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Comparative Effectiveness of Angiotensin-Converting Enzyme Inhibitors and Angiotensin-Receptor Blockers on Cardiovascular Disease Prevention

A thesis By

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BSc, MSc

Submitted in fulfilment of the requirements for the degree of Doctor of Philosophy (PhD) to the Institute of Cardiovascular and Medical Sciences, College of Medical, Veterinary and Life Sciences, University of Glasgow

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ABSTRACT

Background

The renin-angiotensin-aldosterone system (RAAS) plays a crucial role in the development of hypertension, and in the pathogenesis and progression of atherosclerosis, leading to cardiovascular diseases (CVD). ACEIs and ARBs inhibit the RAAS at different targets and achieve comparable BP reductions. Of the two groups, ARBs have a superior safety and tolerability profile. However, there are reports of divergent effects from ACEI and ARBs based on the meta-analyses of clinical trials. ACEIs reduce the risk of MI, cardiovascular (CV) mortality and all-cause mortality, whereas ARBs do not. Clinical practice guidelines consider ACEIs and ARBs equivalent, and a comprehensive and up to date assessment of the 'ARB paradox' is important to inform future guidelines and ensure safe clinical practice.

Objectives: The main objectives of the current thesis are: 1) to investigate the comparative effectiveness of ACEIs and ARBs for preventing CV morbidity and mortality in patients with or at high-risk of CVDs; and 2) to assess the relative contribution of BP-dependent and independent mechanisms on reducing the risk of CV morbidity and mortality, as achieved by ACEIs and ARBs.

Methodologies for answering the research questions: A systematic review and meta-analysis of randomized-control trials (RCTs), was performed in addition to a random-effects meta-regression analysis. Pre-specified outcomes, including, myocardial infarction (MI), angina pectoris, stroke, heart failure (HF), all-cause mortality, and CV death were assessed. In addition, specific pre-specified subgroups of patients, including drug subclasses, comparator drugs, population clinical setting, and mean age (years), were evaluated to demonstrate the differential benefits when comparing ACEIs and ARBs.

Results:

The results for the meta-analysis and meta-regression analysis are divided here into four chapters (4 to 7) according to the CV outcomes for ACEIs and ARBs. In total, 97 RCTs, with 317,984 participants with or at high-risk of CVDs were included in this systematic review, over an average duration of 3.03 years.

ACEIs and ARBs with risk of coronary artery disease events: The pooled data shows that there was a significant 16% (RR, 0.84; 95% CI 0.79-0.90; p<0.00001)

reduction in the risk of incident MI in relation to ACEI therapy compared control group with no evidence of statistical heterogeneity among the trials ($I^2=0\%$.). In contrast, there was no overall benefit identified from ARB therapy (RR, 0.97; 95% CI 0.89-1.06; p= 0.55; $I^2=30\%$). The evidence from the direct comparison trials showed no distinction between ACEIs and ARBs in terms of MI risk (RR 1.02; 95% CI 0.95-1.09; p=0.64; $I^2=0\%$)). Furthermore, I have shown through a meta-regression analysis that nearly half (9% relative risk reduction) of the protective effect of ACEI on MI risk occurs independently of any BP lowering effect. Both ACEI and ARB therapies have no impact in terms of their capacity to reduce the risk of angina pectoris. Considerable heterogeneity was observed among the effect estimates for ACEIs and ARBs (I^2 : 58% and 61% respectively), which limits the author's capacity to formulate definitive conclusions.

ACEIs and ARBs in preventing stroke: According to this systematic review, the analyses reveal that both ACEIs and ARBs provide a reduction in stroke risk compared with placebo; by 14% (RR, 0.86; 95% CI 0.76-0.98; p=0.02; l²=26%) and 9% (RR, 0.91; 95% CI 0.85-1.00; p=0.05; l²=0%) respectively. Based on direct comparison trials, there appear to be a 4% lesser stroke lowering affect from ARB therapy than noted for ACEI (RR, 0.96; 95% CI 0.87-1.06; p=0.42; l²=0%), but this finding did not achieve statistical significance. In the meta-regression analysis, both ACEI and ARB therapies have respective risk ratios for stroke reduction that are significantly related to the magnitude of the BP reduction.

ACEIs versus ARBs for HF prevention: This overview suggests that ACEIs showed a 20% lower HF risk compared with placebo (RR, 0.80; 95% CI 0.74, 0.87; P= 0.00001). Similarly, ARBs had a 14% lower HF risk compared with placebo (RR, 0.86; 95% CI 0.80-0.92; p< 0.00001). This comparable finding was confirmed in direct comparison trials (RR,1.03; 95% CI 0.97-1.09; p=0.37; l²=0%). However, when analyzing trials with active therapy as the comparator group, ARB appeared to be beneficial, with a 13% significant reduction of HF risk, and no added benefit emerging for ACEIs. BP reduction was a major determinant of the risk reduction achieved by ACEIs, while the ARB effect occurred independently of BP reduction.

ACEIs versus ARBs with risk of CV and all-cause mortality: ACEIs are associated with a 9% (RR, 0.91; 95% CI 0.86- 0.97; P=0.002) and 5% (RR, 0.95; 95% CI 0.91- 0.98; p=0.003) relative risk reduction in CV and all-cause mortality respectively. No statistical variation was apparent across the studies (I²=0%). Meanwhile, no

such benefit was seen with ARB-based therapy. Direct comparison trials showed that both ACEIs and ARBs were equivalent in terms of the CV (RR, 1.04; 95% CI 0.98-1.10; p=0.16; l²=0%) and all mortality risk (RR, 1.03; 95% CI 0.98-1.08; p=0.20; l²=0%). The magnitude of the observed risk-reduction seen with ACEIs could be attributed to the magnitude of the BP reduction. Consistent findings involving a series of sensitivity analyses were expected to support the strength of this association.

Conclusions:

In summary, this study used data from 317,984 participants with or at high-risk of CVDs, suggesting that ARBs are as effective as ACEIs at mitigating potential risk from CV events and mortality. The finding from the direct comparison trials also supports the view that ARBs may be slightly more protective than ACEIs against risk of stroke. The reduction in stroke risk brought about by ACEI and ARB is largely attributable to BP reduction. The magnitude of the risk reduction for HF, CV and all-mortality by ACEIs appear to have largely been driven by the magnitude of the BP reduction. The beneficial effect independent of BP reduction of ACEI on MI risk and ARB on HF risk warrants further study.

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Author's declaration

I declare that this thesis and the work presented in it are my own work, unless specified otherwise in the text, and that this thesis has not been submitted previously for a degree or any other qualification at this University or any other institution.

Definitions/abbreviations

=	Equal to
- <	Greater than
>	Less than
<u><</u>	Less than or equal to
⊒ ≥	Greater than or equal to
4 C	Candesartan for Prevention of Cardiovascular Events After Cypher or
- C	Taxus Coronary Stenting
AASK	African American Study of Kidney Disease and Hypertension
ABCD	Appropriate Blood Pressure Control in Diabetes
ABPM	Ambulatory Blood Pressure Monitoring
ACC/AHA	American College of Cardiology/American Heart Association
ACE	Angiotensin-converting enzyme
ACE	Angiotensin-converting enzyme inhibitor
ACTIVE I	Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of
ACTIVET	Vascular Events I
AF	Atrial fibrillation
AHT	Antihypertensive therapy
ALLHAT	Antihypertensive and Lipid-Lowering Treatment to Prevent Heart
	Attack Trial
ALPINE	Antihypertensive Treatment and Lipid Profile in A North of Sweden
	Efficacy Evaluation
ANBP-2	Australian National Blood Pressure Study
Ang	Angiotensin
ANTIPAF	Angiotensin II-Antagonist in Paroxysmal Atrial Fibrillation
ARB	Angiotensin receptor blockers
ASCOT-BPLA	Anglo-Scandinavian Cardiac Outcomes Trial- Blood Pressure Lowering
· - ·	Arms
AT receptor	Angiotensin-II receptors
BB	Beta-blocker
BENEDICT	Bergamo Nephrologic Diabetes Complications Trial
BP	Blood pressure
BHF	British Heart Foundation
BPLTTC	The Blood Pressure Lowering Treatment Trialists Collaboration
CABG	Coronary Artery Bypass Grafting
CAD	Coronary artery disease
CAMELOT	Comparison of Amlodipine Versus Enalapril to Limit Occurrences of
	Thrombosis
CARMEN	Carvedilol And ACE-Inhibitor Remodeling Mild Heart Failure Evaluation
	Trial
CARP	Coronary Atherosclerosis Reduction Project
CASE-J	Candesartan Antihypertensive Survival Evaluation in Japan
CASE-J Ex	Candesartan Antihypertensive Survival Evaluation Extension Study
ССВ	Calcium channel blockers
CDER	Center for Drug Evaluation and Research
CHARM-Overall	Candesartan in Heart Failure Assessment of Reduction in Mortality & Morbidity
CHIEF	Chinese Hypertension Intervention Efficacy
	childse hypertension intervention Effedey

	Congrestive heart failure				
CHF	Congestive heart failure				
	Consolidated Standards of Reporting Trials				
CORD 1 B	COmparison of Recommended Doses				
COPE	Combination Therapy of Hypertension to Prevent Cardiovascular				
-	Events				
CI	Confidence Interval				
CVA	Cerebrovascular accident				
CVD	Cardiovascular Disease				
CVDC	Cardiovascular diseases continuum				
DALY	Disability-Adjusted Life Year				
DBP	Diastolic blood pressure				
DEMAND	Delapril And Manidipine For Nephroprotection In Diabetes				
DETAIL	Diabetics Exposed to Telmisartan And Enalapril				
DHP	Dihydropyridine				
DIABHYCAR	Non-Insulin Dependent Diabetes, Hypertension, Microalbuminuria or				
	Proteinuria, Cardiovascular Events, And Ramipril				
DIRECT	Diabetic Retinopathy Candesartan Trials				
DREAM	Diabetes Reduction Assessment with Ramipril And Rosiglitazone				
	Medication Dutch				
E-COST	Efficacy of Candesartan on Outcome in Saitama Trial EIS European				
	Infarction Study				
E-COST-R	Efficacy of Candesartan on Outcome in Saitama Trial in Renal Disease				
ESH/ESC	European Society of Hypertension/European Society of Cardiology				
EUROPA					
Lonor	Stable Coronary Artery Disease				
ELITE II	Losartan Heart Failure Survival Study				
ELVERA	Effects of amlodipine and lisinopril on left ventricular mass and				
	diastolic function				
ESPIRAL					
	Efecto del tratamiento antihipertensivo Sobre la Progresion de la Insuficiencia RenAL en pacientes no diabeticos				
FDA	FDA Food and Drug Administration				
FEM	Fixed-effect model				
GISSI-AF	Gruppo Italiano Per Lo Studio Della Sopravvienza Nell'infarto				
GISSI-AF	Miocardico-Atrial Fibrillation				
HBPM	Home Blood Pressure Monitoring				
HCTZ	Hydrochlorothiazide				
HFrEF	HF with reduced ejection fraction				
•	IFpEF HF with preserved ejection fraction				
HIJ-CREATE	Heart Institute of Japan Candesartan Randomized Trial for Evaluation				
	in Coronary Artery Disease				
HMOD	Hypertension-Mediated Organ Damage				
HOMED-BP	Hypertension Objective Treatment Based on Measurement by				
	Electrical Devices Blood Pressure Trial				
HONG-KONG	Hong Kong diastolic heart failure				
DHF					
HOPE	PE Heart Outcomes Prevention Evaluation				
HOPE-3	Heart Outcomes Prevention Evaluation-3				
HYVET	Hypertension in The Very Elderly Trial				
IDNT	Irbesartan Idiopathic Nephropathy Trial				

IGT	Impaired glucose tolerance
IHD IMAGINE	Ischemic heart disease Ischemia Management with Accupril Post- Bypass Graft Via Inhibition
IMAGINE	of The Converting Enzyme
I-PRESERVE	Irbesartan In Patients with Heart Failure and Preserved Ejection Fraction
IRMA-2	Irbesartan In Patients with Type 2 Diabetes and Microalbuminuria -2
ISH	International Society of Hypertension
ITT	Intention-to-treat
J- RHYTHM	Japanese Rhythm Management Trial for Atrial Fibrillation
JAMP	Japanese Acute Myocardial Infarction Prospective Study
JMIC-B	Japan Multicenter Investigation for Cardiovascular Diseases-B
J-MIND	Japan Multicenter Investigation of Antihypertensive Treatment for Nephropathy in Diabetics
JNC	Joint National Committee
KACT-MetS	Kagoshima Collaborate Trial in Metabolic Syndrome
	Losartan Vascular Regression Study
LIFE	Losartan Intervention for Endpoint
LIRICO	Long-Term Impact of RAS Inhibition on Cardiorenal Outcomes
LVH	Left Ventricular Hypertrophy
M-H	Mantel-Haenszel
MI	Myocardial infarct
MITEC	Media Intima Thickness Evaluation with Candesartan Cilexetil
MOSES	Morbidity and Mortality After Stroke, Eprosartan Compared with
MRC	Nitrendipine for Secondary Prevention Medical Research Council Trial of Treatment for Mild Hypertension
NAGOYA	Comparison between valsartan and amlodipine regarding morbidity
HEART	and mortality in patients with hypertension and glucose intolerance
NAVIGATOR	Nateglinide And Valsartan in Impaired Glucose Tolerance Outcomes Research
NESTOR	Natrilix SR Versus Enalapril Study in Hypertensive Type 2 Diabetics with Microalbuminuria
NHLBI	National Heart, Lung, And Blood Institute
NICE	National Institute for Care and Health Excellence
NIDDM	Non-Insulin Dependent Diabetes Mellitus
NR	Not reported
NTP-AF	Nifedipine versus Telmisartan on Prevention of AF recurrence in hypertensive patients with AF
NYHA	New York Heart Association
OCTOPUS	Olmesartan Clinical Trial in Okinawan Patients Under
OLIVUS	Impact of Olmesartan On Progression of Coronary Atherosclerosis: Evaluation by Intravascular Ultrasound
ONTARGET	Ongoing Telmisartan Alone and In Combination with Ramipril Global Endpoint Trial
OPTIMAAL	Optimal Trial in Myocardial Infarction with The Angiotensin II
	Antagonist Losartan
ORIENT	Olmesartan Reducing Incidence of End stage Renal Disease in Diabetic
	Nephropathy Trial

PART-2	Prevention of Atherosclerosis with Ramipril PAT Propranolol Aneurysm
PAI-1	Trial Plasminogen Activator Inhibitor-1
PCI	Percutaneous Coronary Intervention
PEACE	Prevention of Events with Angiotensin Converting Enzyme Inhibition
PEP-CHF	Perindopril in Elderly People with Chronic Heart Failure
PHARAO	Prevention of hypertension with the angiotensin converting enzyme inhibitor ramipril in patients with high-normal blood pressure
PHYLLIS	Plaque Hypertension Lipid-Lowering Italian Study PIP2 Phosphatidylinositol Biphosphate POST Prevention of Syncope Trial
PREAMI	Perindopril and Remodeling in Elderly with Acute Myocardial Infarction
PRESERVE	Prospective Randomized Enalapril Study Evaluating Regression of Ventricular Enlargement
PREVENT-IT	Prevention of Renal and Vascular End-Stage Disease Intervention Trial
PREVER-	Prevention of Hypertension in Patients with Pre-Hypertension
treatment	
PROBE	Prospective, randomized open blinded-endpoint
PRoFESS	Prevention Regimen for Effectively Avoiding Second Strokes
PROGRESS	Perindopril Protection Against Recurrent Stroke Study
ΡΤϹΑ	Percutaneous Transluminal Coronary Angioplasty
PVD	Peripheral vascular disease
QUIET	Quinapril Ischemic Event Trial
QUO VADIS	QUinapril on Vascular Ace and Determinants of Ischemia
RAAS	Renin Angiotensin Aldosterone System
RAS	Renin-Angiotensin System
RCTs	Randomized-controlled trials
REM	Random-effects model
REIN	Ramipril Efficacy in Nephropathy
RENAAL	Reduction of Endpoints in NIDDM (Non-Insulin Dependent Diabetes
	Mellitus) With the Angiotensin II Antagonist Losartan
ROAD	Reno protection Of Optimal Antiproteinuric Doses
ROADMAP	Randomized Olmesartan And Diabetes Microalbuminuria Prevention
RR	Relative risk
SAVE	Survival and Ventricular Enlargement
SBP	Systolic blood pressure
SCAT	Simvastatin/Enalapril Coronary Atherosclerosis Trial
SCOPE	Study on Cognition and Prognosis in The Elderly
SCORE	Systematic COronary Risk Evaluation
SUPPORT	SUPPlemental benefit of ARB in hypertensive patients with stable heart
	failure using Olmesartan Trial.
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
TRANSCEND	Telmisartan Randomized Assessment Study in ACE Intolerant Subjects
	with Cardiovascular Disease
Val-HeFT	Valsartan Heart Failure Trial
VALIANT	Valsartan in Acute Myocardial Infarction
VALUE	Valsartan Antihypertensive Long-Term Use Evaluation
WHO	World Health Organization

Poster's presentations

Abstracts for Poster Presentation

Alosaimi, Manal; Roos, Nur Aishah Che; Alnakhli, Anwar Mansour; Cleland, John G.F.; Padmanabhan, Sandosh. Angiotensin-Converting Enzyme Inhibitors & Angiotensin Receptor Blockers on Risk of Mortality: A Meta-Analysis of Randomized-Controlled Trials Involving 317,984 Patients, Journal of Hypertension: April 2021 - Volume 39 - p e200-e201.

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1 Introduction

1.1 Cardiovascular diseases

1.1.1 Epidemiology of cardiovascular diseases

Cardiovascular disease (CVD) is a medical term for conditions affecting the heart and blood vessels, including coronary heart disease (CHD), cerebrovascular accident (CVA), peripheral arterial disease (PAD), rheumatic heart disease, congenital heart disease, deep vein thrombosis (DVT) and pulmonary embolism (Mensah et al., 2019). According to the WHO, CVDs are the most common cause of death worldwide, with approximately 17.9 million people dying from CVDs in 2019, representing 32% of all global deaths. An 85% of these deaths were from ischemic heart disease (IHD) and stroke. IHD is ranked as the leading cause of global mortality, increasing by more than 2 million since 2000 to nearly 8.9 million in 2019 (WHO, 2020). Moreover, global CV-related mortality rate is projected to increase (from 16.7 million in 2002) to an estimated 23.3 million in 2030 (Mathers and Loncar, 2006). Therefore, the WHO has recommended that at least half of all eligible patients (≤40 years or at high-risk of CVDs) should be provided with counselling or drug therapy by 2025 (WHO, 2013).

In the United Kingdom, about 7.6 million people live with heart and circulatory diseases, and this number is rising. In total, 27% of deaths were attributed to heart and circulatory diseases, representing approximately 160,000 deaths annually (BHF, 2021). According to a BHF statistical report, early deaths from heart and circulatory diseases (under the age of 75) are most common in the north of England, central Scotland and the south of Wales, and lowest in the south of England. The estimating health care cost relating to CVD in UK are £9 billion per year (BHF, 2021).

1.1.2The cardiovascular diseases continuum (CVDC)

In 1991, experts presenting advances in CVD research and applied practice assembled at a workshop to interpret the then state of knowledge about CVD to improve therapeutic strategies (Dzau and Braunwald, 1991). A hypothesis was generated that CVD arises from a chain of events precipitated by several CV risk factors, which follow a process involving a number of pathophysiology pathways.

If each stage remains untreated, the individual will experience end-stage HF and ultimately death. The CVD progressive process is termed the Cardiovascular Diseases Continuum (CVDC) (Figure 1.1) (Dzau and Braunwald, 1991). Additionally, CV risk factors such as dyslipidaemia, HTN and DM are known to promote oxidative stress, endothelial dysfunction which then initiate a cascade of events, including alterations in vasoactive mediators, inflammatory responses, and vascular remodelling that terminates in target-organ pathology (Figure1.1). Therefore, a further hypothesis was generated, suggesting that any intervention anywhere along a given chain of events could disrupt the pathophysiological process and provide cardioprotective effects (Carey and Siragy, 2003).

The renin-angiotensin-aldosterone system (RAAS), when overexpressed, has long been recognized as a prime contributor to the development and progression of CVDs. It is now recognized that Ang II is the primary effector; it acts via AT₁receptors, and plays a vital role at all stages of this continuum (Ferrario, 2006). In addition to elevated BP through vasoconstriction and sodium and water retention, Ang II contributes to other pathophysiological processes, such as the development of atherosclerosis, also promoting CV remodelling by induction of cardiac hypertrophy and fibrosis (Ma et al., 2010). Thus, RAAS blockers are an important therapeutic target.

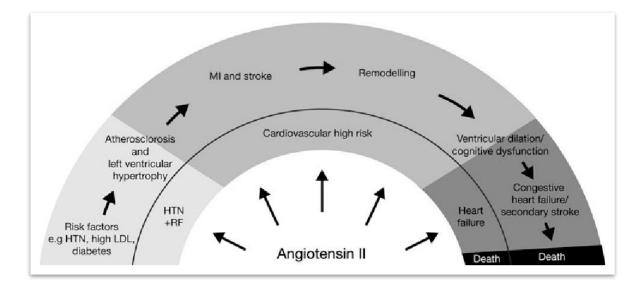


Figure 1-1 Cardiovascular Diseases Continuum (CVDC)

Adapted from Dzau and Braunwald (1991)

1.1.3 Risk factors for CVD

In 1957, the concept of risk factors in CVD was first described by findings in the Framingham heart study (FHS) (Dawber et al., 1957) . The FHS and other epidemiological studies were responsible for improving our knowledge of the association between CVDs and potential risk factors. There are many known risk factors linked to CVD, which are classified as modifiable and non-modifiable risk factors. Modifiable risk factors comprise elevated BP, high blood cholesterol levels, smoking, obesity, lack of physical activity, dietary habit, and stress. Meanwhile, non-modifiable risk factors include age, gender, ethnicity and family history (Hajar, 2017). The presence of a particular risk factor in an individual patient does not necessarily impose to CVD, however, the presence of more risk factor will increase the likelihood. Besides conventional risk factors, recent research has identified novel biomarkers for CV risk prediction that would facilitate a new targeted approach to CVDs, including growth differentiation factor-15, C-reactive protein, fibrinogen and micro-RNA. Each risk marker has a certain level of involvement in the pathophysiology of CVDs such as dyslipidaemia, thrombosis, inflammation, fibrosis, and hemodynamic stress (Wang et al., 2017, Thomas and Lip, 2017)

1.2 Hypertension

Maintenance of a normal blood pressure (BP) is dependent on the balance between cardiac output (CO) and systemic vascular resistance (SVR) (also known as total peripheral vascular resistance (PVR)). The majority of patients diagnosed with essential hypertension have a normal CO but a raised PVR. PVR is determined not by large arteries or capillaries but by small arterioles, the walls of which contain smooth muscle cells. Contractions in the smooth muscle cells are thought to lead to elevated intracellular calcium concentration, which might explain the vasodilatory effect of drugs that block the calcium channels. Prolonged smooth muscle constriction is thought to induce structural changes, with thickening of the arteriolar vessel walls possibly mediated by angiotensin, leading to an irreversible rise in peripheral resistance (Beevers et al., 2001). Many of these mechanisms have been postulated to contribute to a rise in peripheral resistance in cases of hypertension. Two mechanisms have been studied extensively here, disturbances in salt and water excretion from the kidneys (abnormalities in the intrarenal RAS

or abnormalities of the sympathetic nervous system). It has also been suggested that endothelial dysfunction, vascular inflammation, and vasoactive substances might contribute to increased peripheral resistance and vascular damage in incidences of hypertension (Beevers et al., 2001)

According to the WHO, hypertension is one of the most serious CV risks leading to CV and renal events across the CVD continuum (WHO, 2020). Hypertension is diagnosed when an office or clinic systolic blood pressure (SBP) is \geq 140 mm Hg and/or their diastolic blood pressure (DBP) is \geq 90 mm Hg following repeated examination (Unger et al., 2020). High-risk conditions such as diabetes, coronary heart disease, chronic kidney disease and stroke are commonly associated with hypertension (Beevers et al., 2001).

1.2.1 Classification of hypertension

Recent guidelines recommend classifying BP on an office value that is evaluated as either optimal, normal, high-normal, or hypertension ranging from grades 1-3. The definition of hypertension, based on various methods of measurement, is similar in the National Institute for Health and Care Excellence (NICE, 2019), the European Society of Hypertension/ European Society of Cardiology (ESH/ESC) (Williams et al., 2018) and the Eighth Joint National Committee (JNC 8) guidelines (James et al., 2014). Meanwhile, the updated American College of Cardiology/ American Heart Association (ACC/AHA) guideline modified the definition of hypertension in the clinic/office as SBP \geq 130 and/or DBP \geq 80 instead of SBP 140 and/or DBP 90 mmHg (Whelton et al., 2018). Table 1-1 summarizes the diagnosis of hypertension according to methods of measurement established in scientific guidelines. Based on recommendations set out in hypertension guidelines, a diagnosis of hypertension is based on either office or clinic measurement and must also be confirmed by home or ambulatory BP monitoring. In a large cohort study, over a period of 24-hours, daytime and night-time ambulatory BP (ABPM) are better predictors for CV mortality than clinic BP after adjustment of potential confounders including age and sex. Moreover, ABPM highlights the white coat and masked hypertension phenomena (Banegas et al., 2018)

NICE (2019) - United Kingdom				
Clinic	SBP ≥140 and/or DBP ≥90			
ABPM (Daytime)	SBP ≥135 and/or DBP ≥85			
НВРМ	SBP ≥135 and/or DBP ≥85			
ESH/ESC (2018) [‡] - European				
Office BP	SBP ≥140 and/or DBP ≥90			
ABPM				
Daytime	SBP ≥135 and/or DBP ≥85			
Night time	SBP ≥120 and/or DBP ≥70			
24-hour	SBP ≥130 and/or DBP ≥80			
НВРМ	SBP ≥135 and/or DBP ≥85			
JNC 8 (2014) - US				
Clinic/Office	SBP ≥140 and/or DBP ≥90			
ACC/AHA (2017) - US				
Clinic/Office	SBP ≥130 and/or DBP ≥80			
ABPM SBP ≥130 and/or DBP ≥80				
НВРМ	SBP ≥130 and/or DBP ≥80			
Abbreviation: ABPM: ambulatory blood pressure monitoring; ACC/AHA: American College of				
Cardiology/the American Heart Association. HBPM: home blood pressure monitoring; JNC: Joint				
National Committee;	ESH/ESC: European Society of Cardiology/European Society of			
Hypertension; NICE: The National Institute for Health and Care Excellence.				
‡ Diagnostic values of hypertension remain unchanged from previous guideline				
See list of definitions/abbreviation				

Table 1-1 Diagnosis of hypertension based of	on measurement technique from guidelines
--	--

1.2.2Global burden of hypertension

Generally, an elevated level of systolic blood pressure (SBP) of \geq 140 mmHg accounted for 7.8 million deaths (14 % of total deaths), and 143 million disabilityadjusted life-years lost (DALYs) (Forouzanfar et al., 2017). Despite improvements in therapeutic approaches, the deaths associated with hypertension have increased by 40% since 1990. The CVD is accounted for by a majority of SBP-related deaths (41%), among which 54.4% of cases were caused by IHD, 58.3% to haemorrhagic stroke and 50% to ischemic stroke (Forouzanfar et al., 2017). In Global Burden of Disease (GBD) analysis, elevated BP is the first and second global attributable death in female and male causes of all deaths; accounting for 20.3% and 18.2% respectively (GBD 2019 Risk Factors Collaborators, 2020). Therefore, management of CVDs risk factors includes hypertension as the main way to interrupt the CVD continuum (Williams et al., 2018, NICE, 2019).

1.2.3 Hypertension and cardiovascular risk assessment

Hypertension is commonly clustered with other CV risk factors as diabetes, lipid disorders, obesity and hyperuricemia. The association of one or more risk factors with hypertension is likely to increase the risk of CV, cerebrovascular and renal events (GBD 2019 Risk Factors Collaborators, 2020). Therefore, stratification of hypertensive patients based on their CV risk assessment scores is a crucial component of clinical decision making; the higher the risk, the more intense the action required (Unger et al., 2020).

Many CV risk assessment systems have been developed for clinical practice in apparently healthy individuals such as Framingham (Ralph B. D'Agostino et al., 2008) and ASSIGN scores (ASSIGN score, 2014). In 2003, European Guideline on CV prevention in clinical practice recommended use of the Systematic Coronary Risk Estimation (SCORE) system (De Backer et al., 2003). The validity of the SCORE system was based on a large data from 12 representative European cohort studies across different European countries with varying CV risk levels (Conroy et al., 2003). Previously, the SCORE system only estimated the risk for patients aged 40-65 years, while an updated version later developed for patients aged 65 years or more (Cooney et al., 2016). Moreover, the system predicts fatal atherosclerotic CVD events over 10-years based on gender, age, smoking, SBP and total cholesterol. The guidelines recommended avoiding estimates of CV risk for hypertensives with established CVD, DM, CKD (stages 3-5) because they are automatically considered to be at very high-risk ($\geq 10\%$) or high-risk (5-10\%) (Piepoli et al., 2016). The simplest chart for assessing CV risk level for hypertensives was proposed by ESC/ESH guideline. This chart facilitates diagnosis of each patient based on BP level and known additional risk factors, such as age (>65 years), gender (male/female), high LDL/triglyceride, hypertension-mediated organ damage (HMOD) such as LVH and CKD and documented CVD (Williams et al., 2018). Table 1.2 illustrates the classification of risk level for hypertensives (low, moderate, and high risk) based on additional risk factors, HMOD and established diseases for middle-aged male.

	BP (mmHg) grading			
Other risk factor,	High-normal	Grade 1	Grade 2	Grade 3
HMOD or disease	SBP 130-139	SBP 140-159	SBP 160-179	SBP ≥ 180
	DBP 85-89	DBP 90-99	DBP 100-109	DBP ≥ 110
No risk factors	Low risk	Low risk	Moderate risk	High risk
1-2 risk factors	Low risk	Moderate risk	Moderate to	High risk
			high risk	
≥ 3 risk factors	Low to	Moderate to	High risk	High risk
	moderate risk	high risk		
HMOD, CKD (grade 3) or	Moderate to	High risk	High risk	High to very
DM without organ	high risk			high risk
damage				
Established CVD, CKD	Very high risk	Very high risk	Very high risk	Very high risk
(grade \geq 4) or DM with				
organ damage				

Table 1-2 Classification of hypertension risk based on additional risk factors, HMOD and comorbidity

Adapted from ESC/ESH 2018 (Williams et al., 2018) & ISH 2020 (Unger et al., 2020) The CV risk illustrated is for 60 years old males, HMOD: Hypertension-Mediated Organ Damage See list of definitions/abbreviations

1.2.4 Management of hypertension

Prospective Studies Collaboration (2002) revealed a linear relationship between BP, vascular morbidity, and mortality. In middle aged patients, a reduction of 20 mmHg of SBP (or 10 mmHg DBP) is associated with a more than twofold difference in the stroke death rate, with two fold differences in the death rates from IHD and other vascular causes (Lewington et al., 2002). A meta-analysis of antihypertensive agents in 147 cohort and RCTs demonstrated that a benefit of these drugs is arisen as result of BP reduction. Specifically, a reduction of 10 mmHg SBP (5 mmHg DBP) accounted for a 22% and 41% lower incidence of CHD and stroke events respectively (Law et al., 2009). Therefore, a well-controlled BP is essential for all hypertensives to avoid the consequences of complications.

Established guidelines such as the National Institute for Health and Care Excellence (NICE), the European Society of Hypertension/ European Society of Cardiology (ESH/ESC), and the Eighth Joint National Committee (JNC) recommend angiotensin-converting enzyme inhibitor (ACEI), angiotensin-receptor blocker

(ARB), calcium channel blocker (CCB), and thiazide diuretics for the initial management of hypertension unless there is another compelling indication (NICE, 2019, Williams et al., 2018, James et al., 2014). Furthermore, the strategies for using these agents have been generated by guidelines to improve BP level and prevent potential complications. Previous ESH/ESC guideline emphasizes the need to initiate monotherapy and then increase dosage or substitute another monotherapy if BP is not controlled (Mancia et al., 2013). However, increasing the dose of monotherapy might be increase the possibility of side effects. Additionally, switching to other agents can decrease compliance with therapy and so might be ineffective. Therefore, the most recent guidelines focus on a stepcare approach, in which monotherapy is used as a first-step, and as an add-on therapy when required. Despite this, control of BP remains poor. The observational study showed that of 142,042 participants, 40% had treated hypertension; of these, 30% had controlled HTN of less than 140/90 mmHg (Chow et al., 2013). Failure to achieve target BP suggested a need for substantial improvements to guarantee effective outcomes. Therefore, a newer guideline prefers a combination of therapies to manage hypertension by an ACEI or ARB with either CCB and/or a thiazide or thiazide-like diuretic. However, monotherapy would be considered to manage low risk grade 1 hypertension (SBP < 150 mmHg) and patients aged 80 years or more (Williams et al., 2018). Table 1.3 shows recommendations from international guidelines to manage uncomplicated hypertension by clinically available agents. Thorough knowledge of each class of antihypertensives in regard to efficacy and safety would improve clinical decision making. Nevertheless, hypertension is commonly clustered with one or more other diseases, especially with advanced age. A large retrospective observational study using data on 86,100 participants in the General Practice Research Database in UK showed hypertension was the main disease co-occurring with other medical conditions, principally CHD, CKD, and diabetes (Brilleman et al., 2013). Therefore, selecting an appropriate antihypertensive agent to identify patients with a medical history of chronic disease would improve the quality of life. Table 1.4 outlines the selection steps for therapy according to the presence of comorbidities.

Guideline	Initial Recommended therapy
NICE (2019)	Age<55 years but NOT of black African or African-Caribbean family origin:
	ACEI or ARB
	Age≥55 years or black African or African-Caribbean family origin at any
	age: CCBs (in case of oedema or evidence of HF, offer thiazide-like diuretic)
ESH/ESC (2018)	ACEI or ARB+CCB or diuretic +BB ^a
JNC-8 (2014)	Black: TZ or CCB alone or in combination
	Non-black: ACEI, ARB, CCB alone or in combination
ACC/AHA (2017)	TZ, CCB, ACEI or ARB

Table 1-3 Guideline recommendations for initial therapy for uncomplicated hypertension

See list of definitions/abbreviations

^a Consider BB at any treatment stage for specific indication as HF, post-MI, or AF

Table 1-4	Compelling	indications f	for antih	vpertensive	agents [‡]
	- 5				

		Recommended Drugs								
Compelling indications	Diuretic	BB	ACEI	ARB	ССВ					
HFrEF	● ^a	•	•	•						
Post-MI		٠	•	•						
High coronary diseases risk	•	•	•	•						
DM	● ^a		•	•	•					
CKD	● ^a		•	٠	•					
Recurrent stroke prevention	● ^b		•							
AF		•	•	•	●C					
PAD										

See list of definitions/abbreviations

[‡]Adapted from ESC/ESH guidelines for the management off arterial hypertension (2018) and JNC 8 (2014).

 $^{\rm a}$ Using a loop-diuretic when eGFR is <30ml/min/1.72m²; $^{\rm b}$ Thiazide-like diuretic; $^{\rm c}$ non-dihydropyridine CCB

1.3 The renin-angiotensin aldosterone system (RAAS) in CVDs: an overview

1.3.1 Historical perspective

The RAAS was discovered more than a century ago. In 1898, Tigerstedt and Bergman first demonstrated that a substance was extracted from the renal cortex of rabbits (later named renin) that elevated BP when injected intravenously to recipient rabbits (Tigerstedt and Bergman, 1898). However, the discovery of renin by Tigerstedt was widely disputed and ignored until research published in 1934 by Goldblatt and colleagues. It took another 40 years for scientists to realize that renin as an enzyme acts on a protein substrate to produce a peptide that mediates the vasopressor effect of renin. This protein substrate was later named angiotensinogen and the peptide became known as angiotensin. Two distinct forms of angiotensin II (Ang II), where Ang I was cleaved by ACE to generate biologically active Ang II. These findings have augmented the research and improved our understanding of RAAS. The pathway of RAAS and its components can be classified into a classic pathway or a non-classic pathway.

1.3.2 Classic pathway of RAAS

1.3.2.1 Principal effector: Ang II

The classical RAAS hormonal cascade begins with biosynthesis of renin (Figure 1.2). Renin is an inactive prohormone formed by the proteolysis of a 43-aminoacid prosegment peptide from the N-terminus of prorenin, the proenzyme or renin precursor. Mature renin is stored in the granules of the juxtaglomerular cells of the kidney and is released by an exocytic process involving stimulus-secretion coupling with the renal and then the systemic circulation (Mascolo et al., 2017). Renin, an aspartyl protease produced by the juxtaglomerular cells of the kidney, regulates the initial and rate-limiting steps of RAAS by cleaving to the N-terminal portion of a large molecular weight globulin, angiotensinogen, to form the Ang I or Ang-(1-10). Ang-I is a biologically inert decapeptide, which requires further activation by ACE, a dipeptidyl carboxypeptidase, to form the biologically active octapeptide Ang II. Angiotensinogen is an alpha-2-globulin mainly produced by the liver, but the mRNA expression of angiotensinogen was also detected in other tissue, such as the kidney, brain, heart, vascular, adrenal gland, ovary, placenta, and adipose tissue (Carey and Siragy, 2003, Mascolo et al., 2017). The biologically inert decapeptide Ang-I is activated by the hydrolysis process via angiotensinconverting enzyme (ACE), which removes the C-terminal dipeptide to form the octapeptide Ang II (Ang-1-8). Octapeptide Ang II is a biologically active potent vasoconstrictor. The ACE is a membrane-bound exopeptidase that is localized on the plasma membranes of several cell types, including the vascular endothelial cells, microvillar brush border epithelial cells (e.g., renal proximal tubule cells), and the neuroepithelial cells. ACE also metabolizes other peptides to create the inactive metabolites bradykinin and kallidin. Therefore, the enzymatic function of ACE is potentially augmented by increased vasoconstriction and decreased vasodilation. Ang II can bind to and signal through the AT₁ and AT₂ receptors (Carey and Siragy, 2003)

1.3.2.2 Bradykinin

ACE also metabolizes other peptides, such as bradykinin (BK), a potent endothelium-dependent vasodilator, to create an inactive form. Functionally, BK exerts cardioprotective effects via vasodilation, antiproliferative, and antiapoptotics, and stimulates tissue plasminogen activator (tPA) from endothelium and fibrinolysis (Atlas, 2007). The vasodilation effect of bradykinin occurs as a result of stimulating the production of prostaglandin, nitric oxide (NO) and endothelium-derived hyperpolarizing factor (Francolini et al., 2007).

1.3.2.3 Angiotensin (AT) receptor subtypes

Four angiotensin receptor subtypes have been described (figure 1.2). The bulk of the established action of Ang II is mediated by the AT_1 receptor. It is widely expressed at a constant level in adults, and is located in various tissues as blood vessels, heart, kidneys, adrenal glands, brain and liver. These mediate CV effects (vasoconstriction, increased BP, increased cardiac contractility, vascular and cardiac hypertrophy), kidney (renal tubular sodium reabsorption, inhibition of renin release), sympathetic nervous system, and adrenal cortex (stimulation of aldosterone synthesis), cell growth and proliferation, inflammatory responses, and oxidative stress (Mascolo et al., 2017, Atlas, 2007).

The second subtype is the AT_2 receptor, which is mainly limited to embryogenesis and/or early development. Despite its low levels of expression in adult, it has

been proposed that AT_2 plays a role in opposing the action of the AT_1 receptor (Levy, 2004). It mediates vasodilation via a release of NO, antiproliferative, apoptotic effects and regulates BP. However, recent data suggested that the actions of AT_2 -mediated are less beneficial than previously expected and might have deleterious effects through growth promotion, fibrosis, and hypertrophy, proatherogenic and proinflammatory effects. Moreover, they are located in the uterus, the adrenal glands, the CNS, the heart (cardiomyocytes and fibroblasts), and the kidney (D'Amore et al., 2005).

The biological actions of AT₄ remain uncertain, but a link has been proposed to plasminogen activator inhibitor-1 (PAI-1) expression. Whereas the functions of AT3 receptors is unknown. PAI-1 is released by stimulation of the AT₄ receptor by Ang II, Ang III and Ang IV (Kramar et al., 1998, Atlas, 2007). Moreover, excessive PAI-1 was found in atherosclerotic plaques, and their role is a mediated fibrinolysis inhibition and a powerful independent predictor of death after transmural MI (Nikolopoulos et al., 2014). Whereas, some studies suggest it plays a role in improving cerebral blood flow, thereby conferring cerebro-protective effects (Chai et al., 2004).

1.3.3 Non-classical pathway and tissue RAAS

The non-classical pathway of RAAS involves enzymes, peptides, and receptors, i.e., ACE2, Ang-III, Ang-IV and Ang 1-7. The two main axes of the pathway recognized ACE2/Ang 1-7/Mas axis and Ang IV/AT axis (Mascolo et al., 2017). **Figure 1.2** illustrates non-classic pathways in the system.

1.3.3.1 The aminopeptidase products of Ang-II: Ang III and IV

Although Ang-II is recognized as a vital product of RAAS, recent evidence has identified novel peptides with potential biological activities, particularly in the tissue, known as Ang III and Ang IV. In the Ang IV/AT axis, Ang III and IV are formed by the action of aminopeptidases involving the sequential removal of amino acids from the N-terminus of Ang II. High levels of these aminopeptidases are likely to be produced in the brain and kidney tissues for example. Heptapeptide Ang-III is formed firstly by the removal of the first N-terminal amino acid from Ang-II. Moreover, Ang III is present in CNS where it is thought to play an important role in tonic BP maintenance and hypertension. Further enzymatic degradation of Ang III

produces a hexapeptide Ang IV (Mascolo et al., 2017). Ang IV generally opposes the action of Ang II by facilitating vasodilation in the cerebral and renal vascular area, and attenuation of Ang II-induced vasoconstriction. Its actions are mediated by the AT_1 and AT_4 receptors (Atlas, 2007, Chai et al., 2004).

1.3.3.2 Ang 1-7

ACE2/Ang 1-7/Mas axis involved the formation of Ang 1-7 directed from Ang-II via a newly discovered carboxypeptidase enzyme called ACE2. ACE2 has a significantly similar structural homology to ACE; however, this enzyme does not convert Ang-I to Ang-II. Ang 1-7 is known to play a critical role in CV homeostasis and alterations to its function contribute to the pathogenesis of CVD (Dzau et al., 2002). Additionally, Ang-I can also be converted by prolyl endopeptidase (PEP) and neutral endopeptidase (NEP) to the heptapeptide Ang 1-7. ACE2 can be cleaved Ang I to form Ang 1-9, which in sequence is converted to Ang 1-7 by ACE. Ang 1-9 is a peptide that currently has no known function. Ang 1-7 is activated a unique receptor called the Mas receptor that was found to promote vasodilation via NO release, Akt phosphorylation, and anti-inflammatory effects. New evidence has shown that the ACE2/Ang1-7/MAS axis is located in the CNS of humans, and provides cerebrovascular protective effects, mediated by the release of bradykinin and NO (Mascolo et al., 2017).

1.3.3.3 Tissue RAAS and Alternative Pathways of Angiotensin Biosynthesis

ACE is considered the main generator of Ang II from Ang I in systematic circulation. Whereas, in tissue-based RAS, novel non-ACE dependent Ang II formation was identified in the heart by dodecapeptide Ang 1-12 (Atlas, 2007). In 2006, Ang 1-12 was first isolated by Nagata et al. (2006) in the small intestine of a Japanese strain of Wistar rats. Their observations showed that the expression of Ang 1-12 is increased in cardiac myocytes in spontaneously hypertensive rats, and that cardiac chymase expression has a potential role in cardiac hypertrophy. Moreover, vasoconstrictor effects were abolished by captopril and ARBs. This conversion may be facilitated by serine proteinases, such as kallikrein, cathepsin G and chymase. Chymase is more potent, and a specific Ang II-generator, identified from all known serine proteases. Numerous studies have suggested that 40% of Ang II is generated by the non-ACE pathway in the human kidney. The chymase primarily generates Ang-II in atrial cardiac myocytes and atherosclerotic aorta (Ihara et al., 1999, Ahmad et al., 2011). Therefore, alteration to tissue-RAAS might contribute to pathogenesis in CV diseases.

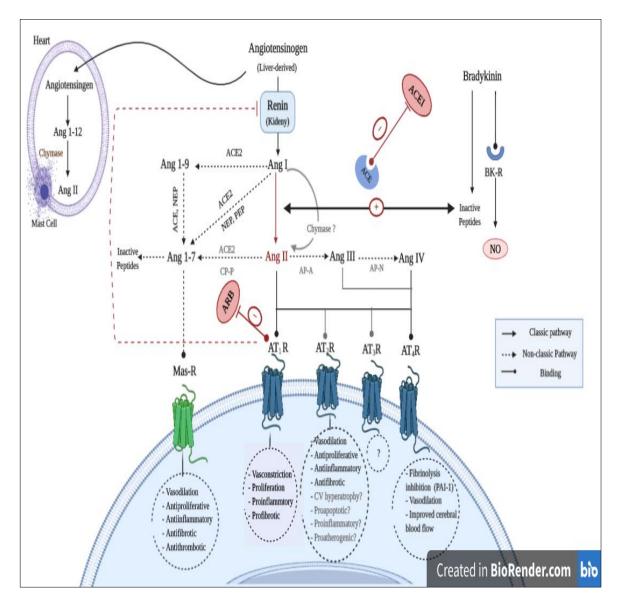


Figure 1-2 Classical and non-classical renin-angiotensin system (RAS) pathway and its inhibition

Red lines indicate inhibition by ACEI and ARB. The red dashed line indicates a negative feedback loop of renin secretion. Abbreviation: Ang; angiotensin; AT-R: Angiotensin receptor subtype; R: receptor; BK-R: Bradykinin receptor; NEP: neutral-endopeptidase; PEP: prolyl-endopeptidase; ACE: Angiotensin-converting enzyme; ACEI: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin-receptor blockers; PAI-1: Plasminogen activator inhibitor-1; AP-A: aminopeptidase-A; AP-N: aminopeptidase-N

Scientific information is adapted from (Atlas, 2007, Carey and Siragy, 2003, Mascolo et al., 2017).

1.4 RAS blockers: an important therapeutics target

1.4.1 Angiotensin-converting enzyme inhibitors (ACEIs)

In the 1960s, a study extracted a peptide from the venom of the Brazilian arrowhead viper (Bothrops jararaca), this peptide inhibited kinase II, an enzyme involved in the degradation of bradykinin. Later, it was shown to be identical to ACE (Ferreira, 1965). A synthetic analogues peptide fraction of snake venom (nonapeptide teprotide) was shown to have a beneficial effect in patients with hypertension and HF through its BP lowering and hemodynamic effects (Fau et al., 1977). Consequently, numerous research has been carried-out on orally active competitive ACEIs, the first of these being captopril (Cushman et al., 1977). Captopril was designed based on known inhibitors of another zinc-containing metalloprotease, carboxypeptidase A, and included a sulfhydryl-containing amino acid to serve as a ligand for the zinc moiety (Cushman et al., 1977). The sulfhydryl in the captopril group contributes to undesirable side effects, such as proteinuria, allergic reactions, and altered taste. Therefore, other active oral ACEIs were synthesized to replace this group with a carboxyl group (e.g., lisinmopril, benazepril, quinapril, ramipril, perindopril, cilazapril, trandolapril) or phosphoryl group (fosinopril) (Atlas, 2007, Ferrario, 2006).

1.4.1.1 ACEIs classification

ACEIs are classified into three categories according to the group that binds the zinc atom of the ACE molecule, giving a sulfhydril, a carboxyl or a phosphoryl group as a zinc ligand. **Table 1-5** summarises the pharmacological properties of ACEIs.

1.4.1.2 Pharmacodynamics: High versus low-affinity tissue ACEIs

ACEIs vary in their binding affinity to tissue-based ACE, where it is based on the strength affinity of a functional group that allows drugs to adhere to ACE. The binding strength of ACEI to tissue ACE is dependent on the binding of sulfhydryl-, carboxyl-, or phosphinyl-containing groups at the N-terminus of the ACEI with zinc ion, and the binding of the negatively charged C-terminus of the ACEI with positively charged carboxylate dock residue of ACE (Unger and Gohlke, 1994). Quantitatively, more than 90% of tissue-based ACE is found in tissues such as blood vessels, the myocardium, kidneys, brain, and adrenal glands. Whereas 10% of ACE

circulates in plasma, where it contributes to acute changes in BP (Dzau et al., 2002). Numerous experimental studies have been proven that tissue ACE plays a vital role in altering the pathophysiology of CVDs, and thus its inhibition may restore endothelial function or prevent endothelial dysfunction. Furthermore, tissue-based ACE produces a local Ang II that is responsible for changes in the myocardium and vascular structures leading to the development of arteriosclerosis and ischemic events (Dzau et al., 2002, Unger and Gohlke, 1994).

A radioligand inhibitor binding study demonstrated that 24-hrs after treatment with quinapril, ACE was still inhibited by 25% in plasma, by 30% in aorta, by 35% in the kidneys and by more than 40% in the cardiac atria and ventricles (Fabris et al., 1990). Therefore, quinapril has the strongest affinity to tissue-ACE and it was suggested that high-affinity tissue ACEIs in the heart, vasculature, and kidneys might have important cardioprotective effects. Moreover, researchers have ranked potency of ACEIs as following: quinaprilat=benazeprilat > ramiprilat > perindoprilat > lisinopril > enalaprilat > fosinopril > captopril. Quinaprilat also has the highest tissue retention among ACE inhibitors (Fabris et al., 1990, Dzau et al., 2002). Various studies have showed that ACEI-members are not homogeneous in terms of their selectivity to bradykinin and Ang-I binding sites. At an equivalent dose, perindoprilat had a high affinity to bradykinin versus the Ang-I binding site, whereas enalapril has the lowest profile (Francolini et al., 2007).

1.4.1.3 Pharmacokinetics (PK) profile

Although ACEIs share a common active mechanism and many of their therapeutic profiles, they differ in terms of their physiochemical and PK properties. Bioavailability is an important factor determining the clinical efficacy of individual ACEIs (Lopez-Sendon et al., 2004). Lipophilicity is a vital factor affecting bioavailability and may contribute to the differences in tissue penetration among ACEIs. A study has demonstrated that with similar structural ACEIs, drugs with a highly lipophilicity property penetrate well into target organs, such as the brain. Fosinopril has the most lipophilic properties, and therefore has highest potential for diffusion into the brain. Whereas, captopril and zofenopril are less lipophilic, with the result that their inhibition capacity typically persists for 6 hours or less (Ranadive et al., 1992). The majority of ACEIs are administered as pro-drugs and hepatic or via gastrointestinal tissue hydrolysis for conversion into active

metabolites. Whereas captopril and lisinopril are not activated by hepatic metabolism into active metabolites. The chief route of extraction of most ACEIs is the renal route, whereas fosinopril, zofenopril, trandolapril and spirapril display balanced elimination via hepatic and renal routes. Therefore, they are not significantly affected by renal impairment. The elimination of captopril is rapid and thus, the duration of its action is short (>6 hour). Whereas tandrolaprilat (prodrug of Trandolapril) is eliminated more slowly than other ACEIs (Lopez-Sendon et al., 2004, Brown and Vaughan, 1998). Newly approved ACEIs, such as quinapril and trandolapril, are known for their strong binding to proteins, relative to older generics. Thus, they have a prolonged terminal half-life and a greater affinity with tissue-ACE (Dzau et al., 2002).

	Drug	Active	Protein-	Elimination	Renal	Bradykinin/Ang-
		metabolite	bound	Half-life	elimination	l selectivity
			fraction	(h)	(%)	ratio
			(%)			
Sulfhydryl-	Captopril	None	25-30	2	95	NA
containing	Zofenopril*	Zofenoprilat	NA	4.5	60**	NA
	Cilazapril	None	NA	10	80	NA
	Benazepril*	Benazeprilat	97	11	85	NA
	Enalapril*	Enalaprilat	20-89	11	88	1
	Lisinopril	None	0	12	70	NA
Carboxyl-	Perindopril*	Perindoprilat	60	>24	75	1.44
containing	Quinapril*	Quinaprilat	97	2-4	75	1.09
	Ramipril*	Ramiprilat	73	8-14	85	1.16
	Spirapril	None	NA	1.6	50**	NA
	Trandolapril*	Trandolaprilat	65-94	16-24	15**	1.08
Phosphinyl-	Fosinopril*	Fosinoprilat	NA	12	50**	NA
containing						

Table 1-5 Summary of pharmacological properties of ACEIs

*Prodrug; **Significant hepatic elimination

Data are adapted from (Lopez-Sendon et al., 2004, Lala and McLaughlin, 2008, Brown and Vaughan, 1998, Francolini et al., 2007)

1.4.1.4 Individualization of ACEI-based therapy indications

Previous RCTs have provided evidence that each ACEI has a unique clinical efficacy for use treating patients across the spectrum of cardiac disease. Minimal data shows the superiority of one ACEI over another for controlling HTN; therefore, all ACEIs are indicated for the management of hypertension (Lala and McLaughlin, 2008). Based on the results of the EUROPA and HOPE trials, perindopril and ramipril are recommended to reduce the risk of CV events in high-risk patients with a history CAD, stroke, PVD, or diabetes accompanied by at least one other CV risk factor (Fox et al., 2003, Yusuf et al., 2000). Captopril and lisinopril show kidney-protective properties, reducing the progression rate of renal insufficiency and the development of serious adverse clinical outcomes (death or need for renal transplantation or dialysis) (Lewis et al., 1993). Therefore, they are indicated for the treatment of diabetic nephropathy in patients with T1DM.

ACEIs are well established as improving survival following acute MI in clinically stable patients with LVD or HF; although, not all ACEIs show a comparable benefit. Captopril, enalapril, ramipril, trandolapril and lisinopril have been indicated for post-MI with LVD or/and clinical signs of HF to improve survival and prevent progress to overt HF. For the management of symptomatic CHF, seven ACEIs, including captopril, enalapril, lisinopril, ramipril, fosinopril, quinapril and perindopril (in Europe) are indicated for treating symptomatic HF as an adjunctive therapy (Lopez-Sendon et al., 2004). **Table 1-6** summarizes the indications for the currently available ACEIs and their approval years.

		Indications							
Generic name	FDA Approval	HTN	HF	Post-MI	Nephropathy (T1DM)	High-risk CV			
Captopril	1981	•	•	●ab	•				
Enalapril	1985	•	•	● ^a					
Lisinopril	1987	•	•	● ^b	• ^c				
Ramipril	1991	•	•	● ^d		• ^e			
Fosinopril	1991	•	•						
Benazepril	1991	•							
Quinapril	1991	•	•						
Perindopril	1993	•	● ^c			● ^f			
Moexipril	1995	•							
Trandolapril	1996	•		● ^a					

Table 1-6 Approval year and indications for currently available ACEIs

Abbreviations: HTN: hypertension; HF: heart failure; MI: myocardial infarction; T1DM: type1 diabetic.

Approval date and indications are taken from: <u>https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm</u>. (FDA, 2020) and (Joint Formulary

Committee, 2020)

 $^{\rm a}\, with$ LVD and/ or HF

^b within 24 hours of MI onset; ^c approved in Europe.

^d with clinical signs of CHF (started at least 48 hours after acute infarction).

^e recommended in patients ≥ 55 years old at high risk of developing a major CV event because of a history of CAD, stroke, PVD, or diabetes with at

least one CV risk factor

^f Indicated in patients with stable CAD to reduced risk of CV mortality and MI.

1.4.2 Angiotensin-receptor blockers (ARBs)

The concept of the treatment of hypertension and its consequences by blocking the action of Ang II on its receptor was first established in the 1970s with the use of a nonselective antagonist of Ang II receptors: saralasin. However, saralasin had a partial agonist effect similar to Ang II's effects at high doses (Brunner et al., 1971). Subsequently, numerous studies have been carried out. In the 1990s, the first orally active, selective, and potent nonpeptide ARB was developed and approved, losartan (Duncia et al., 1990). Subsequently, numerous "sartans" were introduced into clinical practice, including valsartan, irbesartan, candesartan, eprosartan, telmisartan, and olmesartan (Ferrario, 2006, Burnier, 2001). ARBs are non-peptide compounds with some similarities in chemical structure: (a) tetrazolobiphenyl structure (candesartan, irbesartan, losartan, and valsartan); (b) benzimidazole group (candesartan and telmisartan); (c) apart from irbesartan, all active ARBs have a free carboxylic acid group. The variations in chemical structure might affect the pharmacodynamic and pharmacokinetic properties of each ARB, such as lipid solubility, affinity to AT₁ receptors and pharmacokinetics profile (Ferrario, 2006).

1.4.2.1 Pharmacological actions unique to individual ARBs

As shown in **table 1.7**, some ARBs act as surmountable antagonists, that its antagonism action can be overcome by increasing the concentration of Ang II such as losartan. Meanwhile others are insurmountable antagonists that bind to the AT₁ receptor irreversibly, such as candesartan and telmisartan (Burnier, 2001, Taylor et al., 2011). Therefore, telmisartan is the longest acting agent among various ARBs (elimination half-life ~ 24h). A study ranked the order of affinity of ARBs as follows: telmisartan > olmesartan > candesartan > EXP3174 > or = valsartan > or = losartan (Kakuta et al., 2005). Their findings suggested that agents with the strongest AT₁ antagonize ability are associated with a longer duration of action, and thus might provide a long-lasting BP lowering effect with superior cardioprotective effects.

1.4.2.2 Pharmacokinetics (PK)

Table 1.7 summarises the major PK properties of commercially available ARBs. All ARBs are highly protein-bound (>85%). The majority have a long elimination half-life,

thus they need to be administered once daily. Telmisartan is the longest acting ARBs available in market (~ 24 hour). However, losartan and eprosartan have a short elimination half-life, thus twice daily dosing is required to meet target efficacy. Regarding excretion, the majority of them are extracted via the bile route with a small fraction extracted via the kidney. Whereas eprosartan and candesartan are excreted mainly vis renal route (Taylor et al., 2011, Israili, 2000). Among all the ARBs, losartan and candesartan cilexetil are prodrug and require bioactivation. The active metabolite of losartan, EXP 3174, is more potent and has a longer duration of action. However, the lower bioavailability of EXP 3174 is limited in its use in the market. Meanwhile, candesartan cilexetil is converted to candesartan (an active form) directly after gastrointestinal absorption (by ester hydrolysis) (Burnier, 2001).

Drug	Antagonism	Active	Half-	Dosing	Protein	Bioavailability	Route of
	type	metabolite	life	frequency	binding	(%)	elimination
			(h)	(h)	(%)		(%)
Losartan	S	Yes	2	q.d. or	98.7	33	b: 70; r: 30
				b.i.d.			
Eprosartan	S	No	5-7	q.d.	98	63	b: 10; r: 90
Irbesartan	I	No	11-15	q.d.	90-95	60-80	b: 75; r: 25
Valsartan	S	No	9	q.d.	95	23	b: 80; r : 20
Telmisartan	I	No	24	q.d.	>99	43	b: 100
Olmesartan	I	No	14-16	q.d.	>99	26	b: 60; r: 40
Candesartan	I	Yes	9-12	q.d. or	99.5	42	b: 40; r: 60
cilexetil				b.i.d.			
Azilsartan	S	No	11	q.d.	>99	60	b: 55; r: 42

Abbreviations: r (renal); b (biliary); h (hour); S or I (Surmountable or Insurmountable antagonism); q.d. (once daily) and b.i.d. (twice daily).

Data adapted (Taylor et al., 2011, Burnier, 2001)

1.4.2.3 Individualization of ARBs-based therapy

All currently available ARBs have BP lowering efficacy, despite their variability in extent of lowering of BP and the duration of actions. Therefore, these agents have been licensed for the treatment of hypertension. Different indications have been approved for each agent based on clinical trials conducted in patients at different stages of CV and renal diseases (Table 1.8). Olmesartan, azilsartan and eprosartan

are only approved for the management of HTN. In patients with T2DM, with or without nephropathy, losartan and irbesartan are indicated (Joint Formulary Committee, 2020). Based on the results of ONTARGET and TRANSCENT trials, telmisartan is only ARB indicated for the prevention of CV events across high-risk patients, including those with manifest atherosclerotic CVD or T2DM with target-organ damage (FDA, 2020). Moreover, losartan reduced the risk of stroke by 25% relative to atenolol in the LIFE trial; therefore, it was approved for management of HTN with LVH. According to the results of the CHARM, VALIANT, Val-HeFT and HEAAL trials, candesartan, valsartan and losartan (in Europe) can be used in patients with HF (FDA, 2020).

Drug	Approval	Indications								
		HTN	HTN+LVH	Post-MI	HF+LVSD	Nephropathy (T2DM)	CV high-risk*			
Losartan	1995	•	• ^b		eac	•				
Valsartan	1996	•		•	● ^a					
Irbesartan	1997	•				•				
Eprosartan	1997	•								
Candesartan	1998	•			• ^a					
Telmisartan	1998	•					•			
Olmesartan	2002	•								
Azilsartan	2011	•								

Table 1-8 Approved indications for eight currently available ARBs

Abbreviation: LVD: left ventricular systolic dysfunction; LVH; left ventricular hypertrophy; HTN: hypertension; HF: heart failure; T2DM:

type 2 diabetics mellitus.

Approved date and indications are adapted from: <u>https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm</u> (FDA, 2020, 2020) and

(Joint Formulary Committee, 2020)

* Including those with established atherosclerotic CVD (i.e., history of CAD, stroke or PAD) or T2DM with documented target-organ

damage); ^a Considered when ACEIs are not tolerated

^b for stroke prevention

^c Approved in Europe

1.4.3 The unique mechanisms of ACEIs and ARBs

Despite ACEIs and ARBs having a comparable BP reduction action, only ACEIs appear to improve coronary outcomes, suggesting that ACEIs, but not ARBs, reduce the progression of atherosclerosis and incidence of coronary thrombosis (Yusuf et al., 2000, Yusuf et al., 2008b). The differentiation in observed clinical benefits cannot simply relate to a reduction in BP, but might be a more complex biological action affecting the in coronary artery and the endometrium. Although both ACEI and ARB attenuate the well-known effects of Ang-II, each uses a unique mechanism. ACEIs competitively inhibit the action of ACE that converts Ang-I to Ang-II, thereby decreasing circulating and local Ang-II. Whereas ARB prevents blocking activation of AT₁ by Ang-II, thereby preventing actions mediated by the Ang-II (Aponte and Francis, 2012). Moreover, various unique mechanisms of ACEI and ARBs has been identified in experimental studies. These differential actions could be translated into clinical practice. Long-term blockage of the AT₁ receptor by ARB inhibits a negative feedback loop leading to increased renin secretion and raising the circulating level of Ang-II severalfold above the baseline. As a consequence of the rising levels of Ang-II, possible overstimulation of the AT_2 , AT_3 , and AT_4 receptors could occur (Levy, 2005). Previously, the activation of AT_2 was known to be beneficial via NO-mediate vasodilation. However, accumulating data suggests that it may exert more harmful effects rather than previously proposed. AT₂ stimulation may have proinflammatory, hypertrophic, proatherogenic and proapoptotic actions on CV tissue. The expression of AT₂ in isolated cardiomyocytes resulted cardiac hypertrophy. Moreover, the overexpression of AT₂ does not antagonize AT₁ receptor-mediated hypertrophy by Ang-II (D'Amore et al., 2005).

One of main concerns related to the activation of the AT₂ receptor is that it promotes an apoptosis. Inappropriate apoptosis has been recognized as a chief contributor to pathogenesis of cardiac diseases, and is involved in CV remodelling (Goldenberga et al., 2001). Involvement of AT₂ in apoptosis of cardiomyocytes has been proven in various studies using antagonists (Levy, 2005). In 2001, Goldenberg and colleagues demonstrated that stimulation of both the AT₁ and AT₂ receptors by Ang-II enhanced apoptosis in rat cardiomyocytes (Goldenberga et al., 2001). Additionally, recent evidence in human myocytes suggests that Ang-II might be involved in the development of atherosclerosis and induce atherosclerotic plaque rupture by enhancing matrix metalloproteinase-1 (MMP-1) production through AT_2 receptor activation (Kim et al., 2005). This observation provides a possible mechanism by which ARBs might promote plaque vulnerability and rupture, leading to acute coronary syndrome. Additionally, one of the proposed biological actions of long-term ARBs is the activation of AT_4 by Ang-II, Ang-III and Ang-IV. Activation of AT_4 is linked to facilitating the release of plasminogen activator inhibitor-1 (PAI-1). Moreover, excessive PAI-1 was found in atherosclerotic plaques, and their role mediated fibrinolysis inhibition and proved to be a powerful independent predictor of death after transmural MI (Nikolopoulos et al., 2014). Whereas, some studies suggested it has a role in improving cerebral blood flow, thus, confers cerebro-protective effects (Chai et al., 2004). **Details of non-classical pathway and tissue RAAS is described in section 1.3.3**

One of the biological actions of ACEIs not shared by ARBs is that they augment bradykinin (BK)-induced beneficial effects by inhibiting its degradation (section **1.3.2.2 bradykinin).** Some data has proposed that ACEIs have a high-affinity to BK than Ang-I binding site; thus, the main actions of these agents might primarily involve preventing bradykinin degradation. During a plaque rupture, the BK is liberated as a potent stimulant for the release of tissue-type plasminogen activator (t-PA) from the endothelium, which then inhibits thrombus formation (Francolini et al., 2007) . In PERTINENT (PERindopril-Thrombosis, InflammatioN, Endothelial Dysfunction and Neurohormonal Activation Trial), blood was withdrawn from 1200 CAD patients at baseline and after 1 year of treatment with either perindopril or placebo to measure level of BK. There was a significant in increased BK level by 17% (P<0.05) and this exerted anti-apoptotic effects on the endothelium (Ceconi et al., 2007). This might in part explain the anti-ischemic benefits for ACEIs patients with or at risk-of CVDs is mediated by BK-induced t-PA release (Witherow et al., 2002). Therefore, ACEIs might offer greater cardioprotective effects than ARBs. The apoptosis effects mediated by AT₂ & reduced by BK, are the major biological differences between ACEIs and ARBs. In an experimental study, perindopril reduced endothelial apoptosis and increased endothelial renewal in patients with ACS. Therefore, ACEI is likely to reduce the progress of atherosclerosis. Whereas, valsartan failed to show similar properties (Cangiano et al., 2011).

1.5 Clinical effects of ACEIs and ARBs: review of the evidence

1.5.1 The ARB-MI paradox: early evidence

Based on the available clinical evidence, both ACEIs and ARBs achieve a comparable BP reduction, and ARBs have a superior safety profile (Li et al., 2014). However, the majority of contemporary ARB-trials have demonstrated a complete lack of MI and mortality reduction among patients with comorbidities (Yusuf et al., 2011, Califf et al., 2010). Paradoxically, the incidence of MI appears to increase with the use of ARBs (Julius et al., 2004). Therefore, this suggests the cardioprotective effects of both classes might be not identical in patients with or at risk of CVD. The unexpected relationship between MI and ARB was first raised as an issue in 2004 following VALUE trials (Julius et al., 2004). The VALUE trial reported a 19% relative increase in incidence of MI with valsartan, as compared to amlodipine, among 15,245 participants with HTN. Similarly, in the CHARM-Alternative trial, candesartan was associated with a 52% increase in risk of MI compared with placebo (p=0.025) despite a reduction in BP of 4.4/3.9 mmHg in favour of candesartan (Granger et al., 2003). Paradoxically, a complete lack of benefit was reported against MI. For example, ACTIVE-I (2011) reported a nonbeneficial effect for irbesartan on risk of MI compared with placebo in 9016 patients with AF, despite a mean reduction of SBP that was 2.8 mmHg greater with irbesartan (Yusuf et al., 2011).

1.5.2 Randomized clinical trials (RCTs)

1.5.2.1 Patients with hypertension with target-organ damage

In hypertension with LVH, more prospective RCTs assessed the ACEI and ARB on CV morbidity and mortality risk compared with other antihypertensive agents. The majority of these trials did not clearly prove the expected relationship between CV events and BP reduction. In 2002, the LIFE trial involving 9193 hypertensives showed that losartan lowers mean SBP by 1.7 mmHg compared with atenolol (Dahlöf et al., 2002). However, the losartan-based regimen resulted in a 5% non-significant increased risk of MI (RR 1.05; 95% CI 0.86-1.28) and a non-significant decreased risk of CV mortality relative to atenolol, with a major reduction in incidence of stroke. Similarly, in SCOPE candesartan showed a lack of CV and all

mortality benefit compared with placebo, despite a mean reduction of 3.2/1.7 mmHg in SBP favouring candesartan (Lithell et al., 2003).

1.5.2.2 Patients with diabetes

Hypertension as a one of the main risk factors of CV is highly prevalent in diabetes. Although both ACEI and ARB reduce the onset of diabetes and have renoprotective effects, clinical trials exhibited discordant results with regard to CV outcomes (Gillespie et al., 2005). In Lewis' study, enrolled patients with T1DM nephropathy showed that captopril was associated with a 50% reduced risk of combined end points involved in death, despite a small disparity in BP (Lewis et al., 1993). The IDNT trial involved patients with T2DM nephropathy where 30% of them had previous CVD and demonstrated that Irbesartan had protective effects on the development of CHF, either compared with placebo or amlodipine (Lewis et al., 2001). Nevertheless, in this case a complete lack of CV mortality and MI was evident. A similar result was demonstrated by the RENAAL trial in patients with T2DM nephropathy, even with 2.7 mmHg lower in mean SBP favoured losartan (Brenner et al., 2001). However, these trials were not adequately designed to effectively detect the CV endpoint. Moreover, some claimed that it was not possible to compare trials of ACEI and ARB, due to the comparator groups being different.

1.5.2.3 Patients with coronary heart diseases (CHD)

In patients with CHD, the cardioprotective benefits of ARB over ACEIs remains unproven. In fact, the CAMELOT trial showed a reduction in clinical events with amlodipine but not enalapril (Nissen et al., 2004). However, this evidence was taken from a study involving an indirect comparison. Despite this, the data from head-to-head comparison trials should not be ignored. The contemporary trial, ONTARGET in high-risk patients reported a greater reduction in SBP favouring ARBs of 0.9 mmHg as compared with ACEI (Yusuf et al., 2008d). Therefore, it could be assumed that mortality risk might reduce further with an ARBs-based regimen than with ACEIs. Despite this, no differences between the two drugs have been proven in terms of mortality reduction. It should be notice that telmisartan has a longer duration of action than ramipril.

1.5.2.4 Patients with cerebrovascular disease

Telmisartan 80 mg daily was evaluated in a PRoFESS trial and compared with placebo in 20392 patients who previously had an ischemic stroke with follow-up of 2.5 years (Yusuf et al., 2008a). Although mean BP at baseline was 144.1/83.8 mmHg, and was further reduced in the telmisartan group (-3.8/2.0 mmHg), incidence of major CV events was not significantly lower.

1.5.2.5 Patients with heart failure

Conflicting findings regarding the CV benefits of ARBs for patients with CHF have been reported previously. In an ELITE II trial, patients with symptomatic CHF assessed the superiority of losartan 50 mg to captopril 50 mg three times daily on survival improvement (Pitt et al., 2000). Based on the ELITE (1997) trial findings (Pitt et al., 1997), a mortality benefit had been expected. However, the losartanbased group had a non-significant 12% increase in mortality risk compared to captopril. Moreover, losartan was associated with a 15% non-significant increase in sudden death and resuscitated arrest (9% vs. 7.3%). Notably, the ELITE trial was not powered to detect the CV endpoint. Placebo comparators would have providing a true measure of drug efficacy (Castro, 2007). In the CHARM-overall program, patients with symptomatic CHF were allocated to candesartan 32mg once daily or placebo and followed up for at least 2 years (Pfeffer et al., 2003b). The survival risk is improved by candesartan compared with placebo (adjusted HR 0.90; 95% CI 0.82-0.99; p=0.032). Therefore, the authors conclude that candesartan generally had beneficial effects on mortality compared with placebo. However, the observed benefit resulted mainly from CHARM-Added effects, as all involved patients with a background therapy of ACEI which might mask the real effect of ARBs. A recent network meta-analysis on the risk of mortality in patients with HF with a reduced ejection fraction demonstrated that monotherapy with ACEIs reduced the risk of all-deaths by 17%, whereas ARB therapy did not (Burnett et al., 2017). Furthermore, indirect comparison revealed no differences between ACEI and ARB on risk of mortality 0.941 (95% CI 0.679-1.292; p=0.66). However, these findings should be interpreted in a cautionary manner, as more patientyears in ACEI therapy (23,293) than those of ARBs (5880) compared with placebo.

1.5.3 Systematic review and meta-analyses

Conflicting findings from parallel meta-analyses have been reported previously regarding the efficacy of ARB compared to ACEIs across clinical condition. The majority of meta-analyses of ARB trials have showed a complete lack of reduction in MI, or do not improve the survival rate compared with placebo (Bangalore et al., 2016, Ricci et al., 2016). Whereas, the other reviewers concluded that increases occurred in the rates of MI despite BP reduction and a good tolerability profile (Volpe et al., 2005, McDonald et al., 2005). Theses conflicting results might result from methodological variation as an eligibility criteria, or even be considered a true effect. A meta-analysis of Zanchetti was performed in hypertensives (3 trials, n=17,728) and concluded that ARBs are as effective as ACEIs, in terms of outcomes for MI (RR 1.07, 95% CI 0.94-1.22), CV death (RR 1.00, 95% CI 0.98-1.12) and total mortality (RR, 0.98 95% CI 0.90-1.07) (Thomopoulos et al., 2015a). In 2014, similar results were found by Cochrane Hypertension Group (8 trials, n= 10081). However, 96.5% and 91.8% respectively of included patients were from the ONTARGET trial. Therefore, these meta-analyses may ultimately have reflected the results of ONTARGET. A parallel meta-analysis by Savarese and colleagues (2013) conducted on 26 RCTs enrolled 108,212 high-CV risk participants without HF, and demonstrated that ACEIs significantly reduced the risk of MI and HF, whereas ARB did not (Savarese et al., 2013). They concluded that ARB represents a viable option for high-risk patients who do not tolerate ACEIs therapy. Nevertheless, based on their inclusion criteria, the ACTIVE-I (2011) trial was not incorporated (Yusuf et al., 2011). Moreover, a study by Cheng et al revealed that ACEIs reduced the risk of MI in patients with DM, whereas ARBs had no such benefits, and thus they concluded that ACEIs should be considered as first-line therapy to limit excess mortality and morbidity in this population (Cheng et al., 2014). However, the aforementioned studies were not based on a head-to-head comparison, but on an indirect inference comparing ACEI or ARB or with a placebo. Table 1-9 summarizes the RR of MI, HF, CV, and all-cause mortality from parallel meta-analyses of ACEIs and ARBs.

1.6 Rationale for the present study

During the past decade, RAAS blockers, especially ACEIs and ARBs have been clearly indicated for several CV conditions. However, there was a difference in

their mechanism of actions; thus, a similarity in clinical, particularly CV outcomes, cannot be presumed. As a previous review of clinical evidence shows in **section 1.5**, these two drug classes appeared to have divergent effects when preventing CV mortality and morbidity. Although the benefits of ACEI and ARB have long been established in RCTs and meta-analyses of patients with HTN, their effects in the presence of comorbidities have been less certain. Despite this, ARBs are widely used in clinical practice and often considered a substitution for ACEIs due to their reputation for having fewer side effects and comparable BP reduction. The differences in the efficacy of these agents and their therapeutic interchangeability remains a subject of controversy. Therefore, the current study has generally investigated the validity of this substitution, by reviewing CV outcomes in patients with or at high-risk of CVDs.

		AC	El vs. placebo)		ARB vs placebo					
Study	MI	CV mortality	All- mortality	HF	N	MI	CV mortality	All- mortality	HF	Ν	
Bangalore et al. (2016); High risk without HF	0.83 (0.78-0.90)	0.83 (0.70-0.99)	0.89 (0.80-1.00)	0.76 (0.67-0.87)	62 398	0.93 (0.85-1.03)	1.02 (0.92-1.14)	1.01 (0.96-1.06)	0.89 (0.82- 0.96)		
Savarese et al. (2013); High-risk	0.81 (0.75-0.88)	0.9 (0.78-1.03)	0.91 (0.85-0.98)	0.78 (0.68- 0.90)	53,791	0.9 (0.8-1.02)	1.03 (0.85-1.26)	1.01 (0.94-1.08)	0.89 (0.76- 1.04)	54,421	
Cheng et al. (2014); DM	0.79 (0.65-0.95)	0.83 (0.70-0.99)	0.89 (0.79-0.99)	0.70 (0.59-0.82)	32 827	0.89 (0.74-1.07)	1.21 (0.81-1.8)	1.03 (0.89-1.18)	0.81 (0.71- 0.93)	23,867	
Salvador et al. (2017); HTN	0.78 (0.71-0.86)	0.77 (0.69, 0.87)	0.85 (0.78, 0.93)	0.76 (0.68- 0.86)	12,170	0.91, (0.83-0.99)	0.95 (0.86, 1.06)	1.02 (0.96, 1.09)	0.80 (0.72- 0.88)	24,697	
Bangalore et al. (2011); High risk	0.94 (0.85-1.03)	0.97 (0.92-1.02)	0.99 (0.95-1.03)	0.87 (0.81-0.93)	182830		1	NA	I I		

Table 1-9 Risk of myocardial infarction, heart failure, cardiovascular and all-cause mortality in parallel meta-analyses

Values indicate risk ratio (95% confidence interval)

1.7 Aim and objectives of the thesis

1.7.1Aims

- To investigate the comparative effectiveness of ACEIs and ARBs on preventing CV morbidity and mortality in patients with or at high-risk of CVDs.
- 2) To assess the relative contribution of BP-dependent and independent mechanisms to reducing the risk of CV morbidities and mortalities achieved by ACEIs and ARBs.

1.7.2 Methodologies for answering the research questions

A systematic review and meta-analysis of RCTs:

- To assess whether ARBs and ACEIs have similar effects on MI, angina, stroke, HF, CV and all-cause mortality risk reduction.
- 2) To investigate whether specific pre-specified subgroups of patients show differential benefits with ACEIs and ARBs.
- 3) To investigate whether the effect estimates of ACEIs, and ARBs are consistent across different subgroups.

A meta-regression analysis:

- 1) To investigate whether the risk reduction of MI, stroke, HF, CV, and all-cause mortality by ACEIs or ARBs is related to achieved BP reduction or not.
- 2) To explore the potential source of heterogeneity among the included trials.

2 Methods

2.1 Systematic review and meta-analysis

This section describes those strategies applied to systematically review and quantitively synthesize data from randomized-controlled trials (RCTs) to illustrate the comparative efficacy of ACEIs and ARBs for cardiovascular and cerebrovascular morbidity and mortality outcomes. This systematic review is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA-P) statement-2015 (Moher et al., 2015). The protocol is registered with PROSPERO (ID: 42019127785) and published at https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=127785

2.1.1 Eligibility and exclusion criteria (PICOS)

The criteria for considering and excluding studies adhere to the Population Intervention Comparison Outcome Study (PICOS) design framework (Santos et al., 2007). The PICOS framework was also used to develop the literature search strategies.

2.1.1.1 Population (P)

All adult men and women aged 18 years and over with/at risk of CVD, who have received outpatient ARBs or ACEIs therapy, with outcomes of interest that are eligible for inclusion.

Trials were excluded if they included the following populations: pregnant women, those aged below 18 years old, those with secondary hypertension, accelerated or malignant hypertension, congenital heart disease, hospitalized patients, or those with cancer, heart, kidney or liver transplantation, hepatic dysfunction, end stage renal disease (ESRD) (eGFR 15-19 ml/min/1.73 m2), haemodialysis, autoimmune diseases (i.e. IgA nephropathy and lupus nephritis), inherited diseases (i.e. Duchenne muscular dystrophy (DMD), ribbing disease, polycystic kidney disease, Marfan Syndrome (MFS)). Furthermore, studies with information missing regarding key population characteristics or healthcare settings were excluded.

2.1.1.2 Interventions and comparators (I & C)

The review included trials that evaluated ACEIs or ARBs in monotherapy, or as combination therapy, whether a stepped-care approach was applied or not. Combination drug regimens including other antihypertensives (e.g., diuretics, CCBs or beta-blockers) were permitted: **1]** if one of the combined drugs in control group (e.g., ACEI+ drug X vs. drug X), **2]** the combined drug was the same for both the intervention and comparator arms (ACEI + drug X vs. ARB+ drug X) or (ACEI or ARB+ drug X vs drug X+ drug Y). Drug X should be delivered with the same fixed or titrated doses in both arms.

Comparators allowed were placebo, no treatment, or other antihypertensives (diuretics, CCBs, beta-blockers, ACEIs or ARBs). Likewise, conventional BP lowering therapy (e.g., centrally acting drugs, alpha-blockers and vasodilators) were also considered eligible. The intervention and comparator agents must be administered orally and continued in outpatient settings if the patients had been hospitalized. In addition, supplemental drugs after randomization from other classes were allowed as part of a stepped therapy. However, these had to be prespecified and follow the same protocol in both arms. Moreover, trials with a background of RAS blockers were deemed eligible.

Trials with the following interventions and controls were excluded: **1**] **Intervention:** BP-lowering drugs other than ACEI and ARB. In addition, trials comparing drugs that belonged to the same class, either combination or monotherapy at different doses, as well as trials examining combined therapy including ACEI and ARB. **2**] **comparators:** trials comparing interventions with non-pharmacological agents (herbs, diet, exercises, and surgical procedures), other pharmacological agents (non-AHT; hormonal therapy, and vitamins) and other RAS blockers agents (e.g., renin and neprilysin inhibitors) as well as ACEI + drug X vs ARB + drug Y (e.g., enalapril + manidipine vs. irbesartan + HCTZ).

These exclusion criteria were applied to obtain an unbiased effect. Background combination therapy including treatment with non-ACEI or non-ARB was permitted in both arms. This strategy minimizes bias in the results of the included studies. Since the conclusions of a review rely on the results of the included studies, if these results are biased, then a meta-analysis will produce a misleading conclusion. Another bias arises from the exclusion of studies that should have been

included in the synthesis; a common reason for which is publication bias. Our exclusion criteria minimize bias in the results of the included studies in a manner that is critical for the study question, as risk of bias was assessed using standard methods, as described in **chapter 2, section 2.1.9.7.**

2.1.1.3 Outcome measures (O)

Primary outcome: as defined based on the 11th revision of the International Classification of Diseases- (ICD-11) from the WHO (World Health Organization):

- 1. Total mortality: death from all causes
- CV mortality: defined as per study, often defined as CHD mortality (fatal MI and sudden or rapid cardiac death) or/and cerebrovascular mortality (fatal stroke) combined.
- 3. Coronary heart disease outcomes (ICD- BA40-60):
 - Fatal and non-fatal myocardial infarction (ICD-BA41-42, 50 and 60)
 - Fatal and nonfatal angina.
- 4. Fatal and non-fatal stroke: including ischemic stroke (infarction) and haemorrhagic stroke (intracerebral haemorrhages and subarachnoid haemorrhages) but excluding transient ischemic attack (TIA). (ICD-8B00-11)
- 5. Heart failure (death due to HF, hospitalized or worsening of signs or symptoms of HF, NYHA Functional Classification) (ICD-BD10-13).

Only the first event of a relevant outcome type was included in each analysis. Studies that do not report relevant clinical endpoints (at least one of MI, all-cause mortality, CV mortality, stroke and HF) were also excluded. In some cases, insufficient data were found, and so these studies' researchers were contacted for further information (if none was forthcoming, they were excluded).

2.1.1.4 Study type (S)

Only RCTs that fulfilled the following criteria were included in this review: 1] double-blind RCTs or Prospective Randomized Open Blinded-Endpoint (PROBE) trials; 2] parallel or factorial-design and explanatory or pragmatic trials; 3] single-or multicentre RCTs; 4] randomized with at least 100 participants; 5] median or

average follow-up time of at least 52 weeks or one year; and 6] conference abstracts and other so-called 'grey literature'.

Trials with the following study designs were excluded: where the unit of randomization was not at the individual level (cluster-randomized), when the same individual acts as a control (cross-over studies), quasi-experimental designs where participants were not randomly allocated to a study treatment, all types of observational studies (cohorts, case control, cross-sectional, and case-reports), subgroup study and post hoc analyses. Retracted studies and any study design involving animals were ineligible.

2.1.1.5 Geographical location

The review included studies conducted in other countries, as RAS blockers are widely prescribed. Therefore, no language restriction was applied, and translation was sought where necessary.

2.1.2 Search strategy for identification of relevant studies

2.1.2.1 Electronic searching

Searching was completed utilising the following bibliographic databases for published trials: The Cochrane Central Register of Controlled Trials (CENTRAL), Medical Literature Analysis and Retrieval System Online (MEDLINE Ovid (1946 onwards)), Excerpta Medica Database (EMBASE Ovid (1974 onwards)), Web of Science-Core of Collection [Conference Proceedings Citation Index-Science (CPCI-S)-1990-present]. Also, the Cochrane Database of Systematic Reviews was searched to identify relevant reviews. No language restriction was implemented. The search was performed to find published articles dated between 1 January 2000 and December 2018 (the search was updated run on 17th July 2020).

Search filters are optimal strategies developed to maximize the effectiveness of searches and identify higher quality evidence from a vast quantity of literature indexed in selected medical databases (Lefebvre et al., 2017a). A comprehensive search for studies was conducted using Medical Subject Heading (MeSH) terms and appropriate subject keywords, as "angiotensin receptor antagonists", "arb", "angiotensin enzyme inhibitors", "acei", "randomized controlled trial", "drug therapy", "controlled clinical trial". Moreover, the search was completed using a

strategy termed the Cochrane Highly Sensitive Search Strategy for identifying RCTs in MEDLINE: sensitivity- and precision-maximising version (2008 revision), as described in the Cochrane Handbook for systematic reviews of the Intervention Version 5.1.0. Box 6.4b. (Lefebvre et al., 2017b). The detailed search strategy implemented here is detailed in the **Appendix A**.

2.1.2.2 Searching non-bibliographic databases

Unpublished or ongoing trials were identified through the following sources: ClinicalTrials.gov (www.clinicaltrials.gov), World Health Organization International Clinical Trials Registry Platform (ICTR-P) (www.who.it.trialsearch) and pharmaceutical industry trials registers (via the registration number provided in primary trial).

Moreover, a manual search was conducted of the reference lists of previously published articles, abstracts and editorials, to identify additional potentially eligible RCTs. The following reviews and meta-analyses were searched as follows: Bangalore et al. (2017); Bangalore et al. (2016); Tai et al. (2017); Heran et al. (2012); Cheng et al. (2014), Li et al. (2014); Bangalore et al. (2011); Salvador et al. (2017); Savarese et al. (2013); Thomopoulos et al. (2015); Verdecchia et al. (2005); Strippoli et al. (2006)

2.1.3 References management

The records and references generated from the selected electronic databases were imported and organized using reference management software, EndNote version X8, in the form of a bibliographic library. All citations were imported from electronic databases through Research Information Systems (RIS) or endnote export (.enw) format. The EndNote X8 deduplication tool was used to identify and then remove duplicates. Duplicate records were saved in duplicate references library. In addition, manual identification of duplicates was also performed by scanning the references after sorting them by title.

For the purpose of scanning, the records were imported into Rayyan QCRI (the Systematic Reviews web application), available on <u>http://rayyan.qcri.org</u> (Ouzzani et al., 2016). Rayyan QCRI is a free screening software, designed to help expedite the initial screening of abstracts and titles with the further detection of

duplicates. This web application allows identification of eligible studies based on PICOS, by labelling a decision as excluded, included or undecided attributing reasons. Subsequently, included and undecided citations that required full text screening were exported into EndNote format (.enw) and exported into a Microsoft Excel (version 2016) spreadsheet for labelling. Only the main author (Manal Alosaimi) of this review was responsible for maintenance and adjustments made to the bibliographic library.

2.1.4 Study selection process

2.1.4.1 Screening of titles and/or abstracts

Independently, the primary author (Manal) screened the titles and/or abstracts of the studies based on predefined inclusion criteria, as outlined in **section 2.1.1**. During the screening process using Rayyan QCRI, a number of rejected articles were recorded with reasons. These records were mainly rejected for one of two reasons: they were clearly not related to the review question or did not meet the pre-defined criteria. When the eligibility criterion was not clear from the title and/or abstract, the full text of the paper was obtained. Two review authors (MA and NA) independently assessed the full texts of all eligible papers. A list of rejected papers and the reasons for their rejection were documented.

2.1.4.2 Obtaining documents

Full-text articles were obtained from the University of Glasgow Library via the university of Glasgow account of the main author. When the full text article was not held by the library, the librarian team requested it (usually) from the British Library Document Supply Service (BLDSS)-The British Library. Additional sources were searched such as the 'Google' web search engine by title of article or name of journal to obtain full-text articles.

2.1.5 Data extraction

Two reviewers (Manal Alosaimi, and Nur Aishah) independently decided whether a trial was to be included. The included trials were then extracted independently by three reviewers (Manal, Nur Aishah and Anwar). Any enduring uncertainty was resolved in discussion with supervising author (Prof Sandosh Padmanabhan) if needed. The data collection form was designed after evaluating how much information needed to be collected. A standardized Microsoft Excel 2016 worksheet was designed as a collection form to record the data required to assess study quality and evidence for synthesis. The data was extracted and collected according to the PICOS framework: population, intervention and comparators, outcome measures and study design.

For participant characteristics we assessed: 1] Overall number of participants based on ITT approaches, 2] Number randomized to each arm, 3] Populations' clinical settings, 4] Baseline and achieved mean SBP/DBP; 6] CV risk at baseline (mean age (years), male (%), current smokers (%), HTN (%), DM (%), LVH (%)); and 7] Patients with established or CV history ((%) CAD, CVA, and HF).

Intervention and comparators characteristics were extracted as follows: 1] class of drug; 2] Generic name of drug; 3] Control group; 4] Dose of drug; 5] Background of RAS blockers at randomization (%); 6] Concomitant non-study RAS blockers at end of the trial (%); 7] Supplemental agents; and 8] Adherence to therapy (%)

For outcome measures: 1] Outcomes as pre-defined or adverse events; 2] Number of events in each assigned arm; 3] Number of fatal and nonfatal events; 4] Outcome diagnosis adjudication; 5] Source of data (published or unpublished).

Study methodology: 1] Study acronym; 2] Study full name; 3] First author's name; 4] Publication year; 5] Journal published; 6] Study duration (total, mean or median); 7] methodology quality domains; 8] Type of analysis (ITT or per protocol); 9] Predefined primary and secondary outcomes; and 10] Sponsor.

For each trial, the mean between-group difference in SPB (mmHg) during followup was extracted in two ways: 1] mean of the between-group difference achieved may be reported already in trial or 2] when not reported directly in the study, a calculation was performed. Calculation of the mean between-group difference in SBP was carried out as follows:

$$\Delta SBP = (SBP_0 - SBP_2) - (SBP_0 - SBP_1)$$

Where;

 Δ SBP= mean between-group difference in SBP (mmHg)

 SBP_0 = Baseline mean SBP (at randomization)

SBP₁= SBP of final follow-up for intervention arm

SBP₂ = SBP of final follow-up for control group

One review author (MA) double-checked the data entered by comparing the data presented in the systematic review with the data extraction sheet. When more than one publication of one study existed, only the publication with the most complete data set was included.

2.1.6 Assessment of methodological quality

2.1.6.1 Risk of bias across domains

According to the recommendation from the Cochrane Collaboration, risk of bias was assessed utilising the "risk of bias" tool, domain-based evaluation tool (Higgins et al., 2017a). This tool permits the critical assessment of bias through seven separate and specific domains: (1) random sequence generation; (2) allocation sequence concealment; (3) blinding of participants and personnel; (4) blinding of outcome assessment; (5) completeness of outcome data; (6) selective outcome reporting; and (7) other sources of bias. Each domain was assigned a rating of high, low or unclear risk of bias with the justification for the judgement adhering to protocol provided by Higgins et al. (2017a)

2.1.6.2 Overall risk of bias assessment

Overall, each trial was deemed as low, high or unclear, and assessed differently for each outcome. Specifically, all the domains were assessed similarly for all outcomes, except for all-cause mortality. Based on the empirical evidence, objectively measured outcome such as all-cause mortality is not exaggerated by the lack of outcome assessment blinding, whereas trials with subjectively assessed outcomes, such as physician assessed disease outcomes (vascular events) might be affected (Wood et al., 2008). Therefore, the bias risk of outcome assessment blinding domain was assessed according to the subjective or objective nature of the outcome.

For each RCT, risk of bias across domains was summarized to obtain overall risk of bias according to the recommendations of the Cochrane Collaboration. Sequence generation, allocation concealment and outcome assessment blinding were considered key domains. Methodological studies were conducted to assess the importance of these domains, sequence generation, allocation concealment (Schulz et al., 1995, Wood et al., 2008) and blinding (Hrobjartsson et al., 2012). Therefore, the bias of the RCT was scored as low if all the key domains had a low

risk of bias, as high if at least 1 key domain had a high risk of bias, or unclear if at least 1 key domain carried an unclear risk of bias in the absence of high risk. Trials with high or unclear risk of bias in one key domain were deemed to represent the highest risk of bias. Otherwise, they were considered as carrying a low risk of bias. Two review authors (Manal and Nur Aisha) independently assessed the risk of bias with disagreements resolved by discussion to reach a consensus. It is noteworthy that study quality was not considered a reason for exclusion from the whole review.

2.1.7 Approach to missing data

The meta-analysis was performed using an intension-to-treat (ITT) approach based on recommendations from the Cochrane Collaboration (Higgins et al., 2017b). In cases of missing data of interest in published works or supplementary material, the following steps were undertaken as required: 1] other peer-reviewed publications were searched; 2] data from previous meta-analyses were checked; 3] data was obtained from ClinicalTrial.gov and pharmaceutical industry trials registers (via the registration number provided in primary trial). In addition, documents submitted by the Centre for Drug Evaluation and Research (CDER), is a division of Food and drug administration (FDA) that regulates drug approval or safety labelling changes (www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm); was searched and 4) investigators were contacted by correspondence email. Otherwise, the study was excluded.

2.1.8 Dealing with unit-of-analysis issues

Relevant studies including multiple intervention groups were addressed based on Cochrane Collaboration, overcoming a unit-of-analysis error (Higgins et al., 2017b). Firstly, any trial designed to include three active arms (e.g., ramipril vs amlodipine vs metoprolol), the number of participants, and events reported by active groups were combined into a single pairwise comparison (i.e., ramipril vs amlodipine plus metoprolol), as well as taking the weighted average for baseline BP, and achieved BP. However, the combined active groups were separated for the subgroup analyses (i.e., ramipril versus amlodipine and ramipril versus metoprolol). Additionally, for trials with three arms: ACEI or ARBs, AHT and placebo (e.g., enalapril vs amlodipine vs placebo) the arms were split and dealt with independently (i.e., enalapril vs amlodipine and enalapril vs placebo) regarding number of participants and events. Similarly, in cases of two monotherapies and one combination therapy (ACEI vs CCB vs ACEI+CCB) these were dealt with independently (ACEI vs CCB and ACEI+CCB vs CCB). If a study was comparing different doses of either ACEI or ARB with a control group (e.g., the study had three arms, irbesartan 150mg vs irbesartan 300mg vs placebo), number of patients and outcomes were combined when there were corresponding ARBs (i.e., ARR versus placebo). For studies enrolling three arms, one pair of relevant interventions was selected, and irrelevant options excluded.

2.1.9 Meta-analysis

2.1.9.1 Meta-analysis software

Review Manager 5 (RevMan 5) software was used to perform a meta-analysis. This program is used for preparing and maintaining Cochrane Reviews developed by the Cochrane Collaboration Group. It is available free for all Cochrane authors and for academic use. This software generates two statistical models: a fixed-effect model (FEM) and a random-effects model (REM).

2.1.9.2 Fixed-effect model (FEM) meta-analysis

Under the fixed-effect model (FEM) we assume all studies share an identical true (common) effect size, and that all differences in observed effects are a consequence of sampling error (error in estimating the effect size). Therefore, when assigning weights to different studies we can largely ignore information from smaller studies, since we have better information regarding the same effect size in larger studies. The combined effect estimate generated from the FEM reflects the one true effect size. A weight assigned to each study is the inverse of within-study variance. Distribution of points observed in the meta-analysis indicates sampling error and within-study error, and this can be reduced by assigning weights to each study in the analysis (Borenstein et al., 2010).

2.1.9.3 Random-effects model (REM) meta-analysis

Random-effects model (REM) involves incorporating assumptions that all studies in a meta-analysis estimate a study-specific true effect. Unlike FEM, the REM does not estimate one true effect, although it does help to estimate the mean distribution of effects. The null hypothesis for the summary is that the mean of these effects is zero for difference (equivalent to 1.0 for ratio). As REM estimates the mean distribution of effects, two types of variance should be considered: within-study error and between study-variance (Tau²) (Borenstein et al., 2010). The method developed by DerSimonian and Laird (method of moment) is used to estimate Tau² (DerSimonian and Laird, 1986). Moreover, the CI generated from REM will always be wider, and the weights of studies will always be more similar to one another than in the FEM. Therefore, different results will become apparent as we explore the differences between the two models. As we shift from FEM to REM, extreme studies will lose influence if they are large, and gain influence if they are small.

2.1.9.4 Data synthesis: Measures of treatment effect and model-used

A trial-level meta-analysis was performed as per recommendation from the Cochrane Collaboration and PRISMA. The aggregated data detailing outcomes was treated as dichotomous data and the intervention risk expressed according to a risk ratio (relative risk). Meta-analytic summary estimates the risk ratio (RR) and 95% confidence interval (CI) using REM as per DerSimonian and Laird calculated by RevMan 5 (DerSimonian and Laird, 1986). FEM is preferred when two conditions are met: [1] there is a good reason to believe that all the studies are functionally identical; and [2] our goal is to compute the common effect size of a narrowly defined population, which cannot be generalized to a wider range of situations. In the current review, studies differ in terms of their combination of participants and in the implementations of interventions among other reasons, they may have different effect sizes underlying the different studies. Hence, REM would be more appropriate to compute the summary effect size (Borenstein et al., 2010, Barili et al., 2018). The results were confirmed by a Mantel-Haenszel FE model to avoid small studies becoming overly weighted. The Mantel-Haenszel FER have better statistical properties when some event rates and study sizes are low. In the absence of heterogeneity, the RE model yields identical results to the FE model. An equivalent z test was performed for each pooled RR, and where P<0.05 it is considered statistically significant. Continuity correction was used for the trial with zero events (corrected automatically by RevMan 5) (Borenstein et al., 2010). Moreover, the results were expressed according to percentage relative risk ratio (RRR): RRR = $100\% \times (1 - RR)$. From the model, a pooled RR of 1 (or close to 1)

suggests no difference or little difference in risk, a RR > 1 suggests an increased risk of a particular outcome in the exposed group and a RR < 1 suggests a reduced risk in the exposed group. Publication bias was evaluated according to a visual evaluation of funnel plots.

2.1.9.5 Precision of the treatment effect: Confidence intervals

The 95% confidence interval (CI) for a relative risk (RR) estimate describes the range within which we are 95% confident the true population effect will lie. The width of the 95% CI indicates the precision of the estimate. A narrow CI indicates a more precise population estimate, and a wider CI lower precision. When conducting a meta-analysis, the width 95% CI is based on the precision of the individual study estimates and the number of studies included. As more studies are incorporated into a meta-analysis, the width of the 95% CI decreases. However, if heterogeneity increases following the inclusion of additional studies, the width of the 95% CI will widen in accordance with the random-effects model (see section 2.1.9.3). There is logical relationship between the CI and the P value. If 95% CI includes 1, the test of significance yields a P value of more than 0.05. Alternatively, if the 95% CI does not contain the value 1, the p-value is strictly below 0.05. When the p-value is exactly 0.05, then either the upper or lower limit of the 95% CI will include the null value of RR of 1 (Schünemann et al., 2021).

2.1.9.6 Assessment of heterogeneity

Heterogeneity is the term used to describes variability among the studies included in a systematic review. These variabilities might be clinical, as diversity is present in the participants, interventions and outcomes studied, and/or methodological diversity in the study design and risk of bias (Higgins et al., 2017b). The statistical heterogeneity among risk estimates might arise from clinical or/and methodological diversity. The traditional statistical test to identify and quantify heterogeneity is Cochrane's chi-squared (x^2 , or Chi²) test, also known as the Qstatistic test (Borenstein et al., 2009a). It tests assumptions including homogeneity, the null hypothesis, that all studies share a common effect size (Higgins and Thompson, 2002). In the current review, a statistically significant pvalue of <0.05 provides evidence of heterogeneity as regards intervention effects. It is widely appreciated that the Q-statistic test for heterogeneity can be low when one study is much more precise than the rest, or that excessive power can detect clinically unimportant heterogeneity across multiple studies (Hardy and Thompson, 1998). So, no test would be expected to provide a relevant summary of the extent to which heterogeneity impacts a meta-analysis. Therefore, a further test was used to quantify inconsistency across studies, called the l² statistic. According to Higgins and Thompson (2002), this describes the percentage of variability in effect estimates arising from heterogeneity rather than sampling error (chance). It is not affected by the number of studies included in the meta-analysis. The I² value lies between 0% (indicates no observed heterogeneity) and 100% (indicates increasing heterogeneity). The following is a rough guide to an interpreted I² (Higgins et al., 2017b): 0% to 40%: might not be important; 30% to 60%: may represent moderate heterogeneity; 50% to 90%: may represent substantial heterogeneity; and 75% 100%: to considerable heterogeneity.

Significant heterogeneity is typically considered present if I^2 is \geq 50%. In situations where heterogeneity is present, the RE meta-analysis method facilitates incorporation of between-study variability into an overall estimate. This model does not fix the heterogeneity, rather it accounts for differences in treatment effect among studies. This model used Tau² statistics to estimate between-studies variance from the observed effect. It is important to recognize that a non-significant test for heterogeneity does not guarantee homogeneity between all the trials included in a meta-analysis (Thompson and Higgins, 2002). In the current study, heterogeneity is explored, by conducting subgroup, sensitivity, and meta-regression analyses.

2.1.9.7 Publication bias assessment

Publication bias arises from the failure to include all relevant trials, as they might then remain unpublished (Sterne et al., 2006). In this review, a visual examination of a funnel plot was used to detect publication bias. A funnel plot is a simple scatter plot showing intervention effect estimates from individual studies against some measure describing each study's size or precision. In a graphical plot, a horizontal line represents the effect estimate, whereas study size is shown on the vertical axis as well as a triangular 95% confidence region based on a fixed-effect model (Higgins et al., 2017b). Therefore, effect estimates for smaller studies would be located at the bottom of any plot, with the spread being narrower for larger studies. Larger or those with the greatest power will be located toward the top of plot. If bias is absent, the plot will resemble a symmetrical inverted funnel. In the presence of bias, the model appeared symmetrical at the top (reflecting large studies) with more studies missing (small studies) nearer the bottom.

2.1.9.8 Sensitivity analysis

The robustness of the results was tested using several sensitivity analyses. The analysis excluding certain trials are described in detail in the methods section of each result chapter.

2.1.9.9 Subgroup analysis

Subgroup analyses were performed to investigate possible sources of clinical and statistical heterogeneity, as well as to identify consistency in treatment effects. The stratified analysis is described in detail in the methods section of each result chapter.

2.1.10 Meta-regression

2.1.10.1 Meta-regression software

The meta-regression analyses were performed using the Comprehensive Meta-Analysis version 2 (Biostat, Englewood, New Jersey, USA).

2.1.10.2 Statistical analysis

Meta-regression is a statistical technique used to identify any impact from triallevel covariates on study effect (Thompson and Higgins, 2002). Moreover, it is used to investigate whether covariates could explain any of the heterogeneity in the between-study effect estimate. Meta regression is similar in essence to simple linear regression, in which a dependent variable (outcome variable) is the observed log-RR from each study, and the independent variables (explanatory variable) are covariates at the study-level that might influence the size of intervention effect (Thompson and Higgins, 2002). In this review, the univariate and multivariate (adjusted) linear meta-regression random-effects (RE) analysis were performed for two reasons (Thompson and Sharp, 1999): 1] to evaluate the assumption that risk ratio reduction is proportional to the SBP reduction achieved, and to explore any BP independent effects on clinical outcomes. The slope of the regression line was used to estimate the RR of outcome for each unit of change in achieved mean SBP differences (BP-dependent effects). The intercept of the regression line was used to estimate the RR of stroke when the achieved SBP differences is zero mmHg (BP-independent effects); and 2] to explore the potential sources of heterogeneity among the trials.

The RR is logarithmically transformed and weighted by the inverse of the sum of the within-trial and residual between-trial variance. The log RR for each trial was regressed against between-group reduction in SBP. To estimate the additive (between-study) component of variance (Tau²), the restricted maximum likelihood (REML) method was used. Tau² denotes heterogeneity not explained by the potential effect modifier (Thomposon and Sharp, 1999). To estimate the relationship between achieved reduction in SBP to a log RR of outcome (Thomposon and Sharp, 1999):

$$In (RR) = \alpha + \beta x_i, v_i + \tau^2$$

In (RR)=Predicted value of outcomes RR

 α = The intercept for the regression line estimates log-RR when between-group difference in SBP is 0 mmHg (blood pressure-independent pharmacological effect)

 β = the slope of each regression line estimates the log-risk ratio for one unit of change in follow-up SBP difference achieved (Blood-pressure dependent effect)

 x_i = Achieved reduction in SBP

 $1/v_i + \tau^2$ = each trial weighted by the inverse of the sum of the within-trial variance (v_i) and the residual between-trial variance (τ^2)

The P value of each regression coefficient was used to test whether there is a linear relationship between treatment effect and between-group difference in SBP. A two-tailed p-value of < 0.05 is considered significant. The R^2 index is generated from meta-regression model, which was defined as a proportion of the between-trial variance explained by covariates. It can be interpreted as

percentage and range from 0% to 100% (Borenstein et al., 2009b). Firstly, a univariate meta-regression was performed by considered potential explanatory variables. Then, potential confounders are accounted for in a multivariate (adjusted) model. The covariate was first added to the model applying a forward stepwise approach based on the following criteria: 1] if it explained the largest proportion of variability in the data (R^2) in univariate model; and 2] if it significantly reduced the between-study variance (reduced the Tau² statistical value, or by testing the hypothesis of Tau²=0). The process was then repeated by adding the next variable explaining most of the remaining residual (unexplained) heterogeneity (I^2 residual) in the data. The best model should explain most of the between-study variance (Tau² reduced). Moreover, covariates showing a collinearity with one another were deleted from the multivariate model (correlation matrix value is close to -1 or 1), and to check whether the main result was dependent upon another comparator, a series of sensitivity analyses were performed.

3 Angiotensin-converting enzyme inhibitors (ACEIs) versus Angiotensin-receptor blockers (ARBs) in cardiovascular risk: Screening, Eligibility and Quality assessment

3.1 Aim

This chapter describes the results of the systematic review, including details returned by the literature search regarding the excluded and included studies, and the risk of bias in RCTs assessing the effects of ACEIs and ARBs therapy on risk of CV morbidity and mortality.

3.2 Results of the search

The literature search revealed 25,440 records using the search strategies described in **Appendix**, as attained from bibliographic and non-bibliographic database sources. The process implemented for the search strategy, and the identification of the literature is summarized in the PRISMA study flow diagram (see **Figure 3-1**).

After excluding duplicates, the remaining 12,931 citations and/or abstracts were screened for inclusion criteria. About 98% (12,721) of these were excluded based on title and/or abstract, as pre-defined by PICOS criterion. The remaining 210 publications were identified as potentially eligible studies, in which 113 RCTs were excluded after a full-text screening. Finally, 97 trials enrolled 317,984 eligible participants for the qualitative and quantitative synthesis of this review. The excluded and included studies were described in Section 3.2.1 and Section 3.2.2.

Studies reported in non-English language journals were translated prior to assessment. One study required full-text translation from the Chinese Journal of Gerontology (CJG); however, the duration of follow-up was 9 months (Yuanying and Yanling, 2011). Moreover, six trials required translation of their abstracts and were then found to not meet the inclusion criteria: 6 Chinese studies were excluded due to having fewer than 100 participants (4 trials) or a follow-up period of less than 52 weeks (2 trials) (see Table 3-1).

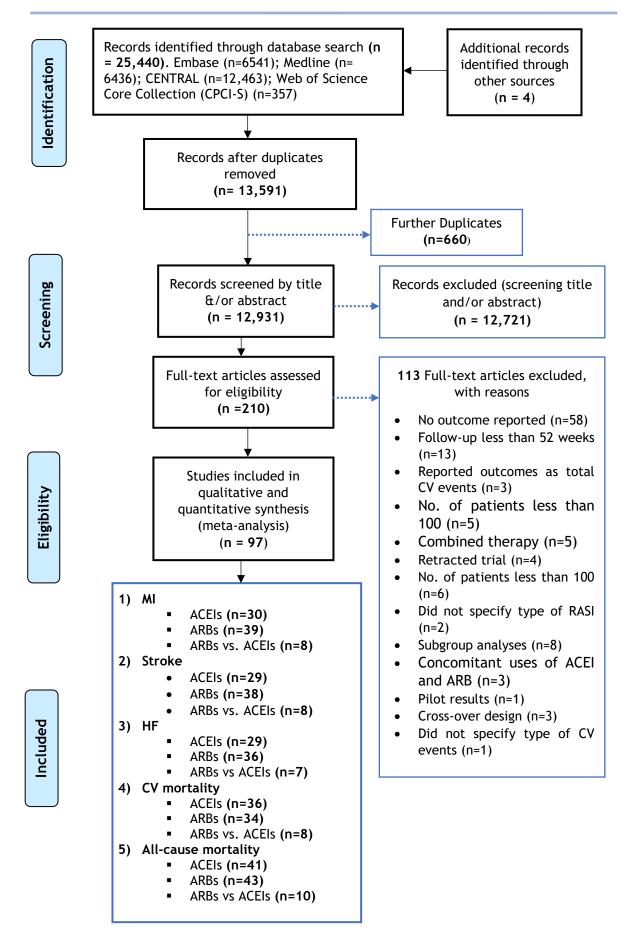


Figure 3-1 PRISMA Study flow diagram

3.2.1 Description of excluded studies

The reasons for excluding the trials that were eliminated are provided in **Table 3**-**1**. Overall, a total of 113 RCTs were excluded after eligibility screening of the full text. Ineligible trials were excluded for the following reasons. Four trials (COOPERATE, KYOTO HEART; VART; JIKEI HEART and NAGOYA HEART) were retracted due to ethical issues and inaccuracies in the data. GEMINI and HOMED-BP did not specify type of RAAS blocker. The combined regimens of ACEIs and ARBs led to the elimination of three trials (ADVANCED-J; Cocco et al.; PROTECT-CKD). Three trials reported outcomes as total CV event (ABCD 2V; RIAS and TROPHY) and so excluded. Also, BENEDICT-B'S CAMUI's and Tang et al.'s trials were conducted on the wrong control group. The remainder of excluded trials were disqualified for failure to report outcomes of interest.

Trial	Reason for exclusion	Reference
AAA	No outcome reported	(Ikeda et al., 2008)
AASK subgroup	Reported the same outcome as original trial	(Thornley-Brown et al., 2006)
ABCD 2V	Reported outcomes as total CV events	(Estacio et al., 2006)
ACCESS	Stopped prematurely	(Schrader et al., 2003)
Adamayn	No outcome reported	(Adamayn et al., 2013)
ADVANCED-J	Compared combined ARB+CCB with ARB	(Kawamori et al., 2006)
CandHeart	No outcome reported	(Aleksova et al., 2012)
ALLHAT subgroup	Reported the same outcome as original trial	(Leenen et al., 2006)
Zoppi	No outcome reported	(Fogari et al., 2012b)
ATTEST	Compared different doses of azelnidipine plus temocapril	(Katayama et al., 2008)
AVER	No outcome reported	(Esnault et al.)
Ben Ariff	No. of patients less than 100	(Ariff et al., 2006)
BENEDICT-B	Compared verapamil/trandolapril with trandolapril	(Ruggenenti et al., 2010)
CAMUI	Compared ARB+ccb with ARB+diuretics	(Sato et al., 2013)
CAPTAIN	No outcome reported	(Bainey et al., 2013)
CATCH ²	No outcome reported	(Cuspidia et al., 2002)
Chen	Follow-up less than 52 weeks (Translated)	(Chen et al., 2000)
CHIEF	No outcome reported	(L et al., 2011)
CIBIS III	Bisoprolol vs enalopril for 6 months followed by their combination for 12 months	(Krum et al., 2011)
Cocco G	Concomitant uses of ACEI and ARB	(Vizir and Berezin, 2002)
COLM	Compared Olmesartan plus CCB group with Olmesartan plus diuretic group	(Ogihara et al., 2014)
COOPERATE	Retracted trial	(Nakao et al., 2003)
CSPPT	Post-hoc of CSPPT trials (folic acid/Enalopril vs Enalopril)	(Li et al., 2017)

Derosa	No outcome reported	(Fogari et al., 2008a)
Derosa	No outcome reported	(Derosa et al., 2015)
Derosa	No outcome reported	(Derosa et al., 2004)
Didangelos T	No outcome reported	(Didangelos et al., 2017)
ELITE II subgroup	Demographic subgroup of ELITE Reported the same outcomes of original trial	(Konstam et al., 2005)
Evdokimov	No outcome reported	(Vladimir et al., 2018)
Fogari	No outcome reported	(Fogari et al., 2005)
Fogari	No outcome reported	(Fogari et al., 2008b)
Fogari	No outcome reported	(Fogari et al., 2011)
Fogari	No outcome reported	(Fogari et al., 2012a)
Galzerano	Follow-up less than 1 year	(Galzerano et al., 2007)
GEMINI	Not specify the type of RASI	(Jr et al., 2007)
GENRES	Cross-over design	(Hiltunen et al., 2007)
HOMED-BP	Did not specify the ACEI or ARB	(Hosohata et al., 2007)
Huang	No outcome reported (translated)	(J et al., 2000)
HYVET	Compared indapamide vs. placebo (perindopril may add as needed)	(Beckett et al., 2008)
HYVET-COG	No outcome reported	(Peters et al., 2008)
INNOVATION	No outcome reported	(Makino et al., 2008)
Jaffar Naqvi	No outcome reported	(Naqvi et al., 2016)
Jianfeng	No outcome reported	(Jianfeng et al., 2012)
JIKEI HEART	Retracted	(Mochizuki et al., 2007)
JLIGHT	No outcome reported	(lino et al., 2004)
JMIC-B	Reported other outcomes	(Yui et al., 2010)
SILVHIA	No outcome reported	(Karin et al., 2001)
Kawamura	Number of patients less than 100	(Kawamura et al., 2013)
Kinouchi	No outcomes reported	(Kinouchi et al., 2010)
Kjeldsen	Non-randomized trial	(Kjeldsen et al., 2016)
Kumar	No outcome reported	(Kumar et al., 2015)
Kvetny	No outcome reported	(Kvetny et al., 2001)
KYOTO HEART	Retracted trial	(Sawada et al., 2009)
LIFE subgroup	Reported the same outcomes as original trials	(Wachtell et al., 2005)
Ling	No. of patients less than 100 (translated)	(Ling and Tao, 2003)
LIVE	Follow-up less than 1 year	(Gosse et al., 2000)
LOTHAR	No outcome reported	(Jr et al., 2006)
Min et al	No. of patients (n=68) (translated)	(Min et al., 2002)
MORE	No outcome reported	(Stumpe et al., 2007)
MOSES subgroup	Reported the same outcomes of original trials	(Schrade et al., 2006)
NAGOYA HEART	Retracted Trial in Aug 2018	(Muramatsu et al., 2012)
NAVIGATOR	Renal outcomes of NAVIGATOR trial	(Currie et al., 2017)
Nephros	No outcome reported	(Herlitz et al., 2001)
OCTOPUS	Hemodialysis patients	(Iseki et al., 2013)
Ogawa S	No outcome reported	(Ogawa et al., 2007)
Onodera	No outcome reported	(Onodera et al., 2005)
PARAMOUNT	Follow-up less than 52 weeks	(Solomon et al., 2012)

Parrinello	No. of patients less than 100	(Parrinello et al., 2009)
PATHWAY	Cross-over design	(MacDonald et al., 2017)
Peng et al	No outcome reported	(Peng et al., 2015)
PERFECT	No outcome reported	(52)
PERSPECTIVE	Subgroup of EUROPA trial- reported other outcomes	(Rodriguez-Granillo et al., 2007)
PIL-FAST	Pilot results of new study but no. of patients=14	(Shaw et al., 2013)
PRESERVE	No outcomes reported	(Devereux et al., 2001)
PREVEND IT subgroup	Subgroup of PREVENT IT trial reported other outcomes	(Asselbergs et al., 2005)
PRoFESS	Reported other outcomes	(Diener et al., 2008)
PRONEDI	No. of patients less than 100	(Juarez et al., 2013)
PROTECT-CKD	Concomitant used of ACEI & ARB	(Hayashi et al., 2015)
Shang	No outcome reported	(Shang et al., 2016)
Raja M et al	No outcome reported	(Raja et al., 2016)
REASON	No outcome reported	(Protogerou et al., 2009)
REIN	No outcome reported	(Ruggenenti et al., 2000)
Ren	No outcome reported (translated)	(Ren et al., 2006)
RIAS	Reported as total cardiac events	(Bull et al., 2015)
Rosei	No outcome reported	(Ciulla et al., 2005)
Rosendorff	No outcome reported	(Rosendorff et al., 2009)
Sapojnic	No outcome reported	(Nadejda et al., 2015)
Sapojnic	No outcome reported	(Sapojnic et al., 2018)
SCAST	Follow-up less than 1 year	(Jusufovic et al., 2014)
SILK	Duration of follow-up (6 months)	(Yamabe, 2018)
SILVHIA	No outcome reported	(Mortsell et al., 2007)
SMART	No outcome reported	(Uzu et al., 2007)
Song	Duration of follow-up (9 months)- full text of Chinese language was translated	(Yuanying and Yanling, 2011)
SPICE	Follow-up less than 52 weeks	(Granger et al., 2000)
STAR	No outcome reported	(Bakris et al., 2006)
STRONG	Observational study	(Ahmed et al., 2016)
SUPPORT subgroup	Reported other outcomes	(Nochioka et al., 2017)
Tang	Wrong control group (aliskiren/ARB versus ARB)	(Tang et al., 2018)
TRAIN	Cross-over design	(Cesari et al., 2008)
TROPHY	Did not specify type of CV events	(Julius et al., 2006)
Tumasyan	No outcome reported	(Liana et al., 2015)
VALISH	One arm, valsartan, then divided into two groups based on BP level	(Ogihara et al., 2004)
VALVACE	Non-randomized trial	(Peters et al., 2005)
VART	Retracted trial	(Narumi et al., 2011)
VENTURE	Follow-up less than 52 weeks	(Oh et al., 2015)
VIvID	Wrong control drug (aliskiren/valsartan vs valsartan)	(Bakris et al., 2012)
Williams	No outcome reported	(Williams et al., 2004)
Yingkai	No outcome reported	(Cui et al., 2015)
Yuehui Yin	No outcome reported	(Yin et al., 2006)

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Yz Li	No. of patient less than 100 (Translated)	(Li et al., 2002)
ZAMES	No outcome was reported	(Napoli et al., 2016)

3.2.2 Description of included studies

Utilizing the PRISMA-P statement recommendations, 97 RCTs were identified as fulfilling all the selection criteria for this review. In total these reviews represent 317,984 participants over an average of 3.03 years. The trials were either placebo or active-controlled. Of the 97 trials, 42 trials randomized 127,331 (43.2%) participants to an ACEIs versus a control (placebo or active) group and followed them for an average of 3 years. Similarly, 45 trials randomized 157,020 (46.3%) patients to an ARB versus control (placebo or active) and followed them for an average of 3.2 years. Regarding trials directly comparing ACEIs with ARBs, 10 trials randomized 41,106 (10.7%) participants allowing an average follow-up of 3.1 years. The characteristics for the included studies are tabulated in **Appendix B**.

Generally, the clinical trials were described according to methodological design, clinical history at entry, the pre-randomization background of ACEI and ARBs, pre-specified outcomes, source and type of relevant outcomes and comparator agents. Regarding clinical history at entry: more of the ARBs trials included patients without vascular diseases than the ACEI trials did. 21 of the ACEIs trials enrolled patients with no established, or history of, vascular diseases (AARDVARK, ADVANCE, ATLANTIS, AASK, ABCD, ANBP2, BENEDICT, Chan et al., DEMAND, DIABHYCAR, DREAM, ESPIRAL, ELVERA, Fogari et al., Hou et al. (group 2), HYVET, PHARAO, PREVEND IT, RASS, J-MIND, PHYLLIS). Whereas, 30 of the ARBs trials included this group (ACTIVE-I, ANTIPAF, ALPINE, ATTEMPT-CVD, CASE-, Dahl et al., DIRECT-Protect 2, DIRECT-Prevent 1, DIRECT-Protect 1, EFFERVESCENT, E-COST, Fang Wu et al., GISSI-AF, IDNT, IRMA-2, NAVIGATOR, ORIENT, RAS, RENAAL, ROADMAP, SCOPE, HOPE-3, KACT-MetS, LAARS, LIFE, MITEC, NTP-AF study, COPE, J-RHYTHM II and PREVER-treatment). In addition, four head-to-head trials enrolled patients with a history of vascular diseases (CORD 1 B, LIRICO, RASS and ROAD).

By stratified trials, the majority of the trials (60%) enrolled high-risk patients as T1DM, T2DM, hypertension, diabetic and nondiabetic nephropathy, atrial fibrillation (AF), abnormal carotid intima-media thickness (CIMT). Six of the ACEI trials mainly focused on hypertensive patients without co-morbidities (AARDVARK, ANBP2, ELVERA, HYVET, PHARAO and PHYLLIS). Whereas, eight of the ARBs trials

involved these patients (SCOPE, ALPINE, COPE, E-COST, Fang Wu et al., LAARS, LIFE and PREVER-treatment). One head-to-head trial enrolled this group of patients (CORD 1 B).

The remaining 83 trials enrolled hypertensive and non-hypertensive patients with specific co-morbidities present as entry criteria. Hypertensive participants with at least one CVD risk factor were enrolled in eight ACEIs trials (AASK, BENEDICT, DEMAND, Hou et al., Chan et al., Fogari et al., JMIC-B, J-MIND), whereas 13 trials used ARB as one of the randomized arms (CASE-J, E-COST-R, IDNT, IRMA-2, ORIENT, HIJ-CREATE, J-RHYTHM II, KACT-MetS, MOSES, NTP-AF study, OLIVUS, VALUE, CHIEF). However, one head-to head trial enrolled high-risk HTN patients (DETAIL).

More trials were conducted on patients with T1DM and T2DM in the absence or presence of hypertension and nephropathy, and these were randomized to ARBs. There were eleven ARB trials (DIRECT-Protect 2, DIRECT-Prevent 1, DIRECT-Protect 1, IDNT, IRMA-2, ORIENT, RASS, RENAAL, ROADMAP, MITEC, Weil et al.), ten ACEI trials (ADVANCE, ABCD, BENEDICT, DEMAND, RASS, Fogari et al., J-MIND, Chan et al., ATLANTIS, DIABHYCAR), and three head-to-head trials (DETAIL, RASS, LIRICO).

Numerous trials enrolled participants with established, or a history of, CV diseases at entry (e.g., CAD, CVA or HF). Firstly, CAD either stable or acute was the most common morbidity in the twelve trials of ACEIs enrolled patients (CAMELOT, CARMEN, CCS-I, APRES, EUROPA, HOPE, IMAGINE, PART-2, PEACE, PREAMI, QUIET, QUO VADIS, SCAT, ALLHAT, JAMP, JMIC-B, Cai et al.). Some trials enrolled more than 50% of patients with CAD as CARMEN, HOPE and PART-2. Compared to the ARBs trials, six trials included patients with CAD (TRANSCEND, CARP, 4 C, HIJ-CREATE, Kondo et al., OLIVUS), and TRANSCEND enrolled more than 50% with CAD. Two head-to-head trials enrolled patients with acute CAD (OPTIMAAL, VALIANT).

This was followed by inclusion of patients who previously experience HF in four trials of ACEIs (CARMEN, PEP-CHF) and seven trials of ARBs (CHARM-Preserved, CHARM-Alternative, CHARM-Added, Val-HeFT, I-PRESERVE, HONG-KONG DHF, SUPPORT). Overall, fewer trials were conducted on patients with a cerebrovascular history, whether ACEI trials (PROGRESS) or ARB trials (PRoFESS and MOSES).

With regard to the ACEIs subclassification: ACEIs were categorized into highaffinity and low-affinity tissue ACEIs. Five high-affinity tissue ACEIs (benazepril, delapril, quinapril, ramipril, and trandolapril) and four low-affinity tissue ACEIs (captopril, enalapril, fosinopril, and lisinopril) were used. Moreover, the four trials did not specify the ACEI subclasses used (HYVET, LIRICO, JAMP, JMIC-B). Among the ACEI subclasses, ramipril was studied extensively, as 26.7% of patients were assigned to ramipril in the eleven trials (AASK, APRES, ATLANTIS, CORD 1 B, DIABHYCAR, DREAM, HOPE, HONG-KONG DHF, ONTARGET, PART-2, PHARAO), and fewer patients were randomized to delapril (0.2%) in the DEMAND trial.

ARBs subclassification: Generally, seven ARBs subclasses were studied (candesartan, eprosartan, irbesartan, olmesartan, telmisartan, losartan, valsartan). Of these, telmisartan was used most frequently, as it was assigned to 25.2% of the participants in the six largest trials (ATTEMPT-CVD, CHIEF, DETAIL, ONTARGET, PROFESS, TRANSCEND). Whereas fewer patients were allocated to eprosartan (MOSES).

With regard to active comparators: In the ACEI trials, the majority of trials used CCBs then beta-blockers. Three DHP-CCBs were used (amlodipine, nisoldipine & nifedpine) in ten trials (AARDVARK, ABCD, ALLHAT, AASK, Chan et al., ELVERA, ESPIRAL, Fogari , JMIC-B, J-MIND) and non-DHP CCBs (verapamil) in BENEDICT. Only two trials compared beta-blockers, whether cardioselective or non-cardioselective (metoprolol and carvedilol), in the AASK and CARMEN trials. In addition, ACEI was compared with a combination regimen of thiazide-like diuretics (chlorthalidone) and amlodipine in ALLHAT, and thiazide diuretics (HCTZ) were used in PHYLLIS and ANBP2.

Similarly, CCBs was common comparators in the ARB trials. Mainly DHP-CCBs were compared with ARBs as amlodipine (CASE-J, J-RHYTHM II, MITEC, IDNT, Fang Wu, VALUE), nifedipine (NTP-AF) and bepridil (COPE and Kawamura). Three types of diuretics were used, thiazide (HCTZ) in ALPINE, and a combination regimen of thiazide-like diuretics combined with potassium-sparing diuretics (chlorthalidone+ amiloride) were studied in the PREVER-treatment study. However, the HONG-KONG DHF study did not specify type of diuretic used. In terms of methodological designs: The majority of included trials were designed as a parallel group. Meanwhile, a 2-by-2 factorial design was used in five ACEIs trials (NAVIGATOR, DREAM, HOPE, PREVEND IT, SCAT) and three of the ARBs trials (NAVIGATOR,

PRoFESS, HOPE-3). One of the ACEIs trial was designated as a 3-by-2 factorial, AASK. In addition, JAMP, JMIC-B and LIRICO were designed as a pragmatic trial.

The CV event was pre-defined as an outcome: CV mortality was pre-specified in 71 RCTs (89.8%), MI in 70 (92.1%), and HF in 71 trials (91.5%), all causes mortality in 64 trials (69.5%), and 36 trials (80%) reported stroke. The source of relevant outcomes was described in each results chapter and **tables E-1 and E-2 Appendix E.**

3.2.3 Dealing with unit-of-analysis issues

Details of the method used for dealing with units of analysis issues have been described in **Chapter 2, Section 2.1.8.** A relevant study with multiple intervention groups was addressed as follows. Firstly, five trials randomized participants into three arms, an intervention, placebo or active control (AARDVARK, CAMELOT, HYVET, IDNT and RASS). They were then treated as independent arms for primary analysis. Secondly, the active arms were combined in the four trials (ALLHAT, AASK, COPE, HONG-KONG DHF). Thirdly, three trials including arms with a combination regimen of ACEI and ARB were excluded (ONTARGET, LIRICO and VALIANT). Fourthly, six trials enrolled participants into three arms, in which combination therapy was dealt with as an independent arm (BENEDICT, DEMAND, PROGRESS, Fogari et al., CARMEN). Lastly, ATLANTIS and IRMA-2 assessed different doses of ramipril and irbesartan; thus, the active arms were combined.

3.2.4 Discussion

This chapter has described the protocol for identifying studies used in a systematic review of ACEIs and ARBs therapies so as to determine the risk of CV morbidity and mortality. Hypertension (HTN) is a prominent risk factor for CV diseases and subsequently might ultimately lead to mortality (Ezzati et al., 2002, Forouzanfar et al., 2017). Therefore, HTN guidelines and CV societies have emphasized managing HTN using antihypertensive agents to reduce the long-term risks of complications (NICE, 2019, Williams et al., 2018). Although BP-lowering remains a crucial target for effective CV therapy, the ancillary effects of RAAS blockers have an additional target. The majority of the included trials were non-intentional BP lowering studies, even though the trial design was not intended to investigate the effects of BP fluctuations. Our target is patients at high risk of CV events who have an established or high-risk of CVD. Therefore, it is important to note that trials

were selected across various morbidities, namely DM with or without nephropathy, acute and stable CAD, HF or CVA.

Studying high risk patients as a specific group was a novel idea prior to the HOPE trial (Yusuf et al., 2000). The trial enrolled fewer than 50% hypertensives; therefore, arguments arose relating to the benefits of the BP-lowering effects of ACEI. Contrasting this with previous analyses, the current review did not exclude trials with baseline co-morbidities, to allow generalization of the findings and assessment of the drug's benefits by conducting stratified analyses. Some claim that a true treatment effect might be undetected as a result of heterogeneity in the patient population (Bangalore et al., 2016, Savarese et al., 2013).

3.2.4.1 Treatment strategies

Guidelines and cardiac societies have outlined the principal of initiation steps for the treatment and individualization of drug therapy (Williams et al., 2018, NICE, 2019, James et al., 2014). The majority of the included trials initiate monotherapy with ACEI or ARBs and add-on therapy as necessary. Trials included in this systematic review investigated the impact of ACEIs and ARBs on participants with various co-morbidities. Significantly, 60% of the included trials were designed to assess the efficiency of ACEI and ARBs as a form of primary prevention. According to the Cardiovascular Disease Continuum (CVDC), hypertension is described as one of main underlying causes of CV complications. Therefore, CV endpoints such as mortality, myocardial infarction (MI) and stroke, are termed "hard-endpoints" and of greater clinical importance in clinical trials. A meta-analysis of 147 randomized trials assessed the efficacy of different classes of BP lowering agents as a primary prevention strategy, and showed that for every 10-mmHg reduction in SPB, there was a 22% reduction in CHD events and a 41% reduction in stroke (Law et al., 2009). However, each class of BP-lowering agent fails to provide an equivalent reduction in "hard-endpoints". Moreover, hypertension is a common co-morbidity with diabetes mellitus (DM) in the presence or absence of nephropathy. ESC/ESH for hypertension management (2018) recommended that hypertensive diabetes, particularly in the presence of proteinuria or micro-albuminuria with office BP of \geq 140/90 mmHg (grade I hypertension), is a way to initiate treatment by combining an ACEI or ARB with a CCB or thiazide/thiazide-like diuretic.

The first ACE inhibitor, captopril, was approved by the U.S. Food and Drug Administration (FDA) in 1981 to treat hypertension. It maintained exclusivity in the marketplace for almost 5 years, at which point a second ACE inhibitor, enalapril, was introduced at the end of 1985. The cardioprotective effects of ramipril were studied in one of the largest contemporary trial, HOPE. The HOPE trial was designed to assess the hypothesis that two preventive intervention strategies, ramipril or vitamin E, would improve morbidity and mortality in patients at high risk of CV events when compared with a placebo. Significantly, ramipril reduced the risk of MI, stroke, and CV death by 22% (P value <0.001) at the 5-year follow-up. Therefore, the FDA approved a new indication for ramipril in patients at risk of MI, stroke, and death (FDA, 2000). Ramipril has already been approved for the management of hypertension and post-MI with clinical signs of HF. Although, ramipril showed cardioprotective effects when compared with a placebo, it was equivalent to telmisartan in patients with vascular disease or at high-risk of diabetes in the ONTARGET trial (Yusuf et al., 2008d). Telmisartan was the broadly used ARB in four large pivotal RCTs (CHIEF, DETAIL, ONTARGET, PROFESS, TRANSCEND). It was approved by the FDA for the treatment of HTN in November 1998 (FDA, 1998). In October 2009, based on the results of the ONTARGET trial, telmisartan was the first ARB to be granted FDA approval to reduce CV risk in high-risk patients who did not tolerate ACEIs (FDA, 2009). Moreover, the cardioprotective effects of telmisartan was proven in the TRANSCEND trial, which included 5926 high-risk patients intolerant to ACEIs (Yusuf et al., 2008c). After 56 months, telmisartan reduced the composite outcomes of CV death, MI, and stroke by (P = 0.045). The high lipophilicity of telmisartan might be expected to enhance tissue penetration, intracellular absorption and bioavailability, consequently conferring greater vascular protection when compared to other ARBs (Wolfgang Wienen, 2000).

The majority of the included trials were designed as explanatory trials, and three trials (JAMP, JMIC-B and LIRICO) as pragmatic trials. The pragmatic trials were designed to test interventions within a typical care setting to maximize applicability and generalization. Differentiation between the two designs was first described by Schwartz and Lellouch (Daniel Schwartz, 1967). A Pragmatic-Explanatory Continuum Indicator Summary (PRECIS) tool was designed and updated in 2015 to facilitate the designation of trials acknowledging explanatory/pragmatic data (Loudon et al., 2015). In pragmatic trials, the

intervention should be delivered in the form of normal real clinical practice. Firstly, the participants and investigators were not masked; therefore, those trials followed a Prospective Randomized Open Blinded Endpoint (PROBE) design. Moreover, those trials focused on the most common care settings and were less commonly focused on highly specialized care settings. The most important point here is that there is flexibility involved in deciding which subclasses of ACEI or ARB should be delivered. However, these trials tend to neglect causality; i.e., the causal link between specific interventions and observable clinical outcomes becomes weakened.

3.2.4.2 Cardiovascular (CV) endpoint reported in clinical trials

CV endpoints are critical in assessing the therapeutic approaches in clinical research. However, a major limitation when trialling therapeutic approaches is that there is a lack of uniform definition of a key endpoint. Therefore, uniform definitions for CV and stroke outcomes have been developed by the Standardized Data Collection for Cardiovascular Trials Initiative (SCTI) and the FDA. The SCTI publicly posted these definitions on the Clinical Data Interchange Standards Consortium (CDISC) website and then published them in the ACC/AHA (Hicks et al., 2015, Karen A. Hicks, August 2014). By ranking the pre-specification of outcomes in the current review, it was found that a high percentage of trials reported MI (92%), and 69.5% of these reported all causes mortality as pre-defined outcome measures. It is of interest to note that trials reporting relevant outcomes as adverse events were designed and powered to measure a "surrogate endpoint". Surrogate endpoints, such as change in SBP and DBP, pathological cardiac hypertrophy, carotid intima-media thickness (CIMT), albuminuria and change in eGFR might act as strong predictors of increments in CV and all-cause mortality (Cohn et al., 2004). One point to highlight here is that those trials with surrogateendpoints had a much shorter duration, a smaller sample sizes and low costs.

The majority of the included clinical trials used a composite primary or secondary endpoint to achieve adequate statistical power. FDA guidance for reporting endpoints have emphasized that the results for each component event should be individually examined and always included in study (FDA, 2017b). Despite this, few of the trials reported in the current systematic review did not follow that guidance. For example, the COPE trial was designed and powered to detect a primary composite endpoint (sudden death, fatal or nonfatal stroke, fatal or

nonfatal MI, hospitalization due to unstable angina, new onset of HF) in hypertensives (Matsuzaki et al., 2011). Moreover, individual component data was not reported. The importance of component endpoints rose because those endpoints might not share a similar relative risk reduction. For example, in the LIFE trial, losartan and atenolol were evaluated in hypertensive patients with LVH (Dahlöf et al., 2002). Although the trial reported a significant reduction in the primary composite endpoint, this had risen from a significant reduction in incidence of stroke among other components. Adjudication of the potential CV endpoint by Endpoint Adjudication Committees (EACs) is vital to enhance the validity of CV outcome measures. Nevertheless, the role of EACs was not reported in 16.5% of the included trials. The FDA and the European Medicine Agency (EME) implemented the responsibilities of EACs (European Medicines Agency, 2005, FDA, 2006). Lack of a clear definition of outcomes or even the absence of a qualified independent adjudication committee might lead to bias. In the ALLHAT and VALUE trials, for example, HF events were higher in amlodipine relative to RAS blockers. These findings prompted debate on whether the events detected in these trials were from HF, or due to peripheral oedema of amlodipine.

3.2.4.3 Strengths and Limitations

In addition to the extensive searching strategy applied to bibliographic databases, other sources were searched for unpublished data and ongoing trials, i.e., Pharmaceutical Industry Clinical Trials database, ClinicalTrials.gov register and Drugs@FDA. However, the possibility of missing evidence from a smaller study is high, as grey literature. Despite applying an unrestricted searching strategy, there is a possibility that some RCTs were not published in English, which might have led to selection bias. An empirical study demonstrated that excluding non-English trials generally has little impact on treatment effect estimates (Jüni et al., 2002, Moher et al., 2000). Moreover, many trials were excluded as they did not report the outcomes of interest; thus, the results may be susceptible to outcome-reporting bias. However, a larger number of included trials would minimize selection bias and increase external validity.

3.3 Risk of bias in included studies

Methodological quality was assessed across all domains of bias for each trial (see **Appendix C: Methodological quality of included trials**). Figure 3-2 was used to summarize the risks of bias in percentage form across all the included studies. Other bias domains were defined as playing a sponsorship role. As previously mentioned, the risk of bias was assessed for each domain and then the key domains were selected to assess the overall quality of each study (Tables E-1 and E-2 presented in Appendix E summarizing the overall quality of each trial).

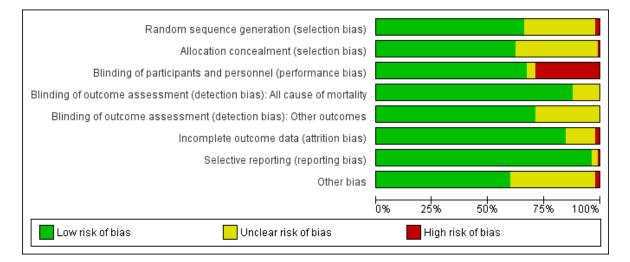


Figure 3-2 Risk of bias graph review authors' judgements about each risk of bias item presented as percentages across all included studies.

3.3.1 Randomization and allocation

The random sequence generation method was performed adequately for 64 trials (65.9% of total trials). We assessed 31 studies as having an unclear risk of bias for this domain because no information had been provided in study reports (ABCD, ALPINE, ANBP2, BENEDICT, Cai et al., CARMEN, CARP, Chan et al., Dahl et al., E-COST-R, ELITE II, ELVERA, ESPIRAL, EUROPA, Fang Wu et, HOPE, IRMA-2, JAMP, J-MIND, KACT-MetS, Kawamura, Kondo et al., OLIVUS, ONTARGET, PEACE, PROFESS, QUIET, QUO VADIS, SUPPORT, TRANSCEND, Val-HeFT). Two trials (E-COST and CORD 1 B) were judged as carrying a high-risk of bias with the report generation method being inadequate.

Allocation concealment was rated as of low risk of bias in 59 trials (60.8%). Meanwhile, 37 trials were judged as conveying an unclear risk of bias, which was not reported as the chief method of allocation concealment (4 C, ALPINE, BENEDICT, Cai et al., CAMELOT, CARP, Chan et al., CORD 1 B, Dahl et al., E-COST-R, ELITE II, ELVERA, ESPIRAL, EUROPA, Fang Wu, Fogari et al., HIJ-CREATE, HONG-KONG DHF, Hou et al. (group 2), IRMA-2, JAMP, J-MIND, J-RHYTHM II, KACT-MetS, Kawamura, Kondo et al., LAARS, MITEC, NTP-AF study, OLIVUS, PEACE, QUIET, QUO VADIS, SUPPORT, Val-HeFT, Weil et al.). One trial, E-COST, was judged to carry a high-risk of bias due to the inadequate allocation concealment method.

3.3.2Blinding

More than half of the included trials (65 trials) used blinded participants and personnel for the intervention or control group (active or placebo). Hence, they were assessed as conveying a low risk of performance bias. Twenty-nine studies had open-label designs, and were therefore judged to carry a high risk of bias for this domain (4 C, AARDVARK, ANBP2, ATTEMPT-CVD, CARP, CASE-J, CHIEF, COPE, CORD 1 B, Dahl et al., E-COST, E-COST-R, ESPIRAL, Fogari et al., HIJ-CREATE; HONG-KONG DHF, HYVET, JAMP, JMIC-B, J-MIND, J-RHYTHM II, KACT-MetS, PHARAO, Kondo et al., LIRICO, MOSES, NTP-AF study, ROAD, SUPPORT), as both the participants and personnel were aware of the treatment assigned. The remaining four studies were assessed as having unclear risk of bias because no information was provided regarding blinding (Cai et al., Fang Wu et, Kawamura, OLIVUS).

The blinding of the outcome assessment was deemed adequate in more than half (71%) of the included studies. Of these, many were designed as prospective, randomized, open-label, and blinded-endpoint (PROBE). The PROBE design was used mainly to avoid detection bias. Nevertheless, the blinding of the outcome assessment in all 25 trials was judged as carrying an unclear risk, as no information was provided (ALLHAT, ALPINE, Cai et al., CARP, CCS-I, Dahl et al., DETAIL, E-COST, E-COST-R, ESPIRAL, ELVERA, EUROPA, Fogari et al., Fang Wu et, GISSI-AF, HYVET pilot, JAMP, J-MIND, KACT-MetS, Kawamura, Kondo et al., NTP-AF, RASS, SCAT, Weil et al.). Although this domain is unimportant for all-cause mortality outcome, it is a critical domain for subjectively assessing outcomes such as MI, stroke, HF, and CV death (See Appendix C: Methodological quality of included studies).

3.3.3 Incomplete outcome data

Attrition bias was judged as a low risk in 94.5% (82) of the included trials. Of those, eight trials (ALPINE, Dahl et al., DEMAND; Fang Wu et; OLIVUS, PHARAO, PREVEND IT, Weil et al.) had complete outcome data and no participant was unavailable for follow-up. The trials were judged as having a low risk of attrition bias because: [1] overall follow-up loss was insignificant between 0.01% to 17.2% (less than 20%); [2] the rate of loss was equal between the study arms; or [3] analysis was done according to ITT principles. Two trials were rated as having a high-risk of attrition bias due to: [1] rate of follow-up (loss was high in the intervention group (19.8%) compared to the control (17.4%) in Cai et al.), [2] the discontinuation rate was reported only for the valsartan group and not reported for the control group and number of enrolled patients was less than planned without reasons reported (CARP).

Participants lost to follow-up was not reported in 12 trials (4 C, ANTIPAF, E-COST; E-COST-R, J-RHYTHM II, ELVERA; ESPIRAL, GISSI-AF, Kawamura, Kondo et al., PHYLLIS, SUPPORT). However, ITT analysis was performed; thus, they were judged to carry a low risk of attrition bias. Eleven studies (ABCD, ATTEMPT-CVD, CCS-I, Chan et al., CORD 1 B, Fogari et al., HONG-KONG DHF, JAMP, Val-HeFT, VALIANT, VALUE) were assessed as having an unclear risk of bias, as insufficient information was provided to allow a judgement.

3.3.4 Selective reporting

Overall, 93 of the included RCTs (95.5%) reported all outcomes as specified in the methodology section or in the pre-study protocols where available. However, three trials were assessed as having unclear reporting bias. Firstly, HONG-KONG DHF and Kawamura did not pre-specify the study outcomes in the methodology and the respective study protocol was unpublished. Also, the VALIANT study failed to report the result of coronary revascularization procedures as pre-defined in the methodology part. The PREVER-treatment trial was judged to carry a high-risk of reporting bias, in which HF hospitalization was pre-defined in the protocol but was not published.

3.3.5 Other potential sources of bias

3.3.5.1 Source of funding

Sponsorship bias was considered as a potential source of bias. Generally, funding sources were classified as profit, non-profit or mixed profit and non-profit organizations. In total, 45 trials were funded by pharmaceutical companies in the form of grants provision, study materials or manpower (authorship, statistical analysis, other assistance). Meanwhile, twenty studies were funded by non-profit or partially from profit organizations (ADVANCE, APRES, DIABHYCAR, DREAM, HOPE, Hou et al. (group 2), PART-2, PROGRESS, RASS, ABCD, ALLHAT, ANBP2, ANTIPAF, EFFERVESCENT, HOPE-3, Weil et al., ATTEMPT-CVD, CARP). Another 14 studies were supported by non-profit organizations, such as independent academic institutions.

More than half of the included trials were decided to have a low risk of sponsorship bias as the study sponsors were not directly involved in the design of the studies, or the collection, analysis, and interpretation of data. Thirty-two trials were rated as demonstrating unclear sponsorship bias for the following reasons. Firstly, where the role of sponsor was not reported (CHARM-Overall, ANTIPAF, IDNT, RENAAL, ALPINE, CASE-J, E-COST, E-COST-R, Kondo et al., MITEC, APRES, ATLANTIS, DIABHYCAR, HYVET, PART-2, PREAMI, QUO VADIS, SCAT, AASK, ABCD, ABCD, Cai et al, Chan et al, ELVERA, Fogari, PHYLLIS, ELITE II), and secondly, where funding resource was not reported, in the OLIVUS-Ex, ESPIRAL, LAARS, J-MIND trials. Three studies were judged as at high risk of sponsorship bias (VALUE; Val-HeFT; CAMELOT) which data monitoring, collection, and analysis were performed directly by the sponsor.

3.3.6 Overall assessment risk of bias

Tables E-1 to E-2 presented in Appendix E summarize the overall risk of bias of each trial. For vascular events, 52 of the included studies were judged to carry a high risk of bias, whereas the remaining 43 studies were rated as having a low risk of bias (AASK, ABCD, ACTIVE-I, ADVANCE, APRES, ATLANTIS, ANTIPAF, COPE, CHARM-overall, DEMAND, DIABHYCAR, DREAM, IMAGINE, PART-2, PEP-CHF, PHARAO, PREAMI, PREVEND IT, PROGRESS, AASK, JMIC-B, PHYLLIS, EFFERVESCENT, HOPE-3, IDNT, I-PRESERVE, NAVIGATOR, ORIENT, ONTARGET, OPTIMAAL RENAAL,

ROADMAP, RASS, ROAD, SCOPE, CASE-J, LIFE, MOSES, PREVER-treatment, VALUE, LIRICO, VALIANT).

With regard to trials reporting all-cause mortality outcome, 33 were deemed to carry a high risk of bias, whereas the remaining 49 trials had a low risk of bias (AARDVARK, ADVANCE, ACTIVE-I, APRES, ATLANTIS, DEMAND, DETAIL, DIABHYCAR, DREAM, HYVET, IMAGINE, PART-2, PEP-CHF, PHARAO, PREAMI, PREVEND IT, PROGRESS, RASS, SCAT, AASK, ALLHAT, JMIC-B, ANTIPAF, CHARM-overall, DIRECT-overall, EFFERVESCENT, GISSI-AF, HOPE-3, IDNT, I-PRESERVE, NAVIGATOR, ORIENT, ONTARGET, OPTIMAAL, RASS, RENAAL, ROADMAP, SCOPE, TRANSCEND, CASE-J, COPE, LIFE, MOSES, PREVER-treatment, LIRICO, ROAD, VALIANT, VALUE).

3.3.7 Discussion

Randomized-controlled trials (RCTs) present one of the highest levels of evidence in clinical practice, evaluating healthcare interventions when appropriately designed, conducted, and reported. However, randomized trials that lack methodological rigour can be unreliable. The Consolidated Standards of Reporting Trials (CONSORT) statement was developed to improve quality when reporting data and to support the quality of newly designed clinical trials. It was firstly introduced in 1996 (Begg et al., 1996) and then finally updated in 2010 (Moher et al., 2010). Although it provides guidance for all the designs of trials including clusters, noninferiority, equivalence, and pragmatic trials, it emphasizes individually randomized, two group, parallel trials more. An additional large database for clinical trials registry has recently been developed for the United States National Library of Medicine (NLM) at the National Institute of Health (ClinicalTrial.gov). It provides information to track changes between a planned study and when it is published to keep researchers up to date about ongoing clinical trials. Section 801 of the FDA-Amendments Act (FDAAA) mandate sponsors to register the clinical trial, and report basic summary results either within 1 year of completion of data collection or upon the date of early termination at ClinicalTrials.gov (Dingell and John, 2007). In addition, the EU Clinical Trials Database (EudraCT) is designed by the European Medicines Agency (EMA) to register clinical trials that are authorized in the EU, and to publish results information that is publicly available for approved and unapproved drugs in the European Union (Bucher et al., 2019). Despite these improvements, several trials

in this review are methodologically weak which might lead to overestimates or underestimates the true treatment effects (Deborah A. Zarin, 2011).

A key aspect of RCTs is the method of randomization. The principal aim of a welldesigned randomization method is to avoid selection bias by ensuring that all participants' known, and unknown characteristics are similar and balanced between groups at the beginning of the RCTs (Higgins et al., 2017a). Of all RCTs published from 2000 onwards, approximately 30% of included trials carried uncertain risk of selection bias, as they had failed to report the method used for the random allocation process. E-COST and CORD 1 B trials were assessed as carrying a high risk of selection bias, as they used unsealed envelopes, which might allow researchers to predict the group to which a patient will be randomized. Methodological study sought to assess differences in the estimated intervention effects for 15 of 22 comparisons of randomized and nonrandomized trials (Kunz R, 2002). The authors concluded that randomized trials with inadequate concealment of allocation tend to result in a larger effect estimate than randomized trials with adequately concealed allocation. The optimal strategy to minimize likelihood of performance bias and detection bias is to keep participants, health-care providers, data collectors, outcome assessors, or data analysts unaware of the assigned intervention (Higgins et al., 2017a). The purpose of blinding is to prevent bias associated with patients' and investigators' expectations. Additionally, the blinding of outcomes assessors is crucial for subjectively assessing outcomes which minimize detection bias. Simply put, more than 70% of the RCTs included had adequately blinded patients, investigators and outcome assessors. The remainder were open-label trials that either followed the PROBE design or did not. Since endpoint in PROBE design is evaluated by a blinded end-point committee, there should be no difference between the two types of trials in this regard. A meta-analysis compared the impact of a double-blind and open-label designs on the observed treatment effects of CV mortality, all types of stroke, MI, all cause and CV mortality (JC et al., 2013). They found no significant interaction between study design for chief efficacy and safety outcomes. Attrition bias refers to systematic differences between groups when there are withdrawals from a study (Higgins et al., 2017a). Attrition bias can influence the statistical power of the study and balance the confounders between the groups. Therefore, ITT was introduced as a statistical solution (Fergusson et al., 2002). The attrition rate for all the included trials ranged from between 0.01% and 17.2%; however,

the majority used the ITT principle. Unsurprisingly, the follow-up loss rate for the included trials increased for trials with a longer follow-up duration. The ITT approach preserved randomization balance, minimized type I errors and allowed for greater generalizability (Fergusson et al., 2002).

An important source of potential bias relates to the influence of pharmaceutical industry sponsorship on trial findings, called sponsorship bias. The majority (80%) of the included studies received assistance in form of provision grants, study material or manpower. However, the sponsors were not directly involved in the designing of studies, or the collection, analysis, and interpretation of data. Remarkably, the industry-sponsored studies in this review showed a slight preference for comparing study drugs against a placebo (58.6%), rather than against similarly effective drugs (30.1%) that were usually intended for approval purposes. One of main reasons for considering sponsor as source of bias is that the quality of a study sponsored by an industrial profit-oriented organization might be poor. A meta-analysis conducted by Cochrane collaboration reviewers revealed that studies sponsored by a manufacturing company more frequently reported positive results (e.g., those with significant P values) and conclusions than those sponsored by other organizations (Lundh et al., 2012). Additionally, failure to publish unfavourable data can lead to publication bias.

4 Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) with risk of coronary artery disease events

4.1 Introduction

Atherosclerosis is a highly complex biological process that has been the subject of intense study over the past decades. Although the renin-angiotensin-aldosterone system (RAAS) is known to regulate blood pressure (BP) and sodium homeostasis, it also has a crucial role in pathogenesis of coronary atherosclerosis (Grote et al., 2004). Drugs designed to interfere with this system, particularly ACEIs and ARBs, have been shown to be beneficial in reducing the risk of coronary atherosclerosis and its sequelae (Aponte and Francis, 2012).

4.1.1 Hypothesis from basic science

Despite data confirming the similar abilities of ACEIs and ARBs to lower BP, the two classes differ in their pharmacological properties at the molecular/cellular level (Heran et al., 2008). Both of classes diminish the harmful effects of Ang II, but by unique mechanisms: the pharmacological actions of ACEIs are mediated through inhibition of Ang II synthesis, whereas ARBs preferentially inhibit its action on the AT₁ receptor. Long-term exposure to ARBs leads to increases in the circulating Ang II levels above baseline, by uncoupling a negative-feedback loop. As a result, overstimulation of AT_2 and AT_4 receptors may occur - this is not seen with ACEI therapy (Levy, 2004, Nikolopoulos et al., 2014). AT_2 receptors can induce vasodilatation via nitric oxide (NO) release, an opposite effect to the AT_1 -mediated effects; thereby ARBs have a dual action. However, more recent studies have suggested that the effects of chronic overstimulation of AT_2 under certain conditions might be parallel to those evoked by AT_1 stimulation, through mediation of growth promotion, fibrosis, and cardiac hypertrophy (D'Amore et al., 2005).

Ang II-mediated AT_4 stimulation has been linked to release of plasminogen activator inhibitor-1 (PAI-1), a major inhibitor of fibrinolysis. One of the unique properties of ACEIs not shared by ARBs is increased bioavailability of bradykinin. Bradykinin is known to exert favourable biologic effects via inhibition of both platelet aggregation and circulating PAI-I levels, as well as promotion of vasodilatation via the release of prostacyclin I_2 and endothelium-derived NO (Witherow et al., 2002, Aponte and Francis, 2012). Therefore, it is not fully established whether this unique pharmacological property of ACEIs, distinct from ARBs, could have clinical implications. The detail of the unique mechanisms of ACEIs and ARBs have been described in **Chapter 1, Section 1.4.3**.

4.1.2 Rationale behind the current study

Two major RCTs have shown an increase in risk of myocardial infarction (MI) in the ARB arm compared to the control. The results of the VALUE trial showed that valsartan was associated with a 19% relative increase in risk of MI compared with amlodipine in 15,245 high-risk hypertensive subjects (Julius et al., 2004). Similarly, in the CHARM-Alternative trial, candesartan was associated with a 52% increase in risk of MI compared to the placebo (p=0.025), despite a 4.4/3.9 mmHg BP reduction in the candesartan-treated group (Granger et al., 2003). On the other hand, other major ARBs trials in high-risk patients have shown no impact on MI reduction. For example, the ACTIVE-I (2011) study reported a non-beneficial effect of irbesartan on risk of MI compared with the placebo, in 9,016 participants with AF, despite a 2.8 mmHg greater reduction of (systolic blood pressure) SBP in the irbesartan group (Yusuf et al., 2011). This unexpected lack of efficacy of ARBs on MI raised concerns about the safety of this class of drugs, later described as the "ARB-MI paradox". The paradox was first raised as an issue in a 2004 editorial (Subodh Verma, 2004), followed by further discussions, debates, and commentaries (Strauss and Hall, 2017, Messerli and Bangalore, 2017). Despite the potential divergent effects of the two pharmacological agents on coronary artery outcomes, many guidelines and clinicians consider them equivalent and interchangeable. The aim of this study is to evaluate the effectiveness of ARB and ACEI on MI and angina pectoris risk in participants with various co-morbidities, through a systematic review of RCTs. A secondary objective is to evaluate whether pharmacological properties or BP reduction account for any differences in MI outcome.

4.2 Methodology

4.2.1 Search strategy and selection criteria

The methods used for this systematic review and meta-analysis have been described in **Chapter 2, Section 2.1.**

4.2.2 Data extraction and source of data

The primary outcome is MI and angina pectoris. The data from published RCTs extracted for evidence synthesis included the percentage of patients with previous or established cardiovascular disease (CVD), whether the MI and angina were prespecified outcomes, the source of data, and the quality of each trial. The details of the source data and overall quality of each trial are summarized in **tables E-1** and E-2 in Appendix E.

Data on MI for the ADVANCE trial was available as tabulated data on the sponsor's clinical data website, Servier Laboratories Pharmaceutical Company (Servier Laboratories, 2009). The data for the IRMA-2, VALIANT, and Val-HEFT trials were obtained from a report submitted by the sponsor company to the U.S. Food and Drug Administration (FDA) website (Targum et al., 2004, Novartis Advisory Committee, 2002, FDA, 2001a). The data on non-fatal MI for the ROADMAP and fatal MI for the ORIENT trials were unpublished and obtained from a safety announcement report released by the U.S FDA website (FDA, 2010b). Data for the CHIEF trial was presented at the International Academy of Cardiology Annual Scientific Sessions 2018 conference (Lu et al., 2018). Data for the remaining studies was obtained from the primary study publications.

The PREAMI, DEMAND, QUO VADIS, and Chan et al. trials reported MI as a prespecified composite endpoint and individually as total events in a manner that prevented meaningful extraction of MI events. In addition, fatal MI was reported overall across both arms in the HYVET-Pilot. Two trials reported zero MI events: the J-RHYTHM II and NTP-AF studies.

Regarding unpublished data of angina pectoris events, data from the CHARM-Added, CHARM-Alternative, and CHARM-Preserved trials were reported on the Clinical Trial Results website of the sponsor, being AstraZeneca pharmaceutical company (CHARM Preserved investigators, 2004, CHARM Added investigators, 2004, CHARM Alternative investigators, 2004). Similarly, data for angina pectoris in the ADVANCE study was available as tabulated data on the clinical data website of the sponsor, being Servier Laboratories Pharmaceutical Company (Servier Laboratories, 2009). Data from the IDNT, IRMA-2, RENAAL, and Val-HeFT trials was obtained from a report submitted by the sponsor company to the U.S. FDA (Hung et al., 2002, Novartis Advisory Committee, 2002, FDA, 2001a). Angina data in the PEACE trial was retrieved from a previous meta-analysis (Bangalore et al., 2017). Data on angina events in the PREVER-Treatment study was supplied by the trial's primary author (Dr Flávio D. Fuchs of Hospital de Clinicas de Porto Alegre, Brazil).

Angina pectoris outcomes in the PREAMI, COPE and QUO VADIS trials were reported as a pre-specified composite endpoint and individually as total events in a manner that was unextractable.

4.2.3 Statistical analysis

4.2.3.1 Meta-analysis

The statistical analysis methods used in this study have been described in **Chapter 2, Section 2.1.9.** Sensitivity analyses were carried out, excluding trials with: (1) non-background usage of RAS blockers; (2) poor methodological quality; (3) small sample sizes with total participants less than 1,000 (to minimize the small study effect) (Dechartres et al., 2013, Kjaergard et al., 2001); (4) post-MI with signs and symptoms of HF. For risk of MI, subgroup analyses for ACEI and ARBs were conducted as follows: (1) ACEIs and ARB subclass; (2) comparator drugs; (3) clinical setting; (4) group mean of age.

4.2.3.2 Meta-regression analysis

A full description of the meta-regression analysis has been described in **Chapter 2**, **Section 2.1.10**.

4.3 Results

The search results have been described in **Chapter 3, Section 3.1.2**. A total of 77 (78.3% of included trials) trials comprising 297,251 participants and reported MI events either as a predefined outcome or as an adverse event. The average followup was 3.6 years (range 1 to 6.2 years) and average age of participants across all studies was 65 years. Angina pectoris events were reported in 48 RCTs with 231,091 participants, followed up over 3.6 years (range 1 to 6.2 years) and with an average age of 64 years.

Data regarding the effect of ACEIs on risk of MI was available from 30 trials that enrolled 109,843 participants and reported 4,256 MI events, whereas data on MI in ARBs trials was available from 39 trials that enrolled 146,593 participants and reported 3,840 MI events. Eight trials compared ACEI directly with ARB, enrolling 40,815 patients with 2,899 events reported.

Almost all trials had pre-defined MI as an outcome, except for nine trials which reported it as an adverse event (ATLANTIS, ANTIPAF, ALPINE, CORD 1 B, Hou et al. (group 2), IRMA-2, KACT-MetS, PHYLLIS, and ROAD). Fourteen trials reported only non-fatal MI events (4 C, ABCD, ADVANCE, CAMELOT, CASE-J, Hou et al. (group 2), IMAGINE, PEACE, PHARAO, TRANSCEND, HIJ-CREATE, KACT-MetS, Kondo et al., OLIVUS-Ex) and three trials reported only fatal events (ALLHAT, ANTIPAF, and ESPIRAL). The remaining trials reported combined fatal and non-fatal MI events.

Data for angina pectoris were pooled from 20 ACEIs trials that included 102,104 participants with 8,346 angina events reported. For ARB trials, 26 RCTs randomized 102,043 participants. Two trials directly compared ACEI with ARB in 26,936 participants. The majority of included trials (~73%) included angina pectoris as an outcome, while eleven trials reported it as serious adverse event. Details of the population characteristics and risk of bias in the RCTs included in this review have been described in **Appendix B and Appendix C**, respectively.

4.4 ACEIs and risk of MI

4.4.1 Overall treatment effect

Figure 4-1 shows RE overall estimates of MI risk pooled from ACEI trials, stratified by comparison group (placebo and active). Thirty RCTs assessed the ACEI therapy on occurrence of MI in 109,843 participants and reported 3,968 events. Altogether, the incidence rate of MI in patients assigned to ACEIs group was slightly lower than those in control group (3.5% and 3.7% respectively). Treatment with ACEIs was associated with a statistically significant 16% reduction in MI compared with control therapy (RR, 0.84; 95% CI 0.79-0.90; P< 0.00001).

Within the placebo subgroup, data pooled from 17 placebo-controlled trials that enrolled 62,790 participants and 3,016 MI events reported contributed 79.9% of the overall effects. ACEIs significantly reduced the risk of MI by 16% when compared with the placebo (RR, 0.84; 95% CI 0.78-0.90; p<0.00001). The most heavily weighted trials in this group were the HOPE (28.5%) and EUROPA (19.2%) trials.

In the active comparator subgroup, data was available from 13 RCTs with 47,053 participants and reported 952 events. The ACEIs showed a 14% lower risk of MI compared to the active group (RR, 0.86; 95% CI 0.75-0.99; p=0.03).

Pooled estimates of RR and 95% CI were similar between the two models, FE and RE, as there was no heterogeneity (Figures 4-1 and 4-2). The heterogeneity of the two models, assessed by $I^2=0\%$ for the placebo and active-controlled trials, indicating no statistical heterogeneity and hence did not require further exploration.

Assessment of the funnel plot (presented in **Figure D-1** in **Appendix D**) shows an asymmetrical appearance at the top and bottom of the funnel. The gap to the top-right of the area of non-significance is likely due to reporting bias (studies with non-significant effects might remain unpublished) and outliers. The outliers were identified as trials with a small sample size and significant effects (PHYLLIS, Fogari et al., and Cai et al.).

	ACE	-	Cont	. al		Risk Ratio	Risk Ratio	Risk of Bias	
Study or Subgroup	Events		Events		Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl	ABCDEFG	
1.1.1 ACEIs vs Placebo	Lycins	Total	LVCIILS	Total	weight	M-H, Random, 55% CI	M-H, Kandolli, 35% Cl	ADCDLIG	
ADVANCE 2007	136	5569	135	5571	6.9%	1.01 [0.80, 1.27]			
APRES 2000	1.50	80	4	79	0.1%	0.25 [0.03, 2.16]	•		
ATLANTIS 2000	3	92	1	48	0.1%	1.57 [0.17, 14.65]	· · · · · · · · · · · · · · · · · · ·		
CAMELOT (Placebo) 2004	11	673	19	655	0.7%	0.56 [0.27, 1.17]			
DIABHYCAR 2004	61	2443	78	2469	3.5%	0.79 [0.57, 1.10]	_ - +		
DREAM 2006	13	2623	11	2646	0.6%	1.19 [0.54, 2.66]			
EUROPA 2003	320	6110	418	6108	19.2%	0.77 [0.66, 0.88]		??	
HOPE 2000	459	4645	570	4652	28.5%	0.81 [0.72, 0.91]		?	
Hou et al (group 2) 2006	5	112	8	112	0.3%	0.63 [0.21, 1.85]			
IMAGINE 2008	16	1280	21	1273	0.9%	0.76 [0.40, 1.45]			
PART-2 2000	22	308	33	309	1.4%	0.67 [0.40, 1.12]	+		
PEACE 2004	222	4158	220	4132	11.6%	1.00 [0.84, 1.20]	_ + _	??	
PHARAO 2008	4	505	5	503	0.2%	0.80 [0.22, 2.95]			
PREVEND IT 2007	12	431	11	433	0.6%	1.10 [0.49, 2.46]			
PROGRESS (monotherapy) 2001	48	1281	52	1280	2.6%	0.92 [0.63, 1.35]			
QUIET 2001	36	878	40	872	2.0%	0.89 [0.58, 1.39]		??	
SCAT 2000	8	229	13	231	0.5%	0.62 [0.26, 1.47]		$\bullet \bullet \bullet ? \bullet \bullet ?$	
Subtotal (95% CI)		31417		31373	79.9%	0.84 [0.78, 0.90]	•		
Total events	1377		1639						
 Heterogeneity: Tau² = 0.00; Chi² = 1 Test for overall effect: Z = 4.98 (P < 		16 (P =	0.60); I² =	0%					
1.1.2 ACEIs vs Active									
AASK 2002	19	436	23	658	1.1%	1.25 [0.69, 2.26]		$\bullet \bullet \bullet \bullet \bullet \bullet \bullet ?$	
ABCD (normotensive) 2002	16	246	18	234	0.9%	0.85 [0.44, 1.62]		? • • • ? • ?	
ALLHAT 2002	157	9054	466	24303	11.9%	0.90 [0.76, 1.08]		$\bullet \bullet \bullet ? \bullet \bullet \bullet$	
ANBP2 2003	58	3044	82	3039	3.5%	0.71 [0.51, 0.98]		?	
Caietal 2001	1	478	2	344	0.1%	0.36 [0.03, 3.95]	• • •	?????	
CAMELOT (Active) 2004	11	673	14	663	0.6%	0.77 [0.35, 1.69]		$\bullet ? \bullet \bullet \bullet \bullet ?$	
ESPIRAL 2001	2	129	1	112	0.1%	1.74 [0.16, 18.90]	• • • • •	• ?? 🖨 ? 🖶 ?	
Fogari et al (combination) 2002	1	104	4	103	0.1%	0.25 [0.03, 2.18]	•	• ? • ? ? • ?	
Fogari et al (monotherapy) 2002	3	102	4	103	0.2%	0.76 [0.17, 3.30]	· · · · · · · · · · · · · · · · · · ·	• ? • ? ? • ?	
J-MIND 2001	1	208	1	228	0.1%	1.10 [0.07, 17.41]	· · · · · · · · · · · · · · · · · · ·	· ?? @ ? @ ?	
JAMP 2004	17	466	18	422	0.9%	0.86 [0.45, 1.64]		?? ? ? ? • •	
JMIC-B 2004	13	822	16	828	0.7%	0.82 [0.40, 1.69]			
PHYLLIS 2004	0	127	4	127	0.0%	0.11 [0.01, 2.04]		$\bullet \bullet \bullet \bullet \bullet \bullet \bullet ?$	
Subtotal (95% CI)		15889		31164	20.1 %	0.86 [0.75, 0.99]	•		
Total events	299		653						
Heterogeneity: Tau ² = 0.00; Chi ² = 7		2 (P = 0	.84); I ² = ()%					
Test for overall effect: Z = 2.16 (P =	0.03)								
Total (95% CI)		47306		62537	100.0%	0.84 [0.79, 0.90]	•		
Total events	1676		2292						
Heterogeneity: Tau ² = 0.00; Chi ² = 2	21.35, df =	29 (P =	0.85); l² =	0%			0.5 0.7 1 1.5 2	-	
Test for overall effect: Z = 5.42 (P ≤	0.00001)						Favours ACEL Favours control		
Test for subgroup differences: Chi ²	= 0.09, df	= 1 (P =	0.76), l² =	= 0%			Tavours AGEL Tavours control		
Risk of bias legend									
(A) Random sequence generation (selection bias)									
(B) Allocation concealment (selection bias)									
(C) Blinding of participants and personnel (performance bias)									
(D) Blinding of outcome assessme	nt (detecti	on bias)	: Other ou	utcomes					
(E) Incomplete outcome data (attriti	on bias)								
(F) Selective reporting (reporting bia	as)								
(G) Other bias									

(G) Other bias

Figure 4-1 Forest plot showing effect of ACEIs on risk of MI, stratified by comparison group (placebo vs. active). Overall: 30 trials [RE model]

The **diamond** indicates the pooled risk ratio (and 95% CI) or the overall effect for MI risk. CI: confidence interval; RE: random-effects; M-H: Mantel-Haenszel. For studies acronyms, see list of definition/ abbreviations

	ACE		Cont	rol		Risk Ratio	Risk Ratio	Risk of Bias
Study or Subgroup	Events		Events		Moight	M-H, Fixed, 95% Cl	M-H. Fixed, 95% Cl	ABCDEFG
1.1.1 ACEIs vs Placebo	Events	Total	Events	TUtal	weight	Wi-fi, Fixeu, 95% Ci	M-H, FIXEU, 95% CI	ABCDEFG
ADVANCE 2007	136	5569	135	5571	6.5%	1.01 (0.80, 1.27)		
APRES 2000	130	5569	135	5571	0.5%	0.25 [0.03, 2.16]	•	
ATLANTIS 2000	3	92	4	48	0.2%	1.57 [0.17, 14.65]		+
CAMELOT (Placebo) 2004	11	673	19	655	0.1%	0.56 [0.27, 1.17]		
DIABHYCAR 2004	61	2443	78	2469	3.7%	0.79 [0.57, 1.10]		
DREAM 2006	13	2623	11	2405	0.5%	1.19 [0.54, 2.66]		
EUROPA 2003	320	6110	418	6108	20.1%	0.77 [0.66, 0.88]		7707000
HOPE 2000	459	4645	570	4652	20.1%	0.81 [0.72, 0.91]		2000000
Hou et al (group 2) 2006	408	4045	570	4052	0.4%	0.63 [0.21, 1.85]		
IMAGINE 2008	16	1280	21	1273	1.0%	0.76 [0.40, 1.45]		ă ă ă ă ă ă ă ă
PART-2 2000	22	308	33	309	1.6%	0.67 [0.40, 1.12]		
PEACE 2004	222	4158	220	4132	10.6%	1.00 [0.84, 1.20]		2200002
PHARAO 2008	4	4156	220	503	0.2%	0.80 [0.22, 2.95]		
PREVEND IT 2007	12	431	11	433	0.2%	1.10 [0.49, 2.46]		
PROGRESS (monotherapy) 2001	48	1281	52	1280	2.5%	0.92 [0.63, 1.35]		
QUIET 2001	40	878	52 40	872	2.5%	0.89 [0.58, 1.39]		??
SCAT 2000	30	229	40	231	0.6%	0.89 [0.58, 1.39]		
Subtotal (95% CI)	8	31417	13	31373	78.9%	0.84 [0.78, 0.90]	· •	
	4077	51417	1639	51575	10.970	0.04 [0.78, 0.90]	•	
Total events	1377							
Heterogeneity: Chi ² = 13.96, df = 16), 1- = 0%)					
Test for overall effect: Z = 4.97 (P ≺	0.00001)							
1.1.2 ACEIs vs Active								
AASK 2002	19	436	23	658	0.9%	1.25 [0.69, 2.26]		
ABCD (normotensive) 2002	16	246	18	234	0.9%	0.85 [0.44, 1.62]		2000202
ALLHAT 2002	157	9054		24303	12.2%	0.90 [0.76, 1.08]		.
ANBP2 2003	58	3044	82	3039	4.0%	0.71 [0.51, 0.98]		2000000
Caletal 2001	1	478	2	344	0.1%	0.36 [0.03, 3.95]	•	22220002
CAMELOT (Active) 2004	11	673	14	663	0.7%	0.77 [0.35, 1.69]		<u><u><u></u></u></u> <u></u>
ESPIRAL 2001	2	129	1	112	0.1%	1.74 [0.16, 18,90]	• •	+ ?? •? • •?
Fogari et al (combination) 2002	1	104	4	103	0.2%	0.25 [0.03, 2.18]	←	• • • • • • • • • • • • • • • • • • •
Fogari et al (monotherapy) 2002	3	102	4	103	0.2%	0.76 [0.17, 3.30]	•	• • • • • • • • • • • • • • • • • • •
J-MIND 2001	1	208	1	228	0.0%	1.10 [0.07, 17.41]	•	+ ?? •? •?
JAMP 2004	17	466	18	422	0.9%	0.86 [0.45, 1.64]		2202200
JMIC-B 2004	13	822	16	828	0.8%	0.82 [0.40, 1.69]		
PHYLLIS 2004	0	127	4	127	0.2%	0.11 [0.01, 2.04]	←	AAAAAAAAAAAAA
Subtotal (95% CI)	0	15889	-	31164	21.1%	0.85 [0.74, 0.98]	•	
Total events	299		653				•	
Heterogeneity: Chi ² = 7.30, df = 12		I ² = 0.%	000					
Test for overall effect: Z = 2.26 (P =		0.0						
	0.02,							
Total (95% CI)		47306		62537	100.0%	0.84 [0.79, 0.90]	•	
Total events	1676		2292					
Heterogeneity: Chi ² = 21.35, df = 29		1° $I^{\circ} = 0.9$						_
Test for overall effect: Z = 5.45 (P <		// - 0 /	, 				0.5 0.7 1 1.5 2	
Test for subgroup differences: Chi ²		- 1 (P -	0.83) 18-	- 0%			Favours ACEI Favours control	
Risk of bias legend	= 0.00, ai		0.00/,1	0.0				
(A) Random sequence generation	(eoloction	hine)						
(B) Allocation concealment (selecti		blas)						
(C) Blinding of participants and per		orformar	re hias)					
(D) Blinding of outcome assessme				iteomos				
(E) Incomplete outcome data (attriti		on bias)	. Julei 0	acomes				
(F) Selective reporting (reporting bia								
(G) Other bias	a3)							
(a) outer blas								

Figure 4-2 Forest plot showing effect of ACEIs on risk of MI, stratified by comparison group (placebo vs. active). Overall: 30 trials (FE model)

The **diamond** indicates the pooled risk ratio (and 95% CI) or the overall effect for MI risk. CI: confidence interval; FE: fixed-effect; M-H: Mantel-Haenszel. For studies acronyms, see list of definition/ abbreviations

4.4.2 Sensitivity analysis

Figure 4-3 demonstrates the summary effect of ACEIs compared to the control (placebo or active) after excluding 10 trials with non-background usage of RAS blockers (naïve). The majority of trials that compared ACEIs with a placebo included naïve participants, particularly those that contributed most to the pooled treatment effect, such as the HOPE and EUROPA trials. The pooled estimate showed ACEIs significantly reduced the risk of MI when compared with placebo or active comparators (RR, 0.87; 95% CI 0.78-0.97; p=.0.01). The test of heterogeneity indicated no variation between studies.

Figure 4-4 shows the forest plot after excluding 17 trials with poor methodological guality (seven placebo and 10 active-controlled trials). The pooled point estimate favoured a protective effect of ACEI on MI risk, though this did not reach statistical significance at RR 0.91 (95% CI 0.79-1.05; p=0.19). Moderate heterogeneity was detected, likely due to the PHYLLIS trial, which was not designed and powered to detect CV outcomes.

Figure 4-5 presents the results after excluding 14 RCTs with small sample sizes (six placebo and eight active-controlled RCTs). The pooled effect estimates were similar for both comparators: placebo (RR, 0.85; 95% CI 0.79-0.91) or active control (RR, 0.87; 95% CI 0.75-1.00). HOPE and EUROPA trials contributed 30.1% and 20.3% of the overall treatment effect and, consequently, influenced the direction of the overall treatment effect.

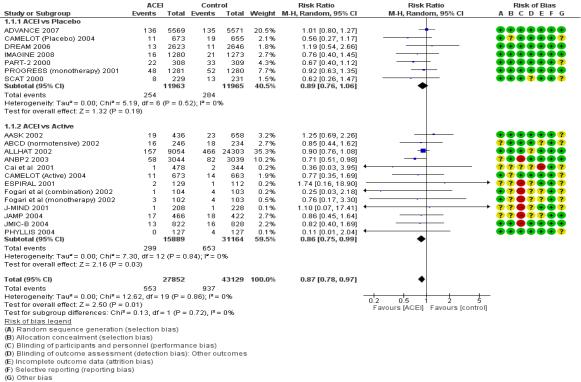


Figure 4-3 Forest plot showing the effect of ACEIs on risk of MI [Sensitivity analysis: Excluding trials with naïve participants]. Overall: 20 trials (RE model).

CI: confidence interval; RE: random-effects; M-H: Mantel-Haenszel. For studies acronyms, see list of definition/ abbreviations

	ACE	s	Contr	ol		Risk Ratio	Risk Ratio	Risk of Bias	
Study or Subgroup	Events		Events		Weight	M-H, Random, 95% Cl	M-H, Random, 95% CI	ABCDEFG	
1.1.2 ACEIs vs Placebo									
ADVANCE 2007	136	5569	135	5571	36.8%	1.01 [0.80, 1.27]	-		
APRES 2000	1	80	4	79	0.4%	0.25 [0.03, 2.16]	←		
ATLANTIS 2000	3	92	1	48	0.4%	1.57 [0.17, 14.65]			
DIABHYCAR 2004	61	2443	78	2469	18.7%	0.79 [0.57, 1.10]			
DREAM 2006	13	2623	11	2646	3.2%	1.19 [0.54, 2.66]			
IMAGINE 2008	16	1280	21	1273	4.9%	0.76 [0.40, 1.45]			
PART-2 2000	22	308	33	309	7.7%	0.67 [0.40, 1.12]			
PHARAO 2008	4	505	5	503	1.2%	0.80 [0.22, 2.95]			
PREVEND IT 2007	12	431	11	433	3.1%	1.10 [0.49, 2.46]			
PROGRESS (monotherapy) 2001	48	1281	52	1280	13.8%	0.92 [0.63, 1.35]			
Subtotal (95% CI)		14612		14611	90.1%	0.90 [0.77, 1.05]	•		
Total events	316		351						
Heterogeneity: Tau ² = 0.00; Chi ² = 5		(P = 0.8)	30); I² = 09	6					
Test for overall effect: Z = 1.37 (P =	0.17)								
1.1.3 ACEIs vs Active									
AASK 2002	19	436	23	658	5.7%	1.25 [0.69, 2.26]			
JMIC-B 2004	13	822	16	828	3.9%	0.82 [0.40, 1.69]			
PHYLLIS 2004	0	127 1385	4	127 1613	0.2%	0.11 [0.01, 2.04]			
Subtotal (95% Cl)		1385		1015	9.9%	0.93 [0.49, 1.77]			
Total events	32	~ ~ ~ ~	43	~					
Heterogeneity: Tau ² = 0.11; Chi ² = 3		(P = 0.∡	(2); F= 35	9%					
Test for overall effect: Z = 0.22 (P =	0.82)								
Total (95% CI)		15997		16224	100.0%	0.91 [0.79, 1.05]	•		
Total events	348		394			. , ,			
Heterogeneity: Tau ² = 0.00; Chi ² = 8		2 (P = 0		196			+ + + + + + + + + + + + + + + + + + + +		
Test for overall effect: Z = 1.31 (P =							0.1 0.2 0.5 1 2 5 10 Favours (ACEIs) Favours (control)		
Test for subgroup differences: Chi*		= 1 (P =	0.92), ² =	0%			Favours (ACEIS) Favours (control)		
Risk of bias legend									
(A) Random sequence generation	(selection	bias)							
(B) Allocation concealment (selection	on bias)	,							
(C) Blinding of participants and per	sonnel (pe	rformar	nce bias)						
(D) Blinding of outcome assessme	nt (detecti	on bias)	: Other ou	Itcomes					
(E) Incomplete outcome data (attrition bias)									
(F) Selective reporting (reporting bia	as)								
(G) Other bias									

Figure 4-4 Forest plot showing effect of ACEIs on risk of MI [Sensitivity analysis: Excluding trials with low methodological quality]. Overall: 13 trials (RE model)

CI: confidence interval; RE: random-effects; M-H: Mantel-Haenszel. For studies acronyms, see list of definition/ abbreviations

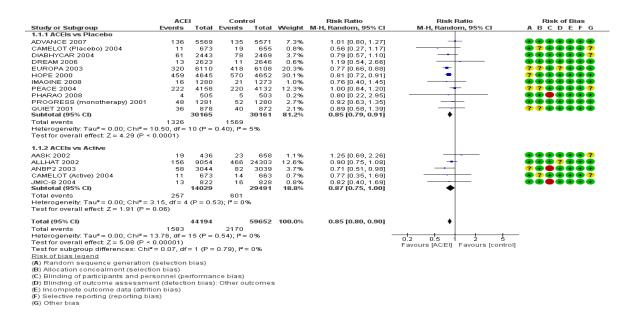


Figure 4-5 Forest plot showing effect of ACEIs on risk of MI [Sensitivity analysis: Excluding trials with small sample size]. Overall: 16 trials (RE model)

CI: confidence interval; RE: random-effects; M-H: Mantel-Haenszel. For studies acronyms, see list of definition/ abbreviations

4.4.3 Subgroup analysis

Table 4-1 summarizes the subgroup analyses of the effectiveness of ACEIs on riskof MI.

4.4.3.1 High- versus low-tissue affinity ACEIs

Figure 4-6 shows the RE meta-analytical summary of high- versus low-tissue affinity ACEIs compared with the control (placebo or active). Overall, high-tissue affinity ACEIs had a 15% lower risk of MI compared with the control group (RR, 0.85; 95% CI 0.79-0.91; p <0.00001). The significance level of pooled effect estimates was greatly influenced by the EUROPA and HOPE trials, which studied perindopril and ramipril, respectively. There was no heterogeneity among trials. Similarly, low-affinity tissue ACEIs were associated with a significant 17% reduction in MI (RR, 0.83; 95% CI 0.73-0.96; p value=0.010). No heterogeneity was detected.

4.4.3.2 Class of active control

Figure 4-7 shows nine RCTs that compared ACEIs with DHP CCBs. The model yielded an RR estimate of 0.92 (95% CI 0.77, 1.11 p=0.40). The direction of the pooled effect estimate was mainly driven by the ALLHAT (CCB) trial, as it had the most weight (73%). No heterogeneity was detected. Compared with diuretics, ACEI showed no apparent benefit (RR, 0.80; 95% CI 0.61-1.05; p=0.11). The direction of the overall effect estimate was mainly influenced by the ALLHAT (diuretic) trial. The heterogeneity test suggested a moderate statistical variation between trials, likely due to PHYLLIS (which was not designed and powered to assess CV outcomes). Compared with the active control, the model yielded an RR of 0.93 (95 CI% 0.59-1.45, p=0.74). No heterogeneity was detected.

4.4.3.3 Clinical setting

Figure 4-8 depicts an RE model of ACEIs' effects, stratified by population setting. Trials of high-risk hypertensive patients showed that ACEIs were associated with a significant 13% reduction in MI (RR, 0.87; 95% CI 0.81-0.93; p=0.0001). The significant pooled effect estimate was driven mainly by the HOPE (39.1%) and ANBP2 (4.8%) trials. The assessment of heterogeneity showed no statistical variation between studies. Among patients with underlying CAD, ACEI therapy showed an 18% risk reduction in MI (RR, 0.82; 95% 0.76-0.88; p<0.00001). This result was largely driven by the HOPE and EUROPA trials, which contributed 42.6% and 28.8% to the overall combined RR, respectively. No heterogeneity was detected.

ACEI therapy was associated with a non-significant 9% reduction in MI risk in patients with DM \pm nephropathy (RR, 0.91; 95% CI 0.76-1.10, p=0.33). The non-significant direction of RR was influenced by the ADVANCE (59%) study, which showed a null effect. However, the 95% CI limit was relatively wide and the possible existence of an effect cannot be excluded. Assessment of heterogeneity indicating no statistical variation between trials.

From the forest plot in **Figure 4-8**, no clear benefit of ACEIs on the risk of MI was evident in patients with non-diabetic nephropathy (RR, 0.94; 95% CI 0.50, 1.75; p=0.84). However, the wide 95% CI limit may indicate a low precise point of estimate. The PREVEND IT trial showed an unfavourable effect of ACEI on MI and contributed of 60% of the pooled effect estimate. Only one trial included patients with CVA: PROGRESS (monotherapy).

4.4.3.4 Mean age group

Pooled data for studies with a younger mean age (< 65 years) yielded a RR estimate of 0.84 (95% CI 0.76, 0.93; p=0.0004). Significantly, the EUROPA trial strongly influenced the direction of the effect estimate (45.9%). Assessment of heterogeneity indicating no statistical variations between studies.

Similar results were seen in studies with a mean age of participants of 65 years or older, with RR 0.85 (95% CI 0.78- 0.92; p < 00001). The direction of the treatment effect was mainly driven by the HOPE study. There was no evidence of heterogeneity across trials.

Table 4-1 Summary of a meta-analytical subgroup analysis by RE model shows the effect of ACEIs compared with control (placebo or active) on risk of MI[†]

					MI Incic	lence (%)			
Su	bgroup analysis	Studies	Participant	Event	ACEI	Control	RR (M-H, Random, 95% CI)	P value*	(l ² %) ‡
Overall	RE	30	109843	3968	3.54	3.81	0.84 [0.79-0.89]	<0.00001*	0
Subclass	High-tissue affinity	15	61232	2984	4.47	5.27	0.85 (0.79-0.91)	<0.00001*	0
	Low-tissue affinity	14	47935	973	1.86	2.11	0.83 (0.73-0.96)	0.010*	0
	DHP CCBs	9	23310	543	1.88	2.00	0.92 (0.77-1.11)	0.40	0
Active	Diuretics	3	30646	453	1.75	2.00	0.80 (0.61-1.05)	0.11	0
control	Active control	3	2587	75	2.68	3.14	0.93 (0.59-1.45)	0.74	0
	CAD	12	40692	2514	5.59	6.74	0.82 [0.76-0.88]	<0.00001*	0
	High-risk hypertensive	17	84495	2930	3.54	3.41	0.87 [0.81-0.93]	0.0001*	0
	DM± Nephropathy	7	17520	462	2.52	2.75	0.91 [0.76-1.10]	0.33	0
Clinical	Non- nephropathy	3	1329	39	2.82	3.05	0.94 [0.50-1.75]	0.84	0
setting	CVA**	1	2561	100	3.74	4.07	0.92 [0.63-1.35]**	0.68	
Mean age	< 65 years	22	40170	1626	3.70	4.37	0.84 [0.76-0.93]	0.0004*	0
group	≥ 65 years	7	69000	2331	3.47	3.31	0.85 [0.78-0.92]	<0.0001*	0

Study or Subgroup Events Total Weight M.H., Random, 95% Cl A. B. C. D. E. F. G. AASK 2002 19 436 23 659 1.4% 1.25 (0.69, 2.26)									
1.1 ftligh-fissue affinity ACEIs AASK 2002 19 436 23 659 14% 1.25 [0.69, 2.26] APRES 2000 1 80 4 79 0.1% 0.25 [0.3, 2.16] APRES 2000 1 80 4 79 0.1% 0.25 [0.3, 2.16] APRES 2000 1 80 4 79 0.1% 0.25 [0.3, 2.16] DIASHYCAR 2004 61 2443 78 2469 4.4% 0.79 [0.57, 1.10] DREAM 2006 13 2623 11 2646 0.8% 1.91 [0.4, 2.66] 77 0.78 PECAM 2003 320 6110 418 6162 3.0% 0.81 [0.72, 0.91] 7 <td< td=""><td></td><td></td><td></td><td></td><td></td><td></td><td>Risk Ratio</td><td>Risk Ratio</td><td>Risk of Bias</td></td<>							Risk Ratio	Risk Ratio	Risk of Bias
AASK 2002 19 436 23 656 1.4% 1.25 (0.69, 2.26) APPERS 2000 1 80 4 79 0.1% 0.25 (0.03, 2.16) APRES 2000 1 80 4 79 0.1% 0.25 (0.03, 2.16) ATAMTS 2000 6 1243 78 2460 0.4% 0.79 (0.57, 1.16) DREAM 2006 13 2623 112 646 0.8% 0.71 (0.66, 0.88) • <td></td> <td>Events</td> <td>Total</td> <td>Events</td> <td>Total</td> <td>Weight</td> <td>M-H, Random, 95% Cl</td> <td>M-H, Random, 95% Cl</td> <td>ABCDEFG</td>		Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl	ABCDEFG
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Hou et al (group 2) 2006 5 112 8 112 0.4% 0.63 [0.21, 1.85] IMAGINE 2008 16 1280 21 1273 1.2% 0.76 [0.40, 1.45] PART-2000 22 308 33 309 1.8% 0.67 [0.40, 1.42] PEACE 2004 222 4158 220 4132 14.7% 1.00 [0.84, 1.20] PHARAO 2008 4 505 5 503 0.3% 0.80 [0.22, 295] PROGRESS (monotherapy) 2001 48 1281 52 1280 3.3% 0.92 [0.63, 1.35] OUIET 2001 30520 30712 100.0% 0.85 [0.79, 0.91] Total events 1365 1619 Heterogeneity. Tau" = 0.00; Ch" = 1.5.8% 0.44 1.462 ALLHAT 2002 16 246 18 234 4.5% 0.85 [0.44, 1.62] ALLHAT 2002 16 246 18 234 4.5% 0.85 [0.44, 1.62] ALLHAT 2002 157 9054 466 24303 58.6% 0.90 [0.76, 1.08] ALLHAT 2002 157 9054 466 24303 58.6% 0.90 [0.76, 1.08] ALLHAT 2002 157 9054 466 24303 58.6% 0.90 [0.76, 1.08] ALLHAT 2002 157 9054 466 24303 58.6% 0.90 [0.76, 1.08] ALLHAT 2002 157 9054 466 24303 58.6% 0.90 [0.76, 1.08] ALLHAT 2002 157 9054 466 24303 58.6% 0.90 [0.76, 1.08] ALLHAT 2002 157 9054 406 24303 98.0% 0.71 [0.51, 0.98] Calletal 2001 1 478 2 344 0.3% 0.38 [0.033, 1.28] Fogari et al (combination) 2002 1 104 4 103 0.4% 0.25 [0.03, 2.18] Fogari et al (combination) 2002 1 104 4 103 0.4% 0.26 [0.03, 2.18] Fogari et al (combination) 2002 1 102 4 103 0.9% 0.76 [0.47, 7.330] JAMIC 2004 17 466 18 422 4.5% 0.88 [0.45, 1.64] JAMIC 2004 17 466 18 422 4.5% 0.88 [0.45, 1.64] JAMIC 2004 17 466 18 422 4.5% 0.88 [0.45, 1.64] PREVEND IT 2007 1 2 431 11 433 2.9% 1.10 [0.07, 7.30] PREVEND IT 2007 1 2 431 11 433 2.9% 1.10 [0.01, 2.04] PREVEND IT 2007 1 2 431 11 433 2.9% 1.10 [0.01, 2.04] PREVEND IT 2007 1 2 431 11 433 2.9% 1.10 [0.49, 2.46] Subtotal (95% CI) 16113 31822 100.0% 0.63 [0.73, 0.96] PHEVEND IT 2007 1 2 431 11 433 2.9% 1.10 [0.49, 2.46] Subtotal (95% CI) 16113 31822 100.0% 0.63 [0.73, 0.96] PREVEND IT 2007 1 2 4.31 11 433 2.9% 1.01 [0.49, 2.46] Subtotal (95% CI) 16113 31822 100.0% 0.63 [0.73, 0.96] PREVEND IT 2007 1 2 4.31 11 433 2.9% Total events 300 673 Heterogeneity: Tau" = 0.00; Ch" = 7.10, d"= 13 (P = 0.90); P = 0% Test for overall effect Z = 2.59 (P = 0.010)	EUROPA 2003	320	6110	418	6108	24.3%	0.77 [0.66, 0.88]		
IMAGINE 2008 16 1280 21 1273 1.2% 0.76 0.40 1.45 PART-2 2000 22 308 33 309 1.8% 0.67 0.40 1.12 PHARE 2004 222 4158 200 4132 14.7% 1.00 10.84 1.00 0.84 1.00 0.84 1.00 0.84 1.00 0.84 1.00 0.84 1.00 0.84 1.00 0.84 1.00 0.84 1.00 0.84 1.00 0.84 1.00 0.84 1.00 0.85 0.89 0.85 0.89 0.85 0.89 0.85 0.89 0.85 0.89 0.85 0.89 0.85 0.99 0.85 0.99 0.85 0.99 0.85 0.90 0.85 0.90 0.85 0.90 0.85 0.90 0.85 0.90 0.79 0.91 0.76 0.00 0.79 0.91 0.76 0.00 0.76 0.00 0.76 0.76 0.76 0.76 0.76 0.76 0.76 0.76 0.76 0.76 0.76 0.76 </td <td>HOPE 2000</td> <td>459</td> <td>4645</td> <td>570</td> <td>4652</td> <td>36.0%</td> <td>0.81 [0.72, 0.91]</td> <td>+</td> <td></td>	HOPE 2000	459	4645	570	4652	36.0%	0.81 [0.72, 0.91]	+	
PART-2 2000 22 308 33 309 1.8% 0.67 [0.40, 1.12] PEACE 2004 222 4158 220 4132 14.7% 1.00 [0.84, 1.20] PHARAO 2008 4 505 5 503 0.3% 0.80 [0.22, 2.95] OUET 2001 36 878 40 872 2.5% 0.89 [0.58, 1.39] OUET 201 36 878 40 872 2.5% 0.89 [0.58, 1.39] OUET 201 36 878 40 872 2.5% 0.89 [0.58, 1.39] OUET 201 36 878 40 872 2.5% 0.89 [0.58, 1.39] OUET 201 36 878 40 872 2.5% 0.89 [0.58, 1.39] OUET 201 36 878 40 872 2.5% 0.89 [0.58, 1.39] OUET 201 36 878 40 872 2.5% 0.89 [0.58, 1.39] OUET 201 36 878 40 872 2.5% 0.85 [0.44, 1.62] ALLHAT 202 16 246 18 234 4.5% 0.85 [0.44, 1.62] ALLHAT 202 157 9054 466 24303 58.6% 0.90 [0.76, 1.08] ALLHAT 202 157 9054 466 24303 58.6% 0.90 [0.76, 1.08] ALLHAT 202 157 9054 466 24303 58.6% 0.90 [0.33, 3.128] Calietal 2001 1 478 2 344 0.3% 0.71 [0.51, 0.98] Calietal 2001 2 102 4 103 0.4% 0.25 [0.33, 1.28] Fogari et al (combination) 2002 1 104 4 103 0.4% 0.25 [0.33, 1.28] Fogari et al (combination) 2002 1 102 4 103 0.4% 0.26 [0.33, 1.64] JMIC-B 2004 17 466 18 422 45% 0.88 [0.40, 1.69] JMIND 2001 1 208 1 228 0.2% 11.10 [0.7, 1.741] JMIND 2001 1 208 1 228 0.2% 11.10 [0.7, 1.741] JMIND 2004 17 46 18 422 45% 0.88 [0.40, 1.69] JMIND 2001 1 22 41 113 3 1282 168 28 3.6% 0.82 [0.40, 1.69] JMIC-B 2004 17 46 18 422 45% 0.88 [0.40, 1.69] JMIC-B 2004 17 46 18 422 45% 0.88 [0.40, 1.69] JMIC-B 2004 17 46 18 422 45% 0.88 [0.40, 1.69] JMIC-B 2004 17 46 18 422 45% 0.88 [0.40, 1.69] JMIC-B 2004 17 46 18 422 45% 0.88 [0.40, 1.69] JMIC-B 2004 17 4 127 0.2% 0.11 [0.01, 2.04] JMIC-B 2004 673 Heterogeneity. Tau" = 0.00; Ch" = 7.10, d" = 13 (P = 0.90); P = 0% Test for overall effect Z = 2.59 (P = 0.010)	Hou et al (group 2) 2006	5	112	8	112	0.4%	0.63 [0.21, 1.85]		
PEACE 2004 222 4158 220 4132 14.7% 1.00 [0.84, 1.20] PHARAO 2008 4 505 5 503 0.3% 0.80 [0.22, 2.95] PROGRESS (monotherapy) 2001 4 505 5 0.3% 0.89 [0.58, 1.39] QUIET 2001 36 878 40 872 2.5% 0.89 [0.58, 1.39] Subtotal (95% (1) 30520 30712 100.0% 0.85 [0.79, 0.91] 7 Total events 1365 1619 Heterogeneity: Tau ² = 0.00; Chi ² = 13.59, df = 14 (P = 0.48); P = 0% 0.85 [0.74, 1.62] 7 7 7 Cai etal 2001 16 246 18 234 4.5% 0.85 [0.44, 1.62] 7	IMAGINE 2008	16	1280	21	1273	1.2%	0.76 [0.40, 1.45]		
PHARAO 2008 4 505 5 503 0.3% 0.80 (0.22, 2.95) PROGRESS (monotherapy) 2001 48 1281 52 1280 3.3% 0.92 (0.63, 1.35) Subtotal (95% CI) 30520 30712 100.0% 0.85 [0.79, 0.91] 7 7 7 7 7 Total events 1365 1619 Heterogeneity: Tau" = 0.00; Chi" = 13.59, df = 14 (P = 0.48); P = 0% 0.85 [0.79, 0.91] 7	PART-2 2000	22	308	33	309	1.8%	0.67 [0.40, 1.12]		
PROGRESS (monotherapy) 2001 48 1281 52 1280 3.3% 0.92 [0.83, 1.35] QUIET 2001 36 878 40 872 2.5% 0.89 [0.58, 1.39] Subtotal (95% C) 30520 30712 100.0% 0.89 [0.58, 1.39] Total events 1365 1619 Heterogeneity: Tau" = 0.00; Chi" = 13.59, df = 14 (P = 0.48); I" = 0% Testfor overall effect: Z = 4.70 (P < 0.00001) 1.1.2 Low-tissue affinity ACEIs ABCD (normotensive) 2002 16 246 18 234 4.5% 0.85 [0.44, 1.62] ALLAT 2002 157 9054 466 24303 58.6% 0.90 [0.76, 1.08] ANBP2 2003 68 3044 82 3039 17.0% 0.71 [0.51, 0.88] CAMELOT (Overall) 2004 11 673 33 1315 4.1% 0.65 [0.33, 1.28] Fogari et al (combination) 2002 1 104 4 103 0.4% 0.25 [0.03, 2.18] Fogari et al (combination) 2002 3 102 4 103 0.9% 0.76 [0.17, 3.30] JAMP 2004 17 466 18 422 4.5% 0.86 [0.45, 1.84] JAMC-B 2004 13 822 16 828 3.6% 0.82 [0.40, 1.69] JAMP 2004 17 466 18 422 4.5% 0.86 [0.45, 1.84] JAMC-B 2004 13 822 16 828 3.6% 0.82 [0.40, 1.68] JAMC-B 2004 13 822 16 828 3.6% 0.82 [0.40, 1.68] JAMC-B 2004 13 822 16 828 3.6% 0.82 [0.40, 1.68] JAMC-B 2004 17 466 18 422 4.5% 0.86 [0.45, 1.84] JAMC-B 2004 13 822 16 828 3.6% 0.82 [0.40, 1.68] JAMC-B 2004 13 822 16 828 3.6% 0.82 [0.40, 1.68] JAMC-B 2004 13 822 16 828 3.6% 0.82 [0.40, 1.68] JAMC-B 2004 13 822 16 828 3.6% 0.62 [0.26, 1.47] JAMC-B 2004 8 229 13 231 2.5% 0.62 [0.26, 1.47] JAMC-B 2004 7 7 4 61 13 31822 100.0% 0.83 [0.73, 0.96] Total events 300 673 Heterogeneity: Tau" = 0.00; Chi" = 7.10, df = 13 (P = 0.90); P = 0% Testfor overall effect: Z = 2.59 (P = 0.010)	PEACE 2004	222	4158	220	4132	14.7%	1.00 [0.84, 1.20]	+	??
QUET 2001 36 878 40 872 2.5% 0.89 0.58 1.39 Subtotal (95% CI) 30520 30712 100.0% 0.85 0.89 0.58 1.39 Total events 1365 1619 Heterogeneity: Tau ² = 0.00; Chi ² = 13.59, df = 14 (P = 0.48); P = 0% 0.85 0.44, 162] 0.85 0.90 0.76, 1.08] ALLHAT 2002 16 246 18 234 4.5% 0.85 0.44, 162] 0.76, 1.08] Cai et al 2001 1 478 2 344 0.3% 0.36 (0.3, 3.45) 0.76 (0.3, 3.45) Fogari et al (comolnation) 2002 1 114 0.3% 0.46 (0.3, 3.45) 0.76 (0.17, 3.30) Fogari et al (comolnation) 2002 1 1.04 4 103 0.9% 0.76 (0.17, 3.30) J-MiND 2001 1 2.08 1.28 0.2% 0.11 (0.01, 2.04) 0.76 (0.17, 3.30) J-MiND 2004 17 466 828 3.6% 0.82 (0.40, 1.68) 0.76 (0.17, 7.41) 0.76 (0.7, 7.41) J-MAP 2004 12 12 12 1.28 0.2% 0.11 (PHARAO 2008	4	505	5	503	0.3%	0.80 [0.22, 2.95]		
Subtotal (95% CI) 30520 30712 100.0% 0.85 [0.79, 0.91] Total events 1365 1619 Heterogeneity: Tau ² = 0.00; Chi ² = 13.59, df = 14 (P = 0.48); P = 0% Test for overall effect: Z = 4.70 (P < 0.00001)	PROGRESS (monotherapy) 2001	48	1281	52	1280	3.3%	0.92 [0.63, 1.35]		
Subtral (95% Cl) 30520 30712 100.0% 0.85 [0.79, 0.91] Total events 1365 1619 Heterogeneily: Tau ² = 0.00; Ch ² = 13.59, df = 14 (P = 0.48); P = 0% 0.85 [0.79, 0.91] 1.12 Low-tissue affinity ACEIs 0.85 [0.79, 0.91] ALLHAT 2002 16 246 18 234 4.5% 0.85 [0.44, 1.62] Caite al 2001 14 478 2 3039 17.0% 0.71 [0.51, 0.98] 7 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	QUIET 2001	36	878	40	872	2.5%	0.89 [0.58, 1.39]		??
Heterogeneity: Tau ² = 0.00; Chi ² = 13.59, df = 14 (P = 0.48); i ² = 0% Test for overall effect: Z = 4.70 (P < 0.00001)	Subtotal (95% CI)		30520		30712	100.0%		•	
Heterogeneity: Tau ² = 0.00; Chi ² = 13.59, df = 14 (P = 0.48); i ² = 0% Test for overall effect: Z = 4.70 (P < 0.00001)	Total events	1365		1619					
Test for overall effect: Z = 4.70 (P < 0.00001)			14 (P =		0%				
1.1.2 Low-tissue affinity ACEIs ABCD (normotensive) 2002 16 246 18 234 4.5% 0.85 [0.44, 1.62]									
ABCD (normotensive) 2002 16 246 18 234 4.5% 0.85 [0.44, 1.62] ALLHAT 2002 157 9054 466 24303 58.8% 0.90 [0.76, 1.08] ANBP2 2003 58 3044 82 3039 17.0% 0.71 [0.51, 0.98] Cai etal 2001 1 478 2 344 0.3% 0.36 [0.03, 3.95] CAMELOT (Overall) 2004 11 673 33 1315 4.1% 0.66 [0.33, 1.28] ESPIRAL 2001 2 129 1 112 0.3% 1.74 [0.16, 18.90] Fogari et al (combination) 2002 1 104 4 103 0.4% 0.26 [0.03, 2.18] Fogari et al (combination) 2002 3 102 4 103 0.9% 0.76 [0.17, 3.30] J-MIND 2001 1 208 1 228 0.2% 1.10 [0.07, 17.41] JAMP 2004 17 466 18 422 4.5% 0.86 [0.45, 1.64] JAMP 2004 17 466 18 422 4.5% 0.82 [0.40, 1.69] PHYLLIS 2004 0 127 4 127 0.2% 0.11 [0.01, 2.04] PREVEND IT 2007 12 431 11 433 2.9% 1.10 [0.07, 37, 0.96] PAYLIS 2004 0 127 4 127 0.2% 0.11 [0.01, 2.04] PREVEND IT 2007 12 431 11 433 2.9% 1.00 [0.49, 2.46] SCAT 2000 8 229 13 231 2.5% 0.83 [0.73, 0.96] Total events 300 673 Heterogeneity: Tau ² = 0.00; Ch ² = 7.10, df = 13 (P = 0.90); P = 0% Test for overall effect: Z = 2.59 (P = 0.010)		,							
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ANBP2 2003 58 3044 82 3039 17.0% 0.71 [0.51, 0.98] Cai et al 2001 1 478 2 344 0.3% 0.36 [0.03, 3.95] CAMELOT (Overall) 2004 11 673 33 1315 4.1% 0.66 [0.33, 1.28] ESPIRAL 2001 2 129 1 112 0.3% 1.74 [0.16, 18.90] Fogari et al (combination) 2002 1 104 4 103 0.4% 0.25 [0.03, 2.18] Fogari et al (combination) 2002 3 102 4 103 0.4% 0.25 [0.03, 2.18] Fogari et al (combination) 2002 1 104 4 103 0.4% 0.25 [0.03, 2.18] Fogari et al (combination) 2002 1 104 4 103 0.4% 0.25 [0.03, 2.18] Fogari et al (combination) 2002 1 104 4 103 0.4% 0.25 [0.03, 2.18] Fogari et al (combination) 2002 1 104 4 103 0.4% 0.25 [0.03, 2.18] Fogari et al (combination) 2002 1 104 4 103 0.4% 0.25 [0.03, 2.18] Fogari et al (combination) 2002 1 102 4 103 0.4% 0.25 [0.03, 2.18] Fogari et al (combination) 2002 1 1 208 1 228 0.2% 1.10 [0.07, 17.41] JAMP 2004 17 466 18 422 4.5% 0.88 [0.45, 1.64] PHYLLIS 2004 0 127 4 127 0.2% 0.11 [0.01, 2.04] PREVEND IT 2007 12 431 11 433 2.9% 1.10 [0.49, 2.46] SCAT 2000 8 229 13 231 2.5% 0.62 [0.26, 1.47] Subtotal (95% CI) 16113 31822 100.0% 0.73 0.96] Total events 300 673 Heterogeneity: Tau ² = 0.00; Ch ² = 7.10, df = 13 (P = 0.90); P = 0% Test for overall effect: Z = 2.59 (P = 0.010)								-	
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Fogari et al (monotherapy) 2002 3 102 4 103 0.9% 0.76 [0.17, 3.30] ••••••••••••••••••••••••••••••••••••								←	
J-MIND 2001 1 208 1 228 0.2% 1.10 [0.07, 17.41] ? ? • • ? ? ? • • ? ? • • • • • ? ? • • • • • ? ? • • • • • • ? ? • • • • • • • • • • • • • • • • • • •									
JAMP 2004 17 466 18 422 4.5% 0.86 [0.45, 1.64] JMIC-B 2004 13 822 16 828 3.6% 0.82 [0.40, 1.69] PHYLLIS 2004 0 127 4 127 0.2% 0.11 [0.01, 2.04] PREVEND IT 2007 12 431 11 433 2.9% 1.10 [0.49, 2.46] SCAT 2000 8 229 13 231 2.5% 0.62 [0.26, 1.47] Subtotal (95% CI) 16113 31822 100.0% 0.83 [0.73, 0.96] Total events 300 673 Heterogeneity. Tau ² = 0.00; Ch ² = 7.10, df = 13 (P = 0.90); I ² = 0% Test for overall effect: Z = 2.59 (P = 0.010)								•	
JMIC-B 2004 13 822 16 828 3.6% 0.82 [0.40, 1.69] PHYLLIS 2004 0 127 4 127 0.2% 0.11 [0.01, 2.04] PREVEND IT 2007 12 431 11 433 2.9% 1.10 [0.49, 2.46] SCAT 2000 8 229 13 231 2.5% 0.62 [0.26, 1.47] Subtotal (95% CI) 16113 31822 100.0% 0.83 [0.73, 0.96] ● Total events 300 673 ●<									
PHYLLIS 2004 0 127 4 127 0.2% 0.11 [0.01, 2.04] PREVEND IT 2007 12 431 11 433 2.9% 1.10 [0.49, 2.46] SCAT 2000 8 229 13 231 2.5% 0.62 [0.26, 1.47] Subtotal (95% Cl) 16113 31822 100.0% 0.83 [0.73, 0.96] ● Total events 300 673 + + ● <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td>									
PREVEND IT 2007 12 431 11 433 2.9% 1.10 [0.49, 2.46] ScAT 2000 8 229 13 231 2.5% 0.62 [0.26, 1.47] Subtotal (95% CI) 16113 31822 100.0% 0.83 [0.73, 0.96] Total events 300 673 Heterogenetly: Tau ² = 0.00; Chi ² = 7.10, df = 13 (P = 0.90); I ² = 0% Test for overall effect: Z = 2.59 (P = 0.010)								<u>ــــــــــــــــــــــــــــــــــــ</u>	
SCAT 2000 8 229 13 231 2.5% 0.62 [0.26, 1.47] Subtotal (95% CI) 16113 31822 100.0% 0.83 [0.73, 0.96] ◆ Total events 300 673 Heterogeneity. Tau ² = 0.00; Chi ² = 7.10, df = 13 (P = 0.90); I ² = 0% Test for overall effect: Z = 2.59 (P = 0.010)		-							
Subtotal (95% Cl) 16113 31822 100.0% 0.83 [0.73, 0.96] Total events 300 673 Heterogeneity: Tau ² = 0.00; Chi ² = 7.10, df = 13 (P = 0.90); I ² = 0% Test for overall effect: Z = 2.59 (P = 0.010)									
Total events 300 673 Heterogeneity: Tau ² = 0.00; Chi ² = 7.10, df = 13 (P = 0.90); i ² = 0% Test for overall effect: Z = 2.59 (P = 0.010)		0		15					
Heterogeneity: Tau ² = 0.00; Chi ² = 7.10, df = 13 (P = 0.90); i ² = 0% Test for overall effect: Z = 2.59 (P = 0.010)		200	10115	070	J 1022	100.070	0.05 [0.75, 0.50]	•	
Test for overall effect: Z = 2.59 (P = 0.010)			2 /D – 0		- ov				
			3 (P = 0	.90), I== (7.20				
	Test for overall effect. $z = 2.59$ (P = 0	5.010)							
									_
0.2 0.3 1 2 3								0.2 0.5 1 2 5	
Favours [ACEI] Favours [Control]	To show only successful differences of the	0.00 **	4.00	0.000 17	0.07			Favours (ACEI) Favours (control)	
Test for subgroup differences: Chi ² = 0.03, df = 1 (P = 0.86), P = 0%		= 0.03, df	= 1 (P =	0.86), F=	= 0%				
Risk of bias legend									
(A) Random sequence generation (selection bias)			pias)						
(B) Allocation concealment (selection bias)		,							
(C) Blinding of participants and personnel (performance bias) DD Blinding of participants and personnel (detection bias): Other automas									

(C) Blinding of participants and personnel (performance bias)
 (D) Blinding of outcome assessment (detection bias): Other outcomes
 (E) Incomplete outcome data (attrition bias)
 (F) Selective reporting (reporting bias)
 (G) Other bias

Figure 4-6 Forest plot showing effect of ACEIs on risk of MI (RE model). [Subgroup: Low vs. high-tissue affinity ACEIs]

CI: confidence interval; RE: random-effects; M-H: Mantel-Haenszel. For studies acronyms, see list of definition/ abbreviations

	ACE	le	Cont	rol		Risk Ratio	Risk Ratio	Risk of Bias
Study or Subgroup	Events		Events		Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl	ABCDEFG
1.1.1 Dihydropyridine CCBs								
AASK (CCB) 2002	19	436	5	217	3.6%	1.89 [0.72, 5.00]		
ABCD (normotensive) 2002	16	246	18	234	8.1%	0.85 [0.44, 1.62]		?
ALLHAT (CCB) 2002	157	9054	168	9048	73.0%	0.93 [0.75, 1.16]		
CAMELOT (Active) 2004	11	673	14	663	5.5%	0.77 [0.35, 1.69]	_	
ESPIRAL 2001	2	129	1	112	0.6%	1.74 [0.16, 18.90]		?? \varTheta ? 🖶 😌 ?
Fogari et al (combination) 2002	1	104	4	103	0.7%	0.25 [0.03, 2.18]	·	•? •? •?
Fogari et al (monotherapy) 2002	3	102	4	103	1.6%	0.76 [0.17, 3.30]		9? \varTheta ? ? 8 ?
J-MIND 2001	1	208	1	228	0.4%	1.10 [0.07, 17.41]	← →	?? 🗧 ? 🖶 ?
JMIC-B 2004	13	822	16	828	6.5%	0.82 [0.40, 1.69]		
Subtotal (95% CI)		11774		11536	100.0%	0.92 [0.77, 1.11]	◆	
Total events	223		231					
Heterogeneity: Tau ² = 0.00; Chi ² =	4.24, df =	8 (P = 0	.84); I ² = I	3%				
Test for overall effect: Z = 0.83 (P =	0.40)							
1.1.2 Diuretics								
ALLHAT (Diuretic) 2002	157	9054	298	15255	60.9%	0.89 [0.73, 1.08]	-	
ANBP2 2003	58	3044	82	3039	38.2%	0.71 [0.51, 0.98]		? • • • • • •
PHYLLIS 2004	0	127	4	127	0.9%	0.11 [0.01, 2.04]	·	
Subtotal (95% CI)		12225		18421	100.0%	0.80 [0.61, 1.05]	•	
Total events	215		384					
Heterogeneity: Tau ² = 0.02; Chi ² =		2 (P = 0	.20); I² = 3	38%				
Test for overall effect: Z = 1.60 (P =	: 0.11)							
1.1.3 Active control								
AASK (Beta-blocker) 2002	19	436	18	441	49.7%	1.07 [0.57, 2.01]		
Caietal 2001	1	478	2	344	3.4%	0.36 [0.03, 3.95]	← · · · · · · · · · · · · · · · · · · ·	?????
JAMP 2004	17	466	18	422	46.9%	0.86 [0.45, 1.64]		?? 🔴 ? ? 🖶 🔁
Subtotal (95% CI)		1380		1207	100.0%	0.93 [0.59, 1.45]	-	
Total events	37		38					
Heterogeneity: Tau ² = 0.00; Chi ² =		2 (P = 0	.65); I² = I	3%				
Test for overall effect: Z = 0.33 (P =	: 0.74)							
							0.2 0.5 1 2 5	
							Favours [ACEIs] Favours [control]	
Test for subgroup differences: Chi	r = 0.79, c	f = 2 (P	= 0.67), P	°= 0%				
Risk of bias legend								
(A) Random sequence generation		n bias)						
(B) Allocation concealment (select	,							
(C) Blinding of participants and pe								
(D) Blinding of outcome assessm		tion bias	s): Other (outcome	s			
(E) Incomplete outcome data (attri								
(F) Selective reporting (reporting b	ias)							
(G) Other bias								

Figure 4-7 Forest plot showing effect of ACEIs on risk of MI (RE model). [Subgroup: Class of active control]

CI: confidence interval; RE: random-effects; M-H: Mantel-Haenszel. For studies acronyms, see list of definition/ abbreviations

Chapter 4: ACEIs and ARBs with risk of CAD

Events 19 136 157	436 5569	23	Total 658	1.5%	M-H, Random, 95% Cl 1.25 [0.69, 2.26]	M-H, Random, 95% Cl	
136			658	1.5%	1 25 10 69 2 261		
136			658	1.5%			
	5569		C C 7 4				
157		135	5571	9.5%	1.01 [0.80, 1.27]		
	9054	466	24303	16.4%	0.90 [0.76, 1.08]		
58	3044	82	3039	4.8%	0.71 [0.51, 0.98]		200000
11	673	33	1318	1.2%	0.65 [0.33, 1.28]		
61	2443	78	2469	4.8%	0.79 [0.57, 1.10]		
2	129	1	112	0.1%	1.74 [0.16, 18.90]		
1	104	4	103	0.1%	0.25 [0.03, 2.18] 👎		•?•?•
3	102	4	103	0.2%	0.76 [0.17, 3.30]		•?•?•
459	4645	570	4652	39.1%	0.81 [0.72, 0.91]		? • • • • • •
	112	8	112	0.4%			
		21		1.3%			
	208						
						_ _	226666
		52					
	J4 107	4740	30308	100.0%	0.87 [0.81, 0.95]	•	
3.84, df = 1	16 (P = 1		0%				
3)							
	00	,	70	0.40	0.0510.00.0401 4		
							?
17	466	18	422	1.4%	0.86 [0.45, 1.64]		2 2 🖨 2 2 🖶
13	822	16	828	1.1%	0.82 [0.40, 1.69]		
22	308	33	309	2.2%	0.67 [0.40, 1.12]	+	
222	4158	220	4132	17.4%	1.00 [0.84, 1.20]	_ + _	??
							??
						•	
		1388				•	
.02, df = 11	1 (P = 0.)%				
ropathy							
	246	10	224	7 7 96	0.95 (0.44, 1.62)		?
						T	\rightarrow
3							• ? • ? • •
1		1				•	
	8764		8756	100.0 %	0.91 [0.76, 1.10]	•	
221		241					
	(P = 0.7	'9); I² = 04	%				
2	179	1	112	6 9%	174 0 16 18 901		→ ??₽? ₽₽(
12		11					
10	312		007	100.0%	0.34 [0.30, 1.73]		
94, df = 2	(P = 0.6		%				
48	1281	52	1280	100.0%	0.92 [0.63, 1.35]		
	1281				0.92 [0.63, 1.35]		
48		52				-	
40		52					
168)							
					-	0.2 0.5 1 2	5
		0.74% /5	00		Fav	ours [experimental] Favours [control	1
		11 7 1 Y 14 -					
= 2.14, df=	- 4 (F -	200 M.C	- 0 %				
		0.117,114	- 0 %				
= 2.14, df= selection I in bias)		0.11),115	- 0 %				
	1 3 459 5 16 1 13 222 0 48 1212 3.84, df= 10,0001) 1 1 1 1 1 320 48 1212 3.84, df= 1 1 3.84, df= 5 18 10 1 1 1 1 2 2 2 2 2 2 19 94, df= 2 19 19 19 5 19 5 19 19 5 19 19 19 19 19 19 19 19 19 19	$\begin{array}{c} 1 & 104 \\ 3 & 102 \\ 459 & 4645 \\ 5 & 112 \\ 16 & 1280 \\ 1 & 208 \\ 13 & 822 \\ 222 & 4158 \\ 0 & 127 \\ 48 & 1281 \\ 34187 \\ 1212 \\ 3.84, df = 16 (P = 1, 0, 0, 0, 0) \\ 1 & 80 \\ 1 & 478 \\ 320 & 6110 \\ 459 & 4645 \\ 16 & 1280 \\ 17 & 466 \\ 13 & 822 \\ 22 & 308 \\ 222 & 4158 \\ 8 & 229 \\ 20127 \\ 1126 \\ .02, df = 11 (P = 0, 0, 0, 0, 0, 0) \\ .00001) \\ \textbf{mopathy} \\ 16 & 246 \\ 136 & 5569 \\ 3 & 92 \\ 20127 \\ 1126 \\ .00001) \\ \textbf{mopathy} \\ 16 & 246 \\ 136 & 5569 \\ 3 & 92 \\ 20127 \\ 1126 \\ .00001) \\ \textbf{mopathy} \\ 16 & 246 \\ 136 & 5569 \\ 3 & 92 \\ 20127 \\ 1126 \\ .00001) \\ \textbf{mopathy} \\ 16 & 246 \\ 136 & 5569 \\ 3 & 92 \\ 20127 \\ 1126 \\ .00001) \\ \textbf{mopathy} \\ 16 & 246 \\ 136 & 5569 \\ 3 & 92 \\ 20127 \\ .00001) \\ \textbf{mopathy} \\ 16 & 246 \\ .00001 \\ \textbf{mopathy} \\ \textbf{mopathy} \\ 16 & 246 \\ .00001 \\ \textbf{mopathy} \\ \textbf{mopathy} \\ 16 & 246 \\ .00001 \\ \textbf{mopathy} \\ mopa$	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$

(C) Blinding of participants and personnel (performance bias)
 (D) Blinding of outcome assessment (detection bias): Other outcomes
 (E) Incomplete outcome data (attrition bias)
 (F) Selective reporting (reporting bias)
 (G) Other bias

Figure 4-8 Forest plot showing effect of ACEIs on risk of MI (RE model). [Subgroup analysis: Clinical setting].

CI: confidence interval; RE: random-effects; M-H: Mantel-Haenszel. For studies acronyms, see list of definition/ abbreviations

4.5 ARBs and risk of MI

4.5.10verall treatment effect

Figure 4-9 presents an RE meta-analysis of ARBs and risk of MI, stratified by comparison group (placebo and active).

A total of 39 trials were analysed to prospectively test the effectiveness of ARBs against MI in a total of 146,593 participants, and 3,840 reported MI. Altogether, the MI event rate in patients assigned to the ARBs group was similar to that in the control group (2.63% and 2.60% respectively). Overall, there was no clearly beneficial effect of ARBs compared to the control group for MI, with an RR of 0.97 (95% CI 0.89-1.06; p= 0.55). Placebo-controlled trials contributed 65.5% of the overall pooled effect estimates.

Compared to the placebo, ARBs did not reduce the risk of MI (RR 0.94; 95% CI, 0.85-1.05, p= 0.29). This result was mainly influenced by the three most heavily weighted trials: PRoFESS, NAVIGATOR, and ACTIVE-I (6.9%, 6.4% and 6.4%, respectively). The remaining trials were individually weighted <10%. The assessment of heterogeneity indicates moderate between-trial variation (chi-square p value = 0.09 and $I^2 = 34\%$). This is likely due to statistical diversity from the CHARM-Alternative and CHARM-Added trials. The CHARM-Alternative trial, which contributed 4.1% of the overall weight, was the only study that showed a statistically significant increase in MI rate with use of ARB. In contrast, CHARM-Added showed a significant reduction in MI with ARB therapy.

Data on MI events was available from 22 active-controlled trials that included 58,924 participants. No obvious benefit on risk of MI was seen with ARB therapy compared to active therapy (RR 1.03; 95% CI 0.88-1.20, p=0.66). This was largely driven by the VALUE (8.7%) and LIFE (7.4%) trials. The remaining trials were individually weighted <3% and the heterogeneity was low (Chi-test p value = 0.20 and I^2 =20%). The observed heterogeneity was likely due to trials that used amlodipine as a comparator therapy: IDNT (CCB) and VALUE. After excluding these trials, the heterogeneity diminished (I^2 =3%) as did the point estimate of RR 0.96 (95% CI 0.82-1.12).

FE model is presented in **Figure 4-10** showing similar results to the RE model. Subgroup analysis of placebo-controlled trials assigned slightly more weight to ACTIVE-I, NAVIGATOR, and PRoFESS, and the combined effect estimate yielded an RR of 0.95 (95% CI 0.88, 1.03; p=0.22), coming close to the RE model. In activecontrolled trials, the combined RR increased (RR, 1.08; 95% CI 0.98, 1.19; p= 0.13) compared to that generated by RE, with a narrower 95% CI. This is likely because the majority of active-controlled trials contributed <1% to the pooled effect estimate, with only two trials contributing higher weights: VALUE (16.4%) and LIFE (9.8%).

A visual inspection of the funnel plot (Figure D-1 in Appendix D) shows a symmetrical appearance. However, outliers were detected outside the triangular region in the area of beneficial effects, which may indicate heterogeneity. These outliers are trials with markedly different intervention estimates: CHARM-Added 4C, E-COST and Fang Wu et al.

(G) Other bias

	AR	-	Cont	rol		Risk Ratio	Risk Ratio	Risk of Bias
Study or Subgroup	Events		Events		Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl	ABCDEFG
1.1.2 ARB vs Placebo								
ACTIVE-I 2011	143	4518	135	4498	6.4%	1.05 [0.84, 1.33]	_ -	
ANTIPAF 2012	1	214	1	211	0.1%	0.99 [0.06, 15.66]	•	+ @@@@@@@ ?
CHARM-Added 2003	44	1276	69	1272	3.8%	0.64 [0.44, 0.92]		
CHARM-Alternative 2003	75	1013	48	1015	4.1%	1.57 [1.10, 2.23]	—•—	$\bullet \bullet \bullet \bullet \bullet \bullet \bullet \circ$
CHARM-Preserved 2003	57	1514	73	1509	4.2%	0.78 [0.55, 1.09]		
HOPE-3 2016	52	6356	62	6349	3.8%	0.84 [0.58, 1.21]		
I-PRESERVE 2008	60	2067	54	2061	3.9%	1.11 [0.77, 1.59]		
IDNT (Placebo) 2003	44	579	46	569	3.4%	0.94 [0.63, 1.40]		
IRMA-2 2001	5	404	5	207	0.5%	0.51 [0.15, 1.75]	·	
NAVIGATOR 2010 ORIENT 2011	138 4	4631 282	140 8	4675 284	6.4% 0.5%	1.00 [0.79, 1.25] 0.50 [0.15, 1.65]	· · · · · · · · · · · · · · · · · · ·	
PRoFESS 2008	168	10146	169	204 10186	0.5%	1.00 [0.81, 1.23]	· ·	?
RENAAL 2001	50	751	68	762	4.1%	0.75 [0.53, 1.06]		
ROADMAP 2011	22	2232	26	2215	2.0%	0.84 [0.48, 1.48]		<u>ăăăăăăă</u>
SCOPE 2003	70	2477	63	2460	4.3%	1.10 [0.79, 1.54]	_ -	
TRANSCEND 2008	116	2954	147	2972	6.3%	0.79 [0.63, 1.01]		2000000
Val-HeFT 2001	83	2511	73	2499	4.7%	1.13 [0.83, 1.54]	_ -	??
Subtotal (95% CI)		43925		43744	65.5%	0.94 [0.85, 1.05]	◆	
Total events	1132		1187					
Heterogeneity: Tau ² = 0.02;	Chi ² = 24	14, df =	16 (P = 0)	1.09); I ² =	34%			
Test for overall effect: Z = 1.	07 (P = 0.	29)						
1.1.3 ARB vs Active								
4C 2016	1	585	4	534	0.2%	0.23 [0.03, 2.04]		
ALPINE 2003	1	197	1	196	0.1%	0.99 [0.06, 15.79]		+ ?? ! ? !! ? + !!!!
ATTEMPT-CVD 2016	5 4	615 90	1	613	0.2% 0.5%	4.98 [0.58, 42.53]		220200
CARP 2011 CASE-J 2008	4	2354	18	101 2349	0.5%	0.64 [0.19, 2.12] 0.94 [0.49, 1.82]		
CHIEF 2018	38	6766	35	6776	2.8%	1.09 [0.69, 1.72]		
COPE 2011	5	1110		2183	2.6%	1.40 [0.45, 4.42]		
E-COST 2005	10	1053	23	995	1.3%	0.41 [0.20, 0.86]		
E-COST-R 2005	4	69	20	72	0.3%	2.09 [0.39, 11.03]		+ ?? • ? • ? • ?
Fang Wu et 2015	11	140	12	70	1.2%	0.46 [0.21, 0.99]		? ? ? ? • • •
HIJ-CREATE 2009	29	1024	26	1025	2.3%	1.12 [0.66, 1.88]		• ? • • ? • •
IDNT (CCB) 2003	44	579	27	567	2.7%	1.60 [1.00, 2.54]		
J-RHYTHM II 2010	0	158	0	160		Not estimable		• ? • • • • •
KACT-MetS 2012	1	79	0	71	0.1%	2.70 [0.11, 65.23]	• •	+ ??●?●+
Kondo et al 2003	2	203	1	203	0.1%	2.00 [0.18, 21.88]		+ ?? 🛑 ? 🖶 🔁 ?
LIFE 2002	198	4605	188	4588	7.4%	1.05 [0.86, 1.28]		
MOSES 2005	39	681	48	671	3.3%	0.80 [0.53, 1.20]	+	
NTP-AF study 2013	0	74	0	75		Not estimable		
OLIVUS 2010	2	126	1	121	0.1%	1.92 [0.18, 20.91]		+ ????
PREVER-treatment 2016	1	322	1	333	0.1%	1.03 [0.06, 16.46]	•	
SUPPORT 2015	13	578	12	568	1.2%	1.06 [0.49, 2.31]		
VALUE 2004 Subtotal (95% CI)	369	7649 29057	313	7596 29867	8.7% 34.5%	1.17 [1.01, 1.36] 1.03 [0.89, 1.20]		
Total events	794	25057	727	25007	J4.J70	1.05 [0.85, 1.20]	Ť	
Heterogeneity: Tau ² = 0.02;		82 df-		1201) IZ -	20%			
Test for overall effect: Z = 0.			19 (1 - 0	.20),1 -	20 %			
]	
Total (95% CI)		72982		73611	100.0%	0.97 [0.89, 1.06]	•	
Total events	1926		1914					
Heterogeneity: Tau ² = 0.02;			зы (Р = 0	1.04); l ² =	30%		0.2 0.5 1 2	 5
Test for overall effect: Z = 0.			- 1 /0 - 1	1 2 2 1 2			Favours ARB Favours control	
Test for subgroup differenc	es: Chif=	0.95, df	= 1 (P = I	u.33), F=	:U%			
Risk of bias legend	anation (-	ala ati c -	hine)					
(A) Random sequence gen			pias)					
(B) Allocation concealment (C) Blinding of participants			utorman	na hian'				
(D) Blinding of participants (D) Blinding of outcome as:					itcomer			
(E) Incomplete outcome da			on ulda).	Julei UL	acomes			
(F) Selective reporting (repo								
(G) Other bias	ang bida	/						

Figure 4-9 Forest plot showing effect of ARBs on risk of MI, stratified by comparison group (placebo vs. active). Overall: 39 trials (RE model)

The **diamond** indicates the pooled risk ratio (and 95% CI) or the overall effect for MI risk. CI: confidence interval; RE: random-effects; M-H: Mantel-Haenszel. For studies acronyms, see list of definition/ abbreviations

	ARE	-	Cont			Risk Ratio	Risk Ratio	Risk of Bias
tudy or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl	ABCDEF
.1.2 ARB vs Placebo								
CTIVE-I 2011	143	4518	135	4498	7.0%	1.05 [0.84, 1.33]		
NTIPAF 2012	1	214	1	211	0.1%	0.99 [0.06, 15.66]	•	+ ••••••
HARM-Added 2003	44	1276	69	1272	3.6%	0.64 [0.44, 0.92]		
HARM-Alternative 2003	75	1013	48	1015	2.5%	1.57 [1.10, 2.23]		
HARM-Preserved 2003	57	1514	73	1509	3.8%	0.78 [0.55, 1.09]		
IOPE-3 2016	52	6356	62	6349	3.2%	0.84 [0.58, 1.21]		
PRESERVE 2008	60	2067	54	2061	2.8%	1.11 [0.77, 1.59]	_ 	
ONT (Placebo) 2003	44	579	46	569	2.4%	0.94 [0.63, 1.40]		
RMA-2 2001	5	404	5	207	0.3%	0.51 [0.15, 1.75]	· · · · · · · · · · · · · · · · · · ·	? ? • • • •
IAVIGATOR 2010	138	4631	140	4675	7.3%	1.00 [0.79, 1.25]	-+-	
RIENT 2011	4	282	8	284	0.4%	0.50 [0.15, 1.65]	• • • • • • • • • • • • • • • • • • •	
RoFESS 2008	168	10146	169	10186	8.8%	1.00 [0.81, 1.23]	-+-	? • • • • •
ENAAL 2001	50	751	68	762	3.5%	0.75 [0.53, 1.06]		
OADMAP 2011	22	2232	26	2215	1.4%	0.84 [0.48, 1.48]		
COPE 2003	70	2477	63	2460	3.3%	1.10 [0.79, 1.54]	_ 	
RANSCEND 2008	116	2954	147	2972	7.6%	0.79 [0.63, 1.01]		? • • • • • •
al-HeFT 2001	83	2511	73	2499	3.8%	1.13 [0.83, 1.54]		?? 🔁 🔁 ? 🔁 (
ubtotal (95% CI)		43925		43744	61.9 %	0.95 [0.88, 1.03]	•	
otal events	1132		1187					
eterogeneity: Chi² = 24.14,			; I ² = 34%	6				
est for overall effect: Z = 1.2	2 (P = 0.2	22)						
1.3 ARB vs Active								
C 2016	1	585	4	534	0.2%	0.23 [0.03, 2.04]	•	• ? • • • •
LPINE 2003	1	197	4	196	0.2%		4	+ ??
						0.99 [0.06, 15.79]	·	+
TTEMPT-CVD 2016 ARP 2011	5 4	615 90	1	613 101	0.1% 0.3%	4.98 [0.58, 42.53]		220200
				2349		0.64 [0.19, 2.12]		
ASE-J 2008 HIEF 2018	17 38	2354 6766	18 35	2349	0.9% 1.8%	0.94 [0.49, 1.82] 1.09 [0.69, 1.72]		
OPE 2011	5	1110		2183	0.2%	1.40 [0.45, 4.42]		
	10	1053	23	2183	1.2%			
-COST 2005		1053	23		0.1%	0.41 [0.20, 0.86]		+ ?? • ? • •
-COST-R 2005	4	140	12	72 70		2.09 [0.39, 11.03]		22224
ang Wulet 2015	11 29	1024	26	1025	0.8% 1.4%	0.46 [0.21, 0.99]		
IJ-CREATE 2009	29 44	579	26	567	1.4%	1.12 [0.66, 1.88]		
DNT (CCB) 2003	44	158	27	160	1.4 %	1.60 [1.00, 2.54]		
-RHYTHM II 2010 ACT-MetS 2012	1	79	0	71	0.0%	Not estimable 2.70 (0.11, 65.23)	•	+ ?? . ?
	2	203	1	203	0.0%			+ 22020
iondo et al 2003		4605		4588	9.8%	2.00 [0.18, 21.88]		
IFE 2002 IOSES 2005	198 39	4605	188 48	4000	9.0%	1.05 [0.86, 1.28]		
		74	40	75	2.3%	0.80 [0.53, 1.20]		
TP-AF study 2013	2	126	1		0.40	Not estimable	•	+ ???
LIVUS 2010 REVER-treatment 2016	2 1	322	1	121 333	0.1% 0.1%	1.92 [0.18, 20.91] 1.03 [0.06, 16.46]		+
UPPORT 2015	13	578	12	568	0.1%			
ALUE 2004	369	7649	313	7596	16.4%	1.06 [0.49, 2.31] 1.17 [1.01, 1.36]	_	
ubtotal (95% CI)	209	29057	313	29867	38.1%	1.08 [0.98, 1.19]	•	
otal events	794	20001	727	20007	50.170	1.00 [0.00, 1.10]	•	
leterogeneity: Chi ² = 23.82,		- 0 201		6				
eterogeneity. Chi= = 23.82, est for overall effect: Z = 1.5			, 1 – 20%	•				
	2.0 - 0.1	/						
otal (95% CI)		72982		73611	100.0%	1.00 [0.94, 1.06]	♦	
otal events	1926		1914					
eterogeneity: Chi ² = 51.71,	df = 36 (F	^o = 0.04)	; I ² = 30%	6				+
est for overall effect: Z = 0.0	11 (P = 0.9)	99)					Favours ARB Favours control	5
est for subgroup difference			= 1 (P = 0	0.05), I ^z =	73.6%		avouis AND Favouis control	
lisk of bias legend								
(A) Random sequence gene	eration (se	election	bias)					
B) Allocation concealment (/					
C) Blinding of participants a			rformand	e bias)				
) Blinding of outcome ass					Itcomes			
E) Incomplete outcome data		-		24151 00				
	a variation							
) Selective reporting (repor	ting higel)						

Figure 4-10 Forest plot showing effect of ARBs on risk of MI, stratified by comparison group (placebo vs. active). Overall: 38 trials (FE model)

The diamond indicates the pooled risk ratio (and 95% CI) or the overall effect for MI risk. CI: confidence interval; FE: fixed-effect; M-H: Mantel-Haenszel. For studies acronyms, see list of definition/ abbreviations

4.5.2 Sensitivity analysis

Figure 4-11 depicts the meta-analytical summary generated by the RE model after excluding 13 trials that included patients with concomitant ACEIs therapy from the overall analysis. The RR of ARB compared with the placebo was 0.96 (95% CI 0.81-1.13; p=0.63). Moderate heterogeneity was detected. Compared with active treatment, the RE model generated a RR of 1.03 (95% CI 0.83-1.27; p=0.82). The heterogeneity test showed an I² of 23%, likely due to E-COST (judged as high risk of bias).

Figure 4-12 shows the RE meta-analytical summary after excluding 17 RCTs deemed to have poor methodological quality (four placebo and 13 active-controlled trials). The pooled effect estimate did not change for ARB compared with placebo (RR, 0.94; 95% CI 0.83-1.08; p=0.4). However, when compared to active treatment, ARB therapy showed a 12% increased risk of MI (RR, 1.12; 95% CI 1.01-1.24; p=0.04). This estimate was driven mainly by VALUE, which showed unfavourable effects of valsartan on MI risk. Overall, the effect of ARB on MI risk was neutral.

Figure 4-13 presents a meta-analytical summary of the effect of ARB on risk of MI after excluding 13 trials with a sample size less than 1,000 (three placebocontrolled trials and ten active-controlled trials). The overall effect estimate was neutral, with RR 0.99 (95% CI; 0.90-1.08, p=0.76). Similarly, the relative MI risk reduction by ARB was not affected by the exclusions in either placebo or active subgroups. There was evidence for between-trial heterogeneity (p value is 0.01 and $I^2 = 42\%$), likely due to the statistical diversity of CHARM-Added (concomitant therapy with ACEIs), CHARM-Alternative, and E-COST (judged as a high-risk trial).

	ARE		Cont			Risk Ratio	Risk Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl	ABCDEFG
1.1.2 ARB vs Placebo								
ANTIPAF 2012	1	214	1	211	0.2%	0.99 [0.06, 15.66]	• •	
CHARM-Alternative 2003	75	1013	48	1015	7.4%	1.57 [1.10, 2.23]		
HOPE-3 2016	52	6356	62	6349	7.0%	0.84 [0.58, 1.21]		
IDNT (Placebo) 2003	44	579	46	569	6.4%	0.94 [0.63, 1.40]		
IRMA-2 2001	5	404	5	207	1.0%	0.51 [0.15, 1.75]	• · · · · · · · · · · · · · · · · · · ·	??
RENAAL 2001	50	751	68	762	7.4%	0.75 [0.53, 1.06]		
ROADMAP 2011	22	2232	26	2215	3.9%	0.84 [0.48, 1.48]		
SCOPE 2003	70	2477	63	2460	7.8%	1.10 [0.79, 1.54]		
TRANSCEND 2008	116	2954	147	2972	10.7%	0.79 [0.63, 1.01]		?
Val-HeFT 2001	83	2511	73	2499	8.5%	1.13 [0.83, 1.54]		?? ? 🗣 🗣 ? 🗣 🛑
Subtotal (95% CI)		19491		19259	60.3%	0.96 [0.81, 1.13]	+	
Total events	518		539					
Heterogeneity: Tau ² = 0.03;	Chi ² = 15.	35, df =	9 (P = 0.0	08); I ^z = 4	11%			
Test for overall effect: Z = 0.	49 (P = 0.6)	53) [.]						
1.1.3 ARB vs Active								
ALPINE 2003	1	197	1	196	0.2%	0.99 [0.06, 15.79]	•	• ?? • ? • ? ?
ATTEMPT-CVD 2016	5	615	1	613	0.3%	4.98 [0.58, 42.53]		
CASE-J 2008	17	2354	18	2349	3.0%	0.94 [0.49, 1.82]		
CHIEF 2018	38	6766	35	6776	5.3%	1.09 [0.69, 1.72]		
COPE 2011	5	1110	7	2183	1.1%	1.40 [0.45, 4.42]		
E-COST 2005	10	1053	23	995	2.5%	0.41 [0.20, 0.86]		•••?
Fang Wu et 2015	11	140	12	70	2.4%	0.46 [0.21, 0.99]		?????
HIJ-CREATE 2009	29	1024	26	1025	4.4%	1.12 [0.66, 1.88]		• ? • • ? • •
IDNT (CCB) 2003	44	579	27	567	5.2%	1.60 [1.00, 2.54]		
J-RHYTHM II 2010	0	158	0	160		Not estimable		
KACT-MetS 2012	1	79	0	71	0.2%	2.70 [0.11, 65.23]	• • •	• ?? 🔴 ? 🖶 🔁 😣
LIFE 2002	198	4605	188	4588	12.2%	1.05 [0.86, 1.28]		
NTP-AF study 2013	0	74	0	75		Not estimable		• ? 🛑 ? • • •
OLIVUS 2010	2	126	1	121	0.3%	1.92 [0.18, 20.91]	•	• ????
PREVER-treatment 2016	1	322	1	333	0.2%	1.03 [0.06, 16.46]	• •	
SUPPORT 2015	13	578	12	568	2.3%	1.06 [0.49, 2.31]		• ? • • • • •
Subtotal (95% CI)		19780		20690	39.7%	1.03 [0.83, 1.27]	•	
Total events	375		352					
Heterogeneity: Tau ² = 0.03;	Chi ² = 16.	87, df =	13 (P = 0	.21); I ² =	23%			
Test for overall effect: Z = 0.3	23 (P = 0.1	32)						
T-4-1 (05%) CD		2027		20045	400.00	0.0010.07		
Total (95% CI)		39271		39949	100.0%	0.99 [0.87, 1.12]	•	
Total events	893		891					
Heterogeneity: Tau ² = 0.02;			23 (P = 0	.08); I ^z =	31%		0.2 0.5 1 2 5	-
Test for overall effect: $Z = 0$.							Favours ARB Favours control	
Test for subgroup difference	es: Chi ^z =	0.24, df	= 1 (P = 0)	J.63), I²=	= 0%			
Risk of bias legend								
(A) Random sequence gen			bias)					
(B) Allocation concealment								
(C) Blinding of participants :								
(D) Blinding of outcome ass			on bias):	Other ou	utcomes			
(E) incomplete outcome dat	 (attrition) 	(hige)						

(E) Incomplete outcome data (attrition bias) (F) Selective reporting (reporting bias) (G) Other bias

Figure 4-11 Forest plot showing effect of ARBs on risk of MI [Sensitivity analysis: Excluding trials with concomitant non-study RAS blockers]. Overall: 26 trials (RE model)

CI: confidence interval; RE: random-effects; M-H: Mantel-Haenszel. For studies acronyms, see list of definition/ abbreviations

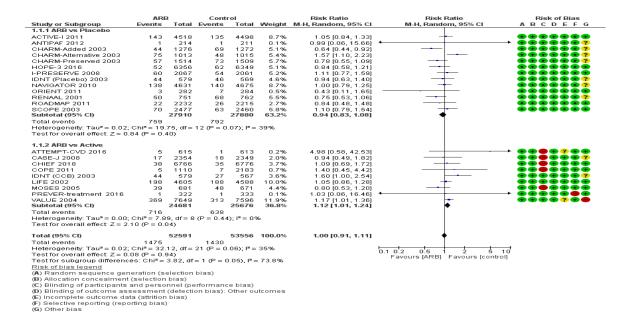


Figure 4-12 Forest plot showing effect of ARBs on risk of MI [Sensitivity analysis: Excluding trials with low methodological quality]. Overall: 22 trials (RE model)

CI: confidence interval; RE: random-effects; M-H: Mantel-Haenszel. For studies acronyms, see list of definition/ abbreviations

	ARE		Cant			Dials Datia	Diale Datia	Diels of Dies
Study of Subarrows			Cont		the induct	Risk Ratio	Risk Ratio	Risk of Bias
Study or Subgroup 1.1.1 ARB vs Placebo	Events	Total	Events	Total	vveigni	M-H, Random, 95% CI	M-H, Random, 95% Cl	ABCDEFG
ACTIVE-I 2011	143	4518	135	4498	6.5%	1.05 [0.84, 1.33]		
CHARM-Added 2003	44	1276	69	1272	4.0%	0.64 [0.44, 0.92]		$\bullet \bullet $
CHARM-Alternative 2003	75	1013	48	1015	4.3%	1.57 [1.10, 2.23]		$\bullet \bullet $
CHARM-Preserved 2003	57	1514	73	1509	4.5%	0.78 [0.55, 1.09]		
HOPE-3 2016	52	6356	62	6349	4.0%	0.84 [0.58, 1.21]		
I-PRESERVE 2008	60	2067	54	2061	4.1%	1.11 [0.77, 1.59]		
IDNT (Placebo) 2003	44	579	46	569	3.6%	0.94 [0.63, 1.40]		••••••
NAVIGATOR 2010	138	4631	140	4675	6.5%	1.00 [0.79, 1.25]	-	$\bullet \bullet \bullet \bullet \bullet \bullet \bullet \circ \circ$
PRoFESS 2008		10146		10186	7.0%	1.00 [0.81, 1.23]	_ _ _	? • • • • • • •
RENAAL 2001	50	751	68	762	4.3%	0.75 [0.53, 1.06]		$\bullet \bullet \bullet \bullet \bullet \bullet \bullet ?$
ROADMAP 2011	22	2232	26	2215	2.2%	0.84 [0.48, 1.48]		
SCOPE 2003	70	2477	63	2460	4.5%	1.10 [0.79, 1.54]		
TRANSCEND 2008	116	2954	147	2972	6.4%	0.79 [0.63, 1.01]		?
Val-HeFT 2001 Subtotal (95% Cl)	83	2511 43025	73	2499 43042	4.9% 66.8%	1.13 [0.83, 1.54] 0.95 [0.85, 1.06]	•	??**?*
Total events	1122		1173				1	
Heterogeneity: Tau ² = 0.02		0.05 df-		0.06\-18-	- 4196			
Test for overall effect: $Z = 0$			- 13 (F =	0.00), 1	- 41 %			
Test for overall effect. $Z = 0$	1.00 (F = U	.30)						
1.1.2 ARB vs Active								
4C 2016	1	585	4	534	0.2%	0.23 [0.03, 2.04]	•	
ATTEMPT-CVD 2016	5	615	1	613	0.2%	4.98 [0.58, 42.53]		
CASE-J 2008	17	2354	18	2349	1.7%	0.94 [0.49, 1.82]		
CHIEF 2018	38	6766	35	6776	3.0%	1.09 [0.69, 1.72]		
COPE 2011	5	1110	7	2183	0.6%	1.40 [0.45, 4.42]		
E-COST 2005	10	1053	23	995	1.4%	0.41 [0.20, 0.86]		•••?
HIJ-CREATE 2009	29	1024	26	1025	2.4%	1.12 [0.66, 1.88]		• ? • • ? • •
IDNT (CCB) 2003	44	579	27	567	2.9%	1.60 [1.00, 2.54]		
LIFE 2002	198	4605	188	4588	7.4%	1.05 [0.86, 1.28]	+-	
MOSES 2005	39	681	48	671	3.5%	0.80 [0.53, 1.20]		
SUPPORT 2015	13	578	12	568	1.3%	1.06 [0.49, 2.31]		
VALUE 2004	369	7649	313	7596	8.6%	1.17 (1.01, 1.36)		••••
Subtotal (95% CI)		27599		28465	33.2%	1.05 [0.90, 1.24]		
Total events	768		702					
Heterogeneity: Tau ² = 0.02		= 1h 287		0 11): P:	= 35%			
Test for overall effect: Z = 0				0.117,1	00.0			
		.52)						
Total (95% CI)		70624		71507	100.0%	0.99 [0.90, 1.08]	•	
Total events	1890		1875				1	
Heterogeneity: Tau ² = 0.02		00 df-		0.043-18-	- 1200			
Test for overall effect: $Z = 0$			- 25 (1	0.01),1	- 42.0		0.2 0.5 1 2 5	
Test for subgroup difference			f = 1 /P =	0.043 18	- 2.0%		Favours [ARB] Favours [control]	
	tes. Chi-=	= 1.03, u	1 = 1 (P =	0.31), 15	= 2.9%			
Risk of bias legend								
(A) Random sequence ge			i bias)					
(B) Allocation concealment								
(C) Blinding of participants								
(D) Blinding of outcome as			ion bias)	: Other o	outcomes			
(E) Incomplete outcome da		n bias)						

 ⁽F) Selective reporting (reporting bias)
 (G) Other bias

Figure 4-13 Forest plot showing effect of ARBs on risk of MI [Sensitivity analysis: Excluding trials with small sample size]. Overall: 26 trials (RE model)

CI: confidence interval; RE: random-effects; M-H: Mantel-Haenszel. For studies acronyms, see list of definition/ abbreviations

4.5.3 Subgroup analysis

Table 4-2 summarizes the subgroup analyses of effectiveness of ARB on risk of MI.

4.5.3.1 Class of active control

The results after stratifying by type of active control are presented in **Figure 4-14.** Seven RCTs used CCB as a randomised treatment. The RR of the most weighted trials - VALUE (33.1%) and IDNT (CCB) (19.9%) - had an RR point estimate >1 in contrast to the remaining trials, thus resulting in an overall neutral effect in the pooled effect estimate on the null hypothesis (RR, 1.00; 95% CI 0.73-1.36, P=1.00). The heterogeneity test showed significant heterogeneity between studies, which may have been driven by clinical and methodological differences in the VALUE and IDNT (CCB) trials. When these were excluded, the I² and RR reduced to 7% and 0.75 (95% CI 0.54-1.05), respectively.

Likewise, ARB therapy did not reduce the risk of MI as compared to diuretics (RR, 1.10; 95% CI 0.7-1.67; P=0.66). No heterogeneity was detected. Also, no apparent benefit was seen with ARBs as compared to the active control in regard to risk of MI with RR, 0.97 (95% CI, 0.73-1.29; p value=0.85).

4.5.3.2 Clinical setting

Figure 4-15 shows **the** RE meta-analytical summary of the ARB effect stratified by population clinical setting.

Data from trials that included participants with high-risk hypertension was available from 11,2966 participants enrolled in 27 RCTs, with 3,064 MI events reported. ARB was not associated with a decrease in MI in this cohort (RR, 0.99; 95% CI 0.90-1.08, p=0.84). Although 50% of trials reported RR point estimates >1, only two trials showed significant results (E-COST and Fang Wu et al.), resulting in low heterogeneity (chi-square test p value =0.18 and $I^2 = 20\%$).

For patients with HF, no apparent benefit was seen in risk of MI from ARB therapy (RR, 1.00; 95% CI 0.76-1.32; p=0.98). Importantly, the CHARM-Alternative study greatly influenced the magnitude and direction of the pooled effect estimate. There was significant heterogeneity between trials, due to the statistical and methodological diversity between CHARM-Alternative and CHARM-Added studies

(patients with background ACEI before randomization) (Chi-square test p value=0.01 and I^2 = 67%).

For diabetic patients, ARB therapy was associated with a non-significant 14% reduction in MI (RR, 0.86; 95% CI, 0.65-1.14, p=0.30). The non-significant reduction in MI was mainly driven by IDNT (CCB). There was low heterogeneity (Chi-square test p value=0.26 and I² statistics =24%).

Pooled data for patients with pre-existing CAD showed no benefit of ARB therapy in regard to MI (RR, 0.85; 95% CI 0.68-1.05; p=0.12). The TRANSCEND trial contributed 78.9% of the pooled treatment effect.

Data for patients with AF was available from four RCTs with a total of 9,908 participants. However, only two trials reported an event. There was no apparent benefit of ARB therapy for MI with RR, 1.05 (95% CI 0.84-1.33; p=0.65). Similarly, ARB therapy did not significantly affect the MI risk of patients with CVA (RR, 0.95; 95% CI 0.79-1.15, p=0.61).

4.5.3.3 Mean age group

Almost all studies with a younger mean age (< 65 years) and 95% CI cross the line null effect except for the CHARM-Added study. Thus, the overall effect was null for ARB on MI risk in younger patients (RR, 0.94; 95% CI 0.83-1.06; p=0.29). CHARM-Added included patients with background of ACEI at baseline, which may have masked any possible deleterious effects of ARBs. No evidence of heterogeneity was detected.

For studies with patients with a mean age of 65 years or older, pooled data yielded an RR of 0.99 [95% CI 0.88, 1.11; P=0.83]. The chi-square test p value =0.02 and the I^2 =44% indicate statistically significant inconsistency across studies. The observed heterogeneity is likely due to the statistical and methodological diversity of the CHARM-Preserved, E-COST, and TRANSCEND studies.

analysis desartan artan nisartan sartan artan	Studies 39 13 6 5 4	Participants 146593 36418 30112 41177	Events 3840 752 1060	ARB 2.63 1.98	Control 2.60 2.15	RR (M-H, Random, 95% CI) 0.97 [0.94, 1.06] 0.91 (0.71-1.15)	P value* 0.55 0.43	l ² %‡ 32
artan nisartan sartan	13 6 5	36418 30112	752	1.98				
artan nisartan sartan	6 5	30112			2.15	0.91 (0.71-1.15)	0.42	
nisartan sartan	5		1060				0.45	52
sartan		41177		4.00	3.63	1.05 (0.87, 1.25)	0.63	34
	4		679	1.59	1.70	0.94 (0.75, 1.18)	0.61	39
artan		15470	519	3.32	3.37	1.08 (0.91, 1.28)	0.38	0
	3	11361	506	4.38	4.52	0.93 (0.72, 1.20)	0.59	28
esartan	5	6831	90	1.22	1.41	0.87 (0.57, 1.32)	0.51	0
dropyridine CCBs	7	23123	898	4.12	3.63	1.00 (0.73-1.36)	1	62¶
etics	3	14590	77	0.55	0.50	1.08 (0.69-1.69)	0.72	0
ve control	11	17918	534	2.97	2.98	0.97 (0.73-1.29)	0.85	18
n-risk hypertensive	27	112966	3064	2.73	2.69	0.99 (0.91-1.08)	0.84	20
	6	17883	661	3.70	3.68	1.00 [0.76, 1.32]	0.98	67
Nephropathy	5	8852	303	2.91	3.88	0.86 (0.65-1.14)	0.30	24
	5	8819	335	3.47	4.11	0.85 (0.68-1.05)	0.12	0
	4	9908	280	2.90	2.75	1.05 (0.84, 1.33)	0.65	0
	2	21684	424	1.91	1.99	0.95 (0.79-1.15)	0.61	0
i years	17	49217	990	1.91	2.09	0.94 [0.83, 1.06]	0.29	0
i years	21	96797	2806	2.93	2.86	0.99 (0.88-1.11)	0.83	44
v v i i j	etics e control risk hypertensive Nephropathy years years	etics 3 e control 11 rrisk hypertensive 27 6 Nephropathy 5 5 4 2 years 17 years 21 abbreviation. Cl: confidence interview.	etics 3 14590 e control 11 17918 risk hypertensive 27 112966 6 17883 Nephropathy 5 8852 5 8819 4 9908 2 21684 years 21 96797 abbreviation. Cl: confidence interval; RE: random RE: random	atics 3 14590 77 e control 11 17918 534 risk hypertensive 27 112966 3064 6 17883 661 Nephropathy 5 8852 303 5 8819 335 4 9908 280 2 21684 424 years 17 49217 990 years 21 96797 2806	atics 3 14590 77 0.55 e control 11 17918 534 2.97 risk hypertensive 27 112966 3064 2.73 6 17883 661 3.70 Nephropathy 5 8852 303 2.91 5 8819 335 3.47 4 9908 280 2.90 2 21684 424 1.91 years 17 49217 990 1.91 years 21 96797 2806 2.93	Petics 3 14590 77 0.55 0.50 e control 11 17918 534 2.97 2.98 risk hypertensive 27 112966 3064 2.73 2.69 6 17883 661 3.70 3.68 Nephropathy 5 8852 303 2.91 3.88 5 8819 335 3.47 4.11 4 9908 280 2.90 2.75 2 21684 424 1.91 1.99 years 17 49217 990 1.91 2.09 years 21 96797 2806 2.93 2.86	Attics 3 14590 77 0.55 0.50 1.08 (0.69-1.69) e control 11 17918 534 2.97 2.98 0.97 (0.73-1.29) rrisk hypertensive 27 112966 3064 2.73 2.69 0.99 (0.91-1.08) 6 17883 661 3.70 3.68 1.00 [0.76, 1.32] Nephropathy 5 8852 303 2.91 3.88 0.86 (0.65-1.14) 5 8819 335 3.47 4.11 0.85 (0.68-1.05) 4 9908 280 2.90 2.75 1.05 (0.84, 1.33) 2 21684 424 1.91 1.99 0.95 (0.79-1.15) years 17 49217 990 1.91 2.09 0.94 [0.83, 1.06] years 21 96797 2806 2.93 2.86 0.99 (0.88-1.11)	Attics 3 14590 77 0.55 0.50 1.08 (0.69-1.69) 0.72 e control 11 17918 534 2.97 2.98 0.97 (0.73-1.29) 0.85 risk hypertensive 27 112966 3064 2.73 2.69 0.99 (0.91-1.08) 0.84 6 17883 661 3.70 3.68 1.00 [0.76, 1.32] 0.98 Nephropathy 5 8852 303 2.91 3.88 0.86 (0.65-1.14) 0.30 4 9908 280 2.90 2.75 1.05 (0.84, 1.33) 0.65 2 21684 424 1.91 1.99 0.95 (0.79-1.15) 0.61 years 17 49217 990 1.91 2.09 0.94 [0.83, 1.06] 0.29

Table 4-2 Summary of RE meta-analytical subgroup analysis shows the effect of ARBs compared with placebo or active control on risk of MI[†]

Study or Subgroup	ARB Events		Cont Events		Weinht	Risk Ratio M-H, Random, 95% Cl	Risk Ratio M-H, Random, 95% Cl	Riskof Bias ABCDEFG
1.1.1 Dihydropyridine CCBs	Lycinta	Total	Lycinta	Total	weight	M-1, Rundon, 33% of	in-n, random, 55% er	ADCDLIG
CASE-J 2008	17	2354	18	2349	13.7%	0.94 [0.49, 1.82]		
Fang Wu et 2015	11	140	12	2349	11.3%	0.46 [0.21, 0.99]		2222000
IDNT (CCB) 2003	44	579	27	567	19.9%	1.60 [1.00, 2.54]		
J-RHYTHM II 2010	44	158	27	160	13.370	Not estimable		
MOSES 2005	39	681	48	671	22.1%	0.80 [0.53, 1.20]		
NTP-AF study 2013	39 0	74	40 0	75	22.190	Not estimable	-	
VALUE 2004	369	7649	313	7596	33.1%	1.17 [1.01, 1.36]	_	
Subtotal (95% CI)	209	11635	515	11488	100.0%	1.00 [0.73, 1.36]	_	
Total events	480	11055	418	11400	100.070	100 [0.75, 1.50]	Ť	
Heterogeneity: Tau ² = 0.07; (5 df - 4		2)+ IZ – 61	206			
Test for overall effect: Z = 0.0			- (i = 0.0.	5),1 = 0.	2.70			
1.1.2 Diuretics								
ALPINE 2003	1	197	1	196	2.3%	0.99 [0.06, 15.79]	← →	??
CHIEF 2018	38	6766	35	6776	85.0%	1.09 [0.69, 1.72]	_ 	
COPE (Diuretic) 2011	30 5	1110		1094	10.4%	1.23 [0.33, 4.58]		
PREVER-treatment 2016	1	322	4	333	2.3%	1.03 [0.06, 16,46]	·	
Subtotal (95% CI)		8395	'	8399	100.0%	1.10 [0.72, 1.67]	· · · · · · · · · · · · · · · · · · ·	
Total events	45	0000	41	0000			T	
Heterogeneity: Tau ² = 0.00; (df = 27		· IZ = 100				
Test for overall effect: Z = 0.4			,i — 1.00,	,1 - 0 /0	I			
1.1.3 Active control								
4C 2016	1	585	4	534	1.6%	0.23 [0.03, 2.04]	←	
ATTEMPT-CVD 2016	5	615	1	613	1.7%	4.98 [0.58, 42.53]		
CARP 2011	4	90	7	101	5.1%	0.64 [0.19, 2.12]		220200
E-COST 2005	10	1053	23	995	11.6%	0.41 [0.20, 0.86]		
E-COST-R 2005	4	69	23	72	2.7%	2.09 [0.39, 11.03]		220200
HIJ-CREATE 2009	29	1024	26	1025	19.1%	1.12 [0.66, 1.88]	_	
KACT-MetS 2012	1	79	20	71	0.8%	2.70 [0.11, 65.23]		22020
Kondo et al 2003	2	203	1	203	1.4%	2.00 [0.18, 21.88]		22020200
LIFE 2002	198	4605	188	4588	44.1%	1.05 [0.86, 1.28]	+	
OLIVUS 2010	2	126	100	121	1.4%	1.92 [0.18, 20.91]	,	2224442
SUPPORT 2015	13	578	12	568	10.7%	1.06 [0.49, 2.31]		
Subtotal (95% CI)	15	9027	12	8891	100.0%	0.97 [0.73, 1.29]	•	
Total events	269		265				Ţ	
Heterogeneity: Tau ² = 0.04; (7 df = 1		27)· I ≥ = 1	18%			
Test for overall effect: Z = 0.1			0 (1 - 0	217,1 -	1070			
1.1.4 Beta-blockers								
COPE (Beta-blocker) 2011	5	1110	3	1089	100.0%	1.64 [0.39, 6.83]		
Subtotal (95% CI)		1110		1089	100.0%	1.64 [0.39, 6.83]		
Total events	5		3					
Heterogeneity: Not applicabl	е							
Test for overall effect: Z = 0.6	7 (P = 0.5)	D)						
							0.1 0.2 0.5 1 2 5 10 Favours (ARB) Favours (control)	
Test for subgroup difference	s: Chi² = 0	.66, df=	3 (P = 0.	88), I² =	0%		Favours (Arco) Favours (control)	
Risk of bias legend								
(A) Random sequence gene	ration (se	lection b	ias)					
(B) Allocation concealment (,					
(C) Blinding of participants a			formance	e bias)				
(D) Blinding of outcome ass					comes			
(E) Incomplete outcome data								

(F) Selective reporting (reporting bias) (G) Other bias

Figure 4-14 Forest plot showing effect of ARBs on risk of MI (RE model). [Subgroup analysis: Class of active group].

CI: confidence interval; RE: random-effects; M-H: Mantel-Haenszel. For studies acronyms, see list of definition/ abbreviations

1.1.1 High-risk hypertensive voTivE-12011 U_PINE 2003 ATTEMPT-CVD 2016 CASE-J 2008 SHIEF 2018 SOPE 2011 S-COST 2005 -cOST-R 2005 -cOST-R 2005 -cOST-R 2005 -COST-R 2005 -PRESERVE 2009 -PRESERVE 2008 DNT (Overall) 2003	143 5 17 38 5 10	4518 197 615 2354 6766	135 1 1 18 35	4498 196 613 2349	9.2% 0.1% 0.2% 1.7%	1.05 [0.84, 1.33] 0.99 [0.06, 15.79] 4.98 [0.58, 42.53]	+	
LPINE 2003 ATTEMPT-CVD 2016 CASE-J 2008 CHIEF 2018 COPE 2011 E-COST 2005 E-COST 2005 F-COST-R 2005 F-COST-R 2005 F-COST-R 2005 HJ-CREATE 2009 PRESERVE 2008	1 5 17 38 5	197 615 2354 6766	1 1 18	196 613 2349	0.1% 0.2%	0.99 [0.06, 15.79] 4 4.98 [0.58, 42.53]		
2ASE-J 2008 CHIEF 2018 5OPE 2011 E-COST 2005 E-COST-R 2005 Fang Wu et 2015 HJJ-CREATE 2009 -PRESERVE 2008	5 17 38 5	615 2354 6766	1 18	613 2349	0.2%	4.98 [0.58, 42.53]		
CHIEF 2018 COPE 2011 COST 2005 COST-R 2005 -ang Wu et 2015 HJJ-CREATE 2009 -PRESERVE 2008	38 5	6766			17%			
COPE 2011 E-COST 2005 E-COST-R 2005 Fang Wu et 2015 HU-CREATE 2009 -PRESERVE 2008	5		35			0.94 [0.49, 1.82]		
E-COST 2005 E-COST-R 2005 Fang Wu et 2015 HJJ-CREATE 2009 -PRESERVE 2008			7	6776 2183	3.3% 0.6%	1.09 [0.69, 1.72] 1.40 [0.45, 4.42]		
E-COST-R 2005 Fang Wu et 2015 HIJ-CREATE 2009 -PRESERVE 2008		1110	23	2183	1.4%	0.41 [0.20, 0.86]		
HIJ-CREATE 2009 -PRESERVE 2008	4	69	2	72	0.3%	2.09 [0.39, 11.03]		2 2 9 2 9 9 2
-PRESERVE 2008	11	140	12	70	1.3%	0.46 [0.21, 0.99]		?????
	29	1024	26	1025	2.6%	1.12 [0.66, 1.88]		
	60 44	2067 579	54 73	2061 1136	4.8% 4.9%	1.11 [0.77, 1.59] 1.18 [0.82, 1.70]		
RMA-2 2001	5	404	5	207	0.5%	0.51 [0.15, 1.75]		2200000
FRHYTHM II 2010	ō	158	ō	160		Not estimable		
<act-mets 2012<="" td=""><td>1</td><td>79</td><td>0</td><td>71</td><td>0.1%</td><td>2.70 [0.11, 65.23]</td><td></td><td>?? 🔴 ? 🖶 🛨 🛨</td></act-mets>	1	79	0	71	0.1%	2.70 [0.11, 65.23]		?? 🔴 ? 🖶 🛨 🛨
_IFE 2002	198	4605	188	4588	11.2%	1.05 [0.86, 1.28]		
MOSES 2005 NAVIGATOR 2010	39 138	681 4631	48 140	671 4675	4.0% 9.2%	0.80 [0.53, 1.20] 1.00 [0.79, 1.25]		
NTP-AF study 2013	0	74	0	75	3.2 %	Not estimable		
DLIVUS 2010	2	126	1	121	0.1%	1.92 [0.18, 20.91]		????***?
DRIENT 2011	3	282	7	284	0.4%	0.43 [0.11, 1.65]		
REVER-treatment 2016	1	322	1	333	0.1%	1.03 [0.06, 16.46] 👎	• • •	
PROFESS 2008	168 50	10146 751	169 68	10186 762	10.2% 5.1%	1.00 [0.81, 1.23]		
RENAAL 2001 SCOPE 2003	70	2477	63	2460	5.5%	0.75 [0.53, 1.06] 1.10 [0.79, 1.54]	-	
FRANSCEND 2008	116	2954	147	2972	8.9%	0.79 [0.63, 1.01]		2000000
/ALUE 2004	369	7649	313	7596	14.5%	1.17 [1.01, 1.36]	<u>}</u> −-	••••
Subtotal (95% CI)		55831		57135	100.0%	0.99 [0.91, 1.08]	•	
Fotal events Heterogeneity: Tau² = 0.01; Cf Fest for overall effect: Z = 0.21			1537 24 (P = 0	.18); I²=	20%			
I.1.2 Heart Failure (HF)								
HARM-Added 2003	44	1276	69	1272	17.6%	0.64 [0.44, 0.92]		
CHARM-Alternative 2003	75	1013	48	1015	18.2%	1.57 [1.10, 2.23]	_ _ _	
CHARM-Preserved 2003	57	1514	73	1509	18.6%	0.78 [0.55, 1.09]		
-PRESERVE 2008 SUPPORT 2015	60 13	2067 578	54 12	2061 568	17.8% 8.3%	1.11 [0.77, 1.59] 1.06 [0.49, 2.31]		
/al-HeFT 2001	83	2511	73	2499	0.3%	1.13 [0.83, 1.54]	_ _	2288288
Subtotal (95% CI)	00	8959	10	8924	100.0%	1.00 [0.76, 1.32]	◆	
Fotal events Heterogeneity: Tauª = 0.07; Cł Fest for overall effect: Z = 0.02			329 5 (P = 0.0	01); I² = €	67%			
I.1.3 Diabetes Mellitus (DM) ± DNT (Overall) 2003				1400	25.20	4 49 10 00 4 70	_ _	
DNT (Overall) 2003 RMA-2 2001	44 5	579 404	73 5	1136 207	35.3% 5.0%	1.18 [0.82, 1.70] 0.51 [0.15, 1.75]		2244444
DRIENT 2011	3	282	5	284	4.2%	0.43 [0.11, 1.65]		
RENAAL 2001	50	751	68	762	36.4%	0.75 [0.53, 1.06]		
ROADMAP 2011	22	2232	26	2215	19.2%	0.84 [0.48, 1.48]		
Subtotal (95% CI)	404	4248	470	4604	100.0%	0.86 [0.65, 1.14]	-	
Fotal events Heterogeneity: Tau² = 0.02; Cł	124 hi≅ = 5.29	9 df= 4	179 (P = 0.26	i): I≊ = 24	196			
Fest for overall effect: Z = 1.04	(P = 0.3		0 = 0.20	.,, - 2°				
I.1.4 Coronary Artey Disease CARP 2011	e (CAD) 4	90	7	101	3.1%	0.64 [0.19, 2.12]		228282
HJ-CREATE 2009	4 29	90 1024	26	101	3.1%	0.64 [0.19, 2.12] 1.12 [0.66, 1.88]		
Condo et al 2003	23	203	20	203	0.8%	2.00 [0.18, 21.88]		220202
DLIVUS 2010	2	126	1	121	0.8%	1.92 [0.18, 20.91]		222888
RANSCEND 2008	116	2954	147	2972	78.9%	0.79 [0.63, 1.01]		?
Subtotal (95% CI)		4397		4422	100.0%	0.85 [0.68, 1.05]	-	
Fotal events Heterogeneity: Tau² = 0.00; Cł Fest for overall effect: Z = 1.55			182 (P = 0.64	l); l² = 09	%			
4 5 Atrial Fibrillation (AF)								
I.1.5 Atrial Fibrillation (AF)	140	4640	105	4400	00.20	1.05 (0.04, 4.22)		
ACTIVE-I 2011 ANTIPAE 2012	143 1	4518 214	135 1	4498 211	99.3% 0.7%	1.05 [0.84, 1.33] 0.99 [0.06, 15.66] 4	· · · · · · · · · · · · · · · · · · ·	
I-RHYTHM II 2010	o i	158	, o	160	0.7.20	Not estimable		
NTP-AF study 2013	õ	74	Ő	75		Not estimable	l	•••••
Subtotal (95% CI)		4964		4944	100.0%	1.05 [0.84, 1.33]	•	
Fotal events	144	о <i>н</i> е – -	136					
Heterogeneity: Tau² = 0.00; CH Fest for overall effect: Z = 0.45			(P = 0.96	i); I* = U4	80			
I.1.6 Cerebrovascular diseas	se (CVD))						
408ES 2005	39	681	48	671	21.2%	0.80 [0.53, 1.20]	— • <u>+</u>	
PROFESS 2008		10146	169	10186		1.00 [0.81, 1.23]	—	? • • • • • •
Subtotal (95% CI)	207	10827	217	10857	100.0%	0.95 [0.79, 1.15]	₹	
otal evente		8. df = 1		i): I ≅ = ∩ 9	16			
Fotal events Heterogeneity: Tau ² = 0.00: Ct			0.50	= 0s	-			
Heterogeneity: Tau ² = 0.00; Ch		i1)						
		1)						
Heterogeneity: Tau ² = 0.00; Ch		51)				ā		
Heterogeneity: Tau ² = 0.00; Ch	(P = 0.6		= 5 (P - 0	169) ¤ -	- 0%	ā	0.1 0.2 0.5 1 2 5 10 Favours [ARB] Favours [control]	

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias): Other outcomes
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Figure 4-15 Forest plot showing effect of ARBs on risk of MI (RE model). [Subgroup analysis: Clinical setting].

CI: confidence interval; RE: random-effects, M-H: Mantel-Haenszel. For studies acronyms, see list of definition/ abbreviations

4.6 Direct comparison between ARBs and ACEIs on risk of MI

4.6.10verall treatment effect

Figure 4-16 shows the RE meta-analytical summary of a direct comparison of the effect of ARBs and ACEIs on risk of MI. Relevant data was available from eight trials that enrolled 40,815 participants, with 2,899 events reported. The overall result indicated a null effect, favouring neither ACEIs or ARBs on incident MI with RR 1.02 (95% CI 0.95-1.09; p=0.64). This was mainly driven by the VALIANT, ONTARGET, and OPTIMAAL studies, contributing 41.8%, 27.8%, and 27.4% of the overall weight, respectively. Each of the remaining five trials contributed <2% of the overall weight.

The test of heterogeneity showed no between-trial variation ($I^2=0\%$). Therefore, the relative risk of MI was similar between RE and FE models (Figure 4-17).

Assessment of the funnel plot is presented in **Appendix D** (Figure D-1) and shows an asymmetrical appearance at top and bottom of the funnel plot. The gap to the top left of the area of significance is likely due to reporting bias, as studies with significant effects might remain unpublished. No outliers were observed.

Figures 4-19 and 4-20 show a flowchart summarizing the RE meta-analytical effectiveness of ACEIs and ARBs compared with the control (either placebo or active) on risk of MI.

	ARB	s	ACE	ls		Risk Ratio	Risk Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl	ABCDEFG
CORD 1 B 2009	3	1887	4	1926	0.2%	0.77 [0.17, 3.42]	· · · ·	
DETAIL 2004	9	120	6	130	0.5%	1.63 [0.60, 4.43]		
ELITE II 2000	31	1578	28	1574	1.9%	1.10 [0.67, 1.83]		?? • • • • ?
LIRICO 2018	4	414	4	413	0.3%	1.00 [0.25, 3.96]		
ONTARGET 2008	440	8542	413	8576	27.8%	1.07 [0.94, 1.22]	-	
OPTIMAAL 2002	384	2744	379	2733	27.4%	1.01 [0.88, 1.15]	+	
ROAD 2007	4	180	4	180	0.3%	1.00 [0.25, 3.94]		
VALIANT 2003	587	4909	599	4909	41.8%	0.98 [0.88, 1.09]	+	$\bullet \bullet $
Total (95% CI)		20374		20441	100.0%	1.02 [0.95, 1.09]	•	
Total events	1462		1437					
Heterogeneity: Tau ² =	: 0.00; Chi	² = 2.13	, df = 7 (P	^e = 0.95);	I² = 0%			ł
Test for overall effect:	Z=0.46 (P = 0.64	4)				0.2 0.5 1 2 5 Favours [ARBs] Favours [ACEIs]	I
<u>Risk of bias legend</u>								

(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias): Other outcomes

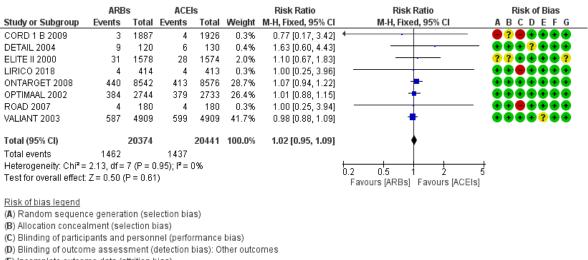
(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

Figure 4-16 Forest plot showing the effect of ARBs versus ACEIs on risk of MI. Overall: 8 trials (RE model)

The diamond indicates the pooled risk ratio (and 95% CI) or the overall effect for MI risk. CI: confidence interval; RE: random-effects; M-H: Mantel-Haenszel. For studies acronyms, see list of definition/ abbreviations



(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

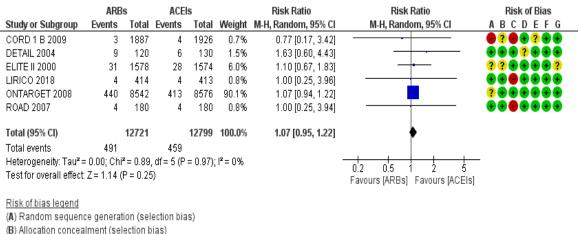
(G) Other bias

Figure 4-17 Forest plot showing effect of ARBs versus ACEIs on risk of MI. Overall: 8 trials (FE model)

The **diamond** indicates the pooled risk ratio (and 95% CI) or the overall effect for MI risk. CI: confidence interval; FE: fixed-effect; M-H: Mantel-Haenszel. For studies acronyms, see list of definition/ abbreviations.

4.6.2 Sensitivity analysis

Figure 4-18 demonstrates a meta-analytic summary of ACE versus ARB after excluding two trials that enrolled patients with signs and symptoms of HF within 10 days of an MI, OPTIMAAL and VALIANT. The incidence of MI in patients allocated to the ARB group (3.85%) was similar to that of those who used ACE therapy (3.58%) with an RR of 1.07 (95% CI 0.95-1.22; p=0.25). The largest trial in this group was the ONTARGET study, accounting for 90.1% of the overall effect estimate. There was no evidence of heterogeneity.



(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias): Other outcomes

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

Figure 4-18 Forest plot showing effect of ARBs vs. ACEIs on risk of MI [Sensitivity analysis: Excluding OPTIMAAL and VALIANT trials]. Overall: 6 trials (RE model)

CI: confidence interval; M-H: Mantel-Haenszel. For studies acronyms, see list of definition/ abbreviations

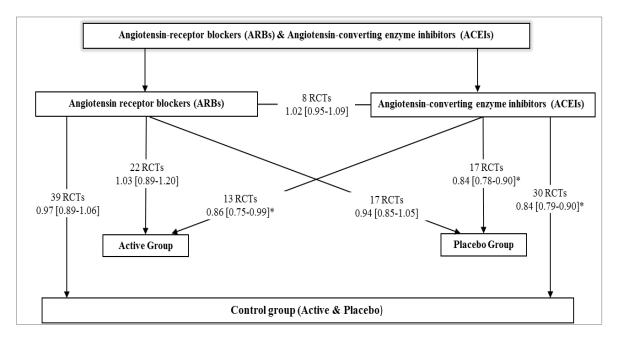


Figure 4-19 Flowchart represents a random-effects (RE) meta-analytical summary of the ACEIs versus ARBs on risk of MI

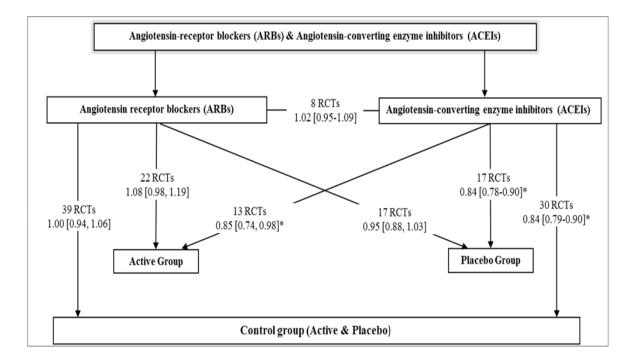


Figure 4-20 Flowchart represents a fixed-effect (FE) meta-analytical summary of the effectiveness of ACEIs versus ARB on risk of MI

4.7 Meta-regression analyses of the effect of ACEIs and ARBs on MI risk in relation to SBP reduction

4.7.1ACEIs

4.7.1.1 Overall effect

Figure 4-21 shows a plot of log RR of MI regressed against difference in achieved SBP mmHg between the ACEI and control group in 24 trials. These studies consisted of ten active-controlled trials and 14 placebo-controlled trials. The achieved SBP difference ranged from -8.3 mmHg (ESPIRAL) to 2 mmHg (JMIC-B). The intercept of the regression line shows that the reduction in risk of MI achieved by ACEI therapy was greater than can be expected from BP-lowering alone. At 0 mmHg SBP reduction, ACEIs result in an estimated 12% relative reduction of MI (predicated RR, 0.88; 95% CI; 0.81-0.98; p=0.02). However, treatment by ACEIs achieved a non-significant 13% lower MI risk for each 1 mmHg reduction in mean achieved SBP between the two groups (predicated RR, 0.87; 95% CI 0.78-1.04; p=0.22).

4.7.1.2 Sensitivity analysis

Sensitivity analysis was performed by applying the following exclusions: [1] ALLHAT (diuretics); [2] trials that used CCB as comparator group; and [3] trials with a sample size less than 1,000. Although ALLHAT (diuretics) showed a superior effect of chlorthalidone to lisinopril in BP lowering (2 mmHg), the incidence of MI was lower in the lisinopril group. Excluding the ALLHAT (diuretics) trial altered the zero SBP reduction from significant to non-significant, though the point estimate remained <1 (RR, 0.90; 95% 0.80-1.01; P=0.09). Excluding nine trials that used CCBs as one of the randomized arms did not modify either the intercept (RR,0.88; 95% CI 0.78-0.98; p=0.02) or slope of the meta-regression line (p=0.36). Similarly, excluding ten trials with small sample sizes did not affect either the intercept (RR,0.88; 95% CI 0.78-0.99; p=0.04) or slope of the meta-regression line (p=0.57).

4.7.2ARBs

4.7.2.1 Overall effect

A total of 35 ARBs trials that reported mean SBP reduction were included in the meta-regression analysis (Figure 4-21). The average SBP reduction was, ranged from -5.7 mmHg for HOPE-3 trial to 2.3 mmHg for OLIVUS trial. Meta-regression demonstrated no apparent benefit of ARB, either independently of BP reduction (RR, 1.07; 95% CI 0.94-1.19; p=0.27) or dependent on BP reduction (RR,1.02; 95% CI 0.99-1.07; p=0.06). However, for each 5-mmHg reduction in SBP, ARB achieved a 12% reduction in MI risk that was close to significant (RR, 0.88; p=0.06).

4.7.2.2 Sensitivity analysis

Sensitivity analyses were carried out by excluding trials that used CCBs. Excluding four trials that allocated patients to CCBs did not alter the estimated RR of MI generated from intercept (RR, 1.11; 95% CI 0.91-1.36 p=0.27) or the regression line slope (RR,1.06 p=0.09).

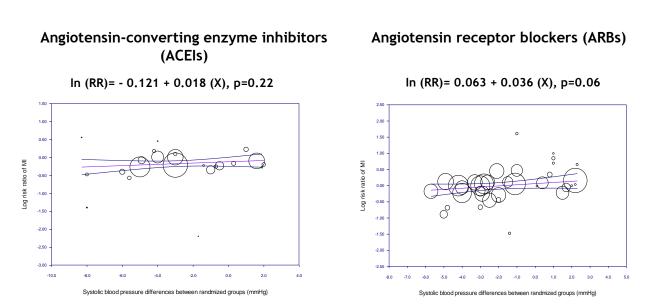


Figure 4-21 meta-regression analysis of relationship between RR of MI and difference in achieved SBP (mmHg) between randomized groups for trials of ACEIs and ARBs

Each study is represented by a circle. The size of each circle is proportional to that study's weight in the analysis (inverse-variance weighted). A negative value in the x-axis indicates lower achieved SBP in the treatment group than in the control group.

4.8 Risk of angina pectoris

4.8.1 ACEIs and risk of angina pectoris

4.8.1.1 Overall treatment effects

Figure 4-22 presents an RE meta-analytical summary of the effect of ACEIs therapy on angina risk, stratified by comparator arms (placebo or active). A total of 20 studies comprising 102,112 participants were analysed to prospectively test the effectiveness of ACEIs on angina pectoris. Overall, there was no significant effect on the risk of angina when ACEIs therapy was compared with a control therapy (RR,1.02; 95% CI 0.94-1.11, p=0.63).

Fourteen placebo-controlled trials randomized 64,238 participants to either ACEIs therapy or placebo, with 5,018 angina events reported. The incidence of angina was 7.5% and 8% in patients randomized to ACEIs therapy or placebo, respectively. The **forest plot in Figure 4-22** shows a null effect of ACEIs on risk of angina, with RR 0.97 (95% CI 0.89-1.06; p =0.48). However, two trials showed a significant reduction in angina by ACEIs therapy, HOPE and DIABHYCAR. The assessment of heterogeneity showed between-trial variations across IMAGINE, DIABHYCAR, and ATLANTIS (p value= 0.06 and I²=41%). After excluding these trials, the result indicates a beneficial effect of ACEI on risk of angina with RR of 0.93 (95% CI 0.89-0.99; p=0.01 and I²=0).

A subgroup of six active-controlled trials that enrolled 37,874 participants with 3,884 angina events reported were analysed. The incidence of angina in patients assigned to ACEIs was 10.7%, and 10% in those assigned to active control. Remarkably, all trials reported an RR greater than 1. The ACEIs therapy was associated with a non-significant 19% increase in angina risk compared with the active control (RR 1.19; 95% CI 0.98-1.44; p=0.08). The higher risk of angina was mainly due to trials that used DHP CCBs as a comparator therapy, with an RR of 1.25 (95% CI 0.96-1.63; p=0.09) (Figure 4-24; subgroup analysis: active comparator). The heterogeneity test showed 41% variation between trials (Chi-square test P value of 0.13 and I^2 at 41%). The detected statistical heterogeneity was driven by CAMELOT, where amlodipine was used as comparator agent.

Sensitivity analysis after excluding CAMELOT (active) resulted in an I^2 at 0% and an RR of 1.09 (95% CI1.02-1.16; p=0.01).

Figure 4-23 shows a meta-analytical summary generated by the FE model. The results are similar to the RE model but with both placebo and active comparator subgroups showing significant effects. In the placebo-controlled trials subgroup, the HOPE trial contributed 29.7% of the weight to the pooled estimate. As this trial showed a significant reduction in angina by ACEIs, it greatly influenced the direction and magnitude of the pooled effect estimate, reaching significance level with an RR of 0.94 (95% CI 0.89-0.99; P=0.02). Similarly, in active-controlled trials, the weight of ALLHAT was 21% and, with the pooled effect estimate, indicated a detrimental effect of ACEIs with an RR of 1.11 (95% CI 1.04-1.18; p=0.002). A visual examination of the funnel plot (shown in Figure D-1 in Appendix D (358)) demonstrates a gap in the top-right area, indicating asymmetric distribution of studies.

	ACE		Cont			Risk Ratio	Risk Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl	ABCDEFG
1.1.1 ACEI vs Placebo								
ADVANCE 2007	261	5569	295	5571	9.0%	0.89 [0.75, 1.04]		
APRES 2000	34	80	30	79	3.7%	1.12 [0.77, 1.64]	_ 	
ATLANTIS* 2000	4	92	5	48	0.4%	0.42 [0.12, 1.48]	· · · · · · · · · · · · · · · · · · ·	
CAMELOT (Placebo) 2004	86	673	84	655	5.5%	1.00 [0.75, 1.32]		$\bullet ? \bullet \bullet \bullet \bullet ?$
DIABHYCAR* 2004	35	2443	61	2469	3.3%	0.58 [0.38, 0.88]		
DREAM 2006	24	2623	20	2646	1.8%	1.21 [0.67, 2.19]		
EUROPA 2003	342	6110	367	6108	9.7%	0.93 [0.81, 1.07]		??
HOPE 2000	1107	4645	1220	4652	12.2%	0.91 [0.85, 0.98]	+	?
IMAGINE* 2008	141	1280	114	1273	6.7%	1.23 [0.97, 1.55]		
PART-2 2000	45	308	42	309	3.5%	1.07 [0.73, 1.59]		
PEACE 2004	151	4158	139	4132	6.9%	1.08 [0.86, 1.35]		??
PROGRESS 2001	111	3051	134	3054	6.3%	0.83 [0.65, 1.06]		
QUIET 2001	52	878	45	872	3.6%	1.15 [0.78, 1.69]	_ -	??
SCAT 2000	40	229	29	231	2.9%	1.39 [0.89, 2.16]	+	
Subtotal (95% CI)		32139		32099	75.4%	0.97 [0.89, 1.06]	•	
Total events	2433		2585					
Heterogeneity: Tau ² = 0.01; Chi ² =	: 21.96. df	= 13 (P	= 0.06); (² = 41%				
Test for overall effect: Z = 0.71 (P			,,					
1.1.2 ACEI vs Active								
ALLHAT 2002	1019	9054	2517	24303	12.3%	1.09 [1.01, 1.16]	+	
CAMELOT (Active) 2004	86	673	51	663	4.5%	1.66 [1.20, 2.31]		
Fogari et al (combination) 2002	2	104	0	103	0.1%	4.95 [0.24, 101.91]		
J-MIND 2001	2	208	0	228	0.1%	5.48 [0.26, 113.45]		?? 🗧 ? ? 🖷 ?
JAMP 2004	53	466	48	422	3.8%	1.00 [0.69, 1.44]	_	?? 🗧 ? ? 🖶 🧲
JMIC-B 2004	56	822	50	828	3.8%	1.13 [0.78, 1.63]	_ -	
Subtotal (95% CI)		11327		26547	24.6%	1.19 [0.98, 1.44]		
Total events	1218		2666					
Heterogeneity: Tau ² = 0.02; Chi ² =	= 8.43, df =	5 (P = 0).13); P =	41%				
Test for overall effect: Z = 1.76 (P	= 0.08)							
Total (95% CI)		43466		58646	100.0%	1.02 [0.94, 1.11]	•	
Total events	3651		5251					
Heterogeneity: Tau ² = 0.01; Chi ² =	: 45.38, df	= 19 (P	= 0.0006); I² = 5 8	%			
Test for overall effect: Z = 0.47 (P							0.2 0.5 1 2 5 Favours (ACEI) Favours (control)	
Test for subgroup differences: Ch	,	df = 1 (P	= 0.06).	I ² = 72.1	%		Favours (ACEI) Favours (control)	
Risk of bias legend			/1					
(A) Random sequence generatio	n (selectio	n bias)						
(B) Allocation concealment (sele								
(C) Blinding of participants and p	,		ance hia	e)				
(D) Blinding of outcome assessn								
(E) Incomplete outcome data (attr			aj. Ourei	outcom	63			
(F) Selective reporting (reporting I (C) Other bins	nas)							
(G) Other bias								

Figure 4-22 Forest plot showing the effect of ACEIs on risk of angina pectoris, stratified by comparison group (placebo vs active treatment). Overall: 20 trials (RE model).

*Excluding trials yielded RR of 0.93 [0.89, 0.99] & I²=0%. The diamond indicates the pooled risk ratio (and 95% CI) or the overall effect for angina risk. CI: confidence interval; RE: random-effects; M-H: Mantel-Haenszel. For studies acronyms, see list of definition/ abbreviations

	ACE	=1	Cont	rol		Risk Ratio	Risk Ratio	Risk of Bias
Study or Subgroup	Events		Events		Weiaht	M-H, Fixed, 95% Cl	M-H. Fixed, 95% Cl	ABCDEFG
1.1.1 ACEI vs Placebo								
ADVANCE 2007	261	5569	295	5571	7.2%	0.89 [0.75, 1.04]		
APRES 2000	34	80	30	79	0.7%	1.12 [0.77, 1.64]		
ATLANTIS* 2000	4	92	5	48	0.2%	0.42 [0.12, 1.48]	←	
CAMELOT (Placebo) 2004	86	673	84	655	2.1%	1.00 [0.75, 1.32]		
DIABHYCAR* 2004	35	2443	61	2469	1.5%	0.58 [0.38, 0.88]		
DREAM 2006	24	2623	20	2646	0.5%	1.21 [0.67, 2.19]		
EUROPA 2003	342	6110	367	6108	8.9%	0.93 [0.81, 1.07]		??
HOPE 2000	1107	4645	1220	4652	29.7%	0.91 [0.85, 0.98]	-	?
IMAGINE* 2008	141	1280	114	1273	2.8%	1.23 [0.97, 1.55]		
PART-2 2000	45	308	42	309	1.0%	1.07 [0.73, 1.59]		
PEACE 2004	151	4158	139	4132	3.4%	1.08 [0.86, 1.35]	_ _	??
PROGRESS 2001	111	3051	134	3054	3.3%	0.83 [0.65, 1.06]		
QUIET 2001	52	878	45	872	1.1%	1.15 [0.78, 1.69]		??
SCAT 2000	40	229	29	231	0.7%	1.39 [0.89, 2.16]	+	
Subtotal (95% CI)		32139		32099	63.0%	0.94 [0.89, 0.99]	•	
Total events	2433		2585					
Heterogeneity: Chi ² = 21.96, df = 1	13 (P = 0.0	06); I ² = 4	11%					
Test for overall effect: Z = 2.40 (P	= 0.02)							
1.1.2 ACEI vs Active								
ALLHAT 2002	1019	9054	2517	24303	33.3%	1.09 [1.01, 1.16]	-	
CAMELOT (Active) 2004	86	673	51	663	1.3%	1.66 [1.20, 2.31]		$\bullet ? \bullet \bullet \bullet \bullet ?$
Fogari et al (combination) 2002	2	104	0	103	0.0%	4.95 [0.24, 101.91]		• ? • ? ? • ?
J-MIND 2001	2	208	0	228	0.0%	5.48 [0.26, 113.45]		3 3 🖌 3 3 4 3
JAMP 2004	53	466	48	422	1.2%	1.00 [0.69, 1.44]		?? 🛑 ? ? 🖶 🖶
JMIC-B 2004	56	822	50	828	1.2%	1.13 [0.78, 1.63]		
Subtotal (95% CI)		11327		26547	37.0%	1.11 [1.04, 1.18]	•	
Total events	1218		2666					
Heterogeneity: Chi ² = 8.43, df = 5 Test for overall effect: Z = 3.07 (P :		; I ² = 419	%					
Test for overall effect. $\Sigma = 3.07$ (P :	= 0.002)							
Total (95% CI)		43466		58646	100.0 %	1.00 [0.96, 1.04]	•	
Total events	3651		5251					
Heterogeneity: Chi ² = 45.38, df = 1	19 (P = 0.0	0006); P	= 58%					
Test for overall effect: Z = 0.08 (P =	= 0.94)						Favours [ACEI] Favours [control]	
Test for subgroup differences: Ch	i ² = 15.21	, df = 1 (P < 0.000	01), I² = 9	3.4%			
Risk of bias legend								
(A) Random sequence generation	n (selectio	on bias)						
(B) Allocation concealment (selec	tion bias)							
(C) Blinding of participants and pe	ersonnel (perform	ance bia	s)				
(D) Blinding of outcome assessm	nent (dete	ction bia	s): Other	outcom	es			
(E) Incomplete outcome data (attr	ition bias))						
(F) Selective reporting (reporting b	ias)							
(G) Other bias								

Figure 4-23 Forest plot showing the effect of ACEIs on risk of angina pectoris, stratified by the comparison group (placebo vs active treatment). Overall: 20 trials (FE model).

*Excluding trials yielded RR of 0.94 [0.89, 0.99] & 12=0%. The diamond indicates the pooled risk ratio (and 95% CI) or the overall effect for angina risk. CI: confidence interval; FE: fixed-effect; M-H: Mantel-Haenszel. For clinical trial acronyms, see list of definition/ abbreviations

ACEI		ACEI Control				Risk Ratio	Risk Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl	ABCDEFG
1.1.1 DHP-CCBs								
ALLHAT (CCB) 2002	1019	9054	950	9048	46.2%	1.07 [0.99, 1.17]	•	$\bullet \bullet \bullet \bullet \bullet \bullet \bullet$
CAMELOT (Active) 2004	86	673	51	663	27.5%	1.66 [1.20, 2.31]		\bullet ? \bullet \bullet \bullet \bullet ?
Fogari et al (combination) 2002	2	104	0	103	0.7%	4.95 [0.24, 101.91]		• 🖲 ? 🖨 ? ? 🖶 ?
J-MIND 2001	2	208	0	228	0.7%	5.48 [0.26, 113.45]		• ?? 🖲 ? ? 🖶 ?
JMIC-B 2004	56	822	50	828	24.8%	1.13 [0.78, 1.63]		
Subtotal (95% CI)		10861		10870	100.0%	1.25 [0.96, 1.63]	◆	
Total events	1165		1051					
Heterogeneity: Tau ² = 0.04; Chi ² =	= 8.43, df=	: 4 (P = I	0.08); I ² =	53%				
Test for overall effect: Z = 1.69 (P	= 0.09)							
1.1.2 Diuretics								
ALLHAT (Diuretic) 2002	1019	9054	1567	15255	100.0%	1.10 [1.02, 1.18]		$\bullet \bullet \bullet \bullet \bullet \bullet \bullet \bullet$
Subtotal (95% CI)		9054		15255	100.0 %	1.10 [1.02, 1.18]	•	
Total events	1019		1567					
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.40 (P	= 0.02)							
1.1.3 Other Actives								
JAMP 2004	53	466	48	422	100.0%	1.00 [0.69, 1.44]		?? 🗣 ? ? 🗣 🗣
Subtotal (95% CI)		466		422	100.0%	1.00 [0.69, 1.44]		
Total events	53		48					
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.00 (P	= 1.00)							
							0.2 0.5 1 2 5	-
							Favours [ACEI] Favours [Active]	
Test for subgroup differences: Cl	hi≝=1.22,	dt = 2 (P	'= 0.54),	If = 0%				
Risk of bias legend								
(A) Random sequence generatio								
(B) Allocation concealment (sele	ction bias)							

(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias): Other outcomes

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

Figure 4-24 Forest plot showing effect of ACEIs on risk of angina pectoris (RE model). [Subgroup: active comparator].

CI: confidence interval; RE: random-effects; M-H: Mantel-Haenszel. For studies acronyms, see list of definition/ abbreviations

4.8.2ARBs and risk of angina pectoris

4.8.2.1 Overall treatment effect

A total of 26 RCTs assessed the effect of ARBs therapy on occurrence of angina pectoris in 102,043 participants compared with control (placebo and active), and 4,491 events were reported. Incidence of angina was 4.67% in patients assigned to the ARB group and 4.35% in the control group, with an RR of 0.99 (95% CI 0.88-1.11; p=0.87) (Figure 4-25)

Angina events in trials comparing ARBs with placebo were reported in 13 studies involving 48,937 participants and 2,405 events. There was a neutral benefit of ARB on the risk of angina compared with placebo group, with an RR of 0.97 (95% 0.90-1.05; p value=0.43). No heterogeneity was detected.

In the subgroup of 13 active-controlled trials that involved 53,106 participants with 2,086 reported angina events, there was no clear benefit for angina from ARBs therapy compared with the active group (RR 0.93, 95% CI 0.73-1.18; p value=0.54). The test for heterogeneity showed that 71% of variation across the studies was due to heterogeneity rather than chance (Chi-square test p value is <0.0001 and I² 71%). The observed heterogeneity was likely due to the CHIEF and VALUE trial reporting a beneficial effect of CCBs over ARBs on risk of angina pectoris. A sensitivity analysis that excluded them resulted in a narrowing of 95% CI and a marked decreased in I² statistics across studies (RR, 0.85; 95% CI 0.70-1.05; I²=25%).

The FE model shown in **Figure 4-26** depicts the weighting of comparable individual studies and effect estimates. Both FE and RE models agree on the pooled effect estimate of ARB versus placebo. However, the FE model assigned more weight to the VALUE trial (increased by 34%), resulting in a highly significant RR of 1.21 (95% CI 1.11-1.31; p<0.00001).

Figure D-1 (Appendix D) shows the distribution of 25 trials in a funnel plot. Despite the scattering of trials, there is an appearance of symmetry with only one outlier observed. The outlier is VALUE.

	ARE		Cont			Risk Ratio	Risk Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl	ABCDEFG
1.1.1 ARB vs Placebo								
ANTIPAF 2012	1	214	0	211	0.1%	2.96 [0.12, 72.21]		
CHARM-Added 2003	150	1276	169	1272	7.6%	0.88 [0.72, 1.09]		$\bullet \bullet \bullet \bullet \bullet \bullet \bullet ?$
CHARM-Alternative 2003	127	1013	120	1015	7.2%	1.06 [0.84, 1.34]		$\bullet \bullet \bullet \bullet \bullet \bullet \bullet ?$
CHARM-Preserved 2003	213	1514	217	1509	8.2%	0.98 [0.82, 1.17]	-	
HOPE-3 2016	51	6356	69	6349	5.2%	0.74 [0.51, 1.06]		
I-PRESERVE 2008	20	2067	19	2061	2.6%	1.05 [0.56, 1.96]		
IDNT (Placebo) 2003	8	579	5	569	1.0%	1.57 [0.52, 4.78]		
IRMA-2 2001	11	404	6	207	1.3%	0.94 [0.35, 2.50]		?? *****
NAVIGATOR 2010	242	4631	234	4675	8.2%	1.04 [0.88, 1.24]	+	
ORIENT 2011	5	282	3	284	0.6%	1.68 [0.40, 6.96]		
RENAAL 2001	42	751	41	762	4.4%	1.04 [0.68, 1.58]		
TRANSCEND 2008	253	2954	287	2972	8.4%	0.89 [0.75, 1.04]		?
Val-HeFT 2001	63	2511	49	2499	5.0%	1.28 [0.88, 1.85]	+	?? 🗣 🗣 ? 🗣 🛑
Subtotal (95% CI)		24552		24385	59.8%	0.97 [0.90, 1.05]	•	
Total events	1186		1219					
Heterogeneity: Tau ² = 0.00;	Chi ² = 9.5	0. df = 1	2 (P = 0.6)	66); F = (3%			
Test for overall effect: Z = 0.			`					
		,						
1.1.2 ARB vs Active								
4C 2016	16	585	16	534	2.3%	0.91 [0.46, 1.81]		• ? • • • • •
ATTEMPT-CVD 2016	1	615	5	613	0.3%	0.20 [0.02, 1.70]	←	••••
CASE-J 2008	8	2354	14	2349	1.6%	0.57 [0.24, 1.36]		
CHIEF 2018	60	6766	49	6776	4.9%	1.23 [0.84, 1.79]		
COPE 2011	10	1110	25	2183	2.1%	0.79 [0.38, 1.63]		
HIJ-CREATE 2009	151	1024	171	1025	7.7%	0.88 [0.72, 1.08]		• ? • • • • •
IDNT (CCB) 2003	8	579	15	567	1.6%	0.52 [0.22, 1.22]		
Kondo et al 2003	9	203	14	203	1.7%	0.64 [0.28, 1.45]		??
LAARS 2002	1	142	0	138	0.1%	2.92 [0.12, 70.97]		
LIFE 2002	160	4605	141	4588	7.3%	1.13 [0.90, 1.41]	_ _ _	
OLIVUS 2010	6	126	13	121	1.4%	0.44 [0.17, 1.13]		2224442
PREVER-treatment 2016	Ő	322		333	1.1.20	Not estimable		
VALUE 2004	708	7649	485	7596	9.2%	1.45 [1.30, 1.62]	-	
Subtotal (95% CI)		26080	400	27026	40.2%	0.93 [0.73, 1.18]	•	
Total events	1138		948				٦	
Heterogeneity: Tau ² = 0.08;		30 df=		0001)	² = 71%			
Test for overall effect: Z = 0.								
		/						
Total (95% CI)		50632		51411	100.0%	0.99 [0.88, 1.11]	•	
Total events	2324		2167					
Heterogeneity: Tau ² = 0.04;		11. df=	24 (P < 0	.0001):1	r = 61%			-
Test for overall effect: Z = 0.				/1	•		0.2 0.5 1 2 5	
Test for subgroup differenc	Favours [ARB] Favours [control]							
Risk of bias legend		, ui			2.79			
(A) Random sequence gen	eration (e	alaction	hiae)					
(P) Allocation concealment			in a a y					

(B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias) (D) Blinding of outcome assessment (detection bias): Other outcomes

(E) Incomplete outcome data (attrition bias) (F) Selective reporting (reporting bias)

(G) Other bias

Figure 4-25 Forest plot showing the effect of ARBs on risk of angina pectoris, stratified by comparison group (placebo vs active treatment). Overall: 26 trials (RE model).

The diamond indicates the pooled risk ratio (and 95% CI) or the overall effect for angina risk. CI: confidence interval; RE: random-effects; M-H: Mantel-Haenszel. For studies acronyms, see list of definition/ abbreviations

	ARE		Cont			Risk Ratio	Risk Ratio	Risk of Bias			
Study or Subgroup	Events		Events		Moight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl	ABCDEFG			
Study or Subgroup 1.1.1 ARB vs Placebo	Events	Total	Events	Total	weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% CI	ABCDEFG			
				~							
ANTIPAF 2012	1	214	0	211	0.0%	2.96 [0.12, 72.21]					
CHARM-Added 2003	150	1276	169	1272	7.8%	0.88 [0.72, 1.09]					
CHARM-Alternative 2003	127 213	1013 1514	120 217	1015 1509	5.5%	1.06 [0.84, 1.34]	I				
CHARM-Preserved 2003 HOPE-3 2016	213	6356	217	6349	10.0% 3.2%	0.98 [0.82, 1.17]					
I-PRESERVE 2008	20	2067	19	2061	3.2% 0.9%	0.74 [0.51, 1.06] 1.05 [0.56, 1.96]					
IDNT (Placebo) 2003	20	579	19	2001	0.9%	1.57 [0.52, 4.78]					
IRMA-2 2001	11	404	5	207	0.2%	0.94 [0.35, 2.50]		2200000			
NAVIGATOR 2010	242	4631	234	4675	10.8%	1.04 [0.88, 1.24]					
ORIENT 2011	242	282	204	284	0.1%	1.68 [0.40, 6.96]					
RENAAL 2001	42	751	41	762	1.9%	1.04 [0.68, 1.58]					
TRANSCEND 2008	253	2954	287	2972	13.2%	0.89 [0.75, 1.04]		2000000			
Val-HeFT 2001	63	2511	49	2499	2.3%	1.28 [0.88, 1.85]	<u> </u>	· · · · · · · · · · ·			
Subtotal (95% CI)	00	24552	40	24385	56.4%	0.97 [0.90, 1.05]	•				
Total events	1186		1219				1				
Heterogeneity: Chi ² = 9.50,		= 0.66).									
Test for overall effect: Z = 0.											
1.1.2 ARB vs Active											
4C 2016	16	585	16	534	0.8%	0.91 [0.46, 1.81]					
ATTEMPT-CVD 2016	1	615	5	613	0.2%	0.20 [0.02, 1.70]	•				
CASE-J 2008	8	2354	14	2349	0.6%	0.57 [0.24, 1.36]					
CHIEF 2018	60	6766	49	6776	2.3%	1.23 [0.84, 1.79]					
COPE 2011	10	1110	25	2183	0.8%	0.79 [0.38, 1.63]					
HIJ-CREATE 2009	151	1024	171	1025	7.9%	0.88 [0.72, 1.08]					
IDNT (CCB) 2003	8	579	15	567	0.7%	0.52 [0.22, 1.22]					
Kondo et al 2003	9	203	14	203	0.6%	0.64 [0.28, 1.45]					
LAARS 2002	1	142 4605	-	138	0.0%	2.92 [0.12, 70.97]	· · ,				
LIFE 2002 OLIVUS 2010	160 6	4605	141 13	4588 121	6.5% 0.6%	1.13 [0.90, 1.41] 0.44 [0.17, 1.13]		2220002			
PREVER-treatment 2016	0	322	13	333	0.6%	Not estimable	-				
VALUE 2004	708	7649	485	7596	22.5%	1.45 [1.30, 1.62]	-				
Subtotal (95% CI)	700	26080	405	27026	43.6%	1.21 [1.11, 1.31]	▲				
Total events	1138		948								
Heterogeneity: Chi ² = 38.30		o < 0.00	(01) ; $I^2 = 7$	1%							
Test for overall effect: Z = 4.											
T-4-1 (05% OD		50000			100.00	4 07 14 00 4 441					
Total (95% CI)		50632		51411	100.0%	1.07 [1.02, 1.14]	•				
Total events	2324		2167	4.04							
Heterogeneity: Chi ² = 62.11			01); 1* = 6	196			0.2 0.5 1 2 5	-			
Test for overall effect: Z = 2.			K - 4 (D -	0.0000	17 - 02 0	.or	Favours (ARB) Favours (control)				
Test for subgroup differenc	es: Chi r =	14.25, 0	11 = 1 (P =	0.0002)	, if = 93.0	1%					
Risk of bias legend											
(A) Random sequence ger			plas)								
(B) Allocation concealment (selection bias)											
(C) Blinding of participants and personnel (performance bias) (D) Blinding of outcome assessment (detection bias): Other outcomes											
(D) Blinding of outcome as: (E) Incomplete outcome da			on plas):	other of	ncomes						
(F) Selective reporting (repo											
(G) Other bias	a ang pida,	r									
(2) 20101 0100											

Figure 4-26 Forest plot showing the effect of ARBs on risk of angina pectoris, stratified by comparison group (placebo vs active treatment). Overall: 25 trials (FE model).

The diamond indicates the pooled risk ratio (and 95% CI) or the overall effect for angina risk. CI: confidence interval; FE: fixed-effect; M-H: Mantel-Haenszel. For studies acronyms, see list of definition/ abbreviations

4.8.3 Direct comparasion between ACEIs and ARBs

As shown in **Figure 4-27**, data from direct comparisons was obtained from two trials that included 26,936 participants. Pooled data showed similar angina risk between ARBs and ACEIs with an RR of 1.00 (95% CI 0.92-1.08, p=0.95). There was low heterogeneity (chi-square test p value =0.26 and I² statistics =22%). The FE model generated a similar meta-analytical summary to the RE model (**Figure 4-28**).

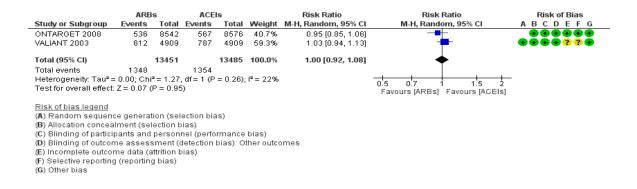


Figure 4-27 Forest plot showing angina outcome in direct comparisons of ACEIs versus ARBs; total of two trials (RE model).

The **diamond** indicates the pooled risk ratio (and 95% CI) or the overall effect for angina risk. CI: confidence interval; RE: random-effects; M-H: Mantel-Haenszel. For studies acronyms, see list of definition/ abbreviations

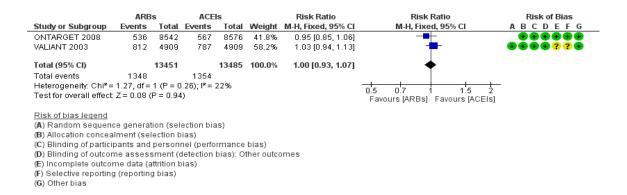


Figure 4-28 Forest plot showing angina outcome in direct comparisons of ACEIs versus ARBs; total of two trials (FE model).

The **diamond** indicates the pooled risk ratio (and 95% CI) or the overall effect for angina risk. CI: confidence interval; FE: fixed-effect; M-H: Mantel-Haenszel. For studies acronyms, see list of definition/ abbreviations

4.9 Discussion

The current meta-analyses of 77 trials using data pooled from 302,251 participants-years of follow-up has sought to evaluate the effects of ACEIs and ARBs on risk of MI and angina for patients with or at high-risk of CVD. This is the largest and most current meta-analysis to address this question. Compared with placebo or active therapy, ACEIs produced marked and consistent reductions in MI across diverse patient populations, whereas ARBs demonstrated no such benefit. In addition, ACEI therapy provide an estimated 12% relative reduction of MI independent of BP reduction. However, data from direct comparison trials suggests no difference exists between ACEIs and ARBs with respect to MI and angina pectoris risk. The consistency of summary estimates, narrow confidence interval, and low or no between-trial heterogeneity would support the validity of the results. Furthermore, sensitivity analyses supported the robustness of the results from the primary analysis.

Although both drug classes interfere with RAAS and may appear similar in their effects, major biological differences exist. Therefore, whether these differences may influence the cardio-protective activity afforded by ACEIs and ARBs has been long debated (Kaplan, 2015). A majority of ARB trials in high-risk patients have demonstrated a consistent lack of reduction in MI, despite a good tolerability profile and effective BP lowering (Yusuf et al., 2011, Diener et al., 2008). More importantly, increased rates of MI have been observed in some trials (Julius et al., 2004, Granger et al., 2003). Thus, the relationship between ARBs and MI has been described as the "ARB-MI paradox" (Subodh Verma, 2004). Consequently, discussions, debate, and commentary continue to raise the question of whether ARBs are clinically equivalent to or even interchangeable with ACEIs (Strauss and Hall, 2017, Messerli and Bangalore, 2017). Placebo comparators have extraordinary advantages in clinical trials by providing the most rigorous test for detecting therapeutic benefit or harmful effects (Castro, 2007). Our analysis of placebo-controlled trials shows that ACEIs lowered the risk of MI by 16% whereas no such benefit was apparent with ARBs. Several interpretations could explain these conflicting results. First, a majority of participants enrolled in ACEI trials were RAS blockers-naïve before randomization, whereas those allocated to ARBs generally received RAS blockers before randomization. Hence, the potential

therapeutic benefits of ARBs may have been masked because of prior ACEI or RAS blocker use. Furthermore, the beneficial effect of ACEIs compared to placebo are mainly influenced by two large trials, HOPE and EUROPA (Yusuf et al., 2000, Fox et al., 2003). Despite using different ACEIs and inclusion criteria, both trials reported the same finding that the rate of subsequent MI was approximately 20% lower among patients randomly assigned to the ACEIs than those assigned to a placebo. These results may be explained by the high event rate in the placebo group, as trials involved RAAS-naïve patients, fewer patients had undergone coronary revascularization before enrolment, and approximately 30% of patients used lipid-lowering treatment, which may have contributed to the clear reduction in MI.

A majority of ARB trials allowed concomitant non-study RAS blockers in either the active or placebo arm, and this was rare in those enrolled in ACEI trials. Thus, the absolute effects of ARB might be attenuated. The protocols of some clinical trials in our meta-analysis permitted using ACEIs for other indications during follow-up, such as ACTIVE-I, PRoFESS, and NAVIGATOR. Although ACTIVE-I and NAVIGATOR trials were designed and powered to detect risk of CV events in relation to irbesartan and valsartan therapy in patients with underlying AF and established CV risk, respectively, no obvious benefit was apparent for MI risk. It should be strongly emphasized that 60% of the participants enrolled in ACTIVE-I and 25% of those enrolled in the NAVIGATOR trial had concomitant ACEIs treatment. Additionally, enrolled participants were on background ACEIs before enrolment, which may have contributed to a lack of a significant reduction in events. It is important to note that the sensitivity analysis, which excluded trials that permitted usage of non-study RAAS blockers did not modify the primary result, with pooled estimates indicating a null effect.

Nevertheless, the dissimilarity between the two classes in MI risk reduction might support the unique physiological actions for coronary protection of ACEIs over ARBs. ARBs and ACEIs attenuate the deleterious effects of Ang II through unique mechanisms: ACEIs decrease the synthesis of Ang II, whereas ARBs block AT₁ receptors, thus preventing their activation. As a result of the blockage of AT₁ receptors by ARBs, the level of circulating Ang II will increase by uncoupling a negative feedback loop, leading to hyperstimulation of AT₂ and AT₄ (Levy, 2004).

It has been proposed that the effects of stimulating AT_2 receptors on the CV system are beneficial, via vasodilation through nitric oxide (NO) and attenuation of the vasoconstrictive effects of AT_1 mediated by Ang II. Recent data has suggested that AT_2 stimulation might be implicated in cardiac and vascular hypertrophic processes (Levy, 2004). In adults, AT_2 is upregulated in various pathological states associated with tissue remodelling or inflammation, including hypertension, HF, post-MI, ischaemia, and diabetes (Matsubara, 1998). Recent evidence in human myocytes suggests that Ang II may induce atherosclerotic plaque rupture via enhancement of matrix metalloproteinase-1 (MMP-1) production through AT_2 receptor activation (Kim et al., 2005). Moreover, a study using cultured neonatal cardiomyocytes showed that overexpression of the AT_2 receptor promotes cardiomyocyte hypertrophy, which is an independent predictor of CV events and death, and AT_2 activation could not directly antagonize the AT_1 receptor in this setting (D'Amore et al., 2005). This suggests it is biologically plausible that ARBs may promote plaque vulnerability and promote its rupture.

Furthermore, ACEIs have a physiological property not shared by ARBs: preventing the breakdown of bradykinin. This may explain the observed MI reduction by ACEIs rather than ARBs. Although bradykinin is implicated in the pathogenesis of ACEIinduced cough and angioedema, it has been shown to have beneficial vascular effects (Yesil et al., 1994). The vascular effects of bradykinin are mediated by its inhibition of both platelet aggregation and circulating PAI-I level. As previously described, elevated level of PAI-1 through Ang II-mediated AT₄ stimulation has been associated with various pathological conditions, including development and recurrence of atherosclerotic disease (Nikolopoulos et al., 2014). A recent systematic meta-analysis identified a relationship between higher PAI-1 antigen levels and CAD risk (OR=1.22 per unit increase of log-transformed PAI-1; 95% CI: 1.01-1.47) (Song et al., 2017). Some studies have shown that interruption of RAAS by either ACEIs or ARBs decreases the PAI antigen, and ACEIs offer a greater PAI-1 reduction than ARBs in insulin-resistant hypertensives (Song et al., 2017). Even though chronic use of ARBs may stimulate AT₄ by Ang II, their role in the observed increase in PAI-1 is still undetermined. Nevertheless, from a biological point of view, the observation that ARBs potentially increase PAI-1 relative to ACEIs, and vice versa, may explain the harmful effects of ARBs on plaque vulnerability.

Another vascular protective effect contributed by ACEIs is that bradykinin plays a key role in ischaemic preconditioning, a cytoprotective phenomenon that protects myocardial cells from prolonged exposure to ischaemia (Ebrahim, 2002). Therefore, infarct size and ischaemic-mediated ventricular arrhythmia can be limited by ischaemic preconditioning and, in turn, might explain the vascular protective effects of ACEIs (Ebrahim, 2002). Moreover, bradykinin facilitates vasodilation via release of recognized vasodilation factors, such as prostacyclin I₂ and nitric oxide (Aponte and Francis, 2012).One study showed that long-term ACEI therapy in patients with NYHA class II-III heart failure secondary to IHD-augmented bradykinin induced endogenous tissue plasminogen activator (t-PA) release from the endothelium (Witherow et al., 2002). These findings would support anti-ischaemic effects being associated with long-term ACEI therapy. However, the relative lack of impact of ARBs on bradykinin might limit the aforementioned cytoprotective effects.

Accordingly, a question arises as to whether the differences between the actions of ACEIs and ARBs could explain the observed differences in coronary vascular protection. The latest meta-regression analysis by the Blood Pressure Lowering Treatment Trialists Collaboration (BPLTTC) involving 21 RCTs and a total of 146,838 participants with HTN or high risk of CVD plotted the difference in followup SBP reduction against pre-defined CV outcomes (Turnbull, 2007). Although this revealed that both classes have similar BP-dependent effects, ACEIs may offer 9% greater coronary vascular protection compared with ARBs (p=0.004) - this effect was independent of BP reduction. However, the confidence limit of the estimated MI risk reduction by ARBs was wider than for ACEIs, with a potential 17% lower risk as well as a 39% greater risk; this may be due to the small sample sizes included. However, according to the study's listed inclusion criteria, the authors did not incorporate large trials, such as HYVET and MOSES. Nevertheless, our comprehensive and up-to-date meta-regression of more than 50 RCTs suggests that the beneficial effects of ACEIs cannot be a consequence of BP reduction, but of a unique coronary protective effect. Thus, our finding may support the observations of superior coronary vascular protective effects of ACEIs over ARBs. The main finding can be confounded by other antihypertensive comparators; however, the series of sensitivity analyses in this study did not suggest that any comparator may have a substantial impact on the main finding.

The findings from 77 trials and 297,251 participants are similar to those of previous meta-analyses, despite the different methodological criteria. A parallel meta-analysis by Savarese et al. (2013) conducted on 26 RCTs that enrolled 108,212 high-CV risk participants without HF, demonstrated that ACEIs significantly reduced the risk of MI whereas ARB did not. Nevertheless, their final conclusion was that ARBs represent a viable option for high-risk patients who do not tolerate ACEIs therapy. Moreover, a study by Cheng et al. (2014) revealed that ACEIs reduced risk of MI in patients with DM, whereas ARBs had no such benefits, and concluded that ACEIs should be considered as first-line therapy to limit excess mortality and morbidity in this population. However, the aforementioned studies are not based on direct comparison but on an indirect inference from comparisons of ACEIs or ARBs with a placebo or active control. Our findings confirm the results of a previous meta-analysis of ACEIs and ARBs by Bangalore et al. (2016), which excluded patients with HF. However, they concluded that in high-risk patients without HF, ARBs are as effective and safe as ACEIs with the advantage of better tolerability.

However, there are contradictory results from other meta-studies which associate ARB therapy with a higher risk of MI (Cheung et al., 2006, Khalaf et al., 2009, Strauss and Hall, 2006). It should be pointed out that these meta-analyses were conducted before the release of the TRANSCEND trial results (Yusuf et al., 2008b), which revealed that a telmisartan-based group experienced a significant reduction in MI (RR, 0.79; 95% CI 0.63-1.01). If this trial were incorporated into these meta-analyses, the trend toward a greater MI event rate with ARB therapy would be markedly attenuated and statistical significance would disappear. Therefore, the conflicting results of other meta-analyses may reflect the high degree of dependence on which trials have been included/excluded.

A comparison of ACEIs with an active control suggests dissimilarity with ARBs on MI risk reduction. Stratified analysis based on the class of active control may explain the superiority of ACEIs over ARBs when compared with other BP-lowering agents. Initially, clinical benefits of ACEIs were mainly driven by the ANBP2 trial, where participants were allocated to diuretic (Wing et al., 2003). The ANBP2 trial enrolled 6,083 hypertensive participants with a relatively low CV risk profile. Although the trial demonstrated a lower MI risk with an ACEI-based regimen than

diuretics, despite a similar BP reduction, this should be interpreted with caution. First, the trial was a PROBE design, which likely had an impact on the choice of appropriate add-on therapies as well as reported events. Moreover, 95% of those assigned were white hypertensive patients, who are known to have increased renin levels and thus a better clinical response to ACEIs (Sagnella, 2001).

Direct comparison trials are the only gold standard way to objectively evaluate the relative CV-protective effects of ACEIs and ARBs. The present meta-analyses establish that the beneficial effects of ACEIs and ARBs on reducing MI and angina pectoris are equivalent. Despite the appearance of equivalent effects, this result should be viewed cautiously. The 69.2% of pooled MI effect estimate was driven by the VALIANT and OPTIMAAL trials (Pfeffer et al., 2003a, Dickstein et al., 2002). These trials enrolled post-MI patients with signs and symptoms of HF and compared losartan 50 mg and valsartan 160 mg twice daily, respectively, to captopril 50 mg three times daily. Both trials concluded that ARBs are as effective as ACEIs in reducing atherosclerosis events. Even though the three-times-daily dose of captopril in both trials was selected from the protocol of SAVE study, it is important to note that the mean follow-up duration of the SAVE study was 3.5 years and reduction of recurrent MI by captopril did not reach statistical significance (Marc A. Pfeffer, 1992, Pfeffer et al., 2000). From this point of view, it would not be surprising that captopril was not superior to ARB in the VALIANT and OPTIMAAL trials, which may partly be due to the short duration of follow-up, 2 and 2.7 years, respectively. Furthermore, the potential benefit of captopril in VALIANT might have been attenuated, because 39% of randomized patients received non-study ACEIs up to 12 hours before randomization as well as 7.7% of patients' concomitant non-study ACEIs during follow-up (Velazquez et al., 2003). A parallel finding was reported by a meta-analysis of trials comparing ARBs with ACEIs directly (Volpe et al., 2005). They reported MI data for VALIANT favoured valsartan, however, unpublished data from the sponsor reported a neutral MI risk between valsartan and captopril (Targum et al., 2004).

Moreover, because of the absence of multiple direct comparisons in large prospective RCTs, a network meta-analysis is required. This is an alternative statistical method to assess the relative effect of interventions using a common comparator. A recent network meta-analysis in high-risk patients without heart failure using a placebo as a common comparator found no significant differences between ACEIs and ARBs in preventing a composite of CV death, MI, and stroke. Therefore, the authors concluded that there was no evidence of statistical superiority of ACEIs, as a class, over ARBs in preventing incident risk of MI (Ricci et al., 2016).

Our findings show a similarity between ACEI and ARB therapies with respect to angina pectoris risk reduction. However, there is considerable heterogeneity among treatment estimates of trials comparing ACEIs with placebos, which is likely due to the statistical diversity of the IMAGINE and DIABHYCAR trials. After excluding IMAGINE, DIABHYCAR, and ATLANTIS, a statistically significant 7% relative risk reduction of angina was evident. This may be due to the subjective nature of angina events, which might affect endpoint assessments. Moreover, heterogeneity also originated from trials where patients were randomized to CCBs, CAMELOT and VALUE. A superiority of amlodipine over ACEIs or ARBs for angina risk reduction might be expected due to amlodipine's pharmacological and clinical profiles, thought to be mediated by the amlodipine-induced dilation of the peripheral vessel and coronary arteries (Sueta et al., 2017).

4.9.1 Strengths and limitations

The comprehensive analyses presented in this chapter provide much more reliable results than previous analyses, as the present analysis incorporates unpublished data (ADVANCE, IDNT, IRMA-2, PREVER-Treatment, VALIANT, Val-HeFT, ROADMAP and ORIENT) and data from CHIEF and PREVER-Treatment studies, which has never been incorporated in previous reviews. Therefore, this study provides more precision to the pooled RR of MI and angina. Unlike previous studies, we did not exclude trials because of baseline co-morbidities, thus allowing for greater generalizability of findings (Bangalore et al., 2016, Savarese et al., 2013). The narrow 95% CI limit and low or no heterogeneity between trials make a type I or II error unlikely.

Nevertheless, several limitations of this analysis must be mentioned. First, this meta-analysis is based on trial-level data, rather than individual patient data. Thus, subgroup and meta-regression analyses are subject to ecological bias, with other potential confounders, and so the results should not be over-interpreted.

Second, the included trials assessed patients at risk of or with CVD, which may introduce clinical heterogeneity, though these clinical conditions are not mutually exclusive. Third, many of the included trials varied in multiple ways, such as background therapy, concomitant use of other RAAS blockers, therapy regimens, and history of diseases, which might lead to random error. However, the large sample size would minimize the risk of random error and thus increase precision. Finally, a collaborative meta-analysis pooling individual data could serve to eliminate many of these limitations.

4.10 Conclusion

In summary, this systematic review and meta-analysis shows that the use of ACEIs therapy is more effective in reducing MI than ARBs for patients with or at risk of major CV events. However, evidence from direct comparison trials suggests similar effects of the two classes. The meta-regression indicates that this observed effect may be a result of the BP-independent coronary vascular benefits of ACEIs.

5 Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) in preventing stroke

5.1 Introduction

According to the World Health Organization's (WHO) estimate of global disease, cerebrovascular accidents (CVA) are the second leading cause of death. They account for approximately 11% of total deaths and are the third leading cause of disability (WHO, 2020). An important modifiable risk factor of stroke is blood pressure (BP); an elevated level of systolic blood pressure (SBP) of at least 110 mmHg accounts for approximately 58% of the population burden of CVA (Forouzanfar et al., 2017). Population mortality trends for stroke parallel those for hypertension. Therefore, effective antihypertensive agents could represent the most cost-effective strategy for the primary and secondary prevention of stroke (Turnbull et al., 2003).

5.1.1 Hypothesis of cerebro-protective superior of ARBs therapy

In 1986, Brown and Brown proposed the challenging hypothesis that Ang II could have a stroke-protective effect (Brown and Brown, 1986). They assumed that the vasoconstrictive effect of Ang II in the proximal cerebral arteries could be responsible for preventing Charcot-Bouchard aneurysms from rupturing. However, the AT₁ receptor-mediated vasoconstrictive effect only explain prevention of haemorrhagic but not ischemic stroke. Their hypothesis arose from results provided in a Medical Research Council (MRC) trial, and was supported by experimental studies (Party, 1985). The MRC trial showed that with a similar BP reduction, diuretics reduce the relative risk of stroke 2.4 times more effectively than beta-blockers. Diuretic-mediated increments of the Ang II level in the cerebral area stimulate renin secretion in response to sodium depletion, resulting in increased Ang II and protecting against stroke through the stimulation of the AT₂ and AT₄ receptors.

ARBs are hypothesized to have superior stroke protection compared to ACEIs, as a consequence of their unique dual actions on the RAAS, blocking AT_1 receptors and sequentially stimulating AT_2 and AT_4 receptors. In the brain, RAAS is attenuated

by ARBs by competitively blocking the binding of Ang II to AT_1 receptors. Consequently, ARBs increase the level of Ang II above the baseline by interrupting negative feedback leading to the stimulation of unoccupied AT_2 and AT_4 receptors (Kramar et al., 1997). As AT_2 are over-expressed in the area of tissue injury, such as the cerebral ischemia (Li et al., 2005, Steckelings et al., 2005), stimulation of them is assumed to protect against cerebral ischemia via recruitment of cerebral collateral vessels, which enhances neuronal resistance to anoxia, and also through attenuating mediators of atherosclerosis (Fournier et al., 2004).

5.1.2 Rationale of the current study

The clinically meaningful cerebrovascular protective effect of ARBs over ACEIs for the primary and secondary prevention of stroke setting has long been debated. This debate arose as a result of direct fallout following the publication of two large-scale trials, PRoFESS and ONTARGET. The ONTARGET trial compared telmisartan with ramipril in 25,620 participants at high-risk of vascular disease (Yusuf et al., 2008d). Although telmisartan slightly lowered the mean BP (0.9/0.6 mmHg), it trended towards reducing the risk of primary stroke by 9% compared with the ramipril. Moreover, post-6-month data of the secondary stroke prevention trial, PRoFESS, showed a 12% significant benefit from telmisartan compared with placebo (Yusuf et al., 2008a). Their findings suggested the superiority of ARBs for the primary and secondary prevention of stroke, which went beyond BP lowering effects. As a result, controversial editorials were published regarding the superiority of ARBs over ACEIs for stroke prevention (Hackam, 2009, Strauss and Hall, 2009). Therefore, the question of whether these classes of RAS blockers had divergent effects on stroke prevention arose.

To compare the effectiveness of ARBs and ACEIs on stroke prevention, we undertook a systematic review, and then quantitatively synthesized data regarding RCTs for ARBs and ACEIs in participants with or at high risk of cardiocerebrovascular events. Moreover, the aim was to examine the impact of BP lowering by ARBs and ACEIs on the risk of stroke reduction according to a metaregression analysis.

5.2 Methodology

5.2.1 Search strategy and selection criteria

A direct and indirect comparison was made between ACEI and ARB therapies to determine their impact on the risk of fatal and non-fatal stroke. Full descriptions of the methods used for this systematic review and meta-analysis have been described in **Chapter 2**, **Section 2.1**.

5.2.2 Data extraction and source of data

Data from the ADVANCE trial was reported as tabulated data regarding non-fatal stroke in sponsor clinical data website, Servier Laboratories Pharmaceutical Company (Servier Laboratories, 2009). Similarly, stroke event in the DETAIL trial was reported in a clinical study data synopsis from their sponsor, Boehringer Ingelheim Pharmaceutical company (Boehringer Ingelheim Pharmaceuticals, 2005). The VALIANT and RENAAL data for stroke was reported in Food and Drug Administration (FDA) website (Hung et al., 2002, Targum et al., 2004). Data for the non-fatal stroke of ROADMAP and fatal stroke of ORIENT were unpublished and obtained from Drug Safety Announcement released from U.S FDA (FDA, 2010b). The PREAMI, DEMAND and QUO-VADIS trials reported strokes as total events for both arms in a way that could not be extracted. Data for the CHIEF trial was posted in conference paper (Lu et al., 2018). The remaining data were reported in the original trials. (Source of data and overall quality of each trial are presented in Tables E-1 and E-2 of Appendix E)

5.2.3 Statistical analysis

5.2.3.1 Meta-analysis

The data synthesis and analysis method have been fully described in **Chapter 2**, **Section 2.1.9**.

5.2.3.2 Meta-regression analysis

A full description of the meta-regression analysis used has been described in **Chapter 2, Section 2.1.10.**

5.3 Results

Altogether, 75 RCTs, involving 297,451 participant-years of follow-up were identified, in which RAS blockers were compared to a control group (placebo or active). For ACEIs therapy, 29 trials with an average follow-up of 3.2 (range from 1 to 5.3) and average patient age of 61.6 years were included. 38 trials used ARBs as an experimental group with an average follow-up of 3.2 (range from 1 to 6) and an average patient age of 64.2 years. Eight trials directly compared ARBs with ACEIs with an average 3.4-year duration for follow-up and an average patient age of 63.4 years.

The baseline characteristics and overall risk of bias of the studies included in this review have been described elsewhere (See Appendix B: baseline characteristics, Appendix C: methodological quality of studies and Appendix E: Overall quality of each trial).

The majority of the trials reported stroke as a pre-defined outcome. This is with the exception of the Hou et al. (group 2), APRES, QUIET, ANTIPAF, EFFERVESCENT, ALPINE, Kawamura, CORD 1 B and ROAD trials, where stroke was reported as an adverse event. 95.8% of the included trials examined primary stroke prevention capabilities. Three trials tested the benefits of ARBs and ACEIs in patients who had already experienced a stroke (PROGRESS, PRoFESS and MOSES). Regarding reporting on incidence of stroke, ten trials reported only on non-fatal stroke, CAMELOT, Hou et al. (group 2), PEACE, PREVEND IT, ABCD, EUROPA, TRANSCEND, CARP, HIJ-CREATE, LIRICO. Two trials, QUIET and OLIVUS reported on fatal stroke. The remaining studies reported on both fatal and nonfatal strokes. Only one trial, ALPINE, reported zero stroke events in both arms. Three ACEIs trials (ADVANCE, ALLHAT and EUROPA), three ARBs trials (CHIEF, HOPE-3, PROFESS and VALUE) and one trial comparing ARBs with ACEIs (ONTARGET) enrolled more than 10,000 participants, thereby contributing the highest number of participants to this review.

With regard to active comparators, 17 studies reporting stroke data randomized patients to DHP-CCBs (amlodipine or nifedipine); including nine ACEIs and eight ARBs trials. Three ACEIs and four ARBs trials assigned patients to chlorthalidone/amiloride, HCTZ or chlorthalidone.

5.4 ACEIs and risk of stroke

5.4.10verall treatment effect

Figure 5.1 presents the RE meta-analytical summary for stroke reduction by ACEIs, compared with a control (placebo or active). In total, 29 RCTs including 116,197 participants and reported 3802 stroke events were included. The incidence rate for stroke was similar between the two arms, 3% in ACEIs and 3.4% in the control arm. There was no significant decrease in risk of stroke with ACEI therapy compared with the control therapy (RR, 0.93; 95% 0.83-1.05; p=0.23). The degree of heterogeneity in the effect of treatment across all the trials was moderate (I^2 : 39%) and significant (chi-square test P value =0.02).

In the stratified analysis, 18 RCTs compared ACEI therapy with a placebo for 70,256 participants with 1920 reported stroke events. More than 70% of the placebo-controlled trials reported RR point estimates of < 1, although their confidence intervals crossed the line of no effect. One trial reported a significant beneficial effect from ACEI on stroke reduction, HOPE trial, which contributed 10.2% of the overall effect estimate. Compared to placebo, the ACEI therapy was significantly associated with a 14% reduction in stroke (RR, 0.86; 0.76-0.98; p=0.02). The chi-square test for heterogeneity yielded a P-value of 0.15 and the $l^2 = 26\%$, indicating a moderate heterogeneity between studies. This heterogeneity is likely driven by the clinical diversity of the HOPE trial (included RAAS-naïve patients).

In eleven actively controlled trials, 45,941 participants and reported 1882 stroke events. The incidence rate for stroke was slightly higher in patients treated with ACEIs compared to active therapies, at 4.3% and 4% respectively. The forest plot shows the ALLHAT trial, demonstrating a significantly unfavourable effect from lisinopril on stroke risk compared with amlodipine and chlorthalidone. This then represented 78% of the overall effect in the pooled analysis (see **Figure 5.5 Section 5.4.3.2**). The pooled effect estimate indicated a significant increase in stroke with ACEIs, RR of 1.14 (95% CI 1.04- 1.26, p=0.006). No heterogeneity was detected (chi-square p value = 0.74 and $I^2 = 0\%$).

Figure 5.2 depicts the FE model results. In the case of the placebo-controlled trials, more weight is assigned to the larger trials, HOPE (22%) and ADVANCE (21.2%), while the weight for DIABHYCAR reduced to 1.9%. In the pooled analysis, the 95% CI became narrower and became statistically more significant. The pooled RR for the FE model was 0.87 (95% CI 0.80-0.95: p value=0.002) for the placebo-controlled trials and remained unchanged for the active-controlled trials. No heterogeneity between-trial was detected.

Visual inspection of the funnel plot (see Figure D-2 in Appendix D) shows it approximately resembled a symmetrical funnel. However, one outlier was detected which represented PREVEND IT trial. Although this trial reported a significant reduction in stroke with fosinopril, possibly explained by a reduction in SBP (-3mmHg), and it was underpowered to detect CV events.

Marcha an Ordennaut	ACE		Conti		104-1-1-1	Risk Ratio	Risk Ratio	Risk of Bias
Study or Subgroup	Events	lotal	Events	lotal	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl	ABCDEFG
I.1.1 ACEI vs Placebo								
ADVANCE 2007	215	5569	218	5571	10.7%	0.99 [0.82, 1.19]	. †	
PRES 2000	0	80	1	79	0.1%	0.33 [0.01, 7.96]	• •	
CAMELOT (Placebo) 2004	8	673	12	655	1.5%	0.65 [0.27, 1.58]		\bullet ? \bullet \bullet \bullet ?
CCS-I 2001	22	3391	28	3358	3.3%	0.78 [0.45, 1.36]		$\bullet \bullet \bullet ? ? \bullet \bullet$
DIABHYCAR 2004	118	2443	116	2469	8.7%	1.03 [0.80, 1.32]	+	
DREAM 2006	4	2623	8	2646	0.9%	0.50 [0.15, 1.67]		
EUROPA 2003	98	6110	102	6108	8.0%	0.96 [0.73, 1.26]	-	????????
HOPE 2000	156	4645	226	4652		0.69 [0.57, 0.84]		?.
Hou et al (group 2) 2006	2	112	3	112	0.4%	0.67 [0.11, 3.91]		
HYVET (Placebo) 2003	12	431	18	426	2.2%	0.66 [0.32, 1.35]		
MAGINE 2008	15	1280	14	1273	2.2%	1.07 [0.52, 2.20]		
PART-2 2000	7	308	4	309	0.8%	1.76 [0.52, 5.94]		
PEACE 2004	71	4158	92	4132	7.2%	0.77 [0.56, 1.04]		? ? • • • • •
PHARAO 2008	3	505	1	503	0.3%	2.99 [0.31, 28.63]		
PREVEND IT 2007	1	431	10	433	0.3%	0.10 [0.01, 0.78]	•	
PROGRESS* (monotherapy) 2001	157	1281	165	1280	10.0%	0.95 [0.78, 1.17]	+	
QUIET 2001	1	878	1	872	0.2%	0.99 [0.06, 15.85]	<→	· ??••••
SCAT 2000	2	229	9	231	0.6%	0.22 [0.05, 1.03]	•	
Subtotal (95% CI)		35147		35109	67.5%	0.86 [0.76, 0.98]	◆	
Fotal events	892		1028					
Heterogeneity: Tau² = 0.01; Chi² = 2		7 (P = 0	.15); I ² = (26%				
Fest for overall effect: Z = 2.32 (P =	0.02)							
.1.2 ACEI vs Active								
WSK 2002	23	436	32	658	3.7%	1.08 [0.64, 1.83]	-	
ABCD (normotensive) 2002	6	246	11	234	1.3%	0.52 [0.20, 1.38]		?
ALLHAT 2002	457	9054	1052	24303	13.0%	1.17 [1.05, 1.30]	-	
ANBP2 2003	112	3044	107	3034	8.4%	1.04 [0.80, 1.35]		2000000
CAMELOT (Active) 2004	8	673	6	663	1.1%	1.31 [0.46, 3.77]		
ESPIRAL 2001	1	129	2	112	0.2%	0.43 [0.04, 4.72]	•	22020
ogari et al (combination) 2002	1	104	2	103	0.2%	0.50 [0.05, 5.38]	• • • • • • • • • • • • • • • • • • •	
ogari et al (monotherapy) 2002	3	102	2	103	0.4%	1.51 [0.26, 8.88]		
	12	431	6	426	1.3%	1.98 [0.75, 5.22]		
HYVEL (diuretics) 2003								
HYVET (diuretics) 2003 I-MIND 2001								
I-MIND 2001	5	208	2	228	0.5%	2.74 [0.54, 13.97]	,	
I-MIND 2001 IMIC-B 2004		208 822		228 828	0.5% 2.4%	2.74 [0.54, 13.97] 1.01 [0.51, 2.00]	,	· ?? • ? • • ?
I-MIND 2001 IMIC-B 2004 Subtotal (95% CI)	5 16	208	2 16	228	0.5%	2.74 [0.54, 13.97]	•	· ?? • ? • • ?
I-MIND 2001 IMIC-B 2004 Subtotal (95% CI) Fotal events	5 16 644	208 822 15249	2 16 1238	228 828 30692	0.5% 2.4%	2.74 [0.54, 13.97] 1.01 [0.51, 2.00]	•	· ?? • ? • • ?
I-MIND 2001 IMIC-B 2004 Subtotal (95% CI)	5 16 644 6.88, df = 10	208 822 15249	2 16 1238	228 828 30692	0.5% 2.4%	2.74 [0.54, 13.97] 1.01 [0.51, 2.00]	· · · · · · · · · · · · · · · · · · ·	· ?? • ? • • ?
I-MIND 2001 IMIC-B 2004 Subtotal (95% CI) Fotal events Heterogeneity: Tau ² = 0.00; Chi ² = 6 Fest for overall effect: Z = 2.75 (P =	5 16 644 6.88, df = 10	208 822 15249) (P = 0.7	2 16 1238	228 828 30692 %	0.5% 2.4% 32.5 %	2.74 (0.54, 13.97) 1.01 (0.51, 2.00) 1.14 [1.04, 1.26]		
I-MIND 2001 IMIC-B 2004 Subtotal (95% CI) Fotal events Heterogeneity: Tau ² = 0.00; Chi ² = 6 Fest for overall effect: Z = 2.75 (P = Fotal (95% CI)	5 16 644 5.88, df = 10 0.006)	208 822 15249	2 16 1238 '4); I ² = 0'	228 828 30692 %	0.5% 2.4%	2.74 [0.54, 13.97] 1.01 [0.51, 2.00]		
I-MIND 2001 IMIC-B 2004 Subtotal (95% CI) Fotal events Heterogeneity: Tau ² = 0.00; Chi ² = 6 Fest for overall effect: Z = 2.75 (P = Fotal (95% CI) Fotal events	5 16 644 6.88, df = 10 0.006) 1536	208 822 15249) (P = 0.7 50396	2 16 1238 '4); I ² = 0' 2266	228 828 30692 % 65801	0.5% 2.4% 32.5 %	2.74 (0.54, 13.97) 1.01 (0.51, 2.00) 1.14 [1.04, 1.26]		· ?? • ? • • ?
I-MIND 2001 IMIC-B 2004 Subtotal (95% CI) Fotal events Heterogeneity: Tau ² = 0.00; Chi ² = 6 Fest for overall effect: Z = 2.75 (P = Fotal (95% CI) Fotal events Heterogeneity: Tau ² = 0.02; Chi ² = 4	5 16 644 6.88, df = 10 0.006) 1536 45.98, df = 2	208 822 15249) (P = 0.7 50396	2 16 1238 '4); I ² = 0' 2266	228 828 30692 % 65801	0.5% 2.4% 32.5 %	2.74 [0.54, 13.97] 1.01 [0.51, 2.00] 1.14 [1.04, 1.26] 0.93 [0.83, 1.05]		
I-MIND 2001 IMIC-B 2004 Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0.00; Chi ² = 6 Fest for overall effect: Z = 2.75 (P = Fotal (95% CI) Fotal events Heterogeneity: Tau ² = 0.02; Chi ² = 4 Fest for overall effect: Z = 1.20 (P =	5 16 644 3.88, df = 10 0.006) 1536 15.98, df = 2 0.23)	208 822 15249) (P = 0.7 50396 ?8 (P = 0	2 16 1238 '4); I ^a = 0 2266 .02); I ^a = 1	228 828 30692 % 65801 39%	0.5% 2.4% 32.5% 100.0%	2.74 [0.54, 13.97] 1.01 [0.51, 2.00] 1.14 [1.04, 1.26] 0.93 [0.83, 1.05]	0.1 0.2 0.5 1 2 5 10 Favours (ACEI) Favours (control)	
I-MIND 2001 IMIC-B 2004 Subtotal (95% CI) Fotal events Heterogeneity: Tau ² = 0.00; Chi ² = 6 Fest for overall effect: Z = 2.75 (P = Fotal (95% CI) Fotal events Heterogeneity: Tau ² = 0.02; Chi ² = 4 Fest for overall effect: Z = 1.20 (P = Fest for subgroup differences: Chi ²	5 16 644 3.88, df = 10 0.006) 1536 15.98, df = 2 0.23)	208 822 15249) (P = 0.7 50396 ?8 (P = 0	2 16 1238 '4); I ^a = 0 2266 .02); I ^a = 1	228 828 30692 % 65801 39%	0.5% 2.4% 32.5% 100.0%	2.74 [0.54, 13.97] 1.01 [0.51, 2.00] 1.14 [1.04, 1.26] 0.93 [0.83, 1.05]		
I-MIND 2001 IMIC-B 2004 Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0.00; Chi ² = B Fest for overall effect: Z = 2.75 (P = Fotal (95% CI) Total events Heterogeneity: Tau ² = 0.02; Chi ² = 4 Fest for overall effect: Z = 1.20 (P = Fest for subgroup differences: Chi ² Risk of bias legend	5 16 644 6.88, df = 10 0.006) 1536 15.98, df = 2 0.23) = 12.37, df	208 822 15249) (P = 0.7 50396 ?8 (P = 0 ?= 1 (P =	2 16 1238 '4); I ^a = 0 2266 .02); I ^a = 1	228 828 30692 % 65801 39%	0.5% 2.4% 32.5% 100.0%	2.74 [0.54, 13.97] 1.01 [0.51, 2.00] 1.14 [1.04, 1.26] 0.93 [0.83, 1.05]		
I-MIND 2001 IMIC-B 2004 Subtotal (95% CI) Fotal events Heterogeneity: Tau ² = 0.00; Chi ² = 6 Fest for overall effect: Z = 2.75 (P = Fotal (95% CI) Fotal events Heterogeneity: Tau ² = 0.02; Chi ² = 4 Fest for overall effect: Z = 1.20 (P = Fest for subgroup differences: Chi ²	5 16 644 6.88, df = 10 0.006) 1536 15.98, df = 2 0.23) = 12.37, df	208 822 15249) (P = 0.7 50396 ?8 (P = 0 ?= 1 (P =	2 16 1238 '4); I ^a = 0 2266 .02); I ^a = 1	228 828 30692 % 65801 39%	0.5% 2.4% 32.5% 100.0%	2.74 [0.54, 13.97] 1.01 [0.51, 2.00] 1.14 [1.04, 1.26] 0.93 [0.83, 1.05]		
I-MIND 2001 IMIC-B 2004 Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0.00; Chi ² = B Fest for overall effect: Z = 2.75 (P = Fotal (95% CI) Total events Heterogeneity: Tau ² = 0.02; Chi ² = 4 Fest for overall effect: Z = 1.20 (P = Fest for subgroup differences: Chi ² Risk of bias legend	5 16 644 6.88, df = 10 0.006) 1536 45.98, df = 2 0.23) 1 = 12.37, df (selection t	208 822 15249) (P = 0.7 50396 ?8 (P = 0 ?= 1 (P =	2 16 1238 '4); I ^a = 0 2266 .02); I ^a = 1	228 828 30692 % 65801 39%	0.5% 2.4% 32.5% 100.0%	2.74 [0.54, 13.97] 1.01 [0.51, 2.00] 1.14 [1.04, 1.26] 0.93 [0.83, 1.05]		
I-MIND 2001 IMIC-B 2004 Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0.00; Chi ² = B Fest for overall effect: Z = 2.75 (P = Total (95% CI) Fotal events Heterogeneity: Tau ² = 0.02; Chi ² = 4 Fest for overall effect: Z = 1.20 (P = Fest for subgroup differences: Chi ² <u>Risk of bias legend</u> A) Random sequence generation	5 16 644 6.88, df = 10 0.006) 1536 15.98, df = 2 0.23) '= 12.37, df (selection k on bias)	208 822 15249 0 (P = 0.7 50396 28 (P = 0 28 (P = 0 2 = 1 (P = 0ias)	2 16 '4); I [#] = 0' 2266 .02); I [#] = 1 0.0004),	228 828 30692 % 65801 39%	0.5% 2.4% 32.5% 100.0%	2.74 [0.54, 13.97] 1.01 [0.51, 2.00] 1.14 [1.04, 1.26] 0.93 [0.83, 1.05]		
I-MIND 2001 IMIC-B 2004 Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0.00; Chi ² = B Fest for overall effect: Z = 2.75 (P = Total (95% CI) Fotal events Heterogeneity: Tau ² = 0.02; Chi ² = 4 Fest for overall effect: Z = 1.20 (P = Fest for subgroup differences: Chi ² <u>Risk of bias legend</u> A) Random sequence generation B) Allocation concealment (selection)	5 16 644 5.88, df = 10 0.006) 1536 15.98, df = 2 0.23) = 12.37, df (selection t on bias) sonnel (per	208 822 15249 0 (P = 0.7 50396 28 (P = 0 28 (P = 0 2 = 1 (P = 0ias) formance	2 16 1238 '4); I ² = 0' 2266 .02); I ² = : 0.0004), re bias)	228 828 30692 % 65801 39% ² = 91.9	0.5% 2.4% 32.5% 100.0%	2.74 [0.54, 13.97] 1.01 [0.51, 2.00] 1.14 [1.04, 1.26] 0.93 [0.83, 1.05]		
I-MIND 2001 IMIC-B 2004 Subtotal (95% CI) Fotal events Heterogeneity: Tau ² = 0.00; Chi ² = B Fost for overall effect: Z = 2.75 (P = Fotal (95% CI) Fotal events Heterogeneity: Tau ² = 0.02; Chi ² = 4 Fost for overall effect: Z = 1.20 (P = Fest for subgroup differences: Chi ² Risk of bias legend A) Random sequence generation B) Allocation concealment (selectii C) Blinding of participants and pers	5 16 644 5.88, df = 10 0.006) 1536 15.98, df = 2 0.23) = 12.37, df (selection t on bias) sonnel (per nt (detectio	208 822 15249 0 (P = 0.7 50396 28 (P = 0 28 (P = 0 2 = 1 (P = 0ias) formance	2 16 1238 '4); I ² = 0' 2266 .02); I ² = : 0.0004), re bias)	228 828 30692 % 65801 39% ² = 91.9	0.5% 2.4% 32.5% 100.0%	2.74 [0.54, 13.97] 1.01 [0.51, 2.00] 1.14 [1.04, 1.26] 0.93 [0.83, 1.05]		
I-MIND 2001 IMIC-B 2004 Subtotal (95% CI) Fotal events Heterogeneity: Tau ² = 0.00; Chi ² = 6 Fost for overall effect: Z = 2.75 (P = Fotal (95% CI) Fotal events Heterogeneity: Tau ² = 0.02; Chi ² = 4 Fost for overall effect: Z = 1.20 (P = Fost for overall effect: Z = 1.20 (P = Fost for subgroup differences: Chi ² Risk of bias legend A) Random sequence generation B) Allocation concealment (selectii C) Blinding of participants and pers D) Blinding of outcome assessme	5 16 644 5.88, df = 10 0.006) 1536 15.98, df = 2 0.23) = 12.37, df (selection t on bias) sonnel (per int (detectio on bias)	208 822 15249 0 (P = 0.7 50396 28 (P = 0 28 (P = 0 2 = 1 (P = 0ias) formance	2 16 1238 '4); I ² = 0' 2266 .02); I ² = : 0.0004), re bias)	228 828 30692 % 65801 39% ² = 91.9	0.5% 2.4% 32.5% 100.0%	2.74 [0.54, 13.97] 1.01 [0.51, 2.00] 1.14 [1.04, 1.26] 0.93 [0.83, 1.05]		

Figure 5-1 Forest plot showing effect of ACEIs on risk of stroke, stratified by comparison group (placebo vs. active). Overall: 29 trials (RE model).

The **diamond** indicates the pooled risk ratio (and 95% CI) or the overall effect for stroke risk. CI: confidence interval; RE: random-effects; M-H: Mantel-Haenszel. For studies acronyms, see list of definition/ abbreviations

	ACE		Cont			Risk Ratio	Risk Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl	ABCDEFG
1.1.1 ACEI vs Placebo								
ADVANCE 2007	215	5569	218	5571	12.2%	0.99 [0.82, 1.19]	. +	
APRES 2000	0	80	1	79	0.1%	0.33 [0.01, 7.96]	• • • • • • • • • • • • • • • • • • • •	$\bullet \bullet \bullet \bullet \bullet \bullet \bullet ?$
CAMELOT (Placebo) 2004	8	673	12	655	0.7%	0.65 [0.27, 1.58]		$\bullet ? \bullet \bullet \bullet \bullet ?$
CCS-I 2001	22	3391	28	3358	1.6%	0.78 [0.45, 1.36]		$\bullet \bullet \bullet ? ? \bullet \bullet$
DIABHYCAR 2004	118	2443	116	2469	6.5%	1.03 [0.80, 1.32]	+	$\bullet \bullet \bullet \bullet \bullet \bullet \bullet ?$
DREAM 2006	4	2623	8	2646	0.4%	0.50 [0.15, 1.67]		
EUROPA 2003	98	6110	102	6108	5.7%	0.96 [0.73, 1.26]		? ? # ? # # #
HOPE 2000	156	4645	226	4652	12.7%	0.69 [0.57, 0.84]		? • • • • • • •
Hou et al (group 2) 2006	2	112	3	112	0.2%	0.67 [0.11, 3.91]		$\bullet ? \bullet \bullet \bullet \bullet \bullet$
HYVET (Placebo) 2003	12	431	18	426	1.0%	0.66 [0.32, 1.35]		
IMAGINE 2008	15	1280	14	1273	0.8%	1.07 [0.52, 2.20]		
PART-2 2000	7	308	4	309	0.2%	1.76 [0.52, 5.94]		$\bullet \bullet \bullet \bullet \bullet \bullet \bullet \circ \circ$
PEACE 2004	71	4158	92	4132	5.2%	0.77 [0.56, 1.04]		??
PHARAO 2008	3	505	1	503	0.1%	2.99 [0.31, 28.63]		
PREVEND IT 2007	1	431	10	433	0.6%	0.10 [0.01, 0.78]	←────	
PROGRESS* (monotherapy) 2001	157	1281	165	1280	9.3%	0.95 [0.78, 1.17]		
QUIET 2001	1	878	1	872	0.1%	0.99 [0.06, 15.85]	· · · · · · · · · · · · · · · · · · ·	· ? ? • • • • •
SCAT 2000	2	229	9	231	0.5%	0.22 [0.05, 1.03]	• · · · · · · · · · · · · · · · · · · ·	$\bullet \bullet \bullet ? \bullet \bullet ?$
Subtotal (95% CI)		35147		35109	57.8%	0.87 [0.80, 0.95]	•	
Total events	892		1028					
Heterogeneity: Chi ² = 22.89, df = 17	(P = 0.15);	I ^z = 26%	ó					
Test for overall effect: Z = 3.17 (P = 0	0.002)							
1.1.2 ACEI vs Active								
AASK 2002	23	436	32	658	1.4%	1.08 [0.64, 1.83]		
ABCD (normotensive) 2002	6	246	11	234	0.6%	0.52 [0.20, 1.38]		? • • • • ? • ?
ALLHAT 2002	457	9054		24303	32.1%	1.17 [1.05, 1.30]	-	
ANBP2 2003	112	3044	107	3034	6.0%	1.04 [0.80, 1.35]	+-	?.............
CAMELOT (Active) 2004	8	673	6	663	0.3%	1.31 [0.46, 3.77]		
ESPIRAL 2001	1	129	2	112	0.1%	0.43 [0.04, 4.72]		330366
Fogari et al (combination) 2002	1	104	2	103	0.1%	0.50 [0.05, 5.38]	•	• ? • ? ? • ?
Fogari et al (monotherapy) 2002	3	102	2	103	0.1%	1.51 [0.26, 8.88]		
HYVET (diuretics) 2003								
	12	431	6	426	0.3%	1.98 [0.75, 5.22]		
J-MIND 2001	5	208	2	228	0.1%	2.74 [0.54, 13.97]		
J-MIND 2001 JMIC-B 2004	. –	208 822	-	228 828	0.1% 0.9%	2.74 [0.54, 13.97] 1.01 [0.51, 2.00]		
J-MIND 2001 JMIC-B 2004 Subtotal (95% CI)	5 16	208	2 16	228	0.1%	2.74 [0.54, 13.97]		
J-MIND 2001 JMIC-B 2004 Subtotal (95% CI) Total events	5 16 644	208 822 15249	2	228 828	0.1% 0.9%	2.74 [0.54, 13.97] 1.01 [0.51, 2.00]	· · · · · · · · · · · · · · · · · · ·	
J-MIND 2001 JMIC-B 2004 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 6.88, df = 10 (5 16 644 (P = 0.74); P	208 822 15249	2 16	228 828	0.1% 0.9%	2.74 [0.54, 13.97] 1.01 [0.51, 2.00]	· · · · · · · · · · · · · · · · · · ·	
J-MIND 2001 JMIC-B 2004 Subtotal (95% CI) Total events	5 16 644 (P = 0.74); P	208 822 15249	2 16	228 828	0.1% 0.9%	2.74 [0.54, 13.97] 1.01 [0.51, 2.00]	•	
J-MIND 2001 JMIC-B 2004 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 6.88, df = 10 (Test for overall effect: Z = 2.75 (P = 0	5 16 644 (P = 0.74); P	208 822 15249 *= 0%	2 16	228 828 30692	0.1% 0.9% 42.2 %	2.74 [0.54, 13.97] 1.01 [0.51, 2.00] 1.14 [1.04, 1.25]	• •	
J-MIND 2001 JMIC-B 2004 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 6.88, df = 10 (Test for overall effect: Z = 2.75 (P = 0 Total (95% CI)	5 16 (P = 0.74); P 0.006)	208 822 15249	2 16 1238	228 828 30692	0.1% 0.9%	2.74 [0.54, 13.97] 1.01 [0.51, 2.00]	• •	
J-MIND 2001 JMIC-B 2004 Subtotal (95% CI) Total events Heterogeneity: Chi [≈] = 6.88, df = 10 (Test for overall effect: Z = 2.75 (P = (Total (95% CI) Total events	5 16 644 P = 0.74); P 0.006) 1536	208 822 15249 *= 0% 50396	2 16 1238 2266	228 828 30692	0.1% 0.9% 42.2 %	2.74 [0.54, 13.97] 1.01 [0.51, 2.00] 1.14 [1.04, 1.25]	* *	
J-MIND 2001 JMIC-B 2004 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 6.88, df = 10 (Test for overall effect: Z = 2.75 (P = 0 Total (95% CI) Total events Heterogeneity: Chi ² = 45.98, df = 28	5 16 644 (P = 0.74); P 0.006) 1536 (P = 0.02);	208 822 15249 *= 0% 50396	2 16 1238 2266	228 828 30692	0.1% 0.9% 42.2 %	2.74 [0.54, 13.97] 1.01 [0.51, 2.00] 1.14 [1.04, 1.25]		?? ?????????????
J-MIND 2001 JMIC-B 2004 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 6.88, df = 10 (Test for overall effect: Z = 2.75 (P = 1 Total events Heterogeneity: Chi ² = 45.98, df = 28 Test for overall effect: Z = 0.51 (P = 1	5 16 644 (P = 0.74); P 0.006) 1536 (P = 0.02); 0.61)	208 822 15249 * = 0% 50396 * = 39%	2 16 1238 2266 6	228 828 30692 65801	0.1% 0.9% 42.2%	2.74 [0.54, 13.97] 1.01 [0.51, 2.00] 1.14 [1.04, 1.25]		?? ?????????????
J-MIND 2001 JMIC-B 2004 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 6.88, df = 10 (Test for overall effect: Z = 2.75 (P = (Total (95% CI) Total events Heterogeneity: Chi ² = 45.98, df = 28 Test for overall effect: Z = 0.51 (P = 1 Test for subgroup differences: Chi ²	5 16 644 (P = 0.74); P 0.006) 1536 (P = 0.02); 0.61)	208 822 15249 * = 0% 50396 * = 39%	2 16 1238 2266 6	228 828 30692 65801	0.1% 0.9% 42.2%	2.74 [0.54, 13.97] 1.01 [0.51, 2.00] 1.14 [1.04, 1.25]	0.1 0.2 0.5 1 2 5 10 Favours [ACEI] Favours [control]	22 0 2 0 2 0 0 0 00
J-MIND 2001 JMIC-B 2004 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 6.88, df = 10 (Test for overall effect: Z = 2.75 (P = 1 Total events Heterogeneity: Chi ² = 45.98, df = 28 Test for overall effect: Z = 0.51 (P = 1	5 16 644 (P = 0.74); P 0.006) 1536 (P = 0.02); 0.61)	208 822 15249 * = 0% 50396 * = 39%	2 16 1238 2266 6	228 828 30692 65801	0.1% 0.9% 42.2%	2.74 [0.54, 13.97] 1.01 [0.51, 2.00] 1.14 [1.04, 1.25]		22 0 2 0 2 0 0 0 00
J-MIND 2001 JMIC-B 2004 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 6.88, df = 10 (Test for overall effect: Z = 2.75 (P = (Total (95% CI) Total events Heterogeneity: Chi ² = 45.98, df = 28 Test for overall effect: Z = 0.51 (P = 1 Test for subgroup differences: Chi ²	5 16 644 (P = 0.74); P 0.006) 1536 (P = 0.02); 0.61) = 17.39, df	208 822 15249 *= 0% 50396 *= 39% = 1 (P <	2 16 1238 2266 6	228 828 30692 65801	0.1% 0.9% 42.2%	2.74 [0.54, 13.97] 1.01 [0.51, 2.00] 1.14 [1.04, 1.25]		22 0 2 0 2 0 0 0 00
J-MIND 2001 JMIC-B 2004 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 6.88, df = 10 (Test for overall effect: Z = 2.75 (P = (Total events Heterogeneity: Chi ² = 45.98, df = 28 Test for overall effect: Z = 0.51 (P = (Test for subgroup differences: Chi ² Risk of bias legend	5 16 644 (P = 0.74); P 0.006) 1536 (P = 0.02); 0.61) = 17.39, df (selection b	208 822 15249 *= 0% 50396 *= 39% = 1 (P <	2 16 1238 2266 6	228 828 30692 65801	0.1% 0.9% 42.2%	2.74 [0.54, 13.97] 1.01 [0.51, 2.00] 1.14 [1.04, 1.25]		22 0 2 0 2 0 0 0 00
J-MIND 2001 JMIC-B 2004 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 6.88, df = 10 (Test for overall effect: Z = 2.75 (P = (Total events Heterogeneity: Chi ² = 45.98, df = 28 Test for overall effect: Z = 0.51 (P = (Test for subgroup differences: Chi ² Risk of bias legend (A) Random sequence generation (5 16 644 P = 0.74); P 0.006) (P = 0.02); 0.61) = 17.39, df (selection b on bias)	208 822 15249 * = 0% 50396 * = 39% * = 1 (P < bias)	2 16 1238 2266 6	228 828 30692 65801	0.1% 0.9% 42.2%	2.74 [0.54, 13.97] 1.01 [0.51, 2.00] 1.14 [1.04, 1.25]		22 0 2 0 2 0 0 0 00
J-MIND 2001 JMIC-B 2004 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 6.88, df = 10 (Test for overall effect: Z = 2.75 (P = 0 Total events Heterogeneity: Chi ² = 45.98, df = 28 Test for overall effect: Z = 0.51 (P = 1 Test for subgroup differences: Chi ² Risk of bias legend (A) Random sequence generation ((B) Allocation concealment (selection	5 16 644 P = 0.74); P 0.006) 1536 (P = 0.02); 0.61) = 17.39, df (selection b on bias) sonnel (per	208 822 15249 * = 0% 50396 * = 39% = 1 (P < bias)	2 16 1238 2266 6 : 0.0001), ce bias)	228 828 30692 65801	0.1% 0.9% 42.2%	2.74 [0.54, 13.97] 1.01 [0.51, 2.00] 1.14 [1.04, 1.25]		22 0 2 0 2 0 0 0 00
J-MIND 2001 JMIC-B 2004 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 6.88, df = 10 (Test for overall effect: Z = 2.75 (P = (Total events Heterogeneity: Chi ² = 45.98, df = 28 Test for overall effect: Z = 0.51 (P = (Test for osubgroup differences: Chi ² <u>Risk of bias legend</u> (A) Random sequence generation ((B) Allocation concealment (selectic (C) Blinding of participants and pers	5 16 644 P = 0.74); P 0.006) 1536 (P = 0.02); 0.61) = 17.39, df (selection b on bias) sonnel (per sonnel (per the detection	208 822 15249 * = 0% 50396 * = 39% = 1 (P < bias)	2 16 1238 2266 6 : 0.0001), ce bias)	228 828 30692 65801	0.1% 0.9% 42.2%	2.74 [0.54, 13.97] 1.01 [0.51, 2.00] 1.14 [1.04, 1.25]		?? ?????????????
J-MIND 2001 JMIC-B 2004 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 6.88, df = 10 (Test for overall effect: Z = 2.75 (P = (Total events Heterogeneity: Chi ² = 45.98, df = 28 Test for overall effect: Z = 0.51 (P = (Test for subgroup differences: Chi ² <u>Risk of bias legend</u> (A) Random sequence generation ((B) Allocation concealment (selectic (C) Blinding of participants and pers (D) Blinding of outcome assessmel	5 16 644 P = 0.74); P 0.006) (P = 0.02); 0.61) = 17.39, df (selection b on bias) sonnel (per nt (detectio on bias)	208 822 15249 * = 0% 50396 * = 39% = 1 (P < bias)	2 16 1238 2266 6 : 0.0001), ce bias)	228 828 30692 65801	0.1% 0.9% 42.2%	2.74 [0.54, 13.97] 1.01 [0.51, 2.00] 1.14 [1.04, 1.25]		?? ?????????????

Figure 5-2 Forest plot showing effect of ACEIs on risk of stroke, stratified by comparison group (placebo vs. active). Overall: 29 trials (FE model).

The **diamond** indicates the pooled risk ratio (and 95% CI) or the overall effect for stroke risk. CI: confidence interval; FE: fixed-effect; M-H: Mantel-Haenszel. For studies acronyms, see list of definition/ abbreviations

5.4.2 Sensitivity analysis

Excluding 18 trials of poor methodological quality did not change the point estimates for stroke RR reduction by ACEI therapy compared with the control (placebo and active) (RR, 0.98; 95% CI 0.88- 1.10, p value=0.78). The heterogeneity test showed no variation between-trials (see **Figure 5.3**)

	ACE	1	Contr	ol		Risk Ratio	Risk Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl	ABCDEFG
1.1.1 ACEI vs Control								
AASK 2002	23	436	32	658	4.7%	1.08 [0.64, 1.83]	_ - _	
ADVANCE 2007	215	5569	218	5571	37.2%	0.99 [0.82, 1.19]	+	
APRES 2000	0	80	1	79	0.1%	0.33 [0.01, 7.96]	←	
DIABHYCAR 2004	118	2443	116	2469	20.3%	1.03 [0.80, 1.32]	+	
DREAM 2006	4	2623	8	2646	0.9%	0.50 [0.15, 1.67]		
IMAGINE 2008	15	1280	14	1273	2.4%	1.07 [0.52, 2.20]		
JMIC-B 2004	16	822	16	828	2.7%	1.01 [0.51, 2.00]		
PART-2 2000	7	308	4	309	0.9%	1.76 [0.52, 5.94]		
PHARAO 2008	3	505	1	503	0.2%	2.99 [0.31, 28.63]		
PREVEND IT 2007	1	431	10	433	0.3%	0.10 [0.01, 0.78]	←	
PROGRESS* (monotherapy) 2001	157	1281	165	1280	30.4%	0.95 [0.78, 1.17]	+	
Subtotal (95% CI)		15778		16049	100.0%	0.98 [0.88, 1.10]	•	
Total events	559		585					
Heterogeneity: Tau ² = 0.00; Chi ² = 8.		(P = 0.9	57); I² = 0'	%				
Test for overall effect: Z = 0.28 (P = 0	.78)							
							0.05 0.2 1 5 2	-
							Favours [ACEI] Favours [control]	
Test for subgroup differences: Not a	pplicable							
Risk of bias legend								
(A) Random sequence generation (selection k	ias)						
(B) Allocation concealment (selectio)	n bias)							
(C) Blinding of participants and pers								
(D) Blinding of outcome assessmer	nt (detectio	n bias):	Other out	comes				
(E) Incomplete outcome data (attritio	n bias)							
(F) Selective reporting (reporting bia	s)							
(G) Other bias								

Figure 5-3 Forest plot showing effect of ACEIs on risk of stroke [Sensitivity analysis: Excluding trials with low methodological quality]. Overall: 11 trials (RE model)

5.4.3 Subgroup analysis

Table 5.1 summarizes the subgroup analyses performed to assess the effect ofACEIs on the risk of stroke.

5.4.3.1 High-affinity versus low-affinity tissue ACEIs

High-tissue affinity ACEIs showed a 10% reduction in stroke (RR, 0.90; 95% CI 0.81, 1.00; p=0.04). This significant reduction was greatly influenced by HOPE, which reported a lower stroke risk by ramipril. Assessment of heterogeneity revealed a low between-trial variation (I^2 =11%). After excluding HOPE, the heterogeneity is disappeared (I^2 =0%) with RR of 0.96 (95% CI 0.87-1.06) (see **Figure 5.4**). No obvious benefit was seen with the low-affinity tissue ACEIs for stroke risk, RR 0.96 (95% CI 0.78-1.19; p=0.71). However, a wide 95% CI might indicate low precision in the effect estimate. ALLHAT and ANBP2 contributed 57.6% to the overall treatment effects, therefore, they had a significant influence. A moderate heterogeneity between-trials was detected (chi-square test p value = 0.14 and I^2 = 31%). This variation is probably due to clinical diversity of ALLHAT trial which used amlodipine & chlorthalidone as comparator group.

5.4.3.2 Class of active control

Figure 5.5 presents a RE meta-analytical summary of effectiveness of ACEI therapy versus an active control stratified based on the class of BP lowering agents. The trials used CCBs, diuretics, beta-blockers and other actives. Combined data from the nine RCTs that used DHP-CCB as one of its randomised treatment arms showed that the ACEIs therapy was associated with a significant 19% increase in stroke, as compared with CCBs (RR, 1.19; 95% CI 1.05-1.35; p=0.006). Importantly, this unfavourable effect was entirely driven by ALLHAT (CCB), as it carried 89.1% of the overall treatment estimate effect. No heterogeneity existed among trials. Similarly, treatment by ACEIs had an 13% increase in stroke risk compared with diuretics (RR, 1.13; 95% CI 1.02- 1.26; p=0.02). All three trials reported an RR for stroke of >1; however, their 95% CI overlapped 1. The significant direction of RR was mainly driven by ALLHAT (Diuretic), as it is carried 82.5% of the overall effect estimates. No heterogeneity existed among the trials. Beta-blocker was used as one of the randomized arms in one trial, AASK (Beta-

blocker) trial. Therefore, this data could not be taken forward for the metaanalysis.

5.4.3.3 Population clinical setting

Figure 5.6 presents the RE meta-analytical summary of effects of ACEIs on the risk of stroke, as stratified by study population clinical setting. Trials that included high-risk hypertensives included 16 RCTs, enrolling 85,674 participants with 3124 stroke events reported. The ALLHAT trial reported an unfavourable effect of ACEI on risk of stroke and carried 18.3% of pooled effect estimate. The overall result was a non-significant reduction in stroke by ACEIs with an RR of 0.95 (95% CI, 0.83-1.09; p=0.48). There was evidence of moderate heterogeneity existing between-trials (chi-square test p value = 0.03 and I² = 43%). This between-trial variation may have arisen from clinical diversity of ALLHAT trial. By excluding the ALLHAT trial, heterogeneity was reduced (I²=4%) and the pooled estimate reached statistical significance, RR of 0.90 (95% CI 0.81-1.00; p=0.05).

Trials including patients with CAD represented 45,734 of participants in eleven trials and reported 907 stroke events. HOPE (weight 42.2%) and PEACE (weight 18%) trials showed a statistically significant reduction in stroke events with ACEI. Therefore, in patients with CAD, ACEIs therapy showed an overall 21% lower risk of stroke (RR, 0.79; 95% CI 0.69- 0.90; p=0.0004). The assessment of heterogeneity showed a non-significant chi-square test (p=0.49), and I² =0%, indicating no between-trial variation.

Data for patients with DM, either with or without nephropathy, revealed a neutral effect from ACEIs therapy on the risk of stroke with an RR of 0.99 (95% CI 0.86-1.15; p =0.94). However, the wide 95% CI limit reflecting a relatively poor precision of the treatment effect estimates, which is likely to be attributable to the small sample size. Only three trials comprising 1329 patients with non-diabetic nephropathy, among whom 19 stroke events were observed. The pooled effect estimates RR of 0.32 (95% CI 0.10-1.07; p=0.07).

5.4.3.4 Mean age group

As shown in Figure 5.7, patients with a mean age group of < 65 years reported a possible protective effect from ACEI on stroke risk, although this did not attain statistical significance. EUROPA contributed 33.9% of the pooled effect estimate, and its null effect on stroke had a notable influence on the pooled result. As a result, therapy with ACEIs in the group of patients aged below 65 years lowered stroke risk by 14%, although not to a level that attained statistical significance (RR, 0.86; 95% CI 0.74-1.01; p=0.07). For group of patients with a mean age of \geq 65 years, all the trials reported non-beneficial effects, except HOPE. The HOPE trial reported a significant reduction in stroke by ACEIs. Meanwhile, in the pooled analysis, there was no significant stroke reduction in older patients receiving ACEIs (RR, 0.97; 95% CI 0.84-1.12; p=0.70). There was a significant heterogeneity among the trials (p= 0.004 and l²= 67%), which is likely to be due to the methodological diversity of HOPE trial (included patients with RAS blocker naivety). By excluding the HOPE trial, the heterogeneity disappeared (l²=0%), and the results neared statistical significance with an RR of 1.08 (95% CI 1.00-1.16; p=0.06).

Table 5-1 Summary of RE meta-analytical subgroup analysis showing the effect of ACEIs compared with control (placebo and active) on risk of stroke[†]

					Stroke In	cidence (%)			
Sub	ogroup analysis	Studies	Participants	Events	ACEI	Control	RR (M-H, Random, 95% CI)	P value*	l² (%) ‡
Overall effects	RE	29	116197	3802	3.04	3.44	0.93 [0.83, 1.05]	0.23	39
Subclass	High-tissue affinity	14	61092	1853	2.85	3.20	0.90 [0.81, 1.00]	0.04*	11
	Low-tissue affinity	13	54001	1929	3.42	3.65	0.96 [0.78, 1.19]	0.71	31 [¥]
	Dihydropyridine CCBs	9	23310	947	4.41	3.70	1.19 [1.05, 1.35]	0.006*	0
Active control	Diuretics	3	31244	1369	4.63	4.21	1.13 [1.02, 1.26]	0.02	0
	Beta-blockers**	1	877	46	5.27	4.21	1.01 [0.58, 1.78]	0.97	NA
	High-risk hypertensive	17	88227	3152	3.40	3.70	0.95 [0.84, 1.09]	0.48	43 ⁿ
	CAD	11	45734	907	1.75	2.20	0.79 [0.69, 0.90]	0.0004*	0
Clinical setting	DM± Nephropathy	6	17380	699	4.01	4.03	0.99 [0.86, 1.15]	0.94	0
	Non-diabetic nephropathy	3	1329	19	0.59	2.23	0.32 [0.10, 1.07]	0.07	4
	CVA**	1	2561	322	1.22	1.28	0.95 [0.78, 1.17]	0.63	NA
Mean age	< 65 years	19	44815	615	1.24	1.49	0.86 [0.74, 1.01]	0.07	0
group	≥ 65 years	8	70278	3167	4.55	4.47	0.97 [0.84, 1.12]	0.70	67¶

[†]See list of definitions/abbreviation. Cl: confidence interval; RE: random-effects; RR: risk ratio; I²: I-square test; M-H: Mantel-Haenszel. *P value of less than 0.05 is considered statistically significant; ‡ I² statistic with <25% considered as low heterogeneity and I2> 75% as high heterogeneity; ** Cannot synthesize data based on one trial

¶ Excluding the HOPE trial results a homogenous RR of 1.08 (95% CI 1.00-1.16; P=0.06).

 π Excluding ALLHAT reduces (l²=4%) with an RR of 0.90 (95% CI 0.81-1.00; p=0.05).

Y Excluding the ALLHAT and PREVEND IT trials, which yield a homogenous RR of 0.94 (95 CI 0.78, 1.15; P=0.57)

	ACE		Cont	rol		Risk Ratio	Risk Ratio	Risk of Bias
Study or Subgroup	Events		Events		Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl	ABCDEFG
1.1.1 High-affinity tissue ACEIs	Lventa	Total	Lycinta	Total	weight	M-11, Taliao11, 35% CI	M-H, Randolli, 55% cr	ADCDLIG
AASK 2002	23	436	32	658	3.6%	1.08 [0.64, 1.83]		
ADVANCE 2007	215	5569	218	5571	21.0%	0.99 [0.82, 1.19]		
APRES 2000	215	3009	210	79	0.1%	0.33 [0.01, 7.96]		
DIABHYCAR 2004	118	2443	116	2469	13.3%	1.03 [0.80, 1.32]		
DREAM 2006	4	2623	8	2646	0.7%	0.50 [0.15, 1.67]		
	98	6110	102					778788
EUROPA 2003 HOPE 2000	156	4645	226	6108 4652	11.4%	0.96 [0.73, 1.26]		2000000
	156	4645	226	4652	18.8%	0.69 [0.57, 0.84]		
Hou et al (group 2) 2006						0.67 [0.11, 3.91]		
IMAGINE 2008	15	1280	14	1273	1.9%	1.07 [0.52, 2.20]		
PART-2 2000	7	308	4	309	0.7%	1.76 [0.52, 5.94]		
PEACE 2004	71	4158	92	4132	9.5%	0.77 [0.56, 1.04]		??@@@@@
PHARAO 2008	3	505	1	503	0.2%	2.99 [0.31, 28.63]		
PROGRESS* (monotherapy) 2001	157	1281	165	1280	18.2%	0.95 [0.78, 1.17]		
QUIET 2001	1	878	1	872	0.1%	0.99 [0.06, 15.85]	•	• ?? ?
Subtotal (95% CI)		30428		30664	100.0%	0.90 [0.81, 1.00]	•	
Total events	870		983					
Heterogeneity: Tau ² = 0.00; Chi ² = 1 Test for overall effect: Z = 2.01 (P = 0		13(P = 0).33); I [≈] =	11%				
1.1.2 Low-affinity tissue ACEIs								
								? • • • • ? • ?
ABCD (normotensive) 2002	6	246	11	234	4.1%	0.52 [0.20, 1.38]		
ALLHAT 2002	457	9054	1052		33.9%	1.17 [1.05, 1.30]		
ANBP2 2003	112	3044	107	3034	23.7%	1.04 [0.80, 1.35]		?
CAMELOT (Overall) 2004	8	673	18	1318	5.5%	0.87 [0.38, 1.99]		\bullet ? \bullet \bullet \bullet \bullet ?
CCS-I 2001	22	3391	28	3358	10.3%	0.78 [0.45, 1.36]		
ESPIRAL 2001	1	129	2	112	0.8%	0.43 [0.04, 4.72]		?? • ? • • ?
Fogari et al (combination) 2002	1	104	2	103	0.8%	0.50 [0.05, 5.38]	• • • • • • • • • • • • • • • • • • • •	• ? • ? ? • ?
Fogari et al (monotherapy) 2002	3	102	2	103	1.4%	1.51 [0.26, 8.88]		• • • • • • • • • • • • • • • • • • • •
HYVET (Overall) 2003	12	431	24	852	7.6%	0.99 [0.50, 1.96]		
J-MIND 2001	5	208	2	228	1.6%	2.74 [0.54, 13.97]		• ?? \varTheta ? 🕒 ?
JMIC-B 2004	16	822	16	828	7.5%	1.01 [0.51, 2.00]		
PREVEND IT 2007	1	431	10	433	1.0%	0.10 [0.01, 0.78]	•	
SCAT 2000	2	229	9	231	1.8%	0.22 [0.05, 1.03]	• • • • • • • • • • • • • • • • • • • •	••••?
Subtotal (95% CI)		18864		35137	100.0%	0.96 [0.78, 1.19]	+	
Total events	646		1283					
Heterogeneity: Tau ² = 0.03; Chi ² = 1	7.35, df = 1	12 (P = 0).14); I [×] =	31%				
Test for overall effect: Z = 0.37 (P = 0	0.71)							
							0.2 0.5 1 2 5	
							Favours (ACEIs) Favours (control)	
Test for subgroup differences: Chi≊:	= 0.30, df=	= 1 (P = 1	0.59), I ≝=	0%			· ····································	
Risk of bias legend								
(A) Random sequence generation (selection	bias)						
(B) Allocation concealment (selection	n bias)							
(C) Blinding of participants and pers	onnel (pe	rforman	ce bias)					
(D) Blinding of outcome assessmer	nt (detectio	n bias):	Other ou	tcomes				
(E) Incomplete outcome data (attritio								
(E) Coloctive reporting (reporting big	-							

(F) Selective reporting (reporting bias) (G) Other bias

Figure 5-4 Forest plot showing effect of ACEIs on risk of stroke (RE model). [Subgroup analysis: Low vs. high-tissue affinity ACEIs]

CI: confidence interval; RE: random-effects; M-H: Mantel-Haenszel. For studies acronyms, see list of definition/ abbreviations

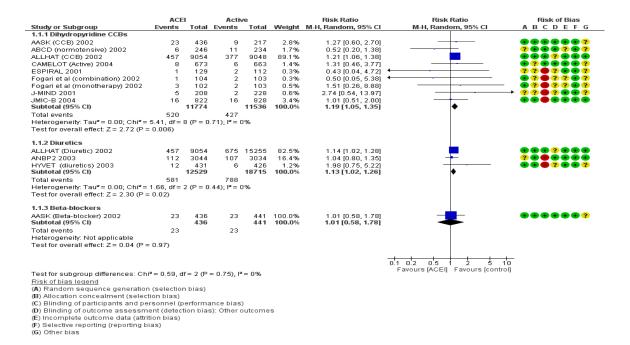


Figure 5-5 Forest plot showing effect of ACEIs on risk of stroke (RE model). [Subgroup analysis: Class of active control].

Study or Subgroup	ACE Events		Contr Events		Weight	Risk Ratio M-H, Random, 95% Cl	Risk Ratio M-H, Random, 95% Cl	Riskof Bias ABCDEFG
1.1.1 High-risk hypertensives								
VASK 2002	23	436	32	658	4.9%	1.08 [0.64, 1.83]		•••••
ADVANCE 2007	215	5569	218	5571	14.8%	0.99 [0.82, 1.19]		
ALLHAT 2002	457	9054		24303	18.3%	1.17 [1.05, 1.30]	-	
ANBP2 2003	112 8	3044 673	107 18	3034 1318	11.5% 2.3%	1.04 [0.80, 1.35] 0.87 [0.38, 1.99]		
CAMELOT (Overall) 2004 DIABHYCAR 2004	118	2443	116	2469	2.3%	1.03 [0.80, 1.32]		
DREAM 2006	4	2623	8	2646	1.1%	0.50 [0.15, 1.67]		
ESPIRAL 2001	1	129	2	112	0.3%	0.43 [0.04, 4.72]	·	?? . ? ?
Fogari et al (combination) 2002	1	104	2	103	0.3%	0.50 [0.05, 5.38]	·	
Fogari et al (monotherapy) 2002	3	102	2	103	0.5%	1.51 [0.26, 8.88]		- • • • • • • • • • • •
HOPE 2000	156	4645	226	4652	14.1%	0.69 [0.57, 0.84]		?
Hou et al (group 2) 2006	2	112	3	112	0.5%	0.67 [0.11, 3.91]		•••••
HYVET (Overall) 2003	12	431	24	852	3.1%	0.99 [0.50, 1.96]		•••?
MAGINE 2008	15	1280	14	1273	2.8%	1.07 [0.52, 2.20]		
J-MIND 2001	5	208	2	228	0.6%	2.74 [0.54, 13.97]		→ ??●?●₽?
JMIC-B 2004	16	822	16	828	3.1%	1.01 [0.51, 2.00]		
PEACE 2004	71	4158	92	4132	9.8%	0.77 [0.56, 1.04]		??
Subtotal (95% CI)		35833		52394	100.0%	0.95 [0.84, 1.09]	•	
Fotal events	1219		1934					
Heterogeneity: Tau² = 0.02; Chi² = 2 Fest for overall effect: Z = 0.70 (P = 0		ь (P = 0.	03); F = 4	1370				
1.1.2 Coronary Artery Dieases (CAI	D)							
APRES 2000	0	80	1	79	0.2%	0.33 [0.01, 7.96]	←	
CAMELOT (Overall) 2004	8	673	18	1318	2.5%	0.87 [0.38, 1.99]	_	
CCS-I 2001	22	3391	28	3358	5.5%	0.78 [0.45, 1.36]	- +	
EUROPA 2003	98	6110	102	6108	22.4%	0.96 [0.73, 1.26]		2292999
HOPE 2000	156	4645	226	4652	42.4%	0.69 [0.57, 0.84]		? • • • • • •
MAGINE 2008	15	1280	14	1273	3.2%	1.07 [0.52, 2.20]		
JMIC-B 2004	16	822	16	828	3.6%	1.01 [0.51, 2.00]		
PART-2 2000	7	308	4	309	1.1%	1.76 [0.52, 5.94]		
PEACE 2004	71	4158	92	4132	18.0%	0.77 [0.56, 1.04]		??•••••
QUIET 2001	1	878	1	872	0.2%	0.99 [0.06, 15.85]		\rightarrow ?? $\bullet \bullet \bullet \bullet \bullet$
SCAT 2000 Subtotal (05% CD	2	229 22574	9	231 23160	0.7% 100.0%	0.22 [0.05, 1.03]		
Subtotal (95% CI) Fotal events	396	22314	511	23100	100.0%	0.79 [0.69, 0.90]	•	
Fest for overall effect: Z = 3.54 (P = 0								
ABCD (normotensive) 2002	ni opatny 6	246	11	234	2.2%	0.52 [0.20, 1.38]		? • • • ? • ?
ADVANCE 2007	215	5569	218	5571	62.1%	0.99 [0.82, 1.19]	_	
DIABHYCAR 2004	118	2443	116	2469	33.9%	1.03 [0.80, 1.32]		
Fogari et al (combination) 2002	1	104	2	103	0.4%	0.50 [0.05, 5.38]	←	
ogari et al (monotherapy) 2002	3	102	2	103	0.7%	1.51 [0.26, 8.88]		- 😑 ? 😑 ? ? 😔 ?
J-MIND 2001	5	208	2	228	0.8%	2.74 [0.54, 13.97]		→ ??●?●₽?
Subtotal (95% CI)		8672		8708	100.0%	0.99 [0.86, 1.15]	•	
Fotal events	348		351					
Heterogeneity: Tau² = 0.00; Chi² = 3. Fest for overall effect: Z = 0.07 (P = 0	.81, df = 5 ((P = 0.58	9); I* = 0%					
	.81, df = 5 ((P = 0.58	i); I* = 0%					
Fest for overall effect: Z = 0.07 (P = 0	.81, df = 5 ((P = 0.58 129	i); I* = 0%	112	24.3%	0.43 (0.04, 4.72)	←	??
Fest for overall effect: Z = 0.07 (P = 0 I.1.4 Non-diabetic nephropathy	8.81, df = 5 (0.94)			112 112	24.3% 43.1%	0.43 [0.04, 4.72] 0.67 [0.11, 3.91]	·	? ? • ? • • ?
Fest for overall effect: Z = 0.07 (P = 0 I.1.4 Non-diabetic nephropathy ESPIRAL 2001 Hou et al (group 2) 2006 PREVEND IT 2007	1.81, df = 5 (0.94) 1	129 112 431	2	112 433	43.1% 32.6%	0.67 [0.11, 3.91] 0.10 [0.01, 0.78]	·	
Fest for overall effect: Z = 0.07 (P = 0 I.1.4 Non-diabetic nephropathy SSPIRAL 2001 Hou et al (group 2) 2006	1.81, df = 5 (0.94) 1 2	129 112	23	112	43.1%	0.67 [0.11, 3.91]		
Fest for overall effect: Z = 0.07 (P = 0 I.1.4 Non-diabetic nephropathy ESPIRAL 2001 Hou et al (group 2) 2006 PREVEND IT 2007	1.81, df = 5 (0.94) 1 2	129 112 431	23	112 433	43.1% 32.6%	0.67 [0.11, 3.91] 0.10 [0.01, 0.78]		
Fest fo ⁻ overall effect: Z = 0.07 (P = 0 I.1.4 Non-diabetic nephropathy ESPIRAL 2001 Hou et al (group 2) 2006 REVEND IT 2007 Subtotal (95% CI)	8.81, df = 5 (0.94) 1 2 1 1 2 1 2 .09, df = 2 (129 112 431 672	2 3 10 15	112 433 657	43.1% 32.6%	0.67 [0.11, 3.91] 0.10 [0.01, 0.78]		
Fest for overall effect: Z = 0.07 (P = 0 I.1.4 Non-diabetic nephropathy ESPIRAL 2001 Hou et al (group 2) 2006 PREVEND IT 2007 Subtotal (95% CI) Fotal events Heterogeneity: Tau ² = 0.05; Chi ² = 2 Fest for overall effect: Z = 1.84 (P = 0	8.81, df = 5 (0.94) 1 2 1 1 2 1 2 .09, df = 2 (129 112 431 672	2 3 10 15	112 433 657	43.1% 32.6%	0.67 [0.11, 3.91] 0.10 [0.01, 0.78]		
Fest for overall effect: Z = 0.07 (P = 0 1.1.4 Non-diabetic nephropathy ESPIRAL 2001 Hou et al (group 2) 2006 REVEND IT 2007 Subtotal (95% CI) Fotal events Heterogeneity: Tau ² = 0.05; Chi ² = 2 Fest for overall effect: Z = 1.84 (P = 0 1.1.5 CVA	8.81, df = 5 (0.94) 1 2 1 1 2.09, df = 2 (0.07)	129 112 431 672 (P = 0.35	2 3 10 15 ;); I ^z = 4%	112 433 657	43.1% 32.6% 100.0 %	0.67 (0.11, 3.91) 0.10 (0.01, 0.78) 0.32 (0.10, 1.07)		
Fest for overall effect: Z = 0.07 (P = 0 I.1.4 Non-diabetic nephropathy ESPIRAL 2001 Hou et al (group 2) 2006 REVEND IT 2007 Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0.05; Chi ² = 2 Test for overall effect: Z = 1.84 (P = 0 I.1.5 CVA PROGRESS* (monotherapy) 2001	8.81, df = 5 (0.94) 1 2 1 1 2 1 2 .09, df = 2 (129 112 431 672 (P = 0.35	2 3 10 15	112 433 657 1280	43.1% 32.6% 100.0 %	0.67 (0.11, 3.91) 0.10 (0.01, 0.78) 0.32 (0.10, 1.07) 0.95 (0.78, 1.17)		
Fest for overall effect: Z = 0.07 (P = 0 I.1.4 Non-diabetic nephropathy ESPIRAL 2001 Hou et al (group 2) 2006 PREVEND IT 2007 Subtotal (95% CI) Fotal events Heterogeneity: Tau ² = 0.05; Chi ² = 2 Fest for overall effect: Z = 1.84 (P = 0 I.1.5 CVA PROGRESS* (monotherapy) 2001 Subtotal (95% CI)	8.81, df = 5 (0.94) 1 2 1 1 2.09, df = 2 (0.07)	129 112 431 672 (P = 0.35	2 3 10 15 ;); I ^z = 4%	112 433 657 1280	43.1% 32.6% 100.0 %	0.67 (0.11, 3.91) 0.10 (0.01, 0.78) 0.32 (0.10, 1.07)		
Fest for overall effect: Z = 0.07 (P = 0 1.1.4 Non-diabetic nephropathy ESPIRAL 2001 Hou et al (group 2) 2006 REVEND IT 2007 Subtotal (95% CI) Fotal events Heterogeneity: Tau ² = 0.05; Chi ² = 2 Fest for overall effect: Z = 1.84 (P = 0 1.1.5 CVA PROGRESS* (monotherapy) 2001 Subtotal (95% CI) Fotal events	8.81, df = 5 (0.94) 1 2 1 1 2.09, df = 2 (0.07) 157	129 112 431 672 (P = 0.35	2 3 10 15); I² = 4% 165	112 433 657 1280	43.1% 32.6% 100.0 %	0.67 (0.11, 3.91) 0.10 (0.01, 0.78) 0.32 (0.10, 1.07) 0.95 (0.78, 1.17)		
Fest for overall effect: Z = 0.07 (P = 0 I.1.4 Non-diabetic nephropathy ESPIRAL 2001 Hou et al (group 2) 2006 PREVEND IT 2007 Subtotal (95% CI) Fotal events Heterogeneity: Tau ² = 0.05; Chi ² = 2 Fest for overall effect: Z = 1.84 (P = 0 I.1.5 CVA PROGRESS* (monotherapy) 2001 Subtotal (95% CI)	1.81, df = 5 (0.94) 1 2 1 1 2 1 1 2 1 1 2 1 1 57 157	129 112 431 672 (P = 0.35	2 3 10 15); I² = 4% 165	112 433 657 1280	43.1% 32.6% 100.0 %	0.67 (0.11, 3.91) 0.10 (0.01, 0.78) 0.32 (0.10, 1.07) 0.95 (0.78, 1.17)		
Fest for overall effect: Z = 0.07 (P = 0 I.1.4 Non-diabetic nephropathy ESPIRAL 2001 Hou et al (group 2) 2006 PREVEND IT 2007 Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0.05; Chi ² = 2 Fest for overall effect: Z = 1.84 (P = 0 I.1.5 CVA PROGRESS* (monotherapy) 2001 Subtotal (95% CI) Fotal events Heterogeneity: Not applicable	1.81, df = 5 (0.94) 1 2 1 1 2 1 1 2 1 1 2 1 1 57 157	129 112 431 672 (P = 0.35	2 3 10 15); I² = 4% 165	112 433 657 1280	43.1% 32.6% 100.0 %	0.67 (0.11, 3.91) 0.10 (0.01, 0.78) 0.32 (0.10, 1.07) 0.95 (0.78, 1.17)		•••••••
Fest for overall effect: $Z = 0.07$ ($P = 0$ 1.1.4 Non-diabetic nephropathy ESPIRAL 2001 Hou et al (group 2) 2006 PREVEND IT 2007 Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0.05; Chi ² = 2 Fest for overall effect: $Z = 1.84$ ($P = 0$ 1.1.5 CVA PROGRESS* (monotherapy) 2001 Subtotal (95% CI) Total events Heterogeneity: Not applicable Fest for overall effect: $Z = 0.48$ ($P = 0$	8.81, df = 5 (0.94) 1 2 1 1 2 1 1 2 1 1 2 1 1 57 157 0.63)	129 112 431 672 (P = 0.35 1281 1281	2 3 10 15); I ^a = 4% 165 165	112 433 657 1280 1280	43.1% 32.6% 100.0 %	0.67 (0.11, 3.91) 0.10 (0.01, 0.78) 0.32 (0.10, 1.07) 0.95 (0.78, 1.17)	0.1 0.2 0.5 1 2 5 Favours [ACEI] Favours [Plac	
Fest for overall effect: $Z = 0.07$ ($P = 0$ 1.1.4 Non-diabetic nephropathy ESPIRAL 2001 Hou et al (group 2) 2006 PREVEND IT 2007 Subtotal (95% CI) Fotal events Heterogeneity: Tau ² = 0.05; Chi ² = 2 Fest for overall effect: $Z = 1.84$ ($P = 0$ 1.1.5 CVA PROGRESS* (monotherapy) 2001 Subtotal (95% CI) Total events Heterogeneity: Not applicable Fest for overall effect: $Z = 0.48$ ($P = 0$ Fotal for overall effect: $Z = 0.48$ ($P = 0$ Fotal for overall effect: $Z = 0.48$ ($P = 0$ Fest for subgroup differences: Chi ² = 0	8.81, df = 5 (0.94) 1 2 1 1 2 1 1 2 1 1 2 1 1 57 157 0.63)	129 112 431 672 (P = 0.35 1281 1281	2 3 10 15); I ^a = 4% 165 165	112 433 657 1280 1280	43.1% 32.6% 100.0 %	0.67 (0.11, 3.91) 0.10 (0.01, 0.78) 0.32 (0.10, 1.07) 0.95 (0.78, 1.17)		
Fest for overall effect: Z = 0.07 (P = 0 I.1.4 Non-diabetic nephropathy ESPIRAL 2001 Hou et al (group 2) 2006 PREVEND IT 2007 Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0.05; Chi ² = 2 Fest for overall effect: Z = 1.84 (P = 0 I.1.5 CVA PROGRESS* (monotherapy) 2001 Subtotal (95% CI) Fotal events Heterogeneity: Not applicable Fest for overall effect: Z = 0.48 (P = 0 Fest for subgroup differences: Chi ² : Rest for subgroup differences: Chi ² :	1.81, df = 5 (0.94) 1 1.09, df = 2 (0.07) 157 157 0.63) = 9.42, df =	129 112 431 672 (P = 0.35 1281 1281 1281	2 3 10 15); I ^a = 4% 165 165	112 433 657 1280 1280	43.1% 32.6% 100.0 %	0.67 (0.11, 3.91) 0.10 (0.01, 0.78) 0.32 (0.10, 1.07) 0.95 (0.78, 1.17)		
Fest for overall effect: Z = 0.07 (P = 0 I.1.4 Non-diabetic nephropathy ESPIRAL 2001 Hou et al (group 2) 2006 REVEND IT 2007 Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0.05; Chi ² = 2 Fest for overall effect: Z = 1.84 (P = 0 I.1.5 CVA PROGRESS* (monotherapy) 2001 Subtotal (95% CI) Fotal events Heterogeneity: Not applicable Fest for overall effect: Z = 0.48 (P = 0 Fest for subgroup differences: Chi ² + Risk of bias legend A) Random sequence generation (1.81, df = 5 (0.94) 1 2 1 1 2 1 1 2 1 1 2 1 1 57 157 157 0.63) = 9.42, df = (selection b	129 112 431 672 (P = 0.35 1281 1281 1281	2 3 10 15); I ^a = 4% 165 165	112 433 657 1280 1280	43.1% 32.6% 100.0 %	0.67 (0.11, 3.91) 0.10 (0.01, 0.78) 0.32 (0.10, 1.07) 0.95 (0.78, 1.17)		
Fest for overall effect: $Z = 0.07$ (P = 0 1.1.4 Non-diabetic nephropathy ESPIRAL 2001 Hou et al (group 2) 2006 PREVEND IT 2007 Subtotal (95% CI) Fotal events Heterogeneity: Tau ² = 0.05; Chi ² = 2 Fest for overall effect: $Z = 1.84$ (P = 0 1.1.5 CVA PROGRESS* (monotherapy) 2001 Subtotal (95% CI) Total events Heterogeneity: Not applicable Fest for subgroup differences: Chi ² = 3 Risk of bias legend A) Random sequence generation (5) PALOREMENT	1.81, df = 5 (0.94) 1 1 1 1 1 1 1 1 1 57 1 57 0.63) = 9.42, df = (selection b on bias)	129 112 431 672 (P = 0.35 1281 1281 1281	2 3 10 15); I ² = 4% 165 165	112 433 657 1280 1280	43.1% 32.6% 100.0 %	0.67 (0.11, 3.91) 0.10 (0.01, 0.78) 0.32 (0.10, 1.07) 0.95 (0.78, 1.17)		
Fest for overall effect: Z = 0.07 (P = 0 I.1.4 Non-diabetic nephropathy ESPIRAL 2001 Hou et al (group 2) 2006 PREVEND IT 2007 Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0.05; Chi ² = 2 Fest for overall effect: Z = 1.84 (P = 0 I.1.5 CVA PROGRESS* (monotherapy) 2001 Subtotal (95% CI) Fotal events Heterogeneity: Not applicable Fest for subgroup differences: Chi ² : Rest for subg	1.81, df = 5 (0.94) 1 1.09, df = 2 (0.07) 157 157 0.63) = 9.42, df = (selection b on blas) sonnel (per	129 112 431 672 (P = 0.35 1281 1281 • 4 (P = 0 vias) formanc	2 3 10 15 ;; ² = 4% 165 165 1.05), ² = 1 e bias)	112 433 657 1280 1280 57.6%	43.1% 32.6% 100.0 %	0.67 (0.11, 3.91) 0.10 (0.01, 0.78) 0.32 (0.10, 1.07) 0.95 (0.78, 1.17)		
Fest for overall effect: Z = 0.07 (P = 0 I.1.4 Non-diabetic nephropathy ESPIRAL 2001 Hou et al (group 2) 2006 REVEND IT 2007 Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0.05; Chi ² = 2 Fest for overall effect: Z = 1.84 (P = 0 I.1.5 CVA PROGRESS* (monotherapy) 2001 Subtotal (95% CI) Fotal events Heterogeneity: Not applicable Fest for overall effect: Z = 0.48 (P = 0 Fest for subgroup differences: Chi ² = <u>Risk of bias legend</u> A) Random sequence generation (B) Allocation concealment (selectio C) Blinding of participants and pers D) Blinding of outcome assessmer	1.81, df = 5 (0.94) 1 2 1 1 2.09, df = 2 (0.07) 157 157 157 157 0.63) = 9.42, df = (selection b soinae) (per nt (detectio	129 112 431 672 (P = 0.35 1281 1281 • 4 (P = 0 vias) formanc	2 3 10 15 ;; ² = 4% 165 165 1.05), ² = 1 e bias)	112 433 657 1280 1280 57.6%	43.1% 32.6% 100.0 %	0.67 (0.11, 3.91) 0.10 (0.01, 0.78) 0.32 (0.10, 1.07) 0.95 (0.78, 1.17)		
Fest for overall effect: Z = 0.07 (P = 0 I.1.4 Non-diabetic nephropathy ESPIRAL 2001 Hou et al (group 2) 2006 PREVEND IT 2007 Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0.05; Chi ² = 2 Fest for overall effect: Z = 1.84 (P = 0 I.1.5 CVA PROGRESS* (monotherapy) 2001 Subtotal (95% CI) Fotal events Heterogeneity: Not applicable Fest for subgroup differences: Chi ² : Rest for subg	1.81, df = 5 (0.94) 1 2 1 1.09, df = 2 (0.07) 157 157 0.63) = 9.42, df = (selection b on bias) sonnel (per nt (detectio	129 112 431 672 (P = 0.35 1281 1281 • 4 (P = 0 vias) formanc	2 3 10 15 ;; ² = 4% 165 165 1.05), ² = 1 e bias)	112 433 657 1280 1280 57.6%	43.1% 32.6% 100.0 %	0.67 (0.11, 3.91) 0.10 (0.01, 0.78) 0.32 (0.10, 1.07) 0.95 (0.78, 1.17)		

Figure 5-6 Forest plot showing effect of ACEIs on risk of stroke (RE model). [Subgroup analysis: Clinical setting].

Chapter 5: ACEIs and ARBs in preventing stroke

	ACE		Cont			Risk Ratio	Risk Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl	ABCDEFG
1.1.1 Mean age < 65 years old								
AASK 2002	23	436	32	658	9.4%	1.08 [0.64, 1.83]		
ABCD (normotensive) 2002	6	246	11	234	2.7%	0.52 [0.20, 1.38]		? • • • ? • ?
APRES 2000	0	80	1	79	0.3%	0.33 [0.01, 7.96]	• • •	
CAMELOT (Overall) 2004	8	673	18	1318	3.7%	0.87 [0.38, 1.99]		$\bullet ? \bullet \bullet \bullet \bullet ?$
CCS-I 2001	22	3391	28	3358	8.3%	0.78 [0.45, 1.36]		
DREAM 2006	4	2623	8	2646	1.8%	0.50 [0.15, 1.67]		
ESPIRAL 2001	1	129	2	112	0.4%	0.43 [0.04, 4.72]	•	?? 🔴 ? 🖶 🔁 ?
EUROPA 2003	98	6110	102	6108	33.9%	0.96 [0.73, 1.26]		??
Fogari et al (combination) 2002	1	104	2	103	0.5%	0.50 [0.05, 5.38]	·	
Fogari et al (monotherapy) 2002	3	102	2	103	0.8%	1.51 [0.26, 8.88]		- 🔒 ? 🛑 ? ? 🖶 ?
Hou et al (group 2) 2006	2	112	3	112	0.8%	0.67 [0.11, 3.91]		
MAGINE 2008	15	1280	14	1273	4.9%	1.07 [0.52, 2.20]	-	
J-MIND 2001	5	208	2	228	1.0%	2.74 [0.54, 13.97]		+ ?? 🛑 ? 🖶 🖶 ?
PART-2 2000	7	308	4	309	1.7%	1.76 [0.52, 5.94]	<u> </u>	
PEACE 2004	71	4158	92	4132	27.3%	0.77 [0.56, 1.04]		??
PHARAO 2008	3	505	1	503	0.5%	2.99 [0.31, 28.63]		* *******
PREVEND IT 2007	1	431	10	433	0.6%	0.10 [0.01, 0.78]	←─────	
QUIET 2001	1	878	1	872	0.3%	0.99 [0.06, 15.85]	• • •	+ ??
SCAT 2000	2	229	9	231	1.1%	0.22 [0.05, 1.03]	← − − − − − − − − − − − − − − − − − − −	
Subtotal (95% CI)		22003			100.0%	0.86 [0.74, 1.01]	•	
Total events	273		342					
Heterogeneity: Tau ² = 0.00; Chi ² = 1	7.21, df = 1	18 (P = 0).51); I ² =	0%				
Test for overall effect: Z = 1.79 (P = 0	0.07)							
1.1.2 Mean age ≥ 65 years old								
	04.5		04.0	6674	40.000	0.00 10.00 1.10		
ADVANCE 2007	215	5569	218	5571	16.2%	0.99 [0.82, 1.19]	T.	
ALLHAT 2002	457	9054		24303		1.17 [1.05, 1.30]		2000000
ANBP2 2003	112	3044	107	3034	12.8%	1.04 [0.80, 1.35]		
DIABHYCAR 2004	118	2443	116	2469	13.2%	1.03 [0.80, 1.32]		
HOPE 2000	156	4645	226	4652		0.69 [0.57, 0.84]		?...........
HYVET (Overall) 2003	12	431	24	852	3.7%	0.99 [0.50, 1.96]		
JMIC-B 2004	16	822	16	828	3.7%	1.01 [0.51, 2.00]		
PROGRESS* (monotherapy) 2001	157	1281	165	1280	15.3%	0.95 [0.78, 1.17]	-	
Subtotal (95% CI)		27289		42989	100.0%	0.97 [0.84, 1.12]	•	
Total events	1243		1924					
Heterogeneity: Tau ² = 0.02; Chi ² = 2		f(P = 0)	004); l ² =	67%				
Test for overall effect: Z = 0.38 (P = 0	J.70)							
								_
							0.2 0.5 1 2 5	_
To al fan an hanna air an an an an	4.40	4.00	0.000 15	40.00			Favours [ACEI] Favours [Contro]
Test for subgroup differences: Chi#	= 1.16, df:	= 1 (P =	0.28), I* =	13.8%				
Risk of bias legend								
(A) Random sequence generation (bias)						
(B) Allocation concealment (selection)	n bias)							

(B) Allocation concealment (selection bias)
 (C) Blinding of participants and personnel (performance bias)
 (D) Blinding of outcome assessment (detection bias): Other outcomes
 (E) Incomplete outcome data (attrition bias)
 (F) Selective reporting (reporting bias)
 (G) Other bias

Figure 5-7 Forest plot showing effect of ACEIs on risk of stroke (RE model). [Subgroup analysis: Mean age group].

5.5 ARBs and risk of stroke

5.5.1 Overall treatment effect

Figure 5.8 presents an RE meta-analytical summary of the therapeutic benefits of ARB on stroke risk, stratified by comparator groups (placebo or active). Data was pooled from 38 RCTs, reported 6211 stroke cases among 142,122 participants. The incidence rate of stroke in patients assigned to ARB therapy was lower when compared to those in the control arm, at 4.2% and 4.5% respectively. Treatment with ARB compared with control (placebo or active) resulted in an 8% relative risk reduction of stroke, which was nominally significant at the meta-analysis level (RR, 0.92; 95% CI 0.85-1.00; p=0.05).

Data pooled from 17 placebo-controlled trials, which enrolled 83,610 participants and reported 4103 stroke events. The meta-analysis result was mainly driven by data from the PRoFESS and ACTIVE-I trials, with the most weight assigned to these trials at 9.6% and 8.3% respectively. Whereas, the remaining trials were assigned a weight of less than 5% each. Therapy with ARBs resulted in a significant 9% reduction in stroke compared with placebo (RR, 0.91; 95% CI 0.86-0.97; p=0.003). The degree of heterogeneity in the treatment effect across all the trials was zero (I^2 : 0%) and nonsignificant (P= 0.80).

Active comparator trials included 21 trials with 58,512 participants and reported 2108 stroke cases. There was no significant reduction in the risk of stroke by ARBs compared with active therapies (RR, 0.94, 95% CI 0.79-1.12; p=0.50). The neutral effect of ARB on stroke observed was mainly driven by trials that used CCBs as one of the randomized comparator groups (**Section 5.5.3.1 Subgroup analysis: active comparator**). In this case, poor overlap among the 95% CI of individual trials indicates statistical heterogeneity. A chi-square test of heterogeneity showed a significant p value (0.0006) and I² statistics = 58%. The between-trial variation was greatly influenced by trials comparing ARB with CCB-based regimens. Excluding these trials diminished the heterogeneity (I²=9%) with an RR 0.80 (95% CI 0.68-0.92; p=0.003).

Figure 5.9 shows the forest plot for the FE model. For placebo-controlled trials, a meta-analytical summary of the FE model is similar to RE as $Tau^2 = 0$. However,

the FE model of pooled data from the active-controlled trials assigned slightly more weight to LIFE (9.6%) and VALUE (8.8%). The combined effect estimates then yielded a RR of 0.96 (95% CI 0.89-1.05; p=0.40).

Assessment of the funnel plot (Figure D-2 in Appendix D) demonstrated asymmetry. However, one outlier was detected, which represented J-RHYTHM II. Although the trial reported a significant stroke reduction with candesartan, it was not designed or powered to detect cerebrovascular events.

(D) Blinding of outcome assessment (detection bias): Other outcomes

(E) Incomplete outcome data (attrition bias)
 (F) Selective reporting (reporting bias)
 (G) Other bias

Study or Subaroup	ARE Events		Cont		Mojakt	Risk Ratio	Risk Ratio	Risk of Bias
Study or Subgroup	Events	lotal	Events	lotal	weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl	ABCDEFG
.1.1 ARB vs Placebo								
ACTIVE-I 2011	379	4518	411	4498	8.3%	0.92 [0.80, 1.05]	-	
NTIPAF 2012	2	214	1	211	0.1%	1.97 [0.18, 21.58]		
HARM-Added 2003	47	1276	41	1272	2.8%	1.14 [0.76, 1.72]		
CHARM-Alternative 2003	36	1013	42	1015	2.5%	0.86 [0.56, 1.33]		
CHARM-Preserved 2003	58	1514	63	1509	3.5%	0.92 [0.65, 1.30]		
FFERVESCENT 2016	1	80	0	40	0.1%	1.52 [0.06, 36.46]	← →	••••••
3ISSI-AF 2009	4	722	0	720	0.1%	8.98 [0.48, 166.40]		
HOPE-3 2016	75	6356	94	6349	4.2%	0.80 [0.59, 1.08]		
PRESERVE 2008	68	2067	79	2061	4.0%	0.86 [0.62, 1.18]		
DNT (Placebo) 2003	28	579	26	569	1.9%	1.06 [0.63, 1.78]		
VAVIGATOR 2010	105	4631	132	4675	5.2%	0.80 [0.62, 1.03]		
RIENT 2011	11	282	11	284	0.9%	1.01 [0.44, 2.29]		
RoFESS* 2008	880	10146	934	10186	9.6%	0.95 [0.87, 1.03]	1	200000
RENAAL 2001	47	751	934 50	762	3.1%			
	47	2232	10	2215	0.9%	0.95 [0.65, 1.40]		
CADMAP 2011						1.59 [0.72, 3.49]		
COPE 2003	89	2477	115	2460	4.8%	0.77 [0.59, 1.01]		
RANSCEND 2008	112	2954	136	2972	5.4%	0.83 [0.65, 1.06]		$? \bullet \bullet \bullet \bullet \bullet \bullet$
Subtotal (95% CI)		41812		41798	57.3%	0.91 [0.86, 0.97]	•	
otal events	1958		2145					
Heterogeneity: Tau² = 0.00;			16 (P = 0	.80); I²=	0%			
est for overall effect: Z = 2.9	39 (P = 0.0	003)						
.1.2 ARB vs Active								
IC 2016	12	585	11	534	0.9%	1.00 [0.44, 2.24]		
LPINE 2003	0	197	0	196		Not estimable		?? +? + ??
TTEMPT-CVD 2016	8	615	11	613	0.7%	0.72 [0.29, 1.79]		
ARP 2011	3	90	1	101	0.1%	3.37 [0.36, 31.79]		· ? ? - ? - • •
ASE-J 2008	60	2354	47	2349	3.1%	1.27 [0.87, 1.86]		
CHIEF 2018	163	6766	127	6776	5.7%	1.29 [1.02, 1.62]		
COPE 2011	17	1110	39	2183	1.7%	0.86 [0.49, 1.51]		
E-COST 2005	47	1053	77	995	3.5%	0.58 [0.41, 0.82]		
	17	69	20	72	1.7%	0.89 [0.51, 1.55]		220200
ang Wu et 2015	9	140	11	70	0.8%	0.41 [0.18, 0.94]		2222000
-		1024		1025	2.9%			
HJ-CREATE 2009	45		49			0.92 [0.62, 1.36]		
DNT (CCB) 2003	28	579	15	567	1.4%	1.83 [0.99, 3.39]		
-RHYTHM II 2010	0	158	3	160	0.1%	0.14 [0.01, 2.78]		
(awamura 2013	0	49	2	95	0.1%	0.38 [0.02, 7.85]	• • •	???????
IFE 2002	232	4605	309	4588	7.4%	0.75 [0.63, 0.88]		
10SES* 2005	36	681	42	671	2.6%	0.84 [0.55, 1.30]		
ITP-AF study 2013	0	74	1	75	0.1%	0.34 [0.01, 8.16]	←	•••••
)LIVUS 2010	0	126	2	121	0.1%	0.19 [0.01, 3.96]	←	????
REVER-treatment 2016	0	322	1	333	0.1%	0.34 [0.01, 8.43]	←	
SUPPORT 2015	34	578	26	568	2.1%	1.29 [0.78, 2.11]		??
/ALUE 2004	322	7649	281	7596	7.7%	1.14 [0.97, 1.33]	-	
Subtotal (95% CI)	022	28824	201	29688	42.7%	0.94 [0.79, 1.12]		
Total events	1033		1075				1	
leterogeneity: Tau ² = 0.06;		23 df-		1.000	² = 52%			
est for overall effect: Z = 0.0			, a (r. – 0	.5550), 1	- 30%			
$\cos(10) \cos(10) \cos(10) \cos(10) = 0.1$,						
otal (95% CI)		70636		71486	100.0%	0.92 [0.85, 1.00]	•	
otal events	2991		3220			cicc [oloo; hou]	1	
leterogeneity: Tau ² = 0.02;		33 AF-		01): 12-	37%			
			50 (F - 0	.01),11=	57.70		0.2 0.5 1 2 5	
est for overall effect: Z = 1.			- 4 (D - 4	7517			Favours (ARB) Favours (control)	
est for subgroup difference	s. uni⁺=	u. i i, dī	= 1 (P = l	urio), if =	-0%0			
<u>Risk of bias legend</u>								
	aration (s	election	bias)					
N) Random sequence gen B) Allocation concealment								

Figure 5-8 Forest plot showing effect of ARBs on risk of stroke, stratified based on control group (placebo vs. active). Overall: 38 trials (RE model)

The **diamond** indicates the pooled risk ratio (and 95% CI) or the overall effect for stroke risk. CI: confidence interval; RE: random-effects; M-H: Mantel-Haenszel. For studies acronyms, see list of definition/ abbreviations

	ARE	:	Cont	rol		Risk Ratio	Risk Ratio	Risk of Bias
Study or Subgroup	Events		Events		Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl	ABCDEFG
1.1.1 ARB vs Placebo								
ACTIVE-I 2011	379	4518	411	4498	12.8%	0.92 [0.80, 1.05]	-	
ANTIPAF 2012	2	214	1	211	0.0%	1.97 [0.18, 21.58]		
CHARM-Added 2003	47	1276	41	1272	1.3%	1.14 [0.76, 1.72]		$\bullet \bullet $
CHARM-Alternative 2003	36	1013	42	1015	1.3%	0.86 [0.56, 1.33]		
CHARM-Preserved 2003	58	1514	63	1509	2.0%	0.92 [0.65, 1.30]		
EFFERVESCENT 2016	1	80	0	40	0.0%	1.52 [0.06, 36.46]		
GISSI-AF 2009	4 75	722 6356	0 94	720 6349	0.0%	8.98 [0.48, 166.40]		
HOPE-3 2016 I-PRESERVE 2008	75 68	2067	94 79	2061	2.9% 2.5%	0.80 [0.59, 1.08]		
IDNT (Placebo) 2003	28	579	26	569	0.8%	0.86 [0.62, 1.18] 1.06 [0.63, 1.78]		
NAVIGATOR 2010	105	4631	132	4675	4.1%	0.80 [0.62, 1.03]		
ORIENT 2011	11	282	11	284	0.3%	1.01 [0.44, 2.29]		
PRoFESS* 2008		10146	934	10186	29.0%	0.95 [0.87, 1.03]	-	?
RENAAL 2001	47	751	50	762	1.5%	0.95 [0.65, 1.40]	<u> </u>	
ROADMAP 2011	16	2232	10	2215	0.3%	1.59 [0.72, 3.49]		
SCOPE 2003	89	2477	115	2460	3.6%	0.77 [0.59, 1.01]		
TRANSCEND 2008	112	2954	136	2972	4.2%	0.83 [0.65, 1.06]		? • • • • • •
Subtotal (95% CI)		41812		41798	66.7%	0.91 [0.86, 0.97]	•	
Total events	1958		2145					
Heterogeneity: Chi ² = 11.07); I² = 0%					
Test for overall effect: Z = 2.	99 (P = 0.0)03)						
1.1.2 ARB vs Active								
4C 2016	12	585	11	534	0.4%	1.00 [0.44, 2.24]		
40 2010 ALPINE 2003	0	197	0	196	0.470	Not estimable		2202002
ATTEMPT-CVD 2016	8	615	11	613	0.3%	0.72 [0.29, 1.79]		
CARP 2011	3	90	1	101	0.0%	3.37 [0.36, 31.79]		
CASE-J 2008	60	2354	47	2349	1.5%	1.27 [0.87, 1.86]	<u> </u>	
CHIEF 2018	163	6766	127	6776	3.9%	1.29 [1.02, 1.62]		
COPE 2011	17	1110	39	2183	0.8%	0.86 [0.49, 1.51]		
E-COST 2005	47	1053	77	995	2.5%	0.58 [0.41, 0.82]		•••?
E-COST-R 2005	17	69	20	72	0.6%	0.89 [0.51, 1.55]		?? \varTheta ? 🕒 🕈 ?
Fang Wu et 2015	9	140	11	70	0.5%	0.41 [0.18, 0.94]		? ? ? ? • • •
HIJ-CREATE 2009	45	1024	49	1025	1.5%	0.92 [0.62, 1.36]		• ? • • • • •
IDNT (CCB) 2003	28	579	15	567	0.5%	1.83 [0.99, 3.39]		
J-RHYTHM II 2010	0	158	3	160	0.1%	0.14 [0.01, 2.78]		
Kawamura 2013	0	49	2	95	0.1%	0.38 [0.02, 7.85]	•	3333434
LIFE 2002	232	4605	309	4588	9.6%	0.75 [0.63, 0.88]	-	
MOSES* 2005	36	681	42	671	1.3%	0.84 [0.55, 1.30]	·	
NTP-AF study 2013	0	74	1	75	0.0%	0.34 [0.01, 8.16]		
OLIVUS 2010 PREVER-treatment 2016	0 0	126 322	2	121 333	0.1%	0.19 [0.01, 3.96]		??? ** *?
SUPPORT 2015	34	578	26	568	0.0% 0.8%	0.34 [0.01, 8.43] 1.29 [0.78, 2.11]	•	2200000
VALUE 2004	34	7649	281	7596	8.8%	1.14 [0.97, 1.33]	-	
Subtotal (95% CI)	522	28824	201	29688	33.3%	0.96 [0.89, 1.05]	•	
Total events	1033		1075				-	
Heterogeneity: Chi ² = 45.23		P = 0.00		8%				
Test for overall effect: Z = 0.			<i>//····</i>					
Total (95% CI)		70636		71486	100.0 %	0.93 [0.89, 0.98]	•	
Total events	2991		3220					
Heterogeneity: Chi ² = 57.33); I² = 37%	b			0.2 0.5 1 2 5	
Test for overall effect: Z = 2.							Favours [ARB] Favours [control]	
Test for subgroup difference	es: Chi ² = 1	1.1U, df	= 1 (P = 0).30), l² =	= 8.8%			
Risk of bias legend		1 21	1-1 ⁵					
(A) Random sequence gen			bias)					
(B) Allocation concealment		-		a biac'				
(C) Blinding of participants a (D) Blinding of outcome ass					teorees			
(D) Blinding of outcome ass (E) Incomplete outcome dat			on pras):	ouner ou	acomes			
(F) Selective reporting (repo								
(G) Other bias	ang bias)							
/-/ - mor wide								

Figure 5-9 Forest plot showing effect of ARBs on risk of stroke, stratified based on control group (placebo or active). Overall: 38 trials (FE model)

The **diamond** indicates the pooled risk ratio (and 95% CI) or the overall effect for stroke risk. CI: confidence interval; FE: fixed-effect; M-H: Mantel-Haenszel. For studies acronyms, see list of definition/ abbreviations

5.5.2 Sensitivity analysis

Figure 5.10 displays the effect estimate after the omission of two trials with stroke at baseline; PRoFESS and MOSES trials. Excluding the PRoFESS trial did not change the pooled effect of ARB compared with the placebo (RR, 0.89; 95% CI 0.82-0.96; p=0.004). No heterogeneity was detected among the trials. Excluding MOSES did not modify the pooled effect estimate of ARB compared with the active control (RR, 0.95; 95% CI 0.79-1.14; p=0.57). There was evidence of heterogeneity (p value is 0.0004) with I²=60%. This is likely to have arisen due to the clinical diversity of trials using CCBs as the comparator group.

Figure 5.11 shows a meta-analytical summary after excluding 16 trials with poor methodological quality, three placebo and thirteen active-controlled trials. Pooled effect estimates did not modify either the placebo controlled (RR,0.89; 95% CI 0.82-0.97; p=0.009) or active control (RR, 1.06; 95% CI 0.85- 1.32; p=0.62) subgroups. By contrast, significant heterogeneity across active-controlled trials was detected (p value = 0.0006 and I² = 73%). This is likely to be due to the clinical diversity of the LIFE (atenolol as a comparator) and IDNT (amlodipine as a comparator) trials, as they reported an opposite RR of stroke. After excluding these, the heterogeneity disappeared (I²=0%) with a RR of 1.15 (95% CI 1.02-1.29).

Church and Carls and an	ARB		Cont		Later Sect 1	Risk Ratio	Risk Ratio	Risk of Bias
Study or Subgroup	Events	lotal	Events	lotal	weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl	ABCDEF
1.1.1 ARB vs Placebo								
ACTIVE-I 2011	379	4518	411	4498	8.3%	0.92 [0.80, 1.05]		
ANTIPAF 2012	2	214	1	211	0.1%	1.97 [0.18, 21.58]		→ ●●●●●● ●
CHARM-Added 2003	47	1276	41	1272	3.4%	1.14 [0.76, 1.72]		
CHARM-Alternative 2003	36	1013	42	1015	3.1%	0.86 [0.56, 1.33]		
CHARM-Preserved 2003	58	1514	63	1509	4.1%	0.92 [0.65, 1.30]	- _	
EFFERVESCENT 2016	1	80	0	40	0.1%	1.52 [0.06, 36.46]	• •	→ ● ●●●●●●
GISSI-AF 2009	4	722	0	720	0.1%	8.98 [0.48, 166.40]		
HOPE-3 2016	75	6356	94	6349	4.9%	0.80 [0.59, 1.08]		
I-PRESERVE 2008	68	2067	79	2061	4.6%	0.86 [0.62, 1.18]		
IDNT (Placebo) 2003	28	579	26	569	2.4%	1.06 [0.63, 1.78]		
NAVIGATOR 2010	105	4631	132	4675	5.7%	0.80 [0.62, 1.03]		
		282		284				
ORIENT 2011	11		11		1.1%	1.01 [0.44, 2.29]		
RENAAL 2001	47	751	50	762	3.7%	0.95 [0.65, 1.40]		
ROADMAP 2011	16	2232	10	2215	1.2%	1.59 [0.72, 3.49]		
SCOPE 2003	89	2477	115	2460	5.4%	0.77 [0.59, 1.01]		
TRANSCEND 2008	112	2954	136	2972	5.9%	0.83 [0.65, 1.06]		?
Subtotal (95% CI)		31666		31612	54.3%	0.89 [0.82, 0.96]	•	
Total events	1078		1211					
Heterogeneity: Tau ² = 0.00;	Chi² = 9.9	3, df = 1	5 (P = 0.8	82); I ² = 0)%			
Test for overall effect: Z = 2.								
1.1.2 ARB vs Active								
4C 2016	12	585	11	534	1.2%	1.00 [0.44, 2.24]		
ALPINE 2003	0	197	0	196		Not estimable		??
ATTEMPT-CVD 2016	8	615	11	613	1.0%	0.72 [0.29, 1.79]		
CARP 2011	3	90	1	101	0.2%	3.37 [0.36, 31.79]		
CASE-J 2008	60	2354	47	2349	3.8%	1.27 [0.87, 1.86]		
CHIEF 2018	163	6766	127	6776	6.2%			
						1.29 [1.02, 1.62]		
COPE 2011	17	1110	39	2183	2.1%	0.86 [0.49, 1.51]		
E-COST 2005	47	1053	77	995	4.1%	0.58 [0.41, 0.82]		
E-COST-R 2005	17	69	20	72	2.2%	0.89 [0.51, 1.55]		220200
Fang Wu et 2015	9	140	11	70	1.1%	0.41 [0.18, 0.94]		????€€ €
HIJ-CREATE 2009	45	1024	49	1025	3.6%	0.92 [0.62, 1.36]		
IDNT (CCB) 2003	28	579	15	567	1.9%	1.83 [0.99, 3.39]		
J-RHYTHM II 2010	0	158	3	160	0.1%	0.14 [0.01, 2.78]	•	• ? • • • • •
Kawamura 2013	0	49	2	95	0.1%	0.38 [0.02, 7.85]	• •	-> ????? ? ?
LIFE 2002	232	4605	309	4588	7.6%	0.75 [0.63, 0.88]		
NTP-AF study 2013	0	74	1	75	0.1%	0.34 [0.01, 8.16]	• •	→ • • • • • • • • •
OLIVUS 2010	Ō	126	2	121	0.1%	0.19 [0.01, 3.96]	←	???
PREVER-treatment 2016	ŏ	322	1	333	0.1%	0.34 [0.01, 8.43]	• • • • • • • • • • • • • • • • • • • •	
SUPPORT 2015	34	578	26	568	2.6%	1.29 [0.78, 2.11]		??
VALUE 2004	322	7649	281	7596	7.8%	1.14 [0.97, 1.33]		
Subtotal (95% CI)	322	28143	201	29017	45.7%	0.95 [0.79, 1.14]		
	997	20145	4000	25017	43.770	0.55 [0.75, 1.14]	T	
Total events		- AF -	1033	00040-1	z _ coor			
Heterogeneity: Tau ² = 0.06; Taatéan anana 11 afrant 7 - 0.			18 (P = 0	1.0004);1	-= 6U%			
Test for overall effect: Z = 0.9	56 (P = 0.5	0						
Total (95% CI)		59809		60620	100.0%	0.93 [0.84, 1.02]		
		29009		00029	100.0%	0.95 [0.84, 1.02]	•	
Total events	2075		2244					
Heterogeneity: Tau ² = 0.02;			34 (P = 0	1.008); l²	= 40%		0.2 0.5 1 2 5	_
Test for overall effect: Z = 1.							Favours [ARB] Favours [control	oll
Test for subgroup difference	es: Chi ^z = I	0.42, df	= 1 (P = 0	0.52), I ² =	- 0%			
<u>Risk of bias legend</u>								
(A) Random sequence gen	eration (se	lection	bias)					
(B) Allocation concealment			,					
(C) Blinding of participants a			rforman	ce bias)				
(D) Blinding of outcome ass					Itcomes			
(E) Incomplete outcome dat				Saler UL				
		ind b)						
(F) Selective reporting (repo	rung blas)							
(G) Other bias								

Figure 5-10 Forest plot showing effect of ARBs on risk of stroke [Sensitivity analysis: Excluding PRoFESS and MOSES]. Overall:36 trials (RE model)

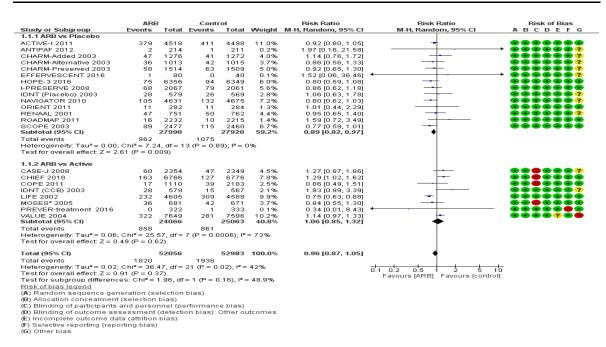


Figure 5-11 Forest plot showing effect of ARBs on risk of stroke [Sensitivity analysis: Excluding trials with low methodological quality]. Overall: 22 trials (RE model)

CI: confidence interval; RE: random-effects; M-H: Mantel-Haenszel. For studies acronyms, see list of definition/ abbreviations

5.5.3 Subgroup analysis

Table 5.2 summarizes the subgroup meta-analyses of the effect of ARBs therapy on risk of stroke.

5.5.3.1 Class of active control

From figure 5-12, ARBs were compared extensively with DHP (amlodipine, benidipine, nitrendipine and nifedipine), as well as non-DHP CCBs (bepridil). These trials contributed to 45.3% of the overall pooled effect estimates. There was no significant stroke risk reduction by ARBs when compared with CCBs with an RR of 1.11 (95% CI 0.90-1.37; p=0.35). There was moderate heterogeneity across trials, and this was likely to be due to the methodological and clinical diversity of IDNT (CCB) (designed and powered to detect renal outcomes) and in Fang Wu et al. (a small number of patients were studied).

Pooled data active comparator trials using diuretics, such as thiazide (hydrochlorothiazide), potassium-sparing diuretic (amiloride) and thiazide-like

(chlorthalidone), yielded a RR of 1.30 (95% CI 0.64-2.66; p=0.47). There was no evidence of heterogeneity among these trials. Stroke data of pertaining to 11,392 participants (two large trials) allocated to beta-blockers as control groups pooled. Together those trials reported a total of 585 stroke cases events. Therapy with ARB was associated with a significant 26% reduction in stroke compared with beta-blockers (RR, 0.74; 95% CI 0.63-0.87; p=0.0002). There was no evidence of heterogeneity among the trials. Compared with the active control group, there was a non-significant decrease in the risk of stroke by ARBs with RR of 0.86 (95% CI, 0.66-1.12; p=0.26). There was also moderate heterogeneity across the trials, probably arising from the methodological and clinical diversity of SUPPORT trial.

5.5.3.2 Population clinical setting

Figure 5.13 presents the RE meta-analytical summary of effects of ARB on the risk of stroke, as stratified by study population clinical setting. Trials including high-risk hypertensive subjects numbered 27, including 114,793 participants and 5665 stroke events. The majority of the trials reported RR point estimates of < 1; however, there was considerable heterogeneity among the included trials. Three trials reporting RR point estimates >1, VALUE, CHIEF and CASE-J trials (CCBs as comparator group). In the case of high-risk hypertensives, treatment with ARBs reduced the risk of stroke by 9% at borderline significance level (RR, 0.91; 95% CI 0.83-1.00; p=0.05). The chi-square test for heterogeneity showed a p value of 0.0003, and I² of 49%, indicating heterogeneity among trials. This variation is potentially due to trials utilizing CCB as a comparator, VALUE, CHIEF and CASE-J. Excluding these resulted in an I^2 of 23% with RR of 0.86 (95% CI 0.79, 0.93; p=0.0002). Trials including those from patients with underlying CVA data were available from two trials involving 21,684 participants with 1892 stroke cases. The PRoFESS trial contributed 96% of pooled effect estimates. In patients with a CVA history, there was no significant decrease in the risk of stroke when ARB therapy was compared with the control (RR, 0.94; 95% CI 0.86-1.03; p=0.17). There was no evidence of heterogeneity among trials. In patients with HF, there was no significant decrease in the risk of stroke by ARB compared with the control group (RR, 0.96; 95% CI 0.81-1.15; p=0.68). There was no heterogeneity between trials. Six RCTs assessed the effect of ARB on 11,494 participants with AF. The ACTIVE-I trial carried of 98.8% of pooled effect estimate. There was a null effect on the risk of stroke by ARB when compared with control group (RR, 0.92; 95% CI 0.801.05; p=0.21). No heterogeneity was detected between the trials. Trials including patients with underlying CAD showed a null effect on the risk of stroke by ARB when compared with control group (RR, 0.86; 95% CI, 0.71-1.06; p=0.15). The pooled effect estimate was mainly derived from TRANSCEND, which accounts for 67% of the combined effect estimate. There was no evidence of heterogeneity among these trials. For participants with DM \pm nephropathy; there was no clear benefit from ARB on the risk of stroke (RR,1.10; 95% CI 0.84-1.44; p=0.48). However, it seems a wide pooled 95% CI indicated a low precise effect estimate. There was no evidence of heterogeneity.

5.5.3.3 Mean age group

Figure 5.14 presents the RE meta-analysis results testing the efficacy of ARB therapy on stroke outcome compared with a control arm (placebo or active) in patients aged < 65 years or \ge 65 years.

In the age group < 65 years, there was a null effect on risk of stroke by ARB compared with the control group (RR, 1.08; 95% CI 0.96-1.22; p=0.21). The trials that showed the RR point estimates >1 for ARBs also used a CCB-based regimen in one of their randomized arms, CASE-J, CHIEF and IDNT (CCB). There was no heterogeneity among the trials.

Pooled data for the age group \geq 65 years showed therapy with ARB in elderly patients was associated with a significant 14% reduction in stroke (RR, 0.87; 95% CI 0.80-0.95; p=0.002). PRoFESS, ACTIVE-I and VALUE greatly influenced treatment estimate effects. There was also moderate heterogeneity among trials (chi-square test p value =0.03 and I² = 41%). The observed heterogeneity was most likely a result of the clinical diversity in VALUE (CCBs used as comparator), PRoFESS (patients with ischemic stroke at baseline) and SUPPORT (81% of patients with background ACEI therapy). When excluding these, the heterogeneity disappeared (I²=0%) with RR of 0.82 (95 CI% 0.77-0.89; p=<0.00001).

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				Stroke Inc	cidence (%)			
analysis	Studies	Participants	Events	ARBs	Control	RR (M-H, Random, 95% CI)	P value*	l² (%) ‡
RE	38	142122	6211	4.23	4.50	0.92 [0.85, 1.00]	0.05	37
Candesartan	13	36156	1050	2.68	3.12	0.86 [0.75, 0.99]	0.04*	21
Telmisartan	5	41177	2372	5.65	5.86	0.98 [0.81, 1.18]	0.83	53
Irbesartan	3	14859	1006	6.63	6.90	0.94 [0.80, 1.12]	0.50	23
Valsartan	6	26514	869	3.33	3.21	0.92 [0.63, 1.35]	0.67	62
Losartan	3	11361	639	4.91	6.33	0.78 [0.67, 0.90]	0.001*	0
Olmesartan	5	6831	110	1.74	1.47	1.20 [0.83, 1.74]	0.34	0
Eprosartan**	1	1352	78	5.28	6.25	0.84 [0.55, 1.30]	0.44	NA
CCBs	9	36809	1147	3.34	2.88	1.11 [0.90, 1.37]	0.35	44
Diuretics	3	3252	30	1.04	0.80	1.30 [0.64, 2.66]	0.47	0
Beta-blockers	2	11392	585	4.35	5.91	0.74 [0.63, 0.87]	0.0002*	0
Active control	8	8169	363	4.00	4.88	0.86 [0.66, 1.12]	0.26	30
	Candesartan Telmisartan Irbesartan Valsartan Losartan Olmesartan Eprosartan** CCBs Diuretics Beta-blockers	RE38Candesartan13Telmisartan5Irbesartan3Valsartan6Losartan3Olmesartan5Eprosartan**1CCBs9Diuretics3Beta-blockers2	RE38142122Candesartan1336156Telmisartan541177Irbesartan314859Valsartan626514Losartan311361Olmesartan56831Eprosartan**11352CCBs936809Diuretics33252Beta-blockers211392	RE381421226211Candesartan13361561050Telmisartan5411772372Irbesartan3148591006Valsartan626514869Losartan311361639Olmesartan56831110Eprosartan**1135278CCBs9368091147Diuretics3325230Beta-blockers211392585	AnalysisStudiesParticipantsEventsARBsRE3814212262114.23Candesartan133615610502.68Telmisartan54117723725.65Irbesartan31485910066.63Valsartan6265148693.33Losartan3113616394.91Olmesartan568311101.74Eprosartan**11352785.28CCBs93680911473.34Diuretics33252301.04Beta-blockers2113925854.35	RE3814212262114.234.50Candesartan133615610502.683.12Telmisartan54117723725.655.86Irbesartan31485910066.636.90Valsartan6265148693.333.21Losartan3113616394.916.33Olmesartan568311101.741.47Eprosartan**11352785.286.25CCBs93680911473.342.88Diuretics33252301.040.80Beta-blockers2113925854.355.91	AnalysisStudiesParticipantsEventsARBsControlRR (M-H, Random, 95% Cl)RE3814212262114.234.500.92 [0.85, 1.00]Candesartan133615610502.683.120.86 [0.75, 0.99]Telmisartan54117723725.655.860.98 [0.81, 1.18]Irbesartan31485910066.636.900.94 [0.80, 1.12]Valsartan6265148693.333.210.92 [0.63, 1.35]Losartan3113616394.916.330.78 [0.67, 0.90]Olmesartan568311101.741.471.20 [0.83, 1.74]Eprosartan**11352785.286.250.84 [0.55, 1.30]CCBs93680911473.342.881.11 [0.90, 1.37]Diuretics33252301.040.801.30 [0.64, 2.66]Beta-blockers2113925854.355.910.74 [0.63, 0.87]	AnalysisStudiesParticipantsEventsARBsControlRR (M-H, Random, 95% CI)P value*RE3814212262114.234.500.92 [0.85, 1.00]0.05Candesartan133615610502.683.120.86 [0.75, 0.99]0.04*Telmisartan54117723725.655.860.98 [0.81, 1.18]0.83Irbesartan31485910066.636.900.94 [0.80, 1.12]0.50Valsartan6265148693.333.210.92 [0.63, 1.35]0.67Losartan3113616394.916.330.78 [0.67, 0.90]0.001*Olmesartan568311101.741.471.20 [0.83, 1.74]0.34Eprosartan**11352785.286.250.84 [0.55, 1.30]0.44CCBs93680911473.342.881.11 [0.90, 1.37]0.35Diuretics33252301.040.801.30 [0.64, 2.66]0.47

Table 5-2 Summary of RE meta-analytical subgroup analysis showing the effect of ARBs on risk of stroke compared with control (placebo or active) †

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Table 5-3 Summary of RE meta-analytical subgroup analysis showing the effect of ARBs on risk of stroke compared with control (placebo or active) (Continued)

					Stroke Inci	dence (%)			
Subgro	oup analysis	Studies	Participant	Events	ACEI	Control	RR (M-H, Random,	P value*	l² (%) ‡
							95% CI)		
Overall effects	RE	38	142122	6211	4.23	4.50	0.92 [0.85, 1.00]	0.05	37
	High-risk hypertensive	27	114793	5665	4.78	5.08	0.91 [0.83, 1.00]	0.05	49¶
	CVA	2	21684	1892	8.46	8.98	0.94 [0.86, 1.03]	0.17	0
	Heart failure	5	12873	494	3.76	3.90	0.96 [0.81, 1.15]	0.68	0
Clinical setting	Atrial fibrillation	6	11494	803	6.71	7.25	0.92 [0.80, 1.05]	0.21	0
	CAD	5	9532	371	3.59	4.18	0.86 [0.71, 1.06]	0.15	0
	DM± Nephropathy	4	8241	111	2.57	2.54	1.10 [0.84, 1.44]	0.48	0
	Non-DM nephropathy**	1	141	37	2.46	2.77	0.89 [0.51, 1.55]	0.67	NA
Mean age group	< 65 years	16	43710	1004	2.38	2.21	1.08 [0.96, 1.22]	0.21	0
	≥ 65 years	21	97833	5179	5.02	5.56	0.87 [0.80, 0.95]	0.002*	41 [¥]

†See list of definitions/abbreviation. Cl: confidence interval; RE: random-effects; RR: risk ratio; I^2 : I-square test; M-H: Mantel-Haenszel. *P value of less than 0.05 is considered statistically significant; ** Cannot synthesise data with one trial; $\ddagger I^2$ statistic with <25% considered as low heterogeneity and I^2 > 75% as high heterogeneity

¶ Excluded trials with CCBs as comparators yield homogenous RR of 0.86 (95% CI 0.79, 0.93; p=0.0002)

¥ Excluded VALUE trial yields RR of 0.82 [95% CI 0.77, 0.89, P<0.00001]

	ARE		Cont			Risk Ratio	Risk Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl	ABCDEFG
1.1.1 CCBs								
CASE-J 2008	60	2354	47	2349	16.4%	1.27 [0.87, 1.86]	+	
CHIEF 2018	163	6766	127	6776	24.7%	1.29 [1.02, 1.62]		
Fang Wu et 2015	9	140	11	70	5.4%	0.41 [0.18, 0.94]		<u>? ? ? ? • • •</u>
IDNT (CCB) 2003	28	579	15	567	8.7%	1.83 [0.99, 3.39]		
J-RHYTHM II 2010	0	158	3	160	0.5%	0.14 [0.01, 2.78] 🔸 🛶		•••••••
Kawamura 2013	0	49	2	95	0.5%	0.38 [0.02, 7.85] 🛛 🕂 🚽		— ???? •?•
MOSES* 2005	36	681	42	671	14.1%	0.84 [0.55, 1.30]		
NTP-AF study 2013	0	74	1	75	0.4%	0.34 [0.01, 8.16] 🛛 🕂 🚽		— •?•?•••
VALUE 2004 Subtotal (95% CI)	322	7649 18450	281	7596 18359	29.2% 100.0 %	1.14 [0.97, 1.33] 1.11 [0.90, 1.37]		••••
Total events	618		529					
Heterogeneity: Tau ² = 0.03;	Chi² = 14.2	2, df = 8	P = 0.08	3); l ² = 4	4%			
Test for overall effect: Z = 0.9	94 (P = 0.3	5)						
1.1.2 Diuretics								
ALPINE 2003	0	197	0	196		Not estimable		?? +? + ?
COPE (Diuretic) 2011	17	1110	12	1094	95.0%	1.40 [0.67, 2.91]		
PREVER-treatment 2016	0	322	1	333	5.0%	0.34 [0.01, 8.43] 🗕 🗕		— ••••••
Subtotal (95% CI)		1629		1623	100.0 %	1.30 [0.64, 2.66]		
Total events	17		13					
Heterogeneity: Tau ² = 0.00;	Chi² = 0.70	, df = 1	(P = 0.40)	; I² = 0%	,			
Test for overall effect: Z = 0.1	72 (P = 0.4)	7)						
1.1.3 Beta-blockers								
COPE (Beta-blocker) 2011	17	1110	27	1089	7.0%	0.62 [0.34, 1.13]		
LIFE 2002	232	4605	309	4588	93.0%	0.75 [0.63, 0.88]		
Subtotal (95% CI)		5715		5677	100.0%	0.74 [0.63, 0.87]	▼	
Total events	249		336					
Heterogeneity: Tau ² = 0.00;	Chi² = 0.36	, df = 1	(P = 0.55)	; I ² = 0%	,			
Test for overall effect: Z = 3.	74 (P = 0.00	002)						
1.1.4 Active control								
4C 2016	12	585	11	534	8.9%	1.00 [0.44, 2.24]	_	
ATTEMPT-CVD 2016	8	615	11	613	7.4%	0.72 [0.29, 1.79]		
CARP 2011	3	90	1	101	1.4%	3.37 [0.36, 31.79]		
E-COST 2005	47	1053	77	995	25.5%	0.58 [0.41, 0.82]	_ _	•••?
E-COST-R 2005	17	69	20	72	15.4%	0.89 [0.51, 1.55]		?? \varTheta ? 🕒 ?
HIJ-CREATE 2009	45	1024	49	1025	22.9%	0.92 [0.62, 1.36]	-	
OLIVUS 2010	0	126	2	121	0.8%	0.19 [0.01, 3.96]		???
SUPPORT 2015	34	578	26	568	17.8%	1.29 [0.78, 2.11]	_ 	??
Subtotal (95% CI)		4140			100.0%	0.86 [0.66, 1.12]	◆	
Total events	166		197				-	
Heterogeneity: Tau ² = 0.04;		5. df = 7		3); ² = 3	0%			
Test for overall effect: Z = 1.					-			
		-						
							··	
							0.2 0.5 1 2 5 is (experimental) Favours (contro	n
Test for subgroup difference	es: Chi ² = 1	0.32. df	= 3 (P = f	0.02). P	= 70,9%	Favour	s (experimental) Favours (contro	IJ

(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)
 (C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias): Other outcomes

(E) Incomplete outcome data (attrition bias) (F) Selective reporting (reporting bias)

(G) Other bias

Figure 5-12 Forest plot showing effect of ARBs on risk of stroke (RE model). [Subgroup analysis: Class of active control].

Study or Subgroup	ARE Events		Cont Events		Weight	Risk Ratio M-H, Randorn, 95% Cl	Risk Ratio M-H, Random, 95% Cl	Riskof Bias ABCDEFG
1.1.1 High-risk hypertensive	2							
ACTIVE-I 2011 ALPINE 2003	379	4518 197	411 0	4498 196	9.4%	0.92 [0.80, 1.05] Not estimable		
ATTEMPT-CVD 2016	8	615	11	613	1.0%	0.72 [0.29, 1.79]		
CASE-J 2008 CHIEF 2018	60 163	2354 6766	47 127	2349 6776	4.0% 6.8%	1.27 [0.87, 1.86] 1.29 [1.02, 1.62]		
COPE 2011	17	1110	39	2183	2.2%	0.86 [0.49, 1.51]		
E-COST 2005	47	1053	77	995	4.3%	0.58 [0.41, 0.82]		
E-COST-R 2005 Fang Wu et 2015	17	69 140	20 11	72 70	2.2% 1.1%	0.89 [0.51, 1.55] 0.41 [0.18, 0.94]		
GISSI-AF 2009	4	722	0	720	0.1%	8.98 [0.48, 166.40]		
HIJ-CREATE 2009 I-PRESERVE 2008	45 68	1024 2067	49 79	1025 2061	3.7% 4.9%	0.92 [0.62, 1.36] 0.86 [0.62, 1.18]		
IDNT (Overall) 2003	28	579	41	1136	4.9%	1.34 [0.84, 2.14]	+	
J-RHYTHM II 2010	0	158	3	160	0.1%	0.14 [0.01, 2.78]	•	
LIFE 2002 MOSES* 2005	232 36	4605 681	309 42	4588 671	8.5% 3.3%	0.75 [0.63, 0.88] 0.84 [0.55, 1.30]		
NAVIGATOR 2010	105	4631	132	4675	6.2%	0.80 [0.62, 1.03]		
NTP-AF study 2013 OLIVUS 2010	0	74	1	75 121	0.1%	0.34 [0.01, 8.16] 0.19 [0.01, 3.96]		
ORIENT 2011	8	282	11	284	1.0%	0.73 [0.30, 1.79]		
PREVER-treatment 2016 PRoFESS* 2008	0 880	322 10146	1 934	333 10186	0.1% 10.6%	0.34 [0.01, 8.43] 0.95 [0.87, 1.03]	•	
RENAAL 2001	47	751	50	762	3.9%	0.95 [0.65, 1.40]		
SCOPE 2003	89	2477	115	2460	5.8%	0.77 [0.59, 1.01]		
SUPPORT 2015 TRANSCEND 2008	34 112	578 2954	26 136	568 2972	2.7% 6.4%	1.29 [0.78, 2.11] 0.83 [0.65, 1.06]		
VALUE 2004	322	7649	281	7596	8.7%	1.14 [0.97, 1.33]	_ - _	••••
Subtotal (95% CI) Total events	2710	56648	2955	58145	100.0%	0.91 [0.83, 1.00]	•	
Heterogeneity: Tau ² = 0.02; C Test for overall effect: Z = 1.9	≎hi² = 49.			.003); I ^z	= 49%			
1.1.2 CVA	~~				~	0.04/0.65 4.05		
MOSES* 2005 PRoFESS* 2008	36 880	681 10146	42 934	671 10186	4.0% 96.0%	0.84 [0.55, 1.30] 0.95 [0.87, 1.03]		200000
Subtotal (95% CI)		10827		10857	100.0%	0.94 [0.86, 1.03]	•	
Total events Heterogeneity: Tau ² = 0.00; 0	916 ∿bi≅ = 0.2	5 df - 1	976 /P = 0.6/	N: 12 - 09	×.			
Test for overall effect: Z = 1.3			(1 0.0	i), i = 0.	••			
1.1.3 Heart failure								
CHARM-Added 2003	47	1276	41	1272	17.8%	1.14 [0.76, 1.72]		
CHARM-Alternative 2003 CHARM-Preserved 2003	36 58	1013 1514	42 63	1015 1509	15.8% 24.6%	0.86 [0.56, 1.33] 0.92 [0.65, 1.30]		
I-PRESERVE 2008	68	2067	79	2061	29.7%	0.86 [0.62, 1.18]		
SUPPORT 2015	34	578 6448	26	568	12.2% 100.0 %	1.29 [0.78, 2.11]		??
Subtotal (95% CI) Total events	243	0440	251	6425	100.0%	0.96 [0.81, 1.15]	Ť	
Heterogeneity: Tau ² = 0.00; C Test for overall effect: Z = 0.4	≎hi ≊ = 2.8			9); I≊ = 09	X6			
1.1.4 Atrial Fibrillation	270	4610	411	4400	00.0%	0.02 (0.00, 4.05)		
ACTIVE-I 2011 ANTIPAF 2012	379 2	4518 214	411 1	4498 211	98.9% 0.3%	0.92 [0.80, 1.05] 1.97 [0.18, 21.58]	_	
GISSI-AF 2009	4	722	0	720	0.2%	8.98 [0.48, 166.40]	· · · · · · · · · · · · · · · · · · ·	
J-RHYTHM II 2010 Kawamura 2013	0	158 49	3	160 95	0.2% 0.2%	0.14 [0.01, 2.78] 0.38 [0.02, 7.85]		
NTP-AF study 2013	ŏ	74	1	75	0.2%	0.34 [0.01, 8.16]	• · · · · · · · · · · · · · · · · · · ·	
Subtotal (95% CI)	385	5735	418	5759	100.0%	0.92 [0.80, 1.05]	•	
Total events Heterogeneity: Tau ² = 0.00; 0		4, df = 5		2); I ^z = 09	x6			
Test for overall effect: $Z = 1.2$								
1.1.5 Coronary Artery Disea	ses (CAE))						
4C 2016	12	585	11	534	6.1%	1.00 [0.44, 2.24]		
CARP 2011	3	90 1024	1	101 1025	0.8% 25.7%	3.37 [0.36, 31.79] 0.92 [0.62, 1.36]		
HIJ-CREATE 2009 OLIVUS 2010	45 0	1024	49 2	1025	25.7%	0.92 [0.62, 1.36] 0.19 [0.01, 3.96]	← — — — — — — — — — — — — — — — — — — —	2220002
TRANSCEND 2008	112	2954	136	2972	67.0%	0.83 [0.65, 1.06]	-	?
Subtotal (95% CI) Total events	172	4779	199	4753	100.0%	0.86 [0.71, 1.06]	-	
Heterogeneity: Tau ² = 0.00; C	>hi⁼ = 2.6			l); I≊ = 09	X6			
Test for overall effect: Z = 1.4	2 (P = 0.1	15)						
1.1.6 Diabetes Mellitus (DM)	± Nephr	opathy						
IDNT (Overall) 2003	28	579	41	1136	32.1%	1.34 [0.84, 2.14]		
ORIENT 2011 RENAAL 2001	8 47	282 751	11 50	284 762	8.8% 47.7%	0.73 [0.30, 1.79] 0.95 [0.65, 1.40]		
ROADMAP 2011	16	2232	10	2215	11.4%	1.59 [0.72, 3.49]		
Subtotal (95% CI) Total events	99	3844	112	4397	100.0%	1.10 [0.84, 1.44]	-	
Heterogeneity: Tau ² = 0.00; C	≎hi ≊ = 2.8			2); I≅ = 09	X6			
Test for overall effect: Z = 0.7		¥8)						
1.1.7 Non-diabetic nephropa						0.0015.5		
E-COST-R 2005 Subtotal (95% CI)	17	69 69	20	72 72	100.0% 100.0 %	0.89 [0.51, 1.55] 0.89 [0.51, 1.55]		??●?●?
Total events	17		20					
Heterogeneity: Not applicable Test for overall effect: Z = 0.4	e 2 (P - 0)	37)						
reactor overall ellect. ∠ = 0.4	z (r = 0.t							
							0.2 0.5 1 2 5 Favours (ARB) Favours (Placebo)	
Test for subgroup difference	s: Chi = =	2.57, df	= 6 (P = 0	0.86), I ² =	0%		i avouis (Artoj Favours (Piacebo)	
<u>Risk of bias legend</u> (A) Random seguence gene	ration (c)	election	hias					
(B) Allocation concealment (selection	bias)	-					
(C) Blinding of participants a					iteome -			
(D) Blinding of outcome asse (E) Incomplete outcome data			on plas):	other of	acomes			
(F) Selective reporting (report								
(G) Other bias								

Figure 5-13 Forest plot showing effect of ARBs on risk of stroke (RE model). [Subgroup analysis: Clinical setting]

	ARE		Cont			Risk Ratio	Risk Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl	ABCDEFG
1.1.1 Mean age <65 years								
ALPINE 2003	0	197	0	196		Not estimable		??
ANTIPAF 2012	2	214	1	211	0.3%	1.97 [0.18, 21.58]		
CARP 2011	3	90	1	101	0.3%	3.37 [0.36, 31.79]		?? • ? • •
CASE-J 2008	60	2354	47	2349	10.7%	1.27 [0.87, 1.86]	+	••••
CHARM-Added 2003	47	1276	41	1272	9.0%	1.14 [0.76, 1.72]	- -	
CHIEF 2018	163	6766	127	6776	28.9%	1.29 [1.02, 1.62]	⊢ ∎−	
COPE 2011	17	1110	39	2183	4.8%	0.86 [0.49, 1.51]		
EFFERVESCENT 2016	1	80	0	40	0.2%	1.52 [0.06, 36.46]	← →	
DNT (Overall) 2003	28	579	41	1136	6.9%	1.34 [0.84, 2.14]		
Kawamura 2013	ō	49	2	95	0.2%	0.38 [0.02, 7.85]	· · · · · · · · · · · · · · · · · · ·	?????
NAVIGATOR 2010	105	4631	132	4675	23.7%	0.80 [0.62, 1.03]		
NTP-AF study 2013	0	74	1 1	4075	0.1%	0.34 [0.01, 8.16]	· · · · · · · · · · · · · · · · · · ·	
DRIENT 2011	11	282	11	284	2.3%			
						1.01 [0.44, 2.29]		
PREVER-treatment 2016	0	322	1	333	0.1%	0.34 [0.01, 8.43]	· · ·	
RENAAL 2001	47	751	50	762	10.2%	0.95 [0.65, 1.40]		
ROADMAP 2011	16	2232	10	2215	2.4%	1.59 [0.72, 3.49]		
Subtotal (95% Cl)		21007		22703	100.0%	1.08 [0.96, 1.22]		
Fotal events	500		504					
Heterogeneity: Tau ² = 0.00;			14 (P = 0	I.46); I² =	0%			
Test for overall effect: Z = 1.3	25 (P = 0.)	21)						
1.1.2 Mean age ≥ 65 years								
4C 2016	12	585	11	534	1.1%	1.00 [0.44, 2.24]		
ACTIVE-I 2011	379	4518	411	4498	12.0%	0.92 [0.80, 1.05]		
TTEMPT-CVD 2016	8	615	11	613	0.9%	0.72 [0.29, 1.79]		••••
CHARM-Alternative 2003	36	1013	42	1015	3.3%	0.86 [0.56, 1.33]		
CHARM-Preserved 2003	58	1514	63	1509	4.6%	0.92 [0.65, 1.30]	- _	
-COST 2005	47	1053	77	995	4.6%	0.58 [0.41, 0.82]		
-COST-R 2005	17	69	20	72	2.2%	0.89 [0.51, 1.55]		?? .
Fang Wu et 2015		140	11	70	1.1%	0.41 [0.18, 0.94]		7777000
GISSI-AF 2009	4	722		720	0.1%	8.98 [0.48, 166.40]		
HIJ-CREATE 2009	45	1024	49	1025	3.8%	0.92 [0.62, 1.36]		
HOPE-3 2016	40	6356	49 94	6349	5.7%			
	68	2067	94 79	2061		0.80 [0.59, 1.08]		
I-PRESERVE 2008					5.3%	0.86 [0.62, 1.18]		
J-RHYTHM II 2010	0	158	3	160	0.1%	0.14 [0.01, 2.78]	•	
LIFE 2002	232	4605	309	4588	10.5%	0.75 [0.63, 0.88]		
MOSES* 2005	36	681	42	671	3.3%	0.84 [0.55, 1.30]		
OLIVUS 2010	0	126	2	121	0.1%	0.19 [0.01, 3.96]	•	?????
PRoFESS* 2008	880	10146	934	10186	14.1%	0.95 [0.87, 1.03]	4	?
SCOPE 2003	89	2477	115	2460	6.5%	0.77 [0.59, 1.01]		
SUPPORT 2015	34	578	26	568	2.7%	1.29 [0.78, 2.11]		??●●●●●
TRANSCEND 2008	112	2954	136	2972	7.3%	0.83 [0.65, 1.06]		?
VALUE 2004	322	7649	281	7596	10.8%	1.14 [0.97, 1.33]	+- -	••••
Subtotal (95% CI)		49050		48783	100.0%	0.87 [0.80, 0.95]	•	
Total events	2463		2716					
Heterogeneity: Tau ² = 0.01;		.99. df =		.03): I ² =	41%			
Test for overall effect: Z = 3.1				,.				
	51 (1 = 0.	002)						
							0.2 0.5 1 2 5	
	o hiz	7 00	- 4 (D)		- 07.0%		Favours [ARB] Favours [Control]	
Test for subgroup difference	as. Chiř =	7.88, df	= 1 (P = 1)	5.005), P	= 87.3%			
Risk of bias legend								
(A) Random sequence gen			bias)					
(B) Allocation concealment								
(C) Blinding of participants a	and perso	onnel (pe	erforman	ce bias)				
(D) Blinding of outcome ass	essment	detecti	on bias):	Other ou	utcomes			
E) Incomplete outcome dat								

(B) Incomplete outcome data (attrition bias)
 (F) Selective reporting (reporting bias)
 (G) Other bias

Figure 5-14 Forest plot showing effect of ARBs on risk of stroke (RE model). [Subgroup analysis: Mean age group].

5.6 Meta-regression analyses of the effect of ACEI and ARB on stroke risk in relation to SBP reduction

5.6.1 ACEIs

5.6.1.1 Overall effect

Four of the included trials did not report achieved SBP reduction (CCS-I, Hou et al. (group 2), IMAGINE and QUIET). Thus, 24 trials were included in the meta-regression analysis. The mean SBP reduction achieved for the ACEI trials ranged from -23 (HYVET) to 2 (ALLHAT) mmHg. As shown in **table 5.4**, the univariate analysis demonstrates the RR reduction in stroke is proportional to the magnitude of mean SBP reduction achieved by ACEIs (an estimated RR, 1.03; 95% CI 1.00-1.05; p=0.029). Each 10-mmHg reduction in mean SBP was estimated to reduce the risk of stroke by 25% (95% CI 0.65-0.87; P=0.029). The achieved SBP differences between the randomized groups explained 47% of the observed between-trial variation in stroke risk.

In the univariate model, a 47% between-study variance was explained by the percentage of males (%) (Tau² reduced from 0.0203 to 0.0107; p=0.093). Therefore, percentage of males (%) as a variable was adjusted in model (1) multivariate analysis. After accounting for males (%), the direction and magnitude of relationship between mean SBP and stroke remained unaltered. A 67% variability among the trials in RR of stroke was substantially explained by the model (1) (Tau² reduced from 0.0203 to 0.0066; p=0.244). Similarly, adjusting for male (%) and baseline SBP (mmHg) in model (2) did not attenuate the association (see Table 5.4). The mean DBP differences achieved were excluded from the multivariate model because it possessed a strong correlation with the achieved mean SBP differences (r=-0.9). At zero mmHg BP reduction, there was no evidence that ACEIs conferred a BP-independent cerebrovascular effect (RR, 1.01; 95% CI 0.89-1.14; p=0.83) (see Figure 5.15)

5.6.1.2 Sensitivity analysis

To investigate the robustness of this finding, I performed a series of sensitivity analyses on the adjusted meta-regression analysis. First, the analysis was performed by excluding nine trials that utilize CCBs as their comparator. The result did not modify the observed BP dependent effect (RR, 1.03; 95% CI 1.00-1.06; p=0.042). Secondly, three trials with diuretics as the comparator (ALLHAT (Diuretic), HYVET (diuretics) and ANBP2) were also omitted from analysis. Once again, the results remained unchanged (RR, 1.04; 95% CI 1.00-1.07; p=0.013). Thirdly, twelve trials with a sample size of less than 1000 were removed, but this did not modify the effect of SBP reduction on the RR of stroke (p=0.05). Finally, one outlier (HYVET) was removed from the analysis which did not alter the point estimate, but instead lost statistical significance (RR, 1.03; 95% CI 0.98-1.08; p=0.21) (see Figure 5.16). Table 5-4 Meta-regression of related and unrelated SBP differences by ACEI on stroke (unadjusted and adjusted models)

		Slope			Between-study variance			
Variable	Studies (n)	RR	95% CI	P value	Tau ²	I ² Residual (%)	P value	R ² (%)
Null model (24 trials)	<u> </u>		Ł	0.0203	47.10	0.006	-	
Univariate analysis (Unadjusted)								
Achieved SBP differences (mmHg)	24	1.03	1.00-1.05	0.029*	0.0118	27.13	0.114	42
Achieved DBP differences (mmHg)**		1.04	0.99-1.11	0.102	0.0166	36.8	0.040	18
Baseline SBP (mmHg)		1.00	0.99-1.01	0.125	0.0172	42.69	0.017	15
Mean age (Years)		1.01	0.98-1.03	0.307	0.0206	46.35	0.008	0
Male (%)		0.99	0.98-1.00	0.060*	0.0107	29.39	0.093	47
DM (%)		1.00	0.99-1.00	0.779	0.0232	49.34	0.004	0
Duration of follow-up (Years)		0.99	0.86-1.13	0.892	0.0225	47.35	0.006	0
Multivariate analysis (Adjusted)	1							
Model 1: Achieved SBP differences (mmHg)	24	1.07	1.00-1.05	0.036	0.0066	16.27	0.244	67
Model 2: Achieved SBP differences (mmHg)		1.03	1.00-1.06	0.025	0.0115	17.98	0.226	43
Abbreviation: Tau ² = estimated amount of het	erogeneity (bet	ween-stu	ldy variance) n	ot explained	l by covaria	te; I ² residual= pro	oportion of r	emaining
observed variance due to true variation in eff	fect size; ** The	DBP diff	erence achieve	d is exclude	ed from mul	tivariate model as	s it highly co	rrelated
with the achieved SBP differences (r=-0.99).								
Madel (4). The surplusion of directed for mod							•• •	

Model (1): The analysis was adjusted for males (%); Model (2): The analysis was adjusted for males (%) and baseline SBP (mmHg)

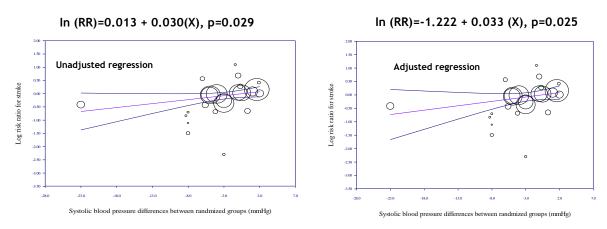


Figure 5-15 Adjusted and unadjusted meta-regression analysis of the relationship between RR for stroke and difference in SBP (mmHg) achieved between the randomized groups for trials of ACEIs.

Each study is represented by a circle. The size of each circle is proportional to that study's weight in the analysis (inverse-variance weighted). A negative value on the x-axis indicates lower achieved SBP in the treatment group than the control group

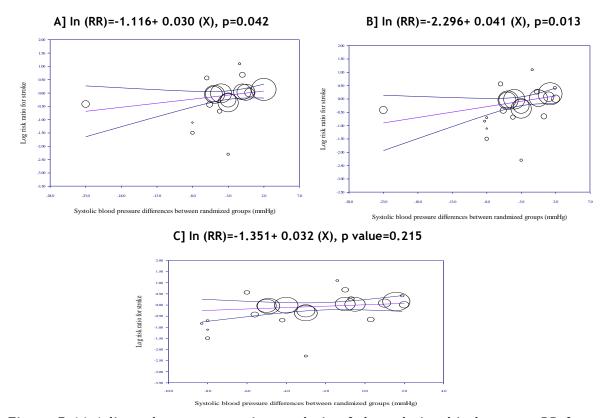


Figure 5-16 Adjusted meta-regression analysis of the relationship between RR for stroke and difference in achieved SBP (mmHg) between randomized groups for the ACEIs trials [Sensitivity analysis].

Excluding trials with A] CCB as comparator; B] Diuretic as comparator and C] HYVET trial (an outlier).

5.6.2ARBs

5.6.2.1 Overall effect

Four of the included trials did not report the SBP differences achieved between the two groups; Fang Wu et al., J-RHYTHM II, Kawamura and SUPPORT trials. The remaining 33 trials of ARBs reported mean SBP reductions. The mean SBP reduction achieved in the ARBs trials ranged from -10 mmHg (EFFERVESCENT) to 2.3 mmHg (OLIVUS). The univariate regression analysis showed a significant (RR, 1.03; 95% CI 1.00-1.06; p=0.020) association between the trial specific mean SBP, and the log relative stroke reduction by ARBs (Figure 5.17 and table 5.6). The mean SBP differences achieved accounted for 43% of the variance of the individual risk ratios. In the adjusted model, DM (%), males (%), and mean age (years) were entered into the multivariate analysis as these factors explained most of the variability between the trials. After accounting for these variables in the multivariate model, the strong linear association in the reduction of SBP by ARBs and stroke (RR, 1.03; 95% CI 1.01-1.06; p=0.001) remained significant. After adjustment, a large proportion of the between-study variance was explained (R²=100%) and the percentage of residual heterogeneity disappeared (the residual $I^2=0\%$ and Tau² reduced from 0.0176 to 0). The correlation matrix showed a high correlation between the SBP and DBP differences achieved; thus, DBP was excluded from the adjusted model. At zero mmHg BP reduction, there was no evidence to suggest that ARBs conferred cerebrovascular effects independent of BP (RR, 1.00; 95% CI 0.90-1.10; p=0.956) (Figure 5.17 and table 5.6)

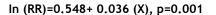
5.6.2.2 Sensitivity analysis

The PRoFESS trial was initially excluded from the adjusted analysis, as it had an extreme outlier percent weight of 30.8% relative to the total weight accorded to study. The result remained unchanged (RR, 1.03; 95% CI 1.01-1.06; p=0.002). Seven trials with CCBs were excluded. The result remained unchanged in terms of directionality, but lost its statistical significance (RR; 1.00; 95% CI 0.96-1.05; p=0.848 Removal of three trials with diuretics comparator arms yielded similar BP dependent effects (RR, 1.03; 95% CI 1.01-1.6; p=0.001) (see Figure 5.18)

Table 5-5 Meta-regression of related and unrelated SBP differences by ARBs on stroke (unadjusted and adjusted models)

			Slope			Intercept		Between study variance					
Variable	Studies	RR	95% CI	P value	RR	95% CI	P value	Tau ²	l ² residual	Р	R ²		
	(n)								(%)	value	(%)		
Null model (no covariates) 0.0176 35.15 0.027 -													
Univariate analysis (Unadjusted)													
Achieved SBP differences (mmHg)	32	1.03	1.00-1.06	0.020	1.00	0.90-1.10	0.956	0.0100	23.27	0.123	43		
Achieved DBP differences (mmHg)**		1.04	0.98-1.11	0.146	0.97	0.87-1.08	0.667	0.0154	32.21	0.045	12		
Baseline SBP (mmHg)		0.99	0.99-1.01	0.417	1.39	0.51-3.73	0.512	0.0180	34.24	0.034	0		
Mean age (Years)		0.97	0.95-0.99	0.025	4.58	1.12-18	0.034	0.0142	26.42	0.091	19		
Male (%)		1.00	0.99-1.08	0.136	0.77	0.60-0.99	0.043	0.0141	27.05	0.085	20		
DM (%)		1	1-1.007	0.009	0.82	0.73-0.92	0.001	0.0119	19.59	0.168	32		
Duration of follow-up (Years)		0.93	0.85-1.01	0.117	1.20		0.286	0.0160	31.66	0.049	9		
Sample size (n)		1.00	1.00-1.01	0.419	0.88	0.77-1.02	0.082	0.0173	33.58	0.037	2		
Multivariate analysis (Adjusted)				L			L	L	L	L			
Achieved SBP differences (mmHg)*	32	1.03	1.01-1.06	0.001	1.72	0.49-5.95	0.386	0	0	0.692	100		
Abbreviation: Tau ² = estimated the a	mount of I	neteroge	eneity (betwe	en-study	varianc	e) not explai	ned by th	e covariat	e; I² residual	= proport	tion of		
remaining observed variance due to t	rue variati	on in eff	fect size										
*The analysis was adjusted for DM (%)	, mean ag	e (years)), Male (%)										
** Achieved DBP differences highly co	rrelated w	ith achie	eved SBP diff	erences (r	=-0.93)								

In (RR)=0.003+ 0.035 (X), p=0.020



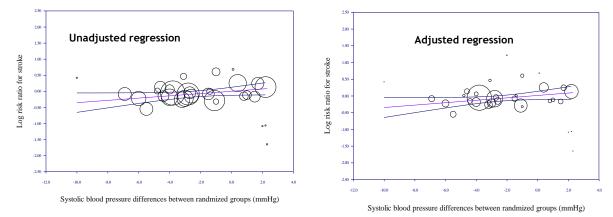
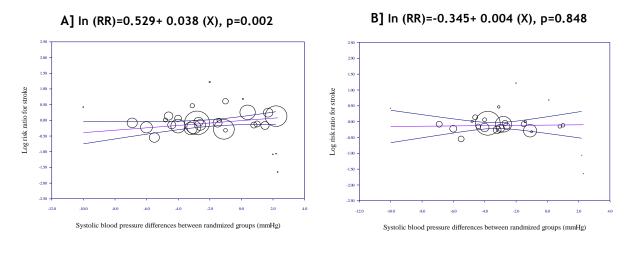
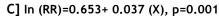


Figure 5-17 Adjusted and unadjusted meta-regression analysis of relationship between RR of stroke and difference in achieved SBP (mmHg) between randomized groups for ARBs trials.

Each study is represented by a circle. The size of each circle is proportional to that study's weight in the analysis (inverse-variance weighted). A negative value in x-axis indicates lower achieved SBP in treatment group than control group





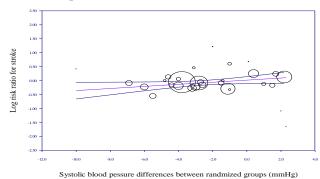
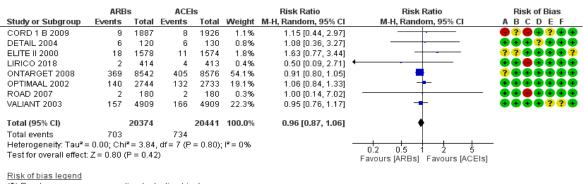


Figure 5-18 Adjusted meta-regression analysis of the relationship between RR for stroke and difference in achieved SBP (mmHg) between randomized groups for ARBs trails [Sensitivity analysis].

Excluding trials with A] PRoFESS; B] Diuretics as comparator, and C] Sample size < 1000.

5.7 Direct comparison of ACEIs and ARBs on risk of stroke: meta-analysis

Figure 5.19 shows a meta-analytical summary of the trials directly comparing ARBs and ACEIs on risk of stroke. Altogether, data were available from 8 trials that enrolled 40,815 participants with 1437 reported to have had a stroke. Individually, the trials reported an equivalent effect from ARBs and ACEIs. The ONTARGET trial accounted for a larger weight (54.1%) and was then followed by VALIANT (22.3%). The point estimate from direct comparison trials indicates a 4% lesser stroke lowering affect from ARB therapy than for ACEI RR, 0.96 (95% CI 0.87-1.06; p=0.42), though the confidence interval crosses the line of null effect. The assessment of heterogeneity showed no variation between the trials (chi-square test p-value =0.80 and $I^2 = 0$ %). As the results of no heterogeneity among the trials Tau²=0, the meta-analytical summary generated by a FE model agreed with the RE model (see Figure 5.20).



(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias) (C) Blinding of participants and personnel (performance bias)

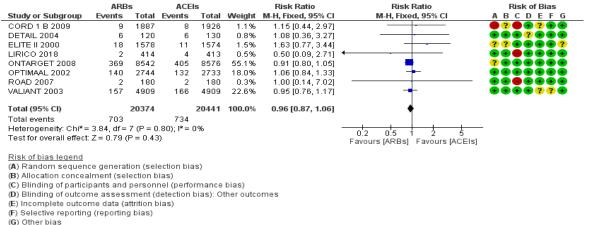
(D) Incomplete outcome data (attrition bias)

(E) Selective reporting (reporting bias)

(F) Other bias

Figure 5-19 Forest plot showing effect of ARBs versus ACEIs on risk of stroke (RE model)

CI: confidence interval; RE: random-effects; M-H: Mantel-Haenszel. For studies acronyms, see list of definition/ abbreviations



(G) Other blas

Figure 5-20 Forest plot showing effect of ARBs versus ACEIs on risk of stroke (FE model)

CI: confidence interval; FE: fixed-effect; M-H: Mantel-Haenszel. For studies acronyms, see list of definition/ abbreviations

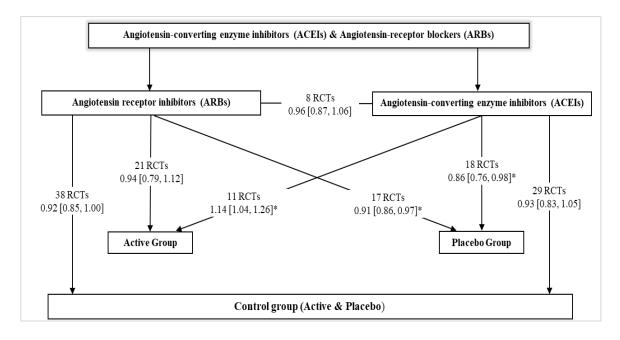


Figure 5-21 Flowchart representing a random-effects (RE) meta-analytical summary of the effectiveness of ACEIs and ARBs on risk of stroke

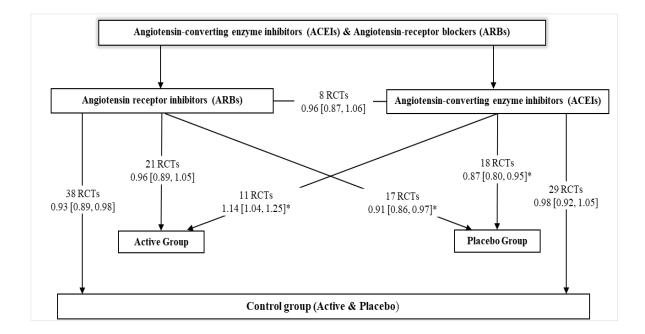


Figure 5-22 Flowchart representing a fixed-effect (FE) meta-analytical summary of the effectiveness of ACEIs and ARBs on risk of stroke

5.8 Discussion

The comprehensive meta-analysis and meta-regression analysis presented here included data from 75 RCTs with 297,451 patients-years of follow-up. The main finding is that when compared to a placebo, ARBs and ACEIs similarly reduced the risk of stroke; however, this was not evident when compared with non-RAS blocker therapy. A meta-regression using data from 58 RCTs showed reductions in stroke risk by ACEI and ARB to be directly associated with BP reduction, with no evidence of any BP-independent effects. Evidence from head-to-head trials demonstrated that ARBs may be slightly more protective than ACEIs against the risk of stroke.

Clinically meaningful differences are detectable in the cerebrovascular activity of ACEIs and ARBs. These emerged from the findings of the PRoFESS and HOPE trials, despite their methodological variation (Yusuf et al., 2008a, Yusuf et al., 2000). This finding was supported by evidence from the experimental data indicating that ARBs therapy, at least theoretically, offers unique dual actions on RAAS. In 1986, researchers first hypothesized that increased Ang-II by stimulating renin secretion through sodium depletion from diuretics or by interruption of the negative feedback from ARBs, might have a beneficial effect on cerebrovascular circulation (Brown and Brown, 1986). The basis for this hypothesis is that the vasoconstriction mediated by Ang II in the proximal cerebral arteries will modulate cerebral blood flow, thereby protecting the smaller, more fragile distal cerebral vessels, which are vulnerable to intracellular haemorrhage. However, this hypothesis can only explain the prevention of haemorrhagic but not ischemic stroke. In normotensive rats, injured by cerebral artery occlusion and pre-treated with candesartan or ramipril at sub hypotensive doses, the infarct size was reduced by ARB, and not by ACEI (Krikova et al., 2008).

Furthermore, it has been postulated experimentally that Ang II is involved in the physiological mechanisms that protect against cerebral ischemia mediated by non- AT_1 receptor - AT_2 and AT_4 receptors. Thus, ARBs elevate the levels of Ang II by blunting the AT_1 -mediated negative feedback with subsequent stimulation of unopposed AT_2 . Thereby, this facilitates the recruitment of collateral vessels, and increases neuronal resistance to anoxia (Fournier et al., 2004) attenuating the pro-thrombosis, inflammation, and endothelial dysfunction that mediates atherosclerosis (Aponte and Francis, 2012). Additionally, it has been suggested

that circulating Ang II is rapidly cleaved to Ang III, which in turn is cleaved to Ang IV, triggering AT₄-mediated nitric-oxide-dependent intracellular hemodynamic mechanisms (Kramar et al., 1998). The hypothesised protective effects of AT_2 and AT₄ blockage were confirmed by study using an experimental rat embolic stroke model pre-treated with lisinopril or candesartan (Faure et al., 2008). This study demonstrated a protective effect from pre-treatment with candesartan after an acute stroke and diminished after administration of AT₂ and AT₄ antagonists. Moreover, dual blockage of AT_2 and AT_4 not only abolishes cerebro-protective effect but also showed a deleterious effect similar to that from lisinopril pretreatment. This hypothesis was followed by a meta-analysis, which examined the relative risk of stroke from drugs, which potentially increased or decreased formation of Ang-II. This study demonstrated that stroke risk reduction was significantly smaller with angiotensin-decreasing drugs than with angiotensinincreasing drugs (P<0.00001) (Boutitiea et al., 2007). In contrast, the benefit of ACEIs on AT₂ receptor-dependent cerebro-protection might be mitigated by reducing the circulating Ang II level.

Our univariate linear meta-regression analysis of 58 trials suggests that stroke risk by ACEI and ARB is largely attributable to BP reduction, with no evidence of any BP-independent effects. These results were consistent with the adjusted model accounting for other predicators that may explain residual heterogeneity, such as DM, mean age, male gender and baseline SBP. Other established risk factors for stroke, such as smoking, BMI, IHD, dyslipidaemia and AF may also have an impact (Poorthuis et al., 2017), but we were limited by the data available from the included trials. Our results are in accordance with & add to meta-regression analyses conducted by the Blood Pressure Lowering Treatment Trialists Collaboration (BPLTTC). The meta-regression by BPLTTC revealed that both classes have a comparable BP-dependent reduction in risk of stroke & no BP independent benefit was apparent for either drug classes (Turnbull, 2007). It is crucial to emphasize that the methodology of the BPLTTC review did not include two large trials (HYVET and MOSES) and had limited exploration of potential confounders.

Furthermore, evidence of the significant heterogeneity of stroke in contributing to trials was seen in one subgroup comparison, i.e. those with ARBs versus active therapy. Nevertheless, the multivariate meta-regression shows that the observed heterogeneity among the RR of stroke in ARBs trials was substantially explained by the SBP differences achieved, males (%), DM (%) and mean age (years). Despite the overall test of heterogeneity across the ACEIs trials being non-significant, the meta-regression reveals that the 67% diversity across trials could be related to achieved SBP differences and the percentage of males in each trial.

It is noteworthy that the protective effect observed from the ACEIs versus placebo on the stroke risk were primarily driven by the HOPE trial, and the overall effect estimate associated with the 7% relative stroke risk reduction. The HOPE trial assessed the role of ramipril in patients at high-risk of CV events with a mean age of 66 years. Ramipril showed a 31% lower stroke risk compared to the placebo and was associated with a reduction in office blood pressure (OBP) of only 3/2 mmHg BP. However, based on previous epidemiological studies, a reduction of 3/2 mmHg BP among middle age patients would be expected to reduce risk of stroke by around 13%, even within the normal range of BP (Collins et al., 1990, Lewington et al., 2002). Thus, the HOPE findings for stroke reduction were substantially more than would be expected based on the BP reduction observed in the trial. This led to the hypothesis that the majority of stroke risk reduction must be attributable to an effect independent of BP. A simpler explanation may be that in the HOPE trial, the OBP underestimates the true BP lowering effect achieved in the trial. According to the HOPE protocol, ramipril was given once daily at bedtime, and OBP measured during the day, and this may result in an underestimation of the 24-hour reduction in BP. In a small sub-study by HOPE, ramipril was taken at night and then followed by 24-hr ambulatory BP measurement which showed an average 24-hour ambulatory BP reduction 10/4 mmHg (Svensson et al., 2001). If a similar reduction occurred in all HOPE participants, the benefits would be associated with about a 40% lower risk of stroke (Lewington et al., 2002); corresponding to actual benefit. A further explanation, which may underpin the cerebrovascular advantage of ARBs and ACEIs, relates to their ability to prevent the onset of atrial fibrillation (Zhao et al., 2015, Wolf et al., 1991) and diabetes mellitus (Bangalore et al., 2016) which are strong risk factors for stroke. However, these were not planned outcomes of our study, making it difficult to draw firm conclusions about their role in mediating stroke reduction.

In our analysis of ACEIs and ARBs compared to active treatment, ARBs therapy was as effective as the active treatment group in terms of stroke outcome, while ACEIs had a detrimental effect. It ought to be highlighted here that the impact of ACEIs and ARBs appears to be dependent on the comparator drug, namely in trials using long-acting DHP CCBs and diuretics. Although active therapies were superior to ACEIs in terms of the prevention of stroke, this result was mainly driven by the ALLHAT trial. When ALLHAT was excluded from the analysis, the risk ratio for stroke decreased to a non-significant 8%. In ALLHAT, the lisinopril arm showed a 21% and 14% higher incidence of stroke compared to amlodipine and chlorthalidone, respectively. However, the SBP in the lisinopril group was 1.2 and 2 mmHg higher than in the amlodipine and chlorthalidone groups respectively, suggesting a possible reason for the higher stroke risk arising with lisinopril. Although the differences in SBP appeared to be clinically negligible, data from an individual-patient study of one million patients without vascular diseases reported that a 2 mmHg lower than usual SBP would clinically translate to a 10% lower risk of stroke mortality (Lewington et al., 2002). Additionally, long-duration DHP CCBs may provide better cerebrovascular protection through their unique properties that reduce carotid intima-media thickening (CIMT), when compared with RAS blockers independent of BP reduction (Mason, 2002, Verdecchia et al., 2005b, Wang et al., 2006). Moreover, ARBs, diuretics and to some extent long-acting DHP CCBs are hypothetically able to elevate circulating Ang-II, by stimulating renin secretion, diminishing negative feedback, sodium depletion (Martinez-Maldonado et al., 1990) and sympathetic activation (Grossman and Messerli, 1997). Consequently, these may hypothetically activate AT_2 and AT_4 receptors (Fournier et al., 2004).

Despite methodological differences, our finding corroborates the results from previous meta-analyses. For example, pooled stroke data from 19 RCTs in patients with DM by Cheng and colleagues showed that both ACEIs and ARBs were not associated with any decrease in the risk of stroke in patients with DM (Cheng et al., 2014). They found ACEIs but not ARBS reduced all-cause mortality, CV mortality, and major CV events, and concluded that ACEIs therapy should be considered a first-line therapy to limit excess mortality and morbidity in this population. An explanation of their results may be that they combined both comparators, placebo and active treatments in their analysis. Another, conflicting result arose from a recently published meta-analysis of 37 ARBs RCTs in patients with various co-morbidities, which demonstrated a significant 9% stroke reduction with ARBs therapy compared with active therapy (Bangalore et al., 2011). However, this meta-analysis included trials that directly compared ARBs with ACEIs, and the effects were largely contributed to by ONTARGET, OPTIMAAL, VALIANT and ROAD; thereby they were able to influence the overall evidence.

The superior cerebrovascular protective benefits of ARBs than ACEIs were first demonstrated by a BPLTTC meta-analysis of six head-to-head trials (Reboldi et al., 2008). This meta-analysis assessed the effect of ARBs versus ACEIs on CV events among patients at high CV risk with or without HTN. They reported an 8% lower stroke risk with ARBs compared to ACEIs (OR, 0.92; 95% CI 0.85-0.99; p=0.036). However, in their meta-analysis, the results appear to be driven by stroke data from VALIANT which favoured valsartan. However, published stroke data from VALIANT showed that they included multiple events per patient, and unpublished data from VALIANT subsequently provided by the FDA showed the number of events in both arms were almost similar (Targum et al., 2004). Furthermore, they included the ARB and ACEI combined-regimen arms of the ONTARGET and VALIANT trials. Despite these limitations, the authors concluded that the observed benefits might slightly support ARB's unique cerebrovascular protection beyond any expected BP reduction. Our meta-analysis compared ARBs to ACEI from eight RCTs, and included unpublished data from VALIANT, demonstrating a slightly more protective from ARBs over ACEIs on preventing stroke but did not achieve the significance level.

Although ACEIs are as effective as ARBs at preventing stroke, our subgroup analysis did not find any reduction in stroke-risk with ACEIs in patients aged \geq 65 years when compared with either the placebo or active control. In contrast to ACEIs, ARBs showed a benefit in the form of reduction in stroke risk in such populations. A possible explanation may be that the cerebrovascular protection of ACEIs, in contrast to ARBs, in the older population is attenuated by a reduction in circulating Ang-II levels, and thus decreased AT₂ receptor-dependent cerebrovascular protection (Fournier et al., 2004). These results are consistent with the other previous meta-analysis. In 2016, a meta-analysis was conducted by

Bavishi et al. (2016) to assess the long-term efficacy and safety of ACEIs in patients aged 65 or more with various comorbidities. Even though they demonstrated that ACEIs failed to prevent stroke in this population, they included trials compared with ARBs as VALIANT, OPTIMAAL and ONTARGET. Moreover, Elgendy et al. (2015) conducted a meta-analysis of 14 RCTs showed that benefit of ARBs compared with control in older patients was strongest for stroke reduction (RR: 0.93, 95% CI: 0.87-0.99, P = 0.03).

5.8.1 Strengths and limitations

To the best of author's knowledge, this meta-analysis has included up-to-date RCTs (ATTEMPT-CVD, CHIEF, EFFERVESCENT, LIRICO and PREVER-Treatment) which has never been incorporated into most recent review (Bangalore et al., 2016). Moreover, this meta-analysis included unpublished stroke data from ADVANCE, DETAIL, ROADMAP, ORIENT, RENAAL and VALIANT trials, which will increase the quality of evidence. Therefore, the results should increase the precision of the stroke estimates with a narrow overall 95% CI, making type I errors unlikely. The consistency of the results across a series of sensitivity analyses would be support the robustness of the primary results.

However, some limitations have to be mentioned in our analysis. There is significant heterogeneity among the trials of ARBs versus the active group. Nevertheless, heterogeneity was managed by using a RE model for meta-analyses and then investigated by subgroup and meta-regression analyses. Moreover, for ethical reasons, the majority of the included trials clearly permitted usage of non-study RAS blockers and other antihypertensive agents when indicated. Therefore, it is difficult to discern whether these medications could influence the observed results. It is noteworthy that despite the possibility of variation among specific subgroups, subgroup analyses would have been underpowered to detect it. Moreover, the current meta-analyses and meta-regression are based on aggregate data, which limited our ability to investigate other trials' characteristics. Therefore, the possibility of ecological bias cannot be excluded. Since meta-regression is based on published trial-level data, the relationship described by a meta-regression is an observational association across trials and not a causal relationship. The adjusted R² and residual heterogeneity (Tau²) value from the

multivariate regression of ACEIs trials is only 67%, suggesting a possibility of residual heterogeneity which might be due to other uncontrolled variables. Therefore, an individual-patient data meta-analysis is essential to eliminate many of these limitations. Although a comprehensive search of databases and clinical trials registers was carried-out, there remained the possibility of missing studies that have not been published.

5.9 Conclusion

This meta-analysis of RCTs, using data from 297,451 patient-years of follow-up confirms the beneficial effects of ARBs and ACEIs on the risk of stroke when compared with a placebo in patients with high CV risk. The finding from direct comparison trials also supports the view that ARBs may be slightly more protective than ACEIs against the risk of stroke However, no additional benefit was seen for ACEIs or ARBs when compared with other BP lowering agents. The observed benefit of both classes appeared to be related directly to the magnitude of SBP reduction.

6 Angiotensin-converting enzyme inhibitors (ACEIs) versus angiotensin receptor blockers (ARBs) for heart failure (HF) prevention

6.1 Introduction

A recent population-based study of around 4 million individuals showed that newly diagnosed HF in UK increased by 12% from 2002 to 2014. This is comparable to the total number of the most common new cases of cancer (breast, prostate, lung, and bowel) combined (Conrad et al., 2018). The most important risk factor for HF is elevated blood pressure (BP). In the Framingham Heart Study (FHS) cohort of 5,143 subjects, hypertension (HTN) had a high population-attributable risk of HF, accounting for 91% of all newly diagnosed HF patients during the 20 years of follow-up (mean 14.1 years) (Levy et al., 1996). Moreover, multivariable analyses revealed that 39% of HF cases in men and 59% in women are a result of elevated BP. At 80 years of age, the lifetime risk of HF was about 20% in the Framingham cohort; this risk doubled for patients with a BP of 160/100 mm Hg compared to 140/90 mm Hg (Lloyd-Jones et al., 2002). Among hypertensive subjects, myocardial infarction (MI), diabetes, left ventricular hypertrophy (LVH), and valvular heart disease were also predictive of increased risk of CHF in both sexes (Conrad et al., 2018). Despite major improvements in the detection and treatment of these conditions, HF incidence remains high.

6.2 Rationale of the present study

The rationale for therapeutic indications for ACEIs and ARBs across a variety of CV morbidities is their ability to attenuate the harmful effects of Ang II. While both drug classes inhibit stimulation of AT₁, there are significant differences between them. For instance, ACEIs reduce Ang II but may also stimulate Ang II formation to shift to a novel non-ACEI enzymatic pathway, which can potentially reduce the efficacy of long-term ACEIs therapy. ARBs antagonize the actions of Ang II mediated by AT₁ but can increase circulating Ang II levels and, consequently, activate other receptor subtypes, AT_2 and AT_4 (Levy, 2004). The non-classical pathway and tissue RAAS are described in **Chapter 1, Section 1.3.3**.

The differences in the pharmacological actions of ACEIs and ARBs suggest that their efficacies may not be equivalent and, hence, they are not interchangeable. A comparable BP-lowering effect of ACEIs and ARBs have been inferred by their similar effects on CV protective outcomes in hypertensive subjects (Thomopoulos et al., 2015b). Clinical studies have demonstrated conflicting results in regard to the efficacy of ACEIs and ARBs in reducing risk of HF in a wide spectrum of patients (Yusuf et al., 2008b, Yusuf et al., 2000). Nevertheless, the use of ARBs is recommended in the case of ACEIs intolerance in most international guidelines on the management of HTN and its compelling indications (Knuuti et al., 2019, Williams et al., 2018).

There is considerable evidence supporting a beneficial effect of ACEIs on HF outcomes. In the HOPE trial, ramipril reduced the risk of HF by 22% in 9,297 participants with high CV risk (80.4 % with CAD, 46.8% HTN and 38.4% diabetes) (Yusuf et al., 2000). There was a greater reduction in HF rate in patients with a baseline systolic blood pressure (SBP) above the median (139 mmHg) (RR, 0.67) compared with those below the median (RR, 0.91); P_{interaction}=0.024. There was no difference in HF outcomes based on CAD status - ramipril reduced HF rate both in those with (RR, 0.87) and without MI (RR, 0.78). In the EUROPA trial, perindopril showed a 39% lower risk of HF compared with the placebo which was greater than expected from the observed reduction in BP achieved by perindopril (mean 5/2 mmHg) (Fox et al., 2003). A meta-regression analysis showed that an antihypertensive-induced reduction in SBP of 10 mmHg could be expected to lower HF by 28% (Ettehad et al., 2016). Although these studies broaden the identified CV-protection role of ACEIs, it remains uncertain whether the observed effects are related to BP lowering or not.

The relationship between BP reduction by ARBs and HF risk is not always straightforward. The ACTIVE-I trial assessed the efficacy of irbesartan 300mg daily among patients with AF and history of HTN, followed up for a mean of 4.1 years. There was a 13% reduction of HF risk by irbesartan (RR, 0.87;95% 0.78-0.98), despite a modest reduction in mean SBP (-2.9 mmHg). This suggests that a mechanism independent of BP lowering may play a role. However, in this trial, 60% of participants in each group also received ACEIs. Conversely, the PRoFESS and TRANSCEND trials did not show any benefit of ARBs on HF risk, though the

achieved mean SBP was lower in the ARBs group compared to the placebo, by 3.8 mmHg in the PRoFESS study and 4.2 mmHg in the TRANSCEND trial.

The main aims of this study are: (1) to compare the relative efficacy of ACEIs and ARBs in reducing HF risk in patients with or at high risk of CVD, by meta-analysis of all prospective RCTs; and (2) to investigate whether the observed effects of ACEIs and ARBs can be explained by BP reduction using meta-regression analysis.

6.3 Methodology

6.3.1 Search strategy and selection criteria

Direct and indirect comparisons between ACEI and ARB therapies were conducted on risk of HF. Full descriptions of the methods used for this systematic review have been described previously in **Chapter 2, Section 2.1.**

6.3.2 Data extraction and source of data

The outcome of interest is HF risk. The extracted baselines from included RCTs were percentage of patients with history or current evidence of HF, NYHA Classes of HF, whether the HF is a predefined outcome or not, and adjudication of HF events.

HF data for the ADVANCE trial was available as tabulated data on the sponsor's clinical data website: Servier Laboratories Pharmaceutical Company (Servier Laboratories, 2009). HF event data for the VALIANT trial was reported by the Center for Drug Evaluation and Research (CDER) of the FDA (Targum et al., 2004). Data for the remaining studies was published as tabulated data in the primary studies. HF outcome in the PREVER-Treatment study was supplied by the trial's primary author (Dr Flávio D. Fuchs of Hospital de Clinicas de Porto Alegre, Brazil). In Chan et al.'s study, data was pre-defined in protocol and HF events was reported as a combined endpoint in way that cannot be extracted. The J-RHYTHM II, NTP-AF, PREVER-treatment, and ROADMAP trials, zero HF events were reported. Source of data and overall quality of included trials are summarized in **tables E-1 and E-2 (Appendix E)**

6.3.3 Statistical analysis

6.3.3.1 Meta-analysis

The data synthesis and analysis procedures used have been fully described in **Chapter 2, Section 2.1.9.** To check the robustness of the primary findings, a series of sensitivity analyses were carried out, as follows: excluded trials with 1) poor methodological quality; 2) naïve participants (without background use of study drugs); and 3) participants with symptomatic HF (NYHA class II-IV). To check whether the primary analyses were dependent upon certain characteristics of trials, the main results were stratified as follows: 1) subclasses of ACEIs and ARBs; 2) type of active comparator; 3) population clinical setting; 4) mean age of patients.

6.3.3.2 Meta-regression analysis

A full description of the meta-regression analysis method used has been described previously in **Chapter 2, Section 2.1.10.** To determine the validity of the main meta-regression results, a series of sensitivity analyses were conducted by omitting trials with: 1) CCBs as comparator group; 2) considerable weight; and 3) participants with symptomatic HF (NYHA class II-IV).

6.4 Results

HF events were reported in 70 RCTs that enrolled 295,450 participants with an average follow-up of 3.4 years (range 1 to 5 years) comparing ACEIs and ARBs with a placebo, active control, or with each other. Of these, 29 RCTs compared ACEIs with a control, with an average follow-up of 3.5 years (ranging from 1 to 6 years) and an average patient age of 63.3, while 36 RCTs were ARB trials with an average follow-up of 3.3 years (range 1 to 6 years) and average patient age of 64.2. In addition, 7 trials compared ARBs to ACEIs directly, with an average follow-up of 3.6 years (range 1 to 6 years) and an average patient age of 64.2. In addition, 7 trials compared ARBs to ACEIs directly, with an average follow-up of 3.6 years (range 1 to 6 years) and an average patient age of 64.2 (see Appendix B: Characteristics of included studies, and Appendix C: Methodological quality of included studies). HF events were reported as predefined outcomes or adverse events: 1) 91.5% of the included trials reported HF as a pre-specified outcome; 2) seven RCTs reported HF as an adverse event (ROAD, COPE, Hou et al. (group 2), QUO VADIS, ANTIPAF, HIJ-CREATE, and Kawamura).

6.5 ACEIs and risk of HF

6.5.10verall treatment effects

Figure 6.1 shows a random effects (RE) meta-analysis summary of the efficacy of ACEIs on HF risk compared to placebo or active control. HF data was reported in 29 RCTs comprising 119,211 participants with 5,520 reported events. Overall, the HF incidence was lower in the ACEIs compared to the control group, at 4% and 5%, respectively. ACEIs therapy reduced the risk of HF by 17% compared to the control (RR, 0.83; 95% CI, 0.76-0.92; P=0.0003). The results from placebo-controlled trials contributed 70.9% of the overall combined weight, driving the overall pooled effect estimate.

For stratification of control groups, 18 RCTs used a placebo as a comparator; these enrolled 72,983 participants and reported 2,955 HF events. The incidence of HF was higher in patients allocated to the placebo compared to those treated with ACEIs, at 4.5% and 3.6% respectively. Remarkably, the error bars of larger weighted trials (CCS-I, EUROPA, HOPE, PEACE, and PROGRESS) did not cross the null effect line, representing a greater contribution to the pooled effect estimate in the meta-analysis. ACEIs showed a 20% lower HF risk compared with placebo (RR, 0.80; 95% CI 0.74, 0.87; P= 0.00001). The assessment of heterogeneity showed no evidence of variation among studies (p value of chi-square test=0.36 and $I^2 = 8\%$).

Eleven RCTs randomized patients to ACEIs or active treatment. These RCTs enrolled 46,909 participants and reported 2563 HF events. The incidence of HF was lower in ACEI-treated patients (4.9%) compared to active control (5.7%). There was no clear beneficial effect on HF from ACEIs compared to the active control (RR 0.92; 95% CI 0.76-1.10; P=0.36). The pooled RR was mainly influenced by the ALLHAT study, which contributed 11.7% of the overall estimate. The sensitivity analysis after omitting ALLHAT yielded an RR of 0.85 (95% CI 0.67-1.07; p=0.16) (see Figure 6.3).

The chi-square test of heterogeneity showed low variation between trials, which may be due to the statistical variety of the Cai et al. trial (P value=0.19 and $I^2=27\%$)

(judged as a high risk of bias trial). After excluding the Cai et al. trial, I^2 reduced to 0% (RR, 1.03; 95% CI 0.95-1.12)

The FE model presented in **Figure 6.2** shows that summary estimates of placebo RCTs was not influenced by the low heterogeneity among trials. However, the HOPE trial weight increased from 10.8% to 19.8%. The summary effect estimates of active-controlled trials changed, likely due to the presence of small study effects, as this group had only one large trial, ALLHAT. The ALLHAT trial was assigned more weight (31.7%), thus it greatly influenced the pooled effect estimates (RR 1.00; 95% CI 0.93-1.09; p=0.92).

Finally, assessment of the funnel plot shown in **Figure D-2** (**Appendix D**) demonstrated a symmetrical distribution of studies at the top of the plot. A gap at the bottom graph appears because small studies might be missing, likely due to reporting bias.

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Study or Coloran	ACE		Cont		187-1-1-4	Risk Ratio	Risk Ratio	Risk of Bias
Study or Subgroup	Events	lotal	Events	Total	weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl	ABCDEFG
1.1.1 ACEIs vs Placebo								
ADVANCE 2007	197	5569	199	5571	8.5%	0.99 [0.82, 1.20]		
APRES 2000	6	80	12	79	1.0%	0.49 [0.19, 1.25]		$\bullet \bullet $
CAMELOT (Placebo) 2004	4	673	5	655	0.5%	0.78 [0.21, 2.89]		$\bullet ? \bullet \bullet \bullet \bullet ?$
CCS-I 2001	139	3391	186	3358	7.9%	0.74 [0.60, 0.92]		$\bullet \bullet \bullet ? ? \bullet \bullet$
DIABHYCAR 2004	85	2443	102	2469	6.2%	0.84 [0.64, 1.12]		$\bullet \bullet $
DREAM 2006	12	2623	4	2646	0.7%	3.03 [0.98, 9.37]		
EUROPA 2003	63	6110	103	6108	5.5%	0.61 [0.45, 0.83]		??
HOPE 2000	417	4645	535	4652	10.7%	0.78 [0.69, 0.88]	-	?
Hou et al (group 2) 2006	3	112	5	112	0.5%	0.60 [0.15, 2.45]		\bullet ? \bullet \bullet \bullet \bullet
IMAGINE 2008	15	1280	14	1273	1.6%	1.07 [0.52, 2.20]		
PART-2 2000	7	308	9	309	0.9%	0.78 [0.29, 2.07]		•••••
PEACE 2004	115	4158	152	4132	7.2%	0.75 [0.59, 0.95]		??
PEP-CHF 2006	97	424	106	426	7.2%	0.92 [0.72, 1.17]		
PHARAO 2008	14	505	19	503	1.8%	0.73 [0.37, 1.45]		
PREAMI 2006	22	631	30	621	2.6%	0.72 [0.42, 1.24]		
PREVEND IT 2007	0	431	2	433	0.1%	0.20 [0.01, 4.17]	←	
PROGRESS 2001	113	3051	151	3054	7.2%	0.75 [0.59, 0.95]		
QUO VADIS 2001	6	75	6	73	0.8%	0.97 [0.33, 2.88]		??
Subtotal (95% CI)		36509		36474	70.9%	0.80 [0.74, 0.87]	•	
Total events	1315		1640					
Heterogeneity: Tau ² = 0.00; Chi ²		lf = 17 (F		I² = 8%				
Test for overall effect: Z = 5.48 (F	•		,					
1001101 0101011 010002 2 - 0.40 (·/						
1.1.2 ACEIs vs Active								
AASK 2002	20	436	30	658	2.5%	1.01 [0.58, 1.75]		
ABCD (normotensive) 2002	12	246	11	234	1.3%	1.04 [0.47, 2.31]		2
ALLHAT 2002	612	9054		24303	11.6%	1.04 [0.95, 1.14]	_	
ANBP2 2003	69	3034	78	3039	5.4%	0.88 [0.64, 1.22]		2000000
Cai et al* 2001	21	478	34	344	2.7%	0.44 [0.26, 0.75]		2222002
CAMELOT (Active) 2004	4	673	34	663	0.4%			6 ? 6 6 6 ?
	4	191				1.31 [0.30, 5.85]		2000000
CARMEN (combination) 2004			12	191	1.0%	0.58 [0.23, 1.45]		2000000
CARMEN (monotherapy) 2004	16	190	12	191	1.6%	1.34 [0.65, 2.76]		
J-MIND 2001	0	208	1	228	0.1%	0.37 [0.01, 8.92]	· · · · · · · · · · · · · · · · · · ·	220200
JAMP 2004	14	466	10	422	1.3%	1.27 [0.57, 2.82]		3 3 6 3 3 6 6
JMIC-B 2004	9	822	12	828	1.2%	0.76 [0.32, 1.78]		
Subtotal (95% CI)		15808		31101	29.1%	0.92 [0.76, 1.10]	-	
Total events	784		1779					
Heterogeneity: Tau² = 0.02; Chi²	•	lf = 10 (F	? = 0.19);	I ² = 27%)			
Test for overall effect: Z = 0.91 (F	P = 0.36)							
T-1-1/05% OB		50047		07575	100.00	0.0010 70.0001	•	
Total (95% CI)		52317		67575	100.0%	0.83 [0.76, 0.92]	•	
Total events	2099		3419					
Heterogeneity: Tau² = 0.02; Chi²			? = 0.008); I² = 43'	%		0.2 0.5 1 2 5	
Test for overall effect: Z = 3.65 (F	P = 0.0003)					Favours [ACEI] Favours [control]	
Test for subgroup differences: C	>hi² = 1.65	, df = 1 (i	P = 0.20)	, I² = 39.4	4%		rateale plozif i ateale [control]	
Risk of bias legend								
(A) Random sequence generati	on (select	ion bias))					
(B) Allocation concealment (sel	ection bias	;)						
(C) Blinding of participants and			nance bia	as)				
(D) Blinding of outcome assess					nes			
(E) Incomplete outcome data (a								

(E) Incomplete outcome data (attrition bias) (F) Selective reporting (reporting bias)

(G) Other bias

Figure 6-1 Forest plot showing of ACEIs on risk of HF, stratified by comparison group (placebo vs. active). Overall: 29 trials (RE model).

* Trial responsible for heterogeneity, excluding it resulted an I² of 0% (RR, 1.03; 95% CI 0.95-1.12) compared with active group. The diamond indicates the pooled risk ratio (and 95% CI) or the overall effect for HF risk. CI: confidence interval; RE: random-effects; M-H: Mantel-Haenszel. For studies acronyms, see list of definition/ abbreviations

	ACE		Cont	rol		Risk Ratio	Risk Ratio	Risk of Bias
Study or Subgroup	Events		Events		Woight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl	ABCDEFG
1.1.1 ACEIs vs Placebo	LVCIIIS	Total	LVCIILS	Total	weight	M-11, 11ACu, 5570 CI	m-n, nzeu, 55% ci	ADCDLIG
ADVANCE 2007	197	5569	199	5571	7.4%	0.99 [0.82, 1.20]		
APRES 2000	197	5569	199	79	0.4%	• • •		
CAMELOT (Placebo) 2004	4	673	5	655	0.4%	0.49 [0.19, 1.25] 0.78 [0.21, 2.89]		
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HOPE 2000	417	4645	535	4652	3.0% 19.8%	0.78 [0.69, 0.88]	+	2000000
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QUO VADIS 2001	6	75	6	5054	0.2%	0.97 [0.33, 2.88]		??
Subtotal (95% Cl)	0	36509	0	36474	60.8%	0.80 [0.75, 0.86]	•	
Total events	1315	50505	1640	50474	00.070	0.00 [0.1 0, 0.00]	•	
Heterogeneity: Chi ² = 18.41, df =		263118-						
Test for overall effect: Z = 6.21 (F			0.20					
restion overall ellect. Z = 0.21 (r	~ ~ 0.0000	0						
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ABCD (normotensive) 2002	12	246	11	234	0.4%	1.04 [0.47, 2.31]		? • • • ? • ?
ALLHAT 2002	612	9054	1576	24303	31.7%	1.04 [0.95, 1.14]	+	
ANBP2 2003	69	3044	78	3039	2.9%	0.88 [0.64, 1.22]	<u> </u>	? • • • • • •
Cai et al* 2001	21	478	34	344	1.5%	0.44 [0.26, 0.75]		?????
CAMELOT (Active) 2004	4	673	3	663	0.1%	1.31 [0.30, 5.85]		•?••••?
CARMEN (combination) 2004	7	191	12	191	0.4%	0.58 [0.23, 1.45]		?
CARMEN (monotherapy) 2004	16	190	12	191	0.4%	1.34 [0.65, 2.76]		? • • • • • •
J-MIND 2001	0	208	1	228	0.1%	0.37 [0.01, 8.92]	· · · · · · · · · · · · · · · · · · ·	?? 🛑 ? 🗣 ?
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Test for overall effect: Z = 0.11 (F	P = 0.92)							
Total (95% CI)		52317		67575	100.0%	0.88 [0.84, 0.93]	•	
Total events	2099	52517	3419	01515	100.070	0.00 [0.04, 0.00]	•	
Heterogeneity: Chi ² = 49.01, df =		0003-18						
Test for overall effect: Z = 4.67 (F			- 4370				0.2 0.5 1 2 5	
Test for subgroup differences: C			/D ~ 0.00	011 8-	0/10		Favours (ACEI) Favours (control)	
= .	/11 - 10.0	/, ui – i	(F < 0.00	101), 11–	94.170			
Risk of bias legend		a na la i a ari	、 、					
(A) Random sequence generati)					
(B) Allocation concealment (sel								
(C) Blinding of participants and (
(D) Blinding of outcome assess			as): Othe	routcon	162			
(E) Incomplete outcome data (at		9						
(F) Selective reporting (reporting (C) Other bias	uas)							
(G) Other bias								

Figure 6-2 Forest plot showing effect of ACEIs on risk of HF, stratified by comparison group (placebo vs. active). Overall: 29 (FE model)

*Trial responsible for heterogeneity, excluding it resulted an I² of 0% (RR, 1.03; 95% CI 0.95-1.12) compared with active group. The **diamond** indicates the pooled risk ratio (and 95% CI) or the overall effect for HF risk. CI: confidence interval; FE: fixed-effect; M-H: Mantel-Haenszel. For studies acronyms, see list of definition/ abbreviations

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	20 12	436 246	30	234	0.6%	1.01 [0.58, 1.75]		2
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		3044	78 34	3039		0.88 [0.64, 1.22]		2222002
Cai et al 2001 CAMELOT (Active) 2004	21 4	4/8	34	344 663	2.1% 0.2%	0.44 [0.26, 0.75]		
	4				0.2%	1.31 [0.30, 5.85]		2000000
CARMEN (combination) 2004	16	191 190	12	191 191	0.7%	0.58 [0.23, 1.45]		2000000
CARMEN (monotherapy) 2004	16	208		228	0.6%	1.34 [0.65, 2.76]		220202
J-MIND 2001			1		0.1%	0.37 [0.01, 8.92]	· · · · · · · · · · · · · · · · · · ·	2202200
JAMP 2004	14	466	10	422		1.27 [0.57, 2.82]		
JMIC-B 2004 Subtotal (95% Cl)	9	822 6754	12	828 6798	0.6% 11.0%	0.76 [0.32, 1.78] 0.85 [0.69, 1.03]		
	4.70	0754	202	0790	11.0%	0.85 [0.09, 1.05]		
Total events	172	0.12 4	203					
Heterogeneity: Chi ² = 10.30, df =		(3); I* = 1	3%					
Test for overall effect: Z = 1.66 (F	$^{2} = 0.10$							
Total (95% CI)		43263		43272	100.0%	0.81 [0.75, 0.86]	•	
Total events	1487	40200	1843	45212	100.070	0.01 [0.1 0, 0.00]	•	
Heterogeneity: Chi ² = 28.95, df=		202118-						
Test for overall effect: Z = 6.40 (F			7 70				0.2 0.5 1 2 5	
Test for subgroup differences: C			n – o eox	17 - 0.00			Favours [ACEI] Favours [control]	
	∠ni== 0.25,	ui = 1 (i	P = 0.62)	, 1- = 0 %				
Risk of bias legend								
(A) Random sequence generati)					
(B) Allocation concealment (sel								
(C) Blinding of participants and								
(D) Blinding of outcome assess			as): Othe	r outcon	nes			
(E) Incomplete outcome data (a		;)						
(F) Selective reporting (reporting	i bias)							
(G) Other bias								

Figure 6-3 Forest plot showing the effect of ACEIs on risk of HF (RE model). [Sensitivity analysis: Excluding ALLHAT trial]

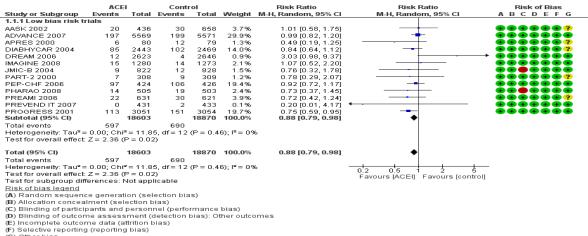
CI: confidence interval; RE: random-effects; M-H: Mantel-Haenszel. For studies acronyms, see list of definition/ abbreviations

6.5.2 Sensitivity analysis

Exclusion of 16 RCTs with poor methodological quality, as shown in **Figure 6.4**, did not make a noticeable difference to the estimates, with an RR of 0.88 (95% CI 0.79-0.98; p=0.02). The PROGRESS trial largely contributed to the statistical direction of the pooled effect estimate. No heterogeneity was detected.

Nine placebo-controlled trials enrolled patients without background usage of RAS blockers before randomisation (naïve patients): APRES, DIABHYCAR, EUROPA, HOPE, Hou et al. (group 2), PEACE, PHARAO, PREVEND IT and QUO VADIS (see **Figure 6.5).** Remarkably, most of the high-weighted trials - EUROPA (10.7%), PEACE (7.2%) and HOPE (5.5%) - enrolled naïve patients. However, exclusion of these trials did not affect the overall estimates (RR, 0.86; 95% CI 0.75-0.99; P=0.04). Minimal heterogeneity was detected (chi-square test p value=0.20 and I²

=28%), most likely driven by the methodological diversity of the DREAM trial. The DREAM trial showed high HF incidence in the ramipril group compared to the placebo, which may be explained by there being more patients in the placebo group on ARBs, lipid-lowering agents, and aspirin at the end of follow-up.



(G) Other bias

Figure 6-4 Forest plot showing the effect of ACEIs on risk of HF (RE model). [Sensitivity analysis: Excluding trials with low methodological quality]

CI: confidence interval; RE: random-effects; M-H: Mantel-Haenszel. For studies acronyms, see list of definition/ abbreviations

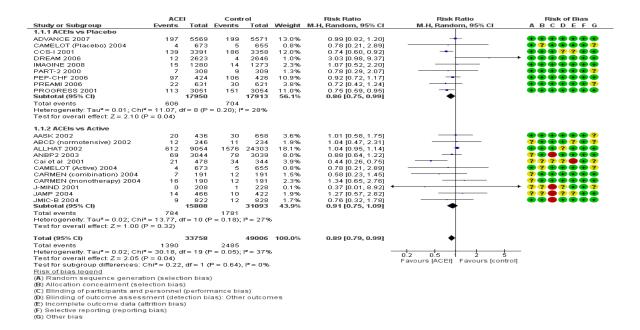


Figure 6-5 Forest plot showing effect of ACEIs on risk of HF (RE model). [Sensitivity analysis: Excluding trials with naive participants]

CI: confidence interval; RE: random-effects; M-H: Mantel-Haenszel. For studies acronyms, see list of definition/ abbreviations

6.5.3 Subgroup analysis

Table 6.1 summarizes the subgroup analyses of the effectiveness of ACEIs on riskof HF.

6.5.3.1 High- versus low-affinity ACEIs

Figure 6.6 shows the RE model summary of ACEIs' effect on HF risk compared with control, stratified based on subclasses of ACEIs: high and low-affinity tissue ACEIs. High-affinity tissue ACEIs showed an 18% reduction in HF risk compared with the control (RR, 0.82; 95% CI 0.75-0.89; p<0.0001). The HOPE trial contributed 25.4% of the pooled effect estimates. Heterogeneity assessment showed no evidence of variation between trials.

Treatment with low-affinity tissue ACEIs showed a statistically non-significant reduced risk of HF (RR, 0.85; 95% CI 0.70-1.04; p=0.11). There was evidence of heterogeneity among trials (p value =0.03 and I²=49%). The non-significant result and heterogeneity were driven by the ALLHAT trial. After excluding ALLHAT, the heterogeneity diminished, with an RR of 0.78 (95% CI 0.66-0.93; p=0.006; I²=7%).

6.5.3.2 Class of active control

Figure 6.7 shows an RE model summary of ACEIs on risk of HF compared with DHP-CCBs, diuretics, beta-blockers, and conventional therapies. When compared with DHP-CCBs (amlodipine and nifedipine), ACEIs had a 13% lower HF risk (RR 0.87; 95% 0.79-0.96; p=0.008). Notably, the ALLHAT trial (CCB) contributed 94% of the pooled effect estimate. No heterogeneity among trials was observed.

Two trials assessed the effects of ACEIs versus diuretics. No benefit of ACEIs in regard to risk of HF compared with diuretics was apparent (RR, 1.07; 95% CI 0.81, 1.41; p=0.65). Statistical heterogeneity was detected (chi-square p value =0.09 and $I^2 = 66\%$).

Data from trials comparing with an active control showed no significant effect of ACEIs compared with other BP-lowering agents (RR, 0.81; 95% 0.52-1.28; p=0.37). There was evidence of heterogeneity (p value=0.07 and $I^2 = 54\%$). The observed heterogeneity was due to the Cai et al. trial (rated as high risk of bias).

6.5.3.3 Population clinical setting

Figure 6.8 displays a RE forest plot of the effect of ACEIs therapy on HF risk compared with a control group (placebo or active), classified by clinical setting. There were 13 RCTs that enrolled high-risk hypertensives, which enrolled 82,279 participants with 4,310 reported HF events. ACEIs therapy showed a 11% reduction in HF risk among high-risk hypertensive patients, with an RR of 0.89 (95% CI 0.79-0.99; p=0.03). The assessment of heterogeneity showed moderate variation between trials (chi-square test p value = 0.07 and I² statistics = 40%). This variation is likely influenced by ALLHAT. The ALLHAT trial carried 23.2% of the overall pooled effect estimates and showed an unfavourable effect of ACEIs on risk of HF (when diuretics was used as comparator) (see subgroup analyses; Section 6.5.3.2). After excluding ALLHAT, the heterogeneity disappeared (I²=0%) with an RR of 0.83 (95% CI 0.76-0.90, p<0.0001).

In patients with CAD (13 trials), treatment with ACEIs reduced HF risk by 25% compared with the control (RR, 0.75; 95% CI 0.69-0.82; p<0.00001). As shown in the forest plot, the HOPE trial was assigned the most weight, at 51% of the pooled effect estimate. Assessment of I^2 indicated no statistical heterogeneity.

Pooled data of patients with underlying DM with or without nephropathy (four trials) showed no clear benefit of ACEIs therapy (RR, 0.94; 95% CI 0.81-1.10; p=0.45). However, the wide 95% CI indicate a less precise estimate. No heterogeneity was detected.

For HF patients (three trials), no obvious benefit was seen with ACEIs therapy (RR, 0.93; 95% CI 0.74-1.16; p=0.51). However, the wide 95% CI and small number of trials indicate a less precise estimate.

Two trials enrolled 1,088 participants with non-diabetic nephropathy. Although ACEIs therapy was associated with non-significant reduction in HF risk in this group of patients, the wide 95% CI indicates low precision of the intervention's effect estimate (RR, 0.49; 95% 0.14-1.77; p=0.28). No variation between trials was detected.

6.5.3.4 Mean age group

As shown in **Figure 6.9**, combined available data on risk of HF with a patient mean age of younger than 65 years demonstrates that ACEI therapy in patients with a mean age < 65 years old was associated with a statistically significant 24% reduction in HF risk (RR, 0.76, 95% CI 0.67-0.85, p<0.00001). The assessment of heterogeneity showed no variation between studies.

In patients with a mean age of \ge 65 years, the pooled point estimate for risk of HF was less than 1 but did not reach statistical significance (RR, 0.90, 95% 0.80-1.01, P=0.09). However, the pooled RR was strongly influenced by the ALLHAT trial, which contributed 23.9% of the overall effect estimate. There was evidence of statistical heterogeneity between trials (I² = 57% and p value=0.02), which was most likely due to the clinical and methodological diversity of ALLHAT. After excluding the ALLHAT trial, the heterogeneity disappeared (I²=0%) and the model yielded an RR of 0.85 (95% CI 0.78-0.92; p=0.0001) (See Figure 6.9)

HF Incidence (%) Subgroup analysis Studies ACEI RR (M-H, Random, 95% CI) P value* l² (%) [‡] **Participants Events** Control 119.892 5.518 5.05 Overall effects RE 29 4.01 0.83 [0.76, 0.92] 0.0003* 43 High-tissue affinity 65,136 2,669 3.67 4.51 0.82 [0.75, 0.89] 15 Subclass 16 <0.0001* **49**[¥] 12 2,845 4.70 5.56 0.85 [0.70, 1.04] Low-tissue affinity 54,080 0.11 **Dihydropyridine CCBs** 22,649 5.74 6.62 0.87 [0.79, 0.96] 1,400 6 0.008* 0 30,392 1,629 5.62 5.18 1.07 [0.81, 1.41] Active control Diuretics 2 0.62 66 0.81 [0.52, 1.28] Active control 5 3,350 168 4.42 5.66 0.37 54 0.89 [0.79, 0.99] High-risk hypertensive 13 82,279 4,310 4.74 5.57 0.03* 40 13 3.62 4.72 CAD 46,634 1,949 0.75 [0.69, 0.82] <0.00001* 0 DM_± nephropathy 3.47 3.68 0.94 [0.81, 1.10] Clinical setting 4 16,968 607 0.45 0 250 14.9 16.08 0.93 [0.74, 1.16] 0.51 HF 3 1,613 0 Non-diabetic nephropathy 2 1,088 0.55 1.28 0.49 [0.14, 1.77] 0 10 0.28 CVA** 1 264 3.70 4.94 0.75 [0.59, 0.95] 6,105 0.02* NA 50,678 3.04 0.76 [0.67, 0.85] Mean age < 65 years 20 1,368 2.34 <0.00001* 8 6.29 ≥ 65 years 8 68,541 4,146 5.66 0.90 [0.80, 1.01] 0.09 **57**[†] group +See list of definitions/abbreviation. Cl: confidence interval; RE: random-effects; RR: risk ratio; 1²: I-square test; M-H: Mantel-Haenszel. *P value of less than 0.05 considered statistically significant; ** Cannot synthesize data from one trial; $\pm 1^2$ statistic with <25% considered as low heterogeneity and 1^2 > 75% as high heterogeneity

Table 6-1 Summary of an RE meta-analytical subgroup analysis shows the effect of ACEIs compared with placebo or active on risk of HF

¥ Excluding ALLHAT trial resulted in a significant RR of 0.78 (95% CI 0.66-0.93; p=0.006; I²=7%)

† Excluding ALLHAT yielded an RR of 0.85 (95% CI 0.78-0.92; p=0.0001).

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	ACE		Cont	rol		Risk Ratio	Risk Ratio	Risk of Bias
Study or Subgroup	Events		Events		Weight	M-H, Random, 95% Cl	M-H. Random, 95% Cl	ABCDEFG
1.1.2 High-affinity tissue ACEIs	Lvents	Total	Lvents	Totai	weight	Man, Kandoni, 35% Ci	Mi-fi, Randoni, 35% Cl	ABCDEIG
AASK 2002	20	436	30	658	2.5%	1.01 [0.58, 1.75]		
ADVANCE 2007	197	5569	199	5571	14.8%	0.99 [0.82, 1.20]		
APRES 2000	197	5569	133	79	0.9%	0.49 [0.19, 1.25]		
DIABHYCAR 2004	85	2443	102	2469	8.3%	0.49 [0.19, 1.25]		
DREAM 2006	12	2623	4	2646	0.6%	3.03 [0.98, 9.37]		
EUROPA 2003	63	6110	103	6108	7.1%	0.61 [0.45, 0.83]		? ?
HOPE 2000	417	4645	535	4652	25.4%	0.78 [0.69, 0.88]	-	2000000
Hou et al (group 2) 2006	417	112	535	4652	25.4%	0.60 [0.15, 2.45]		
IMAGINE 2008	15	1280	14	1273	1.5%	1.07 [0.52, 2.20]		
PART-2 2000	7	308	9	309	0.8%	0.78 [0.29, 2.07]		
PEACE 2004	115	4158	152	4132	10.9%	0.75 [0.29, 2.07]		? ?
PEP-CHF 2006	97	4158	106	4132	10.8%			
PHARAO 2008	97	424 505	19	426 503	1.7%	0.92 [0.72, 1.17]		
PREAMI 2006	22	631	30	621	2.6%	0.73 [0.37, 1.45]		
PROGRESS 2001	113	3051	151	3054	10.9%	0.72 [0.42, 1.24] 0.75 [0.59, 0.95]		
QUO VADIS 2001	113	3051	151	3054	0.7%			? ? @@@@ ?
Subtotal (95% CI)	6	32450	0	32686	100.0%	0.97 [0.33, 2.88] 0.82 [0.75, 0.89]	▲]	
Total events	1192	52450	1477	52000	100.070	0.02 [0.7 5, 0.05]	•	
Heterogeneity: Tau ² = 0.00; Chi ² :		H - 1 5 /5		18 - 1 6 00				
Test for overall effect: Z = 4.40 (P			0.28),	1 = 15%	,			
restion overall ellect. Z = 4.40 (P	~ 0.0001	,						
1.1.3 Low-affinity tissue ACEIs								
ABCD (normotensive) 2002	12	246	11	234	5.1%	1.04 [0.47, 2.31]		?
ALLHAT 2002*	612	9054	1576	24303	25.9%	1.04 (0.95, 1.14)	-	
ANBP2 2003	69	3044	78	3039	16.0%	0.88 [0.64, 1.22]		?
Caietal 2001	21	478	34	344	9.4%	0.44 [0.26, 0.75]	I	????
CAMELOT (Overall) 2004	4	673	8	1315	2.5%	0.98 [0.30, 3.23]		
CARMEN (combination) 2004	7	191	12	191	4.1%	0.58 [0.23, 1.45]		?
CARMEN (monotherapy) 2004	16	190	12	191	6.0%	1.34 [0.65, 2.76]		7000000
CCS-I 2001	139	3391	186	3358	20.7%	0.74 [0.60, 0.92]		
J-MIND 2001	0	208	1	228	0.4%	0.37 [0.01, 8.92]		?? 😑 ? 🕒 ?
JAMP 2004	14	466	10	422	5.0%	1.27 [0.57, 2.82]		?? 🔴 🔁 ? 🖷 🖶
JMIC-B 2004	9	822	12	828	4.5%	0.76 (0.32, 1.78)		
PREVEND IT 2007	0	431	2	433	0.4%	0.20 (0.01, 4.17)	←	
Subtotal (95% CI)		19194		34886	100.0%	0.85 [0.70, 1.04]	•	
Total events	903		1942					
Heterogeneity: Tau ² = 0.04; Chi ² :	= 21.48, c	If = 11 (F	P = 0.03;	$I^{2} = 49\%$,			
Test for overall effect: Z = 1.60 (P	= 0.11)							
							Favours [ACEI] Favours [Control]	
Test for subgroup differences: C	hi≊ = 0.13	, df = 1 (i	P = 0.72)	, I≊ = 0 %				
Risk of bias legend								
(A) Random sequence generation	on (select	ion bias))					
(B) Allocation concealment (sele	ction bias	;)						

(b) Allocation concealment (selection blas)
 (C) Blinding of participants and personnel (performance blas)
 (D) Blinding of outcome assessment (detection blas): All cause of mortality
 (E) Incomplete outcome data (attrition blas)
 (F) Selective reporting (reporting blas)
 (G) Other blas

Figure 6-6 Forest plot showing the effect of ACEIs on risk of HF (RE model). [Subgroup analysis: Low vs. high tissue-affinity ACEIs].

*After excluding ALLHAT, the heterogeneity was diminished ($I^2=7\%$) with an RR within the significance level (RR, 0.78; 95% CI 0.66-0.93; p=0.006). CI: confidence interval; RE: randomeffects; M-H: Mantel-Haenszel. For studies acronyms, see list of definition/ abbreviations

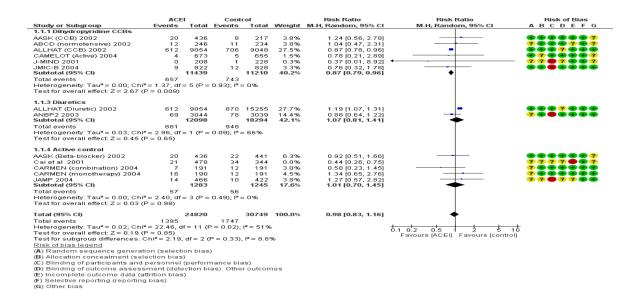


Figure 6-7 Forest plot showing the effect of ACEIs on risk of HF (RE model). [Subgroup analysis: Class of active control].

CI: confidence interval; RE: random-effects; M-H: Mantel-Haenszel. For studies acronyms, see list of definition/ abbreviations

Chapter 6: ACEIs versus ARBs for HF prevention

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Study or Subgroup	ACE Events		Cont Events		Moight	Risk Ratio M-H, Random, 95% Cl	Risk Ratio M-H, Random, 95% Cl	Riskof Bias ABCDEFG
Study or Subgroup 1.2.1 High-risk hypertensive	Events	TULAI	Events	TUTAI	weight	m-n, Rahuom, 95% Ci	M-H, Randolli, 95% Cl	ABCDEFG
AASK 2002	20	436	30	658	3.4%	1.01 [0.58, 1.75]		
ADVANCE 2007	197	5569	199	5571	14.7%	0.99 [0.82, 1.20]	-+-	
ALLHAT 2002*	612	9054	1576	24303	23.2%	1.04 [0.95, 1.14]	+	
ANBP2 2003	69	3044	78	3039	8.1%	0.88 [0.64, 1.22]		
CAMELOT (Overall) 2004 DIABHYCAR 2004	4 85	673 2443	8 102	1318 2469	0.8% 9.6%	0.98 [0.30, 3.24] 0.84 [0.64, 1.12]		
HOPE 2000	417	4645	535	4652	20.5%	0.78 [0.69, 0.88]		?
Hou et al (group 2) 2006	3	112	5	112	0.6%	0.60 [0.15, 2.45]		
IMAGINE 2008	15	1280	14	1273	2.1%	1.07 [0.52, 2.20]		
JMIC-B 2004	9	822	12	828	1.5%	0.76 [0.32, 1.78]		
J-MIND 2001	0	208	1	228	0.1%	0.37 [0.01, 8.92]		→ ??●?●?
PEACE 2004 PREAMI 2006	115 22	4158 631	152 30	4132 621	11.8% 3.5%	0.75 [0.59, 0.95] 0.72 [0.42, 1.24]		
Subtotal (95% Cl)	~~	33075	50	49204	100.0%	0.89 [0.79, 0.99]	•	
Total events	1568		2742				-	
Heterogeneity: Tau ² = 0.01; Chi ²	² = 20.07, d	f = 12 (F	P = 0.07);	l² = 40%				
Test for overall effect: Z = 2.20 (° = 0.03)							
1.2.2 Coronary Heart Disease (CADI							
APRES 2000	CAD) 6	80	12	79	0.9%	0.49 [0.19, 1.25]		
Cai et al 2001	21	478	34	344	2.7%	0.44 [0.26, 0.75]		22220002
CAMELOT (Overall) 2004	4	673	8	1318	0.5%	0.98 [0.30, 3.24]		
CCS-I 2001	139	3391	186	3358	16.3%	0.74 [0.60, 0.92]		
EUROPA 2003	63	6110	103	6108	7.7%	0.61 [0.45, 0.83]	—— <u> </u>	220200
HOPE 2000	417	4645	535	4652	51.0%	0.78 [0.69, 0.88]		?
IMAGINE 2008	15	1280	14	1273	1.4%	1.07 [0.52, 2.20]		
JAMP 2004 JMIC-B 2004	14 9	466 822	10 12	422 828	1.2% 1.0%	1.27 [0.57, 2.82] 0.76 [0.32, 1.78]		
PART-2 2000	7	308	9	309	0.8%	0.78 [0.29, 2.07]		
PEACE 2004	115	4158	152	4132	13.2%	0.75 [0.59, 0.95]		??
PREAMI 2006	22	631	30	621	2.6%	0.72 [0.42, 1.24]		
QUO VADIS 2001	6	75	6	73	0.6%	0.97 [0.33, 2.88]		?? ? 🗣 🗣 🗣 ?
Subtotal (95% Cl)		23117		23517	100.0%	0.75 [0.69, 0.82]	•	
Total events Heterogeneity: Tau ² = 0.00; Chi ²	838 - 0.65 df	- 12 /D	1111 - 0.653 B	- 00				
Test for overall effect: Z = 6.54 (I			- 0.03), 1	- 0 %				
1.2.3 Diabetic mellitus (DM) ± N		-						
ABCD (normotensive) 2002	12	246	11	234	3.8%	1.04 [0.47, 2.31]		3000303
ADVANCE 2007 DIABHYCAR 2004	197 85	5569 2443	199 102	5571 2469	65.3% 30.6%	0.99 [0.82, 1.20]		
J-MIND 2001	0	2443	102	2409	0.2%	0.84 [0.64, 1.12] 0.37 [0.01, 8.92]		
Subtotal (95% Cl)		8466		8502	100.0%	0.94 [0.81, 1.10]	◆	
Total events	294		313					
Heterogeneity: Tau ² = 0.00; Chi ²		= 3 (P =	0.74); l² =	= 0%				
Test for overall effect: Z = 0.75 (I	P = 0.45)							
1.2.4 Heart failure								
CARMEN (combination) 2004	7	191	12	191	6.0%	0.58 [0.23, 1.45]		? • • • • • •
CARMEN (monotherapy) 2004	16	190	12	191	9.5%	1.34 [0.65, 2.76]		? • • • • • • •
PEP-CHF 2006	97	424	106	426	84.6%	0.92 [0.72, 1.17]		
Subtotal (95% CI)		805		808	100.0%	0.93 [0.74, 1.16]	•	
Total events	120 - 2.00. df		130	- 00				
Heterogeneity: Tau ² = 0.00; Chi ² Test for overall effect: Z = 0.66 (I		- 2 (P =	0.37), 1*=	- U%				
	0.017							
1.2.6 CVA								
PROGRESS 2001	113	3051	151		100.0%	0.75 [0.59, 0.95]		
Subtotal (95% CI)		3051		3054	100.0%	0.75 [0.59, 0.95]	-	
Total events Heterogeneity: Not applicable	113		151					
Test for overall effect: Z = 2.37 (I	P = 0.02)							
2.01 (. ,							
1.2.7 Non-diabetics nephropati							_	
Hou et al (group 2) 2006	3	112	5	112	82.3%	0.60 [0.15, 2.45]		••••
PREVEND IT 2007 Subtotal (95% CI)	0	431 543	2	433 545	17.7% 100.0%	0.20 [0.01, 4.17] 0.49 [0.14, 1.77]		
Total events	3	545	7	545	100.0%	0.49 [0.14, 1.77]		
Heterogeneity: Tau ² = 0.00; Chi ²		= 1 (P =		= 0%				
Test for overall effect: Z = 1.08 (I		· • • =						
						(0.2 0.5 1 2 5	
Test for subgroup differences: (Chi² = 11 40	a df= 5	(P = 0.04)) F= 56	5%	Favo	urs [experimental] Favours [control]	
Risk of bias legend		-,	. 0.04	,, 00				
(A) Random sequence generati	ion (selecti	on hias	\ \					

 Risk of bias legend

 (A) Random sequence generation (selection bias)

 (B) Allocation concealment (selection bias)

 (C) Blinding of participants and personnel (performance bias)

 (D) Blinding of outcome assessment (detection bias): Other outcomes

 (E) Incomplete outcome data (attrition bias)

 (F) Selective reporting (reporting bias)

 (G) Other bias

Figure 6-8 Forest plot showing the effect of ACEIs on risk of HF (RE model). [Subgroup analysis: Clinical setting]

*After excluding the ALLHAT trial, the heterogeneity disappeared (I²=0%) with an RR of 0.83 (95% CI 0.76-0.90; p<0.0001). CI: confidence interval; RE: random-effects; M-H: Mantel-Haenszel. For studies acronyms, see list of definition/ abbreviations

Chapter	6: ACEIs	versus	ARBs f	for HF	prevention
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C (()	ACE		Cont			Risk Ratio	Risk Ratio	Risk of Bias
Study or Subgroup	Events	lotal	Events	lotal	weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl	ABCDEFG
1.1.1 Mean age < 65 years								
AASK 2002	20	436	30	658	4.3%	1.01 [0.58, 1.75]		
ABCD (normotensive) 2002	12	246	11	234	2.2%	1.04 [0.47, 2.31]		? • • • • ? • ?
APRES 2000	6	80	12	79	1.6%	0.49 [0.19, 1.25]		
Cai et al 2001	21	478	34	344	4.8%	0.44 [0.26, 0.75]		???? @@ ? @ @ @@@
CAMELOT (Overall) 2004	4	673	8	1318	1.0%	0.98 [0.30, 3.24]		
CARMEN (combination) 2004	7	191	12	191	1.7%	0.58 [0.23, 1.45]		? • • • • • • •
CARMEN (monotherapy) 2004	16	190	12	191	2.6%	1.34 [0.65, 2.76]		?...........
CCS-I 2001	139	3391	186	3358	21.1%	0.74 [0.60, 0.92]		
DREAM 2006	12	2623	4	2646	1.1%	3.03 [0.98, 9.37]		
EUROPA 2003	63	6110	103	6108	12.0%	0.61 [0.45, 0.83]		? ? O ? O O O
Hou et al (group 2) 2006	3	112	5	112	0.7%	0.60 [0.15, 2.45]		• ? • • • • •
IMAGINE 2008	15	1280	14	1273	2.6%	1.07 [0.52, 2.20]		
J-MIND 2001	0	208	1	228	0.1%	0.37 [0.01, 8.92]	•	220200
JAMP 2004	14	466	10	422	2.1%	1.27 [0.57, 2.82]		3 3 🖨 3 3 4 🖉
PART-2 2000	7	308	9	309	1.5%	0.78 [0.29, 2.07]		$\bullet \bullet \bullet \bullet \bullet \bullet \bullet \circ \circ$
PEACE 2004	115	4158	152	4132	18.2%	0.75 [0.59, 0.95]		??@@@@
PHARAO 2008	14	505	19	503	2.9%	0.73 [0.37, 1.45]		
PREVEND IT 2007	0	431	2	433	0.2%	0.20 [0.01, 4.17]	•	
PROGRESS 2001	113	3051	151	3054	18.2%	0.75 [0.59, 0.95]		
QUO VADIS 2001	6	75	6	73	1.2%	0.97 [0.33, 2.88]		??
Subtotal (95% CI)	587	25012	781	25666	100.0%	0.76 [0.67, 0.85]	•	
Total events Heterogeneitly: Tau ² = 0.01; Chi ² Test for overall effect: Z = 4.60 (F 1.1.2 Mean age ≥ 65 years	²= 20.59, d			I ² = 8%				
	407		400		45.000			
ADVANCE 2007	197	5569	199	5571	15.9%	0.99 [0.82, 1.20]	T	
ALLHAT 2002*	612	9054		24303	23.9%	1.04 [0.95, 1.14]	T	2000000
ANBP2 2003	69	3044	78	3039	9.2%	0.88 [0.64, 1.22]		
DIABHYCAR 2004 HOPE 2000	85 417	2443 4645	102 535	2469 4652	10.8%	0.84 [0.64, 1.12]		2000000
JMIC-B 2004	417	4645	535	465Z 828	21.5% 1.8%	0.78 [0.69, 0.88]		
DWIC-B 2004 PEP-CHF 2006	97	424	106	426		0.76 [0.32, 1.78]		
PREAMI 2006	22	424	30	420	12.9% 4.1%	0.92 [0.72, 1.17]		
Subtotal (95% CI)	22	26632	30	41909	4.1% 100.0%	0.72 [0.42, 1.24] 0.90 [0.80, 1.01]	•	
Total events	1508		2638					
Heterogeneity: Tau ² = 0.01; Chi ² Test for overall effect: Z = 1.72 (F		lf = 7 (P :	= 0.02); l ^a	²= 57%				
Test for subgroup differences: C <u>Risk of bias legend</u> (A) Random sequence generati (B) Allocation concealment (sel- (C) Blinding of participants and (D) Blinding of outcome assess (E) Incomplete outcome data (a) (F) Selective reporting (reporting (G) Other bias	Chi ^z = 4.18 ion (select ection bias personnel iment (dete ttrition bias	ion bias) ;) (perforn ection bi	nance bia	as)			0.2 0.5 1 2 5 Favours (ACEI) Favours (control)	

Figure 6-9 Forest plot showing the effect of ACEIs on risk of HF (RE model). [Subgroup analysis: Mean age group]

* After excluded ALLHAT trial, the heterogeneity disappeared ($I^2=0\%$) & the model yields RR within statistical level (RR, 0.85; 95% CI 0.78-0.92; p=0.0001). CI: confidence interval; RE: random-effects; M-H: Mantel-Haenszel. For studies acronyms, see list of definition/ abbreviations

6.6 ARBs and risk of HF

6.6.10verall treatment effects

Figure 6.10 shows the RE model of the effects of ARBs versus placebo or active control on HF risk. Altogether, 36 RCTs compared ARBs with either placebo or active treatment including 140,542 participants and reported 7,251 HF events. The incidence of HF was lower in patients treated with ARBs compared to those in control group, at 4.82% versus 5.49%, respectively. Overall, ARBs were associated with a statistically significant 14% reduction in HF compared with the control group (RR, 0.86; 95% CI 0.81-0.91; P<0.00001).

Placebo-controlled RCTs included 15 RCTs with 82,121 participants and 5,420 reported HF events. The incidence of HF was lower in patients treated with ARBs (6.10%) compared to the placebo (7.09%). All large RCTs (Val-HeFT, ACTIVE-I, and CHARM-Added) reported an RR of less than 1 and their 95% CIs did not cross the line of null effect. Treatment with ARBs was associated with a statistically significant 14% reduction in HF compared to the placebo (RR, 0.86; 95% CI 0.80-0.92; p< 0.00001). The assessment of statistical heterogeneity detected moderate variation among placebo-controlled trials (p value of chi-square = 0.13 and $l^2=31\%$). The observed heterogeneity was most likely due to the statistical diversity of the CHARM-Alternative and Val-HeFT trials. The favourable observed effects are likely due to the fact that 84% of subjects in the Val-HeFT and 60% of those in the CHARM-Alternative trials received the target dose of ARBs. After excluding these trials, the heterogeneity disappeared and the results remained significant (RR, 0.90; 95% CI 0.85-0.95; $l^2 = 0\%$).

There were 21 RCTs that randomized participants to ARBs or an active comparator; these included 58,421 participants with 1,831 reported HF events. The incidence of HF was lower in patients treated with ARBs compared to those treated with the active comparator drugs, at 2.98% and 3.27%, respectively. Therapy with ARBs reduced the risk of HF significantly, by 13%, compared with active treatment (RR, 0.87; 95% CI 0.76-0.99; p=0.03). The significance level of the pooled effect estimate was mainly driven by IDNT (CCB), which carried 3% of the overall combined weight, however, the remaining studies carried less than 2% each. Moderate heterogeneity existed between trials for this endpoint (p value of chi-

square was 0.17 and $I^2 = 24\%$). The observed heterogeneity was due to clinical the diversity of IDNT (CCB) and CHIEF trials (comparing ARBs with amlodipine). After excluding these, the heterogeneity disappeared and the results were maintained (RR, 0.90; 95% CI 0.82-0.99; $I^2=0\%$) (see Section 6.6.2.1, subgroup analysis: type of active control)

In the FE model in **Figure 6.11**, the overall effect estimates did not change for ARBs compared either with placebo (RR, 0.86; 95% CI 0.82-0.90; p<0.00001) or active control (RR, 0.88; 95% CI 0.81-0.96; p=0.005). However, the pooled 95% CI narrowed, as there was moderate variation among trials. Slightly more weight was assigned to the ACTIVE-I, Val-HeFT, and VALUE trials.

Assessment of the funnel plot as shown in **Figure D-2** (**Appendix D**) demonstrated a symmetrical distribution of studies at the top of the plot. A gap in the bottom corner of the plot occurred because small studies might be missing, likely due to reporting bias.

	ARE	3	Cont	rol		Risk Ratio	Risk Ratio	Risk of Bias
Study or Subgroup	Events		Events		Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl	ABCDEFG
1.1.1 ARBs vs Placebo					-			
ACTIVE-I 2011	482	4518	551	4498	9.7%	0.87 [0.78, 0.98]	-	
ANTIPAF 2012	1	214	1	211	0.0%	0.99 [0.06, 15.66]	←	+
CHARM-Added 2003	309	1276	356	1272	8.7%	0.87 [0.76, 0.99]	-	
CHARM-Alternative 2003*	207	1013	286	1015	7.3%	0.73 [0.62, 0.85]		
CHARM-Preserved 2003	241	1514	276	1509	7.3%	0.87 [0.74, 1.02]		
HOPE-3 2016	24	6356	22	6349	0.9%	1.09 [0.61, 1.94]		
I-PRESERVE 2008	325	2067	336	2061	8.2%	0.96 [0.84, 1.11]		
IDNT (Placebo) 2003	60	579	72	569	2.7%	0.82 [0.59, 1.13]		
NAVIGATOR 2010	91	4631	94	4675	3.3%	0.98 [0.73, 1.30]		
ORIENT 2011	18	282	25	284	0.9%	0.73 [0.40, 1.30]		
PRoFESS 2008	121	10146		10186	3.9%	• • •		2000000
						1.04 [0.81, 1.34]		
RENAAL 2001	89	751	127	762	4.0%	0.71 [0.55, 0.91]	-	
ROADMAP 2011	0	2232	0	2215	5.000	Not estimable		
TRANSCEND 2008	191	2954	197	2972	5.8%	0.98 [0.80, 1.18]		
Val-HeFT 2001*	346	2511	455	2499	8.9%	0.76 [0.67, 0.86]	-	?? 🗣 🗣 ? 🗣 🛑
Subtotal (95% CI)		41044		41077	71.7%	0.86 [0.80, 0.92]	•	
Total events	2505		2915					
 Heterogeneity: Tau² = 0.00; Test for overall effect: Z = 4. 			13 (P = 0	.13); I ^z =	31%			
Test for overall effect. $\Sigma = 4$.	00 (F < 0.)	50001)						
1.1.2 ARBs vs Active								
4C 2016	9	585	16	534	0.5%	0.51 [0.23, 1.15]		• ? • • • • •
ATTEMPT-CVD 2016	3	615	6	613	0.2%	0.50 [0.13, 1.98]	←	••••
CARP 2011	1	90	3	101	0.1%	0.37 [0.04, 3.53]	· · · · · · · · · · · · · · · · · · ·	?? \varTheta ? 🕒 🛨 🛨
CASE-J 2008	20	2354	16	2349	0.7%	1.25 [0.65, 2.40]		•••••
CHIEF 2018*	16	6766	6	6776	0.4%	2.67 [1.05, 6.82]		
COPE 2011	5	1110	11	2183	0.3%	0.89 [0.31, 2.57]		
E-COST 2005	35	1053	41	995	1.5%	0.81 [0.52, 1.26]		
E-COST-R 2005	11	69	17	72	0.7%	0.68 [0.34, 1.34]		? ? .?..?
HIJ-CREATE 2009	40	1024	44	1025	1.7%	0.91 [0.60, 1.38]		
HONG-KONG DHF 2007	.0	56	6	50	0.3%	0.89 [0.31, 2.59]		• ? • • ? ? •
IDNT (CCB) 2003*	60	579	93	567	3.0%	0.63 [0.47, 0.86]		
J-RHYTHM II 2010	0	158	0	160	3.0 %	Not estimable		
Kawamura 2013	1	49	4	95	0.1%	0.48 [0.06, 4.22]	<u> </u>	2222020
Kondo et al 2003	, 0	203	2	203	0.0%			220200
						0.20 [0.01, 4.14]	· ·	
LIFE 2002	153	4605	161	4588	4.9%	0.95 [0.76, 1.18]]	
MOSES 2005	30	681	46	671	1.5%	0.64 [0.41, 1.01]		
NTP-AF 2013	0	74	0	75		Not estimable		
OLIVUS 2010	2	126	1	121	0.1%	1.92 [0.18, 20.91]		+ ?????
PREVER-treatment 2016	0	322	0	333		Not estimable		
SUPPORT 2015	113	578	99	568	4.2%	1.12 [0.88, 1.43]	_ T •	
VALUE 2004 Subtotal (95% CI)	354	7649 28746	400	7596 29675	8.2% 28.3 %	0.88 [0.76, 1.01] 0.87 [0.76, 0.99]	•	••••
Total events	859	_0.10	972	200.0	201070	5151 [511 5, 5155]	•	
Heterogeneity: Tau ² = 0.01;		49 df=		17): P=	24%			
Test for overall effect: Z = 2.					-170			
T-4-1 (05% CI)		0700		70753	400.0%	0.0010.04.0.041		
Total (95% CI)		69790	0000	70752	100.0%	0.86 [0.81, 0.91]	•	
Total events	3364		3887					
Heterogeneity: Tau ² = 0.01;			31 (P = 0	.10); I ^z =	26%		0.2 0.5 1 2 5	_
Test for overall effect: Z = 4.							Favours [ARB] Favours [control	1
Test for subgroup differenc	es: Chi²=	0.03, df	= 1 (P = 0	0.87), I ² =	:0%			,
<u>Risk of bias legend</u>								
(A) Random sequence gen	eration (s	election	bias)					
(B) Allocation concealment	(selection	bias)	-					

(B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias): Other outcomes

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

Figure 6-10 Forest plot showing the effect of ARBs on risk of HF, stratified by comparison group (placebo vs active). Overall: 36 trials (RE model).

*Trial responsible for heterogeneity. The **diamond** indicates the pooled risk ratio (and 95% CI) or the overall effect for HF risk. CI: confidence interval; RE: random-effects; M-H: Mantel-Haenszel. For studies acronyms, see list of definition/ abbreviations

	AR		Cont			Risk Ratio	Risk Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl	ABCDEFG
1.1.1 ARBs vs Placebo								
ACTIVE-I 2011	482	4518	551	4498	18.9%	0.87 [0.78, 0.98]		
ANTIPAF 2012	1	214	1	211	0.0%	0.99 [0.06, 15.66]	•	→ •••• •••?
CHARM-Added 2003	309	1276	356	1272	12.2%	0.87 [0.76, 0.99]		
CHARM-Alternative 2003*	207	1013	286	1015	9.8%	0.73 [0.62, 0.85]	-	
CHARM-Preserved 2003	241	1514	276	1509	9.5%	0.87 [0.74, 1.02]		$\bullet \bullet \bullet \bullet \bullet \bullet \bullet ?$
HOPE-3 2016	24	6356	22	6349	0.8%	1.09 [0.61, 1.94]		
I-PRESERVE 2008	325	2067	336	2061	11.5%	0.96 [0.84, 1.11]	-	
IDNT (Placebo) 2003	60	579	72	569	2.5%	0.82 [0.59, 1.13]	+	$\bullet \bullet $
NAVIGATOR 2010	91	4631	94	4675	3.2%	0.98 [0.73, 1.30]	-+-	$\bullet \bullet \bullet \bullet \bullet \bullet \bullet ?$
ORIENT 2011	18	282	25	284	0.9%	0.73 [0.40, 1.30]		
PRoFESS 2008	121	10146	117	10186	4.0%	1.04 [0.81, 1.34]	+	?
RENAAL 2001	89	751	127	762	4.3%	0.71 [0.55, 0.91]		
ROADMAP 2011	0	2232	0	2215		Not estimable		
TRANSCEND 2008	191	2954	197	2972	6.7%	0.98 [0.80, 1.18]	-+	?
Val-HeFT 2001*	346	2511	455	2499	15.6%	0.76 [0.67, 0.86]		?? ? 🗣 🕈 ? 🖶 🛑
Subtotal (95% CI)		41044		41077	100.0%	0.86 [0.82, 0.90]	•	
Total events	2505		2915					
Heterogeneity: Chi ² = 18.83); I ^z = 319	6				
Test for overall effect: Z = 6.	08 (P ≤ 0.	00001)						
1.1.2 ARBs vs Active								
4C 2016	9	585	16	534	1.7%	0.51 [0.23, 1.15]		• ? • • • • •
ATTEMPT-CVD 2016	3	615	6	613	0.6%	0.50 [0.13, 1.98]	←	
CARP 2011	1	90	3	101	0.3%	0.37 [0.04, 3.53]	←	220200
CASE-J 2008	20	2354	16	2349	1.6%	1.25 [0.65, 2.40]		
CHIEF 2018*	16	6766	6	6776	0.6%	2.67 [1.05, 6.82]		
COPE 2011	5	1110	11	2183	0.8%	0.89 [0.31, 2.57]		
E-COST 2005	35	1053	41	995	4.3%	0.81 [0.52, 1.26]		
E-COST-R 2005	11	69	17	72	1.7%	0.68 [0.34, 1.34]		? ? • ? • • ?
HIJ-CREATE 2009	40	1024	44	1025	4.5%	0.91 [0.60, 1.38]		•••••
HONG-KONG DHF 2007	6	56	6	50	0.7%	0.89 [0.31, 2.59]		• ? • • ? ? •
IDNT (CCB) 2003*	60	579	93	567	9.7%	0.63 [0.47, 0.86]		
J-RHYTHM II 2010	0	158	0	160		Not estimable		
Kawamura 2013	1	49	4	95	0.3%	0.48 [0.06, 4.22]	← − −	? ? ? ? • ? •
Kondo et al 2003	Ó	203	2	203	0.3%	0.20 [0.01, 4.14]	←	220200
LIFE 2002	153	4605	161	4588	16.6%	0.95 [0.76, 1.18]		
MOSES 2005	30	681	46	671	4.8%	0.64 [0.41, 1.01]		
NTP-AF 2013	0	74	0	75		Not estimable		
OLIVUS 2010	2	126	1	121	0.1%	1.92 [0.18, 20.91]		→ ? ? ? • • • ?
PREVER-treatment 2016	Ū	322	0	333		Not estimable		
SUPPORT 2015	113	578	99	568	10.3%	1.12 [0.88, 1.43]	- - -	220000
VALUE 2004	354	7649	400	7596	41.2%	0.88 [0.76, 1.01]	-	
Subtotal (95% CI)		28746			100.0%	0.88 [0.81, 0.96]	◆	
Total events	859		972				-	
Heterogeneity: Chi ² = 22.49		P = 0.17); I ² = 249	6				
Test for overall effect: Z = 2.	• •							
							0.2 0.5 1 2 5	
							Favours [ARB] Favours [control	0]
Test for subgroup differenc	es: Chi ^z =	0.24, df	= 1 (P = 0	0.63), l²∶	= 0%			-
<u>Risk of bias legend</u> (A) Random sequence gen	eration (s	election	bias)					

(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias): Other outcomes

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

Figure 6-11 Forest plot showing the effect of ARBs on risk of HF, stratified by comparison group (placebo vs active). Overall: 36 trials (FE model).

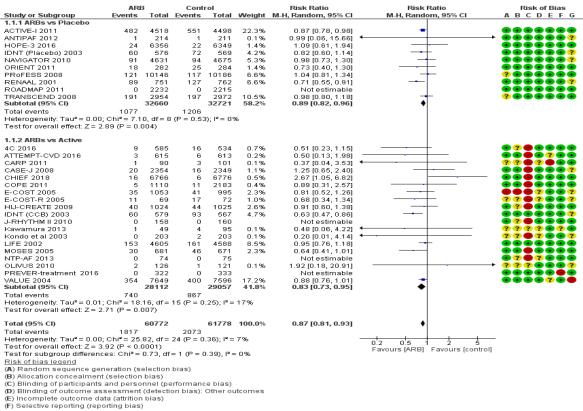
*Trial responsible for heterogeneity. The **diamond** indicates the pooled risk ratio (and 95% CI) or the overall effect for HF risk. CI: confidence interval; FE: fixed-effect; M-H: Mantel-Haenszel. For clinical trial acronyms, see list of definition/ abbreviations

6.6.2 Sensitivity analysis

Exclusion of seven trials that included patients with symptomatic HF (NYHA class II-IV) did not modify the treatment effect estimate, either compared with placebo (RR, 0.89; 95% CI, 0.82-0.96; p=0.004) or active control (RR, 0.83; 95% CI 0.73-0.95; p=0.007) (see Figure 6.12). No heterogeneity was detected among placebo-controlled trials. However, there was evidence of low variation among active-controlled trials.

The results after the exclusion of 15 RCTs with poor methodological quality are shown in **Figure 6.13**. The pooled estimate compared to placebo was 0.86 (95% CI 0.80-0.93; p=0.0002), and 0.86 (95% CI 0.70-1.07; p=0.13) when compared with active control. The high heterogeneity among active-controlled trials ($I^2 = 50\%$) was most likely influenced by statistical and methodological variation of trials that used DHP-CCB as a randomized arm (CHIEF and IDNT (CCB)).

Six RCTs that enrolled patients without a background of ACEIs use before randomization (naïve patients) were excluded (see Figure 6.14); two trials were placebo-controlled trials (ANTIPAF and ROADMAP) and four trials used active agents as the comparator group (E-COST, HONG-KONG DHF, Kawamura, and OLIVUS). The reduction in risk of HF by ARB therapy was not affected, either compared with placebo (RR,0.86; 95% CI 0.80-0.92) or with active agents (RR,0.87; 95% CI 0.74-1.01).



```
(G) Other bias
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Figure 6-12 Forest plot showing the effect of ARBs on risk of HF (RE model). [Sensitivity analysis: Excluding trials of symptomatic HF (NYHA class II-IV]

CI: confidence interval; RE: random-effects; M-H: Mantel-Haenszel. For studies acronyms, see list of definition/ abbreviations

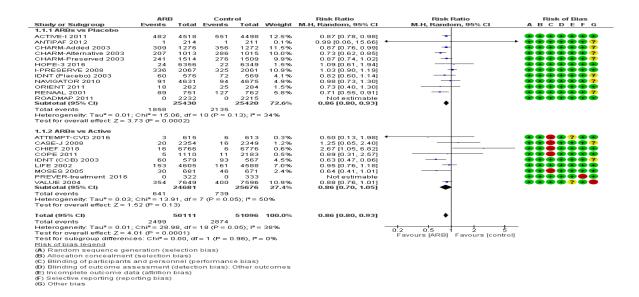


Figure 6-13 Forest plot showing the effect of ARBs on risk of HF (RE model). [Sensitivity analysis: Excluding trials with low methodological quality]

CI: confidence interval; RE: random-effects; M-H: Mantel-Haenszel. For studies acronyms, see list of definition/ abbreviations

		-						
	ARE		Cont			Risk Ratio	Risk Ratio	Risk of Bias
Study or Subgroup	Events	lotal	Events	lotal	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl	ABCDEFG
1.1.1 ARBs vs Placebo								
ACTIVE-I 2011	482	4518	551	4498	9.2%	0.87 [0.78, 0.98]	-	
CHARM-Added 2003	309	1276	356	1272	8.4%	0.87 [0.76, 0.99]		$\bullet \bullet \bullet \bullet \bullet \bullet \bullet \bullet \bullet$
CHARM-Alternative 2003	207	1013	286	1015	7.3%	0.73 [0.62, 0.85]	-	$\bullet \bullet \bullet \bullet \bullet \bullet \bullet \circ \circ$
CHARM-Preserved 2003	241	1514	276	1509	7.3%	0.87 [0.74, 1.02]		
HOPE-3 2016	24	6356	22	6349	1.1%	1.09 [0.61, 1.94]		
I-PRESERVE 2008	325	2067	336	2061	8.0%	0.96 [0.84, 1.11]	-	
IDNT (Placebo) 2003	60	576	72	569	3.0%	0.82 [0.60, 1.14]		$\bullet \bullet \bullet \bullet \bullet \bullet \bullet \circ \circ$
NAVIGATOR 2010	91	4631	94	4675	3.6%	0.98 [0.73, 1.30]		$\bullet \bullet \bullet \bullet \bullet \bullet \bullet ?$
ORIENT 2011	18	282	25	284	1.1%	0.73 [0.40, 1.30]		
PRoFESS 2008	121	10146		10186	4.3%	1.04 [0.81, 1.34]		?
RENAAL 2001	89	751	127	762	4.3%	0.71 [0.55, 0.91]		$\bullet \bullet \bullet \bullet \bullet \bullet \bullet \circ \circ$
TRANSCEND 2008	191	2954	197	2972	5.9%	0.98 [0.80, 1.18]		? • • • • • • •
Val-HeFT 2001	346	2511 38595	455	2499 38651	8.6% 72.0%	0.76 [0.67, 0.86]		?? ? 🖲 🖶 ? 🖶 🖨
Subtotal (95% CI)		38595		10086	72.0%	0.86 [0.80, 0.92]	•	
Total events	2504		2914					
Heterogeneity: Tau ² = 0.00;			12 (P = 0	.09); F=	36%			
Test for overall effect: Z = 4.	.50 (P < 0.)	00001)						
1.1.2 ARBs vs Active								
4C 2016	9	585	16	534	0.6%	0.51 [0.23, 1.15]		
ATTEMPT-CVD 2016	3	615	6	613	0.0%	0.50 [0.13, 1.98]		
CARP 2011	1	90	3	101	0.2%	0.37 [0.04, 3.53]	•	220200
CASE-J 2008	20	2354	16	2349	0.9%	1.25 [0.65, 2.40]		
CHIEF 2018	16	6766	6	6776	0.4%	2.67 [1.05, 6.82]		
COPE 2011	5	1110	11	2183	0.4%	0.89 [0.31, 2.57]		
E-COST-R 2005	11	69	17	72	0.8%	0.68 [0.34, 1.34]		? ? • ? • • ?
HIJ-CREATE 2009	40	1024	44	1025	1.9%	0.91 [0.60, 1.38]		
IDNT (CCB) 2003	60	579	93	567	3.3%	0.63 [0.47, 0.86]		.
J-RHYTHM II 2010	0	158	0	160	0.070	Not estimable		
Kondo et al 2003	ŏ	203	2	203	0.0%	0.20 [0.01, 4.14]	←	? ? . ? . . ?
LIFE 2002	153	4605	161	4588	5.2%	0.95 [0.76, 1.18]		
MOSES 2005	30	681	46	671	1.7%	0.64 [0.41, 1.01]		
NTP-AF 2013	ō	74		75		Not estimable		
PREVER-treatment 2016	ŏ	322	ŏ	333		Not estimable		
SUPPORT 2015	113	578	99	568	4.5%	1.12 [0.88, 1.43]		??
VALUE 2004	354	7649	400	7596	8.0%	0.88 [0.76, 1.01]		
Subtotal (95% CI)		27462		28414	28.0%	0.87 [0.74, 1.01]	•	
Total events	815		920				-	
Heterogeneity: Tau ² = 0.02;	Chi ² = 21	63. df =	13(P = 0	.06): I ^z =	40%			
Test for overall effect: Z = 1								
	t							
Total (95% CI)		66057		67065	100.0%	0.86 [0.81, 0.92]	•	
Total events	3319		3834					
Heterogeneity: Tau ² = 0.01;			26 (P = 0	.03); I ^z =	36%		0.2 0.5 1 2 5	
Test for overall effect: Z = 4.							Favours [ARB] Favours [control]	
Test for subgroup differenc	es: Chi⁼=	0.01, df	= 1 (P = 0	0.91), I₹=	= 0%			
Risk of bias legend								
(A) Random sequence ger			bias)					
(B) Allocation concealment								
(C) Blinding of participants								
(D) Blinding of outcome as:			on bias):	Other ou	utcomes			
(E) Incomplete outcome da	ta (attritior	i bias)						

(E) Incomplete outcome data (attrition bias)
 (F) Selective reporting (reporting bias)
 (G) Other bias

Figure 6-14 Forest plot showing the effect of ARBs on risk of HF (RE model). [Sensitivity analysis: Excluding trials with RAAS-blockers naïve]

CI: confidence interval; RE: random-effects; M-H: Mantel-Haenszel. For studies acronyms, see list of definition/ abbreviations

6.6.3 Subgroup analysis

Tables 6.2 and 6.3 summarize the subgroup analyses of the effectiveness of ARBs on risk of MI.

6.6.3.1 Class of active control

Figure 6.15 reveals the RE model of 20 trials assessing the effects of ARBs therapy on risk of HF with patients randomized to either DHP-CCBs, diuretics, or other active control.

A majority of active-controlled trials compared ARBs with DHP-CCBs (amlodipine, nifedipine, bepridil, and nitrendipine). Pooled analysis showed ARB therapy had a 15% reduction in HF risk compared with CCBs, but this did not reach statistical significance (RR, 0.85; 95% CI 0.64-1.13; p=0.26). The direction and magnitude of pooled RR was mainly driven by the VALUE trial, which contributed 33.2% of the overall combined effect estimates. Heterogeneity assessment with the chi-square test (p value= 0.03) and I² statistics (59%) suggested evidence of variation among studies. The heterogeneity observed was contributed by the CHIEF and IDNT (CCB) trials, likely due to methodological and clinical diversity. After excluding these, heterogeneity diminished I²=3% (RR, 0.84; 95% CI 0.73-0.98; p=0.02).

Trials that assessed the effects of ARBs compared with beta-blockers showed no apparent benefit of ARBs compared with beta-blockers on risk of HF (RR, 0.95; 95% CI 0.77-1.17; p=0.62). No heterogeneity between trials was detected.

Diuretics was one of the randomized arms in three trials that enrolled 2,965 participants with 23 HF events. There was a non-significant 14% reduction in risk of HF compared with diuretics (RR, 0.86; 95% CI 0.39-1.90; p=0.71). However, the wider 95% CI may indicate low precision of effect estimates. No between-trial heterogeneity was detected.

In trials that used another conventional therapy as one of their randomized arms, there was no clear beneficial effect of ARBs therapy compared with control (RR, 0.91; 95% CI 0.75-1.11; p=0.36). No evidence of heterogeneity between trials was detected.

6.6.3.2 Population clinical setting

A shown in **Figure 6.16**, pooled data of high-risk hypertensives resulted in an RR of 0.91 (95% CI, 0.84-0.98; p=0.01). The ACTIVE-I and VALUE trials were assigned the most weighting (25.9%) in the pooled effect estimates. Moderate heterogeneity between trials was detected, likely due to the statistical and methodological diversity of CHIEF trial; after excluding it, the value of I² statistics diminished (I²=16%) with an RR of 0.90 (95% CI 0.85-0.97).

For patients with underlying symptomatic HF, the ARBs therapy showed a 14% lower risk of HF compared with control (RR, 0.86; 95% CI, 0.77-0.96; p=0.005). There was evidence of heterogeneity between trials (p value =0.02 and I^2 = 61%). The observed statistical heterogeneity was most likely due to the methodological

diversity of the CHARM-Alternative and Val-HeFT trials. Excluded these resulted in a homogeneous RR of 0.92 (95% CI 0.85-1.00; $I^2=7\%$).

Pooled data of DM patients with or without nephropathy resulted in an RR of 0.71 (95% 0.60-0.85; p=0.0002). Heterogeneity assessment showed a chi-square p value of 1 and I^2 statistics of 0%, indicating no statistical difference was present between these studies. Similarly, ARBs therapy showed a 13% lower HF risk when compared with other control group in patients with AF (RR, 0.87; 95% 0.78-0.98; p= 0.02). No evidence of heterogeneity between trials was detected.

Data of patients with CAD demonstrated that no clearly apparent benefit was seen with ARBs therapy when compared with the control group (RR, 0.93; 95% CI 0.79-1.10; p=0.41). This analysis was mainly driven by the TRANSCEND study, which carried 77.8% of the overall weight. The assessment of heterogeneity suggested no statistical heterogeneity between studies. In patients with underlying CVA, treatment by ARBs showed a 15% lower HF risk when compared with the control group (RR, 0.85; 95% CI 0.53-1.35; p=0.49). The assessment of heterogeneity showed substantial variation among trials (chi-square test p value =0.07 and l^2 =70%). This was likely due to the statistical and methodological diversity between the MOSES and PRoFESS trials. Unlike MOSES, PRoFESS showed an unfavourable effect of ARBs, possibly due to poor adherence to telmisartan compared with the placebo (68.3% versus 70.8%) and more patients in the placebo group using BP-lowering agents.

6.6.3.3 Mean age group

For studies with a patient mean age < 65 years, ARBs therapy showed an 18% reduction in HF risk compared with the control group (RR, 0.82; 95% 0.73-0.91; p=0.0003). Moderate heterogeneity between trials was detected. Similarly, pooled data on HF events for a patient mean age of \geq 65 years showed that therapy with ARBs significantly reduced the risk of HF in this group, by 10% (RR, 0.89; 95% CI 0.84-0.95; p=0.0003).

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Table 6-2 Summary of an RE meta-analytical subgroup analysis showing the effect of ARBs on risk of HF compared with control (placebo and active

					HF Inc	idence (%)			l² (%) :
Subgroup	o analysis	Studies	Participant	Events	ARBs	Control	RR (M-H, Random, 95% CI)	P value*	
Overall effects	RE	36	140,542	7251	4.82	5.49	0.86 [0.81, 0.91]	<0.00001*	26
	Candesartan	12	31,232	1,977	5.73	6.93	0.83 [0.76, 0.90]	<0.00001*	0
	Irbesartan	4	14,962	1,931	12.04	13.6	0.88 [0.80, 0.98]	0.02*	19
	Valsartan	4	29,752	1,644	5.32	6.40	0.83 [0.74, 0.95]	0.004*	31
	Telmisartan	5	41,177	657	1.61	1.58	1.05 [0.81, 1.36]	0.72	43
Subclass	Losartan	3	11,361	530	4.26	5.06	0.83 [0.62, 1.09]	0.18	65
	Olmesartan	5	6,831	260	3.90	3.70	1.06 [0.85, 1.32]	0.63	0
	Eprosartan**	1	1,352	76	4.40	6.85	0.64 [0.41, 1.01]	0.05	NA
	DHP-CCBs	8	36,599	1,037	2.57	3.08	0.85 [0.64, 1.13]	0.26	59 [¥]
Active control	Beta-blockers	2	11,392	324	2.76	2.92	0.95 [0.77, 1.17]	0.62	0
	Diuretics	3	2,965	23	0.73	0.81	0.86 [0.39, 1.90]	0.71	0
	Active control	9	8,575	443	4.92	5.71	0.91 [0.75, 1.11]	0.36	5

heterogeneity.

Y Excluding CHIEF and IDNT yields an RR of 0.84 (95% CI 0.73-0.98; p=0.02; I² =3%)

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Table 6-3 Summary of an RE meta-analytical subgroup analysis showing the effect of ARBs on risk of HF compared with control (placebo and active (Continued)[†]

					HF Incid	ence (%)			l ² (%)		
Subgi	roup analysis	Studies	Participants	Events	ACEI	Control	RR (M-H, Random, 95% CI)	P value*	+		
Overall effects	RE	36	140,542	7251	4.82	5.49	0.86 [0.81, 0.91]	<0.00001*	26		
	High-risk hypertensive	25	10,9121	4,648	4.05	4.46	0.91 [0.84, 0.98]	0.01*	27		
	HF	7	17,989	3,361	17.1	20.2	0.86 [0.77, 0.96]	0.005*	61 [†]		
	DM± nephropathy	4	8,241	483	4.34	7.20	0.71 [0.60, 0.85]	0.0002*	0		
Clinical setting	Atrial fibrillation	5	10,052	1,040	9.65	11.03	0.87 [0.78, 0.98]	0.02*	0		
	CAD	6	9,938	506	4.87	5.30	0.93 [0.79, 1.10]	0.41	0		
	CVA	2	21,684	314	1.39	1.50	0.85 [0.53, 1.35]	0.49	70		
Mean age group	< 65 years	15	48,207	2,220	4.11	5.05	0.82 [0.73, 0.91]	0.0003*	23		
	≥ 65 years	20	91,756	4,971	5.10	5.73	0.89 [0.84, 0.95]	0.0003*	16		
[†] See list of definitions/abbreviation. Cl: confidence interval; RE: random-effects; RR: risk ratio; I ² : I-square test; M-H: Mantel-Haenszel. *P value of											
< 0.05 considered statistically significant; ‡ I ² statistic with <25% considered as low heterogeneity and I ² > 75% as high heterogeneity											
† Excluding CHAR/	M-Alternative and Val-HeF	T results in	an RR of 0.92 (9	95% CI 0.85	5-1.00; l ² =7	%).					

	ARE		Cont	rol		Risk Ratio	Risk Ratio	Risk of Bias
Study or Subgroup	Events		Events		Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl	ABCDEFG
1.1.1 Dihydropyridine CCBs							,	
CASE-J 2008	20	2354	16	2349	3.3%	1.25 [0.65, 2.40]		
CHIEF* 2018	16	6766	6	6776	1.7%	2.67 [1.05, 6.82]		
IDNT (CCB)* 2003	60	579	93	567	11.1%	0.63 [0.47, 0.86]	_ _	
J-RHYTHM II 2010	0	158	0	160		Not estimable		
Kawamura 2013	1	49	4	95	0.3%	0.48 [0.06, 4.22]	·	???? ~ ? • ?•
MOSES 2005	30	681	46	671	6.3%	0.64 [0.41, 1.01]		
NTP-AF 2013	0	74	0	75	0.070	Not estimable		
VALUE 2004	345	7649	400	7596	23.1%	0.86 [0.74, 0.99]	-	
Subtotal (95% CI)	040	18310	400	18289	45.7%	0.85 [0.64, 1.13]	•	
Total events	472		565				•	
Heterogeneity: Tau ² = 0.06; C		5 df - 6		s): I≊ – 60	206			
Test for overall effect: Z = 1.13			/() = 0.0.	5,1 = 5.	, ,0			
	5 (1 - 0.20	<i>"</i>						
1.1.2 Beta-blockers								
COPE (Beta-blocker) 2011	5	1110	5	1089	1.0%	0.98 [0.28, 3.38]		
LIFE 2002	153	4605	161	4588	16.4%	0.95 [0.26, 3.38]		
Subtotal (95% CI)	105	5715	101	4000 5677	17.3%	0.95 [0.77, 1.17]	→	
Total events	158	57 15	166	5077	11.570	0.00 [0.11, 1.11]	•	
		df = 1		12 - 000				
Heterogeneity: Tau ² = 0.00; C			(P = 0.96)	i, i= = 0%				
Test for overall effect: Z = 0.49	9 (P = 0.64	9						
1.1.3 Diuretics								
	-			4004	4.4.00			
COPE (Diuretic) 2011	5	1110	6	1094	1.1%	0.82 [0.25, 2.68]		
HONG-KONG DHF 2007	6	56	6	50	1.3%	0.89 [0.31, 2.59]		
PREVER-treatment 2016	0	322	0	333	2.40	Not estimable		
Subtotal (95% CI)		1488		1477	2.4%	0.86 [0.39, 1.90]		
Total events	11		12					
Heterogeneity: Tau ² = 0.00; C			(P = 0.92)	; I* = 0%				
Test for overall effect: Z = 0.33	7 (P = 0.71	0						
1.1.4 Active control								
4C 2016	9	585	16	534	2.2%	0.51 [0.23, 1.15]		
ATTEMPT-CVD 2016	3	615	6	613	0.8%	0.50 [0.13, 1.98]		
CARP 2011	1	90	3	101	0.3%	0.37 [0.04, 3.53]	• • • • • • • • • • • • • • • • • • • •	???????
E-COST 2005	35	1053	41	995	6.4%	0.81 [0.52, 1.26]		
E-COST-R 2005	11	69	17	72	3.0%	0.68 [0.34, 1.34]		? ? • ? • • ?
HIJ-CREATE 2009	40	1024	44	1025	6.9%	0.91 [0.60, 1.38]		
Kondo et al 2003	0	203	2	203	0.2%	0.20 [0.01, 4.14]	• • • • • • • • • • • • • • • • • • • •	3 5 6 5 6 6 5
OLIVUS 2010	2	126	1	121	0.3%	1.92 [0.18, 20.91]		???!!!! ?
SUPPORT 2015	113	578	99	568	14.5%	1.12 [0.88, 1.43]	_ 	?? 🗧 🖶 🖶 🖶
Subtotal (95% CI)		4343		4232	34.6%	0.91 [0.75, 1.11]	•	
Total events	214		229					
Heterogeneity: Tau ² = 0.00; C	hi² = 8.40	df = 8 ((P = 0.40)	; I² = 5%				
Test for overall effect: Z = 0.93	2 (P = 0.36	5)						
Total (95% CI)		29856		29675	100.0%	0.86 [0.76, 0.98]	•	
Total events	855		972					
Heterogeneity: Tau ² = 0.01; C	hi² = 22.6	4, df = 1	8 (P = 0.)	20); I ² = 2	21%			
Test for overall effect: Z = 2.29	9 (P = 0.02	2)					Favours [ARB] Favours [control]	
Test for subgroup differences	s: Chi² = 0	40, df=	: 3 (P = 0.	94), l² =	0%			
Risk of bias legend								
(A) Random sequence gene	ration (sel	ection b	pias)					
(B) Allocation concealment (s								
(C) Blinding of participants ar			formance	e bias)				
(D) Blinding of outcome asse					comes			
(E) Incomplete outcome data								
(F) Selective reporting (report		,						
(G) Other hiss								

(G) Other bias

Figure 6-15 Forest plot showing the effect of ARBs on risk of HF (RE model). [Subgroup analysis: Class of comparator]

* Excluding CHIEF and IDNT trials yields an RR of 0.84 (95% CI 0.73-0.98; p=0.02) and I² of 3%. CI: confidence interval; RE: random-effects; M-H: Mantel-Haenszel. For studies acronyms, see list of definition/ abbreviations

	ARE		Cont			Risk Ratio	Risk Ratio	Risk of Bias
Study or Subgroup 1.1.1 High-risk hypertensive	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl	ABCDEFG
4C 2016	9	585	16	534	0.8%	0.51 [0.23, 1.15]	+	• ? • • • • •
ACTIVE-I 2011 ATTEMPT-CVD 2016	482 3	4518 615	551 6	4498 613	14.2% 0.3%	0.87 [0.78, 0.98] 0.50 [0.13, 1.98]	•	
CARP 2011	1	90	3	101	0.1%	0.37 [0.04, 3.53]	←	220200
CASE-J 2008	20	2354	16	2349	1.3%	1.25 [0.65, 2.40]		
CHIEF 2018 COPE 2011	16 5	6766 1110	6 11	6776 2183	0.6% 0.5%	2.67 [1.05, 6.82] 0.89 [0.31, 2.57]		
E-COST 2005	35	1053	41	995	2.6%	0.81 [0.52, 1.26]		
E-COST-R 2005 HIJ-CREATE 2009	11 40	69 1024	17 44	72 1025	1.2% 2.8%	0.68 [0.34, 1.34] 0.91 [0.60, 1.38]		
I-PRESERVE 2008	336	2067	325	2061	12.3%	1.03 [0.90, 1.19]	+	
IDNT (Overall) 2003	60	579	165	1136	5.5%	0.71 [0.54, 0.94]		
J-RHYTHM II 2010 LIFE 2002	0 153	158 4605	0 161	160 4588	7.7%	Not estimable 0.95 [0.76, 1.18]		
MOSES 2005	30	681	46	671	2.5%	0.64 [0.41, 1.01]		
NAVIGATOR 2010 NTP-AF 2013	91 0	4631 74	94 0	4675 75	5.3%	0.98 [0.73, 1.30] Not estimable	-+-	
OLIVUS 2010	2	126	1	121	0.1%	1.92 [0.18, 20.91]		2220002
ORIENT 2011	18	282	25	284	1.6%	0.73 [0.40, 1.30]		
PREVER-treatment 2016 PRoFESS 2008	0 121	322 10146	0 117	333 10186	6.3%	Not estimable 1.04 [0.81, 1.34]		
RENAAL 2001	89	751	127	762	6.3%	0.71 [0.55, 0.91]		
SUPPORT 2015	113	578	99	568	6.6%	1.12 [0.88, 1.43]	+	??@@@@
TRANSCEND 2008 VALUE 2004	191 354	2954 7649	197 400	2972 7596	8.9% 12.3%	0.98 [0.80, 1.18] 0.88 [0.76, 1.01]		
Subtotal (95% CI)		53787		55334	100.0%	0.91 [0.84, 0.98]	•	
Total events	2180	75 46-	2468	1.00.18	270			
Heterogeneity: Tau² = 0.01; 0 Test for overall effect: Z = 2.5			21 (P = 0	.12);1*=	27%			
1.1.2 Heart failure								
CHARM-Added 2003	309	1276	356	1272	18.5%	0.87 [0.76, 0.99]		
CHARM-Alternative 2003* CHARM-Preserved 2003	207 241	1013 1514	286 276	1015 1509	16.6% 16.5%	0.73 [0.62, 0.85] 0.87 [0.74, 1.02]		
HONG-KONG DHF 2007	6	56	6	50	0.9%	0.89 [0.31, 2.59]		• ? • • ? ? •
I-PRESERVE 2008 SUPPORT 2015	325	2067	336	2061	17.8%	0.96 [0.84, 1.11]	<u>+</u>	
Val-HeFT 2001*	113 346	578 2511	99 455	568 2499	10.9% 18.8%	1.12 [0.88, 1.43] 0.76 [0.67, 0.86]	-	2200200
Subtotal (95% CI)		9015		8974	100.0%	0.86 [0.77, 0.96]	•	
Total events Heterogeneity: Tau ² = 0.01: 0	1547 `hi≊−15	30 df-	1814 6 (P - 0 (12118 - 6	3196			
Test for overall effect: Z = 2.7			0 () = 0.0					
1.1.3 Diabetes mellitus (DM)	± Nephr	opathy						
IDNT (Overall) 2003	60	579	165	1136	40.8%	0.71 [0.54, 0.94]		
ORIENT 2011 RENAAL 2001	18 89	282 751	25 127	284 762	9.3% 49.9%	0.73 [0.40, 1.30] 0.71 [0.55, 0.91]		
ROADMAP 2011	0	2232	0	2215		Not estimable		
Subtotal (95% CI)	4.07	3844		4397	100.0%	0.71 [0.60, 0.85]	•	
Total events Heterogeneity: Tau² = 0.00; 0	167 hi⁼= 0.0	0, df = 2	317 P = 1.00)); I² = 0°	%			
Test for overall effect: Z = 3.7								
1.1.4 Atrial Fibrillation (AF)								
ACTIVE-I 2011	482	4518	551	4498	99.5%	0.87 [0.78, 0.98]	_ <mark> </mark>	
ANTIPAF 2012 J-RHYTHM II 2010	1 0	214 158	1	211 160	0.2%	0.99 [0.06, 15.66] Not estimable		
Kawamura 2013	1	49	4	95	0.3%	0.48 [0.06, 4.22]	· · · · · · · · · · · · · · · · · · ·	2222929
NTP-AF 2013 Subtotal (95% CI)	0	74 5013	0	75 5039	100.0%	Not estimable 0.87 [0.78, 0.98]		•?•?••
Total events	484	5015	556	3035	100.0%	0.87 [0.78, 0.98]	•	
Heterogeneity: Tau ² = 0.00; C			(P = 0.87	?); I² = 0°	%			
Test for overall effect: Z = 2.3								
1.1.6 Coronary Artery Disea			10			0.54 10.00 4.45		
4C 2016 CARP 2011	9	585 90	16 3	534 101	4.4% 0.6%	0.51 [0.23, 1.15] 0.37 [0.04, 3.53]	· · · · · · · · · · · · · · · · · · ·	220200
HIJ-CREATE 2009	40	1024	44	1025	16.4%	0.91 [0.60, 1.38]		
Kondo et al 2003 OLIVUS 2010	0	203 126	2	203 121	0.3% 0.5%	0.20 [0.01, 4.14]		22 8 2 88 2 • 222 8 2
TRANSCEND 2008	191	2954	197	2972	77.8%	1.92 [0.18, 20.91] 0.98 [0.80, 1.18]	-	2000000
Subtotal (95% CI)		4982		4956	100.0%	0.93 [0.79, 1.10]	•	
Total events Heterogeneity: Tau ² = 0.00; 0	243 ≿hi≊ = 4.3	0 df= 5	263 (P = 0.51	Y = 0	*			
Test for overall effect: Z = 0.8								
1.1.7 CVA								
MOSES 2005	30	681	46		42.3%	0.64 [0.41, 1.01]		
PRoFESS 2008 Subtotal (95% CI)	121	10146	117		57.7% 100.0%	1.04 [0.81, 1.34] 0.85 [0.53, 1.35]		$? \bullet \bullet \bullet \bullet \bullet \bullet$
Total events	151	10027	163	10657	100.0%	0.65 [0.55, 1.55]		
Heterogeneity: Tau² = 0.08; 0	⊳hi² = 3.3			?); I₹ = 70	0%			
Test for overall effect: Z = 0.7	0 (P = 0.4)	49)						
							0.2 0.5 1 2 5	-
T 16 1 100					~~ ~~		Favours [ARB] Favours [control]	
Test for subgroup difference Risk of bias legend	s: Chi≝=	6.54, df	= 5 (P = l	J.26), I* =	= 23.6%			
(A) Random sequence gene			bias)					
(B) Allocation concealment (selection	bias)						
(C) Blinding of participants a (D) Blinding of outcome asse					itcomes			
(E) Incomplete outcome data	(attrition	i bias)		Salar of				
(F) Selective reporting (repor	ting bias))						
(G) Other bias								

Figure 6-16 Forest plot showing the effect of ARBs on risk of HF (RE model). [Subgroup analysis: Clinical setting]

*Trial responsible for heterogeneity. CI: confidence interval; RE: random-effects; M-H: Mantel-Haenszel. For studies acronyms, see list of definition/ abbreviations

6.7 Meta-regression analyses of the effect of ACEI and ARB on HF risk in relation to SBP reduction

6.7.1ACEIs

6.7.1.1 Overall effect

Eight of the trials included in the current meta-analysis did not report achieved SBP: CCS-I, Hou et al., IMAGINE, Cai et al., CARMEN, J-MIND, and JAMP. Thus, a total of 19 RCTs of ACEIs were included in meta-regression: 13 placebo-controlled trials and 6 active-controlled trials. The achieved SBP reduction ranged from -8 mmHg in APRES to 3.4 mmHg in QUO VADIS. Using a univariate model, the magnitude of HF risk reduction achieved by ACEIs was directly associated with magnitude of BP reduction. ACEIs achieved a 12% lower risk of HF for each 1 mmHg reduction in SPB (RR, 0.88; 95% CI 0.92-0.85; p=<0.0001), whereas no benefit for HF risk was seen independent of BP reduction (RR, 0.94; 95% CI 0.88-1.01; p=0.06) (see Figure 6.17 and table 6.4). The percentage of male subjects and baseline SBP (mmHg) contributed a greater proportion of between-study variance in HF risk estimates, at 91% and 22% respectively. Therefore, these variables were entered into the final multivariate (adjustment) regression model. After accounting for these covariates in the multivariate model, the association between SBP difference and HF risk was consistent (RR, 1.04; 95% CI 1.00-1.08; p=0.038). The final model largely explained the between-study variance, estimated at $R^2 = 100\%$. Moreover, there was no evidence of residual heterogeneity (p=0.936) and Tau² value reduced from 0.0154 to 0 (see Figure 6.17 and table 6.4).

6.7.1.2 Sensitivity analysis

To examine the strength of the association between risk reduction by ACEIs and reduction in SBP, a series of sensitivity analyses were carried out (see **Figure 6.18**). Excluding five trials that used CCBs as one of the randomized groups from univariate and multivariate models did not modify the impact of BP reduction by ACEIs on HF risk (univariate estimated an RR of 1.06; 95% CI 1.05-1.11; p=0.000 or multivariate estimated an RR of 1.06; 95% CI 1.03-1.10; p=0.001). Second, after omitting the ALLHAT trial (contributed considerable weight (44.6%)), RR did not reach statistical significance at trial level (univariate: RR, 1.05; 95% CI 0.99-1.10; p=0.082 and multivariate: RR, 1.03; 95% CI 0.97-1.10; P=0.281).

			Slope		Between-study variance				
Variable	Studies	RR	95% CI	P value	Tau2	Residual I ² (%)	P value	R ² (%)	
Null model (without covariates)			I		0.0154	44.81	0.019	-	
Univariate analysis (unadjusted)									
Achieved SBP differences (mmHg)	19	1.06	1.03-1.00	0.000	0	0	0.845	100	
Achieved DBP differences (mmHg)**		1.17	1.09-1.25	0.00001	0	0	0.752	100	
Baseline SBP (mmHg)		1.00	0.99-1.09	0.174	0.0121	30.51	0.107	22	
Mean age (Years)		1.00	0.98-1.06	0.695	0.0155	45.11	0.020	0	
Male (%)		0.98	0.98-0.99	0.0001	0.0014	0	0.797	91	
DM (%)		1.00	0.99-1.00	0.647	0.0168	47.67	0.013	0	
Duration of follow-up (years)		1.00	0.94-1.11	0.852	0.0171	0	0.022	0	
Multivariate analysis (adjusted)*									
Achieved SBP differences (mmHg)*		1.04	1.00-1.08	0.038	0	0	0.936	100	
Abbreviations: Tau ² = estimated amount of	heterogeneity (b	etween-stu	udy variance) not	explained by c	covariate; l ² res	idual= proportion of rema	ining observed varia	ance due to tru	
variation in effect size.									
*The analysis was adjusted for male (%) and	d baseline SBP (n	nmHg)							
**Achieved DBP and SBP is highly correlated	1 (r=-0.8)								

Table 6-4 Meta-regression of related and unrelated SBP differences by ACEI on risk of HF (unadjusted and adjusted models)

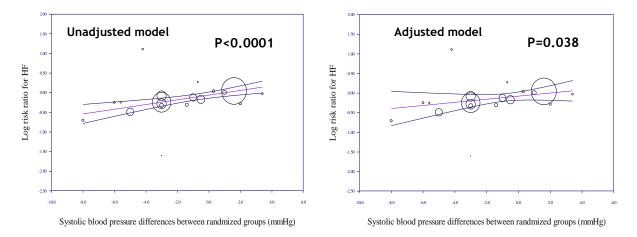


Figure 6-17 Meta-regression analysis of the relationship between RR of HF and difference in achieved SBP (mmHg) between randomized groups for trials of ACEIs.

Each study is represented by a circle. The size of each circle is proportional to that study's weight in the analysis (inverse-variance weighted). A negative value in the x-axis indicates lower achieved SBP in the treatment group than the control group.

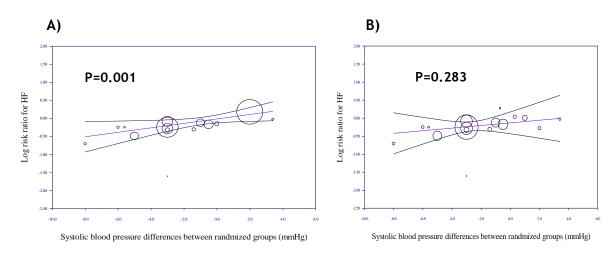


Figure 6-18 Multivariate meta-regression analysis of relationship between RR of HF and difference in achieved SBP (mmHg) between randomized groups for ACEIs trials [Sensitivity analysis].

Excluding, A) trials with CCB as comparator; and B) ALLHAT trial (an extreme weight).

6.7.2ARBs

6.7.2.1 Overall effect

In total, six trials were excluded from the meta-regression analysis for the following reasons: 1) two trials did not report SBP reduction for both groups (Kawamura and SUPPORT); 2) four trials reported zero HF events (ROADMAP, J-RHYTHM II, NTP-AF, and PREVER-Treatment). A total of 30 RCTs were included: 18 active comparator trials and 12 placebo-controlled trials. The achieved SBP reduction ranged from -5.7 mmHg in HOPE-3 to 2.3 mmHg in the OLIVUS trial. From the univariate model, the intercept of meta-regression line of differences in achieved SBP demonstrates that ARBs therapy conferred additional protection for HF beyond that expected by BP reduction alone. ARBs therapy had an estimated 15% lower risk of HF beyond the BP differences (RR, 0.86; 95% CI 0.78-0.94; p=0.003), whereas there was no relationship between the HF risk-reduction caused by ARBs and SBP reduction (RR, 1.00; 95% CI 0.97-1.02; p=0.796). In the univariate model, mean age (years) explained a large proportion of between-study variance ($R^2=94\%$), followed by percentage of male gender ($R^2=43\%$) (see **Figure 6.19**).

6.7.2.2 Sensitivity analysis

As shown in **Figure 6.20**, a series of sensitivity analyses were performed to examine the stability of the above findings. First, five trials that used CCBs as the comparator group were omitted. The direction and magnitude of RR of HF at zero BP reduction (mmHg) did not change; however, it did not reach statistical significance at trial level (RR, 0.89; 0.75-1.04; p=0.158). Moreover, the direction and magnitude of the slope of the meta-regression line was not affected. Second, excluding six trials that enrolled participants with symptomatic HF did not alter the main results for the BP-independent effect (RR, 0.86; 95% CI 0.79-0.93; p=0.0003) or dependent effect (RR, 0.99; 95% CI 0.97-1.02 p=0.56). Lastly, omitting seven trials with a sample size of less than 1,000 did not change either the intercept (RR, 0.86; 95% CI 0.77-0.94; p=0.005) or the slope of the regression line (RR, 1.00; 95% 0.98-1.02; p=0.75).

In (RR)=-0.147 + 0.003 (X), P=0.782

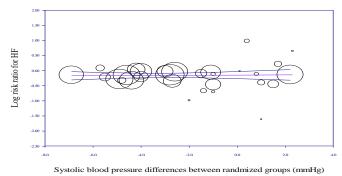
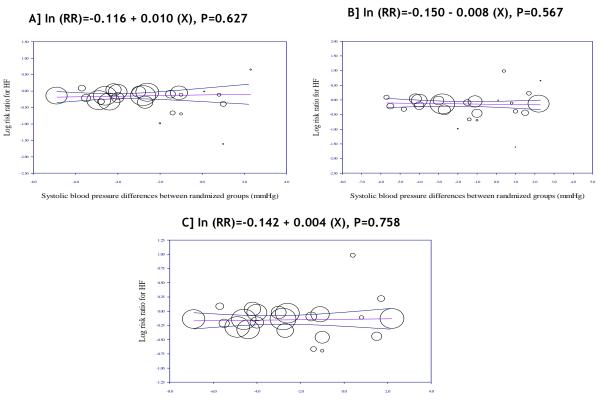


Figure 6-19 Meta-regression analysis of the relationship between RR of HF and difference in achieved SBP (mmHg) between randomized groups for trials of ARBs.

Each study is represented by a circle. The size of each circle is proportional to that study's weight in the analysis (inverse-variance weighted). A negative value in the x-axis is indicates a lower achieved SBP in the treatment group than the control group



Systolic blood pressure differences between randmized groups (mmHg)

Figure 6-20 Multivariate meta-regression analysis of the relationship between RR of HF and difference in achieved SBP (mmHg) between randomized groups for ARBs trials. [Sensitivity analysis].

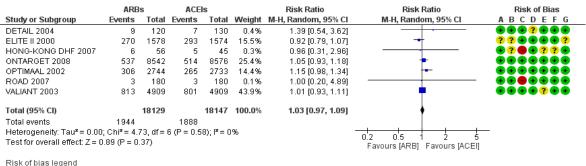
Excluding trials with, A) CCB as comparator; B) symptomatic HF and C) a sample size less

6.8 Direct comparison between ARBs and ACEIs

6.8.10verall treatment effect

Figure 6.21 shows the RE meta-analytical summary of ARBs versus ACEIs head-tohead in occurrence of HF. Seven RCTs directly assessed the effects of ARBs versus ACEIs on risk of HF in 36,276 participants, among whom 3,832 HF events were reported. The incidence of HF in patients allocated to the ARBs group was similar to those allocated to the ACEIs group: 10.72% versus 10.40%, respectively. Almost all trials reported an RR of 1 or more, however, their confidence intervals cross the line of null effects. Therefore, the reduction of HF risk by ARBs appeared similar to ACEIs therapies, with an RR of 1.03 (95% CI 0.97-1.09; p=0.37). The VALIANT trial contributed 43.9% of the overall effect. Tests for heterogeneity yielded a chi-square p value of 0.65 and $I^2 = 0\%$, which suggests no observed statistical heterogeneity among trials.

As a result of no between-trial variation (Tau²=0), the FE meta-analysis model agrees with the RE estimates (RR, 1.03; 95% CI 0.97-1.09; p=0.34). However, less weight was assigned to ONTARGET (27.2%) (see **Figure 6.22**)



(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias) (D) Blinding of outcome assessment (detection bias): Other outcomes

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

Figure 6-21 Forest plot showing the effect of ARBs versus ACEIs on risk of HF (RE model). Overall: 8 RCTs

The diamond indicates the pooled risk ratio (and 95% CI) or the overall effect for HF risk. CI: confidence interval; RE: random-effects; M-H: Mantel-Haenszel. For studies acronyms, see list of definition/ abbreviations

	ARB	s	ACE	ls		Risk Ratio	Risk Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl	ABCDEFG
DETAIL 2004	9	120	7	130	0.4%	1.39 [0.54, 3.62]		$\bullet \bullet \bullet ? \bullet \bullet \bullet$
ELITE II 2000	270	1578	293	1574	15.5%	0.92 [0.79, 1.07]		?? • • • • ?
HONG-KONG DHF 2007	6	56	5	45	0.3%	0.96 [0.31, 2.96]		•? • • •? ? •
ONTARGET 2008	537	8542	514	8576	27.2%	1.05 [0.93, 1.18]	+	
OPTIMAAL 2002	306	2744	265	2733	14.1%	1.15 [0.98, 1.34]		
ROAD 2007	3	180	3	180	0.2%	1.00 [0.20, 4.89]		
VALIANT 2003	813	4909	801	4909	42.4%	1.01 [0.93, 1.11]	†	
Total (95% CI)		18129		18147	100.0%	1.03 [0.97, 1.09]	•	
Total events	1944		1888					
Heterogeneity: Chi ² = 4.73,	df = 6 (P =	= 0.58);	I² = 0%				0.2 0.5 1 2 5	
Test for overall effect: Z = 0	.96 (P = 0.	.34)					Favours [ARB] Favours [ACEI]	
Risk of bias legend								
(A) Random sequence ge	neration (s	election	n bias)					
(B) Allocation concealment	t (selectior	n bias)						
(C) Blinding of participants	and perso	onnel (p	erforman	ce bias))			

(D) Blinding of outcome assessment (detection bias): Other outcomes

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

Figure 6-22 Forest plot showing the effect of ARBs versus ACEIs on risk of HF (FE model). Overall: 8 RCTs

The diamond indicates the pooled risk ratio (and 95% CI) or the overall effect for HF risk. CI: confidence interval; FE: fixed-effect; M-H: Mantel-Haenszel. For studies acronyms, see list of definition/ abbreviations

6.8.2 Sensitivity analysis

Sensitivity analysis was carried out by excluding trials with an HF cohort: two trials enrolled patients with symptomatic HF (NYHA class II-IV) (ELITE II and HONG-KONG DHF) and two trials enrolled patients with acute MI and clinical signs of HF (OPTIMAAL and VALIANT) (see **Figure 6.2**). Excluding these did not modify the pooled effect estimate, with an RR of 1.05 (95% CI 0.94-1.18; p=0.38). However, the combined 95% CI became wider. Remarkably, the ONTARGET study carried the most weight (98.0%) and, hence, had the greatest influence in this meta-analysis. No statistical heterogeneity was observed (chi-square test p value = 0.84 and $l^2=0\%$).

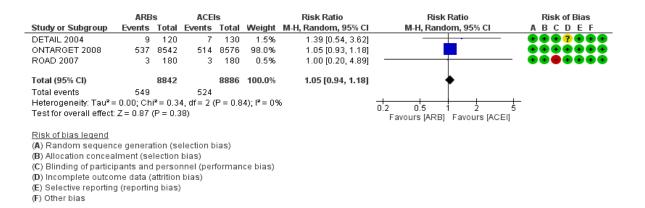


Figure 6-23 Forest plot showing the effect of ARBs versus ACEIs on risk of HF [Sensitivity analysis: Excluding HF trials]. Overall: 3 RCTs (RE model).

CI: confidence interval; RE: random-effects; M-H: Mantel-Haenszel. For studies acronyms, see list of definition/ abbreviations

6.9 Discussion

The present study demonstrates three main findings. First, it provides clear evidence that both ACEIs and ARBs are able to reduce risk of HF when compared with a placebo or active group. The observed reduction is broadly consistent across various clinical conditions, suggesting that the two drug classes would provide a broadly generalisable benefit. Moreover, a series of sensitivity analyses confirmed the strength of the overall benefit of ARBs and ACEIs. Second, this study suggests that ARBs therapy confers protection against HF independently of BP reduction, whereas the benefit of ACEIs on HF risk is explained by SBP reduction.

While basic scientific research continues to show the differential pharmacological actions of ACEIs and ARBs, increasing clinical data has demonstrated contradictory results in terms of the efficacy of ACEIs and ARBs in reducing the risk of HF in a wide spectrum of patients (Yusuf et al., 2008d, Dickstein et al., 2002). Many studies have theoretically postulated that ACEIs are unable to fully supress the formation of Ang II by angiotensin-converting enzyme (ACE) during chronic treatment with these agents, and have suggested recovery of Ang II via an alternative pathway called a non-ACE dependent pathway (chymase) (Ferrario and Mullick, 2017). The chymase pathway has been implicated as the primary generator of Ang II (Ahmad et al., 2011). Ang II reactivation has been found in 50% of patients with HF chronically treated by ACEIs. (Roig et al., 2000). However, the reactivation in subjects with HTN or at high risk of CV diseases is still unknown. ARBs block the binding of Ang II to the AT₁ receptor, regardless of its formation pathway (ACEI or non-ACEI pathway).

The meta-analysis by Savarese et al. (2013) demonstrated a significant reduction of HF by ACEIs therapy but not ARBs compared with placebo in high-risk patients without overt HF. However, based on their inclusion criteria, the ACTIVE-I (2011) trial was not included (Yusuf et al., 2011). This trial showed a beneficial effect of irbesartan on risk of HF compared with placebo in patients with AF (RR, 0.87; 95% CI 0.78-0.98) and so would have exerted a major influence on the pooled effect estimates. Furthermore, other findings reported in a recent meta-analysis of 21 RCTs involving 58,722 participants with underlying various baseline co-morbidities (Ettehad et al., 2016). Even though the design of that analysis was similar to this review, the authors found no beneficial effect of ACEIs or ARBs compared with control group (placebo or active) in preventing HF. This result is a reflection of their inclusion and exclusion criteria, which may have influenced the overall effect estimate. They included a larger trial, the ONTARGET, involving 8,576 participants with or at risk of vascular disease without HF, and assessed whether telmisartan was at least as effective as ramipril or not (Yusuf et al., 2008d). The trial showed no significant differences between the two groups in relative risk of HF; thus, this might mask a potential benefit. Furthermore, an important trial, the VALUE, was not included. In this trial, the risk of HF was lower in the group allocated to the valsartan-based regimen than those on amlodipine, although it did not reach statistical significance (-12% (+1 to -24%)). However, our analysis shows that ACEIs and ARBs are associated with a significant reduction in HF risk. It important to note that, despite the possibly heterogenous high-risk population in our review, there was proportional similarity of ACEI benefits in placebocontrolled trials.

In line with our findings, Bangalore et al. (2011) pooled data from 20 RCTs that enrolled 147,020 individuals with various medical conditions, and demonstrated that ARBs therapy reduced the risk of HF compared with either placebo or active control. Though the heterogeneity across effect estimates of ARBs trials for the HF outcome was significant (I²=58.4%, p<0.001), no further investigation was carried out. This statistical heterogeneity might be a result of including trials that directly compared ARBs with ACEIs to primary analysis. In contrast to our review, they also included trials of haemodialysis patients.

The safety profile as well as tolerability of ARB therapy could explain the apparent benefit. From direct comparisons by eight trials in patients without HF, the withdrawal rate was 23% lower in the ARBs group compared to the ACEIs group (Bangalore et al., 2016). Thomopoulos et al. (2016) found that treatment with ARBs had a significant 29% lower risk of discontinuation when compared with all other BP-lowering agents. Furthermore, they demonstrated that ARBs, among all commonly used BP-lowering agents, did not have a higher discontinuation rate than the placebo.

Although there was superiority of ARBs over ACEIs when compared with active control for prevention of HF, subgroup analysis explained the lack of benefits of

ACEIs. The absent benefits of ACEIs compared with active control was largely determined by one trial that used diuretics as the comparator arm, ALLHAT (diuretic). In this trial, the superiority of chlorthalidone over lisinopril in preventing HF may have been due to the 2-mmHg reduction in SBP by chlorthalidone. Moreover, 71.2% of patients randomized to thiazide-like diuretics continued with treatment, compared to only 61.2% of those randomized to lisinopril. This lower persistence with the lisinopril-based regimen may explain the poorer results for this group. Though the ALLHAT (diuretic) trial was assigned high percentage of overall effect estimate (21.8%) of HF, the effects of ACEI on HF risk compared with active control must be interpreted with caution.

Though the protective effect of ACEIs and ARBs against HF have been confirmed previously (Bangalore et al., 2016), the conflicting results of association between BP reduction and HF were apparent in individual trials of ACEIs or ARBs. In 2000, the HOPE trial enrolled patients of whom 90% had previous CV diseases, 80.4% had a history of CAD, 46.8% of HTN, and 38.4% diabetes. Treatment with ramipril led to a 22% reduction in HF risk with SBP differences of -3.3 mmHg between the two randomized groups. According to a recent meta-regression, a reduction in SBP of 10 mmHg by antihypertensives would be expected to lower HF risk by 28% (Ettehad et al., 2016). Accordingly, the HOPE trial gave rise to the hypothesis that ACEIs might additionally reduce the risk of HF beyond BP control in high-risk patients (Yusuf et al., 2000, Arnold et al., 2003). However, the results of our metaregression suggest that the observed HF reduction in the HOPE trial (RR=0.78) for the group assigned to ramipril might be explained mainly by differences in SBP, as the predicated RR is 0.76. Furthermore, the RENAAL and IDNT trials, which involved hypertensive patients with diabetic nephropathy, reported a significantly lower risk of HF in the ARB-based regimen groups (Brenner et al., 2001, Lewis et al., 2001). Nevertheless, the mechanism that underlines this reduction may be a result of a decline in the progress of proteinuria, an independent risk of HF, or attributed to BP reduction (Currie and Delles, 2013). Meta-regression by Verdecchia et al. (2009) revealed that ACEIs and ARBs provide an additional 19% reduction in HF independently of BP reduction in patients with hypertension or high CV risk. However, they dealt with ACEIs and ARBs as one group. In 2007, a report from the Blood Pressure Lowering Treatment Trialist's Collaboration (BPLCT) demonstrated that the magnitude of HF risk reduction of both classes was

positively related to BP reduction and no BP-independent effect was seen for either drug class in patients with various medical conditions (Turnbull, 2007). However, the ARBs analysis is likely underpowered, as the 95% CI was wider than that of ACEIs, likely due to a smaller number of included participants. Moreover, trials that directly compared ARBs with ACEIs were included (VALIANT, OPTIMAAL, and LITE II), which might have attenuated the effect of ARBs therapy.

Interestingly, our comprehensive meta-regression analyses of 50 trials found that ARBs but not ACEIs provided protection from HF independently of BP reduction, whereas the beneficial effect of ACEIs on HF risk could be explained by SBP reduction. As the limitation of CCBs in preventing HF is well recognised, a series of sensitivity analyses were conducted by excluding trials with CCBs as the comparator. The results were consistent for ACEIs and would support the primary findings. The direction and magnitude of the BP-independent effect of ARBs is consistent but does not reach the level of significance. This finding might be the result of the harmful effects of CCBs on HF risk: CCBs reduce left ventricular afterload and neurohormonal activation in response to arterial vasodilatation, and the direct negative inotropic action on the myocardium may elicit HF in predisposed patients (Rousseau et al., 1994). Additionally, a common adverse event associated with dihydropyridine CCBs is ankle oedema, which could be misinterpreted as CHF. The meta-regression also explains the variation among trials either observed statistically or not in the meta-analysis. While the benefit of ACEIs was remarkably consistent for the HF outcome (between-trial heterogeneity 1² ranging from 8% to 27%), the meta-regression showed that differences in achieved SBP (mmHg) largely explains the variation between study estimates. Whereas the observed heterogeneity among the effect estimates of ARBs trials might be attributable to mean age (years) and percentage of male gender.

Several RCTs and meta-analyses have demonstrated the beneficial effects of ACEIs and ARBs on risk of HF; however, none of these studies targeted primarily older populations. In the current analysis, the subgroup analyses of trials that predominately enrolled patients \geq 65 years of age showed that ARBs reduced HF risk whereas ACEIs did not. However, pooled estimates of ACEIs must be interpreted with caution, as there was evidence of heterogeneity among ACEIs trials, largely due to the ALLHAT trial. After excluding this trial, the magnitude and direction of pooled estimates shifted to a significant reduction at metaanalysis level. In this trial, lisinopril had a 19% higher risk of HF than chlorthalidone. The lisinopril group had a 2 mmHg higher SBP than the group allocated to chlorthalidone over the 5-year follow-up period, which could explain the higher incidence of HF. Moreover, this might have been the result of study population characteristics: the study enrolled older patients and had a large proportion of black patients (35%), who are known to have low plasma renin activity and, thus, a better clinical response to diuretics (Sagnella, 2001). A metaanalysis of RCTs by Bavishi et al. (2016) was published on the efficacy and safety of ACEIs in patients \geq 65 years of age, which found a similar conclusion, despite including trials that compared ACEIs with ARBs (ELITE II, OPTIMAAL, ONTARGET, and VALIANT). Whereas, Elgendy et al. (2015) conducted a meta-analysis of studies in older patients with or at high risk of CV diseases and concluded that ARBs failed to reduce HF compared with the control. However, there was a marked heterogeneity among treatment estimates of HF outcome (I²=90.0%). This heterogeneity could be attributable to the inclusion of trials that used ACEIs as the comparator, which might have attenuated the beneficial effects of ARBs.

Despite the inclusion of a heterogenous high-risk population in our review, there was proportional similarity of ACEIs and ARBs benefits among trials. The presence of clinical variation between ACEIs and ARBs on HF risk among medical conditions is possible. Therefore, the primary overall effect estimates of both ACEIs and ARBs were stratified based on population clinical setting for further investigation. A similar benefit of ARBs and ACEIs on preventing of HF was clearly observed in highrisk hypertensives, at -9% (-2% to -16%) and -11% (-1% to -21%), respectively. The meta-analysis by Thomopoulos et al. (2015b) in high-risk hypertensives reported similar results; however, we included more five trials that were published after 2013 when their search period ended. In 2017, a meta-analysis assessed the effect of RAS blocker with stable CAD without HF (Bangalore et al., 2017). Despite demonstrating a beneficial effect of this class on risk of HF, a study was designed to assess RAS blocker as a class. Our subgroup shows that ACEIs seem to lead to a decreased risk of HF in patients with underlying CAD, whereas ARBs did not. However, the lack of benefit of ARBs in reducing risk of HF in patients with CAD was mainly as a result of the TRANSCEND trial, which contributed 77.8% of the

overall weight. Although the benefit of ARBs was superior to ACEIs therapy on HF in diabetic patients, the pooled confidence limit of ACEI was wide, due to low events rates; thus, it may not have sufficient statistical power to detect an actual effect, and also might be influenced by the ADVANCE trial.

Our reported results are supported by trials directly comparing ARBs to ACEIs, showing an equivalent effect between both classes. Notably, the heterogeneity analyses support a statistical consistently among trials $(1^2=0\%)$. A comparable result was demonstrated in a recent network meta-analysis that assessed the superiority of ACEIs versus ARBs in reducing risk of CV morbidity and mortality in high-risk patients without HF (Ricci et al., 2016). In contrast, direct comparison of common BP-lowering agents including ACEIs and ARBs in high-risk hypertensives reported that ACEIs therapy led to a 10% non-significant reduction in hospitalization of HF compared with ARBs (Thomopoulos et al., 2015a). However, 96.6% of the included participants were from the ONTARGET trial; thus, their findings largely reflected the results of the ONTARGET trial. Nevertheless, our result should not be overestimated, as an equivalent effect may be a result of aggressive use of therapy in the included trials, such as higher rates of concomitant use of B-blockers and statins (Yusuf et al., 2008d). Moreover, some trials used relatively low doses of ARBs, which may have led to suboptimal therapeutic effects (Pitt et al., 2000, Dickstein et al., 2002).

6.9.1 Strengths and limitations

The main strength of the analyses presented here is that data was pooled from 295,450 participants involved in 70 trials, making it more comprehensive than other previous analyses. Unlike previous meta-analyses (Bangalore et al., 2016, Savarese et al., 2013), the trials with baseline co-morbidities were not excluded, thus allowing for generalisability of the findings and assessment of treatment effect stratified based on clinical settings. To the best of our knowledge, the HF events of the ADVANCE, CHIEF, and PREVER-Treatment studies were first incorporated in this analysis. Furthermore, unpublished data was extracted from FDA and sponsors' clinical data websites. Our meta-regression analysis is the first to date that documents the BP-independent effect of ARBs therapy, whereas the effect of ACEIs is BP dependent on relative risk of HF. Subgroup and sensitivity

analyses confirmed consistent findings, and the statistical heterogeneity indicated by I² remained at an appropriate level.

The present study also has a number of limitations. The first and main drawback is that the aggregate patient data (APD) was only available for this review, which may lead to ecological bias. Second, lack of important data in each trial did not allow the meta-regression analysis to be adjusted for potential confounders and to explore possible heterogeneity. Third, HF is an outcome that strongly requires adjudication in a blinded fashion by an Event Adjudication Committee (EAC). However, in a number of RCTs it was unclear whether HF was among the outcomes adjudicated or not. Moreover, the definition of HF events might be inconsistent across different trials. A majority of RCTs considered in this meta-analysis followed a double-blind design, which guarantees some homogeneity of betweentreatment comparisons of HF risk.

6.10 Conclusion

The findings of the current meta-analysis suggest that the risk of HF decreases through use of either ACEIs or ARBs therapy. ARBs therapy appears to prevent HF independently of BP reduction in patients with or at-risk of CVD, whereas the HF reduction by ACEI therapy is associated with the BP reduction.

7 Angiotensin-converting enzyme inhibitors (ACEIs) versus angiotensin receptor blockers (ARBs) with risk of mortality

7.1 Introduction

Hypertension (HTN) is considered to be the main leading cause of cardiovascular (CV) and renal events, including ischemic heart disease (IHD), cerebrovascular diseases, and renal failure (WHO, 2020). In 2015, an elevated level of systolic blood pressure (SBP) of \geq 140 mmHg accounted for 7.8 million deaths (14% of total deaths), and 143 million disability-adjusted life-years lost (DALYs) (Forouzanfar et al., 2017). The largest numbers of SBP-related deaths were caused by IHD (54.4%), 58.3% haemorrhagic stroke (58.3%) and ischemic stroke (50.8%) (Forouzanfar et al., 2017). According to a Global Burden of Disease (GBD) analysis (2019), globally, an elevated BP was the primary risk factor for death in females (20.3% of all female deaths) and the second risk factor males in 2019 (18.2% of all male deaths) (GBD 2019 Risk Factors Collaborators, 2020). Although the ultimate goal of hypertension management is to prevent mortality, the guidelines emphasise adequate control of blood-pressure (BP) (Williams et al., 2018, NICE, 2019)

7.2 Rationale of the study

An overactive renin-angiotensin aldosterone system (RAAS) is strongly linked to pathogenesis of HTN; thus, RAAS inhibitors, including ARBs and ACEIs, are the most widely prescribed medications for the management of hypertension and its complications. Study data has shown that the two classes of medication have a comparable clinical profile in terms of lowering BP (Dahlöf et al., 2002, Lithell et al., 2003). However, these medications have differentiated pharmacological properties and, thus, may have different clinical consequences (Ferrario and Mullick, 2017). The unique mechanisms of ACEIs and ARBs have been described in **Chapter 1, Section 1.4.3**.

Two contemporary trials showed no differences between ACEI and ARB in terms of mortality reduction. The ONTARGET trial (high-risk patients) and DETAIL trial (patients with diabetic nephropathy) reported a greater reduction of SBP favoured ARBs compared with ACEI, 0.9 and 3 mmHg, respectively (Barnett et al., 2004, Yusuf et al., 2008d). Therefore, it is indicated that mortality risk is more effectively reduced with an ARBs-based regimen than an ACEIs-based one. It should be noted that telmisartan remains active longer than the medications used in the trials, that is, ramipril and enalapril, respectively.

In trials using ARBs compared with a placebo, the observed reduction in SBP did not always translate into mortality reduction. The achieved mean SBP was lower in the ARB group than in the placebo group by 3.2 mmHg in the SCOPE study and 4.2 mmHg in the TRANSCEND study; no benefit in the mortality risk were observed in either of the studies (Lithell et al., 2003, Yusuf et al., 2008c). In the SCOPE trial, the majority of participants (66%) assigned to the placebo received openlabel antihypertensive agents including diuretics, beta-blockers and CCBs than in those assigned to candesartan (44%).

A meta-analysis of the mortality reduction by RAAS in hypertensives found that the ACEIs lowered the risk of CV mortality by 12% toward the significant level and reduced the risk of all-cause mortality by 10% (van Vark et al., 2012). No benefits were seen in the case of ARB therapy. The effect of both ACEIs and ARBs on CV mortality was statistically non-significant (P interaction= 0.227); however, the difference between ARB and ACEI in terms of reducing the risk of all-cause mortality was significant (P interaction= 0.036). It is worth noting that mortality reduction by ACEIs was mainly driven from ASCOT-BPLA trial that assessed amlodipine with and without perindopril and the HYVET trial that used indapamide with and without perindopril. Moreover, the CV mortality data of CASE-J, IDNT and RENAAL were not included in van Vark et al. (2012) review. Their metaregression analysis revealed an association between achieved SBP reduction and mortality risk. However, the authors dealt with ACEIs and ARBs as one class.

In light of these conflicting results, this chapter aims to assess the efficacy of ACEIs and ARBs in lowering both all-cause and CV mortality risk of patients with or at high-risk of CVD. Moreover, the meta-regression is also being carried out to investigate the impact of BP reduction on observed effects by ACEIs and ARBs.

7.3 Methodology

7.3.1 Search strategy and selection criteria

This chapter presents a comparison between ACEIs and ARBs using placebo and active comparators to explore risk of all and CV mortality. A full description of the methods used for this systematic review and meta-analysis has been explained in **Chapter 2 Section 2.1**.

7.3.2Data extraction and source of data

The outcomes of this study are CV and all-cause mortality risks. The data extracted for evidence synthesis included number of events, baseline characteristics, whether the mortality was prespecified outcome, source of data and quality of each trial. The majority of CV and all-mortality data was published. The total mortality data of the IRMA-2 trial was reported by the Center for Drug Evaluation and Research (CDER) of the FDA (FDA, 2001a). CV mortality was prespecified in the Val-HeFT trial as a primary endpoint and only CV death due to HF was reported. Therefore, CV death data was extracted from the FDA website (Novartis Advisory Committee, 2002). Also, data relating to CV mortality in the DEMAND, COPE and PREAMI trials were reported as a pre-specified combined endpoint in a manner that prevented meaningful extraction. So, in the DEMAND trial, sudden death was reported and extracted. The source of data, whether the outcome was predefined, and the overall quality of trials are reported in **Tables E-1 and E-2 presented in Appendix E.**

The CARP, J-RHYTHM II, QUO VADIS, J-RHYTHM II, PHARAO, MITEC and NTP-AF trials reported zero CV death events; however, these trials were not designed and powered to detect CV mortality. Also, the CARP, QUO VADIS 2001 and ROAD trials reported zero all-cause mortality events. The ATTEMPT-CVD, CASE-J and DEMAND trials reported only sudden cardiac death.

7.3.3 Statistical analysis

7.3.3.1 Meta-analysis

The data synthesis and analysis method used have been fully described in **Chapter 2 Section 2.1.9**

7.3.3.2 Meta-regression analysis

A full description of meta-regression analysis used has been described in **Chapter 2, Section 2.1.10**

7.4 Results

7.4.1Search results

A total of 73 (85.2% of included trials) trials reported CV deaths and 86 RCTs (88% of included trials) reported all-mortality events either as a predefined outcome or as an adverse event (these trials were described in detail in Chapter 3, Section 3.1.2). To gather data on CV mortality, 36 ACEIs RCTs involving 123,899 participants were analysed to prospectively test the effectiveness of ACEIs when compared with a placebo or active control. These RCTs had an average follow-up of 3.4 years (ranging from 1 to 6 years) and the average patients' age across all of the studies was 66.6 years.

34 ARB RCTs reported CV mortality events among 139,988 participants with various co-morbidities. The average follow-up of these RCTs was 3.5 years (ranging from 1 to 5.9 years) and the average patients' age across all of the studies was 63.3 years. 8 trials involving 37,103 participants directly compared ARB with ACEI.

In regard to all-cause mortality, 41 RCTs involved 125,824 participants were randomised to an ACEI-based therapy group versus a control group (placebo or active). The studies had an average follow-up of 3.5 years (ranging from 1 to 6 years). The average patients' age across all of the studies was 63.4 years. In an additional 43 trials, 151,721 participants were allocated to an ARB-based or control group (placebo or actives). These studies had an average follow-up of 3.2 years. 10 trials (n=41,106) directly compared ACEIs with ARBs therapies on all

mortality. Details on the population characteristics and the risk of bias of RCTs included in this review are given in **Appendices B and C.**

Almost all the trials included in this study reported CV mortality data as a predefined endpoint. The BENEDICT, ROAD, Weil et al., HONG-KONG DHF and MITEC trials mortality was reported as an adverse event. 19 RCTs reported all-cause mortality as an adverse event (namely AARDVARK, ATLANTIS, BENEDICT, DEMAND, Hou et al (group 2), RASS, ELVERA, Fogari et al, ANTIPAF, DIRECT (Overall), EFFERVESCENT, IRMA-2, RASS, Weil et al, Dahl et al., HONG-KONG DHF, MITEC, CORD 1 B and ROAD).

7.5 ACEIs and risk of CV mortality

7.5.10verall treatment effect

The data of 36 RCTs were pooled to assess the effectiveness of ACEI on occurrence of CV mortality (n= 123,899 participants) and reported 6224 CV deaths. **Figure 7-**1 shows a RE meta-analytical summary of ACEI on the risk of CV death compared with either a placebo or an active therapy group. Altogether, the incidence rate of CV death was significantly lower in patients using ACEIs than those in the control group (4.57% and 5.36%, respectively). ACEIs was associated with a significant 9% reduction in CV death as compared to the control group (RR, 0.91; 95% CI 0.86-0.97; P=0.002).

A total of 21 RCTs involving 75,429 subjects assessed the effect of ACEI when compared to a placebo. The incidence rate of CV death in patients assigned to the ACEI group (4.45%) was lower than that in the placebo group (5.15%). The ACEI group had a 13% lower risk of CV death (RR, 0.87; 95% CI 0.81-0.94; p= 0.0003). There was no evidence of statistical heterogeneity among the trials (chi-square p value = 0.31 and I²=12%).

Data on the effectiveness of ACEIs compared with active control was obtained from 16 RCTs involving 48,470 participants and 2600 observed events. The ALLHAT trial was assigned a higher weighting (23.1%) and showed a neutral effect. No benefit was seen for ACEI therapy compared to active drugs with an RR of 1.02 (95% CI 0.94, 1.11; p=0.56). No evidence of heterogeneity was found (chi-square

p value = 0.99 and $I^2 = 0\%$). In light of the no statistical heterogeneity result, the summary effect estimates generated by a FE were almost similar to RE with a higher weighting assigned to the HOPE and ALLHAT trials (see Figure 7-2). A visual examination of the funnel plot (Appendix D, figure D-3) reveals missing data in a nonsignificant area (gap in bottom right side) that may be the due to unpublished smaller studies that yielded no statistically significant effects. No outlier was detected.

	ACE	3	Cont	rol		Risk Ratio	Risk Ratio	Risk of Bias
Study or Subgroup	Events		Events		Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl	ABCDEFG
1.1.1 ACEI vs Placebo	Luoino	Total	Lionto	Total	roight	in fight and only obtained		N B C B E I G
ADVANCE 2007	211	5569	257	5571	8.8%	0.82 [0.69, 0.98]		
APRES 2000	- 1	80	7	79	0.0%	0.14 [0.02, 1.12]	•	
BENEDICT (monotherapy) 2004	. 1	301	3	300	0.1%	0.33 [0.03, 3.18]	· · · · · · · · · · · · · · · · · · ·	??
CAMELOT (Placebo) 2004	5	673	2	655	0.1%	2.43 [0.47, 12.50]		+
CCS-I 2001	340	3391	395	3358	13.3%	0.85 [0.74, 0.98]	-	
DEMAND (monotherapy) 2011	0	127	2	127	0.0%	0.20 [0.01, 4.12]	←	
DIABHYCAR 2004	179	2443	175	2469	7.2%	1.03 [0.85, 1.26]	_ _	
DREAM 2006	12	2623	10	2646	0.5%	1.21 [0.52, 2.80]		
EUROPA 2003	215	6110	249	6108	8.7%	0.86 [0.72, 1.03]	-	??
HOPE 2000	282	4645	377	4652	11.7%	0.75 [0.65, 0.87]		2000000
HYVET (Placebo) 2003	22	431	19	426	0.9%	1.14 [0.63, 2.08]		
IMAGINE 2008	18	1280	15	1273	0.7%	1.19 [0.60, 2.36]		
PART-2 2000	8	308	18	309	0.5%	0.45 [0.20, 1.01]		
PEACE 2004	146	4158	152	4132	6.0%	0.95 [0.76, 1.19]	_ _	
PEP-CHF 2006	38	424	40	426	1.8%	0.95 [0.63, 1.46]		
PHARAO 2008	0	505	0	503		Not estimable		
PREVEND IT 2007	5	431	3	433	0.2%	1.67 [0.40, 6.96]		
PROGRESS 2001	181	3051	198	3054	7.5%	0.92 [0.75, 1.11]		
QUIET 2001	13	878	14	872	0.6%	0.92 [0.44, 1.95]		??
QUO VADIS 2001	0	75	0	73	0.070	Not estimable		??
SCAT 2000	4	229	7	231	0.2%	0.58 [0.17, 1.94]		
Subtotal (95% CI)	-	37732		37697	68.7%	0.87 [0.81, 0.94]	•	
Total events	1681		1943				•	
Heterogeneity: Tau ² = 0.00; Chi ² =		= 18 (P =		= 17%				
Test for overall effect: Z = 3.63 (P =		- 10 (1 -	0.017,1	- 12.0				
	ŕ							
1.1.2 ACEI vs Active								
AASK 2002	12	436	19	658	0.7%	0.95 [0.47, 1.94]		
ABCD (normotensive) 2002	14	246	8	234	0.5%	1.66 [0.71, 3.89]		$\bullet \bullet \bullet \bullet \bullet \circ \bullet \circ \circ$
ALLHAT 2002	618	9054	1599	24303	23.1%	1.04 [0.95, 1.13]		
ANBP2 2003	84	3044	82	3039	3.5%	1.02 [0.76, 1.38]	. +	?
BENEDICT (combination) 2004	0	300	1	303	0.0%	0.34 [0.01, 8.23]		- ??
BENEDICT (monotherapy) 2004	1	301	1	303	0.0%	1.01 [0.06, 16.02]	4	* ??@@@@@@
CAMELOT (Active) 2004	5	673	5	663	0.2%	0.99 [0.29, 3.39]		\bullet ? \bullet \bullet \bullet \bullet ?
CARMEN (combination) 2004	9	191	13	191	0.5%	0.69 [0.30, 1.58]		?
CARMEN (monotherapy) 2004	14	190	13	191	0.6%	1.08 [0.52, 2.24]		?
Chan et al 2000	2	50	2	52	0.1%	1.04 [0.15, 7.10]		? ? • • ? • ?
ESPIRAL 2001	3	129	6	112	0.2%	0.43 [0.11, 1.70]	•	2 2 🖨 2 🔒 3
Fogari et al (combination) 2002	1	104	2	103	0.1%	0.50 [0.05, 5.38]	·	🔁 ? 🖨 ? ? 🖶 ?
Fogari et al (monotherapy) 2002	2	102	2	103	0.1%	1.01 [0.15, 7.03]		• ? • ? ? • ?
HYVET (diuretics) 2003	22	431	23	426	1.0%	0.95 [0.54, 1.67]		••••?
JAMP 2004	11	466	14	422	0.5%	0.71 [0.33, 1.55]		3 3 🖨 3 3 🖶 🗣
JMIC-B 2004	6	822	6	828	0.3%	1.01 [0.33, 3.11]		
Subtotal (95% CI)		16539		31931	31.3%	1.02 [0.94, 1.11]	•	
Total events	804		1796					
Heterogeneity: Tau ² = 0.00; Chi ² =		15 (P = 0	0.99); I² =	0%				
Test for overall effect: Z = 0.58 (P =	= 0.56)							
Total (95% CI)		54271		69628	100.0%	0.91 [0.86, 0.97]	•	
Total events	2485	54271	3739	00020	100.070	01011[0100, 0101]	•	
Heterogeneity: Tau ² = 0.00; Chi ² =		= 34 (P =		= 6%				_
Test for overall effect: Z = 3.07 (P =		010	0.017,1	- 0 /0			0.2 0.5 1 2 5	
Test for subgroup differences: Ch		f= 1 (P -	= 0.004\	I ² = 87 9	96		Favours [ACE] Favours [control]	
Risk of bias legend	. – 0.20, u	0	0.004),	. – 07.8				
(A) Random sequence generation	(selection	n hias)						
(B) Allocation concealment (selec		n bias)						
(C) Blinding of participants and pe		orformo	nce bice	、 、				
(D) Blinding of outcome assessm					e			
(E) Incomplete outcome data (attri		uon pias	y. other i	sacome	3			
(c) meaniplete outcome data (attri	uon pias)							

(E) Incomplete outcome data (attrition (F) Selective reporting (reporting bias) ion bias)

(G) Other bias

Figure 7-1 Forest plot showing effect of ACEIs on risk of CV mortality, stratified by comparison group (placebo vs active). Overall: 36 trials (RE model).

The diamond indicates the pooled risk ratio (and 95% CI) or the overall effect for CV mortality risk. CI: confidence interval; RE: random-effects; M-H: Mantel-Haenszel. For studies acronyms, see list of definition/ abbreviations

Study or Subgroup	ACE Events		Cont Events		Moight	Risk Ratio M-H, Fixed, 95% Cl	Risk Ratio M-H, Fixed, 95% Cl	Risk of Bias
1.1.1 ACELVS Placebo	Events	TULAI	Evenus	TULAI	weight	WI-FI, FIXeu, 95% CI	M-H, Fixed, 95% Cl	ABCDEFG
ADVANCE 2007	211	5569	257	5571	8.5%	0.82 [0.69, 0.98]		
APRES 2000	- 1	80	237	79	0.2%	0.14 [0.02, 1.12]	•	
BENEDICT (monotherapy) 2004	1	301	3	300	0.1%	0.33 [0.03, 3.18]		??
CAMELOT (Placebo) 2004	5	673	2	655	0.1%	2.43 [0.47, 12.50]		
CCS-I 2001	340	3391	395	3358	13.2%	0.85 [0.74, 0.98]		
DEMAND (monotherapy) 2011	0	127	2	127	0.1%	0.20 [0.01, 4.12]	←	
DIABHYCAR 2004	179	2443	175	2469	5.8%	1.03 [0.85, 1.26]	+	
DREAM 2006	12	2623	10	2646	0.3%	1.21 [0.52, 2.80]		
EUROPA 2003	215	6110	249	6108	8.3%	0.86 [0.72, 1.03]		? ? . ? . . .
HOPE 2000	282	4645	377	4652	12.5%	0.75 [0.65, 0.87]	-	? • • • • • • •
HYVET (Placebo) 2003	22	431	19	426	0.6%	1.14 [0.63, 2.08]		$\bullet \bullet \bullet \circ \circ$
IMAGINE 2008	18	1280	15	1273	0.5%	1.19 [0.60, 2.36]		
PART-2 2000	8	308	18	309	0.6%	0.45 [0.20, 1.01]		$\bullet \bullet $
PEACE 2004	146	4158	152	4132	5.1%	0.95 [0.76, 1.19]		$\bullet \bullet $
PEP-CHF 2006	38	424	40	426	1.3%	0.95 [0.63, 1.46]		
PHARAO 2008	5	505	3	503	0.1%	Not estimable		
PREVEND IT 2007 PROGRESS 2001	181	431 3051	198	433 3054	6.6%	1.67 [0.40, 6.96] 0.92 [0.75, 1.11]		
QUIET 2001	13	878	198	872	0.5%	0.92 [0.44, 1.95]		? ?
QUO VADIS 2001	0	75	0	73	0.5%	Not estimable	-	2200000
SCAT 2000	4	229	7	231	0.2%	0.58 [0.17, 1.94]		
Subtotal (95% CI)	-	37732		37697	64.7%	0.86 [0.81, 0.92]	•	
Total events	1681		1943				•	
Heterogeneity: Chi ² = 20.45. df = 1		$1) \cdot 1^2 = 1^2$						
Test for overall effect: Z = 4.53 (P								
	0.00001,							
1.1.2 ACEI vs Active								
AASK 2002	12	436	19	658	0.5%	0.95 [0.47, 1.94]		
ABCD (normotensive) 2002	14	246	8	234	0.3%	1.66 [0.71, 3.89]		
ALLHAT 2002	618	9054	1599	24303	28.9%	1.04 [0.95, 1.13]	+	
ANBP2 2003	84	3044	82	3039	2.7%	1.02 [0.76, 1.38]	_ _	? • • • • • •
BENEDICT (combination) 2004	0	300	1	303	0.0%	0.34 [0.01, 8.23]	• • •	???
BENEDICT (monotherapy) 2004	1	301	1	303	0.0%	1.01 [0.06, 16.02]	· · · · · ·	• • • • • • • •
CAMELOT (Active) 2004	5	673	5	663	0.2%	0.99 [0.29, 3.39]		\bullet ? \bullet \bullet \bullet \bullet ?
CARMEN (combination) 2004	9	191	13	191	0.4%	0.69 [0.30, 1.58]		? • • • • • • •
CARMEN (monotherapy) 2004	14	190	13	191	0.4%	1.08 [0.52, 2.24]		? • • • • • • •
Chan et al 2000	2	50	2	52	0.1%	1.04 [0.15, 7.10]		??!!?!?!?!?!!?!!?!!?!!?!!!!!!!!!!!!!
ESPIRAL 2001	3	129	6	112	0.2%	0.43 [0.11, 1.70]		3303303
Fogari et al (combination) 2002	1	104	2	103	0.1%	0.50 [0.05, 5.38]	•	$\bullet \circ \bullet \circ \circ \bullet \circ \circ$
Fogari et al (monotherapy) 2002	2	102	2	103	0.1%	1.01 [0.15, 7.03]		
HYVET (diuretics) 2003	22	431	23	426	0.8%	0.95 [0.54, 1.67]		
JAMP 2004	11	466	14	422	0.5%	0.71 [0.33, 1.55]		
JMIC-B 2004 Subtotal (95% CI)	6	822 16539	ь	828 31931	0.2% 35.3%	1.01 [0.33, 3.11] 1.02 [0.94, 1.11]		
Total events	804	10559	1796	51951	33.3%	1.02 [0.94, 1.11]	Ť	
Heterogeneity: Chi ² = 5.53, df = 15								
Test for overall effect: Z = 0.56 (P =), I-= 0%	•					
Testion overall ellect. Z = 0.50 (F -	. 0.50)							
Total (95% CI)		54271		69628	100.0%	0.92 [0.88, 0.97]	•	
Total events	2485		3739					
Heterogeneity: Chi ² = 36.19, df = 3		$7): I^2 = 6!$						
Test for overall effect: Z = 3.25 (P =							0.2 0.5 1 2 5	
Test for subgroup differences: Ch		df = 1 (F	9 = 0.001), I [≈] = 90,	3%		Favours [ACE] Favours [control]	
Risk of bias legend								
(A) Random sequence generation	1 (selectio	n bias)						
(B) Allocation concealment (selec								
(C) Blinding of participants and pe	rsonnel (r	performa	nce bias	.)				
(D) Blinding of outcome assessm		tion bias): Other	outcome	s			
(E) Incomplete outcome data (attri	tion bias)							
(F) Selective reporting (reporting b	ias)							
(G) Other bias								

Figure 7-2 Forest plot showing effect of ACEIs on risk of CV mortality, stratified by comparison group (placebo vs active). Overall: 36 trials (FE model).

The **diamond** indicates the pooled risk ratio (and 95% CI) or the overall effect for CV mortality risk. CI: confidence interval; FE: fixed-effect; M-H: Mantel-Haenszel. For studies acronyms, see list of definition/ abbreviations

7.5.2Sensitivity analysis

Figure 7-3 displays a RE summary of ACEI treatment effect estimates following the exclusion of 9 placebo-controlled trials involving participants without background use of RAS blockers (naïve) (APRES; DIABHYCAR; EUROPA; HOPE; PEACE; PHARAO; PREVEND IT; QUIET; QUO VADIS). All RCTs involving naïve patients had mainly allocated participants to the placebo group. Excluding those RCTs did not change the RR of ACEI on CV death reduction (RR, 0.87; 95% CI 0.79-0.95; p=0.002). No evidence of heterogeneity was detected. The exclusion of 24 RCTs with poor methodology hand no impact on the RR of CV death. However, the 95% CI became wider as the sample size decreased (RR, 0.91; 95% CI 0.82-1.02; p=0.11). No evidence of heterogeneity was found among the trials (see Figure 7-4)

Study or Subarows	ACE Events		Cont		Moight	Risk Ratio	Risk Ratio	Risk of Bias
Study or Subgroup	Events	rotal	Events	rotal	vveight	M-H, Random, 95% Cl	M-H, Random, 95% Cl	ABCDEFG
1.1.1 ACEI vs Placebo							_	
ADVANCE 2007	211	5569	257	5571	11.4%	0.82 [0.69, 0.98]		
BENEDICT (monotherapy) 2004	1	301	3	300	0.1%	0.33 [0.03, 3.18]		??•••••
CAMELOT (Placebo) 2004	5	673	2	655	0.1%	2.43 [0.47, 12.50]		
CCS-I 2001	340	3391	395	3358	19.3%	0.85 [0.74, 0.98]		
DEMAND (monotherapy) 2011	0	127	2	127	0.0%	0.20 [0.01, 4.12]		
DREAM 2006	12	2623	10	2646	0.5%	1.21 [0.52, 2.80]		
HYVET (Placebo) 2003	22	431	19	426	1.0%	1.14 [0.63, 2.08]		
MAGINE 2008	18	1280	15	1273	0.8%	1.19 [0.60, 2.36]		
PART-2 2000	8	308	18	309	0.5%	0.45 [0.20, 1.01]		
PEP-CHF 2006	38	424	40	426	2.0%	0.95 [0.63, 1.46]		
PROGRESS 2001	181	3051	198	3054	9.5%	0.92 [0.75, 1.11]		
SCAT 2000	4	229	7	231	0.2%	0.58 [0.17, 1.94]		$\bullet \bullet \bullet ? \bullet \bullet ?$
Subtotal (95% CI)		18407		18376	45.6%	0.87 [0.79, 0.95]	•	
Total events	840		966					
Heterogeneity: Tau² = 0.00; Chi² =	9.28, df=	11 (P =	0.60); l² =	:0%				
Test for overall effect: Z = 3.13 (P =	= 0.002)							
1.1.2 ACEI vs Active								
AASK 2002	12	436	19	658	0.7%	0.95 [0.47, 1.94]		
ABCD (normotensive) 2002	14	246	.0	234	0.5%	1.66 [0.71, 3.89]		
ALLHAT 2002	618	9054		24303	45.1%	1.04 [0.95, 1.13]	_	
ANBP2 2003	84	3044	82	3039	4.0%	1.02 [0.76, 1.38]		2000000
BENEDICT (combination) 2004	0	300	1	303	0.0%	0.34 [0.01, 8.23]	·····	
BENEDICT (monotherapy) 2004	1	301	1	303	0.0%	1.01 [0.06, 16.02]	· · · · · · · · · · · · · · · · · · ·	
CAMELOT (Active) 2004	5	673	5	663	0.2%	0.99 [0.29, 3.39]		
CARMEN (combination) 2004	9	191	13	191	0.2%	0.69 [0.30, 1.58]		2000000
CARMEN (complitation) 2004	14	190	13	191	0.5%	1.08 [0.52, 2.24]		2000000
Chan et al 2000	2	50	2	52	0.1%	1.04 [0.15, 7.10]		2200202
ESPIRAL 2001	3	129	6	112	0.1%	0.43 [0.11, 1.70]		220200
Fogari et al (combination) 2002	1	104	2	103	0.2%	0.50 [0.05, 5.38]		
Fogari et al (combination) 2002 Fogari et al (monotherapy) 2002	2	104	2	103	0.1%	1.01 [0.15, 7.03]		
HYVET (diuretics) 2003	22	431	23	426	1.1%			
JAMP 2004	11	451	23 14	420	0.6%	0.95 [0.54, 1.67] 0.71 [0.33, 1.55]		2202200
JAMP 2004 JMIC-B 2004	6		14	828	0.0%			
Subtotal (95% CI)	0	822 16539	6	828 31931	0.3% 54.4%	1.01 [0.33, 3.11] 1.02 [0.94, 1.11]		
	004	10559	4700	21921	34.470	1.02 [0.94, 1.11]	Ť	
Total events	804	4.5 (5)	1796					
Heterogeneity: Tau² = 0.00; Chi² = Test for overall effect: Z = 0.58 (P =		15 (P =	0.99); 11=	:0%				
		34040		50207	100.0%	0.05 (0.00, 4.04)		
Fotal (95% CI)		34946		20307	100.0%	0.95 [0.89, 1.01]	٦	
Total events	1644	07.7	2762					
Heterogeneity: Tau ² = 0.00; Chi ² =		= 27 (P =	= 0.73); l ^e	= 0%		-	0.2 0.5 1 2 5	
Test for overall effect: Z = 1.69 (P =					~		Favours [ACEI] Favours [control]	
Test for subgroup differences: Ch	r* = 7.30, o	tt = 1 (P	= 0.007),	If = 86.3	%			
Risk of bias legend								
(A) Random sequence generatior		n bias)						
(B) Allocation concealment (selec								
(C) Blinding of participants and pe				-				
(D) Blinding of outcome assessm	ent (detec	tion bias	s): Other	outcome	S			
(E) Incomplete outcome data (attri	tion bias)							
F) Selective reporting (reporting b	ias)							
G) Other bias								

Figure 7-3 Forest plot showing effect of ACEIs on risk of CV mortality (RE model). [Sensitivity analysis: Excluding trials with naïve participants].

CI: confidence interval; RE: random-effects; M-H: Mantel-Haenszel. For studies acronyms, see list of definition/ abbreviations

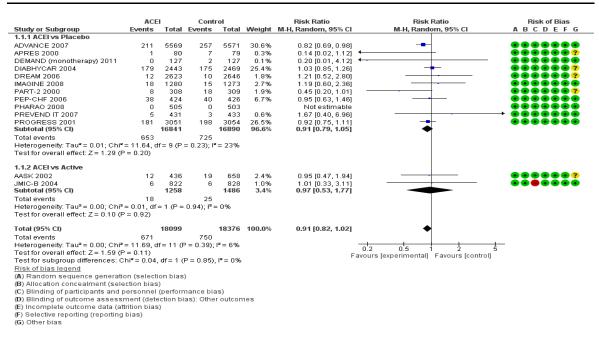


Figure 7-4 Forest plot showing effect of ACEIs on risk of CV mortality (RE model). [Sensitivity analysis: Excluding trials with low methodological quality].

CI: confidence interval; RE: random-effects; M-H: Mantel-Haenszel. For studies acronyms, see list of definition/ abbreviations

7.5.3 Subgroup analysis

Table 7-1 and 2 summarises the overall results of the subgroup analysis.

7.5.3.1 High and low-affinity tissue ACEI

Overall, 18 RCTs assessed the high-affinity tissue ACEIs (quinapril, ramipril, perindopril, trandolapril and delapril) by comparing them with either a placebo or active therapies. The high-affinity tissue ACEIs were associated with a significant 13% reduction in CV mortality compared with the control group (RR, 0.87; 95% CI 0.80-0.94, p=0.0008).

Four low-affinity tissue ACEIs were assessed (lisinopril, enalapril, fosinopril and captopril). Overall, low-affinity tissue ACEIs appeared to have no advantages compared with control (RR, 0.98; 95% CI 0.91, 1.05, p=0.56). The overall effect was mainly reflected the ALLHAT trial (61.2%) (see **Figure 7-5**)

7.5.3.2 Class of active control

As shown in **Figure 7-6**, 11 RCTs randomised patients to CCBs (DHPs or non-DHPs). The risk of CV death reduction of the ACEI and CCB group was similar (RR, 1.02; 95% CI 0.92-1.14; p=0.65). The direction of pooled RR was mainly driven by the ALLHAT trial (CCB) that contributed 93.8% of the overall pooled weighting. The test of heterogeneity showed no statistical variation. Compared with diuretics, the overall effect estimate was neutral (RR, 1.03; 95% CI 0.94-1.13; p=0.51). ALLHAT (diuretic) greatly contributed to the pooled treatment effect (88.1%). No heterogeneity was detected. Three trials comparing ACEI to beta-blockers. ACEIs appeared to be of more benefit than beta-blockers with RR of 0.93 (95% CI 0.59-1.45; p=0.74). No heterogeneity was detected.

7.5.3.3 Clinical setting

Figures 7-7 and 8 represent the meta-analytical summary estimates of ACEIs on occurrence of CV mortality in comparison to placebo or active therapy groups, stratified based on the clinical setting.

For high-risk hypertensives, ACEIs therapy was associated with a 10% lowering in CV death compared with the placebo but this was not a statistically significant result with an RR of 0.89 (95% CI 0.79-1.01; p=0.06). The pooled estimate was greatly driven by the HOPE trial as it carried 26.3% of the overall weighting. There was no significant decrease in risk when compared with the active group (RR, 1.03; 95% CI 0.95-1.12; p=0.53). There was no evidence of statistical heterogeneity.

For patients with underlying CAD, ACEI-based therapy led to a 16% lowering in the risk of CV death compared with the placebo (RR, 0.84; 95% CI 0.75- 0.94; p=0.002). in contrast, there was no significant decrease in risk compared with the active group (RR, 0.83; 95% CI 0.47-1.47; p=0.53). However, a wide confidence limit may indicate a low precise point.

For patients with DM with or without nephropathy, the ACEIs did not reduce risk of CV death when compared with the placebo (RR, 0.90; 0.73-1.11; p=0.34) or active group (RR, 1.23; 95% CI 0.64, 2.38; p=0.53). However, when the DIABHYCAR trial is excluded, I^2 statistics becomes zero with a significant RR of 0.81 [95% CI 0.68, 0.97]. However, the result should not be underestimated as the confidence limit is wide.

7.5.3.4 Mean age group

Compared with placebo, ACEIs reduce the risk of CV mortality in patients with a mean age of < 65 years but not for patients within the \geq 65 group. However, when the DIABHYCAR trial data is excluded from the trials that included patients whose mean age fell in the \geq 65 group, the RR became significant (RR, 0.80; 95% CI 0.72-0.89; p<0.0001). When compared with active control, the pooled data relating to both groups of patients shows that ACEIs have a neutral effect. There was no evidence of heterogeneity (I² = 0%).

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	ACI		Cont			Risk Ratio	Risk Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl	ABCDEF
1.1.1 High-affinity tissue ACEIs								
AASK 2002	12	436	19	658	1.3%	0.95 [0.47, 1.94]		
ADVANCE 2007	211	5569	257	5571	15.8%	0.82 [0.69, 0.98]		
APRES 2000	1	80	7	79	0.2%	0.14 [0.02, 1.12]	•	
BENEDICT (combination) 2004	0	300	1	303	0.1%	0.34 [0.01, 8.23]	•	- ??
BENEDICT (monotherapy) 2004	1	301	4	603	0.1%	0.50 [0.06, 4.46]		??
DEMAND (monotherapy) 2011	0	127	2	127	0.1%	0.20 [0.01, 4.12]	•	
DIABHYCAR 2004	179	2443	175	2469	13.2%	1.03 [0.85, 1.26]	+	
DREAM 2006	12	2623	10	2646	0.9%	1.21 [0.52, 2.80]		
EUROPA 2003	215	6110	249	6108	15.7%	0.86 [0.72, 1.03]		??
HOPE 2000	282	4645	377	4652	20.5%	0.75 [0.65, 0.87]	-	?
IMAGINE 2008	18	1280	15	1273	1.4%	1.19 [0.60, 2.36]		
PART-2 2000	8	308	18	309	1.0%	0.45 [0.20, 1.01]		
PEACE 2004	146	4158	152	4132	11.1%	0.95 [0.76, 1.19]	-	
PEP-CHF 2006	38	424	40	426	3.5%	0.95 [0.63, 1.46]	-	
PHARAO 2008	0	505	0	503		Not estimable		
PROGRESS 2001	181	3051	198	3054	13.8%	0.92 [0.75, 1.11]	-+	
QUIET 2001	13	878	14	872	1.2%	0.92 [0.44, 1.95]		??
QUO VADIS 2001	0	75	0	73		Not estimable		??
Subtotal (95% CI)		33313		33858	100.0%	0.87 [0.80, 0.94]	•	
Total events	1317		1538					
Heterogeneity: Tau ² = 0.00; Chi ² = Test for overall effect: Z = 3.34 (P :		= 15 (P :	= 0.33); I*	= 10%				
1.1.2 Low-affinity tissue ACEIs					0.7%	4 00 /0 74 0 001		
ABCD (normotensive) 2002	14	246	8	234	0.7%	1.66 [0.71, 3.89]		
ALLHAT 2002	618	9054		24303	61.2%	1.04 [0.95, 1.13]		
ANBP2 2003	84	3044	82	3039	5.5%	1.02 [0.76, 1.38]		? • • • • • • •
CAMELOT (Overall) 2004	5	673	7	1318	0.4%	1.40 [0.45, 4.39]		
CARMEN (combination) 2004	9	191	13	191	0.7%	0.69 [0.30, 1.58]		200000
CARMEN (monotherapy) 2004	14	190	13	191	0.9%	1.08 [0.52, 2.24]		? • • • • • •
CCS-I 2001	340	3391	395	3358	26.3%	0.85 [0.74, 0.98]	•	
Chan et al 2000	2	50	2	52	0.1%	1.04 [0.15, 7.10]		2 2 9 9 2 9
ESPIRAL 2001	3	129	6	112	0.3%	0.43 [0.11, 1.70]		220200
Fogari et al (combination) 2002	1	104	2	103	0.1%	0.50 [0.05, 5.38]	•	
Fogari et al (monotherapy) 2002	2	102	2	103	0.1%	1.01 [0.15, 7.03]		
HYVET (Overall) 2003	22	431	42	852	1.9%	1.04 [0.63, 1.71]		
JAMP 2004	11	466	14	422	0.8%	0.71 [0.33, 1.55]		220230
JMIC-B 2004	6	822	6	828	0.4%	1.01 [0.33, 3.11]		
PREVEND IT 2007	5	431	3	433	0.2%	1.67 [0.40, 6.96]		
SCAT 2000	4	229	7	231	0.3%	0.58 [0.17, 1.94]		•••
Subtotal (95% CI)		19553		35770	100.0%	0.98 [0.91, 1.05]	Ţ	
Total events Heterogeneity: Tau² = 0.00; Chi² = Test for overall effect: Z = 0.58 (P :		= 15 (P :	2201 = 0.69); I ²	= 0%				
								_
								n
Test for subgroup differences: Ch	ni² = 4.65, d	if=1 (P	= 0.03), P	°= 78.59	6		Favours [ACEI] Favours [contro	1]

(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)
 (C) Blinding of participants and personnel (performance bias)

(E) Selective reporting (reporting bias) (F) Other bias

Figure 7-5 Forest plot showing effect of ACEIs on risk of CV mortality (RE model) [Subgroup analysis: High-affinity tissue vs low-affinity ACEIs].

CI: confidence interval; RE: random-effects; M-H: Mantel-Haenszel. For studies acronyms, see list of definition/ abbreviations

~	ACE		Cont			Risk Ratio	Risk Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl	ABCDEFG
1.1.1 CCBs								
AASK (CCB) 2002	12	436	7	217	1.3%	0.85 [0.34, 2.14]		•••• •••
ABCD (normotensive) 2002	14	246	8	234	1.6%	1.66 [0.71, 3.89]		$\bullet \bullet \bullet \bullet \circ \circ$
ALLHAT (CCB) 2002	609	9054	592	9048	93.8%	1.03 [0.92, 1.15]	. –	
BENEDICT (combination) 2004	0	300	1	303	0.1%	0.34 [0.01, 8.23]		??•••••
BENEDICT (monotherapy) 2004	1	301	1	303	0.1%	1.01 [0.06, 16.02]	• • •	??•••••
CAMELOT (Active) 2004	5	673	5	663	0.7%	0.99 [0.29, 3.39]		020000000000000
Chan et al 2000	2	50	2	52	0.3%	1.04 [0.15, 7.10]		33003003
ESPIRAL 2001	3	129	6	112	0.6%	0.43 [0.11, 1.70]		3303005
Fogari et al (combination) 2002	1	104	2	103	0.2%	0.50 [0.05, 5.38]		
Fogari et al (monotherapy) 2002	2	102	2	103	0.3%	1.01 [0.15, 7.03]	,	• ? • ? ? • ?
JMIC-B 2004	6	822	6	828	0.9%	1.01 [0.33, 3.11]		
Subtotal (95% CI)		12217		11966	100.0%	1.02 [0.92, 1.14]	•	
Total events	655		632					
Heterogeneity: Tau² = 0.00; Chi² = Test for overall effect: Z = 0.45 (P		10 (P =	0.96); I² =	0%				
1.1.2 Diuretics								
ALLHAT (Diuretic) 2002	609	9054	992	15255	88.1%	1.03 [0.94, 1.14]		$\bullet \bullet \bullet ? \bullet \bullet \bullet$
ANBP2 2003	84	3044	82	3039	9.3%	1.02 [0.76, 1.38]	_ _	? • • • • • •
HYVET (diuretics) 2003	22	431	23	426	2.6%	0.95 [0.54, 1.67]		•••?
Subtotal (95% CI)		12529		18720	100.0 %	1.03 [0.94, 1.13]	*	
Total events	715		1097					
Heterogeneity: Tau² = 0.00; Chi² = Test for overall effect: Z = 0.65 (P		2 (P = 0	.95); I² = ()%				
1.1.3 Beta-blockers								
AASK (Beta-blocker) 2002	12	436	12	441	32.4%	1.01 [0.46, 2.23]	+	$\bullet \bullet \bullet \bullet \bullet \bullet \bullet \circ \circ$
CARMEN (combination) 2004	9	191	13	191	29.6%	0.69 [0.30, 1.58]		? • • • • • • •
CARMEN (monotherapy) 2004	14	190	13	191	38.1%	1.08 [0.52, 2.24]		? • • • • • •
Subtotal (95% CI)		817		823	100.0 %	0.93 [0.59, 1.45]		
Total events	35		38					
Heterogeneity: Tau² = 0.00; Chi² = Test for overall effect: Z = 0.33 (P		2 (P = 0	.70); I² = ()%				
1.1.4 Active control								
JAMP 2004 Subtotal (95% CI)	11	466 466	14		100.0% 100.0 %	0.71 [0.33, 1.55] 0.71 [0.33, 1.55]		??●??●
Total events	11		14					
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.86 (P	= 0.39)							
	0.00)							
							0.2 0.5 1 2 5	
							Favours [ACEI] Favours [control]	
Test for subgroup differences: Ch	ni² = 1.04, c	lf = 3 (P	= 0.79), l ^a	'= 0%			ratears (robil ratears (control)	
<u>Risk of bias legend</u>								
(A) Random sequence generatio	n (selectio	n bias)						
(B) Allocation concealment (seled		-						
(C) Blinding of participants and p	,	erforma	ance bias)				
(D) Blinding of outcome assessm					s			
(E) Incomplete outcome data (attr					-			

(E) Incomplete outcome data (attrition bias) (F) Selective reporting (reporting bias)

(G) Other bias

Figure 7-6 Forest plot showing effect of ACEIs on risk of CV mortality (RE model) [Subgroup analysis: Class of active comparator].

CI: confidence interval; RE: random-effects; M-H: Mantel-Haenszel. For studies acronyms, see list of definition/ abbreviations

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	ACI	FI	Place	ho		Risk Ratio	Risk Ratio	Risk of Bias
Study or Subgroup	Events		Events		Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl	ABCDEFG
1.1.1 High-risk hypertensive								
ADVANCE 2007	211	5569	257	5571	22.4%	0.82 [0.69, 0.98]		
BENEDICT (monotherapy) 2004	1	301	3	300	0.3%	0.33 [0.03, 3.18]	←	??
CAMELOT (Placebo) 2004	5	673	2	655	0.5%	2.43 [0.47, 12.50]		
DEMAND (monotherapy) 2011	Ō	127	2	127	0.2%	0.20 [0.01, 4.12]	←	
DIABHYCAR* 2004	179	2443	175	2469	19.9%	1.03 [0.85, 1.26]	+	
DREAM 2006	12	2623	10	2646	2.0%	1.21 [0.52, 2.80]		
HOPE 2000	282	4645	377	4652	26.3%	0.75 [0.65, 0.87]		? • • • • • •
HYVET (Placebo) 2003	22	431	19	426	3.8%	1.14 [0.63, 2.08]		•••?
PEACE 2004	146	4158	152	4132	17.7%	0.95 [0.76, 1.19]	-	
PEP-CHF 2006	38	424	40	426	7.0%	0.95 [0.63, 1.46]	_	
Subtotal (95% CI)		21394		21404	100.0%	0.89 [0.79, 1.01]	◆	
Total events	896		1037					
Heterogeneity: Tau ² = 0.01; Chi ² =	12.48, df	= 9 (P =	0.19); l ^z =	28%				
Test for overall effect: Z = 1.88 (P =	= 0.06)							
112 Coronany Artony Diseases (CAD							
1.1.2 Coronary Artery Diseases (00		70	0.00	0.40.00.00.0.002		
APRES 2000	1	80 673	8	79 655	0.3% 0.5%	0.12 [0.02, 0.96]	`	
CAMELOT (Placebo) 2004						2.43 [0.47, 12.50]		
CCS-I 2001 EUROPA 2003	340 215	3391 6110	395 249	3358 6108	27.6% 21.6%	0.85 [0.74, 0.98]		220200
						0.86 [0.72, 1.03]		2000000
HOPE 2000 IMAGINE 2008	282 18	4645 1280	377 15	4652 1273	25.7% 2.7%	0.75 [0.65, 0.87]	-	
	18	308	15	309	2.7%	1.19 [0.60, 2.36]		
PART-2 2000 PEACE 2004	0 146	4158	152	4132	16.7%	0.45 [0.20, 1.01]		
	140	4156	152	872	2.2%	0.95 [0.76, 1.19]		2200000
QUIET 2001 QUO VADIS 2001	13	75	14	73	2.270	0.92 [0.44, 1.95]	-	2200000
	4		7	231	0.9%	Not estimable		
SCAT 2000 Subtotal (95% CI)	4	229 21827		21742		0.58 [0.17, 1.94] 0.84 [0.75, 0.94]	•	
Total events	1032	21021	1237	21142	100.070	0.04 [0.1 0, 0.04]	•	
Heterogeneity: Tau ² = 0.01; Chi ² = Test for overall effect: Z = 3.03 (P =	12.35, df	= 9 (P =		: 27%				
1.1.3 Diabetes Mellitus ± Nephroj	pathy							
ADVANCE 2007	211	5569	257	5571	51.6%	0.82 [0.69, 0.98]		
BENEDICT (monotherapy) 2004	1	301	3	300	0.9%	0.33 [0.03, 3.18]	← <u></u>	??
DEMAND (monotherapy) 2011	O	127	2	127	0.5%	0.20 [0.01, 4.12]	←─────	
DIABHYCAR* 2004	179	2443	175	2469	47.0%	1.03 [0.85, 1.26]	-	
Subtotal (95% CI)		8440		8467	100.0%	0.90 [0.73, 1.11]	•	
Total events	391		437				-	
Heterogeneity: Tau ² = 0.01; Chi ² = Test for overall effect: Z = 0.96 (P =		3 (P = 0	.21); I² = :	34%				
1.1.7 Non-diabetics nephropathy								
PREVEND IT 2007	5	431	3	422	100.0%	1.67 [0.40, 6.96]		
Subtotal (95% Cl)	5	431	5	433	100.0%	1.67 [0.40, 6.96]		
Total events	5		3					
Heterogeneity: Not applicable	5		5					
Test for overall effect: Z = 0.71 (P =	= 0.48)							
4.4.9.01/8								
1.1.8 CVA	181	3051	198	2054	100.0%	0 0 2 70 75 4 4 4 1		
PROGRESS 2001 Subtotal (95% CI)	181	3051 3051	198	3054 3054	100.0% 100.0%	0.92 [0.75, 1.11] 0.92 [0.75, 1.11]		
	104	5031	100	5054	100.070	0.52 [0.15, 1.11]	T	
Total events Heterogeneity: Not applicable	181		198					
Test for overall effect: Z = 0.89 (P =	= 0.37)							
v	,							
							0.2 0.5 1 2 5	
The state of the second st		10					Favours (ACEI) Favours (Placebo]
Test for subgroup differences: Ch	r= 1.70, 0	аг = 4 (P	= 0.79), P	-= U%				
Risk of bias legend		- 1-1						
(A) Random sequence generation		n bias)						
(B) Allocation concealment (selec	uon plas)							

(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias): Other outcomes
 (E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

Figure 7-7 Forest plot showing effect of ACEIs versus placebo on risk of CV mortality (RE model) [Subgroup analysis: Population clinical setting].

*Trial responsible for heterogeneity. CI: confidence interval; RE: random-effects; M-H: Mantel-Haenszel. For studies acronyms, see list of definition/ abbreviations

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	ACE	1	Acti	ve		Risk Ratio	Risk Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl	ABCDEFG
1.1.1 High-risk hypertensive								
AASK 2002	12	436	19	658	1.4%	0.95 [0.47, 1.94]		
ALLHAT 2002	618	9054	1599	24303	86.7%	1.04 [0.95, 1.13]		
ANBP2 2003	84	3044	82	3039	7.7%	1.02 [0.76, 1.38]		?
BENEDICT (combination) 2004	0	300	1	303	0.1%	0.34 [0.01, 8.23]	· · · · · · · · · · · · · · · · · · ·	??
BENEDICT (monotherapy) 2004	1	301	1	303	0.1%	1.01 [0.06, 16.02]	· · · · · · · · · · · · · · · · · · ·	??
CAMELOT (Active) 2004	5	673	5	663	0.5%	0.99 [0.29, 3.39]		
Chan et al 2000	2	50	2	52	0.2%	1.04 [0.15, 7.10]		2244242
ESPIRAL 2001	3	129	6	112	0.4%	0.43 [0.11, 1.70]		226269
Fogari et al (combination) 2002	1	104	2	103	0.1%	0.50 [0.05, 5.38]	·	
Fogari et al (monotherapy) 2002	2	102	2	103	0.2%	1.01 [0.15, 7.03]		
HYVET (diuretics) 2003	22	431	23	426	2.2%	0.95 [0.54, 1.67]		
JMIC-B 2004	6	822	20	828	0.5%	1.01 [0.33, 3.11]		
Subtotal (95% CI)	0	15446	0	30893		1.03 [0.95, 1.12]	•	
Total events	756		1748					
Heterogeneity: Tau ² = 0.00; Chi ² =		11 /D -		- 006				
Test for overall effect: Z = 0.64 (P =			1.00),1 -	- 0 %				
1.1.2 Coronary Artery Diseases (CAD)							
CAMELOT (Active) 2004	5	673	5	663	21.2%	0.99 [0.29, 3.39]		\bullet ? \bullet \bullet \bullet ?
JAMP 2004	11	466	14	422	53.3%	0.71 [0.33, 1.55]		?? 🛑 ? ? 🖶 🛨
JMIC-B 2004	6	822	6	828	25.4%	1.01 [0.33, 3.11]	+	
Subtotal (95% CI)		1961		1913	100.0 %	0.83 [0.47, 1.47]	-	
Total events	22		25					
Heterogeneity: Tau ² = 0.00; Chi ² = Test for overall effect: Z = 0.63 (P =		2 (P = 0	.84); I² =	0%				
1.1.3 Diabetes Mellitus ± Nephrop	pathy							
ABCD (normotensive) 2002	14	246	8	234	59.5%	1.66 [0.71, 3.89]		$\bullet \bullet \bullet \bullet \bullet ? \bullet ?$
BENEDICT (combination) 2004	0	300	1	303	4.2%	0.34 [0.01, 8.23]	• • •	??
BENEDICT (monotherapy) 2004	1	301	1	303	5.6%	1.01 [0.06, 16.02]	· •	??
Chan et al 2000	2	50	2	52	11.7%	1.04 [0.15, 7.10]		?? • • ? • ?
Fogari et al (combination) 2002	1	104	2	103	7.6%	0.50 [0.05, 5.38]	• • •	••••••
Fogari et al (monotherapy) 2002	2	102	2	103	11.4%	1.01 [0.15, 7.03]		🔒 ? 🖨 ? ? 🖶 ?
Subtotal (95% CI)		1103		1098	100.0 %	1.23 [0.64, 2.38]	-	
Total events	20		16					
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = Test$ for overall effect: $Z = 0.63$ (P =		5 (P = 0	.88); I² =	0%				
1.1.4 Non-diabetics nephropathy								
ESPIRAL 2001	3	129	6	110	100.00	0 42 10 44 4 701		??
Subtotal (95% CI)	3	129	ь		100.0% 100.0%	0.43 [0.11, 1.70] 0.43 [0.11, 1.70]		
	~	129	~	112	100.0%	0.45 [0.11, 1.70]		
Total events	3		6					
Heterogeneity: Not applicable	0.000							
Test for overall effect: Z = 1.20 (P =	= 0.23)							
Test for subgroup differences of	ສຸລາຊ -	H _ 1 / P	- 0 500 "	8 - 00 ⁷			Favours [ACEI] Favours [Active]	
Test for subgroup differences: Ch	r= ∠.35, 0	a = 3 (P	= 0.50), h	-=0%				
Risk of bias legend								
(A) Random sequence generation	-	n blas)						
(B) Allocation concealment (selec								
(C) Blinding of participants and pe								
(D) Blinding of outcome assessm		tion bias	s): Other	outcome	S			
(E) Incomplete outcome data (attri	tion bias)							

(F) Selective reporting (reporting bias) (G) Other bias

Figure 7-8 Forest plot showing effect of ACEIs versus active on risk of CV mortality (RE model). [Subgroup analysis: Population clinical setting].

** Excluding ALLHAT trial yields RR of 0.89 [95% CI 0.80-1.00; p=0.05]

Table 7-1 Summary of RE meta-analytical subgroup analysis showing the effect of ACEIs compared with control (placebo or active) on risk of CV death[†]

					CV death	n Incidence			
Subgro	oup analysis	Studies	Participant	Events		(%)	RR (M-H, Random, 95%	P value*	l² (%) ‡
					ACEI	Control	CI)		
	Overall effects	36	123,899	6224	4.57	5.36	0.91 [0.86-0.97]	0.002*	6
	Placebo	21	75,429	3624	4.45	5.15	0.87 [0.81-0.94]	0.0003*	12
	Active	16	48,470	2600	4.86	5.54	1.02 [0.94, 1.11]	0.56**	0
Subclass	High-tissue affinity	18	67,171	2855	3.95	4.54	0.87 [0.80-0.94]	0.0008*	10
	Low-tissue affinity	16	55,323	3341	5.83	6.15	0.98 [0.91-1.05]	0.56	0
	CCBs	11	24,183	1287	5.37	5.28	1.02 [0.92-1.14]	0.65	0
Active control	Diuretics	3	31,249	1812	5.70	5.86	1.03 [0.94-1.13]	0.51	0
	Beta-blockers	3	1640	73	4.28	4.61	0.93 [0.59-1.45]	0.51	0
	Other^	1	888	25	2.36	3.31	0.71 [0.33-1.55]	0.39	NA

Table 7-2 Summary of RE a meta-analytical subgroup analysis shows the effect of ACEIs compared with control (placebo or active) on risk of CV mortality (Continued)[†]

					CV death	Incidence (%)			
	Subgroup analysis	Studies	Participant	Events	ACEI	Control	RR (M-H, Random, 95% CI)	P value*	l² (%) ‡
		-	•	Placebo	-	-	-		
	High-risk hypertensive	10	42,798	1933	4.18	4.84	0.87 [0.79-1.01]	0.06**	28
	CAD	11	43,569	2269	4.72	5.68	0.84 [0.75, 0.94]	0.002*	27
Clinical	DM± Nephropathy	4	16,907	828	4.63	5.16	0.90 [0.73-1.11]	0.34	34¶
setting	Non-diabetic nephropathy^	1	864	8	1.16	0.69	1.67 [0.40-6.96]	0.48	NA
	CVA^		6105	379	5.93	6.48	0.92 [0.75-1.11]	0.37	NA
Mean age	< 65 years	16	48,373	2025	3.91	4.45	0.88 [0.81-0.96]	0.003*	0
group	≥ 65 years	5	27,056	1600	5.41	6.40	0.87 [0.75-1.02]	0.08	49 [¥]
				Active					
	High-risk hypertensive	12	46,339	2504	4.89	5.65	1.03 [0.95, 1.12]	0.53	0
Clinical	CAD	3	3874	47	1.12	1.30	0.83 [0.47, 1.47]	0.53	0
Clinical	DM± Nephropathy	6	2201	36	1.81	1.45	1.23 [0.64, 2.38]	0.53	0
setting	Non-diabetic nephropathy^	1	241	9	2.32	5.35	0.43 [0.11, 1.70]	0.23	NA
	CVA		1	1		NA			
Mean age	< 65 years	12	6523	160	2.32	2.57	0.91 [0.67, 1.24]	0.54	0
group	≥ 65 years	4	41,947	2440	5.46	5.97	1.03 [0.95, 1.13]	0.44	0

statistically significant; ^ Cannot synthesis data by one trial; ‡ I² statistic with <25% considered as low heterogeneity and I²> 75% as high heterogeneity.

** By excluding DIABHYCAR, pooled RR became significant at meta-analysis level of 0.84 [95% CI 0.75-0.94; p=0.002]

[¶] By excluding DIABHYCAR trial, I² is disappeared (0%) with a significant pooled RR of 0.81 [95% CI 0.68, 0.97, p=0.02]

⁴ By excluding DIABHYCAR trial, I² is disappeared (0%) with a significant pooled RR of 0.80 [95% CI 0.72-0.89; p<0.0001]

7.6 ARBs and risk of CV mortality

7.6.10verall treatment effect

Figure 7-9 presents a summary of the treatment effect of ARBs with risk of CV death in a RE model, stratified by control group (placebo or active). Data regarding the effects of ARB on occurrence of CV death were available from 34 RCTs involving 139,988 participants and 7,768 CV deaths were reported. Overall, the incidence of CV death in ARB was almost similar to that of the control group, 5.5% and 5.5% respectively. Clearly, more than 50% of individual trials reported unfavourable effects of ARB on CV death. There were no apparent benefits of ARBs in reducing CV death compared to the control group (RR, 0.99; 95% CI 0.94-1.05; p=0.73). The heterogeneity assessment shows a chi-square p-value of 0.10 and $l^2 = 26\%$ indicating low statistical differences between studies.

By stratifying control group, the data available from 16 placebo controlled RCTs that included 86,802 participants and 6,333 observed CV events. The horizontal lines of 95% CI of each trial crossed the line of no effect, indicating non-statistical significance at the meta-analysis level. Thus, this indicates that there was no clear benefit attributable to ARB on reducing CV death when compared to the placebo group (RR 0.98; 95% CI 0.92, 1.04; P=0.55). The chi-square test for heterogeneity yielded a P-value=0.08 and I²=35% indicating a moderate variability between studies. The degree of heterogenicity was driven by data from the ROADMAP and ORIENT trials. Excluding these trials, an RR of 0.97 (0.93-1.02; p=0.28) is obtained and I² =0%

The data available from 18 active-controlled RCTs that involved 53,186 participants indicated 1,340 CV death events. The incidence of CV deaths in the ARB and active-treated group was almost the same, 3.3% and 3.4% respectively. The VALUE and LIFE are largely contributed of overall weighting, 7.4% and 5.9% respectively. The distribution of weightings among the remaining 13 studies was < 2% each. There was no reduction in CV death by ARB compared with the active control group (RR 1.04; 95% CI 0.90-1.20; P=0.58). No evidence of heterogeneity (P value of chi-square test =0.27 and $I^2 = 17\%$).

Figure 7-10 presents the results generated by the FE model. In the case of the placebo-controlled trials, a higher weighting was given to the ACTIVE-I trials and slightly less weighting to the Val-HeFT trials. The pooled effect estimate was similar to that generated from the RE model and the 95% CI narrowed (RR 0.98; 95% CI 0.94, 1.02; P=0.4). In the active-controlled trials, the FE model was given data that was slightly weighted in favour of the VALUE and LIFE trials and the 95% CI also narrowed.

The funnel plot (Appendix D, figure D-3) indicates a symmetric appearance at the top of the graph. However, an outlier was detected on the left side of the graph (the Kondo et al. trial).

(E) Incomplete outcome data (attrition bias) (F) Selective reporting (reporting bias)

(G) Other bias

Study or Studgroup Events Total Weight M.H., Random, 95% Cl M.H., Random, 95% Cl A.B. C. D. E.F. G ACTME1 2011 666 4518 648 4448 10.7% 10.01 09.1.131 ACTME2 2011 666 4518 648 4448 10.7% 10.01 09.1.131 CHARM-Attendev 2003 127 154 170 59.07 1.01 0.91 0.71 0.01 09.1.131 CHARM-Attendev 2003 126 126 127 1.01 0.00 0.00		ARE	2	Cont	rol		Risk Ratio	Risk Ratio	Risk of Bias
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(B) Allocation concealment (selection bias) (C) Blinding of participants and personnel (performance bias)									
(C) Blinding of participants and personnel (performance bias)				n bias)					
(D) Blinding of outcome assessment (detection bias): Other outcomes									
(E) Incomplete outcome data (attrition bias)			-	ion bias)	: Other o	utcomes			

Figure 7-9 Forest plot showing effect of ARBs on risk of CV mortality, stratified by comparison group (placebo vs active). Overall: 34 trials (RE model).

*Trial responsible for heterogeneity. The **diamond** indicates the pooled risk ratio (and 95% CI) or the overall effect for CV mortality risk. CI: confidence interval; RE: random-effects; M-H: Mantel-Haenszel. For studies acronyms, see list of definition/ abbreviations

~	ARE		Cont			Risk Ratio	Risk Ratio	Risk of Bias
Study or Subgroup	Events	lotal	Events	lotal	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl	ABCDEFG
1.1.1 ARB vs Placebo							L	
ACTIVE-I 2011	666	4518	646	4498	16.6%	1.03 [0.93, 1.13]	Ť	
CHARM-Added 2003	302	1276	347	1272	8.9%	0.87 [0.76, 0.99]		
CHARM-Alternative 2003	219	1013	252	1015	6.4%	0.87 [0.74, 1.02]	-•1	
CHARM-Preserved 2003	170	1514	170	1509	4.4%	1.00 [0.82, 1.22]	+	••••••
HOPE-3 2016	155	6356	170	6349	4.4%	0.91 [0.73, 1.13]		
I-PRESERVE 2008	311	2067	302	2061	7.7%	1.03 [0.89, 1.19]	+	
IDNT (Placebo) 2003	52	579	46	569	1.2%	1.11 [0.76, 1.62]	- <u>+</u>	
NAVIGATOR 2010	128	4631	116	4675	3.0%	1.11 [0.87, 1.43]	+	•••••
ORIENT 2011*	10	282	3	284	0.1%	3.36 [0.93, 12.07]	+•	
PRoFESS 2008	223	10146	263	10186	6.7%	0.85 [0.71, 1.02]		?••••
RENAAL 2001	90	751	79	762	2.0%	1.16 [0.87, 1.54]	+	$\bullet \bullet \bullet \bullet \bullet \bullet \bullet \circ \circ$
ROADMAP 2011*	15	2232	3	2215	0.1%	4.96 [1.44, 17.12]		••••??•••
SCOPE 2003	145	2477	152	2460	3.9%	0.95 [0.76, 1.18]		$\bullet \bullet \bullet \bullet \bullet \bullet \bullet \circ \circ$
TRANSCEND 2008	227	2954	223	2972	5.7%	1.02 [0.86, 1.22]	+	
Val-HeFT 2001	427	2511	419	2499	10.7%	1.01 [0.90, 1.15]	+	??
Weil et al 2013	1	84	1	85	0.0%	1.01 [0.06, 15.91]	· · · · · · · · · · · · · · · · · · ·	• • • • • • • • • • • •
Subtotal (95% CI)		43391		43411	81.7%	0.98 [0.94, 1.03]		
Total events	3141		3192					
Heterogeneity: Chi² = 23.0 Test for overall effect: Z = 0			3); I² = 35	%				
1.1.2 ARB vs Active								
4C 2016	6	585	5	534	0.1%	1.10 [0.34, 3.57]	_	
ATTEMPT-CVD 2016	2	615	2	613	0.1%	1.00 [0.14, 7.05]		
CARP 2011	0	90	0	101		Not estimable		??
CASE-J 2008	11	2354	15	2349	0.4%	0.73 [0.34, 1.59]		
CHIEF 2018	58	6766	37	6776	0.9%	1.57 [1.04, 2.37]		
E-COST 2005	1	1053	0	995	0.0%	2.83 [0.12, 69.51]	· · · · · · · · · · · · · · · · · · ·	
E-COST-R 2005	4	69	4	72	0.1%	1.04 [0.27, 4.01]		220200
HIJ-CREATE 2009	28	1024	25	1025	0.6%	1.12 [0.66, 1.91]	_ 	\bullet ? ? \bullet ? \bullet ?
HONG-KONG DHF 2007	1	56	1	50	0.0%	0.89 [0.06, 13.90]	· · · · · · · · · · · · · · · · · · ·	• • ? • • ? ? •
IDNT (CCB) 2003	52	579	37	567	1.0%	1.38 [0.92, 2.06]	<u>+</u>	
J-RHYTHM II 2010	0	158	0	160		Not estimable		
Kondo et al 2003	2	203	9	203	0.2%	0.22 [0.05, 1.02]	<	220200
LIFE 2002	204	4605	234	4588	6.0%	0.87 [0.72, 1.04]	-+-	
MITEC 2009	0	100	0	109		Not estimable		
NTP-AF study 2013	Ō	74	Ō	75		Not estimable		
OLIVUS 2010	1	126	2	121	0.1%	0.48 [0.04, 5.23]	←	2224442
SUPPORT 2015	48	578	38	568	1.0%	1.24 [0.82, 1.87]		
VALUE 2004	304	7649	304	7596	7.8%	0.99 [0.85, 1.16]	+	
Subtotal (95% CI)		26684		26502	18.3%	1.01 [0.91, 1.11]	♦	
Total events	722		713					
Heterogeneity: Chi ² = 15.7 Test for overall effect: Z = 0		•	7); I² = 17	%				
Total (95% CI)		70075		69913	100.0%	0.99 [0.95, 1.03]		
Total events	3863		3905				1	
Heterogeneity: Chi ² = 38.9		P = 0.10		%				
Test for overall effect: Z = 0		•		~			0.2 0.5 1 2 5	
Test for subgroup differen		· ·	f = 1 (P =	0.69) 12	= 0%		Favours [ARB] Favours [control]	
Risk of bias legend		50, u		5.00/11	0.0			
(A) Random sequence ge	neration /s	election	hiae)					
(B) Allocation concealmen			10103/					
(C) Blinding of participants			erformer	nce hise)				
(D) Blinding of participants (D) Blinding of outcome as				2				
(E) Incomplete outcome as			uon bias)	. outer o	acomes			
(E) Incomplete outcome a (F) Selective reporting (rep								
	orung bias	7						
(G) Other bias								

Figure 7-10 Forest plot showing effect of ARBs on risk of CV mortality, stratified by comparison group (placebo vs active). Overall: 34 trials (FE model).

*Trial responsible for heterogeneity. The **diamond** indicates the pooled risk ratio (and 95% CI) or the overall effect for CV mortality risk. CI: confidence interval; FE: fixed-effect; M-H: Mantel-Haenszel. For clinical trials acronyms, see list of definition/ abbreviations

7.6.2 Sensitivity analysis

All the placebo-controlled trials that were included in this study, with the exception of the ROADMAP trial, reported the CV death events, included participants with a background use of RAS blockers before randomisation. The ROADMAP trial carried 0.2% of the overall combined weighting so its exclusion did not have an impact on the pooled effect estimates (RR, 0.98; 95% CI 0.93, 1.03; P=0.35). Similarly, three active-controlled trials (E-COST, HONG-KONG DHF and OLIVUS) involved naive patients. These trials had a minimal effect on the overall combined weighting and excluding them did not have an impact on relative risk of CV death (RR, 1.05; 95% CI 0.90, 1.24; p=0.52) (see Figure 7-11)

When the data from 19 trials with poor methodology were excluded, the analysis of the RR of CV mortality by ARBs showed that ARBs had no effect compared with the placebo (RR, 0.98; 95% CI 0.92-1.05; p=0.54) and with the active group (RR, 1.09; 95% CI 0.87-1.36; p=0.45) (see Figure 7-12)

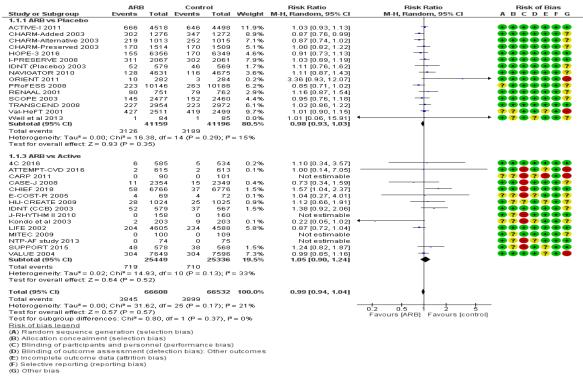


Figure 7-11 Forest plot showing effect of ARBs on risk of CV mortality (RE model) [Sensitivity analysis: Excluding trials with naive participants].

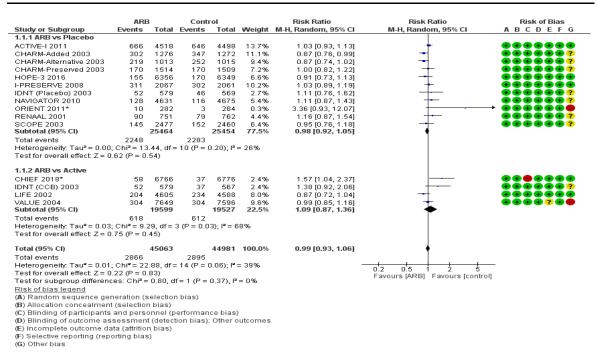


Figure 7-12: Forest plot showing effect of ARBs on risk of CV mortality (RE model) [Sensitivity analysis: Excluding trials with low methodological quality].

*Trials responsible for heterogeneity. CI: confidence interval; RE: random-effects; M-H: Mantel-Haenszel. For studies acronyms, see list of definition/ abbreviations

7.6.3 Subgroup analysis

Table 7-3 summarises the results of the subgroup analyses.

7.6.3.1 Class of active control

As shown in **Figure 7-13**, no significant differences were observed in CV death between ARBs and CCBs (RR, 1.16; 95% CI 0.88-1.53; p=0.30). The RR of the IDNT (CCB) and CHIEF trials indicated superiority of CCBs over ARB therapy. Therefore, a moderate heterogeneity among trials is indicated ($I^2 = 55\%$).

Data on CV death of ARB group compared with the diuretic or beta-blocker groups was available from two trials, namely the HONG-KONG DHF and LIFE trials. No significant lowering of the risk of CV mortality with the use of ARB therapy was indicated (RR, 0.87; 95% CI 0.72- 1.04; p=0.67).

Nine RCTs involving 8575 participants compared the use of ARBs with control comparators and 177 CV mortality observed. There was no significant reduction of CV death in the ARB therapy group compared with the control group (RR, 1.10;

95% CI 0.82-1.47; p=0.53). The assessment of heterogeneity showed no variation among trials.

7.6.3.2 Clinical setting

Figure 7-14 shows the effects of ARB on occurrence of CV mortality stratified based on clinical setting, compared with the control group (placebo or active).

Data on high-risk hypertensive patients was available from 26 trials involving 109,242 participants and reported 5056 events. There was no clearly apparent benefit of ARB therapy on lowering risk of CV death in high-risk hypertensives compared with the control group (RR, 1.01; 0.96-1.07; p=0.69). There was no evidence of heterogeneity ($I^2=0\%$).

Data on patients with underlying CAD was obtained from the TRANSCEND trial which had an 75.2% pooled treatment effect. When compared with the control group, ARB therapy did not reduce the CV mortality risk with an RR of 1.00 (95% CI 0.79- 1.27; p=0.99). There was no evidence of heterogeneity.

For patients with underlying DM with or without nephropathy, the model yielded an RR of 1.45 (95% CI 0.98-2.14; p=0.06). However, the assessment of heterogeneity shows a 46% statistical variation among trials. The degree of heterogeneity was due to the ORIENT and ROADMAP trials that reported excessive CV deaths in the ARB group. When these trials are excluded, the heterogeneity disappears (I²=0%) with an RR of 1.19 (95% CI 0.96-1.47; p=0.12).

Data of patients with HF was available from 7 trials that indicated that treatment with ARB did not reduce the risk of CV mortality compared with the control group (RR, 0.96; 95% CI 0.90-1.03, p=0.26). There was no evidence of heterogeneity.

Although there were 3 trials that assessed the effectiveness of ARB for patients with AF, one only reported events (ACTIVE-I). Thus, this data could not be included in the meta-analysis.

7.6.3.3 Mean age group

Data for patients aged \ge 65 years indicated no significant mortality reduction by ARB (RR, 0.97; 95% CI 0.92-1.02, p=0.21). The assessment of heterogeneity shows no statistical differences between studies.

Data of patients aged <65 years indicated no clear reduction of CV death by ARBs as compared with the control group (RR, 1.12; 95% CI 0.95-1.32; p=0.18). The assessment of heterogeneity detected a significant statistical variation between studies (chi-square P=0.007 and I²=61%). This degree of statistical heterogenicity was driven by the ROADMAP, ORIENT and CHARM-Added trials. The ROADMAP and ORIENT trials reported high CV deaths in the ARB group; however, the CHARM-Added study indicated superiority of ARB. When these trials are excluded, the I² becomes zero.

	ARI		Cont	rol		Risk Ratio	Risk Ratio	Risk of Bias
Study or Subgroup	Events		Events		Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl	ABCDEFG
1.1.1 Dihydropyridine CCI		istai	Lvents	iotai	weight	m-n, nanu011, 95% CI	M-1, Nandolli, 95% Cl	ADCDEFU
CASE-J 2008	11	2354	15	2349	10.2%	0.73 [0.34, 1.59]		
CHIEF 2018*	58	6766	37	6776	23.6%	1.57 [1.04, 2.37]		
IDNT (CCB) 2003*	52	579	37	567	24.0%	1.38 [0.92, 2.06]	+ -	
J-RHYTHM II 2010	0	158	0	160	21.070	Not estimable		A ? A A A A A
MITEC 2009	Ō	100	Ō	109		Not estimable		
NTP-AF study 2013	0	74	0	75		Not estimable		••••
VALUE 2004	304	7649	304	7596	42.1%	0.99 [0.85, 1.16]	+	••••
Subtotal (95% CI)		17680		17632	100.0%	1.16 [0.88, 1.53]	*	
Total events	425		393					
Heterogeneity: Tau ² = 0.0-	4; Chi² = 6.	63, df=	3 (P = 0.0	18); I ° = 6	55%			
Test for overall effect: Z =	1.04 (P = 0	.30)						
1.1.2 Diuretics / Beta-blo								
HONG-KONG DHF 2007	1	56	1	50	0.4%	0.89 [0.06, 13.90]	• • • • • • • • • • • • • • • • • • • •	
LIFE 2002 Subtatel (05% CI)	204	4605 4661	234	4588	99.6% 100.0 %	0.87 [0.72, 1.04]		$\bullet \bullet \bullet \bullet \bullet \bullet \bullet \bullet$
Subtotal (95% CI)	005	4001	005	4030	100.0%	0.87 [0.72, 1.04]		
Total events Heterogeneity: Tau ² = 0.00	205 0: 0: 0: 7	00 df-	235 1 /D = 0.0	0.12 - 0	nov.			
Test for overall effect: Z =	•	•	T (P = 0.9	18), I [_] = U	170			
restion overall ellect. Z -	1.51 (F = 0	.13)						
1.1.3 Active control								
4C 2016	6	585	5	534	6.1%	1.10 [0.34, 3.57]		
ATTEMPT-CVD 2016	2	615	2	613	2.2%	1.00 [0.14, 7.05]		
CARP 2011	0	90	0	101		Not estimable		??
E-COST 2005	1	1053	0	995	0.8%	2.83 [0.12, 69.51]		• • • • • ? • • ?
E-COST-R 2005	4	69	4	72	4.7%	1.04 [0.27, 4.01]		?? \varTheta ? 😼 😯 ?
HIJ-CREATE 2009	28	1024	25	1025	30.1%	1.12 [0.66, 1.91]		• ? ? • ? • ?
Kondo et al 2003	2	203	9	203	3.7%	0.22 [0.05, 1.02]	<	?? 🔴 ? 🗣 🤋 ?
OLIVUS 2010	1	126	2	121	1.5%	0.48 [0.04, 5.23]	•	?????
SUPPORT 2015	48	578	38	568	50.8%	1.24 [0.82, 1.87]	-t -	•?•••
Subtotal (95% CI)		4343		4232	100.0%	1.10 [0.82, 1.47]	•	
Total events	92		85					
Heterogeneity: Tau ² = 0.0	•	•	7 (P = 0.6	i1); I² = 0)%			
Test for overall effect: Z =	0.63 (P = 0	.53)						
							0.2 0.5 1 2 5	-
Toot for outparoup differen	one: Chiz-	- 266 -	f = 0 /P -	0.46\ 12	- 45.2%		Favours [ARB] Favours [control]	
Test for subgroup differer	ices. Chira	= 3.66, u	I = 2 (P =	0.16), 1-	= 40.3%			
Risk of bias legend			- 1-11					
(A) Random sequence ge			i plas)					
(B) Allocation concealmer			a rfa rna	a his-				
(C) Blinding of participant								
 (D) Blinding of outcome a (E) Incomplete outcome d 			uon bias)	. other c	nucomes			
(E) Incomplete outcome d								

(F) Selective reporting (reporting bias)

(G) Other bias

Figure 7-13 Forest plot showing effect of ARBs on risk of CV mortality (RE model) [Subgroup analysis: Class of active comparator].

*Trial responsible for heterogeneity. CI: confidence interval; RE: random-effects; M-H: Mantel-Haenszel. For studies acronyms, see list of definition/ abbreviations

	ARE Events		Place Events	ebo Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% Cl	Risk of Bias ABCDEFG
1.1.1 High-risk hypertensive 4C 2016	e 6	585	5	534	0.2%	1.10 [0.34, 3.57]		
ACTIVE-I 2011	666	4518	5 646	534 4498	27.8%	1.03 [0.93, 1.13]	_	
ATTEMPT-CVD 2016	2	615	2	613	0.1%	1.00 [0.14, 7.05]		
CARP 2011	0	90	0	101		Not estimable		?? ?????????????
CASE-J 2008	11	2354	15	2349	0.5%	0.73 [0.34, 1.59]		
CHIEF 2018 E-COST 2005	58 1	6766 1053	37 0	6776 995	1.6%	1.57 [1.04, 2.37] 2.83 [0.12, 69.51]	· · · · · · · · · · · · · · · · · · ·	
E-COST-R 2005	4	69	4	72	0.2%	1.04 [0.27, 4.01]	· · _ · · ·	? ? • ? • ?
HIJ-CREATE 2009	28	1024	25	1025	1.0%	1.12 [0.66, 1.91]		• ? ? • ? • ?
HONG-KONG DHF 2007	1	56	1	50	0.0%	0.89 [0.06, 13.90]	• • • •	
IDNT (Overall) 2003 I-PRESERVE 2008	52 311	579 2067	83 302	1136 2061	2.5% 13.0%	1.23 [0.88, 1.71] 1.03 [0.89, 1.19]		
J-RHYTHM II 2010	311	158	302	160	13.0%	Not estimable	Γ	
LIFE 2002	204	4605	234	4588	8.3%	0.87 [0.72, 1.04]		
MITEC 2009	0	100	0	109		Not estimable		
NAVIGATOR 2010	128	4631	116	4675	4.5%	1.11 [0.87, 1.43]	- +- -	
NTP-AF study 2013 OLIVUS 2010	0	74 126	0	75 121	0.0%	Not estimable 0.48 [0.04, 5.23]	· · · · · · · · · · · · · · · · · · ·	2 2 2
ORIENT 2011*	10	282	3	284	0.2%	3.36 [0.93, 12.07]	· · · · · · · · · · · · · · · · · · ·	
PRoFESS 2008	223	10146	263	10186	8.9%	0.85 [0.71, 1.02]		?
RENAAL 2001	90	751	79	762	3.4%	1.16 [0.87, 1.54]	+	
SCOPE 2003 SUPPORT 2015	145 48	2477 578	152 38	2460 568	5.7% 1.7%	0.95 [0.76, 1.18]		
TRANSCEND 2008	227	2954	223	2972	8.8%	1.24 [0.82, 1.87] 1.02 [0.86, 1.22]		ă ă ă ă ă ă ă ă
VALUE 2004	304	7649	304	7596	11.5%	0.99 [0.85, 1.16]	-	
Weil et al 2013	1	84	1	85	0.0%	1.01 [0.06, 15.91]	· · · · · · · · · · · · · · · · · · ·	• • ? • ? • • ?
Subtotal (95% CI)		54391		54851	100.0%	1.01 [0.96, 1.07]	•	
Total events Heterogeneity: $Tau^2 = 0.00$; (Test for overall effect: $Z = 0.4$			2535 21 (P = 1	0.52); l² :	= 0%			
1.1.2 Coronary Artery Disea			-				_	
4C 2016 CARP 2011	6	585 90	5 0	534 101	4.0%	1.10 [0.34, 3.57] Not estimable	 	
HIJ-CREATE 2009	28	1024	25	1025	17.4%	1.12 [0.66, 1.91]	_	
Kondo et al 2003	2	203	- 9	203	2.4%	0.22 [0.05, 1.02]	←	22020
OLIVUS 2010	1	126	2	121	1.0%	0.48 [0.04, 5.23]	•	??????
TRANSCEND 2008	227	2954 4982	223	2972	75.2%	1.02 [0.86, 1.22]		
Subtotal (95% CI) Total events	264	4982	264	4956	100.0%	1.00 [0.79, 1.27]	—	
Heterogeneity: Tau ² = 0.01; 0 Test for overall effect: Z = 0.0	Chi² = 4.3			86); I² = 9	%			
1.1.3 DM ± Nehropathy		,						
IDNT (Overall) 2003	52	579	83	1136	39.3%	1.23 [0.88, 1.71]	+	
MITEC 2009 ORIENT 2011*	0 10	100	0	109	7.00	Not estimable		
RENAAL 2001	90	282 751	3 79	284 762	7.9% 42.5%	3.36 [0.93, 12.07] 1.16 [0.87, 1.54]	,	
ROADMAP 2011*	15	2232	3	2215	8.4%	4.96 [1.44, 17.12]	- →	
Weil et al 2013	1	84	1	85	1.9%	1.01 [0.06, 15.91]	· · · · · · · · · · · · · · · · · · ·	• • • • • • • • • • •
Subtotal (95% CI)		4028		4591	100.0%	1.45 [0.98, 2.14]		
Total events Heterogeneity: Tau ² = 0.07; 0	168 25 - 7 -	11 df -	169 4 /D = 0.1	13:18 - 4	en			
Test for overall effect: Z = 1.8			4 (F = 0.1	1),1 = 4	0.70			
1.1.4 HF								
CHARM-Added 2003	302	1276	347	1272	22.8%	0.87 [0.76, 0.99]		
CHARM-Alternative 2003	219	1013	252	1015	17.2%	0.87 [0.74, 1.02]		
CHARM-Preserved 2003 HONG-KONG DHF 2007	170	1514 56	170	1509 50	11.5% 0.1%	1.00 [0.82, 1.22] 0.89 [0.06, 13.90]	· · · · · ·	
I-PRESERVE 2008	311	2067	302	2061	19.7%	1.03 [0.89, 1.19]	· · · · · · · · · · · · · · · · · · ·	
SUPPORT 2015	48	578	38	568	3.0%	1.24 [0.82, 1.87]		• ? • • ? • •
Val-HeFT 2001	427	2511	419	2499	25.8%	1.01 [0.90, 1.15]	, 1	?? 🔁 🔁 ? 🖶 🛑
Subtotal (95% CI)		9015		8974	100.0%	0.96 [0.89, 1.03]	•	
Total events Heterogeneity: Tau ² = 0.00; 0 Test for overall effect: Z = 1.1			1529 6 (P = 0.3	33); I⁼ = 1	3%			
1.1.5 AF								
ACTIVE-I 2011	666	4518	646	4498	100.0%	1.03 [0.93, 1.13]		
J-RHYTHM II 2010	0	158	0	160		Not estimable	T	
NTP-AF study 2013	0	74 4750	0	75	100.0%	Not estimable		•?•?••
Subtotal (95% CI) Total events	666	4750	646	4733	100.0%	1.03 [0.93, 1.13]	T	
Heterogeneity: Not applicabl Test for overall effect: Z = 0.5	le	.61)	040					
1.1.6 Non-diabetics nephron								
E-COST-R 2005	patriy 4	69	4	72	100.0%	1.04 [0.27, 4.01]		??
Subtotal (95% Cl)	-	69	+	72	100.0%	1.04 [0.27, 4.01]		
Total events	4		4			-		
Heterogeneity: Not applicabl								
Test for overall effect: Z = 0.0	ο (P = 0.	.90)						
1.1.7 CVA							1	
PRoFESS 2008	223	10146	263	10186	100.0%	0.85 [0.71, 1.02]		?
Subtotal (95% CI)		10146		10186	100.0%	0.85 [0.71, 1.02]	•	
Total events Heterogeneity: Not applicabl	223		263					
Test for overall effect: Z = 1.7		.07)						
						E	0.2 0.5 i ż ś avours [experimental] Favours [control]	
Test for subgroup difference	s: Chi ^z =	8.33, di	f=6(P=	0.22), I²	= 28.0%		testermental, i avoura fromtoll	
Risk of bias legend (A) Random sequence gene	eration (s	election	n bias)					
(D) Allocation concolment (e o lo otio		-					

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias): Other outcomes
(E) Incomplete outcome data (attrition bias)
(G) Other bias

Figure 7-14 Forest plot showing effect of ARBs on risk of CV mortality (RE model) [Subgroup analysis: Clinical setting].

*Trial responsible heterogeneity. CI: confidence interval; RE: random-effects; M-H: Mantel-Haenszel. For studies acronyms, see list of definition/ abbreviations

Table 7-3 Summary of RE a meta-analytical subgroup analysis showing the effect of ARBs on risk of CV death compared with control (placebo and active) †

					CV death	Incidence (%)			l² (%)
Sut	ogroup analysis	Studies	Participants	Events	ARBs	Control	RR (M-H, Random, 95% CI)	Р	‡
								value*	
Overall effects	RE	34	139,988	7768	5.51	5.58	0.99 [0.95, 1.03]	0.53	26
	DHP-CCBs	7	35312	818	2.40	2.22	1.16 [0.88, 1.53]	0.30	55
Active control	Diuretics/Beta-blockers	2	9299	440	4.39	5.06	0.87 [0.72, 1.04]	0.13	0
	Active control	9	8575	177	2.11	2.00	1.10 [0.82, 1.47]	0.53	0
	High-risk hypertensive	26	109,242	5056	4.63	4.62	1.01 [0.96, 1.07]	0.69	0
	CAD	6	9938	528	5.29	5.32	1.00 [0.79, 1.27]	0.99	9
-	DM± Nephropathy	6	8619	337	4.17	3.68	1.45 [0.98, 2.14]	0.06	46**
Clinical setting	Heart failure	7	17,989	3007	16.3	17.0	0.96 [0.89, 1.03]	0.26	13
	Atrial fibrillation	3	9483	1312	14.0	13.7	1.03 [0.93, 1.13]	0.61	NA
	Non-diabetic nephropathy^	1	141	8	5.79	5.55	1.04 [0.27, 4.01]	0.95	NA
	CVA^	1	20,332	486	2.19	2.58	0.85 [0.71, 1.02]	0.07	NA
Mean age	< 65 years	13	44,068	2197	5.03	4.93	1.12 [0.95, 1.32]	0.18	61¥
group	≥ 65 years	20	95,341	5519	5.68	5.88	0.97 [0.92, 1.02]	0.21	0

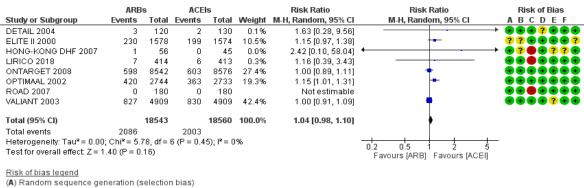
¥ By excluding ORIENT and ROADMAP, the heterogeneity is disappeared (i2=0%) with RR of 1.08 (95% CI 0.98-1.19; p=0.11).

7.7 Direct comparison between ACEIs and ARBs on risk of CV mortality

7.7.10verall treatment effect

Data regarding direct comparisons between ARBs and ACEIs on CV death risk were available from 8 RCTs that involved 37,103 participants and 4,089 reported CV death events. The incidence of CV deaths between patients treated by ACE and ARB was similar (11.24% and 10.79%, respectively) (see **Figure 7-15**). The reduction of risk of CV deaths in patients treated with ARBs and ACEIs was similar (RR, 1.04; 95% CI 0.98-1.10; p=0.16). The direction and magnitude of the pooled effect estimates were mainly influenced by the VALIANT and ONTARGET trials that contributed 69.8% of the weighting. There was no evidence of statistical heterogeneity among trials (chi-square p value =0.45 and I² = 0%).

As there was no variation among trials, the summary effect estimates generated by the FE model are similar to those generated by the RE model (see Figure 7-16).



(B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias)

(D) Incomplete outcome data (attrition bias) (E) Selective reporting (reporting bias)

(F) Other bias

Figure 7-15 Forest plot showing effect of ARBs versus ACEIs on risk of CV mortality (RE model).

The diamond indicates the pooled risk ratio (and 95% CI) or the overall effect for CV mortality risk. CI: confidence interval; RE: random-effects; M-H: Mantel-Haenszel. For studies acronyms, see list of definition/ abbreviations

	ARB	s	ACE	Is		Risk Ratio	Risk Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl	ABCDEFG
DETAIL 2004	3	120	2	130	0.1%	1.63 [0.28, 9.56]		→ ••• • ? •••
ELITE II 2000	230	1578	199	1574	9.9%	1.15 [0.97, 1.38]	+	??
HONG-KONG DHF 2007	1	56	0	45	0.0%	2.42 [0.10, 58.04]	•	→ • ? • • ? ? •
LIRICO 2018	7	414	6	413	0.3%	1.16 [0.39, 3.43]		
ONTARGET 2008	598	8542	603	8576	30.0%	1.00 [0.89, 1.11]	+	
OPTIMAAL 2002	420	2744	363	2733	18.2%	1.15 [1.01, 1.31]	-	
ROAD 2007	0	180	0	180		Not estimable		
VALIANT 2003	827	4909	830	4909	41.4%	1.00 [0.91, 1.09]	†	€€€€?€€
Total (95% CI)		18543		18560	100.0%	1.04 [0.98, 1.10]	•	
Total events	2086		2003					
Heterogeneity: Chi ² = 5.78	, df = 6 (P =	= 0.45);	I²=0%					_
Test for overall effect: Z = 1	.40 (P = 0.	.16)					0.2 0.5 1 2 5 Favours [ARB] Favours [ACEI]	
Dick of high logand							Taroalo (Fito) Taroalo (Fiozi)	

Risk of bias legend

(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias): Other outcomes

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

Figure 7-16 Forest plot showing effect of ARBs versus ACEIs on risk of CV mortality (FE model).

The diamond indicates the pooled risk ratio (and 95% CI) or the overall effect for CV mortality risk. CI: confidence interval; FE: fixed-effect; M-H: Mantel-Haenszel. For studies acronyms, see list of definition/ abbreviations

7.7.2 Sensitivity analysis

Excluding 4 trials that involved patients with signs and symptoms of HF within 10 days of an MI (OPTIMAAL & VALIANT) and with symptomatic CHF (ELITE II & HONG-KONG DHF) did not modify the direction and magnitude of treatment effect with an RR of 1.00 (95% CI 0.90- 1.11; p=0.99). There was evidence of heterogeneity (See Figure 7-17).

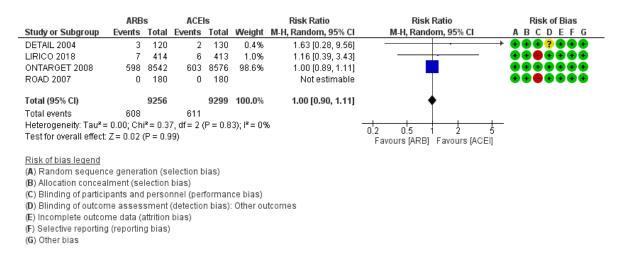


Figure 7-17 Forest plot showing effect of ARBs versus ACEIs on risk of CV mortality (RE model). [Sensitivity analysis: Excluding trials with HF),

7.8 Meta-regression analyses of the effect of ACEI and ARB on CV mortality risk in relation to SBP reduction

7.8.1 ACEIs

7.8.1.1 Overall effect

Nine of the trials included did not report the SBP reduction achieved (CARMEN, CCS-I, PROGRESS, Hou et al. (group 2), IMAGINE and QUIET) and two reported zero CV mortality cases (PHARAO, QUO VADIS). Thus, 25 trials were included in the meta-regression analysis. The mean achieved SBP reduction of the ACEI trials were in the range of -8 (ESPIRAL) to 4.8 mmHg (Chen et al.). As shown in Table 7-4, the univariate analysis indicates that the relative risk of CV mortality reduction was proportional to the mean SBP reduction achieved by ACEIs (an estimated RR, 1.04; 95% CI 1.01-1.08; p=0.002). Mortality reduction was larger in trials with the largest difference in the achieved mean SBP. Achieved SBP differences between randomised groups explained 77% of the observed between-trial variations for CV mortality risk.

In the univariate model, a 14% of between-study variance was explained by percentage of male and 9% by baseline SBP (mmHg). Therefore, percentage of male and baseline SBP were adjusted on the multivariate analysis. After accounting for these variables, the direction and magnitude of the relationship between a mean SBP and CV mortality risk remained unaltered. A 99% variability among trials in the RR of mortality was substantially explained by the adjusted model (Tau² reduced from 0.0114 to 0.0001; p=0.777 and Residual I²=0%). Although the achieved mean DBP (mmHg) differences explained 66% of the variabilities, it was excluded from the multivariate model because it possessed a strong correlation with the achieved mean SBP differences (r=-0.9). At zero mmHg BP reduction achieved, there was no evidence that ACEIs conferred a BP-independent cerebrovascular effect (RR, 0.98; 95% CI 0.90-1.07; p=0.767). **Figure 7-18** shows adjusted meta-regression plot of the mean difference in SBP between groups of ACEIs trials compared with the control group and log RR of CV mortality.

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Table 7-4 Meta-regression of related and unrelated SBP differences by ACEIs on CV mortality (unadjusted and adjusted models).

			Slope			Between stu	Between study variance					
Variable	Studies	RR	95% CI	P value*	Tau ²	Residual I ² (%)	P value*	R ² (%)				
Null model	<u></u>		<u> </u>		0.0114	26.37	0.113					
Univariate analysis (Unadjusted)												
Achieved SBP differences (mmHg)	25	1.04	1.01-1.08	0.002	0.0026	0	0.768	77				
Achieved DBP differences (mmHg)**		1.09	1.02-1.17	0.010	0.0039	0	0.628	66				
Baseline SBP (mmHg)		1.00	0.99-1.02	0.409	0.0104	21.07	0.176	9				
Mean age (Years)		1.00	0.97-1.03	0.823	0.0124	26.79	0.113	0				
Male (%)		0.99	0.98-1.00	0.124	0.0098	8.15	0.348	14				
DM (%)		1.00	0.99-1.02	0.858	0.0138	29.34	0.089	0				
Duration of follow-up (Years)		1.03	0.84-1.24	0.762	0.0121	23.69	0.145	0				
Multivariate analysis (Adjusted)‡			1		1							
Achieved SBP differences (mmHg)		1.05	1.02-1.08	0.0003	0.0001	0	0.777	99				

Abbreviation: Tau²= estimated amount of heterogeneity (between-study variance) not explained by covariate; I² residual= proportion of remaining observed variance due to true variation in effect size.

* P value less of than 0.05 is significant

** The achieved DBP difference is excluded from multivariate model as it highly correlated with achieved SBP differences (r=-0.99).

⁺ The analysis was adjusted for male (%) and baseline SBP (mmHg)

7.8.2ARBs

7.8.2.1 Overall effect

Two trials did not report the mean SBP reduction (SUPPORT, Weil et al.) and four trials reported zero cases (CARP, J-RHYTHM II, MITEC, NTP-AF study). Thus, a total of 28 ARB trials that reported a mean SBP reduction were included in the meta-regression analysis (see **Figure 7-18**). The average SBP reduction ranged from - 5.7 mmHg in the HOPE-3 trial to 2.3 mmHg in the OLIVUS trial. A meta-regression demonstrated no apparent benefit related to ARB either dependent on or independent from BP reduction, with a p value=0.81 and 0.83, respectively.

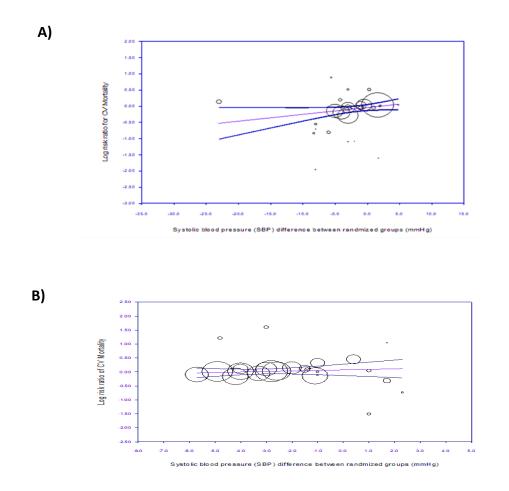


Figure 7-18 Adjusted meta-regression analysis of the relationship between RR for CV mortality and difference in SBP (mmHg) achieved between the randomized groups for trials of A) ACEIs and B) ARBs

Each study is represented by a circle. The size of each circle is proportional to that study's weight in the analysis (inverse-variance weighted). A negative value on the x-axis indicates lower achieved SBP in the treatment group.

7.9 ACEIs and risk of all-cause mortality

7.9.10verall effect

Figure 7-19 displays the RE meta-analytical summary of the effect of ACEI -based treatment on all-cause mortality risk stratified according to control group, placebo or active group. Data on all-cause mortality was reported in 41 RCTs that involved 125,824 participants and reported 11,646 events. Altogether, therapy with ACEIs was found to significantly reduce the risk of all-cause mortality by 5% (RR,0.95; 95% CI 0.91-0.98; p=0.003). The chi-square test resulted in a P-value of 0.76 and $l^2 = 0\%$.

By stratifying the control group into placebo and active comparators, the data on all-cause mortality of ACEI compared with the placebo groups could be extracted from 26 RCTs involving 77,386 subjects and 6045 all-cause mortality events. More than 50% of the trials reported RR < 1. Thus, ACEI was associated with a significant 9% reduction of all-cause mortality compared with the placebo (RR, 0.91; 95% CI 0.86-0.95; p <0.0001). The largest mortality reductions were observed in four trials that greatly contributed to the pooled treatment effects, namely HOPE (9.8%), CCS-I (8.3%), ADVANCE (7.9%) and EUROPA (7.1%). The chi-square test P-value is 0.71 and the $I^2 = 0\%$ indicating no statistical heterogeneity between studies.

In 16 active-controlled trials involving 48,438 participants and reporting 5,601 events. The incidence of all-cause mortality was lower in the ACEIs group (10.3%) than the active group (12.2%). A 58.8% of trials reported RR < 1 and an interrupted line of null hypothesis. Compared with the active therapy group, the benefit of ARB therapy was neutral (RR, 1.00; 95% CI 0.95-1.06; p=1.00). There was no evidence of statistical heterogeneity among trials (chi-square p value = 0.97 and $l^2=0\%$). The FE model shown in **Figure 7-20** indicates that a slightly higher weighting was assigned to the ALLHAT (2.9%) and HOPE (0.6%) trials. However, the direction and magnitude of the pooled effect estimates was not affected as a result of no variation among trials ($l^2=0\%$). A visual examination of the funnel plot (**Figure D-3 presented in Appendix D**) shows a symmetric distribution of data in the top area. However, a gap appears in the bottom right side of the plot (a non-

significant area) that may be due to publication bias as smaller trials without positive results are not published. No outliers were detected.

to the set Conference of	ACE		Contr		104-1-1-4	Risk Ratio	Risk Ratio	Risk of Bias
itudy or Subgroup .1.1 ACEI vs Placebo	Events	lotal	Events	lotal	weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl	ABCDEF
ARDVARK (Placebo) 2017	2	73	3	79	0.0%	0 72 [0 12 4 20]	<u>ــــــــــــــــــــــــــــــــــــ</u>	
DVANCE 2007	408	5569	471	5571	7.9%	0.72 [0.12, 4.20] 0.87 [0.76, 0.98]	· · ·	
PRES 2000	2	80	8	79	0.1%	0.25 [0.05, 1.13]	•••	
TLANTIS 2000	5	92	0	48	0.0%	5.80 [0.33, 102.66]	*	
ENEDICT (monotherapy) 2004	4	301	8	300	0.1%	0.50 [0.15, 1.64]	• • • • • • • • • • • • • • • • • • • •	??
AMELOT (Placebo) 2004	8	673	6	655	0.1%	1.30 [0.45, 3.72]		
CS-I 2001	404	3391	463	3358	8.3%	0.86 [0.76, 0.98]		
EMAND (monotherapy) 2011	1	127	3	127	0.0%	0.33 [0.04, 3.16]	• • • • • • • • • • • • • • • • • • •	
IABHYCAR 2004	334	2443	324	2469	6.3%	1.04 [0.90, 1.20]	+	
REAM 2006	31	2623	32	2646	0.5%	0.98 [0.60, 1.60]		
JROPA 2003	375	6110	420	6108	7.1%	0.89 [0.78, 1.02]	-	226666
OPE 2000	482	4645	569	4652	9.8%	0.85 [0.76, 0.95]	-	200000
ou et al (group 2) 2006	402	112	0	112	0.0%	3.00 [0.12, 72.86]	· · · · · · · · · · · · · · · · · · ·	
				426	0.0%			
YVET (Placebo) 2003	27	431	22		0.170	1.21 [0.70, 2.10]		
AGINE 2008	28	1280	28	1273	0.5%	0.99 [0.59, 1.67]		
ART-2 2000	16	308	25	309	0.3%	0.64 [0.35, 1.18]		
EACE 2004	299	4158	334	4132	5.7%	0.89 [0.77, 1.03]	-+	
EP-CHF 2006	56	424	53	426	1.0%	1.06 [0.75, 1.51]	_ 	
HARAO 2008	5	505	2	503	0.0%	2.49 [0.49, 12.78]		
REAMI 2006	40	631	37	621	0.7%	1.06 [0.69, 1.64]	_ 	
REVEND IT 2007	5	431	4	433	0.1%	1.26 [0.34, 4.64]		
ROGRESS 2001	306	3051	319	3054	5.8%	0.96 [0.83, 1.11]	+	
JIET 2001	27	878	27	872	0.5%	0.99 [0.59, 1.68]		??
UO VADIS 2001	27	878	27	73	0.0%	Not estimable		220000
			-					
ASS 2009	1	94	1	95	0.0%	1.01 [0.06, 15.92]	•	6?6666
CAT 2000	8	229	11	231	0.2%	0.73 [0.30, 1.79]		
ubtotal (95% Cl)		38734		38652	55.5%	0.91 [0.86, 0.95]	•	
otal events eterogeneity: Tau² = 0.00; Chi² =	2875		3170					
est for overall effect: Z = 4.03 (P <	(0.0001)							
1.2 ACEI vs Active								
ARDVARK (Active) 2016	2	73	3	72	0.0%	0.66 [0.11, 3.82]	• • • • • • • • • • • • • • • • • • • •	
ASK 2002	34	436	71	658	0.8%	0.72 [0.49, 1.07]	+	
3CD (normotensive) 2002	19	246	19	234	0.3%	0.95 [0.52, 1.75]		
LLHAT 2002	1314	9054	3459	24303	37.2%	1.02 [0.96, 1.08]	•	
NBP2 2003	195	3044	210	3039	3.6%	0.93 [0.77, 1.12]	-+	2
ENEDICT (combination) 2004	2	300	3	303	0.0%	0.67 [0.11, 4.00]	· · · · · · · · · · · · · · · · · · ·	22444
ENEDICT (monotherapy) 2004	4	301	3	303	0.1%	1.34 [0.30, 5.95]		220000
AMELOT (Active) 2004	8	673	7	663	0.1%	1.13 [0.41, 3.09]		
ARMEN (combination) 2004	0 14	191	14	191	0.1%			
						1.00 [0.49, 2.04]	1	200000
ARMEN (monotherapy) 2004	14	190	14	191	0.3%	1.01 [0.49, 2.05]		
LVERA 2001	0	85	1	81	0.0%	0.32 [0.01, 7.69]	•	??.....
ogari et al (combination) 2002	2	104	4	103	0.0%	0.50 [0.09, 2.64]	• • • • • • • • • • • • • • • • • • • •	
		102	4	103	0.1%	0.76 [0.17, 3.30]		
ogari et al (monotherapy) 2002	3	102						
	3 27	431	30	426	0.5%	0.89 [0.54, 1.47]		
YVET (diuretics) 2003				426 422				
YVET (diuretics) 2003 MP 2004	27	431	30		0.5%	0.89 [0.54, 1.47]		
YVET (diuretics) 2003 AMP 2004 MIC-B 2004	27 47	431 466	30 47	422	0.5% 0.9%	0.89 [0.54, 1.47] 0.91 [0.62, 1.33]		
YVET (diuretics) 2003 AMP 2004 MIC-B 2004 ubtotal (95% CI)	27 47	431 466 822	30 47	422 828	0.5% 0.9% 0.2%	0.89 [0.54, 1.47] 0.91 [0.62, 1.33] 1.26 [0.59, 2.67]		
VVET (diuretics) 2003 MP 2004 MIC-B 2004 Jubtotal (95% CI) Datal events	27 47 15 1700	431 466 822 16518	30 47 12 3901	422 828 31920	0.5% 0.9% 0.2%	0.89 [0.54, 1.47] 0.91 [0.62, 1.33] 1.26 [0.59, 2.67]		
VET (diuretics) 2003 MP 2004 (IC-B 2004 (Job 195% CI) tal events eterogeneity: Tau ² = 0.00; Chi ² =	27 47 15 1700 6.48, df =	431 466 822 16518	30 47 12 3901	422 828 31920	0.5% 0.9% 0.2%	0.89 [0.54, 1.47] 0.91 [0.62, 1.33] 1.26 [0.59, 2.67]	•	
VET (diuretics) 2003 MP 2004 IIC-B 2004 Ibitotal (95% CI) Ital events sterogeneity: Tau ² = 0.00; Chi ² = Ist for overall effect: Z = 0.00 (P =	27 47 15 1700 6.48, df =	431 466 822 16518	30 47 12 3901	422 828 31920 0%	0.5% 0.9% 0.2%	0.89 [0.54, 1.47] 0.91 [0.62, 1.33] 1.26 [0.59, 2.67] 1.00 [0.95, 1.06]		
ÑET (diuretics) 2003 MP 2004 IIC-B 2004 Ibtotal (95% CI) tal events sterogeneity: Tau ² = 0.00; Chi ² = ist for overall effect: Z = 0.00 (P = tal (95% CI)	27 47 15 1700 6.48, df = 1 = 1.00)	431 466 822 16518 15 (P = 1	30 47 12 3901 0.97); I ² =	422 828 31920 0%	0.5% 0.9% 0.2% 44.5%	0.89 [0.54, 1.47] 0.91 [0.62, 1.33] 1.26 [0.59, 2.67]	•	
VET (diuretics) 2003 MP 2004 (IC-B 2004 (Ibtotal (95% CI) tal events eterogeneity: Tau ² = 0.00; Chi ² = st for overall effect: Z = 0.00 (P = tal (95% CI) tal events eterogeneity: Tau ² = 0.00; Chi ² =	27 47 15 1700 6.48, df = = 1.00) 4575 33.51, df =	431 466 822 16518 15 (P = 1 55252	30 47 12 3901 0.97); I ² = 7071	422 828 31920 0% 70572	0.5% 0.9% 0.2% 44.5%	0.89 [0.54, 1.47] 0.91 [0.62, 1.33] 1.26 [0.59, 2.67] 1.00 [0.95, 1.06]		
WET (diuretics) 2003 MP 2004 MIC-B 2004 ubtotal (95% CI) otal events eterogeneity: Tau ² = 0.00; Chi ² = est for overall effect: Z = 0.00 (P = otal (95% CI) otal events eterogeneity: Tau ² = 0.00; Chi ² = staf or overall effect: Z = 0.00; Chi ² = staf or overall effect: Z = 0.00; Chi ² =	27 47 15 6.48, df = = 1.00) 4575 33.51, df = = 0.003)	431 466 822 16518 15 (P = 1 55252 = 40 (P =	30 47 12 3901 0.97); I ² = 7071 : 0.76); I ²	422 828 31920 0% 70572 = 0%	0.5% 0.9% 0.2% 44.5%	0.89 [0.54, 1.47] 0.91 [0.62, 1.33] 1.26 [0.59, 2.67] 1.00 [0.95, 1.06]	0.2 0.5 1 2 5 Favours [ACE] Favours [control]	
VVET (diuretics) 2003 AMP 2004 MIC-B 2004 ubtotal (95% CI) otal events leterogeneity: Tau ² = 0.00; Chi ² = est for overall effect: Z = 0.00 (P = otal events leterogeneity: Tau ² = 0.00; Chi ² = est for overall effect: Z = 0.00; Chi ² = est for overall effect: Z = 3.00 (P = est for overall effect: Z = 3.00 (P =	27 47 15 6.48, df = = 1.00) 4575 33.51, df = = 0.003)	431 466 822 16518 15 (P = 1 55252 = 40 (P =	30 47 12 3901 0.97); I ² = 7071 : 0.76); I ²	422 828 31920 0% 70572 = 0%	0.5% 0.9% 0.2% 44.5%	0.89 [0.54, 1.47] 0.91 [0.62, 1.33] 1.26 [0.59, 2.67] 1.00 [0.95, 1.06]		
INVET (diuretics) 2003 AMP 2004 MIC-B 2004 ubtotal (95% CI) otal events leterogeneity: Tau ² = 0.00; Chi ² = est for overall effect: Z = 0.00 (P = otal events leterogeneity: Tau ² = 0.00; Chi ² = est for overall effect: Z = 3.00 (P = est for subgroup differences: Ch tisk of bias legend	27 47 15 6.48, df = = 1.00) 4575 33.51, df = = 0.003) i [≠] = 7.22, d	431 466 822 16518 15 (P = 1 55252 = 40 (P = f = 1 (P =	30 47 12 3901 0.97); I ² = 7071 : 0.76); I ²	422 828 31920 0% 70572 = 0%	0.5% 0.9% 0.2% 44.5%	0.89 [0.54, 1.47] 0.91 [0.62, 1.33] 1.26 [0.59, 2.67] 1.00 [0.95, 1.06]		
ogari et al (monotherapy) 2002 fYVET (diuretics) 2003 AMP 2004 MIC-B 2004 MIC-B 2004 iubtotal (95% CI) otal events leterogeneity: Tau ² = 0.00; Chi ² = est for overall effect: Z = 0.00 (P = otal (95% CI) iotal events leterogeneity: Tau ² = 0.00; Chi ² = est for overall effect: Z = 3.00 (P = iest for subgroup differences: Ch lisk of bias legend A) Random sequence generation	27 47 15 1700 6.48, df = • = 1.00) 4575 33.51, df = = 0.003) i [≠] = 7.22, d n (selectior	431 466 822 16518 15 (P = 1 55252 = 40 (P = f = 1 (P =	30 47 12 3901 0.97); I ² = 7071 : 0.76); I ²	422 828 31920 0% 70572 = 0%	0.5% 0.9% 0.2% 44.5%	0.89 [0.54, 1.47] 0.91 [0.62, 1.33] 1.26 [0.59, 2.67] 1.00 [0.95, 1.06]		
tyvET (diuretics) 2003 AMP 2004 MIC-B 2004 MIC-B 2004 (ubtotal (95% CI)) total events est for overall effect: Z = 0.00; Chi² = est for overall effect: Z = 0.00; Chi² = est for overall effect: Z = 0.00; Chi² = est for overall effect: Z = 0.00; Chi² = est for overall effect: Z = 0.00; Chi² = est for overall effect: Z = 0.00; Chi² = est for overall effect: Z = 0.00; Chi² = est for overall effect: Z = 0.00; Chi² = est for overall effect: Z = 3.00 (P = est for overall effect: A = 0.00; Chi² = est for overall effect: Z = 3.00 (P = a) Allocation concealment (selection of the selection overall effection (selection overallement overallement overallement overallement overallement overallement overallement overallement	27 47 15 1700 6.48, df = = 1.00) 4575 33.51, df = = 0.003) i ² = 7.22, d n (selection tion bias)	431 466 822 16518 15 (P = 1 55252 = 40 (P = f = 1 (P = n bias)	30 47 12 3901 0.97); I ² = 7071 : 0.76); I ² = 0.007),	422 828 31920 0% 70572 = 0% ² = 86.2	0.5% 0.9% 0.2% 44.5%	0.89 [0.54, 1.47] 0.91 [0.62, 1.33] 1.26 [0.59, 2.67] 1.00 [0.95, 1.06]		
tivET (diuretics) 2003 AMP 2004 MIC-B 2004 ubtotal (95% CI) total events eleterogeneity: Tau ² = 0.00; Chi ² = est for overall effect: Z = 0.00 (P = otal events eleterogeneity: Tau ² = 0.00; Chi ² = est for overall effect: Z = 0.00; Chi ² = est for overall effect: Z = 3.00 (P = est for subgroup differences: Ch tisk of bias legend Andom sequence generation B) Allocation concealment (select) D) Blinding of participants and pe	27 47 15 1700 6.48, df = = 1.00) 4575 33.51, df = 0.003) i ² = 7.22, d n (selection tion bias) rsonnel (p	431 466 822 16518 15 (P = 1 55252 = 40 (P = f = 1 (P = n bias) eerforma	30 47 12 3901 0.97); I ² = 7071 0.76); I ² = 0.007), nce bias;	422 828 31920 0% 70572 = 0% ² = 86.2	0.5% 0.9% 0.2% 44.5%	0.89 [0.54, 1.47] 0.91 [0.62, 1.33] 1.26 [0.59, 2.67] 1.00 [0.95, 1.06]		
try ET (diuretics) 2003 AMP 2004 MIC-B 2004 ubtotal (95% CI) total events leterogeneity: Tau ² = 0.00; Chi ² = est for overall effect: Z = 0.00 (P = otal events leterogeneity: Tau ² = 0.00; Chi ² = est for overall effect: Z = 0.00; Chi ² = est for overall effect: Z = 3.00 (P = est for subgroup differences: Ch tisk of bias legend a) Random sequence generation a) Rancon concealment (select) D) Blinding of participants and pe b) Blinding of outcome assessm	27 47 15 1700 6.48, df = = 1.00) 4575 33.51, df = = 0.003) i ² = 7.22, d n (selection tion bias) ersonnel (p	431 466 822 16518 15 (P = 1 55252 = 40 (P = f = 1 (P = n bias) eerforma	30 47 12 3901 0.97); I ² = 7071 0.76); I ² = 0.007), nce bias;	422 828 31920 0% 70572 = 0% ² = 86.2	0.5% 0.9% 0.2% 44.5%	0.89 [0.54, 1.47] 0.91 [0.62, 1.33] 1.26 [0.59, 2.67] 1.00 [0.95, 1.06]		
Total (diuretics) 2003 AMP 2004 MIC-B 2004 ubtotal (95% CI) (bit of all events) teterogeneity: Tau ² = 0.00; Chi ² = est for overall effect: Z = 0.00; Chi ² = otal events est for overall effect: Z = 0.00; Chi ² = est for overall effect: Z = 0.00; Chi ² = est for overall effect: Z = 3.00 (P = est for overall effect: Z = 3.00 (P = est for overall effect: Z = 3.00 (P = 9.1 Rondom sequence generation 3) Allocation concealment (select) Silnding of participants and pe 0.1 Bilinding of participants and pe Sessessm 0.2 Bilinding of outcome assessm Silncomplete outcome data (attri	27 47 15 1700 6.48, df = = 1.00) 4575 33.51, df = = 0.003) I [*] = 7.22, d n (selection tion bias) resonnel (p tent (detect tion bias)	431 466 822 16518 15 (P = 1 55252 = 40 (P = f = 1 (P = n bias) eerforma	30 47 12 3901 0.97); I ² = 7071 0.76); I ² = 0.007), nce bias;	422 828 31920 0% 70572 = 0% ² = 86.2	0.5% 0.9% 0.2% 44.5%	0.89 [0.54, 1.47] 0.91 [0.62, 1.33] 1.26 [0.59, 2.67] 1.00 [0.95, 1.06]		
VVET (diuretics) 2003 AMP 2004 MIC-B 2004 ubtotal (95% CI) otal events eterogeneity: Tau ² = 0.00; Chi ² = est for overall effect: Z = 0.00 (P = otal (95% CI) otal events eterogeneity: Tau ² = 0.00; Chi ² = est for overall effect: Z = 3.00 (P = est for overall effect: Z = 3.00 (P = set for ove	27 47 15 1700 6.48, df = = 1.00) 4575 33.51, df = = 0.003) I [*] = 7.22, d n (selection tion bias) resonnel (p tent (detect tion bias)	431 466 822 16518 15 (P = 1 55252 = 40 (P = f = 1 (P = n bias) eerforma	30 47 12 3901 0.97); I ² = 7071 0.76); I ² = 0.007), nce bias;	422 828 31920 0% 70572 = 0% ² = 86.2	0.5% 0.9% 0.2% 44.5%	0.89 [0.54, 1.47] 0.91 [0.62, 1.33] 1.26 [0.59, 2.67] 1.00 [0.95, 1.06]		

Figure 7-19 Forest plot showing effect of ACEIs on risk of all-cause mortality, stratified by comparison group (placebo vs active). Overall: 41 trials (RE model).

The diamond indicates the pooled risk ratio (and 95% CI) or the overall effect for all-cause mortality risk. CI: confidence interval; RE: random-effects; M-H: Mantel-Haenszel. For studies acronyms, see list of definition/ abbreviations

Chapter 7: ACEIs and ARBs with risk of mortality	Chapter 7	: ACEIs	and ARBs	with	risk	of	mortality
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tudy or Subgroup .1.1 ACEI vs Placebo	Evente	Total	Cont		Moight	Risk Ratio	Risk I M H Eixo		Risk of Bias
I.I ACEIVS PIACEDU	Events	lotal	Events	Total	weight	M-H, Fixed, 95% Cl	M-H, Fixe	a, 95% CI	ABCDEF
ARDVARK (Placebo) 2017	2	73	3	79	0.1%	0.72 [0.12, 4.20]	,		
DVANCE 2007	408	5569	471	5571	8.6%	0.87 [0.76, 0.98]	, 7		
PRES 2000	2	80	8	79	0.1%	0.25 [0.05, 1.13]	•	-	
TLANTIS 2000	5	92	0	48	0.0%	5.80 [0.33, 102.66]		.,	
ENEDICT (monotherapy) 2004	4	301	8	300	0.1%	0.50 [0.15, 1.64]			??+++++++++++++
AMELOT (Placebo) 2004	8	673	6	655	0.1%	1.30 [0.45, 3.72]			$\bullet ? \bullet \bullet \bullet \bullet \bullet$
CS-I 2001	404	3391	463	3358	8.5%	0.86 [0.76, 0.98]			$\bullet \bullet \bullet \bullet \bullet ? \bullet \bullet$
EMAND (monotherapy) 2011	1	127	3	127	0.1%	0.33 [0.04, 3.16]	•		
IABHYCAR 2004	334	2443	324	2469	5.9%	1.04 [0.90, 1.20]	1	-	
REAM 2006	31	2623	32	2646	0.6%	0.98 [0.60, 1.60]			
UROPA 2003	375	6110	420	6108	7.7%	0.89 [0.78, 1.02]	-		?? ••••
OPE 2000	482	4645	569	4652	10.4%	0.85 [0.76, 0.95]	-		?.
ou et al (group 2) 2006	1	112	0	112	0.0%	3.00 [0.12, 72.86]	•		\bullet
YVET (Placebo) 2003	27	431	22	426	0.4%	1.21 [0.70, 2.10]	-		
IAGINE 2008	28	1280	28	1273	0.5%	0.99 [0.59, 1.67]			
ART-2 2000	16	308	25	309	0.5%	0.64 [0.35, 1.18]		_	
EACE 2004	299	4158	334	4132	6.1%	0.89 [0.77, 1.03]	-		
EP-CHF 2006	56	424	53	426	1.0%	1.06 [0.75, 1.51]	-		
HARAO 2008	5	505	2	503	0.0%	2.49 [0.49, 12.78]		,	
REAMI 2006	40	631	37	621	0.7%	1.06 [0.69, 1.64]			
REVEND IT 2007	5	431	4	433	0.1%	1.26 [0.34, 4.64]		<u> </u>	
ROGRESS 2001	306	3051	319	3054	5.8%	0.96 [0.83, 1.11]	_	-	
UIET 2001	27	878	27	872	0.5%	0.99 [0.59, 1.68]			??
UO VADIS 2001	0	75	0	73	0.070	Not estimable			??
ASS 2009	1	94	1	95	0.0%	1.01 [0.06, 15.92]	•	,	
CAT 2000	. 8	229	11	231	0.2%	0.73 [0.30, 1.79]			
ubtotal (95% CI)	, v	38734		38652	57.9%	0.91 [0.86, 0.95]	•		
otal events	2875		3170						
1.2 ACEI vs Active ARDVARK (Active) 2016	2	73	3	72	0.1%	0.66 [0.11, 3.82]	•		
ASK 2002	34	436	71	658	1.0%	0.72 [0.49, 1.07]			
	4.0	246							
BCD (normotensive) 2002	19	240	19	234	0.4%	0.95 [0.52, 1.75]			
BCD (normotensive) 2002 LLHAT 2002	19	9054	19 3459	234 24303		0.95 [0.52, 1.75] 1.02 [0.96, 1.08]		•	
LLHAT 2002	1314	9054	3459		34.3%	1.02 [0.96, 1.08]	_	-	
LLHAT 2002 NBP2 2003	1314 195	9054 3044	3459 210	24303 3039	34.3% 3.8%	1.02 [0.96, 1.08] 0.93 [0.77, 1.12]			
LLHAT 2002 NBP2 2003 ENEDICT (combination) 2004	1314	9054	3459 210 3	24303	34.3% 3.8% 0.1%	1.02 [0.96, 1.08] 0.93 [0.77, 1.12] 0.67 [0.11, 4.00]			
LLHAT 2002 NBP2 2003 ENEDICT (combination) 2004 ENEDICT (monotherapy) 2004	1314 195 2 4	9054 3044 300 301	3459 210 3 3	24303 3039 303 303	34.3% 3.8% 0.1% 0.1%	1.02 [0.96, 1.08] 0.93 [0.77, 1.12] 0.67 [0.11, 4.00] 1.34 [0.30, 5.95]		- - 	
LLHAT 2002 NBP2 2003 ENEDICT (combination) 2004 ENEDICT (monotherapy) 2004 AMELOT (Active) 2004	1314 195 2 4 8	9054 3044 300 301 673	3459 210 3 3 7	24303 3039 303 303 663	34.3% 3.8% 0.1% 0.1% 0.1%	1.02 [0.96, 1.08] 0.93 [0.77, 1.12] 0.67 [0.11, 4.00] 1.34 [0.30, 5.95] 1.13 [0.41, 3.09]			
LLHAT 2002 NBP2 2003 ENEDICT (combination) 2004 ENEDICT (monotherapy) 2004 AMELOT (Active) 2004 ARMEN (combination) 2004	1314 195 2 4 8 14	9054 3044 300 301 673 191	3459 210 3 3 7 14	24303 3039 303 303 663 191	34.3% 3.8% 0.1% 0.1% 0.1% 0.3%	1.02 [0.96, 1.08] 0.93 [0.77, 1.12] 0.67 [0.11, 4.00] 1.34 [0.30, 5.95] 1.13 [0.41, 3.09] 1.00 [0.49, 2.04]			
LLHAT 2002 NBP2 2003 ENEDICT (combination) 2004 ENEDICT (monotherapy) 2004 AMELOT (Active) 2004 ARMEN (combination) 2004 ARMEN (monotherapy) 2004	1314 195 2 4 8 14 14	9054 3044 300 301 673 191 190	3459 210 3 7 14 14	24303 3039 303 303 663 191 191	34.3% 3.8% 0.1% 0.1% 0.3% 0.3%	1.02 (0.96, 1.08) 0.93 (0.77, 1.12) 0.67 (0.11, 4.00) 1.34 (0.30, 5.95) 1.13 (0.41, 3.09) 1.00 (0.49, 2.04) 1.01 (0.49, 2.05)			
LLHAT 2002 NBP2 2003 ENEDICT (combination) 2004 ENEDICT (monotherapy) 2004 AMELOT (Active) 2004 ARMEN (combination) 2004 ARMEN (monotherapy) 2004 LVERA 2001	1314 195 2 4 8 14 14 0	9054 3044 300 301 673 191 190 85	3459 210 3 7 14 14 14	24303 3039 303 303 663 191 191 81	34.3% 3.8% 0.1% 0.1% 0.3% 0.3% 0.0%	1.02 [0.96, 1.08] 0.93 [0.77, 1.12] 0.67 [0.11, 4.00] 1.34 [0.30, 5.95] 1.13 [0.41, 3.09] 1.00 [0.49, 2.04] 1.01 [0.49, 2.05] 0.32 [0.01, 7.69]		 	
LLHAT 2002 NBP2 2003 ENEDICT (combination) 2004 ENEDICT (monotherapy) 2004 AMELOT (Active) 2004 ARMEN (combination) 2004 ARMEN (monotherapy) 2004 LVERA 2001 ogari et al (combination) 2002	1314 195 2 4 8 14 14 0 2	9054 3044 300 301 673 191 190 85 104	3459 210 3 7 14 14 1 4	24303 3039 303 303 663 191 191 81 103	34.3% 3.8% 0.1% 0.1% 0.3% 0.3% 0.0% 0.1%	1.02 [0.96, 1.08] 0.93 [0.77, 1.12] 0.67 [0.11, 4.00] 1.34 [0.30, 5.95] 1.13 [0.41, 3.09] 1.00 [0.49, 2.04] 1.01 [0.49, 2.05] 0.32 [0.01, 7.69] 0.50 [0.09, 2.64]		 	
LLHAT 2002 NBP2 2003 ENEDICT (combination) 2004 ENEDICT (monotherapy) 2004 AMELOT (Active) 2004 ARMEN (combination) 2004 ARMEN (monotherapy) 2004 LVERA 2001 ogari et al (combination) 2002 ogari et al (monotherapy) 2002	1314 195 2 4 8 14 14 0 2 3	9054 3044 300 301 673 191 190 85 104 102	3459 210 3 7 14 14 1 4 4	24303 3039 303 663 191 191 81 103 103	34.3% 3.8% 0.1% 0.1% 0.3% 0.3% 0.0% 0.1%	1.02 (0.96, 1.08) 0.93 (0.77, 1.12) 0.67 (0.11, 4.00) 1.34 (0.30, 5.95) 1.00 (0.49, 2.04) 1.01 (0.49, 2.05) 0.32 (0.01, 7.69) 0.50 (0.09, 2.64) 0.76 (0.17, 3.30)			
LLHAT 2002 NBP2 2003 ENEDICT (combination) 2004 ENEDICT (monotherapy) 2004 AMELOT (Active) 2004 ARMEN (combination) 2004 ARMEN (monotherapy) 2004 LVERA 2001 ogari et al (combination) 2002 ogari et al (monotherapy) 2002 YVET (diuretics) 2003	1314 195 2 4 8 14 14 0 2 3 27	9054 3044 300 673 191 190 85 104 102 431	3459 210 3 7 14 14 14 4 4 30	24303 3039 303 663 191 191 81 103 103 426	34.3% 3.8% 0.1% 0.1% 0.3% 0.3% 0.0% 0.1% 0.1% 0.6%	1.02 [0.96, 1.08] 0.93 [0.77, 1.12] 0.67 [0.11, 4.00] 1.34 [0.30, 5.95] 1.13 [0.41, 3.09] 1.00 [0.49, 2.04] 1.01 [0.49, 2.05] 0.32 [0.01, 7.69] 0.50 [0.09, 2.64] 0.76 [0.17, 3.30] 0.89 [0.54, 1.47]			
LLHAT 2002 NBP2 2003 SNEDICT (combination) 2004 ENEDICT (monotherapy) 2004 AMELOT (Active) 2004 ARMEN (combination) 2004 ARMEN (monotherapy) 2004 JVERA 2001 Ogari et al (combination) 2002 Ogari et al (combination) 2002 Ogari et al (duretics) 2003 MP 2004	1314 195 2 4 8 14 14 0 2 3 27 47	9054 3044 300 301 673 191 190 85 104 102 431 466	3459 210 3 7 14 14 1 4 4 30 47	24303 3039 303 663 191 191 81 103 103 426 422	34.3% 3.8% 0.1% 0.1% 0.3% 0.3% 0.3% 0.1% 0.1% 0.6% 0.9%	1.02 [0.96, 1.08] 0.93 [0.77, 1.12] 0.67 [0.11, 4.00] 1.34 [0.30, 5.95] 1.13 [0.41, 3.09] 1.00 [0.49, 2.04] 1.01 [0.49, 2.05] 0.32 [0.01, 7.69] 0.50 [0.09, 2.64] 0.76 [0.17, 3.30] 0.89 [0.54, 1.47] 0.91 [0.62, 1.33]			
LHAT 2002 UBP2 2003 ENEDICT (combination) 2004 ENEDICT (monotherapy) 2004 AMELOT (Active) 2004 ARMEN (combination) 2004 ARMEN (monotherapy) 2004 VERA 2001 ogari et al (combination) 2002 orgari et al (monotherapy) 2002 rVET (diuretics) 2003 MP 2004 MP 2004	1314 195 2 4 8 14 14 0 2 3 27	9054 3044 300 301 673 191 190 85 104 102 431 466 822	3459 210 3 7 14 14 14 4 4 30	24303 3039 303 663 191 191 81 103 103 426 422 828	34.3% 3.8% 0.1% 0.1% 0.3% 0.3% 0.3% 0.1% 0.1% 0.6% 0.9% 0.2%	$\begin{array}{c} 1.02 & [0.96 & 1.08] \\ 0.93 & [0.77 , 1.12] \\ 0.67 & [0.11 & 4.00] \\ 1.34 & [0.30 & 5.95] \\ 1.13 & [0.41 & 3.09] \\ 1.00 & [0.49 & 2.04] \\ 1.01 & [0.49 & 2.05] \\ 0.32 & [0.01 & 7.69] \\ 0.50 & [0.09 & 2.64] \\ 0.76 & [0.17 & 3.30] \\ 0.89 & [0.54 & 1.47] \\ 0.91 & [0.62 & 1.33] \\ 1.26 & [0.59 & 2.67] \end{array}$			
LLHAT 2002 NBP2 2003 ENEDICT (combination) 2004 ENEDICT (monotherapy) 2004 AMELOT (Active) 2004 ARMEN (combination) 2004 ARMEN (monotherapy) 2004 .VERA 2001 ogari et al (combination) 2002 ogari et al (combination) 2002 or VET (diuretics) 2003 MP 2004 IIIC-B 2004 Ibtotal (95% CI)	1314 195 2 4 8 14 14 0 2 3 3 27 47 15	9054 3044 300 301 673 191 190 85 104 102 431 466	3459 210 3 7 14 14 14 4 30 47 12	24303 3039 303 663 191 191 81 103 103 426 422	34.3% 3.8% 0.1% 0.1% 0.3% 0.3% 0.3% 0.1% 0.1% 0.6% 0.9%	1.02 [0.96, 1.08] 0.93 [0.77, 1.12] 0.67 [0.11, 4.00] 1.34 [0.30, 5.95] 1.13 [0.41, 3.09] 1.00 [0.49, 2.04] 1.01 [0.49, 2.05] 0.32 [0.01, 7.69] 0.50 [0.09, 2.64] 0.76 [0.17, 3.30] 0.89 [0.54, 1.47] 0.91 [0.62, 1.33]			
LLHAT 2002 NBP2 2003 ENEDICT (combination) 2004 ENEDICT (monotherapy) 2004 ARMEN (combination) 2004 ARMEN (combination) 2004 ARMEN (monotherapy) 2004 _VER 2001 gari et al (combination) 2002 gari et al (combination) 2002 gari et al (combination) 2002 VET (diuretics) 2003 MP 2004 MC-B 2004 MD 2004 Lototal (95% CI) total events eterogeneity: Chi ⁼ = 6.48, df = 15	1314 195 2 4 8 14 14 0 2 3 27 47 15 1700 ((P = 0.97)	9054 3044 300 301 673 191 190 85 104 405 431 466 822 16518	3459 210 3 7 14 14 14 4 30 47 12 3901	24303 3039 303 663 191 191 81 103 103 426 422 828	34.3% 3.8% 0.1% 0.1% 0.3% 0.3% 0.3% 0.1% 0.1% 0.6% 0.9% 0.2%	$\begin{array}{c} 1.02 & [0.96 & 1.08] \\ 0.93 & [0.77 , 1.12] \\ 0.67 & [0.11 & 4.00] \\ 1.34 & [0.30 & 5.95] \\ 1.13 & [0.41 & 3.09] \\ 1.00 & [0.49 & 2.04] \\ 1.01 & [0.49 & 2.05] \\ 0.32 & [0.01 & 7.69] \\ 0.50 & [0.09 & 2.64] \\ 0.76 & [0.17 & 3.30] \\ 0.89 & [0.54 & 1.47] \\ 0.91 & [0.62 & 1.33] \\ 1.26 & [0.59 & 2.67] \end{array}$			
LLHAT 2002 NBP2 2003 ENEDICT (combination) 2004 ENEDICT (monotherapy) 2004 ARMEN (combination) 2004 ARMEN (combination) 2004 ARMEN (monotherapy) 2004 VERA 2001 ogari et al (combination) 2002 ogari et al (combination) 2002 ogari et al (combination) 2002 VET (diuretics) 2003 MP 2004 MD 2004 Ibtotal (95% CI) tal events eterogeneity: Chi ² = 6.48, df = 15 est for overall effect: Z = 0.06 (P =	1314 195 2 4 8 14 14 0 2 3 27 47 15 1700 ((P = 0.97)	9054 3044 300 301 673 191 190 85 104 405 431 466 822 16518	3459 210 3 7 14 14 14 4 30 47 12 3901	24303 3039 303 663 191 191 81 103 103 426 422 828 31920	34.3% 3.8% 0.1% 0.1% 0.3% 0.3% 0.3% 0.1% 0.1% 0.6% 0.9% 0.2%	$\begin{array}{c} 1.02 & [0.96 & 1.08] \\ 0.93 & [0.77 , 1.12] \\ 0.67 & [0.11 & 4.00] \\ 1.34 & [0.30 & 5.95] \\ 1.13 & [0.41 & 3.09] \\ 1.00 & [0.49 & 2.04] \\ 1.01 & [0.49 & 2.05] \\ 0.32 & [0.01 & 7.69] \\ 0.50 & [0.09 & 2.64] \\ 0.76 & [0.17 & 3.30] \\ 0.89 & [0.54 & 1.47] \\ 0.91 & [0.62 & 1.33] \\ 1.26 & [0.59 & 2.67] \end{array}$			
LLHAT 2002 NBP2 2003 ENEDICT (combination) 2004 ENEDICT (monotherapy) 2004 AMELOT (Active) 2004 ARMEN (combination) 2004 ARMEN (monotherapy) 2004 LVERA 2001 ogari et al (combination) 2002 ogari et al (combination) 2002 ogari et al (combination) 2002 yVET (diuretics) 2003 MP 2004 diC-B 2004 ubtotal (95% CI) otal events eterogeneity: Chi ² = 6.48, df = 15 est for overall effect: Z = 0.06 (P = stal (95% CI)	1314 195 2 4 8 14 14 0 2 3 27 47 15 1700 ((P = 0.97) ; 0.95)	9054 3044 300 301 673 191 190 85 104 102 431 466 822 16518	3459 210 3 7 14 14 14 4 300 47 12 3901	24303 3039 303 663 191 191 81 103 103 426 422 828 31920	34.3% 3.8% 0.1% 0.1% 0.3% 0.3% 0.0% 0.1% 0.1% 0.9% 0.2% 42.1%	1.02 [0.96, 1.08] 0.93 [0.77, 1.12] 0.67 [0.11, 4.00] 1.34 [0.30, 5.95] 1.13 [0.41, 3.09] 1.00 [0.49, 2.04] 1.01 [0.49, 2.05] 0.32 [0.01, 7.69] 0.50 [0.09, 2.64] 0.76 [0.17, 3.30] 0.89 [0.54, 1.47] 0.91 [0.62, 1.33] 1.26 [0.59, 2.67] 1.00 [0.95, 1.05]			
LLHAT 2002 NBP2 2003 ENEDICT (combination) 2004 ENEDICT (monotherapy) 2004 AMELOT (Active) 2004 ARMEN (combination) 2004 ARMEN (monotherapy) 2004 LVERA 2001 ogari et al (combination) 2002	1314 195 2 4 8 14 14 0 2 3 3 27 45 15 1700 ((P = 0.97) 5 0.95) 4575 0 (P = 0.7) 5 0.002)	9054 3044 300 301 673 191 190 85 104 102 431 466 822 16518); ² = 0% 6); ² = 0%	3459 210 3 7 14 14 4 30 47 12 3901 3901	24303 3039 303 663 191 191 191 81 103 103 426 422 828 31920 70572	34.3% 3.8% 0.1% 0.1% 0.3% 0.3% 0.1% 0.1% 0.1% 0.1% 0.6% 0.2% 42.1%	1.02 [0.96, 1.08] 0.93 [0.77, 1.12] 0.67 [0.11, 4.00] 1.34 [0.30, 5.95] 1.13 [0.41, 3.09] 1.00 [0.49, 2.04] 1.01 [0.49, 2.05] 0.32 [0.01, 7.69] 0.50 [0.09, 2.64] 0.76 [0.17, 3.30] 0.89 [0.54, 1.47] 0.91 [0.62, 1.33] 1.26 [0.59, 2.67] 1.00 [0.95, 1.05]	0.2 0.5 1 Favours (ACE)		

Figure 7-20 Forest plot showing effect of ACEIs on risk of all-cause mortality, stratified by comparison group (placebo vs active). Overall: 41 trials (FE model).

The diamond indicates the pooled risk ratio (and 95% CI) or the overall effect for all-cause mortality risk. CI: confidence interval; FE: fixed-effect; M-H: Mantel-Haenszel. For studies acronyms, see list of definition/ abbreviations

7.9.2Sensitivity analysis

Figure 7-21 presents a summary of the effect estimates of ACEIs after excluding 23 RCTs with a sample size of less than 1,000 patients, 13 placebo and 11 active-controlled trials. The exclusion did not modify the effect estimates compared with the placebo (RR, 0.91; 95% CI 0.86-0.95; p<0.0001) or with active (RR, 1.00; 95% CI 0.94-1.07; p=0.94). There was no evidence of heterogeneity.

Excluding 19 trials with poor methodological quality did not change the effect of ACEIs on risk of all-mortality compared with the placebo (RR, 0.95; 95% CI 0.89-1.02; p=0.19) or with active therapy (RR, 1.01; 95% CI 0.95-1.07; p=0.71). The assessment of heterogeneity showed no statistical variation among trials (see **Figure 7-22**)

	ACE	1	Cont	rol		Risk Ratio	Risk Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl	ABCDEF
1.1.1 ACEI vs Placebo								
ADVANCE 2007	408	5569	471	5571	10.1%	0.87 [0.76, 0.98]		
CAMELOT (Placebo) 2004	8	673	6	655	0.2%	1.30 [0.45, 3.72]		\bullet ? \bullet \bullet \bullet \bullet ?
CCS-I 2001	404	3391	463	3358	10.4%	0.86 [0.76, 0.98]	-	
DIABHYCAR 2004	334	2443	324	2469	8.6%	1.04 [0.90, 1.20]	+-	
DREAM 2006	31	2623	32	2646	1.0%	0.98 [0.60, 1.60]		$\bullet \bullet \bullet \bullet \bullet \bullet \bullet \circ \circ$
EUROPA 2003	375	6110	420	6108	9.3%	0.89 [0.78, 1.02]		??
HOPE 2000	482	4645	569	4652	11.6%	0.85 [0.76, 0.95]		?
IMAGINE 2008	28	1280	28	1273	0.9%	0.99 [0.59, 1.67]		
PEACE 2004	299	4158	334	4132	8.0%	0.89 [0.77, 1.03]		
PHARAO 2008	5	505	2	503	0.1%	2.49 [0.49, 12.78]		
PREAMI 2006	40	631	37	621	1.2%	1.06 [0.69, 1.64]		
PROGRESS 2001	306	3051	319	3054	8.1%	0.96 [0.83, 1.11]	-	
QUIET 2001	27	878	27	872	0.8%	0.99 [0.59, 1.68]		??
Subtotal (95% CI)		35957		35914	70.3%	0.91 [0.86, 0.95]	•	
Total events	2747		3032					
Heterogeneity: Tau ² = 0.00;			2 (P = 0.6	6); I ² = 0	%			
Test for overall effect: Z = 3.9	98 (P < 0.0	001)						
1.1.2 ACEI vs Active								
AASK 2002	34	436	71	658	1.5%	0.72 [0.49, 1.07]		
ALLHAT 2002	1314	9054	3459	24303	22.0%	1.02 [0.96, 1.08]	<u>†</u>	
ANBP2 2003	195	3044	210	3039	5.5%	0.93 [0.77, 1.12]		? • • • • • • •
CAMELOT (Active) 2004	8	673	7	663	0.2%	1.13 [0.41, 3.09]		$\bullet ? \bullet \bullet \bullet \bullet ?$
JMIC-B 2004	15	822	12	828	0.4%	1.26 [0.59, 2.67]		
Subtotal (95% CI)		14029		29491	29.7%	1.00 [0.94, 1.07]	Ţ	
Total events	1566		3759					
Heterogeneity: Tau ² = 0.00;			(P = 0.40)); I² = 2%	5			
Test for overall effect: Z = 0.1	08 (P = 0.9	4)						
Total (95% CI)		49986		65405	100.0%	0.93 [0.89, 0.98]	•	
Total events	4313		6791	00.00	1001070	0000 [0000; 0000]	·	
Heterogeneity: Tau ² = 0.00;		26 df - 1		211:12-	20%			
Test for overall effect: Z = 2.3			I7 (F = 0.	21),1 =	20%		0.2 0.5 1 2 5	
Test for subgroup difference			- 1 /P - 0	01) 12-	91 7%		Favours [ACE] Favours [control]	
Risk of bias legend	63. Offi – C	, ur-	- 1 (1 - 0	.017,1 =	04.2 /0			
(A) Random sequence gen	aration (ea	laction	hige)					
(B) Allocation concealment			ulasj					
(C) Blinding of participants :			formance	e hias)				
(D) Incomplete outcome dat			normaniu	s bias)				
(E) Selective reporting (repo		ulas)						
(E) Other bias	nung bias)							

(F) Other bias

Figure 7-21 Forest plot showing effect of ACEIs on risk of all-cause mortality (RE model) [Sensitivity analysis: Excluding trials with sample size less than 1000].

	ACE		Cont			Risk Ratio	Risk Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl	ABCDEFG
1.1.1 ACEI vs Placebo								
AARDVARK (Placebo) 2017	2	73	3	79	0.1%	0.72 [0.12, 4.20]		
ADVANCE 2007	408	5569	471	5571	12.6%	0.87 [0.76, 0.98]	· · ·	
APRES 2000	2	80	8	79	0.1%	0.25 [0.05, 1.13]	•	•••••
ATLANTIS 2000	5	92	0	48	0.0%	5.80 [0.33, 102.66]		••••••••
DEMAND (monotherapy) 2011	1	127	3	127	0.0%	0.33 [0.04, 3.16]	• • • • • • • • • • • • • • • • • • • •	
DIABHYCAR 2004	334	2443	324	2469	10.1%	1.04 [0.90, 1.20]	+	•••••
DREAM 2006	31	2623	32	2646	0.8%	0.98 [0.60, 1.60]		
HYVET (Placebo) 2003	27	431	22	426	0.7%	1.21 [0.70, 2.10]		
IMAGINE 2008	28	1280	28	1273	0.8%	0.99 [0.59, 1.67]		
PART-2 2000	16	308	25	309	0.6%	0.64 [0.35, 1.18]		$\bullet \bullet \bullet \bullet \bullet \bullet \bullet ?$
PEP-CHF 2006	56	424	53	426	1.7%	1.06 [0.75, 1.51]	— .	
PHARAO 2008	5	505	2	503	0.1%	2.49 [0.49, 12.78]		
PREAMI 2006	40	631	37	621	1.1%	1.06 [0.69, 1.64]		$\bullet \bullet \bullet \bullet \bullet \bullet \bullet ?$
PREVEND IT 2007	5	431	4	433	0.1%	1.26 [0.34, 4.64]		
PROGRESS 2001	306	3051	319	3054	9.3%	0.96 [0.83, 1.11]		
RASS 2009	1	94	1	95	0.0%	1.01 [0.06, 15.92]	,	
SCAT 2000	8	229	11	231	0.3%	0.73 [0.30, 1.79]		
Subtotal (95% CI)		18391		18390	38.3%	0.95 [0.89, 1.02]	•	
Total events	1275		1343					
Heterogeneity: Tau ² = 0.00; Chi ²		t=16(н	' = 0.60);	1*= 0%				
Test for overall effect: Z = 1.31 (F	² = 0.19)							
1.1.2 ACEI vs Active								
AARDVARK (Active) 2016	2	73	3	72	0.1%	0.66 [0.11, 3.82]	←	
AASK 2002	34	436	71	658	1.3%	0.72 [0.49, 1.07]		
ALLHAT 2002	1314	9054	3459	24303	59.2%	1.02 (0.96, 1.08)		
HYVET (diuretics) 2003	27	431	30	426	0.8%	0.89 [0.54, 1.47]		•••••
JMIC-B 2004	15	822	12	828	0.4%	1.26 [0.59, 2.67]		
Subtotal (95% CI)		10816		26287	61.7%	1.01 [0.95, 1.07]	•	
Total events	1392		3575					
Heterogeneity: Tau ² = 0.00; Chi ²	= 3.73, df	= 4 (P =	0.44); I ² :	= 0%				
Test for overall effect: Z = 0.37 (F	P = 0.71)							
Total (95% CI)		29207		44677	100.0%	0.99 [0.94, 1.03]	1	
Total events	2667		4918					
Heterogeneity: Tau ² = 0.00; Chi ²		f= 21 (F	? = 0.56);	I ² = 0%			0.2 0.5 1 2 5	
Test for overall effect: Z = 0.52 (F							Favours [ACE] Favours [control]	
Test for subgroup differences: C	¢hi² = 1.59	df = 1 (P = 0.21)	² = 37.1	%			
Risk of bias legend								
(A) Random sequence generati)					
(B) Allocation concealment (sel								
(C) Blinding of participants and								
(D) Blinding of outcome assess			as): All ca	ause of r	nortality			
(E) Incomplete outcome data (at		i)						
(F) Selective reporting (reporting	(bias)							
(G) Other bias								

Figure 7-22 Forest plot showing effect of ACEIs on risk of all-cause mortality (RE model) [Sensitivity analysis: Excluding trials with low methodological quality].

CI: confidence interval; RE: random-effects; M-H: Mantel-Haenszel. For studies acronyms, see list of definition/ abbreviations

7.9.3 Subgroup analysis

Tables 7-5 and 7-6 summarise the subgroup estimates of ACEI-based therapy on risk of all-mortality.

7.9.3.1 High and low-affinity tissue ACEI

Figure 7-23 represents an RE meta-analytical summary of relative risk of allmortality reduction by high or low -affinity tissue ACEIs. Overall, 22 RCTs assessed the high-affinity tissue ACEIs (quinapril, ramipril, perindopril, trandolapril and delapril). The high-affinity tissue ACEIs had a 9% lower in risk of all-cause mortality compared with the control group (RR, 0.91; 95% CI 0.86-0.96; p=0.0002). There was no evidence of heterogeneity. Data were available in relation to four low-affinity ACEIs (lisinopril, enalapril, fosinopril and captopril). The low-affinity ACEIs did not reduce risk of all-mortality compared with the control group (RR, 0.98; 95% CI 0.94-1.03; p=0.52). The non-beneficial effect was especially evident in the ALLHAT trial. Excluding this trial yields a significant RR of 0.90 (95% CI 0.82-0.99; p=0.03).

7.9.3.2 Class of active control

Figure 7-24 presents the meta-analytical summary provided by an RE model indicating the effectiveness of ACEIs on the occurrence of all mortality when compared with active therapy, stratified by class of active therapy (CCBs, diuretics, beta-blockers and other active control).

Firstly, the CCBs indicated in the trials are DHP CCBs (amlodipine, nisoldipine and nifedipine) or non-DHP (verapamil). 40.8% of the overall pooled treatment effects was derived by the trials using CCBs as a comparator. As the forest plot clearly shows, the ALLHAT (CCB) had a greater impact on the pooled effect estimates (94.5%). There was no significant decrease in the risk of total mortality when ACEIs was compared to CCBs (RR,1.04; 95% CI 0.97-1.11; p=0.31). There was no heterogeneity among trials.

ACEI does not reduce the risk of total mortality when compared with diuretics (RR, 1.00; 95% CI 0.94-1.06, p=0.87). However, the pooled effect estimate (88.6%) reflects the results obtained by the ALLHAT (Diuretic) trial. Although a non-significant reduction was detected in comparison with beta-blockers, a wide confidence limit led to low precision.

7.9.3.3 Clinical setting

Figures 7-25 and 26 demonstrate the effectiveness of ACEIs on reducing the risk of all-mortality compared with placebo or active therapy groups based on population clinical setting. Data from 13 placebo-controlled trials (n=46,129) and 12 trials with active comparator (n=46,307) were pooled for high-risk hypertension. In comparison with the placebo, the ACEIs achieved 8% reduction in all-mortality (RR, 0.91; 95% CI 0.85-0.97; p=0.003). No such benefit was seen in comparison with the active therapy group (RR, 1.00; 95% CI 0.95-1.06; p=0.93). There was no evidence of heterogeneity across the trials.

Data on patients with underlying CAD were obtained from 12 placebo-controlled trials (n=44,821) and 3 actively controlled trials (n=3874). The benefit of ACEI therapy on all-mortality was indicated when compared with the placebo (RR, 0.87; 95% CI 0.82-0.93; p<0.0001). While the ACEIs did not reduce the risk of all-mortality when compared with active therapy. However, due to a wide confidence limit a significant true point of estimation cannot be excluded.

For diabetic patients with or without nephropathy, the combined data did not demonstrate any benefit obtained through ACEI in terms of reducing the risk of all mortality. However, due to a wide confidence limit a significant true point of estimation cannot be excluded.

7.9.3.4 Mean age group

Compared with placebo group, the ACEIs had a 12% impact on lowering the risk of all-mortality in a group of patients with a mean age < 65 years (RR, 0.88; 95% CI, 0.84- 0.94; p<0.0001). The pooled effect estimates were mainly driven by the HOPE trial (17.7%) that indicated that ACEI-based therapy was significantly superior. No evidence of heterogeneity was detected. For patients with a mean age of \geq 65 years, there was no significant decrease in all-mortality due to ACEI therapy when compared with the placebo group (RR, 0.96; 95% CI, 0.88-1.05; p=0.38). No heterogeneity was detected.

Compared with active therapy group, the ACEIs reduced risk of all mortality for the mean age group < 65 years (RR, 0.87; 95% CI 0.70-1.07; p=0.11) but the results were not at significance level. There was no evidence of heterogeneity. In the case of patients with a mean age \geq 65 years, the ALLHAT trial contributed a significant 89.4% of pooled treatment that greatly influenced the pooled RR. There was no apparent benefit of ACEI-based therapy on the reduction of all mortality compared with active therapy (RR, 1.01; 95% CI, 0.96-1.07; p=0.73). No heterogeneity was detected.

	A.C.F.		Cont			Diels Detie	Diel: Detie	Dials of Diag
Study or Subgroup	ACE Events		Cont Events		Weight	Risk Ratio M-H, Random, 95% Cl	Risk Ratio M-H, Random, 95% Cl	Riskof Bias ABCDEFG
1.1.1 High-affinity tissue ACEIs	LVCIRS	Total	Lvents	Total	weight	M-H, Kaluoli, 55% Ci	M-H, Kandolli, 55% Cl	ABCDEFG
AARDVARK (Overall) 2017	2	73	6	151	0.1%	0.69 [0.14, 3.33]	·	
AASK 2002	34	436	71	658	1.8%	0.72 [0.49, 1.07]		
ADVANCE 2007	408	5569	471	5571	16.7%	0.87 [0.76, 0.98]		
APRES 2000	2	80	8	79	0.1%	0.25 [0.05, 1.13]	←	
ATLANTIS 2000	5	92	0	48	0.0%	5.80 [0.33, 102.66]		
BENEDICT (combination) 2004	2	300	3	303	0.1%	0.67 [0.11, 4.00]	• • • • • • • • • • • • • • • • • • • •	??
BENEDICT (monotherapy) 2004	4	301	11	603	0.2%	0.73 [0.23, 2.27]		??
DEMAND (monotherapy) 2011	1	127	3	127	0.1%	0.33 [0.04, 3.16]	• · · · · · · · · · · · · · · · · · · ·	
DIABHYCAR 2004	334	2443	324	2469	13.4%	1.04 [0.90, 1.20]	+	•••••
DREAM 2006	31	2623 6110	32	2646	1.1%	0.98 [0.60, 1.60]		
EUROPA 2003 HOPE 2000	375 482	4645	420 569	6108 4652	14.9% 20.7%	0.89 [0.78, 1.02]	-	200000
Hou et al (group 2) 2006	402	4045	569	4052	20.7%	0.85 [0.76, 0.95] 3.00 [0.12, 72.86]		
IMAGINE 2008	28	1280	28	1273	1.0%	0.99 [0.59, 1.67]		
PART-2 2000	16	308	25	309	0.7%	0.64 [0.35, 1.18]		
PEACE 2004	299	4158	334	4132	12.0%	0.89 [0.77, 1.03]		
PEP-CHF 2006	56	424	53	426	2.2%	1.06 [0.75, 1.51]		
PHARAO 2008	5	505	2	503	0.1%	2.49 [0.49, 12.78]		
PREAMI 2006	40	631	37	621	1.4%	1.06 [0.69, 1.64]		
PROGRESS 2001	306	3051	319	3054	12.3%	0.96 [0.83, 1.11]	-	
QUIET 2001	27	878	27	872	1.0%	0.99 [0.59, 1.68]		??
QUO VADIS 2001	0	75	0	73		Not estimable		?? • • • ?
Subtotal (95% CI)		34221		34790	100.0%	0.91 [0.86, 0.96]	•	
Total events	2458		2743					
Heterogeneity: Tau ² = 0.00; Chi ² =		= 20 (P =	= 0.60); I*	= 0%				
Test for overall effect: Z = 3.68 (P =	= 0.0002)							
1.1.2 Low-affinity tissue ACEIs								
ABCD (normotensive) 2002	19	246	19	234	0.7%	0.95 [0.52, 1.75]		
ALLHAT 2002	1314	9054	3459	24303	71.2%	1.02 [0.96, 1.08]	_	
ANBP2 2003	195	3044	210	3039	6.9%	0.93 [0.77, 1.12]	T	2000000
CAMELOT (Overall) 2004	8	673	13	1318	0.3%	1.21 [0.50, 2.89]		
CARMEN (combination) 2004	14	191	14	191	0.5%	1.00 [0.49, 2.04]		2000000
CARMEN (monotherapy) 2004	14	190	14	191	0.5%	1.01 [0.49, 2.05]		? • • • • • • •
CCS-I 2001	404	3391	463	3358	15.8%	0.86 [0.76, 0.98]		
ELVERA 2001	0	85	1	81	0.0%	0.32 [0.01, 7.69]	· · · · · · · · · · · · · · · · · · ·	?? ? 🔁 🔁 🔁 ?
Fogari et al (combination) 2002	2	104	4	103	0.1%	0.50 [0.09, 2.64]	• • • • • • • • • • • • • • • • • • •	• ? • • ? • ?
Fogari et al (monotherapy) 2002	3	102	4	103	0.1%	0.76 [0.17, 3.30]	• · · · · · · · · · · · · · · · · · · ·	• ? • • ? • ?
HYVET (Overall) 2003	27	431	52	852	1.2%	1.03 [0.65, 1.61]		
JAMP 2004	47	466	47	422	1.7%	0.91 [0.62, 1.33]		? ? ● ● ? ● ●
JMIC-B 2004	15	822	12	828	0.4%	1.26 [0.59, 2.67]		
PREVEND IT 2007 RASS 2009	5	431 94	4	433 95	0.1% 0.0%	1.26 [0.34, 4.64] 1.01 [0.06, 15.92]		
SCAT 2000	8	229	11	231	0.0%	0.73 [0.30, 1.79]	,,	
Subtotal (95% Cl)	0	19553			100.0%	0.98 [0.94, 1.03]	4	
Total events	2076		4328				1	
Heterogeneity: Tau ² = 0.00; Chi ² =	8.63. df =	15 (P =	0.90); I ² =	0%				
Test for overall effect: Z = 0.65 (P =								
							0.2 0.5 1 2 5	
							Favours [ACEIs] Favours [control]	
Test for subgroup differences: Ch	i² = 4.90, d	f=1 (P	= 0.03), P	°= 79.69	6		- · · · · · · · · · · · · · · · · · · ·	
Risk of bias legend								
(A) Random sequence generation		n bias)						
(B) Allocation concealment (selec								
(C) Blinding of participants and pe (D) Blinding of outcome assessm					ante liter			
(E) Incomplete outcome data (attri		ion pias	s). All cau	se u mo	manty			
(F) Selective reporting (reporting b								
(G) Other bias								
(-,								

Figure 7-23 Forest plot showing effect of ACEIs on risk of all-cause mortality (RE model) [Subgroup analysis: high-affinity tissue vs low-affinity ACEIs].

	ACE	3	Cont	rol		Risk Ratio	Risk Ratio	Risk of Bias
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl	ABCDEFG
1.1.1 Dihydropyridine (DHP) CCBs								
AARDVARK (Active) 2016	2	73	3	72	0.2%	0.66 [0.11, 3.82]	<u>الم</u>	
AASK (CCB) 2002	34	436	22	217	1.9%	0.77 [0.46, 1.28]		
ABCD (normotensive) 2002	19	246	19	234	1.3%	0.95 [0.52, 1.75]		
ALLHAT (CCB) 2002	1314	9054	1256	9048	94.5%	1.05 [0.97, 1.12]		
BENEDICT (combination) 2004	2	300	3	303	0.2%	0.67 [0.11, 4.00]	· · · · · · · · · · · · · · · · · · ·	??
BENEDICT (monotherapy) 2004	4	301	3	303	0.2%	1.34 [0.30, 5.95]		- ??+++++
CAMELOT (Active) 2004	8	673	7	663	0.5%	1.13 [0.41, 3.09]		$\bullet ? \bullet \bullet \bullet \bullet ?$
ELVERA 2001	0	85	1	81	0.0%	0.32 [0.01, 7.69]	4	+ <mark>??++++?</mark>
Fogari et al (combination) 2002	2	104	4	103	0.2%	0.50 [0.09, 2.64]	•	• ? • • ? • ?
Fogari et al (monotherapy) 2002	3	102	4	103	0.2%	0.76 [0.17, 3.30]		•?••?
JMIC-B 2004	15	822	12	828	0.9%	1.26 [0.59, 2.67]		
Subtotal (95% CI)		12196		11955	100.0 %	1.04 [0.97, 1.11]	•	
Total events	1403		1334					
Heterogeneity: Tau ² = 0.00; Chi ² = Test for overall effect: Z = 1.01 (P =		10 (P =	0.96); l² =	0%				
1.1.2 Diuretics								
ALLHAT (Diuretic) 2002	1314	9054	2203	15255	88.6%	1.00 [0.94, 1.07]		
ANBP2 2003	195	3044	210	3039	10.0%	0.93 [0.77, 1.12]		?
HYVET (diuretics) 2003 Subtotal (95% CI)	27	431 12529	30	426 18720	1.4% 100.0 %	0.89 [0.54, 1.47] 1.00 [0.94, 1.06]		•••••
Total events	1536		2443					
Heterogeneity: Tau ² = 0.00; Chi ² = Test for overall effect: Z = 0.16 (P =		2 (P = 0	.66); I² = I)%				
1.1.3 Beta-blockers								
AASK (Beta-blocker) 2002	34	436	49	441	59.4%	0.70 [0.46, 1.06]		$\bullet \bullet \bullet \bullet \bullet \bullet \bullet ?$
CARMEN (combination) 2004	14	191	14	191	20.3%	1.00 [0.49, 2.04]	+	? • • • • • •
CARMEN (monotherapy) 2004 Subtotal (95% CI)	14	190 817	14	191 823	20.3% 100.0 %	1.01 [0.49, 2.05] 0.81 [0.59, 1.12]	•	?
Total events	62		77					
Heterogeneity: Tau ² = 0.00; Chi ² = Test for overall effect: Z = 1.28 (P =		2 (P = 0	.57); I² = I)%				
1.1.4 Active control								
JAMP 2004 Subtotal (95% CI)	47	466 466	47		100.0% 100.0 %	0.91 [0.62, 1.33] 0.91 [0.62, 1.33]	1	?? ?????
		400		422	100.0%	0.91[0.02, 1.33]		
Total events	47		47					
Heterogeneity: Not applicable	0.043							
Test for overall effect: Z = 0.51 (P =	0.01)							
								L
							0.2 0.5 1 2 5	5
Test for subaroup differences: Chi	² = 2.85 d	f= 3 (P	= 0.41) P	²= 0%			Favours [ACEI] Favours [contro	1]
Risk of bias legend	= 2.00, 0		5.417,1	0.10				
(A) Random sequence generation	(selectio	n hiae\						
(B) Allocation concealment (select								

(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias): All cause of mortality

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

Figure 7-24 Forest plot showing effect of ACEIs on risk of all-cause mortality (RE model) [Subgroup analysis: class of active comparator].

Chapter 7: ACEls a	and ARBs with	risk of	mortality
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ACE Events				Weight		RISK Ratio M-H, Random, 95% Cl	Riskof Bias ABCDEFG
2	73	3	79	0.1%	0.72 [0.12, 4.20]	4	
408	5569	471	5571	24.6%	0.87 [0.76, 0.98]		
4	301	8	300	0.3%	0.50 [0.15, 1.64]	•	??
8	673	6	655	0.4%	1.30 [0.45, 3.72]		• ? • • • • ?
1	127	3	127	0.1%	0.33 [0.04, 3.16]	•	
334	2443	324	2469	19.7%	1.04 [0.90, 1.20]		
31	2623	32	2646	1.7%	0.98 [0.60, 1.60]		
482	4645	569	4652	30.5%	0.85 [0.76, 0.95]	-	? • • • • • •
1	112	0	112	0.0%	3.00 [0.12, 72.86]	•	→ ●?●●●●
27	431	22	426	1.3%	1.21 [0.70, 2.10]		
28	1280	28	1273	1.5%	0.99 [0.59, 1.67]		
299	4158	334	4132	17.7%	0.89 [0.77, 1.03]		
40	631	37	621	2.1%	1.06 [0.69, 1.64]		
	23066		23063	100.0%	0.91 [0.85, 0.97]	•	
1665		1837					
	= 12 (P =	0.61); I ^z	= 0%				
0.003)							
						•	
8	673	6	655	0.3%	1.30 [0.45, 3.72]		•••••
	3391	463			0.86 [0.76, 0.98]		
375	6110	420	6108	21.3%	0.89 [0.78, 1.02]		??
482	4645	569	4652	29.6%	0.85 [0.76, 0.95]	-	? • • • • • •
28	1280	28	1273	1.4%	0.99 [0.59, 1.67]		
16	308	25	309	1.0%	0.64 [0.35, 1.18]		
299	4158	334	4132	17.2%	0.89 [0.77, 1.03]	-=	
40	631	37	621	2.1%	1.06 [0.69, 1.64]		
27	878	27	872	1.4%			??
0	75	0	73		Not estimable		??
8	229	11	231	0.5%	0.73 [0.30, 1.79]		
	22458		22363	100.0%	0.87 [0.82, 0.93]	•	
1689		1928					
6.04, df =	10 (P = 0	0.81); I ² =	0%				
0.0001)							
							\rightarrow \bullet \bullet \bullet \bullet \bullet \bullet \bullet \bullet
						•	
						. –	
1		1			1.01 [0.06, 15.92]		→ €?€€ €€
	8020		8010	100.0%	0.94 [0.80, 1.10]	-	
	5 (P = 0.	22); I* = 3	29%				
· ·							
5	431	4	433	100.0%	1.26 [0.34, 4.64]		
	431		433	100.0%	1.26 [0.34, 4.64]		
5		4					
0.73)							
306	3051	319	3054	100.0%	0.96 [0.83, 1.11]	-	
	3051		3054	100.0%	0.96 [0.83, 1.11]	•	
306		319					
0.59)							
56	424	53	426	100.0%	1.06 (0.75, 1.51)		
	424		426	100.0%			
56		53	-			T	
0.74)							
0.74)							
0.74)						0.2 0.5 1 2	5
		- 0 60\ "	2 – 0°			0.2 0.5 1 2 Favours [ACEI] Favours [Place	
*= 3.06, c	lf= 5 (P =	= 0.69), lª	²= 0%				
	Events 2 408 4 5 1 334 482 1 334 482 299 40 1665 10.12, df: 0.003) 2 8 404 1665 10.12, df: 0.003) 2 8 400 299 40 299 40 1665 10.12, df: 0.003) 2 8 402 28 402 28 40 299 40 299 40 299 40 299 40 299 40 299 40 299 40 299 40 299 40 299 40 299 40 299 40 299 40 299 40 299 40 299 40 299 40 27 0 8 5 6 0.0001) 5 6 306 0.59) 56	Events Total 2 73 408 5569 4 301 8 673 1 127 334 2443 31 2623 482 4645 1 112 27 431 28 280 1665 23066 1665 10.12, df = 12 (P = 0.003) 2 80 8 673 39 375 6110 482 404 3391 375 375 6110 482 482 4645 28 28 168 308 404 3391 375 304 631 27 8 229 22458 1689 92 4 1 127 334 408 5569 5 5 92 4 1 <	Events Total Events 2 73 3 408 5569 471 4 301 8 8 673 6 1 127 3 334 2443 324 31 2623 32 482 4645 569 1 112 0 27 431 22 28 1280 28 299 4158 334 40 631 37 1665 1837 10.12, df = 12 (P = 0.61); P 0.003) 2 80 8 673 6 404 336 25 29 16 308 25 29 4158 344 40 631 37 6 302 11 28 280 14 40 631 37 16 <td< td=""><td>Events Total Events Total 2 73 3 79 408 5569 471 5571 4 301 8 300 8 673 6 655 1 127 3 127 334 2423 322 2646 482 4645 569 4652 1 112 0 112 29 4168 334 4132 40 631 37 6 299 4158 334 4132 40 631 37 6 2066 123063 1683 3056 10.12, df = 12 (P = 0.61); P = 0% 0.003) 1633 335 2066 2180 28 1273 207 78 270 75 073 2120 28 1280 28 1273 240 631 376 6110 23063</td><td>Events Total Events Total Weight 2 73 3 79 0.1% 408 5569 471 5571 24.6% 4 301 8 300 0.3% 8 673 6 655 0.4% 1 127 3 127 0.1% 334 2443 324 2469 19.7% 31 2623 32 2646 1.7% 48 652 30.5% 1 112 0.4652 299 4158 334 4132 1.7% 40 631 37 621 2.1% 23063 100.0% 1665 1837 1.43 100.0% 1.43 463 3358 24.9% 375 6110 420 6108 21.3% 422 4645 569 4652 29.6% 28 1280 28 1273 1.4% 16 308 <</td><td>$\begin{array}{cccccccccccccccccccccccccccccccccccc$</td><td>Events Total Weight M-H, Random, 95% CI M-H, Random, 95% CI 2 73 3 79 0.1% 0.72 (0.12, 4.20) </td></td<>	Events Total Events Total 2 73 3 79 408 5569 471 5571 4 301 8 300 8 673 6 655 1 127 3 127 334 2423 322 2646 482 4645 569 4652 1 112 0 112 29 4168 334 4132 40 631 37 6 299 4158 334 4132 40 631 37 6 2066 123063 1683 3056 10.12, df = 12 (P = 0.61); P = 0% 0.003) 1633 335 2066 2180 28 1273 207 78 270 75 073 2120 28 1280 28 1273 240 631 376 6110 23063	Events Total Events Total Weight 2 73 3 79 0.1% 408 5569 471 5571 24.6% 4 301 8 300 0.3% 8 673 6 655 0.4% 1 127 3 127 0.1% 334 2443 324 2469 19.7% 31 2623 32 2646 1.7% 48 652 30.5% 1 112 0.4652 299 4158 334 4132 1.7% 40 631 37 621 2.1% 23063 100.0% 1665 1837 1.43 100.0% 1.43 463 3358 24.9% 375 6110 420 6108 21.3% 422 4645 569 4652 29.6% 28 1280 28 1273 1.4% 16 308 <	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	Events Total Weight M-H, Random, 95% CI M-H, Random, 95% CI 2 73 3 79 0.1% 0.72 (0.12, 4.20)

(B) Allocation concealment (selection bias)
 (C) Blinding of participants and personnel (performance bias)
 (D) Blinding of outcome assessment (detection bias): All cause of mortality
 (E) Incomplete outcome data (attrition bias)
 (F) Selective reporting (reporting bias)
 (G) Other bias

Figure 7-25 Forest plot showing effect of ACEIs versus placebo on risk of all-cause mortality (RE model) [Subgroup analysis: Clinical setting].

Study or subgroup Events Total Events Total Weight Mul, Random, 95% CI M.H. Random, 95% CI A.B. C. D. E.F. G AABC 2016 2 73 3 72 0.1% 0.66 [0.11, 32.0] AABC 2012 134 435 17 658 0.20 % 72 [0.4], 107 ALLHAT 2002 134 435 420 82.03 87.0% 1.02 [0.6], 108 ALLHAT 2002 134 4054 4210 93.03 97.0% 1.02 [0.6], 108 ALHPC 2003 195 3040 13 303 01% 0.67 [0.1], 41.00 BENEDICI Crombination 2002 2 104 4 103 0.1% [0.6], 0.61 [0.6], 0.61 [0.7], 300 CAMELOT (Active) 2004 8 673 7 663 10.2% 0.69 [0.6], 1.47] Piparie al (combination) 2002 2 12 128 0.05 % 1.03 [0.6], 0.59, 267] 1.00 [0.95, 1.06] VICI-E 2004 8 673 7 663 10.2% 1.13 [0.4], 3.09] 0.98 [0.52, 1.75] 0.98 [0.59, 267]		ACE		Acti	10		Risk Ratio	Risk Ratio	Risk of Bias
1.12 (Hg) risk typerference 4.20 VARK (Calve) 2016 2 73 3 72 0.1% 0.66 (0.11, 3.82) AABX X002 34 438 71 658 2.0% 0.26 (0.14, 3.82) ALHAT 2002 1194 9054 3455 2.03% 0.21 (0.16, 0.16) 0.66 (0.11, 3.82) ANER 22 003 1194 9054 3455 2.03% 0.72 (0.46, 1.07) ANER 22 001 1194 9053 3.033 0.1% 0.66 (0.11, 3.82) BEHEDICT (combination) 2004 2 9073 7.663 0.3% 1.31 (0.15%, 0.56) 0.32 (0.01, 7.68) CAMELOT (Achive) 2004 0 95 1 91 0.46 1.03 0.1%, 0.56 (0.19, 2.84) CAMELOT (Achive) 2003 22 1.02 4 103 0.1%, 0.56 (0.19, 2.84) 0.56 (0.15, 2.67) Total events 15425 30807 0.862 1.02 (0.59, 2.67) 1.03 (0.59, 2.67) Total events 15425 30807 6.63 1.02 (0.59, 2.67) 1.03 (0.59, 2.67) Total events 10.66 1.44 10.00, 0.57 1.06 (0.28, 2.67)	Study or Subaroup					Weight			
Acid Scale 2002 34 436 71 663 20% 0.72 [0 43 [1 07] 102 [0 68, 103] 107 (1 12) 102 [0 68, 103] 107 (1 12) 102 [0 68, 103] 107 (1 12) 102 [0 68, 103] 107 (1 12) 103 [1 12] 103 [1 12] 103 [1 13] 104 [1 30] 105 [1 14] 103 [1 15] 104 [1 30] 105 [1 14] 103 [1 15] 104 [1 30] 105 [1 14] 103 [1 15] 104 [1 30] 105 [1 14] 103 [1 15] 104 [1 30] 105 [1 14] 103 [1 15] 104 [1 30] 105 [1 14] 103 [1 15] 104 [1 30] 105 [1 14] 103 [1 15] 104 [1 30] 105 [1 14] 104 [1 130] 115 [1 14] 104 [1 130] 115 [1 14] 104 [1 130] 115 [1 14] 104 [1 15] 104 [1 14] 115 [1 14] 104 [14] 115 [1 14] 104									
Acid Scale 2002 34 406 71 658 2.0% 0.72 [0 49, 107] 107 ALLHAT 2002 1314 906 4369 2430 87.0% 0.93 [0.77, 112] 40.000 57, 112 BENEDICT (combination) 2004 2 300 3 303 01% 0.97 [0 11, 100] 0.95, 103] BENEDICT (combination) 2004 4 301 3 303 01% 1.34 [0 30, 5.96] LEVERA 2001 0 85 1 81 0.0% 0.32 [0 01, 7.89] Fogari et al (comotherapy) 2002 3 1102 4 103 01% 0.76 [0 17, 3.30] Fogari et al (comotherapy) 2002 3 1102 4 103 01% 0.76 [0 17, 3.30] Fogari et al (comotherapy) 2002 3 1102 4 103 01% 0.76 [0 17, 3.30] Total events 1506 3500 1.26 [0 .98, 2.67] Heterogenelly, Tau ² = 0.00; Ch ² = 0.80; P = 0	AARDVARK (Active) 2016	2	73	3	72	0.1%	0.66 [0.11, 3.82]	4 · · ·	
$\begin{array}{c} AVEP 22003 & 196 & 9044 & 210 & 9039 & 16.5\% \\ EVEPCIAC(romotherap) 2004 & 2 & 300 & 33 & 33 & 01\% \\ EVEPCIAC(romotherap) 2004 & 4 & 301 & 3 & 303 & 01\% \\ EVEPCIAC(romotherap) 2004 & 4 & 301 & 3 & 303 & 01\% \\ EVEPCIAC(romotherap) 2004 & 4 & 301 & 3 & 303 & 01\% \\ Fogart et al(combination) 2002 & 2 & 104 & 4 & 103 & 0.1\% \\ Fogart et al(combination) 2002 & 2 & 104 & 4 & 103 & 0.1\% \\ Fogart et al(combination) 2002 & 2 & 104 & 4 & 103 & 0.1\% \\ Fogart et al(combination) 2002 & 2 & 104 & 4 & 103 & 0.1\% \\ HYVEF(duretics) 2003 & 27 & 431 & 30 & 426 & 1.2\% \\ Fogart et al(combination) 2002 & 2 & 102 & 4 & 103 & 0.1\% \\ HVEF(duretics) 2003 & 27 & 431 & 30 & 426 & 1.2\% \\ Total events & 1606 & 3007 \\ Hetrogenetity(Tau^{*}= 0.00, Ch^{*}= 0.5\%); F= 0\% \\ Test for overall effect Z = 0.10, \mathsf{Ch^{*}= 0.5\%; f= 3(P= 0.72); P= 0\% \\ Total events & 70 & 66 \\ Heterogenetity; Tau^{*}= 0.00, Ch^{*}= 0.5\%; f= 19 \\ Total events & 70 & 66 \\ Heterogenetity; Tau^{*}= 0.00; Ch^{*}= 0.5\%; f= 19 \\ Fogart et al(combination) 2002 & 2 & 104 & 4 & 103 & 10.8\% \\ Total events & 70 & 66 \\ Heterogenetity; Tau^{*}= 0.00; Ch^{*}= 0.5\%; f= 4(P= 0.92); P= 0\% \\ Test for overall effect Z = 0.10 (\mathsf{P= 0.95); f= 0.05 \\ Test for overall effect Z = 0.00 (\mathsf{Ch^{*}= 0.5\%; f= 4(P= 0.92); P= 0\% \\ Total events & 30 & 33 \\ Total events & 30 & 33 \\ Total events & 30 & 33 \\ Total events & 28 & 28 \\ Heterogenetity; Tau^{*}= 0.00; Ch^{*}= 0.05; d= 4(P= 0.92); P= 0\% \\ Test for overall effect Z = 0.01 (\mathsf{P= 0.05); d= 4(P= 0.92); P= 0\% \\ Test for overall effect Z = 0.01 (\mathsf{P= 0.05); d= 4(P= 0.92); P= 0\% \\ Test for overall effect Z = 0.01 (\mathsf{P= 0.05); d= 4(P= 0.92); P= 0\% \\ Test for overall effect Z = 0.01 (\mathsf{P= 0.05); d= 4(P= 0.92); P= 0\% \\ Test for overall effect Z = 0.00 (\mathsf{Ch^{*}= 0.02); P= 0\% \\ Test for overall eff$		34	436	71	658	2.0%			$\bullet \bullet \bullet \bullet \bullet \bullet \bullet \circ \circ$
EENEDICT (combination) 2014 12 1001 3 133 0.15% 0.87 0.114 101 EENEDICT (combination) 2004 4 301 3 0.35% 1.34 0.34 0.39% CAMELOT (Attive) 2004 8 673 7 663 0.35% 1.34 0.34 0.39% Fogari et al (combination) 2002 2 104 4 103 0.15% 0.58 0.58 0.59	ALLHAT 2002	1314	9054	3459	24303	87.0%	1.02 [0.96, 1.08]		
$ \begin{array}{c} \label{eq:constraints} \\ \begin{tabular}{lllllllllllllllllllllllllllllllllll$	ANBP2 2003	195	3044	210	3039	8.5%	0.93 [0.77, 1.12]		? • • • • • •
CAMELOT Active 2004	BENEDICT (combination) 2004	2	300	3	303	0.1%	0.67 [0.11, 4.00]	←	
ELVERA 201 0 1 65 1 61 1 61 0.0% 0.22 (2017, 26) Fegari et al (monotherany) 2002 3 102 4 103 0.1% 0.56 (0.07, 3.30) HYVET (diuretics) 2003 27 431 30 426 1.2% 0.58 (0.54, 1.47] JMIC-B 2004 15 622 12 828 0.5% 1.26 (0.55, 1.66] Heterogeneity, Tau ² = 0.00, Ch ² = 6.19, df = 11 (P = 0.86), P = 0% Test for verall effect Z = 0.00 (Ch ² = 6.19, df = 11 (P = 0.86), P = 0% Test for verall effect Z = 0.00 (Ch ² = 6.19, df = 11 (P = 0.86), P = 0% Test for verall effect Z = 0.00 (Ch ² = 6.19, df = 11 (P = 0.92), P = 0% Test for verall effect Z = 0.10 (Ch ² = 6.19, df = 11 (P = 0.92), P = 0% Test for verall effect Z = 0.10 (Ch ² = 6.19, df = 11 (P = 0.92), P = 0% Test for verall effect Z = 0.10 (Ch ² = 0.63) 333 7.4% BENEDICT (monotherany) 2004 4 301 3 303 7.4% BENEDICT (monotherany) 2004 4 301 3 303 7.4% BENEDICT (monotherany) 2004 4 109 103 10.0% Total events 70 66 Heterogeneity, Tau ² = 0.00, Ch ² = 0.65, df = 2 (P = 0.72), P = 0% Test for verall effect Z = 0.10 (P = 0.92); P = 0% Test for verall effect Z = 0.10 (P = 0.92); P = 0% Test for verall effect Z = 0.01 (P = 0.92); P = 0% Test for verall effect Z = 0.00, ch ² = 0.65, df = 4 (P = 0.92); P = 0% Test for verall effect Z = 0.00, ch ² = 0.65, df = 4 (P = 0.92); P = 0% Test for verall effect Z = 0.00, ch ² = 0.65, df = 4 (P = 0.92); P = 0% Test for verall effect Z = 0.01 (P = 0.93) 1.5 f CARMEN (combination) 2004 14 191 14 191 50.0% Total events 28 28 28 Heterogeneity, Tau ² = 0.00; Ch ² = 0.65, df = 4 (P = 0.92); P = 0% Test for verall effect Z = 0.01 (P = 0.93) 1.5 f Heterogeneity, Tau ² = 0.00; Ch ² = 0.65, df = 4 (P = 0.92); P = 0% Test for verall effect Z = 0.01 (P = 0.93) 1.6 (D Total events 28 28 28 Heterogeneity, Tau ² = 0.00; Ch ² = 0.55, df = 3 (P = 0.97), P = 0% Test for verall effect Z = 0.01 (P = 0.93) Total events 28 28 26 Heterogeneity, Tau ² = 0.01; Ch ² = 0.55, df = 3 (P = 0.97), P = 0% Test for verall effect Z = 0.01 (P = 0.93) 1.0 (D 0.61, 1.66] 1.0 (D 0.61, 1.66] 1.0 (D 0.61,							1.34 [0.30, 5.95]		
Fegari et al (combination) 2002 2 104 4 103 0.1% 0.56 0.03 0.56 0.03 2.64 0.76 0.76 0.73 0.76 0.73 0.76 0.73 0.76 0.73 0.76 0.73 0.76 0.73 0.76 0.73 0.76 0.73 0.76 0.73 0.76 0.73 0.76 0.73 0.76 0.73 0.76 0.73 0.76 0.73 0.76 0.73 0.76 0.73 0.76 0.73 0.76 0.76 0.76 0.73 0.76	CAMELOT (Active) 2004			7	663		1.13 [0.41, 3.09]		
$ \begin{array}{c} \mbox{Figure 1al} (monother app) 2002 & 3 & 102 & 4 & 103 & 0.1\% \\ \mbox{HVTET} (dimension) 2003 & 27 & 431 & 30 & 426 & 1.2\% \\ \mbox{HVTET} (dimension) 2003 & 27 & 431 & 30 & 426 & 1.2\% \\ \mbox{Subtrail} (95) (2) & 15 & 822 & 12 & 828 & 0.5\% \\ \mbox{Subtrail} (95) (2) & 15 & 822 & 12 & 828 & 0.5\% \\ \mbox{Subtrail} (95) (2) & 15 & 822 & 12 & 828 & 0.5\% \\ \mbox{Heterogeneity}. Tau" = 0.00, Chi" = 0.19, df = 11 (P = 0.80); P = 0\% \\ \mbox{Test for versall effect Z = 0.09 (P = 0.93) \\ \mbox{Heterogeneity}. Tau" = 0.00, Chi" = 0.61, df = 2 & 422 & 71.4\% \\ \mbox{JAMP 2004} & 47 & 466 & 47 & 422 & 71.4\% \\ \mbox{JAMP 2004} & 15 & 822 & 12 & 828 & 18.4\% \\ \mbox{JAMP 2004} & 15 & 822 & 12 & 828 & 18.4\% \\ \mbox{JAMP 2004} & 15 & 822 & 12 & 828 & 18.4\% \\ \mbox{JaMP 2004} & 15 & 822 & 12 & 828 & 18.4\% \\ \mbox{JaMP 2004} & 15 & 822 & 12 & 828 & 18.4\% \\ \mbox{JaMP 2004} & 15 & 822 & 12 & 828 & 18.4\% \\ \mbox{JaMP 2004} & 15 & 822 & 12 & 828 & 18.4\% \\ \mbox{JaMP 2004} & 15 & 822 & 12 & 62.9\% \\ \mbox{JamP 2004} & 15 & 822 & 12 & 62.9\% \\ \mbox{JaMP 2004} & 15 & 822 & 12 & (P = 0.72); P = 0\% \\ \mbox{Test for overall effect Z = 0.10 (P = 0.92) \\ \mbox{JamP 2004} & 2 & 300 & 3 & 303 & 7.4\% \\ \mbox{BENEDICT (combination) 2002} & 2 & 104 & 4 & 103 & 8.3\% \\ \mbox{Log on order sinely 2004} & 16 & 102.5\% \\ \mbox{JamP 2004} & 1053 & 1006 & 100.0\% \\ \mbox{JamP 2004} & 14 & 191 & 14 & 191 & 50.0\% \\ \mbox{Subtrail (95) Cl)} & 1053 & 1046 & 100.0\% \\ Tast error overall effect Z = 0.49 (P = 0.83); P = 0\% \\ \mbox{Test for overall effect Z = 0.01 (P = 0.89); P = 0\% \\ \mbox{Test for overall effect Z = 0.01 (P = 0.92); P = 0\% \\ \mbox{Test for overall effect Z = 0.01 (P = 0.89); P = 0\% \\ \mbox{Test for overall effect Z = 0.01 (P = 0.89); P = 0\% \\ \mbox{Test for overall effect Z = 0.01 (P = 0.89); P = 0\% \\ \mbox{Test for overall effect Z = 0.01 (P = 0.89); P = 0\% \\ \mbox{Test for overall effect Z = 0.01 (P = 0.89); P = 0\% \\ \mbox{Test for overall effect Z = 0.01 (P = 0.89); P = 0\% \\ \mbox{Test for overall effect Z = 0.01 (P = 0.89); P =$							• • •	• · · · · · · · · · · · · · · · · · · ·	
$\begin{array}{c} \text{HV}\text{CF} \ (\text{dim}\text{e}\text{fice}) 2003 & 27 & 431 & 30 & 426 & 1.2\% \\ \text{JMC-B 2004} & 15 & B22 & 12 & B28 & 0.5\% \\ \text{JMC-B 2004} & 15 & B22 & 12 & B28 & 0.5\% \\ \text{I-26} \ (\text{J} \text{I-26}) \ (\text{J} \text{I-26})$								• · · · · · · · · · · · · · · · · · · ·	
$ \begin{array}{c} LM(C=2CO4 & 15 & 822 & 12 & 828 & 0.5\% & 1.26 [D.59, 2.67] \\ LO10(D.55, 1.06] \\ LO10(D.55, 1.06) \\ LO10(D$									
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Total events 1606 3807 Heterogeneity: Tau"= 0.00; Ch"= 0.8], d"= 11 (P = 0.86); P= 0% Test for overall effect Z = 0.09 (P = 0.93) 1.13 CAD CAMEN (CAtive) 2004 8 673 7 663 10.2% JAMP 2004 47 466 47 422 71.4% Subtotal (95% CI) 1961 1913 100.0% JMIC-B 2004 15 822 12 828 18.4% 1.26 [0.59, 2.67] Subtotal (95% CI) 1961 1913 100.0% Test for overall effect Z = 0.10 (P = 0.92) 1.14 DM ± Nephropathy ABCC (normotensive) 2002 19 246 19 234 62.9% ABCC (normotensive) 2002 19 246 19 234 62.9% Dest[0.71, 1.36] Heterogeneity: Tau"= 0.00; Chi"= 0.95, df = 2 (P = 0.72); I" = 0% Test for overall effect Z = 0.10 (P = 0.92) 1.14 DM ± Nephropathy ABCC (normotensive) 2002 19 246 19 234 62.9% Dest[0.71, 1.36] Dest[0.71, 1.36] Dest[0.72, 1.75] Dest[0.70 coreside 2002 3 102 4 103 10.8% Dest[0.74, 3.30] Dest[0.75, 1.44] Dest[0.76; CI) 1.51 H CARNEN (combination) 2004 14 191 14 191 50.0% Dest[0.75, 1.44] Dest[0.70 coreside 14 (P = 0.92); I" = 0% Test for overall effect Z = 0.01 (P = 0.99); I" = 0% Test for overall effect Z = 0.01 (P = 0.99); I" = 0% Test for overall effect Z = 0.01 (P = 0.99); I" = 0% Test for overall effect Z = 0.01 (P = 0.99); I" = 0% Test for overall effect Z = 0.01 (P = 0.99); I" = 0% Test for overall effect Z = 0.01 (P = 0.99); I" = 0% Test for overall effect Z = 0.01 (P = 0.99); I" = 0% Test for overall effect Z = 0.01 (P = 0.99); I" = 0% Test for overall effect Z = 0.01 (P = 0.99); I" = 0% Test for overall effect Z = 0.01 (P = 0.99); I" = 0% Test for overall effect Z = 0.01 (P = 0.99); I" = 0% Test for overall effect Z = 0.01 (P = 0.99); I" = 0% Test for overall effect Z = 0.01 (P = 0.99); I" = 0% Test for overall effect Z = 0.01 (P = 0.99); I" = 0% Test for overall effect Z = 0.01 (P = 0.99); I" = 0% Test for overall effect Z = 0.01		15		12					
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Test for subgroup differences: Chi ² = 0.25, df = 3 (P = 0.97), I ² = 0% Favours [ACEI] Favours [ACEI]									-
Test for subgroup differences: Chi≅ = 0.25, df = 3 (P = 0.97), I² = 0%									
Risk of higs legend	Test for subgroup differences: Ch	i² = 0.25, c	lf= 3 (P	= 0.97), l ^a	²= 0%			rationa (nord) i atoma (netive)	
	Risk of bias legend								
(A) Random sequence generation (selection bias)	(A) Random sequence generation	n (selectio	n bias)						
(B) Allocation concealment (selection bias)									
(C) Blinding of participants and personnel (performance bias) (D) Blinding of outcome assessment (detection bias): All cause of modelity									

(D) Blinding of outcome assessment (detection bias): All cause of mortality (E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

Figure 7-26 Forest plot showing effect of ACEIs versus active on risk of all-cause mortality (RE model) [Subgroup analysis: Clinical setting].

Table 7-5 Summary of a RE meta-analytical subgroup analysis shows the effect of ACEIs compared with control (placebo or active) on risk of all-cause mortality[†]

					All-death	n Incidence			
Subg	roup analysis	Studies	Participants	Events		(%)	RR (M-H, Random, 95% CI)	P value*	l² (%) ‡
					ACEI	Control			
(Overall effects	41	125,824	11,646	8.28	10.0	0.94 [0.91, 0.98]	0.002*	0
F	Placebo	26	77,386	6045	7.42	8.20	0.91 [0.86, 0.95]	<0.0001*	0
1	Active	16	48,438	5601	10.2	12.2	1.00 [0.95, 1.05]	0.95	0
Subclass H	High-tissue affinity	22	69,011	5201	7.18	7.88	0.91 [0.86, 0.96]	0.0002*	0
I	Low-tissue affinity	16	55,335	6404	10.6	12.0	0.98 [0.94, 1.03]	0.52 [†]	0
(CCBs	11	24,151	2737	11.5	11.1	1.04 [0.97, 1.11]	0.31	0
Active control	Diuretics	3	31,249	3979	12.2	13.0	1.00 [0.94, 1.06]	0.87	0
F	Beta-blockers	3	1640	139	7.58	9.3	0.81 [0.59, 1.12]	0.20	0
(Other	1	888	94	10.0	11.1	0.91 [0.62, 1.33]	0.61	NA

** Cannot synthesis data by one trial.

 $\pm I^2$ statistic with <25% considered as low heterogeneity and I²> 75% as high heterogeneity.

 \dagger Excluding ALLHAT trial yields a RR of 0.90 (95% CI 0.82- 0.99, p=0.03) and I^2=0%

Table 7-6 Summary of a RE meta-analytical subgroup analysis shows the effect of ACEIs compared with control (placebo or active) on risk of all-cause mortality[†]

					All-mortali	ty Incidence (%)			
S	Subgroup analysis	Studies	Participants	Events	ACEI	Control	RR (M-H, Random, 95% CI)	P value*	l² (%) ‡
Placebo									
	High-risk hypertensive	13	46,129	3502	7.21	7.96	0.91 [0.85, 0.97]	0.003*	0
	CAD	12	44,821	3617	7.52	8.62	0.87 [0.82, 0.93]	<0.0001*	0
Clinical	DM± Nephropathy	6	17,236	1560	8.72	9.37	0.94 [0.80, 1.10]	0.43	29
setting	Non-diabetic nephropathy	1	864	9	1.16	0.92	1.26 [0.34, 4.64]	0.73	NA
	HF	1	850	109	13.2	12.4	1.06 [0.75, 1.51]	0.74	NA
Mean age	< 65 years	20	58,223	4268	6.88	7.77	0.88 [0.84, 0.94]	<0.0001*	0
group	≥ 65 years	6	19,163	1777	9.05	9.48	0.96 [0.88, 1.05]	0.38	2
Active									
	High-risk hypertensive	12	46,307	5413	10.4	12.3	1.00 [0.95, 1.06]	0.93	0
	CAD	3	3874	136	3.56	3.45	0.98 [0.71, 1.36]	0.92	0
Clinical	DM± Nephropathy	5	2099	63	2.84	3.16	0.89 [0.55, 1.44]	0.63	0
setting	Non-diabetic nephropathy					NA			
	CVA					NA			
	HF	2	763	56	7.34	7.32	1.00 [0.61, 1.66]	0.99	0
Mean age	< 65 years	26	77,386	333	4.88	5.86	0.91 [0.86, 0.95]	0.19	0
group	≥ 65 years	16	48,438	5268	11.4	12.9	1.00 [0.95, 1.05]	0.73	0

7.10 ARBs and risk of all-cause mortality

7.10.1 Overall treatment effects

Figure 7-27 shows the RE of the meta-analysis on the effectiveness of ARB-based therapy on the risk of total mortality stratified according to control group, placebo or active therapy group. Data of all-mortality of ARBs were reported in 43 RCTs that included 151,721 participants and 13,945 total mortality events. The incidence rate of total mortality was similar between patients treated by ARB and those within the control group, 9.1% and 9.1% respectively. There was no noticeable benefit of ARBs on the total mortality compared with the control group (RR, 0.99; 95% CI 0.96-1.02; p=0.55). There was no heterogeneity among trials (chi-square test p value = 0.98 and $I^2 = 0\%$).

The effect of ARB therapy on the occurrence of total mortality when compared with a placebo was assessed on the basis of 24 studies stratified by control group. The trials involved 94,816 participants and 10,333 all mortality events. More than 50% of the trials reported RR > 1. Therapy with ARB indicated no benefit on total mortality risk compared with the placebo (RR, 0.99; 95% CI 0.96-1.03; p=0.63). The chi-square test resulted in a P-value of 0.96 and I²= 0% indicating no statistical heterogeneity between studies.

A total of 19 studies were analysed to test the effectiveness of ARB therapy for total mortality in 56,905 participants in active-controlled trials. These trials reported 3,612 total mortality events in which the incidence of all-mortality was similar between patients randomised to the ARBs or active therapy groups, 6.3% and 6.3% respectively. The weighting of the trials was 1% or less, except for VALUE (11.3%) and LIFE (5.4%). Therapy with ARBs indicated no benefits on total mortality compared with active therapy group (RR, 0.98; 95% CI 0.93-1.05; p=0.63). The assessment of heterogeneity shows no statistical variation (chi-square test p value = 0.78 and $l^2 = 0\%$).

The FE model shown in **Figure 7-28** indicates that the summary effect estimate was similar to that generated by the RE model. However, a slightly higher weighting was assigned to PRoFESS and LIFE.

	AR	D	Cont	ral		Risk Ratio	Risk Ratio	Risk of Bias
Study or Subgroup	Events		Events		Weight	M-H, Random, 95% Cl		ABCDEFG
1.1.1 ARB vs Placebo								
ACTIVE-I 2011	949	4518	929	4498	14.5%	1.02 [0.94, 1.10]	+	
ANTIPAF 2012	2	214	1	211	0.0%	1.97 [0.18, 21.58]		
CHARM-Added 2003	377	1276	412	1272	6.9%	0.91 [0.81, 1.02]		
CHARM-Alternative 2003 CHARM-Preserved 2003	265 244	1013 1514	296 237	1015 1509	4.7% 3.5%	0.90 [0.78, 1.03] 1.03 [0.87, 1.21]		
DIRECT-Prevent 1 2008	244	710	237	710	0.1%	1.40 [0.45, 4.39]		
DIRECT-Protect 1 2008	. 7	951	8	951	0.1%	0.88 [0.32, 2.40]		
DIRECT-Protect 2 2008	37	949	35	954	0.5%	1.06 [0.68, 1.67]		
EFFERVESCENT 2016	1	80	0	40	0.0%	1.52 [0.06, 36.46]	• •	• • • • • • • • • • • • • • • • • • • •
GISSI-AF 2009	8	722	7	720	0.1%	1.14 [0.42, 3.13]		
HOPE-3 2016	342	6356	349	6349	4.5%	0.98 [0.85, 1.13]	-+-	
I-PRESERVE 2008	445	2067	436	2061	6.8%	1.02 [0.91, 1.14]	+	
IDNT (Placebo) 2003	87	579 404	93 5	569 207	1.3%	0.92 [0.70, 1.20]		
IRMA-2 2001 NAVIGATOR 2010	11 295	404	327	4675	0.1% 4.1%	1.13 [0.40, 3.20] 0.91 [0.78, 1.06]		
ORIENT 2011*	235	282	20	284	0.3%	0.96 [0.52, 1.75]		
PRoFESS 2008	755	10146	740	10186	9.8%	1.02 [0.93, 1.13]	+	2000000
RASS 2009	1	96	1	95	0.0%	0.99 [0.06, 15.59]	،	
RENAAL 2001	158	751	155	762	2.4%	1.03 [0.85, 1.26]		
ROADMAP 2011*	26	2232	15	2215	0.2%	1.72 [0.91, 3.24]		
SCOPE 2003	259	2477	266	2460	3.6%	0.97 [0.82, 1.14]	-	
TRANSCEND 2008	364	2954	349	2972	4.9%	1.05 [0.91, 1.20]		
Val-HeFT 2001	495	2511	484	2499	7.4%	1.02 [0.91, 1.14]	· · · · · · · · ·	?? ** ? **
VVeil et al 2013 Subtotal (95% CI)	3	84 47517	6	85 47299	0.1% 75.8%	0.51 [0.13, 1.96] 0.99 [0.96, 1.03]		
Total events	5157	47517	5176	47233	13.070	0.33 [0.30, 1.03]	1	
Heterogeneity: Tau ² = 0.00		.65. df=		.96); I ^z =	0%			
Test for overall effect: Z = 0								
1.1.3 ARB vs Active								
4C 2016	22	585	20	534	0.3%	1.00 [0.55, 1.82]		
CARP 2011	7	90	6	101	0.1%	1.31 [0.46, 3.75]		
CASE-J 2008 CHIEF 2018	73 98	2354 6766	86 110	2349 6776	1.0% 1.3%	0.85 [0.62, 1.15]		
COPE 2010	25	1110	46	2183	0.4%	0.89 [0.68, 1.17] 1.07 [0.66, 1.73]		
Dahl et al 2010	23	57	40	2103	0.1%	1.40 [0.47, 4.15]		2200000
E-COST 2005	4	1053	4	995	0.0%	0.94 [0.24, 3.77]		
E-COST-R 2005	4	69	4	72	0.1%	1.04 [0.27, 4.01]		?? 🗧 🖲 🖷 ?
HIJ-CREATE 2009	69	1024	59	1025	0.8%	1.17 [0.84, 1.64]		••••
HONG-KONG DHF 2007	1	56	3	50	0.0%	0.30 [0.03, 2.77]	• • • • • • • • • • • • • • • • • • • •	•?••
IDNT (CCB) 2003*	87	579	83	567	1.2%	1.03 [0.78, 1.35]	. —	
Kondo et al 2003	4	203	11	203	0.1%	0.36 [0.12, 1.12]	•	2200000
LIFE 2002 MITEC 2009	383 0	4605 100	431 0	4588 109	5.4%	0.89 [0.78, 1.01] Not estimable		
MOSES 2005	57	681	52	671	0.7%	1.08 [0.75, 1.55]		
OLIVUS 2010	4	126	4	121	0.1%	0.96 [0.25, 3.75]		? ? ?•••?
PREVER-treatment 2016	1	322	o	333	0.0%	3.10 [0.13, 75.87]	۰ · · · · · · · · · · · · · · · · · · ·	
SUPPORT 2015	98	578	85	568	1.3%	1.13 [0.87, 1.48]		
VALUE 2004	841	7649	818	7596	11.3%	1.02 [0.93, 1.12]	+	••••
Subtotal (95% CI)		28007		28898	24.2%	0.98 [0.93, 1.05]	•	
Total events	1785		1827					
Heterogeneity: Tau ² = 0.00			17 (P = 0	.78); I ^z =	0%			
Test for overall effect: Z = 0	.48 (P = U.	03)						
Total (95% CI)		75524		76197	100.0%	0.99 [0.96, 1.02]		
Total events	6942		7003			,]	
Heterogeneity: Tau ² = 0.00	; Chi ² = 25	.07, df=	41 (P = 0	.98); I ^z =	0%		0.2 0.5 1 2 5	-
Test for overall effect: Z = 0.59 (P = 0.55) Test for overall effect: Z = 0.59 (P = 0.55) Favours [ARB] Favours [control]								
Test for subgroup differences: Chi² = 0.05, df = 1 (P = 0.83), l² = 0%								
Risk of bias legend								
(A) Random sequence generation (selection bias)								
(B) Allocation concealment (C) Blinding of participants			former	a bise'				
(C) Blinding of participants (D) Blinding of outcome as					e of mort	ality		
(D) Blinding of outcome assessment (detection bias): All cause of mortality (E) Incomplete outcome data (attrition bias)								

(B) incomplete outcome assessment (detect)
 (E) incomplete outcome data (attrition bias)
 (F) Selective reporting (reporting bias)
 (G) Other bias

Figure 7-27 Forest plot showing effect of ARBs on risk of all-cause mortality, stratified by comparison group (placebo vs active). Overall: 43 trials: (RE model).

The diamond indicates the pooled risk ratio (and 95% CI) or the overall effect for all-cause mortality risk. CI: confidence interval; RE: random-effects; M-H: Mantel-Haenszel. For studies acronyms, see list of definition/ abbreviations

Chapter	7:	ACEIs	and	ARBs	with	risk	of	mortali	ty
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			C			Diele Defie	Dials Datia	Diele of Die o
Study or Subgroup	ARI Events		Cont Events		Weight	Risk Ratio M-H, Fixed, 95% Cl	Risk Ratio M-H, Fixed, 95% Cl	Riskof Bias ABCDEFG
1.1.1 ARB vs Placebo								
ACTIVE-I 2011	949	4518	929	4498	13.3%	1.02 [0.94, 1.10]	+	
ANTIPAF 2012	2	214	1	211	0.0%	1.97 [0.18, 21.58]		+ •••••••
CHARM-Added 2003	377	1276	412	1272	5.9%	0.91 [0.81, 1.02]		
CHARM-Alternative 2003 CHARM-Preserved 2003	265 244	1013 1514	296 237	1015 1509	4.2% 3.4%	0.90 [0.78, 1.03] 1.03 [0.87, 1.21]		
DIRECT-Prevent 1 2008	244	710	237	710	0.1%	1.40 [0.45, 4.39]		
DIRECT-Protect 1 2008	. 7	951	8	951	0.1%	0.88 [0.32, 2.40]		
DIRECT-Protect 2 2008	37	949	35	954	0.5%	1.06 [0.68, 1.67]		
EFFERVESCENT 2016	1	80	0	40	0.0%	1.52 [0.06, 36.46]	• •	* •••••••
GISSI-AF 2009	8	722	7	720	0.1%	1.14 [0.42, 3.13]		
HOPE-3 2016 I-PRESERVE 2008	342 445	6356 2067	349 436	6349 2061	5.0% 6.2%	0.98 [0.85, 1.13]		
IDNT (Placebo) 2003	445	579	430	2001	1.3%	1.02 [0.91, 1.14] 0.92 [0.70, 1.20]		
IRMA-2 2001	11	404	5	207	0.1%	1.13 [0.40, 3.20]		??
NAVIGATOR 2010	295	4631	327	4675	4.7%	0.91 [0.78, 1.06]		
ORIENT 2011*	19	282	20	284	0.3%	0.96 [0.52, 1.75]		
PRoFESS 2008	755	10146	740	10186	10.6%	1.02 [0.93, 1.13]	. +	? • • • • • • ?
RASS 2009	1	96	1	95	0.0%	0.99 [0.06, 15.59]		+ 8 ? 8888 888888
RENAAL 2001 ROADMAP 2011*	158 26	751 2232	155 15	762 2215	2.2% 0.2%	1.03 [0.85, 1.26] 1.72 [0.91, 3.24]	T	
SCOPE 2003	259	2477	266	2460	3.8%	0.97 [0.82, 1.14]		
TRANSCEND 2008	364	2954	349	2972	5.0%	1.05 [0.91, 1.20]		
Val-HeFT 2001	495	2511	484	2499	6.9%	1.02 [0.91, 1.14]	+	??••?•
Weil et al 2013	3	84	6	85	0.1%	0.51 [0.13, 1.96]	←	• ? • • • • ?
Subtotal (95% CI)		47517		47299	74.0%	0.99 [0.96, 1.03]	1	
Total events	5157 5 df = 22.4	n – o oe	5176					
Heterogeneity: Chi ² = 12.65 Test for overall effect: Z = 0), 1- = 0 %					
	.20 (i = 0.	,						
1.1.3 ARB vs Active								
4C 2016	22	585	20	534	0.3%	1.00 [0.55, 1.82]		
CARP 2011 CASE-J 2008	7	90 2354	6 86	101 2349	0.1% 1.2%	1.31 [0.46, 3.75] 0.85 [0.62, 1.15]		
CHIEF 2018	98	2304 6766	110	2349 6776	1.2%	0.89 [0.68, 1.17]		
COPE 2011	25	1110	46	2183	0.4%	1.07 [0.66, 1.73]		
Dahl et al 2010	7	57	5	57	0.1%	1.40 [0.47, 4.15]		?? 🛑 🗣 🗣 🗣
E-COST 2005	4	1053	4	995	0.1%	0.94 [0.24, 3.77]		
E-COST-R 2005	4	69	4	72	0.1%	1.04 [0.27, 4.01]		??.....?
HIJ-CREATE 2009	69	1024	59	1025	0.8%	1.17 [0.84, 1.64]	· — —	
HONG-KONG DHF 2007 IDNT (CCB) 2003*	1 87	56 579	3 83	50 567	0.0% 1.2%	0.30 [0.03, 2.77] 1.03 [0.78, 1.35]	•	
Kondo et al 2003	4	203	11	203	0.2%	0.36 [0.12, 1.12]	←─────────────────────────────	2200000
LIFE 2002	383	4605	431	4588	6.2%	0.89 [0.78, 1.01]	-	
MITEC 2009	0	100	0	109		Not estimable		
MOSES 2005	57	681	52	671	0.7%	1.08 [0.75, 1.55]		
OLIVUS 2010	4	126	4	121	0.1%	0.96 [0.25, 3.75]		???•••?
PREVER-treatment 2016 SUPPORT 2015	1 98	322 578	0 85	333 568	0.0% 1.2%	3.10 [0.13, 75.87]	·	
VALUE 2004	90 841	7649	818	7596	11.7%	1.13 [0.87, 1.48] 1.02 [0.93, 1.12]	+	
Subtotal (95% CI)	0	28007	0.0	28898	26.0%	0.98 [0.92, 1.05]	•	
Total events	1785		1827					
Heterogeneity: Chi ² = 12.40); I² = 0%					
Test for overall effect: Z = 0	.56 (P = 0.)	58)						
Total (95% CI)		75524		76197	100.0%	0.99 [0.96, 1.02]		
Total events	6942		7003					
Heterogeneity: Chi ² = 25.07); I² = 0%					-
lest for overall effect: Z = 0.54 (P = 0.59) Eavours (ABB) Eavours (control)								
Test for subgroup differences: Chi ² = 0.12, df = 1 (P = 0.73), i ² = 0%								
<u>Risk of bias legend</u> (A) Random sequence generation (selection bias)								
(B) Allocation concealment			2.00/					
(C) Blinding of participants and personnel (performance bias)								
(D) Blinding of outcome assessment (detection bias): All cause of mortality								
(E) Incomplete outcome data (attrition bias)								

(F) Selective reporting (reporting bias)

(G) Other bias

Figure 7-28 Forest plot showing effect of ARBs on risk of all-cause mortality, stratified by comparison group (placebo vs active). Overall: 43 trials (FE model).

The **diamond** indicates the pooled risk ratio (and 95% CI) or the overall effect for all-cause mortality risk. CI: confidence interval; FE: fixed-effect; M-H: Mantel-Haenszel. For studies acronyms, see list of definition/ abbreviations

7.10.2 Sensitivity analysis

Figure 7-29 shows summary effects of ARB on occurrence of all-cause mortality after excluding 14 RCTs with sample size less than 1000 (six placebo and eight active- controlled RCTs). The pooled treatment effects of trials, either randomized to placebo or active, was not affected by exclusion with RR 0.99 (95% CI, 0.96-1.02; p=0.58). There was no heterogeneity among trials. Exclusion of 15 RCTs with poor methodology quality, four placebo and eleven active controlledtrial, did not alter the pooled treatment effects or heterogeneity compared with placebo (RR, 0.98; 95% CI 0.95-1.02; P=0.45) or with active (RR, 0.97; 95% CI 0.91-1.04]; p=0.40) (see Figure 7-30)

	40		Cant			Diel: Detie	Dials Datia	Diels of Dies
Study or Subgroup	AR Events		Cont Events		Mojaht	Risk Ratio M-H, Random, 95% Cl	Risk Ratio M-H, Random, 95% Cl	Riskof Bias ABCDEFG
1.1.1 ARB vs Placebo	Evenus	TULAI	Events	TUtal	weight	M-H, Random, 95% CI	M-H, Rahuolii, 95% Ci	ABCDEFG
ACTIVE-I 2011	949	4518	929	4498	14.6%	1.02 [0.94, 1.10]		
CHARM-Added 2003	349	1276	412	1272	7.0%	0.91 [0.81, 1.02]	-	
CHARM-Added 2003 CHARM-Alternative 2003	265	1013	296	1015	4.7%	0.90 [0.78, 1.03]		
CHARM-Preserved 2003	203	1514	230	1509	3.5%	1.03 [0.87, 1.21]	<u> </u>	
DIRECT-Prevent 1 2008	7	710	201	710	0.1%	1.40 [0.45, 4.39]		
DIRECT-Protect 1 2008	7	951	8	951	0.1%	0.88 [0.32, 2.40]		
DIRECT-Protect 2 2008	37	949	35	954	0.5%	1.06 [0.68, 1.67]		
GISSI-AF 2009	8	722	7	720	0.1%	1.14 [0.42, 3.13]		
HOPE-3 2016	342	6356	349	6349	4.5%	0.98 [0.85, 1.13]	+	
I-PRESERVE 2008	445	2067	436	2061	6.9%	1.02 [0.91, 1.14]	+	
IDNT (Placebo) 2003	87	579	93	569	1.3%	0.92 [0.70, 1.20]		
NAVIGATOR 2010	295	4631	327	4675	4.1%	0.91 [0.78, 1.06]	-+	
PRoFESS 2008	755	10146	740	10186	9.9%	1.02 [0.93, 1.13]	+	?
RENAAL 2001	158	751	155	762	2.4%	1.03 [0.85, 1.26]	+-	
ROADMAP 2011*	26	2232	15	2215	0.2%	1.72 [0.91, 3.24]		
SCOPE 2003	259	2477	266	2460	3.6%	0.97 [0.82, 1.14]	-	
TRANSCEND 2008	364	2954	349	2972	5.0%	1.05 0.91, 1.20	+-	
Val-HeFT 2001	495	2511	484	2499	7.5%	1.02 [0.91, 1.14]	+	?? 🗣 🗣 ? 🗣 🖶
Subtotal (95% CI)		46357		46377	76.0%	0.99 [0.96, 1.03]	+	
Total events	5120		5143					
Heterogeneity: Tau ² = 0.00	l; Chi ² = 11	1.24, df=	= 17 (P =	0.84); I ² :	= 0%			
Test for overall effect: Z = 0	.40 (P = 0	1.69)						
1.1.3 ARB vs Active								
4C 2016	22	585	20	534	0.3%	1.00 [0.55, 1.82]		
CASE-J 2008	73	2354	86	2349	1.0%	0.85 [0.62, 1.15]		
CHIEF 2018	98	6766	110	6776	1.3%	0.89 [0.68, 1.17]		
COPE 2011	25	1110	46	2183	0.4%	1.07 [0.66, 1.73]		
E-COST 2005	4	1053	4	995	0.0%	0.94 [0.24, 3.77]		
HIJ-CREATE 2009	69 87	1024 579	59 83	1025	0.8% 1.2%	1.17 [0.84, 1.64]		
IDNT (CCB) 2003* LIFE 2002	383	4605	83 431	567	1.2%	1.03 [0.78, 1.35]		
MOSES 2005	383	4605	431	4588 671	5.5% 0.7%	0.89 [0.78, 1.01] 1.08 [0.75, 1.55]		
SUPPORT 2015	57 98	578	52 85	568	1.3%	1.13 [0.87, 1.48]		
VALUE 2004	90 841	7649	818	7596	11.4%	1.02 [0.93, 1.12]		
Subtotal (95% CI)	041	26984	010	27852	24.0%	0.99 [0.93, 1.05]	4	
Total events	1757	20004	1794	21002	241070	0.00 [0.00, 1.00]	1	
Heterogeneity: Tau ² = 0.00		10 df=		72): I ² =	0%			
Test for overall effect: Z = 0			.50 -0	27, 1 =	0.0			
Total (95% CI)		73341		74229	100.0%	0.99 [0.96, 1.02]	1	
Total events	6877		6937					
Heterogeneity: Tau ² = 0.00	l; Chi² = 1	8.36, df=	= 28 (P =	0.92); I²:	= 0%			•
Test for overall effect: Z = 0							Favours [ARB] Favours [control]	
Test for subgroup differen	ces: Chi⁼∶	= 0.03, d	f=1 (P=	0.86), I ^z	= 0%			
Risk of bias legend								
(A) Random sequence ge			n bias)					
(B) Allocation concealmen	t (selectio	n bias)						
(C) Blinding of participants	and pers	onnel (p	erformar	nce bias)				
(D) Blinding of outcome as			tion bias)	: All cau	se of mort:	ality		
(E) Incomplete outcome da	ata (attritic	n bias)						
(F) Selective reporting (rep	orting bia	s)						
(G) Other bias								

Figure 7-29 Forest plot showing effect of ARBs on risk of all-cause mortality (RE model) [Sensitivity analysis: Excluding trials with sample size less than 1000].

CI: confidence interval; RE: random-effects; M-H: Mantel-Haenszel. For studies acronyms, see list of definition/ abbreviations

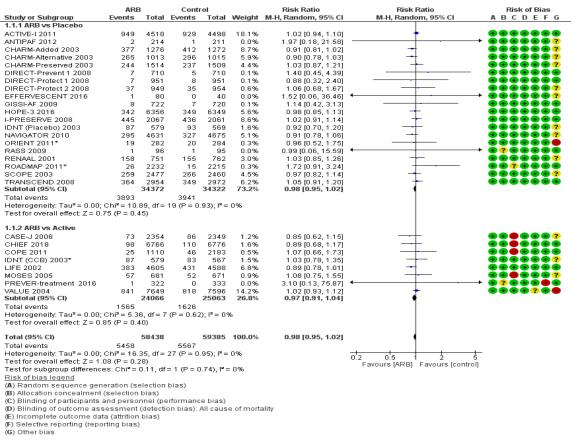




Figure 7-30 Forest plot showing effect of ARBs on risk of all-cause mortality (RE model) [Sensitivity analysis: Excluding trials with low methodology quality].

CI: confidence interval; RE: random-effects; M-H: Mantel-Haenszel. For studies acronyms, see list of definition/ abbreviations

7.10.3 Subgroup analysis

 Table 7-7 summarises the subgroup analyses of ARB on all-cause mortality.

7.10.3.1 Class of active control

Figure 7-31 shows the RE of the meta-analysis on the effectiveness of ARB therapy compared with active therapies, stratified to DHP CCBs, diuretics, beta-blockers and other active therapies. The trials assessing the effectiveness of ARB compared with DHP CCBs contributed 65.9% to the overall pooled treatment effects. All the trials reported RR >1 and its 95% CIs included 1 indicating non-significant pooled treatment effects. The analysis shows that ARB-based therapy has a neutral effect on all-cause mortality compared with CCBs of RR, 1.00 (95% CI 0.93-1.08; p=0.95). No heterogeneity was detected.

Diuretics or beta-blockers were used with the control group in three trials, HONG-KONG DHF, PREVER-treatment and LIFE. The pooled estimate was driven by LIFE that contributed 80.5%. ARB-based therapy achieved an 11% reduction in total mortality compared with diuretics and/or beta-blockers (RR, 0.88; 95% CI 0.78-1.01; p=0.06). However, this result was not statistically significant. No heterogeneity was detected. Compared with the other control groups, ARBs did not reduce the risk of all mortality (RR,1.10; 95% CI 0.92-1.32; p=0.30). No heterogeneity was detected.

7.10.3.2 Clinical setting

Figure 7-32 shows the RE of the meta-analysis on the effect of ARB-based therapy on the risk of mortality compared with the control group based on baseline population clinical setting. High-risk hypertensives were studied in 29 trials involving 115,479 participants and 10,304 events. No benefits were indicated of ARB therapy for high-risk hypertensives in terms of lowering the risk of allmortality (RR, 1.00; 95% CI 0.96-1.04; p= 0.98). There was no evidence of heterogeneity.

Similarly, treatment by ARBs for diabetics with or without nephropathy did not reduce the risk of all-mortality with an RR of 1.02 (95% CI 0.90-1.16; p=0.73). No variation among trials was indicated ($I^2 = 0\%$).

For patients with underlying CAD, a pooled estimate resulted in an RR of 1.05 (95% CI 0.93-1.19). The pooled estimate however reflected the result of the TRANSCEND trial that contributed 79.2% to the overall effect. Two trials involving 1,867 participants with AF and 18 all-mortality cases indicated no benefit attributable to an ARB-based regimen on risk of all-mortality. However, a significant effect estimate cannot be excluded due to a broad 95% CI.

7.10.3.3 Mean age group

In the analysis of the data relating to participants with **a mean age < 65 years**, the direction of pooled RR close to 1 was mainly influenced by the Val-HeFT trial that contributed 27.9% of the pooled treatment effect. There was no apparent benefit attributed to ARB-based therapy in terms of the reduction of all-mortality

compared with the control group (RR, 0.96; 95% CI 0.91-1.02; p=0.23). No heterogeneity was detected among the trials.

In the analysis of the data relating to participants with **a mean age** \geq **65 years** the pooled data of all mortality shows that therapy with ARB had no favourable effects on the reduction of total mortality compared with control (RR, 1.00; 95% CI 0.97-1.04; p=0.96). No heterogeneity was detected among the trials.

	ACI		Cont			Risk Ratio	Risk Ratio	Risk of Bias
Study or Subgroup	Events	lotal	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl	ABCDEFG
1.1.1 Dihydropyridine (DHP	-						_	
CASE-J 2008	73	2354	86	2349	6.2%	0.85 [0.62, 1.15]		
CHIEF 2018	98	6766	110	6776	8.0%	0.89 [0.68, 1.17]		
COPE 2011	25	1110	46	2183	2.5%	1.07 [0.66, 1.73]		
IDNT (CCB) 2003	87	579	83	567	7.6%	1.03 [0.78, 1.35]		$\bullet \bullet \bullet \bullet \bullet \bullet \bullet \circ \circ$
MITEC 2009	0	100	0	109		Not estimable	_	$\bullet ? \bullet \bullet \bullet \bullet ?$
MOSES 2005	57	681	52	671	4.5%	1.08 [0.75, 1.55]		
VALUE 2004	841	7649 19239	818	7596	71.1%	1.02 [0.93, 1.12]	—	••••
Subtotal (95% CI)		19239		20251	100.0%	1.00 [0.93, 1.08]	•	
Total events	1181		1195					
Heterogeneity: Tau ² = 0.00;			(P = 0.8)	i); i*= 04	%			
Test for overall effect: Z = 0.	.06 (P = 0.	95)						
1.1.2 Diuretics & beta-bloc	kers							
HONG-KONG DHF 2007	легэ 1	56	3	50	0.3%	0.30 [0.03, 2.77]	←	•?••
LIFE 2002	383	4605	431	4588	99.5%	0.89 [0.78, 1.01]	· · · · · · · · · · · · · · · · · · ·	
PREVER-treatment 2016	303	4005	431	4088	0.2%	3.10 [0.13, 75.87]	• • • • • • • • • • • • • • • • • • •	
Subtotal (95% CI)	1	4983	U		100.0%	0.88 [0.78, 1.01]	•	
Total events	385	4505	434	4371	100.070	0.00 [0.70, 1.01]	•	
Heterogeneity: Tau ² = 0.00;		1 df = 3		2) IZ = 00	v.			
Test for overall effect: Z = 1.			(F = 0.4)	0,1 = 0	20			
Test for overall effect. $Z = 1$.	.00 (F = 0.	00)						
1.1.3 Active control								
4C 2016	22	585	20	534	9.5%	1.00 [0.55, 1.82]		
CARP 2011	7	90	6	101	3.0%	1.31 [0.46, 3.75]		??
Dahl et al 2010	7	57	5	57	2.8%	1.40 [0.47, 4.15]		??
E-COST 2005	4	1053	4	995	1.7%	0.94 [0.24, 3.77]		
E-COST-R 2005	4	69	4	72	1.8%	1.04 [0.27, 4.01]		??
HIJ-CREATE 2009	69	1024	59	1025	29.5%	1.17 [0.84, 1.64]	_	
Kondo et al 2003	4	203	11	203	2.6%	0.36 [0.12, 1.12]	←	??
OLIVUS 2010	4	126	4	121	1.8%	0.96 [0.25, 3.75]		???
SUPPORT 2015	98	578	85	568	47.1%	1.13 [0.87, 1.48]		
Subtotal (95% CI)		3785		3676	100.0%	1.10 [0.92, 1.32]	•	
Total events	219		198				-	
Heterogeneity: Tau ² = 0.00;		36. df = 8		2): IF = 0.9	ж			
Test for overall effect: Z = 1.								
								-
							0.5 0.7 1 1.5 2 Ferreure MCEII Ferreure Mativel	
Test for subgroup differenc	es: Chi ² =	4.24, df	= 2 (P = 0).12), I² =	= 52.8%		Favours [ACEI] Favours [Active]	
Risk of bias legend								
(A) Random sequence ger	neration (s	election	bias)					
(B) Allocation concealment								
(C) Blinding of participants			erforman	e bias)				
(D) Blinding of outcome as:					e of mort	ality		
(E) Incomplete outcome da			on oras).	, in cado	s srmon	any		
(F) Selective reporting (repo								
(G) Other bias	arang pida	/						

(G) Other bias

Figure 7-31 Forest plot showing effect of ARBs on risk of all-cause mortality [Subgroup analysis: Type of active comparator].

CI: confidence interval; RE: random-effects; M-H: Mantel-Haenszel. For studies acronyms, see list of definition/ abbreviations

Study or Subgroup	ARE Events	B Total	Place Events		Weight	Risk Ratio M-H, Random, 95% Cl	Risk Ratio M-H, Random, 95% Cl	Riskof Bias ABCDEFG
1.1.2 High-risk hypertensive 4C 2016	22	585	20	534	0.4%	1.00 [0.55, 1.82]		
ACTIVE-I 2011 CARP 2011	949 7	4518 90	929 6	4498 101	20.1% 0.1%	1.02 [0.94, 1.10] 1.31 [0.46, 3.75]	†	
CASE-J 2008 CHIEF 2018	73 98	2354 6766	86 110	2349 6776	1.4% 1.8%	0.85 [0.62, 1.15] 0.89 [0.68, 1.17]		
COPE 2011 E-COST 2005	25	1110	46	2183	0.6%	1.07 [0.66, 1.73] 0.94 [0.24, 3.77]		
E-COST-R 2005	4	69	4	72	0.1%	1.04 [0.27, 4.01]		2200002
GISSI-AF 2009 HIJ-CREATE 2009	8 69	722 1024	7 59	720 1025	0.1% 1.1%	1.14 [0.42, 3.13] 1.17 [0.84, 1.64]		
HONG-KONG DHF 2007 I-PRESERVE 2008	1 445	56 2067	3 436	50 2061	0.0% 9.5%	0.30 [0.03, 2.77] 1.02 [0.91, 1.14]		
IDNT (CCB) 2003	87	579	83	567	1.7%	1.03 [0.78, 1.35]		
IDNT (Placebo) 2003 IRMA-2 2001	87 11	579 404	93 5	569 207	1.8% 0.1%	0.92 [0.70, 1.20] 1.13 [0.40, 3.20]		
LIFE 2002 MITEC 2009	383 0	4605 100	431 0	4588 109	7.5%	0.89 [0.78, 1.01] Not estimable	-	
MOSES 2005 NAVIGATOR 2010	57 295	681 4631	52 327	671 4675	1.0% 5.6%	1.08 [0.75, 1.55] 0.91 [0.78, 1.06]		
OLIVUS 2010	4	126	20	121	0.1%	0.96 [0.25, 3.75]		2220002
ORIENT 2011* PREVER-treatment 2016	1	322	0	333	0.0%	0.96 [0.52, 1.75] 3.10 [0.13, 75.87]		
PRoFESS 2008 RENAAL 2001	755 158	10146 751	740 155	10186 762	13.7% 3.3%	1.02 [0.93, 1.13] 1.03 [0.85, 1.26]	<u></u>	
SCOPE 2003 SUPPORT 2015	259 98	2477 578	266 85	2460 568	5.0% 1.8%	0.97 [0.82, 1.14] 1.13 [0.87, 1.48]	*	
TRANSCEND 2008	364	2954	349	2972	6.9%	1.05 [0.91, 1.20]	ł	GGGGGG
VALUE 2004 Weil et al 2013	841 3	7649 84	818 6	7596 85	15.8% 0.1%	1.02 [0.93, 1.12] 0.51 [0.13, 1.96]		
Subtotal (95% CI) Total events	5127	57362	5144	58117	100.0%	1.00 [0.96, 1.04]		
Heterogeneity: Tau ² = 0.00; C Test for overall effect: Z = 0.0	>hi² = 13.	.34, df = 2		.99); l²=	0%			
1.1.3 HF	2 (F = 0.:	90)						
CHARM-Added 2003	377	1276	412	1272	22.3%	0.91 [0.81, 1.02]	4	
CHARM-Alternative 2003 CHARM-Preserved 2003	265 244	1013 1514	296 237	1015 1509	15.6% 11.7%	0.90 [0.78, 1.03] 1.03 [0.87, 1.21]	1	
HONG-KONG DHF 2007 I-PRESERVE 2008	1 445	56 2067	3	50 2061	0.1%	0.30 [0.03, 2.77]		
SUPPORT 2015	98	578	85	568	4.6%	1.02 [0.91, 1.14] 1.13 [0.87, 1.48]	—	• ? • • ? • •
Val-HeFT 2001 Subtotal (95% CI)	495	2511 9015	484	2499 8974	23.7% 100.0%	1.02 [0.91, 1.14] 0.98 [0.92, 1.04]	t	??
Total events Heterogeneity: Tau ² = 0.00; C	1925 3hi≅ = 6 3	86 df = 6 i	1953 P = 0.38	0: I ₹ = 69	×.			
Test for overall effect: Z = 0.7	3 (P = 0.	46)			-			
1.1.4 CAD 4C 2016		505				4 00 10 55 4 00		
CARP 2011	22 7	585 90	20 6	534 101	4.3% 1.4%	1.00 [0.55, 1.82] 1.31 [0.46, 3.75]		2200000
HIJ-CREATE 2009 Kondo et al 2003	69 4	1024 203	59 11	1025 203	13.3% 1.2%	1.17 [0.84, 1.64] 0.36 [0.12, 1.12]		
MITEC 2009 OLIVUS 2010	0	100	0	109	0.8%	Not estimable		
TRANSCEND 2008	364	2954	349	2972	79.2%	0.96 [0.25, 3.75] 1.05 [0.91, 1.20]	—	
Subtotal (95% CI) Total events	470	5082	449	5065	100.0%	1.05 [0.93, 1.19]	Ť	
Heterogeneity: Tau ² = 0.00; C Test for overall effect: Z = 0.8	Chi⁼ = 4.0 1 (P = 0)1,df=5 42)	P = 0.55	5); I² = 09	X6			
1.1.5 DM ± Nephropathy								
DIRECT-Prevent 1 2008	7	710 951	5 8	710 951	1.2% 1.5%	1.40 [0.45, 4.39]		
DIRECT-Protect 1 2008 DIRECT-Protect 2 2008	37	949	35	954	7.4%	0.88 [0.32, 2.40] 1.06 [0.68, 1.67]		
IDNT (CCB) 2003 IDNT (Placebo) 2003	87 87	579 579	83 93	567 569	19.7% 21.0%	1.03 [0.78, 1.35] 0.92 [0.70, 1.20]		
IRMA-2 2001 MITEC 2009	11 0	404	5	207 109	1.4%	1.13 [0.40, 3.20] Not estimable		
ORIENT 2011*	19	282	20	284	4.1%	0.96 [0.52, 1.75]		
RASS 2009 RENAAL 2001	1 158	96 751	1 155	95 762	0.2% 38.9%	0.99 [0.06, 15.59] 1.03 [0.85, 1.26]		
ROADMAP 2011* Weil et al 2013	26 3	2232 84	15 6	2215 85	3.8% 0.8%	1.72 [0.91, 3.24] 0.51 [0.13, 1.96]		
Subtotal (95% CI) Total events	443	7717	426	7508	100.0%	1.02 [0.90, 1.16]	+	
Heterogeneity: Tau ² = 0.00; C	>hi≊ = 4.7			91); I ≈ = 0)%			
Test for overall effect: Z = 0.3	5 (P = 0.1	73)						
1.1.6 CVA MOSES 2005	57	681	52	671	6.8%	1.08 [0.75, 1.55]		
PRoFESS 2008 Subtotal (95% CI)	755	10146 10827	740	10186 10857	93.2% 100.0%	1.02 [0.93, 1.13] 1.03 [0.94, 1.13]	—	?
Total events Heterogeneity: Tau ² = 0.00; C	812		792					
Test for overall effect: Z = 0.5			F = 0.78	5), T = 0 -	10			
1.1.7 AF								
ANTIPAF 2012 GISSI-AF 2009	2	214 722	1 7	211 720	15.1% 84.9%	1.97 [0.18, 21.58] 1.14 [0.42, 3.13]		
Subtotal (95% CI) Total events	10	936	8	931	100.0%	1.24 [0.49, 3.14]	-	
Heterogeneity: Tau ² = 0.00; C	Chi² = 0.1	7, df = 1		9); I ² = 09	K 6			
Test for overall effect: Z = 0.4		65)						
1.1.8 Non-diabetics nephrop E-COST-R 2005	pathy 4	69	4	72	100.0%	1.04 [0.27, 4.01]		??
Subtotal (95% CI) Total events	4	69	4	72	100.0%	1.04 [0.27, 4.01]		
Heterogeneity: Not applicable	e	96)	-					
Test for overall effect: Z = 0.0	5 (F = 0.9	53)						
							.01 0.1 1 10 100 ours [experimental] Favours [control]	
Test for subgroup difference: Risk of bias legend	s: Chi²=	1.84, df=	6 (P = 0).93), I² =	:0%	1 619	,	
(A) Random sequence gene (B) Allocation concealment (s			ias)					
(C) Blinding of participants a	nd perso	onnel (per						
(D) Blinding of outcome asse (E) Incomplete outcome data	a (attrition	ı bias)	n bias): .	All caus	e of morta	IITy		
(F) Selective reporting (report (G) Other bias	ting bias)						

Figure 7-32 Forest plot showing effect of ARBs on risk of all-cause mortality; [Subgroup analysis: Clinical setting].

CI: confidence interval; RE: random-effects; M-H: Mantel-Haenszel. For studies acronyms, see list of definition/ abbreviations

Table 7-7 Summary of RE a meta-analytical subgroup analysis shows the effect of ARBs on risk of all-mortality compared with control (placebo and active)[†]

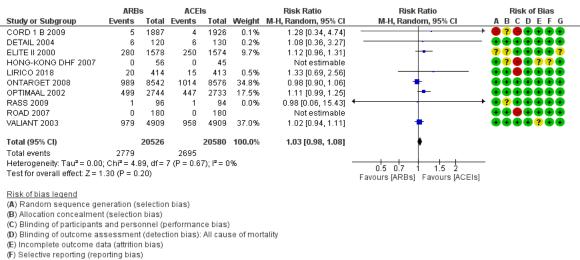
					All-me	ortality			l ² (%) ‡
Su	ıbgroup analysis	Studies	Participants	Events	Incide	nce (%)	RR (M-H, Random,	Р	
					ARBs	Control	95% CI)	value*	
Overall	RE	43	151,721	13,945	9.19	9.19	0.99 [0.96-1.02]	0.59	0
	DHP-CCBs	6	25,948	2168	8.68	8.05	1.01 [0.93-1.10]	0.76	0
Active control	Diuretics/Beta-blockers	4	23,496	1027	4.11	4.63	0.89 [0.79-1.00]	0.04	0
	Active control	9	7461	417	5.78	5.38	1.10 [0.92-1.32]	0.30	0
	High-risk hypertensive	29	115479	10,271	8.93	8.85	1.00 [0.96-1.04]	0.98	0
	HF	7	17989	3878	21.3	21.7	0.98 [0.92-1.04]	046	6
	CAD	7	10147	919	9.24	8.86	1.05 [0.93-1.19]	0.42	0
Clinical	DM± Nephropathy	12	15225	869	5.74	5.67	1.02 [0.90-1.16]	0.73	0
setting	CVA	2	21684	1604	7.49	7.29	1.03 [0.94-1.13]	0.57	0
	AF	2	1867	18	1.06	0.85	1.24 [0.49-3.14]	0.65	0
	Non-diabetic nephropathy^	1	141	8			NA		1
Mean age	< 65 years	21	54,439	3628	6.53	6.79	0.96 [0.91-1.02]	0.23	0
group	≥ 65 years	21	96,703	10,230	10.5	10,5	1.00 [0.97-1.04]	0.96	0
	tions/abbreviation. Cl: confidence					•			

7.11 Direct comparison between ARBs and ACEIs on risk of all-cause mortality

7.11.1 Overall treatment effect

Figure 7-33 demonstrates a meta-analytical RE model of effectiveness of ARBs compared with ACEIs from 10 head-to-head trials. These trials involved 41,106 participants with or at risk of CVD and 5,474 all-mortality events. The majority of the trials reported an RR of more than 1 and a confidence interval that interrupted the line of null hypothesis indicating a non-significant level. The pooled data showed similar all-mortality risk relating to ARBs and ACEIs with an RR of 1.03 (95% CI 0.98-1.08; p=0.20). The direction and magnitude of the pooled effect estimates was mainly influenced by the VALIANT and ONTARGET trials that contributed 71.8% of the overall effect estimates.

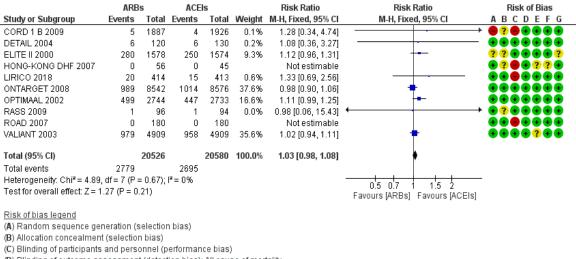
There was no evidence of heterogeneity. As a result, the summary of the overall effect estimate generated from the RE model is similar to that generated from the FE model. However, a higher weighting was assigned to the ONTARGET trial (see Figure 7-34).



(G) Other bias

Figure 7-33 Forest plot showing effect of ARBs versus ACEIs on risk of all-cause mortality (RE model).

The diamond indicates the pooled risk ratio (and 95% CI) or the overall effect for all-cause mortality risk. CI: confidence interval; RE: random-effects; M-H: Mantel-Haenszel. For studies acronyms, see list of definition/ abbreviations



(D) Blinding of outcome assessment (detection bias): All cause of mortality

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

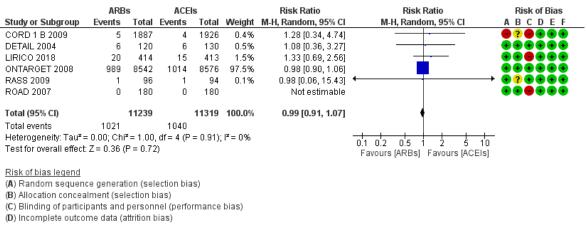
(G) Other bias

Figure 7-34 Forest plot showing effect of ARBs versus ACEIs on risk of all-cause mortality (FE model).

The diamond indicates the pooled risk ratio (and 95% CI) or the overall effect for all-cause mortality risk. CI: confidence interval; FE: fixed-effect; M-H: Mantel-Haenszel. For clinical trials acronyms, see list of definition/ abbreviations

7.11.2 Sensitivity analysis

The exclusion of four trials, two of which involved patients with signs and symptoms of HF within 10 days of an MI (OPTIMAAL and VALIANT) and two of which involved patients with symptomatic CHF (ELITE II and HONG-KONG DHF), did not impact the pooled effect estimates with an RR of 0.99 (95% CI 0.91-1.07; p=0.72). A 97.5% pooled effect estimate is reflected a result of ONTARGET trial (See **Figure 7-35**)



(E) Selective reporting (reporting bias)

(F) Other bias

Figure 7-35 Forest plot showing effect of ARBs versus ACEIs on risk of all-cause mortality (RE model) [Sensitivity analysis: Excluding trials with HF].

CI: confidence interval; RE: random-effects; M-H: Mantel-Haenszel. For studies acronyms, see list of definition/ abbreviations

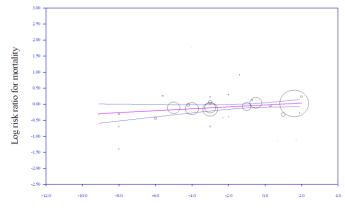
7.12 Meta-regression analyses of the effect of ACEI and ARB on all-cause mortality risk in relation to SBP reduction

7.12.1 ACEIs

7.12.1.1 Overall effect

Eight of the trials included did not report the achieved SBP reduction (CARMEN, CCS-I, JAMP, PROGRESS, Hou et al. (group 2), IMAGINE and QUIET) and one trial reported zero cases (QUO VADIS). Thus, 30 trials were included in the meta-regression analysis. The mean achieved SBP reduction in the ACEI trials were in the range of -8 to 3.4 mmHg, achieved in the APRES and QUO VADIS trials respectively. As shown in **table 7-8**, the univariate analysis shows that the magnitude of mortality risk reduction was positively associated with a reduction of BP (an estimated RR, 1.02; 95% CI 1.01-1.04; p=0.0004). Achieved SBP differences between randomised groups explained 100% of the observed between-trial variation in mortality risk (Tau² reduced from 0.0041 to 0; p=0.951, residual $l^2=0\%$).

In the univariate model, a 26% and 5% between-study variance were explained by male (%) and mean age (%). Therefore, these variables were added to the multivariate analysis. Once the variables were accounted for, the direction and magnitude of the relationship between a mean SBP and mortality remained unaltered. A 100% variability among trials in RR of mortality was substantially explained by the model (Tau² reduced from 0.0041 to 0; p=0.951). The achieved mean DBP differences were excluded from the multivariate model because they had a strong correlation with the achieved mean SBP differences (r=-0.9). At zero mmHg BP reduction achieved, there was no evidence that ACEIs conferred a BP-independent effect on mortality risk (RR, 0.97; 95% CI 0.93-1.07; p=0.227) (See **Figure 7-36**)



Systolic blood pressure (SBP) differences between randmized groups (mmHg)

Figure 7-36 Adjusted meta-regression analysis of relationship between RR of allmortality and difference in achieved SBP (mmHg) between randomized groups for trials of ACEIs

Each study is represented by a circle. The size of each circle is proportional to that study's weighting in the analysis (inverse-variance weighted). Negative value in x-axis is indicates lower achieved SBP in treatment group than control group

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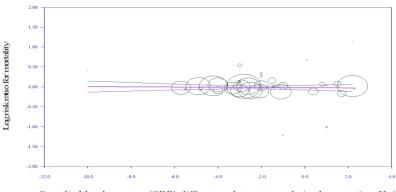
Table 7-8 Meta-regression of related and unrelated SBP differences by ACEI on all-cause mortality risk (adjusted and unadjusted models)

			Slope			Betw	een study varia	nce
Variable	Studies	RR	95% CI	P value	Tau ²	Residual I ²	P value	R ² (%)
Null model					0.0041	1.37	0.444	
Univariate analysis (Unadjusted)								
Achieved SBP differences (mmHg)	30	1.02	1.01-1.04	0.0004*	0	0	0.951	100
Achieved DBP difference (mmHg)		1.06	1.02-1.10	0.001*	0	0	0.981	100
Baseline SBP (mmHg)		1.00	0.99-1.00	0.817	0.0044	0.67	0.455	0
Mean age (Years)		1.00	0.99-1.02	0.435	0.0039	0	0.514	5
Male (%)		0.99	0.99-1.00	0.139	0.0030	0	0.712	26
DM (%)		1.00	0.99-1.02	0.620	0.0046	4.61	0.395	0
Duration of follow-up (Years)		0.98	0.89-1.08	0.718	0.0048	2.25	0.431	0
Multivariate analysis (Adjusted)		I						
Achieved SBP differences (mmHg)**		1.04	1.01-1.06	0.010*	0	0	0.951	100
Abbreviation: Tau ² = estimated amount of h	eterogeneity (between-	study variance)	not explained	d by covariate;	12 residual= propo	rtion of remaining	g observed
variance due to true variation in effect size.								
* P value less of than 0.05 is significant								
**The analysis was adjusted for male (%) and	d age (mean)							

7.12.2 ARBs

7.12.2.1 Overall effect

Five trials did not report a mean SBP reduction (SUPPORT, Weil et al., DIRECT-Prevent 1, DIRECT-Protect 1, DIRECT-Protect 2) and one trial reported zero cases (MITEC). Thus, a total of 37 ARBs trials that reported a mean SBP reduction were included in the meta-regression analysis (see **Figure 7-37**). The average SBP reduction ranged from -5.7 mmHg in the HOPE-3 trial to 2.3 mmHg in the OLIVUS trial. A meta-regression demonstrated no apparent benefit of ARB either depending on or independently from BP reduction with a p value=0.72 and 0.46, respectively.



Systolic blood pressure (SBP) differences between randmized groups (mmHg)

Figure 7-37 Meta-regression analysis of relationship between RR of all-mortality and difference in achieved SBP (mmHg) between randomized groups for trials of ARB.

Each study is represented by a circle. The size of each circle is proportional to that study's weighting in the analysis (inverse-variance weighted). A negative value in x-axis is indicates lower achieved SBP in treatment group than control group

7.13 Discussion

The comprehensive meta-analysis presented in this study involved 317,984 participants with an average follow-up of 3.5 years. It sought to evaluate the effect of ACEIs and ARBs on total and CV mortality on patients with or at high-risk of CVD. This is the largest and most current meta-analysis to address this question. It was found that, overall, ACEIs significantly reduce total and CV mortality by 5% and 9% respectively across diverse high-risk patients. The robustness of the results was supported by a sensitivity analysis. The size of these reductions was broadly consistent across population clinical settings and mean age groups, which suggests that the results can be generalised. In contrast, there was no significant relative risk mortality reduction attributable to ARB-based therapy. Furthermore, the narrow 95% CI with minimal or absence of heterogeneity across the effect estimates confirm the validity of this study's results.

Accumulating data have proved a comparable clinical profile of ACEIs and ARBs including the lowering of BP (Dahlöf et al., 2002, Lithell et al., 2003) although the distinct effects of ACEIs and ARBs on mortality risk are still controversial (Strauss and Hall, 2006). Two contemporary trials, ONTARGET on high-risk patients and DETAIL on patients with diabetic nephropathy, showed a greater reduction of SBP favoured ARBs of 0.9 and 3 mmHg, respectively, compared with ACEI. Despite this result, no differences between the two drugs in terms of mortality reduction have been proved. It should be noted that telmisartan has a longer duration of action than the ramipril and enalapril that was used in the two trials. The different pharmacological modes of action of the ACEIs and ARBs might have contributed to these findings (Strauss and Hall, 2006). Also, similarities and differences in the trial design, such as a heterogenous background antihypertensives regimen, could have played a role.

The observed reduction in SBP by ARB versus placebo have not always resulted in mortality reduction. The achieved mean SBP was lower in the ARB group than in the placebo group by 3.2 mmHg in the SCOPE study and 4.2 mmHg in the TRANSCEND study. However, a lack of benefit to all and CV mortality risk were observed. It should be noted that a considerable proportion of participants (66%) assigned to the placebo group in the SCOPE trial received open-label

antihypertensive agents including diuretics, beta-blockers and CCBs than in those assigned to candesartan (44%).

The findings arising from our analysis are in agreement and build on the findings of Bangalore et al. (2011) review. They pooled data from 30 ARB studies involving 147,020 individuals with broad clinical conditions. The review failed to detect reduction in risk of all and CV mortality through ARB-based therapy compared with placebo or active control therapy. In spite of this, they incorporate trials directly comparing ARBs with ACEIs in primary analyses which might attenuate the real exact effect of ARBs, ONTARGET, OPTIMAAL, VALIANT and ELITE. They also include the JIKEI Heart Study (Mochizuki et al., 2007) and the KYOTO Heart Study (Sawada et al., 2009) which were subsequently retracted due to unreliable data. Our review incorporated updated data taken from the CHIEF, LIRICO, SUPPORT, PREVER-TREATMENT, ORIENT and ROADMAP trials. Therefore, the current analysis presents more comprehensive and reliable evidence relating to the impact of ARBbased therapy on mortality risk.

Contradictory results were reported by previous reviews (Verdecchia et al., 2005a, Savarese et al., 2013, Ettehad et al., 2016). Verdecchia et al. (2005a) pooled data from 11 trials that included diverse high-risk patients which revealed a 9% lowering of risk reduction in CV fatal events through ARBs when compared with the placebo (OR, 0.91; 95% CI 0.83-0.99; P=0.042). This result was based on cardiac death data taken from the Val-HeFT trial that favoured valsartan (OR 0.72; 95% CI 0.45-1.16). However, the FDA reported that the number of CV mortality events in the valsartan group was in fact similar to the number in the placebo group (427 and 419, respectively) (Novartis Advisory Committee, 2002). The discordant results of the effects of ACEI on mortality risk on high-risk patients were reported by Savarese et al. (2013) and Ettehad et al. (2016) reviews. Their results are dependent on which trials were included or excluded. Among the trials on the efficacy of ARB-based therapy included in the Savarese et al. (2013) review, there was a significant heterogeneity on risk of CV mortality (p=0.012 and $I^2 = 61.3\%$). Furthermore, the Ettehad et al. (2016) meta-analysis suffered from the limitation of pooling the data relating to ACEIs and ARBs irrespective of comparator group. However, our analysis involved trials greater than those used in the mentioned

reviews and draw on evidence from placebo, active-controlled and head-to-head comparison trials.

The effect of ARBs and ACEIs compared with antihypertensives on mortality have been previously evaluated. A recent meta-analysis involving hypertensives found that ACEIs have beneficial effects on mortality risk when compared with other antihypertensive therapies (van Vark et al., 2012). Of note is that the treatment effect of ACEIs and ARBs on CV mortality was statistically non-significant (P interaction= 0.227), whereas, the all-mortality reduction was significant (P interaction= 0.036). The observed mortality reduction of ACEI-based treatment when compared with active therapy was mainly driven by the ASCOT-BPLA and HYVET trials that assessed amlodipine and indapamide with the optional addition of perindopril. Therefore, these trials do not completely evaluate ACEIs. In line with van Vark et al. (2012) review, the ASCOT-BPLA and HYVET trials were incorporated in Brugts et al. (2015) review. Moreover, the CV mortality data of the CASE-J, CHIEF, IDNT and RENAAL trials that assessed ARB-based therapy were not included in their review. Our analysis excluded the ASCOT-BPLA and HYVET trials that demonstrated that ACEI is as effective as other antihypertensive therapy on all or CV mortality risk. It should be noted that the unclear mortality effect of ACEIs on DM with or without nephropathy and CVA are uncertain due to the lack of statistical power. There is a moderate non-significant heterogeneity among trials of ARBs versus placebo on risk of CV mortality (1²=35%). The stratified analysis revealed that heterogeneity is completely the result of trials using olmesartan such as the ROADMAP and ORIENT trials. These trials reported excessive mortality cases in diabetics receiving olmesartan. In 2014, an observational study of more than 300,000 patient-years examined the mortality risk of olmesartan in comparison with other ARBs (Graham et al., 2014). They revealed that a high-dose of olmesartan for 6 months or more was associated with increased risk of CV mortality in diabetics (HR 2.03, 95% CI 1.09-3.75, p = 0.02) and a reduced risk in non-diabetics (HR 0.46, 95%CI 0.24-0.86, p = 0.01). In 2016, an individual-patient level meta-analysis was conducted by the manufacturer of Benicar, Daiichi-Sankyo, that provided data from 46 trials showed that, once the ROADMAP and ORIENT trials were excluded, no differences were found in the mortality risk of olmesartan and the active control group (Wang et al., 2016). Therefore, the last

US FDA review indicates that the benefits of olmesartan outweigh the potential risks (FDA, 2017a).

Our reported results have been confirmed by trials that directly compare ARB with ACEIs showing an equivalent effect between them on the risk of mortality. Of note, the heterogeneity test supports a statistical consistently among trials (I²=0%). A comparable result was demonstrated in a recent network meta-analysis assessing the superiority of ACEIs to ARBs on reducing risk of CV morbidity and mortality in high-risk patients without HF (Ricci et al., 2016). Likewise, Thomopoulos et al. (2015a) provided a comparison between ACEIs and ARBs that obtained similar results to the results of this study. However, it must be noted that 96.6% of the participants included were from the ONTARGET study; thus, their findings reflected the results of the ONTARGET trial. In contrast, our analysis includes new head-to-head trial data that have been never incorporated in other reviews, namely the LIRICO (2018) trial. Nevertheless, the results of this study should not be overestimated as an equivalent effect may be a result of aggressive use of therapy in trials, such as higher rates of concomitant use of B-blockers and statins (Yusuf et al., 2008d). Moreover, the use of relatively low doses of ARBs may lead to suboptimal therapeutic effects (Pitt et al., 2000, Dickstein et al., 2002).

The mortality reductions by ACEIs and ARBs have been previously confirmed; it is still unclear, however, if mortality reduction is dependent on or independent of BP reduction. A meta-regression analysis by van Vark et al. (2012) based on the data of 20 trials revealed a significant association between trial-specific mean difference in SBP (mmHg) and relative mortality reduction by RAAS blockers (p=0.008). However, their analysis was focused on finding out whether RAAS blockers as a class have a beneficial effect on mortality. Thus, to the best of our knowledge, our meta-regression is the largest analysis that has yet been done.

7.13.1Strengths and limitations

The major strength of this analysis is the inclusion of a large number of data and trials carried out to date (ATTEMPT-CVD, CHIEF, LIRICO and PREVER-treatment) as well as unpublished data (IRMA-2 and Val-HeFT) making it a more comprehensive and precise analysis of mortality estimates so far. Moreover, the

absence of statistical heterogeneity supports the strength of pooling data across various trials. To the best of our knowledge, the current meta-regression is the largest that has yet been done.

Our review must be interpreted within the context of its limitations. Firstly, this review is based on trial-level data rather than individual-patient data. Therefore, the adjustment of potential clinical variation, such as concomitant drugs or conditions, among trials is difficult. However, the statistical heterogeneity (I^2) is on an appropriate level. Although unique pharmacological properties within a class of ACEIs or ARBs may exist, the validity of this concept is missed due to lack of statistical power. Thirdly, some trials exert a remarkable influence on primary pooled treatment effect such as in the case of ACEIs being compared with active controls which are greatly dominated by the ALLHAT study. Fourthly, the majority of trials only report an aggregate data of mortality; thus, the mortality-specific cause and time-to-event analyses are limited. Despite the comprehensive literature non-restricted search, there is the possibility that some RCTs that were not published in English were missed, which would lead to selection bias. However, the large number of trials included minimises this selection bias and increases internal validity. An empirical study demonstrated that excluding non-English trials has generally little impact on treatment effect estimates (Jüni et al., 2002, Moher et al., 2000). Finally, although the variables data are on a trial level, the number of studies (>10) is sufficient to allow a meta-regression of aggregate data of statistical value (Schmid et al., 2004).

7.13.2 Conclusion

Across a broad range of clinical conditions, ACEIs appear to be effective in reducing mortality; the evidence for ARBs appears less secure. However, the evidence from head-to-head trials suggests that ARBs are as effective as ACEIs in reducing the risk of mortality. Thus, ARBs appear to be a possible option for high-risk patients who are intolerant to ACEI therapy. The effect of ACEIs is associated with and may be due to a reduction in SBP

8 General discussion and implications

The current chapter summarizes the main findings of this study in comparison with other studies; also detailing its strengths and limitations and clinical and research implications.

This comprehensive review was performed to:

1) Investigate the comparative effectiveness of ACEIs and ARBs on preventing CV morbidity and mortality (including MI, angina pectoris, stroke, HF, CV and all-cause mortality) in patients with or at high-risk of CVDs by employing a meta-analysis; and

2) Assess the relative contribution of BP-dependent and independent mechanisms on reducing the risk of CV morbidity and mortality achieved by ACEIs and ARBs, and explore the potential sources of heterogeneity in trials.

8.1 Summary of the main results

Table 8.1 summarizes the main findings of the meta-analysis and meta-regressionstudies.

8.1.1 Comparative effectiveness of ACEI and ARB therapies on CV outcomes.

In total, 97 trials were evaluated to explore the effect of ACEIs and ARBs on CV outcomes (MI, angina pectoris, stroke, HF, CV and all-cause mortality). The total number of participants with or at high-risk of CVDs was 317,984, and studies were conducted over an average period of 3.03 years. The summary of the risk of bias assessment for each trial was performed based on the subjective or objective nature of outcome. Overall, 45% of the trials reported data concerning vascular events, and 55 % reported all-mortality data as having a low risk of bias. While the remainder were evaluated as high-risk trials. For additional details, see **Chapter 3, Section 3.3.6**.

This review integrates more data than previous analyses have done, and the evidence collated suggested that ACEIs, compared with a control group, reduce

the risk of MI by 16%, CV and all-mortality by 9% and 5% respectively. Notably, these effects proved consistent across a broad spectrum of patients; however, predefined subgroup analyses of diabetic participants with or without nephropathy and CVA were hampered by low availability of data with which to assess the specific subgroups. In contrast, this review was unable to demonstrate a comparable overall benefit from ARB-based therapy on risk of MI, CV and all-mortality. These obvious differences between the two classes might be a result of chance, confounders or even genuine differences. However, the absence of ARB benefits is unlikely to be explained by chance alone, due to the summary point estimate being close to unity 1.00 and the limit of 95% CLs being narrow. Moreover, the effect estimates are or nearly homogenous (I² ranged from 0% to 26%). The evidence from the direct comparison trials confirms there is no difference between ACEIs and ARBs on any of the relevant outcomes.

Both ACEI and ARB therapies had no impact on angina pectoris risk reduction when compared with placebo group. Nevertheless, the considerable heterogeneity observed across the effect estimates for ACEI and ARB limit the possibility of reaching definitive conclusions, I²: 58% and 61% respectively. This is most likely due to the subjective nature of angina events, which might affect the endpoint assessment.

The analyses revealed that both ACEI and ARBs provide benefits in terms of preventing stroke when compared with placebo; 14% and 9% respectively. This reduction is consistent across the diverse patient population. However, the wide 95% CI limit of effect estimates for non-diabetic nephropathy and CVA reflects relatively poor precision, which is likely attributable to the small sample size. When compared to each other using direct comparison trials, there was a lesser 4% stroke lowering by ARB therapy over ACEI (RR, 0.96; 95% CI 0.87-1.06; p=0.42), although this did not achieve statistical significance. Notably, the majority of the pooled data (54%) was derived from a single large study ONTARGET. When the participant data were split according to age, ARB therapy, not ACEI, appeared to reduce the risk of stroke in patients aged \geq 65 years.

Similarly, this overview suggests ARBs are as effective as ACEIs at preventing HF, when compared with a placebo. This comparable finding was confirmed in direct

comparison trials. Contrasted with the active group, ARB but not ACEI therapy reduced the risk of HF by 13%. Although a cardioprotective effect from individual ARBs have been assumed previously (Tsoi et al., 2018), in this review comparisons between them were too underpowered to provide a meaningful subgroup analysis. For all outcomes, a series of sensitivity analyses confirmed the robustness of the results.

8.1.2 Relationships between outcome risk reduction and the achieved BP reduction

To the best of our knowledge, this is the most comprehensive meta-regression analysis conducted to date to investigate the relative contribution of BP reduction achieved by ACEI and ARB on the risk of CV morbidity and mortality. For both ACEI and ARB, the risk ratio of stroke reduction was related significantly to the size of the BP reduction; p=0.029 and 0.02; respectively. Adjusting the meta-regression model to account for variables that explaining the large amount of variability did alter the association between mean SBP and stroke. Notably, the differences in SBP contribute to the amount of variance explained for stroke brought about by ACEI (67%) and ARB (100%). Sensitivity analyses provide evidence that the observed association with BP reduction is not dependent on trials with a particular comparator, thus it supports the main findings.

For HF, the size of the BP reduction achieved by ACEI therapy is the major determinant in the size of the reduction of HF risk. Whereas ARB therapy provided a reduction that is independent of the BP reduction. Employing sensitivity analyses, in which trials with CCB comparators and symptomatic HF were excluded, did not alter the results.

The meta-regression analysis shows ACEI provides a reduction in relative risk of MI independently of lowering-BP at approximately 9% (95% CI 2-8%, p=0.02). While no similar effect was observed for ARB-based therapy. Moreover, the magnitude of risk reduction for CV and all-mortality by ACEIs appears to be largely attributable to BP reduction. Consistent findings following a series of sensitivity analyses would support the strength of association.

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Table 8-1 Summary of answers to research questions

Myocardial Infarction (Chapter 4)	 Q1: Do the ACEI and ARB have similar effectiveness at preventing MI in patients at risk of CV events compared with the control group? No. Pooled data from 30 RCTs (n=109,843) shows that ACEI had a 16% lower risk of MI (RR, 0.84; 95% CI 0.79-0.90; I²:0%). While data analyzed from 39 ARB trials (n=146,593) demonstrates clearly that there are no apparent benefits of ARBs on MI risk with an RR of 0.97 (95% CI 0.89-1.06; I²:30%) Q2: From direct comparison trials, do ARBs provide a protective effect equivalent to ACEI-based regimen on risk of MI? Yes. Pooled data from 8 RCTs with (n=40,815) and observed 2899 events revealed that ARB therapy had a similar effect on MI risk of RR =1.02 (95% CI 0.95-1.09; I²=0%) Q3: Does BP reduction alone explain the preventive effect of ACEI and ARB therapies? The meta-regression analysis shows that the ACEI provide a reduction in the relative risk of MI, independently of lowering-BP of approximately 9% (95 CI 2-8%, p=0.02). While no similar effect was observed for ARB-based therapy.
Angina Pectoris (Chapter 4)	 Q1: Do ACEI and ARB have similar effectiveness at preventing angina pectoris in patients at risk for CV events compared with control group? Combined estimates of 20 ACEI studies (n=102,112) reporting 8902 events reveal no significant decreases in risk of angina. Similarly, there was no apparent benefit of ARB on risk of angina (RR, 0.97; 95% 0.90- 1.05; 12: 61%). Q2: From direct comparison trials, do ARBs provide a protective effect equivalent to ACEI-based regimen on risk of angina? Yes. A pooled effect estimate shows a similar angina risk between ARBs and ACEIs with an RR of 1.00 (95% CI 0.92-1.08; l²: 22%).
Stroke (Chapter 5)	 Q1: Do ACEI and ARB have a similar effectiveness at preventing stroke in patients at risk of CV events compared with the control group? Yes. Pooled effect estimates of total of 29 RCTs (n= 116,197) exhibit that ACEI therapy was significantly associated with a 14% reduction in stroke compared with placebo (RR, 0.86; 0.76-0.98; l²: 26%). While there was a higher risk of stroke compared with the active group. Similarly, based on data from 38 RCTs (n=142,122), ARB therapy had an 8% lower risk of stroke compared with the placebo (95% CI 3-14%; l²: 0%). While there was no benefit compared with the active group (l²:58%). Q2: From direct comparison trials, do ARBs provide a protective effect equivalent to an ACEI-based regimen on risk of stroke? Pooled data from eight RCTs (n=40,815) with 1437 stroke events reveals that there was a lesser 4% stroke lowering by ARB therapy over ACEI (RR 0.96; 95% CI 0.87-1.06; l²:0%). Q3: Does BP reduction alone explain the preventive effect of the ACEI and ARB? Yes, the multivariate analysis shows that magnitude of relative risk reduction for stroke was proportional to the size of the BP reduction achieved by ACEIs and ARBs; p=0.036 and 0.001, respectively.

Heart Failure (Chapter 6)	 Q1: Do the ACEI and ARB have similar effectiveness at preventing of HF in patients at risk for CV events compared with a control group? Yes. A meta-analysis of data from 29 RCTs (n=119,211) shows that ACEIs therapy reduced the risk of HF by 17% (RR, 0.83; 95% CI, 0.76-0.92, 1²: 43%). For ARBs, data from 36 RCTs (n=140,542) enrolled resulted in a statistically significant 14% reduction in HF (95% CI 9-19%; 1²: 26%). Q2: From direct comparison trials, do ARBs provide a protective effect equivalent to an ACEI-based regimen on risk of HF? Yes. Based on data from 36,276 participants, ARB therapy appears to provide a similar effect to ACEI therapy on risk of HF with an RR of 1.03 (95% CI 0.97-1.09; 1²: 0%). Q3: Does BP reduction alone explain the preventive effect of the ACEI and ARB? Based on the meta-regression analysis, the relative risk reduction for HF by ACEIs is associated with the size of the BP reduction (p=0.03). Whereas the reduction by ARB appears to be independent of BP reduction, which might be due to pleiotropic effects (p=0.003).
CV mortality (Chapter 7)	 Q1: Do ACEI and ARB have similar effectiveness at preventing CV mortality in patients at risk of CV events compared with a control group? No. Across a high-risk group of 123,899 participants from 36 trials, treatment by ACEI reduced the risk of CV mortality by 9% compared with a control group (95% CI 3-14%; I²:6%). Based on evidence from 34 RCTs, there were no apparent benefits from ARBs in terms of reducing CV death compared to control group (RR, 0.99; 95% CI 0.94-1.05; I²: 26%). Q2: From direct comparison trials, do ARBs provide a protective effect equivalent to an ACEI-based regimen on risk of CV mortality? Yes. Data from eight trials revealed that ARB therapy might provide a protective effect against CV death similar to ACEI (RR, 1.04; 95% CI 0.98-1.10; I²:0%). Q3: Does BP reduction alone explain the preventive effect of ACEI and ARB? The effect of ACEIs is associated with, and may be due, to a reduction in SBP (p=0.002). While this did not appear to be the case for ARBs
All-cause mortality (Chapter 7)	 Q1: Do the ACEI and ARB have similar effectiveness at preventing of all-cause mortality in patients at risk for CV events compared with control group? No. Combined data from 41 RCTs (n=125,824), reported 11,646 events, showing that ACEIs had a 5% lower on risk of all-cause mortality (RR,0.95; 95% CI 0.91-0.98; l²:0%). While 43 RCTs (n=151,721) reporting on 13,945 events shows no noticeable benefit from ARB therapy (RR, 0.99; 95% CI 0.96-1.02; l²: 0%). Q2: From direct comparison trials, do ARBs provide a protective effect equivalent to an ACEI-based regimen on risk of all-mortality? Yes. Evidence from ten trials comparing ARB with ACEI 41,106 participants enrolled (5474 events) found equivalent results between ARB and ACEI in terms of risk of all-mortality (RR, 1.03; 95% CI 0.98-1.08; l²: 0%). Q3: Does BP reduction alone explain the preventive effect of ACEIs and ARBs? For ACEI therapy, the magnitude of mortality risk reduction was positively associated with a reduction in BP (p=0.0004). Conversely, no apparent benefit was observed for ARB therapy.

8.2 Study strengths

The specific strengths of this review are described in each individual results chapter. To the best of this author's knowledge, this is the largest, most comprehensive meta-analysis and meta-regression study with the potential contribute important insights into the effectiveness of ACEI and ARB therapy in individuals belonging to a wide range of conditions as characterized by high CV risk. Generally, the main strength of the current review is that data from RCTs are viewed as the gold-standard in study design. Moreover, in addition to applying an extensive search strategy using bibliographic databases, other nonbibliographic database sources were applied, including pharmaceutical industry trials registers, ClinicalTrials.gov register, World Health Organization International Clinical Trials Registry Platform (ICTR-P) and Drugs@FDA. Implementing these search strategies allowed me to incorporate additional articles and unpublished data. Another strength of the current review is that rigorous methodological quality assessments were applied based on the subjective or objective nature of the outcomes. Moreover, no language restriction was applied. It also incorporates unpublished data and additional trials that have been never included in similar reviews previously; thus, the current review provides much more reliable results than previous analyses. Unlike previous studies, we excluded no trials due to baseline co-morbidities, thereby allowing for a greater generalizability of findings, and thus potentially increasing the external validity and delivering a more precise effect estimate (Bangalore et al., 2016, Savarese et al., 2013). Meanwhile, stratified analyses of patients' characteristics were performed to check whether the effect estimates are externally and internally valid or not. The multivariable meta-regression analysis is the first, largest and most comprehensive to date, addressing the research question by taking into account potential confounders that explaining more of between-study variance.

8.3 Study limitations

Specifically, the limitations identified were described and discussed in each chapter. In general, the chief main potential limitation of the current meta-analyses and meta-regression analyses are that the study was carried out with aggregate data, so a risk of the ecological bias is suspected. This bias arises when the average of the patient's characteristics fail to properly reflect the true effect

from individual-level properties. Although the doses of ACEI and ARB might have impacted on the study outcomes, meta-regression or subgroup analyses would be limited, as the average doses across trials would be approximately similar, and thus there would be minimal potential to discriminate between trials. Therefore, pooling individual-patient data could serve to eliminate these limitations. Applying an ITT analysis to overcome attrition bias might result in a tendency to underestimate the treatment effect. However, a sensitivity analysis was performed excluding high-risk trials. A potential limitation of this review is the possibility of clinical heterogeneity among the enrolled participants with hypertension, diabetes, CVDs, or other conditions. Even though the impact of subgroup populations on pooled effect size were investigated, there was a lack of power with some subgroups that might limit the conclusions elicited. Generally, there was homogeneity in the majority of the effect estimates, as expressed by an I² value of 0%, and only a few outcomes were associated with I² >50%, which supported the validity of the findings.

Since some of the included trials allowed concomitant use of non-study ACEIs or ARBs, statins and antihypertensives during follow-up, the results may have been confounded, leading to a type II error. Therefore, the potential impact could not be ignored due of the lack of individual data. Nevertheless, a sensitivity analysis was conducted by omitting those trials. Moreover, certain assumptions were proposed, suggesting that individual compounds belonging to a specific class might each have unique cardioprotective effects, due to their distinguishing pharmacological features. However, subgroup analyses testing this assumption lacked adequate statistical power. Moreover, in a number of RCTs, it is unclear whether the events were adjudicated or not by. Another possible limitation is that the definition of events and their validation might be inconsistent across the different trials. For instance, all subtypes of stroke were grouped together. Stroke is a heterogeneous condition, and stroke subtypes may have different associations with BP reduction. Nevertheless, a majority of RCTs considered in this metaanalysis followed a double-blind design, which guarantees some homogeneity between-treatment comparisons. Since meta-regression is based on trial-level variables, the meta-regression might be confounded by the characteristics of each trial. Although each trial is randomized, the association across trials in a metaregression arises from an observational not a causal relationship. Therefore,

findings should be interpreted with caution and further confirmation is required. Small values for adjusted R_2 and presence of residual heterogeneity (Tau²) in multivariate regression suggest the possibility of other undefined study-level variables that may not be available, e.g., background of antihypertensive agents and dosage of interventions.

8.4 Comparison of other reviews

8.4.1 Meta-analysis

The appraisal of available evidence in the current review has shown several studies concluded consistent findings, despite methodological diversity. The majority of them assessed both or one of the classes, and their inclusion criteria were based on certain clinical conditions. For example, a more recent meta-analyses by Savarese et al. (2013) and Bangalore et al. (2016) compared the effects of ACEI and ARB, including trials of high-risk participants without overt HF. Likewise, meta-analyses assessed ACEIs and ARBs in patients with stable, DM, hypertension (Cheng et al., 2014, Thomopoulos et al., 2015b, Bangalore et al., 2017). To the best of our knowledge, no previous meta-analysis has focused on evaluating the comparative effectiveness of ACEI and ARB on risk of CV morbidity and mortality in various groups of patients.

Indeed, the methodology design herein is comparable to a previous study by Bangalore et al. (2011) including a group of high-risk patients . However, they mainly focused on the efficacy of ARB therapy compared with placebo or active control. Pubmed, Embase, and CENTRAL were searched for RCTs, to August 2010, which yielded 37 RCTs enrolled 147,020 participants. While our review incorporated 15 additional trials. Firstly, by updating the data set to include trials after 2010 (ANTIPAF, CHIEF, CARP, COPE, CORD 1 B, LIRICO, SUPPORT, OLIVUS, 4C, ACTIVE-I, Kawamura; PREVER-TREATMENT, ATTEMPT-CVD, ORIENT, ROADMAP and Weil et al. trials). Secondly, by using unpublished data from trials prior to 2010 such as MI and angina pectoris data of Val-HEFT trial. Even though their findings were consistent with our review, they demonstrated a significant 9% stroke reduction with the ARB-based regimen compared with active therapy. This might be as a result of pooled data in the JIKEI Heart and KYOTO Heart studies that reported fewer stroke cases with valsartan compared with the non-ARB group of an RR 0.58 (95% CI 0.36-0.95) and 0.45 (95% CI 0.26-0.77); respectively. However, these trials were excluded from our study as they were retracted for reasons described in **Chapter 3, Section 3.2.1**. Although the heterogeneity degree across the effect estimates of HF for ARB-trials was significant (I²=58.4%, p<0.001), no further investigation has been performed. This statistical heterogeneity might be a consequence of included trials directly comparing ARBs with ACEIs (ONTARGET, OPTIMAAL, VALIANT and ROAD trials). Therefore, the current analysis affords a more comprehensive review, and more reliable evidence concerning the influence of ARB therapy on morbidity and mortality risk.

More recently, there was an analysis by Bangalore et al. (2016) of 106 RCTs with 254,301 high-risk participants enrolled. Contrasting with the current review, these authors excluded trials with HF. In our analysis, nevertheless, the sensitivity analyses were performed excluding the trials with HF showing the measured treatment effects did not differ. Their search was up to 2015 with no language restriction and trials with a sample size of at least 100 were eligible. A comparable electronic databases search strategy was applied in the current review. Instead of PubMed, however, a search using Medline was performed, because it allows a more focused search. Additionally, I searched the Web of Science-Core of Collection (CPCI-S), ClinicalTrials.gov, WHO International Clinical Trials Registry Platform (ICTR-P) and CDER-FDA for unpublished or ongoing trials. In comparison with the Bangalore et al. (2016) review, unpublished data from trials prior to 2016 was pooled. For instance, MI and stroke data of ORIENT, ROADMAP and RENAAL trials from CDER-FDA. Also, stroke data of the DETAIL trial from Boehringer Ingelheim Pharmaceutical trials registry. Extension of the period of the search up to 2020 yielded four trials: CHIEF, PREVER-Treatment, ATTEMPT-CVD, and LIRICO trials. Despite the addition of almost 50,000 participants to our study, similar findings were observed.

In line with Bangalore et al. (2016), the methodological qualities of each and overall trials were assessed in accordance with the Cochrane risk of bias tool. For overall risk-of-bias judgement, three key domains were selected to assess the trial for CVD and death outcomes: allocation sequence generation, allocation concealment and blinding of outcome assessors. Conversely, the outcome assessment blinding domain in my study was assessed based on the subjective and objective nature of the outcomes. In accordance with the meta-epidemiological study, all-cause mortality is not affected if outcome assessors are blinded or not, while other outcomes are influenced (Wood et al., 2008).

8.4.2 Meta-regression

In this section, two meta-regression studies were identified as having a comparable method with the current analysis in regard to study design, objective, and outcomes of interest (Turnbull, 2007, Verdecchia et al., 2009). Similarly, both studies included participants with broad clinical conditions, such as HTN, diabetes, a history of CHD or cerebrovascular disease. Moreover, both investigated the association between BP reduction achieved by ACEIs or ARB and relative CV outcomes reduction through a trial-level random effects meta-regression with inverse variance weighting. Nevertheless, they did not account for any potential confounders that might explain the residual heterogeneity (residual I²). Moreover, a similar search strategy was applied utilizing electronic databases. In the current review, additional searching was performed through non-bibliographical databases included in the ClinicalTrials.gov, ICTR-P, Drugs@FDA (CDER), and pharmaceutical industry trial registers, as well as hand-searched for relevant trials. Furthermore, the search was extended to 2020. To the best of our knowledge, no previous study has examined the association between BP lowering on relative mortality reduction by ACEIs or ARBs.

In 2007, The Blood Pressure Lowering Treatment Trialists Collaboration (BPLTTC) carried-out the first meta-regression study to evaluate the impact of the BP dependent and independent effects of ACEI and ARB on the risk of CV events compared with placebo or another drug class (Turnbull, 2007). In their analysis, data from 26 large-scale trials, conducted with a total of 146,838 individuals with hypertension or at risk of CVDs was pooled. The reviewers included trials with a treatment group assigned to an ACEI or an ARB until the end-of 2004. In comparison with my analysis, additional trials were included: six trials published prior to 2004 (APRES, ALPINE, CCS-I, HYVET, IRMS-2, Hou et al., ESPRIAL) and 22 trials after 2004. In the BPLTTC analysis, the reduction in achieved SBP was plotted against the relative risk from the pre-specified endpoints of stroke, HF, and CHD. In accordance with the current analysis, they demonstrated that ACEIs and ARB offer BP-dependent effects on the risk of stroke. For ACEI, but not ARB,

there is an additional 9% relative risk reduction of MI above that expected from the BP reduction achieved. In contrast with the current review, however, an independent effect from ARBs on HF risk was not detected. Conversely, the BPLTTC study has been unable to demonstrate the contribution of BP reduction from these therapies on mortality risk. My multivariate meta-regression analysis is comprehensive to date and sought to investigate of whether the observed effects of ACEIs and ARBs on risk of mortality are related or unrelated to BP reduction, included 30 ACEI and 37 ARB trials.

Although the current results confirm and extend the BPLTTC analyses, they did not account for potential confounders that explaining most of the remaining residual heterogeneity (I² residual). Furthermore, the confidence limits around stroke, CHD and HF estimates by ARB were wider than that for ACEI; this may perhaps be a result of the small sample size included. According to their listed inclusion criteria, they did not incorporate large trials, HYVET and MOSES (Schrader et al., 2005, Bulpitt et al., 2003). Although the stroke and HF data from the AASK trial were incorporated, CHD data was not (Wright et al., 2002). Additionally, incorporating data regarding the ACTIVE-I (2011) trial in my study would support the findings; thus, it carries a considerable weight (approx. 10%) of overall HF, stroke and MI (Yusuf et al., 2011). Moreover, they included trials comparing ACEI to ARB, such as ELITE II, OPTIMAAL and VALIANT that might attenuate the real effect. For these reasons, the present analyses would be expected to provide more reliable results about the effect of BP reduction achieved with ACEI and ARBs.

A much more similar study was performed by Verdecchia et al. (2009). They performed a meta-regression to assess the BP-related and unrelated effects of ACEIs and ARBs compared with CCBs in the prevention of CHF for patients with hypertension or at high risk of CVD. The reviewers searched electronic databases until September 2008. Their study included 16 eligible trials (12 ACEI and 4 ARB trials) enrolled 225,764 participants and reported 6469 HF cases. They also restricted the inclusion criteria to only trials with a median or average follow-up of at least 2-years. Meanwhile my review adds 17 more trials. Consistent with my review, they revealed that ACEI and ARB provide an additional 19% reduction in HF, which is independent of BP reduction in patients with hypertension or at high

risk of CV. Nevertheless, they dealt with ACEIs and ARBs as a single group. In the current review, moreover; a sensitivity analysis was performed by omitting the ALLHAT trial, as it carries considerable weight along with known methodological limitations. In the Verdecchia et al. (2009) study, the HF data from the HOPE trial (146 vs. 173 events) was incorporated, showing ramipril had a non-significant 15% lower in HF compared with placebo (Yusuf et al., 2000). However, the HOPE trial investigators reported that ramipril lowers HF risk by 23% (p<0.0001) in patients at high-risk of CV events (Arnold et al., 2003). Furthermore, based on their inclusion criteria, the AASK trial data for HF was not included.

8.5 Implications for research

In the current review, a persistent gap in the evidence regarding the comparative efficacy of ACEI and ARB is highlighted. Despite the availability of data from the 317,984 participants included in this review, it is difficult to determine the true effect of ACEI and ARB on the risk of CVDs. This review pooled aggregate-data from studies that are not sufficiently similar. Estimates may be biased due to imbalances between the studies in terms of the distribution of trial or patient-level characteristics that affect the relative effectiveness of the interventions being compared. Furthermore, the majority of the large-scale trials enrolled participants with background or concomitant usage of RAS blockers, which may attenuate the true effect estimate. Therefore, it is vital to conduct a well-designed individual patient-data (IPD) study to control potential confounders and to provide vital insights to guide the design of future clinical trials.

In the current review, a number of RCTs are unclear as to whether events were adjudicated or not. Thus, there is a great need for blinded end-point adjudication (EPA) committees and consensus definitions of CV outcomes for both CV and non-CV trials. Despite EPA now being a gold standard in design of registry-based trials, the lack of a scientific adjudication strategy in small trials is warranted. Additionally, the definition of HF events varies widely across the spectrum of non-HF clinical trials. Specific definitions are not provided in many publications (even when defined in the trial protocol), and this might be contributing to the heterogeneity of pooled data and misinterpretation. Ultimately, well-designed RCTs are needed to convincingly confirm the substitutability of ARBs for ACEIs. It

is noteworthy that most of the stroke data from head-to-head comparison in this review was derived from the ONTARGET trial, as it carried 54% of pooled effect estimates. Additionally, the majority of the direct comparison trials included are industry sponsored. A meta-analysis conducted by Cochrane collaboration reviewers revealed that studies sponsored by a manufacturing company more frequently report positive results (e.g., those with significant P values) and conclusions than those sponsored by other organizations (Lundh et al., 2012). Given the criticality of large long-term direct comparison trials, comparative evidence obtained under the auspices of non-profit organizations is vital. The majority of the included clinical trials used a composite endpoint mainly to achieve adequate statistical power. FDA guidance for reporting endpoints emphasizes that results for each component event should be individually examined and always included in study reports (FDA, 2017b). Despite this, few of the trials in current review did not follow the guidance and thus this may alter the findings. For instance, despite the COPE trial being designed and powered to detect the composite endpoint in hypertensives, individual components were not reported (Matsuzaki et al., 2011). Therefore, following FDA guidance should be emphasized.

8.6 Implications for clinical practice

Overall, the results of this thesis, derived from large aggregate data from randomized trials provide reassurance that ACEI and ARBs are equivalent in terms of their efficacy, as they allay concerns that ARBs may represent a risk to patients. Moreover, evidence was provided indicating the superiority of ARBs over ACEI for stroke prevention. Therefore, the recommendation would be extending the use of ACEIs as first-line therapy to either ACEIs or ARBs. Furthermore, it supports the individualization of therapy when the risk of stroke is more prevalent than other CVD events, such as in Asian patients (GBD 2016 Stroke Collaborators, 2019) or patients with a history of a prior cerebrovascular accident (CVA) (Vickrey et al., 2002). Nevertheless, the relative effects of ACE and ARBs on certain clinical population subgroups are limited, owing principally to the lack of adequate headto-head trials. This recommendation is supported by the availability of generic formulations of ARBs and hence is a cost-effective treatment. Previously the main issue that would have impacted more widespread prescription of ARBs was cost, as these were newer agents protected by patents and as a consequence more expensive. However, the cost differentials between ACEIs and ARBs are now non-existent, as both classes are off patent and produced in widely available cheap generic formulations. In 1995, the off-patent captopril entered the market, but losartan had only just been introduced and was much more expensive (FDA, 1995). However, after April 2010, the FDA approved the first generic ARB, losartan, for the management of hypertension and CVDs (FDA, 2010a). Therefore, the availability of generic formulations of ARBs is now making it a cost-effective treatment, and there is a wide selection available for starting or switching therapy. Additionally, this choice is supported by the evidence that ARBs are better tolerated (Bangalore et al., 2016).

8.7 Conclusion

In summary, this study used data from 317,984 participants with or at high-risk of CVDs suggesting that ARBs are as effective as ACEIs at mitigating the risk of CV events and mortality. The findings also support the view that ARBs may be slightly more protective than ACEIs against the risk of stroke. This reduction in stroke risk by ACEI and ARB is largely attributable to BP reduction. The magnitude of risk reduction for HF, CV and all-mortality by ACEIs is largely attributable to BP reduction of ACEI on MI risk and ARB on heart failure risk warrants further study.

Appendices

Appendix A: Electronic database search strategies

MP indicates multi-purpose search terms in the title, original title, abstract, subject heading, the name of substance and registry word fields; "tw" indicates that the term is a text word meaning and title and abstract; "Pt." Indicates publication types, such as reviews, clinical trials, directories, and letters; "ab" indicates all searchable words from the abstract; "/" indicates that it is a Medical Subject Heading (MeSH) term; "\$" indicates all possible suffix variations of the root words; "?" indicates the retrieval of documents with British or American word variants; "adj" plus a number between any two terms returns records that contain both terms, within the specified number of words from each other.

	NE search strategy ase: Ovid MEDLINE(R)
DalaDa	Keywords searches
1	angiotensin receptor antagonists.mp
2	(angiotensin adj2 (receptor antagon\$ or receptor block\$)).tw.
3	arb?.tw.
4	(eprosartan or Azilsartan or candesartan or irbesartan or losartan or fimasartan or
	olmesartan or telmisartan or valsartan).tw.
5	1 or 2 or 3 or 4
6	angiotensin enzyme inhibitors.mp
7	angiotensin converting enzyme inhibit\$.tw
8	(ace adj2 inhibit\$).tw.
9	acei.tw.
10	(captopril or enalapril or benazepril or zofenopril or quinapril or perindopril or ramipril or trandolapril or fosinopril or moexipril or Lisinopril).tw
11	6 or 7 or 8 or 9 or 10
12	randomized controlled trial.pt
13	Controlled clinical trial.pt.
14	randomized.ab.
15	placebo.tw.
16	drug therapy.tw.
17	randomly.ab.
18	trial.ab
19	12 or 13 or 14 or 15 or 16 or 17 or 18
20	animals/ not (humans/ and animals/)
21	19 not 20
22	5 or 11
23	21 and 22
24	Limit 23 to " all adult (19 plus years)"

ENTRAL search strategy
atabase: Cochrane Central Register of Controlled Trials
Keywords searches

Mesh descriptor: [Angiotensin Receptor Antagonist] explode all trees
(angiotensin near/3 receptor next block*):ti,ab,kw
(angiotensib near/3 receptor next antagonist*):ti,ab,kw
(eprosartan or azilsartan or candesartan or irbesartan or losartan or olmesartn or telmisartan or valsartan):ti,ab,kw
#1 or #2 or #3 or #4
MeSH descriptor: [Angiotensin-converting Enzyme Inhibitors]:ti,ab,kw
(angiotensin next converting next enzyme next inhibitor*):ti,ab,kw
ace near/2 inhibit*:ti,ab,kw
(captopril or enalapril or benazepril or zofenopril or quinapril or perindopril or
ramipril or trandolapril or fosinopril or moexipril or Lisinopril):ti,ab,kw
#6 or #7 or #8 or #9
#5 or #10 publication year to 2018 (word variations have been searched)

	e search strategy
Databa	se: Embase
	Keywords searches
1	angiotensin receptor antagonists.mp
2	(angiotensin adj2 (receptor antagon\$ or receptor block\$)).tw.
3	arb?.tw.
4	(eprosartan or Azilsartan or candesartan or irbesartan or losartan or fimasartan or
-	olmesartan or telmisartan or valsartan).tw. 1 or 2 or 3 or 4
5	
6	angiotensin enzyme inhibitors.mp
7	angiotensin converting enzyme inhibit\$.tw
8	(ace adj2 inhibit\$).tw.
9	acei.tw.
10	(captopril or enalapril or benazepril or zofenopril or quinapril or perindopril or ramipril or trandolapril or fosinopril or moexipril or Lisinopril).tw
11	6 or 7 or 8 or 9 or 10
12	randomized controlled trial/
13	crossover procedure/
14	double-blind procedure/
15	(randomi\$ or randomly).tw.
16	(crossover\$ or cross-over\$).tw.
17	placebo\$.tw.
18	(doubl\$ adj blind\$).tw.
19	assign\$. <mark>ab.</mark>
20	allocat <mark>\$.a</mark> b.
21	trial.ti.
22	12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21
23	(animal\$ not (human\$ and animal\$)).mp.
24	22 not 23
25	5 or 11
26	24 and 25
27	Limit 26 to (adult <18 to 64 years > or aged < 65+ years>)

	Keywords searches
#1	TS="angiotensin receptor antagonist"
#2	TS= (angiotensin adj2 (receptor antagon\$ or receptor block\$))
#3	TS=angiotensin converting enzyme inhibit\$
#4	TS=(eprosartan or Azilsartan or eprosartan or irbesartan or losartan or fimasartan or
	olmesartan or telmisartan or valsartan)
#5	TS=(captopril or enalapril or benzaepril or zofenopril or quinapril or perindopril or
	ramipril or captopril or benazepril or trandolapril or fosinopril or moexipril or
	Lisinopril)
#6	TS=arb?
#7	TS=(ace adj2 inhibit\$)
#8	TS=acis
#9	TS=angiotensin receptors block\$
#10	#9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1
#11	TI= randomized controlled trial
#12	TI=crossover procedure
#13	TI=controlled clinical trial
#14	TI=double blind
#15	TI=randomized
#16	TI=(randomi\$ or randomly)
#17	TI=placebo
#18	TI=trial
#19	TI=(doubl\$ adj blind\$)
#20	TI=(meta?analys\$ or systematic review\$)
#21	TI=(meta analy* or metanaly* or metaanaly*)
#22	#21 OR #20 OR #19 OR #18 OR #17 OR #16 OR #15 OR #14 OR #13 OR #12 OR #11
#23	#22 AND #10
	DocType=All document types; Language=All languages;

Appendix B: Characteristics of the included studies (ordered by study ID)

For acronyms (see 'list of definitions/abbreviations)

4 C (Sakamoto et al., 2016)
Design: Prospective, randomized, open-label, blinded-endpoint trial (PROBE)
Mean duration of follow-up: 3 years
Participants: 1119
Clinical setting: Patients with CAD undergoing percutaneous coronary intervention (PCI) with drug-eluting stents
(DESs) within 48 hours
Mean baseline BP: 136/75 mmHg
Age range: 20 or more (mean age: 69 years)
Hypertensive patients (%): 75.5
Baseline co-morbidities (%): DM (34.5)
Intervention: Two groups
ARB: Candesartan 4-12 mg/day vs. control
Co-intervention: If the BP still high, other BP-lowering agents was added (except ACEI)
Concomitant non-study RAS blockers:
Primary and secondary outcomes: Total mortality, composite & individual of major CV events
Funding Source: Japan Heart Foundation
AARDVARK (2016) (Kiru et al., 2016)
Design: Prospective, single-centre, randomized, open-label trial
Mean duration of follow-up: 2 years
Participants (n): 224
Clinical setting: Abdominal aortic aneurysm (AAA)
Mean baseline BP: 131/77 mmHg
Mean age: 70.7 years
Hypertensive patients (%): 100
Baseline co-morbidities (%): None
Intervention: Three groups
ACEI: Perindopril (10 mg/day) vs. amlodipine (5 mg/day) vs. placebo
Co-intervention: NR
Concomitant non-study RAS blockers: None
Primary and secondary outcomes: Growth rate of abdominal aortic aneurysm (AAA) & Tolerance of study medication
(measured by compliance, adverse events, and quality of life)
Funding Source: Imperial College London
AASK (2002) (Wright et al., 2002, Norris et al., 2006)
Design: Prospective, multicentre, randomized, single-blinded trial with a 3-by-2 factorial design
Mean duration of follow-up: 3.8 years
Participants: 1094
Clinical setting: African Americans with hypertension & GFR between 20-65 ml/min/1.73 m ²
Mean baseline BP: 151/96 mmHg
Age range: 18-70 years (mean age: 54.4 years)
Hypertensive patients (%): 100
Baseline co-morbidities (%): CKD
Intervention:
ACEI: Ramipril 2.5-10 mg/day vs. amlodipine 5-10 mg/day vs. metoprolol 50-200 mg/day
Co-intervention: If BP goal was not achieved, other BP-lowering agents were added sequentially.
Concomitant non-study RAS blockers: NR
Primary and secondary outcomes: Rate of change in GFR, total death & CV events.
Funding Source: National institute of Diabetes & Digestive & Kidney Diseases
ABCD, normotensive (2002) (Schrier et al., 2002)
Design: Prospective, multicentre, randomized, double-blinded, parallel trial
Mean duration of follow-up: 5.3 years
Participants: 480
Clinical setting: Normotensive with T2DM
Mean baseline BP: 136/84.5 mmHg
Age range: 40-older (mean age: 59 years)
Hypertensive patients (%): 0
Baseline co-morbidities (%): None
Baseline co-morbidities (%): None
Baseline co-morbidities (%): None Intervention: Two groups
Baseline co-morbidities (%): None Intervention: Two groups ACEI: Enalapril 5-40 mg/day vs. nisoldipine 10-60 mg/day
Baseline co-morbidities (%): None Intervention: Two groups ACEI: Enalapril 5-40 mg/day vs. nisoldipine 10-60 mg/day Co-intervention: To achieve BP goal, open-labelled antihypertensive agents were added as stepwise fashion
Baseline co-morbidities (%): None Intervention: Two groups ACEI: Enalapril 5-40 mg/day vs. nisoldipine 10-60 mg/day Co-intervention: To achieve BP goal, open-labelled antihypertensive agents were added as stepwise fashion Concomitant non-study RAS blockers: None
Baseline co-morbidities (%): None Intervention: Two groups ACEI: Enalapril 5-40 mg/day vs. nisoldipine 10-60 mg/day Co-intervention: To achieve BP goal, open-labelled antihypertensive agents were added as stepwise fashion Concomitant non-study RAS blockers: None Primary and secondary outcomes: Change in 24hr creatinine clearance, CV events retinopathy, neuropathy & urinary albumin secretion
Baseline co-morbidities (%): None Intervention: Two groups ACEI: Enalapril 5-40 mg/day vs. nisoldipine 10-60 mg/day Co-intervention: To achieve BP goal, open-labelled antihypertensive agents were added as stepwise fashion Concomitant non-study RAS blockers: None Primary and secondary outcomes: Change in 24hr creatinine clearance, CV events retinopathy, neuropathy & urinary
Baseline co-morbidities (%): None Intervention: Two groups ACEI: Enalapril 5-40 mg/day vs. nisoldipine 10-60 mg/day Co-intervention: To achieve BP goal, open-labelled antihypertensive agents were added as stepwise fashion Concomitant non-study RAS blockers: None Primary and secondary outcomes: Change in 24hr creatinine clearance, CV events retinopathy, neuropathy & urinary albumin secretion Funding Source: Bayer Pharmaceutical Company and the National Institute of Diabetes, Digestive, and Kidney Diseases
Baseline co-morbidities (%): None Intervention: Two groups ACEI: Enalapril 5-40 mg/day vs. nisoldipine 10-60 mg/day Co-intervention: To achieve BP goal, open-labelled antihypertensive agents were added as stepwise fashion Concomitant non-study RAS blockers: None Primary and secondary outcomes: Change in 24hr creatinine clearance, CV events retinopathy, neuropathy & urinary albumin secretion Funding Source: Bayer Pharmaceutical Company and the National Institute of Diabetes, Digestive, and Kidney

Mean duration of follow-up: 4.1 years
Participants (N): 9016 participants
Clinical setting: A history of risk factor for stroke and permanent atrial fibrillation (AF) or had at least two episode
intermittent AF in last 6 months
Mean baseline BP: 138.3/82.5 mmHg
Age range: 75-older (mean: 69.6 yrs.)
Hypertensive patients (%): 88
Baseline co-morbidities (%): HF (32.2), DM (20)
Intervention: 2 groups
ARB: Irbesartan 300mg/day vs Placebo
Co-intervention: ACTIVE W: clopidogrel plus aspirin vs anticoagulants; ACTIVE A: clopidogrel vs placebo
Concomitant non-study RAS blockers: Intervention: 60% ACEI & 5% ARB. Control: 61% ACEI & 4.7% ARB
Primary outcomes: Composite of (stroke, MI or CV death) & (stroke, MI, CV death or hosp. HF)
Secondary outcomes: total mortality, stroke, hospitalized HF
Funding Source: Bristol-Myers Squibb and Sanofi-Aventis
ADVANCE (2007) (Patel et al., 2007, Servier Laboratories, 2009)
Design: Prospective, multicentre, randomized, double-blinded trial with a 2-by-2 factorial design.
Mean duration of follow-up: 4.3 years
Participants (n): 11,140
Clinical setting: T2DM with at least one history of CV disease or CV risk factor
Mean baseline BP: 145/81 mmHg
Age range: 55 years or older (mean age: 55 years)
Hypertensive patients (%): 69
Baseline co-morbidities (%): CVD (32%)
Intervention: Four groups
ACEI: Perindopril 2-4 mg/day plus indapamide 0.625-1.25 mg/day vs. placebo AND intensive
Co-intervention: The use of BP-lowering agents was allowed
Concomitant non-study RAS blockers: Intervention: 5% ACEI & 10% ARB. Control: 5% ACEI & 13% ARB
Primary and secondary outcomes: Composites & individual of major macrovascular (CV death, nonfatal MI, nonfat
stroke) & microvascular events (new or worsening nephropathy)
Funding Source: Servier and the National Health and Medical Research Council of Australia
ALLHAT (2002) (Curt D. Furberg et al., 2002, Yamal et al., 2014)
Design: Prospective, randomized, double-blinded, parallel trial
Mean duration of follow-up: 4.9 years
Participants (n): 33 357
Clinical setting: Hypertensive patients with at least one risk factor for coronary heart disease events.
Mean baseline BP: 146/84 mmHg
Age range: 55-older (mean: 67 years)
Hypertensive patients (%): 100
Baseline co-morbidities (%): CAD (51), DM (36)
Intervention: 3 treatment groups
ACEI: Lisinopril 10-40 mg/day vs CCB: amlodipine 2.5-10 mg/day vs TZ: chlorthalidone 25 mg/day
Co-intervention: if BP goal was not achieved, other BP-lowering agents were added consecutively (atenolol,
reserpine, clonidine, or hydralazine)
Addition of non-study drugs was allowed in low doses
Concomitant non-study RAS blockers: NR
Primary outcomes: Fatal CHD or non-fatal MI combined
Secondary outcomes: All-cause mortality, stroke, combined CHD, and combined CVD
Funding Source: Pfizer
ALPINE (2003) (Lindholm et al., 2003)
Design: Prospective, randomized, double-blinded, parallel trial
Mean duration of follow-up: 1 year
Participants (n): 392
Clinical setting: Newly diagnosed HTN
Mean baseline BP: 155/968 mmHg
Age range: Not reported (mean: 55 yrs)
Hypertensive patients (%): 100
Baseline co-morbidities (%): None
Baseline co-morbidities (%): None Intervention: Two groups
Baseline co-morbidities (%): None Intervention: Two groups ARB: Candesartan cilexetil 16mg/day vs HTCZ 25mg/day
Baseline co-morbidities (%): None Intervention: Two groups ARB: Candesartan cilexetil 16mg/day vs HTCZ 25mg/day Co-intervention: if BP goal was not achieved, other BP-lowering agents were added consecutively (felodipine was
Baseline co-morbidities (%): None Intervention: Two groups ARB: Candesartan cilexetil 16mg/day vs HTCZ 25mg/day Co-intervention: if BP goal was not achieved, other BP-lowering agents were added consecutively (felodipine was added to the candesartan group and Atenolol was added to the hydrochlorothiazide group). The use of non-study A
Baseline co-morbidities (%): None Intervention: Two groups ARB: Candesartan cilexetil 16mg/day vs HTCZ 25mg/day Co-intervention: if BP goal was not achieved, other BP-lowering agents were added consecutively (felodipine was added to the candesartan group and Atenolol was added to the hydrochlorothiazide group). The use of non-study A or ARB was prohibited.
Baseline co-morbidities (%): None Intervention: Two groups ARB: Candesartan cilexetil 16mg/day vs HTCZ 25mg/day Co-intervention: if BP goal was not achieved, other BP-lowering agents were added consecutively (felodipine was added to the candesartan group and Atenolol was added to the hydrochlorothiazide group). The use of non-study A or ARB was prohibited. Concomitant non-study RAS blockers: None
Baseline co-morbidities (%): None Intervention: Two groups ARB: Candesartan cilexetil 16mg/day vs HTCZ 25mg/day Co-intervention: if BP goal was not achieved, other BP-lowering agents were added consecutively (felodipine was added to the candesartan group and Atenolol was added to the hydrochlorothiazide group). The use of non-study A or ARB was prohibited. Concomitant non-study RAS blockers: None Primary and secondary outcomes: Glucose and lipoprotein metabolism, electrolytes, BP, and subjective symptom
Baseline co-morbidities (%): None Intervention: Two groups ARB: Candesartan cilexetil 16mg/day vs HTCZ 25mg/day Co-intervention: if BP goal was not achieved, other BP-lowering agents were added consecutively (felodipine was added to the candesartan group and Atenolol was added to the hydrochlorothiazide group). The use of non-study A or ARB was prohibited. Concomitant non-study RAS blockers: None Primary and secondary outcomes: Glucose and lipoprotein metabolism, electrolytes, BP, and subjective symptom Funding Source: Department of Public Health and Clinical Medicine, Umea [®] University, Sweden together with
Baseline co-morbidities (%): None Intervention: Two groups ARB: Candesartan cilexetil 16mg/day vs HTCZ 25mg/day Co-intervention: if BP goal was not achieved, other BP-lowering agents were added consecutively (felodipine was added to the candesartan group and Atenolol was added to the hydrochlorothiazide group). The use of non-study A or ARB was prohibited. Concomitant non-study RAS blockers: None Primary and secondary outcomes: Glucose and lipoprotein metabolism, electrolytes, BP, and subjective symptom Funding Source: Department of Public Health and Clinical Medicine, Umea [®] University, Sweden together with AstraZeneca R&D, Molndal, Sweden and Hassle Lakemedel AB, Sweden.
Baseline co-morbidities (%): None Intervention: Two groups ARB: Candesartan cilexetil 16mg/day vs HTCZ 25mg/day Co-intervention: if BP goal was not achieved, other BP-lowering agents were added consecutively (felodipine was added to the candesartan group and Atenolol was added to the hydrochlorothiazide group). The use of non-study A or ARB was prohibited. Concomitant non-study RAS blockers: None Primary and secondary outcomes: Glucose and lipoprotein metabolism, electrolytes, BP, and subjective symptom Funding Source: Department of Public Health and Clinical Medicine, Umea [®] University, Sweden together with
Baseline co-morbidities (%): None Intervention: Two groups ARB: Candesartan cilexetil 16mg/day vs HTCZ 25mg/day Co-intervention: if BP goal was not achieved, other BP-lowering agents were added consecutively (felodipine was added to the candesartan group and Atenolol was added to the hydrochlorothiazide group). The use of non-study A or ARB was prohibited. Concomitant non-study RAS blockers: None Primary and secondary outcomes: Glucose and lipoprotein metabolism, electrolytes, BP, and subjective symptom Funding Source: Department of Public Health and Clinical Medicine, Umea [®] University, Sweden together with AstraZeneca R&D, Molndal, Sweden and Hassle Lakemedel AB, Sweden. ANBP2 (2003) (Wing et al., 2003)
Baseline co-morbidities (%): None Intervention: Two groups ARB: Candesartan cilexetil 16mg/day vs HTCZ 25mg/day Co-intervention: if BP goal was not achieved, other BP-lowering agents were added consecutively (felodipine was added to the candesartan group and Atenolol was added to the hydrochlorothiazide group). The use of non-study A or ARB was prohibited. Concomitant non-study RAS blockers: None Primary and secondary outcomes: Glucose and lipoprotein metabolism, electrolytes, BP, and subjective symptom Funding Source: Department of Public Health and Clinical Medicine, Umea [®] University, Sweden together with AstraZeneca R&D, Molndal, Sweden and Hassle Lakemedel AB, Sweden. ANBP2 (2003) (Wing et al., 2003) Design: Prospective, randomized, open-label, blinded-endpoint trial (PROBE)
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Baseline co-morbidities (%): None Intervention: Two groups ARB: Candesartan cilexetil 16mg/day vs HTCZ 25mg/day Co-intervention: if BP goal was not achieved, other BP-lowering agents were added consecutively (felodipine was added to the candesartan group and Atenolol was added to the hydrochlorothiazide group). The use of non-study A or ARB was prohibited. Concomitant non-study RAS blockers: None Primary and secondary outcomes: Glucose and lipoprotein metabolism, electrolytes, BP, and subjective symptom Funding Source: Department of Public Health and Clinical Medicine, Umea [®] University, Sweden together with AstraZeneca R&D, Molndal, Sweden and Hassle Lakemedel AB, Sweden. ANBP2 (2003) (Wing et al., 2003) Design: Prospective, randomized, open-label, blinded-endpoint trial (PROBE) Mean duration of follow-up: 4.1 Participants: 6083
Baseline co-morbidities (%): None Intervention: Two groups ARB: Candesartan cilexetil 16mg/day vs HTCZ 25mg/day Co-intervention: if BP goal was not achieved, other BP-lowering agents were added consecutively (felodipine was added to the candesartan group and Atenolol was added to the hydrochlorothiazide group). The use of non-study A or ARB was prohibited. Concomitant non-study RAS blockers: None Primary and secondary outcomes: Glucose and lipoprotein metabolism, electrolytes, BP, and subjective symptom Funding Source: Department of Public Health and Clinical Medicine, Umea [®] University, Sweden together with AstraZeneca R&D, Molndal, Sweden and Hassle Lakemedel AB, Sweden. ANBP2 (2003) (Wing et al., 2003) Design: Prospective, randomized, open-label, blinded-endpoint trial (PROBE) Mean duration of follow-up: 4.1 Participants: 6083 Clinical setting: Elderly hypertension
Baseline co-morbidities (%): None Intervention: Two groups ARB: Candesartan cilexetil 16mg/day vs HTCZ 25mg/day Co-intervention: if BP goal was not achieved, other BP-lowering agents were added consecutively (felodipine was added to the candesartan group and Atenolol was added to the hydrochlorothiazide group). The use of non-study A or ARB was prohibited. Concomitant non-study RAS blockers: None Primary and secondary outcomes: Glucose and lipoprotein metabolism, electrolytes, BP, and subjective symptom Funding Source: Department of Public Health and Clinical Medicine, Umea [®] University, Sweden together with AstraZeneca R&D, Molndal, Sweden and Hassle Lakemedel AB, Sweden. ANBP2 (2003) (Wing et al., 2003) Design: Prospective, randomized, open-label, blinded-endpoint trial (PROBE) Mean duration of follow-up: 4.1 Participants: 6083 Clinical setting: Elderly hypertension Mean baseline BP: 167/91 mmHg
Baseline co-morbidities (%): None Intervention: Two groups ARB: Candesartan cilexetil 16mg/day vs HTCZ 25mg/day Co-intervention: if BP goal was not achieved, other BP-lowering agents were added consecutively (felodipine was added to the candesartan group and Atenolol was added to the hydrochlorothiazide group). The use of non-study A or ARB was prohibited. Concomitant non-study RAS blockers: None Primary and secondary outcomes: Glucose and lipoprotein metabolism, electrolytes, BP, and subjective symptom Funding Source: Department of Public Health and Clinical Medicine, Umea [®] University, Sweden together with AstraZeneca R&D, Molndal, Sweden and Hassle Lakemedel AB, Sweden. ANBP2 (2003) (Wing et al., 2003) Design: Prospective, randomized, open-label, blinded-endpoint trial (PROBE) Mean duration of follow-up: 4.1 Participants: 6083 Clinical setting: Elderly hypertension Mean baseline BP: 167/91 mmHg Age range: 65-84 years (mean age: 71.9 years)
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Baseline co-morbidities (%): None Intervention: Two groups ARB: Candesartan cilexetil 16mg/day vs HTCZ 25mg/day Co-intervention: if BP goal was not achieved, other BP-lowering agents were added consecutively (felodipine was added to the candesartan group and Atenolol was added to the hydrochlorothiazide group). The use of non-study A or ARB was prohibited. Concomitant non-study RAS blockers: None Primary and secondary outcomes: Glucose and lipoprotein metabolism, electrolytes, BP, and subjective symptom Funding Source: Department of Public Health and Clinical Medicine, Umea [®] University, Sweden together with AstraZeneca R&D, Molndal, Sweden and Hassle Lakemedel AB, Sweden. ANBP2 (2003) (Wing et al., 2003) Design: Prospective, randomized, open-label, blinded-endpoint trial (PROBE) Mean duration of follow-up: 4.1 Participants: 6083 Clinical setting: Elderly hypertension Mean baseline BP: 167/91 mmHg Age range: 65-84 years (mean age: 71.9 years)

ACE: Enalgeri Vs. hydrochorothiaride Contervention: To achieved Bread, other BP-lowering agents was added in stepwise fashion. Concontant non-study RAS blockers: Intervention: 148 Ad8. Centrol: 12.46 Ad8. Primary and secondary outcomes: Composite & Individual of all CV events (fatal or nonfatai) or all mortality Primary and secondary outcomes: Composite & Individual of all CV events (fatal or nonfatai) or all mortality Primary and secondary outcomes: Composite & Individual of all CV events (fatal or nonfatai) or all mortality Primary and secondary outcomes: Composite & Individual of all CV events (fatal setting: Prospective, randomized, double-blinded, parallel trial Mean duration of follow-up: 1 year Participants (p): 430 Clinical setting: Pransysmal atrial fibrillation (AF). Mean duration of follow-up: 1 year Participants (p): 430 Clinical setting: 2070 mmHg Age range: 18 douter (mean: 61 s years) Hypertensive patients (K): 49 Hypertensive patients (K): 49 Hypertensive patients (K): 49 ABB: Olinearizan 400mg/day vs Placebo Co-intervention: 18 Pg oal was to achieved, other BP-lowering agents were added (diuretics, CCBs, and antiadrenergic agents Concomitant non-study RAS blockers: None Primary outcomes: Percentage of days with documented episodes of paroxysmal or with suspected persistent or Primary outcomes: Three to first of fusion counces of the America distribution for Adm atrice, auality of life Funding Source: German Ministry of Research and Education, Duich Sankyo Deutschland GmbH (Munich, Germany) APEES 2000) Design: Prospective, randomized, moncentre, double-blinded, parallel trial Mean duration of follow-up: 2. Syears Participants (p): 159 Clinical setting: Pice (First 3) ACE: Rampire 15: 2057 Ads) OR Post-PTCA (1-2 days) for chronic stable angina pectoris Mean duration of follow-up: 2. Syears Participants (p): 159 Clinical setting: Pice (First 3) AGE: Rampire 15: 100 m/ day vs. placebo Co-intervention: NB Concomitant non-study RAS blockers: NR Primary and secondary outcomes: CV mortality, AMI, rec	
Concomitant non-study RAS blockers: Intervention: 14% ARB. Control: 12.4% ARB Primary and secondary outcomes: Composite & Lindividual of all (CV events (fatal or nonfatal) or all mortality Funding Source: Australian Commonwealth Department of Health and Aging: the National Health and Medical Research Council of Australia; and Merck Shape I (bolme, Australia ANTIPAF (2012) (Goette et al., 2012) Design: Prospective, randomized, double-blinded, parallel trial Mean duration of follow-up: 1 year Paticipa setting: Prospective ration of the Set Set Set Set Set Set Set Set Set Se	
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Funding Source: Australian Commonwealth Department of Health and Aging the National Health and Medical Research Council of Australia: and Merk Sharp & Dohme, Australia Australia (Control Australia: and Merk Sharp & Dohme, Australia (Control Australia: and Merk Sharp & Dohme, Australia (Control Australia: and Merk Sharp & Dohme, Australia) (Control Australia: and Australia (Control Australia: and Australia) (Control Australia: and Australia) (Control Australia: and Australia) (Control Australia: and Australia: Au	Concomitant non-study RAS blockers: Intervention: 14% ARB. Control: 12.4% ARB
Funding Source: Australian Commonwealth Department of Health and Aging the National Health and Medical Research Council of Australia: and Merk Sharp & Dohme, Australia Australia (Control Australia: and Merk Sharp & Dohme, Australia (Control Australia: and Merk Sharp & Dohme, Australia (Control Australia: and Merk Sharp & Dohme, Australia) (Control Australia: and Australia (Finite Australia) (Control Australia: and Australia (Finite Australia) (Control Australia: and Australia) (Control Australia: and Australia:	Primary and secondary outcomes: Composite & individual of all CV events (fatal or nonfatal) or all mortality
Research Council of Australia; and Merck Sharp & Dohme, Australia ANTIPAF (2012) (Goette et al., 2012) Design: Prospective, randomized, double-blinded, parallel trial Mean duration of follow-up: 1 year Participants (n): 430 Clinical setting: Paroxysmal atrial fibrillation (AF). Mean baseline BP: 132/79 mmHg Age range: 16-0der (mean: 61.5 years) Hypertensive patients (8): 49 Baseline co-morbitities (K): Intervention: 2 groups Concomitant non-study RAS blockers; None Primary outcomes: Percentage of days with documented episodes of paroxysmal or with suspected persistent or permanent AF Secondary outcomes: Percentage of days with documented episodes of paroxysmal or with suspected persistent or permanent AF Secondary outcomes: Percentage of days with documented episodes of paroxysmal or with suspected persistent or permanent AF Secondary outcomes: Percentage of days with documented episodes of paroxysmal or with suspected persistent or permanent AF Secondary outcomes: Percentage of days with documented episodes of paroxysmal or with suspected persistent or permanent AF Secondary outcomes: Percentage of AP, number of hospitalizations for AF and stroke, quality of Iffer Secondary outcomes: Percentage of Jops with documented parallel trial Mean duration of follow-up: 2, 5 years Participants (n): 199 Clinical setting: Post-EAG (5-7 days) OR post-PTCA (1-2 days) for chronic stable angina pectoris Mean baseline BP: 129/79 Age range: 18-75 yeas (mean age: 6) years) Hypertensive patients (6): 24 Age range: 10000 (Othare et al., 2000) Design: Prospective, randomized, multicentre, double-blinded, parallel trial Mean duration of follow-up: 2, years Participants: 100 Contenvention: RR Concomitant non-study RAS blockers; NR Primary and secondary outcomes: CV morality, AM, recurrent HF or angina Funding Source: AstraZeneca, Albertslund, Denmark and agrant from Rigshospitalet, Copenhagen, Denmark. ATLANTE (2000) (Othare et al., 2000) Design: Prospective, randomized, multicentre, double-blinded, parallel trial Mean duration of fo	
ANTPRA (2012) (Goette et al., 2012) Design: Prospective, randomized, double-blinded, parallel trial Mean duration of follow-up: 1 year Participants (n): 430 Clinical setting: Paroxysmal atrial fibrillation (AF). Mean baseline BF: 132/79 mmilg Age range: 18-0der (mean: 61.5 years) Hypertensive patients (s): 49 Baseline co-morbiolities (s): ABB: Olinearia doing (day ve Placebo Co-intervention: if: BF goal was not achieved, other BP-lowering agents were added (diuretics, CCBs, and antidarenergic agents Concomitant non-study RAS blockers: None Primary outcomes: Percentage of days with documented episodes of paroxysmal or with suspected persistent or permanent AF Secondary outcomes: Time to first occurrence of AF, number of hospitalizations for AF and stroke, quality of life Funding Source: German Ministry of Research and Education. Darich Sankyo Deutschland GmbH (Munch, Germany) APRES (2000) (Kyllert-Hansen et al., 2000) Design: Prospective, randomized, monocentre, double-blinded, parallel trial Mean duration of folow-up: 2.5 years Participants (n): 159 Co-intervention: Two groups ACE: Rampin 15-10 mg/day vs. placebo Co-intervention: NR Concomitant non-study RAS blockers: NR Primary outcomes: CV mortality, AMI, recurrent HF or angina. Frimary and secondary outcomes: CV mortality, AMI, recurrent HF or angina. Frimary and secondary outcomes: CV mortality, AMI, recurrent HF or angina. Frimary and secondary outcomes: CV mortality, AMI, recurrent HF or angina. Frimary and secondary outcomes: CV mortality, AMI, recurrent HF or angina. Frimary and secondary outcomes: CV mortality, AMI, recurrent HF or angina. Frimary and secondary outcomes: CV mortality, AMI, recurrent HF or angina. Frimary and secondary outcomes: CV mortality, AMI, recurrent HF or angina. Frimary and secondary outcomes: CV mortality, AMI, recurrent HF or angina. Frimary and secondary outcomes: CV mortality, AMI, recurrent HF or angina. Frimary and secondary outcomes: CV mortality, AMI, recurrent HF or angina. Frimary a	
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Mean duration of follow-up: 1 year Participants (n): 430 Clinical setting: Paroxysmal atrial fibrillation (AF). Mean baseline BP: 132/79 mm/lg Age range: IB-older (mean: 61.5 years) Hypertensive patients (8): Intervention: If BP goal was not achieved, other BP-lowering agents were added (diuretics, CCBs, and Co-Intervention: If BP goal was not achieved, other BP-lowering agents were added (diuretics, CCBs, and Co-Intervention: If BP goal was not achieved, other BP-lowering agents were added (diuretics, CCBs, and Co-Intervention: If BP goal was not achieved, other BP-lowering agents were added (diuretics, CCBs, and Co-Intervention: If BP goal was not achieved, other BP-lowering agents were added (diuretics, CCBs, and Co-Intervention: If BP goal was not achieved, other BP-lowering agents were added (diuretics, CCBs, and Co-Intervention: If BP goal was not achieved, other BP-lowering agents were added (diuretics, CCBs, and Co-Intervention: If BP goal was not achieved, other BP-lowering agents were added (diuretics, CCBs, and Co-Intervention: If BP goal was not achieved, approaches of paroxysmal or with suspected persistent or permanent AF Secondary outcomes: There to first occurrence of AF, number of hospitalizations for AF and stroke, quality of life Funding Source: German Ministry of Research and Education. Datichi Sankyo Deutschland GmbH (Munich, Germany) PARES (2000 () (Selier et Amano Participants (1): 159 Participants (1): 159 Participants (1): 159 Clinical setting: Post-CABC (5-7 days) OR post-PTCA (1-2 days) for chronic stab	
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Participants (n): 430 Clinical setting: Paroxysmal atrial fibrillation (AF). Mean baseline BP: 132/79 mmHg Age range: 18-016kr (mean: 61: 5 years) Hypertensive patients (K): 49 Baseline co-mothdities (K): Intervention: If BP goal was not achieved, other BP-lowering agents were added (diuretics, CCBs, and antidarenergic agents Concintant non-study RAS blockers: None Primary outcomes: Percentage of days with documented episodes of paroxysmal or with suspected persistent or permanent AF Secondary outcomes: Percentage of days with documented episodes of paroxysmal or with suspected persistent or permanent AF Secondary outcomes: Percentage of days with documented episodes of paroxysmal or with suspected persistent or permanent AF Secondary outcomes: Percentage of days with documented episodes of paroxysmal or with suspected persistent or permanent AF Secondary outcomes: Percentage of days with documented episodes of paroxysmal or with suspected persistent or permanent AF Secondary outcomes: Percentage of days with documented episodes of paroxysmal or with suspected persistent or permanent AF Secondary outcomes: Percentage of days with documented episodes of paroxysmal or with suspected persistent or permanent AF Secondary outcomes: Percentage of days with documented episodes of paroxysmal or with suspected persistent or Participants (n): 89 Participants (n): 89 Participants (n): 89 Participants (n): 80 Co-intervention: NR Co-intervention: NR Co-interv	Mean duration of follow-up: 1 year
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Mean baseline BP; 132/79 mmig Age range: 18-016er (mean: 61: 5 years) Hypertensive patients (%): 49 Baseline c-morbidities (%): Intervention: If BP goal was not achieved, other BP-lowering agents were added (diuretics, CCBs, and antidarenergic agents Concontrant non-study RAS blockers: None Primary outcomes: Percentage of days with documented episodes of paroxysmal or with suspected persistent or permanent AF Secondary outcomes: Time to first occurrence of AF, number of hospitalizations for AF and stroke, quality of life Funding Source: German Ministry of Research and Education. Dalichi Sankyo Deutschland GmbH (Munich, Germany) APRES (2000) (Kyleiter-Hansen et al., 2000) Design: Prospective, randomized, monocentre, double-blinded, parallel trial Mean duration of follow-up: 2 years Participants (h): 139 Concontraint non-study RAS blockers: NR Printery and secondary outcomes: CV montality, AM, recurrent HF or angina Printary and secondary outcomes: CV montality, AM, recurrent HF or angina Printery and secondary outcomes: CV montality, AM, recurrent HF or angina Printery and secondary outcomes: CV montality, AM, recurrent HF or angina Printery and secondary outcomes: CV montality, AM, recurrent HF or angina Printery and secondary outcomes: CV montality, AM, recurrent HF or angina Printery and secondary outcomes: CV monta	
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Hypertensive patients (\$): 49 Baseline co-morbidities (\$): Intervention: 2 groups ARB: Olineartan 40mg/day vs Placebo Co-intervention: if BP goal was not achieved, other BP-lowering agents were added (diuretics, CCBs, and antiadrenergic agents Concontlant non-study RAS blockers: None Firmary outcomes: Percentage of days with documented episodes of paroxysmal or with suspected persistent or permanent AF Secondary outcomes: Three to first occurrence of AF, number of hospitalizations for AF and stroke, quality of life Funding Source: German Ministry of Research and Education. Daichi Sankyo Deutschland GmbH (Munich, Germany) APRES (2000) (Kigliet-Hansen et al., 2000) Design: Prospective, randomized, monocentre, double-blinded, parallel trial Mean duration of follow-up: 2. Syears Participants (n): 159 Participants (n): 159 Participants (A): 75 years (mean age: 61 years) Hypertensive patients (\$): 34 Concontlant non-study RAS blockers: NR Firmary and secondary outcomes: CY mortality, AMI, recurrent HF or angina Funding Source: AstraZeneca, Albertslund, Denmark and a grant from Rigshospitalet, Copenhagen, Denmark. ATLANINS (2000) (O'Hare et al., 2000) Design: Prospective, randomized, multicentre, double-blinded, parallel trial Mean duration of follow-up: 2 years Participants: 140 Clinical setting: 110M with microabuminuria & normotensive. Mean baseline BP: 137/5 mmHg Age range: 16 years) Hypertensive patients (\$): Not Seisen: Prospective, randomized, multicentre, open-label, blinded-endpoint trial (PROBE) Mean duration of follow-up: 2 years Participants: 140 Clinical setting: 110M with microabuminuria & normotensive. Mean baseline BP: 133/76 mmHg Age range: (Mean age: 40 years) Hypertensive patients (\$): None Intervention: Three groups ACE: Ramipril: 1.25 mg/day vs. placebo Co-intervention: Three groups ACE: Ramipril: 1.25 mg/day vs. placebo Co-intervention: Three groups ACE: Ramipril: 1.25 mg/day vs. placebo Co-intervention: Three groups ACE: Ramipril: 1.25 mg/day vs. placebo Co-intervention: Three groups ACE: Ramipr	
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AR8: Olmesartan 40mg/day vs Placebo Co-Intervention: If BP goal was not achieved, other BP-lowering agents were added (diuretics, CCBs, and antiadrenergic agents Concomitant non-study RAS blockers: None Primary outcomes: Percentage of days with documented episodes of paroxysmal or with suspected persistent or permanent AF Secondary outcomes: Time to first occurrence of AF, number of hospitalizations for AF and stroke, quality of Iffe Funding Source: German Ministry of Research and Education. Dalichi Sankyo Deutschland GmbH (Munich, Germany) APRES (2000) (Kjøller-Hansen et al., 2000) Design: Prospective, randomized, monocentre, double-blinded, parallel trial Mean duration of follow-up: 2.5 years Participants (1): 159 Clinical setting: Post-CABG (5:7 days) 0R post-PTCA (1-2 days) for chronic stable angina pectoris Mean baseline BP: 129/79 Age range: 18-75 years (mean age: 61 years) Hypertensive patients (8): 214 Intervention: Two groups ACEI: Ramipril 5-10 mg/day vs. placebo Co-intervention: Ng aroups ACEI: Ramipril 5-10 mg/day vs. placebo Co-intervention: Ng aroups ACEI: Ramipril 5-10 mg/day vs. placebo Co-intervention: Ng Proups ACEI: Ramipril 5-10 mg/day vs. placebo Co-intervention: Ng Proups ACEI: Ramipril 5-10 mg/day vs. placebo Co-intervention: Ng Primary and secondary outcomes: CV mortality, AMI, recurrent HF or angina Primary and secondary outcomes: CV mortality, AMI, recurrent HF or angina Participants: 140 Clinical setting: 11M with microalbuminuria & normotensive. Mean baseline BP: 133/76 mmfig Age range: mean age: 40 years) Hypertensive patients (%): Obse Baseline Co-mortNidtite K§): None Intervention: Three groups ACEI: Ramipril 1.25 mg/day vs. placebo Co-intervention: NR Gencomitant non-study RAS blockers: NR Primary and secondary outcomes, Progression of albumin excretion rate (AER) from microalbuminuria to macroalbuminuria, progression to normoabuminuria, eurum creatinne, GFR & BP. Funding Source: Hocchist Marion Roussel (Aventis) Primery and secondary outcomes; NR Gencomitant non-study RAS blocke	Baseline co-morbidities (%):
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Secondary outcomes: Time to first occurrence of AF, number of hospitalizations for AF and stroke, quality of life Funding Source: German Ministry of Research and Education. Dalichi Sankyo Deutschland GmbH (Munich, Germany) APRES (2000) (Kjeller-Hansen et al., 2000) Design: Prospective, randomized, monocentre, double-blinded, parallel trial Mean duration of follow-up: 2.5 years Participants (n): 159 Clinical setting: Post-CA8G (5-7 days) OR post-PTCA (1-2 days) for chronic stable angina pectoris Mean baseline BP: 129/79 Age range: 18-75 years (mean age: 61 years) Hypertensive patients (%): 34 Intervention: Two groups ACEI: Ramipril 5-10 mg/day vs. placebo Co-intervention: NR Concomitant non-study RAS blockers: NR Primary and secondary outcomes: CV mortality, AMI, recurrent HF or angina Frunding Source: AstraZeneca, Albertslund, Denmark and a grant from Rigshospitalet, Copenhagen, Denmark. ATLANTIS (2000) (O'Hare et al., 2000) Design: Prospective, randomized, multicentre, double-blinded, parallel trial Mean duration of follow-up: 2 years Participants: 140 Clinical setting: T1DM with microalbuminuria & normotensive. Mean baseline BP: 133/76 mmHg Age range: (mean age: 40 years) Hypertensive patients (%): 0 Baseline co-morbidities (%): None Intervention: Three groups ACEI: Ramipril Sing/day vs. ramipril 1.25 mg/day vs. placebo Co-intervention: NR Concomitant non-study RAS blockers: NR Primary and secondary outcomes: Progression of albumin excretion rate (AER) from microalbuminuria to macroalbuminuria, progression to normoalbuminuria, serum creatinine, GFR & BP. Funding Source: Hoecht Karion Roussel (Aventis) ATLEMPT-CVD (2015) (Ogawa et al., 2016) Design: Prospective, randomized, multicentre, open-label, blinded-endpoint trial (PROBE) Mean duration of follow-up: 3 years Participants: 12/8 Clinical setting: HTN with at least one CV risk factor (DM, renal, cerebral peripheral artery factor) Mean baseline BP: 151/34 mmHg Age range: (mean age: 6 years) Hypertensive patients (%): 100 Baseline. co-morbidities (%):DM (66.5	
Funding Source: German Ministry of Research and Education. Dailchi Sankyo Deutschland GmbH (Munich, Germany) APRES (2000) (Kjeller-Hansen et al., 2000) Design: Prospective, randomized, monocentre, double-blinded, parallel trial Mean duration of follow-up: 2.5 years Participants (n): 159 Clinical setting: Post-CABG (5-7 days) OR post-PTCA (1-2 days) for chronic stable angina pectoris Mean baseline BP: 129/79 Age range: 18-75 years (mean age: 61 years) Hypertensive patients (%): 34 Intervention: Two groups ACEI: Ramipril: 510 mg/day vs. placebo Co-intervention: Toto groups ACEI: Ramipril: T10W with microalbuminuria & normotensive. Mean baseline BP: 133/76 mmHg Age range: (mean age: 40 years) Hypertensive patients (%): 00 Baseline co-morbidities (%): None Intervention: Three groups ACEI: Ramipril: 5mg/day vs. ramipril 1.25 mg/day vs. placebo Co-intervention: NR Concomitant non-study RAS blockers: NR Primary and secondary outcomes: Progression of albumin excretion rate (AER) from microalbuminuria to macroalbuminuria, progression to normoalbuminuria, secondary outcomes: Progression of albumin excretion rate (AER) from microalbuminuria to macroalbuminuria, progression to normoalbuminuria, secondary outcomes: Charges albumine excretion rate (AER) from microalbuminuria to macroalbuminuria, progression to normoalbuminuria, secondary outcomes: Charges and the day of lob-weils ATTEMPT-CVD (2015) (Ogawa et al., 2016) Design: Prospective, randomized, multic	
APRES (2000) (Kjeller-Hansen et al., 2000) Design: Prospective, randomized, monocentre, double-blinded, parallel trial Mean duration of follow-up: 2.5 years Participants (n): 159 Clinical setting: Post-CABG (5-7 days) OR post-PTCA (1-2 days) for chronic stable angina pectoris Mean baseline BP: 129/79 Age range: 16.75 years (mean age: 61 years) Hypertensive patients (%): 34 Intervention: Two groups Co-intervention: NR Concomitant non-study RAS blockers: NR Primary and secondary outcomes: CV mortality. AML, recurrent HF or angina Funding Source: AstraZeneca, Albertslund, Denmark and a grant from Rigshospitalet, Copenhagen, Denmark. ATLATTS (2000) (OHare et al., 2000) Design: Prospective, randomized, multicentre, double-blinded, parallel trial Mean baseline BP: 133/76 mmHg Age range: (mean age: 40 years) Hypertensive patients (%): 0 Baseline co-morbidities (%): None Intervention: NR Concomitant non-study RAS blockers: NR Primary and secondary outcomes: Primary and secondary outcomes: Mean baseline BP: 133/76 mmHg Age range: (mean age: 40 years) Hypertensive patients (%): None Intervention: NR	Secondary execonds, the to this occurrence of Ar, number of hospitalizations for Ar and stoke, quarty of the
Design: Prospective, randomized, monocentre, double-blinded, parallel trial Mean duration of follow-up: 2.5 years Participants (n): 159 Clinical setting: Post-CABG (5-7 days) OR post-PTCA (1-2 days) for chronic stable angina pectoris Mean Daseline BP: 129/79 Age range: 18-75 years (mean age: 61 years) Hypertensive patients (%): 34 Intervention: Two groups ACEI: Ramipril 5-10 mg/day vs. placebo Co-intervention: NR Concomitant non-study RAS blockers: NR Primary and secondary outcomess: CV mortality. AML, recurrent HF or angina Funding Source: AstraZeneca, Albertslund, Denmark and a grant from Rigshospitalet, Copenhagen, Denmark. ATLANTIS (2000) (O'Hare et al., 2000) Design: Prospective, randomized, multicentre, double-blinded, parallel trial Mean duration of follow-up: 2 years Participants: 140 Clinical setting: T1DM with microalbuminuria & normotensive. Mean baseline BP: 133/76 mmHg Age range: (mean age: 40 years) Hypertensive patients (%): 0 Baseline co-morbidities (%): None Intervention: Three groups ACEI: Ramipril Smg/day vs. ramipril 1.25 mg/day vs. placebo Co-intervention: RR Concomitant non-study RAS blockers: NR Primary and secondary outcomes: Progression of albumin excretion rate (AER) from microalbuminuria to macroalbuminuria, progression to normoalbuminuria, serum creatinine, GFR & BP. Funding Source: Hocht Mariano Roussel (Aventis) ATTEMPT-CVD (2015) (Ogawa et al., 2016) Design: Prospective, randomized, multicentre, open-label, blinded-endpoint trial (PROBE) Mean duration of follow-up: 3 years Participants: 1228 Clinical setting: HTN with at least one CV risk factor (DM, renal, cerebral peripheral artery factor) Mean baseline BP: 151/84 mmHg Age range: (mean age: 66 years) Hypertensive patients (%): 100 Baseline co-morbidities (%): DM (66.5), CVD (32) Intervention: TP-0 groups ARB: Teimisartan vs. non-ARB Co-intervention: PD-lowering agents was added to control BP level. Concomitant non-study RAS blockers: Intervention: 0.41% ACEI. Control: 12.6% ACEIs Primary and secondary outcomes: Charges in unitar	
Mean duration of follow-up: 2.5 years Participants (n): 159 Clinical setting: Post-CABG (5-7 days) OR post-PTCA (1-2 days) for chronic stable angina pectoris Mean baseline BP: 129/79 Age range: 18-75 years (mean age: 61 years) Hypertensive patients (%): 34 Intervention: Two groups Co-intervention: RR Concomitant non-study RAS blockers: NR Primary and secondary outcomes: CV mortality, AMI, recurrent HF or angina Funding Source: AstraZeneca, Albertstund, Denmark and a grant from Rigshospitalet, Copenhagen, Denmark. ATLANTIS (2000) (O'Hare et al., 2000) Design: Prospective, randomized, multicentre, double-blinded, parallel triat Mean baseline BP: 133/76 mmltg Age range: (mean age: 40 years) Hypertensive patients (%): 0 Baseline co-morbidities (%): None Intervention: Three groups ACEI: Ramipril Smg/day vs. ramipril 1.25 mg/day vs. placebo Co-intervention: RR Concomitant non-study RAS blockers: NR Primary and secondary outcomes: Progression of albumin excretion rate (AER) from microalbuminuria to macroalbuminuria, progression to normoalbuminuria, serum creatinine, GFR & BP. Funding Source: Horekits Marion Roussel (Aventis) ATTEMPT-CVD (2015) (Digawa et al., 2016)	
Mean duration of follow-up: 2.5 years Participants (n): 159 Clinical setting: Post-CABG (5-7 days) OR post-PTCA (1-2 days) for chronic stable angina pectoris Mean baseline BP: 129/79 Age range: 18-75 years (mean age: 61 years) Hypertensive patients (%): 34 Intervention: Two groups Co-intervention: RR Concomitant non-study RAS blockers: NR Primary and secondary outcomes: CV mortality, AMI, recurrent HF or angina Funding Source: AstraZeneca, Albertstund, Denmark and a grant from Rigshospitalet, Copenhagen, Denmark. ATLANTIS (2000) (O'Hare et al., 2000) Design: Prospective, randomized, multicentre, double-blinded, parallel triat Mean baseline BP: 133/76 mmltg Age range: (mean age: 40 years) Hypertensive patients (%): 0 Baseline co-morbidities (%): None Intervention: Three groups ACEI: Ramipril Smg/day vs. ramipril 1.25 mg/day vs. placebo Co-intervention: RR Concomitant non-study RAS blockers: NR Primary and secondary outcomes: Progression of albumin excretion rate (AER) from microalbuminuria to macroalbuminuria, progression to normoalbuminuria, serum creatinine, GFR & BP. Funding Source: Horekits Marion Roussel (Aventis) ATTEMPT-CVD (2015) (Digawa et al., 2016)	Design: Prospective, randomized, monocentre, double-blinded, parallel trial
Participants (n): 159 Clinical setting: Post-CABC (5-7 days) OR post-PTCA (1-2 days) for chronic stable angina pectoris Mean baseline BP: 129/79 Age range: 18-75 years (mean age: 61 years) Hypertensive patients (%): 34 Intervention: Two groups Co-intervention: Two groups Concomitant non-study RAS blockers: NR Primary and secondary outcomes: CV mortality, AMI, recurrent HF or angina Funding Source: AstraCareca, Albertstund, Denmark and a grant from Rigshospitalet, Copenhagen, Denmark. ATLANTIS (2000) (O'Hare et al., 2000) Design: Prospective, randomized, multicentre, double-blinded, parallel trial Mean duration of follow-up: 2 years Participants: 140 Clinical setting: T1DM with microalbuminuria & normotensive. Mean baseline BP: 133/76 mmHg Age range: (mean age: 40 years) Hypertensive patients (%): 0 Baseline co-morbidities (%): None Intervention: Three groups ACEI: Ramipril Smg/day vs. ramipril 1.25 mg/day vs. placebo Co-intervention: NR Concomitant non-study RAS blockers: NR Primary and secondary outcomes: Progression of albumin excretion rate (AER) from microalbuminuria to macroalbuminuria, progression to normoalbuminuria, serum creatinine, GFR & BP. Funding Source: Hoechst Marino Rousset (Aventis) ATTEMPT-CVD (2015) (Ogawa et al., 2016) Design: Prospective, randomized, multicentre, open-label, blinded-endpoint trial (PROBE) Mean duration of follow-up: 3 years Participants: 1228 Clinical setting: HTN with at least one CV risk factor (DM, renal, cerebral peripheral artery factor) Mean baseline BP: 151/84 mmHg Age range: (mean age: 60 years) Hypertensive patients (%): 100 Baseline co-morbidities (%): 100 Baseline co-morbidities (%): 100 Baseline co-morbidities (%): 200 Patiensi RAS blockers: Intervention: 0.41% ACEI. Contol: 12.6% ACEIs Primary and secondary outcomes: Cranges in uninary albumin creatinine ration (UACR) & plasma BNP levels from baseline, Occurrence of cerebral events, cardiac, aortic/peripheral arterial events, complication of diabetes and aggravation of re	
Clinical setting: Post-CABC (5-7 days) OR post-PTCA (1-2 days) for chronic stable angina pectoris Mean baseline BP: 120/79 Age range: 18-75 years (mean age: 61 years) Hypertensive patients (%): 34 Intervention: Two groups ACEI: Ramipril 5-10 mg/day vs. placebo Co-intervention: NM Concomitant non-study RAS blockers: NR Primary and secondary outcomes: CV mortality, AML, recurrent HF or angina Funding Source: AstraZeneca, Albertslund, Denmark and a grant from Rigshospitalet, Copenhagen, Denmark. ATLANTIS (2000) (O'Hare et al., 2000) Design: Prospective, randomized, multicentre, double-blinded, parallel trial Mean duration of follow-up: 2 years Participants: 140 Clinical setting: T10M with microalbuminuria & normotensive. Mean baseline BP: 133/76 mmHg Age range: (mean age: 40 years) Hypertensive patients (%): 0 Baseline co-morbidities (%): None Intervention: Three groups ACEI: Ramipril Smg/day vs. ramipril 1.25 mg/day vs. placebo Co-intervention: Three groups ACEI: Ramipril Smg/day vs. ramipril 1.25 mg/day vs. placebo Co-intervention: RR Concomitant non-study RAS blockers: IR Primary and secondary outcomes: Progression of albumin excretion rate (AER) from microalbuminuria to macroalbuminuria, progression to normoalbuminuria, serum creatinine, GFR & BP. Funding Source: Hoechs tharion Roused (Ventis) ATTEMPT-CVD (2015) (Ogawa et al., 2016) Design: Prospective, randomized, multicentre, open-label, blinded-endpoint trial (PROBE) Mean duration of follow-up: 3 years Participants: 1228 Clinical setting: FTN with at least one CV risk factor (DM, renal, cerebral peripheral artery factor) Mean baseline BP: 151/24 mmHg Age range: (mean age: 64 mHg Baseline co-morbidities (%): 100 Baseline co-morbidit	
Mean baseline ² BF: 129/79 An and a set of years) Hypertensive patients (%): 34 Intervention: Two groups ACEI: Ramipril 5-10 mg/day vs. placebo Co-normitant non-study RAS blockers: NR Primary and secondary outcomes: CV mortality, AMI, recurrent HF or angina Funding Source: AstraZeneca, Albertstund, Demmark and a grant from Righospitalet, Copenhagen, Denmark. ATLANTIS (2000) (CHare et al., 2000) Design: Prospective, randomized, multicentre, double-blinded, parallel trial Mean duration of follow-up: 2 years Participants: 140 Clinical setting: T1DM with microalbuminuria & normotensive. Mean baseline BP: 133/76 mmHg Age range: (mean age: 40 years) Hypertensive patients (%): 0 Baseline co-morbidities (%): None Intervention: Three groups ACEI: Ramipril 5mg/day vs. ramipril 1.25 mg/day vs. placebo Co-normitant non-study RAS blockers: NR Primary and secondary outcomes: Progression of albumin excretion rate (AER) from microalbuminuria to macroalbuminuria, progression to normoalbuminuria, serum creatinine, GFR & BP. Funding Source: Hoechst Marion Roussel (Aventis) ATTEMPT-CVD (2015) (Ogawa et al., 2016) Design: Prospective, randomized, multicentre, open-label, blinded-endpoint trial (PROBE) Mean baseline BP:	
Age range: 18-75 years (mean age: 61 years) Hypertensive patients (%): 34 Intervention: Two groups ACEI: Ramipril 5-10 mg/day vs. placebo Co-intervention: NR Concomitant non-study RAS blockers: NR Primary and secondary outcomes: CV mortality, AMI, recurrent HF or angina Funding Source: AstraZeneca, Albertslund, Denmark and a grant from Rigshospitalet, Copenhagen, Denmark. ATLANTIS (2000) (O'Hare et al., 2000) Design: Prospective, randomized, multicentre, double-blinded, parallel trial Mean baseline BP: 133/76 mmlg Mean baseline BP: 133/76 mmlg Age range: (mean age: 40 years) Hypertensive patients (%): 0 Baseline co-morbidities (%): None Intervention: Three groups ACEI: Ramipril Smg/day vs. ramipril 1.25 mg/day vs. placebo Co-normitant non-study RAS blockers: NR Primary and secondary outcomes: Progression of albumin excretion rate (AER) from microalbuminuria to macroalbuminuria, progression to normoalbuminuria, serum creatinine, GFR & BP. Funding Source: Hoechst Marion Roussel (Aventis) ATEMPT-CVD (2015) (Ogawa et al., 2016) Design: Prospective, randomized, multicentre, open-label, blinded-endpoint trial (PROBE) Mea maseline BP: 151/24 mmlig Age range: (mean age: 64 years)	
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Intervention: Two groups ACEI: Ramipril 5-10 mg/day vs. placebo Co-intervention: NR Concomitant non-study RAS blockers: NR Primary and secondary outcomes: CV mortality, AMI, recurrent HF or angina Funding Source: AstraZeneca, Albertslund, Denmark and a grant from Rigshospitalet, Copenhagen, Denmark. ATLANTIS (2000) (O'Hare et al., 2000) Design: Prospective, randomized, multicentre, double-blinded, parallel trial Mean duration of follow-up: 2 years Participants: 140 Clinical setting: T1DM with microalbuminuria & normotensive. Mean baseline BP: 133/76 mmHg Age range: (mean age: 40 years) Hypertensive patients (%): 0 Baseline co-morbidities (%): None Intervention: Three groups ACEI: Ramipril Smg/day vs. ramipril 1.25 mg/day vs. placebo Co-intervention: NR Concomitant non-study RAS blockers: NR Primary and secondary outcomes: Progression of albumin excretion rate (AER) from microalbuminuria to macroalbuminuria, progression to normoalbuminuria, serum creatinine, GFR & BP. Funding Source: Hoechst Marion Roussel (Aventis) ATTEMPT-CVD (2015) (Ogawa et al., 2016) Design: Prospective, randomized, multicentre, open-label, blinded-endpoint trial (PROBE) Mean duration of follow-up: 3 years Participants: 1228 Clinical setting: HTN with at least one CV risk factor (DM, renal, cerebral peripheral artery factor) Mean baseline co-morbidities (%): 100 Baseline co-morbi	Age range: 18-75 years (mean age: 61 years)
Intervention: Two groups ACEI: Ramipril 5-10 mg/day vs. placebo Co-intervention: NR Concomitant non-study RAS blockers: NR Primary and secondary outcomes: CV mortality, AMI, recurrent HF or angina Funding Source: AstraZeneca, Albertslund, Denmark and a grant from Rigshospitalet, Copenhagen, Denmark. ATLANTIS (2000) (O'Hare et al., 2000) Design: Prospective, randomized, multicentre, double-blinded, parallel trial Mean duration of follow-up: 2 years Participants: 140 Clinical setting: T1DM with microalbuminuria & normotensive. Mean baseline BP: 133/76 mmHg Age range: (mean age: 40 years) Hypertensive patients (%): 0 Baseline co-morbidities (%): None Intervention: Three groups ACEI: Ramipril Smg/day vs. ramipril 1.25 mg/day vs. placebo Co-intervention: NR Concomitant non-study RAS blockers: NR Primary and secondary outcomes: Progression of albumin excretion rate (AER) from microalbuminuria to macroalbuminuria, progression to normoalbuminuria, serum creatinine, GFR & BP. Funding Source: Hoechst Marion Roussel (Aventis) ATTEMPT-CVD (2015) (Ogawa et al., 2016) Design: Prospective, randomized, multicentre, open-label, blinded-endpoint trial (PROBE) Mean duration of follow-up: 3 years Participants: 1228 Clinical setting: HTN with at least one CV risk factor (DM, renal, cerebral peripheral artery factor) Mean baseline co-morbidities (%): 100 Baseline co-morbi	Hypertensive patients (%): 34
ACEI: Ramipril 5-10 mg/day vs. placebo Co-intervention: NR Concomitant non-study RAS blockers: NR Primary and secondary outcomes: CV mortality, AMI, recurrent HF or angina Funding Source: AstraCareae, Albertstund, Denmark and a grant from Rigshospitalet, Copenhagen, Denmark. ATLANTIS (2000) (O'Hare et al., 2000) Design: Prospective, randomized, multicentre, double-blinded, parallel trial Mean duration of follow-up: 2 years Participants: 140 Clinical setting: T1DM with microalbuminuria & normotensive. Mean baseline BP: 133/76 mmHg Age range: (mean age: 40 years) Hypertensive patients (%): 0 Baseline co-morbidities (%): None Intervention: Three groups ACEI: Ramipril 5mg/day vs. ramipril 1.25 mg/day vs. placebo Co-intervention: Three groups ACEI: Ramipril 5mg/day vs. ramipril 1.25 mg/day vs. placebo Co-intervention: NR Concomitant non-study RAS blockers: NR Primary and secondary outcomes: Progression of albumin excretion rate (AER) from microalbuminuria to macroalbuminuria, progression to normoalbuminuria, serum creatinine, GFR & BP. Funding Source: Hoechst Marion Roussel (Aventis) ATTEMPT-(VD (2015) (Ogawa et al., 2016) Design: Prospective, randomized, multicentre, open-label, blinded-endpoint trial (PROBE) Mean duration of follow-up: 3 years Participants: 1228 Clinical setting: HTN with at least one CV risk factor (DM, renal, cerebral peripheral artery factor) Mean baseline BP: 1511/48 mmHg Age range: (mean age: 66 years) Hypertensive patients (%): 100 Baseline co-morbidities (%):DM (66.5), CVD (32) Intervention: Two groups ARB: Telmisatran vs. non-ARB Co-intervention: BP-lowering agents was added to control BP level. Concomitant non-study RAS blockers: Intervention: 0.41% ACEI. Control: 12.6% ACEIs Primary and secondary outcomes: Changes in urinary albumin creatinine ration (UACR) & plasma BNP levels from baseline. Occurrence of cerebral events, cardiac, aortic/peripheral arterial events, complication of diabetes and aggravation of renal function) Funding Source: Boehringer Ingelheim BHENDICT (2004) (Ruggenenti	
Co-intervention: NR Funding Source: AstraZeneca, Albertslund, Denmark and a grant from Rigshospitalet, Copenhagen, Denmark. ATLANTIS (2000) (O'Hare et al., 2000) Design: Prospective, randomized, multicentre, double-blinded, parallel trial Mean duration of follow-up: 2 years Participants: 140 Clinical setting: T1DM with microalbuminuria & normotensive. Mean baseline BP: 1337/6 mmHg Age range: (mean age: 40 years) Hypertensive patients (%): 0 Baseline co-morbidities (%): None Intervention: Three groups ACEI: Ramipril Smg/day vs. ramipril 1.25 mg/day vs. placebo Co-intervention: NR Concomitant non-study RAS blockers: NR Primary and secondary outcomes: Progression of albumin excretion rate (AER) from microalbuminuria to macroalbuminuria, progression to normoalbuminuria, serum creatinine, GFR & BP. Funding Source: Hocktis Marion Roussel (Aventis) ATTEMPT-CVD (2015) (Ogawa et al., 2016) Design: Prospective, randomized, multicentre, open-label, blinded-endpoint trial (PROBE) Mean duration of follow-up: 3 years Participants: 128 Clinical setting: HTN with at least one CV risk factor (DM, renal, cerebral peripheral artery factor) Mean baseline Co-morbidities (%): 100 Baseline co-morbidities (%):	
Concomitant non-study RAS blockers: NR Primary and secondary outcomes: CV mortality, AMI, recurrent HF or angina Funding Source: AstraZeneca, Albertslund, Denmark and a grant from Rigshospitalet, Copenhagen, Denmark. ATLANTIS (2000) (O'Hare et al., 2000) Design: Prospective, randomized, multicentre, double-blinded, parallel trial Mean duration of follow-up: 2 years Participants: 140 Clinical setting: T1DM with microalbuminuria & normotensive. Mean baseline BP: 133/76 mmHg Age range: (mean age: 40 years) Hypertensive patients (%): On Baseline co-morbidities (%): None Intervention: Three groups ACEI: Ramipril Smg/day vs. ramipril 1.25 mg/day vs. placebo Co-intervention: NR Concomitant non-study RAS blockers: NR Primary and secondary outcomes: Progression of albumin excretion rate (AER) from microalbuminuria to macroalbuminuria, progression to normoalbuminuria, serum creatinine, GFR & BP. Funding Source: Heechst Marion Roussel (Aventis) ATTEMPT-CVD (2015) (Ogawa et al., 2016) Design: Prospective, randomized, multicentre, open-label, blinded-endpoint trial (PROBE) Mean duration of follow-up: 3 years Participants: 1228 Coincitaisetting: HTN with at least one CV risk factor (DM, renal, cerebral peripheral artery factor) Mean baseline BP: 151/84 mmHg Age range: (mean age: 66 years) Hypertensive patients (%): 100 Baseline co-morbidities (%): 100 Baseline co-morbidities (%): 200 ARB: Telmisartan vs. non-ARB Co-intervention: Two groups ARB: Telmisartan vs. non-ARB Co-intervention: BP-lowering agents was added to control BP level. Concomitant non-study RAS blockers: Intervention: 0.41% ACEI. Control: 12.6% ACEIs Primary and secondary outcomes: Changes in urinary albumin creatinine ration (UACR) & plasma BNP levels from baseline Co-currence of cerebral events, cardiac, aortic/peripheral arterial events, complication of diabetes and aggravation of renal function) Funding Source: Behringer Ingelheim BENEDICT (2004) (Ruggenenti et al., 2004) Design: Prospective, randomized, multicentre,	
Primary and secondary outcomes: CV mortality, AMI, recurrent HF or angina Funding Source: AstraZeneca, Albertslund, Denmark and a grant from Rigshospitalet, Copenhagen, Denmark. ATLANTIS (2000) (O'Hare et al., 2000) Design: Prospective, randomized, multicentre, double-blinded, parallel trial Mean duration of follow-up: 2 years Participants: 140 Clinical setting: T1DM with microalbuminuria & normotensive. Mean baseline BP: 133/76 mmHg Age range: (mean age: 40 years) Hypertensive patients (%): O Baseline co-morbidities (%): None Intervention: Three groups ACEI: Ramipril 5mg/day vs. ramipril 1.25 mg/day vs. placebo Co-intervention: NR Concomitant non-study RAS blockers: NR Primary and secondary outcomes: Progression of albumin excretion rate (AER) from microalbuminuria to macroalbuminuria, progression to normoalbuminuria, serum creatinine, GFR & BP. Funding Source: Hoechst Marion Roussel (Aventis) ATTEMPT-CVD (2015) (Ogawa et al., 2016) Design: Prospective, randomized, multicentre, open-label, blinded-endpoint trial (PROBE) Mean duration of follow-up: 3 years Participants: 1228 Clinical setting: HTN with at least one CV risk factor (DM, renal, cerebral peripheral artery factor) Mean baseline BP: 151/34 mmHig Age range: (mean age: 6 years) Hypertensive patients (%): D0 Baseline co-morbidities (%):DM (66.5), CVD (32) Intervention: BP-lowering agents was added to control BP level. Concomitant non-study RAS blockers: Intervention: 0.41% ACEI. Control; 12.6% ACEIs Primary and secondary outcomes: Changes in urinary albumin creatinine ration (UACR) & plasma BNP levels from baseline Courrence of cerebral events, cardiac, aortic/peripheral arterial events, complication of diabetes and aggravation of renal function) Funding Source: Boehringer Ingelheim BENEDICT (2004) (Ruggenenti et al., 2004) Design: Prospective, randomized, multicentre, double-blinded, parallel trial Median duration of follow-up: 3.6 years	
Funding Source: AstraZeneca, Albertslund, Denmark and a grant from Rigshospitalet, Copenhagen, Denmark. ATLANTIS (2000) (O'Hare et al., 2000) Design: Prospective, randomized, multicentre, double-blinded, parallel trial Mean duration of follow-up: 2 years Participants: 140 Clinical setting: T1DM with microalbuminuria & normotensive. Mean baseline BP: 133/76 mmHg Age range: (mean age: 40 years) Hypertensive patients (%): 0 Baseline co-morbidities (%): None Intervention: Three groups ACEI: Ramipril Smg/day vs. ramipril 1.25 mg/day vs. placebo Co-intervention: RR Concomitant non-study RAS blockers: NR Primary and secondary outcomes: Progression of albumin excretion rate (AER) from microalbuminuria to macroalbuminuria, progression to normoalbuminuria, serum creatinine, GFR & BP. Funding Source: Hoechst Marion Roussel (Aventis) ATTEMPT-CVD (2015) (Ogawa et al., 2016) Design: Prospective, randomized, multicentre, open-label, blinded-endpoint trial (PROBE) Mean duration of follow-up: 3 years Participants: 1228 Clinical setting: HTN with at least one CV risk factor (DM, renal, cerebral peripheral artery factor) Mean baseline 6: %(): 100 Baseline co-morbidities (%): 200 (Ch	
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aggravation of renal function) Funding Source: Boehringer Ingelheim BENEDICT (2004) (Ruggenenti et al., 2004) Design: Prospective, randomized, multicentre, double-blinded, parallel trial Median duration of follow-up: 3.6 years Participants (n): 1024	Design: Prospective, randomized, multicentre, double-blinded, parallel trial Mean duration of follow-up: 2 years Participants: 140 Clinical setting: T1DM with microalbuminuria & normotensive. Mean baseline BP: 133/76 mmHg Age range: (mean age: 40 years) Hypertensive patients (%): 0 Baseline co-morbidities (%): None Intervention: Three groups ACEI: Ramipril 5mg/day vs. ramipril 1.25 mg/day vs. placebo Co-intervention: NR Concomitant non-study RAS blockers: NR Primary and secondary outcomes: Progression of albumin excretion rate (AER) from microalbuminuria to macroalbuminuria, progression to normoalbuminuria, serum creatinine, GFR & BP. Funding Source: Hoechst Marion Roussel (Aventis) ATTEMPT-CVD (2015) (Ogawa et al., 2016) Design: Prospective, randomized, multicentre, open-label, blinded-endpoint trial (PROBE) Mean duration of follow-up: 3 years Participants: 1228 Clinical setting: HTN with at least one CV risk factor (DM, renal, cerebral peripheral artery factor) Mean baseline BP: 151/84 mmHg Age range: (mean age: 66 years) Hypertensive patients (%): 100 Baseline co-morbidities (%):DM (66.5), CVD (32) Intervention: Two groups ARB: Telmisartan vs. non-ARB Co-intervention: BP-lowering agents was added to control BP level. Concomitant non-study RAS blockers: Intervention: 0.41% ACEI. Control: 12.6% ACEIs
Funding Source: Boehringer Ingelheim BENEDICT (2004) (Ruggenenti et al., 2004) Design: Prospective, randomized, multicentre, double-blinded, parallel trial Median duration of follow-up: 3.6 years Participants (n): 1024	Design: Prospective, randomized, multicentre, double-blinded, parallel trial Mean duration of follow-up: 2 years Participants: 140 Clinical setting: T1DM with microalbuminuria & normotensive. Mean baseline BP: 133/76 mmHg Age range: (mean age: 40 years) Hypertensive patients (%): 0 Baseline co-morbidities (%): None Intervention: Three groups ACEI: Ramipril 5mg/day vs. ramipril 1.25 mg/day vs. placebo Co-intervention: NR Concomitant non-study RAS blockers: NR Primary and secondary outcomes: Progression of albumin excretion rate (AER) from microalbuminuria to macroalbuminuria, progression to normoalbuminuria, serum creatinine, GFR & BP. Funding Source: Hoechst Marion Roussel (Aventis) ATTEMPT-CVD (2015) (Ogawa et al., 2016) Design: Prospective, randomized, multicentre, open-label, blinded-endpoint trial (PROBE) Mean duration of follow-up: 3 years Participants: 1228 Clinical setting: HTN with at least one CV risk factor (DM, renal, cerebral peripheral artery factor) Mean baseline BP: 151/84 mmHg Age range: (mean age: 66 years) Hypertensive patients (%): 100 Baseline co-morbidities (%): 100 Baseline co-morbidities (%): M (66.5), CVD (32) Intervention: Two groups ARB: Telmisartan vs. non-ARB Co-intervention: BP-lowering agents was added to control BP level. Concomitant non-study RAS blockers: Intervention: 0.41% ACEI. Control: 12.6% ACEIS Primary and secondary outcomes: Changes in urinary albumin creatinine ration (UACR) & plasma BNP levels from
BENEDICT (2004) (Ruggenenti et al., 2004) Design: Prospective, randomized, multicentre, double-blinded, parallel trial Median duration of follow-up: 3.6 years Participants (n): 1024	Design: Prospective, randomized, multicentre, double-blinded, parallel trial Mean duration of follow-up: 2 years Participants: 140 Clinical setting: T1DM with microalbuminuria & normotensive. Mean baseline BP: 133/76 mmHg Age range: (mean age: 40 years) Hypertensive patients (%): 0 Baseline co-morbidities (%): None Intervention: Three groups ACEI: Ramipril 5mg/day vs. ramipril 1.25 mg/day vs. placebo Co-intervention: Three groups ACEI: Ramipril 5mg/day vs. ramipril 1.25 mg/day vs. placebo Co-intervention: NR Concomitant non-study RAS blockers: NR Primary and secondary outcomes: Progression of albumin excretion rate (AER) from microalbuminuria to macroalbuminuria, progression to normoalbuminuria, serum creatinine, GFR & BP. Funding Source: Hoechst Marion Roussel (Aventis) ATTEMPT-CVD (2015) (Ogawa et al., 2016) Design: Prospective, randomized, multicentre, open-label, blinded-endpoint trial (PROBE) Mean duration of follow-up: 3 years Participants: 1228 Clinical setting: HTN with at least one CV risk factor (DM, renal, cerebral peripheral artery factor) Mean baseline BP: 151/84 mmHg Age range: (mean age: 66 years) Hypertensive patients (%): 100 Baseline co-morbidities (%):DM (66.5), CVD (32) Intervention: Two groups ARB: Telimisartan vs. non-ARB Co-intervention: BP-lowering agents was added to control BP level. Concomitant non-study RAS blockers: Intervention: 0.41% ACEI. Control: 12.6% ACEIs Primary and secondary outcomes: Changes in urinary albumin creatinine ration (UACR) & plasma BNP levels from baseline. Occurrence of cerebral events, cardiac, aortic/peripheral arterial events, complication of diabetes and
Design: Prospective, randomized, multicentre, double-blinded, parallel trial Median duration of follow-up: 3.6 years Participants (n): 1024	Design: Prospective, randomized, multicentre, double-blinded, parallel trial Mean duration of follow-up: 2 years Participants: 140 Clinical setting: T1DM with microalbuminuria & normotensive. Mean baseline BP: 133/76 mmHg Age range: (mean age: 40 years) Hypertensive patients (%): 0 Baseline co-morbidities (%): None Intervention: Three groups ACEI: Ramipril 5mg/day vs. ramipril 1.25 mg/day vs. placebo Co-intervention: NR Concomitant non-study RAS blockers: NR Primary and secondary outcomes: Progression of albumin excretion rate (AER) from microalbuminuria to macroalbuminuria, progression to normoalbuminuria, serum creatinine, GFR & BP. Funding Source: Hoechst Marion Roussel (Aventis) ATTEMPT-CVD (2015) (Ogawa et al., 2016) Design: Prospective, randomized, multicentre, open-label, blinded-endpoint trial (PROBE) Mean duration of follow-up: 3 years Participants: 1228 Clinical setting: HTN with at least one CV risk factor (DM, renal, cerebral peripheral artery factor) Mean aseline BP: 151/84 mmHg Age range: (mean age: 66 years) Hypertensive patients (%): 100 Baseline co-morbidities (%):DM (66.5), CVD (32) Intervention: Two groups ARB: Telmisartan vs. non-ARB Co-intervention: BP: Owering agents was added to control BP level. Concomitant non-study RAS blockers: Intervention: 0.41% ACEI. Control: 12.6% ACEIs Primary and secondary outcomes: Changes in urinary albumin creatinine ration (UACR) & plasma BNP levels from baseline. Occurrence of cerebral events, cardiac, aortic/peripheral arterial events, complication of diabetes and aggravation of renal function)
Median duration of follow-up: 3.6 years Participants (n): 1024	Design: Prospective, randomized, multicentre, double-blinded, parallel trial Mean duration of follow-up: 2 years Participants: 140 Clinical setting: T1DM with microalbuminuria & normotensive. Mean baseline BP: 133/76 mmHg Age range: (mean age: 40 years) Hypertensive patients (%): 0 Baseline co-morbidities (%): None Intervention: Three groups ACEI: Ramipril 5mg/day vs. ramipril 1.25 mg/day vs. placebo Co-intervention: NR Concomitant non-study RAS blockers: NR Primary and secondary outcomes: Progression of albumin excretion rate (AER) from microalbuminuria to macroalbuminuria, progression to normoalbuminuria, serum creatinine, GFR & BP. Funding Source: Hoechst Marion Roussel (Aventis) ATTEMPT-CVD (2015) (Ogawa et al., 2016) Design: Prospective, randomized, multicentre, open-label, blinded-endpoint trial (PROBE) Mean duration of follow-up: 3 years Participants: 1228 Clinical setting: HTN with at least one CV risk factor (DM, renal, cerebral peripheral artery factor) Mean baseline BP: 151/84 mmHg Age range: (mean age: 66 years) Hypertensive patients (%): 100 Baseline co-morbidities (%):100 (66.5), CVD (32) Intervention: Two groups ARB: Telmisartan vs. non-ARB Co-intervention: BP-lowering agents was added to control BP level. Concomitant non-study RAS blockers: Intervention: 0.41% ACEI. Control: 12.6% ACEIS Primary and secondary outcomes: Changes in urinary albumin creatinine ration (UACR) & plasma BNP levels from baseline. Occurrence of cerebral events, cardiac, aortic/peripheral arterial events, complication of diabetes and aggravation of renal function) Funding Source: Boehringer Ingelheim
Median duration of follow-up: 3.6 years Participants (n): 1024	Design: Prospective, randomized, multicentre, double-blinded, parallel trial Mean duration of follow-up: 2 years Participants: 140 Clinical setting: T1DM with microalbuminuria & normotensive. Mean baseline BP: 133/76 mmHg Age range: (mean age: 40 years) Hypertensive patients (%): 0 Baseline co-morbidities (%): None Intervention: Three groups ACEI: Ramipril Simg/day vs. ramipril 1.25 mg/day vs. placebo Co-intervention: NR Concomitant non-study RAS blockers: NR Primary and secondary outcomes: Progression of albumin excretion rate (AER) from microalbuminuria to macroalbuminuria, progression to normoalbuminuria, serum creatinine, GFR & BP. Funding Source: Hoechst Marion Roussel (Aventis) ATTEMPT-CVD (2015) (Ogawa et al., 2016) Design: Prospective, randomized, multicentre, open-label, blinded-endpoint trial (PROBE) Mean duration of follow-up: 3 years Participants: 1228 Clinical setting: HTN with at least one CV risk factor (DM, renal, cerebral peripheral artery factor) Mean baseline 69: 151/84 mmHg Age range: (mean age: 66 years) Hypertensive patients (%): 100 Baseline co-morbidities (%):DM (66.5), CVD (32) Intervention: Two groups ARB: Telmisartan vs. non-ARB Co-intervention: BP-lowering agents was added to control BP level. Concomitant non-study RAS blockers: Intervention: 0.41% ACEI. Control: 12.6% ACEIS Primary and secondary outcomes: Changes in urinary albumin creatinine ration (UACR) & plasma BNP levels from baseline. Occurrence of cerebral events, cardiac, aortic/peripheral arterial events, complication of diabetes and aggravation of renal function) Funding Source: Boehringer Ingelheim BENEDICT (2004) (Ruggenenti et al., 2004)
Participants (n): 1024	Design: Prospective, randomized, multicentre, double-blinded, parallel trial Mean duration of follow-up: 2 years Participants: 140 Clinical setting: T1DM with microalbuminuria & normotensive. Mean baseline BP: 133/76 mmHg Age range: (mean age: 40 years) Hypertensive patients (%): 0 Baseline co-morbidities (%): None Intervention: Three groups ACEI: Ramipril Simg/day vs. ramipril 1.25 mg/day vs. placebo Co-intervention: NR Concomitant non-study RAS blockers: NR Primary and secondary outcomes: Progression of albumin excretion rate (AER) from microalbuminuria to macroalbuminuria, progression to normoalbuminuria, serum creatinine, GFR & BP. Funding Source: Hoechst Marion Roussel (Aventis) ATTEMPT-CVD (2015) (Ogawa et al., 2016) Design: Prospective, randomized, multicentre, open-label, blinded-endpoint trial (PROBE) Mean duration of follow-up: 3 years Participants: 1228 Clinical setting: HTN with at least one CV risk factor (DM, renal, cerebral peripheral artery factor) Mean baseline 69: 151/84 mmHg Age range: (mean age: 66 years) Hypertensive patients (%): 100 Baseline co-morbidities (%):DM (66.5), CVD (32) Intervention: Two groups ARB: Telmisartan vs. non-ARB Co-intervention: BP-lowering agents was added to control BP level. Concomitant non-study RAS blockers: Intervention: 0.41% ACEI. Control: 12.6% ACEIS Primary and secondary outcomes: Changes in urinary albumin creatinine ration (UACR) & plasma BNP levels from baseline. Occurrence of cerebral events, cardiac, aortic/peripheral arterial events, complication of diabetes and aggravation of renal function) Funding Source: Boehringer Ingelheim BENEDICT (2004) (Ruggenenti et al., 2004)
	Design: Prospective, randomized, multicentre, double-blinded, parallel trial Mean duration of follow-up: 2 years Participants: 140 Clinical setting: T1DM with microalbuminuria & normotensive. Mean baseline BP: 133/76 mmHg Age range: (mean age: 40 years) Hypertensive patients (%): 0 Baseline co-morbidities (%): None Intervention: Three groups ACEI: Ramipril 5mg/day vs. ramipril 1.25 mg/day vs. placebo Co-intervention: NR Concomitant non-study RAS blockers: NR Primary and secondary outcomes: Progression of albumin excretion rate (AER) from microalbuminuria to macroalbuminuria, progression to normoalbuminuria, serum creatinine, GFR & BP. Funding Source: Hoechts Marion Roussel (Aventis) ATTEMPT-CVD (2015) (Ogawa et al., 2016) Design: Prospective, randomized, multicentre, open-label, blinded-endpoint trial (PROBE) Mean duration of follow-up: 3 years Participants: 1228 Clinical setting: HTN with at least one CV risk factor (DM, renal, cerebral peripheral artery factor) Mean baseline BP: 151/84 mmHg Age range: (mean age: 66 years) Hypertensive patients (%): 100 Baseline co-morbidities (%):DM (66.5), CVD (32) Intervention: Two groups AR8: Telmisartan vs. non-AR8 Co-intervention: BP-160vering agents was added to control BP level. Concomitant non-study RAS blockers: Intervention: 0.41% ACEI. Control: 12.6% ACEIs Primary and secondary outcomes: Changes in urinary albumin creatinine ration (UACR) & plasma BNP levels from baseline. Courrence of cerebral events, cardiac, aortic/peripheral arterial events, complication of diabetes and aggravation of renal function) Funding Source: Boehringer Ingelheim BENEDICT (2004) (Ruggenenti et al., 2004) Design: Prospective, randomized, multicentre, double-blinded, parallel trial
	Design: Prospective, randomized, multicentre, double-blinded, parallel trial Mean duration of follow-up: 2 years Participants: 140 Clinical setting: T1DM with microalbuminuria & normotensive. Mean baseline BP: 133/76 mmHg Age range: (mean age: 40 years) Hypertensive patients (%): 0 Baseline co-morbidities (%): None Intervention: Three groups ACEI: Ramipril 5mg/day vs. ramipril 1.25 mg/day vs. placebo Co-intervention: R Concomitant non-study RAS blockers: NR Primary and secondary outcomes: Progression of albumin excretion rate (AER) from microalbuminuria to macroalbuminuria, progression to normoalbuminuria, serum creatinine, GFR & BP. Funding Source: Hoechst Marion Roussel (Aventis) ATTEMPT-CVD (2015) (Ogawa et al., 2016) Design: Prospective, randomized, multicentre, open-label, blinded-endpoint trial (PROBE) Mean duration of follow-up: 3 years Participants: 1228 Clinical setting: HTN with at least one CV risk factor (DM, renal, cerebral peripheral artery factor) Mean baseline BP: 151/84 mmHg Age range: (mean age: 66 years) Hypertensive patients (%): D0 Baseline co-morbidities (%):DM (66.5), CVD (32) Intervention: Two groups ARB: Telmisartan vs. non-ARB Co-intervention: BP-lowering agents was added to control BP level. Concomitant non-study RAS blockers: Intervention: 0.41% ACEI. Control: 12.6% ACEIS Primary and secondary outcomes: Changes in urinary albumin creatinine ration (UACR) & plasma BNP levels from baseline. Occurrence of cerebral events, cardiac, aortic/peripheral arterial events, complication of diabetes and aggravation of renal function) Funding Source: Boehringer Ingelheim BENEDICT (2004) (Ruggenenti et al., 2004) Design: Prospective, randomized, multicentre, double-blinded, parallel trial Median duration of follow-up: 3.6 years
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Age range: 40-older (mean age: 61 years) Hypertensive patients (%): 100 Baseline co-mortidities (%): T20M (100) Intervention: 70 control 8P, other BP-lowering agents were added in steps Concomitant non-study RAS blockers: None Primary and secondary outcomes: Progression to microalbuminuria Funding Source: Abbott (Ludwighafen, Germany). Cat et al. (2001) (Cat et al., 2001) Design: Prospective, randomized, multicentre, open label, parallel trial Mean duration of follow-up: 2.3 years Participants (n): 822 Clinical setting: 2001 (Cat et al., 2001) Design: Prospective, randomized, multicentre, open label, parallel trial Mean duration of follow-up: 2.3 years Mean baseline BP: RR Mean age: 64 years (%): 51 Baseline co-mortidities (%): NR Intervention: NR Concomitant non-study RAS blockers: NR Primary outcomes: Re-infraction, HF, sever arrythmia Concomitant non-study RAS blockers: NR Primary outcomes: Re-infraction, HF, sever arrythmia Concomitant non-study RAS blockers: NR Primary outcomes: Re-infraction, HF, sever arrythmia Concomitant non-study RAS blockers: NR Participants (1): 1977 Clinical setting: zeptify five Mational Project CAMELIOT (2004) (Missen et al., 2004) Design: Prospective, randomized, ouble-binded, parallel trial Participants (1): 1977 Clinical setting: zeptify five Mational Project CAMELIOT (2004) (Missen et al., 2004) Design: Prospective, randomized, ouble-binded, parallel trial Participants (1): 1977 Clinical setting: zeptify five Mational Project CAMELIOT (2004) (Missen et al., 2004) Design: Prospective, randomized, ouble-binded, parallel trial Participants (1): 1977 Clinical setting: Zeptify five Mational Project Concomitant non-study RAS blockers: intervention: ZAB (El 2 & RAB, Control: 33; RACE (El 2 & RAB, Clinical SETIN) Resenter co-motive KBP lowering agents were added Concomitant non-study RAS blockers: intervention: ZAB (El 2 & RAB, Control: 35, RACE (El 2 & RAB, Clinical SETIN) Resenter co-motive KBP lowering agents were added Concomitant non-st	Mean baseline BP: 150.5/87.5 mmHg
Hypertensive patients (%): 100 Baseline co-morbidities (%): 120(100) Intervention: Four groups Transloppint (2mg (ady) vs. verapamit (240 mg/day) vs. trandolapril+ sustained released verapamit (180/2 mg per day) of patients four groups Consomitant non-study PAS blockers: hore Primary and secondary outcomes: Progression to microalbuminuria Primary outcomes: Primary outcomes: Progression to microalbuminuria Primary outcomes: All & CV mortality. Secondary outcomes: All & CV mortality. Secondary outcomes: All & CV mortality. Secondary outcomes: All & CV mortality. Callect outpoint (12): 252 mg TID Construct more size infraction. Hf, sever arrythmia Funding Source: Eight Fire National Project CALMELDT (2004) (Nissen et al., 2004) Design: Prospective: randomized, double-blinded, parallel trial Mage and section Project. CALMELDT (2004) (Nissen et al., 2004) Design: Prospective: randomized, double-blinded, parallel trial Mage and baseline Bir (13): Micro (5
Intervention: Four groups concentration: To control BP, other BP-lowering agents were added in steps Concentration: To control BP, other BP-lowering agents were added in steps Concentration: To control BP, other BP-lowering agents were added in steps Concentration on study RAS blockers: None Primary and secondary outcomes: Progression to microalbuminuria Tunding Source: Abbett (Ludwigsbalen, Germany). Cal et al. (2001) (Cal et al., 2001) Design: Prospective: randonized, multicentre, open label, parallel trial Mean duration of forw-up: 2.3 years Mean baseline BP: NR Mean duration of follow-up: 2.7 yrs) Hypertonsive patients (%): 00 Baseline co-morbidities (%): NR Intervention: 1997 Clinical setting: Anglographically documented CAD Mean baseline BP: 1297/77. mmHg Age range: 30-7 (mean: 57.7, 7). Hypertonsive patients (%): 60 Baseline co-morbidities (%): 40 Baseline co-morbidities (%): 40 Committer interververver, the groups were analysed sparalely as enalapril vs., placebo 4 sna	Hypertensive patients (%): 100
Trandologni (2 mg/day) ix, verapami (240 mg/day) vs. trandolapril- sustained released verapamil (180/2 mg per day) vs. placebo Go-intervention: To control BP, other BP-lowering agents were added in steps Concomitant non-study RAS blockers: Ikne Primary and secondary outcomes: Progression to microalbuminuria Frinding Source: Abbit (Ludvighalen, Germany). Cal et al. (2001) (Cal et al., 2001) Design: Prospective, randomized, multicentre, open label, parallel trial Mean duration of follow-up: 2.37 years Mean baseline BP: IRR Primary adjective, randomized, multicentre, open label, parallel trial Mean duration of follow-up: 2.37 years Mean baseline BP: IRR Primary adjective, randomized, Sp. NR Intervention: Two groups ACEI: Catyoni 1.2, 75.25 mg TID Co-intervention: NR Concomitant non-study RAS blockers: IRR Primary outcomes: All & CV mortality. Secondary outcomes: Re-infraction, HF, sever arrythmia Funding Source: Eight-Five National Project CAKELOT (2004) (Nissen et al., 2004) Design: Prospective, randomized, double-blinded, parallel trial Mean duration of follow-up: 2 years Participants (p): 1997 Cincla setting: rangiographically documented CAD Mean baseline BP: (2077) 7 mm ² (p) Baseline co-morbidities (Sb): M (37.7). DM (17) Intervention: No other BP lowering agents were added Concomitant non-study RAS blockers: Intervention: 7% ACEI & 2% ARB. Control: 13% ACEI & 2.8 (15) ARB Primary outcomes: Inclined: V/77.0 mm ² (p) Baseline co-morbidities (Sb): M (37.7). DM (17) Intervention: No other BP lowering agents were added Concomitant non-study RAS blockers: Intervention: 7% ACEI & 2.8 (AB. Control: 13% ACEI & 2.8 (15) ARB Primary outcomes: Inclined: V/77.0 mm ² (p) Baseline co-morbidities (Sb): M (37.7). DM (17) Intervention: No other BP lowering agents were added Concomitant non-study RAS blockers: Intervention: 7% ACEI & 2.8 (AB. Control: 13% ACEI & 2.8 (15) ARB Primary outcomes: Inclined the start of	Baseline co-morbidities (%): T2DM (100)
vs. placeb vs. placeb Concentrate non-study RAS blockers: None Frimary and secondary outcomes: Progression to microalbuminuria Funding Source: Abbott (Ludwigshafen, Germany). Cal et al. (2001) (Cal et al., 2001) Design: Prospective, randomized, multicentre, open label, parallel trial Mean duration of follow-up: 2.37 years Participants (n): 822 Clinical setting: 2.4M within 75 years Clinical setting: 2.4M within 75 years Clinical setting: 2.4M within 75 years Clinical setting: 2.4M within 75 years Design: Prospective, randomized, multicentre, open label, parallel trial Mean age: C4 years Mean age: C4 year	
Co-intervention: To control &P, other &P-lowering agents were added in steps Concomitant non-study RAS blockers: None Primary and secondary outcomes: Progression to microalbuminuria Funding Source: Abbott (Ludvigshafen, Germany). Cal et al. (2001) (Cal et al., 2001) Design: Prospective, randomized, multicentre, open label, parallel trial Mean Justice (P), randomized, multicentre, open label, parallel trial Mean Justice (P), randomized (P), ra	
Concomitant non-study RAS blockers: None Finary and secondary outcomes: Progression to microalbuminuria Funding Source: Abbott (Ludwigshafen, Germany). Cai et al. (2001) (Cai et al., 2001) Design: Prospective, randomized, multicentre, open label, parallel trial Mean duration of follow-up: 2.37 years Mean baseline BP: NR Mean age: 64 years (Signal Stresson, 2000) Mean Stresson, 2000) Mean Stresson, 2000, 2000, 2000) Mean Stresson, 2000, 2000, 2000, 2000) Mean Stresson, 2000, 20	
Primary and secondary outcomes: Progression to microalbuminuria Finding Source: Abbott (Ludvigshafen, Germany). Cal et al. (2001) (Gal et al., 2001) Design: Prospective, randomized, multicentre, open label, parallel trial Mean duration of follow-up: 2.37 years Participants (n): 822 Clinical setting: AMI within 75 years Mean baseline BP: NR Mean baseline BP: NR Mean abseline BP: NR Mean abseline BP: NR Mean abseline BP: NR Mean abseline GP: NR Me	
Funding Source: Abbott (Ludwigshafen, Germany). Cali et al. (2001) (Gai et al., 2001) Design: Prospective, randomized, multicentre, open label, parallel trial Mean duration of follow-up: 2.7 years Mean baseline BP: NR Mean age: 64 years Hypertensive patients (8): 51 Baseline co-morbitities (8): 78 Prospective, randomized, double-blinded, parallel trial Mean baseline BP: NR Mean baseline BP: NR Prospective, randomized, double-blinded, parallel trial Mean baseline EBP: 18/77. Contact States (8): 78 Baseline co-morbitities (8): 78 Baseline co-morbitities (8): 78 Baseline co-morbitities (8): 78 Contact States (7): 78 Contact States (7)	
Design: Prospective, randomized, multicentre, open label, parallel trial Mean duration of follow-up: 2.17 years Mean baseline BP: NR Mean age: 64 years Hypertensive patients (%): 51 Baseline co-morbitities (%): 18 Intervention: Two groups ACEI: catopint 12.5.25 mg TiD Co-intervention: NR Concomitant non-study ARS blockers: NR Frimary outcomes: Aul & CV mortality. Secondary outcomes: Re-infraction, HF, sever arrythmia Funding Source: Eight-Five National Project CAMELOT (2004) (Nissen et al., 2004) Design: Prospective, randomized, double-blinded, parallel trial Mean duration of follow-up: 2 years Participants (n): 1997 Chicka setting: anglographically documented CAD Mean duration of follow-up: 2 years Participants (n): 1997 Chicka setting: anglographically documented CAD Mean duration of follow-up: 2 years Participants (n): 1997 Chicka setting: anglographically documented CAD Mean duration of follow-up: 2 years Participants (n): 1997 Chicka setting: anglographically documented CAD Mean baseline BP: 129/77.7 mmilg Age range: 30-70 (mean: 37.7 yrs) Hypertensive patients (%): 60 Baseline co-morbitites (%): MI (37.7), DM (17) Intervention: 3 groups Co-intervention: 0 other BP lowering agents were added Concomitant non-study RAS blockers: Intervention: ACEI & 2 % (15) ARB Frimary outcomes: Incleme of CV events (CV death, nonfatal MI, resuscitated cardica arrest, hospitalized anglina & Secondary nontainas Incleme of CV events (CV death, nonfatal MI, resuscitated cardica arrest, hospitalized anglina & Secondary nontainas (RI): 14, 2004) Design: Prospective, randomized, multicentre, double-blinded, parallel trial Median duration follow-up: 1.4 years Participants: 572 CARMEN (2004) (Komaj det al., 2004) Concentration: follow-up: 1.4 years Participants: 572 CARMEN (2004) (Komaj det al., 2004) Concentration: follow-up: 1.4 years Participants: 572 CARMEN (2004) (Komaj det al., 2011) Design: Prospective, randomized (Except non-situdy drugs) Concentration: follow-up: 4.4 years Participants: 572 CARMEN (2011) (Ckada et al., 201	Funding Source: Abbott (Ludwigshafen, Germany).
Mean duration of follow-up: 2.37 years Participants (i): 822 Clinical setting: ANI within 75 years Mean baseline BP: NR Mean age: 64 years Hypertensive patients (%): 51 Baseline co-morbidities (%): NR Intervention: Two groups ACEI: Captopril 12.5-25 mg TD Co-intervention: NR Concomitant non-study RAS blockers: NR Primary outcomes: All & CV mortality. Secondary outcomes: All & CV mortality. Age range: 30-79 (mean: 57.7 yrs) Hypertensive petients (%): 60 Baseline co-morbidities (%): MI (37.7), DM (17) Intervention: 1N other & B lowering agents were added Concomitant non-study RAS blockers: Intervention: 7% ACEI & 2% ARB. Control: 13% ACEI & 2 % (15) ARB Primary outcomes: Incidence of CV events (CV death, nonfatal MI, resuscitated cardiac arrest, hospitalized angina & Hr, fatal & nonfatal stroke, TIA, PVD) Secondary outcomes: All-cause mortality and the incidence of revascularization for PCI previous history Funding Source: Firter CARMEN (2004) (Komajd et al., 2004) Secondary outcomes: All-cause mortality and the incidence of revascularization for PCI previous history Funding Source: Firter CARMEN (2004) (Komajd et al., 2004) Secondary outcomes: All-cause mortality and the incidence of revascularization for PCI previous history Funding Source: Firter CARMEN (2004) (Komajd et al., 2004) Secondary outcomes: All-cause mortality and the incidence of revascularization for PCI previous history Funding Source: Sitter (Firter CARMEN (2004) (Source) (S) 4 Baseline co-morbidities (%): CAD (64.4) Intervention:	Cai et al. (2001) (Cai et al., 2001)
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Clinical setting: AMI within 75 years Mean baseline BP: NR Mean baseline BP: NR Mean baseline BP: NR Mean baseline BP: NR Mean baseline BP: NR Mathematical State	
Mean abseline BP: NR Mean age: 64 years Hypertensive patients (%): 51 Baseline co-morbidities (%): NR Intervention: Two groups ACEI: Captopril 12-525 mg TID Co-intervention: NR Concomitant non-study RAS blockers: NR Primary outcomes: Re-infraction, HF, sever anrythmia Funding Source: Eight-Thev National Project: CAMELOT (2004) (Nissen et al., 2004) Design: Prospective, randomized, double-blinded, parallel trial Mean duration of follow-up: 2 years. Participants (n): 1997 Chincla setting: Anglographically documented CAD Mean baseline BP: 1277.7 mmHg Age range: 30-79 (mean: 57.7 yrs) Hypertensive patients (%): 60 Baseline co-morbidities (%): MI (37.7), DM (17) Intervention: 3 groups Co-intervention: 10 mg/day +1 tab placebo vs Placebo & amlodpine Smg/day +1 tab placebo vs placebo In current review, the groups were analysed separately as enalapril vs, placebo & enalapril vs, amlodpine. Co-intervention: 10 order BP (1827, 7), RAB Primary outcomes: Incidence of CV events (CV death, nonfatal MI, resuscitated cardiac arrest, hospitalized anglina & HF, fatal & nonfatal stroke, TA, PVD) Euroding Source: Pfiler CARMEN (2004) (Komaj et al., 2004) Design: Prospective, randomized, multicentre, double-blinded, parallel triat Mean baseline BP: 131/80 mmHg Age range: 30-60der (Michael al., 2004) Design: Prospective, randomized, multicentre, double-blinded, parallel triat Mean baseline BP: 131/80 mmHg Age range: 10-60der (mean age: 62 years) Hypertensive patients (%): CAD (64.4) Intervention: Filder (Maria age: 62 years) Hypertensive patients (%): CAD (64.4) Intervention: Sile (S): CAD (64.4) Intervention: File (S): MICH (S): MICH (S): M	
Mean age: 64 years Hypertensive patients (%): 51 Baseline co-morbidities (%): NR Intervention: Two groups ACEI: Captopril 12.5-25 mg TID Contervention: RR Concomitant non-study RAS blockers: NR Primary outcomes: All & CV mortality. Secondary outcomes: All & CV mortality. Mean duration of follow-up: 2 years Participants (n): 1997 Clincial setting: Angiographically documented CAD Mean baseline BP: 12977.7 mmHg Age: range: 30-79 (mean: 57.7 yrs) Hypertensive patients (%): 60 Baseline co-morbidities (%): M(127.7), DM (17) Intervention: 3 groups ACEI: Enalapril Umg/day + 1 tab placebo vs Placebo & analodipine Smg/day + 1 tab placebo vs placebo in current review, the groups were analysed separately as enalapril vs. placebo & enalapril vs. aniodipine. Co-intervention: No other BP lowering agents were added Concomitant non-study RAS blockers: Intervention: 7% ACEI & 2 X ABB. Control: 13% ACEI & 2 X (15) ABB Firmary outcomes: Incleance of CV events (CV death, nonfatal M, resuscitated cardiac arrest, hospitalized angina & HF, fatal & nonfatal stroke, TIA, PVD) Secondary outcomes: All-cause mortality and the incidence of revascularization for PCI previous history Funding Source: Pfizer CARKEN (2004) (Komajd et al., 2004) Design: Prospective, randomized, multicentre, double-blinded, parallel trial Median duration of follow-up: 1.4 years Participants (72) Chical setting: Pospective, randomized, multicentre, open-label trial Mean baseline BP: 131/36 mmHg Age range: (Boder mean age: 62 years) Hypertensive patie	
Hypertensive patients (%): 51 Baseline c-morbidities (%): NR Concomitant non-study RAS blockers: NR Primary outcomes: Alk G.V. mortality. Secondary outcomes: Alk G.V. mortality. Mean baseline BP: 1297.77. mmHg Age range: 30-79 (mean: 57.7 yrs) Hypertensive patients (%): All (37.7), DM (17) Intervention: 3 groups ACEI: Enalapril 10mg/day + 1 tab placebo vs Placebo & malapril vs. placebo & malapril vs. andodpine. Co-intervention: No other BP lowering agents were added Concomitant non-study RAS blockers: Intervention: 7% ACEI & 2% ARB. Control: 13% ACEI & 2 % (15) ARB Primary outcomes: Incidence of CV events (CV death, nonfatal MI, resuscitated cardiac arrest, hospitalized angina & HF, frata It anontal stroke, T.A. PVD) Secondary outcomes: All-cause mortality and the incidence of revascularization for PCI previous history Funding Source: Pfteer CARMEN (2004) (Komajd et al., 2004) Design: Prospective, randomized, multicentre, double-blinded, parallel trial Median duration of follow-up: 1.8 years Participants: 572 CARMEN (2004) (Komajd et al., 2004) Design: Prospective, randomized, multicentre, double-blinded, parallel trial Median duration of follow-up: 1.8 years Participants: 572 CARMEN (2004) (Komajd et al., 2004) Design: Prospective, randomized, multicentre, double-blinded, parallel trial Median duration of follow-up: 1.8 years Participants: 572 CARMEN (2004) (Komajd et al., 2004) Design: Prospective, randomized, multicentre, open-label trial Mean duration of follow-up: 4.9 years Participants: (Dider mean age: 6.2 years) Hypertensive patients (%): 2.1 CARP (2011) (Dokada et al., 2011) Design: Prospective, randomized, mu	
Intervention: Two groups ACEI: catporth 125: 525 mg TID Co-intervention: NR Concomitant non-study RAS blockers: NR Primary outcomes: Relinfraction, HF, sever arrythmia Funding Source: Eight-Five National Project CAMELOT (2004) (Missen et al., 2004) Design: Prospective, randomized, double-blinded, parallel trial Mean duration of follow-up: 2 years Participants (1): 1997 Clinical setting: Angiographically documented CAD Mean baseline BP: 1297/77. 7mHg Mean baseline BP: 1297/77. 7mHg Mage range: 30-79 (mean: 57.7 yrs) Hypertensive patients (%): 41 (37.7), DN (17) Intervention: 3 groups ACEI: Enalapril 10mg/day + 1 tab placebo vs Placebo & anidolipine Smg/day + 1 tab placebo vs placebo in current review, the groups were analysed separately as enalapril vs. Jalaeob & enalapril vs. amiodipine. Co-intervention: No other BP lowering agents were added Concomitant non-study RAS blockers: intervention: 7% ACEI & 2 % ARB. Control: 13% ACEI & 2 % (15) ARB Primary outcomes: Incidence of CV events (CV death, nonfatal MI, resuscitated cardiac arrest, hospitalized angina & HF, fatal & nonfatal stroke, T.A. PVD) Secondary outcomes: All-cause mortality and the incidence of revascularization for PCI previous history Finding Source: Prizer CARMEN (2004) (Komajd et al., 2004) Design: Prospective, randomized, multicentre, double-blinded, parallel trial Median duration of follow-up: 1.8 years Participants: S72 Clinical setting: Nid CHF (NYHA Class I-III) Mean baseline BP: 131/80 mmHg Age range: 16-older (mean age: 62 years) Hypertensive patients (%): CAD (64.4) Intervention: Three groups ACEI: Enalapril 10mg bid vs. carveditol 25-50 mg bid vs. enalapril plus carveditol Co-intervention: added as needed (Except non-study drugs) Concomitant non-study RAS blockers: NR Primary and secondary outcomes: Absolute change in LV end systolic volume index (LVESVI) & all & CV mortality, CV events Funding Source: SmithKline Beecham & Roche CARP (2011) (Dokada et al., 2011) Design: Prospective, randomized, multicentre, open-label trial Mean baseline	Hypertensive patients (%): 51
ACEI: captopril 12.5-25 mg TID Contenvention: NR Concomitant non-study RAS blockers: NR Primary outcomes: All & CV mortality. Secondary outcomes: Re-infraction. <i>HF</i> , sever arrythmia Funding Source: Eight-Five National Project CARELOT (2004) (Nissen et al., 2004) Design: Prospective, randomized, double-blinded, parallel trial Mean duration of follow-up: 2 years Participants (n): 1997 Clinical setting: Angiographically documented CAD Mean baseline BF: 1297/7.7 mmHg Age range: 30-79 (mean: 57.7 yrs) Hypertensive patients (%): 60 Baseline co-morbidities (%): MI (37.7), DM (17) Intervention: 3 groups ACEE: Enalapril 10mg/day + 1 tab placebo vs Placebo & analopti vs. placebo & analopti vs. placebo & ncurrent review, the groups were analysed separately as enalapri vs. placebo & analopti vs. placebo & analopti vs. placebo & Contenvention: No other BP lowering agents were added Concomitant non-study RAS blockers: Intervention: 7% ACEI & 2% ARB. Control:13% ACEI & 2 % (15) ARB Primary outcomes; Incidence of CV events (CV deatin, nonfatal MI, resuscitated cardiac arrest, hospitalized angina & Hr, fatal & nonfatal stroke, TA, PVD) Secondary outcomes; All-cause mortality and the incidence of revascularization for PCI previous history Funding Source: Pitzer CARMEN (2004) (Komajd et al., 2004) Design: Prospective, randomized, multicentre, double-blinded, parallel trial Median duration of follow-up: 1.8 years Participants: 72 Clinical setting: Mid CHF (WTHA Class I-III) Mean baseline BP: 131/80 mmHg Age range: 18-Older (mean age: 62 years) Hypertensive patients (%): 4 Baseline co-morbidities (%): CAD (64.4) Intervention: added as needed (Except non-study drugs) Concomitant non-study AS blockers: NR Primary and secondary outcomes: Absolute change in LV end systolic volume index (LVESVI) & all & CV mortality, CV events Funding Source: SmithKline Beecham & Roche CARP (2011) (Okada et al., 2011) Design: Prospective, randomized, multicentre, open-label trial Mean duration of follow-up: 4.4 years Participants (h): 191 Design: Prosp	Baseline co-morbidities (%): NR
Co-intervention: NR Concomitant non-study RAS blockers; NR Primary outcomes: All G.V. mortality. Secondary outcomes: Reinforation, HF, sever arrythmia Funding Source: Eight Five National Project CAMELOT (2004) (Nissen et al., 2004) Design: Prospective, randomized, double-blinded, parallel trial Mean baseline BP: 129/77. 7mmlg Mean baseline BP: 129/77. 7mmlg Mean baseline BP: 129/77. 7mmlg Mean baseline BP: 129/77. 7mmlg Mage range: 30-79 (mean: 57.7 yrs) Hypertensive patients (%): 60 Baseline co-morbidities (%): MI (37.7), DM (17) Intervention: 3 groups ACEI: Enalapril 10mg /day + 1 tab placebo vs Placebo & anidotipine Smg /day + 1 tab placebo vs placebo In current review, the groups were analysed separately as enalapril vs. placebo & enalapril vs. anidotipine. Co-intervention: No other BP lowering agents were added Concomitant non-study RAS blockers: Intervention: 7% ACEI & 2% ARB. Control: 13% ACEI & 2 % (15) ARB Primary outcomes: Incidence of CV events (CV death, nonfatal MI, resuscitated cardiac arrest, hospitalized angina & HF, fatal & nonfatal stroke, TA, PVD) Secondary outcomes: All-cause mortality and the incidence of revascularization for PCI previous history Funding Source: Prizer CARMEN (2004) (Komajd et al., 2004) Besign: Prospective, randomized, multicentre, double-blinded, parallel trial Median duration of follow-up: 1.8 years Participants: 572 Clinical strike, Fill Mean baseline BP: 131/80 mmHg Age range: 18-01der (mean age: 62 years) Hypertensive patients (%): CAD (64.4) Easeline co-morbidities (%): CAD (64.4) Easeline co-morbidities (%): CAD (64.4) Easeline co-morbidities (%): CAD (64.4) Easeline co-morbidities (%): CAD (64.4) Baseline Co-morbidities (%): CAD (64.4) Easeline co-morbidities (%): CAD (64.4) Baseline C	
Concomitant non-study RAS blockers: NR Primary outcomes: All & CV mortality. Secondary outcomes: Re-infraction, HF, sever arrythmia Funding Source: Eight-Five National Project CARELOT (2004) (Nissen et al., 2004) Design: Prospective, randomized, double-blinded, parallel trial Mean duration of follow-up: 2 years Participants (n): 1997 Clinical setting: Angiographically documented CAD Mean baseline BP: 129/77.7 mmHg Age range: 30-79 (mean: S7. Yrs) Hypertensive patients (%): 60 Baseline co-morbidities (%): M (37.7), DM (17) Intervention: 3 groups ACEI: Enalgori 10mg/day + 1 tab placebo vs Placebo & analogipine 5mg/day + 1 tab placebo vs placebo In current review, the groups were analysed separately as enalgority vs. placebo & enalgority vs. analodipine. Co-intervention: No other BP lowering agents were added Concomitant non-study RAS blockers: Intervention: 7% ACEI & 2% ARB. Control: 13% ACEI & 2 % (15) ARB Primary outcomes: All-cause mortality and the incidence of revascularization for PCI previous history Funding Source: Prizer CARENC (2004) (Komajd et al., 2004) Design: Prospective, randomized, multicentre, double-blinded, parallel trial Media duration of follow-up: 1.8 years Participants: 72 Clinical setting: Mild CHF (NYHA Class I-III) Mean baseline BP: 131/80 mmHg Age range: 18-older (mean age: 62 years) Hypertensive patients (%): 43 Baseline co-morbidities (%): CAD (64.4) Intervention: Three groups ACEI: Enalgoritic 10 mg bid vs. carvediiol 25-50 mg bid vs. enalapril plus carvediiol Co-intervention: added as needed (Except non-study drugs) Concomitant non-study ARS blockers: NR Primary and secondary outcomes: Absolute change in LV end systolic volume index (LVESVI) & all & CV mortality, CV events Funding Source: SmithKline Beecham & Roche CARP (2011) (Okada et al., 2011) Design: Prospective, randomized, multicentre, open-label trial Mean duration of follow-up: 4.4 years Participants (P): 104, Secondary outcomes: Absolute change in LV end systolic volume index (LVESVI)	
Primary outcomes: Re-informative. Secondary outcomes: Re-informative. Eunding Source: Eight-Five National Project CAMELOT (2004) (Nissen et al., 2004) Design: Prospective, randomized, double-blinded, parallel trial Mean duration of follow-up; 2 years Participants (b): 1997 Clinical setting: Angiographically documented CAD Mean baseline BP: 129/77. 7mmilg Age range: 30-79 (mean: 57.7 yrs) Hypertensive patients (%): 60 Baseline co-morbidities (%): MI (37.7), DM (17) Intervention: 3 groups ACEI: Enalapril 10mg/day + 1 tab placebo vs Placebo & amolopipine Sing/day + 1 tab placebo vs placebo In current review, the groups were analysed separately as enalapril vs. placebo & enalapril vs. amolopipine. Co-intervention: No other BP lowering agents were added Concomitant non-study RAS blockers: Intervention; 7% ACEI & 2% ARB. Control: 13% ACEI & 2% (15) ARB Primary outcomes: Incidence of CV events (CV death, nonfatal M, resuscitated cardica carrest, hospitalized angina & HF, fatal & nonfatal stroke, TIA, PVD) Secondary outcomes: Incidence of CV events (CV death, nonfatal M, resuscitated cardica carrest, hospitalized angina & HF, fatal & nonfatal stroke, TIA, PVD) Secondary outcomes: Incidence of CV events (Nonfatal M, resuscitated cardica carrest, hospitalized angina & HF, fatal & nonfatal stroke, TIA, PVD) Secondary outcomes: Incidence of Vevents Funding Source: Prizer CARMEN (2004) (Komgdi et al., 2004) Design: Prospective, randomized, multicentre, double-blinded, parallel trial Median duration of follow-up: 1.8 years Participants: 572 Clinical setting: Mild OHF (NYHA Class I-III) Mean baseline BP: 131/30 mmilg Age range: 18-older (mean age: 62 years) Hypertensive patients (%): 24 Baseline co-morbidities (%): CAD (64.4) Intervention: added as needed (Except non-study drugs) Conomitant non-study RAS blockers: NR Primary and secondary outcomes: Absolute change in LV end systolic volume index (LVESVI) & all & CV mortality, CV events Primary and secondary outcomes: Absolute change in LV	
Secondary outcomes: Re-infraction, ^I F, sever arrythmia Funding Source: Eight-Five National Project CAMELOT (2004) (Nissen et al., 2004) Design: Prospective, randomized, double-blinded, parallel trial Mean duration of follow-up: 2 years Participants (n): 1997 Clinical settine; Angiographically documented CAD Mean baseline BP: 129/77.7 mmHg Age range: 30-79 (mean: 57.7 yrs) Hypertensive patients (%): 60 Baseline co-morbidities (%): MI (37.7), DM (17) Intervention: 3 groups ACEI: Enalapril 10mg/day - 1 tab placebo vs Placebo & amlodpine 5mg/day + 1 tab placebo vs placebo Intervention: 3 groups ACEI: Enalapril 10mg/day - 1 tab placebo vs Placebo & amlodpine 5mg/day + 1 tab placebo vs placebo Incurrent review, the groups were analysed separately as enalapril vs. placebo & enalapril vs. amlodpine. Co-intervention: No other BP lowering agents were added Concomitant non-study RAS blockers: Intervention: 7% ACEI & 2% ABE. Control:13% ACEI & 2 % (15) ARB Primary outcomes: Incidence of CV events (CV death, nonfatal MI, resuscitated cardiac arrest, hospitalized angina & HF, fatal & nonfatal stroke, TA, PVD) Secondary outcomes: All-cause mortality and the incidence of revascularization for PCI previous history Funding Source: Prizer CARMEN (2004) (Komajd et al., 2004) Design: Prospective, randomized, multicentre, double-blinded, parallel trial Median duration of follow-up: 1.8 years Participants: 572 Clinical setting: Mild CH (NYHA Class I-III) Mean baseline BP: 131/80 mmHg Age range: 16-older (mean age: 62 years) Hypertensive patients (%): CAD (64.4) Intervention: Three groups ACEI: Enalapril 10 mg bid vs. carvediol 25-50 mg bid vs. enalapril plus carvediol Co-intervention: Three groups ACEI: Enalapril 10 mg bid vs. carvediol 25-50 mg bid vs. enalapril plus carvediol Co-intervention: Three groups ACEI: Enalapril 10 mg bid vs. carvediol 25-50 mg bid vs. enalapril plus carvediol Co-intervention: Three groups ACEI: Enalapril 10 mg bid vs. carvediol 25-50 mg bid vs. enalapril plus carvedi	Primary outcomes: All & CV mortality.
Funding Source: Eight-Five National Project CAMELOT (2004) (Nissen et al., 2004) Design: Prospective, randomized, double-blinded, parallel trial Mean duration of follow-up; 2 years Participants (b): 1997 Clinical setting: Angiographically documented CAD Mean baseline BP: 129/77.7 mmlg Age range: 30-79 (mean: 57.7 yrs) Hypertensive patients (%): A0 (37.7), DM (17) Intervention: 3 groups ACEI: Enalapril 10mg/day + 1 tab placebo vs Placebo & amlodpipne 5mg/day + 1 tab placebo vs placebo Intervention: 3 groups ACEI: Enalapril 10mg/day + 1 tab placebo vs Placebo & amlodpipne 5mg/day + 1 tab placebo vs placebo Intervention: No other BP lowering agents were added Concomitant non-study RAS blockers: Intervention; 7% ACEI & 2% ARB. Control: 13% ACEI & 2 % (15) ARB Primary outcomes: Incidence of CV events (CV death, nonfatal MI, resuscitated carleat arrest, hospitalized angina & HF, fatal & nonfatal stroke, TIA, PVD) Secondary outcomes: Incidence of CV events (CV death, nonfatal MI, resuscitated carleat rest, hospitalized angina & HF, fatal & nonfatal stroke, TIA, PVD) Secondary outcomes: Incidence of CV events (CV death, nonfatal MI, resuscitated carleat arrest, hospitalized angina & HF, fatal & nonfatal stroke, TIA, PVD) Secondary outcomes: All-cance mortality and the incidence of revascularization for PCI previous history Funding Source: Prizer CARMEN (2004) (Komajd et al., 2004) Design: Prospective, randomized, multicentre, double-blinded, parallel trial Meetian duration of follow-up: 1.8 years Participants: 572 Clinical setting: Mild CHF (NYHA Class I-III) Mean baseline BP: 131/30 mmlig Age range: 16-older (mean age: 62 years) Hypertensive patients (%): 24 Baseline co-morbidities (%): CAD (64.4) Intervention: added as needed (Except non-study drugs) Concomitant non-study RAS blockers: NR Primary and secondary outcomes: Absolute change in LV end systolic volume index (LVESVI) & all & CV mortality, CV events Funding Source: SmithKline Beecham & Roche CARP (2011) (Okada et al., 2011	Secondary outcomes: Re-infraction, HF, sever arrythmia
Design: Prospective, randomized, double-blinded, parallel trial Mean duration of follow-up: 2 years Participants (n): 1997 Clinical setting: Angiographically documented CAD Mean baseline BP: 129/77. 7mmHg Age range: 30-79 (mean: 57.7 yrs) Hypertensive patients (%): 60 Baseline co-morbidities (%): MI (37.7), DM (17) Intervention: 3 groups ACEI: Enalapril 10mg/day + 1 tab placebo vs Placebo & amlodipine 5mg/day + 1 tab placebo vs placebo in current review, the groups were analysed separately as enalapril vs. placebo & enalapril vs. amlodipine. Co-intervention: No other BP lowering agents were added Concomitant non-study RAS blockers: Intervention: 7% ACEI & 2% ARB. Control: 13% ACEI & 4 (15) ARB Primary outcomes: Incidence of CV events (CV death, nonfatal MI, resuscitated cardiac arrest, hospitalized angina & HF, fatal & nonfatal stroke, TIA, PVD) Secondary outcomes: Incidence of CV events (CV death, nonfatal MI, resuscitated cardiac arrest, hospitalized angina & HF, fatal & nonfatal stroke, TIA, PVD) Secondary outcomes: Incidence of CV events (CV death, nonfatal MI, resuscitated cardiac arrest, hospitalized angina & HF, fatal & nonfatal stroke, TIA, PVD) Secondary outcomes: Incidencetre, double-blinded, parallel trial Median duration of follow-up: 1.8 years Participants; 572 Clinical setting: Mild CHF (NYHA Class I-III) Mean baseline BP: 131/80 mmHg Age range: 18-older (mean age: 62 years) Hypertensive patients (%): CAD (64.4) Intervention: Three groups CAEI: Enalapril 10 mg bid vs. carvedilol 25-50 mg bid vs. enalapril plus carvedilol Co-intervention: added as needed (Except non-study drugs) Concomitant non-study RAS blockers: NR Primary and secondary outcomes: Absolute change in LV end systolic volume index (LVESVI) & all & CV mortality, CV Events Participants (n): 191 Clinical setting: Post-percutaneous coronary interventions (PCI) (next day) with bare-metal stents (BMS) Mean baseline BP: 134/76 mmHg Age range: (mean age: 65 years) Hypertensive patients (%): 7.2.3 Baseline	Funding Source: Eight-Five National Project
Mean duration of follow-up: 2 years Participants (n): 1997 Clinical setting: Angiographically documented CAD Mean baseline BP: 129/77.7 mmHg Age range: 30-79 (mean: 57.7 yrs) Hypertensive patients (%): 60 Baseline co-morbidities (%): 60 Baseline co-morbidities (%): 60 Co-intervention: 3 groups ACEI: Enalapril 10mg/day + 1 tab placebo vs Placebo & anilodipine 5mg/day + 1 tab placebo vs placebo in current review, the groups were analysed separately as enalapril vs. placebo & enalapril vs. anilodipine. Co-intervention: No other BP lowering agents were added Concomitant non-study RAS blockers: Intervention: 7% ACEI & 2% ARB. Control: 13% ACEI & 2 % (15) ARB Primary outcomes: Incidence of CV events (CV death, nonfatal MI, resuscitated cardiac arrest, hospitalized angina & HF, fatal & fnorfatal stroke, TA, PVD) Secondary outcomes: All-cause mortality and the incidence of revascularization for PCI previous history Funding Source: Pizer CARMEN (2004) (Komajd et al., 2004) Design: Prospective, randomized, multicentre, double-blinded, parallel trial Meedina duration of follow-up: 1.8 years Participants: 572 Clinical setting: Mild CHF (NYHA Class I-III) Mean baseline BP: 131/80 mmHg Age range: 18-older (mean age: 62 years) Hypertensive patients (%): CAD (64.4) Intervention: Three groups ACEI: Enalapril 10 mg bid vs. carvedilol 25-50 mg bid vs. enalapril plus carvedilol Co-intervention: added as needed (Except non-study drugs) Concomitant non-study RAS blockers: NR Primary and secondary outcomes: Absolute change in LV end systolic volume index (LVESVI) & all & CV mortality, CV events Funding Source: SmithKline Beecham & Roche CARP (2011) (Okada et al., 2011) Design: Prospective, randomized, multicentre, open-label trial Mean duration of follow-up: 4.4 years Participants (%): 72.3 Baseline co-morbidities (%): MI (41), DM (40) Intervention: Two groups ABB: valsatriat 40-80 mg/day vs. non-ARB Co-intervention: NR Conconstiant non-study RAS blockers: Intervention: 13% ACEI & 2% ARB. Contr	CAMELOT (2004) (Nissen et al., 2004)
Participants (n): 1997 Clinical setting: Angiographically documented CAD Mean baseline BP: 129/77. 7 mrlig Age range: 30-79 (mean: 57.7 yrs) Hypertensive patients (%): 40 (37.7), DM (17) Intervention: 3 groups ACEI: Enalapril 10mg/day + 1 tab placebo vs Placebo & anilodripine 5mg/day + 1 tab placebo vs placebo In current review, the groups were analysed separately as enalapril vs. placebo & enalapril vs. anilodipine. Co-intervention: No other BP lowering agents were added Concomitant non-study RAS blockers: Intervention: 7% ACEI & 2% ARB. Control: 13% ACEI & 2 % (15) ARB Primary outcomes: Incidence of CV events (CV death, nonfatal MI, resuscitated cardiac arrest, hospitalized angina & HF, fatal & nonfatal stroke, TIA, PVD) Secondary outcomes: Incidence of CV events (CV death, nonfatal MI, resuscitated cardiac arrest, hospitalized angina & HF, fatal & nonfatal stroke, TIA, PVD) Secondary outcomes: Incidence of CV events (CV death, nonfatal MI, resuscitated cardiac arrest, hospitalized angina & HF, fatal & nonfatal stroke, TIA, PVD) Secondary outcomes: Incidence of CV events (CV death, nonfatal MI, resuscitated Cardiac arrest, hospitalized angina & HF, fatal & nonfatal stroke, TIA, PVD) Secondary outcomes: Incidence of CV events CARMEN (2004) (Komajd et al., 2004) Design: Prospective, randomized, multicentre, double-blinded, parallel trial Mean baseline BP: 131/80 mmhg Age range: (B-older (mean age: 62 years) Hypertensive patients (%): 24 Baseline co-morbidities (%): CAD (64.4) Intervention: Three groups CARE Chalapril 10 mg bid vs. carveditol 25-50 mg bid vs. enalapril plus carveditol Co-intervention: added as needed (Except non-study drugs) Concomitant non-study RAS blockers: NR Primary and secondary outcomes: Absolute change in LV end systolic volume index (LVESVI) & all & CV mortality, CV events Participants (n): 191 Clincia setting: Post-percutaneous coronary interventions (PCI) (next day) with bare-metal stents (BMS) Mean baseline BP: 131/76 mmHg Age range: (mean age: 65 ye	Design: Prospective, randomized, double-blinded, parallel trial
Clinical setting: Angiographically documented CAD Mean baseline BP: 129/77.7 mmHg Age range: 30-79 (mean: 57.7 yrs) Hypertensive patients (%): 60 Baseline co-morbidities (%): MI (37.7), DM (17) Intervention: 3 groups ACEI: Enalapril 10mg/day + 1 tab placebo vs Placebo & anlodipine 5mg/day + 1 tab placebo vs placebo In current review, the groups were analysed separately as enalapril vs. placebo & enalapril vs. amlodipine. Co-intervention: No other BP lowering agents were added Concomitant non-study RAS blockers: Intervention: 7% ACEI & 2% ARB. Control: 13% ACEI & 2 % (15) ARB Primary outcomes: Incidence of CV events (CV death, nonfatal MI, resuscitated cardiac arrest, hospitalized angina & HF, fatal & nonfatal stroke, TIA, PVD) Secondary outcomes: All-cause mortality and the incidence of revascularization for PCI previous history Funding Source: Pfizer CARMEN (2004) (Komajd et al., 2004) Design: Prospective, randomized, multicentre, double-blinded, parallel trial Median duration of follow-up: 1.8 years Participants: 572 Clinical setting: Mild CHF (NYHA Class I-III) Mean baseline DP: 131/30 mmHg Age range: 18-older (mean age: 62 years) Hypertensive patients (%): 34 Baseline co-morbidities (%): 240 (64.4) Intervention: Three groups ACEI: Enalapril 10 mg bid vs. carvedilol 25-50 mg bid vs. enalapril plus carvedilol Co-intervention: added as needed (Except non-study drugs) Concomitant non-study RAS blockers: NR Primary and secondary outcomes; Absolute change in LV end systolic volume index (LVESVI) & all & CV mortality, CV events Funding Source: SmithKline Beecham & Roche CARP (2011) (Okada et al., 2011) Design: Prospective, randomized, multicentre, open-label trial Mean duration of follow-up: 4.4 years Participants (%); 172. 3 Baseline co-morbidities (%); 172. 3 Baseline co-morbidities (%); 174. 7 Baseline co-morbidities (%); 174. 7	Mean duration of follow-up: 2 years
Mean baseline BP: 129/77.7 mmHg Age range: 30-79 (mean: 57.7 yrs) Hypertensive patients (%): 60 Baseline co-morbidities (%): MI (37.7), DM (17) Intervention: 3 groups ACEI: Enalapril 10mg/day + 1 tab placebo vs Placebo & amlodipine 5mg/day + 1 tab placebo vs placebo In current review, the groups were analysed separately as enalapril vs. placebo & enalapril vs. amlodipine. Co-intervention: No other BP lowering agents were added Concomitant non-study RAS blockers: Intervention: 7% ACEI & 2% ARB. Control: 13% ACEI & 2 % (15) ARB Primary outcomes: Incidence of CV events (CV death, nonfatal MI, resuscitated cardiac arrest, hospitalized angina & HF, fatal & nonfatal stroke, TIA, PVD) Secondary outcomes: Incidence of CV events (CV death, nonfatal MI, resuscitated cardiac arrest, hospitalized angina & HF, fatal & nonfatal stroke, TIA, PVD) Secondary outcomes: ALI-cause mortality and the incidence of revascularization for PCI previous history Funding Source: Pfizer CARMEN (2004) (Komajd et al., 2004) Design: Prospective, randomized, multicentre, double-blinded, parallel trial Median duration of follow-up: 1.8 years Participants: 572 Clinical setting: Mild CHF (NYHA Class I-III) Mean baseline BP: 131/80 mmHg Age range: 18-Iolder (mean age: 62 years) Hypertensive patients (%): 34 Baseline co-morbidities (%): CAD (64.4) Intervention: Three groups ACEI: Enalapril 10 mg bid vs. carvedilol 25-50 mg bid vs. enalapril plus carvedilol Co-intervention: added as needed Except non-study drugs) Concomitant non-study RAS blockers: NR Primary and secondary outcomes: Absolute change in LV end systolic volume index (LVESVI) & all & CV mortality, CV events Funding Source: SmithKline Beecham & Roche CARP (2011) (Okada et al., 2011) Design: Prospective, randomized, multicentre, open-label trial Mean duration of follow-up; 4.4 years Participants (%): 72.3 Baseline co-morbidites (%): 74.3 Baseline co-morbidites	
Age range: 30-79 (mean: 57.7 yrs) Hypertensive patients (%): 60 Baseline co-morbidities (%): MI (37.7), DM (17) Intervention: 3 groups ACEI: Enalapril 100mg/day + 1 tab placebo vs Placebo & amlodipine 5mg/day + 1 tab placebo vs placebo In current review, the groups were analysed separately as enalapril vs. placebo & enalapril vs. amlodipine. Co-intervention: No other DP lowering agents were added Concomitant non-study RAS blockers: Intervention: 7% ACEI & 2% ARB. Control: 13% ACEI & 2 % (15) ARB Primary outcomes: Incidence of CV events (CV death, nonfatal MI, resuscitated cardiac arrest, hospitalized angina & Hr, fatal & nonfatal stroke, TIA, PVD) Secondary outcomes: All-cause mortality and the incidence of revascularization for PCI previous history Funding Source: Prizer CARMEN (2004) (Komajd et al., 2004) Beesign: Prospective, randomized, multicentre, double-blinded, parallel trial Median duration of follow-up: 1.8 years Participants: 572 Clinical setting: Mild CHF (NYHA Class I-III) Mean baseline BP: 131/80 mmHg Age range: 18-older (mean age: 62 years) Hypertensive patients (%): 244 Baseline co-morbidities (%): CAD (64.4) Intervention: Indreg orups ACEI: Enalapril 10 mg bid vs. carveditol 25-50 mg bid vs. enalapril plus carveditol Co-intervention: added as needed (Except non-study drugs) Conomitant non-study RAS blockers: NR Primary and secondary outcomes: Absolute change in LV end systolic volume index (LVESVI) & all & CV mortality, CV events Funding Source: SmithKline Beecham & Roche CARP (2011) (Okada et al., 2011) Design: Prospective, randomized, multicentre, open-label trial Mean duration of follow-up: 4.4 years Participants (%): 72.3 Baseline co-morbidities (%): 72.3 Baseline co-morbidities (%): 74.78 Byertensive patients (%): 72.3 Baseline co-morbidities (%): 74.78 Design: Prospective, randomized, multicentre, open-label trial Mean duration of follow-up: 4.4 years Participants (0: 91) Clinical setting: Post-percutaneous coronary interventions (PCI) (next day) wit	Clinical setting: Angiographically documented CAD
Hypertensive patients (%): 60 Baseline co-morbidities (%): MI (37.7), DM (17) Intervention: 3 groups ACEI: Enalapril 10mg/day + 1 tab placebo vs Placebo £ amlodipine 5mg/day + 1 tab placebo vs placebo In current review, the groups were analysed separately as enalapril vs. placebo £ enalapril vs. amlodipine. Co-intervention: No other BP lowering agents were added Concomitant non-study RAS blockers: Intervention: 7% ACEI & 2% ARB. Control:13% ACEI & 2 % (15) ARB Primary outcomes: Incidence of CV events (CV death, nonfatal MI, resuscitated cardiac arrest, hospitalized angina £ Secondary outcomes: Incidence of CV events (CV death, nonfatal MI, resuscitated cardiac arrest, hospitalized angina £ Secondary outcomes: Incidence of CV events (CV death, nonfatal MI, resuscitated cardiac arrest, hospitalized angina £ Secondary outcomes: Incidence of CV events (CV death, nonfatal MI, resuscitated cardiac arrest, hospitalized angina £ Secondary outcomes: All-Cause mortality and the incidence of revascularization for PCI previous history Funding Source: Pfizer CARMEN (2004) (Komajd et al., 2004) Design: Prospective, randomized, multicentre, double-blinded, parallel trial Median duration of follow-up: 1.8 years Participants: 572 Clinical setting: Mild CHF (NYHA Class I-III) Mean baseline BP: 131/80 mmHg Age range: 18-loder (mean age: 62 years) Hypertensive patients (%): 34 Baseline co-morbidities (%): CAD (64.4) Intervention: raded as needed (Except non-study drugs) Concomitant non-study RAS blockers: NR Primary and secondary outcomes: Absolute change in LV end systolic volume index (LVESVI) & all & CV mortality, CV events Funding Source: SmithKline Beecham & Roche CARP (2011) (Okada et al., 2011) Design: Prospective, randomized, multicentre, open-label trial Mean duration of follow-up: 4.4 years Participants (%): 172.3 Baseline co-morbidities (%): M(41), DM (40) Intervention: Two groups ABE: valaarate 40-80 mg/day vs. non-ARB Co-intervention: NR Concomitant non-study RAS blockers: Intervention: 13% ACEI & 2% ARB. Control: 39	
Baseline co-morbidities (%): MI (37.7), DM (17) Intervention: 3 groups ACEI: Enalapril 10mg/day + 1 tab placebo vs Placebo f: amlodipine 5mg/day + 1 tab placebo vs placebo In current review, the groups were analysed separately as enalapril vs. placebo f: enalapril vs. amlodipine. Co-intervention: No other BP lowering agents were added Concomitant non-study RAS blockers: Intervention: 7% ACEI & 2% ARB. Control:13% ACEI & 2 % (15) ARB Primary outcomes: Incidence of CV events (CV death, nonfatal MI, resuscitated cardiac arrest, hospitalized angina & HF, fatal & nonfatal stroke, TIA, PVD) Secondary outcomes: All-cause mortality and the incidence of revascularization for PCI previous history Funding Source: Pfizer CARMEN (2004) (Komajd et al., 2004) Design: Prospective, randomized, multicentre, double-blinded, parallel trial Meedian duration of follow-up: 1.8 years Participants: 572 Clinical setting: Mild CHF (NYHA Class I-III) Meean baseline BP: 131/80 mmHg Age range: 18-older (mean age: 62 years) Hypertensive patients (%): 2AD (64.4) Intervention: Three groups ACEI: Enalapril 10 mg bid vs. carvedilol 25-50 mg bid vs. enalapril plus carvedilol Co-intervention: added as needed (Except non-study drugs) Concomitant non-study RAS blockers: NR Primary and secondary outcomes: Absolute change in LV end systolic volume index (LVESVI) & all & CV mortality, CV events Participants (n): 191 Clinical setting: Prospective, randomized, multicentre, open-label trial Meean duration of follow-up: 4.4 years Participants (n): 191 Clinical setting: Post-percutaneous coronary interventions (PCI) (next day) with bare-metal stents (BMS) Mge range: (mean age: 65 years) Hypertensive patients (%): 7.2.3 Baseline co-morbidities (%): All (41), DM (40) Intervention: Two groups Age: range: (mean age: 65 years) Hypertensive patients (%): MI (41), DM (40) Intervention: Two groups Age: yaas: Ade Age Mg/day vs. non-ARB Co-intervention: NR Concomitant non-study RAS blockers: Intervention: 13% ACEI & 2% ARB. Contr	
ACEI: Enalapril 1 ⁰ mg ² /day + 1 tab placebo x Placebo & malodripine Smg/day + 1 tab placebo x placebo In current review, the groups were analysed separately as enalapril vs. placebo & enalapril vs. amlodripine. Co-intervention: No other B lowering agents were added Concomitant non-study RAS blockers: Intervention: 7% ACEI & 2% ARB. Control:13% ACEI & 2 % (15) ARB Primary outcomes: Incidence of CV events (CV death, nonfatal MI, resuscitated cardiac arrest, hospitalized angina & HF, fatal & nonfatal stroke, TIA, PVD) Secondary outcomes: All-cause mortality and the incidence of revascularization for PCI previous history Funding Source: Pfizer CARMEN (2004) (Komajd et al., 2004) Design: Prospective, randomized, multicentre, double-blinded, parallel trial Median duration of follow-up: 1.8 years Participants: 572 Clinical setting: Mild CHF (NYHA Class I-III) Mean baseline BP: 131/80 mmHg Age range: 18-older (mean age: 62 years) Hypertensive patients (%): 2AD (64.4) Intervention: Three groups ACEI: Enalapril 10 mg bid vs. carvedilol 25-50 mg bid vs. enalapril plus carvedilol Co-intervention: added as needed (Except non-study drugs) Concomitant non-study RAS blockers: NR Primary and secondary outcomes: Absolute change in LV end systolic volume index (LVESVI) & all & CV mortality, CV events Participants (n): 191 Clinical setting: Post-percutaneous coronary interventions (PCI) (next day) with bare-metal stents (BMS) Mean duration of follow-up: 4.4 years Participants (n): 191 Clinical setting: Post-percutaneous coronary interventions (PCI) (next day) with bare-metal stents (BMS) Mean baseline BP: 134/76 mmHg Age range: (mean age: 65 years) Hypertensive patient (%): 72.3 Baseline co-morbidities (%): MI (41), DM (40) Intervention: Two groups AB: Valastra 40-80 mg/day vs. non-ARB Co-intervention: RR Concomitant non-study RAS blockers: Intervention: 13% ACEI & 2% ARB. Control: 39% ACEI & 7% ARB Primary and secondary outcomes: Composite & individual of death from any cause, nonfatal MI, target lesion	Baseline co-morbidities (%): MI (37.7), DM (17)
In current review, the groups were analysed separately as enalapril vs. placebo & enalapril vs. amlodipine. Co-intervention: No other BP lowering agents were added Concomitant non-study RAS blockers: Intervention: 7% ACEI & 2% ARB. Control: 13% ACEI & 2 % (15) ARB Primary outcomes: Incidence of CV events (CV death, nonfatal MI, resuscitated cardiac arrest, hospitalized angina & HF, fatal & nonfatal stroke, TIA, PVD) Secondary outcomes: All-cause mortality and the incidence of revascularization for PCI previous history Funding Source: Pfizer CARMEN (2004) (Komajd et al., 2004) Design: Prospective, randomized, multicentre, double-blinded, parallel trial Median duration of follow-up: 1.8 years Participants: 572 Clinical setting: Mild CHF (NYHA Class I-III) Mean baseline BP: 131/80 mmHg Age range: 18-older (mean age: 62 years) Hypertensive patients (%): 34 Baseline co-morbidities (%): CAD (64.4) Intervention: Three groups ACEI: Enalapril 10 mg bid vs. carvedilol 25-50 mg bid vs. enalapril plus carvedilol Co-intervention: added as needed (Except non-study drugs) Concomitant non-study RAS blockers: NR Primary and secondary outcomes: Absolute change in LV end systolic volume index (LVESVI) & all & CV mortality, CV events Prinary and secondary outcomes: Absolute change in LV end systolic volume index (LVESVI) & all & CV mortality, CV events Primary and secondary outcomes: Absolute change in LV end systolic volume index (LVESVI) & all & CV mortality, CV events Primary not secondary outcomes: Absolute change in LV end systolic volume index (LVESVI) & all & CV mortality, CV events Primary and secondary outcomes: Absolute change in LV end systolic volume index (LVESVI) & all & CV mortality, CV events Primary and secondary outcomes: Absolute change in LV end systolic volume index (LVESVI) & all & CV mortality, CV events Primary and secondary outcomes: Absolute change in LV end systolic volume index (LVESVI) & all & CV mortality, CV events Primary and secondary outcomes: Absolute change in L	Intervention: 3 groups
Co-intervention: No other BP lowering agents were added Concomitant non-study RAS blockers: Intervention: 7% ACEI & 2% ARB. Control:13% ACEI & 2 % (15) ARB Primary outcomes: Incidence of CV events (CV death, nonfatal MI, resuscitated cardiac arrest, hospitalized angina & HF, fatal & nonfatal stroke, TIA, PVD) Secondary outcomes: All-cause mortality and the incidence of revascularization for PCI previous history Funding Source: Pfizer CARMEN (2004) (Komajd et al., 2004) Design: Prospective, randomized, multicentre, double-blinded, parallel trial Median duration of follow-up: 1.8 years Participants: 572 Clinical setting: Mild CHF (NYHA Class I-III) Mean baseline BP: 131/30 mmHg Age range: 18-older (mean age: 62 years) Hypertensive patients (%): CAD (64.4) Intervention: Three groups ACEI: Enalapril 10 mg bid vs. carvedilol 25-50 mg bid vs. enalapril plus carvedilol Co-intervention: added as needed (Except non-study drugs) Concomitant non-study RAS blockers: NR Primary and secondary outcomes: Absolute change in LV end systolic volume index (LVESVI) & all & CV mortality, CV events Funding Source: SmithKline Beecham & Roche CARP (2011) (Okada et al., 2011) Design: Prospective, randomized, multicentre, open-label trial Mean duration of follow-up: 4.4 years Participants (n): 191 Clinical setting: Post-percutaneous coronary interventions (PCI) (next day) with bare-metal stents (BMS) Mean baseline BP: 134/76 mmHg Age range: (mean age: 65 years) Hypertensive patients (%): 7.2.3 Baseline co-morbidities (%): MI (41), DM (40) Intervention: Two groups AB: Valastran 40-80 mg/day vs. non-ARB Co-intervention: RR Concomitant non-study RAS blockers: Intervention: 13% ACEI & 2% ARB. Control: 39% ACEI & 7% ARB Primary and secondary outcomes: Composite & individual of death from any cause, nonfatal MI, target lesion	
Concomitant non-study RAS blockers: Intervention: 7% ACEI & 2% ARB. Control:13% ACEI & 2 % (15) ARB Primary outcomes: Incidence of CV events (CV death, nonfatal MJ, resuscitated cardiac arrest, hospitalized angina & HF, fatal & nonfatal stroke, TIA, PVD) Secondary outcomes: All-cause mortality and the incidence of revascularization for PCI previous history Funding Source: Pfizer CARMEN (2004) (Komajd et al., 2004) Design: Prospective, randomized, multicentre, double-blinded, parallel trial Median duration of follow-up: 1.8 years Participants: 572 Clinical setting: Mild CHF (NYHA Class I-III) Mean baseline BP: 131/80 mmHg Age range: 18-older (mean age: 62 years) Hypertensive patients (%): 34 Baseline co-morbidities (%): CAD (64.4) Intervention: Three groups ACEI: Enalapril 10 mg bid vs. carvedilol 25-50 mg bid vs. enalapril plus carvedilol Co-intervention: added as needed (Except non-study drugs) Concomitant non-study RAS blockers: NR Primary and secondary outcomes: Absolute change in LV end systolic volume index (LVESVI) & all & CV mortality, CV events Funding Source: SmithKline Beecham & Roche CARP (2011) (Okada et al., 2011) Design: Prospective, randomized, multicentre, open-label trial Mean duration of follow-up: 4.4 years Participants (n): 191 Clinical setting: Post-percutaneous coronary interventions (PCI) (next day) with bare-metal stents (BMS) Mean baseline BP: 134/76 mmHg Age range: (mean age: 65 years) Hypertensive patients (%): 7.3 Baseline co-morbidities (%): MI (41), DM (40) Intervention: Two groups ABB: Valastra 40-80 mg/day vs. non-ARB Co-intervention: NR Concomitant non-study RAS blockers: Intervention: 13% ACEI & 2% ARB. Control: 39% ACEI & 7% ARB Primary and secondary outcomes: Composite & individual of death from any cause, nonfatal MI, target lesion	
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Funding Source: Pfizer CARMEN (2004) (Komajd et al., 2004) Design: Prospective, randomized, multicentre, double-blinded, parallel trial Median duration of follow-up: 1.8 years Participants: 572 Clinical setting: Mild CHF (NYHA Class I-III) Mean baseline BP: 131/80 mmHg Age range: 18-older (mean age: 62 years) Hypertensive patients (%): 34 Baseline co-morbidities (%): CAD (64.4) Intervention: Three groups ACEI: Enalapril 10 mg bid vs. carvedilol 25-50 mg bid vs. enalapril plus carvedilol Co-intervention: added as needed (Except non-study drugs) Concomitant non-study RAS blockers: NR Primary and secondary outcomes: Absolute change in LV end systolic volume index (LVESVI) & all & CV mortality, CV events Funding Source: SmithKline Beecham & Roche CARP (2011) (Okada et al., 2011) Design: Prospective, randomized, multicentre, open-label trial Mean duration of follow-up: 4.4 years Participants (n): 191 Clinical setting: Post-percutaneous coronary interventions (PCI) (next day) with bare-metal stents (BMS) Mean baseline BP: 134/76 mmHg Age range: (mean age: 65 years) Hypertensive patients (%): 72.3 Baseline co-morbidities (%): 72.4 Baseline co-morbidit	HF, fatal & nonfatal stroke, TIA, PVD)
CARMEN (2004) (Komajd et al., 2004) Design: Prospective, randomized, multicentre, double-blinded, parallel trial Median duration of follow-up: 1.8 years Participants: 572 Clinical setting: Mild CHF (NYHA Class I-III) Mean baseline BP: 131/80 mmHg Age range: 18-older (mean age: 62 years) Hypertensive patients (%): 34 Baseline co-morbidities (%): CAD (64.4) Intervention: Three groups ACEI: Enalapril 10 mg bid vs. carvedilol 25-50 mg bid vs. enalapril plus carvedilol Co-intervention: added as needed (Except non-study drugs) Concomitant non-study RAS blockers: NR Primary and secondary outcomes: Absolute change in LV end systolic volume index (LVESVI) & all & CV mortality, CV events Funding Source: SmithKline Beecham & Roche CARP (2011) (Okada et al., 2011) Design: Prospective, randomized, multicentre, open-label trial Mean duration of follow-up: 4.4 years Participants (n): 191 Clinical setting: Post-percutaneous coronary interventions (PCI) (next day) with bare-metal stents (BMS) Mean baseline BP: 134/76 mmHg Age range: (mean age: 65 years) Hypertensive patients (%): 72.3 Baseline co-morbidities (%): MI (41), DM (40) Intervention: Two groups ARB: Valsartan 40-80 mg/day vs. non-ARB Co-intervention: NR Concomitant non-study RAS blockers: Intervention: 13% ACEI & 2% ARB. Control: 39% ACEI & 7% ARB Primary and secondary outcomes: Composite & individual of death from any cause, nonfatal MI, target lesion	Secondary outcomes: All-cause mortality and the incidence of revascularization for PCI previous history
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Funding Source: Hiroshima University Faculty of Medicine & Novartis Pharma Japan CASE-J (2008) (Ogihara et al., 2008) Design: Multicentre, randomized controlled, open-label study Mean duration of follow-up: 3.2 years Participants (N): 4,728 Clinical setting: High-risk HTN ((at least one risk factor for CVD) Mean baseline BP: 163/91.6 mmHg Age range: 25-85 (mean 63.9 yrs) Hypertensive patients (%): 100 Baseline co-morbidities (%): DM (41), CVD (42) Intervention: 2 groups ACEI: Candesartan (4-12 mg OD) or amlodipine (2.5-10 mg OD) Co-intervention: no other BP-lowering agents were added Concomitant non-study RAS blockers: NR Primary outcomes: (composite of the following events): sudden death. CVEs: stroke or TIA. Cardiac events: HF, angina pectoris, or acute MI. Renal events: serum creatinine concentration or end-stage renal disease. Vascular events: dissecting aortic aneurysm or arteriosclerotic occlusion of a peripheral artery. Secondary outcomes: All-cause deaths, new-onset T2DM, discontinuance of treatment because of adverse events Funding Source: Takeda Pharmaceutical and Pfizer Japan. CCS-1 (2001) (Liu et al., 2001) Design: Prospective, randomized, multicentre, double-blinded, parallel trial Mean duration of follow-up: 1.11 years Participants (n): 6749 Clinical setting: (%): NR <td< th=""></td<>
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Clinical setting: High-risk HTN ((at least one risk factor for CVD) Mean baseline BP: 163/91.6 mmHg Age range: 25-85 (mean 63.9 yrs) Hypertensive patients (%): 100 Baseline co-morbidities (%): DM (41), CVD (42) Intervention: 2 groups ACEI: Candesartan (4-12 mg OD) or amlodipine (2.5-10 mg OD) Co-intervention: no other BP-lowering agents were added Concomitant non-study RAS blockers: NR Primary outcomes: (composite of the following events): sudden death. CVEs: stroke or TIA. Cardiac events: HF, angina pectoris, or acute MI. Renal events: serum creatinine concentration or end-stage renal disease. Vascular events: dissecting aortic aneurysm or arteriosclerotic occlusion of a peripheral artery. Secondary outcomes: All-cause deaths, new-onset T2DM, discontinuance of treatment because of adverse events Funding Source: Takeda Pharmaceutical and Pfizer Japan. CCS-I (2001) (Liu et al., 2001) Design: Prospective, randomized, multicentre, double-blinded, parallel trial Mean duration of follow-up: 1.11 years Participants (n): 6749 Clinical setting: AMI Mean baseline BP: NR Mean age: 63.6 years Hypertensive patients (%): 12 Baseline co-morbidities (%): NR Intervention: Two groups ACEI: Captopril (12.5-50 TID) vs. placebo Co-intervention: NR Concomitant non-study RAS blockers: NR Primary outcomes: All & CV mortality Funding Source: NR Chan et al. (2000) Design: Prospective, randomized, multicentre, double-blinded, parallel trial
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Chan et al. (2000) Design: Prospective, randomized, multicentre, double-blinded, parallel trial
Design: Prospective, randomized, multicentre, double-blinded, parallel trial
Mean duration of follow-up: 1 year
Participants (n): 102
Clinical setting: HTN & T2DM with normo/micro/macroalbuminuria Mean baseline BP: 169.2/92.5 mmHg
Mean Age: 58 years
Hypertensive patients (%): 100
Baseline co-morbidities (%): None
Intervention: Two groups
ACEI: Enalapril (10-40 mg/day) vs. nifedipine slow release (20-40 mg twice daily) Co-intervention: To achieved BP level, indapamide or frusemide was added after doubled doses
Co-intervention: To achieved BP level, indepande or trusemide was added after doubled doses Concomitant non-study RAS blockers: NR
Primary outcomes: 24-hour UAE, plasma creatinine Concentration
Secondary outcomes: Death, CV (MI, stroke, hospitalization HF, revascularization procedures), renal events
Funding Source: Merck, Sharpe, and Dohme
CHARM-Added (2003) (McMurray et al., 2003) (CHARM Added investigators, 2004)
Design: Prospective, randomized, double-blinded, parallel trial
Median duration of follow-up: 3.4 years
Participants (N): 2548 patients
Clinical setting: NYHA class II-IV and LVEF= 40% or lower, and who are being treated with ACEI Mean baseline BP: 125.6/75 mmHg
Age range: 18-older (mean: 64.1 years)
Hypertensive patients (%): 47.7
Baseline co-morbidities (%): CAD (62.2)
Intervention: 2 treatment groups
ARB: Candesartan 4-32mg/day vs Placebo
Co-intervention: no other BP-lowering agents were added Primary outcomes: Composite of CV death or worsening HF
Secondary outcomes: CV death, hospitalized HF, nonfatal MI, nonfatal stroke, or coronary revascularization
Concomitant non-study RAS blockers: Intervention group:100% ACEI & 2.3% ARBs. Control group: 99% ACEI & 5% ARB
Funding Source: AstraZeneca
CHARM-Alternative (2003) (Granger et al., 2003) (CHARM Alternative investigators, 2004)
Design: Prospective, randomized, double-blinded, parallel trial
Median duration of follow-up: 2.8 years
Participants (N): 2028
Clinical setting: NYHA class II-IV and LVEF= 40% or lower, and who are intolerance to ACEI. Mean baseline BP: 130.3/76.8 mmHg
Age range: 18-older (mean: 67 Years)
Hypertensive patients (%): 50
inspercensive pacience (10), 50
Baseline co-morbidities (%): Intervention: 2 treatment groups

ARB: Candesartan 4-32mg/day or Placebo
Co-intervention: no other BP-lowering agents were added
Note: Baseline therapy with an ACE inhibitor at least 30 days before randomization is mandatory. Protocol allowed
added of ACEIs if appropriate
Concomitant non-study RAS blockers: Intervention: 6% ACEI & 9% ARB. Control: 6% ACEI & 9% ARB
Primary outcomes: Composite of CV death or worsening HF
Secondary outcomes: CV death, hospitalized HF, nonfatal MI, nonfatal stroke, or coronary revascularization
Funding Source: AstraZeneca
CHARM-Preserved (2003) (Yusuf et al., 2003) (CHARM Preserved investigators, 2004)
Design: Prospective, randomized, double-blinded, parallel trial
Median duration of follow-up: 3.1 years
Participants (N): 3023 patients
Clinical setting: NYHA functional class II-IV and had LVEF higher than 40%
Mean baseline BP: 136/77.8 mmHg
Mean age: 67.1 years
Hypertensive patients (%): 65
Baseline co-morbidities (%): CAD (40)
Intervention: 2 treatment groups
ARB: Candesartan 4-32mg/day vs Placebo
Co-intervention: no other BP-lowering agents were added
Concomitant non-study RAS blockers: Intervention: 20% ACEI & 3% ARB. Control: 23% ACEI & 3% ARB
Primary outcomes: Composite of CV death or worsening HF
Secondary outcomes: CV death, hospitalized HF, nonfatal MI, nonfatal stroke, or coronary revascularization
Funding Source: AstraZeneca
CHIEF (2018) (Lu et al., 2018)
Design Dromotive rendemized multicentry area label blinded and a statistic (DDODE)
Design: Prospective, randomized, multicentre, open-label, blinded-endpoint trial (PROBE)
Median duration of follow-up: 3.5 years
Participants: 13,542
Clinical setting: High-risk HTN
Mean baseline BP: 157/93 mmHg
Age range: 50-79 years (mean age: 61.5 years)
Hypertensive patients (%): 100
Intervention: Two groups
ARB: Telmisartan (40-80 mg) + amlodipine (2.5-5 mg) vs. telmisartan + amlodipine
Co-intervention: To achieved BP goal, other BP-lowering agents were added
Concomitant non-study RAS blockers: NR (Protocol allowed add non-study RAS blockers)
Primary and secondary outcomes: Non-fatal stroke, non-fatal MI, CV death, hospitalization for heart failure, angina,
coronary revascularization, & all-death
Euroding Courses Ministry of science & Technology of China
Funding Source: Ministry of science & rechnology of China
Funding Source: Ministry of science & Technology of China
COPE (2011) (Matsuzaki et al., 2011)
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COPE (2011) (Matsuzaki et al., 2011) Design: Prospective, randomized, multicentre, open-label, blinded-endpoint trial (PROBE)
COPE (2011) (Matsuzaki et al., 2011) Design: Prospective, randomized, multicentre, open-label, blinded-endpoint trial (PROBE) Median duration of follow-up: 3.61 Participants: 3292
COPE (2011) (Matsuzaki et al., 2011) Design: Prospective, randomized, multicentre, open-label, blinded-endpoint trial (PROBE) Median duration of follow-up: 3.61 Participants: 3292 Mean baseline BP: 153.8/89.6 mmHg
COPE (2011) (Matsuzaki et al., 2011) Design: Prospective, randomized, multicentre, open-label, blinded-endpoint trial (PROBE) Median duration of follow-up: 3.61 Participants: 3292 Mean baseline BP: 153.8/89.6 mmHg Age range: 40-85 years (mean age: 63 years)
COPE (2011) (Matsuzaki et al., 2011) Design: Prospective, randomized, multicentre, open-label, blinded-endpoint trial (PROBE) Median duration of follow-up: 3.61 Participants: 3292 Mean baseline BP: 153.8/89.6 mmHg
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Baseline co-morbidities (%): CAD (33)
Intervention: Two groups
ARB: Candesartan 8-32 mg/day vs. conventional therapy
CCB & diuretics are preferred drugs in conventional group
Co-intervention: NR. However, patients on ACEI or ARB were excluded
Concomitant non-study RAS blockers: NR
Primary and secondary outcomes: Change in left ventricular (LV) & left atrial (LA) mass index
Funding Source: The Danish Heart Foundation, Denmark, Family Hede Nielsen's Fund.
DEMAND (2011) (Ruggenenti et al., 2011)
Design: Prospective, randomized, double-blinded, parallel trial
Mean duration of follow-up: 3.8 years
Participants (n): 380 participants
Clinical setting: hypertension and T2DM (with albuminuria <200mg/min)
Mean baseline BP: 148.5/86.9 mmHg
Age range: 40-older (mean: 61.2 years)
Hypertensive patients (%): 100
Baseline co-morbidities (%): T2DM (100)
Intervention: Three groups
ACEI: Delapril (30 mg/day) vs Delapril-Manidipine (30/10 mg/day) vs placebo
Co-intervention: Additional BP-lowering agents were allowed: 1) indapamide, frusemide or HCTZ; 2) BB; 3)
doxazocin, prazosin
Concomitant non-study RAS blockers: NR
Primary outcomes: Rate of GFR decline
Secondary outcomes: Composite end point of death from cardiovascular causes, sudden death, nonfatal myocardial
infarction or stroke, coronary revascularization, amputation, or vascular surgery for peripheral atherosclerotic artery
disease; and new onset, progression, or regression of retinopathy and peripheral neuropathy.
Funding Source: Independent academic trial
DETAIL (2004) (Barnett et al., 2004, Boehringer Ingelheim Pharmaceuticals, 2005)
Design: Prospective, randomized, multicentre, double-blinded, parallel trial
Mean duration of follow-up: 5 years
Participants (n): 250
Clinical setting: HTN & T2DM with early nephropathy
Mean baseline BP: 152/85.5 mmHg
Age range: 40-older (mean age: 61)
Hypertensive patients (%): 100
Baseline co-morbidities (%): CVD (49)
Intervention: Two treatment groups
Telmisartan 40-80 mg vs. enalapril 10-20 mg
Co-intervention: Antihypertensive agents were allowed except of non-study ACEI or ARB
Concomitant non-study RAS blockers: None
Primary & secondary outcomes: Change in glomerular filtration rate, eGFR, urinary albumin excretion, serum
creatining level & BP rates of clinical events (ESRD ML stroke CHE) all cause death rate of adverse events, and
creatinine level & BP, rates of clinical events (ESRD, MI, stroke, CHF), all cause death, rate of adverse events; and
laboratory abnormalities
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Funding Source: AstraZeneca and Takeda
DIRECT-Protect 1 (2008) (Chaturvedi et al., 2008)
Design: Prospective, randomized, double-blinded, parallel trial
Mean duration of follow-up: 4.8 years
Participants (n): 1905
Clinical setting: Normotensive, normoalbuminuric DM type 1 with retinopathy
Mean baseline BP: 117/73 mmHg Age: 18-55 (mean: 31.7 years)
Hypertensive patients (%): None
Baseline co-morbidities (%): DM (100)
Intervention: Two groups
ARB: Candesartan 32 mg/day vs Placebo
Co-intervention: no additional BP-lowering agents
Concomitant non-study RAS blockers: Intervention: 5.5% ACEI & 0.5% ARB. Control: 8% ACEI & 1% ARB Primary & secondary outcomes: Incidence and progression of retinopathy.
Funding Source: AstraZeneca and Takeda
DIRECT-Protect 2 (2008) (Sjolie et al., 2008)
Design: Prospective, randomized, double-blinded, parallel trial
Median duration of follow-up: 4.7 years
Participants (n): 1905
Clinical setting: normoalbuminuric, normotensive, or treated hypertensive people with T2DM with mild to moderately
severe retinopathy Mean baseline BP: 139/79 mmHg
Age: 37-75 (mean: 56.9 years)
Hypertensive patients (%): 62
Baseline co-morbidities (%): DM (100)
Intervention: Two groups
ARB: Candesartan 32 mg/day vs placebo Co-intervention: No additional BP-lowering agent used
Concomitant non-study RAS blockers: Intervention: 21% RAS blockers. Control: 28% RAS blockers, p<0.0001
Primary & Secondary outcomes: Incidence and progression of retinopathy.
Funding Source: AstraZeneca and Takeda
DREAM (2006) (Dagenais et al., 2008)
Design: Prospective, multicentre, randomized, double-blinded trial with a 2-by-2 factorial design
Median duration of follow-up: 3 years
Participants (n): 5269 Clinical setting: Patients with impaired fasting glucose level (IFG) &/or impaired glucose tolerance (IGT)
Mean baseline BP: 136/83.4 mmHg
Age range: 30-older (mean age: 57 years)
Hypertensive patients (%): 43.5
Baseline co-morbidities (%): None
Intervention: Four treatment groups ACEI: ramipril (5-15 mg/day) vs. placebo & rosiglitazone (4-8 mg/day) vs. placebo
Co-intervention: NR
Concomitant non-study RAS blockers: NR
Primary secondary outcomes: Newly diagnosed diabetes or all mortality & Composite of cardiac and renal events
(clinical or silent MI, stroke, CV death, revascularization procedures, HF, newly angina, AF), renal events
Funding Source: Canadian Institutes of Health Research, Sanofi-Aventis, GlaxoSmithKline, and King Pharmaceuticals.
E-COST (2005) (Suzuki et al., 2005)
Design: Prospective, multicentre, randomized, open label with parallel group trial Mean duration of follow-up: 3 years
Participants (n): 2,048
Clinical setting: HTN
Mean baseline BP: 165/93 mmHg
Age range: (mean age: 65 years)
Hypertensive patients (%): 100 Baseline co-morbidities (%): None
Intervention: Two treatment groups
ARB: Candesartan (4-8 mg/day) vs conventional therapy
In conventional-based group, CCBs are commonly used drugs (93%), then beta-blockers (32%) & diuretics (4%)
Co-intervention: To control BP, other agents were added
Concomitant non-study RAS blockers: None
Primary & secondary outcomes: Fatal/nonfatal of stroke, MI or CHF Funding Source: Saitama Medical School
E-COST-R (2005) (Kanno et al., 2005)
Design: Prospective, multicentre, randomized, open label with parallel group trial
Mean duration of follow-up: 3 years
Participants (n): 141
Clinical setting: HTN with coexisting non-diabetics CKD
Mean baseline BP: 146/80 mmHg Age range: Over 60 years (mean age: 67 years)
Hypertensive patients (%): 100
Baseline co-morbidities (%): CKD (100)
Intervention: Two treatment groups
ARB: Candesartan (4-8 mg/day) vs. conventional therapy (CCB, beta-blockers & diuretics)
Concomitant non-study RAS blockers: Intervention: 25% ACEI. Control: 25% ACEI

Primary & secondary outcomes: CV events (hosp. MI, stroke, or CHF)
Funding Source: Saitama Medical School
EFFERVESCENT (2016) (Ramadan et al., 2016)
Design: Prospective, randomized, single-centre, double-blinded, parallel trial Mean duration of follow-up: 2 years
Participants (n): 120
Clinical setting: Abnormal carotid intima-media thickness (CIMT) over 2 years
Mean baseline BP: 126/72 mmHg
Mean age: 60 years
Hypertensive patients (%): 39
Baseline co-morbidities (%): None
Intervention: Two groups
ARB: Valsartan (160-320 mg/day) vs. placebo Co-intervention: Other BP-lowering agents are permitted except ARB therapy
Concomitant non-study RAS blockers: NR
Primary & secondary outcomes: changes in the mean circumferential carotid wall thickness (WT), the mean vessel
wall area (VWA) of the carotid bulb & vascular events
Funding Source: Novartis & the National Centre for Advancing Translational Sciences of the National Institutes of
Health
ELITE II (2000) (Pitt et al., 2000)
Design: Prospective, randomized, multicentre, double-blinded, parallel trial
Median duration of follow-up: 1.5 years
Participants (n): 3152
Clinical setting: Symptomatic CHF (NYHA class II-IV), LVEF ≤40% Mean baseline BP: 134/78 mmHg
Age range: 60 or older (mean age: 71.4 years)
Hypertensive patients (%): 49
Intervention: Two treatment groups
Intervention: Losartan (12.5-50 mg/day) vs. captopril (12.5-50 mg three times daily)
Co-intervention: NR
Concomitant non-study RAS blockers: NR
Primary & secondary outcomes: All cause mortality, Composite of sudden cardiac death, or resuscitated cardiac
arrest Fundier Gewaard Head Decourte Lebourteries
Funding Source: Merck Research Laboratories
ELVERA (2001) (Terpstra et al., 2001) Design: Prospective, randomized, single-centre, double-blinded, parallel trial
Mean duration of follow-up: 2 years
Participants (n): 166
Clinical setting: Untreated elderly HTN
Mean baseline BP: 175/92 mmHg
Age range: 60-75 years (mean age: 67 years)
Hypertensive patients (%): 100
Baseline co-morbidities (%): None
Intervention: Three treatment groups ACEI: Lisinopril (10-20 mg/day) vs. amlodipine (5-10 mg/day)
Co-intervention: NR
Concomitant non-study RAS blockers: NR
Primary & secondary outcomes: Change in combined mean maximum far wall intima-media thickness (IMT) of the
common carotid artery & the common femoral artery
Funding Source: Pfizer
ESPIRAL (2001) (Marina et al., 2001)
Design: Prospective, multicentre, randomized, open-label, parallel study
Mean duration of follow-up: 3 years
Participants (n): 241
Clinical setting: Hypertension and CKD Mean baseline BP:
Age: 24-74 (mean: 56 years)
Hypertensive patients (%): 100
Baseline co-morbidities (%): DM (Ex), CKD (100)
Intervention: Two groups
ACEI: Fosinopril 10-30 mg/day vs CCB: nifedipine GITS 30-60 mg/day
Co-intervention: Additional antihypertensive agents were allowed in the following steps: (1) Furosemide, (2) atenolol
then, (3) doxazosin Concomitant non-study RAS blockers: NR
Primary & secondary outcomes: Time elapsed until the serum creatinine values doubled, or the need to enter the
dialysis programme; CV events, proteinuria evolution and serum creatinine values
Funding Source: NR
EUROPA (2003) (Fox et al., 2003)
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Design: Prospective, randomized, double-blinded, parallel trial Mean duration of follow-up: 4.2 years Participants (n): 12,218 Clinical setting: Stable CHD Mean baseline BP: 137/82 mmHg

Intervention: Two groups
ACEI: Perindopril 80 mg once daily or placebo
Co-intervention: Added on usual therapy
Concomitant non-study RAS blockers: None
Primary & secondary outcomes: Combined & individual of following endpoints: total mortality, non-fatal MI, angina &
cardiac arrest with successful resuscitation
Funding Source: Servier pharmaceutical company
Fang Wu et (2015) (Wu et al., 2015)
Design: Prospective, randomized, single-centre, open-label, parallel trial
Median duration of follow-up: 18 months
Participants (n): 210
Clinical setting: Elderly HTN
Mean baseline BP: 130/73 mmHg
Age range: > 60 years (mean: 68 years)
Hypertensive patients (%): 100
Baseline co-morbidities (%): CAD (30), DM (35)
Intervention: Two treatment groups
ARB: Valsartan (80-160 mg/day) vs. amlodipine (5-10 mg/day), dose was titrated to reach & maintain target BP
Co-intervention: NR
Concomitant non-study RAS blockers: NR
Primary & secondary outcomes: Changes in levels adiponectin, PAI-1 antigen levels, tumour necrosis factor (TNF)-α &
interleukin-6 (IL-6)
Funding Source: Shanghai Council for Science and Technology, China
Fogari et al. (2002) (Fogari et al., 2002)
Design: Prospective, randomized, multi-centre, open-label, parallel trial
Mean duration of follow-up: 4 years
Participants (n): 309
Clinical setting: HTN & T2DM with micro-albuminuria
Mean baseline BP: 160/99.3 mmHg
Mean age: 62.5 years
Hypertensive patients (%): 100
Baseline co-morbidities (%):
Intervention: Three groups
ACEI: Fosinopril (10-30 mg/day) vs amlodipine (5-15 mg/day) vs. amlodipine plus fosinopril
Note: Based on Cochrane recommendation, the three groups were delt with them as independent groups as following:
1) fosinopril vs amlodipine; 2) fosinopril+ amlodipine vs amlodipine
Co-intervention: NR
Concomitant non-study RAS blockers: NR
Primary & secondary outcomes: Urinary albumin excretion (UAE), CV outcomes (fatal/nonfatal stroke, fatal/nonfatal
MI, other CV events)
Funding Source: University of Pavia, Pavia
GISSI-AF (2009) (Disertori et al.)
Design: Prospective, multicentre, randomized, double-blinded, parallel trial
Median duration of follow-up: 1 year
Participants (n): 1442.
Clinical setting: AF
Mean baseline BP: 139/81
Age: 40 & older (mean: 68 years)
Hypertensive patients (%): 84.5
Intervention: Two groups
ARB: Valsartan 80-320mg/day vs Placebo
Co-intervention: no other BP-lowering agents were added.
Concomitant non-study RAS blockers: NR
Primary & secondary outcomes: time to the first recurrence of AF; the proportion of patients who had more than one
episode of AF over the 1-year follow-up period; total number of episodes of AF per patient, hospitalization for any
reason and for a CV event, the composite of death and thromboembolic events, the number of patients in sinus
rhythm at the time of each study visit, the duration of and ventricular rate at the first recurrence of AF, and a safety
profile
Funding Source: Novartis
HIJ-CREATE (2009) (Kasanuki et al., 2009)
Design: Prospective, randomized, open-label, blinded-endpoint trial (PROBE)
Median duration of follow-up: 4.3 years
Participants (n): 2049
Clinical setting: hypertensives with angiographically documented CAD
Mean baseline BP: 135/75.5
Age: 20-80 (mean: 64.8 years)
Hypertensive patients (%): 100
Baseline co-morbidities (%): DM (38)
Intervention: Two treatment groups
ARB: Candesartan 4-12 mg/day vs Control: Non-ARB
Co-intervention: Additional antihypertensive agents were allowed
Concomitant non-study RAS blockers: Intervention: 2.5% ACEIs. Control: 70.5% ACEIs & 23% ARBs
Primary & secondary outcomes: time to a first major adverse cardiac event, angioplasty, stenting or coronary artery
bypass grafting; new onset diabetes
Funding Source: Japan Research Promotion Society for CV Diseases
HONG-KONG DHF (2006) (Yip et al., 2006)

Design: Prospective, randomized, multicentre, open-label, blinded-endpoint trial (PROBE) Mean duration of follow-up: one year
Participants (n): 151
Clinical setting: Symptomatic CHF (NYHA class II-IV), LVEF> 45%
Mean baseline BP: 145/81 mmHg
Mean age: 73 years
Hypertensive patients (%): 76
Intervention: Three groups
ARB: Irbesartan (18.75-75 mg daily) plus diuretics vs Diuretic (frusemide, thiazide or indapamide) vs. Ramipril (2.5-10 mg daily) plus diuretics
In current review, the groups were separated & analysed as following: 1) irbesartan plus diuretics vs. diuretics; 2)
ramipril plus diuretics vs. diuretics; 3) irbesartan plus diuretics vs. ramipril plus diuretics.
Co-intervention: NR
Concomitant non-study RAS blockers:
Outcomes: Symptoms and quality of life & Doppler echocardiographic measurement of ventricular function
Funding Source: Sanofi-Synthelabo
HOPE (2000) (Teo et al., 2004) (Bosch et al., 2002) (Yusuf et al., 2000)
Design: Prospective, multicentre, randomized, double-blinded, parallel trial
Mean duration of follow-up: 4.5 years Participants (n): 9297
Clinical setting: High risk of CVD without LVD or HF
Mean baseline BP: 139/79 mmHg
Age: 55 & older (mean: 66 years)
Hypertensive patients (%): 47
Baseline co-morbidities (%): CAD (80), CVA (19.9)
Intervention: Two groups
ACEI: Ramipril (2.5-10 mg/day) vs Placebo
Co-intervention: no other BP-lowering agents were added.
Concomitant non-study RAS blockers: Intervention: 14% ACEI & 1.6% ARB. Control: 18% ACE & 1.8% ARB Primary & secondary outcomes: Time to first occurrence of the composite outcome of death or CV hospitalization,
CV death; all-cause mortality, combined vascular endpoint, combined HF endpoint, HF mortality or hospitalization;
quality of life, change in NYHA functional class, change in patient global assessment of symptoms, N-terminal B-type
natriuretic peptide levels in blood
Funding Source: Medical Research Council of Canada, Hoechst-Marion Roussel, AstraZeneca, King Pharmaceuticals
and the Heart and Stroke Foundation of Ontario
HOPE-3 (2016) (Lonn et al., 2016)
Design: Prospective, multicentre, randomized, double-blinded trial with a 2-by-2 factorial design.
Median duration of follow-up: 5.6 years
Participants (n): 12705
Clinical setting: High-risk patients Mean baseline BP: 138.1/81.9 mmHg
Age range: Man: \geq 55 years Women: \geq 65 years (mean: 65.5 years)
Hypertensive patients (%): 38
Baseline co-morbidities (%): None
Intervention: Four groups (2-by-2 factorial design)
ARB: Fixed dose combination of candesartan (16 mg/day) plus HCTZ (12.5 mg) vs. placebo OR rosuvastatin (10
mg/day) vs. placebo
Co-intervention: Open-label ACEIs or ARBs not allowed. Excluded patient with clear indications to ACEIs or ARBs Concomitant non-study RAS blockers: Intervention: 1.7% ACEI & 1.6% ARB. Control: 2.3%ACEI & 2.4% ARB
Primary & secondary outcomes: Composite & individual of CV death, nonfatal MI, nonfatal stroke, and the composite
of these events plus resuscitated cardiac arrest, HF, or revascularization.
Funding Source: AstraZeneca & Canadian Institutes of Health Research
Hou et al. (group 2) (2006) (Hou et al., 2006)
Design: Prospective, single-centre, randomized, double-blinded, parallel trial
Mean duration of follow-up: 3.4
Participants (n): 224
Clinical setting: Non-DM CKD, proteinuria (PER > 300 mg/day)
Mean baseline BP: 152/86 mmHg
Age range: 18-70 (mean: 45 years) Hypertensive patients (%): 91.5
Baseline co-morbidities (%): HTN (91.5)
Intervention: Two groups
ACEI: Benazepril (10 mg bid) vs. placebo
Co-intervention: Open-label antihypertensive agents were added as necessary (diuretics, CCBs, or beta-blockers or
combination of these agents)
Concomitant non-study RAS blockers: None
Primary & secondary outcomes: Time to the first event in the composite end point of doubling of the serum
creatinine level, ESRD, or death AND progression of renal disease Funding Source: National Nature and Sciences Grant for Major Projects and a People's Liberation Army Grant and in
part by Novartis
HYVET pilot (2003) (Bulpitt et al., 2003)
Design: Prospective, multicentre, randomized, open label, parallel, pilot trial
Mean duration of follow-up: 13 months
Participants (n): 1283
Clinical setting: Elderly HTN
Mean baseline BP: 181.9/99.6 mmHg
Age range: 79.5-96.1 years (mean: 83.3 years)

Hypertensive patients (%): 100
Baseline co-morbidities (%): None
Intervention: Three groups ACEI: Lisinopril (2.5 mg) vs. bendrofluazide (2.5 mg) vs. no treatment
Note: Based on Cochrane recommendations, three groups were analysed as independent group.
Co-intervention: Diltiazem slow release added to control BP
Concomitant non-study RAS blockers: None
Primary & secondary outcomes: Stroke events, total and CV mortality, cardiac and stroke mortality
Funding Source: British Heart Foundation (BHF)
I-PRESERVE (2008) (Massie et al., 2008)
Design: Prospective, multicentre, randomized, double-blinded, parallel trial
Mean duration of follow-up: 4.1 years
Participants (n): 4128
Clinical setting: Symptomatic HF (NYHA II-IV) & LVEF $\ge 45\%$
Mean baseline BP: 136/79 mmHg
Age range: 60-older years (mean age: 72 years) Hypertensive patients (%): 88
Baseline co-morbidities (%): CAD (40%)
Intervention: Two groups
ARB: Irbesartan 75-300 mg/day vs. placebo
Co-intervention: The study drugs added on background of ACEIs. Treatment with ACEIs was permitted as needed
Concomitant non-study RAS blockers: Intervention: 39% ACEI. Control: 40% ACEI
Primary & secondary outcomes: Composite & individual of death from any cause, hosp. for CV cause (worsening HF,
MI, stroke, unstable angina, ventricular dysarrthmia.
Funding Source: Bristol-Myers Squibb and Sanofi-Aventis
IDNT (2001) (Lewis et al., 2001) (FDA, 2001a) (Berl et al., 2003)
Design: Prospective, multicentre, randomized, double-blinded, parallel trial
Mean duration of follow-up: 2.6 years
Participants (n): 1715
Clinical setting: T2DM, HTN, nephropathy Mean baseline BP: 160/87 mmHg
Age range: 30-70 years (mean: 59 years)
Hypertensive patients (%): 100
Baseline co-morbidities (%): T2DM (100)
Intervention: Three groups
ARB: Irbesartan (75-300 mg/day) vs. amlodipine (2.5-10 mg/day) vs. placebo
Note: The groups were analysed independently into two comparisons.
Co-intervention: other antihypertensive agents were used as needed in each group except ACEI, ARB & CCB.
Concomitant non-study RAS blockers: Intervention: 6.2% ACEI & 2.3% ARB. Control: 8.5% ACEI & 2.5% ARB
Primary & secondary outcomes: Renal outcomes: composite of a doubling of the base-line serum creatinine concentration, the onset of ESRD or all death. CV outcomes: composite of CV death, nonfatal MI, hosp. HF,
cerebrovascular events
Funding Source: Bristol-Myers Squibb Institute for Medical Research and Sanofi-Synthelabo.
IMAGINE (2008) (Rouleau et al., 2008)
Design: Prospective, multicentre, randomized, double-blinded, parallel trial
Median duration of follow-up: 2.95
Participants (n): 2553
Clinical setting: Post-CABG ≤ 7 days, LFEF≥40%
Mean baseline BP: 121/70
Mean Age: 61 years
Hypertensive patients (%): 47
Baseline co-morbidities (%): MI (39)
Intervention: Two groups ACEI: Quinapril 10-40 mg/day vs. placebo
Co-intervention: NR
Concomitant non-study RAS blockers: Intervention: NR. Control: 11% ACEI
Primary & secondary outcomes: Composite & individual of CV death or resuscitated cardiac arrest, nonfatal MI,
stroke, HF, coronary revascularization, angina.
Funding Source: Pfizer Canada, the Netherlands, Belgium, and France.
IRMA-2 (2001) (Parving et al., 2001) (FDA, 2001a)
Design: Prospective, multicentre, randomized, double-blinded, parallel trial
Median duration of follow-up: 2 years
Participants (n): 590
Clinical setting: Hypertension, T2DM WITH microalbuminuria
Mean baseline BP: 153/90 mmHg
Age: 30-70 (mean: 58 years)
Hypertensive patients (%): 100
Baseline co-morbidities (%): None Intervention: Three groups
ARB: Irbesartan 150mg/day vs. irbesartan 300mg/day vs. Placebo
Co-intervention: If BP goal was not achieved, other BP-lowering agents were added (excluding DHPs and ACEI)
Concomitant non-study RAS blockers: None
Primary & secondary outcomes: Time from the baseline visit to the first detection of overt nephropathy, changes in
Primary & secondary outcomes: Time from the baseline visit to the first detection of overt nephropathy, changes in the level of albuminuria, changes in creatinine clearance, and the restoration of normoalbuminuria by the time of the last visit
Primary & secondary outcomes: Time from the baseline visit to the first detection of overt nephropathy, changes in the level of albuminuria, changes in creatinine clearance, and the restoration of normoalbuminuria by the time of the

L WIND (2001) (Paba et al. 2001)
J-MIND (2001) (Baba et al., 2001) Design: Prospective, multicentre, randomized, open label, parallel trial
Median duration of follow-up: 2 years
Participants (n): 436
Clinical setting: HTN+T2DM+ normo/ microalbuminuria Mean baseline BP: 162/90 mmHg
Mean age: 60 years
Hypertensive patients (%): 100
Baseline co-morbidities (%): None
Intervention: Two groups ACEI: Enalapril (5-20 mg/day) vs. nifedipine retard (20-60 mg/day)
Co-intervention: If the BP is still high after increased doses, frusemide & alpha-blockers were added in stepwise
fashion
Concomitant non-study RAS blockers: NR
Primary outcomes: The onset & progression of diabetic nephropathy Secondary outcomes: Incidence of CV events, diabetic complication, side effects
Funding Source: NR
JAMP (2004) (Ueshima et al., 2004)
Design: Prospective, multicentre, randomized, open label, parallel trial
Mean duration of follow-up: 5.8 years
Participants (n): 888 Clinical setting: Post-MI (within 14 days) + coronary angiography
Mean baseline BP: NR
Mean age: 62.5 years
Hypertensive patients (%): 8.5
Baseline co-morbidities (%): None Intervention: Two groups
ACEI: Enalapril, captopril or cilazapril vs. control
Co-intervention: NR
Concomitant non-study RAS blockers: NR
Outcomes: Death (CV or non-CV causes); nonfatal MI, bypass grafting surgery (CABG) or percutaneous transluminal
coronary angioplasty (PTCA) intervention, angina, hosp. HF
Funding Source: Ministry of Health, Labour and Welfare
J-RHYTHM II (2010) (Yamashita et al., 2010)
Design: Prospective, multicentre, randomized, open label, parallel trial
Mean duration of follow-up: 4.2 years
Participants (n): 318 Clinical setting: Paroxysmal AF, HTN
Mean baseline BP: 140/82 mmHg
Age mean: 69 years
Hypertensive patients (%): 100
Baseline co-morbidities (%): AF (100) Intervention: Two groups
ARB: Candesartan (4-16 mg/day) vs. amlodipine (2.5-10 mg/day)
Co-intervention: To achieved target BP level, other agents were added included, diuretics, alpha-blockers & beta-
blockers, irrespective of maximal dose of assigned drug (except ACEI & CCB).
Concomitant non-study RAS blockers: None Primary outcomes: Frequency (days/months) of AF (symptomatic or not)
Secondary outcomes: CV events (cardiac death, MI, cerebral infraction, CHF. Progression of paroxysmal AF into
persistent AF.
Funding Source: Japanese Heart Foundation (JHF)
KACT-MetS (2012) (Miyata et al., 2012)
Design: Prospective, multicentre, randomized, open label, parallel trial Mean duration of follow-up: 1 year
Participants (n): 150
Clinical setting: HTN with metabolic syndrome
Mean baseline BP: 152/86 mmHg
Mean age: 64.5 years Hypertensive patients (%): 100
Baseline co-morbidities (%): DM (54), IHD (16)
Intervention: Two groups
ARB: Valsartan (80-160 mg/day) vs. conventional therapy (except ACEI or ARB)
Co-intervention: Diuretics, CCBs, BB & alpha-blockers Concomitant non-study RAS blockers: NR
Primary outcomes: Changes in adiponectin and PAI-1 antigen levels
Secondary outcomes: Changes in the levels of tumour necrosis factor (TNF)- α , interleukin-6 (IL-6)
Funding Source: Graduate School of Medical & Dental Science, Kagoshima University
Kawamura (2013) (Kawamura et al., 2013)
Design: Prospective, multicentre, randomized, open label, parallel trial
Mean duration of follow-up: 3 years Participants (n): 144
Clinical setting: Persistent AF
Mean baseline BP: 137/78 mmHg
Mean age: 61 years
Hypertensive patients (%): 34

Baseline co-morbidities (%): None

ABS: Candesartan (6-12 mg/day) plus bepridil (100-200 mg/day) vs. carvedilol (5-20 mg/day) plus bepridil vs. bepridil (100-200 mg/day) (50-00 mg/day) vs. carvedilol (5-20 mg/day) plus bepridil vs. bepridil (50-200 mg/day) (50-00 mg/day) (50-00 mg/day) vs. carvedilol (5-20 mg/day) plus bepridil vs. bepridil (50-20 mg/day) (50-00 mg/	Intervention: Three groups APB: Candesartan (8-12 mg/day) plus bepridil (100-200 mg/day) vs. carvedilol (5-20 mg/day) plus bepridil vs. bepridi
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Baseline co-morbidities (%): MI (62) Intervention: Two groups ARB: Candesartan (4-8 mg/day) vs. control Co-intervention: NR Concomitant non-study RAS blockers: Intervention: 21% ACEI. Control: 28.6% ACEI Primary outcomes: Hosp. of CV causes (worsening angina, HF) Funding Source: Ogaki Municipal Hospital LAARS (2002) (Ludwig et al., 2002) Design: Prospective, multicentre, randomized, double-blinded, parallel trial Mean duration of follow-up: 2 years Participants (n): 280 Clinical setting: HTN Mean baseline BP: 160/100 mmHg Mean age: 59 years Hypertensive patients (%): 100 Baseline co-motbidities (%): None Intervention: Two groups ARB: Loastant (50-100 mg/day) vs. atenolol (50-100 mg/day) Co-intervention: added HCTZ 12.5 mg/day then CCBs to reach & maintain target BP Concomitant non-study RAS blockers: NR Outcomes: Change of MIT over 2 years & BP Funding Source: NR LIFE (2002) (Dahlóf et al., 2002) (FDA, 2001b) Design: Prospective, multicentre, randomized, double-blinded, parallel trial Mean baseline BP: 174.5/97.7 Age: 55.80 (mean: 67 years) Hypertensive patients (%): 100 Baseline co-motbidities (%): 100 B	Mean age: 65 years
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Co-intervention: NR Composite of revascularization, nonfatal MI, CV death Secondary outcomes: Hosp. of CV causes (worsening angina, HF) Funding Source: Ogaki Municipal Hospital LARS (2002) (Ludwig et al., 2002) Design: Prospective, multicentre, randomized, double-blinded, parallel trial Mean duration of follow-up: 2 years Participants (in; 280 Clinical setting: HTN Mean baseline BP: 160/100 mmHg Mean baseline Co-morbidities (%): None Intervention: added HCT 12.5 mg/day then CCBs to reach & maintain target BP Concomitant non-study RAS blockers: NR Outcomes: Change of MT over 2 years & BP Funding Source: NR Unitercention: added HCT 12.5 mg/day then CCBs to reach & maintain target BP Concomitant non-study RAS blockers: NR Outcomes: Change of MT over 2 years & BP Funding Source: NR Uniter vention: added HCT 12.5 mg/day then CCBs to reach & maintain target BP Concomitant non-study RAS blockers: NR Outcomes: Change of MT over 2 years & BP Funding Source: NR Uniter vention: added HCT 12.5 mg/day then CCBs to reach & maintain target BP Concomitant non-study RAS blockers: NR Outcomes: Change of MT over 2 years & BP Funding Source: NR Clinical setting: Essential hypertension and LVH Mean baseline BP: 174.5/97.7 Age: 35-80 (mean: 67 years) Hypertensive patients (%): 100 Baseline co-morbidities (%): 100 Engin: Source: Merck LIRCO (2018) (Saglimbene et al., 2018) Design: Prospective, randomized, multicentre, open-label, blinded-endpoint trial (PROBE) Median duration of follow-up: 2.7 years Participants (n): 817 Concomitant non-study RAS blockers: NR Concomitant non-study RAS blockers: NR Concomitant non-study RAS blo	
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Mean baseline BP: 160/100 mmHg Mean age: 59 years Hypertensive patients (%): 100 Baseline co-morbidities (%): None Intervention: Two groups ARB: Losartan (50-100 mg/day) vs. atenolol (50-100 mg/day) Co-intervention: added HCT 12.5 mg/day then CCBs to reach & maintain target BP Concomitant non-study RAS blockers: NR Ultree (2002) (Dahlöf et al., 2002) (FDA, 2001b) Design: Prospective, multicentre, randomized, double-blinded, parallel trial Mean duration of follow-up: 4.8 years Participants (%): 100 Baseline co-morbidities (%): None Intervention: Two groups ARB: Losartan (%): 100 Baseline co-morbidities (%): 100 Frinding Source: Merck LIRCO (2018) (Saglimbene et al., 2018) Design: Prospective, randomized, multicentre, open-label, blinded-endpoint trial (PROBE) Median duration of follow-up: 2.7 years Participants (%): 103 Baseline co-morbidities (%): 108 Baseline co-morbidities (%)	
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Clinical setting: T2DM & HTN	Participants (n): 817 Clinical setting: DM with moderate to severe albuminuria Mean age: 62.8 years Hypertensive patients (%): 83 Baseline co-morbidities (%): 83 Intervention: Two groups ACEI vs ARB Co-intervention: NR Concomitant non-study RAS blockers: NR Primary outcomes: First occurrence of CV death, nonfatal MI, nonfatal stroke, or hosp. for CV causes Secondary outcomes: composite of ESRD, doubling of serum creatinine, eGFR, progression to sever albuminuria Funding Source: Agenzia Italiana del Farmaco MITEC (2009) (Baguet et al., 2009) Design: Prospective, multicentre, randomized, double-blinded, parallel trial Mean duration of follow-up: 2 years Participants (n): 209

Mean baseline BP: 156/91 mmHg Age range: 40-74 years (mean: 59.7 years)
Ade rande: 40-74 years (mean: 59 / years)
Hypertensive patients (%): 100
Baseline co-morbidities (%): None Intervention: Two groups
ARB: Candesartan (8-16 mg/day) vs. amlodipine (5-10 mg/day)
Co-intervention: the doses of assigned drugs were doubled then followed by HCTZ 12.5 mg
Concomitant non-study RAS blockers: NR
Primary outcomes: Progression of CIMT
Funding Source: Laboratories Takeda, Puteaux, France
MOSES (2005) (Schrader et al., 2005)
Design: Prospective, randomized, open-label, blinded-endpoint trial (PROBE)
Mean duration of follow-up: 2.5 years
Participants (n): 1352
Clinical setting: HTN+ history of CVA (within past 24 months)
Mean baseline BP: 150.5/87 mmHg
Mean age: 67 years
Hypertensive patients (%): 100
Baseline co-morbidities (%): CVA (100), CAD (28), DM (37)
Intervention: Two groups
ARB: Eprosartan (600 mg/day) vs. nitrendipine 10 mg/day
Co-intervention: To achieve target BP level, doses of assigned drugs were increased or combination therapy with diuretics, BB, alpha-blockers (avoided ACEI, ARB & CCB)
Concomitant non-study RAS blockers: Intervention group: 11.3% ACEI & 2.5% ARB; Control group: 21% ACEI & 4.8%
ARB
Primary outcomes: Composite of all-mortality, CV & cerebrovascular events. CV events as MI & new HF.
Cerebrovascular events as intracerebral haemorrhage, TIA, or ischemic neurological deficit
Secondary outcomes: Components of combined 1 ^{ry} endpoints. Assessment of the patients' functional capacity and
mental function.
Funding Source: Solvay Pharmaceuticals GmbH and Aventis Pharma Germany
NAVIGATOR (2010) (Califf et al., 2010)
Design: Prospective, multicentre, randomized, double-blinded trial with a 2-by-2 factorial design.
Median duration of follow-up: 5 years
Participants (n): 9306
Clinical setting: Impaired glucose tolerance and established CVD or CV risk
Mean baseline BP: 139.7/82.5
Age: 18-older (mean: 63.7 years) Hypertensive patients (%): 75
Baseline co-morbidities (%): DM (44)
Intervention: Two groups with additional groups (nateglinide vs placebo)
ARB: Valsartan 80-160 mg/day vs Placebo
Co-intervention: No other BP-lowering agents were added
Concomitant non-study RAS blockers: 15% ACEI & 6% ARB. Control: 17% ACEI & 8% ARB
Primary & secondary outcomes: (1) incidence of T2DM, (2) a composite of death from CV causes, nonfatal MI,
nonfatal stroke, hospitalization for HF, arterial revascularization, or hospitalization for unstable angina, (3) core CV
outcome
outcome Funding Source: Novartis Pharma
outcome Funding Source: Novartis Pharma NTP-AF (2013) (Du et al., 2013)
outcome Funding Source: Novartis Pharma NTP-AF (2013) (Du et al., 2013) Design: Prospective, multicentre, randomized, open-label, parallel trial
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outcome Funding Source: Novartis Pharma NTP-AF (2013) (Du et al., 2013) Design: Prospective, multicentre, randomized, open-label, parallel trial Mean duration of follow-up: 2 years Participants (n): 149
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outcome Funding Source: Novartis Pharma NTP-AF (2013) (Du et al., 2013) Design: Prospective, multicentre, randomized, open-label, parallel trial Mean duration of follow-up: 2 years Participants (n): 149 Clinical setting: Paroxysmal AF, HTN Mean baseline BP: 160/93 mmHg Mean age: 61.8 years Hypertensive patients (%): 100 Baseline co-morbidities (%): None Intervention: Two groups ARB; Telmisartan 80 mg/day vs. nifedipine 30 mg/day Co-intervention: To control BP, metoprolol 50-100 mg/day were added, then the dose of nifedipine increased to 60 mg/day or telmisartan 160 mg/day Concomitant non-study RAS blockers: None Primary outcomes: Incidence of AF (including paroxysmal and persistent) recurrence. Secondary outcomes: CV events as CV death, acute MI, stroke, & CHF Funding Source: Program for Innovative Research Team of the second affiliated hospital of Chongqing medical university OLIVUS (2010) (Hirohata et al., 2010, Hirohata et al., 2012) Design: Prospective, multicentre, randomized, open-label, parallel trial Mean duration of follow-up: 4.1 Participants (n): 247 Clinical setting: Clinically stable angina & HTN scheduled for PCI Mean baseline BP: 143/80 mmHg
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outcome Funding Source: Novartis Pharma NTP-AF (2013) (Du et al., 2013) Design: Prospective, multicentre, randomized, open-label, parallel trial Mean duration of follow-up: 2 years Participants (n): 149 Clinical setting: Paroxysmal AF, HTN Mean daseline BP: 160/93 mmHg Mean age: 61.8 years Hypertensive patients (%): 100 Baseline co-morbidities (%): None Intervention: Two groups ARB; Telmisartan 80 mg/day vs. nifedipine 30 mg/day Co-intervention: To control BP, metoprolol 50-100 mg/day were added, then the dose of nifedipine increased to 60 mg/day or telmisartan 160 mg/day Concomitant non-study RAS blockers: None Primary outcomes: Incidence of AF (including paroxysmal and persistent) recurrence. Secondary outcomes: CV events as CV death, acute MI, stroke, & CHF Funding Source: Program for Innovative Research Team of the second affiliated hospital of Chongqing medical university OLIVUS (2010) (Hirohata et al., 2010, Hirohata et al., 2012) Design: Prospective, multicentre, randomized, open-label, parallel trial Mean duration of follow-up: 4.1 Participants (n): 247 Clinical setting: Clinically stable angina & HTN scheduled for PCI Mean baseline BP: 143/80 mmHg Mean baseline BP: 143/80 mmHg
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outcome Funding Source: Novartis Pharma NTP-AF (2013) (Du et al., 2013) Design: Prospective, multicentre, randomized, open-label, parallel trial Mean duration of follow-up: 2 years Participants (n): 149 Clinical setting: Paroxysmal AF, HTN Mean baseline BP: 160/93 mmHg Mean baseline Co-morbidities (%): None Intervention: Two groups ARB; Telmisartan 80 mg/day vs. nifedipine 30 mg/day Co-intervention: To control BP, metoprolol 50-100 mg/day were added, then the dose of nifedipine increased to 60 mg/day or telmisartan 160 mg/day Concomitant non-study RAS blockers: None Primary outcomes: Incidence of AF (including paroxysmal and persistent) recurrence. Secondary outcomes: ICV events as CV death, acute MI, stroke, & CHF Funding Source: Program for Innovative Research Team of the second affiliated hospital of Chongqing medical university OLIVUS (2010) (Hirohata et al., 2010, Hirohata et al., 2012) Design: Prospective, multicentre, randomized, open-label, parallel trial Mean duration of follow-up: 4.1 Participants (n): 247 Clinical setting: Clinically stable angina & HTN scheduled for PCI Mean age: 68 years Hypertensive patients (%): 100 Baseline co-morbidities (%): None Intervention: Two groups
outcome Funding Source: Novartis Pharma NTP-AF (2013) (Du et al., 2013) Design: Prospective, multicentre, randomized, open-label, parallel trial Mean duration of follow-up: 2 years Participants (n): 149 Clinical setting: Paroxysmal AF, HTN Mean baseline BP: 160/93 mmHg Mean baseline BP: 160/93 mmHg Mean baseline Co-morbidities (%): 100 Baseline co-morbidities (%): None Intervention: Two groups ARB; Telmisartan 80 mg/day vs. nifedipine 30 mg/day Co-intervention: To control BP, metoprolol 50-100 mg/day were added, then the dose of nifedipine increased to 60 mg/day or telmisartan 160 mg/day Conomitant non-study RAS blockers: None Primary outcomes: CV events as CV death, acute MI, stroke, & CHF Funding Source: Program for Innovative Research Team of the second affiliated hospital of Chongqing medical university OLIVUS (2010) (Hirohata et al., 2010, Hirohata et al., 2012) Design: Prospective, multicentre, randomized, open-label, parallel trial Mean duration of follow-up: 4.1 Participants (n): 247 Clinical setting: Clinically stable angina & HTN scheduled for PCI Mean baseline BP: 143/80 mmHg Mean age: 68 years Hypertensive patients (%): 100 Baseline co-morbidities (%): N

Concomitant non-study RAS blockers: NR
Primary outcomes: Coronary atherosclerotic changes evaluated by volumetric IVUS
Secondary outcomes: CV adverse events: CV death, nonfatal MI, nonfatal stroke, non-CV death, unstable angina, HF,
deterioration of renal function
Funding Source: NR
ONTARGET (2008) (Yusuf et al., 2008d) Design: Prospective, multicentre, randomized, double-blinded, parallel trial
Mean duration of follow-up: 4.7 years
Participants (n): 25620
Clinical setting: Patients with coronary, peripheral, or cerebrovascular disease or diabetes with end-organ damage
Mean baseline BP: 141.8/67.9 mmHg
Age: 55 or older (mean: 66.4 years)
Hypertensive patients (%): 69
Baseline co-morbidities (%): CAD (75), DM (38) Intervention: Three groups
ARB: 80mg/day telmisartan vs ACEI: 5-10mg/day ramipril vs ARB+ACEI: 80mg/day telmisartan plus 5-10mg/day
ramipril
Co-intervention:
Concomitant non-study RAS blockers: Intervention: 6.4% ACEI. Control: 3.3% ARBs
Outcomes: Composite & individual of CV death, MI or stroke. New HF, DM, AF, dementia or cognitive decline,
nephropathy, and revascularization procedures.
Funding Source: Boehringer Ingelheim & Heart & Stroke Foundation of Ontario
OPTIMAAL (2002) (Dickstein et al., 2002)
Design: Prospective, multicentre, randomized, double-blinded, parallel trial Mean duration of follow-up: 2.7 years
Participants (n): 5477
Clinical setting: Confirmed acute MI and HF
Mean baseline BP: 123/71.5 mmHg
Age: 50 or older (mean: 67.4 years)
Hypertensive patients (%): 36
Baseline co-morbidities (%): IHD (51)
Intervention: Two groups ARB: losartan 12.5-50 mg/day vs ACEI: captopril 37.5-150 mg/day
Co-intervention: NR (Current usage of ACEI was excluded)
Concomitant non-study RAS blockers: NR
Primary outcomes: Total mortality (cardiac & non-cardiac)
Funding Source: Merck, Sharp and Dohme Research Laboratories
ORIENT (2011) (Imai et al., 2011) (FDA, 2010b)
Design: Prospective, multicentre, randomized, double-blinded, parallel trial
Mean duration of follow-up: 3.2 years
Participants (n): 566 Clinical setting: T2DM & nephropathy
Mean baseline BP: 141/77.5 mmHg
Age range: 30-70 years (mean:59 years)
Hypertensive patients (%): 100
Baseline co-morbidities (%): CAD (21)
Intervention: Two groups
ARB: Olmesartan (10-40 mg/day) vs. placebo Co-intervention: Additional BP-lowering agents were added as diuretics, BB, CCB & alpha-blockers (ACEI, ARB &
potassium-sparing diuretics were prohibited)
Concomitant non-study RAS blockers (%): Intervention group: 73% ACEI & Control group 74% ACEI
Primary outcomes: Renal outcomes: composite of doubling of SCr, ESRD, chronic dialysis, transplantation, & all-cause
of death
Secondary outcomes: CV outcomes: a composite endpoint of first occurrence of any of the following events: CV
death, nonfatal stroke (except TIA), nonfatal MI, angina & HF, revascularization of coronary carotid
Funding Source: Daiichi Sankyo
PART-2 (2000) (MacMahon et al., 2000) Design: Prospective, multicentre, randomized, double-blinded, parallel trial
Mean duration of follow-up: 4.7 years
Mean duration of follow-up: 4.7 years Participants (n): 617
Participants (n): 617 Clinical setting: Patients with coronary, cerebrovascular, or peripheral vascular disease
Participants (n): 617 Clinical setting: Patients with coronary, cerebrovascular, or peripheral vascular disease Mean baseline BP: 133/79 mmHg
Participants (n): 617 Clinical setting: Patients with coronary, cerebrovascular, or peripheral vascular disease Mean baseline BP: 133/79 mmHg Mean age: 60 years
Participants (n): 617 Clinical setting: Patients with coronary, cerebrovascular, or peripheral vascular disease Mean baseline BP: 133/79 mmHg Mean age: 60 years Hypertensive patients (%): NR
Participants (n): 617 Clinical setting: Patients with coronary, cerebrovascular, or peripheral vascular disease Mean baseline BP: 133/79 mmHg Mean age: 60 years Hypertensive patients (%): NR Baseline co-morbidities (%): CAD (60), PVD (20)
Participants (n): 617 Clinical setting: Patients with coronary, cerebrovascular, or peripheral vascular disease Mean baseline BP: 133/79 mmHg Mean age: 60 years Hypertensive patients (%): NR
Participants (n): 617 Clinical setting: Patients with coronary, cerebrovascular, or peripheral vascular disease Mean baseline BP: 133/79 mmHg Mean age: 60 years Hypertensive patients (%): NR Baseline co-morbidities (%): CAD (60), PVD (20) Intervention: Two groups
Participants (n): 617 Clinical setting: Patients with coronary, cerebrovascular, or peripheral vascular disease Mean baseline BP: 133/79 mmHg Mean age: 60 years Hypertensive patients (%): NR Baseline co-morbidities (%): CAD (60), PVD (20) Intervention: Two groups ACEI: Ramipril (5-10 mg/day) vs. placebo Co-intervention: NR Concomitant non-study RAS blockers: Intervention group: 3% ACEI & Control group: 7% ACEI
Participants (n): 617 Clinical setting: Patients with coronary, cerebrovascular, or peripheral vascular disease Mean baseline BP: 133/79 mmHg Mean age: 60 years Hypertensive patients (%): NR Baseline co-morbidities (%): CAD (60), PVD (20) Intervention: Two groups ACEI: Ramipril (5-10 mg/day) vs. placebo Co-intervention: NR Concomitant non-study RAS blockers: Intervention group: 3% ACEI & Control group: 7% ACEI Primary outcomes: Change in common & internal carotid arteries (mm)
Participants (n): 617 Clinical setting: Patients with coronary, cerebrovascular, or peripheral vascular disease Mean baseline BP: 133/79 mmHg Mean age: 60 years Hypertensive patients (%): NR Baseline co-morbidities (%): CAD (60), PVD (20) Intervention: Two groups ACEI: Ramipril (5-10 mg/day) vs. placebo Co-intervention: NR Concomitant non-study RAS blockers: Intervention group: 3% ACEI & Control group: 7% ACEI Primary outcomes: Change in common & internal carotid arteries (mm) Other outcomes: all clinical events resulting in death, hospitalization or withdrawal from study treatment
Participants (n): 617 Clinical setting: Patients with coronary, cerebrovascular, or peripheral vascular disease Mean baseline BP: 133/79 mmHg Mean age: 60 years Hypertensive patients (%): NR Baseline co-morbidities (%): CAD (60), PVD (20) Intervention: Two groups ACEI: Ramipril (5-10 mg/day) vs. placebo Co-intervention: NR Concomitant non-study RAS blockers: Intervention group: 3% ACEI & Control group: 7% ACEI Primary outcomes: Change in common & internal carotid arteries (mm) Other outcomes: all clinical events resulting in death, hospitalization or withdrawal from study treatment Funding Source: Hoechst AG & Health Research Council of New Zealand.
Participants (n): 617 Clinical setting: Patients with coronary, cerebrovascular, or peripheral vascular disease Mean baseline BP: 133/79 mmHg Mean age: 60 years Hypertensive patients (%): NR Baseline co-morbidities (%): CAD (60), PVD (20) Intervention: Two groups ACEI: Ramipril (5-10 mg/day) vs. placebo Co-intervention: NR Concomitant non-study RAS blockers: Intervention group: 3% ACEI & Control group: 7% ACEI Primary outcomes: Change in common & internal carotid arteries (mm) Other outcomes: all clinical events resulting in death, hospitalization or withdrawal from study treatment Funding Source: Hoechst AG & Health Research Council of New Zealand. PEACE (2004) (Braunwald et al., 2004)
Participants (n): 617 Clinical setting: Patients with coronary, cerebrovascular, or peripheral vascular disease Mean baseline BP: 133/79 mmHg Mean age: 60 years Hypertensive patients (%): NR Baseline co-morbidities (%): CAD (60), PVD (20) Intervention: Two groups ACEI: Ramipril (5-10 mg/day) vs. placebo Co-intervention: NR Concomitant non-study RAS blockers: Intervention group: 3% ACEI & Control group: 7% ACEI Primary outcomes: Change in common & internal carotid arteries (mm) Other outcomes: all clinical events resulting in death, hospitalization or withdrawal from study treatment Funding Source: Hoechst AG & Health Research Council of New Zealand. PEACE (2004) (Braunwald et al., 2004) Design: Prospective, multicentre, randomized, double-blinded, parallel trial
Participants (n): 617 Clinical setting: Patients with coronary, cerebrovascular, or peripheral vascular disease Mean baseline BP: 133/79 mmHg Mean age: 60 years Hypertensive patients (%): NR Baseline co-morbidities (%): CAD (60), PVD (20) Intervention: Two groups ACEI: Ramipril (5-10 mg/day) vs. placebo Co-intervention: NR Concomitant non-study RAS blockers: Intervention group: 3% ACEI & Control group: 7% ACEI Primary outcomes: Change in common & internal carotid arteries (mm) Other outcomes: all clinical events resulting in death, hospitalization or withdrawal from study treatment Funding Source: Hoechst AG & Health Research Council of New Zealand. PEACE (2004) (Braunwald et al., 2004)

Clinical setting: Stable CAD (MI or PCI/CABG at least 3 months before enrolment)
Mean baseline BP: 134/78 mmHg Age range: 50 or older (mean: 64 years)
Hypertensive patients (%): 46
Intervention: Two groups
ACEI: Trandolapril (2-4 mg/day) vs. placebo
Co-intervention: NR (Excluded usage of ACEIs and ARBs. ACEIs & ARBs were prohibited)
Concomitant non-study RAS blockers: NR
Primary & secondary outcomes: Time of occurrence the CV death or nonfatal MI & Composite of CV death, non-fatal
MI or coronary revascularization
Funding Source: Bristol-Myers Squibb & Merck
PEP-CHF (2006) (Cleland et al., 2006) Design: Prospective, multicentre, randomized, double-blinded, parallel trial
Median duration of follow-up: 2.1 years
Participants (n): 850
Clinical setting: Elderly HF (NYHA Class I-IV) with LVD
Mean baseline BP: 140/80 mmHg
Age range: 75-96 years (mean: 75 years)
Hypertensive patients (%): 79
Baseline co-morbidities (%):
Intervention: Two groups ACEI: Perindopril (2-4 mg/day) vs. placebo
Co-intervention: NR
Concomitant non-study RAS blockers: Intervention: 35% ACEI. Control: 37% ACEI
Primary & secondary outcomes: Composite & individual of all cause-mortality or HF hospitalization
Funding Source: Servier company
PHARAO (2008) (Luders et al., 2008)
Design: Multicentre, prospective, randomized, open-label, blinded-endpoint trial (PROBE)
Mean duration of follow-up: 3 years
Participants (n): 1008
Clinical setting: Patients with high-normal office BP Mean baseline BP: 134.4/83.6
Age: 50-85 (mean: 62.3 years)
Hypertensive patients (%): None
Baseline co-morbidities (%): None
Intervention: Two groups
ACEI: Ramipril 5 mg daily vs Control
Co-intervention: no other BP-lowering agents were added
Concomitant non-study RAS blockers: NR Primary & secondary outcomes: development of hypertension, reduction in CVA events and CV events, overall
mortality, reasons for admissions to hospital, the occurrence of pathological fasting glucose levels in
serum/pathological HbA1c levels
Funding Source: Sanofi Aventis Pharma GmbH
PHYLLIS (2004) (Zanchetti et al., 2004)
Design: Prospective, multicentre, randomized, double-blinded, parallel trial
Mean duration of follow-up: 2.6 years
Participants (n): 508
Clinical setting: Patients with hypertension, hyperlipidaemia, and asymptomatic carotid atherosclerosis Mean baseline BP: 161/98.4 mmHg
Age: 45-70 (mean: 58.4 years)
Hypertensive patients (%): 100
Baseline co-morbidities (%): None
Intervention: Four groups
1) HCTZ 25 mg OD plus placebo OR, 2) fosinopril 20 mg OD plus placebo OR, 3) HCTZ 25 mg & pravastatin 40 OD plus
1) HCTZ 25 mg OD plus placebo OR, 2) fosinopril 20 mg OD plus placebo OR, 3) HCTZ 25 mg & pravastatin 40 OD plus placebo OR, 4) fosinopril 20 mg OD & pravastatin 40 mg OD plus placebo.
1) HCTZ 25 mg OD plus placebo OR, 2) fosinopril 20 mg OD plus placebo OR, 3) HCTZ 25 mg & pravastatin 40 OD plus placebo OR, 4) fosinopril 20 mg OD & pravastatin 40 mg OD plus placebo. Note: For current review, only fosinopril arm vs. HCTZ was included.
1) HCTZ 25 mg OD plus placebo OR, 2) fosinopril 20 mg OD plus placebo OR, 3) HCTZ 25 mg & pravastatin 40 OD plus placebo OR, 4) fosinopril 20 mg OD & pravastatin 40 mg OD plus placebo. Note: For current review, only fosinopril arm vs. HCTZ was included. Co-intervention: if BP goal was not achieved, other BP-lowering agents were added (Nifedipine GITS 30-60 mg/OD).
1) HCTZ 25 mg OD plus placebo OR, 2) fosinopril 20 mg OD plus placebo OR, 3) HCTZ 25 mg & pravastatin 40 OD plus placebo OR, 4) fosinopril 20 mg OD & pravastatin 40 mg OD plus placebo. Note: For current review, only fosinopril arm vs. HCTZ was included. Co-intervention: if BP goal was not achieved, other BP-lowering agents were added (Nifedipine GITS 30-60 mg/OD). Concomitant non-study RAS blockers: NR
1) HCTZ 25 mg OD plus placebo OR, 2) fosinopril 20 mg OD plus placebo OR, 3) HCTZ 25 mg & pravastatin 40 OD plus placebo OR, 4) fosinopril 20 mg OD & pravastatin 40 mg OD plus placebo. Note: For current review, only fosinopril arm vs. HCTZ was included. Co-intervention: if BP goal was not achieved, other BP-lowering agents were added (Nifedipine GITS 30-60 mg/OD).
 HCTZ 25 mg OD plus placebo OR, 2) fosinopril 20 mg OD plus placebo OR, 3) HCTZ 25 mg & pravastatin 40 OD plus placebo OR, 4) fosinopril 20 mg OD & pravastatin 40 mg OD plus placebo. Note: For current review, only fosinopril arm vs. HCTZ was included. Co-intervention: if BP goal was not achieved, other BP-lowering agents were added (Nifedipine GITS 30-60 mg/OD). Concomitant non-study RAS blockers: NR Primary & secondary outcomes: Rate of change in maximum intimal media thickness (IMT) of the coronary artery wall, changes in BP, changes in lipid level and other laboratory variables Funding Source: : Bristol-Myers Squibb and Menarini
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 1) HCTZ 25 mg OD plus placebo OR, 2) fosinopril 20 mg OD plus placebo OR, 3) HCTZ 25 mg & pravastatin 40 OD plus placebo OR, 4) fosinopril 20 mg OD & pravastatin 40 mg OD plus placebo. Note: For current review, only fosinopril arm vs. HCTZ was included. Co-intervention: if BP goal was not achieved, other BP-lowering agents were added (Nifedipine GITS 30-60 mg/OD). Concomitant non-study RAS blockers: NR Primary & secondary outcomes: Rate of change in maximum intimal media thickness (IMT) of the coronary artery wall, changes in BP, changes in lipid level and other laboratory variables Funding Source: : Bristol-Myers Squibb and Menarini PREAMI (2006) (Ferrari et al., 2006) Design: Prospective, multicentre, randomized, double-blinded, parallel trial Mean duration of follow-up: 1 Participants (n): 1252 Clinical setting: AMI within 20 days & LVEF ≥ 40
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 1) HCTZ 25 mg OD plus placebo OR, 2) fosinopril 20 mg OD plus placebo OR, 3) HCTZ 25 mg & pravastatin 40 OD plus placebo OR, 4) fosinopril 20 mg OD & pravastatin 40 mg OD plus placebo. Note: For current review, only fosinopril arm vs. HCTZ was included. Co-intervention: if BP goal was not achieved, other BP-lowering agents were added (Nifedipine GITS 30-60 mg/OD). Concomitant non-study RAS blockers: NR Primary & secondary outcomes: Rate of change in maximum intimal media thickness (IMT) of the coronary artery wall, changes in BP, changes in lipid level and other laboratory variables Funding Source: : Bristol-Myers Squibb and Menarini PREAMI (2006) (Ferrari et al., 2006) Design: Prospective, multicentre, randomized, double-blinded, parallel trial Mean duration of follow-up: 1 Participants (n): 1252 Clinical setting: AMI within 20 days & LVEF ≥ 40 Mean age: 73 years Hypertensive patients (%): 58
 1) HCTZ 25 mg OD plus placebo OR, 2) fosinopril 20 mg OD plus placebo OR, 3) HCTZ 25 mg & pravastatin 40 OD plus placebo OR, 4) fosinopril 20 mg OD & pravastatin 40 mg OD plus placebo. Note: For current review, only fosinopril arm vs. HCTZ was included. Co-intervention: if BP goal was not achieved, other BP-lowering agents were added (Nifedipine GITS 30-60 mg/OD). Concomitant non-study RAS blockers: NR Primary & secondary outcomes: Rate of change in maximum intimal media thickness (IMT) of the coronary artery wall, changes in BP, changes in lipid level and other laboratory variables Funding Source: : Bristol-Myers Squibb and Menarini PREAMI (2006) (Ferrari et al., 2006) Design: Prospective, multicentre, randomized, double-blinded, parallel trial Mean duration of follow-up: 1 Participants (n): 1252 Clinical setting: AMI within 20 days & LVEF ≥ 40 Mean age: 73 years Hypertensive patients (%): 58 Baseline co-morbidities (%): None
 1) HCTZ 25 mg OD plus placebo OR, 2) fosinopril 20 mg OD plus placebo OR, 3) HCTZ 25 mg & pravastatin 40 OD plus placebo OR, 4) fosinopril 20 mg OD & pravastatin 40 mg OD plus placebo. Note: For current review, only fosinopril arm vs. HCTZ was included. Co-intervention: if BP goal was not achieved, other BP-lowering agents were added (Nifedipine GITS 30-60 mg/OD). Concomitant non-study RAS blockers: NR Primary & secondary outcomes: Rate of change in maximum intimal media thickness (IMT) of the coronary artery wall, changes in BP, changes in lipid level and other laboratory variables Funding Source: : Bristol-Myers Squibb and Menarini PREAMI (2006) (Ferrari et al., 2006) Design: Prospective, multicentre, randomized, double-blinded, parallel trial Mean duration of follow-up: 1 Participants (n): 1252 Clinical setting: AMI within 20 days & LVEF ≥ 40 Mean age: 73 years Hypertensive patients (%): 58 Baseline co-morbidities (%): None Intervention: Two groups
 1) HCTZ 25 mg OD plus placebo OR, 2) fosinopril 20 mg OD plus placebo OR, 3) HCTZ 25 mg & pravastatin 40 OD plus placebo OR, 4) fosinopril 20 mg OD & pravastatin 40 mg OD plus placebo. Note: For current review, only fosinopril arm vs. HCTZ was included. Co-intervention: if BP goal was not achieved, other BP-lowering agents were added (Nifedipine GITS 30-60 mg/OD). Concomitant non-study RAS blockers: NR Primary & secondary outcomes: Rate of change in maximum intimal media thickness (IMT) of the coronary artery wall, changes in BP, changes in lipid level and other laboratory variables Funding Source: : Bristol-Myers Squibb and Menarini PREAMI (2006) (Ferrari et al., 2006) Design: Prospective, multicentre, randomized, double-blinded, parallel trial Mean duration of follow-up: 1 Participants (n): 1252 Clinical setting: AMI within 20 days & LVEF ≥ 40 Mean age: 73 years Hypertensive patients (%): 58 Baseline co-morbidities (%): None Intervention: Two groups ACEI: Perindopril (2-8 mg/day) vs. placebo
1) HCTZ 25 mg OD plus placebo OR, 2) fosinopril 20 mg OD plus placebo OR, 3) HCTZ 25 mg & pravastatin 40 OD plus placebo OR, 4) fosinopril 20 mg OD & pravastatin 40 mg OD plus placebo. Note: For current review, only fosinopril arm vs. HCTZ was included. Co-intervention: if BP goal was not achieved, other BP-lowering agents were added (Nifedipine GITS 30-60 mg/OD). Concomitant non-study RAS blockers: NR Primary & secondary outcomes: Rate of change in maximum intimal media thickness (IMT) of the coronary artery wall, changes in BP, changes in lipid level and other laboratory variables Funding Source: : Bristol-Myers Squibb and Menarini PREAMI (2006) (Ferrari et al., 2006) Design: Prospective, multicentre, randomized, double-blinded, parallel trial Mean duration of follow-up: 1 Participants (n): 1252 Clinical setting: AMI within 20 days & LVEF ≥ 40 Mean baseline BP: 126/74 mmHg Mean age: 73 years Hypertensive patients (%): 58 Baseline co-morbidities (%): 58 Baseline co-morbidities (%): 58 Baseline co-morbidities (%): 58 Baseline co-morbidities (%): 58 Baseline for the groups ACEI: Perindopril (2-8 mg/day) vs. placebo Co-intervention: NR
 1) HCTZ 25 mg OD plus placebo OR, 2) fosinopril 20 mg OD plus placebo OR, 3) HCTZ 25 mg & pravastatin 40 OD plus placebo OR, 4) fosinopril 20 mg OD & pravastatin 40 mg OD plus placebo. Note: For current review, only fosinopril arm vs. HCTZ was included. Co-intervention: if BP goal was not achieved, other BP-lowering agents were added (Nifedipine GITS 30-60 mg/OD). Concomitant non-study RAS blockers: NR Primary & secondary outcomes: Rate of change in maximum intimal media thickness (IMT) of the coronary artery wall, changes in BP, changes in lipid level and other laboratory variables Funding Source: : Bristol-Myers Squibb and Menarini PREAMI (2006) (Ferrari et al., 2006) Design: Prospective, multicentre, randomized, double-blinded, parallel trial Mean duration of follow-up: 1 Participants (n): 1252 Clinical setting: AMI within 20 days & LVEF ≥ 40 Mean age: 73 years Hypertensive patients (%): 58 Baseline co-morbidities (%): None Intervention: Two groups ACEI: Perindopril (2-8 mg/day) vs. placebo Co-intervention: NR Concomitant non-study RAS blockers: 8% ACEI in both groups
1) HCTZ 25 mg OD plus placebo OR, 2) fosinopril 20 mg OD plus placebo OR, 3) HCTZ 25 mg & pravastatin 40 OD plus placebo OR, 4) fosinopril 20 mg OD & pravastatin 40 mg OD plus placebo. Note: For current review, only fosinopril arm vs. HCTZ was included. Co-intervention: if BP goal was not achieved, other BP-lowering agents were added (Nifedipine GITS 30-60 mg/OD). Concomitant non-study RAS blockers: NR Primary & secondary outcomes: Rate of change in maximum intimal media thickness (IMT) of the coronary artery wall, changes in BP, changes in lipid level and other laboratory variables Funding Source: : Bristol-Myers Squibb and Menarini PREAMI (2006) (Ferrari et al., 2006) Design: Prospective, multicentre, randomized, double-blinded, parallel trial Mean duration of follow-up: 1 Participants (n): 1252 Clinical setting: AMI within 20 days & LVEF ≥ 40 Mean baseline BP: 126/74 mmHg Mean age: 73 years Hypertensive patients (%): 58 Baseline co-morbidities (%): None Intervention: Two groups ACEI: Perindopril (2-8 mg/day) vs. placebo Co-intervention: NR Concomitant non-study RAS blockers: 8% ACEI in both groups Primary outcomes: Composite of death, HF hosp., LV remodelling
 1) HCTZ 25 mg OD plus placebo OR, 2) fosinopril 20 mg OD plus placebo OR, 3) HCTZ 25 mg & pravastatin 40 OD plus placebo OR, 4) fosinopril 20 mg OD & pravastatin 40 mg OD plus placebo. Note: For current review, only fosinopril arm vs. HCTZ was included. Co-intervention: if BP goal was not achieved, other BP-lowering agents were added (Nifedipine GITS 30-60 mg/OD). Concomitant non-study RAS blockers: NR Primary & secondary outcomes: Rate of change in maximum intimal media thickness (IMT) of the coronary artery wall, changes in BP, changes in lipid level and other laboratory variables Funding Source: : Bristol-Myers Squibb and Menarini PREAMI (2006) (Ferrari et al., 2006) Design: Prospective, multicentre, randomized, double-blinded, parallel trial Mean duration of follow-up: 1 Participants (n): 1252 Clinical setting: AMI within 20 days & LVEF ≥ 40 Mean age: 73 years Hypertensive patients (%): 58 Baseline co-morbidities (%): None Intervention: Two groups ACEI: Perindopril (2-8 mg/day) vs. placebo Co-intervention: NR Concomitant non-study RAS blockers: 8% ACEI in both groups

Funding Source: Stroder, Florence, Italy, and Servier Italia, Rome, Italy.
PREVEND IT (2004) (Asselbergs et al., 2004)
Design: Prospective, single-centre, randomized, double-blinded trial with a 2-by-2 factorial design.
Mean duration of follow-up: 3.8 years
Participants (n): 864
Clinical setting: Microalbuminuria (UAE of 15-300 mg/24 hr)
Mean baseline BP: 130/76 mmHg
Mean age: 51 years
Hypertensive patients (%): Ex
Baseline co-morbidities (%): None Intervention: Four arms (2-by-2 factorial design)
ACEI: Fosinopril (20 mg/day) vs placebo & pravastatin (40 mg/day) vs. placebo
Co-intervention: NR
Concomitant non-study RAS blockers: 5.2% open label ACEIs
Primary & secondary outcomes: Combined & individual incidence of CV mortality and hospitalization for CV
morbidity (nonfatal MI, myocardial ischemia, HF, PVD, CVA, ESRD)
Funding Source: Dutch Kidney Foundation
PREVER-treatment (2016) (Fuchs et al., 2016)
Design: Prospective, multicentre, randomized, double-blinded, parallel trial
Mean duration of follow-up: 1.5 years Participants (n): 655
Clinical setting: Stage I HTN
Mean baseline BP: 142.6/89.5 mmHg
Age: 30-70 (mean: 54 years)
Hypertensive patients (%): 100
Baseline co-morbidities (%): DM (47)
Intervention: Two groups
ARB: Losartan 50 mg/day vs. chlorthalidone/amiloride 12.5/2.5 mg/day
Co-intervention: if BP goal was not achieved, the dose of study drugs was doubled then other BP-lowering agents were added in the following steps- (1) amlodipine up to 10 mg/day (2) propranolol up to 80 mg/day
Concomitant non-study RAS blockers: NR
Primary & secondary outcomes: mean BP between the two treatment groups, fatal and nonfatal major CV events
Funding Source: Department of Science and Technology (DECIT), Health Ministry; National Council of Research (CNPq)
and Agency for Funding of Studies and Projects (FINEP), Science and Technology Ministry; National Institute of Health
Technology Assessment (IATS); and Funding of Incentive to Research (FIPE), Hospital de Clinicas de Porto Alegre, all in
Brazil
PRoFESS (2008) (Yusuf et al., 2008a)
Design: Prospective, randomized, double-blind, 2x2 factorial, placebo-controlled trial
Mean duration of follow-up: 2.5 years
Participants (n): 20,332
Clinical setting: recent ischaemic stroke (less than 90 days before randomization) Mean baseline BP: 144.1/83.8 mmHg
Age: 50-older (mean: 66.2 years)
Hypertensive patients (%): 74
Baseline co-morbidities (%): DM (28)
Intervention: Four groups (other arms randomized to aspirin and dipyridamole extended release vs clopidogrel)
ARB: telmisartan 80mg/day vs Placebo
Co-intervention: NR
Concomitant non-study RAS blockers: Intervention: 28% ACEI & 2.3% ARB. Control group: 34% ACEI, 2.5 ARB Note: Addition of ACE inhibitors was permitted but ARBs were not allowed
Primary & secondary outcomes: Recurrent stroke of any type and total vascular events
Funding Source: Boehringer Ingelheim, with additional support from Bayer Schering Pharma and GlaxoSmithKline
PROGRESS (2001) (Chalmers et al., 2001) (Arima and Chalmers, 2011) (Chaturvedi et al., 2003)
Design: Prospective, multicentre, randomized, double-blinded, parallel trial
Mean duration of follow-up: 3.9 years
Participants (n): 20,332
Clinical setting: History of CVA
Clinical setting: History of CVA Mean baseline BP: 146/84 mmHg
Clinical setting: History of CVA Mean baseline BP: 146/84 mmHg Mean age: 64 years
Clinical setting: History of CVA Mean baseline BP: 146/84 mmHg Mean age: 64 years Hypertensive patients (%): 54
Clinical setting: History of CVA Mean baseline BP: 146/84 mmHg Mean age: 64 years Hypertensive patients (%): 54 Baseline co-morbidities (%): None
Clinical setting: History of CVA Mean baseline BP: 146/84 mmHg Mean age: 64 years Hypertensive patients (%): 54
Clinical setting: History of CVA Mean baseline BP: 146/84 mmHg Mean age: 64 years Hypertensive patients (%): 54 Baseline co-morbidities (%): None Intervention: Three groups
Clinical setting: History of CVA Mean baseline BP: 146/84 mmHg Mean age: 64 years Hypertensive patients (%): 54 Baseline co-morbidities (%): None Intervention: Three groups ACEI: Perindopril (4 mg) vs. perindopril plus indapamide (4 mg+ 2.5 mg/day) vs. placebo Co-intervention: NR Concomitant non-study RAS blockers: NR
Clinical setting: History of CVA Mean baseline BP: 146/84 mmHg Mean age: 64 years Hypertensive patients (%): 54 Baseline co-morbidities (%): None Intervention: Three groups ACEI: Perindopril (4 mg) vs. perindopril plus indapamide (4 mg+ 2.5 mg/day) vs. placebo Co-intervention: NR Concomitant non-study RAS blockers: NR Primary outcomes: Total stroke (fatal/nonfatal) either ischaemic or haemorrhagic
Clinical setting: History of CVA Mean baseline BP: 146/84 mmHg Mean age: 64 years Hypertensive patients (%): 54 Baseline co-morbidities (%): None Intervention: Three groups ACEI: Perindopril (4 mg) vs. perindopril plus indapamide (4 mg+ 2.5 mg/day) vs. placebo Co-intervention: NR Concomitant non-study RAS blockers: NR Primary outcomes: Total stroke (fatal/nonfatal) either ischaemic or haemorrhagic Secondary outcomes: Fatal or disabling stroke with disability, composite of non-fatal stroke, non-fatal MI, CV deaths,
Clinical setting: History of CVA Mean baseline BP: 146/84 mmHg Mean age: 64 years Hypertensive patients (%): 54 Baseline co-morbidities (%): None Intervention: Three groups ACEI: Perindopril (4 mg) vs. perindopril plus indapamide (4 mg+ 2.5 mg/day) vs. placebo Co-intervention: NR Concomitant non-study RAS blockers: NR Primary outcomes: Total stroke (fatal/nonfatal) either ischaemic or haemorrhagic Secondary outcomes: Fatal or disabling stroke with disability, composite of non-fatal stroke, non-fatal MI, CV deaths, total death
Clinical setting: History of CVA Mean baseline BP: 146/84 mmHg Mean age: 64 years Hypertensive patients (%): 54 Baseline co-morbidities (%): None Intervention: Three groups ACEI: Perindopril (4 mg) vs. perindopril plus indapamide (4 mg+ 2.5 mg/day) vs. placebo Co-intervention: NR Concomitant non-study RAS blockers: NR Primary outcomes: Total stroke (fatal/nonfatal) either ischaemic or haemorrhagic Secondary outcomes: Fatal or disabling stroke with disability, composite of non-fatal stroke, non-fatal MI, CV deaths, total death Funding Source: Servier, the Health Research Council of New Zealand, and the National Health and Medical Research
Clinical setting: History of CVA Mean baseline BP: 146/84 mmHg Mean age: 64 years Hypertensive patients (%): 54 Baseline co-morbidities (%): None Intervention: Three groups ACEI: Perindopril (4 mg) vs. perindopril plus indapamide (4 mg+ 2.5 mg/day) vs. placebo Co-intervention: NR Concomitant non-study RAS blockers: NR Primary outcomes: Total stroke (fatal/nonfatal) either ischaemic or haemorrhagic Secondary outcomes: Fatal or disabling stroke with disability, composite of non-fatal stroke, non-fatal MI, CV deaths, total death Funding Source: Servier, the Health Research Council of New Zealand, and the National Health and Medical Research Council of Australia
Clinical setting: History of CVA Mean baseline BP: 146/84 mmHg Mean age: 64 years Hypertensive patients (%): 54 Baseline co-morbidities (%): None Intervention: Three groups ACEI: Perindopril (4 mg) vs. perindopril plus indapamide (4 mg+ 2.5 mg/day) vs. placebo Co-intervention: NR Concomitant non-study RAS blockers: NR Primary outcomes: Total stroke (fatal/nonfatal) either ischaemic or haemorrhagic Secondary outcomes: Fatal or disabling stroke with disability, composite of non-fatal stroke, non-fatal MI, CV deaths, total death Funding Source: Servier, the Health Research Council of New Zealand, and the National Health and Medical Research Council of Australia QUIET (2001) (Pitt et al., 2001)
Clinical setting: History of CVA Mean baseline BP: 146/84 mmHg Mean age: 64 years Hypertensive patients (%): 54 Baseline co-morbidities (%): None Intervention: Three groups ACEI: Perindopril (4 mg) vs. perindopril plus indapamide (4 mg+ 2.5 mg/day) vs. placebo Co-intervention: NR Concomitant non-study RAS blockers: NR Primary outcomes: Total stroke (fatal/nonfatal) either ischaemic or haemorrhagic Secondary outcomes: Fatal or disabling stroke with disability, composite of non-fatal stroke, non-fatal MI, CV deaths, total death Funding Source: Servier, the Health Research Council of New Zealand, and the National Health and Medical Research Council of Australia QUIET (2001) (Pitt et al., 2001) Design: Prospective, multicentre, randomized, double-blinded, parallel trial
Clinical setting: History of CVA Mean baseline BP: 146/84 mmHg Mean age: 64 years Hypertensive patients (%): 54 Baseline co-morbidities (%): None Intervention: Three groups ACEI: Perindopril (4 mg) vs. perindopril plus indapamide (4 mg+ 2.5 mg/day) vs. placebo Co-intervention: NR Concomitant non-study RAS blockers: NR Primary outcomes: Total stroke (fatal/nonfatal) either ischaemic or haemorrhagic Secondary outcomes: Fatal or disabling stroke with disability, composite of non-fatal stroke, non-fatal MI, CV deaths, total death Funding Source: Servier, the Health Research Council of New Zealand, and the National Health and Medical Research Council of Australia QUIET (2001) (Pitt et al., 2001) Design: Prospective, multicentre, randomized, double-blinded, parallel trial Mean duration of follow-up: 3 years
Clinical setting: History of CVA Mean baseline BP: 146/84 mmHg Mean age: 64 years Hypertensive patients (%): 54 Baseline co-morbidities (%): None Intervention: Three groups ACEI: Perindopril (4 mg) vs. perindopril plus indapamide (4 mg+ 2.5 mg/day) vs. placebo Co-intervention: NR Concomitant non-study RAS blockers: NR Primary outcomes: Total stroke (fatal/nonfatal) either ischaemic or haemorrhagic Secondary outcomes: Fatal or disabling stroke with disability, composite of non-fatal stroke, non-fatal MI, CV deaths, total death Funding Source: Servier, the Health Research Council of New Zealand, and the National Health and Medical Research Council of Australia QUIET (2001) (Pitt et al., 2001) Design: Prospective, multicentre, randomized, double-blinded, parallel trial
Clinical setting: History of CVA Mean baseline BP: 146/84 mmHg Mean age: 64 years Hypertensive patients (%): 54 Baseline co-morbidities (%): None Intervention: Three groups ACEI: Perindopril (4 mg) vs. perindopril plus indapamide (4 mg+ 2.5 mg/day) vs. placebo Co-intervention: NR Concomitant non-study RAS blockers: NR Primary outcomes: Total stroke (fatal/nonfatal) either ischaemic or haemorrhagic Secondary outcomes: Fatal or disabling stroke with disability, composite of non-fatal stroke, non-fatal MI, CV deaths, total death Funding Source: Servier, the Health Research Council of New Zealand, and the National Health and Medical Research Council of Australia QUIET (2001) (Pitt et al., 2001) Design: Prospective, multicentre, randomized, double-blinded, parallel trial Mean duration of follow-up: 3 years Participants (n): 1750

Mean age: 58 years Hypertensive patients (%): 47
Baseline co-morbidities (%):
Intervention: Two groups ACEI: Quinapril (10-20 mg/day) vs. placebo
Co-intervention: NR
Concomitant non-study RAS blockers: Intervention group: 23% ACEIs. Control group: 24% ACEIs
Primary & secondary outcomes: Cardiac event (cardiac death, nonfatal MI, resuscitated cardiac arrest, resuscitated
cardiac arrest, CABG, Angina requiring hospitalization)
Funding Source: Parke-Davis Pharmaceutical Research
QUO VADIS (2001) (Oosterga et al., 2001)
Design: Prospective, multicentre, randomized, double-blinded, parallel trial
Median duration of follow-up: 1 year
Participants (n): 148
Clinical setting: One year after CABG
Mean baseline BP: 145/83 mmHg
Mean age: 62 years
Hypertensive patients (%): 20
Baseline co-morbidities (%): None
Intervention: Two groups
ACEI: Quinapril (40 mg/day) vs. placebo
Co-intervention: NR
Concomitant non-study RAS blockers: NR
Primary outcomes: Change in total exercise time
Secondary outcomes: Ischemic events
Funding Source: Parke-Davis Pharmaceutical Research, Ann Arbor, Michigan
RASS (2009) (Mauer et al., 2009)
Design: Prospective, multicentre, randomized, double-blinded, parallel trial
Mean duration of follow-up: 5 years
Participants (n): 285
Clinical setting: T1DM, normo-albuminuria & normotensive
Mean baseline BP: 120/70 mmHg
Mean age: 30 years
Hypertensive patients (%): Ex
Baseline co-morbidities (%): None
Intervention: Three arms
Losartan (100 mg daily) vs enalapril (20 mg daily) vs. placebo
Note: In current review, three arms were split & RR were estimated separately (losartan vs. placebo, enalapril vs.
placebo & losartan vs. enalapril).
Co-intervention: NR
Concomitant non-study RAS blockers: NR
Primary outcomes: Change in the fraction of glomerular volume occupied by mesangium
Funding Source: National Institutes of Health (NIH), the National Institute of Diabetes and Digestive and Kidney
Diseases, Merck (in the United States)
RENAAL (2001) (Brenner et al., 2001) (Kowey et al., 2005) (Hung et al., 2002)
Design: Prospective, multicentre, randomized, double-blinded, parallel trial
Mean duration of follow-up: 3.4 years
Participants (n): 1513
Clinical setting: T2DM and nephropathy
Mean baseline BP: 152/82 mmHg
Age: 31-70 (mean: 60 years)
Hypertensive patients (%): 94
Baseline co-morbidities (%): None
Intervention: Two groups
ARB: Losartan 50-100 mg/day vs Placebo
ARB: Losartan 50-100 mg/day vs Placebo Co-intervention: Conventional BP-lowering agents were added to groups when required (Excluded ARB & ACEI)
ARB: Losartan 50-100 mg/day vs Placebo Co-intervention: Conventional BP-lowering agents were added to groups when required (Excluded ARB & ACEI) Concomitant non-study RAS blockers: Intervention: 7% RAS blockers. Control: 9% RAS blockers
ARB: Losartan 50-100 mg/day vs Placebo Co-intervention: Conventional BP-lowering agents were added to groups when required (Excluded ARB & ACEI) Concomitant non-study RAS blockers: Intervention: 7% RAS blockers. Control: 9% RAS blockers Primary & secondary outcomes: Composite of a doubling of the base-line serum creatinine concentration, ESRD, or
ARB: Losartan 50-100 mg/day vs Placebo Co-intervention: Conventional BP-lowering agents were added to groups when required (Excluded ARB & ACEI) Concomitant non-study RAS blockers: Intervention: 7% RAS blockers. Control: 9% RAS blockers Primary & secondary outcomes: Composite of a doubling of the base-line serum creatinine concentration, ESRD, or death and composite of morbidity and mortality from CV causes, proteinuria, and the rate of progression of renal
ARB: Losartan 50-100 mg/day vs Placebo Co-intervention: Conventional BP-lowering agents were added to groups when required (Excluded ARB & ACEI) Concomitant non-study RAS blockers: Intervention: 7% RAS blockers. Control: 9% RAS blockers Primary & secondary outcomes: Composite of a doubling of the base-line serum creatinine concentration, ESRD, or death and composite of morbidity and mortality from CV causes, proteinuria, and the rate of progression of renal disease.
ARB: Losartan 50-100 mg/day vs Placebo Co-intervention: Conventional BP-lowering agents were added to groups when required (Excluded ARB & ACEI) Concomitant non-study RAS blockers: Intervention: 7% RAS blockers. Control: 9% RAS blockers Primary & secondary outcomes: Composite of a doubling of the base-line serum creatinine concentration, ESRD, or death and composite of morbidity and mortality from CV causes, proteinuria, and the rate of progression of renal disease. Funding Source: Merck and Company
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Funding Source: National Nature and Sciences Grant for Major Projects
ROADMAP (2011) (Haller et al., 2011b, Haller et al., 2011a) (Haller et al., 2010)
Design: Prospective, multicentre, randomized, double-blinded, parallel trial
Median duration of follow-up: 3.2 years
Participants (n): 4447
Clinical setting: T2DM, normo-albuminuria & at least one CV risk factors Mean baseline BP: 137/81 mmHg
Mean age: 57.7 years
Hypertensive patients (%): NR
Baseline co-morbidities (%): CAD (25),
Intervention: Two groups
ARB: Olmesartan (40m/day) vs. placebo
Co-intervention: Other antihypertensive agents were allowed to reach & maintain the target BP level (except non-
study ACEI & ARB) Concomitant non-study RAS blockers: None
Primary outcomes: Time of first onset of microalbuminuria
Secondary outcomes: CV outcomes: CV death (sudden death, fatal MI, fatal stroke), CV morbidity (silent MI, nonfatal
MI, coronary revascularization) & occurrence and progression of retinopathy
Funding Source: Daiichi Sankyo
SCAT (2000) (Teo et al., 2000)
Design: Prospective, randomized, double-blind, 2x2 factorial, placebo-controlled trial
Mean duration of follow-up: 4 years
Participants (n): 460 Clinical setting: CAD and normal or mildly elevated cholesterol.
Mean baseline BP: 130/77 mmHg
Age: 21-older (mean: 61 years)
Hypertensive patients (%): 36
Baseline co-morbidities (%):
Intervention: Two groups (other randomized drugs included simvastatin vs placebo)
ACEI: Enalapril 2.5 -10 mg/ BID vs Placebo
Co-intervention: No antihypertension agents were added Concomitant non-study RAS blockers: NR
Primary & secondary outcomes: Quantitative coronary angiography (QCA) measures and clinical events (death, MI,
stroke, hospitalization for angina, revascularization, and cancer).
Funding Source: Merck Frost Canada and Company
SCOPE (2003) (Lithell et al., 2003)
Design: Prospective, multicentre, randomized, double-blinded, parallel trial
Mean duration of follow-up: 3.5 years
Participants (n): 4964 Clinical setting: elderly patients with hypertension and a Mini Mental State Examination (MMSE) test score >=24
Mean baseline BP: 166/90.4 mmHg
Age: 70-89 (mean: 76.4 years)
Hypertensive patients (%): 100
Baseline co-morbidities (%): None
Intervention: Two groups
ARB: Candesartan 8 - 16 mg/day vs Placebo
Co-intervention: BP-lowering agents were allowed except RAS blockers Concomitant non-study RAS blockers: Intervention: 8% ACEI & 3% ARB. Control:11% ACEI & 4% ARB
Primary & secondary outcomes: Major CV events, CV death, non-fatal stroke, non-fatal MI, cognitive function
measured by the MMSE and dementia.
Funding Source: AstraZeneca
SUPPORT (2015) (Sakata et al., 2015)
Design: Prospective, randomized, single-centre, open-label, blinded-endpoint trial (PROBE)
Mean duration of follow-up: 4.4 years
Participants (n): 1146
Clinical setting: HTN with Symptomatic CHF (NYHA class II-IV) Mean baseline BP: 128/74 mmHg
Mean age: 65.5 years
Hypertensive patients (%): 100
Baseline co-morbidities (%): IHD (49), DM (51)
Intervention: Two groups
ARB: Olmesartan (10-40 mg/day) vs. placebo
Co-intervention: NR Concomitant non-study RAS blockers: NR
Primary & secondary outcomes: Composite & individual of all cause death, nonfatal MI, nonfatal stroke,
hospitalization due to worsening HF.
Funding Source: Ministry of Health, labour & Welfare
TRANSCEND (2008) (Yusuf et al., 2008c)
Design: Prospective, multicentre, randomized, double-blinded, parallel trial
Mean duration of follow-up: 4.7 years
Participants (n): 5926
Clinical setting: History of CVD or T2DM with end-organ damage intolerant to ACE inhibitors
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Intervention: Two groups
ARB: Telmisartan 80 mg/day vs Placebo
Co-intervention: NR
Concomitant non-study RAS blockers: Intervention: 5.8% ARB. Control: 7.6% ARB.
Primary & secondary outcomes: CV death, MI, stroke, hospitalization for HF, new HF, development of T2DM, AF,
cognitive decline or dementia, nephropathy, and revascularization
Funding Source: Boehringer Ingelheim
Val-HeFT (2001) (Cohan et al., 2001) (Novartis Advisory Committee, 2002)
Design: Prospective, multicentre, randomized, double-blinded, parallel trial
Mean duration of follow-up: 1.9 years
Participants (n): 5010
Clinical setting: HF
Mean baseline BP: 123/76 mmHg
Age: 18-older (mean: 62.7 years)
Hypertensive patients (%): 6.7
Baseline co-morbidities (%): DM (25.9)
Intervention: Two groups
ARB: Valsartan 80-320 mg/day vs Placebo
Co-intervention: No additional drugs was added
Concomitant non-study RAS blockers: NR
Primary & secondary outcomes: all morbidity, CV outcomes, NYHA functional class, quality-of-life scores, and signs
and symptoms of HF.
Funding Source: Novartis Pharmaceuticals
VALIANT (2003) (Pfeffer et al., 2003a) (McMurray et al., 2006) (Targum et al., 2004)
Design: Prospective, multicentre, randomized, double-blinded, parallel trial
Mean duration of follow-up: 2.1 years
Participants (n): 14,703
Clinical setting: HF and/or left ventricular systolic dysfunction (LVSD) after MI
Mean baseline BP: 122.7/72.3 mmHg
Age: 18 or older (mean: 64.8 years)
Hypertensive patients (%): 55
Baseline co-morbidities (%): DM (23)
Intervention: Three groups
ACEI: captopril 150 mg/day vs ARB: valsartan 320 mg/day vs ACEI+ARB: 150/320 mg/day
Note: ACEI group vs. ARB only was included in this review
Co-intervention: no additional BP-lowering agents
Concomitant non-study RAS blockers: Intervention: 7.7% ACEI & 2.9% ARB. Control: 7% ACEI & 1.5% ARB
Primary & secondary outcomes: all-cause mortality, CV death, acute coronary syndromes (fatal and nonfatal), CV
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Appendix C: Methodological quality of included studies (ordered by study ID)

For acronyms (see 'list of definitions/abbreviations)

4 C		
Bias	Authors' judgement	Support for judgement
Random sequence generation	Low risk	Randomization into 2 groups in 1:1 ratio using CTSS through the internet by simple randomization
Allocation concealment	Unclear risk	The method was not described
Blinding of participants and personnel (All outcomes)	High risk	Open-label design
Blinding of outcome assessment		
All-cause mortality	Low risk Low risk	Outcome is unlikely influenced by blinding Blinding of outcome assessment
Other outcomes Incomplete outcome data (attrition bias)	Low risk	Dropped-out rate in both groups was not reported.
All outcomes	LOW HISK	However, the analysis of all outcomes was performed based on ITT approach
Selective reporting	Low risk	Outcomes listed in the methods were all reported
Other bias	Low risk	The trial was supported from research institution
AARDVARK (2016)		
Bias	Authors' judgement	Support for judgement
Random sequence generation	Low risk	Computer- generated randomization code by using SAS computer software (using a 1:1:1 ratio stratified by centre and by baseline size of aneurysm)
Allocation concealment	Low risk	Adequate. The randomization code was generated by an independent statistician
Blinding of participants and personnel (All outcomes)	High risk	Open-label design
Blinding of outcome assessment All-cause mortality 	Low risk	Outcome measurement is not likely to be influenced by lack of blinding.
Other outcomes	None	Other outcomes were not reported
Incomplete outcome data All outcomes	Low risk	Missing data unlikely to affect the outcome results
Selective reporting	Low risk	Reported all outcomes specified in the methods
Other bias	Low risk	
AASK (2002)	T	
Bias	Authors' judgement	Support for judgement
Random sequence generation	Low risk	The randomization was stratified by city using randomly permuted blocks.
Allocation concealment	Low risk	The Data Coordinating Center (DCC) performed randomization centrally.
Blinding of participants and personnel (All outcomes)	Low risk	Participants and personal were blinded.
Blinding of outcome assessment		Outcome is unlikely influenced by blinding
 All-cause mortality Other outcomes 	Low risk Low risk	Outcome is unlikely influenced by blinding Blinding of outcome assessment
Incomplete outcome data	Low risk	Missing data unlikely to affect the outcome results (ITT
All outcomes		analysis were performed)
Selective reporting	Low risk	Reported all outcomes specified in the methods
Other bias	Unclear risk	Authors received grants from pharmaceutical company, and they had a full access to study data. So, the actual role of sponsor was not described
ABCD, normotensive (2002)		
Bias	Authors' judgement	Support for judgement
Random sequence generation	Unclear risk	By using permuted block randomization. However, the method was not specified
Allocation concealment	Low risk	Adequate. Assignment by telephone coordinated by centres

Blinding of participants and personnel (All	Low risk	Participants and personnel were blinded. Study nurses
outcomes)		were blinded to the use of enalapril versus nisoldipine
 Blinding of outcome assessment All-cause mortality 	Low risk	Outcome is unlikely influenced by blinding
Other outcomes	Low risk	Blinding of outcome assessment.
		An Endpoint Committee blinded to randomization
Incomplete euteeme data	Uncloar	assignment
Incomplete outcome data All outcomes	Unclear	The loss of follow-up rate was not reported
Selective reporting	Low	Reported all outcomes specified in the
Other bias	Unclear	methods The sponsor role not reported
	oncical	
ACTIVE-I (2011) Bias	Authors'	Support for judgement
	judgement	support for judgement
Random sequence generation	Low risk	Central randomization service using a block randomization scheme.
Allocation concealment	Low risk	Automated voice response system (AreS)
	1	De division de construction blinded
Blinding of participants and personnel (All outcomes)	Low risk	Participants and personnel were blinded
Blinding of outcome assessment		
All-cause mortality	Low risk	Outcome are unlikely influenced by blinding
Other outcomes	Low risk	Blinded outcome assessment
Incomplete outcome data All outcomes	Low risk	Missing data were unlikely to have an impact on the results of the trial. Used ITT analysis
Selective reporting	Low risk	Outcomes listed in the methods were all reported
Other bias	Low risk	The sponsor was not involved in handling, interpterion
		and analysis data
ADVANCE (2007)	A., 46 a.m. 1	Current for judger at
Bias	Authors' judgement	Support for judgement
Random sequence generation	Low risk	Centre randomization stratified by study centre, history
		of macrovascular disease, history of microvascular
Allo antion ann an Inn ant	L avv. stale	disease, and background use of perindopril at baseline.
Allocation concealment	Low risk	Allocated using a central, computer-based, randomization service accessible by internet, telephone, and facsimile
Blinding of participants and personnel (All outcomes)	Low risk	participants and personnel were blinded
Blinding of outcome assessment	1	
 All-cause Mortality Other outcomes 	Low risk Low risk	Outcome is unlikely influenced by blinding Blinding of outcome assessment.
Incomplete outcome data	Low risk	Only 15 patients (0.2%) were lost follow-up,
All outcomes		4 in the intervention group and 11 in
		the placebo group (All analyses would also be by ITT
Selective reporting	Low risk	principle) Reported all the outcomes described in the
Selective reporting	LOW LISK	protocol
Other bias	Low risk	The sponsor of the study had no role in study
		design, data collection, data analysis, data
		interpretation, or writing of the report.
ALLHAT (2002) Bias	Authors'	Support for judgement
	judgement	
Random sequence generation	Low risk	Computer generated sequence. Stratified block randomization (block sizes of 5 or 9)
Allocation concealment	Low risk	The concealed randomization scheme was generated by
		computer implanted at clinical trial centre (computer- generated).
Blinding of participants and personnel (All	Low risk	Participants and personnel were blinded
outcomes) Blinding of outcome assessment		
All-cause mortality	Low risk	Outcome measurement is not likely to be influenced by
,	المعاممة عام	lack of blinding
Other outcomes	Unclear risk	Blinding of outcome assessment was not described.
Incomplete outcome data	Low risk	Two centres initially reported were excluded, due poor
All outcomes		documentation of informed consent. ITT analysis was performed
Selective reporting	Low risk	All the pre-specified outcomes in the methods
· · · · · · · · · · · · · · · · · · ·	1	were reported

Other bias	Low risk	Industry has not involved in data handling, analysis or interpretation of study data
ALPINE (2003)	•	·
Bias	Authors' judgement	Support for judgement
Random sequence generation	Unclear risk	Generation of random sequence was not reported
Allocation concealment	Unclear Risk	The concealment method was not reported
Blinding of participants and personnel (All outcomes)	Low risk	participants and personnel were blinded
Blinding of outcome assessment All-cause mortality Other outcomes 	None Unclear risk	Outcome was not reported Blinding of outcome assessment was not reported
Incomplete outcome data All outcomes	Low risk	No patient was lost to follow-up.
Selective reporting Other bias	Low Unclear risk	Outcomes listed in the methods were all reported
	Unclear risk	The role of sponsor was not reported
ANBP2 (2003)	A uth a wa?	Current for independent
Bias	Authors' judgement	Support for judgement
Random sequence generation	Unclear risk	The method of random sequence generation was not reported
Allocation concealment	Low risk	Adequate. Central allocation by telephone
Blinding of participants and personnel (All outcomes)	High risk	Open-label design
Blinding of outcome assessment		
 All-cause mortality 	Low risk	Outcome is unlikely influenced by blinding
Other outcomes	Low risk	Blinding of outcome assessment
Incomplete outcome data All outcomes	Low risk	Missing data were unlikely to have an impact on the results of the trial
Selective reporting	Low risk	Outcomes listed in the methods were all reported
Other bias	Low risk	The sponsor has no role
ANTIPAF (2012)		
Bias	Authors'	Support for judgement
	judgement	
Random sequence generation	Low risk	Used internet-based e-Trial Management Service (XTrial [™]). Random lists will be generated by the biometrical advisor for the network and subsequently imported into the XTrial [™] system
Allocation concealment	Low risk	Adequate. Used internet-based e-Trial Management System (XTrial™).
Blinding of participants and personnel (All outcomes)	Low risk	Participants and personnel were blinded
Blinding of outcome assessment All-cause mortality Other outcomes 	Low risk Low risk	Outcome is unlikely influenced by blinding Blinding of outcome assessment
Incomplete outcome data All outcomes	Low risk	The loss of follow-up was not reported. However, ITT was
Selective reporting	Low risk	used Outcomes listed in the methods were all reported
Other bias	Unclear risk	The role of sponsor was not described
APRES (2000)		
Bias	Authors' judgement	Support for judgement
Random sequence generation	Low risk	Computer-generated assignment scheme in blocks of four (two ramipril, two placebo), and with stratification according to type of invasive revascularization (CABG or PTCA).
Allocation concealment	Low risk	Adequate. Central allocation
Blinding of participants and personnel All outcomes	Low risk	Participants and personnel were blinded
Blinding of outcome assessment		
All-cause Mortality	Low risk	Outcome is unlikely influenced by blinding
Other outcomes	Low risk	Blinding of outcome assessment
Incomplete outcome data All outcomes	Low risk	Missing data were unlikely to have an impact on the results of the trial
Selective reporting	Low risk	Outcomes listed in the methods were all reported
Other bias	Unclear risk	The role of sponsor was not reported

ATLANTIS (2000)		
Bias	Authors' judgement	Support for judgement
Random sequence generation	Low risk	A sequence of subject numbers was assigned to each study centre, and the study medication was randomly assigned to the participant numbers on 1:1:1 basis
Allocation concealment	Low risk	The randomization schedule was stored in a set of sealed envelopes.
Blinding of participants and personnel (All outcomes)	Low risk	Participants and personnel
Blinding of outcome assessment		
All-cause mortality	Low risk	Outcome is unlikely influenced by blinding
Other outcomes Incomplete outcome data	Low risk Low risk	Blinding of outcome assessment Missing data were unlikely to have an impact on the
All outcomes	LOW LISK	results of the trial
Selective reporting	Low risk	Outcomes listed in the methods were all reported
Other bias	Unclear risk	The role of sponsor is not described
ATTEMPT-CVD (2015)		
Bias	Authors' judgement	Support for judgement
Random sequence generation	Low risk	Computer-generated stratified randomization sequence in which patients were assigned in a 1:1 ratio
Allocation concealment	Low risk	The independent central allocation by faxes
Blinding of participants and personnel (All outcomes)	High risk	Open-label design
Blinding of outcome assessment		
All-cause mortality	None	Outcome was not reported
Other outcomes	Low risk	Blinding of outcome assessment
Incomplete outcome data	Unclear risk	The discontinuation rate was not reported & the analysis
All outcomes Selective reporting	Low risk	was performed by per-protocol principles Outcomes listed in the methods were all reported
Other bias	Low risk	The funders were not involved in the design and execution of the study, data collection, management, analysis or interpretation or manuscript presentation, review or approval.
BENEDICT (2004)		L
Pipe		
Bias	Authors'	Support for judgement
	judgement	
Random sequence generation	judgement Unclear risk	The method of generate random sequence was reported
Random sequence generation Allocation concealment	judgement	
Random sequence generation Allocation concealment Blinding of participants and personnel (All	judgement Unclear risk Unclear risk	The method of generate random sequence was reported The method of was not reported
Random sequence generation Allocation concealment	judgement Unclear risk	The method of generate random sequence was reported
Random sequence generation Allocation concealment Blinding of participants and personnel (All outcomes) Blinding of outcome assessment	judgement Unclear risk Unclear risk Low risk	The method of generate random sequence was reported The method of was not reported Participants and personnel were blinded
Random sequence generation Allocation concealment Blinding of participants and personnel (All outcomes) Blinding of outcome assessment • All-cause mortality	judgement Unclear risk Unclear risk Low risk	The method of generate random sequence was reported The method of was not reported Participants and personnel were blinded Outcome is unlikely influenced by blinding
Random sequence generation Allocation concealment Blinding of participants and personnel (All outcomes) Blinding of outcome assessment • All-cause mortality • Other outcomes Incomplete outcome data	judgement Unclear risk Unclear risk Low risk	The method of generate random sequence was reported The method of was not reported Participants and personnel were blinded Outcome is unlikely influenced by blinding Blinding outcome assessment. Missing data unlikely to affect the outcome results. 16
Random sequence generation Allocation concealment Blinding of participants and personnel (All outcomes) Blinding of outcome assessment • All-cause mortality • Other outcomes	judgement Unclear risk Unclear risk Low risk Low risk Low risk	The method of generate random sequence was reported The method of was not reported Participants and personnel were blinded Outcome is unlikely influenced by blinding Blinding outcome assessment.
Random sequence generation Allocation concealment Blinding of participants and personnel (All outcomes) Blinding of outcome assessment • All-cause mortality • Other outcomes Incomplete outcome data All outcomes Selective reporting	judgement Unclear risk Unclear risk Low risk Low risk Low risk Low risk Low risk	The method of generate random sequence was reported The method of was not reported Participants and personnel were blinded Outcome is unlikely influenced by blinding Blinding outcome assessment. Missing data unlikely to affect the outcome results. 16 (1.3%) out of 1204 were lost to follow-up Reported all outcomes specified in the methods
Random sequence generation Allocation concealment Blinding of participants and personnel (All outcomes) Blinding of outcome assessment • All-cause mortality • Other outcomes Incomplete outcome data All outcomes Selective reporting	judgement Unclear risk Unclear risk Low risk Low risk Low risk Low risk	The method of generate random sequence was reported The method of was not reported Participants and personnel were blinded Outcome is unlikely influenced by blinding Blinding outcome assessment. Missing data unlikely to affect the outcome results. 16 (1.3%) out of 1204 were lost to follow-up Reported all outcomes specified in the
Random sequence generation Allocation concealment Blinding of participants and personnel (All outcomes) Blinding of outcome assessment • All-cause mortality • Other outcomes Incomplete outcome data All outcomes Selective reporting Other bias Cai et al. (2001)	judgement Unclear risk Low risk Low risk Low risk Low risk Low risk Low risk Low risk	The method of generate random sequence was reported The method of was not reported Participants and personnel were blinded Outcome is unlikely influenced by blinding Blinding outcome assessment. Missing data unlikely to affect the outcome results. 16 (1.3%) out of 1204 were lost to follow-up Reported all outcomes specified in the methods Supported in part by pharmaceutical company
Random sequence generation Allocation concealment Blinding of participants and personnel (All outcomes) Blinding of outcome assessment • All-cause mortality • Other outcomes Incomplete outcome data All outcomes Selective reporting	judgement Unclear risk Low risk Low risk Low risk Low risk Low risk Low risk Low risk Low risk	The method of generate random sequence was reported The method of was not reported Participants and personnel were blinded Outcome is unlikely influenced by blinding Blinding outcome assessment. Missing data unlikely to affect the outcome results. 16 (1.3%) out of 1204 were lost to follow-up Reported all outcomes specified in the methods
Random sequence generation Allocation concealment Blinding of participants and personnel (All outcomes) Blinding of outcome assessment • All-cause mortality • Other outcomes Incomplete outcome data All outcomes Selective reporting Other bias Cai et al. (2001)	judgement Unclear risk Low risk Low risk Low risk Low risk Low risk Low risk Low risk	The method of generate random sequence was reported The method of was not reported Participants and personnel were blinded Outcome is unlikely influenced by blinding Blinding outcome assessment. Missing data unlikely to affect the outcome results. 16 (1.3%) out of 1204 were lost to follow-up Reported all outcomes specified in the methods Supported in part by pharmaceutical company
Random sequence generation Allocation concealment Blinding of participants and personnel (All outcomes) Blinding of outcome assessment • All-cause mortality • Other outcomes Incomplete outcome data All outcomes Selective reporting Other bias Cai et al. (2001) Bias	judgement Unclear risk Unclear risk Low risk Low risk Low risk Low risk Low risk Low risk Low risk	The method of generate random sequence was reported The method of was not reported Participants and personnel were blinded Outcome is unlikely influenced by blinding Blinding outcome assessment. Missing data unlikely to affect the outcome results. 16 (1.3%) out of 1204 were lost to follow-up Reported all outcomes specified in the methods Supported in part by pharmaceutical company Support for judgement
Random sequence generation Allocation concealment Blinding of participants and personnel (All outcomes) Blinding of outcome assessment • All-cause mortality • Other outcomes Incomplete outcome data All outcomes Selective reporting Other bias Cai et al. (2001) Bias Random sequence generation	judgement Unclear risk Unclear risk Low risk Low risk Low risk Low risk Low risk Low risk Low risk Low risk Unclear risk	The method of generate random sequence was reported The method of was not reported Participants and personnel were blinded Outcome is unlikely influenced by blinding Blinding outcome assessment. Missing data unlikely to affect the outcome results. 16 (1.3%) out of 1204 were lost to follow-up Reported all outcomes specified in the methods Supported in part by pharmaceutical company Support for judgement The method of random sequence generation was reported
Random sequence generation Allocation concealment Blinding of participants and personnel (All outcomes) Blinding of outcome assessment • All-cause mortality • Other outcomes Incomplete outcome data All outcomes Selective reporting Other bias Cai et al. (2001) Bias Random sequence generation Allocation concealment Blinding of participants and personnel (All	judgement Unclear risk Unclear risk Low risk Low risk Low risk Low risk Low risk Low risk Low risk Unclear risk Unclear risk	The method of generate random sequence was reported The method of was not reported Participants and personnel were blinded Outcome is unlikely influenced by blinding Blinding outcome assessment. Missing data unlikely to affect the outcome results. 16 (1.3%) out of 1204 were lost to follow-up Reported all outcomes specified in the methods Supported in part by pharmaceutical company Support for judgement The method of random sequence generation was reported The method of allocation concealment was reported
Random sequence generation Allocation concealment Blinding of participants and personnel (All outcomes) Blinding of outcome assessment • All-cause mortality • Other outcomes Incomplete outcome data All outcomes Selective reporting Other bias Cai et al. (2001) Bias Random sequence generation Allocation concealment Blinding of participants and personnel (All outcomes)	judgement Unclear risk Low risk Low risk Low risk Low risk Low risk Low risk Low risk Unclear risk Unclear risk Unclear risk Unclear risk	The method of generate random sequence was reported The method of was not reported Participants and personnel were blinded Outcome is unlikely influenced by blinding Blinding outcome assessment. Missing data unlikely to affect the outcome results. 16 (1.3%) out of 1204 were lost to follow-up Reported all outcomes specified in the methods Supported in part by pharmaceutical company Support for judgement The method of random sequence generation was reported The method of allocation concealment was reported Blinding of participants and personnel were not reported Outcome measurement is not likely to be influenced by lack of blinding.
Random sequence generation Allocation concealment Blinding of participants and personnel (All outcomes) Blinding of outcome assessment • All-cause mortality • Other outcomes Incomplete outcome data All outcomes Selective reporting Other bias Cai et al. (2001) Bias Random sequence generation Allocation concealment Blinding of outcome assessment • All-cause mortality	judgement Unclear risk Low risk Low risk Low risk Low risk Low risk Low risk Low risk Unclear risk Unclear risk Unclear risk Unclear risk	The method of generate random sequence was reported The method of was not reported Participants and personnel were blinded Outcome is unlikely influenced by blinding Blinding outcome assessment. Missing data unlikely to affect the outcome results. 16 (1.3%) out of 1204 were lost to follow-up Reported all outcomes specified in the methods Support for judgement The method of random sequence generation was reported The method of allocation concealment was reported Blinding of participants and personnel were not reported Outcome measurement is not likely to be influenced by lack of blinding. Blinding of outcome assessment was not reported
Random sequence generation Allocation concealment Blinding of participants and personnel (All outcomes) Blinding of outcome assessment • All-cause mortality • Other outcomes Incomplete outcome data All outcomes Selective reporting Other bias Cai et al. (2001) Bias Random sequence generation Allocation concealment Blinding of outcome assessment • All-cause mortality	judgement Unclear risk Low risk Low risk Low risk Low risk Low risk Low risk Low risk Unclear risk Unclear risk Unclear risk Unclear risk	The method of generate random sequence was reported The method of was not reported Participants and personnel were blinded Outcome is unlikely influenced by blinding Blinding outcome assessment. Missing data unlikely to affect the outcome results. 16 (1.3%) out of 1204 were lost to follow-up Reported all outcomes specified in the methods Supported in part by pharmaceutical company Support for judgement The method of random sequence generation was reported The method of allocation concealment was reported Blinding of participants and personnel were not reported Outcome measurement is not likely to be influenced by lack of blinding.
Random sequence generation Allocation concealment Blinding of participants and personnel (All outcomes) Blinding of outcome assessment • All-cause mortality • Other outcomes Incomplete outcome data All outcomes Selective reporting Other bias Cai et al. (2001) Bias Random sequence generation Allocation concealment Blinding of participants and personnel (All outcomes) Blinding of outcome assessment • All-cause mortality • Other outcomes Incomplete outcome data	judgement Unclear risk Low risk Low risk Low risk Low risk Low risk Low risk Low risk Unclear risk Unclear risk Unclear risk Unclear risk	The method of generate random sequence was reported The method of was not reported Participants and personnel were blinded Outcome is unlikely influenced by blinding Blinding outcome assessment. Missing data unlikely to affect the outcome results. 16 (1.3%) out of 1204 were lost to follow-up Reported all outcomes specified in the methods Support for judgement The method of random sequence generation was reported The method of allocation concealment was reported Blinding of participants and personnel were not reported Outcome measurement is not likely to be influenced by lack of blinding. Blinding of outcome assessment was not reported High dropped-out rate (19.8%) in captopril group as compared with control group (17.4%). The ITT analysis
Random sequence generation Allocation concealment Blinding of participants and personnel (All outcomes) Blinding of outcome assessment • All-cause mortality • Other outcomes Incomplete outcome data All outcomes Selective reporting Other bias Cai et al. (2001) Bias Random sequence generation Allocation concealment Blinding of participants and personnel (All outcomes) Blinding of outcome assessment • All-cause mortality • Other outcomes Incomplete outcome data Adl outcomes	judgement Unclear risk Low risk Low risk Low risk Low risk Low risk Low risk Low risk Low risk Unclear risk Unclear risk Unclear risk Unclear risk Unclear risk High risk	The method of generate random sequence was reported The method of was not reported Participants and personnel were blinded Outcome is unlikely influenced by blinding Blinding outcome assessment. Missing data unlikely to affect the outcome results. 16 (1.3%) out of 1204 were lost to follow-up Reported all outcomes specified in the methods Supported in part by pharmaceutical company Support for judgement The method of random sequence generation was reported The method of allocation concealment was reported Blinding of participants and personnel were not reported Outcome measurement is not likely to be influenced by lack of blinding. Blinding of outcome assessment was not reported High dropped-out rate (19.8%) in captopril group as compared with control group (17.4%). The ITT analysis was not used.

Bias	Authors' judgement	Support for judgement
Random sequence generation	Low risk	The randomization code was generated using a block size of 6
Allocation concealment	Unclear risk	Allocation concealment method was not described
Blinding of participants and personnel (All outcomes)	Low risk	Participants and personnel were blinded
Blinding of outcome assessment	Low rick	Outcome is unlikely influenced by blinding
All-Cause MortalityOther outcomes	Low risk Low risk	Outcome is unlikely influenced by blinding Blind outcome assessment
Incomplete outcome data	Low risk	Missing data were unlikely to have an impact on the
All outcomes Selective reporting	Low risk	results of the trial Outcomes listed in the methods were all reported
Other bias	Unclear risk	Primary statistical analysis was performed by Pfizer.
	oneccui risk	(Industrial sponsor). however, their role was not reported
CARMEN (2004)		
Bias	Authors' judgement	Support for judgement
Random sequence generation	Unclear risk	The method was not described
Allocation concealment	Low risk	Adequate. Central telephone randomization (ClinPhone) matched for age (≥70 years and ≤70 years), for ACE inhibitor treatment and β-blockade
Blinding of participants and personnel (All outcomes)	Low risk	Participants and personnel were blinded
Blinding of outcome assessment All-cause mortality 		
Other outcomes	Low risk	Outcome is unlikely influenced by blinding
Incomplete outcome data	Low risk	Blinding of outcome assessment Missing data were unlikely to have an impact on the
Incomplete outcome data All outcomes	Low risk	results of the trial
Selective reporting	Low risk	Outcomes listed in the methods were all reported
Other bias	Low risk	Sponsor representatives participated in steering committee meetings as non-voting members.
CARP (2011)		
Bias	Authors'	Support for judgement
Deadar	judgement Unclear risk	La deserte. Des des l'estites une estate la section
Random sequence generation	Unclear risk	Inadequate. Randomization was undertaken using minimization method. But, the method of sequence generation was not described
Allocation concealment	Unclear risk	The method was not reported
Blinding of participants and personnel (All outcomes)	High risk	Open-label
Blinding of outcome assessment	1	
All-cause mortality	Low risk	Outcome measurement is not likely to be influenced by lack of blinding.
Other outcomes	Unclear risk	The blinding method was not reported
Incomplete outcome data All outcomes	High risk	The discontinuation was reported only for valsartan group, as 14% of patients discontinued valsartan for reported reasons, whereas discontinuation rate was not reported in control group. The trial estimated 210 patients (120 in each group) to validate the hypothesis under the assumption that the valsartan add-on group achieves a 40%r risk reduction compared with control group and gives 80% statistical power for detecting a clinical significance. However, only 191 patients in total were enrolled without reported the reasons.
Selective reporting	Low risk	Outcomes listed in the methods were all reported
Other bias	Low risk	The sponsor not involved in study design, collection, analysis, interpterion data
CASE-J (2008)		
Bias	Authors' judgement	Support for judgement
Random sequence generation	Low risk	computer-generated lists of permutation blocks stratified by 9 regional blocks and complication of type 2 diabetes mellitus.
Allocation concealment	Low risk	Central allocation through the Internet and/or facsimile
Blinding of participants and personnel (All outcomes)	High risk	Study drugs were administered open-label
Blinding of outcome assessment All-cause mortality Other outcomes 	Low risk Low risk	Outcome is unlikely influenced by blinding Blinded-end point assessments

Incomplete outcome data	Low risk	Missing data were unlikely to have an impact on the
Incomplete outcome data All outcomes	LUWTISK	results of the trial. ITT was used
Selective reporting	Low risk	Outcomes listed in the methods were all reported
Other bias	Unclear risk	The role of sponsor was not described
CCS-I (2001)		
Bias	Authors' judgement	Support for judgement
Random sequence generation	Low risk	Computer-generated randomization
Allocation concealment	Low risk	Adequate. By using Sealed envelope system, each coordinating hospital received continuous ordinal number of drug supplies from coordinating office
Blinding of participants and personnel (All outcomes)	Low risk	Participants and personnel were blinded
Blinding of outcome assessment All-cause Mortality 	Low risk	Outcome measurement is not likely to be influenced by lack of blinding.
Other outcomes	Unclear risk	The outcome of assessment blinding was not described.
Incomplete outcome data	Unclear risk	The missing data was not reported. No information
All outcomes Selective reporting	Low risk	available for judgement Outcomes listed in the methods were all reported
Other bias	Low risk	The sponsor was academic research centre
Chan et al. (2000)	1	l
Bias	Authors' judgement	Support for judgement
Random sequence generation	Unclear risk	The method of random sequence generation was not reported
Allocation concealment	Unclear risk	The method of allocation concealment was not reported
Blinding of participants and personnel (All outcomes)	Low risk	Participants and personnel were not reported
Blinding of outcome assessment		
All-cause mortality	None	Outcome was not reported
Other outcomes	Low risk	Blinding of outcome assessment
Incomplete outcome data All outcomes	Unclear risk	The dropped-out rate & type of analysis of missing data were not reported
Selective reporting	Low risk	Outcomes listed in the methods were all reported
Other bias	Unclear risk	The role of sponsor was not reported
CHARM-Overall		
Bias	Authors' judgement	Support for judgement
Random sequence generation	Low risk	Computer-generated random sequence stratified by site and component trial
Allocation concealment	Low risk	Central randomization through a coordinating telephone centre. The assignment code was held at an independent centre and by the data safety monitoring board
Blinding of participants and personnel (All outcomes)	Low risk	Participants and personnel were blinded
Blinding of outcome assessment		Outcome is unlikely influenced by blinding
All-cause mortality Other outcomes	Low risk Low risk	Outcome is unlikely influenced by blinding Blinding of outcome assessment.
Incomplete outcome data All outcomes	Low risk	Missing data were unlikely to have an impact on the results of the trial
Selective reporting (reporting bias)	Low risk	Outcomes listed in the methods were all reported
Other bias	Unclear risk	The pharmaceutical sponsor of the study managed the data, and its representatives were involved in the data analysis and data interpretation.
CHIEF (2018)		
Bias	Authors' judgement	Support for judgement
Random sequence generation	Low risk	Computer-based randomization
Allocation concealment Blinding of participants and personnel (All outcomes)	Low risk High risk	Central allocation Open-label design
Blinding of participants and personnel (All outcomes) Blinding of outcome assessment • All-cause mortality	High risk Low risk	Open-label design Outcome is unlikely influenced by blinding
Blinding of participants and personnel (All outcomes) Blinding of outcome assessment	High risk Low risk Low risk	Open-label design Outcome is unlikely influenced by blinding Blinding of outcome assessment
Blinding of participants and personnel (All outcomes) Blinding of outcome assessment	High risk Low risk	Open-label design Outcome is unlikely influenced by blinding Blinding of outcome assessment The missing data was not reported. However, ITT was
Blinding of participants and personnel (All outcomes) Blinding of outcome assessment	High risk Low risk Low risk	Open-label design Outcome is unlikely influenced by blinding Blinding of outcome assessment

COPE (2011)		
Bias	Authors' judgement	Support for judgement
Random sequence generation	Low risk	Computer-generated (dynamic allocation)
Allocation concealment	Low risk	Adequate. Quote "Allocation was concealed to the investigators until they contacted the Data Center"
Blinding of participants and personnel (All outcomes)	High risk	Open-label design
Blinding of outcome assessment		
All-cause mortality	Low risk Low risk	Outcome is unlikely influenced by blinding Blinding of outcome assessment
Other outcomes Incomplete outcome data	Low risk	The missing data seems not affected the results
All outcomes	LOW TISK	The missing data seems not affected the results
Selective reporting	Low risk	Outcomes listed in the methods were all reported
Other bias	Low risk	The sponsor had no role in data collection and data analysis.
CORD 1 B (2009)		
Bias	Authors' judgement	Support for judgement
Random sequence generation	High risk	Inadequate. Patients were randomized according to their day of birth either to losartan or Ramipril
Allocation concealment	Unclear risk	The method of concealment was not reported
Blinding of participants and personnel (All outcomes)	High risk	Open-label design
Blinding of outcome assessment		
All-cause mortality	Low risk	Outcome is unlikely influenced by blinding
Other outcomes	Low risk	Blinding of outcome assessment
Incomplete outcome data	Unclear risk	The loss of follow-up was not reported and analysis of dealing with missing data was not described
All outcomes Selective reporting	Low risk	dealing with missing data was not described Outcomes listed in the methods were all reported
	LOW TISK	
Other bias	Low risk	The study was not sponsored by pharmaceutical company. The data collection & analysis were done by research institution
Dahl et al. (2010)		
Bias	Authors' judgement	Support for judgement
Random sequence generation	Unclear risk	The method of random sequence generation was not reported
Allocation concealment	Unclear risk	The method was not reported
Blinding of participants and personnel (All outcomes)	High risk	Open-label design
Blinding of outcome assessment All-cause mortality 	Low	Blinding end-point assessment. However, outcome is unlikely influenced by blinding.
Other outcomes	None	Other outcomes were not reported
Incomplete outcome data All outcomes	Low risk	No loss of follow-up during study
Selective reporting	Low risk	Outcomes listed in the methods were all reported
Other bias	Low risk	Funding & conducted by research institution
DEMAND (2011)		
Bias	Authors' judgement	Support for judgement
Random sequence generation	Low risk	Block of 6 patients assigned to each therapy with a 1:1:1 ratio.
Allocation concealment	Low risk	Computer-generated and randomization numbers were blindly assigned
Blinding of participants and personnel (All outcomes)	Low risk	Participants and personnel were blinded
Blinding of outcome assessment		
All-cause mortality	Low risk	Outcome is unlikely influenced by blinding
Other outcomes	Low risk	Blinding outcome assessment
Incomplete outcome data All outcomes	Low risk	No patients were loss to follow-up. Analyses were by intention to treat
Selective reporting	Low risk	Outcomes listed in the methods were all reported
Other bias	Low risk	Funded by pharmaceutical company but not involved in

Bias	Authors' judgement	Support for judgement
Random sequence generation	Low risk	Adequate. Randomization was based on permuted blocks, with a block size of four.
Allocation concealment	Low risk	Adequate. The subjects were randomly assigned at a central location to receive one of two drugs
Blinding of participants and personnel (All outcomes)	Low risk	Participants and personnel were blinded
Blinding of outcome assessment		
All-cause mortality	Low risk	Outcome measurement is not likely to be influenced by
Other outcomes	Unclear risk	lack of blinding. The method of outcome assessment was not reported
Incomplete outcome data All outcomes	Low risk	The loss of follow-up seems not affected the results
Selective reporting	Low risk	Outcomes listed in the methods were all reported
Other bias	Low risk	The data analysis was predetermined by the scientific steering committee & were performed by an independent statistical consultant
DIABHYCAR (2004)		
Bias	Authors' judgement	Support for judgement
Random sequence generation	Low risk	Stratified by centre and balanced by blocks of two treatments, by using a computer-generated random number list.
Allocation concealment	Low risk	Central randomization by telephone
Blinding of participants and personnel (All outcomes)	Low risk	Participants and personnel were blinded
Blinding of outcome assessment		
 All-cause mortality Other outcomes	Low risk Low risk	Outcome is unlikely influenced by blinding Blinded outcome assessment
Incomplete outcome data	Low risk	Missing data were unlikely to have an impact on the
All outcomes Selective reporting	Low risk	results of the trial Outcomes listed in the methods were all reported
Other bias	Unclear risk	Partially supported by pharmaceutical company. Unclear
		the role of sponsor
DIRECT Overall (2008) Bias	Authors'	Current for indeenent
Blds	judgement	Support for judgement
Random sequence generation	Low risk	Randomization is performed centrally by a computerized system.
Allocation concealment	Low risk	Centrally using an interactive voice-response system
Blinding of participants and personnel All outcomes	Low risk	Participants and personnel were blinded
Blinding of outcome assessment		
All-cause mortality	Low risk	Blinding of outcome assessment. However, is unlikely influenced by blinding
Other outcomes	None	Other outcomes were not reported
Incomplete outcome data All outcomes	Low risk	Missing data may not affect the results. Using ITT analysis
Selective reporting	Low risk	Reporting all the outcomes of pre-specified in the methods
Other bias	Low risk	The sponsors of the study did the statistical analysis, with validation by an independent statistician.
DREAM (2006)	I	
Bias	Authors'	Support for judgement
	judgement	
Random sequence generation	Low risk	Computer-generated system stratified according to centre, with a permuted block size of 8.
Allocation concealment	Low risk	Central randomization by computerized telephone
Blinding of participants and personnel (All outcomes)	Low risk	Participants and personnel were blinded
Blinding of outcome assessment		Outcome is unlikely influenced by blinding
All-cause mortality	Low risk	
All-cause mortalityOther outcomes	Low risk	Blinding of outcome assessment
All-cause mortality		

Other bias	Low risk	All sponsors had no role in collection, storage, or analysis the data & were not involved in the decision to submit data for publication.
E-COST (2005)		
Bias	Authors'	Support for judgement
	judgement	
Random sequence generation	High risk	The envelope method. The names of subjects were written on slips of paper, and the physician randomly placed the slips of paper into envelopes representing the different group assignments.
Allocation concealment	High risk	Not adequate.
Blinding of participants and personnel (All outcomes)	High risk	Study drugs were administered open-label
Blinding of outcome assessment All-cause mortality 	Low risk	Outcome measurement is not likely to be influenced by lack of blinding.
Other outcomes	Unclear risk	Blinding of outcome assessment was not described.
Incomplete outcome data All outcomes	Low risk	The reasons of dropped-out was not reported & the loss of follow-up was not reported. The analysis of outcomes was performed by ITT
Selective reporting	Low risk	Outcomes listed in the methods were all reported
Other bias	Unclear risk	Funding source not reported
E-COST-R (2005)		
Bias	Authors' judgement	Support for judgement
Random sequence generation	Unclear risk	The method of random sequence generation was not reported
Allocation concealment	Unclear risk	The randomization was done by envelope method. The method not described well
Blinding of participants and personnel (All outcomes)	High risk	Open-label design
Blinding of outcome assessment		
All-cause mortality	Low risk	Outcome measurement is not likely to be influenced by lack of blinding
Other outcomes	Unclear risk	The blinding of outcome assessment was not reported
Incomplete outcome data All outcomes	Low risk	The dropped-out rates were not reported. The ITT was used
Selective reporting	Low risk	Outcomes listed in the methods were all reported
Other bias	Unclear risk	The role of sponsor not described
EFFERVESCENT (2016)		
Bias	Authors' judgement	Support for judgement
Random sequence generation	Low risk	Computer-generated random sequence. Subjects were randomized (2:1 drug vs. placebo).
Allocation concealment	Low risk	Adequate. The allocation sequence was concealed from all researchers enrolling and assessing participants.
Blinding of participants and personnel (All outcomes)	Low risk	Participants and personnel were blinded
Blinding of outcome assessment		
All-cause mortality	Low risk	Outcome unlikely influenced by blinding
Other outcomes Incomplete outcome data	Low risk Low risk	Blinding of outcome assessment The missing data seems not affected the results
All outcomes		
Selective reporting	Low risk	Outcomes listed in the methods were all reported
Other bias	Unclear risk	The role of sponsor was not reported
ELITE II (2000)		
Bias	Authors' judgement	Support for judgement
Random sequence generation	Unclear risk	The method of random sequence generation was not reported
Allocation concealment	Unclear risk	The method of allocation concealment was not reported
Blinding of participants and personnel (All outcomes)	Low risk	Participants and personnel were blinded
Blinding of outcome assessment All-cause mortality 	Low risk	Outcome is unlikely influenced by blinding.

Incomplete outcome data All outcomes Selective reporting Other bias ELVERA (2001) Bias	Low risk Low risk Unclear risk	High patients taking captopril discontinued the treatment (as compared to losartan group). However, the analysis was performed by ITT Outcomes listed in the methods were all reported
Other bias ELVERA (2001)		Outcomes listed in the methods were all reported
ELVERA (2001)	Unclear risk	The set of an energy of the literation of the li
		The role of sponsor was not described
Bias		
	Authors' judgement	Support for judgement
Random sequence generation	Unclear risk	The method of random sequence generation was not reported
Allocation concealment	Unclear risk	The method of allocation concealment was not reported
Blinding of participants and personnel (All outcomes)	Low risk	Participants and personnel were blinded
Blinding of outcome assessment		
All-cause mortality	Low risk	Blinding of outcome assessment
Other outcomes	None	Other outcomes were not reported
Incomplete outcome data	Low risk	The loss of follow-up was not reported. However, the ITT
All outcomes Selective reporting	Low risk	approach was used as analysis Outcomes listed in the methods were all reported
Other bias	Unclear risk	
ESPIRAL (2001)	Unctear FISK	The role of sponsor was not reported
Bias	Authors'	Support for judgement
	judgement	
Random sequence generation	Unclear risk	Method of random sequence generation was not described
Allocation concealment	Unclear risk	Method of allocation concealment not described.
Blinding of participants and personnel (All outcomes)	High risk	Study drugs were administered open-label
Blinding of outcome assessment		
All-cause mortality	None Unclear risk	Outcome was not reported
Other outcomes		Blinding of outcome assessment was not described
Incomplete outcome data All outcomes	Low risk	The loss of follow-up data was not reported. However, ITT principle of analysis was used
Selective reporting	Low risk	Outcomes listed in the methods were all reported
Other bias	Unclear risk	Funding resource is not reported
EUROPA (2003)		· · · · · · · · · · · · · · · · · · ·
Bias	Authors'	Support for judgement
	judgement	
Random sequence generation	Unclear risk	The method of random sequence generation was not described
Allocation concealment	Unclear risk	The method of concealment was not described
Blinding of participants and personnel (All outcomes)	Low risk	participants and personnel were blinded
Blinding of outcome assessment	Low rick	Outcome measurement is not likely to be influenced by
All-cause mortality	Low risk	Outcome measurement is not likely to be influenced by lack of blinding
Other outcomes	Unclear risk	Blinding of outcome assessment was not reported
Incomplete outcome data	Low risk	Missing data were unlikely to have an impact on the results of the trial.
All outcomes Selective reporting	Low risk	Outcomes listed in the methods were all reported
Other bias	Low risk	Sponsor was not involved in the data collection and data analysis.
Fang Wu et (2015)		
Bias	Authors'	Support for judgement
Random sequence generation	judgement Unclear risk	The method of random sequence generation was not reported
	Unclear risk	The method of allocation concealment was not reported
Allocation concealment		1
Blinding of participants and personnel (All	Unclear risk	Blinding of participants and personnel was not reported
Blinding of participants and personnel (All outcomes)	Unclear risk	Blinding of participants and personnel was not reported
Blinding of participants and personnel (All	Unclear risk None	Blinding of participants and personnel was not reported Outcome was not reported
Blinding of participants and personnel (All outcomes) Blinding of outcome assessment		
Blinding of participants and personnel (All outcomes) Blinding of outcome assessment • All-cause mortality	None	Outcome was not reported

Selective reporting	Low risk	Outcomes listed in the methods were all reported
Other bias	Low risk	Supported by grants from research institution
Forest et al. (2002)		
Fogari et al. (2002) Bias	Authors'	Support for judgement
Dids	judgement	Support for judgement
Random sequence generation	Low risk	Computer-generated random number sequence
Allocation concealment	Unclear risk	The method of allocation concealment was not reported.
Autocation conceament	Unctedi Tisk	The method of allocation concealment was not reported.
Blinding of participants and personnel (All outcomes)	High risk	Open-label
Blinding of outcome assessment All-cause mortality 	Low risk	Outcome measurement is not likely to be influenced by lack of blinding.
Other outcomes	Unclear risk	Blinding of outcome assessment was not reported
Incomplete outcome data All outcomes	Unclear risk	The loss of follow-up was not reported. No information available for judgement
Selective reporting	Low risk	Outcomes listed in the methods were all reported
Other bias	Unclear risk	The role of sponsor was not reported
GISSI-AF (2009)		
Bias	Authors' judgement	Support for judgement
Random sequence generation	Low risk	Computer-generated randomization stratified according to site, with blocks of four patients per site.
Allocation concealment	Low risk	Central randomization by computerized telephone, with the group assignments concealed
Blinding of participants and personnel (All outcomes)	Low risk	Participants and personnel were blinded
Blinding of outcome assessment All-cause mortality 	Low risk	Outcome measurement is not likely to be influenced by lack of blinding;
Other outcomes	Unclear risk	Blinding of outcome assessment was not reported
Incomplete outcome data All outcomes	Low risk	The loss of follow-up was not reported. However, ITT was used
Selective reporting	Low risk	Outcomes listed in the methods were all reported
Other bias	Low risk	The sponsor had no role on design, data collection, analysis & interpterion
HIJ-CREATE (2009)		
Bias	Authors' judgement	Support for judgement
Random sequence generation	Low risk	Computer-generated, stratified, permuted-block randomization code (block size of four).
Allocation concealment	Unclear risk	The method of allocation concealment was not described
Blinding of participants and personnel (All outcomes)	High risk	Open-label design
Blinding of outcome assessment		
 All-cause mortality 	Low risk	Outcome is unlikely influenced by blinding
Other outcomes	Low risk	Blinding of outcome assessment
Incomplete outcome data All outcomes	Low risk	The missing data seems not affected the results
Selective reporting (reporting bias)	Low risk	Outcomes listed in the methods were all reported
Other bias	Low risk	The sponsor had no role for a conduct the study

HONG-KONG DHF (2006)		
Bias	Authors' judgement	Support for judgement
Random sequence generation	Low risk	Patients were randomly allocated using computer- generated random numbers in blocks of 10 (balanced stratification)
Allocation concealment	Unclear risk	The allocation concealment was not reported
Blinding of participants and personnel (All outcomes)	High-risk	Open-label design
Blinding of outcome assessment		
 All-cause mortality 	Low risk	Outcome is unlikely influenced by blinding
	Low risk	Blinding-end point assessment.

Other outcomes		
Incomplete outcome data	Unclear risk	The dropped-out rates were not reported. The approach
All outcomes Selective reporting	Unclear risk	analysis of missing data was not reported The protocol was not published
Other bias	Low risk	The data analysis, design was conducted independently of pharmaceutical sponsor. None of the authors received any lecture, advisory board, or consultancy fees relating to this study from the sponsors
HOPE (2000)	•	
Bias	Authors' judgement	Support for judgement
Random sequence generation	Unclear risk	The method of generate random sequence was not reported
Allocation concealment	Low risk	Central Randomization by a telephone call to centre office
Blinding of participants and personnel (All outcomes)	Low risk	participants and personnel were blinded
Blinding of outcome assessment		
All-cause mortality	Low risk	Outcome is likely influenced by blinding
Other outcomes	Low risk	Blinding of outcome assessment
Incomplete outcome data All outcomes	Low Risk	Missing data unlikely to affect the outcome results
Selective reporting	Low Risk	Reported all outcomes specified in the
		methods
Other bias	Low Risk	Sponsored by government bodies or non-profit organizations
HOPE-3 (2016)		
Bias	Authors'	Support for judgement
Dandom convorte record the	judgement	Description block and excitation start (Codd by sector
Random sequence generation Allocation concealment	Low risk Low risk	Permuted block randomization stratified by centre Adequate. Central concealed randomization
Blinding of participants and personnel (All outcomes)	Low risk	Participants and personnel were blinded
Blinding of outcome assessment	Laur stale	Outcome is unlikely influenced by blinding
 All-cause mortality Other outcomes 	Low risk Low risk	Outcome is unlikely influenced by blinding Blinding of outcome assessment
Incomplete outcome data	Low risk	Missing data were unlikely to have an impact on the
All outcomes		results of the trial
Selective reporting	Low risk	Outcomes listed in the methods were all reported
Other bias	Low risk	Data collection & analysis were performed independently of sponsor
Hou et al. (group 2) (2006)		
Bias	Authors'	Support for judgement
	judgement	
Random sequence generation Allocation concealment	Low risk Unclear risk	Computer-generated list was used for randomization The method of concealment was not described
Blinding of participants and personnel (All outcomes)	Low risk	Participants and personnel were blinded
Blinding of outcome assessment All-cause mortality 	Low risk Low risk	Outcome is unlikely influenced by blinding
Other outcomes Incomplete outcome data	Low risk	Blinding of outcome assessment Missing data were unlikely to have an impact on the
All outcomes		results of the trial Outcomes listed in the methods were all reported
Selective reporting Other bias	Low risk Low risk	Supported by clinical research institution
HYVET pilot (2003) Bias	Authors'	Support for judgement
Dias	judgement	
Random sequence generation	Low risk	Computer-generated randomization (central randomization)
Allocation concealment	Low risk	Adequate. Quote: Restricted random allocation to groups
Blinding of participants and personnel	High risk	Open-label design
(All outcomes)		
	Low risk	Outcome measurement is not likely to be influenced by lack of blinding.

Incomplete outcome data		
All outcomes	Low risk	Missing data unlikely to affect the outcome results
Selective reporting	Low risk	Reported all outcomes specified in the methods
Other bias	Unclear risk	The role of sponsor was not reported
I-PRESERVE (2008)		
Bias	Authors' judgement	Support for judgement
Random sequence generation	Low risk	Automated, central randomization system permuted block and stratified by site and by use of ACE inhibitors at baseline
Allocation concealment	Low risk	Via an interactive voice-response system
Blinding of participants and personnel (All outcomes)	Low risk	Participants and personnel were blinded
 Blinding of outcome assessment All-cause mortality 	Low risk	Outcome is unlikely influenced by blinding
 All-cause mortality Other outcomes 	Low risk	Blind outcome assessment
Incomplete outcome data	Low risk	Missing data were unlikely to have an impact on the
All outcomes Selective reporting	Low risk	results of the trial all planned outcomes were reported
	Low hor	
Other bias	Low risk	The data collection & analysis was performed independently of the sponsors
IDNT (2001)		
Bias	Authors' judgement	Support for judgement
Random sequence generation	Low risk	Computer-generated random sequence.
Allocation concealment	Low risk	Randomization was blocked by centres
Blinding of participants and personnel (All outcomes)	Low risk	Participants and personnel were blinded
Blinding of outcome assessment All-cause mortality 	Low risk	Outcome is unlikely influenced by blinding
 All-cause mortality Other outcomes 	Low risk	Blind outcome assessment
Incomplete outcome data	Low risk	Missing data were unlikely to have an impact on the results of the trial
All outcomes Selective reporting	Low risk	Outcomes listed in the methods were all reported
Other bias	Unclear risk	Role of the sponsor was not described
IMAGINE (2008)		
Bias	Authors' judgement	Support for judgement
Random sequence generation	Low risk	Computer-generated which was un-stratified & block- based
Allocation concealment	Low risk	Adequate. Central allocation
Blinding of participants and personnel	Low risk	Participants and personnel were blinded
(All outcomes)		
 Blinding of outcome assessment All-cause mortality 	Low risk	Outcome is unlikely influenced by blinding
 Other outcomes 	Low risk	Blinding outcome assessment
Incomplete outcome data All outcomes	Low risk	Missing data were unlikely to have an impact on the results of the trial.
Selective reporting	Low risk	Outcomes listed in the methods were all reported
Other bias	Low risk	The data were collected and analysed by an independent clinical research organization
IRMA-2 (2001)		
Bias	Authors' judgement	Support for judgement
Random sequence generation	Unclear risk	Method of random sequence generation was not described.
Allocation concealment	Unclear risk	Method of allocation concealment not described.
Blinding of participants and personnel (All outcomes)	Low risk	participants and personnel were blinded
Blinding of outcome assessment	Low risk	Outcome is unlikely influenced by blinding
 All-cause mortality Other outcomes 	Low risk Low risk	Outcome is unlikely influenced by blinding Blinding outcome assessment
Incomplete outcome data	Low risk	Missing data were unlikely to have an impact on the
All outcomes		results of the trial.
Selective reporting	Low risk	Outcomes listed in the methods were all reported

Other bias	Low risk	the steering committee included two nonvoting members
other blas	LOW LISK	from the sponsoring company who oversaw the study
		design, the conduct of the trial, and the management
		and analysis of the data
J-MIND (2001) Bias	Authors'	Support for judgement
	judgement	
Random sequence generation	Unclear risk	A block of 4 patients (2 per group) was assigned to receive either of two drug. The method of random generation was not described
Allocation concealment	Unclear risk	The method of concealment was not reported
Blinding of participants and personnel (All outcomes)	High risk	Open-label design
Blinding of outcome assessment All-cause mortality 	None Unclear risk	Outcome was not reported
Other outcomes Incomplete outcome data	Low risk	Blinding of outcome assessment was reported Missing data were unlikely to have an impact on the
All outcomes	LOW TISK	results of the trial
Selective reporting	Low risk	Outcomes listed in the methods were all reported
Other bias	Unclear risk	The funding source was not reported
J-RHYTHM II (2010)	I	
Bias	Authors'	Support for judgement
Dandom sociuones consection	judgement	Computer generated water based on startification
Random sequence generation	Low risk	Computer-generated system based on stratification according to age, sex, BP during the observation period, existence of structural
		heart diseases and regular use of any antiarrhythmic drugs
Allocation concealment	Unclear risk	The method of concealment was not described
Blinding of participants and personnel (All outcomes)	High risk	Open-label fashion
Blinding of outcome assessment		
All-cause mortality	None Low risk	Outcome was not reported Blinding of outcome assessment
Other outcomes Incomplete outcome data	Low risk	The loss of follow-up & dis-continuation in both groups
All outcomes	LOW HISK	was not reported. However, the actual sample size was 318 which more than that necessary for the prespecified statistical analysis (n= 240) & ITT method was used for analysis.
Selective reporting	Low risk	Outcomes listed in the methods were all reported
Other bias	Low risk	The funding source had no role in the study design, data collection, analysis and interpretation, or the writing of the report
JAMP (2004)		
Bias	Authors' judgement	Support for judgement
Random sequence generation	Unclear risk	The method of sequence generation was not described.
Allocation concealment	Unclear risk	The method of concealment was not described well.
Blinding of participants and personnel (All outcomes)	High risk	Open-label design
Blinding of outcome assessment All-cause mortality 	Low risk	Outcome measurement is not likely to be influenced by lack of blinding.
Other outcomes	Unclear risk	Blinding of outcome assessment was not reported
Incomplete outcome data All outcomes	Unclear risk	The loss of follow-up was not reported. The ITT analysis was not used
Selective reporting	Low risk	Outcomes listed in the methods were all reported
Other bias	Low risk	Non-pharmaceutical company trial
JMIC-B (2004)		
Bias	Authors' judgement	Support for judgement
Random sequence generation	Low risk	Computer-generated random sequence
	Low risk	Adequate. The sealed envelope method was used for
Allocation concealment	LOW TISK	randomization of the study drug
	High risk	randomization of the study drug Open-label design

Other outcomes	Low risk	Blinding of outcome assessment
ncomplete outcome data (All outcomes)	Low risk	Missing data were unlikely to have an impact on the results of the trial. The analysis was performed by ITT
Selective reporting	Low risk	principles Outcomes listed in the methods were all reported
Other bias	Low risk	The trial was supported by research institution
KACT-MetS (2012)	<u> </u>	
Bias	Authors'	Support for judgement
	judgement	
Random sequence generation	Unclear risk	The method Random sequence generation was not reported
Allocation concealment	Unclear risk	The method Allocation concealment was not reported
Blinding of participants and personnel (All outcomes)	High risk	Open-label design
Blinding of outcome assessment		
 All-cause mortality 	None	Outcome was not reported
Other outcomes	Unclear risk	Blinding of outcome assessment was not reported
Incomplete outcome data	Low risk	Only one patient lost to follow-up in control group. The
All outcomes Selective reporting	Low risk	analysis was done by ITT principle Outcomes listed in the methods were all reported
Other bias	Low risk	Funding by Academic institution
Kawamura (2013)		
Bias	Authors'	Support for judgement
	judgement	
Random sequence generation	Unclear risk	The method of random sequence was not reported
Allocation concealment	Unclear risk	Used envelope method. unclear whether it sealed, opaque or not
Blinding of participants and personnel (All outcomes) Blinding of outcome assessment	Unclear risk	The blinding of participants and personnel was not reported
All-cause mortality	None	Outcome was not reported
Other outcomes	Unclear risk	Outcome assessment was not reported
Incomplete outcome data	Low risk	The loss of follow-up was not reported. However, the IT
All outcomes	LOW HISK	approach was used
Selective reporting	Unclear risk	The protocol was not published
Other bias	Low risk	The sponsor was academic institution
Kondo et al. (2003)	<u> </u>	
Bias	Authors'	Support for judgement
Dids	judgement	Support for Judgement
Random sequence generation	Unclear risk	The method of sequence generation was not reported
Allocation concealment	Unclear risk	The method of concealment was not reported
Blinding of participants and personnel (All outcomes)	High risk	Open-label design
 Blinding of outcome assessment All-cause mortality 	Low risk	Outcome measurement is not likely to be influenced by lack of blinding;
Other outcomes	Unclear risk	Blinding of outcome assessment was not reported
Incomplete outcome data All outcomes	Low risk	The loss of follow-up was not reported. However, ITT method was used
Selective reporting	Low risk	Outcomes listed in the methods were all reported
Other bias	Unclear risk	The role of sponsor was not reported
LAARS (2002)		
Bias	Authors' judgement	Support for judgement
Random sequence generation	Low risk	Computer-generated random sequence
Allocation concealment	Unclear risk	Randomization was accomplished by coding clinical samples. The method of concealment was not described
Blinding of participants and personnel	Low risk	Participants and personnel were blinded

All-cause mortality	None	Outcome was not reported
Other outcomes	Low risk	Blinding of outcome assessment
Incomplete outcome data All outcomes	Low risk	Missing data were unlikely to have an impact on the results of the trial
Selective reporting	Low risk	Outcomes listed in the methods were all reported
Other bias	Unclear risk	The funding source was not reported
LIFE (2002)		
Bias	Authors' judgement	Support for judgement
Random sequence generation	Low risk	Computer-generated random sequence
Allocation concealment	Low risk	Adequate. Central allocation
Blinding of participants and personnel (All outcomes)	Low risk	Participants and personnel were blinded
Blinding of outcome assessment All-cause mortality 	Low risk Low risk	Outcome is unlikely influenced by blinding Blinding of outcome assessment
Other outcomes Incomplete outcome data	Low risk	Missing data were unlikely to have an impact
All outcomes Selective reporting	Low risk	on the results of the trial Outcomes listed in the methods were all reported
		·
Other bias	Low risk	Sponsor provided the study steering committee with free access to all data. Data analysis & interpretation, paper writing and publication was independent of the sponsor.
LIRICO (2018)	•	
Bias	Authors' judgement	Support for judgement
Random sequence generation	Low risk	Electronic generated random list stratified by centre and in randomly permuted blocks
Allocation concealment	Low risk	Central randomization by phone
Blinding of participants and personnel (All outcomes)	High risk	Open-label design
Blinding of outcome assessment	Low rick	Outcome is unlikely influenced by blinding
 All-cause mortality Other outcomes 	Low risk Low risk	Outcome is unlikely influenced by blinding Blinding of outcome assessment
Incomplete outcome data All outcomes	Low	Missing data were unlikely to have an impact on the results of the trial
Selective reporting	Low	Outcomes listed in the methods were all reported
Other bias	Low risk	Sponsored by government agency
MITEC (2009)	1	
Bias	Authors' judgement	Support for judgement
Random sequence generation	Low risk	Randomization was computer generated and balanced by the centre
Allocation concealment	Unclear risk	The method of concealment was not reported
Blinding of participants and personnel (All outcomes)	Low risk	Participants and personnel were blinded
Blinding of outcome assessment All-cause mortality Other outcomes	Low risk Low risk	Outcome is unlikely influenced by blinding Blinding of outcome assessment
Incomplete outcome data	Low risk	Missing data were unlikely to have an impact on the
All outcomes	Low risk	results of the trial. Outcomes listed in the methods were all reported
Selective reporting Other bias	Unclear	The role of sponsor was not reported
MOSES (2005)		
Bias	Authors'	Support for judgement
Pandom coqueres consisting	judgement	Computer generated rendem converse
Random sequence generation	Low risk Low risk	Computer-generated random sequence Adequate. the randomization sequence being blocked from previewing
Allocation concealment		
Blinding of participants and personnel (All outcomes)	High risk	Open-label design
Blinding of participants and personnel (All outcomes) Blinding of outcome assessment • All-cause mortality	Low risk	Open-label design Outcome is unlikely influenced by blinding
Allocation concealment Blinding of participants and personnel (All outcomes) Blinding of outcome assessment		Open-label design

Other bias	Low risk	The sponsor is pharmaceutical company. However, study was designed, conducted, analysed, and interpreted by						
		the investigators independently of all sponsors.						
NAVIGATOR (2010)								
Bias	Authors'	Support for judgement						
	judgement							
Random sequence generation	Low risk	Computer-generated stratified according to centre, with a block size of eight within each centre						
Allocation concealment	Low risk	computerized, interactive voice-response telephone randomization system						
Blinding of participants and personnel (All outcomes)	Low risk	Participants and personnel were blinded						
Blinding of outcome assessment	Law state							
 All-cause mortality Other outcomes 	Low risk Low risk	Outcome is unlikely influenced by blinding Blinded end-point assessment						
Incomplete outcome data	Low risk	212 patients were excluded after randomization because						
All outcomes	Low Hak	of protocol deficiencies at site and they were not included in the final analysis. ITT analysis was performed						
Selective reporting	Low risk	Outcomes listed in the methods were all reported						
Other bias	Unclear risk	Data were collected, managed, and analysed by the sponsor, with oversight from the executive committee, the analyses were replicated by an independent academic statistician.						
NTP-AF study (2013)	1							
Bias	Authors' judgement	Support for judgement						
Random sequence generation	Low risk	Computer-generated random sequence						
Allocation concealment	Unclear risk	The method of concealment was not reported						
Blinding of participants and personnel (All outcomes)	High risk	Open-label design						
Blinding of outcome assessment All-cause mortality 	None	Outcome was not reported Blinding of outcome assessment was not reported						
Other outcomes	Unclear risk	building of outcome assessment was not reported						
Incomplete outcome data (attrition bias)	Low risk	No loss of follow-up. The dis-continuation rates were similar. The data was analysis based on ITT approach						
All outcomes Selective reporting	Low risk	Outcomes listed in the methods were all reported						
Other bias	Low risk	The sponsor is research institution						
OLIVUS (2010)								
Bias	Authors' judgement	Support for judgement						
Random sequence generation	Unclear risk	The method of random sequence generation was not described						
Allocation concealment	Unclear risk	The method was not described						
Blinding of participants and personnel (All outcomes)	Unclear risk	Not reported						
Blinding of outcome assessment All-cause mortality Other outcomer 	Low risk Low risk	Outcome is unlikely influenced by blinding Blinding of outcome assessment						
Other outcomes Incomplete outcome data	Low risk	No loss of follow-up.						
All outcomes								
Selective reporting	Low risk	Outcomes listed in the methods were all reported						
Other bias	Unclear risk	The funding resource was not reported						
ONTARGET (2008) Bias	Authors'	Support for judgement						
כמוע	judgement	Support for judgement						
Random sequence generation	Unclear risk	Randomization was stratified according to site with the use of permuted blocks. However, the method of generation was not specified						
Allocation concealment	Low risk	Randomized via a computerized voice-activated telephone call to a central office						
Blinding of participants and personnel (All outcomes)	Low risk	Participants and personnel were blinded						
Blinding of outcome assessment	Low risk	Outcome is unlikely influenced by blinding						
 All-cause mortality 								

Incomplete outcome data	Low risk	Missing data were unlikely to have an impact on the						
All outcomes Selective reporting	Low risk	results of the trial All outcomes described in the protocol were						
	Low Hak	reported						
Other bias	Low risk	The sponsor is pharmaceutical company, but data were						
		collected independently of sponsors. The study sponsor received the data only after the study had been						
		completed						
OPTIMAAL (2002)	•							
Bias	Authors' judgement	Support for judgement						
Random sequence generation	Low risk	Block randomization was used at each						
		centre.						
Allocation concealment	Low risk	Computer-generated allocation						
Blinding of participants and personnel (All outcomes)	Low risk	Participants and personnel were blinded						
Blinding of outcome assessment All-cause mortality 	Low risk	Outcome is unlikely influenced by blinding						
Other outcomes	Low risk	Blinding outcome assessment						
Incomplete outcome data	Low risk	Missing data were unlikely to have an impact on the						
All outcomes	Low rick	results of the trial Outcomes listed in the methods were all reported						
Selective reporting)	Low risk							
Other bias	Low risk	The scientific conduct of the study and manuscript preparation was independent of the sponsor						
ORIENT (2011)	Authors'	Support for judgement						
Bias	judgement	Support for judgement						
Random sequence generation	Low risk	Dynamic random allocation. The centre assigned each						
		patient by the dynamic allocation method, depending on whether or not they were using ACEIs, further stratified						
		by UACR and SCr.						
Allocation concealment	Low risk	Central randomization by fax.						
Blinding of participants and personnel	Low risk	Participants and personnel were blinded						
(All outcomes)								
 Blinding of outcome assessment All-cause mortality 	Low risk	Outcome is unlikely influenced by blinding						
 Other outcomes 	Low risk	Outcome is unlikely influenced by blinding Blinding of outcome assessment						
Incomplete outcome data	Low risk	The missing data seems not affected the results						
All outcomes Selective reporting	Low risk	Outcomes listed in the methods were all reported						
Other bias	Low risk	Overall study design conduct of the trial, data						
	2000 1000	management and analysis were performed independent of sponsor.						
PART-2 (2000)	•							
Bias	Authors' judgement	Support for judgement						
Random sequence generation	Low risk	Randomization was performed by computer using a						
		minimization algorithm that balanced treatment						
		assignment by centre, disease inclusion criteria and current use of a beta-adrenergic						
		blocking agent						
Allocation concealment	Low risk	Adequate. Treatment assignment was obtained by telephone call to the Clinical Trials Research Unit						
Blinding of participants and personnel	Low risk	randomization service Participants and personnel were blinded						
Blinding of outcome assessment	LOW LISK							
All-cause mortalityOther outcomes	Low risk Low risk	Outcome is unlikely influenced by blinding Blinding of outcome assessment						
Incomplete outcome data	Low risk	Missing data were unlikely to have an impact on the						
All outcomes	Low risk	results of the trial						
Selective reporting		Outcomes listed in the methods were all reported						
Other bias	Unclear risk	The role of sponsor was not reported						
PEACE (2004)	1							
Bias	Authors'	Support for judgement						
Pandom coquence concretion	judgement	Dandomization uses the method of second disclosed						
Random sequence generation	Unclear risk	Randomization uses the method of permuted blocks, stratified according to clinical site. However, the method was not described						
Allocation concealment	Unclear risk	Patients were randomized by a call to the data						
		coordinating centre. However, the method was not described						

Blinding of participants and personnel	Low risk	participants and personnel were blinded						
 Blinding of outcome assessment All-cause mortality Other outcomes 	Low risk Low risk	Outcome is unlikely influenced by blinding Blinding of outcome assessment.						
Incomplete outcome data All outcomes	Low risk	Missing data were unlikely to have an impact on the results of the trial						
Selective reporting	Low risk	All outcomes described in the protocol were reported						
Other bias	Low risk	The sponsor is academic institution						
PEP-CHF (2006)								
Bias	Authors' judgement	Support for judgement						
Random sequence generation	Low risk	Computer-generated list in blocks of four within treatment centres						
Allocation concealment	Low risk	Adequate. Quote "through a centrally administered process, concealed from the study investigators".						
Blinding of participants and personnel (All outcomes)	Low risk	Participants and personnel were blinded						
Blinding of outcome assessment								
 All-cause mortality Other outcomes 	Low risk Low risk	Outcome is unlikely influenced by blinding Blinding of outcome assessment.						
Incomplete outcome data All outcomes	Low risk	Only 4/850 lost to follow-up. All analyses used the ITT principle						
Selective reporting	Low risk	Outcomes listed in the methods were all reported						
Other bias	Low risk	The sponsor had access to the database and participated in the analysis under the supervision of an independent statistician						
PHARAO (2008)								
Bias	Authors' judgement	Support for judgement						
Random sequence generation Allocation concealment	Low risk Low risk	Computer-generated randomization list Central allocation						
Blinding of participants and personnel	High risk	Open-study design						
(All outcomes) Blinding of outcome assessment								
All-cause mortality Other outcomes	Low risk Low risk	Outcome is unlikely influenced by blinding Blinding outcome assessment						
Incomplete outcome data (All outcomes)	Low risk	No patients were loss to follow-up						
Selective reporting	Low risk	Outcomes listed in the methods were all reported						
Other bias	Low risk	The study was conducted independent of all sponsors						
PHYLLIS (2004)								
Bias	Authors' judgement	Support for judgement						
Random sequence generation	Low risk	Computer-generated in a block size of 4						
Allocation concealment	Low risk	Central allocation						
Blinding of participants and personnel (All outcomes)	Low risk	Participants and personnel were blinded						
Blinding of outcome assessment All-cause mortality 	None	Not reported as outcome						
Other outcomes Incomplete outcome data	Low risk Low risk	Blinding outcome assessment The dropped-out rates were not reported. However, the						
All outcomes		analysis was based on ITT principle						
Selective reporting	Low risk	Outcomes listed in the methods were all reported						
Other bias	Unclear risk	The role of sponsor was not described						
PREAMI (2006) Bias	Authors'	Support for judgement						
	judgement							
Random sequence generation	Low risk	Computer-generated randomization code to select random permuted blocks (fixed length of 4 without stratification)						
Allocation concealment	Low risk	Centralized randomization						
Blinding of participants and personnel (All outcomes)	Low risk	Participants and personnel were blinded						
Blinding of outcome assessment All-cause ortality Other outcomes 	Low risk Low risk	Outcome is unlikely influenced by blinding Blinding of outcome assessment						
Other outcomes Incomplete outcome data	Low risk	Missing data were unlikely to have an impact on the						
All outcomes Selective reporting	Low risk	results of the trial Outcomes listed in the methods were all reported						
		succomes discer in the methods were all reported						

Other bias	Unclear risk	The role of sponsor was not reported							
PREVEND IT (2004) Bias	Authors'	Support for judgement							
Dias	judgement								
Random sequence generation	Low risk	Computer-generated randomization performed in blocks of 20							
Allocation concealment	Low risk	Central allocation							
Blinding of participants and personnel (All outcomes)	Low risk	Participants and personnel were blinded							
 Blinding of outcome assessment All-cause mortality 	Low risk	Outcome is unlikely influenced by blinding							
Other outcomes	Low risk	Blind outcome assessment							
Incomplete outcome data All outcomes	Low risk	Missing data were unlikely to have an impact on the							
Selective reporting	Low risk	results of the trial Outcomes listed in the methods were all reported							
Other bias	Low risk	The sponsor of study was academic institution							
PREVER-treatment (2016)									
Bias	Authors'	Support for judgement							
Random sequence generation	judgement Low risk	Computer generated list, with variable block sizes and							
	Lauradala	stratified by centre.							
Allocation concealment	Low risk	Randomization was implemented through a 24-h web- based automated system.							
Blinding of participants and personnel (All outcomes)	Low risk	Blinding of participant and investigators							
 Blinding of outcome assessment All-cause mortality 	Low risk	Outcome is unlikely influenced by blinding							
 All-cause mortality Other outcomes 	Low risk	Blinding of outcome assessment							
Incomplete outcome data	Low risk	Missing data were unlikely to have an impact on the							
All outcomes	High rick	results of the trial							
Selective reporting	High risk	Heart failure requiring hospitalization, & angina was not reported in original trial							
Other bias	Low risk	Sponsored by academic institution							
PRoFESS (2008)	Authors'	Current for independent							
Bias	judgement	Support for judgement							
Random sequence generation	Unclear risk	Inadequate. The method of sequence generation was not described. The randomization to telmisartan was stratified based on whether or not individuals were receiving ACE inhibitors							
Allocation concealment	Low risk	Central telephone randomization system							
Blinding of participants and personnel	Low risk	Participants and personnel were blinded							
(All outcomes) Blinding of outcome assessment									
All-cause mortality	Low risk	Outcome unlikely influenced by blinding							
Other outcomes Incomplete outcome data	Low risk Low risk	Blinding outcome assessment Missing data were unlikely to have an impact on the							
All outcomes		results of the trial							
Selective reporting	Low risk	Outcomes listed in the methods were all reported							
Other bias	Low risk	Industry sponsored. However, data analysis was performed independently of sponsor.							
PROGRESS (2001)									
Bias	Authors' judgement	Support for judgement							
Random sequence generation	Low risk	A minimization algorithm stratifies treatment allocation by study centre, sex, age, & entry systolic blood pressure							
Allocation concealment	Low risk	Central computer-based randomization service accessed by telephone or facsimile							
Blinding of participants and personnel (All outcomes)	Low risk	Participants and personnel were blinded							
Blinding of outcome assessment									
All-cause mortalityOther outcomes	Low risk Low risk	Outcome is unlikely influenced by blinding Blinding of outcome assessment							
Incomplete outcome data All outcomes	Low risk	Missing data were unlikely to have an impact on the results of the trial							
Selective reporting	Low risk	Outcomes listed in the methods were all reported							
Other bias	Low risk	The study was designed, conducted, analysed, and interpreted by the investigators independently of all sponsors							

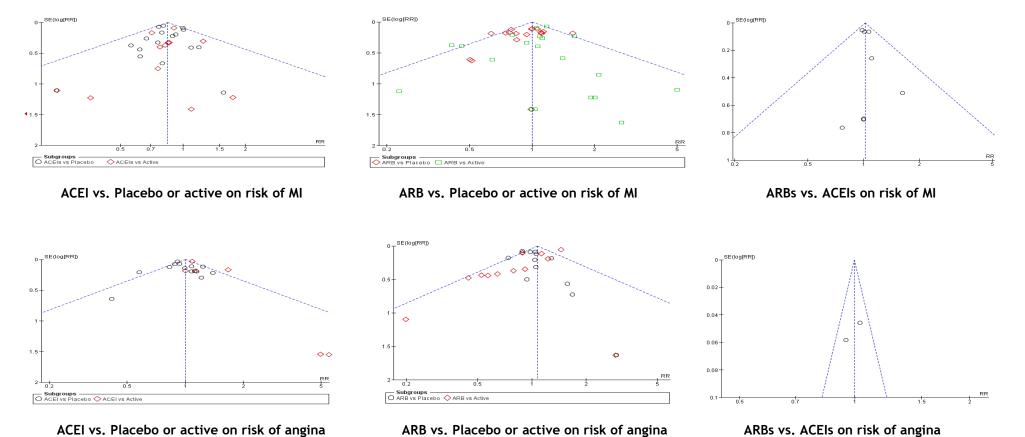
QUIET (2001)	Author-	Current for indrament
Bias	Authors' judgement	Support for judgement
Random sequence generation	Unclear risk	The method of generate random sequence was not reported
Allocation concealment	Unclear risk	The method of allocation concealment was not reported
Blinding of participants and personnel (All outcomes)	Low risk	Participants and personnel were blinded
Blinding of outcome assessment	Laur stale	Outcome is well-table influenced by blinding
All-cause mortalityOther outcomes	Low risk Low risk	Outcome is unlikely influenced by blinding Blinding of outcome assessment
Incomplete outcome data All outcomes	Low risk	Missing data were unlikely to have an impact on the results of the trial. Only 4 patients lost to follow-up during trial
Selective reporting	Low risk	Outcomes listed in the methods were all reported
Other bias	Low risk	The sponsor had not role for data access
QUO VADIS (2001)	•	
Bias	Authors' judgement	Support for judgement
Random sequence generation	Unclear risk	The method of random sequence generation was not described
Allocation concealment	Unclear risk	The method of allocation concealment was not described
Blinding of participants and personnel (All outcomes)	Low risk	Participants and personnel were blinded
Blinding of outcome assessment	امند بنداد	Outcome is unlikely influenced by P.D. Day
All-cause mortality Other outcomes	Low risk Low risk	Outcome is unlikely influenced by blinding Blinding of outcome assessment
Other outcomes Incomplete outcome data	Low risk	Missing data were unlikely to have an impact on the
All outcomes	LOW HISK	results of the trial.
Selective reporting	Low risk	Outcomes listed in the methods were all reported
Other bias	Unclear risk	The role of sponsor was nor reported
RASS (2009)		
Bias	Authors'	Support for judgement
Random sequence generation	judgement Low risk	Computer-generated blocks of six and stratified according to centre and sex
Allocation concealment	Low risk	Computer-generated
Blinding of participants and personnel (All outcomes)	Low risk	Participants and personnel were blinded
Blinding of outcome assessment All-cause mortality Other outcomes 	Low risk None	Outcome unlikely influenced by blinding Other outcomes were not reported
Incomplete outcome data	Low risk	Missing data may not affect the results
All outcomes Selective reporting	Low risk	Reported all outcomes described in the protocol
Other bias	Low risk	Funded by National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Disease (NIH)
RENAAL (2001)		
Bias	Authors' judgement	Support for judgement
Random sequence generation	Low risk	Computer-generated which stratified based on the level of baseline albuminuria.
Allocation concealment	Low risk	Computer-generated random allocation schedule
	Low risk	Participants and personnel were blinded
Blinding of participants and personnel (All outcomes)		
(All outcomes) Blinding of outcome assessment	low rick	Outcome is unlikely influenced by blinding
(All outcomes) Blinding of outcome assessment • All-cause mortality	Low risk	Outcome is unlikely influenced by blinding Blinding of outcome assessment
(All outcomes) Blinding of outcome assessment • All-cause mortality • Other outcomes Incomplete outcome data	Low risk Low risk Low risk	Blinding of outcome assessmentMissing data were unlikely to have an impact on the
(All outcomes) Blinding of outcome assessment • All-cause mortality • Other outcomes Incomplete outcome data All outcomes	Low risk	Blinding of outcome assessment
(All outcomes) Blinding of outcome assessment • All-cause mortality • Other outcomes Incomplete outcome data All outcomes Selective reporting Other bias	Low risk Low risk	Blinding of outcome assessment Missing data were unlikely to have an impact on the results of the trial
(All outcomes) Blinding of outcome assessment • All-cause mortality	Low risk Low risk Low risk	Blinding of outcome assessment Missing data were unlikely to have an impact on the results of the trial Outcomes listed in the methods were all reported

Appendices

Bias	Authors'	Support for judgement
SUPPORT (2015)		
Other bias	Low risk	The study data were entered in the sponsor's database. However, full access to all data by the Executive and Steering Committees & then analyses, interpret results, and write the present paper were independently of the sponsor.
Selective reporting	Low risk	Outcomes listed in the methods were all reported
Incomplete outcome data All outcomes	Low risk	Missing data were unlikely to have an impact on the results of the trial
All-cause mortalityOther outcomes	Low risk Low risk	Outcome is unlikely influenced by blinding Blinded outcome assessment
(All outcomes) Blinding of outcome assessment		
Blinding of participants and personnel	Low risk	Participants and personnel were blinded
Allocation concealment	Low risk	in a 1:1 ratio
Random sequence generation	judgement	Computer-generated randomization schedule,
SCOPE (2003) Bias	Authors'	Support for judgement
Other bias	Unclear risk	The role of sponsor was not reported
Selective reporting	Low risk	Outcomes listed in the methods were all reported
Incomplete outcome data All outcomes	Low risk	Missing data were unlikely to have an impact on the results of the trial
All-cause mortalityOther outcomes	Low risk Unclear risk	Outcome measurement is not likely to be influenced by lack of blinding. Blinding of outcome assessment was not described
Blinding of participants and personnel (All outcomes) Blinding of outcome assessment	Low risk	Participants and personnel were blinded
Allocation concealment	Low risk	Masked allocation codes arranged in consecutive numerical order
Random sequence generation	Low risk	Computer-generated random sequence. (Block- randomization with stratification by centre)
Bias	Authors' judgement	Support for judgement
SCAT (2000)	Authors?	Support for judgement
Other bias	Low risk	Data were collected independently of industry sponsors. Statistical analyses were performed by a clinical research organization
Selective reporting	Low risk	Reported all outcomes described in the protocol
Incomplete outcome data All outcomes	Low risk	Missing data may not affect the results. Used ITT
Other outcomes	Low risk	lack of blinding Blinding of outcome assessment
Blinding of participants and personnel Blinding of outcome assessment • All-cause mortality	Low risk Low risk	Participants and personnel were blinded Outcome measurement is not likely to be influenced by
Allocation concealment	Low risk	Sealed envelopes stored at randomization allocation
Random sequence generation	Low risk	The randomization list will be produced by PRA using SAS software
Bias	Authors' judgement	Support for judgement
ROADMAP (2011)		
Other bias	Low risk	Trial was supported by academic institution
All outcomes Selective reporting	Low risk	the analysis of end-points was done by ITT principles Outcomes listed in the methods were all reported
Incomplete outcome data	Low risk	The withdrawal rates between two groups were similar &
All-cause mortality Other outcomes	Low risk Low risk	Outcome is unlikely influenced by blinding Blinding of outcome assessment
(All outcomes) Blinding of outcome assessment		
Blinding of participants and personnel	High risk	Adequate. Quote: Eligible patients got their sequence numbers from the coordinator Open-label design
Allocation concealment	Low risk	

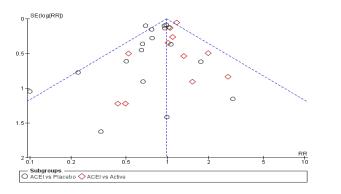
Random sequence generation	Unclear risk	The method of random sequence generation was not described well. Stratified patients by participating institute, sex, and age.
Allocation concealment	Unclear risk	The method of allocation concealment was not reported
Blinding of participants and personnel (All outcomes)	High risk	Open-label design
Blinding of outcome assessment		
 All-cause mortality 	Low risk	Outcome is unlikely influenced by blinding
Other outcomes	Low risk	Blinding end-point assessment
Incomplete outcome data	Low risk	The loss of follow-up was not reported & withdrawal
All outcomes		reasons for treatment group was only reported. Analysis of ITT was used, but after exclusion of some randomized patients
Selective reporting	Low risk	All outcomes reported as planned
Other bias	Low risk	The Statistical Analysis Board will perform statistical analyses independently from all of the sponsors.
TRANSCEND (2008)		
Bias	Authors'	Support for judgement
	judgement	
Random sequence generation	Unclear risk	Inadequate. Randomization was stratified according to site with the use of permuted blocks. However, the method for selecting the blocks was not specified.
Allocation concealment	Low risk	Computerized voice-activated telephone call
Blinding of participants and personnel (All outcomes)	Low risk	Participants and personnel were blinded
Blinding of outcome assessment		
All-cause mortality	Low risk	Outcome is unlikely influenced by blinding
Other outcomes	Low risk	Blinding outcome assessment
Incomplete outcome data	Low risk	Missing data were unlikely to have an impact on the results
All outcomes		of the trial. Analysis was done by ITT
Selective reporting	Low risk	Outcomes listed in the methods were all reported
Other bias	Low risk	Data were collected independently of sponsors. The study sponsor received the data only after the study had been completed
Val-HeFT (2001)		
Bias	Authors'	Support for judgement
	judgement	
Random sequence generation	Unclear risk	Stratified according to whether or not they were receiving a beta-blocker as background therapy. But, the method of generation was not described
Allocation concealment	Unclear risk	Method of allocation concealment not described.
Blinding of participants and personnel (All outcomes)	Low risk	Participants and personnel blinded
Blinding of outcome assessment		
 All-cause mortality Other outcomes 	Low risk Low risk	Outcome is unlikely influenced by blinding Blinding of outcome assessment
Incomplete outcome data	Unclear risk	The loss of follow-up rates was not reported. The type of
•		missing data analysis was not described as ITT. All randomized patients who discontinued prematurely
All outcomes	Low risk	missing data analysis was not described as ITT. All
All outcomes Selective reporting	Low risk High risk	 missing data analysis was not described as ITT. All randomized patients who discontinued prematurely included in analysis. Outcomes listed in the methods were all reported Site monitoring, data collection, and data analysis were
All outcomes Selective reporting Other bias		missing data analysis was not described as ITT. All randomized patients who discontinued prematurely included in analysis. Outcomes listed in the methods were all reported
All outcomes Selective reporting Other bias VALIANT (2003)	High risk	 missing data analysis was not described as ITT. All randomized patients who discontinued prematurely included in analysis. Outcomes listed in the methods were all reported Site monitoring, data collection, and data analysis were performed by Novartis Pharmaceuticals
All outcomes Selective reporting Other bias VALIANT (2003)	High risk Authors'	 missing data analysis was not described as ITT. All randomized patients who discontinued prematurely included in analysis. Outcomes listed in the methods were all reported Site monitoring, data collection, and data analysis were
All outcomes Selective reporting Other bias VALIANT (2003) Bias	High risk	missing data analysis was not described as ITT. All randomized patients who discontinued prematurely included in analysis. Outcomes listed in the methods were all reported Site monitoring, data collection, and data analysis were performed by Novartis Pharmaceuticals Support for judgement Central automated randomization was used to assigned
All outcomes Selective reporting Other bias VALIANT (2003) Bias Random sequence generation	High risk Authors' judgement	missing data analysis was not described as ITT. All randomized patients who discontinued prematurely included in analysis. Outcomes listed in the methods were all reported Site monitoring, data collection, and data analysis were performed by Novartis Pharmaceuticals Support for judgement
All outcomes Selective reporting Other bias VALIANT (2003) Bias Random sequence generation Allocation concealment Blinding of participants and personnel (All outcomes)	High risk Authors' judgement Low risk	missing data analysis was not described as ITT. All randomized patients who discontinued prematurely included in analysis. Outcomes listed in the methods were all reported Site monitoring, data collection, and data analysis were performed by Novartis Pharmaceuticals Support for judgement Central automated randomization was used to assigned study treatment in a 1:1:1 ratio
All outcomes Selective reporting Other bias VALIANT (2003) Bias Random sequence generation Allocation concealment Blinding of participants and personnel (All outcomes)	High risk Authors' judgement Low risk Low risk	missing data analysis was not described as ITT. All randomized patients who discontinued prematurely included in analysis. Outcomes listed in the methods were all reported Site monitoring, data collection, and data analysis were performed by Novartis Pharmaceuticals Support for judgement Central automated randomization was used to assigned study treatment in a 1:1:1 ratio Allocated by interactive voice-response system (IVRS)
All outcomes Selective reporting Other bias VALIANT (2003) Bias Random sequence generation Allocation concealment Blinding of participants and personnel (All outcomes)	High risk Authors' judgement Low risk Low risk Low risk Low risk	missing data analysis was not described as ITT. All randomized patients who discontinued prematurely included in analysis. Outcomes listed in the methods were all reported Site monitoring, data collection, and data analysis were performed by Novartis Pharmaceuticals Support for judgement Central automated randomization was used to assigned study treatment in a 1:1:1 ratio Allocated by interactive voice-response system (IVRS) Participants and personnel were blinded Outcome is unlikely influenced by blinding
All outcomes Selective reporting Other bias VALIANT (2003) Bias Random sequence generation Allocation concealment Blinding of participants and personnel (All outcomes) Blinding of outcome assessment	High risk Authors' judgement Low risk Low risk Low risk	missing data analysis was not described as ITT. All randomized patients who discontinued prematurely included in analysis. Outcomes listed in the methods were all reported Site monitoring, data collection, and data analysis were performed by Novartis Pharmaceuticals Support for judgement Central automated randomization was used to assigned study treatment in a 1:1:1 ratio Allocated by interactive voice-response system (IVRS) Participants and personnel were blinded
All outcomes Selective reporting Other bias VALIANT (2003) Bias Random sequence generation Allocation concealment Blinding of participants and personnel (All outcomes) Blinding of outcome assessment • All-cause mortality • Other outcomes Incomplete outcome data (attrition	High risk Authors' judgement Low risk Low risk Low risk Low risk	missing data analysis was not described as ITT. All randomized patients who discontinued prematurely included in analysis. Outcomes listed in the methods were all reported Site monitoring, data collection, and data analysis were performed by Novartis Pharmaceuticals Support for judgement Central automated randomization was used to assigned study treatment in a 1:1:1 ratio Allocated by interactive voice-response system (IVRS) Participants and personnel were blinded Outcome is unlikely influenced by blinding
All outcomes Selective reporting Other bias VALIANT (2003) Bias Random sequence generation Allocation concealment Blinding of participants and personnel (All outcomes) Blinding of outcome assessment • All-cause mortality • Other outcomes	High risk Authors' judgement Low risk Low risk Low risk Low risk Low risk	missing data analysis was not described as ITT. All randomized patients who discontinued prematurely included in analysis. Outcomes listed in the methods were all reported Site monitoring, data collection, and data analysis were performed by Novartis Pharmaceuticals Support for judgement Central automated randomization was used to assigned study treatment in a 1:1:1 ratio Allocated by interactive voice-response system (IVRS) Participants and personnel were blinded Outcome is unlikely influenced by blinding Blinding of outcome assessment.
All outcomes Selective reporting Other bias VALIANT (2003) Bias Random sequence generation Allocation concealment Blinding of participants and personnel (All outcomes) Blinding of outcome assessment • All-cause mortality • Other outcomes Incomplete outcome data (attrition bias) (All outcomes)	High risk Authors' judgement Low risk Low risk Low risk Low risk Low risk Unclear risk	missing data analysis was not described as ITT. All randomized patients who discontinued prematurely included in analysis. Outcomes listed in the methods were all reported Site monitoring, data collection, and data analysis were performed by Novartis Pharmaceuticals Support for judgement Central automated randomization was used to assigned study treatment in a 1:1:1 ratio Allocated by interactive voice-response system (IVRS) Participants and personnel were blinded Outcome is unlikely influenced by blinding Blinding of outcome assessment. The withdrawal rates were not described. Not all outcomes listed in the method section were

VALUE (2004)	-								
Bias	Authors' judgement	Support for judgement							
Random sequence generation	Low risk	Randomization scheme was generated by computer							
Allocation concealment	Low risk	Computer-generated random sequence centrally prepared by sponsor							
Blinding of participants and personnel (All outcomes)	Low risk	Participants and personnel were blinded							
Blinding of outcome assessment									
 All-cause mortality 	Low risk	Outcome is unlikely influenced by blinding							
Other outcomes	Low risk	Blinding outcome assessment. An endpoint committee blinded to therapy allocation							
Incomplete outcome data All outcomes	Unclear risk	68 patients in 9 centres were excluded after randomization because of good clinical practice deficiencies, and they were not included in intention-to- treat analyses, which might lead some bias							
Selective reporting	Low risk	Outcomes listed in the methods were all reported							
Other bias	High risk	The sponsor managed the data and did all analyses.							
Weil et al. (2013)									
Bias	Authors' judgement	Support for judgement							
Random sequence generation	Low risk	By computer-generated random blocks of <10 subjects stratified by albuminuria category							
Allocation concealment	Unclear risk	The method concealment was not reported							
Blinding of participants and personnel	Low risk	Participants and personnel were blinded							
Blinding of outcome assessment									
All-cause mortality	Low risk	Outcome measurement is not likely to be influenced by lack of blinding							
Other outcomes	Unclear risk	Blinding of outcome assessment not reported							
Incomplete outcome data All outcomes	Low risk	There are no lost to follow-up							
Selective reporting	Low risk	Outcomes listed in the methods were all reported							
Other bias	Low risk	Trial was supported by academic institution							

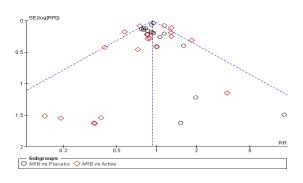


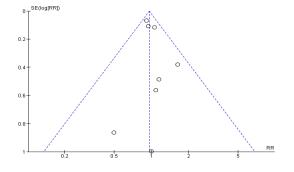
Appendix D: Funnel plots showing comparisons for ACEI versus ARB

Figure D-1 Funnel plots comparing ACEI vs. ARB for risk of myocardial infarction (MI) and angina



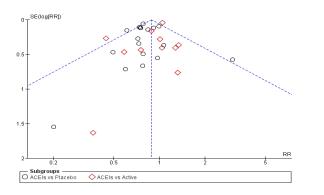
ACEI vs. Placebo or active on risk of stroke



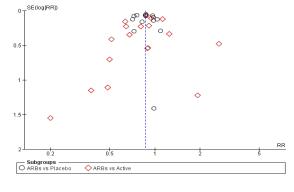


ARB vs. Placebo or active on risk of stroke

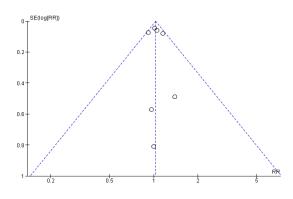
ARBs vs. ACEIs on risk of stroke



ACEIs vs. Placebo or active on risk of HF

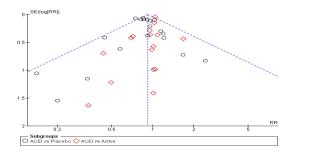


ARB vs. Placebo or active on risk of HF

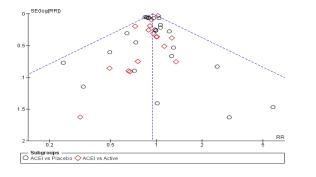


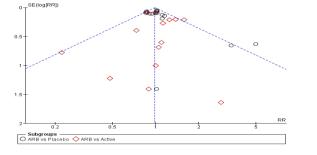
ARB vs ACEI on risk of HF

Figure D-2: Funnel plots comparing ACEI vs. ARB for risk of stroke and

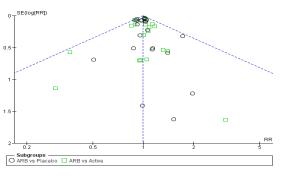




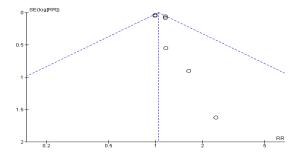




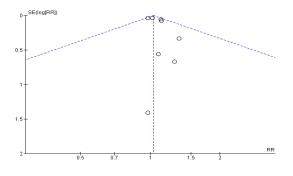
ARB vs. Placebo or active on risk of CV mortality



ARB vs. Placebo or active on risk of all mortality







ARB vs. ACEI on risk of all mortality

ACEI vs. Placebo or active on risk of all- mortality

Figure D- 2 Funnel plots comparing ACEI vs. ARB for risk of CV and all-cause mortality

Appendix E: Source of data and overall quality of each trial

Source of Data						Pre	-defined as))	Overall Quality†					
Trial	All Mortality	CV Mortality	MI	Angina	HF	Stroke	All Mortality	CV Mortality	MI	Angina	HF	Stroke	All Mortality	Other Outcomes
AARDVARK	Published	NR	NR	NR	NR	NR	No						+	NR
ADVANCE	Published	Published	Unpublished	Unpublished	Unpublished	Unpublished	Yes	Yes	Yes‡	Yes‡	Yes‡	Yes‡	+	+
APRES	Published	Published	Published	Published	Published	Published	Yes	Yes	Yes	Yes	Yes	No	+	+
ATLANTIS	Published	NR	Published	Published	NR	NR	No		No	No			+	+
AASK	Published	Published	Published	NR	Published	Published	Yes	Yes	Yes		Yes	Yes	+	+
ABCD	Published	Published	Published	NR	Published	Published	Yes	Yes	Yes		Yes	Yes	±	±
ALLHAT	Published	Published	Published	Published	Published	Published	Yes	Yes	Yes	Yes	Yes	Yes	+	±
ANBP2	Published	Published	Published	NR	Published	Published	Yes	Yes	Yes		Yes	Yes	±	±
BENEDICT	Published	Published	NR	NR	NR	NR	No	No	-				±	±
CCS-I	Published	Published	NR	NR	Published	Published	Yes	Yes			Yes	Yes	±	±
Cai et al	Published	Published	Published	NR	Published	NR	Yes	Yes			Yes		±	±
CAMELOT	Published	Published	Published	Published	Published	Published	Yes	Yes	Yes	Yes	Yes	Yes	±	±
CARMEN	Published	Published	NR	NR	Published	NR	Yes	Yes			Yes		±	±
Chan et al	NR	Published	NR	NR	NR	NR		Yes	Yes‡		Yes‡	Yes‡	NR	±
DEMAND	Published	Published	NR	NR	NR	NR	No	Yes	Yes‡			Yes‡	+	+
DIABHYCAR	Published	Published	Published	Published	Published	Published	Yes	Yes	Yes	Yes	Yes	Yes	+	+
DREAM	Published	Published	Published	Published	Published	Published	Yes	Yes	Yes	Yes	Yes	Yes	+	+
EUROPA	Published	Published	Published	Published	Published	Published	Yes	Yes	Yes	Yes	Yes	Yes	±	±
ELVERA	Published	NR	NR	NR	NR	NR	No						±	NR
ESPIRAL	NR	Published	Published	NR	NR	Published	Yes	Yes	Yes	Yes‡		Yes	NR	±
Fogari et al	Published	Published	Published	Published	NR	Published	No	Yes	Yes			Yes	±	±
HOPE	Published	Published	Published	Published	Published	Published	Yes	Yes	Yes	Yes	Yes	Yes	±	±
Hou et al	Published	NR	Published	NR	Published	Published	No		No		No	No	±	±
HYVET	Published	Published	NR	NR	NR	Published	Yes	Yes				Yes	+	±
IMAGINE	Published	Published	Published	Published	Published	Published	Yes	Yes	Yes	Yes	Yes	Yes	+	+

JAMP	Published	Published	Published	Published	Published	NR	Yes	Yes	Yes	Yes	Yes		±	±
JMIC-B	Published	Published	Published	Published	Published	Published	Yes	Yes	Yes	Yes	Yes	Yes	+	+
J-MIND	NR	NR	Published	Published	Published	Published			Yes	Yes	Yes	Yes	NR	±
PART-2	Published	Published	Published	Published	Published	Published	Yes	Yes	Yes	Yes	Yes	Yes	+	+
PEACE	Published	Published	Published	Uunpublished	Published	Published	Yes	Yes	Yes	Yes	Yes	Yes	±	±
PEP-CHF	Published	Published	NR	NR	Published	NR	Yes	Yes			Yes		+	+
PHARAO	Published	Published	Published	NR	Published	Published	Yes	Yes	Yes		Yes	Yes	+	+
PREAMI	Published	NR	NR	NR	Published	NR	Yes	Yes‡	Yes‡	Yes‡	Yes	Yes‡	+	+
PREVEND IT	Published	Published	Published	NR	Published	Published	Yes	Yes	Yes		Yes	Yes	+	+
PROGRESS	NR	Published	Published	NR	NR	Published	Yes	Yes	Yes	Yes	Yes	Yes	+	+
PHYLLIS	NR	NR	Published	NR	NR	NR			No				NR	+
QUIET	Published	Published	Published	Published	NR	Published	Yes	Yes	Yes	Yes		No	±	±
QUO VADIS	Published	Published	Published [¥]	Published [¥]	Published	Published [¥]	NR	Yes	Yes	Yes	No	Yes	±	±
RASS	Published	NR	NR	NR	NR	NR	No						+	NR
SCAT	Published	Published	Published	Published	NR	Published	Yes	Yes	Yes	Yes		Yes	+	±

Source of data							Pre-defined as outcome (Yes or No)						Overall Quality†	
Trial	All Mortality	CV Mortality	MI	Angina	HF	Stroke	All Mortality	CV Mortality	MI	Angina	HF	Stroke	All Mortality	Other outcomes
4 C	Published	Published	Published	Published	Published	Published	Yes	Yes	Yes	Yes	Yes	Yes	±	±
ACTIVE-I	Published	Published	Published	NR	Published	Published	Yes	Yes	Yes		Yes	Yes	+	+
ANTIPAF	Published	NR	Published	Published	Published	Published	No	No	No	No	No	No	+	+
ALPINE	NR	NR	Published	NR	NR	Published			No			No	NR	±
ATTEMPT- CVD	NR	NR	Published	Published	Published	Published			Yes	Yes	Yes	Yes	NR	+
CHARM-Added	Published	Published	Published	Unpublished	Published	Published	Yes	Yes	Yes	No	Yes	Yes	+	+
CHARM- Alternative	Published	Published	Published	Unpublished	Published	Published	Yes	Yes	Yes	No	Yes	Yes	+	+
CHARM- Preserved	Published	Published	Published	Unpublished	Published	Published	Yes	Yes	Yes	No	Yes	Yes	+	+
CARP	Published	Published	Published	NR	Published	Published	Yes	Yes	Yes		Yes	Yes	±	±
CASE-J	Published	NR	Published	Published	Published	Published	Yes		Yes	Yes	Yes	Yes	+	+
COPE	Published	NR	NR	NR	NR	Published	Yes	Yes‡	Yes‡	Yes‡	Yes‡	Yes	+	+
CHIEF	Published	Published	Published	Published	Published	Published	Yes						+	+
DIRECT- Prevent 1	Published	NR	NR	NR	NR	NR	No						+	NR
DIRECT- Protect 1	Published	NR	NR	NR	NR	NR	No						+	NR
DIRECT- Protect 2	Published	NR	NR	NR	NR	NR	No						+	NR
Dahl et al	Published	NR	NR	NR	NR	NR	No						±	NR
EFFERVESCENT	Published	NR	NR	NR	NR	Published	No					No	+	+
E-COST	Published	Published	Published	NR	Published	Published	Yes	Yes	Yes		Yes	Yes	-	-

Table E- 2 Source of data and overall quality of each ARBs trial

E-COST-R	Published	Published	Published	NR	Published	Published	Yes	Yes	Yes		Yes	Yes	±	±
Fang Wu et	NR	NR	Published	NR	NR	Published			Yes			Yes	NR	±
GISSI-AF	Published	NR	NR	NR	NR	Published	Yes					Yes	+	±
HOPE-3	Published	Published	Published	Published	Published	Published	Yes	Yes	Yes	Yes	Yes	Yes	+	+
HIJ-CREATE	Published	Published	Published	Published	Published	Published	Yes	Yes	Yes	Yes	Yes	Yes	±	±
HONG-KONG	Published	Published	NR	NR	Published	NR	No	No			No		±	±
IDNT	Published	Published	Published	Unpublished	Published	Published	Yes	Yes	Yes	No	Yes	Yes	+	+
I-PRESERVE	Published	Published	Published	Published	Published	Published	Yes	Yes	Yes	Yes	Yes	Yes	+	+
IRMA-2	Unpublished	NR	Unpublished	Unpublished	NR	NR	No		No	No			±	±
J-RHYTHM II	NR	Published	Published	NR	Published	Published		Yes	Yes		Yes	Yes	NR	±
KACT-MetS	NR	NR	Published	NR	NR	NR			No				NR	±
Kawamura	NR	NR	NR	NR	Published	Published					No	No	NR	±
LAARS	NR	NR	NR	Published	NR	NR				No			NR	±
LIFE	Published	Published	Published	Published	Published	Unpublished	Yes	Yes	Yes	Yes	Yes	Yes	+	+
MITEC	Published	Published	NR	NR	NR	NR	No	No					±	±
MOSES	Published	NR	Published	NR	Published	Published	Yes		Yes		Yes	Yes	+	+
NAVIGATOR	Published	Published	Published	Published	Published	Published	Yes	Yes	Yes	Yes	Yes	Yes	+	+
NTP-AF study	NR	Published	Published	NR	Published	Published		Yes	Yes		Yes	Yes	NR	±
ORIENT	Published	Published	Unpublished	Published	Published	Unpublished	Yes	Yes	Yes	Yes	Yes	Yes	+	+
OLIVUS	Published	Published	Published	Published	Published	Published	Yes	Yes	Yes	Yes	Yes	Yes	±	±
PRoFESS	Published	Published	Published	NR	Published	Published	Yes	Yes	Yes		Yes	Yes	±	±
PREVER-	NR	NR	Published	NR	NR	Published	Yes	Yes	Yes	Yes	Yes	Yes	+	+
treatment														
RASS	Published	NR	NR	NR	NR	NR	No						+	NR
RENAAL	Published	Published	Published	Unpublished	Published	Unpublished	Yes	Yes	Yes	Yes	Yes	Yes	+	+
ROADMAP	Published	Published	Unpublished	NR	Published	Unpublished	Yes	Yes	Yes	Yes‡	Yes‡	Yes	+	+
SCOPE	Published	Published	Published	NR	NR	Published	Yes	Yes	Yes			Yes	+	+
SUPPORT	Published	Published	Published	NR	Published	Published	Yes	Yes	Yes		Yes	Yes	±	±
TRANSCEND	Published	Published	Published	Published	Published	Published	Yes	Yes	Yes	Yes	Yes	Yes	+	±

Val-HeFT	Published	Unpublished	Unpublished	Unpublished	Published	NR	Yes	Yes			Yes		±	±	
VALUE	Published	Published	Published	Published	Published	Published	Yes	Yes	Yes	No	Yes	Yes	+	+	
Weil et al	Published	Published	NR	NR	NR	NR	No	No					±	±	

For studies synonyms, see list of abbreviations/abbreviations.

† Represents risk of bias in key domains: sequence generation, allocation concealment and blinding of outcome assessment. (+) low risk of bias, (±) unclear risk & (-) high risk of bias ¥ Reported as total events; ‡ Outcome was reported as composite endpoint; NR=Not Reported

Table E- 3 Source of data and overall quality of each ARBs versus ACEIs trial.

Trial			Sour	Pro	e-defined a	Overall Quality †								
	All Mortality	CV Mortality	MI	Angina	HF	Stroke	All Mortality	CV Mortality	MI	Angina	HF	Stroke	All mortality	Other outcomes
CORD 1 B	Published	NR	Published	NR	NR	Published	No		No			No	-	-
DETAIL	Published	Published	Published	NR	Published	Unpublished	Yes	Yes	Yes		Yes	Yes	+	±
ELITE II	Published	Published	Published	NR	Published	Published	Yes	Yes	Yes	Yes‡	Yes		±	±
HONG-KONG DHF	Published	Published	NR	NR	Published	NR							±	±
LIRICO	Published	Published	Published	Published	NR	Published	Yes	Yes	Yes	Yes		Yes	+	+
ONTARGET	Published	Published	Published	Published	Published	Published	Yes	Yes	Yes	Yes	Yes	Yes	+	+
OPTIMAAL	Published	Published	Published	NR	Published	Published	Yes	Yes	Yes		Yes	Yes	+	+
PARADIGM-HF	Published	Published	Unpublished	Unpublished	Published	Unpublished	Yes	Yes	Yes	No	Yes	Yes	+	+
RASS	Published	NR	NR	NR	NR	NR	No						+	NR
ROAD	Published	Published	Published	NR	Published	Published	No	No	No		No	No	+	+
VALIANT	Published	Published	Unpublished	Unpublished	Unpublished	Published	Yes	Yes	Yes	Yes	Yes	Yes	+	+

For studies synonyms, see list of abbreviations/abbreviations; ‡ Outcome was reported as composite endpoint

† Represents risk of bias in key domains: sequence generation, allocation concealment & blinding of outcome assessment. (+) low risk of bias, (±) unclear risk & (-) high risk of bias

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