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

A thesis By

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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; I^2=26%) and 9% (RR, 0.91; 95% CI 0.85-1.00; p=0.05; I^2=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; I^2=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; I^2=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 (I^2=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; I^2=0%) and all mortality risk (RR, 1.03; 95% CI 0.98-1.08; p=0.20; I^2=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.

Table of Contents

List of Tables

List of Figures

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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
≤	Less than or equal to
≥	Greater than or equal to
4 C	Candesartan for Prevention of Cardiovascular Events After Cypher or 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
ACEI	Angiotensin-converting enzyme inhibitor
ACTIVE I	Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of 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
CCB	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

CHF	Congestive heart failure
CONSORT	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	European Trial on Reduction of Cardiac Events with Perindopril in 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 Miocardico-Atrial Fibrillation
HBPM	Home Blood Pressure Monitoring
HCTZ	Hydrochlorothiazide
HFrEF	HF with reduced ejection fraction
HFpEF	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 DHF	Hong Kong diastolic heart failure
HOPE	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	Ischemic heart disease
IMAGINE	Ischemia Management with Accupril Post– Bypass Graft Via Inhibition 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
LAARS	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 Nitrendipine for Secondary Prevention
MRC	Medical Research Council Trial of Treatment for Mild Hypertension
NAGOYA HEART	Comparison between valsartan and amlodipine regarding morbidity 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 Trial
PAI-1	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-treatment	Prevention of Hypertension in Patients with Pre-Hypertension
PROBE	Prospective, randomized open blinded-endpoint
PRoFESS	Prevention Regimen for Effectively Avoiding Second Strokes
PROGRESS	Perindopril Protection Against Recurrent Stroke Study
PTCA	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.

Alosaimi, Manal; Roos, Nur Aishah Che; Alnakhli, Anwar Mansour; Cleland, John; Padmanabhan, Sandosh. **Impact of Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers on Coronary Heart Disease Events: A Systematic Review and Meta-Analysis of 299,871 Patients**, Journal of Hypertension: April 2021 - Volume 39 - p e200.

Alosaimi, Manal; Roos, Nur Aishah Che; Alnakhli, Anwar Mansour; Cleland, John; Padmanabhan, Sandosh. **Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers in Stroke Prevention: A Systematic Review and Meta-Analysis Involving 297,451 Patients**, Journal of Hypertension: April 2021 - Volume 39 -p e184.

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).

1.1.2 The 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 AT_1-receptors, 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.

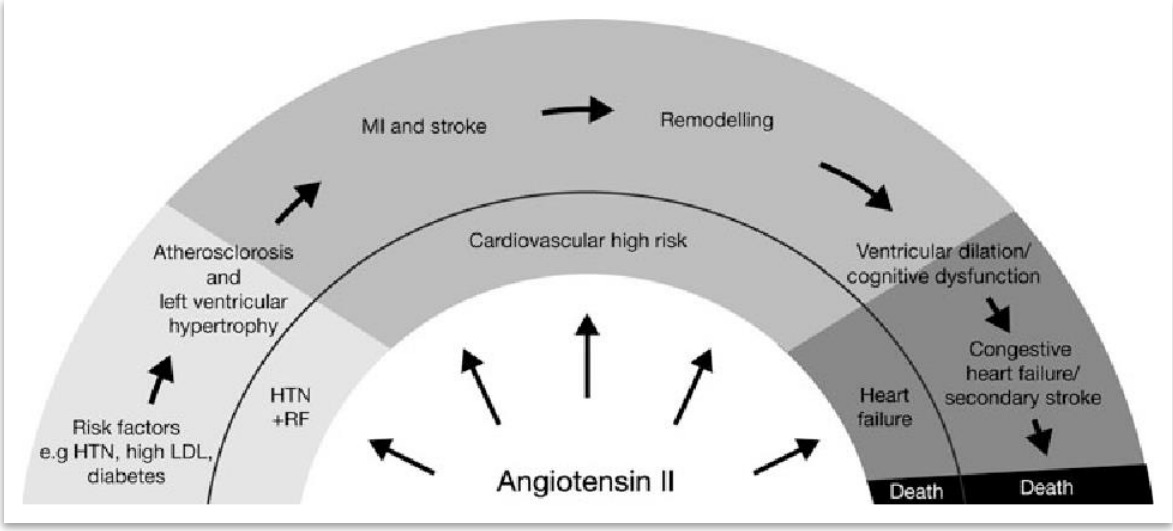


Figure 1-1 Cardiovascular Diseases Continuum (CVDC)

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 ≥140 mm Hg and/or their diastolic blood pressure (DBP) is ≥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 ≥130 and/or DBP ≥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)

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

NICE (2019) - United Kingdom	
Clinic	SBP ≥140 and/or DBP ≥90
ABPM (Daytime)	SBP ≥135 and/or DBP ≥85
HBPM	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
HBPM	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
HBPM	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

1.2.2 Global burden of hypertension

Generally, an elevated level of systolic blood pressure (SBP) of ≥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). 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 (≥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.

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

	BP (mmHg) grading			
Other risk factor, HMOD or disease	**High-normal SBP 130-139 DBP 85-89**	**Grade 1 SBP 140-159 DBP 90-99**	**Grade 2 SBP 160-179 DBP 100-109**	**Grade 3 SBP ≥ 180 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 risk	Moderate to high risk	High risk	High risk
HMOD, CKD (grade 3) or DM without organ damage	Moderate to high risk	High risk	High risk	High to very high risk
Established CVD, CKD (grade ≥ 4) or DM with organ damage	Very high risk	Very high risk	Very high risk	Very high risk

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 step-care 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.

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

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

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 for antihypertensive agents[‡]

	Recommended Drugs				
Compelling indications	**Diuretic**	**BB**	**ACEI**	**ARB**	**CCB**
HFrEF	●[a]	●	●	●	
Post-MI		●	●	●	
High coronary diseases risk	●	●	●	●	
DM	●[a]		●	●	●
CKD	●[a]		●	●	●
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).

[a] Using a loop-diuretic when eGFR is <30ml/min/1.72m^2; [b] Thiazide-like diuretic; [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 were recognized by Skeggs et al. (1954) called: angiotensin I (Ang I) and 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-amino-acid 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 angiotensin-converting 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 AT_1 and AT_2 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 AT_4 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 AT_4 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.

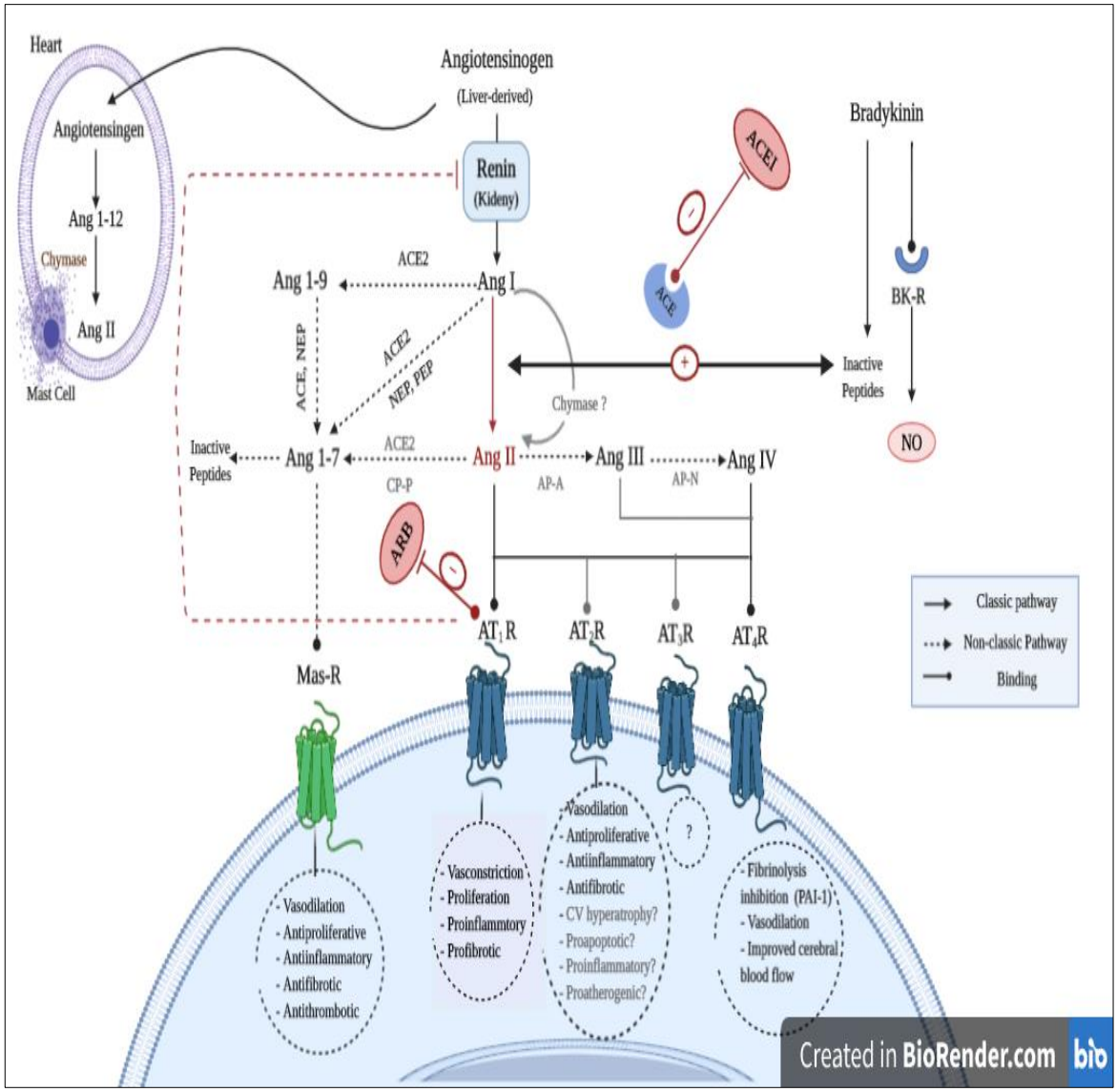


Figure 1-2 Classical and non-classical renin-angiotensin system (RAS) pathway and its inhibition

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).

Table 1-5 Summary of pharmacological properties of ACEIs

	Drug	Active metabolite	Protein-bound fraction (%)	Elimination Half-life (h)	Renal elimination (%)	Bradykinin/Ang-I selectivity ratio
Sulfhydryl-containing	Captopril	None	25-30	2	95	NA
	Zofenopril*	Zofenoprilat	NA	4.5	60**	NA
Carboxyl-containing	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
	Perindopril*	Perindoprilat	60	>24	75	1.44
	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-containing	Fosinopril*	Fosinoprilat	NA	12	50**	NA

*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.

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

		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]		

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

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

[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 AT_1 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 AT_1 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 AT_1 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).

Table 1-7 Summary of pharmacologic characteristics of ARBs

Drug	Antagonism type	Active metabolite	Half-life (h)	Dosing frequency (h)	Protein binding (%)	Bioavailability (%)	Route of elimination (%)
Losartan	S	Yes	2	q.d. or b.i.d.	98.7	33	**b:** 70; **r:** 30
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 cilexetil	I	Yes	9-12	q.d. or b.i.d.	99.5	42	**b:** 40; **r:** 60
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).

Table 1-8 Approved indications for eight currently available ARBs

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

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: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm (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 AT_1 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 AT_1 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. AT_2 stimulation may have proinflammatory, hypertrophic, proatherogenic and proapoptotic actions on CV tissue. The expression of AT_2 in isolated cardiomyocytes resulted cardiac hypertrophy. Moreover, the overexpression of AT_2 does not antagonize AT_1 receptor–mediated hypertrophy by Ang-II (D'Amore et al., 2005).

One of main concerns related to the activation of the AT_2 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 AT_2 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 AT_1 and AT_2 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 cardio-protective effects than ARBs. The apoptosis effects mediated by AT_2 & 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 non-beneficial 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 losartan-based 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 patient-years 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.

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

Study	ACEI vs. placebo					ARB vs placebo				
	MI	CV mortality	All-mortality	HF	N	MI	CV mortality	All-mortality	HF	N
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	**NA**				

Values indicate risk ratio (95% confidence interval)

1.7 Aim and objectives of the thesis

1.7.1 Aims

1) 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:

1) 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 pre-specified 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
2. 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 http://rayyan.qcri.org (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 follow-up 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:

$$\Delta \boldsymbol{SBP} = (\boldsymbol{SBP_0} - \boldsymbol{SBP_2}) - (\boldsymbol{SBP_0} - \boldsymbol{SBP_1})$$

Where;

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

SBP_0= Baseline mean SBP (at randomization)

SBP_1= SBP of final follow-up for intervention arm

SBP_2= 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 (Tau^2) (Borenstein et al., 2010). The method developed by DerSimonian and Laird (method of moment) is used to estimate Tau^2 (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): $\mathrm{RRR} = 100\% \times (1 - \mathrm{RR})$. 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 Chi^2) test, also known as the Q-statistic 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 p-value 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 I^2 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 I^2 value lies between 0% (indicates no observed heterogeneity) and 100% (indicates increasing heterogeneity). The following is a rough guide to an interpreted I^2 (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% to 100%:** considerable heterogeneity.

Significant heterogeneity is typically considered present if I^2 is ≥ 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 Tau^2 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 trial-level 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 (Thomposon 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 (Tau^2), the restricted maximum likelihood (REML) method was used. Tau^2 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 Tau^2 statistical value, or by testing the hypothesis of $Tau^2=0$). 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 (Tau^2 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)**.

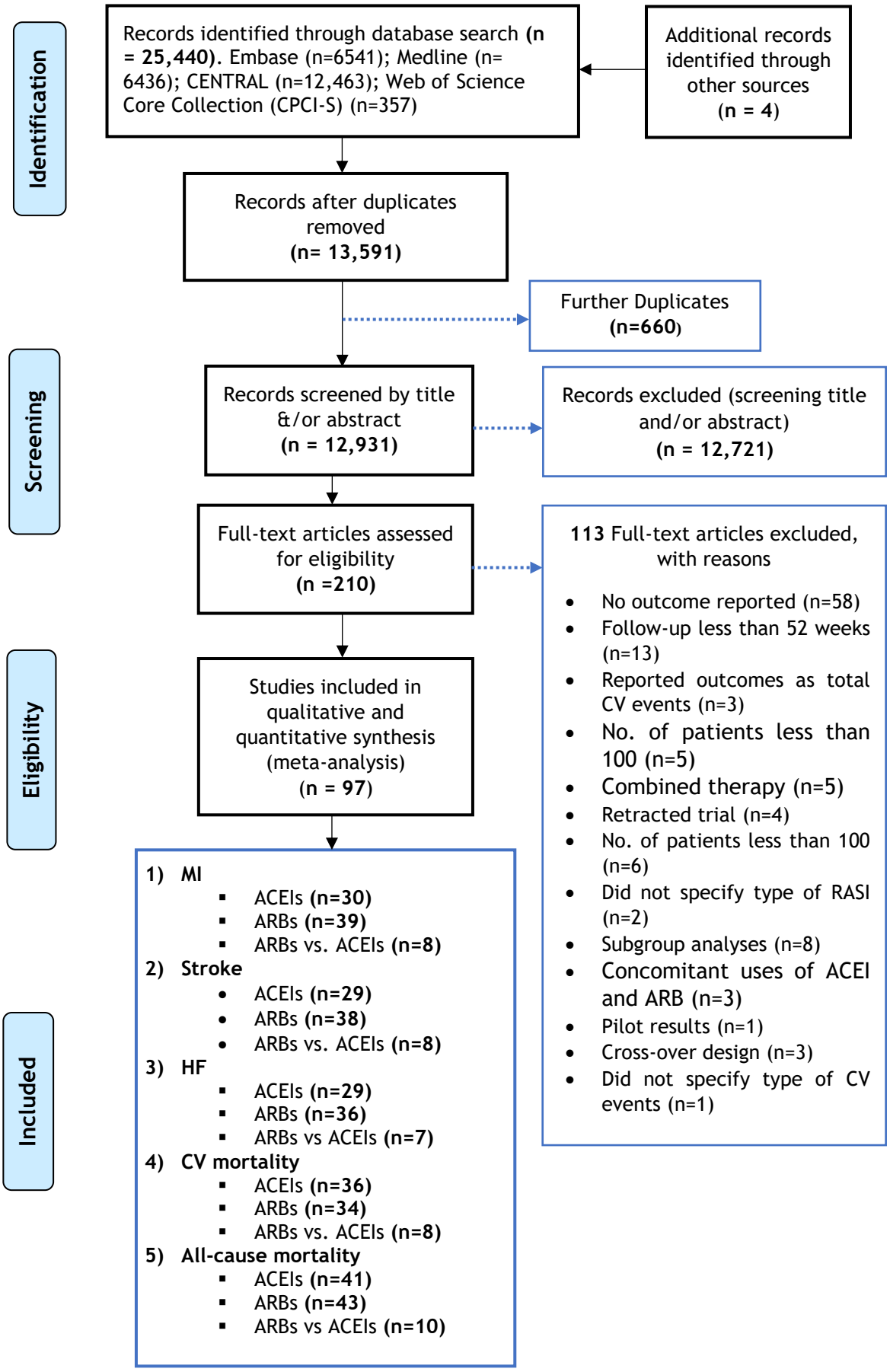


Figure 3-1 PRISMA Study flow diagram

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.

Table 3-1 Reasons for excluding studies (ordered by study ID)

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	(Iino 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)

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 high-affinity 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 (ADVANCE, 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 ≥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 surrogate-endpoints 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).**

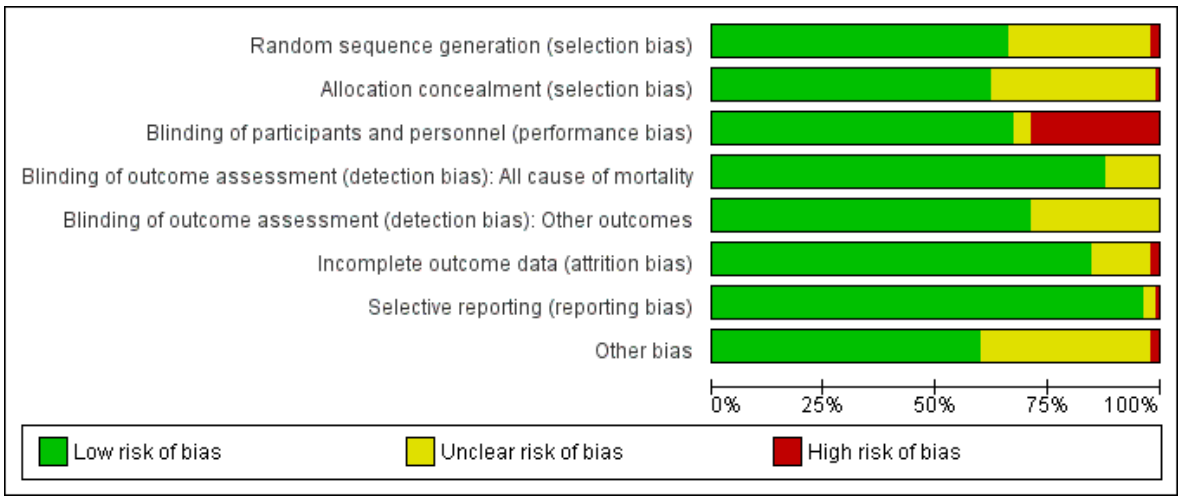


Figure 3-2 Risk of bias graph review authors' judgements about each risk of bias item presented as percentages across all included studies.

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.

3.3.2 Blinding

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 well-designed 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 AT_1 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 pre-specified 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 pre-specified 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 follow-up 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.).

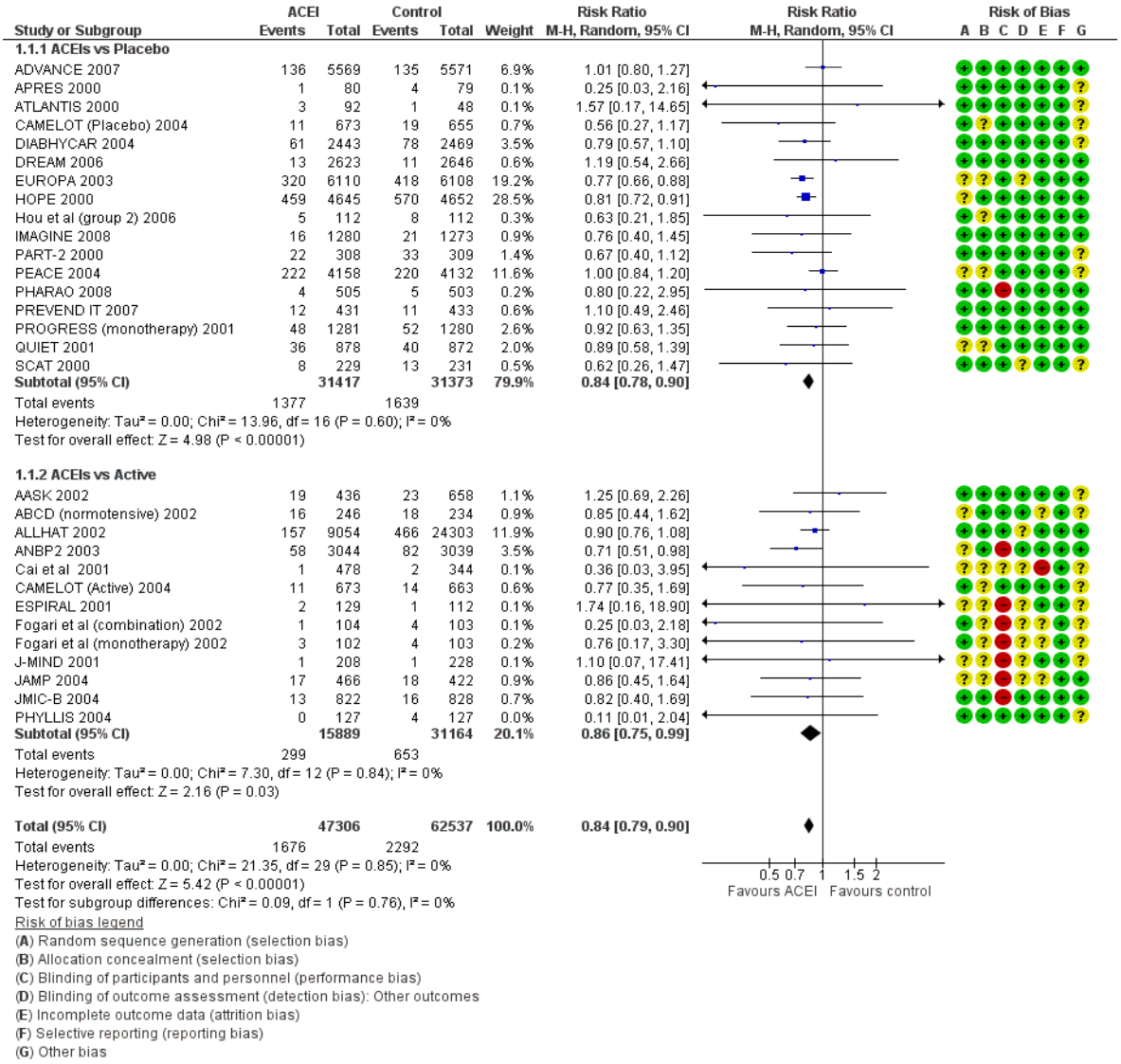


Figure 4-1 Forest plot showing effect of ACEIs on risk of MI, stratified by comparison group (placebo vs. active). Overall: 30 trials [RE model]

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

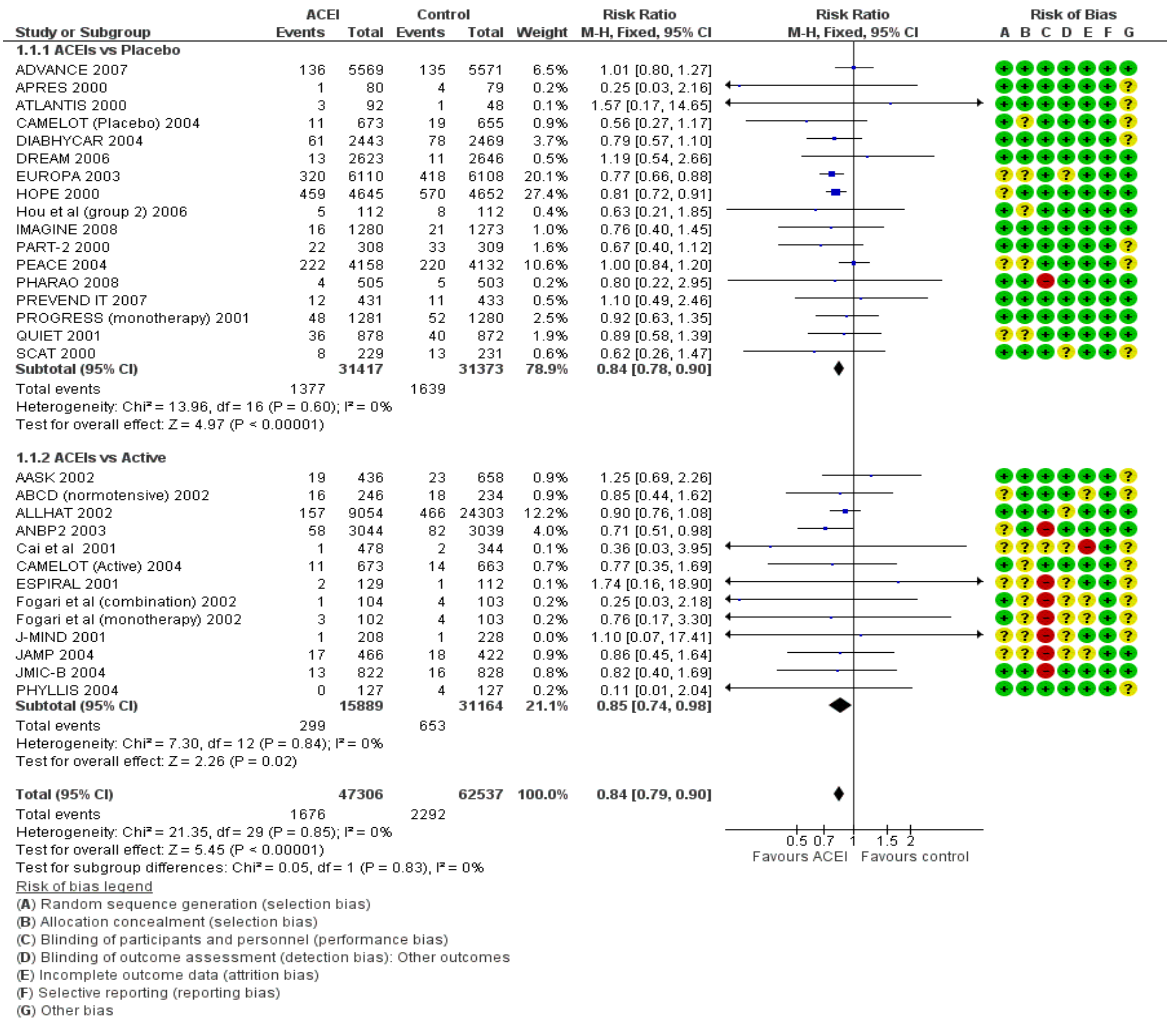


Figure 4-2 Forest plot showing effect of ACEIs on risk of MI, stratified by comparison group (placebo vs. active). Overall: 30 trials (FE model)

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 quality (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.

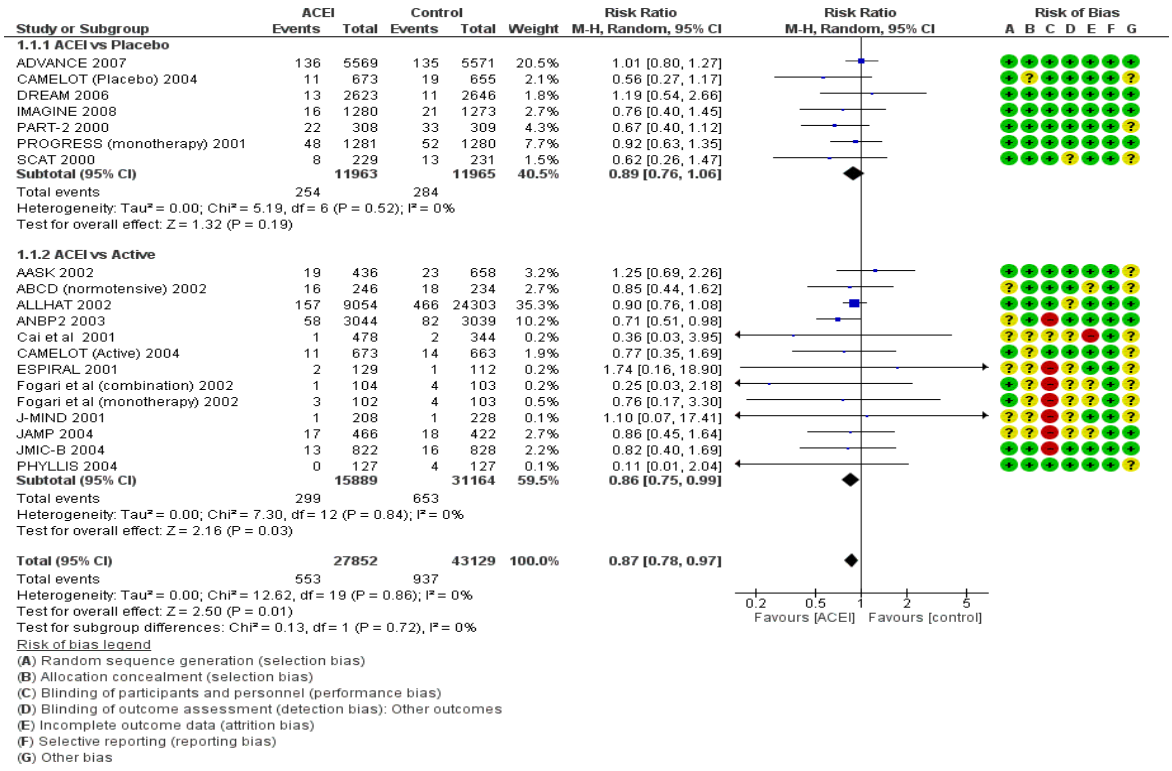


Figure 4-3 Forest plot showing the effect of ACEIs on risk of MI [Sensitivity analysis: Excluding trials with naïve participants]. Overall: 20 trials (RE model).

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

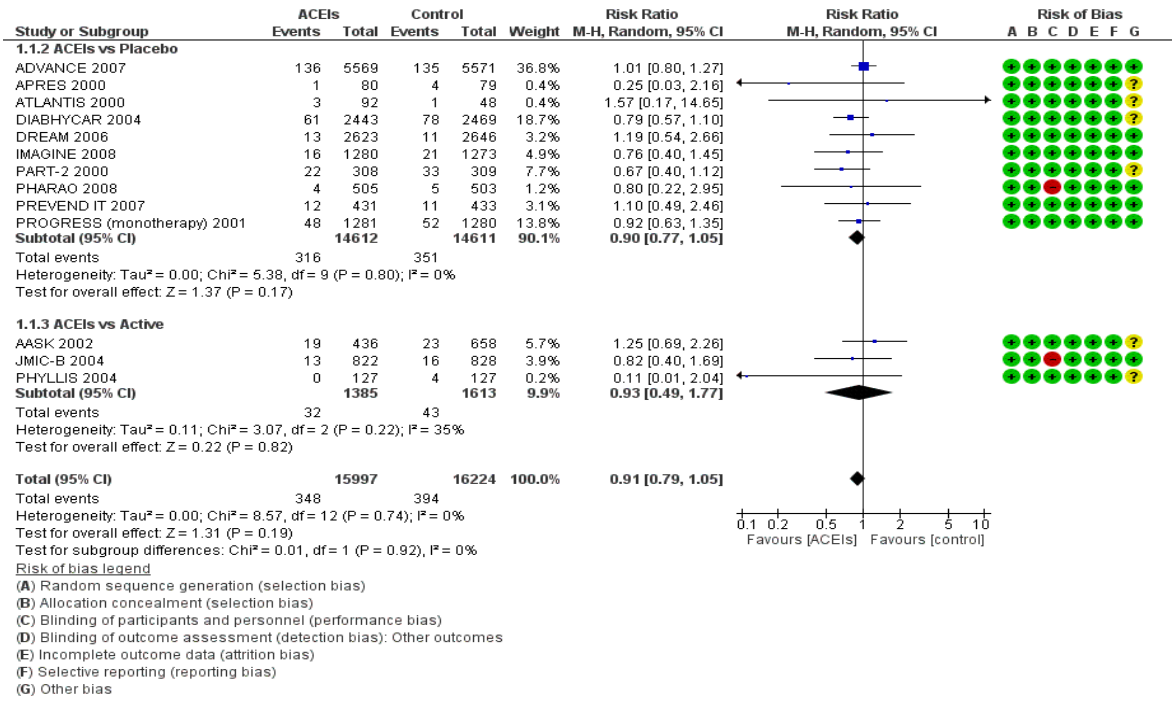


Figure 4-4 Forest plot showing effect of ACEIs on risk of MI [Sensitivity analysis: Excluding trials with low methodological quality]. Overall: 13 trials (RE model)

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

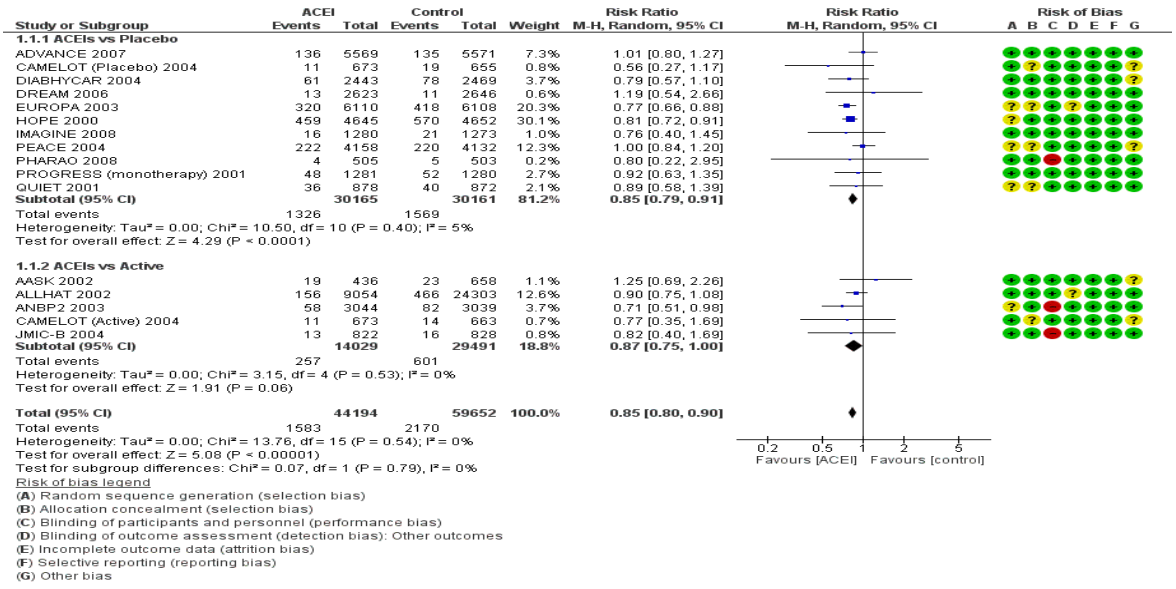


Figure 4-5 Forest plot showing effect of ACEIs on risk of MI [Sensitivity analysis: Excluding trials with small sample size]. Overall: 16 trials (RE model)

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 risk of 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 ± 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 †

Subgroup analysis		Studies	Participant	Event	MI Incidence (%)		RR (M-H, Random, 95% CI)	P value*	(I^2 %) ‡
					ACEI	Control			
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
Active control	**DHP CCBs**	9	23310	543	1.88	2.00	0.92 (0.77-1.11)	0.40	0
	Diuretics	3	30646	453	1.75	2.00	0.80 (0.61-1.05)	0.11	0
	Active control	3	2587	75	2.68	3.14	0.93 (0.59-1.45)	0.74	0
Clinical setting	**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
	Non- nephropathy	3	1329	39	2.82	3.05	0.94 [0.50-1.75]	0.84	0
	CVA**	1	2561	100	3.74	4.07	0.92 [0.63-1.35]**	0.68	--
Mean age group	**< 65 years**	22	40170	1626	3.70	4.37	0.84 [0.76-0.93]	**0.0004***	0
	≥ 65 years	7	69000	2331	3.47	3.31	0.85 [0.78-0.92]	**<0.0001***	0

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

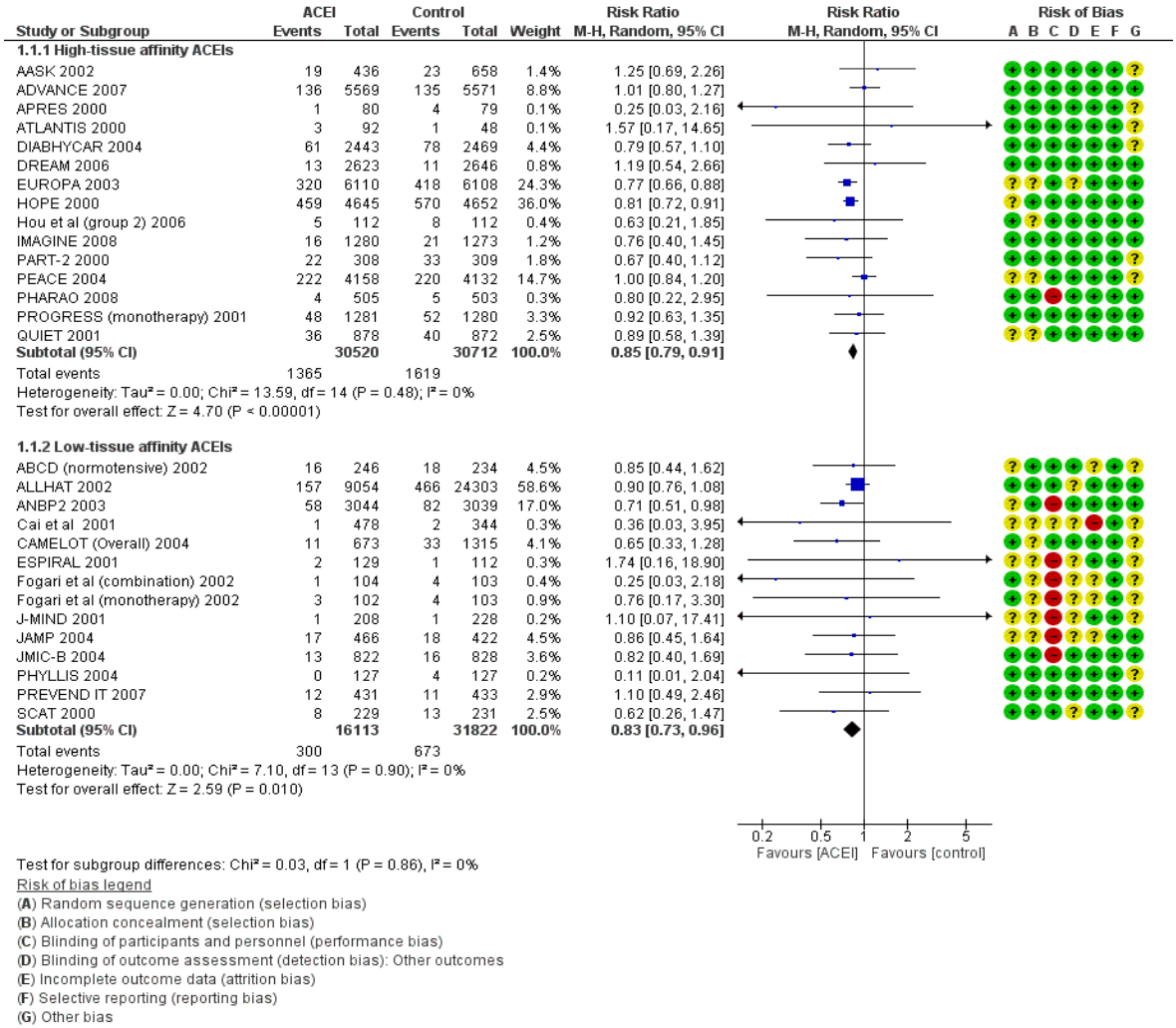


Figure 4-6 Forest plot showing effect of ACEIs on risk of MI (RE model). [Subgroup: Low vs. high-tissue affinity ACEIs]

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

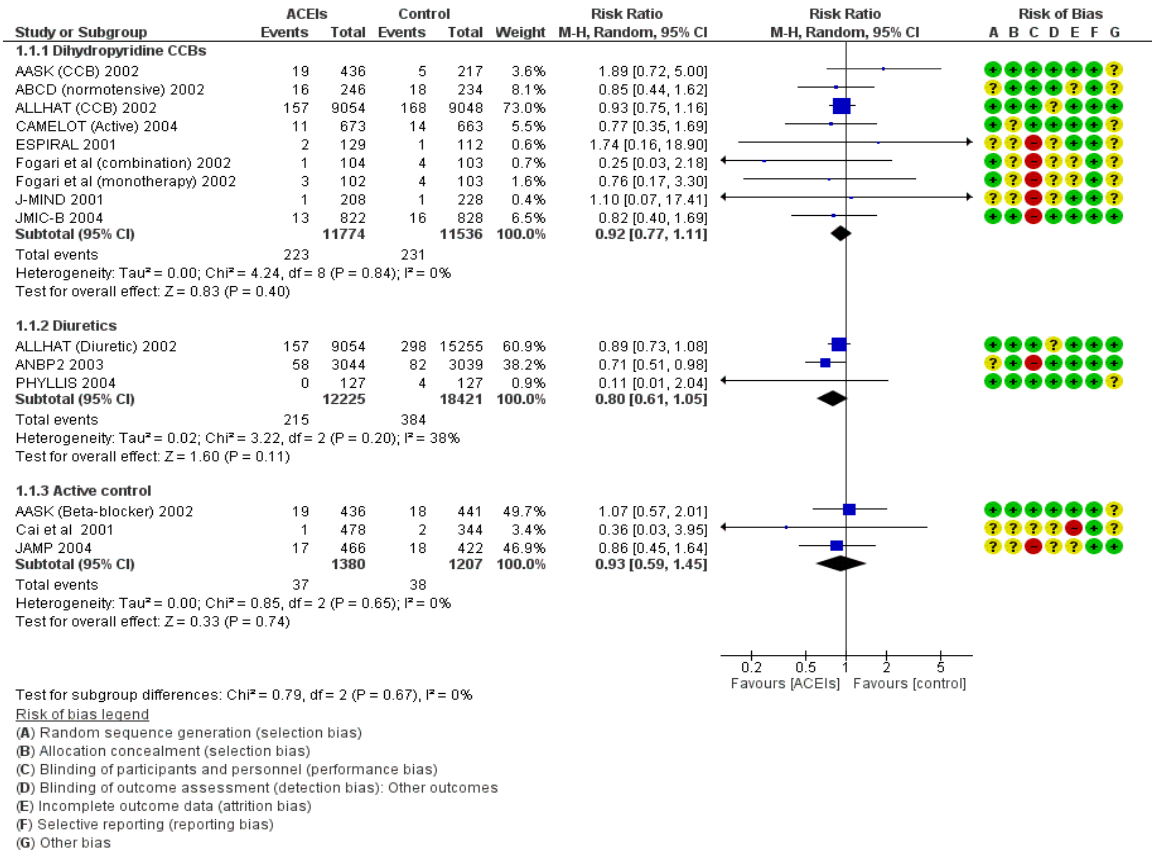


Figure 4-7 Forest plot showing effect of ACEIs on risk of MI (RE model). [Subgroup: Class of active control]

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

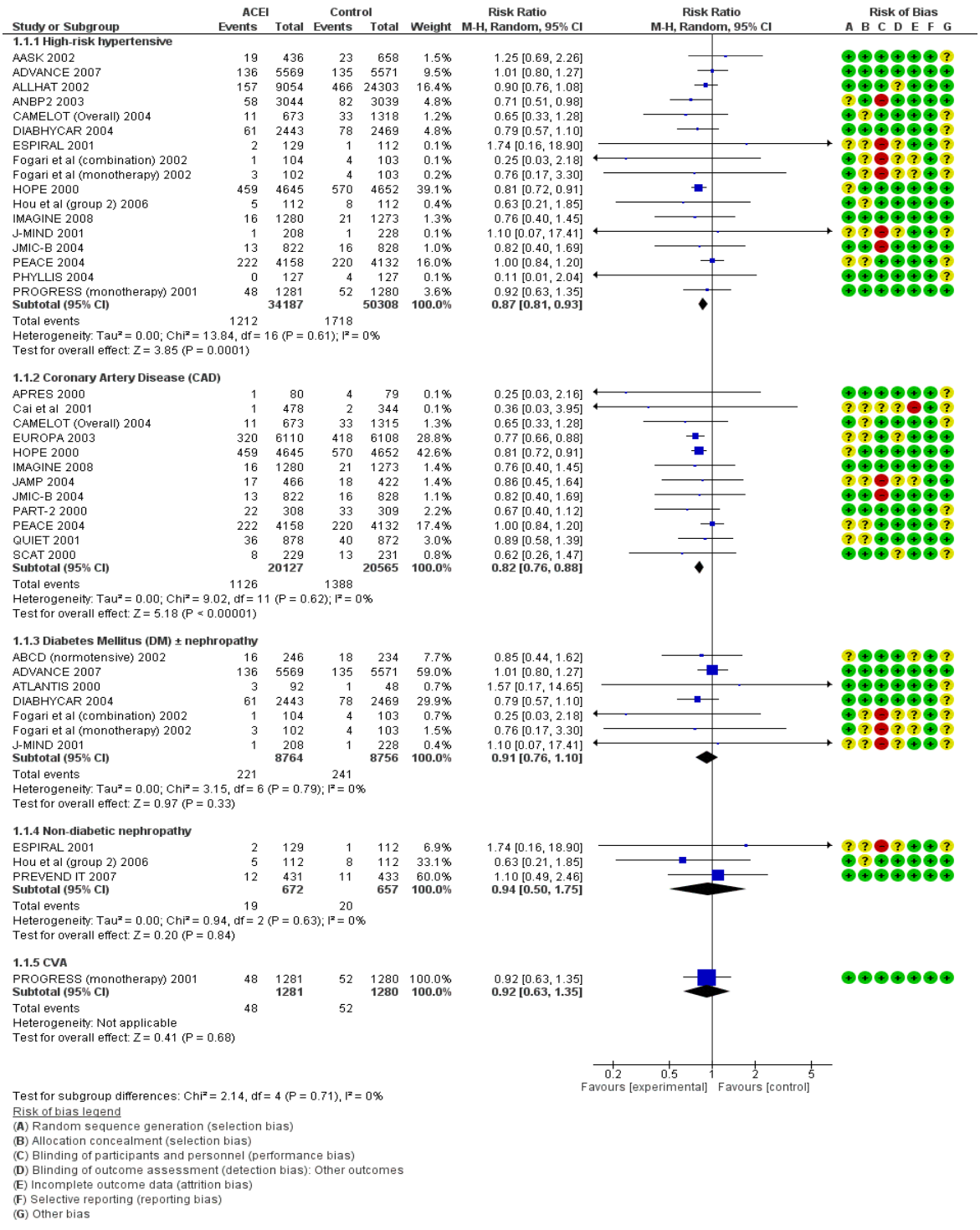


Figure 4-8 Forest plot showing effect of ACEIs on risk of MI (RE model). [Subgroup analysis: Clinical setting].

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

4.5.1 Overall 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**.** Sub-group 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 active-controlled 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.

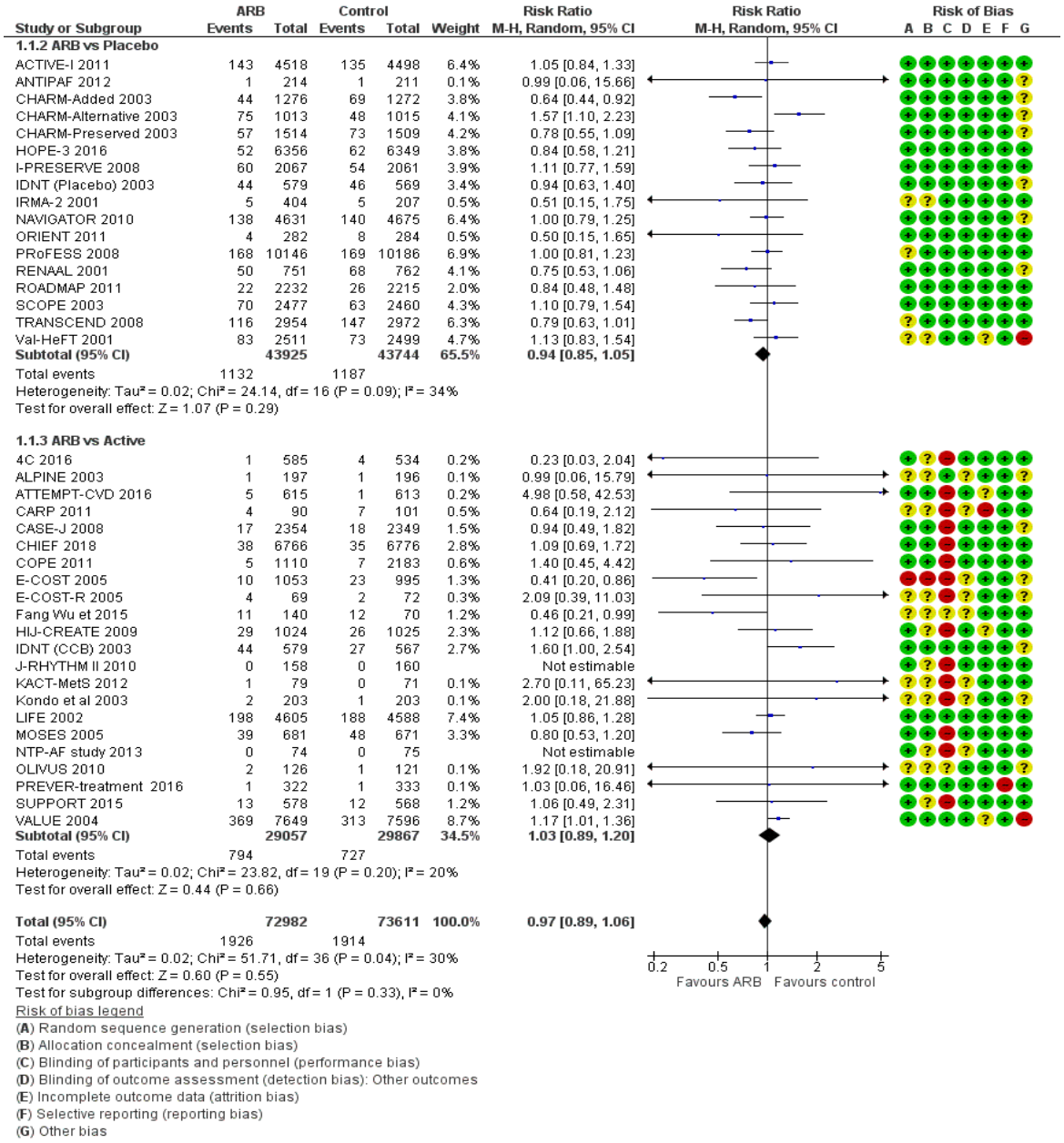


Figure 4-9 Forest plot showing effect of ARBs on risk of MI, stratified by comparison group (placebo vs. active). Overall: 39 trials (RE model)

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

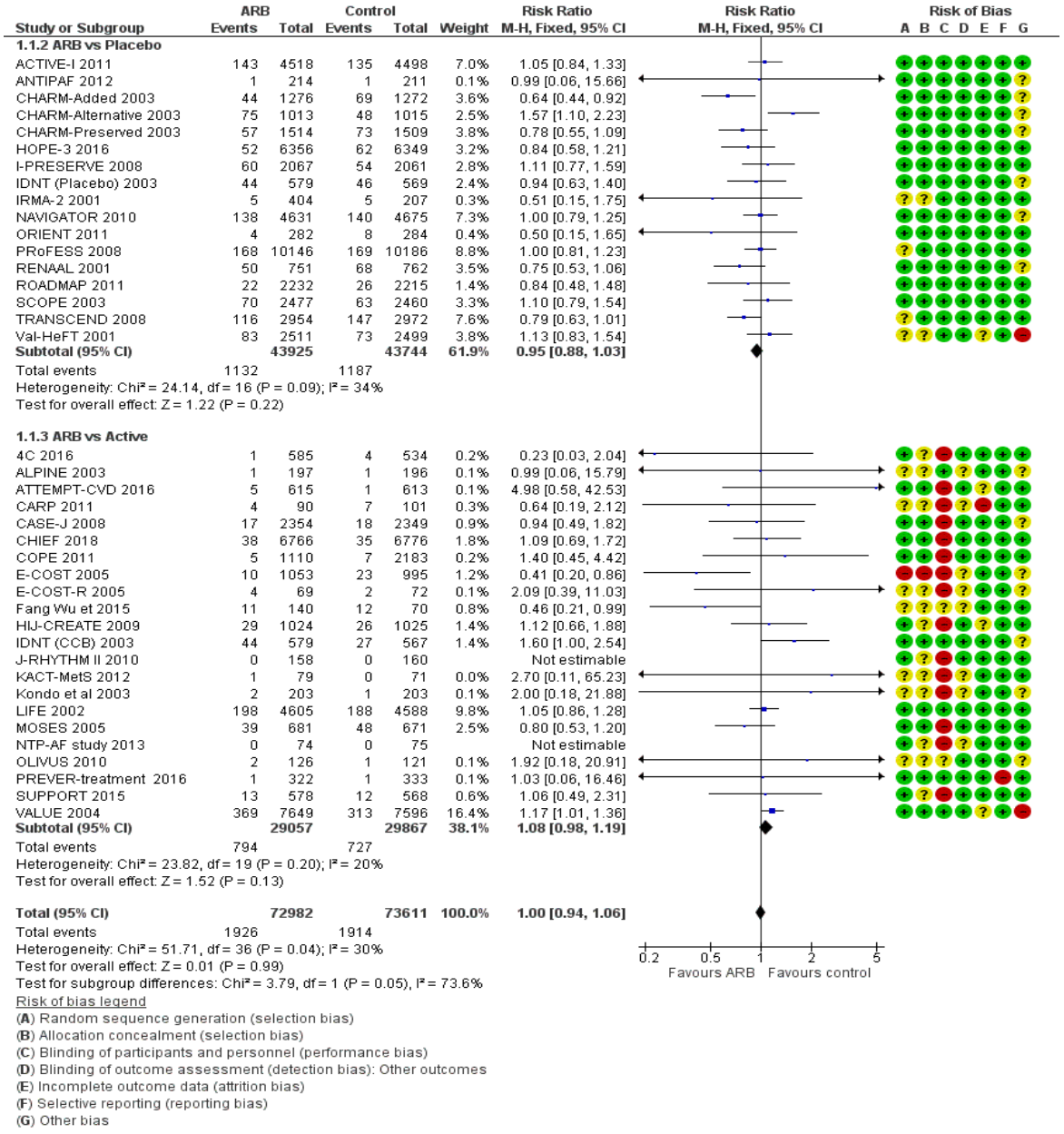


Figure 4-10 Forest plot showing effect of ARBs on risk of MI, stratified by comparison group (placebo vs. active). Overall: 38 trials (FE model)

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 I^2 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 placebo-controlled 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).

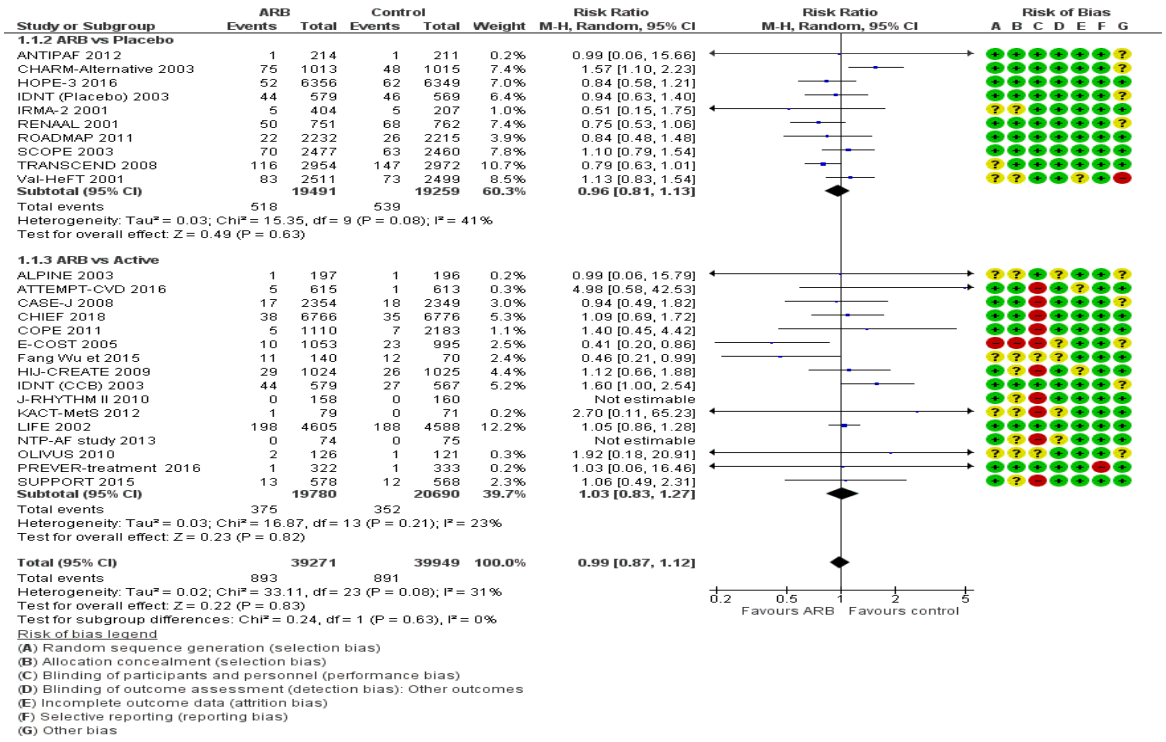


Figure 4-11 Forest plot showing effect of ARBs on risk of MI [Sensitivity analysis: Excluding trials with concomitant non-study RAS blockers]. Overall: 26 trials (RE model)

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

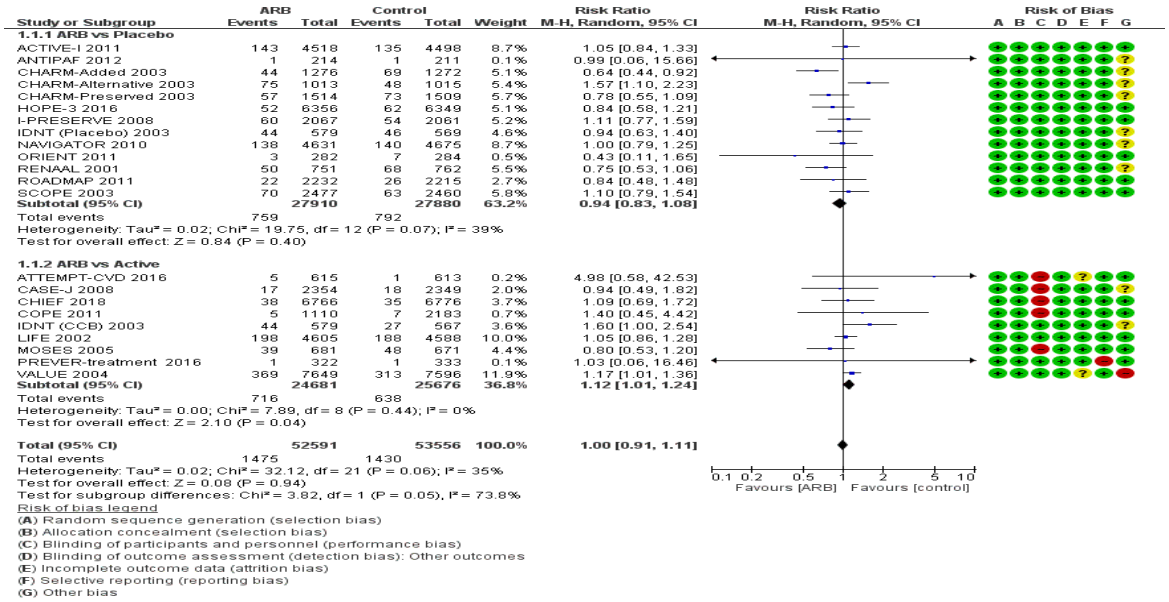


Figure 4-12 Forest plot showing effect of ARBs on risk of MI [Sensitivity analysis: Excluding trials with low methodological quality]. Overall: 22 trials (RE model)

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

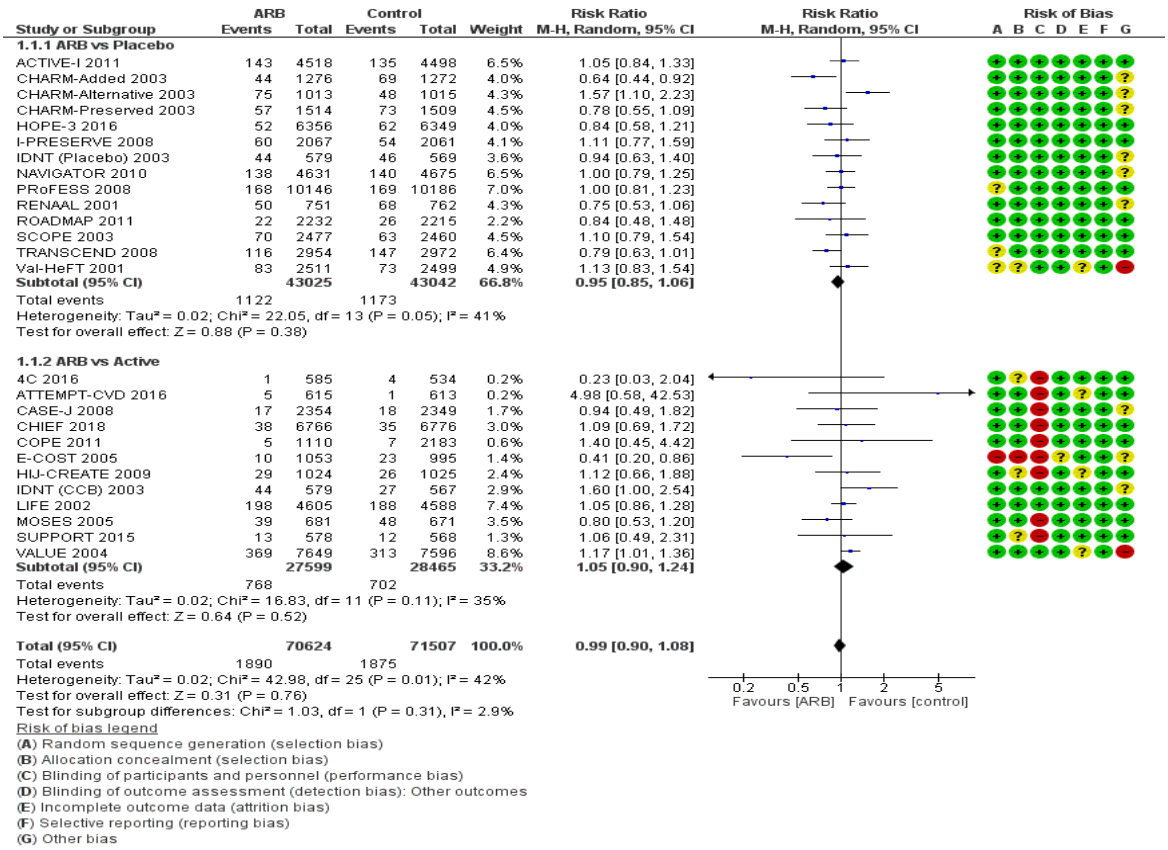


Figure 4-13 Forest plot showing effect of ARBs on risk of MI [Sensitivity analysis: Excluding trials with small sample size]. Overall: 26 trials (RE model)

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 I^2 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 I^2 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.

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 †

Subgroup analysis		Studies	Participants	Events	MI Incidence (%)		RR (M-H, Random, 95% CI)	P value*	I^2 %‡
					ARB	Control			
Overall effects	**RE**	39	146593	3840	2.63	2.60	0.97 [0.94, 1.06]	0.55	32
Subclass	**Candesartan**	13	36418	752	1.98	2.15	0.91 (0.71-1.15)	0.43	52
	Valsartan	6	30112	1060	4.00	3.63	1.05 (0.87, 1.25)	0.63	34
	Telmisartan	5	41177	679	1.59	1.70	0.94 (0.75, 1.18)	0.61	39
	Irbesartan	4	15470	519	3.32	3.37	1.08 (0.91, 1.28)	0.38	0
	Losartan	3	11361	506	4.38	4.52	0.93 (0.72, 1.20)	0.59	28
	Olmesartan	5	6831	90	1.22	1.41	0.87 (0.57, 1.32)	0.51	0
Active control	**Dihydropyridine CCBs**	7	23123	898	4.12	3.63	1.00 (0.73-1.36)	1	62¶
	Diuretics	3	14590	77	0.55	0.50	1.08 (0.69-1.69)	0.72	0
	Active control	11	17918	534	2.97	2.98	0.97 (0.73-1.29)	0.85	18
Clinical setting	**High-risk hypertensive**	27	112966	3064	2.73	2.69	0.99 (0.91-1.08)	0.84	20
	HF	6	17883	661	3.70	3.68	1.00 [0.76, 1.32]	0.98	67
	DM± Nephropathy	5	8852	303	2.91	3.88	0.86 (0.65-1.14)	0.30	24
	CAD	5	8819	335	3.47	4.11	0.85 (0.68-1.05)	0.12	0
	AF	4	9908	280	2.90	2.75	1.05 (0.84, 1.33)	0.65	0
	CVA	2	21684	424	1.91	1.99	0.95 (0.79-1.15)	0.61	0
Mean age group	**< 65 years**	17	49217	990	1.91	2.09	0.94 [0.83, 1.06]	0.29	0
	≥ 65 years	21	96797	2806	2.93	2.86	0.99 (0.88-1.11)	0.83	44

†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 considered statistically significant; ** Cannot synthesize data by one trial; ‡ I^2 statistic with <25% considered as low heterogeneity and I^2> 75% as high heterogeneity. ¶ By excluded VALUE and IDNT (CCB)., the I^2 is reduced (7%) with RR of 0.75 (95% CI 0.54-1.05).

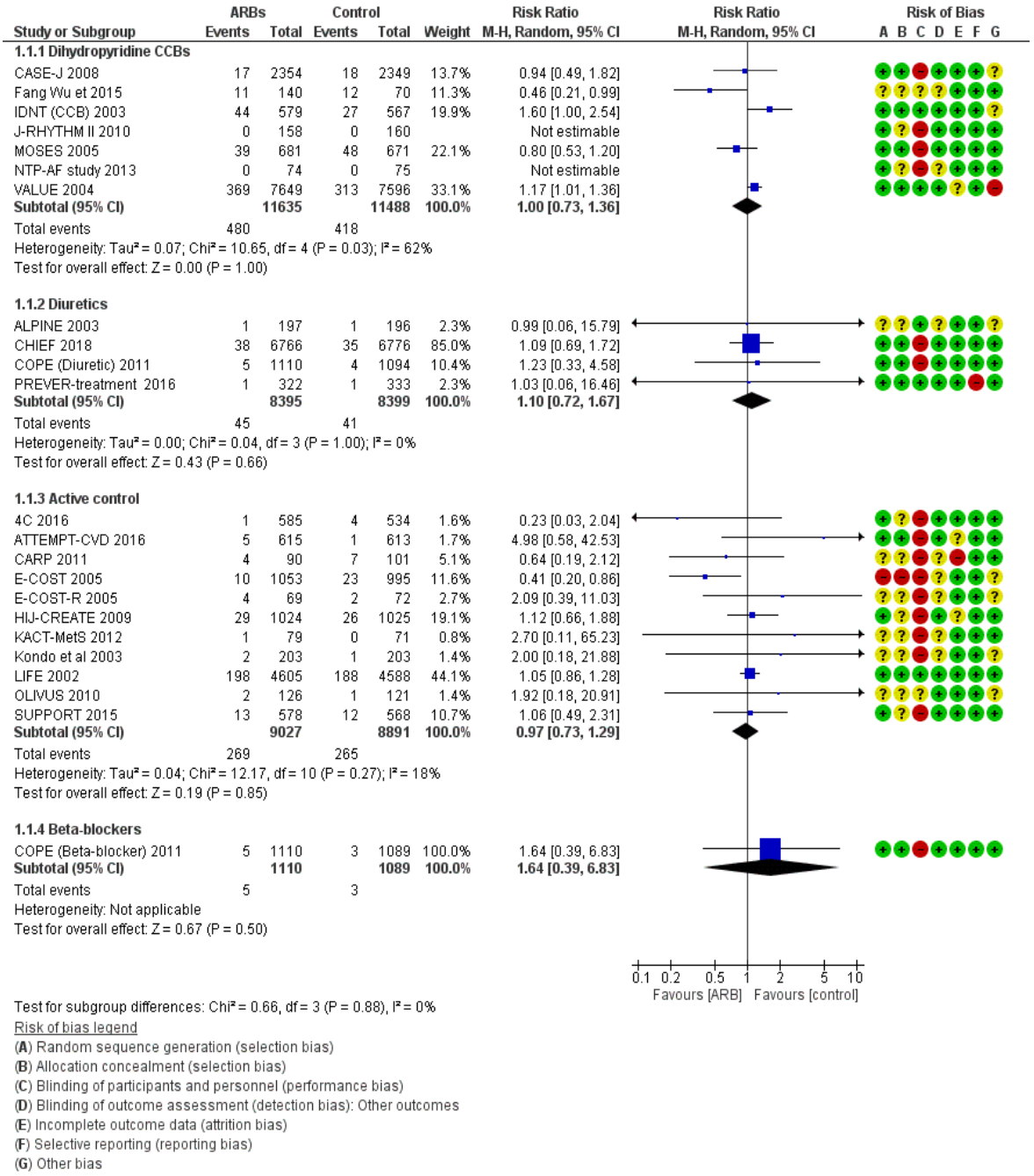


Figure 4-14 Forest plot showing effect of ARBs on risk of MI (RE model). [Subgroup analysis: Class of active group].

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

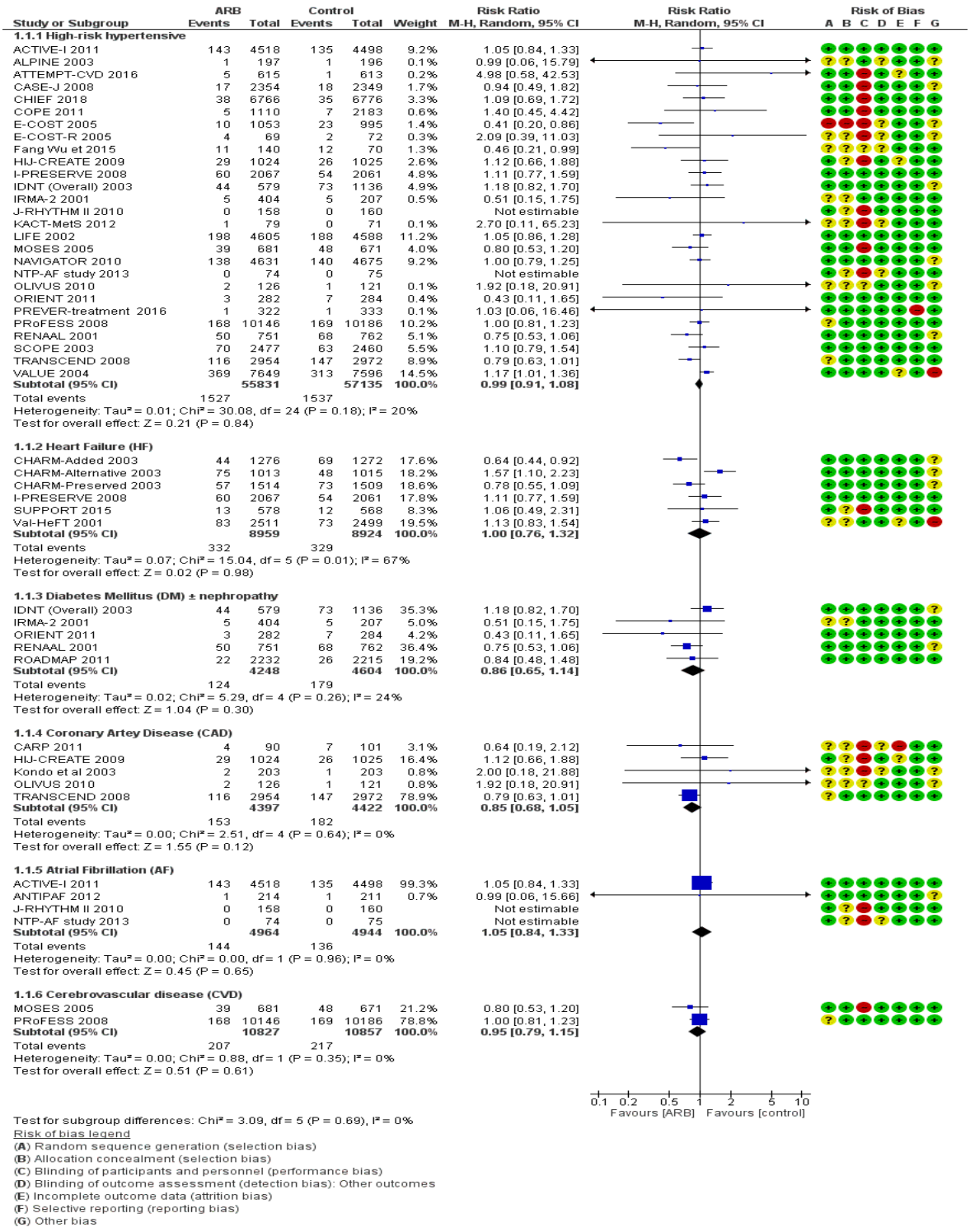


Figure 4-15 Forest plot showing effect of ARBs on risk of MI (RE model). [Subgroup analysis: Clinical setting].

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

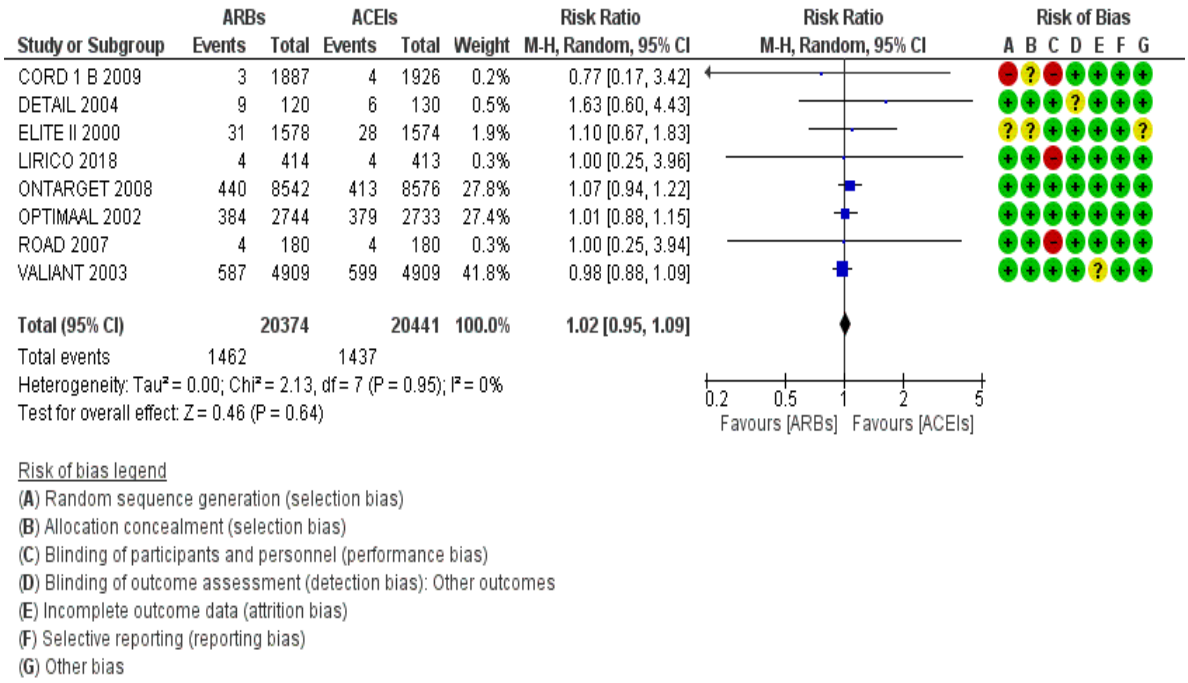
4.6.1 Overall treatment effect

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.

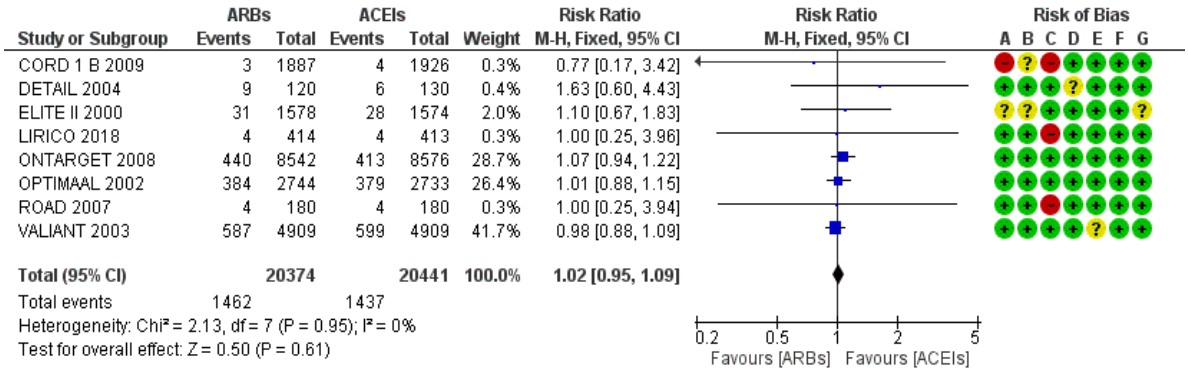
Figures 4-19 and 4-20 show a flowchart summarizing the RE meta-analytical effectiveness of ACEIs and ARBs compared with the control (either placebo or active) on risk of MI.



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 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



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 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.

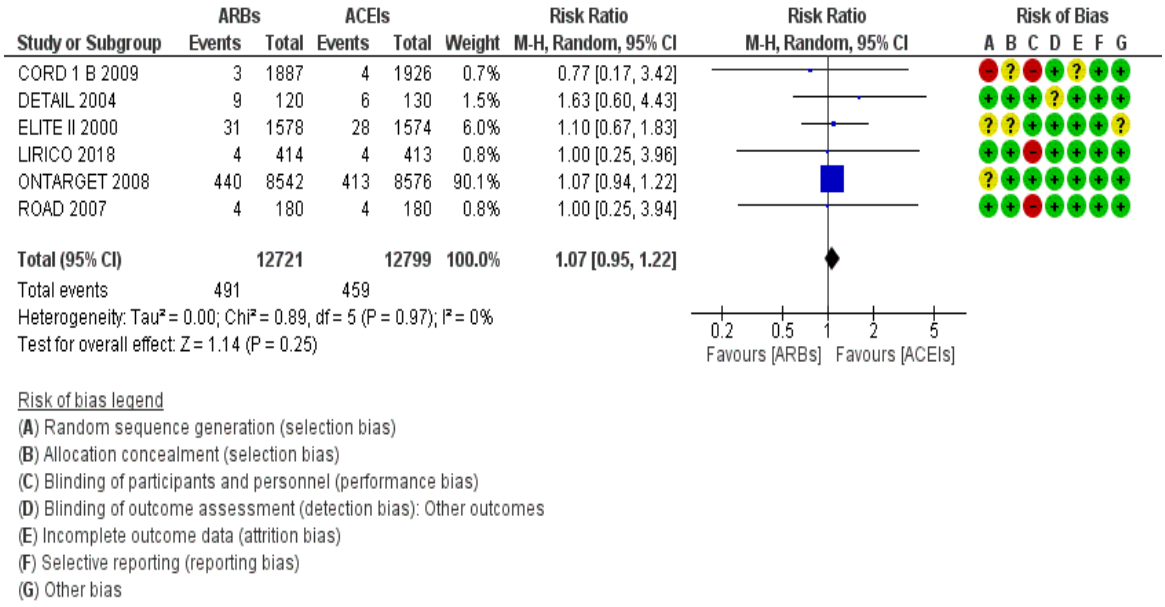


Figure 4-18 Forest plot showing effect of ARBs vs. ACEIs on risk of MI [Sensitivity analysis: Excluding OPTIMAAL and VALIANT trials]. Overall: 6 trials (RE model)

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

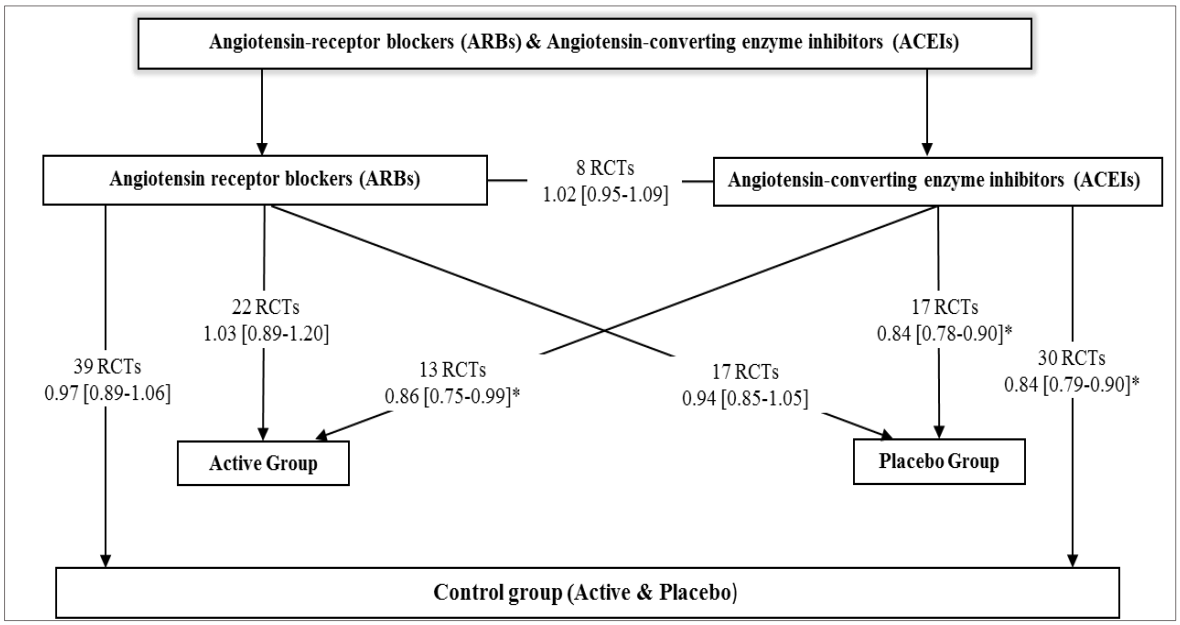


Figure 4-19 Flowchart represents a random-effects (RE) meta-analytical summary of the ACEIs versus ARBs on risk of MI

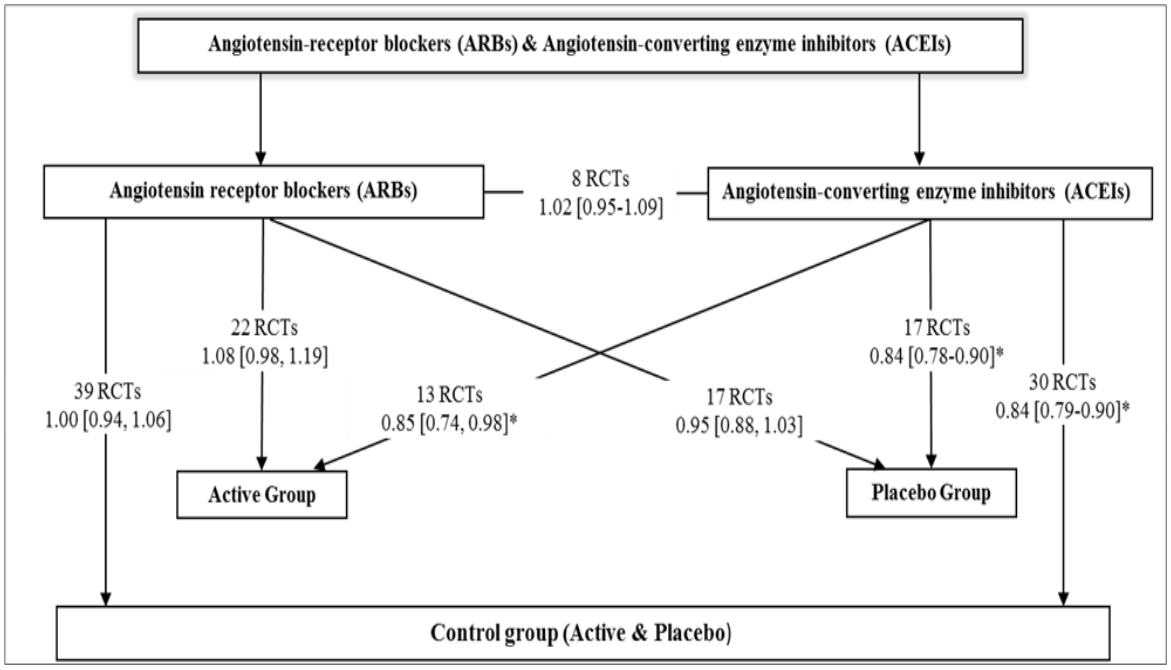


Figure 4-20 Flowchart represents a fixed-effect (FE) meta-analytical summary of the effectiveness of ACEIs versus ARB on risk of MI

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

4.7.1 ACEIs

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).

4.7.2 ARBs

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).

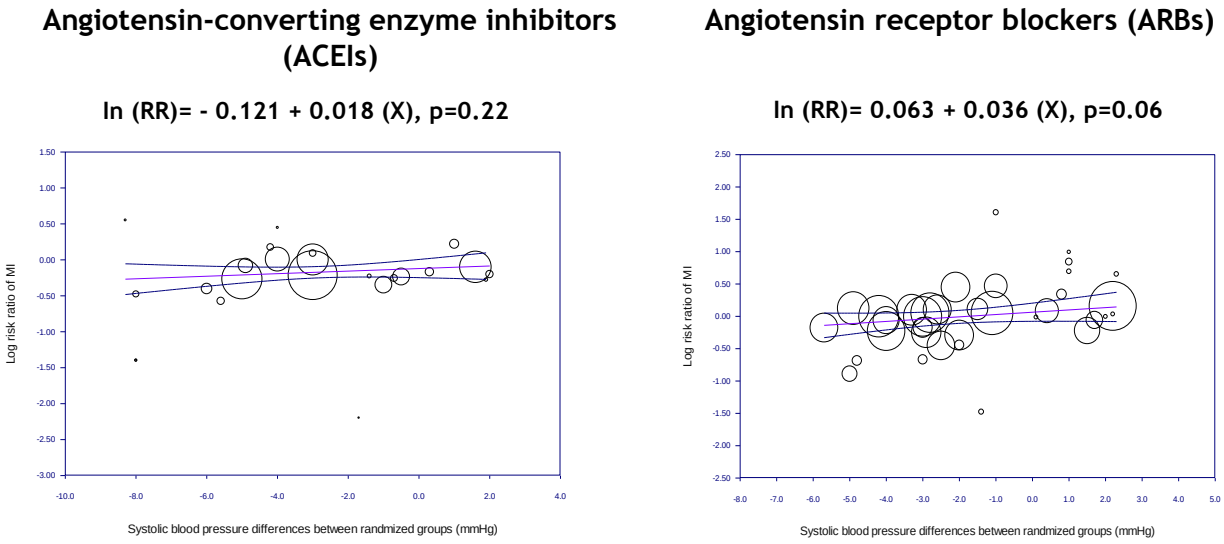


Figure 4-21 meta-regression analysis of relationship between RR of MI and difference in achieved SBP (mmHg) between randomized groups for trials of ACEIs and ARBs

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 I^2=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 I^2=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.

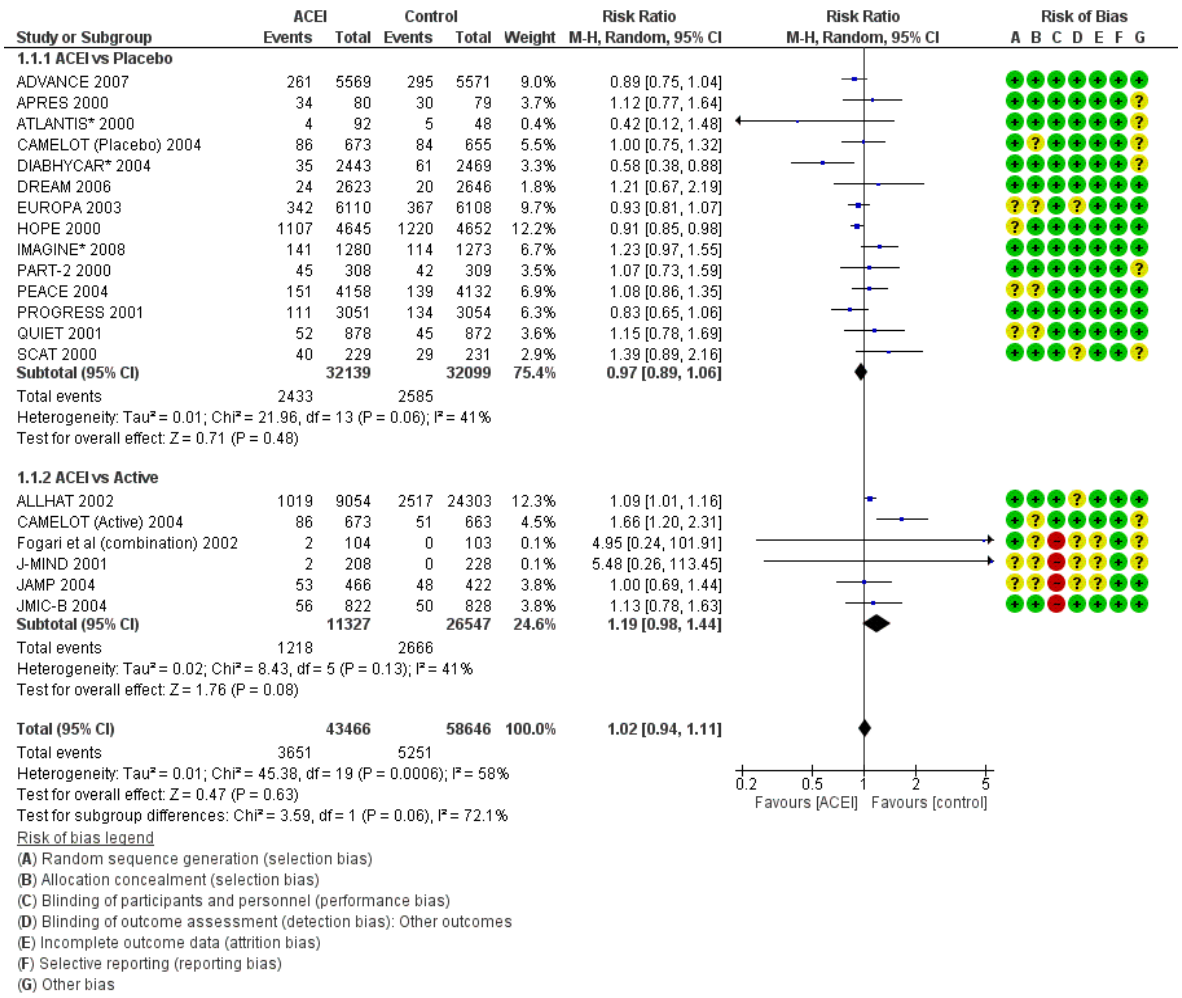


Figure 4-22 Forest plot showing the effect of ACEIs on risk of angina pectoris, stratified by comparison group (placebo vs active treatment). Overall: 20 trials (RE model).

*Excluding trials yielded RR of 0.93 [0.89, 0.99] & I^2=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

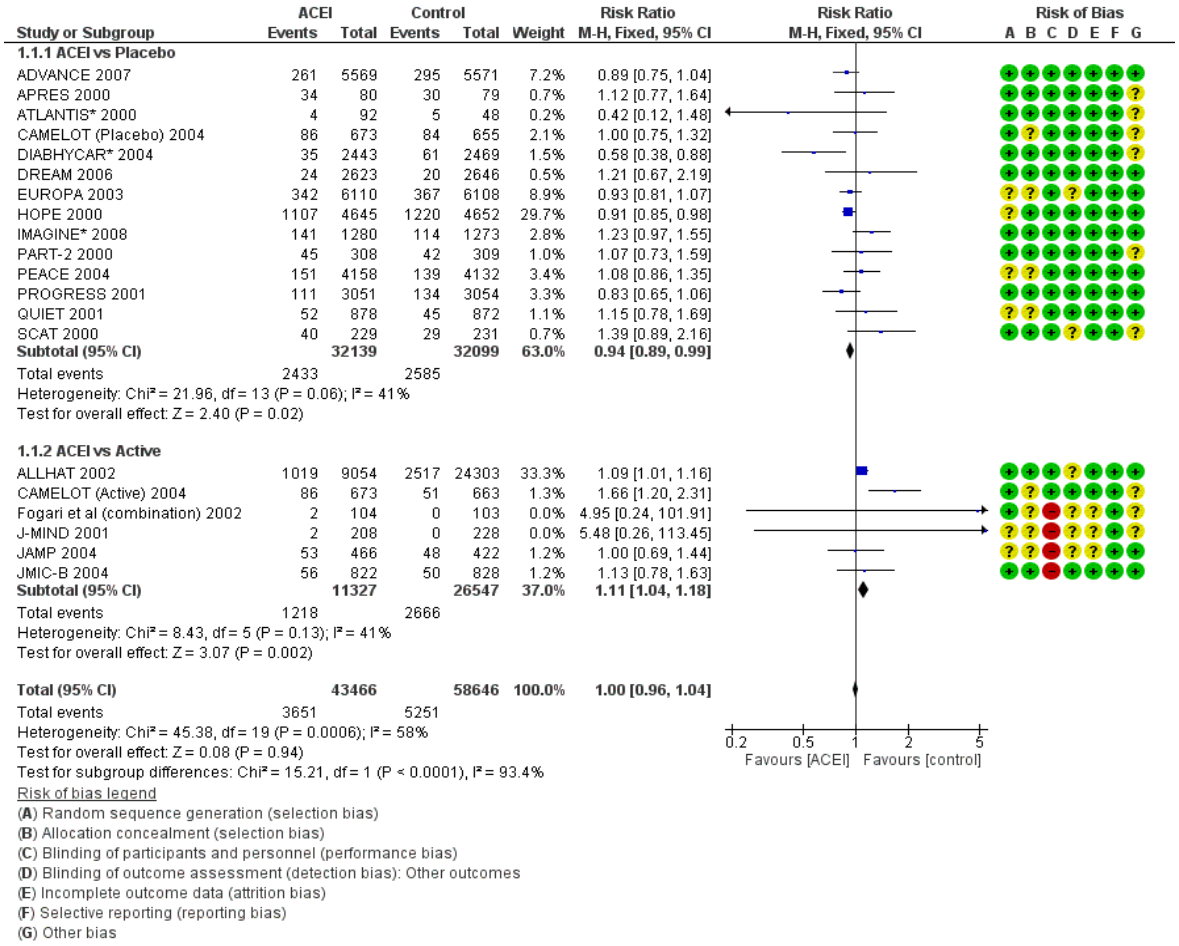


Figure 4-23 Forest plot showing the effect of ACEIs on risk of angina pectoris, stratified by the comparison group (placebo vs active treatment). Overall: 20 trials (FE model).

*Excluding trials yielded RR of 0.94 [0.89, 0.99] & I2=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

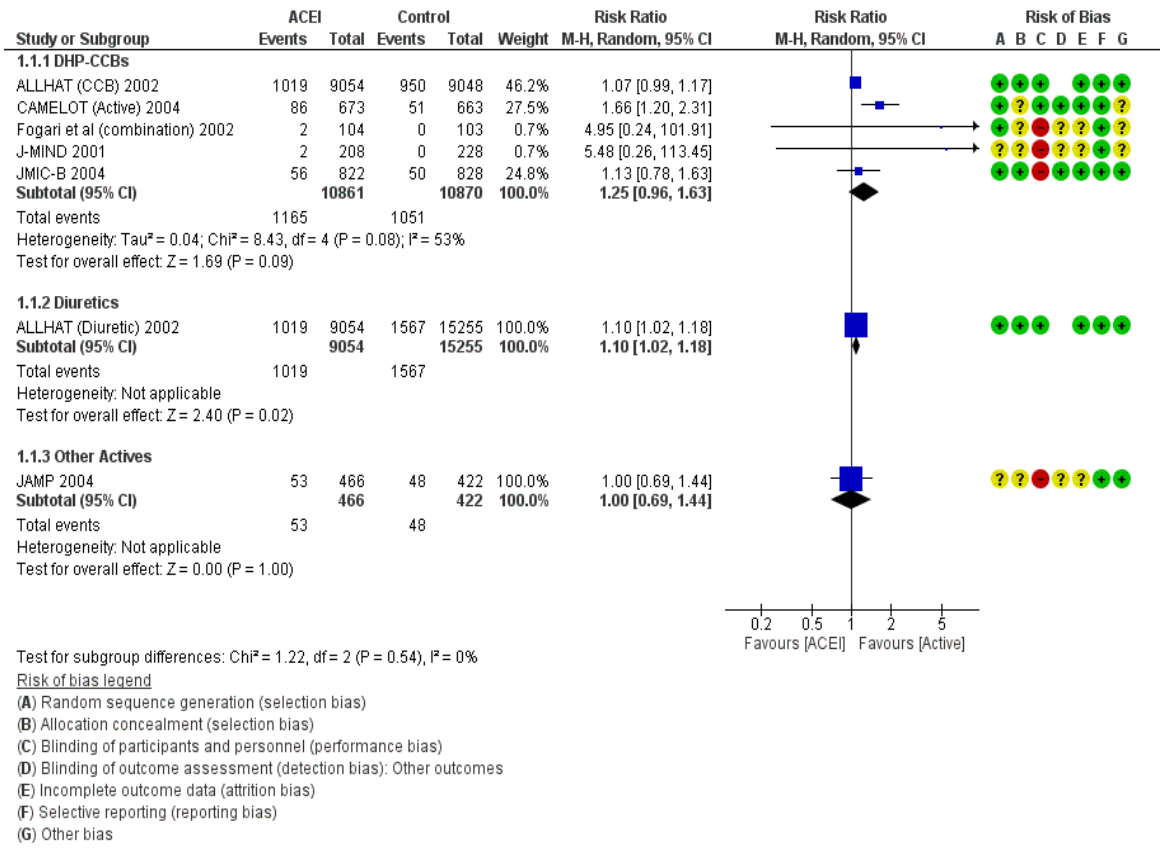


Figure 4-24 Forest plot showing effect of ACEIs on risk of angina pectoris (RE model). [Subgroup: active comparator].

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

4.8.2 ARBs 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 I^2 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 I^2 statistics across studies (RR, 0.85; 95% CI 0.70–1.05; I^2=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.

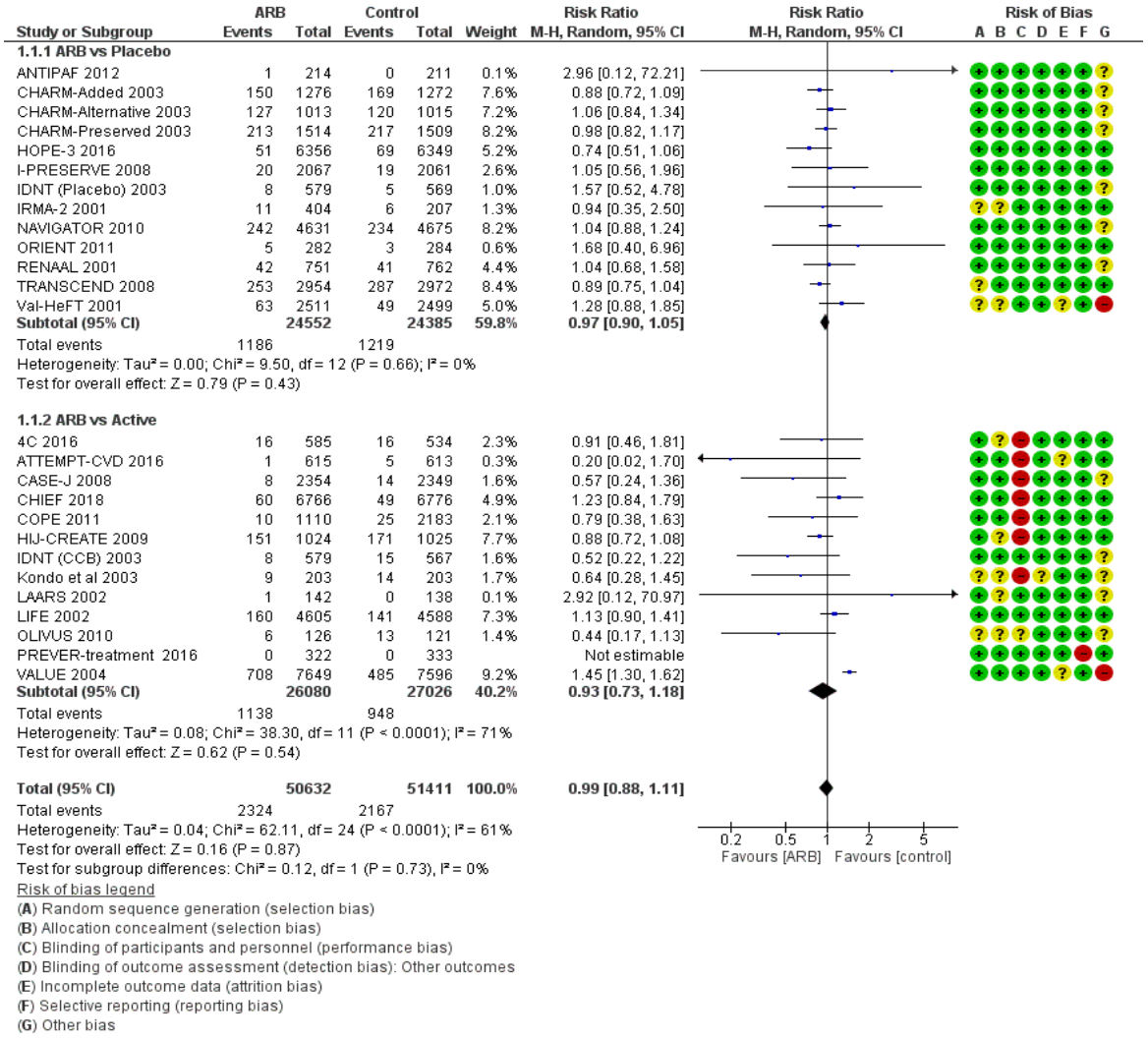


Figure 4-25 Forest plot showing the effect of ARBs on risk of angina pectoris, stratified by comparison group (placebo vs active treatment). Overall: 26 trials (RE model).

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

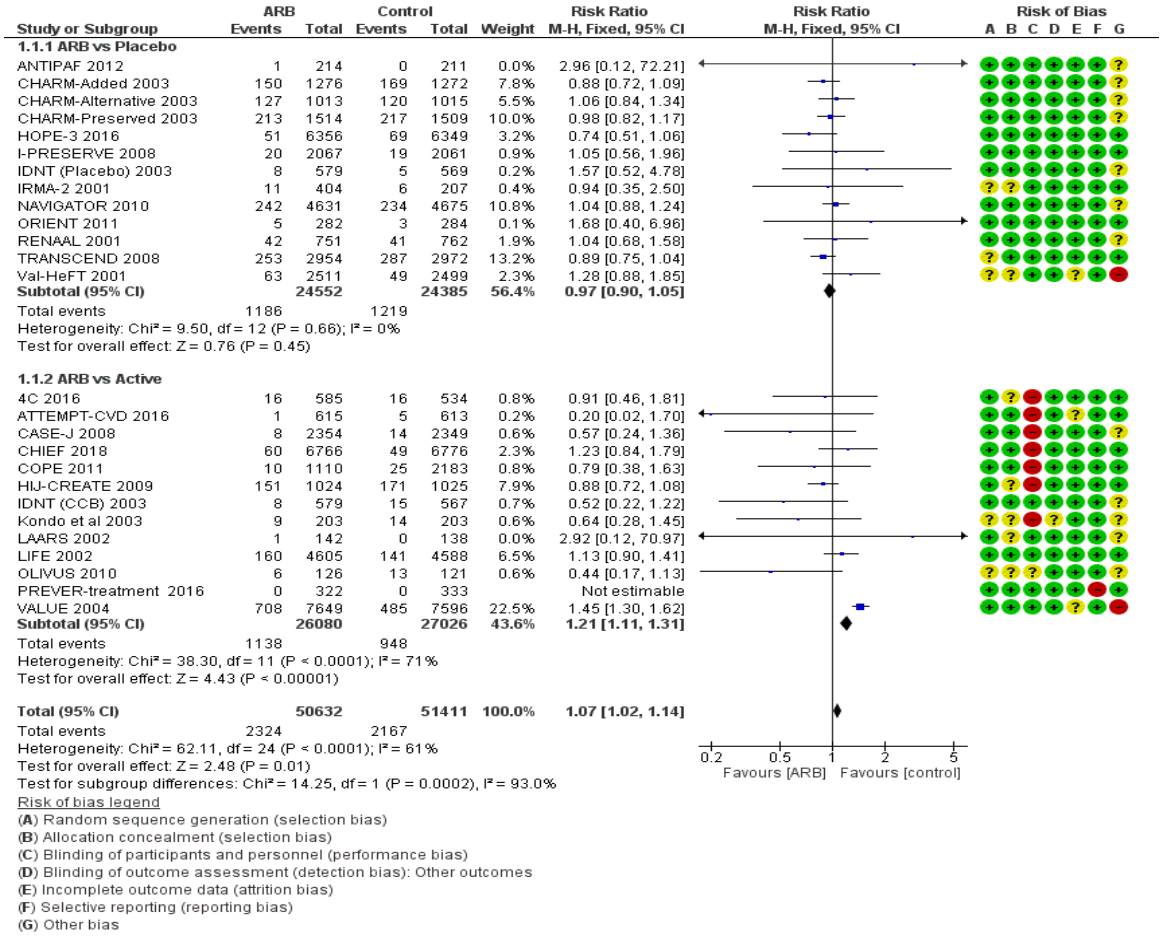


Figure 4-26 Forest plot showing the effect of ARBs on risk of angina pectoris, stratified by comparison group (placebo vs active treatment). Overall: 25 trials (FE model).

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 I^2 statistics =22%). The FE model generated a similar meta-analytical summary to the RE model **(Figure 4-28).**

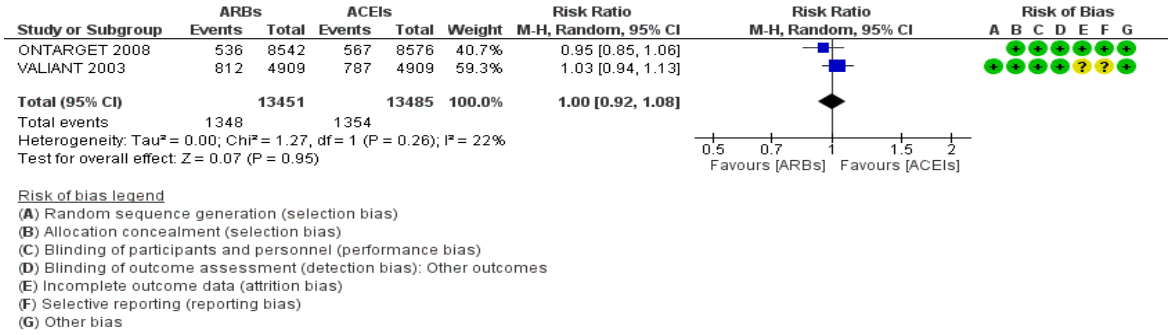


Figure 4-27 Forest plot showing angina outcome in direct comparisons of ACEIs versus ARBs; total of two trials (RE model).

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

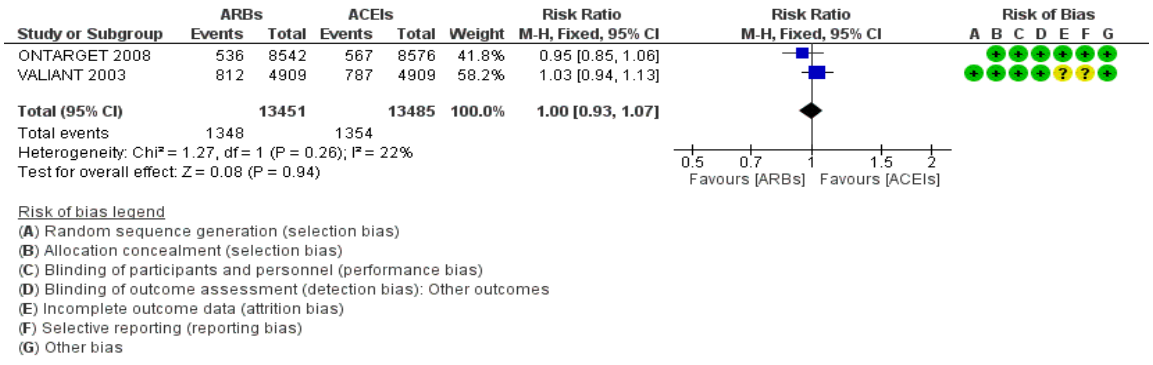


Figure 4-28 Forest plot showing angina outcome in direct comparisons of ACEIs versus ARBs; total of two trials (FE model).

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 AT_1 receptors, thus preventing their activation. As a result of the blockage of AT_1 receptors by ARBs, the level of circulating Ang II will increase by uncoupling a negative feedback loop, leading to hyperstimulation of AT_2 and AT_4 (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 ACEI-induced 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 AT_4 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 AT_4 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 I_2 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 follow-up 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 AT_1 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 AT_2 and AT_4 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 meta-regression 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

5.4.1 Overall 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 I^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.

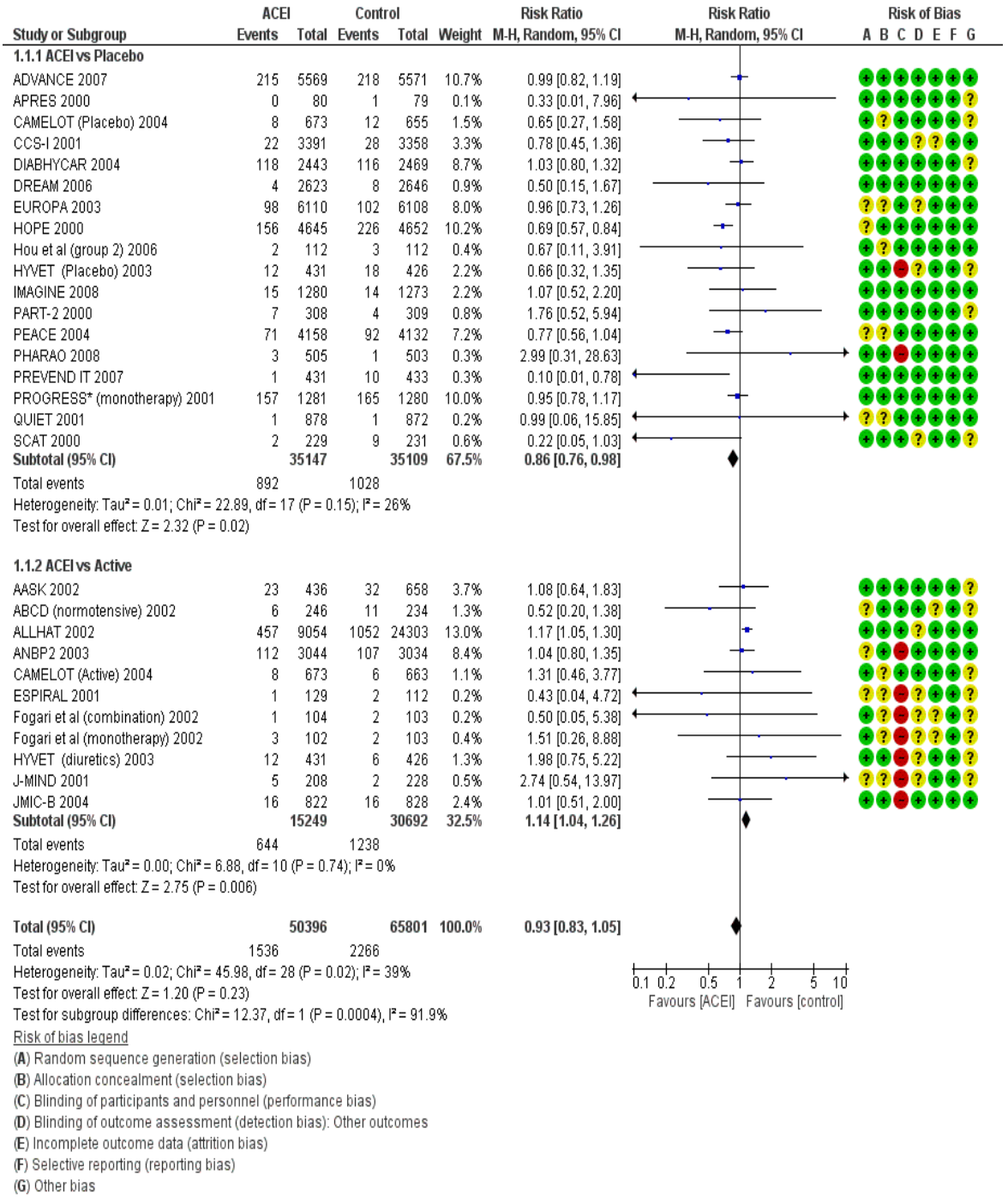


Figure 5-1 Forest plot showing effect of ACEIs on risk of stroke, stratified by comparison group (placebo vs. active). Overall: 29 trials (RE model).

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

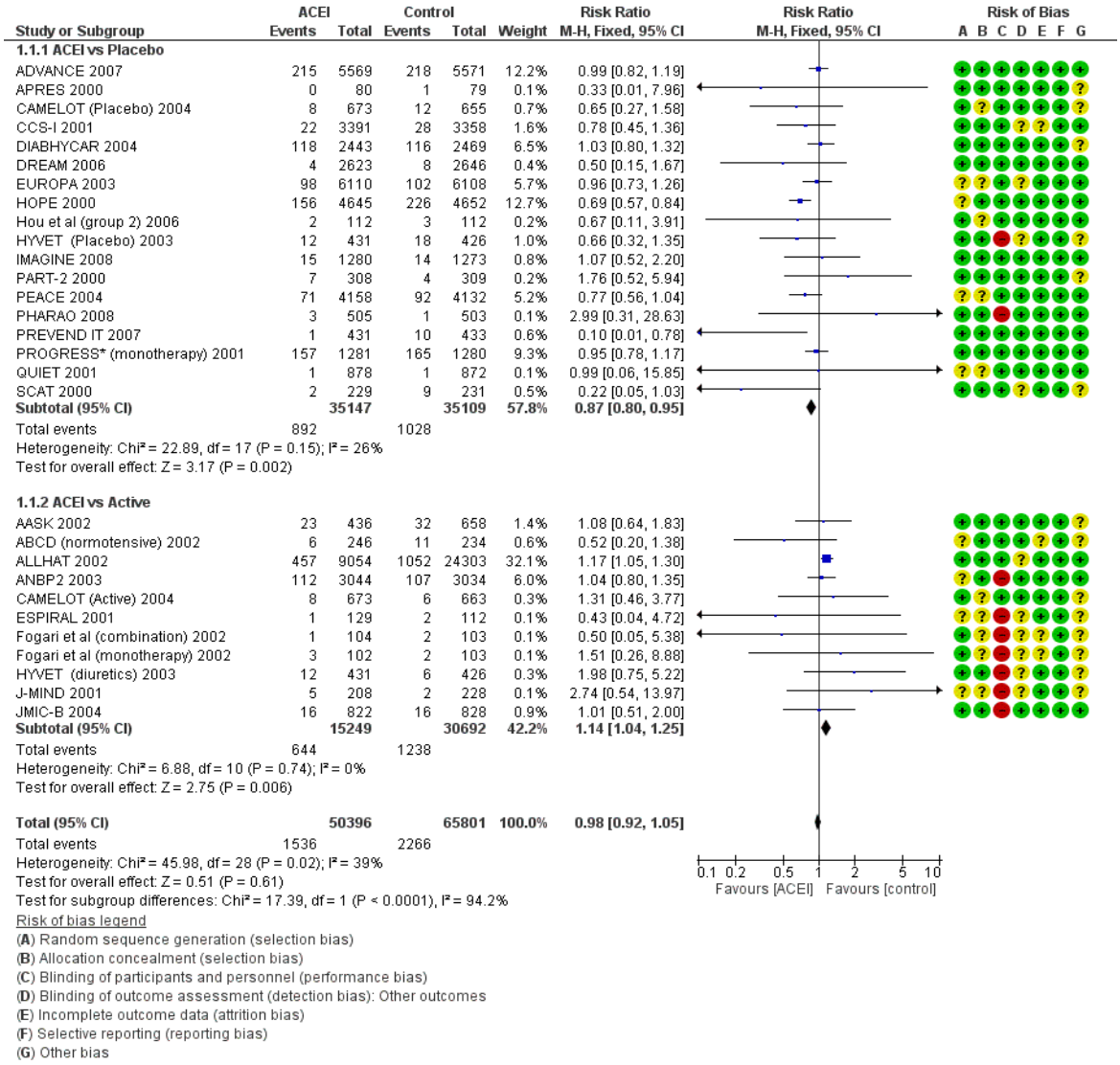


Figure 5-2 Forest plot showing effect of ACEIs on risk of stroke, stratified by comparison group (placebo vs. active). Overall: 29 trials (FE model).

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**)

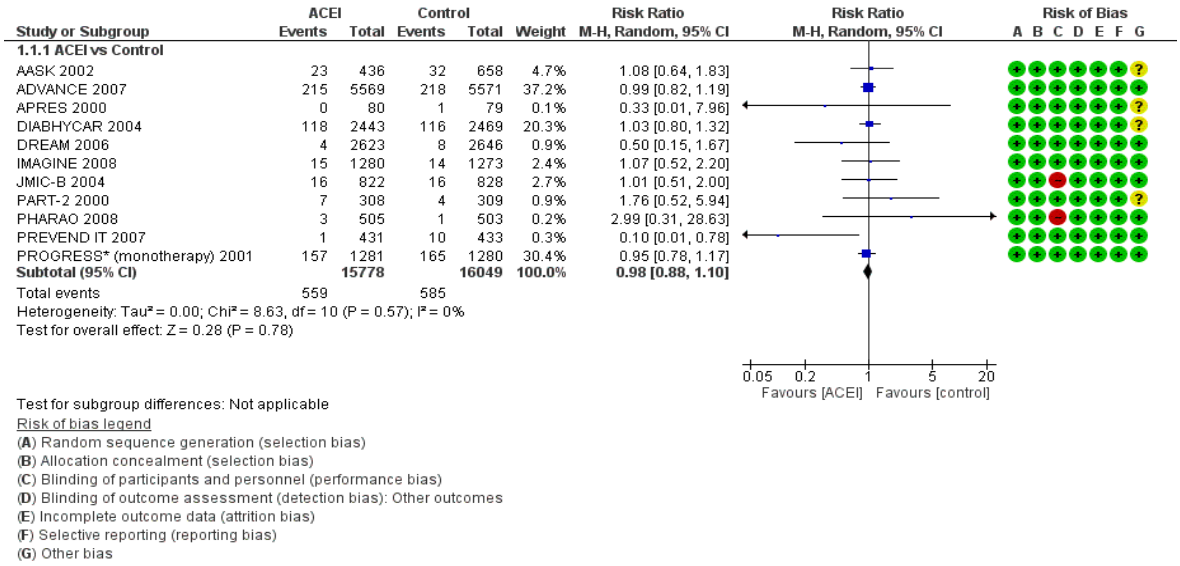


Figure 5-3 Forest plot showing effect of ACEIs on risk of stroke [Sensitivity analysis: Excluding trials with low methodological quality]. Overall: 11 trials (RE model)

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

5.4.3 Subgroup analysis

Table 5.1 summarizes the subgroup analyses performed to assess the effect of ACEIs 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 meta-analysis.

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 I^2 = 43%). This between-trial variation may have arisen from clinical diversity of ALLHAT trial. By excluding the ALLHAT trial, heterogeneity was reduced (I^2=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 I^2 =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 ≥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 I^2= 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 (I^2=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†

Subgroup analysis		Studies	Participants	Events	Stroke Incidence (%)		RR (M-H, Random, 95% CI)	P value*	I^2 (%) ‡
					ACEI	Control			
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¥
Active control	**Dihydropyridine CCBs**	9	23310	947	4.41	3.70	1.19 [1.05, 1.35]	**0.006***	0
	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
Clinical setting	**High-risk hypertensive**	17	88227	3152	3.40	3.70	0.95 [0.84, 1.09]	0.48	43π
	CAD	11	45734	907	1.75	2.20	0.79 [0.69, 0.90]	**0.0004***	0
	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 group	**< 65 years**	19	44815	615	1.24	1.49	0.86 [0.74, 1.01]	0.07	0
	≥ 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; I^2: I-square test; M-H: Mantel-Haenszel. *P value of less than 0.05 is considered statistically significant; ‡ I^2 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 (I^2=4%) with an RR of 0.90 (95% CI 0.81-1.00; p=0.05).

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

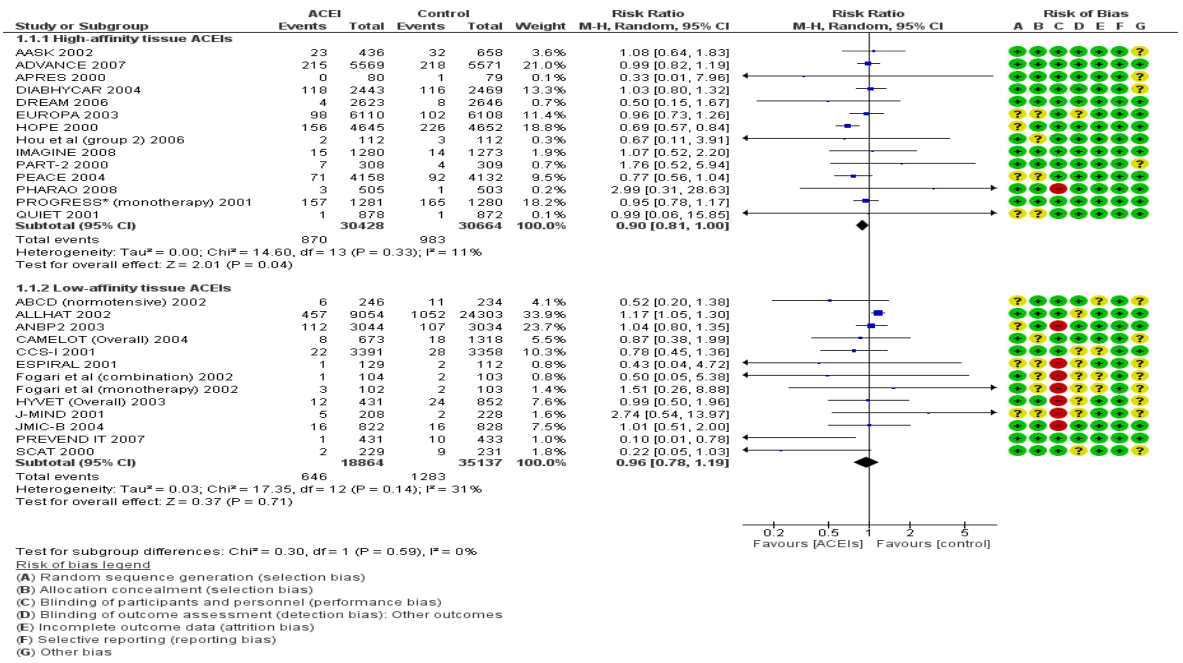


Figure 5-4 Forest plot showing effect of ACEIs on risk of stroke (RE model). [Subgroup analysis: Low vs. high-tissue affinity ACEIs]

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

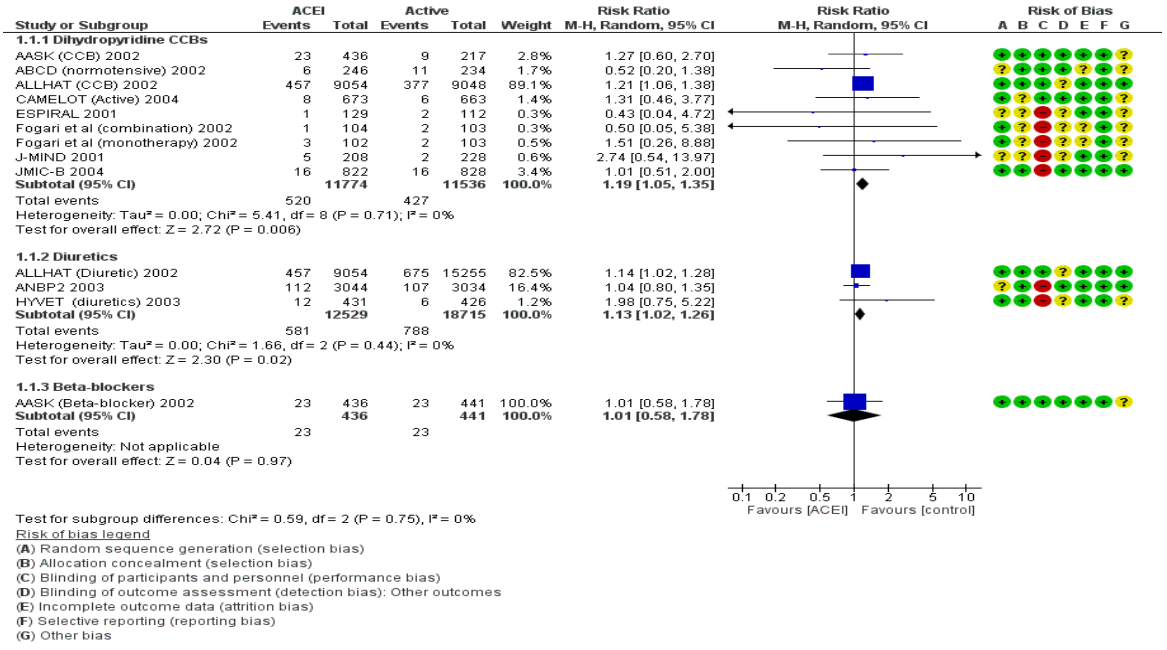


Figure 5-5 Forest plot showing effect of ACEIs on risk of stroke (RE model). [Subgroup analysis: Class of active control].

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

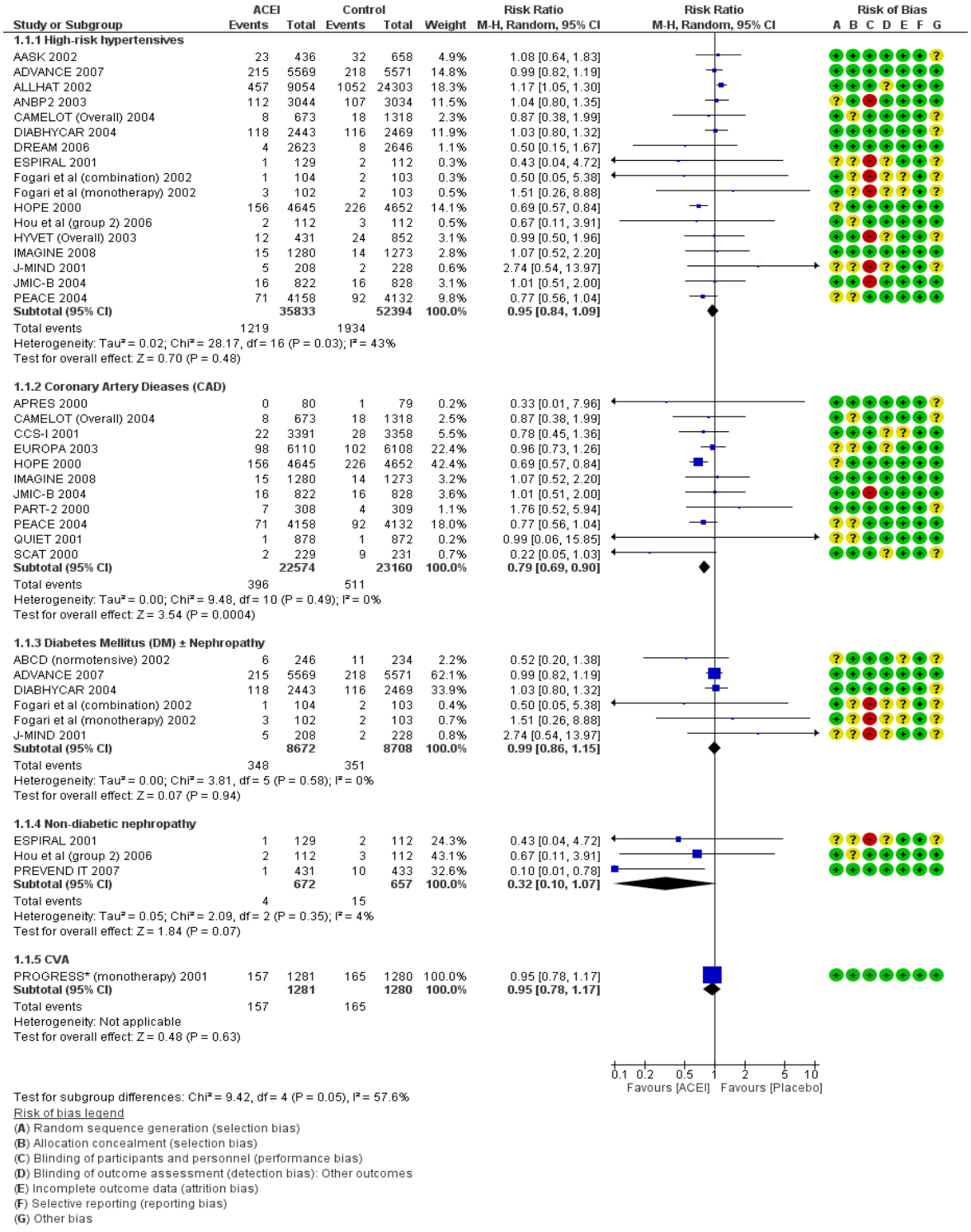


Figure 5-6 Forest plot showing effect of ACEIs on risk of stroke (RE model). [Subgroup analysis: Clinical setting].

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

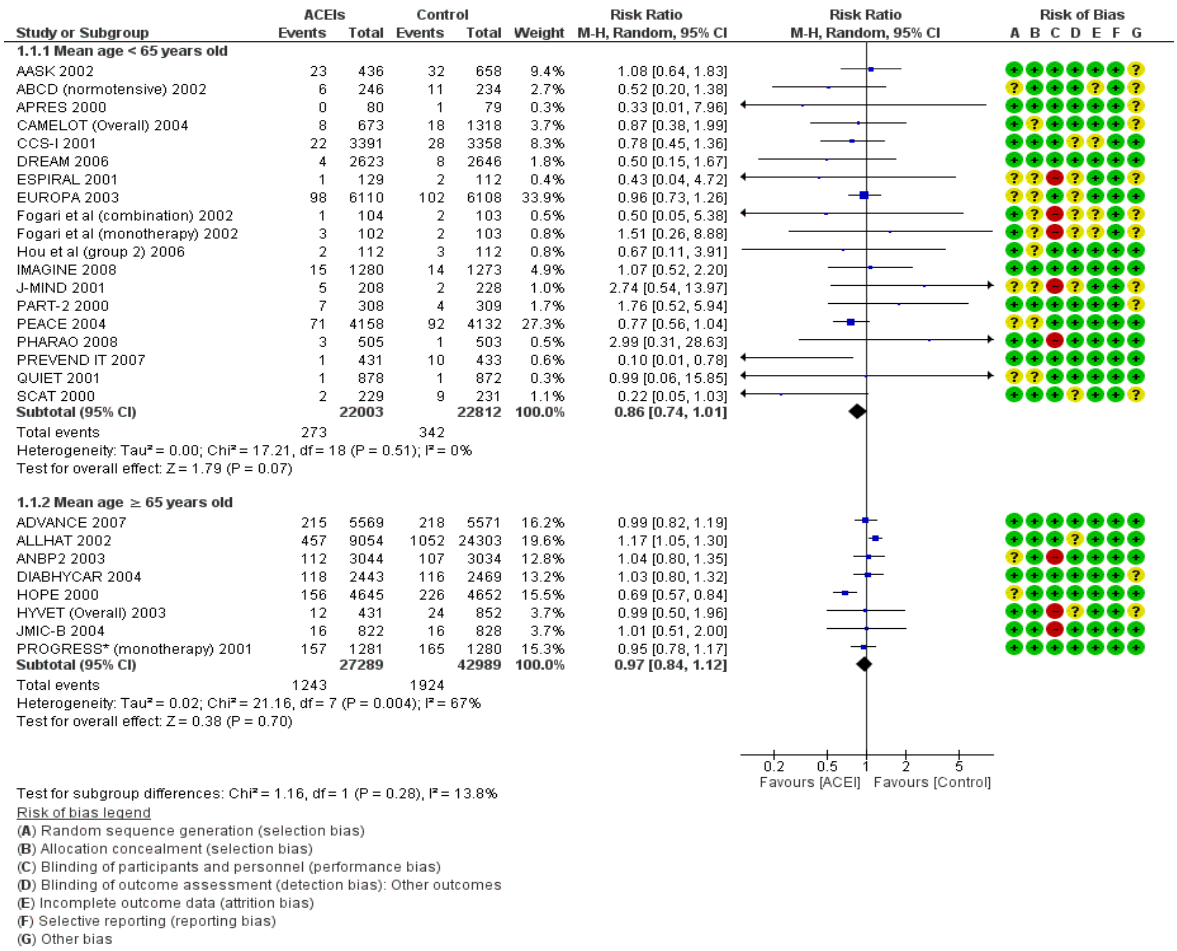


Figure 5-7 Forest plot showing effect of ACEIs on risk of stroke (RE model). [Subgroup analysis: Mean age group].

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

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 I^2 statistics = 58%. The between-trial variation was greatly influenced by trials comparing ARB with CCB-based regimens. Excluding these trials diminished the heterogeneity (I^2=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.

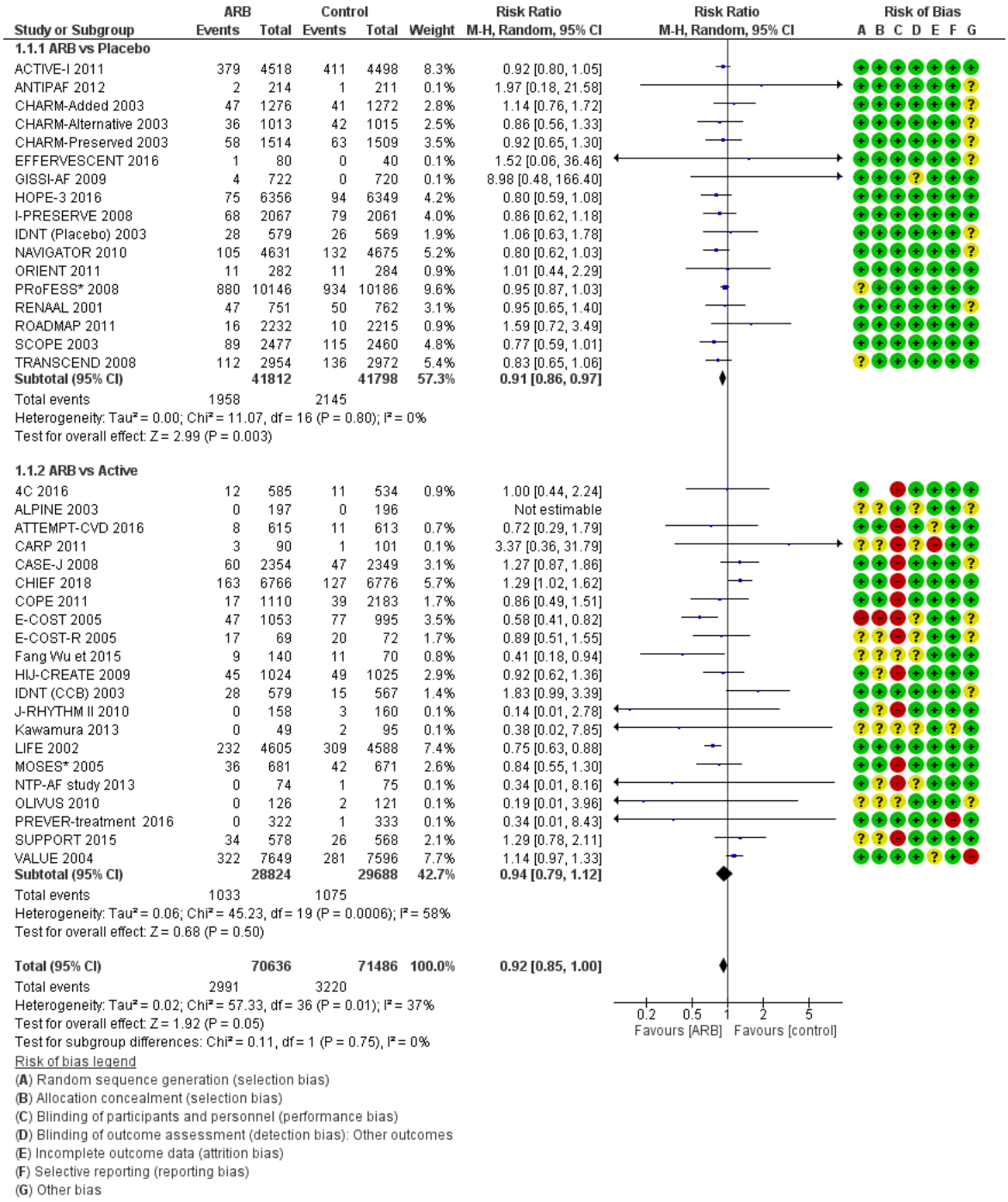


Figure 5-8 Forest plot showing effect of ARBs on risk of stroke, stratified based on control group (placebo vs. active). Overall: 38 trials (RE model)

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

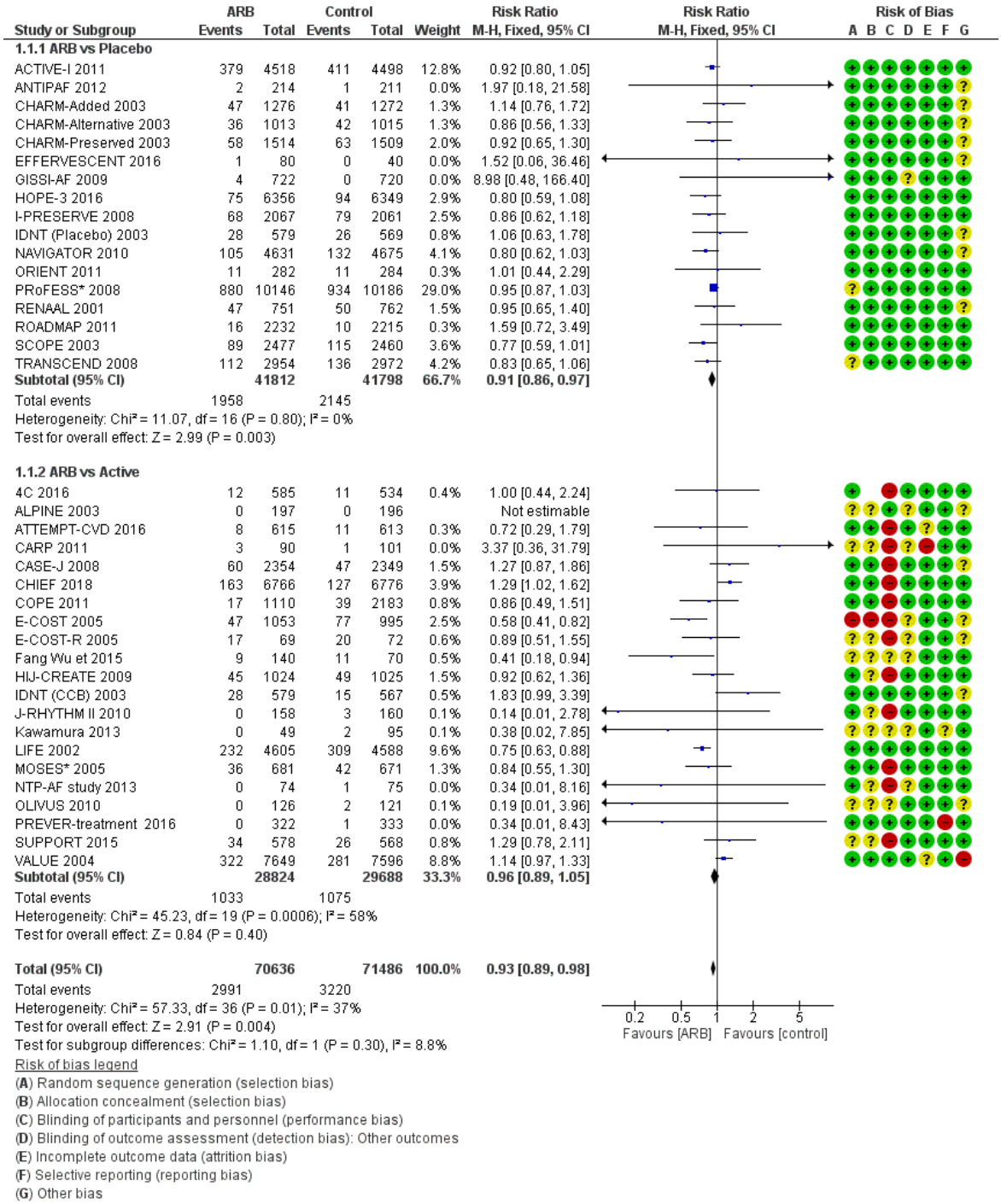


Figure 5-9 Forest plot showing effect of ARBs on risk of stroke, stratified based on control group (placebo or active). Overall: 38 trials (FE model)

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 I^2=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 I^2 = 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 (I^2=0%) with a RR of 1.15 (95% CI 1.02-1.29).

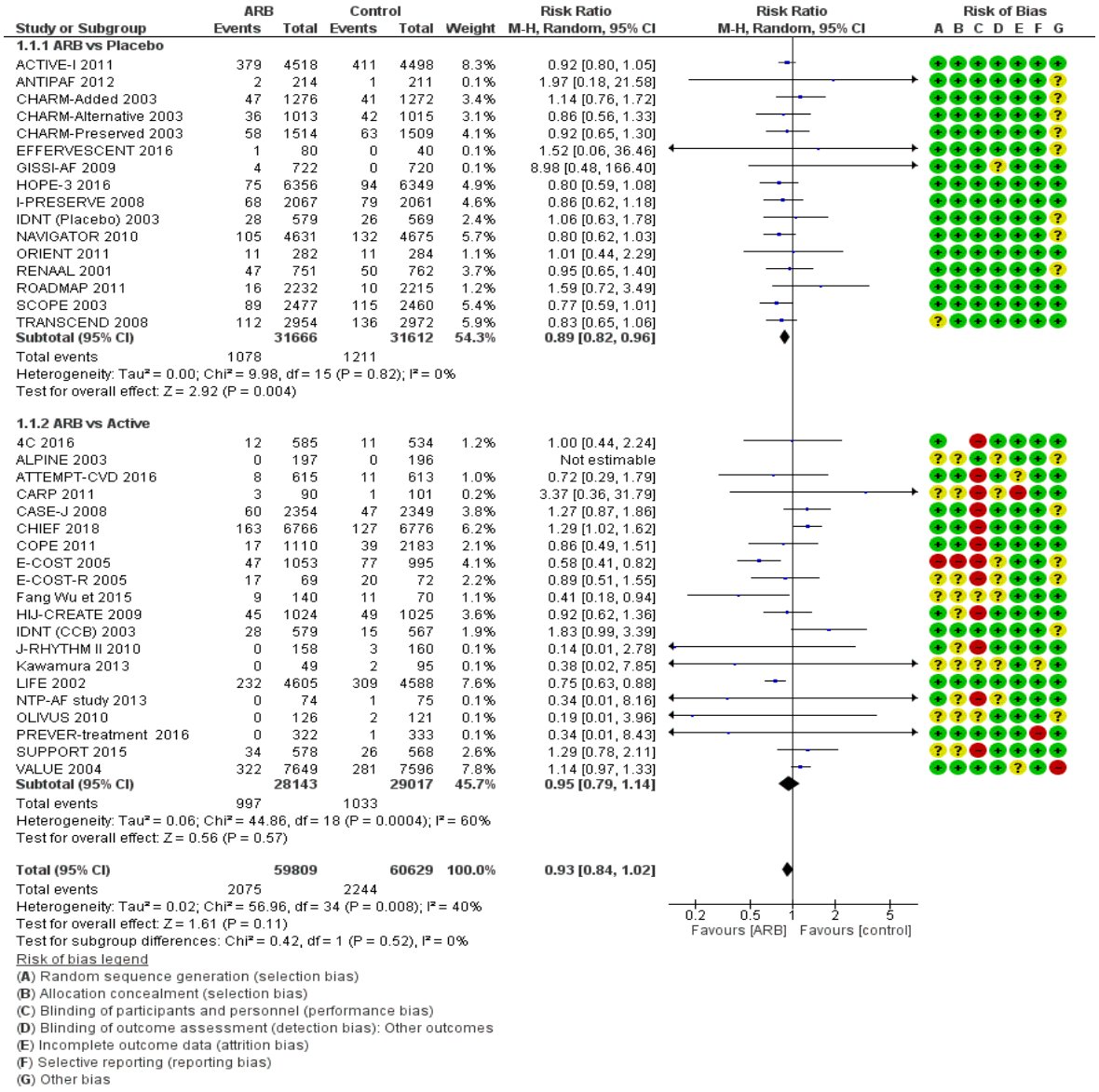


Figure 5-10 Forest plot showing effect of ARBs on risk of stroke [Sensitivity analysis: Excluding PRoFESS and MOSES]. Overall:36 trials (RE model)

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

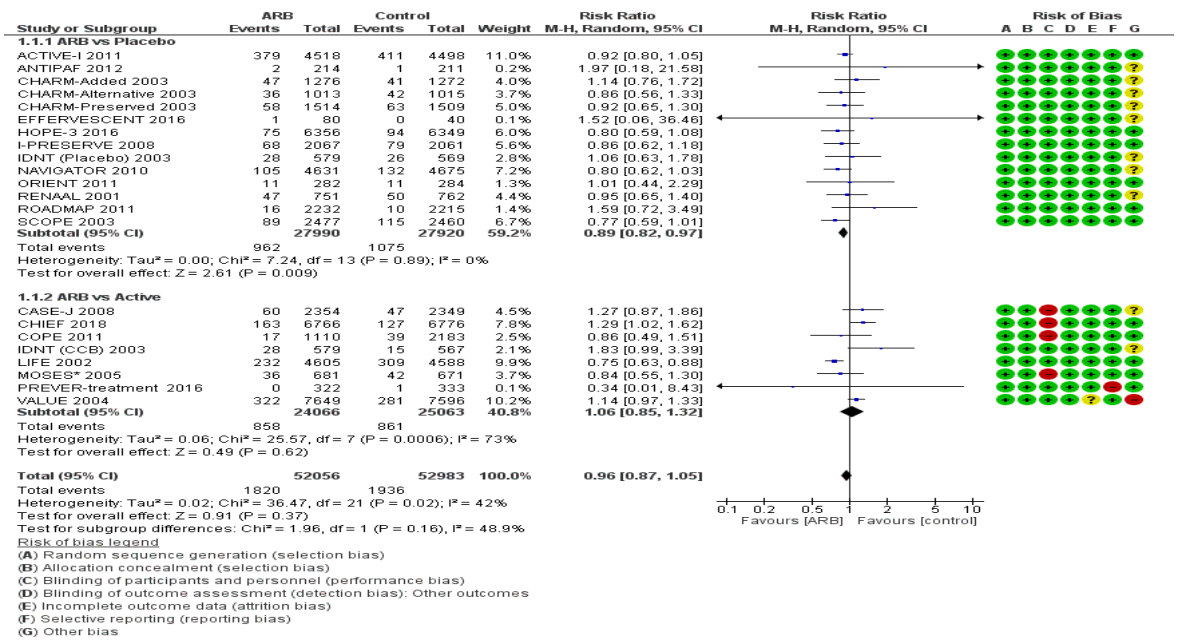


Figure 5-11 Forest plot showing effect of ARBs on risk of stroke [Sensitivity analysis: Excluding trials with low methodological quality]. Overall: 22 trials (RE model)

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 $I^2$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 0.80-

1.05; 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 ± 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 among trials.

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 ≥ 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 ≥ 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 I^2 = 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 (I^2=0%) with RR of 0.82 (95 CI% 0.77-0.89; p=<0.00001).

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) †

Subgroup analysis		Studies	Participants	Events	Stroke Incidence (%)		RR (M-H, Random, 95% CI)	P value*	I^2 (%) ‡
					ARBs	Control			
Overall effects	**RE**	**38**	**142122**	**6211**	**4.23**	**4.50**	**0.92 [0.85, 1.00]**	**0.05**	**37**
Subclass	**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
Active control	**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

† 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; ‡ I^2 statistic with <25% considered as low heterogeneity and I^2> 75% as high heterogeneity

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)

Subgroup analysis		Studies	Participant	Events	Stroke Incidence (%)		RR (M-H, Random, 95% CI)	P value*	I^2 (%) ‡
					ACEI	Control			
Overall effects	**RE**	**38**	**142122**	**6211**	**4.23**	**4.50**	**0.92 [0.85, 1.00]**	**0.05**	**37**
Clinical setting	**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**
	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; ‡ 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]

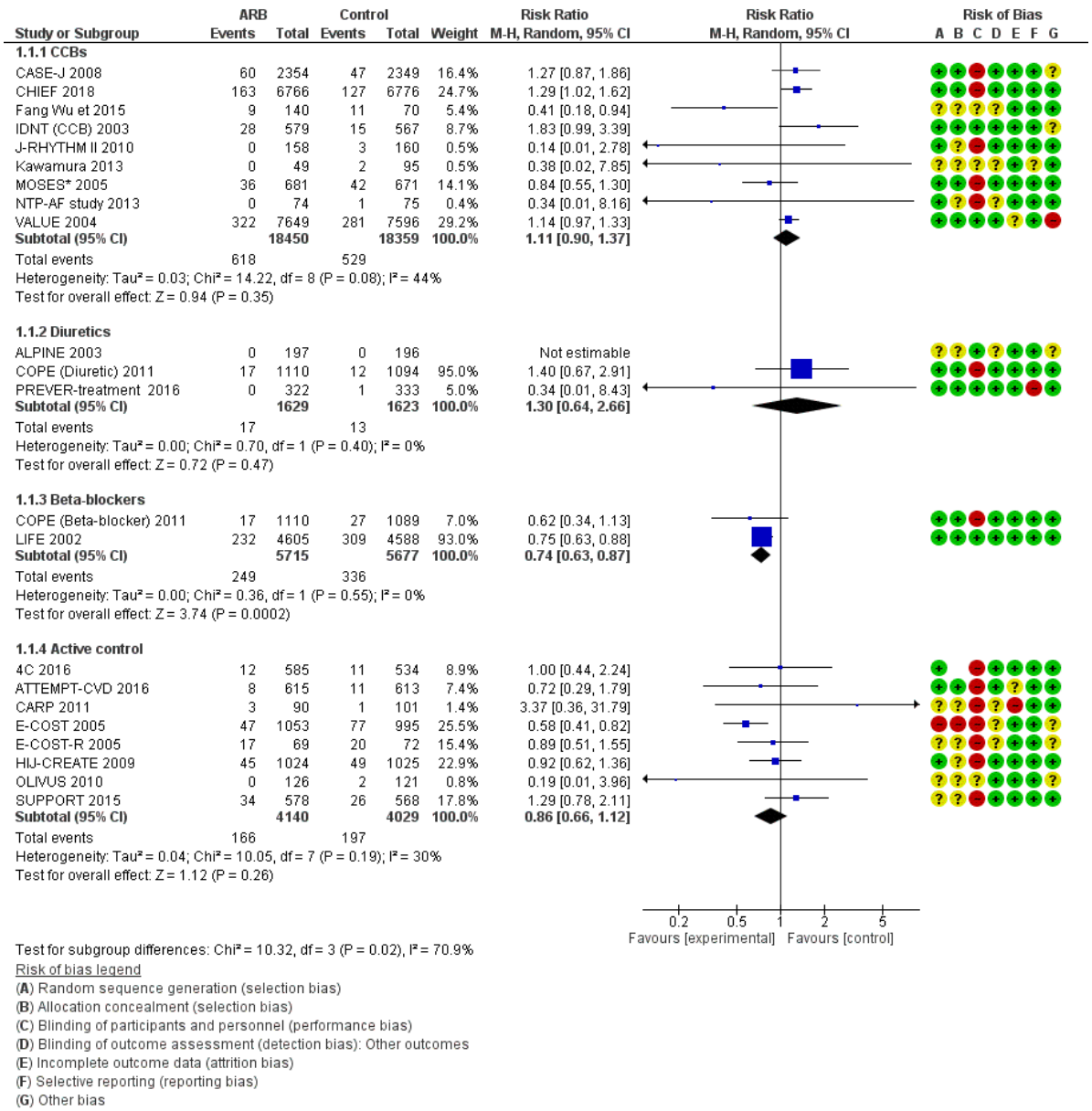


Figure 5-12 Forest plot showing effect of ARBs on risk of stroke (RE model). [Subgroup analysis: Class of active control].

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

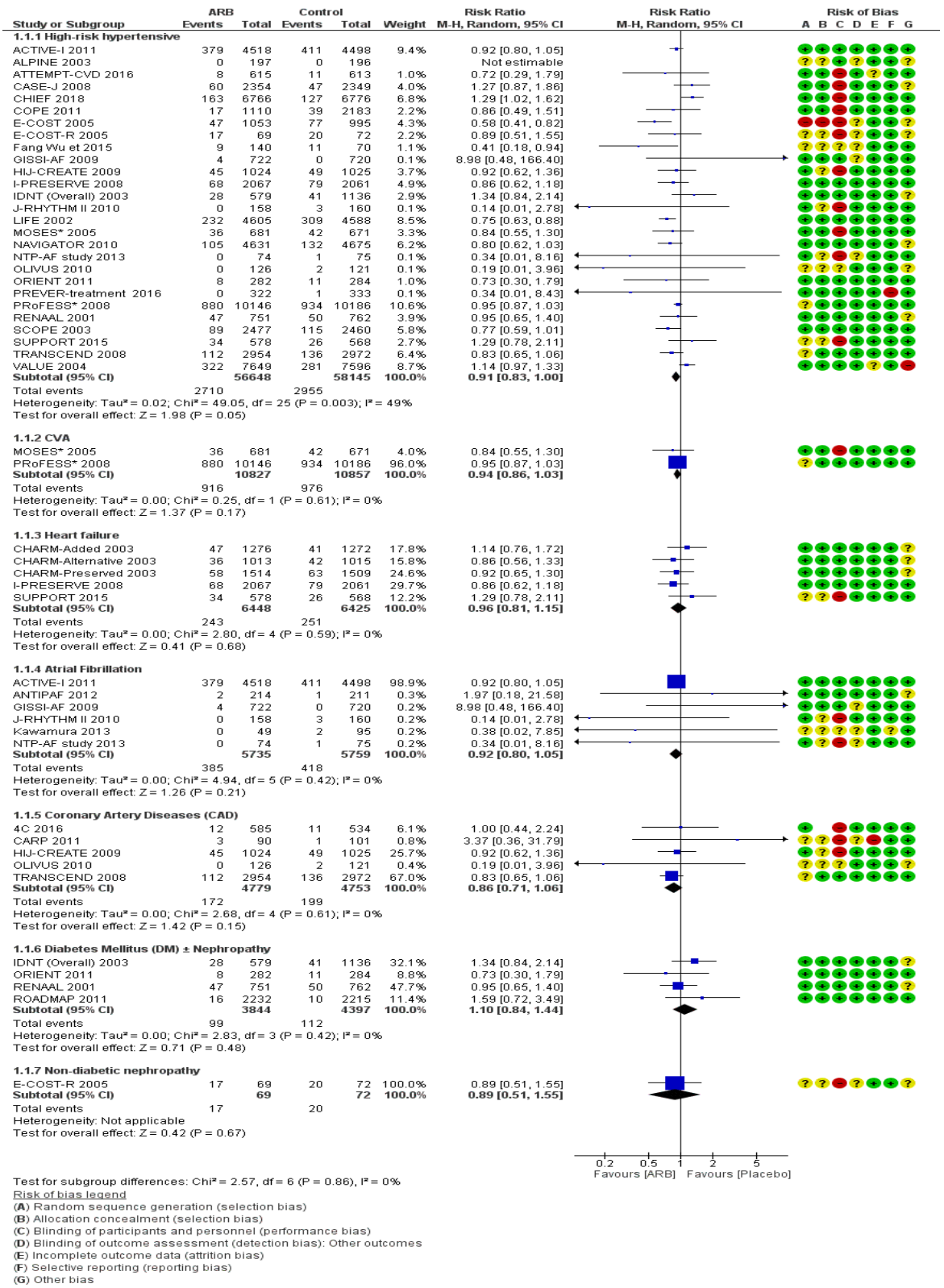


Figure 5-13 Forest plot showing effect of ARBs on risk of stroke (RE model). [Subgroup analysis: Clinical setting]

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

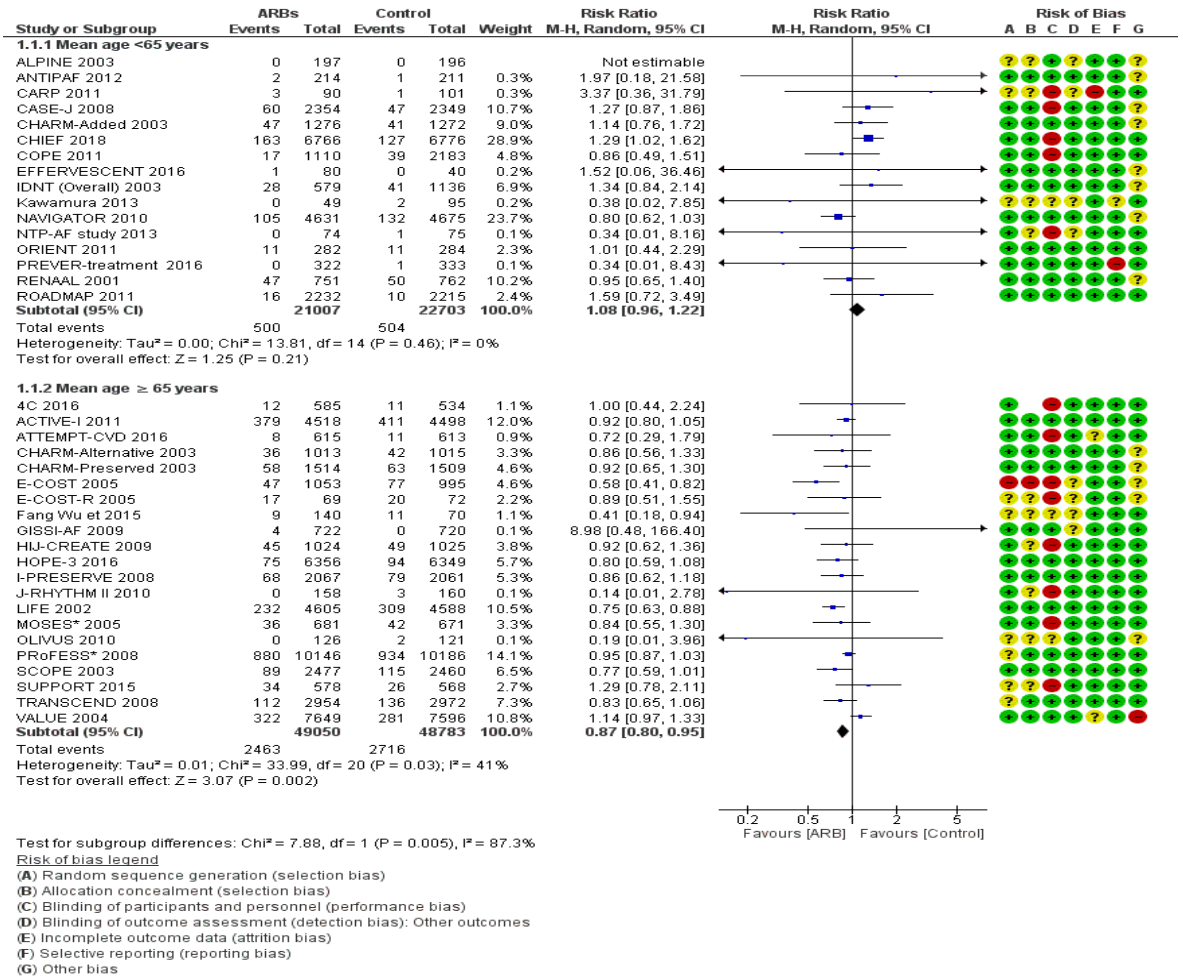


Figure 5-14 Forest plot showing effect of ARBs on risk of stroke (RE model). [Subgroup analysis: Mean age group].

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

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 (%) (Tau^2 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) (Tau^2 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)					**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)								
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 heterogeneity (between-study variance) not explained by covariate; I^2 residual= proportion of remaining observed variance due to true variation in effect size; ** The DBP difference achieved is excluded from multivariate model as it highly correlated with the achieved SBP differences (r=-0.99).

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

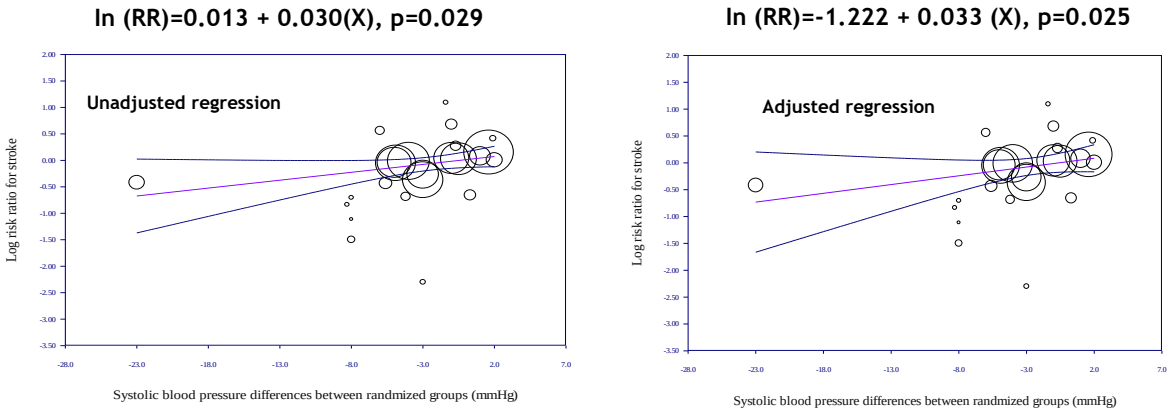


Figure 5-15 Adjusted and unadjusted meta-regression analysis of the relationship between RR for stroke and difference in SBP (mmHg) achieved between the randomized groups for trials of ACEIs.

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

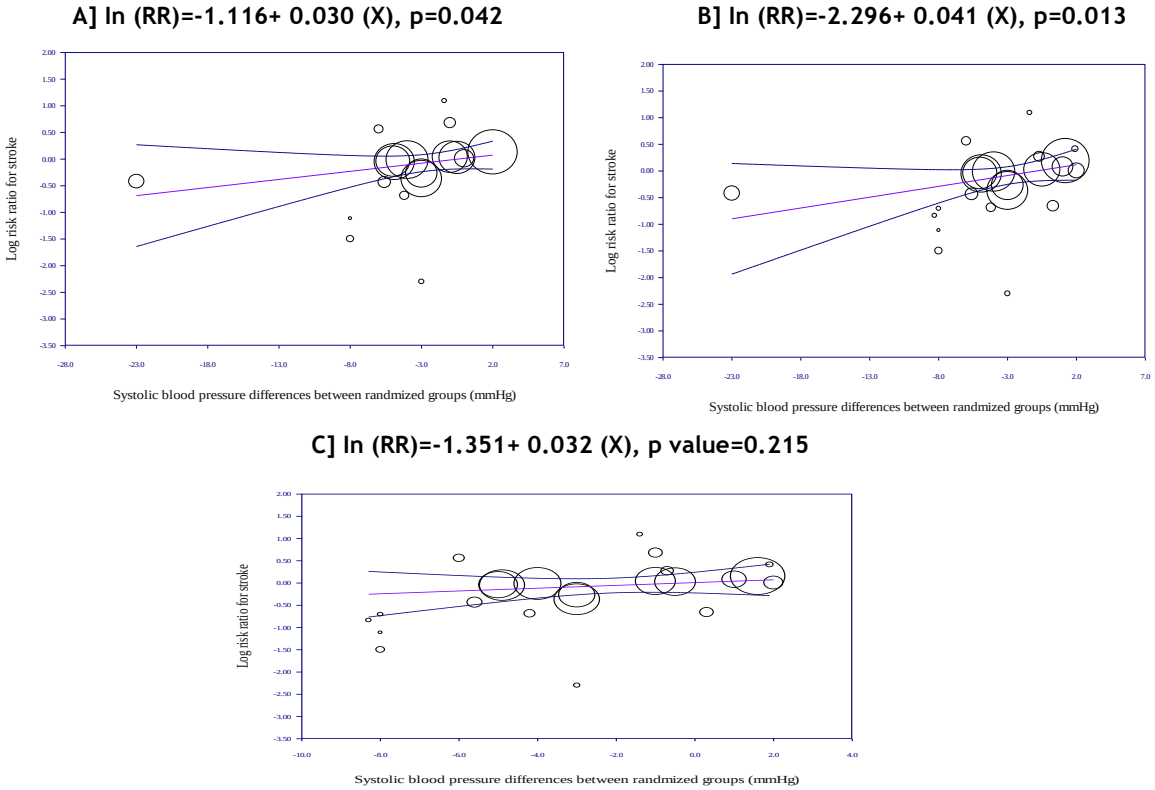


Figure 5-16 Adjusted meta-regression analysis of the relationship between RR for stroke and difference in achieved SBP (mmHg) between randomized groups for the ACEIs trials [Sensitivity analysis].

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 (R^2=100%) and the percentage of residual heterogeneity disappeared (the residual I^2=0% and Tau^2 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=O.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 (n)**	**RR**	**95% CI**	**P value**	**RR**	**95% CI**	**P value**	**Tau^2**	**I^2 residual (%)**	**P value**	**R^2 (%)**
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)											
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 amount of heterogeneity (between-study variance) not explained by the covariate; I^2 residual= proportion of remaining observed variance due to true variation in effect size

*The analysis was adjusted for DM (%), mean age (years), Male (%)

** Achieved DBP differences highly correlated with achieved SBP differences (r=-0.93).

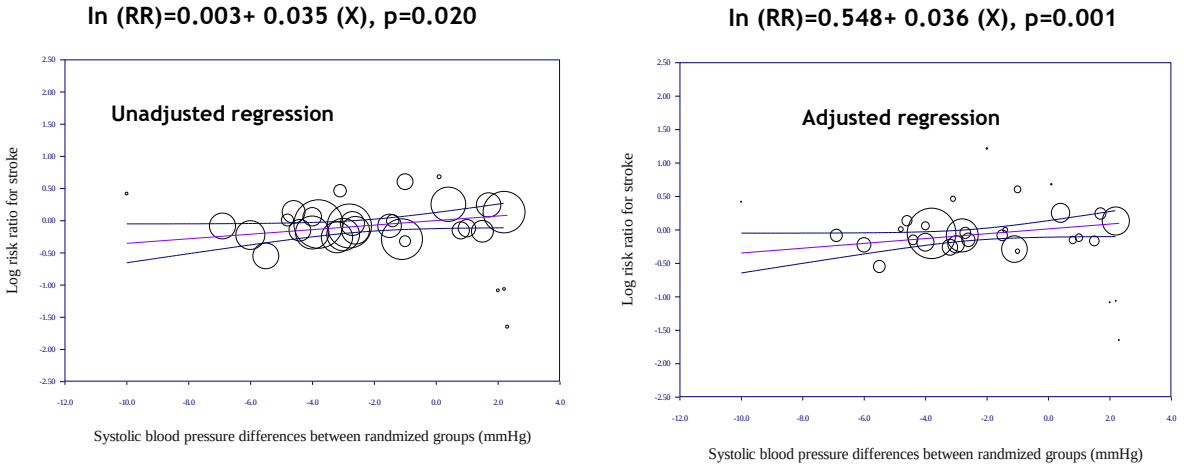


Figure 5-17 Adjusted and unadjusted meta-regression analysis of relationship between RR of stroke and difference in achieved SBP (mmHg) between randomized groups for ARBs trials.

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

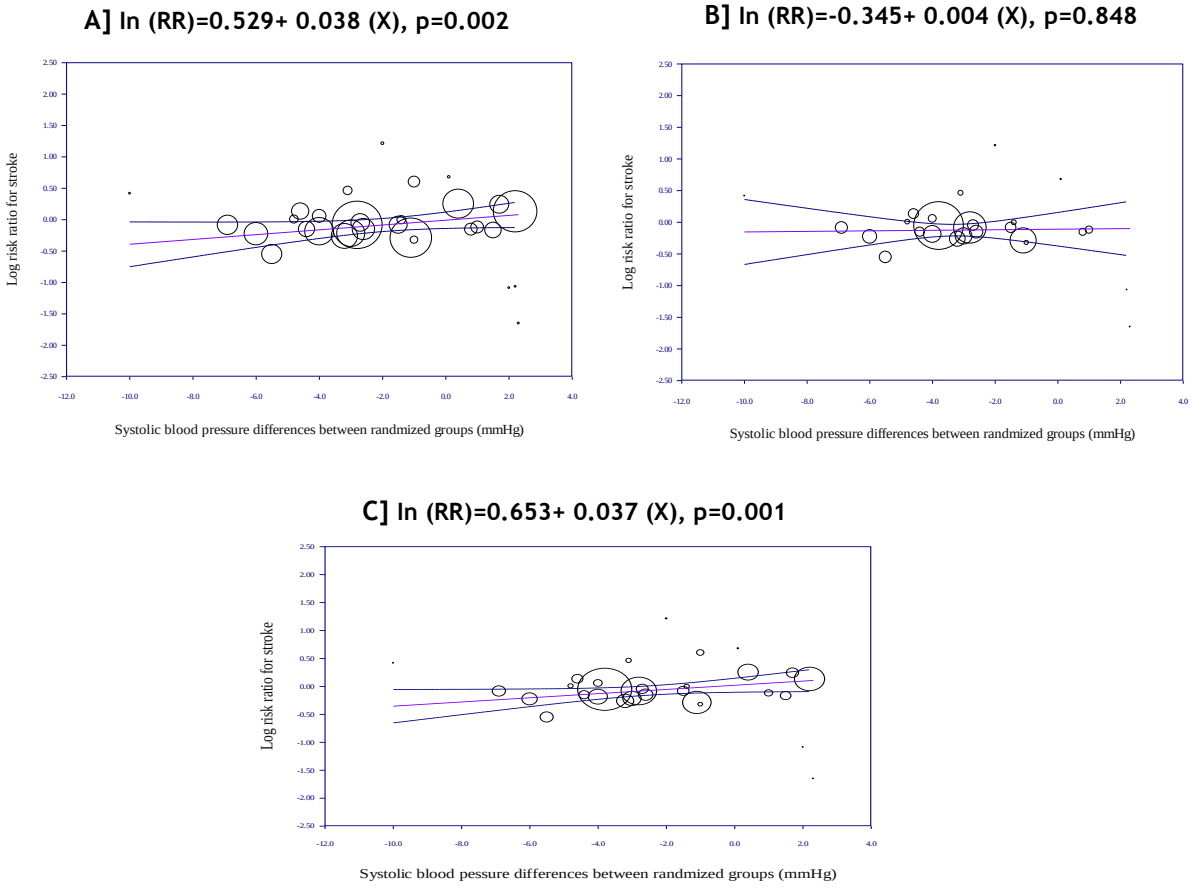


Figure 5-18 Adjusted meta-regression analysis of the relationship between RR for stroke and difference in achieved SBP (mmHg) between randomized groups for ARBs trails [Sensitivity analysis].

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 Tau^2=0, the meta-analytical summary generated by a FE model agreed with the RE model **(**see **Figure 5.20).**

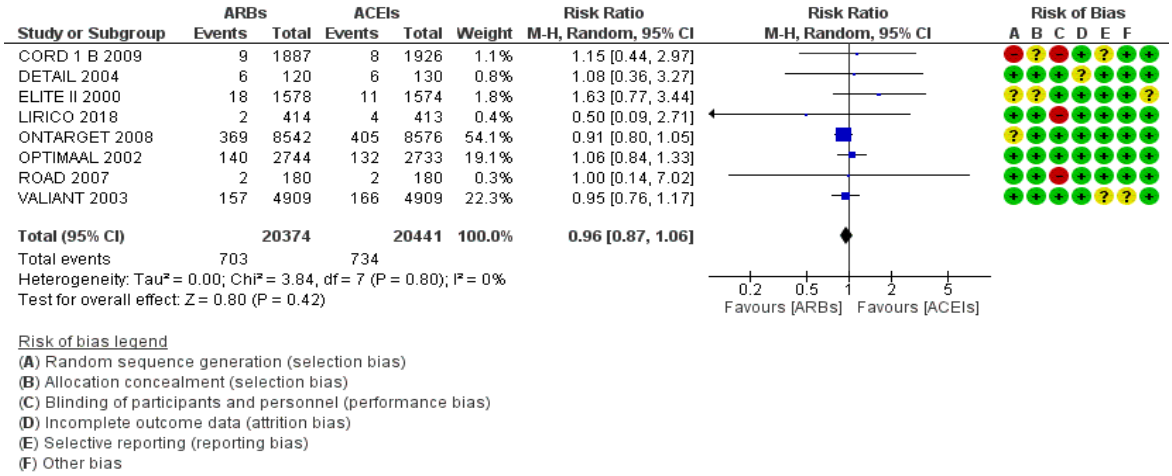


Figure 5-19 Forest plot showing effect of ARBs versus ACEIs on risk of stroke (RE model)

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

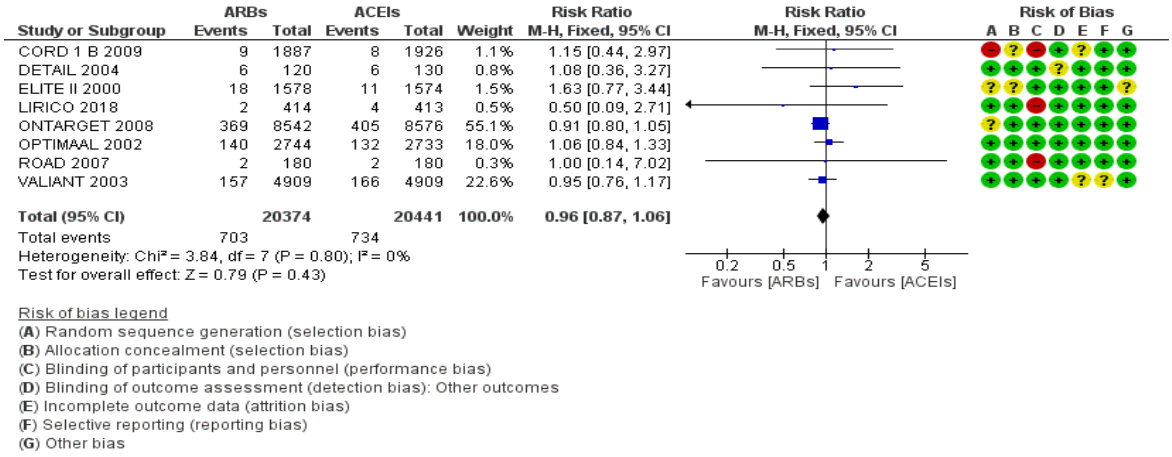


Figure 5-20 Forest plot showing effect of ARBs versus ACEIs on risk of stroke (FE model)

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

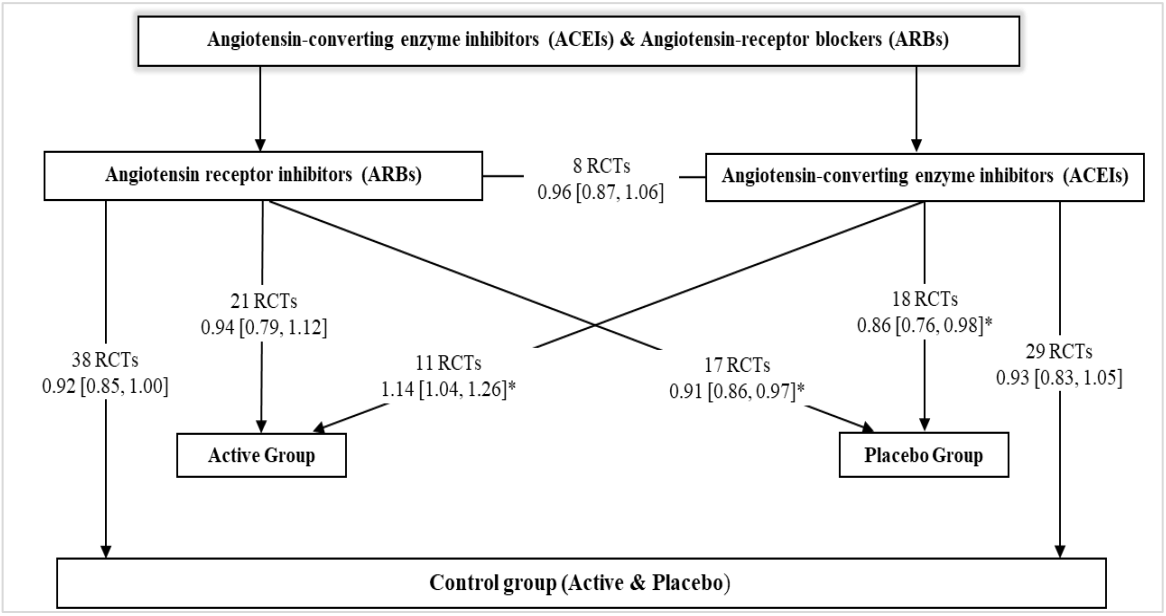


Figure 5-21 Flowchart representing a random-effects (RE) meta-analytical summary of the effectiveness of ACEIs and ARBs on risk of stroke

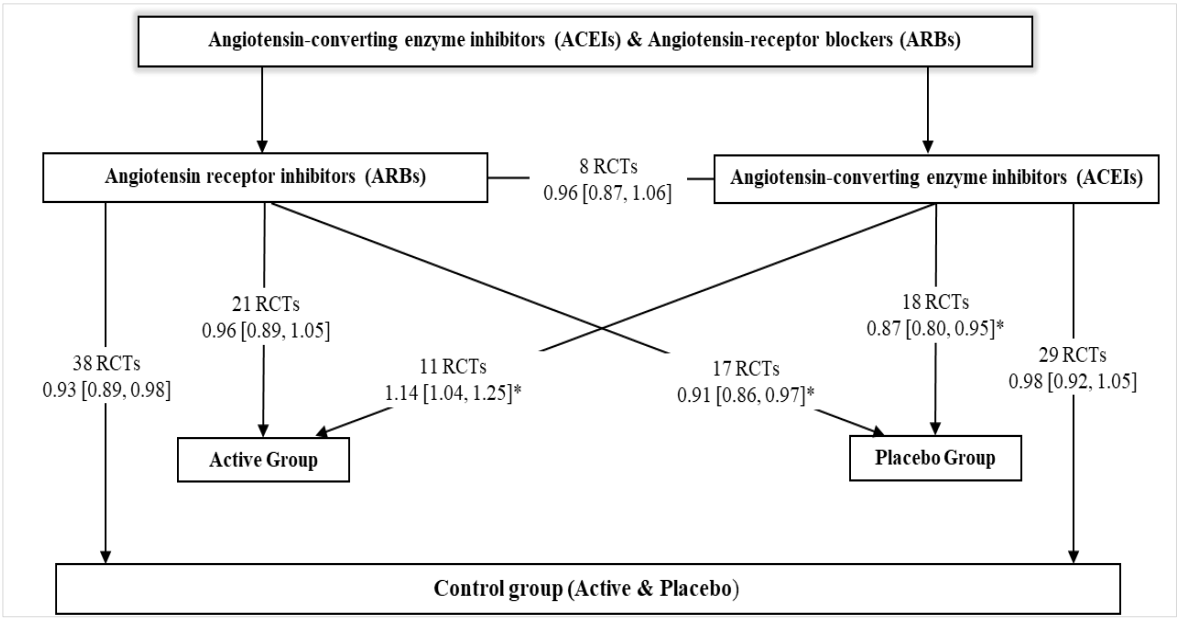


Figure 5-22 Flowchart representing a fixed-effect (FE) meta-analytical summary of the effectiveness of ACEIs and ARBs on risk of stroke

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 AT_4-mediated nitric-oxide-dependent intracellular hemodynamic mechanisms (Kramar et al., 1998). The hypothesised protective effects of AT_2 and AT_4 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 AT_2 and AT_4 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 pre-treatment. 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 angiotensin-increasing drugs ($P<0.00001$) (Boutitiea et al., 2007). In contrast, the benefit of ACEIs on AT_2 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 ≥ 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 AT_2 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 R^2 and residual heterogeneity (Tau^2) 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 AT_1, 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 AT_1 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 **(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

6.5.1 Overall 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.

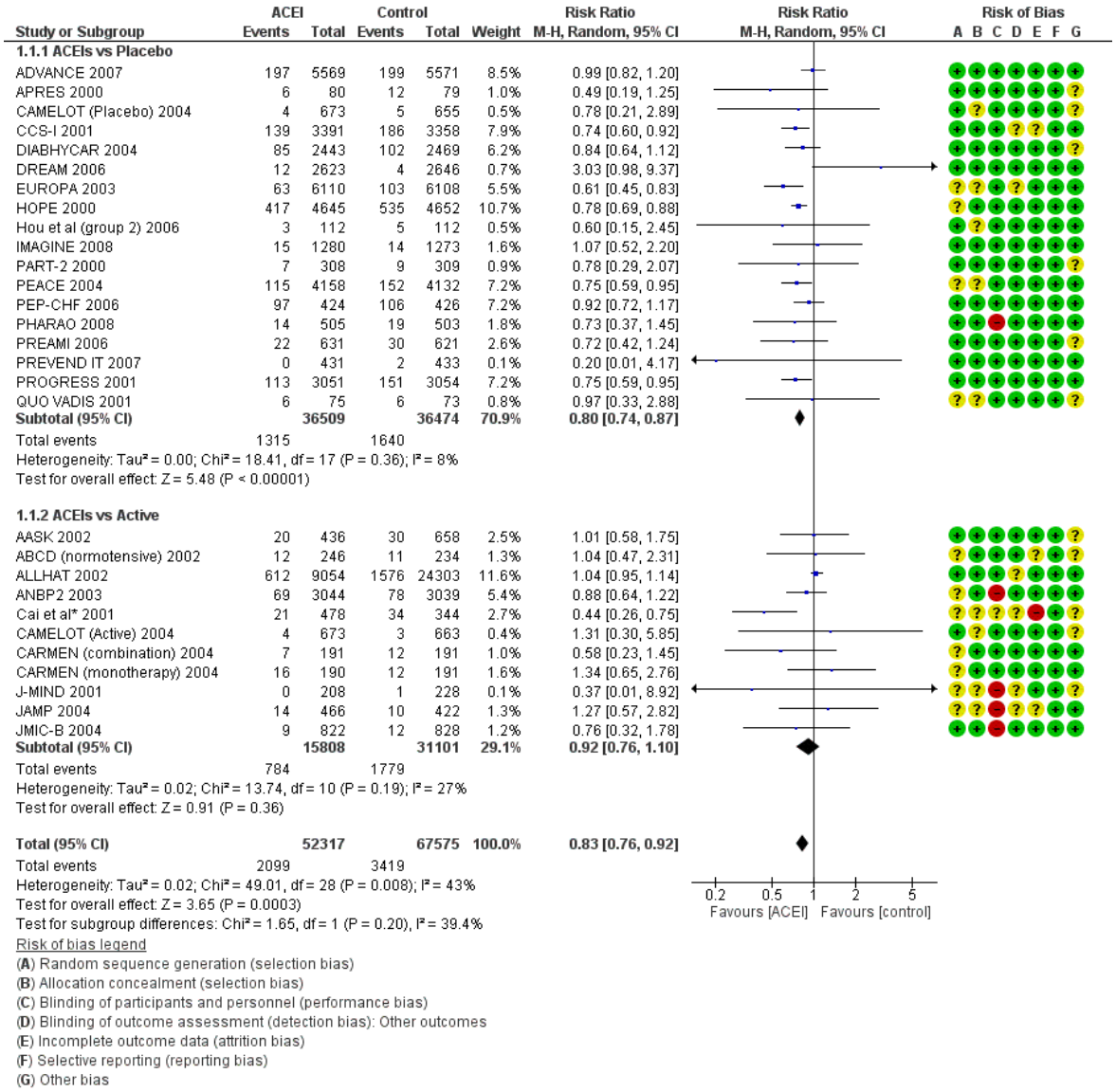


Figure 6-1 Forest plot showing of ACEIs on risk of HF, stratified by comparison group (placebo vs. active). Overall: 29 trials (RE model).

* Trial responsible for heterogeneity, excluding it resulted an I^2 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

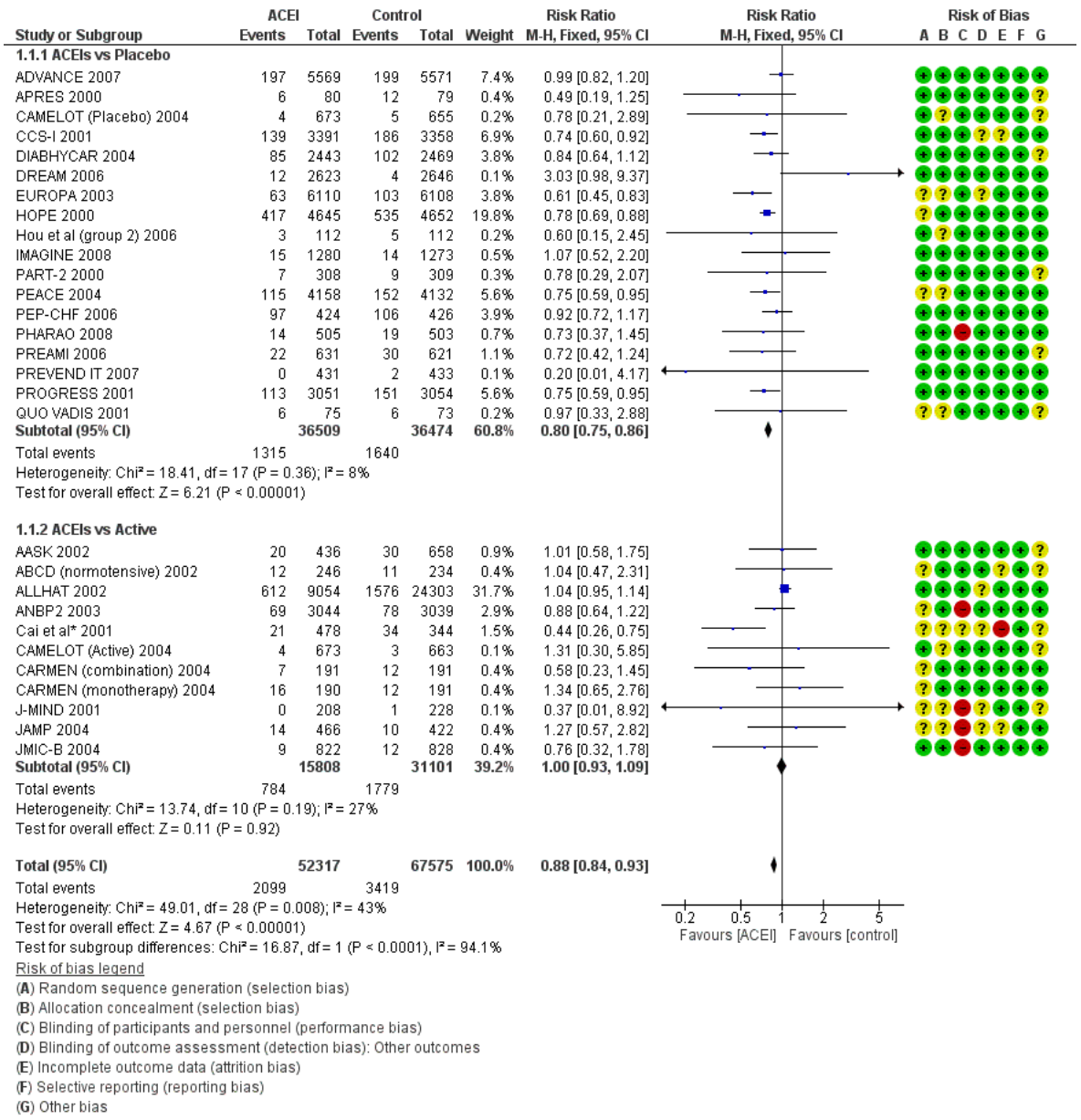


Figure 6-2 Forest plot showing effect of ACEIs on risk of HF, stratified by comparison group (placebo vs. active). Overall: 29 (FE model)

*Trial responsible for heterogeneity, excluding it resulted an I^2 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

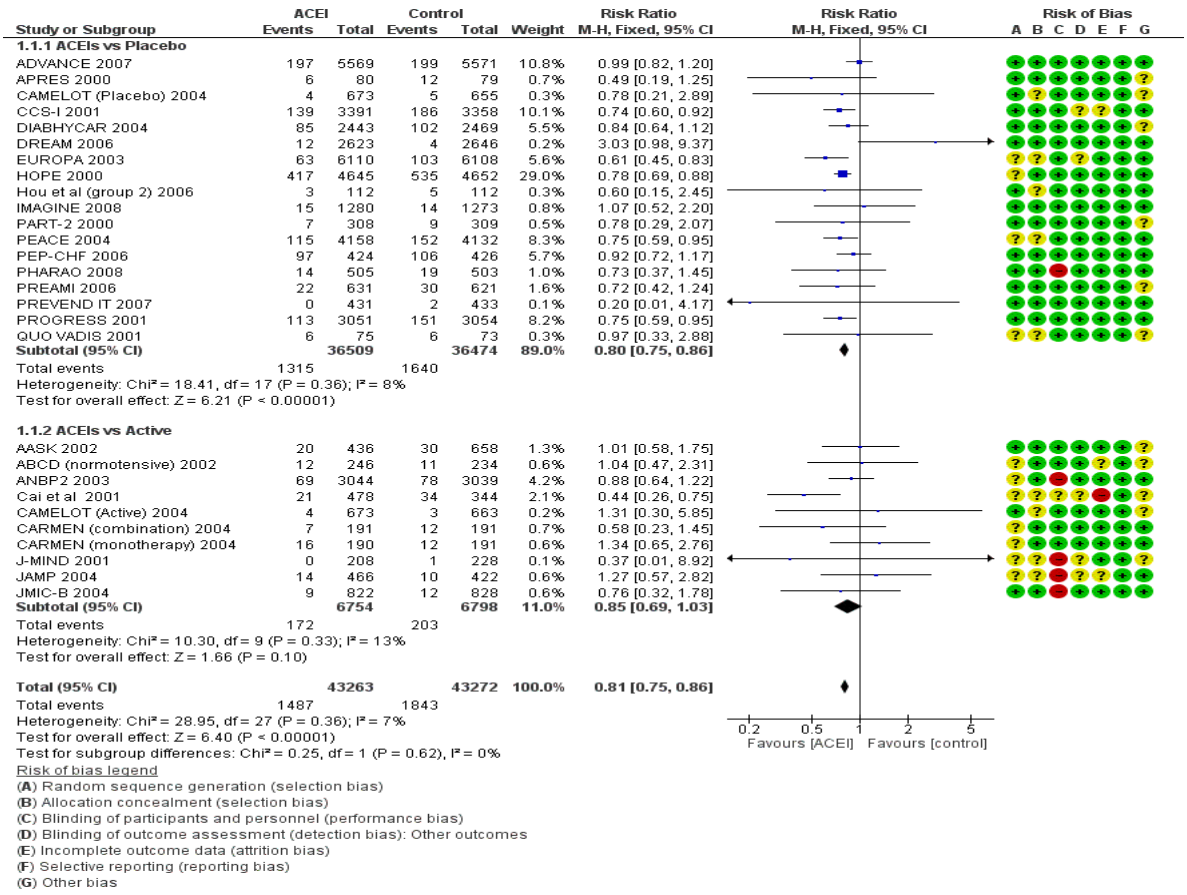


Figure 6-3 Forest plot showing the effect of ACEIs on risk of HF (RE model). [Sensitivity analysis: Excluding ALLHAT trial]

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 I^2

=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.

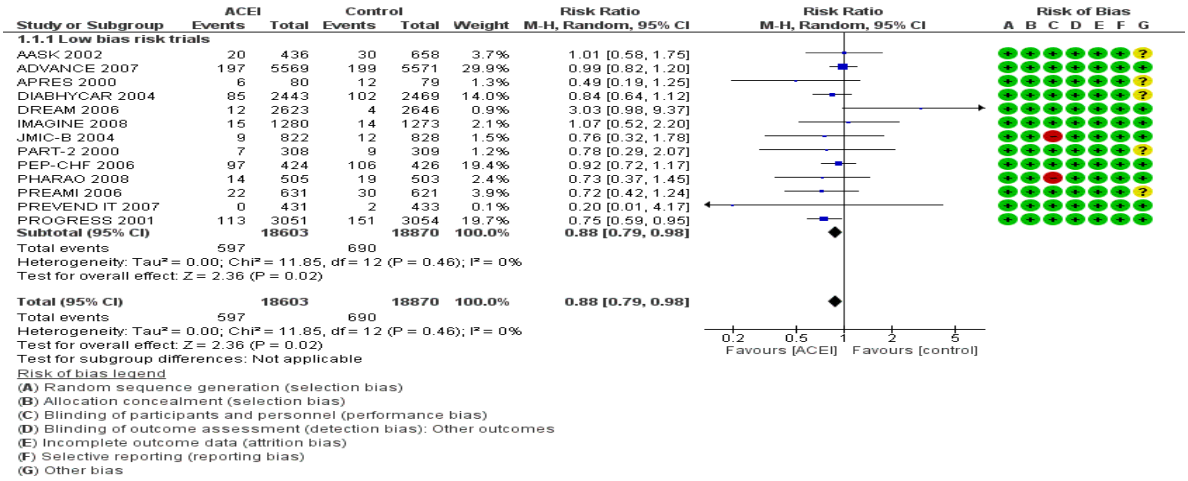


Figure 6-4 Forest plot showing the effect of ACEIs on risk of HF (RE model). [Sensitivity analysis: Excluding trials with low methodological quality]

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

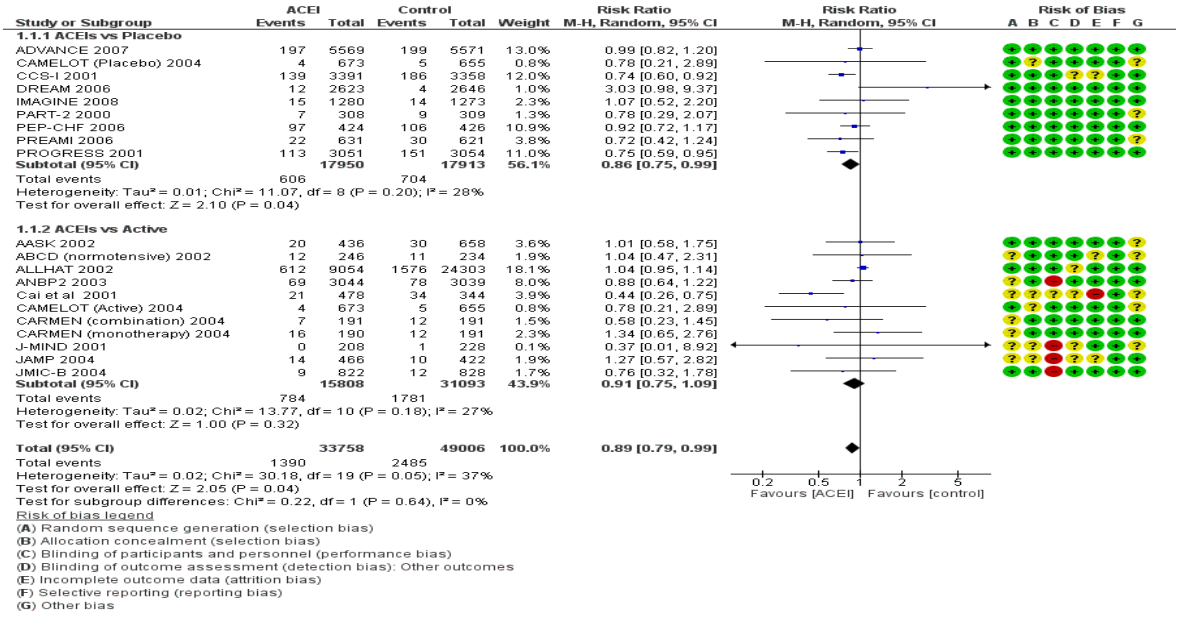


Figure 6-5 Forest plot showing effect of ACEIs on risk of HF (RE model). [Sensitivity analysis: Excluding trials with naive participants]

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 risk of 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 I^2=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; I^2=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 I^2 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 (I^2=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 ≥ 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 (I^2 = 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 (I^2=0%) and the model yielded an RR of 0.85 (95% CI 0.78–0.92; p=0.0001) (See **Figure 6.9**)

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

Subgroup analysis		Studies	Participants	Events	HF Incidence (%)		RR (M-H, Random, 95% CI)	P value*	I^2 (%) ‡
					ACEI	Control			
Overall effects	**RE**	**29**	**119,892**	**5,518**	**4.01**	**5.05**	**0.83 [0.76, 0.92]**	**0.0003***	**43**
Subclass	**High-tissue affinity**	16	65,136	2,669	3.67	4.51	0.82 [0.75, 0.89]	**<0.0001***	15
	Low-tissue affinity	12	54,080	2,845	4.70	5.56	0.85 [0.70, 1.04]	0.11	**49¥**
Active control	**Dihydropyridine CCBs**	6	22,649	1,400	5.74	6.62	0.87 [0.79, 0.96]	**0.008***	0
	Diuretics	2	30,392	1,629	5.62	5.18	1.07 [0.81, 1.41]	0.62	66
	Active control	5	3,350	168	4.42	5.66	0.81 [0.52, 1.28]	0.37	54
Clinical setting	**High-risk hypertensive**	13	82,279	4,310	4.74	5.57	0.89 [0.79, 0.99]	**0.03***	40
	CAD	13	46,634	1,949	3.62	4.72	0.75 [0.69, 0.82]	**<0.00001***	0
	DM± nephropathy	4	16,968	607	3.47	3.68	0.94 [0.81, 1.10]	0.45	0
	HF	3	1,613	250	14.9	16.08	0.93 [0.74, 1.16]	0.51	0
	Non-diabetic nephropathy	2	1,088	10	0.55	1.28	0.49 [0.14, 1.77]	0.28	0
	CVA**	1	6,105	264	3.70	4.94	0.75 [0.59, 0.95]	**0.02***	NA
Mean age group	**< 65 years**	20	50,678	1,368	2.34	3.04	0.76 [0.67, 0.85]	**<0.00001***	8
	≥ 65 years	8	68,541	4,146	5.66	6.29	0.90 [0.80, 1.01]	0.09	**57†**

†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 considered statistically significant; ** Cannot synthesize data from one trial; ‡ I^2 statistic with <25% considered as low heterogeneity and I^2> 75% as high heterogeneity

¥ Excluding ALLHAT trial resulted in a significant RR of 0.78 (95% CI 0.66–0.93; p=0.006; I^2=7%)

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

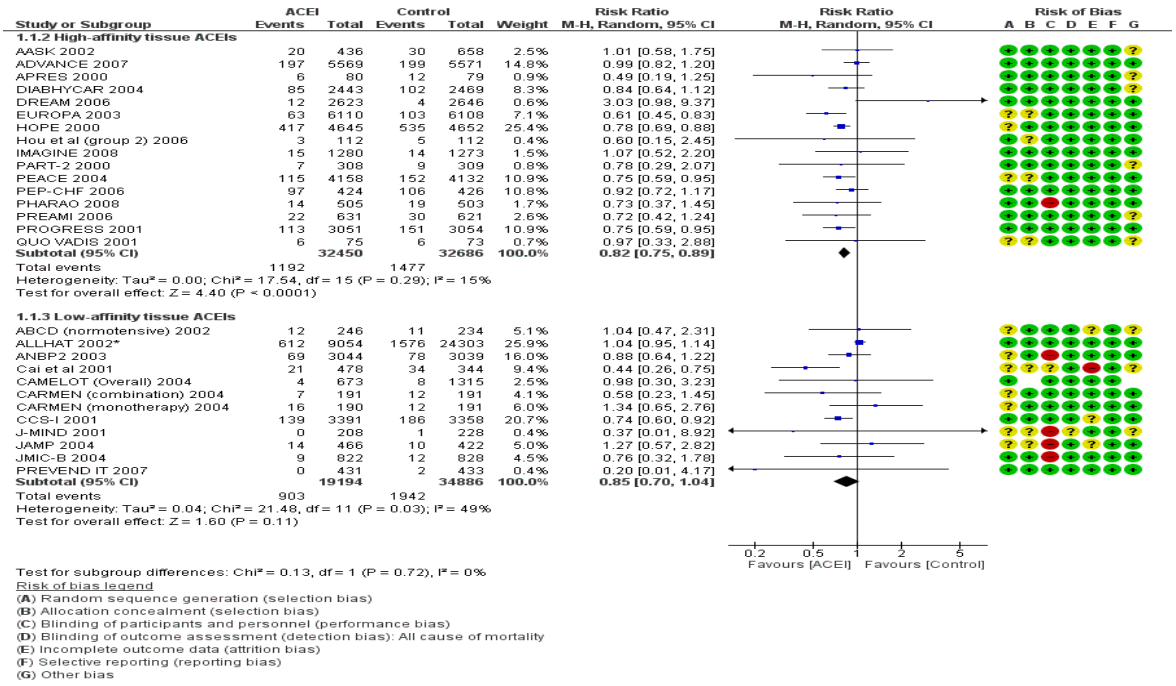


Figure 6-6 Forest plot showing the effect of ACEIs on risk of HF (RE model). [Subgroup analysis: Low vs. high tissue-affinity ACEIs].

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

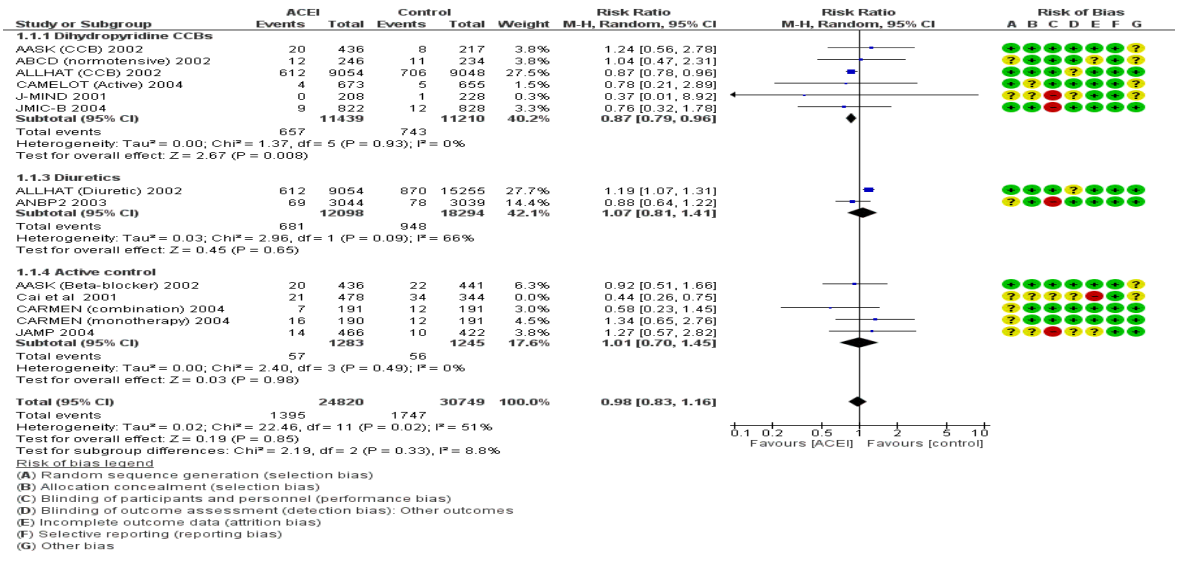


Figure 6-7 Forest plot showing the effect of ACEIs on risk of HF (RE model). [Subgroup analysis: Class of active control].

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

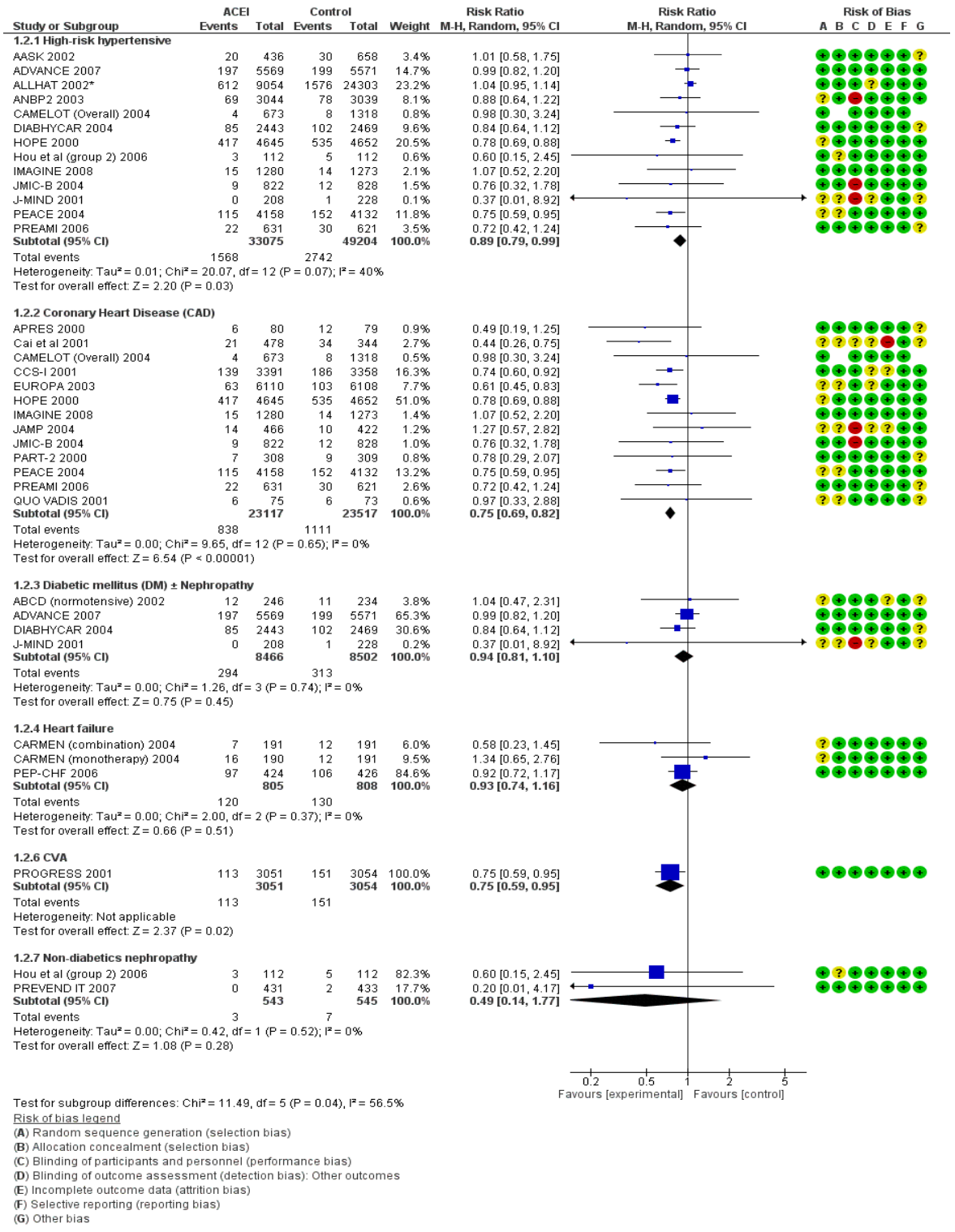


Figure 6-8 Forest plot showing the effect of ACEIs on risk of HF (RE model). [Subgroup analysis: Clinical setting]

*After excluding the ALLHAT trial, the heterogeneity disappeared (I^2=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

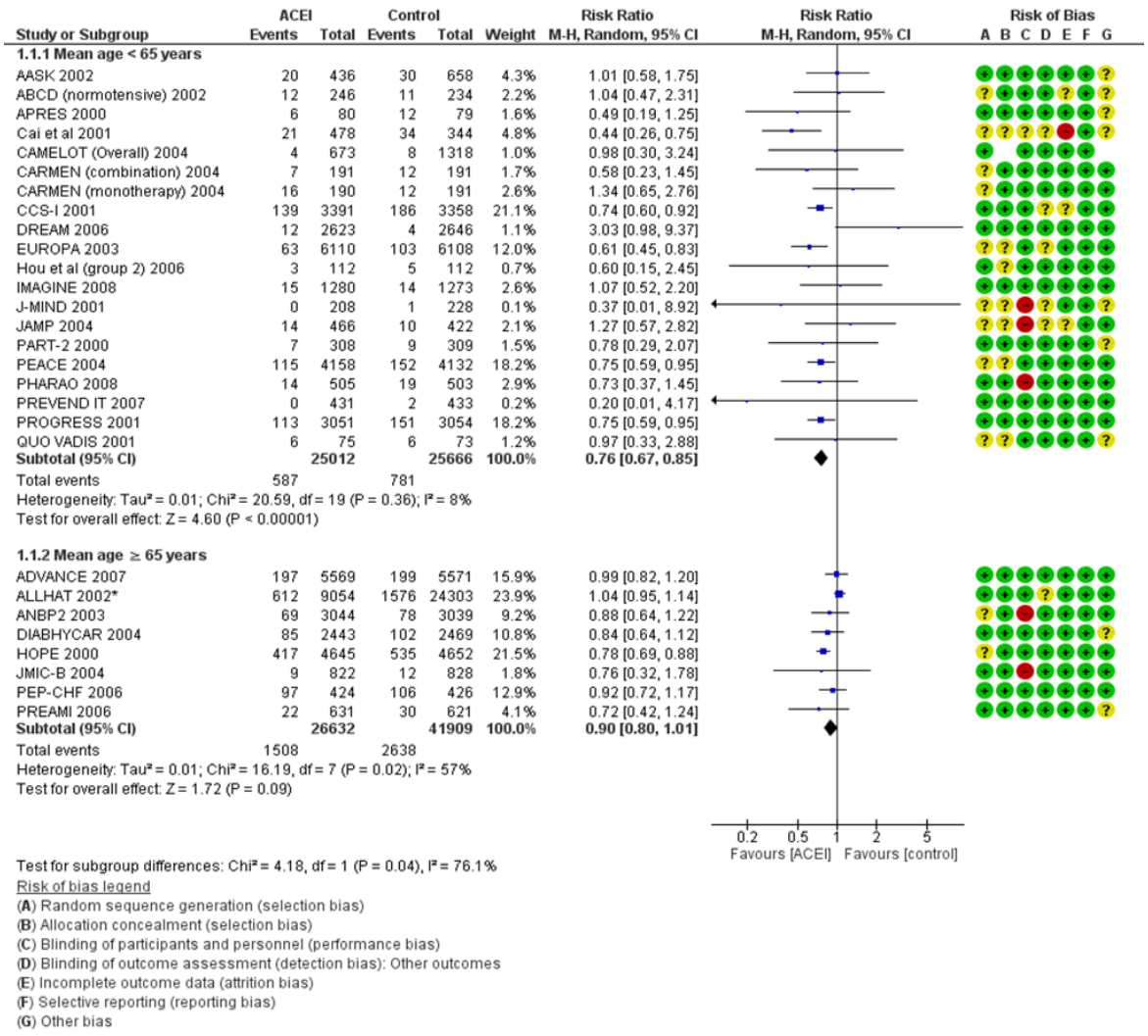


Figure 6-9 Forest plot showing the effect of ACEIs on risk of HF (RE model). [Subgroup analysis: Mean age group]

* 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

6.6.1 Overall 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 I^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; I^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.

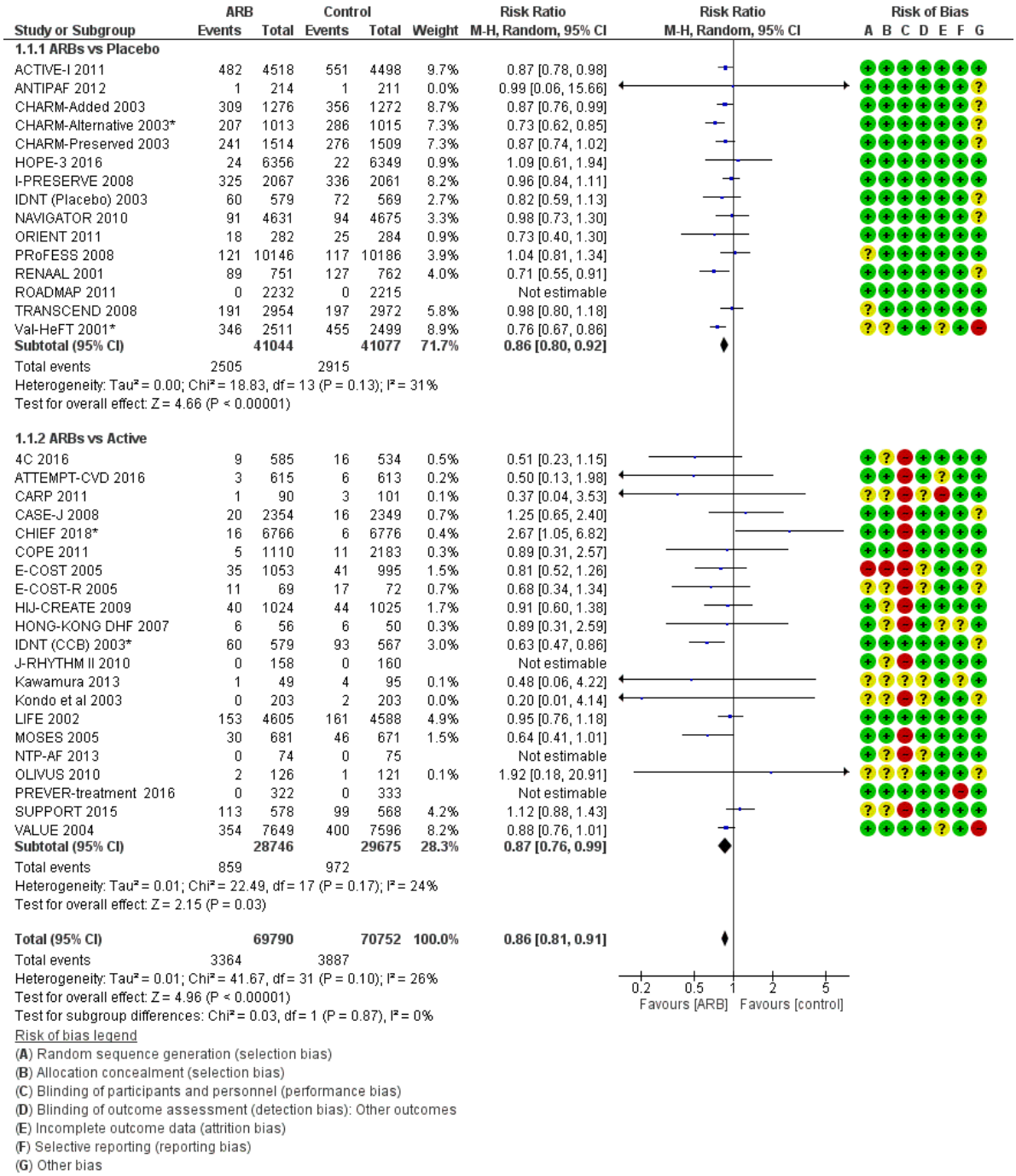


Figure 6-10 Forest plot showing the effect of ARBs on risk of HF, stratified by comparison group (placebo vs active). Overall: 36 trials (RE model).

*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

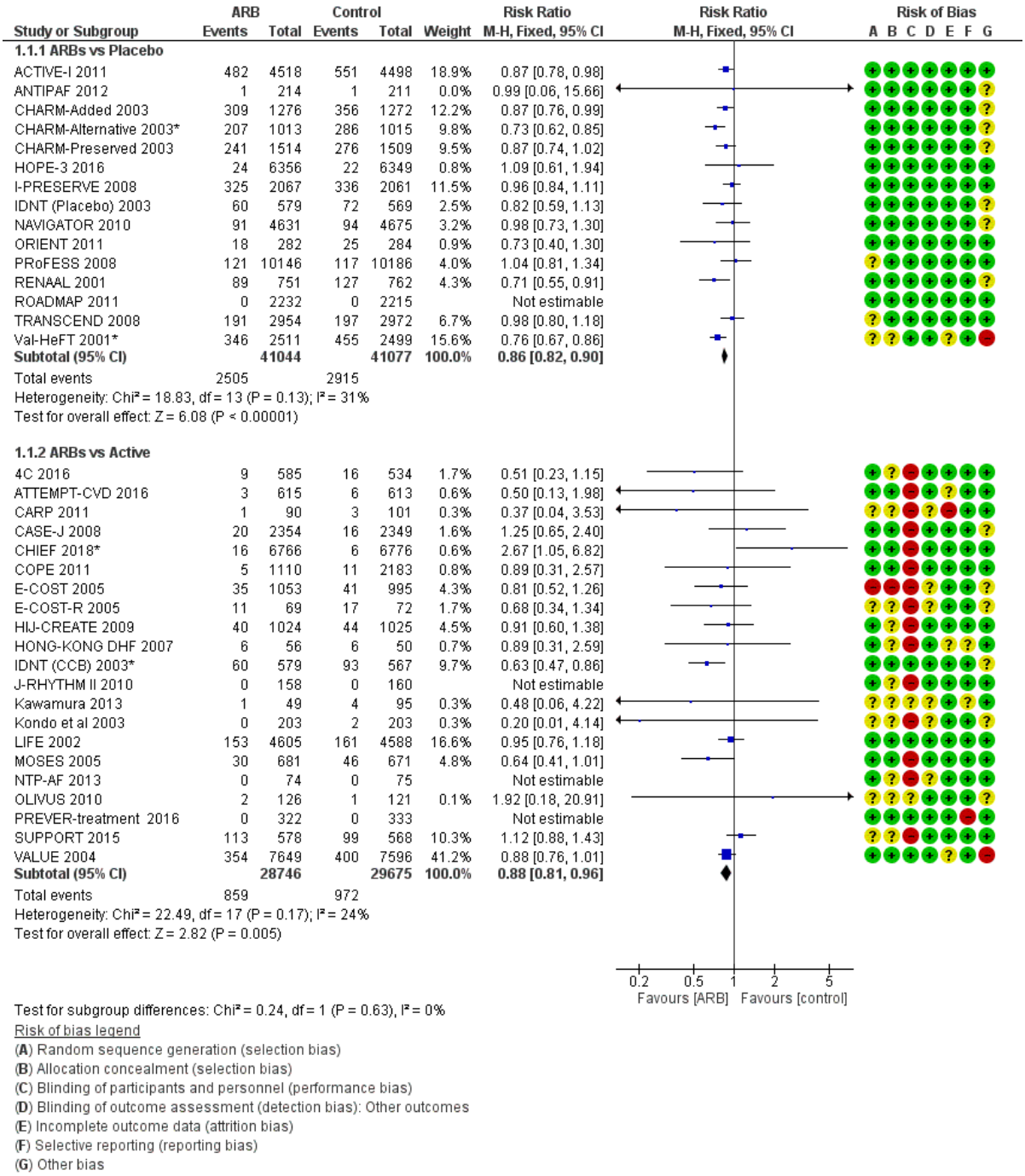


Figure 6-11 Forest plot showing the effect of ARBs on risk of HF, stratified by comparison group (placebo vs active). Overall: 36 trials (FE model).

*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).

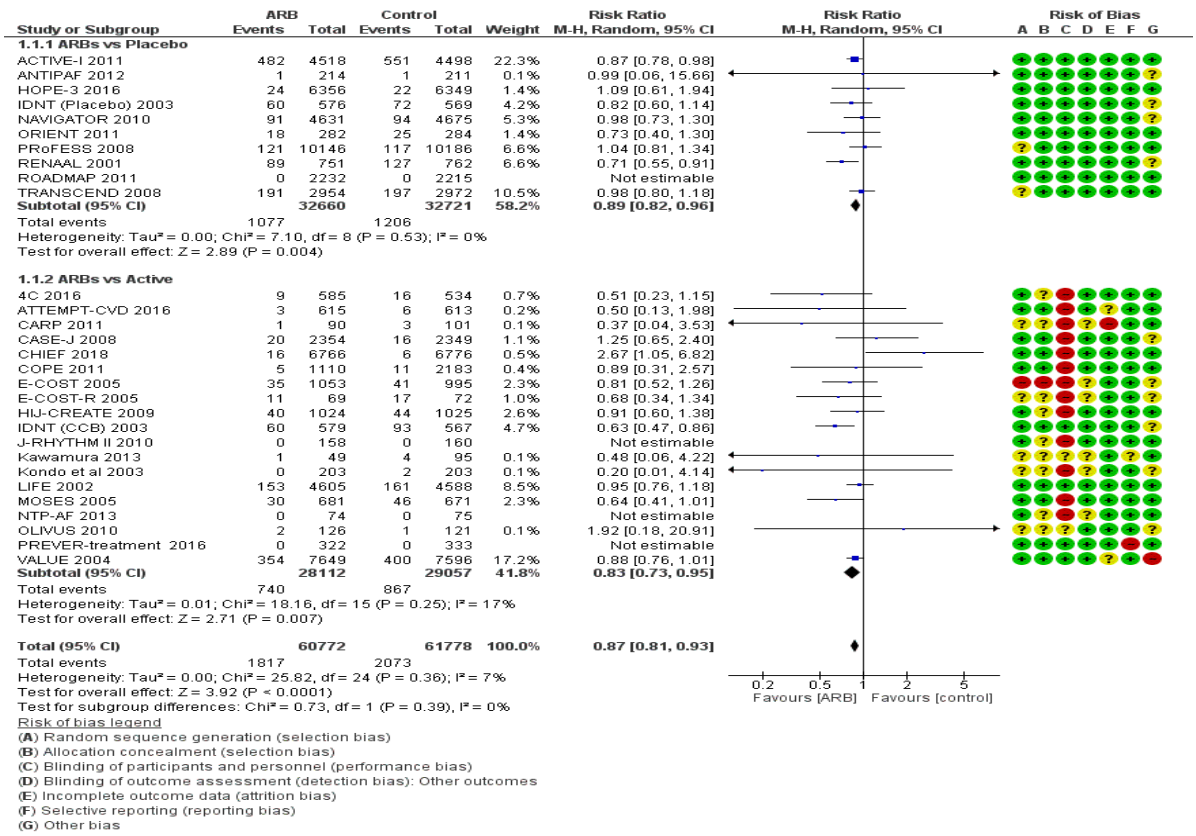


Figure 6-12 Forest plot showing the effect of ARBs on risk of HF (RE model). [Sensitivity analysis: Excluding trials of symptomatic HF (NYHA class II-IV]

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

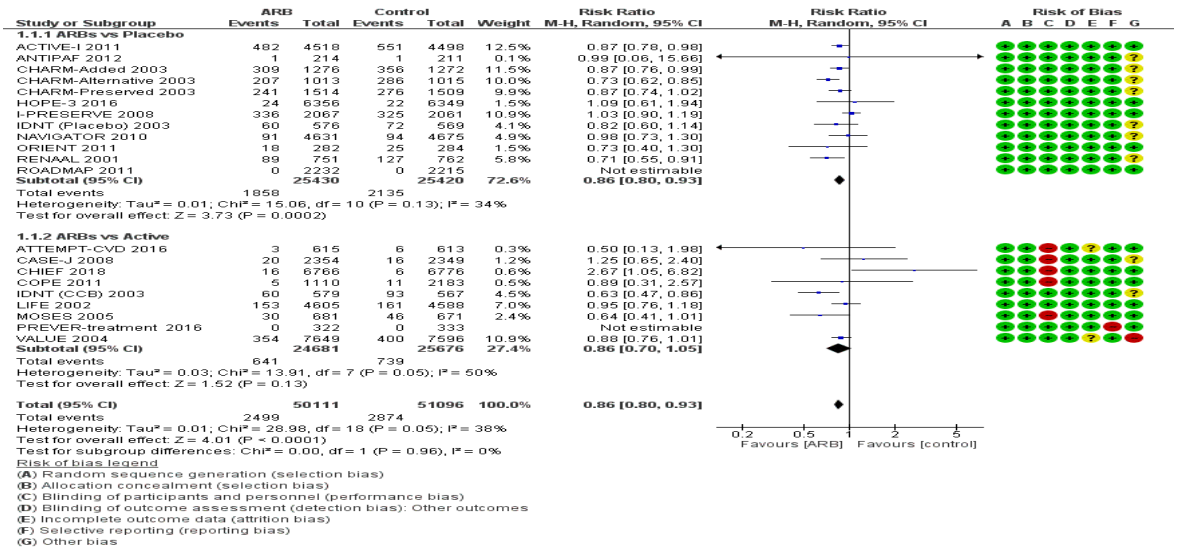


Figure 6-13 Forest plot showing the effect of ARBs on risk of HF (RE model). [Sensitivity analysis: Excluding trials with low methodological quality]

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

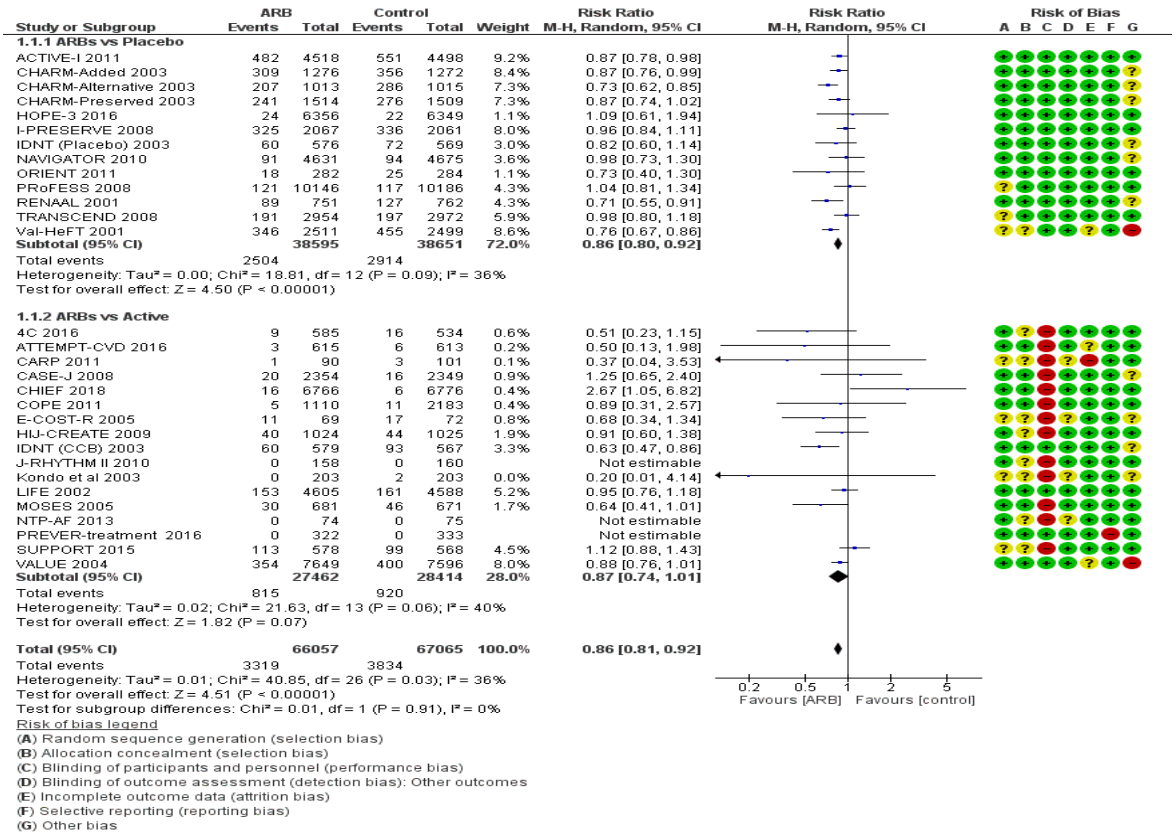


Figure 6-14 Forest plot showing the effect of ARBs on risk of HF (RE model). [Sensitivity analysis: Excluding trials with RAAS-blockers naïve]

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 I^2 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 I^2=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 I^2 statistics diminished (I^2=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 I^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 ≥ 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).

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

Subgroup analysis		Studies	Participant	Events	HF Incidence (%)		RR (M-H, Random, 95% CI)	P value*	I^2 (%) ‡
					ARBs	Control			
Overall effects	**RE**	**36**	**140,542**	**7251**	**4.82**	**5.49**	**0.86 [0.81, 0.91]**	**<0.00001***	**26**
Subclass	**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
	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
Active control	**DHP-CCBs**	8	36,599	1,037	2.57	3.08	0.85 [0.64, 1.13]	0.26	**59¥**
	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

†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 < 0.05 considered statistically significant; ** Cannot synthesize data from one trial; ‡ I^2 statistic with <25% considered as low heterogeneity and I^2> 75% as high heterogeneity.

¥ Excluding CHIEF and IDNT yields an RR of 0.84 (95% CI 0.73–0.98; p=0.02; I^2 =3%)

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)[†]

Subgroup analysis		Studies	Participants	Events	HF Incidence (%)		RR (M-H, Random, 95% CI)	P value*	I^2 (%) ‡
					ACEI	Control			
Overall effects	**RE**	**36**	**140,542**	**7251**	**4.82**	**5.49**	**0.86 [0.81, 0.91]**	**<0.00001***	**26**
Clinical setting	**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
	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. CI: 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 CHARM-Alternative and Val-HeFT results in an RR of 0.92 (95% CI 0.85–1.00; I^2=7%).

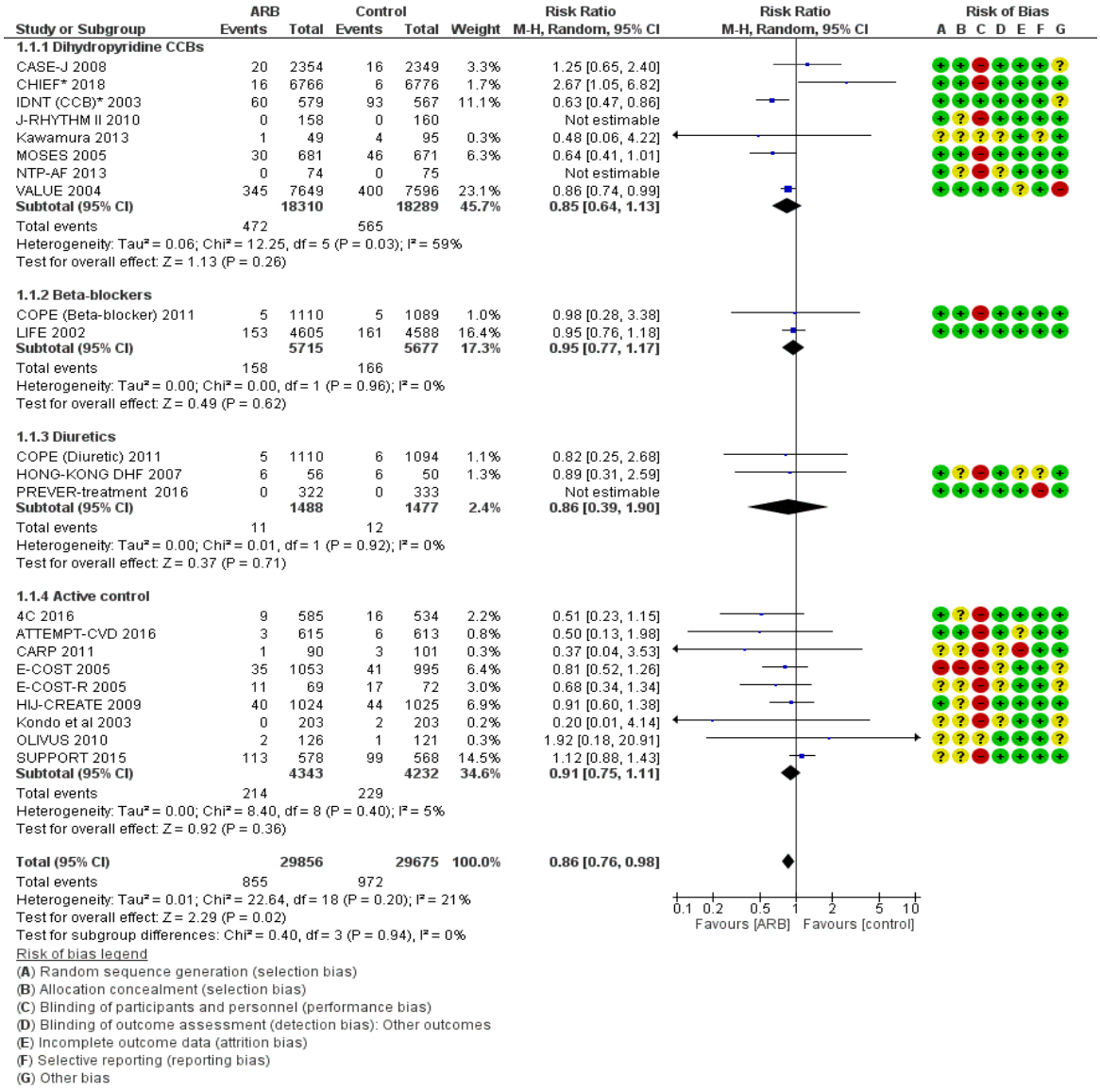


Figure 6-15 Forest plot showing the effect of ARBs on risk of HF (RE model). [Subgroup analysis: Class of comparator]

* Excluding CHIEF and IDNT trials yields an RR of 0.84 (95% CI 0.73–0.98; p=0.02) and I^2 of 3%. CI: confidence interval; RE: random-effects; M-H: Mantel-Haenszel. For studies acronyms, see list of definition/ abbreviations

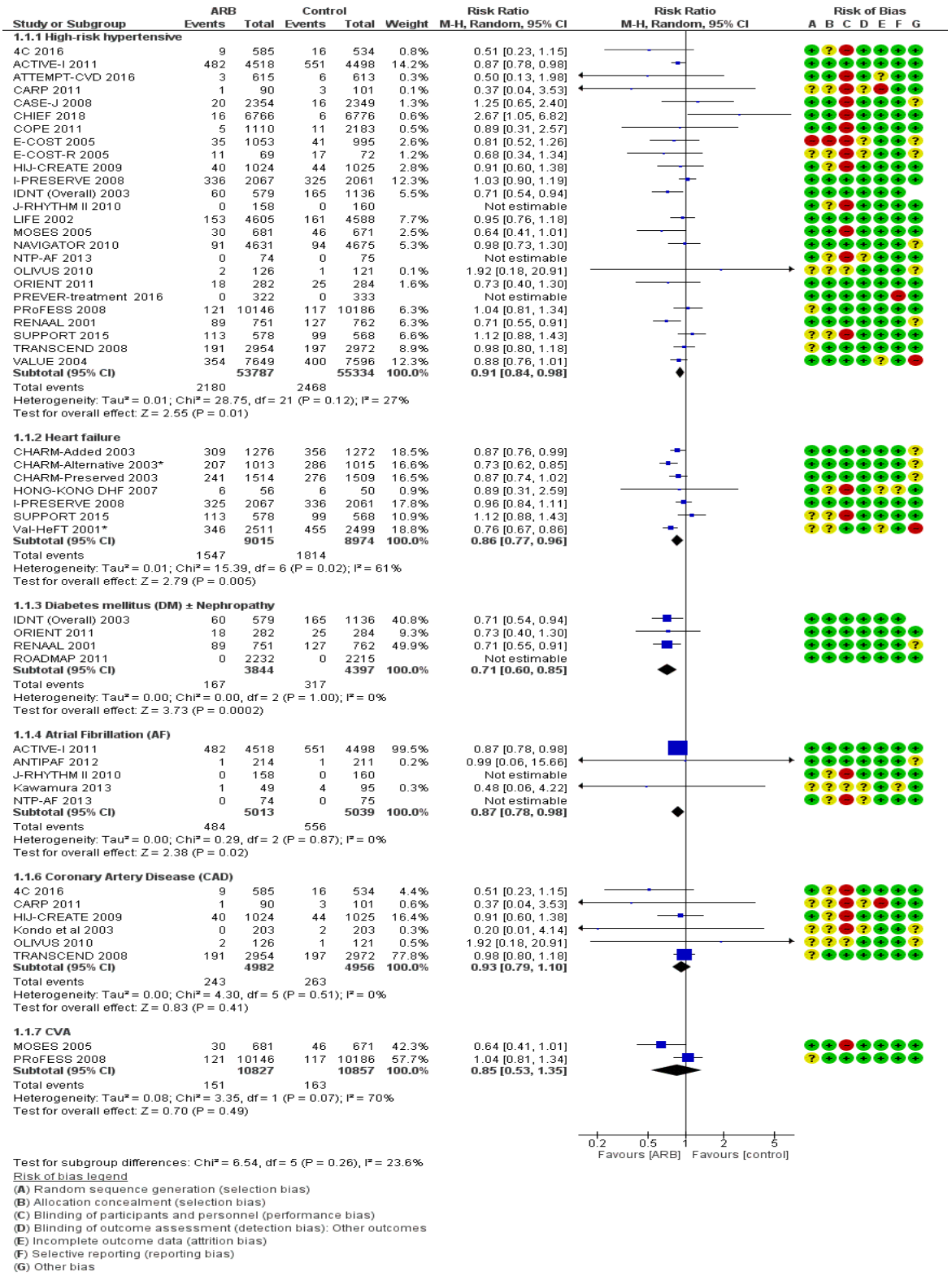


Figure 6-16 Forest plot showing the effect of ARBs on risk of HF (RE model). [Subgroup analysis: Clinical setting]

*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

6.7.1 ACEIs

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 Tau^2 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).

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

		Slope			Between-study variance			
Variable	**Studies**	**RR**	**95% CI**	**P value**	**Tau2**	**Residual I^2 (%)**	**P value**	**R^2 (%)**
Null model (without covariates)					**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 (between-study variance) not explained by covariate; I^2 residual= proportion of remaining observed variance due to true variation in effect size.

*The analysis was adjusted for male (%) and baseline SBP (mmHg)

**Achieved DBP and SBP is highly correlated (r=-0.8)

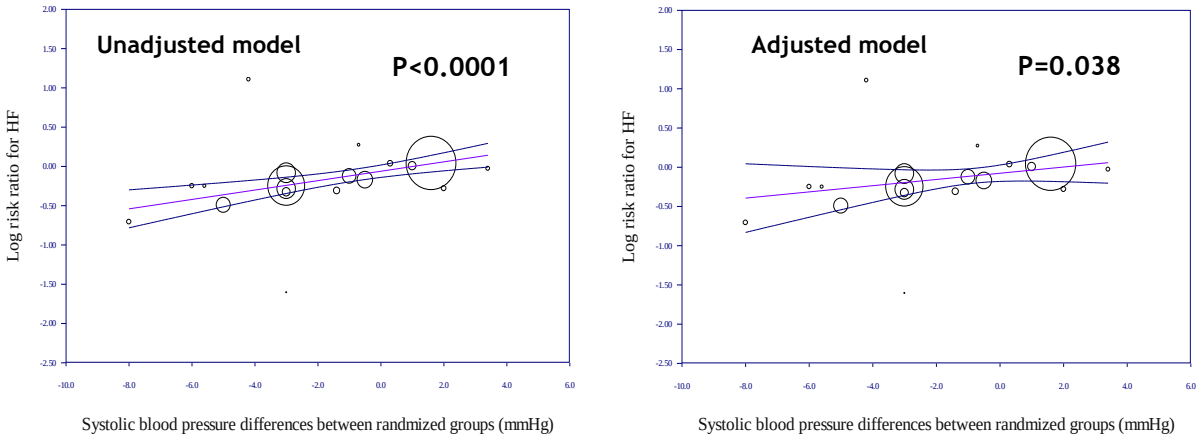


Figure 6-17 Meta-regression analysis of the relationship between RR of HF and difference in achieved SBP (mmHg) between randomized groups for trials of ACEIs.

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.

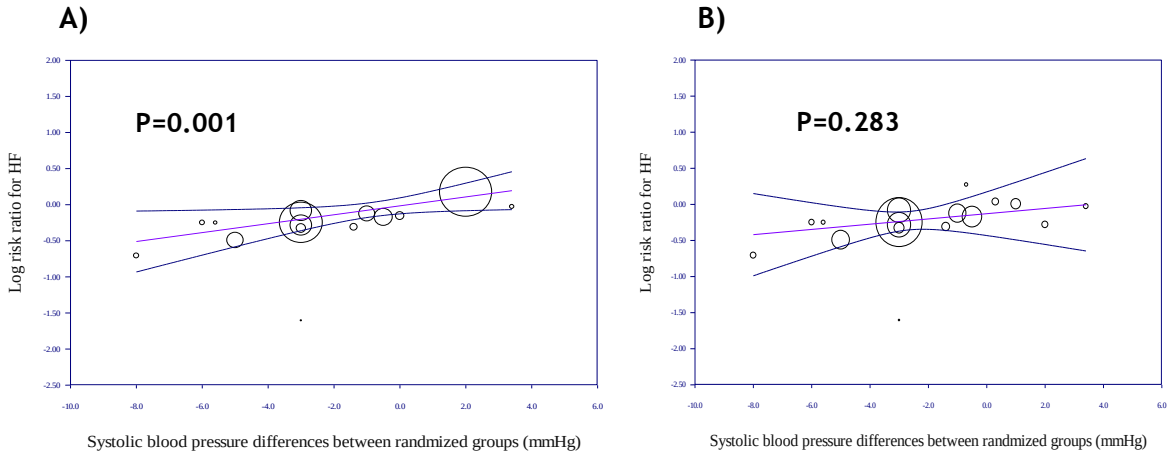


Figure 6-18 Multivariate meta-regression analysis of relationship between RR of HF and difference in achieved SBP (mmHg) between randomized groups for ACEIs trials [Sensitivity analysis].

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

6.7.2 ARBs

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).

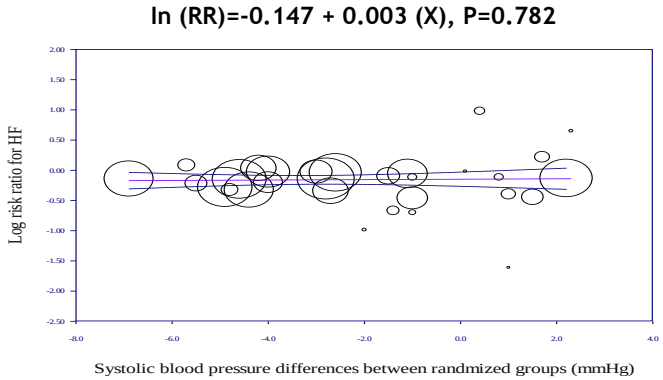


Figure 6-19 Meta-regression analysis of the relationship between RR of HF and difference in achieved SBP (mmHg) between randomized groups for trials of ARBs.

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

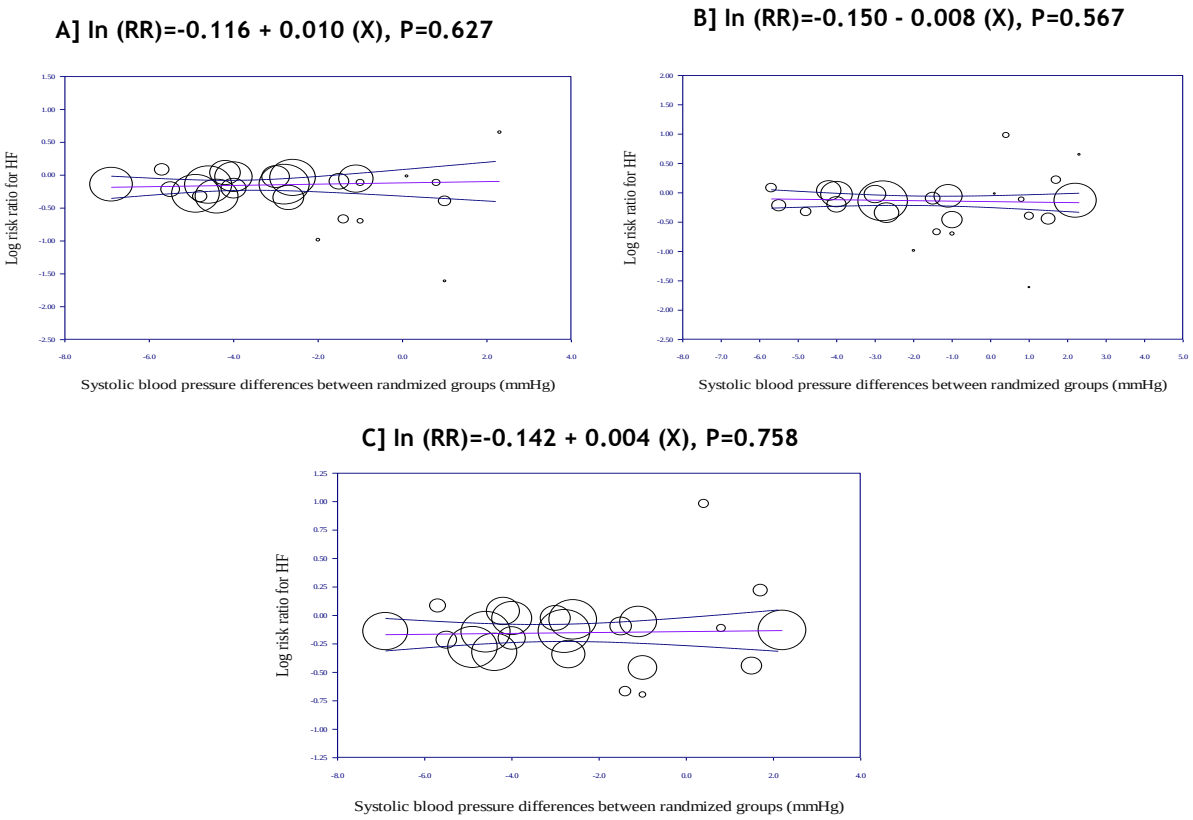


Figure 6-20 Multivariate meta-regression analysis of the relationship between RR of HF and difference in achieved SBP (mmHg) between randomized groups for ARBs trials. [Sensitivity analysis].

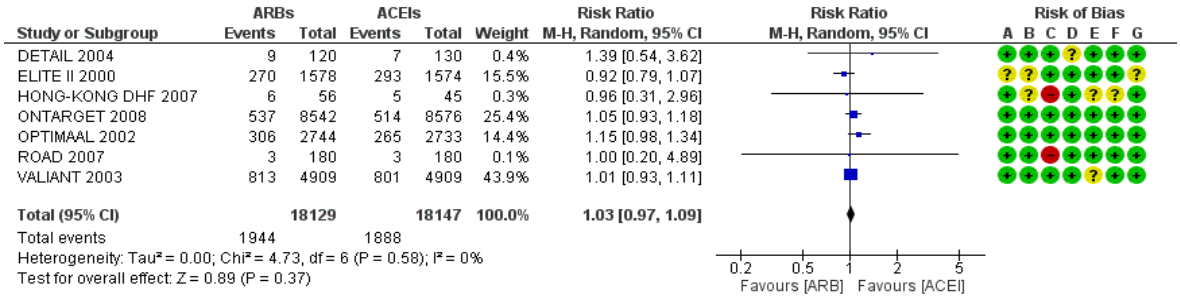
Excluding trials with, **A)** CCB as comparator; **B**) symptomatic HF and **C)** a sample size less

6.8 Direct comparison between ARBs and ACEIs

6.8.1 Overall treatment effect

Figure 6.21 shows the RE meta-analytical summary of ARBs versus ACEIs head-to-head 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.

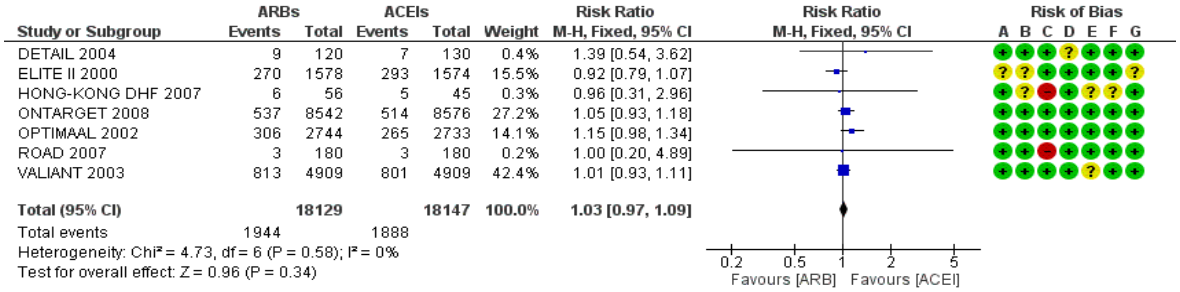
As a result of no between-trial variation (Tau^2=0), the FE meta-analysis model agrees with the RE estimates (RR, 1.03; 95% CI 0.97–1.09; p=0.34). However, less weight was assigned to ONTARGET (27.2%) (see **Figure 6.22**)



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 6-21 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



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 6-22 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 I^2=0%).

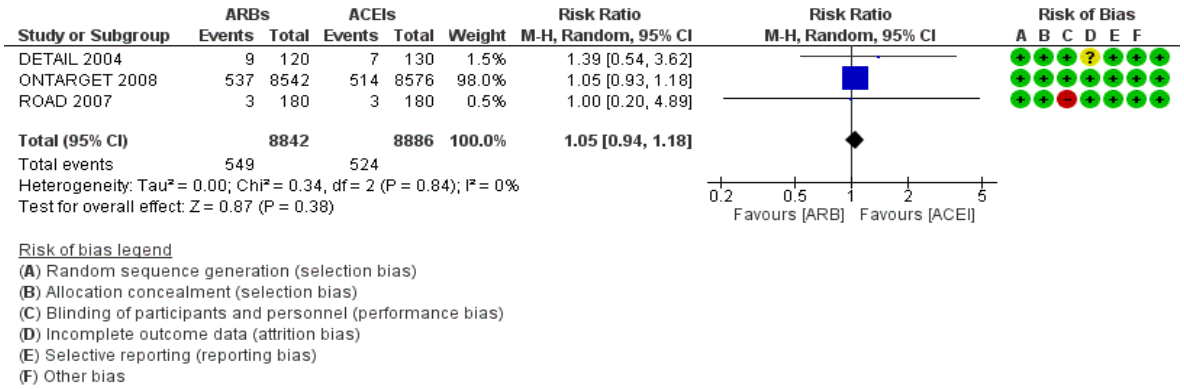


Figure 6-23 Forest plot showing the effect of ARBs versus ACEIs on risk of HF [Sensitivity analysis: Excluding HF trials]. Overall: 3 RCTs (RE model).

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 AT_1 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 placebo-controlled 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 (I^2=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 meta-regression 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 I^2 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 ≥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 meta-analysis 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 meta-analysis of RCTs by Bavishi et al. (2016) was published on the efficacy and safety of ACEIs in patients ≥ 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 (I^2=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 high-risk 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 (I^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 ß-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 I^2 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 between-treatment 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 ≥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 open-label 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 meta-regression 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**.

7.3.2 Data 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 pre-specified 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

7.4.1 Search 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

7.5.1 Overall 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 I^2=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.

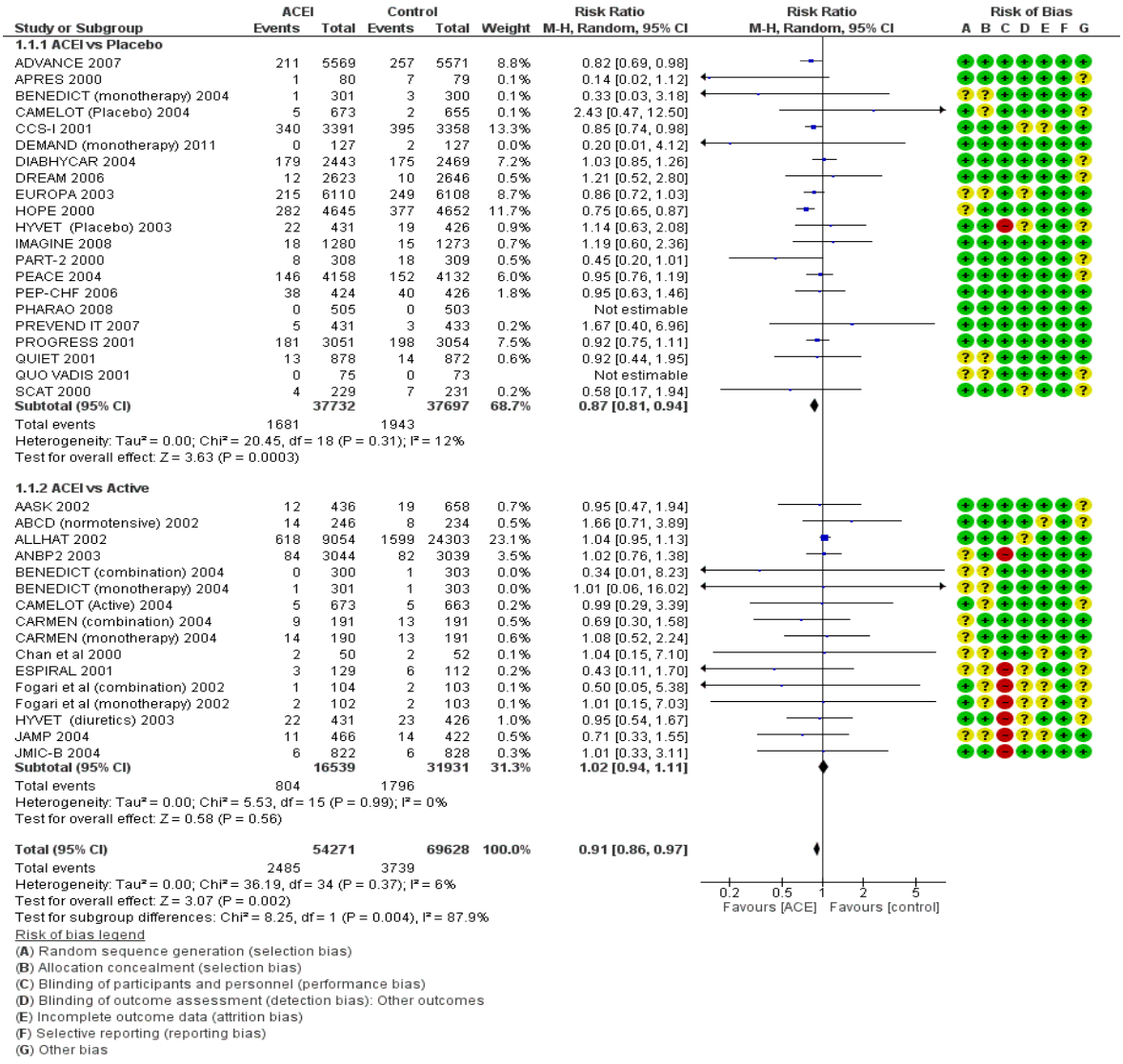


Figure 7-1 Forest plot showing effect of ACEIs on risk of CV mortality, stratified by comparison group (placebo vs active). Overall: 36 trials (RE model).

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

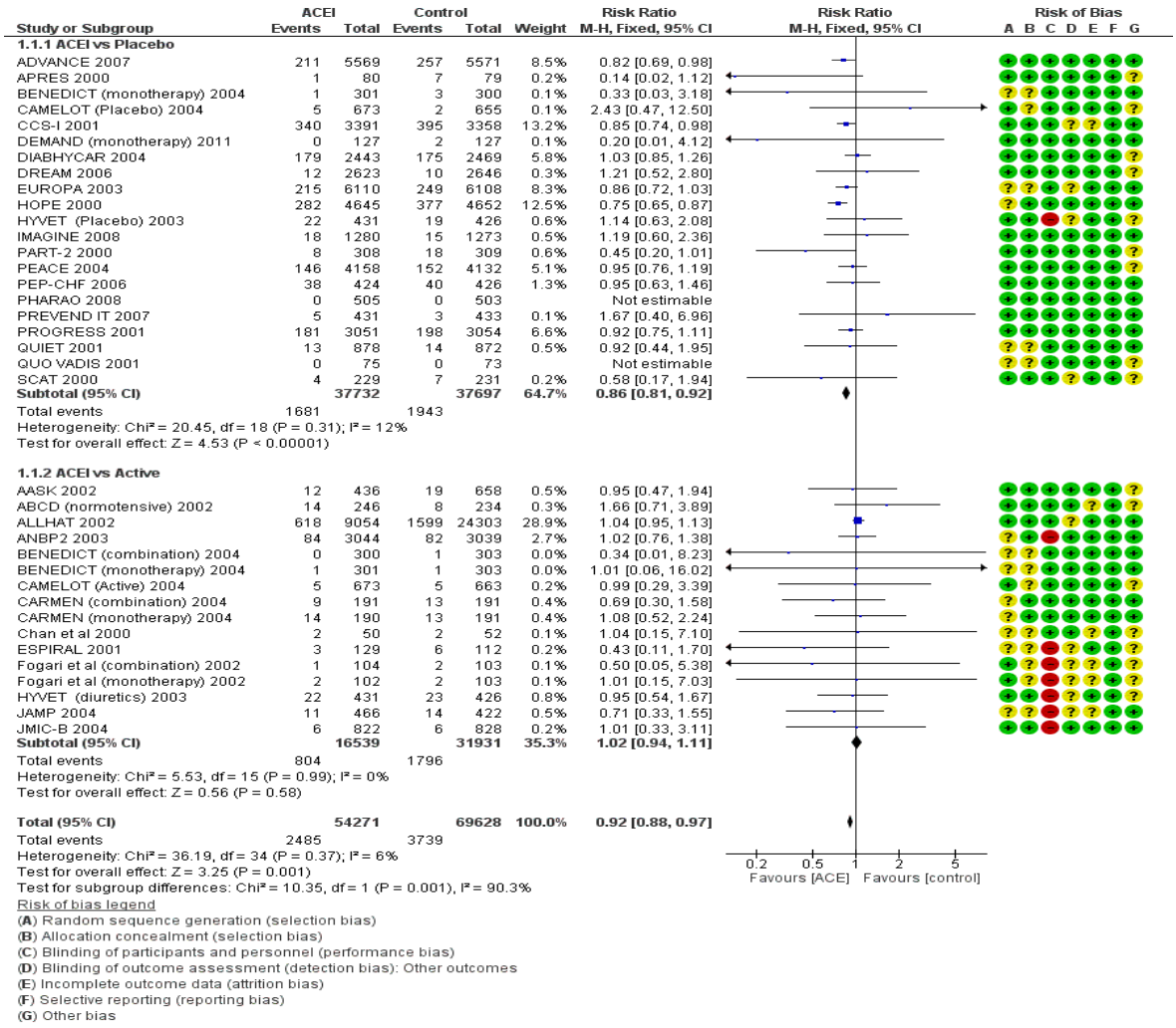


Figure 7-2 Forest plot showing effect of ACEIs on risk of CV mortality, stratified by comparison group (placebo vs active). Overall: 36 trials (FE model).

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

7.5.2 Sensitivity 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)**

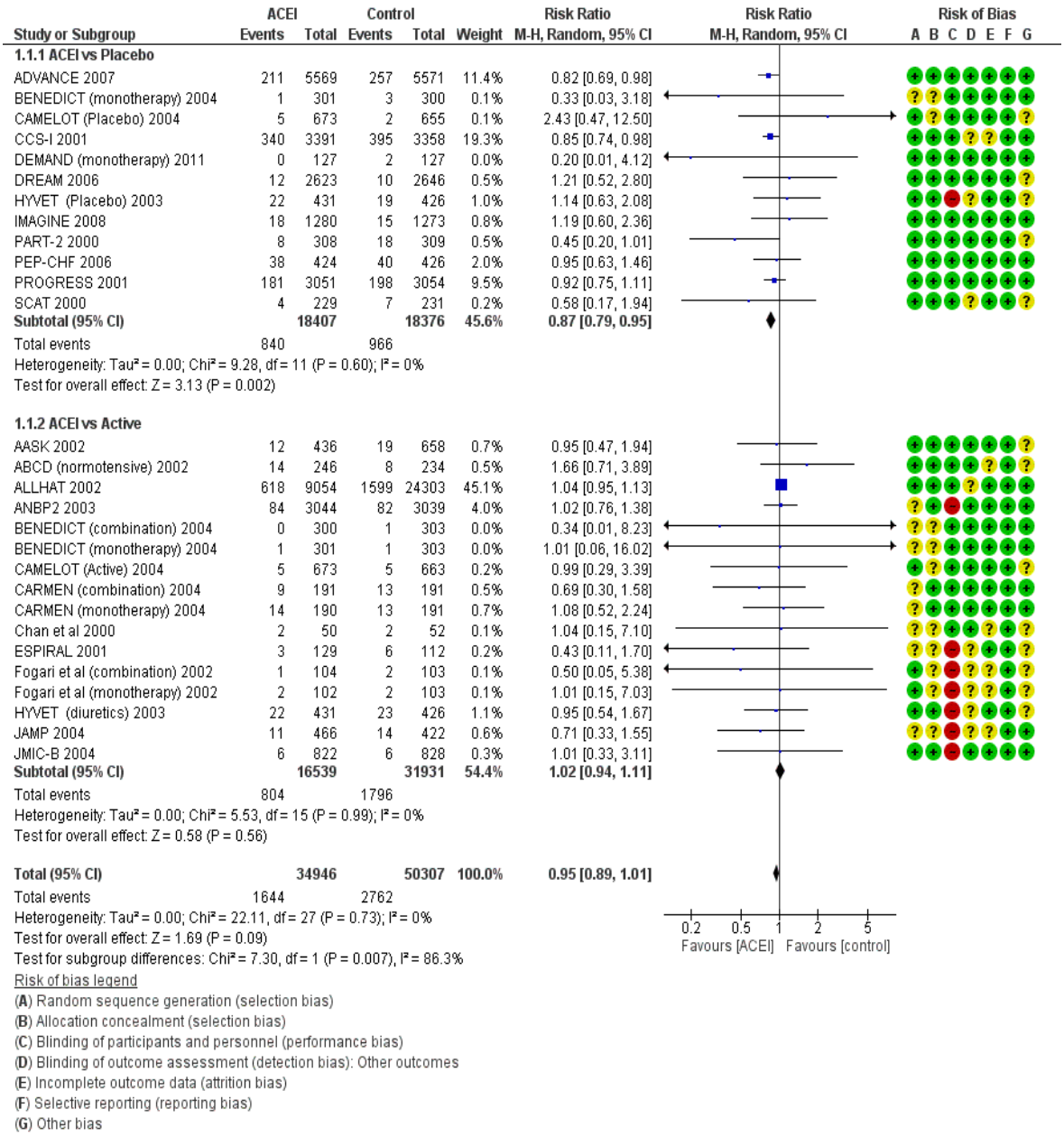


Figure 7-3 Forest plot showing effect of ACEIs on risk of CV mortality (RE model). [Sensitivity analysis: Excluding trials with naïve participants].

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

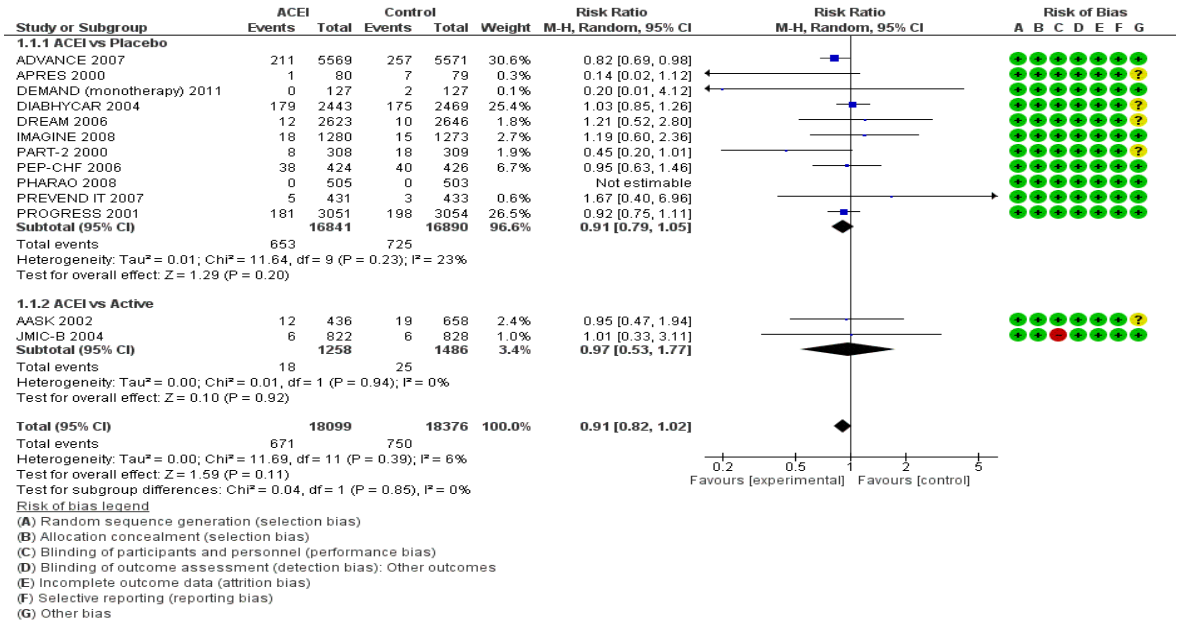


Figure 7-4 Forest plot showing effect of ACEIs on risk of CV mortality (RE model). **[Sensitivity analysis: Excluding trials with low methodological quality].**

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 ≥65 group. However, when the DIABHYCAR trial data is excluded from the trials that included patients whose mean age fell in the ≥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 (I^2 = 0%).

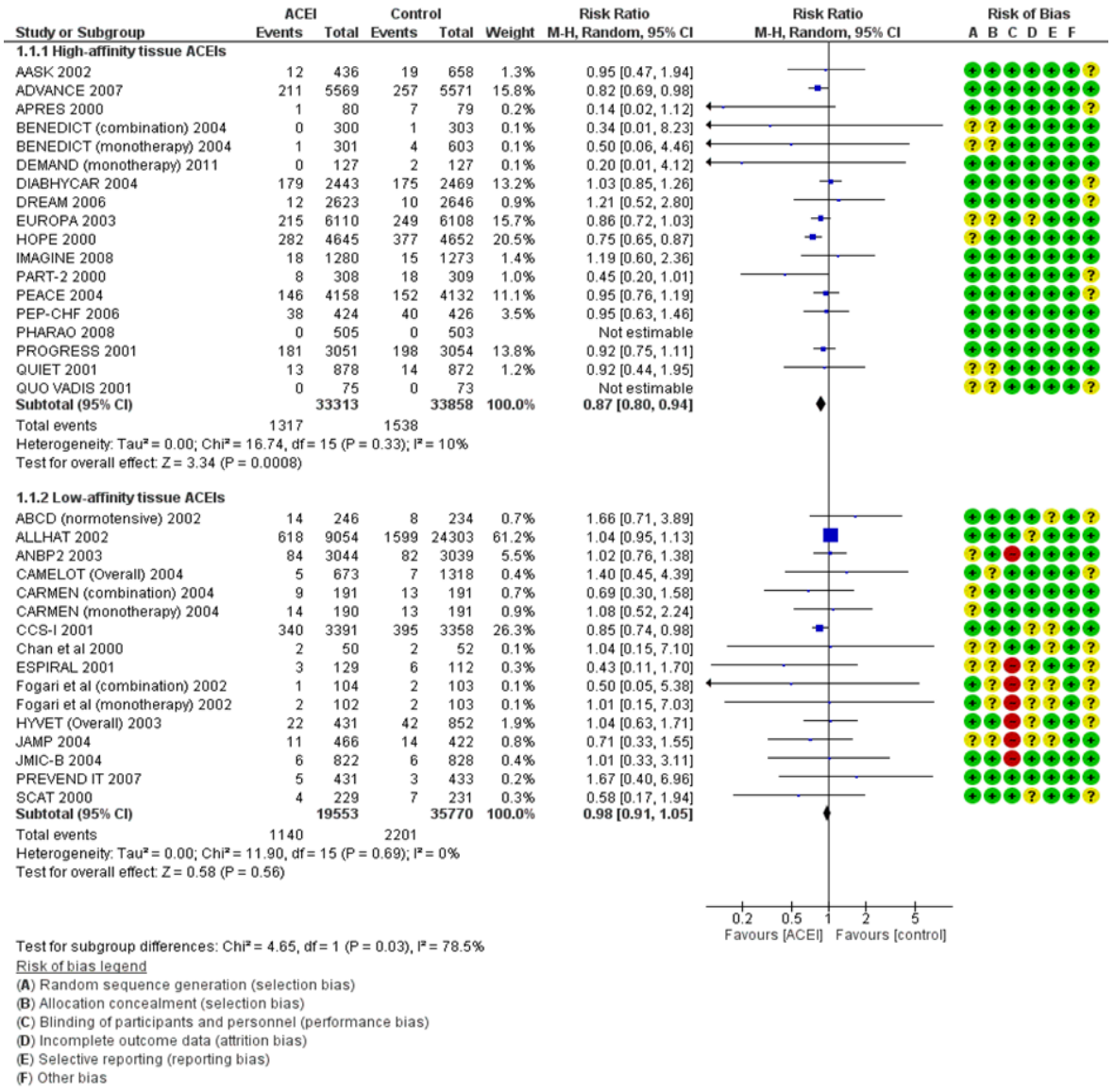


Figure 7-5 Forest plot showing effect of ACEIs on risk of CV mortality (RE model) [Subgroup analysis: High-affinity tissue vs low-affinity ACEIs].

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

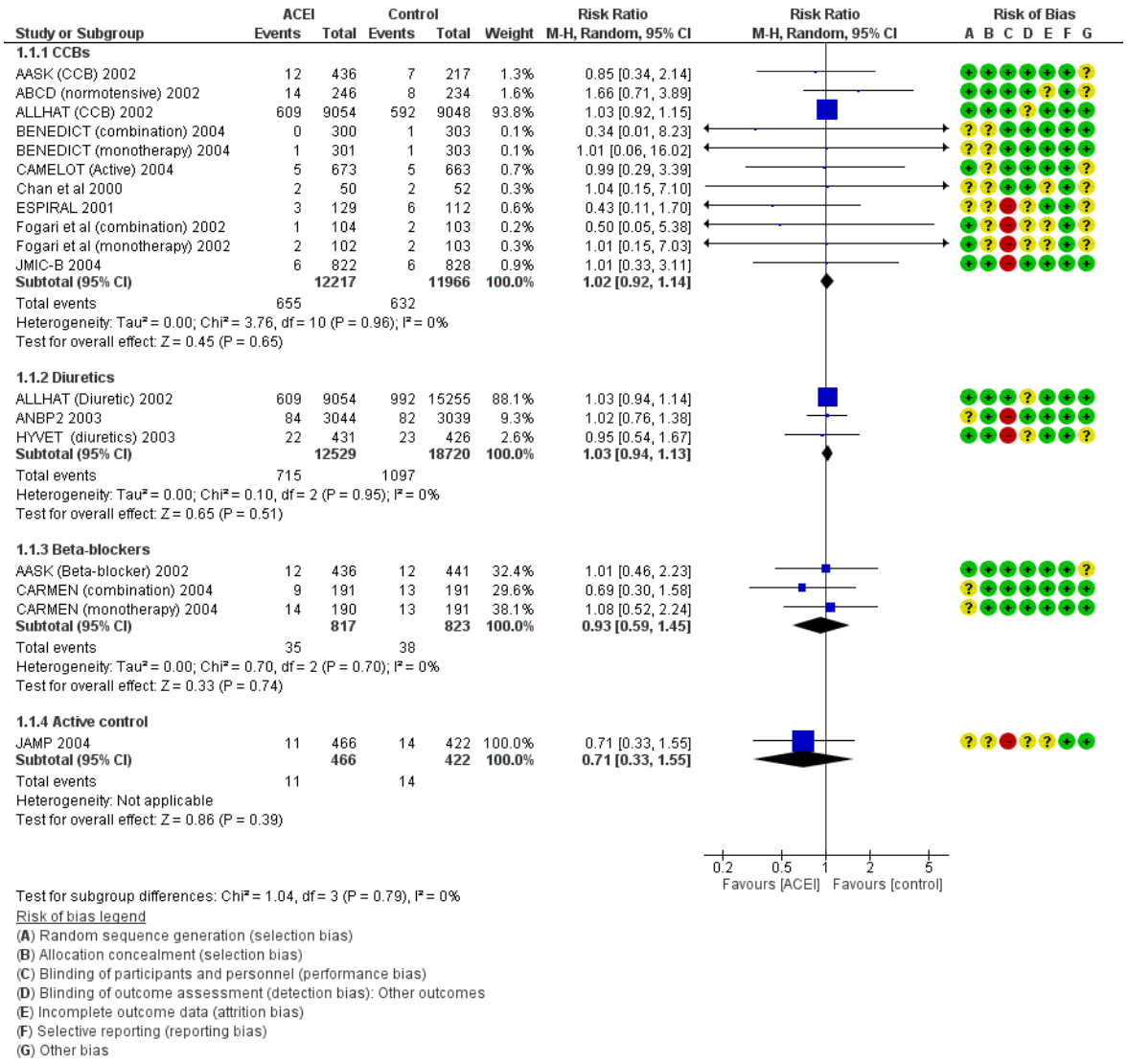


Figure 7-6 Forest plot showing effect of ACEIs on risk of CV mortality (RE model) [Subgroup analysis: Class of active comparator].

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

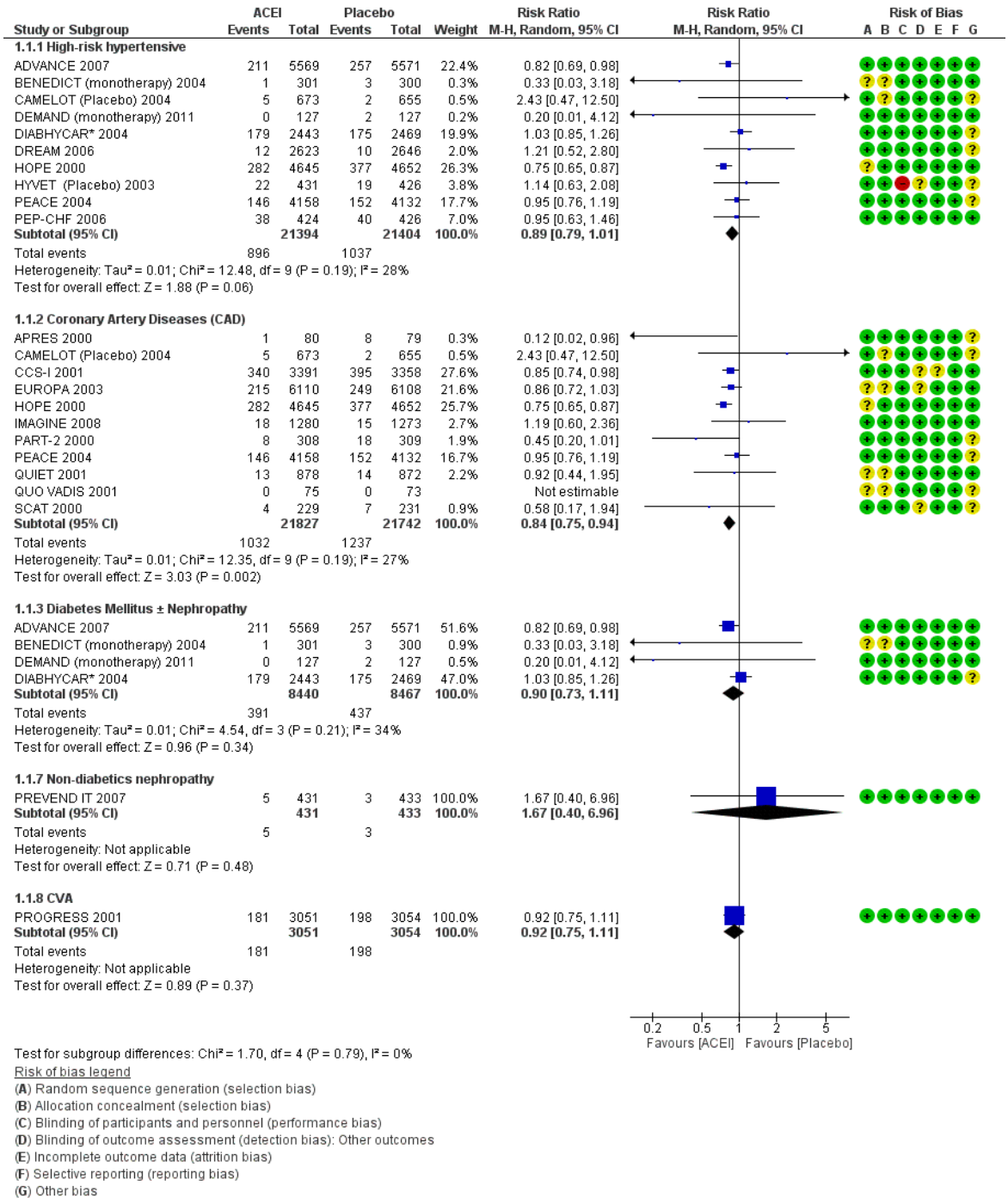


Figure 7-7 Forest plot showing effect of ACEIs versus placebo on risk of CV mortality (RE model) [Subgroup analysis: Population clinical setting].

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

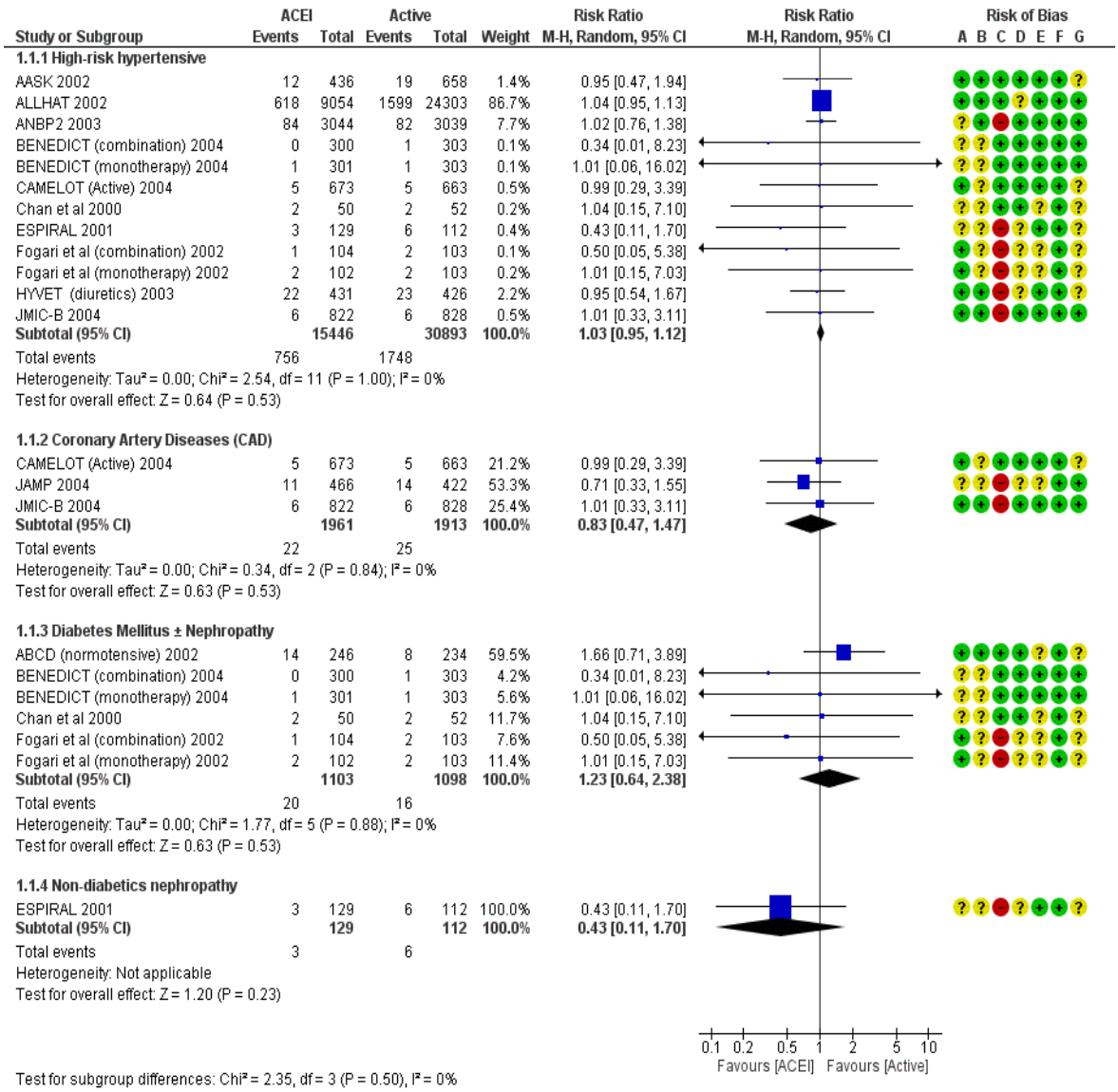


Figure 7-8 Forest plot showing effect of ACEIs versus active on risk of CV mortality (RE model). [Subgroup analysis: Population clinical setting].

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

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†

Subgroup analysis		Studies	Participant	Events	CV death Incidence (%)		RR (M-H, Random, 95% CI)	P value*	I^2 (%) ‡
					ACEI	Control			
	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
Active control	**CCBs**	11	24,183	1287	5.37	5.28	1.02 [0.92-1.14]	0.65	0
	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

†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 considered statistically significant; ^Cannot synthesis data by one trial; ‡ I^2 statistic with <25% considered as low heterogeneity and I^2> 75% as high heterogeneity
** Excluding ALLHAT trial yields RR of 0.89 [95% CI 0.80-1.00; p=0.05]

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)†

Subgroup analysis		Studies	Participant	Events	CV death Incidence (%)		RR (M-H, Random, 95% CI)	P value*	I^2 (%) ‡
					ACEI	Control			
Placebo									
Clinical setting	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
	DM± Nephropathy	4	16,907	828	4.63	5.16	0.90 [0.73-1.11]	0.34	34¶
	Non-diabetic nephropathy^	1	864	8	1.16	0.69	1.67 [0.40-6.96]	0.48	NA
	CVA^	1	6105	379	5.93	6.48	0.92 [0.75-1.11]	0.37	NA
Mean age group	< 65 years	16	48,373	2025	3.91	4.45	0.88 [0.81-0.96]	**0.003***	0
	≥ 65 years	5	27,056	1600	5.41	6.40	0.87 [0.75-1.02]	0.08	49¥
Active									
Clinical setting	High-risk hypertensive	12	46,339	2504	4.89	5.65	1.03 [0.95, 1.12]	0.53	0
	CAD	3	3874	47	1.12	1.30	0.83 [0.47, 1.47]	0.53	0
	DM± Nephropathy	6	2201	36	1.81	1.45	1.23 [0.64, 2.38]	0.53	0
	Non-diabetic nephropathy^	1	241	9	2.32	5.35	0.43 [0.11, 1.70]	0.23	NA
	CVA	NA							
Mean age group	< 65 years	12	6523	160	2.32	2.57	0.91 [0.67, 1.24]	0.54	0
	≥ 65 years	4	41,947	2440	5.46	5.97	1.03 [0.95, 1.13]	0.44	0

†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 considered statistically significant; ^ Cannot synthesis data by one trial; ‡ I^2 statistic with <25% considered as low heterogeneity and I^2> 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, I^2 is disappeared (0%) with a significant pooled RR of 0.81 [95% CI 0.68, 0.97, p=0.02]

¥ By excluding DIABHYCAR trial, I^2 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

7.6.1 Overall 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 I^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 I^2=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 I^2 =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).

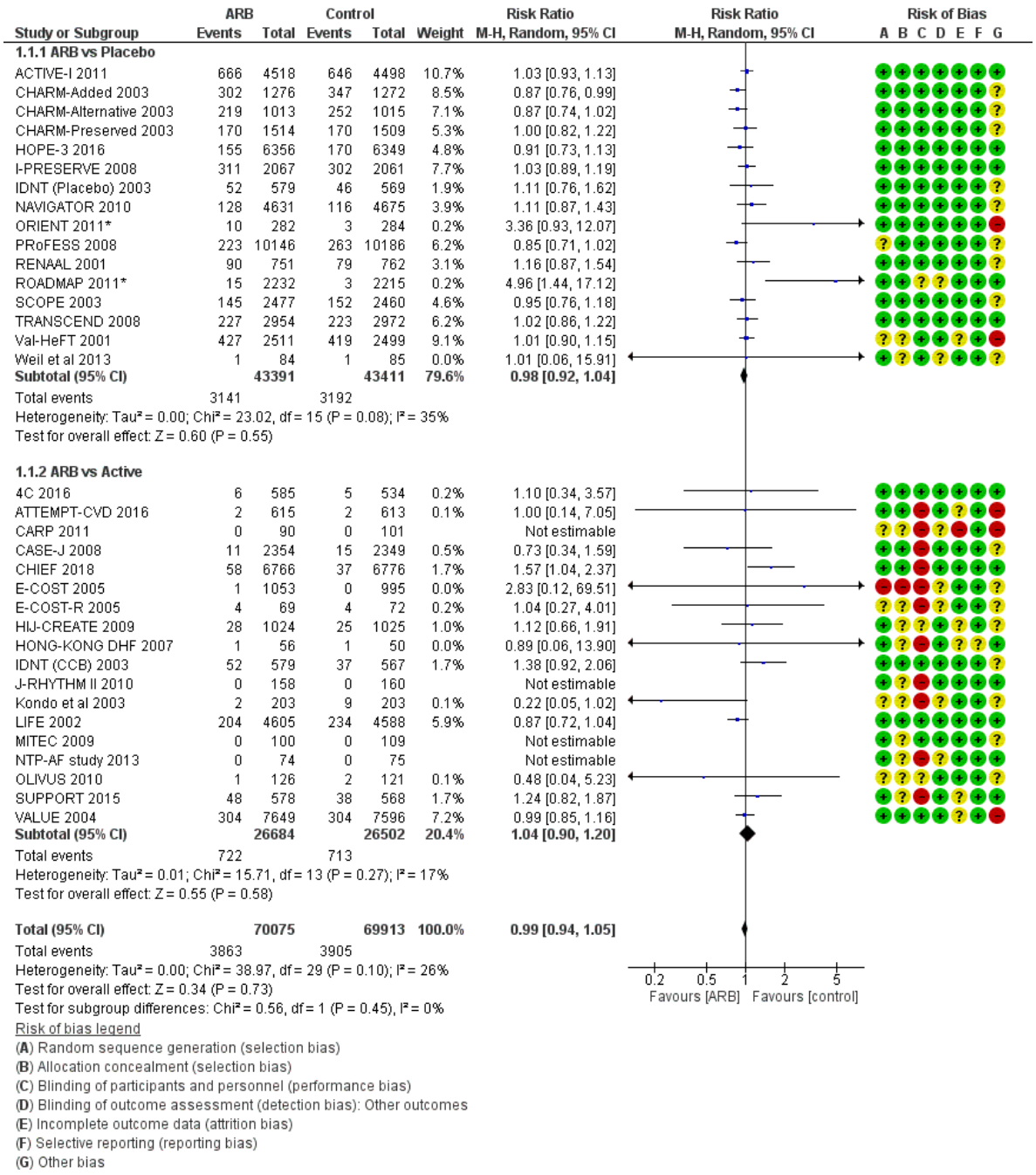


Figure 7-9 Forest plot showing effect of ARBs on risk of CV mortality, stratified by comparison group (placebo vs active). Overall: 34 trials (RE model).

*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

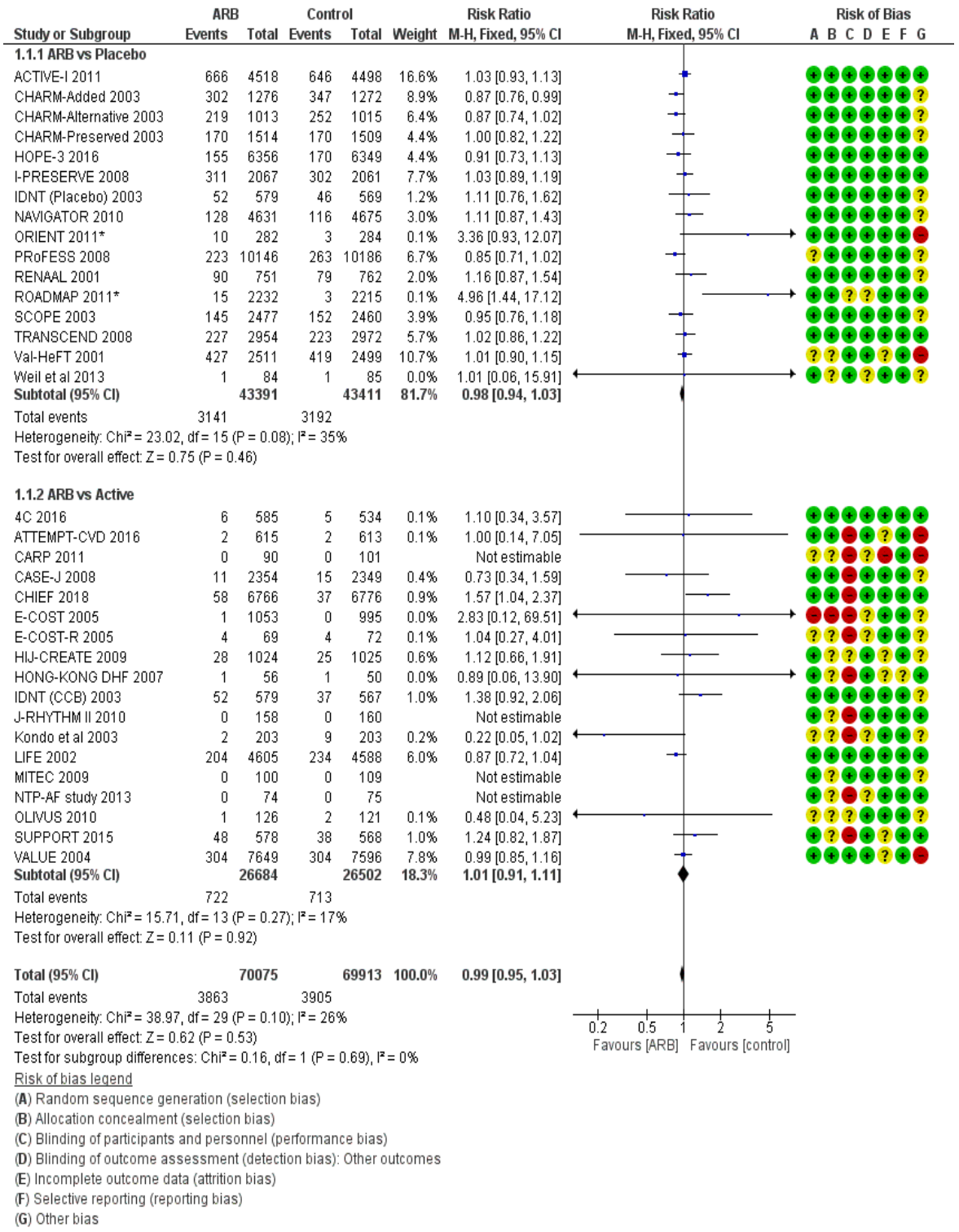


Figure 7-10 Forest plot showing effect of ARBs on risk of CV mortality, stratified by comparison group (placebo vs active). Overall: 34 trials (FE model).

*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)**

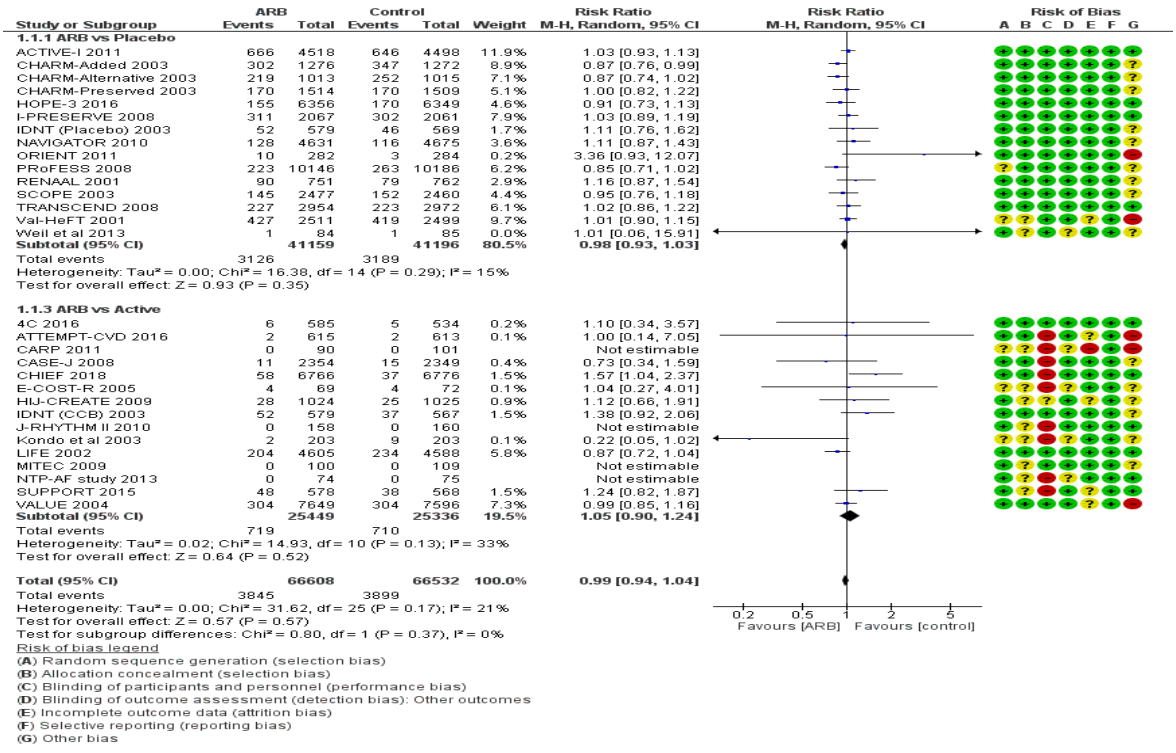


Figure 7-11 Forest plot showing effect of ARBs on risk of CV mortality (RE model) [Sensitivity analysis: Excluding trials with naïve participants].

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

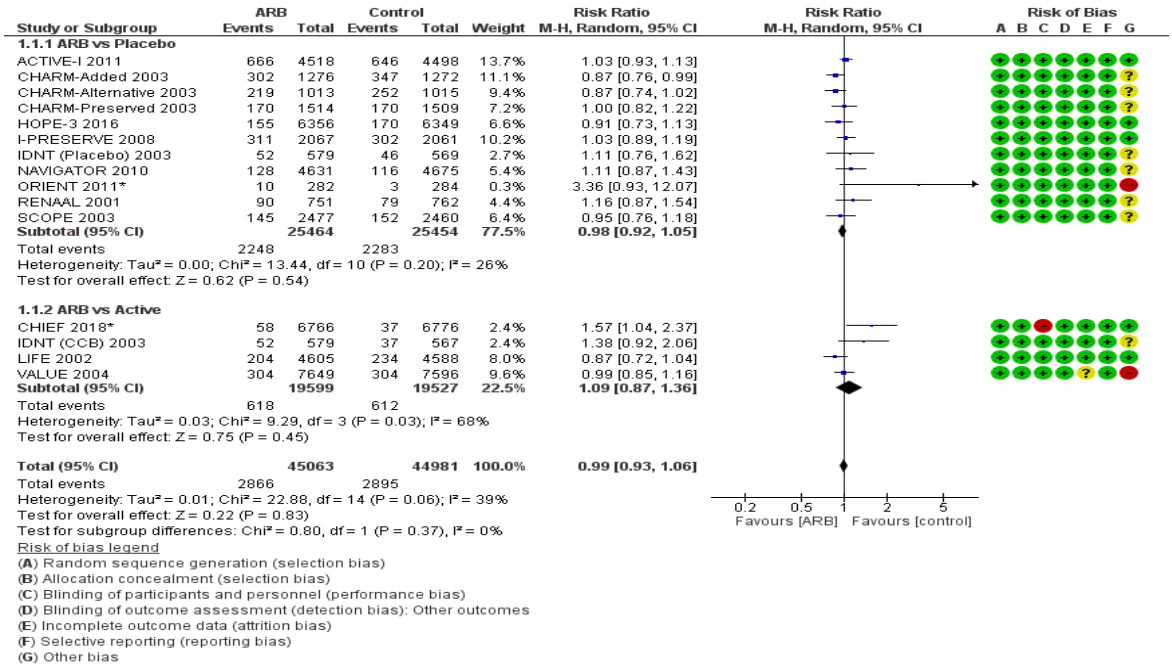


Figure 7-12: Forest plot showing effect of ARBs on risk of CV mortality (RE model) **[Sensitivity analysis: Excluding trials with low methodological quality].**

*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 (I^2=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 ≥ 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 I^2=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 I^2 becomes zero.

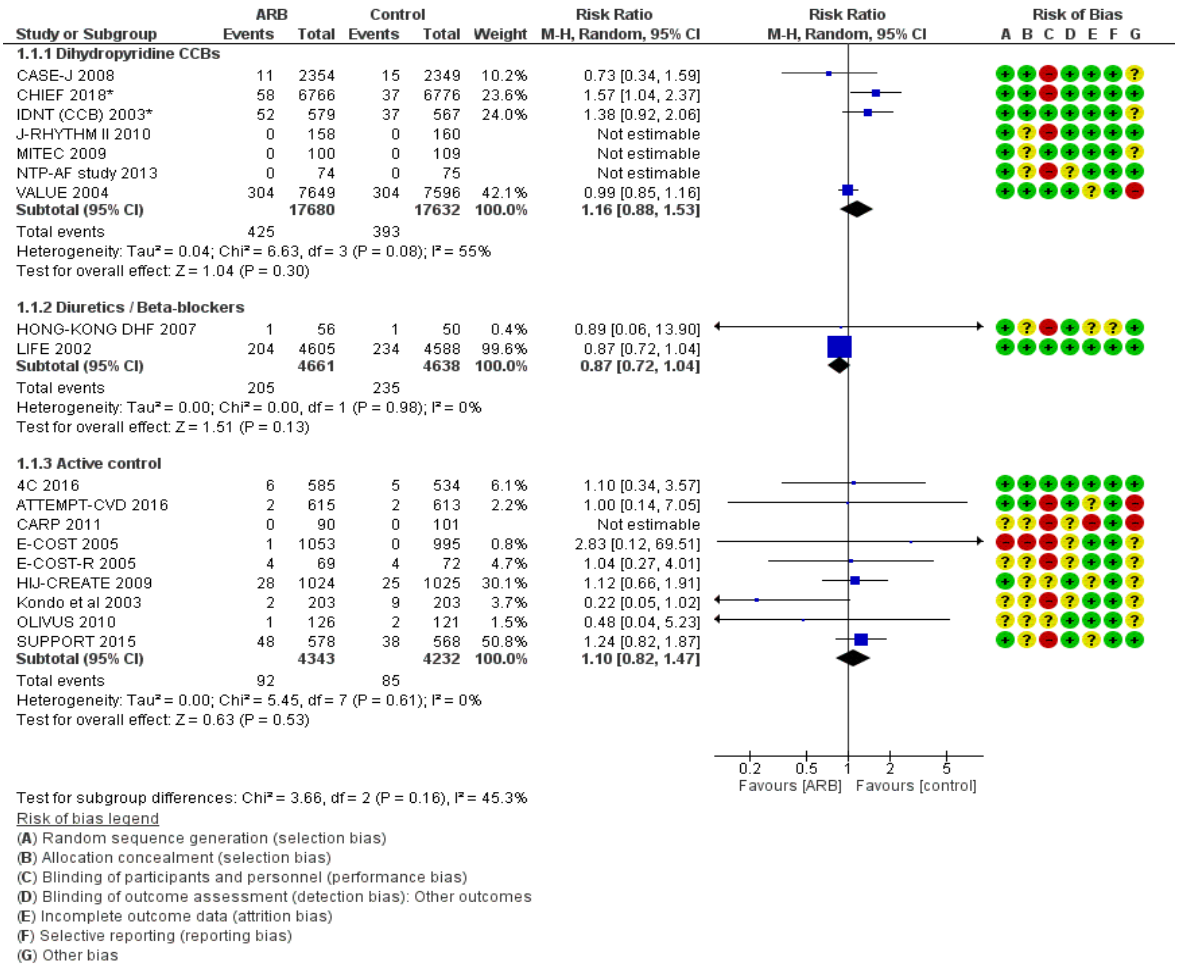


Figure 7-13 Forest plot showing effect of ARBs on risk of CV mortality (RE model) [Subgroup analysis: Class of active comparator].

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

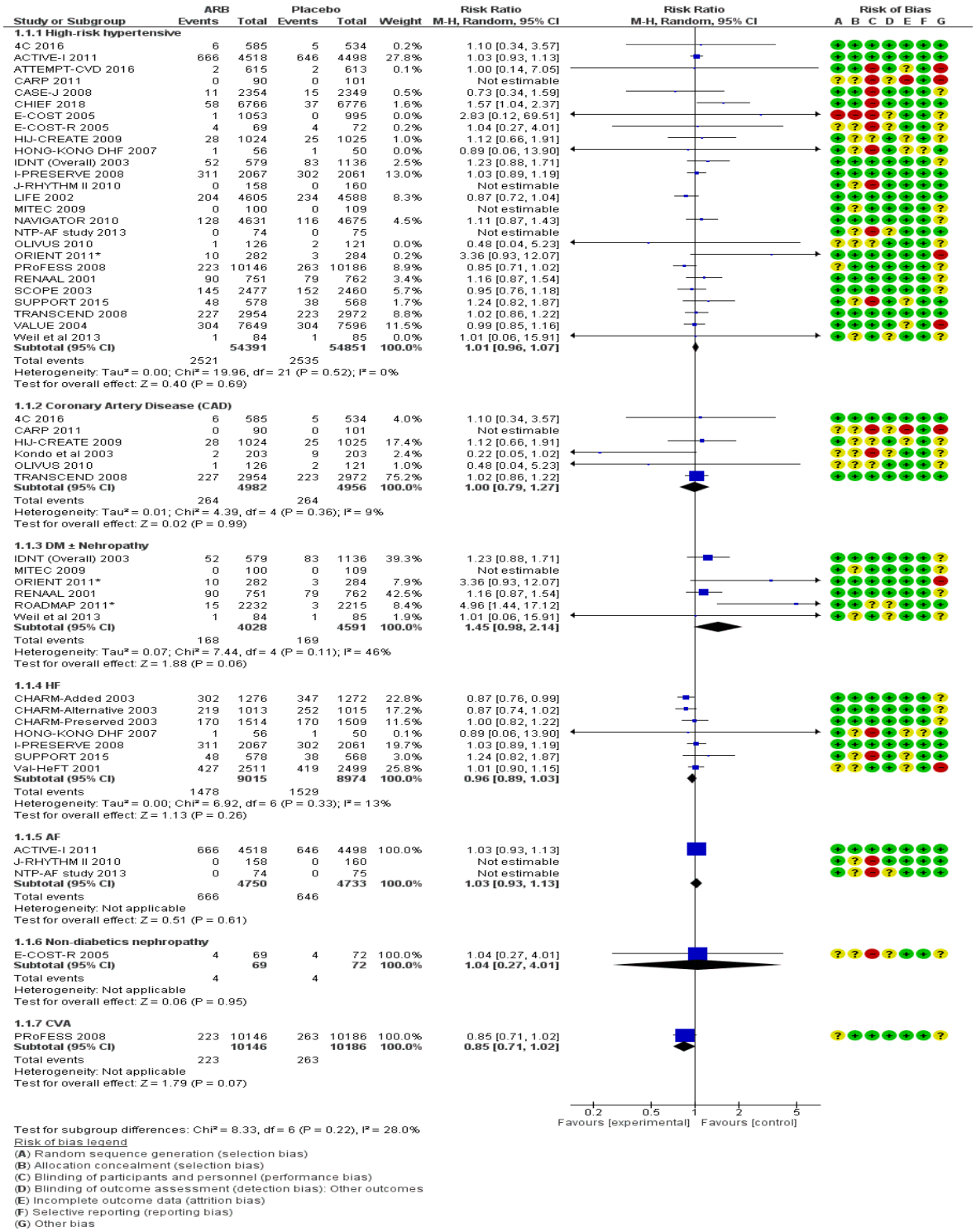


Figure 7-14 Forest plot showing effect of ARBs on risk of CV mortality (RE model) [Subgroup analysis: Clinical setting].

*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) †

Subgroup analysis		Studies	Participants	Events	CV death Incidence (%)		RR (M-H, Random, 95% CI)	P value*	I^2 (%) ‡
					ARBs	Control			
Overall effects	**RE**	**34**	**139,988**	**7768**	**5.51**	**5.58**	**0.99 [0.95, 1.03]**	**0.53**	**26**
Active control	**DHP-CCBs**	7	35312	818	2.40	2.22	1.16 [0.88, 1.53]	0.30	55
	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
Clinical setting	**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**
	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 group	**< 65 years**	13	44,068	2197	5.03	4.93	1.12 [0.95, 1.32]	0.18	61¥
	≥ 65 years	20	95,341	5519	5.68	5.88	0.97 [0.92, 1.02]	0.21	0

†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 considered statistically significant; ^Cannot synthesis data by one trial; ‡ I^2 statistic with <25% considered as low heterogeneity and I^2> 75% as high heterogeneity

** By excluding ORIENT and ROADMAP, the heterogeneity is disappeared (I^2=0%) with RR of 1.19 (95% CI 0.96-1.47; p=0.12).

¥ 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

7.7.1 Overall 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 I^2 = 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).**

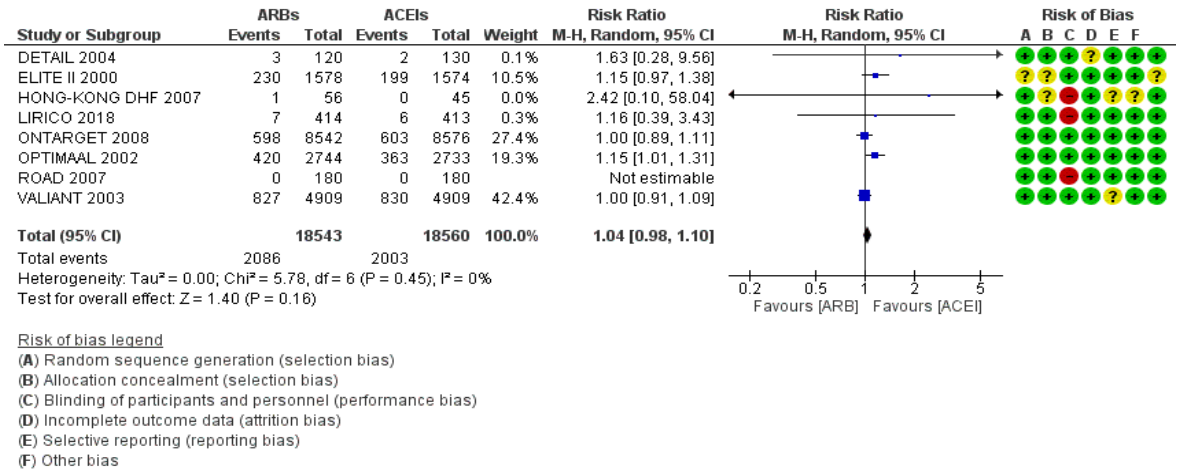


Figure 7-15 Forest plot showing effect of ARBs versus ACEIs on risk of CV mortality (RE model).

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

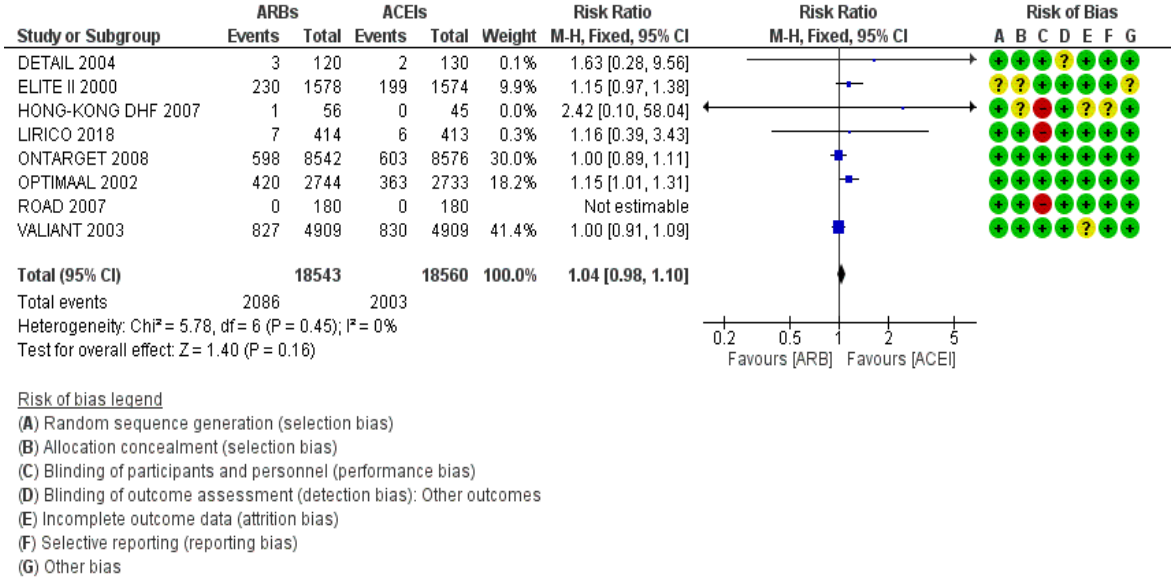


Figure 7-16 Forest plot showing effect of ARBs versus ACEIs on risk of CV mortality (FE model).

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**).

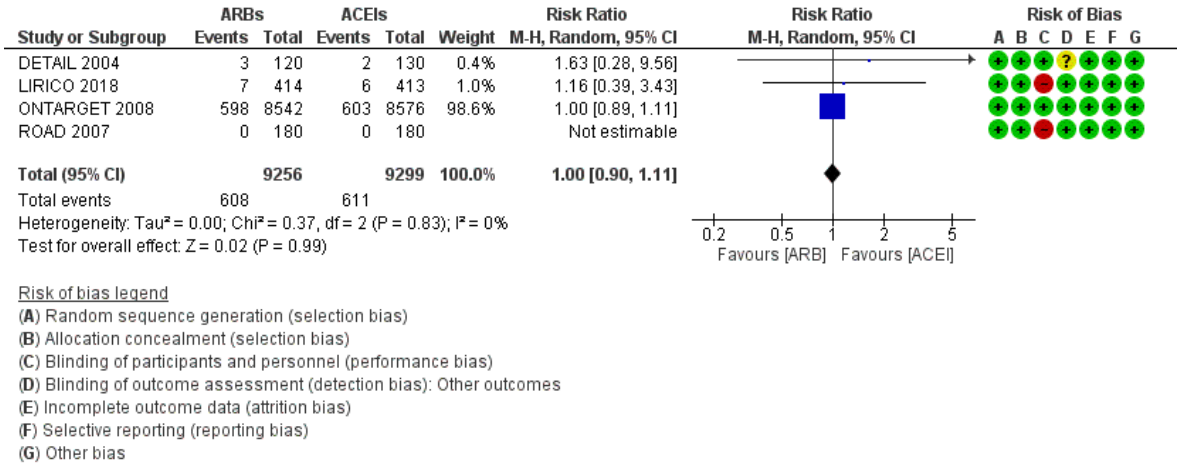


Figure 7-17 Forest plot showing effect of ARBs versus ACEIs on risk of CV mortality (RE model). [Sensitivity analysis: Excluding trials with HF),

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

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 (Tau^2 reduced from 0.0114 to 0.0001; p=0.777 and Residual I^2=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.

Table 7-4 Meta-regression of related and unrelated SBP differences by ACEIs on CV mortality (unadjusted and adjusted models).

		Slope			Between study variance			
Variable	**Studies**	**RR**	**95% CI**	**P value***	**Tau^2**	**Residual I^2 (%)**	**P value***	**R^2 (%)**
Null model					**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)‡								
Achieved SBP differences (mmHg)		1.05	1.02-1.08	0.0003	0.0001	0	0.777	99

Abbreviation: Tau^2= estimated amount of heterogeneity (between-study variance) not explained by covariate; I^2 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).

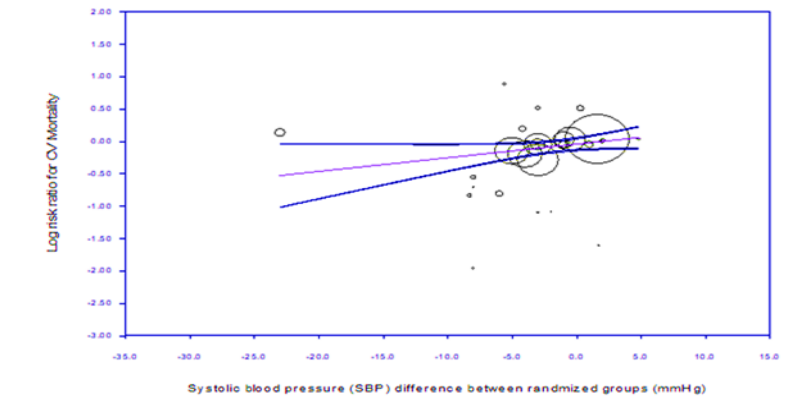
‡ The analysis was adjusted for male (%) and baseline SBP (mmHg)

7.8.2 ARBs

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.

A)



B)

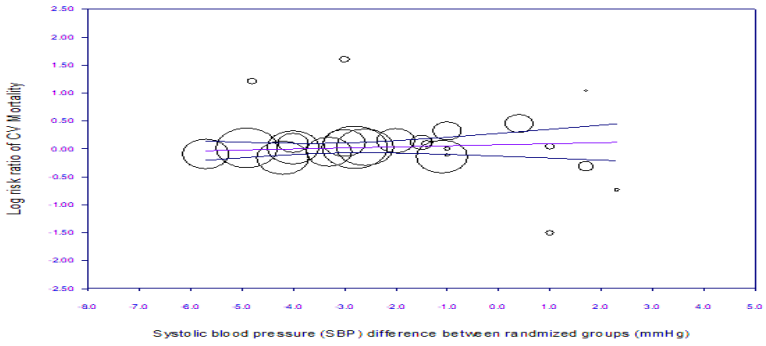


Figure 7-18 Adjusted meta-regression analysis of the relationship between RR for CV mortality and difference in SBP (mmHg) achieved between the randomized groups for trials of A) ACEIs and B) ARBs

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

7.9.1 Overall 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 I^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 I^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 (I^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.

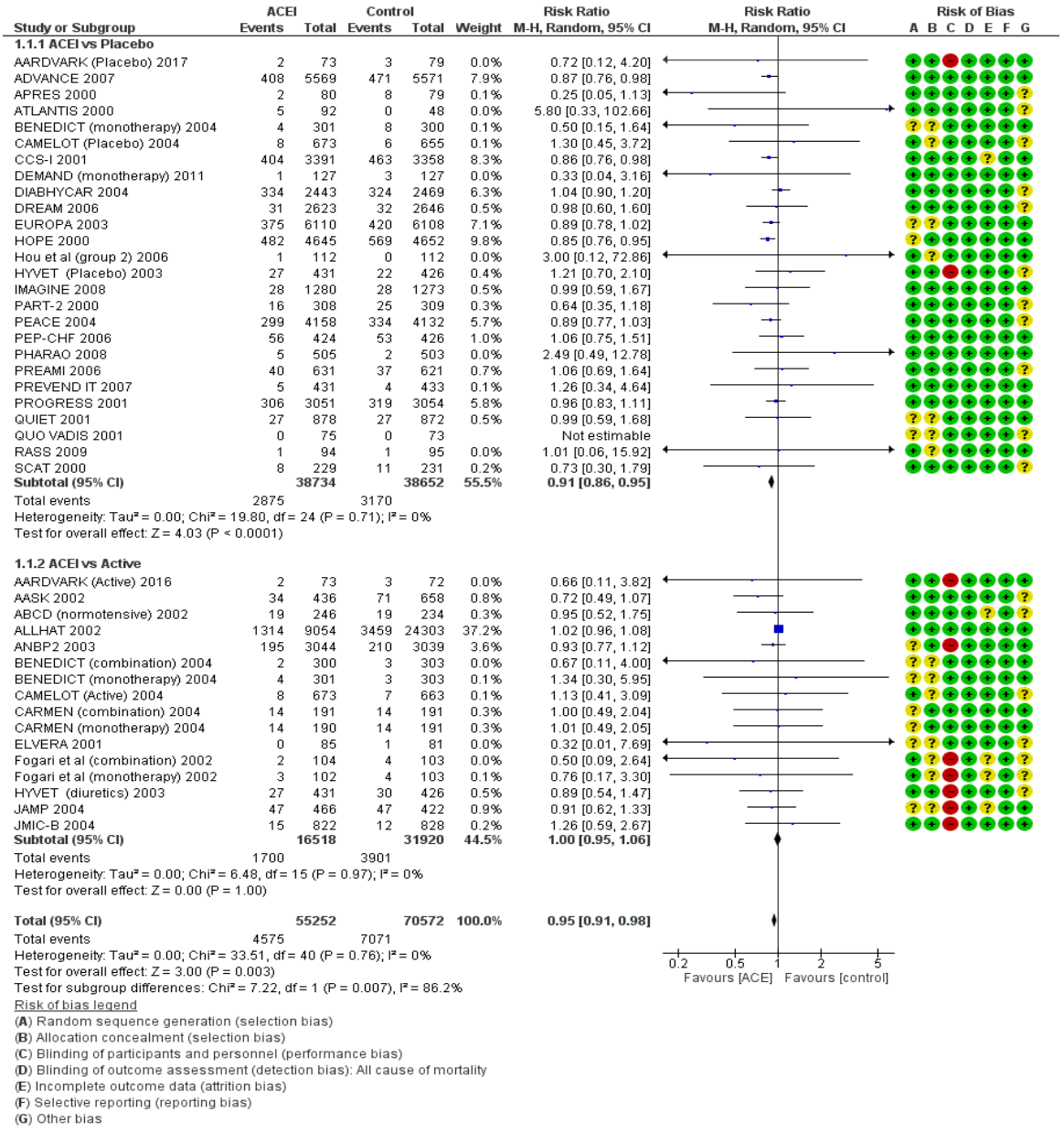


Figure 7-19 Forest plot showing effect of ACEIs on risk of all-cause mortality, stratified by comparison group (placebo vs active). Overall: 41 trials (RE model).

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

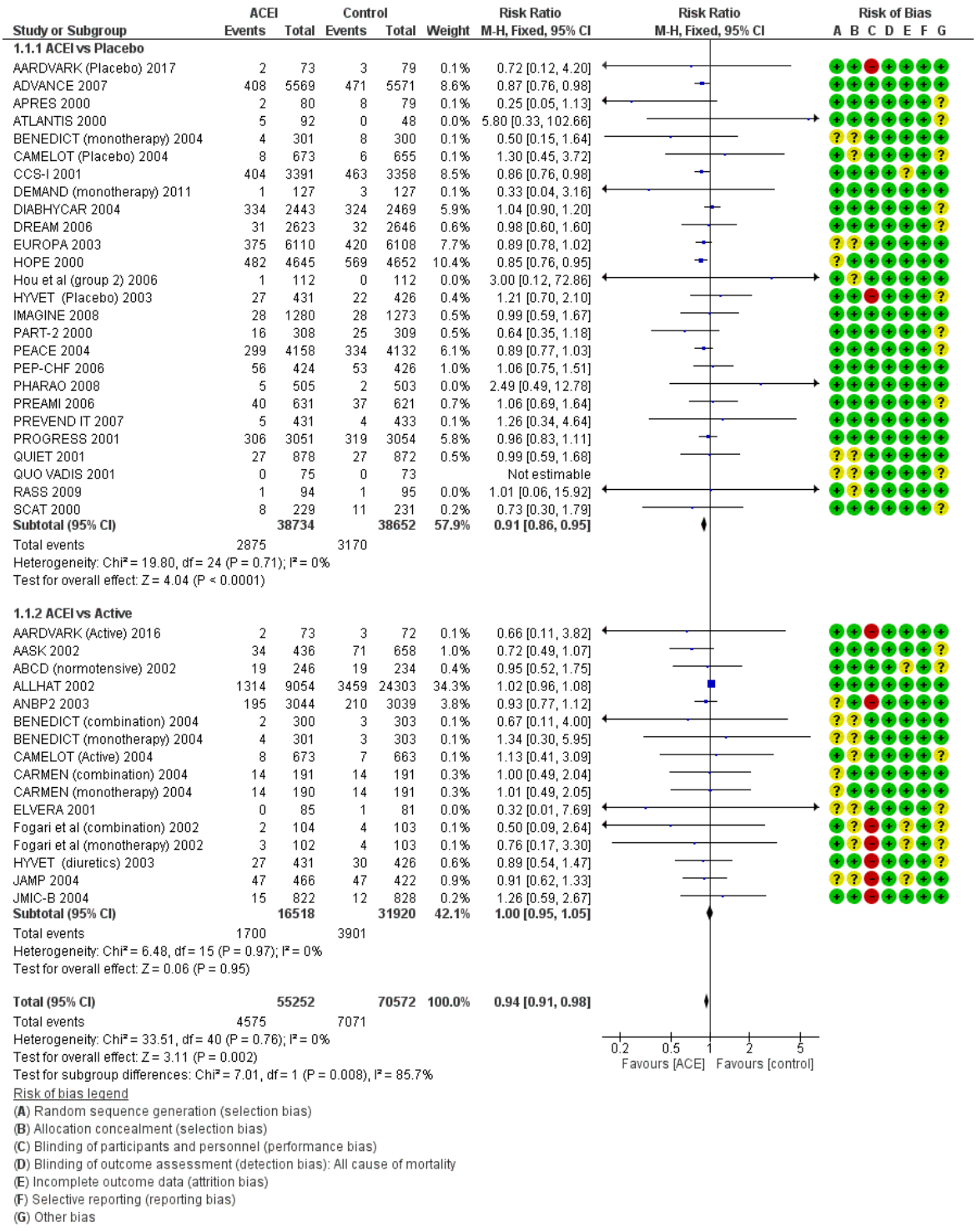


Figure 7-20 Forest plot showing effect of ACEIs on risk of all-cause mortality, stratified by comparison group (placebo vs active). Overall: 41 trials (FE model).

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

7.9.2 Sensitivity 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)**

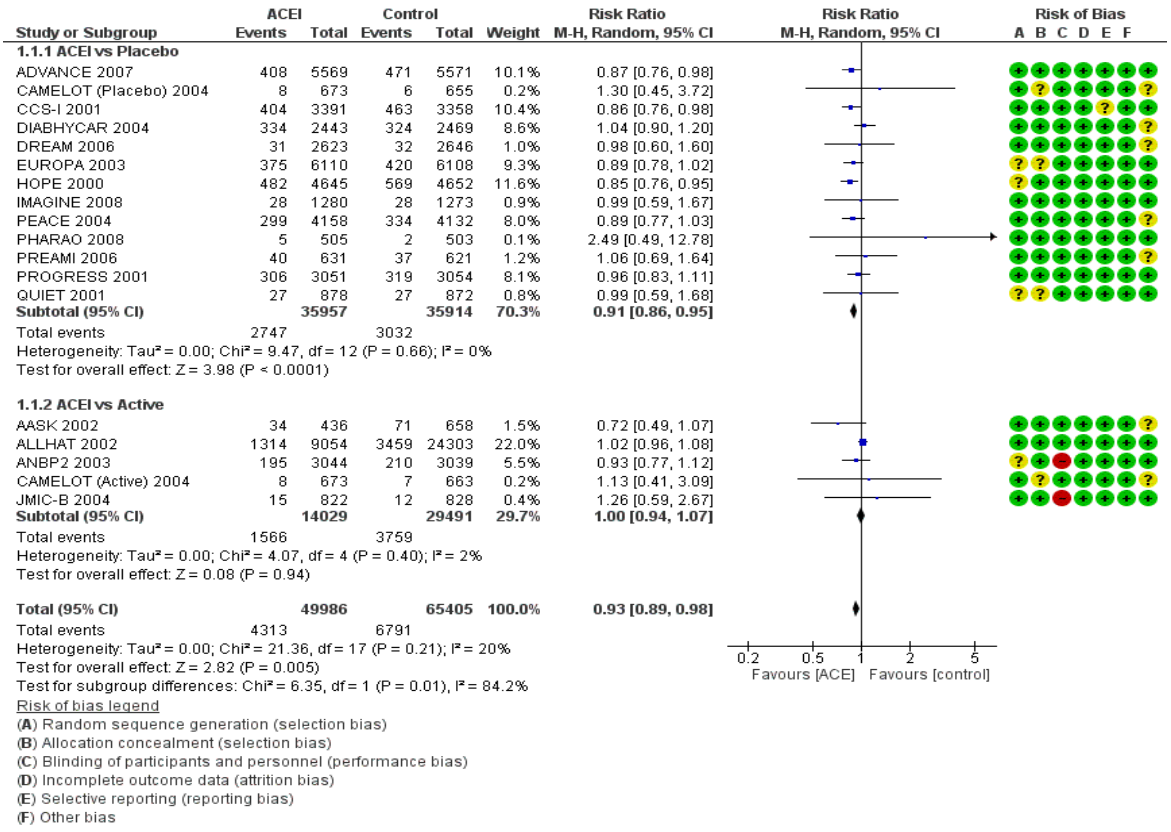


Figure 7-21 Forest plot showing effect of ACEIs on risk of all-cause mortality (RE model) [Sensitivity analysis: Excluding trials with sample size less than 1000].

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

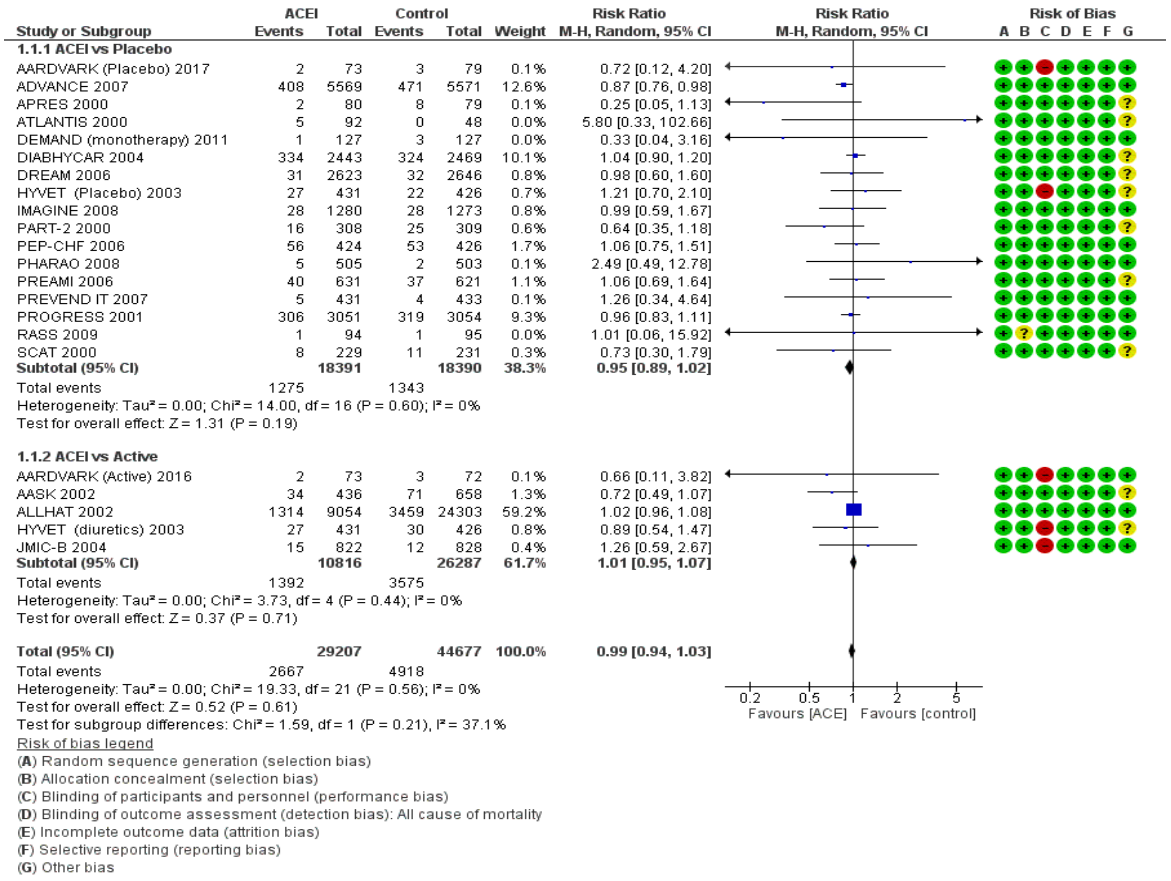


Figure 7-22 Forest plot showing effect of ACEIs on risk of all-cause mortality (RE model) [Sensitivity analysis: Excluding trials with low methodological quality].

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 all-mortality 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 ≥ 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 ≥ 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.

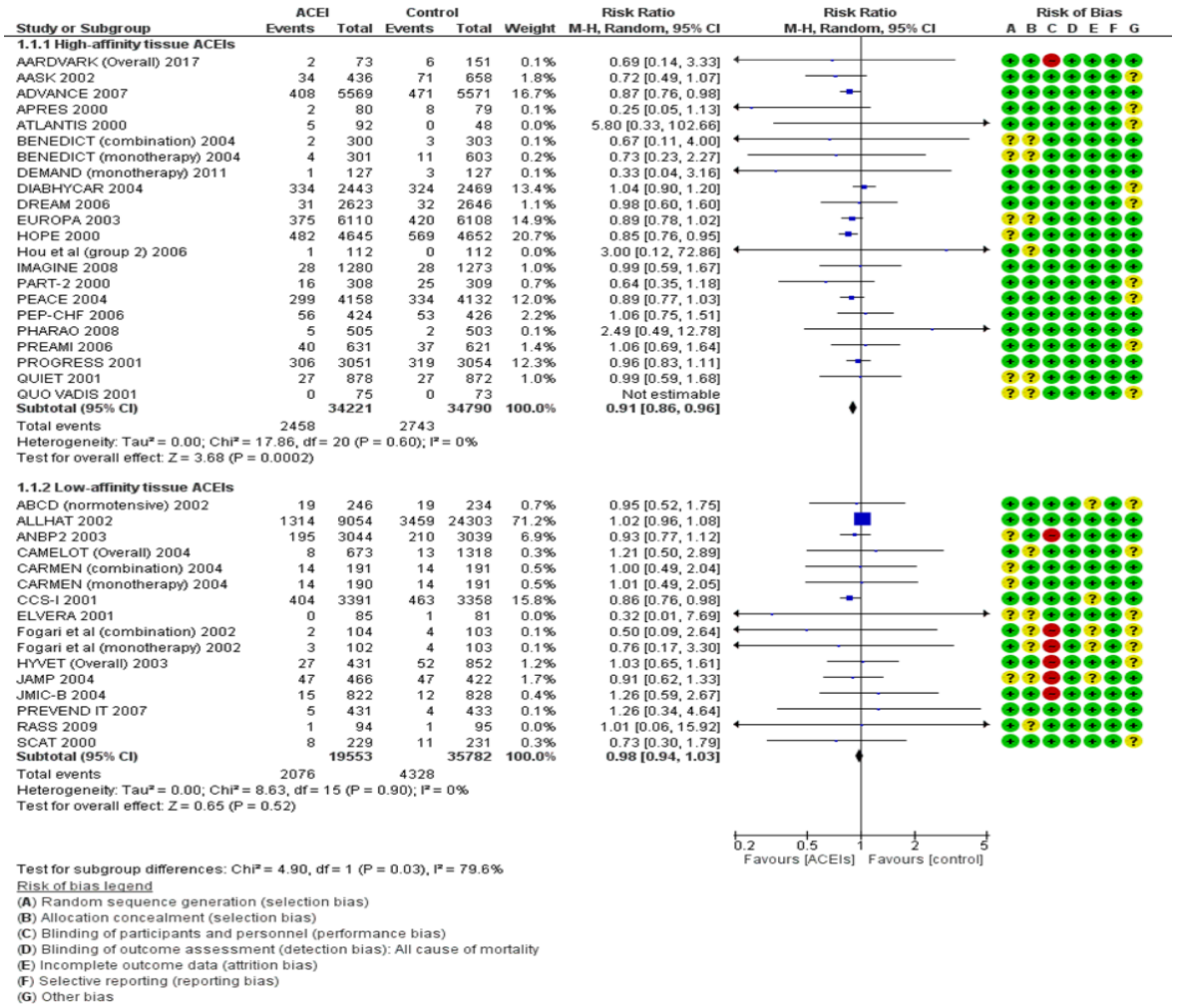


Figure 7-23 Forest plot showing effect of ACEIs on risk of all-cause mortality (RE model) [Subgroup analysis: high-affinity tissue vs low-affinity ACEIs].

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

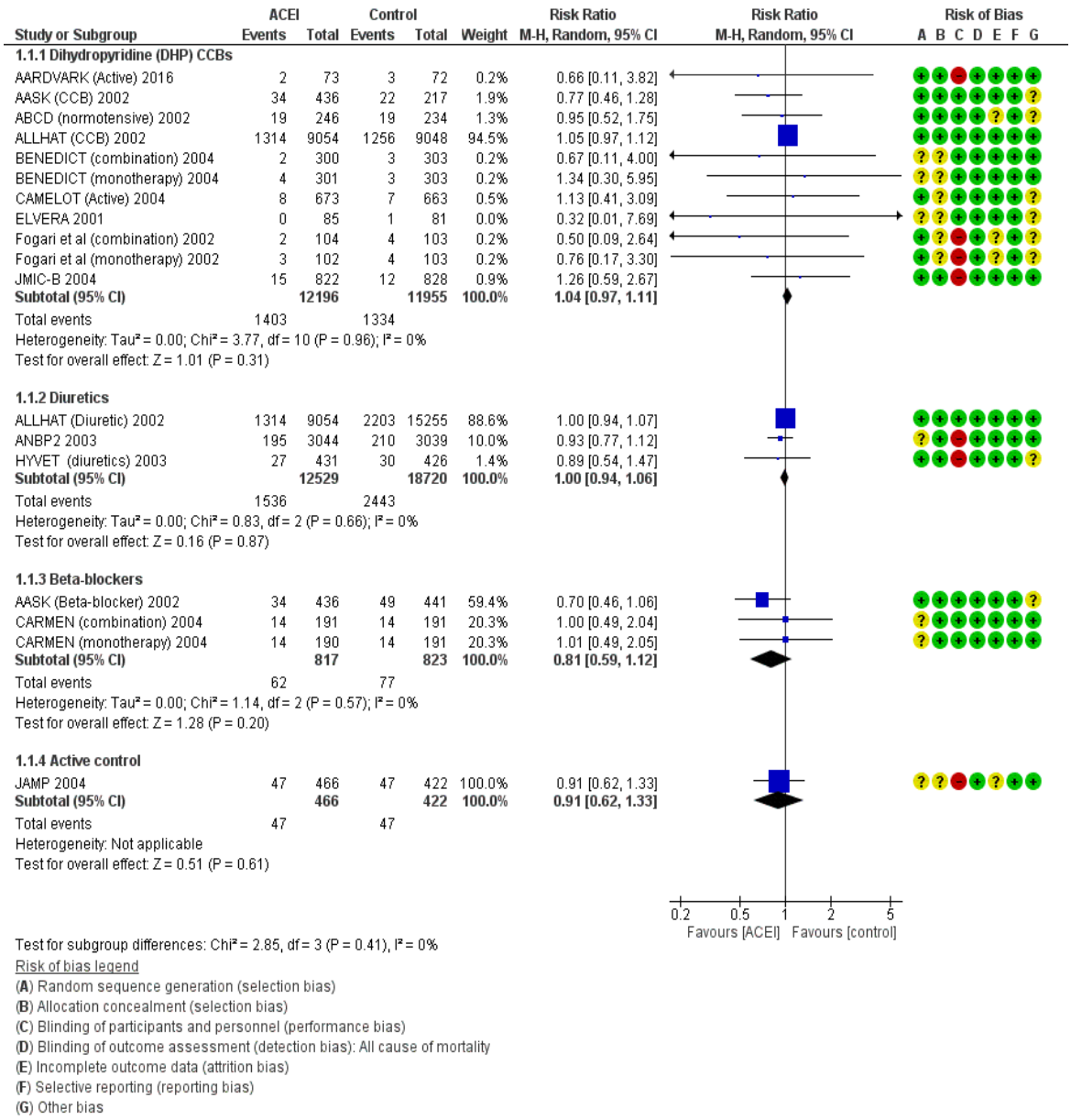


Figure 7-24 Forest plot showing effect of ACEIs on risk of all-cause mortality (RE model) [Subgroup analysis: class of active comparator].

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

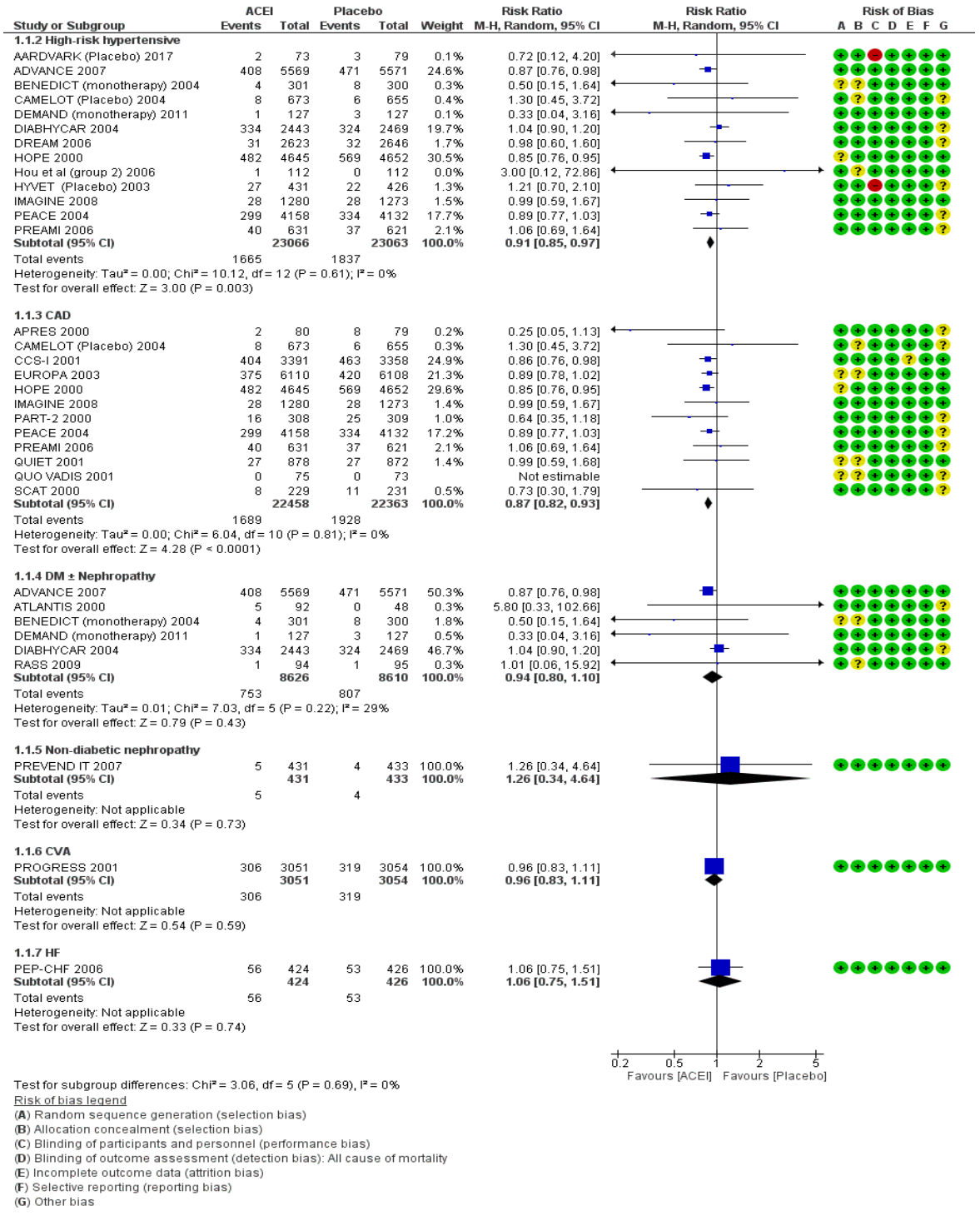


Figure 7-25 Forest plot showing effect of ACEIs versus placebo on risk of all-cause mortality (RE model) [Subgroup analysis: Clinical setting].

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

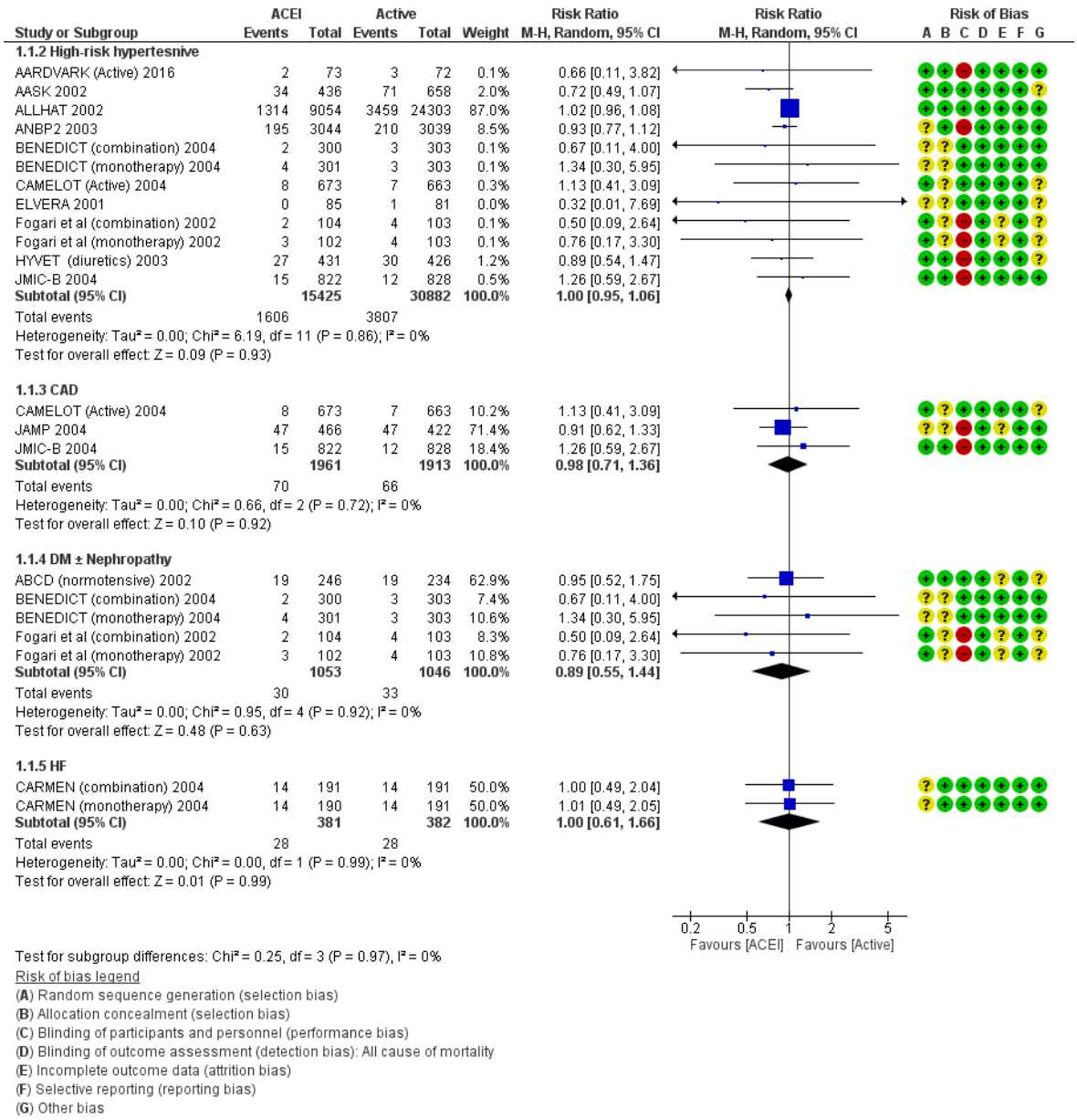


Figure 7-26 Forest plot showing effect of ACEIs versus active on risk of all-cause mortality (RE model) [Subgroup analysis: Clinical setting].

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

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†

Subgroup analysis		Studies	Participants	Events	All-death Incidence (%)		RR (M-H, Random, 95% CI)	P value*	I^2 (%) ‡
					ACEI	Control			
	Overall effects	**41**	**125,824**	**11,646**	**8.28**	**10.0**	**0.94 [0.91, 0.98]**	**0.002***	**0**
	Placebo	26	77,386	6045	7.42	8.20	0.91 [0.86, 0.95]	**<0.0001***	0
	Active	16	48,438	5601	10.2	12.2	1.00 [0.95, 1.05]	0.95	0
Subclass	**High-tissue affinity**	22	69,011	5201	7.18	7.88	0.91 [0.86, 0.96]	**0.0002***	0
	Low-tissue affinity	16	55,335	6404	10.6	12.0	0.98 [0.94, 1.03]	0.52†	0
Active control	**CCBs**	11	24,151	2737	11.5	11.1	1.04 [0.97, 1.11]	0.31	0
	Diuretics	3	31,249	3979	12.2	13.0	1.00 [0.94, 1.06]	0.87	0
	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

†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 considered statistically significant.

** Cannot synthesis data by one trial.

‡ I^2 statistic with <25% considered as low heterogeneity and I^2> 75% as high heterogeneity.

† 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†

Subgroup analysis		Studies	Participants	Events	All-mortality Incidence (%)		RR (M-H, Random, 95% CI)	P value*	I^2 (%) ‡
					ACEI	Control			
Placebo									
Clinical setting	**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
	DM± Nephropathy	6	17,236	1560	8.72	9.37	0.94 [0.80, 1.10]	0.43	29
	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 group	**< 65 years**	20	58,223	4268	6.88	7.77	0.88 [0.84, 0.94]	**<0.0001***	0
	≥ 65 years	6	19,163	1777	9.05	9.48	0.96 [0.88, 1.05]	0.38	2
Active									
Clinical setting	**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
	DM± Nephropathy	5	2099	63	2.84	3.16	0.89 [0.55, 1.44]	0.63	0
	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 group	**< 65 years**	26	77,386	333	4.88	5.86	0.91 [0.86, 0.95]	0.19	0
	≥ 65 years	16	48,438	5268	11.4	12.9	1.00 [0.95, 1.05]	0.73	0

† 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 considered statistically significant; ** Cannot synthesis data by one trial; ‡ I^2 statistic with <25% considered as low heterogeneity and I^2> 75% as high heterogeneity.

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 I^2= 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 I^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.

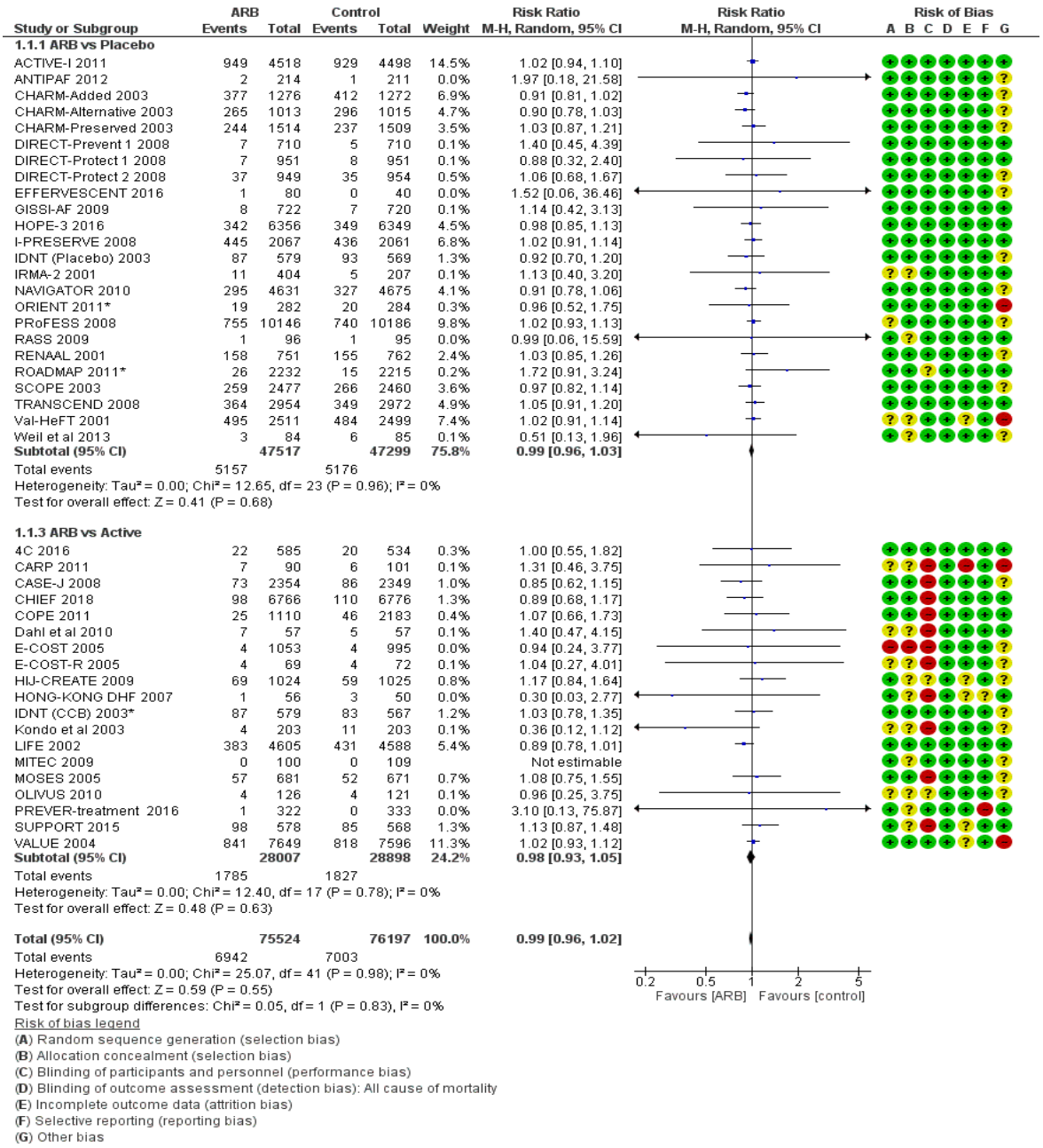


Figure 7-27 Forest plot showing effect of ARBs on risk of all-cause mortality, stratified by comparison group (placebo vs active). Overall: 43 trials: (RE model).

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

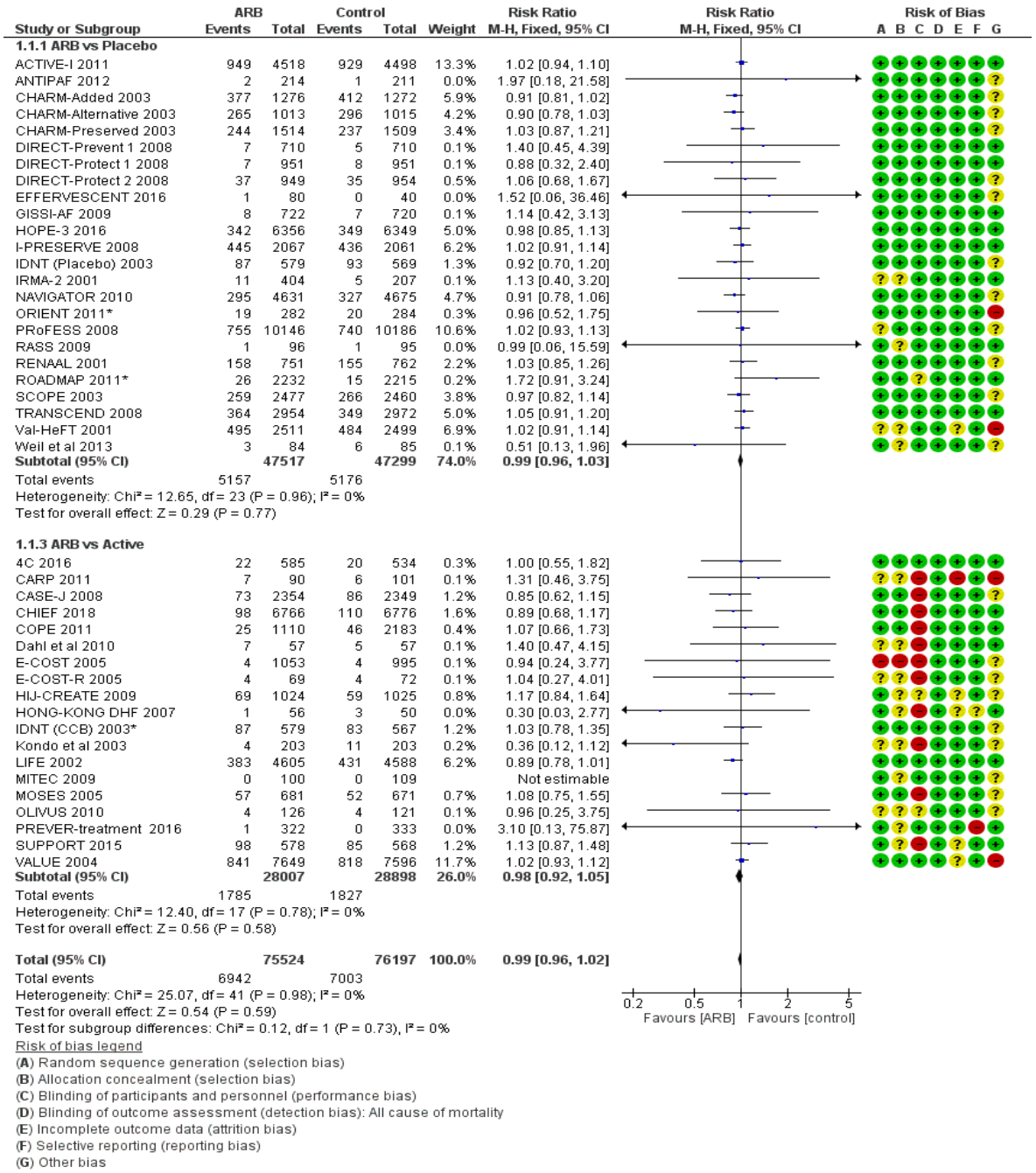


Figure 7-28 Forest plot showing effect of ARBs on risk of all-cause mortality, stratified by comparison group (placebo vs active). Overall: 43 trials (FE model).

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 controlled-trial, 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)**

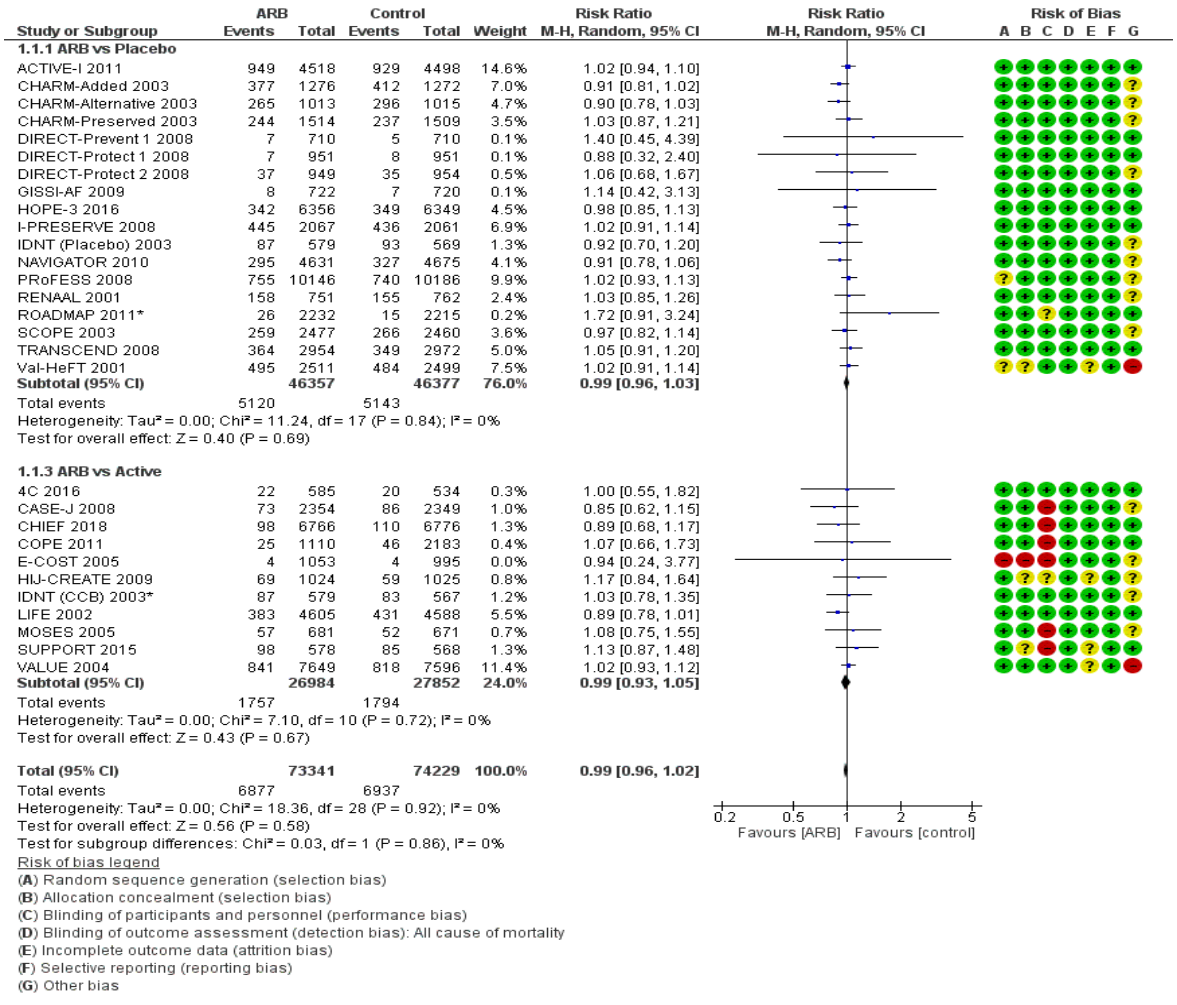


Figure 7-29 Forest plot showing effect of ARBs on risk of all-cause mortality (RE model) **[Sensitivity analysis: Excluding trials with sample size less than 1000].**

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

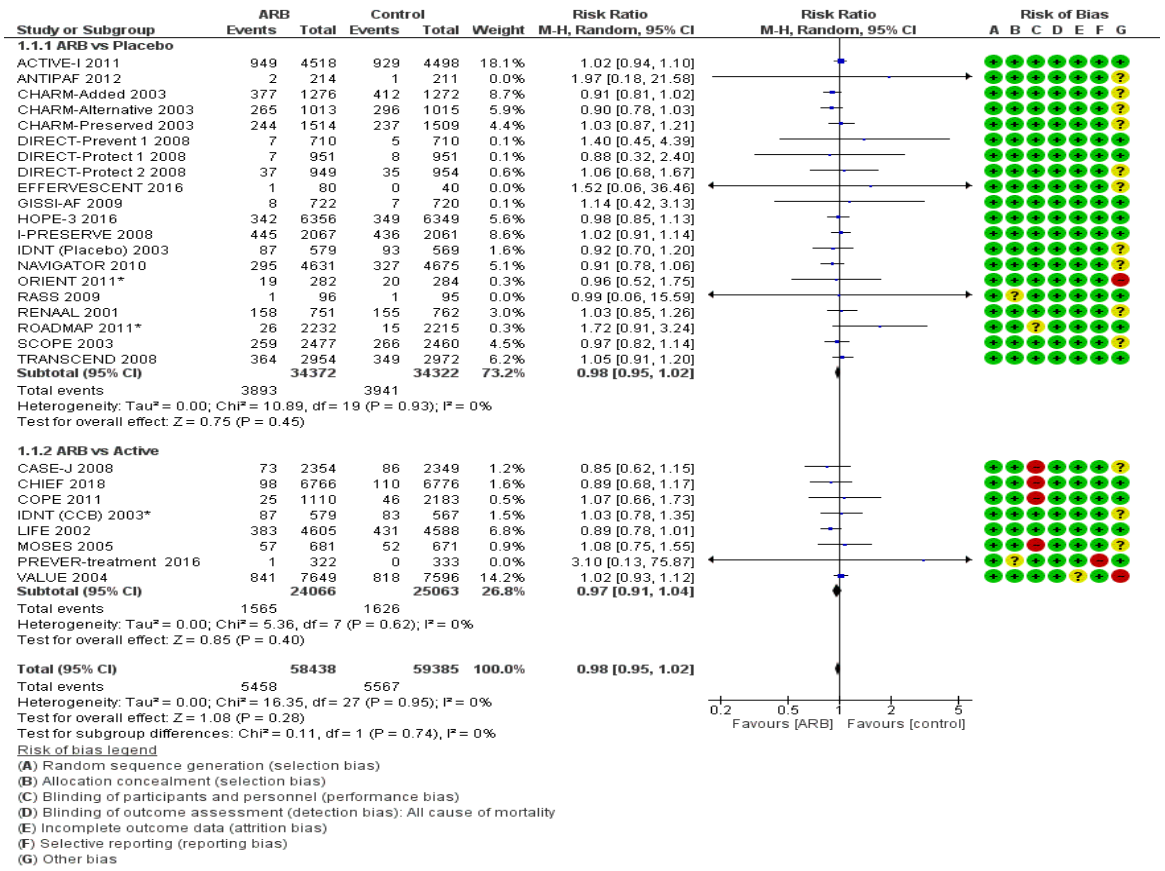


Figure 7-30 Forest plot showing effect of ARBs on risk of all-cause mortality (RE model) **[Sensitivity analysis: Excluding trials with low methodology quality].**

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 all-mortality (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 ≥ 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.

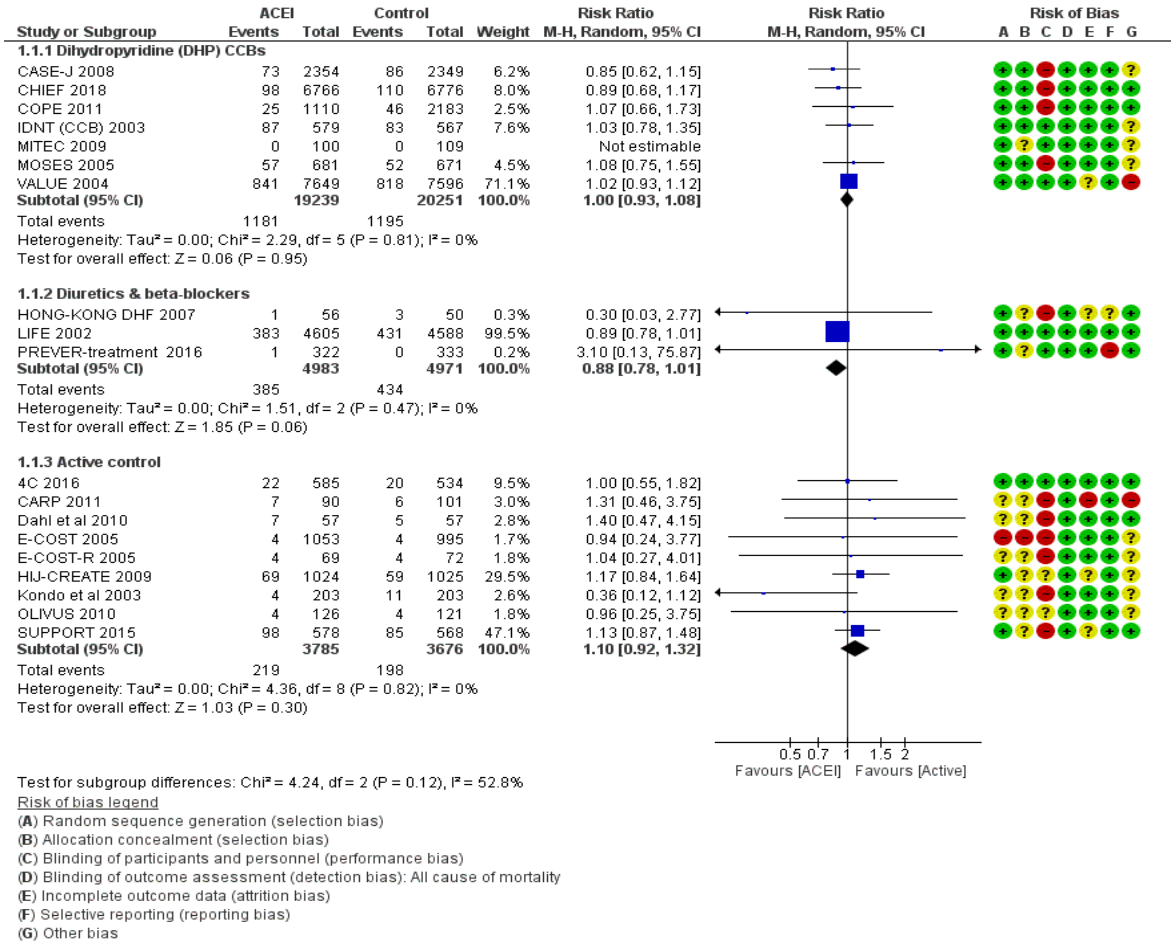


Figure 7-31 Forest plot showing effect of ARBs on risk of all-cause mortality [Subgroup analysis: Type of active comparator].

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

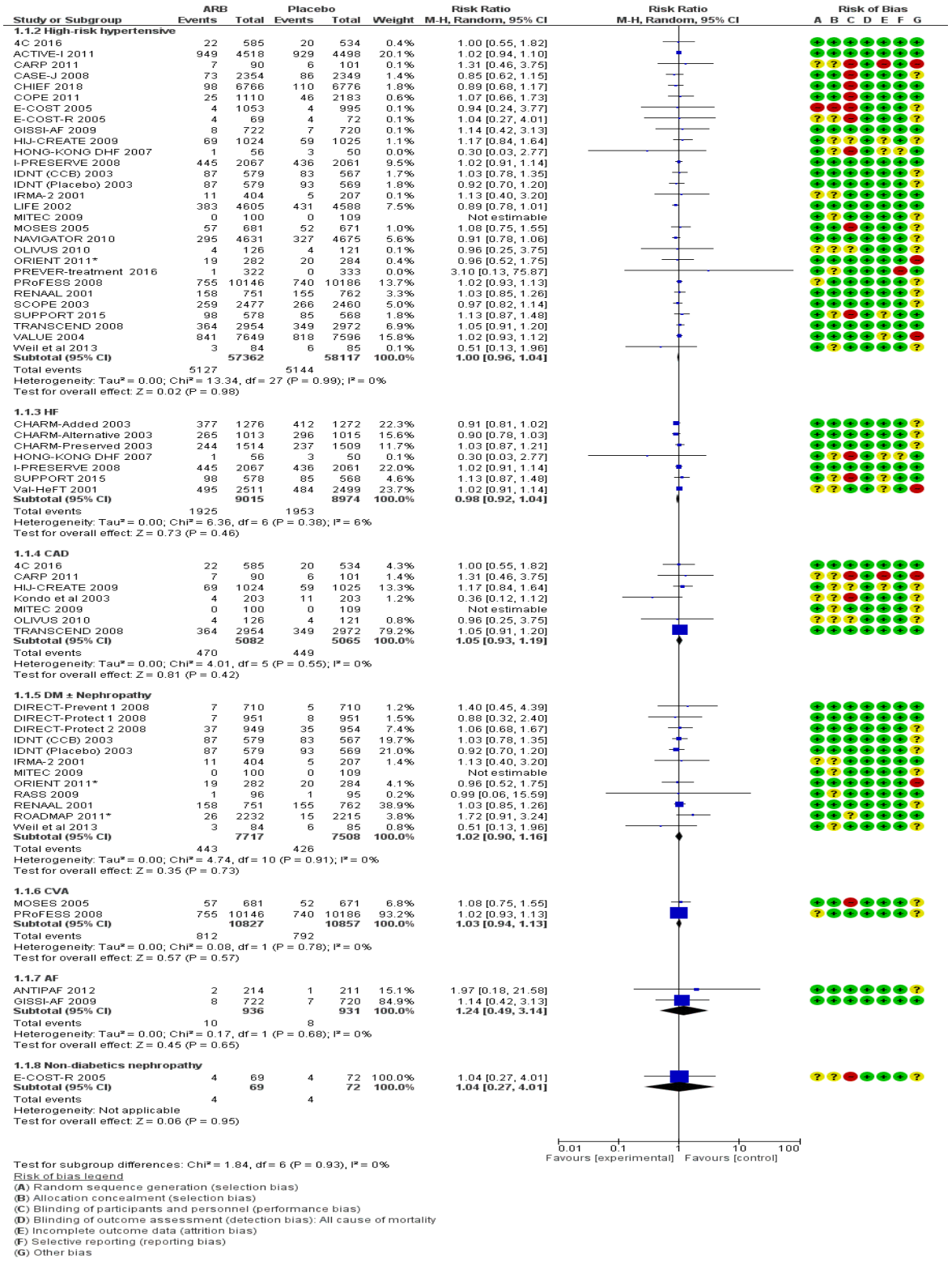


Figure 7-32 Forest plot showing effect of ARBs on risk of all-cause mortality; [Subgroup analysis: Clinical setting].

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)†

Subgroup analysis		Studies	Participants	Events	All-mortality Incidence (%)		RR (M-H, Random, 95% CI)	P value*	I^2 (%) ‡
					ARBs	Control			
Overall	**RE**	**43**	**151,721**	**13,945**	**9.19**	**9.19**	**0.99 [0.96-1.02]**	**0.59**	**0**
Active control	**DHP-CCBs**	6	25,948	2168	8.68	8.05	1.01 [0.93-1.10]	0.76	0
	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
Clinical setting	**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
	DM± Nephropathy	12	15225	869	5.74	5.67	1.02 [0.90-1.16]	0.73	0
	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				
Mean age group	**< 65 years**	21	54,439	3628	6.53	6.79	0.96 [0.91-1.02]	0.23	0
	≥ 65 years	21	96,703	10,230	10.5	10,5	1.00 [0.97-1.04]	0.96	0

†**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 considered statistically significant; ^Cannot synthesis data by one trial; ‡ I^2 statistic with <25% considered as low heterogeneity and I^2> 75% as high heterogeneity.

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).**

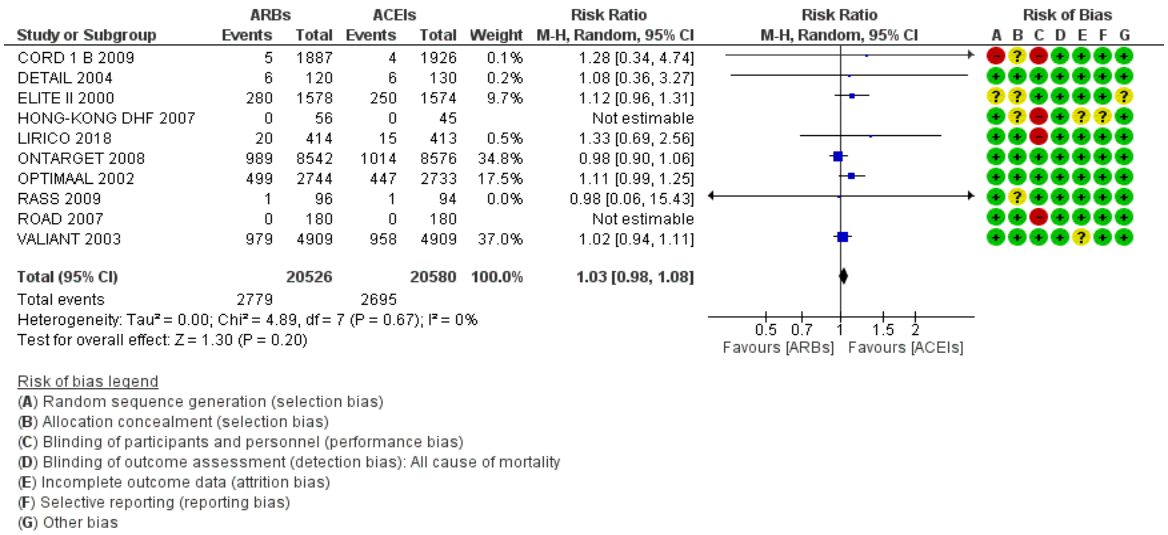


Figure 7-33 Forest plot showing effect of ARBs versus ACEIs on risk of all-cause mortality (RE model).

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

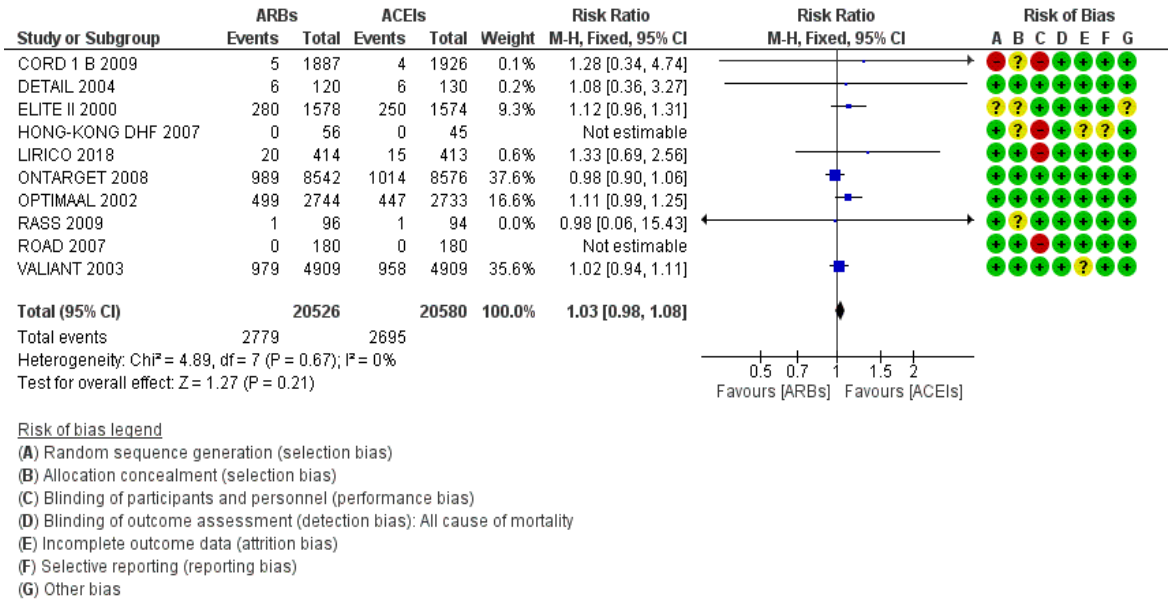


Figure 7-34 Forest plot showing effect of ARBs versus ACEIs on risk of all-cause mortality **(FE model).**

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**)

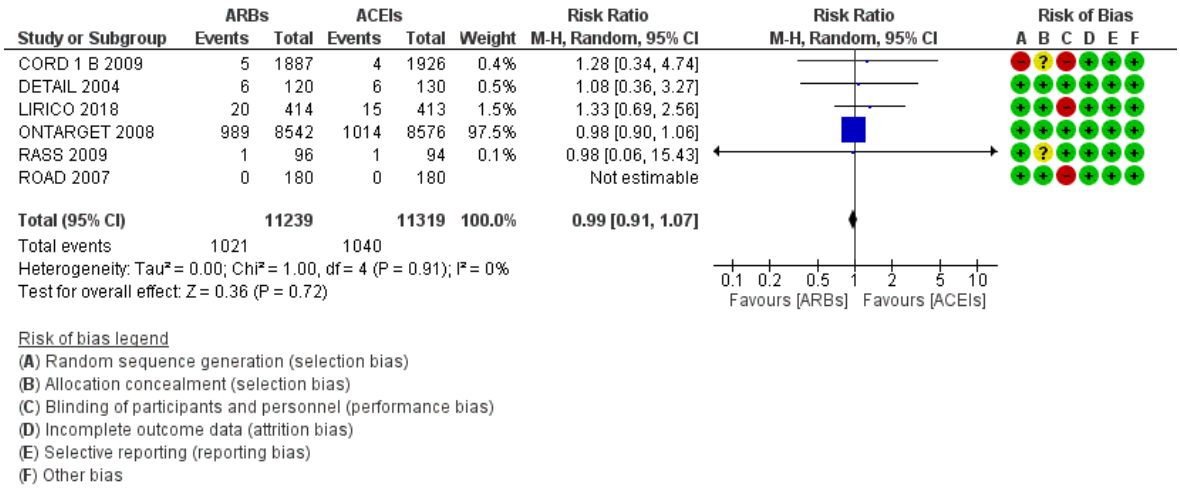


Figure 7-35 Forest plot showing effect of ARBs versus ACEIs on risk of all-cause mortality (RE model) [Sensitivity analysis: Excluding trials with HF].

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 (Tau^2 reduced from 0.0041 to 0; p=0.951, residual I^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 (Tau^2 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)**

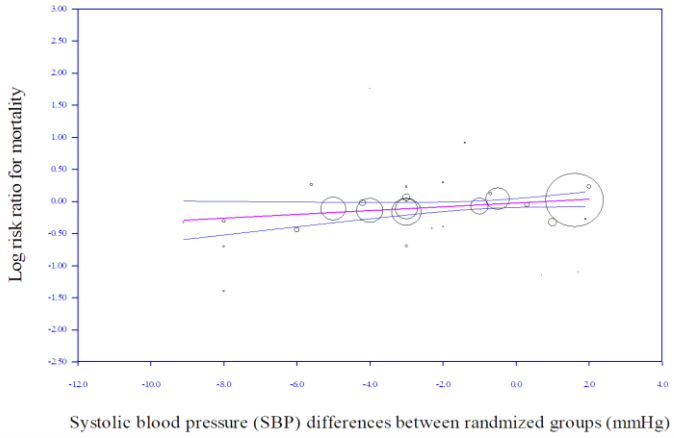


Figure 7-36 Adjusted meta-regression analysis of relationship between RR of all-mortality and difference in achieved SBP (mmHg) between randomized groups for trials of ACEIs

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

Table 7-8 Meta-regression of related and unrelated SBP differences by ACEI on all-cause mortality risk (adjusted and unadjusted models)

		Slope				Between study variance		
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)								
Achieved SBP differences (mmHg)**		1.04	1.01-1.06	**0.010***	0	0	0.951	100

Abbreviation: Tau^2= 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 analysis was adjusted for male (%) and 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.

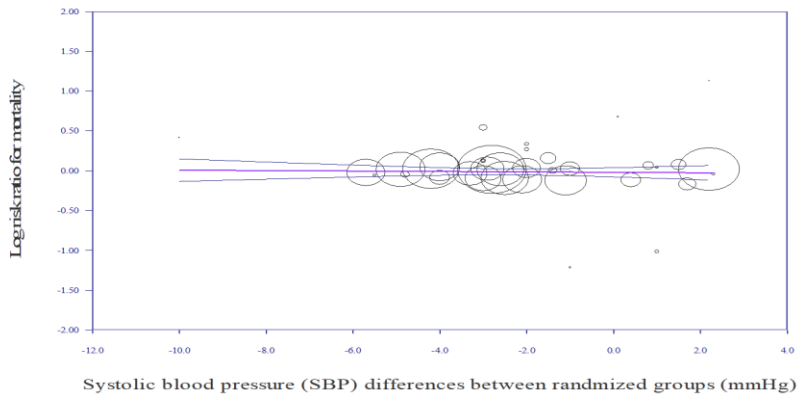


Figure 7-37 Meta-regression analysis of relationship between RR of all-mortality and difference in achieved SBP (mmHg) between randomized groups for trials of ARB.

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 ARB-based 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 (I^2=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 (I^2=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 ß-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-regression studies.

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 (I^2 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, I^2: 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 ≥ 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.

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; I^2:0%). 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; I^2:30%) **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; I^2=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; I2: 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; I^2: 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; I^2: 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%; I^2: 0%). While there was no benefit compared with the active group (I^2:58%). **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; I^2:0%). **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, I^2: 43%). For ARBs, data from 36 RCTs (n=140,542) enrolled resulted in a statistically significant 14% reduction in HF (95% CI 9-19%; I^2: 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; I^2: 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%; I^2:6%). 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; I^2: 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; I^2:0%). **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; I^2:0%). 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; I^2: 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; I^2: 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 non-bibliographic 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 I^2 value of 0%, and only a few outcomes were associated with I^2 >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 meta-analysis 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 meta-regression 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 (Tau^2) 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 (I^2=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 I^2). 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 (I^2 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 head-to-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. The beneficial effect independent of 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.

MEDLINE search strategy **Database:** Ovid MEDLINE(R)	
	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)”

CENTRAL search strategy **Database:** Cochrane Central Register of Controlled Trials	
	Keywords searches

#1	Mesh descriptor: [Angiotensin Receptor Antagonist] explode all trees
#2	(angiotensin near/3 receptor next block*):ti,ab,kw
#3	(angiotensib near/3 receptor next antagonist*):ti,ab,kw
#4	(eprosartan or azilsartan or candesartan or irbesartan or losartan or olmesartn or telmisartan or valsartan):ti,ab,kw
#5	**#1 or #2 or #3 or #4**
#6	MeSH descriptor: [Angiotensin-converting Enzyme Inhibitors]:ti,ab,kw
#7	(angiotensin next converting next enzyme next inhibitor*):ti,ab,kw
#8	ace near/2 inhibit*:ti,ab,kw
#9	(captopril or enalapril or benazepril or zofenopril or quinapril or perindopril or ramipril or trandolapril or fosinopril or moexipril or Lisinopril):ti,ab,kw
#10	**#6 or #7 or #8 or #9**
#11	#5 or #10 publication year to 2018 (word variations have been searched)

Embase search strategy
Database: Embase

	Keywords searches
1	angiotensin receptor antagonists.mp
2	(angiotensin adj2 (receptor antagon$ or receptor block$)).tw.
3	arb?.tw.
4	(eprosartan or Azilsartan or candesartan or irbesartan or losartan or fimasartan or olmesartan or telmisartan or valsartan).tw.
5	**1 or 2 or 3 or 4**
6	angiotensin enzyme inhibitors.mp
7	angiotensin converting enzyme inhibit$.tw
8	(ace adj2 inhibit$).tw.
9	acei.tw.
10	(captopril or enalapril or benazepril or zofenopril or quinapril or perindopril or ramipril or trandolapril or fosinopril or moexipril or Lisinopril).tw
11	**6 or 7 or 8 or 9 or 10**
12	randomized controlled trial/
13	crossover procedure/
14	double-blind procedure/
15	(randomi$ or randomly).tw.
16	(crossover$ or cross-over$).tw.
17	placebo$.tw.
18	(doubl$ adj blind$).tw.
19	assign$.ab.
20	allocat$.ab.
21	trial.ti.
22	**12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21**
23	(animal$ 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>)

Web of Science-Core of Collection [Conference Proceedings Citation Index- Science (CPCI-S) --1990-present]	
	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
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
ACTIVE-I (2011) (Yusuf et al., 2011)
Design: Multicentre, partial factorial, randomized, double-blind, placebo-controlled trial

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 episodes of 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, nonfatal 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
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 ACEI or ARB was prohibited. **Concomitant non-study RAS blockers:** None
Primary and secondary outcomes: Glucose and lipoprotein metabolism, electrolytes, BP, and subjective symptoms
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) **Hypertensive patients (%):** 100 **Baseline co-morbidities (%):** None
Intervention: Two groups

ACEI: Enalapril vs. hydrochlorothiazide **Co-intervention:** To achieved BP goal, other BP-lowering agents was added in stepwise fashion. **Concomitant non-study RAS blockers: Intervention:** 14% ARB. **Control:** 12.4% ARB
Primary and secondary outcomes: Composite & individual 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 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:** 18-older (mean: 61.5 years) **Hypertensive patients (%):** 49 **Baseline co-morbidities (%):**
Intervention: 2 groups **ARB**: 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 life
Funding Source: German Ministry of Research and Education. Daiichi 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 (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 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 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
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
Participants (n): 1024 **Clinical setting:** Subjects with HTN, T2DM & norm-albuminuria

Mean baseline BP: 150.5/87.5 mmHg **Age range:** 40-older (mean age: 61 years) **Hypertensive patients (%):** 100 **Baseline co-morbidities (%):** T2DM (100)
Intervention: Four groups Trandolapril (2 mg/day) vs. verapamil (240 mg/day) vs. trandolapril+ sustained released verapamil (180/2 mg per day) vs. placebo **Co-intervention:** To control BP, other BP-lowering agents were added in steps **Concomitant non-study RAS blockers:** None
Primary 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
Participants (n): 822 **Clinical setting:** AMI 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 TID **Co-intervention:** NR **Concomitant non-study RAS blockers:** NR
Primary outcomes: All & 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 **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 & 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: A**ll-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 (%):** 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 revascularization (TLR)

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-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 (%):** 42 **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 **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 **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 **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: 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
Funding Source: Ministry of science & Technology of China
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) **Hypertensive patients (%):** 100 **Baseline co-morbidities (%):** None
Intervention: Three groups **ARB:** Benidipine (4-8 mg/day)-ARB **vs.** benidipine-BB **vs.** benidipine-TZ **Co-intervention:** Other antihypertensive agents were added to control BP **Concomitant non-study RAS blockers:** NR
Primary and secondary outcomes: Composite & individual of fatal and non-fatal cardiovascular events
Funding Source: Kyowa Hakko Kirin Co., Ltd
CORD 1 B (2009) (Spinar et al., 2009)
Design: Prospective, randomized, multicentre, open-label, blinded-endpoint trial (PROBE) **Mean duration of follow-up:** 1 year
Participants (n): 3813 **Clinical setting:** HTN **Mean baseline BP:** 155.9/93 mmHg **Mean age:** 60.5 years **Hypertensive patients (%):** 100 **Baseline co-morbidities (%):**
Intervention: Two groups Ramipril vs. losartan **Co-intervention:** To control BP, other BP-lowering agents were added **Concomitant non-study RAS blockers:** NR
Primary and secondary outcomes: Decreases in BP, normalization of BP & incidence of clinical events
Funding Source: Ministry of Education of the Czech Republic
Dahl et al. (2010) (Dahl et al., 2010)
Design: Prospective, randomized, single-centre, open-label, blinded-endpoint trial (PROBE) **Mean duration of follow-up:** 1 year
Participants: 114 **Clinical setting:** Aortic Stenosis, post-aortic valve replacement (AVR) **Mean baseline BP:** 146/79 mmHg **Age range:** > 18 years (mean age: 72) **Hypertensive patients (%):** 23

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 creatinine level & BP, rates of clinical events (ESRD, MI, stroke, CHF), all cause death, rate of adverse events; and laboratory abnormalities
Funding Source: Boehringer Ingelheim
DIABHYCAR (2004) (Marre et al., 2004)
Design: Prospective, randomized, double-blinded, parallel trial **Median duration of follow-up: 4 years**
Participants (n): 4912 **Clinical setting:** T2DM who use oral antidiabetic drugs and have persistent microalbuminuria or proteinuria, and serum creatinine ≤ 150 µmol/l. **Mean baseline BP:** 145.5/82.4 mmHg **Age range:** 50-older (mean: 65.1 years) **Hypertensive patients (%):** 56 **Baseline co-morbidities (%):** DM (100%)
Intervention: Two treatment groups **ACEI:** Ramipril 1.25mg/day vs Placebo **Co-intervention:** On top of standard therapy **Concomitant non-study RAS blockers: Intervention:** 20% ACEI. **Control:** 22% ACEI; **P value=0.05**
Primary & primary outcomes: incidence of CV death, fatal and non-fatal MI, stroke, HF, leading to hospital admission, and ESRF; all-cause death; any revascularization procedure on coronary or other arterial vessels, transient neurological ischaemic episodes, doubling of the serum creatinine concentration, loss of vision in one eye, and amputation above the metatarsophalangeal joint
Funding Source: Avantis (Paris) and the French Health Ministry
DIRECT-Prevent 1 (2008) (Chaturvedi et al., 2008)
Design: Prospective, randomized, double-blinded, parallel trial **Median duration of follow-up:** 4.7 years
Participants (n): 1421 participants **Clinical setting:** normotensive, normoalbuminuric type 1 diabetes without retinopathy **Mean baseline BP:** 116/72 mmHg **Age range:** 18-55 (mean: 29.7 years) **Hypertensive patients (%):** Excluded **Baseline co-morbidities (%):** DM (100)
Intervention: 2 treatment groups **ARB**: Candesartan 32 mg/day vs Placebo **Co-intervention**: no other BP-lowering agents were added **Concomitant non-study RAS blockers: Intervention:** 4% ACEI. **Control:** 6% ACEI
Primary & secondary outcomes: incidence and progression of diabetic retinopathy.

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
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)
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 **Age range:** 24-90 (mean: 61 years) **Hypertensive patients (%):** 27 **Baseline co-morbidities (%):** Prior MI (64.7)

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 hospitalizations; 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: ≥55 years Women: ≥ 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 ≥ 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: H**ypertension, 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: I**rbesartan 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 the level of albuminuria, changes in creatinine clearance, and the restoration of normoalbuminuria by the time of the last visit
Funding Source: Sanofi–Synthelabo and Bristol-Myers Squibb

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
Intervention: Three groups **ARB:** Candesartan (8-12 mg/day) plus bepridil (100-200 mg/day) vs. carvedilol (5-20 mg/day) plus bepridil vs. bepridil (100-200 mg/day) **Co-intervention:** Subjects treated with ACEI or ARB were excluded **Concomitant non-study RAS blockers:** None
Outcomes: Recurrence of AF
Funding Source: NR
Kondo et al. (2003) (Kondo et al., 2003)
Design: Prospective, multicentre, randomized, open label, parallel trial **Median duration of follow-up:** 2 years
Participants (n): 406 **Clinical setting:** CAD **Mean baseline BP:** 129/76 mmHg **Mean age:** 65 years **Hypertensive patients (%):** 44 **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: Composite of revascularization, nonfatal MI, CV death **Secondary 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-morbidities (%):** None
Intervention: Two groups **ARB:** Losartan (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 IMT over 2 years & BP
Funding Source: NR
LIFE (2002) (Dahlöf et al., 2002) (FDA, 2001b)
Design: Prospective, multicentre, randomized, double-blinded, parallel trial **Mean duration of follow-up:** 4.8 years
Participants (n): 9193 **Clinical setting:** Essential hypertension and LVH **Mean baseline BP:** 174.5/97.7 **Age:** 55–80 (mean: 67 years) **Hypertensive patients (%):** 100 **Baseline co-morbidities (%):** None
Intervention: Two groups **ARB:** Losartan 50-100mg/day vs BB: atenolol 50-100mg/day **Co-intervention:** If BP goal was not achieved, other BP-lowering agents were added (HCTZ 12.5- 25mg/day, excluding ARB, ACEI and BB). **Concomitant non-study RAS blockers:** NR
Primary & secondary outcomes: CVD mortality and mortality, total mortality, angina pectoris or CHF requiring hospital admission
Funding Source: Merck
LIRICO (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 **Clinical setting:** DM with moderate to severe albuminuria **Mean age:** 62.8 years **Hypertensive patients (%):** 83 **Baseline co-morbidities (%):** None
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 **Clinical setting:** T2DM & HTN

Mean baseline BP: 156/91 mmHg **Age range:** 40-74 years (mean: 59.7 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: I**mpaired 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: V**alsartan 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
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 **Mean age:** 68 years **Hypertensive patients (%):** 100 **Baseline co-morbidities (%):** None
Intervention: Two groups **ARB:** Olmesartan (10-40 mg/day) vs. control **Co-intervention:** Treated with combination of beta-blockers, CCBs, diuretics & nitrates

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: P**atients 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: C**onfirmed 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
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 **Median duration of follow-up: 4.8**
Participants (n): 8290

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: R**amipril 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: P**atients 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 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 **Secondary outcomes:** Individual of 1^{ry} outcomes, CV death, reinfarction or angina, incidence of coronary artery bypass or PCI

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 **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 **Clinical setting:** CAD (Post-PCI, within 72 hr of PCI) **Mean baseline BP:** 123/74 mmHg

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 **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
ROAD (2007) (Hou et al., 2007)
Design: Prospective, randomized, single-centre, open-label, blinded-endpoint trial (PROBE) **Median duration of follow-up:** 3.7 years
Participants (n): 360 **Clinical setting:** Non-DM CKD (stage II-IV) **Mean baseline BP:** 150/86 mmHg **Mean age:** 51 years **Hypertensive patients (%):** 63.6 **Baseline co-morbidities (%):** None
Intervention: Two groups Losartan (50-200 mg daily) vs benazepril (10-40 mg daily) **Co-intervention:** To achieved adequate BP level, additional BP-lowering agents added monotherapy or combination (diuretics, CCBs, BB, centrally acting agents), excluding ACEI & ARB **Concomitant non-study RAS blockers:** NR
Primary & secondary outcomes: Composite or individual end points: doubling of the serum creatinine concentration, ESRD, or death.

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: C**andesartan 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 **Mean baseline BP:** 140.7/82 **Age:** Not reported (mean: 66.9 years) **Hypertensive patients (%):** 76 **Baseline co-morbidities (%):**

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: V**alsartan 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 morbidity, revascularization procedures, CV procedures, hospitalization.
Funding Source: Novartis Pharmaceuticals
VALUE (2004) (Julius et al., 2004)
Design: Prospective, multicentre, randomized, double-blinded, parallel trial **Mean duration of follow-up:** 4.2 years
Participants (n): 15,245 **Clinical setting:** Treated or untreated hypertension and a high risk of cardiac events **Mean baseline BP:** 154.5/87.5 mmHg **Age:** 50 or older (mean: 67 years) **Hypertensive patients (%):** 92 **Baseline co-morbidities (%):**
Intervention: Two groups **ARB:** Valsartan 80 - 160mg/day vs amlodipine 5 - 10mg/day **Co-intervention:** If BP goal was not achieved, other antihypertensive agents were added (excluding ACEI) **Concomitant non-study RAS blockers:** NR
Primary & secondary outcomes: Time to first cardiac event, Fatal and non-fatal MI, fatal and non-fatal HF, and fatal and non-fatal stroke, all-cause mortality, new-onset diabetes.
Funding Source: Novartis Pharma AG
Weil et al. (2013) (Weil et al., 2013)
Design: Prospective, single-centre, randomized, double-blinded, parallel trial **Median duration of follow-up:** 5.9 years
Participants (n): 169 **Clinical setting:** HTN & T2DM with normo/microalbuminuria **Mean baseline BP:** 118/75 mmHg **Mean age:** 42 years **Hypertensive patients (%):** 100 **Baseline co-morbidities (%):** None
Intervention: Two groups **ARB:** Losartan (50-100 mg/day) vs. placebo **Co-intervention:** NR **Concomitant non-study RAS blockers:** NR
Primary outcomes: Decline in GFR to ≤ 60 ml/min or half the baseline subject in patients with GFR < 120 ml/min **Secondary outcomes:** Differences between treatment groups in predefined glomerular structural variables measured on kidney biopsy samples
Funding Source: Intramural Research Program of National Institute of Diabetics, Digestive & Kidney Diseases & by Merck

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** • **Other outcomes**	 Low risk Low risk	 Outcome is unlikely influenced by blinding Blinding of outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropped-out rate in both groups was not reported. 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** • **Other outcomes**	Low risk None	Outcome measurement is not likely to be influenced by lack of blinding. 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)		
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 • **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 unlikely to affect the outcome results (ITT 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 outcomes)	Low risk	Participants and personnel were blinded. Study nurses were blinded to the use of enalapril versus nisoldipine
Blinding of outcome assessment • **All-cause mortality** • **Other outcomes**	 Low risk Low risk	 Outcome is unlikely influenced by blinding Blinding of outcome assessment. An Endpoint Committee blinded to randomization 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 methods
Other bias	Unclear	The sponsor role not reported
ACTIVE-I (2011)		
Bias	**Authors' 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)
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 are unlikely influenced by blinding 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)		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low risk	Centre randomization stratified by study centre, history of macrovascular disease, history of microvascular 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 • **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 15 patients (0.2%) were lost follow-up, 4 in the intervention group and 11 in the placebo group (All analyses would also be by ITT principle)
Selective reporting	Low risk	Reported all the outcomes described in the 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' judgement**	**Support for 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 outcomes)**	Low risk	Participants and personnel were blinded
Blinding of outcome assessment • **All-cause mortality** • **Other outcomes**	 Low risk Unclear risk	 Outcome measurement is not likely to be influenced by lack of blinding Blinding of outcome assessment was not described.
Incomplete outcome data All outcomes	Low risk	Two centres initially reported were excluded, due poor documentation of informed consent. ITT analysis was performed
Selective reporting	Low risk	All the pre-specified outcomes in the methods 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	Low	Outcomes listed in the methods were all reported
Other bias	Unclear risk	The role of sponsor was not reported
ANBP2 (2003)		
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** • **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	Outcomes listed in the methods were all reported
Other bias	Low risk	The sponsor has no role
ANTIPAF (2012)		
Bias	**Authors' judgement**	**Support for 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 used
Selective reporting	Low risk	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** • **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	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** • **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	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** • **Other outcomes**	 None Low risk	 Outcome was not reported Blinding of outcome assessment
Incomplete outcome data All outcomes	Unclear risk	The discontinuation rate was not reported & the analysis was performed by per-protocol principles
Selective reporting	Low risk	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)		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear risk	The method of generate random sequence was reported
Allocation concealment	Unclear risk	The method of 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 outcome assessment.
Incomplete outcome data All outcomes	Low risk	Missing data unlikely to affect the outcome results. 16 (1.3%) out of 1204 were lost to follow-up
Selective reporting	Low risk	Reported all outcomes specified in the methods
Other bias	Low risk	Supported in part by pharmaceutical company
Cai et al. (2001)		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear risk	The method of random sequence generation was reported
Allocation concealment	Unclear risk	The method of allocation concealment was reported
Blinding of participants and personnel (All outcomes)	Unclear risk	Blinding of participants and personnel were not reported
Blinding of outcome assessment • **All-cause mortality** • **Other outcomes**	 Low risk Unclear risk	 Outcome measurement is not likely to be influenced by lack of blinding. Blinding of outcome assessment was not reported
Incomplete outcome data All outcomes	High risk	High dropped-out rate (19.8%) in captopril group as compared with control group (17.4%). The ITT analysis was not used.
Selective reporting	Low risk	Outcomes listed in the methods were all reported
Other bias	Unclear risk	The role of sponsor was not described
CAMELOT (2004)		

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 • **All-Cause Mortality** • **Other outcomes**	 Low risk Low risk	 Outcome is unlikely influenced by blinding Blind 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	Primary statistical analysis was performed by Pfizer. (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 ß-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 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	Sponsor representatives participated in steering committee meetings as non-voting members.
CARP (2011)		
Bias	**Authors' judgement**	**Support for judgement**
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 • **All-cause mortality** • • **Other outcomes**	 Low risk Unclear risk	 Outcome measurement is not likely to be influenced by lack of blinding. 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 All outcomes	Low risk	Missing data were unlikely to have an impact on the 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** • **Other outcomes**	 Low risk Unclear risk	 Outcome measurement is not likely to be influenced by lack of blinding. The outcome of assessment blinding was not described.
Incomplete outcome data All outcomes	Unclear risk	The missing data was not reported. No information available for judgement
Selective reporting	Low risk	Outcomes listed in the methods were all reported
Other bias	Low risk	The sponsor was academic research centre
Chan et al. (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 not reported
Blinding of outcome assessment • **All-cause mortality** • **Other outcomes**	 None Low risk	 Outcome was not reported 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 • **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	Low risk	Central allocation
Blinding of participants and personnel (**All outcomes)**	High risk	Open-label design
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 missing data was not reported. However, ITT was used
Selective reporting	Low risk	Outcomes listed in the methods were all reported
Other bias	Low risk	Sponsored by academic institution

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** • **Other outcomes**	 Low risk Low risk	 Outcome is unlikely influenced by blinding Blinding of outcome assessment
Incomplete outcome data All outcomes	Low risk	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** • **Other outcomes**	 Low risk Low risk	 Outcome is unlikely influenced by blinding Blinding of outcome assessment
Incomplete outcome data All outcomes	Unclear risk	The loss of follow-up was not reported and analysis of dealing with missing data was not described
Selective reporting	Low risk	Outcomes listed in the methods were all reported
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** • **Other outcomes**	 Low None	 Blinding end-point assessment. However, outcome is unlikely influenced by blinding. 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** • **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. 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 data handling & analysis
DETAIL (2004)		

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** • **Other outcomes**	 Low risk Unclear risk	 Outcome measurement is not likely to be influenced by 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 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	Partially supported by pharmaceutical company. Unclear the role of sponsor
DIRECT Overall (2008)		
Bias	**Authors' 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** • **Other outcomes**	 Low risk None	 Blinding of outcome assessment. However, is unlikely influenced by blinding 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)		
Bias	**Authors' judgement**	**Support for 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 • **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	Outcomes listed in the methods were all reported

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' judgement**	**Support for 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** • **Other outcomes**	 Low risk Unclear risk	 Outcome measurement is not likely to be influenced by lack of blinding. 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** • **Other outcomes**	 Low risk Unclear risk	 Outcome measurement is not likely to be influenced by lack of blinding 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** • **Other outcomes**	 Low risk Low risk	 Outcome unlikely influenced by blinding Blinding of outcome assessment
Incomplete outcome data All outcomes	Low risk	The missing data seems not affected the results
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** • **Other outcomes**	 Low risk Low risk	 Outcome is unlikely influenced by blinding. Blinding of outcome assessment

Incomplete outcome data All outcomes	Low risk	High patients taking captopril discontinued the treatment (as compared to losartan group). However, the analysis was performed by ITT
Selective reporting	Low risk	Outcomes listed in the methods were all reported
Other bias	Unclear risk	The role of sponsor was not described
ELVERA (2001)		
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** • **Other outcomes**	 Low risk None	 Blinding of outcome assessment Other outcomes were not reported
Incomplete outcome data All outcomes	Low risk	The loss of follow-up was not reported. However, the ITT approach was used as analysis
Selective reporting	Low risk	Outcomes listed in the methods were all reported
Other bias	Unclear risk	The role of sponsor was not reported
ESPIRAL (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)	High risk	Study drugs were administered open-label
Blinding of outcome assessment • **All-cause mortality** • **Other outcomes**	 None Unclear risk	 Outcome was not reported 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' 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 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** • **Other outcomes**	 Low risk Unclear risk	 Outcome measurement is not likely to be influenced by lack of blinding Blinding of outcome assessment was not reported
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	Sponsor was not involved in the data collection and data analysis.
Fang Wu et (2015)		
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)	Unclear risk	Blinding of participants and personnel was not reported
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 loss of follow-up

Selective reporting	Low risk	Outcomes listed in the methods were all reported
Other bias	Low risk	Supported by grants from research institution
Fogari et al. (2002)		
Bias	**Authors' 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.
Blinding of participants and personnel (All outcomes)	High risk	Open-label
Blinding of outcome assessment • **All-cause mortality** • **Other outcomes**	 Low risk Unclear risk	 Outcome measurement is not likely to be influenced by lack of blinding. 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** • **Other outcomes**	 Low risk Unclear risk	 Outcome measurement is not likely to be influenced by lack of blinding; 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** • **Other outcomes**	 Low risk Low risk	 Outcome is unlikely influenced by blinding 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 Low risk	 Outcome is unlikely influenced by blinding Blinding-end point assessment.

• **Other outcomes**		
Incomplete outcome data All outcomes	Unclear risk	The dropped-out rates were not reported. The approach analysis of missing data was not reported
Selective reporting	Unclear risk	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** • **Other outcomes**	 Low risk Low risk	 Outcome is likely influenced by blinding 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' judgement**	**Support for judgement**
Random sequence generation	Low risk	Permuted block randomization stratified by centre
Allocation concealment	Low risk	Adequate. Central concealed randomization
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	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	Data collection & analysis were performed independently of sponsor
Hou et al. (group 2) (2006)		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low risk	Computer-generated list was used for randomization
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 • **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	Outcomes listed in the methods were all reported
Other bias	Low risk	Supported by clinical research institution
HYVET pilot (2003)		
Bias	**Authors' judgement**	**Support for 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 (All outcomes)	High risk	Open-label design
Blinding of outcome assessment • **All-cause mortality** • **Other outcomes**	 Low risk Unclear risk	 Outcome measurement is not likely to be influenced by lack of blinding. Blinding of outcome assessment was 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	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** • **Other outcomes**	 Low risk Low risk	 Outcome is unlikely influenced by blinding Blind 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 planned outcomes were reported
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** • **Other outcomes**	 Low risk Low risk	 Outcome is unlikely influenced by blinding Blind 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	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 (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 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 • **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	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 steering committee included two nonvoting members 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' judgement**	**Support for 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** • **Other outcomes**	 None Unclear risk	 Outcome was not reported Blinding of outcome assessment was reported
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
J-RHYTHM II (2010)		
Bias	**Authors' judgement**	**Support for judgement**
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** • **Other outcomes**	 None Low risk	 Outcome was not reported Blinding of outcome assessment
Incomplete outcome data All outcomes	Low risk	The loss of follow-up & dis-continuation in both groups 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** • **Other outcomes**	 Low risk Unclear risk	 Outcome measurement is not likely to be influenced by lack of blinding. 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
Allocation concealment	Low risk	Adequate. The sealed envelope method was used for randomization of the study drug
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. The analysis was performed by ITT principles
Selective reporting	Low risk	Outcomes listed in the methods were all reported
Other bias	Low risk	The trial was supported by research institution
KACT-MetS (2012)		
Bias	**Authors' judgement**	**Support for 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** • **Other outcomes**	 None Unclear risk	 Outcome was not reported Blinding of outcome assessment was not reported
Incomplete outcome data All outcomes	Low risk	Only one patient lost to follow-up in control group. The analysis was done by ITT principle
Selective reporting	Low risk	Outcomes listed in the methods were all reported
Other bias	Low risk	Funding by Academic institution
Kawamura (2013)		
Bias	**Authors' judgement**	**Support for 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)	Unclear risk	The blinding of participants and personnel was not reported
Blinding of outcome assessment • **All-cause mortality** • **Other outcomes**	 None Unclear risk	 Outcome was not reported Outcome assessment was not reported
Incomplete outcome data All outcomes	Low risk	The loss of follow-up was not reported. However, the ITT 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)		
Bias	**Authors' 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** • **Other outcomes**	Low risk Unclear risk	Outcome measurement is not likely to be influenced by lack of blinding; 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 (All outcomes)	Low risk	Participants and personnel were blinded
Blinding of outcome assessment		

• **All-cause mortality** • **Other outcomes**	None Low risk	Outcome was not reported 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** • **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	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 • **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)		
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 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	The role of sponsor was not reported
MOSES (2005)		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low risk	Computer-generated random sequence
Allocation concealment	Low risk	Adequate. the randomization sequence being blocked from previewing
Blinding of participants and personnel (All outcomes)	High risk	Open-label design
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 seems not affected the results
Selective reporting	Low risk	Outcomes listed in the methods were all reported

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' judgement**	**Support for 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 • **All-cause mortality** • **Other outcomes**	 Low risk Low risk	 Outcome is unlikely influenced by blinding Blinded end-point assessment
Incomplete outcome data All outcomes	Low risk	212 patients were excluded after randomization because 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)		
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** • **Other outcomes**	 None Unclear risk	 Outcome was not reported Blinding of outcome assessment was not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss of follow-up. The dis-continuation rates were similar. The data was analysis based on ITT approach
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 outcomes**	 Low risk Low risk	 Outcome is unlikely influenced by blinding Blinding of outcome assessment
Incomplete outcome data All outcomes	Low risk	No loss of follow-up.
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' 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 • **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 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** • **Other outcomes**	 Low risk Low risk	 Outcome is unlikely influenced by blinding 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 scientific conduct of the study and manuscript preparation was independent of the sponsor
ORIENT (2011)		
Bias	**Authors' 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 (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 missing data seems not affected the results
Selective reporting	Low risk	Outcomes listed in the methods were all reported
Other bias	Low risk	Overall study design conduct of the trial, data 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 randomization service
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	Outcomes listed in the methods were all reported
Other bias	Unclear risk	The role of sponsor was not reported
PEACE (2004)		
Bias	**Authors' judgement**	**Support for judgement**
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	Low risk	Computer-generated randomization list
Allocation concealment	Low risk	Central allocation
Blinding of participants and personnel (All outcomes)	High risk	Open-study design
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** • **Other outcomes**	 None Low risk	 Not reported as outcome Blinding outcome assessment
Incomplete outcome data All outcomes	Low risk	The dropped-out rates were not reported. However, the 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' judgement**	**Support for 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
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
PREVEND IT (2004)		
Bias	**Authors' judgement**	**Support for 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** • **Other outcomes**	 Low risk Low risk	 Outcome is unlikely influenced by blinding Blind 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 of study was academic institution
PREVER-treatment (2016)		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low risk	Computer generated list, with variable block sizes and 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** • **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	High risk	Heart failure requiring hospitalization, & angina was not reported in original trial
Other bias	Low risk	Sponsored by academic institution
PRoFESS (2008)		
Bias	**Authors' 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 (All outcomes)	Low risk	Participants and personnel were blinded
Blinding of outcome assessment • **All-cause mortality** • **Other outcomes**	 Low risk Low risk	 Outcome unlikely influenced by blinding 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	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 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	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

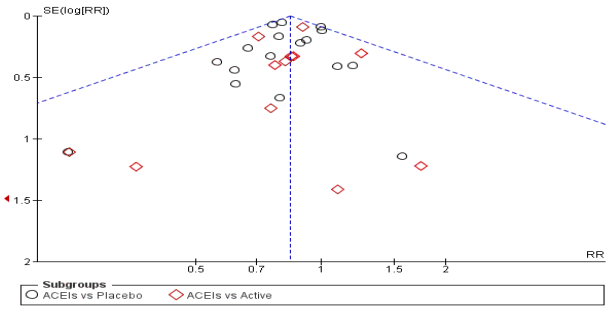
QUIET (2001)		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear risk	The method of generate random sequence was not reported
Allocation concealment	Unclear risk	The method of allocation concealment was not reported
Blinding of participants and personnel (All outcomes)	Low risk	Participants and personnel were blinded
Blinding of outcome assessment • **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. 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 • **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	Outcomes listed in the methods were all reported
Other bias	Unclear risk	The role of sponsor was nor reported
RASS (2009)		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation	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 All outcomes	Low risk	Missing data may not affect the results
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
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	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 described
ROAD (2007)		
Bias	**Authors' judgement**	**Support for judgement**

Random sequence generation	Low risk	Computer-generated randomization sequence list using a blocking size of 8.
Allocation concealment	Low risk	Adequate. Quote: Eligible patients got their sequence numbers from the coordinator
Blinding of participants and personnel (All outcomes)	High risk	Open-label design
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 withdrawal rates between two groups were similar & the analysis of end-points was done by ITT principles
Selective reporting	Low risk	Outcomes listed in the methods were all reported
Other bias	Low risk	Trial was supported by academic institution
ROADMAP (2011)		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low risk	The randomization list will be produced by PRA using SAS software
Allocation concealment	Low risk	Sealed envelopes stored at randomization allocation
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 measurement is not likely to be influenced by lack of blinding Blinding of outcome assessment
Incomplete outcome data All outcomes	Low risk	Missing data may not affect the results. Used ITT
Selective reporting	Low risk	Reported all outcomes described in the protocol
Other bias	Low risk	Data were collected independently of industry sponsors. Statistical analyses were performed by a clinical research organization
SCAT (2000)		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low risk	Computer-generated random sequence. (Block-randomization with stratification by centre)
Allocation concealment	Low risk	Masked allocation codes arranged in consecutive numerical order
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 Unclear risk	 Outcome measurement is not likely to be influenced by lack of blinding. Blinding of outcome assessment was not described
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
SCOPE (2003)		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low risk	Computer-generated randomization schedule, in a 1:1 ratio
Allocation concealment	Low risk	Central allocation via fax
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 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 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.
SUPPORT (2015)		
Bias	**Authors' judgement**	**Support for judgement**

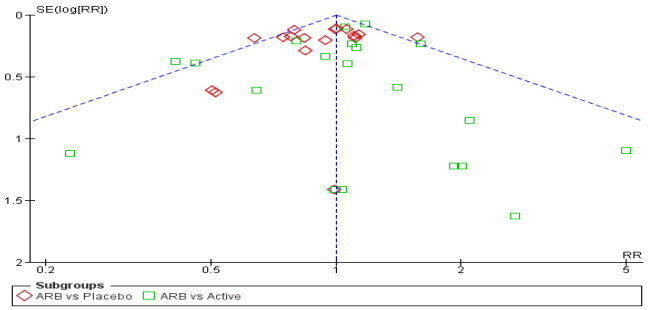
Random sequence generation	Unclear risk	The method of random sequence generation was not described well. Stratified patients by participating institute, sex, and age.
Allocation concealment	Unclear risk	The method of allocation concealment was not reported
Blinding of participants and personnel (All outcomes)	High risk	Open-label design
Blinding of outcome assessment • **All-cause mortality** • **Other outcomes**	 Low risk Low risk	 Outcome is unlikely influenced by blinding Blinding end-point assessment
Incomplete outcome data All outcomes	Low risk	The loss of follow-up was not reported & withdrawal 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' judgement**	**Support for 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** • **Other outcomes**	 Low risk Low risk	 Outcome is unlikely influenced by blinding Blinding outcome assessment
Incomplete outcome data All outcomes	Low risk	Missing data were unlikely to have an impact on the results 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' judgement**	**Support for 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 All outcomes	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 included in analysis.
Selective reporting	Low risk	Outcomes listed in the methods were all reported
Other bias	High risk	Site monitoring, data collection, and data analysis were performed by Novartis Pharmaceuticals
VALIANT (2003)		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low risk	Central automated randomization was used to assigned study treatment in a 1:1:1 ratio
Allocation concealment	Low risk	Allocated by interactive voice-response system (IVRS)
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 (attrition bias) (All outcomes)	Unclear risk	The withdrawal rates were not described.
Selective reporting (reporting bias)	Unclear risk	Not all outcomes listed in the method section were reported i.e., Revascularization procedures
Other bias	Low risk	All analyses were performed independently of sponsor

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** • **Other outcomes**	 Low risk Low risk	 Outcome is unlikely influenced by blinding 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** • **Other outcomes**	 Low risk Unclear risk	 Outcome measurement is not likely to be influenced by lack of blinding 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

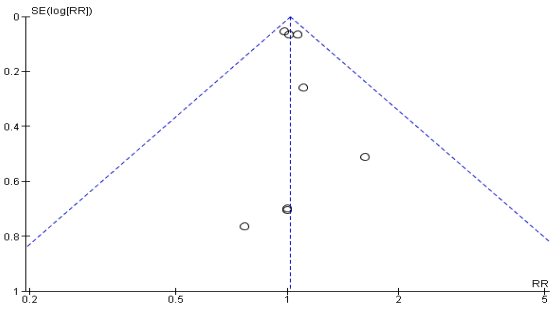
Appendix D: Funnel plots showing comparisons for ACEI versus ARB



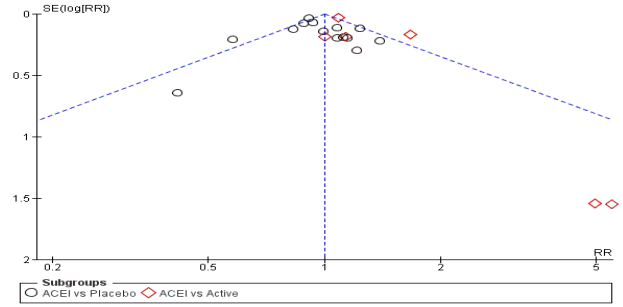
ACEI vs. Placebo or active on risk of MI



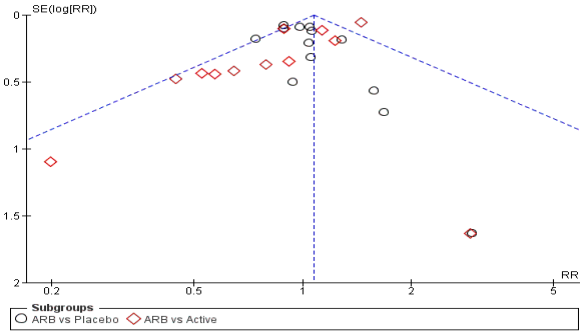
ARB vs. Placebo or active on risk of MI



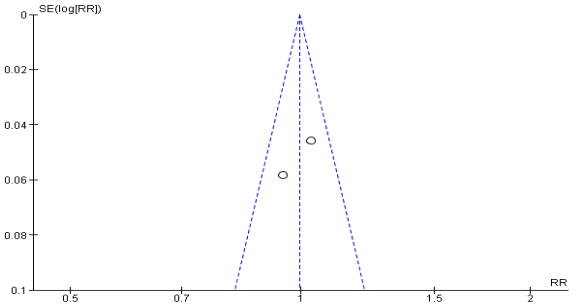
ARBs vs. ACEIs on risk of MI



ACEI vs. Placebo or active on risk of angina

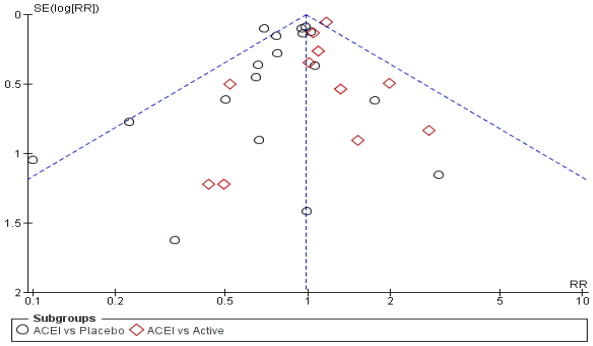


ARB vs. Placebo or active on risk of angina

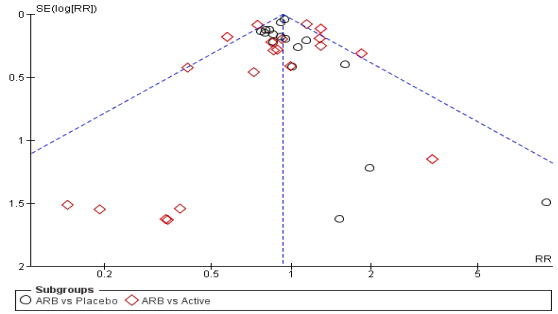


ARBs vs. ACEIs on risk of angina

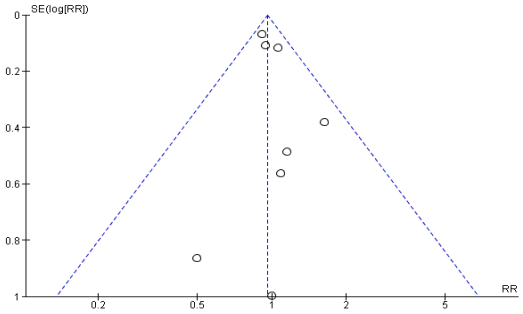
Figure D- 1 Funnel plots comparing ACEI vs. ARB for risk of myocardial infarction (MI) and angina



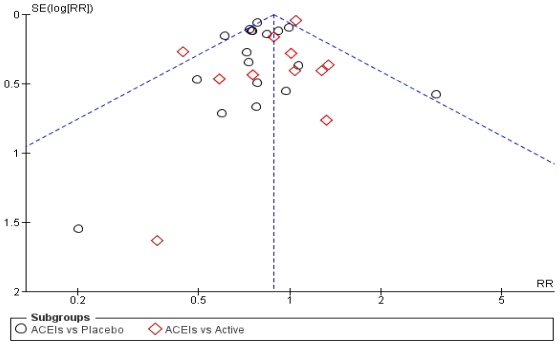
ACEI vs. Placebo or active on risk of stroke



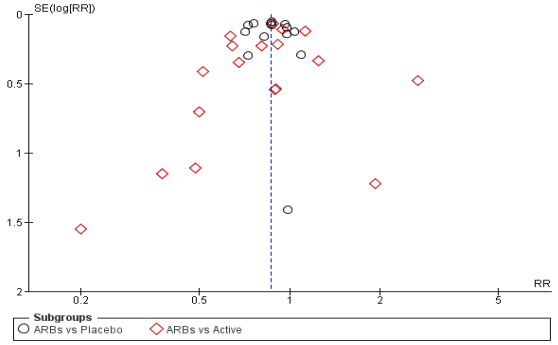
ARB vs. Placebo or active on risk of stroke



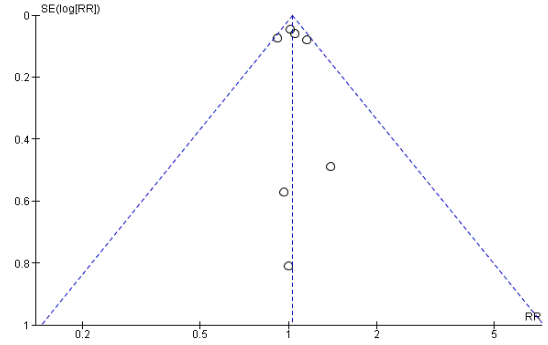
ARBs vs. ACEIs on risk of stroke



ACEIs vs. Placebo or active on risk of HF

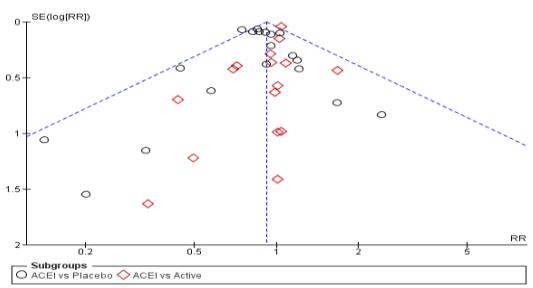


ARB vs. Placebo or active on risk of HF

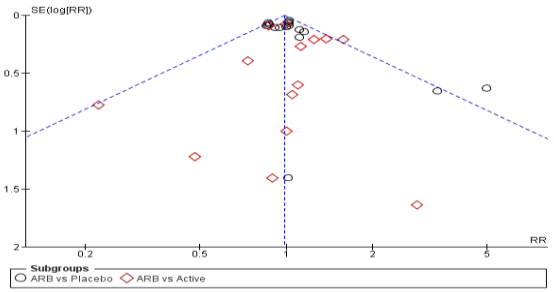


ARB vs ACEI on risk of HF

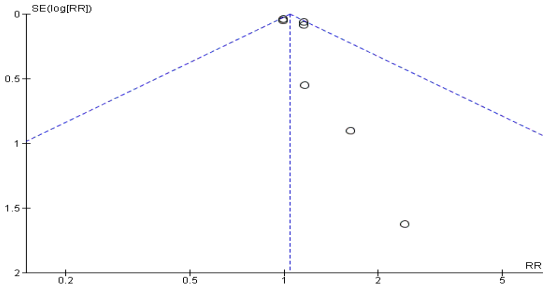
Figure D-2: Funnel plots comparing ACEI vs. ARB for risk of stroke and



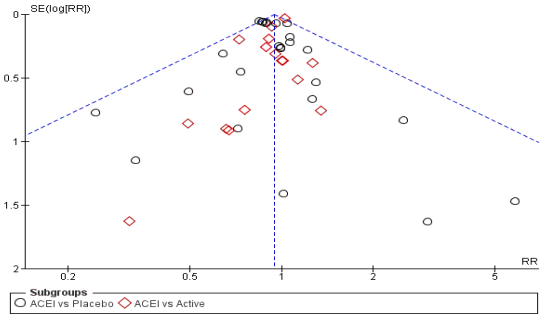
ACEI vs. Placebo or active on risk of CV mortality



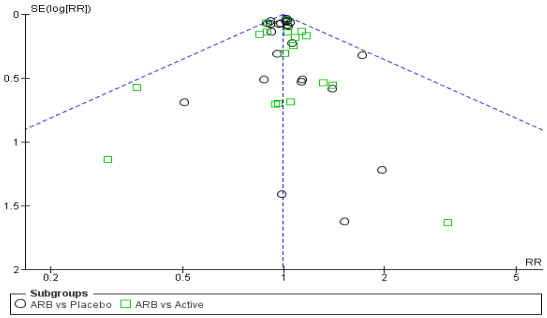
ARB vs. Placebo or active on risk of CV mortality



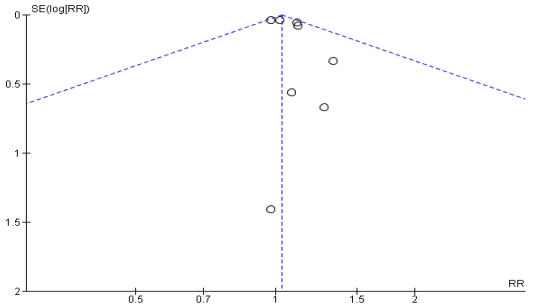
ARBs vs. ACEIs on risk of CV mortality



ACEI vs. Placebo or active on risk of all- mortality



ARB vs. Placebo or active on risk of all mortality



ARB vs. ACEI 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

Table E- 1 Source of data and overall quality of each ACEIs trial

	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**
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	**+**	**±**

Table E- 2 Source of data and overall quality of each ARBs trial

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	-	–

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-treatment	NR	NR	Published	NR	NR	Published	Yes	Yes	Yes	Yes	Yes	Yes	+	+
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.

	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**
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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