Blood pressure-lowering agents response- a systematic review and genome wide study.

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Abstract

In spite of the vast amount of evidence on the benefits of blood pressure (BP) lowering that has accumulated to date, hypertension (HTN) remains the leading risk factor for disease and disability worldwide. Since the first BP-lowering agents became available in the 1950s, their effects have been tested thoroughly by means of the best evidence-providing approach, namely, large randomised controlled trials (RCTs). In the same way, the pharmacogenomics of HTN have the potential to identify genetic biomarkers that predict the response of BP-lowering agents through genome-wide association studies (GWAS), which analyse quantitative traits at millions of markers across the genome to identify genetic variations that could contribute to HTN. For the most part, computational approaches and software tools have played a significant role in translating RCTs and GWAS findings.

This thesis aims first to systematically review the BP responses of main BP-lowering agents, including angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), calcium channel blockers (CCBs), diuretics (DIs) and beta-blockers (BBs) in RCTs, and second to identify the single nucleotide polymorphisms (SNPs) associated with the BP-lowering responses of CCBs and BBs on Nordic Diltiazem (NORDIL) subjects using GWAS.

Description of the research results: Following the Population Intervention Comparison Outcome Study (PICOS) design framework, a literature search of multiple sources resulted in the identification of 10,577 publications, with 5,568 unique records identified after duplicates were excluded. In total, 184 studies were identified as potentially eligible, of which 82 RCTs with a total of 197,684 participants were selected for quantitative synthesis. With regard to BP-lowering strategies, 13 studies with 41,886 participants focused on lowering BP intentionally, while the remaining 69 studies (155,798 participants) were classified as unintentional BP-lowering studies.

Risk of bias in included studies: Using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) framework, all included studies

were described as RCTs; however, most studies did not address how treatment randomization occurred or how allocation of treatment was concealed. All included studies also stated that they were double-blind studies, but again, most did not describe how the double blinding was ensured throughout the studies. The risk of attrition bias was avoided as all randomized participants were included in the analysis. All of the studies had a low risk for reporting bias. BP-lowering agents were added to randomly allocated treatment to control high BP; consequently, one potentially unclear source of bias was present in 13 of the 82 studies. The overall quality was rated to be acceptable to high. In all, 48 studies were rated to be high-quality studies, and 34 studies were rated as acceptable quality.

Effect of intervention: After a systematic search and selection process, 56 studies were included in the analysis of delta BP response, 37 studies were included in the analysis of single-measure BP response and 20 studies were included in the analysis of repeated measures. A number of BP-lowering agents showed a significantly ($P<0.05$) superior BP response in comparison with other agents included in the review; however, the level of BP response was still small. CCBs were superior to ACEIs in lowering both systolic BP (SBP) and diastolic BP (DBP). DIs were superior to ACEIs and CCBs in lowering SBP. ARBs were superior to BBs in lowering SBP. CCBs and DIs were significantly superior to placebos in lowering both SBP and DBP.

Genome-wide study: Following NORDIL quality control standards, a final set of 3,850 samples and 500,905 SNPs was available for analysis. In total, 51 SNPs showed a significant ($P<1X10^{-5}$) association with BP response. The top discordant signals identified in NORDIL included five SNPs for SBP on BB arm, seven SNPs for DBP on BB arm, 12 SNPs for SBP on CCB arm and nine SNPs for DBP on CCB arm. Discordant SNPs from the NORDIL were replicated, based on the interests of five collaborative RCTs; including 11 SNPs for SBP on BB arm, 22 SNPs for DBP on BB arm, 23 SNPs for SBP on CCB arm and 18 SNPs for DBP on CCB arm. However, no SNP achieved a genome-wide significance of ($P<5x10^{-8}$).

Future recommendations: Further systematic reviews of RCTs comparing different BP-lowering agents are required to provide evidence of the options for BP-lowering medication. Specifically, there is a need to study BP response as an

outcome by itself, taking into account different BP-lowering agent combinations, including classes and sub-classes, along with co-morbidities such as type 2 diabetes mellitus, coronary heart disease and chronic renal failure.

Regarding the genome-wide study, further studies are needed to clarify the potential contribution of plausible SNPs in relation to CCB and BB response in HTN. These studies should include comprehensive sequencing of the candidate interval, genotyping of variants in many population samples, testing for association, functional studies and investigation of interactions with other genes or environmental factors. Furthermore, genome-wide studies need to identify directionally discordant signals between SNP and BP response for BB and CCB and confirm the validity of a SNP BP response by analysing the SNP effect on mortality.

Table of Contents

List of Tables

List of Figures

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I dedicate this work to my parents and my siblings. They supported me at each step and stood with me during this journey.

Author's Declaration

I declare that this thesis has been written entirely by myself and is a record of research performed by myself with the exception of discovery cohort genotyping (Dr Wai Kwong Lee, Dr Anna Maria Di Blasio, Stewart Laing, and Dr Davide Gentilini). Genotyping and association analysis of replication cohorts (undertaken by investigators from each cohort, respectively). Any contribution from others has been clearly referenced and reproduced with permission. This work has not been submitted previously for a higher degree and was carried out under the supervision of Padmanabhan, S., and Dominiczak, A.

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List of Abbreviations, Acronyms & Symbols

Δ	Delta
A	Adenine
A1	Major allele
AAA	Amlodipine vs Angiotensin Receptor Blockers in Atherosclerosis
AASK	African American Study of Kidney Disease and Hypertension
ABCD	Appropriate Blood Pressure Control in Diabetes
ABPM	Ambulatory blood pressure monitoring
ACCOMPLISH	Avoiding Cardiovascular Events in Combination Therapy in Patients Living with Systolic Hypertension
ACE	Angiotensin-converting enzyme
ACEI	Angiotensin-converting enzyme inhibitor
ACTION	A Coronary Disease Trial Investigating Outcome with Nifedipine
ADD1	Alpha-adducin
ADRB1	Adrenoceptor Beta 1
ADVANCE	Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation
AF	Atrial fibrillation
AGT	Angiotensinogen
AGTR1	Angiotensinogen II type-1 receptor
AHA	American heart association
ALDH2	Aldehyde dehydrogenase 2
ALLHAT	Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial
ALPINE	Antihypertensive treatment and Lipid Profile in a North of Sweden Efficacy Evaluation
AMA	American Medical Association
ANBP	Australian National Blood Pressure
ANOVA	Analysis of variance
APSIS	Angina Prognosis Study In Stockholm
ARB	Angiotensin receptor blocker
Arg	Arginine
ASCOT-BPLA	Anglo-Scandinavian Cardiac Outcomes Trial — Blood Pressure Lowering Arm
ASH	American society of hypertension
AUC	Area under the curve
BB	Beta blocker
BBD	Beta-blocker + Diuretic
BBD-0	Major homozygous subjects (AA) on BB
BBD-1	Heterozygous (AB) and minor homozygous (BB) subjects on CCB
BENDECT	Bergamo Nephrologic Diabetes Complications Trial
Beta	Standardised regression coefficient
BHS	British hypertension society
BID	Twice-daily
BMI	Body mass index
BMJ	British medical journal
BP	Blood pressure
BRIGHT	British Genetics of Hypertension
C	Cytosine
CACNA1C	Calcium voltage-dependent channels subunit alpha1 C

CACNB2	Calcium voltage-dependent channels subunit beta 2
CALM	Candesartan and Lisinopril Microalbuminuria
CAMELOT	Comparison of Amlodipine vs Enalapril to Limit Occurrences of Thrombosis
CAPPP	Captopril Prevention Project
CARTER	Cilnidipine versus Amlodipine Randomised Trial for Evaluation in Renal Disease
CASE-J	Candesartan Antihypertensive Survival Evaluation in Japan
CCB	Calcium channel blocker
CCB-0	Major homozygous subjects (AA) on BB
CCB-1	Heterozygous (AB) and minor homozygous (BB) subjects on CCB
CCT	Controlled clinical trials
CDCV	Common disease common variant
CDSR	Cochrane database of systematic reviews
CENTRAL	Cochrane Central Register of Controlled Trials
CEU	Utah residents with northern and western European ancestry
CHARGE	Cohorts for Heart and Aging Research in Genomic Epidemiology
CHB	Chinese in Beijing
CHD	Coronary heart disease
CHF	Congestive heart failure
CHL	Chinese hypertension league
CHR	Chromosome
CKD	Chronic Kidney Disease
COLM	Combination of Olmesartan
CONVINCE	Controlled Onset Verapamil Investigation of Cardiovascular End Points
CROSS	Candesartan Role on Obesity and on Sympathetic System
CTNND2	Catenin delta 2
CV	Cardiovascular
CVD	Cardiovascular disease
CVE	Cerebrovascular event
CVIP	Cardiovascular Irbesartan Project
DARE	Database of abstracts of reviews of effects
DASH	Dietary approaches to stop hypertension
DBP	Diastolic blood pressure
DEMAND	Delapril and Manidipine for Nephroprotection in Diabetes
DETAIL	Diabetics Exposed to Telmisartan and Enalapril
DHP	Dihydropyridines
DI	Diuretic
DIABHYCAR	Non-insulin-dependent diabetes, Hypertension, Microalbuminuria or Proteinuria, Cardiovascular events, and Ramipril
DIME	Diuretics In the Management of Essential hypertension
DIRECT-2	Diabetic Retinopathy Candesartan Trial-2
DNA	Deoxyribonucleic acid
DNMT3A	DNA (Cytosine-5-)-Methyltransferase 3 alpha
DREAM	Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication
E-COST	Efficacy of Candesartan on Outcome in Saitama Trial
ELLE	Elderly and Lercanidipine
ELSA	European Lacidipine Study on Atherosclerosis
ELVERA	Effects of Amlodipine and Lisinopril on Left Ventricular Mass and Diastolic Function (E/A Ratio)

EMBASE	Erpta medica database
ENaC	Epithelial sodium channel
ESC	European society of cardiology
ESH	European society of hypertension
EWPHE	European Working Party on High Blood Pressure in the Elderly
FACET	Fosinopril Versus Amlodipine Cardiovascular Events Randomized Trial
FAM110B	Family with sequence similarity 110 member B
FDA	Food and drug administration
FE	Fixed effect model
FHS	Framingham Heart Study
G	Guanine
GALNT2	Polypeptide N-acetylgalactosaminyltransferase 2
GBD	Global Burden of Disease Study
GEMINI	Glycemic Effects in Diabetes Mellitus: Carvedilol-Metoprolol Comparison in Hypertensives
GenHAT	Genetics of Hypertension-Associated Treatments
GENRES	Genetics of Drug Responsiveness in Essential Hypertension Study
GERA	Genetic Epidemiology of Responses to Antihypertensives
GFR	Glomerular filtration rate
GLANT	Study Group on Long-Term Antihypertensive Therapy
Global-BP Gen	Global Blood Pressure Genetics Consortium
Glu	Glutamate
Gly	Glycine
GWAS	Genome wide association studies
HANE	Hydrochlorothiazide, Atenolol, Nitrendipine, and Enalapril in Antihypertensive Treatment
HapMap	Haplotype map
HBPM	Home blood pressure monitoring
HF	Heart failure
HFpEF	Heart failure-preserved ejection fraction
HFrEF	Heart failure- reduced ejection fraction
HOPE	Heart Outcomes Prevention Evaluation
HR	Heart rate
HTN	Hypertension
HWE	Hardy-Weinberg equilibrium
HYVET	Hypertension in the Very Elderly Trial
HYVET-pilot	Hypertension in the Very Elderly Trial- pilot study
I/D	Insertion/ deletion polymorphism
I^2	Inconsistency
IBD	Identity by descent
IBS	Identity by state
IDEAL	Identification of the Determinants of the Efficacy of Arterial Blood Pressure Lowering drugs
IDNT	Irbesartan Diabetic Nephropathy Trial
IMT	Intima media thickness
INSIGHT	International Nifedipine GITS Study Intervention as a Goal in Hypertension Treatment
INTERSALT	International Study of Salt and Blood Pressure
INVEST	International Verapamil SR-Trandolapril Study

INVEST-GENES	International Verapamil SR-Trandolapril Study- genetic sub-study
ISH	Isolated systolic hypertension
ITT	Intention-to-treat
IVRS	Interactive Voice Response System
JMIC-B	Japan Multicenter Investigation for Cardiovascular Diseases-B
JNC	Joint national committee
JPT	Japanese in Tokyo
JSH	Japanese society of hypertension
KCNMB1	Calcium-activated potassium channel subunit beta-1
KHS	KYOTO HEART Study
KM	Kaplan–Meier
LAARS	Losartan Vascular Regression Study
LD	Linkage disequilibrium
Leu	Leucine
LIFE	Losartan Intervention for Endpoint Reduction in Hypertension
LIVE	Left ventricular hypertrophy regression, Indapamide Versus Enalapril
LOTHAR	Amlodipino e Losartana no Tratamento da Hipertensão Arterial
LVH	Left ventricular hypertrophy
LVM	Left ventricular mass
Lys	Lysine
MAF	Minor allele frequency
MAISH	Manidipine versus Amlodipine in Elderly Subjects with Isolated Systolic Hypertention
MAPAVEL	Monitorización Ambulatoria Presión Arterial Aprovel
MARVAL	Microalbuminuria Reduction With valsartan
mBB	Beta blocker monotherapy
mCC	Calcium-channel blocker monotherapy
mDI	Diuretic monotherapy
MDS	Multidimensional scaling
MEDLINE	Medical literature analysis and retrieval system online
Met	Methionine
MI	Myocardial infarction
MIDAS	Multicenter Isradipine Diuretic Atherosclerosis Study
MOSES	Morbidity and Mortality after Stroke, Eprosartan Compared with Nitrendipine for Secondary Prevention
MRC	Medical Research Council trial of treatment of mild hypertension
MRCO	Medical Research Council trial of treatment of mild hypertension in Older adults
mRNA	Messenger ribonucleic acid
N	Number
Na+	Sodium ion
NCI-NHGRI	National Cancer Institute - National Human Genome Research Institute
NEBIS	Nebivolol, Bisoprolol Multicentre Study
NEDD4L	Neural precursor cell expressed a developmentally down-regulated 4-like gene
NICE	National institute for clinical excellence
NICE-Combi	Nifedipine and Candesartan Combination
NICE-EH	National Intervention Cooperative Study in Elderly Hypertensives
NICOLE	Nisoldipine in Coronary Artery Disease in Leuven

NOAAH	Newer Versus Older Antihypertensive Agents in African Hypertensive Patients
Non-DHP	Non-Dihydropyridines
NORDIL	Nordic Diltiazem
OD	Once-daily
ONTARGET	Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial
OR	Odds ratio
ORIENT	Olmesartan Reducing Incidence of End stage renal disease in diabetic Nephropathy Trial
PAMELA	Pressioni Arteriose Monitorate e Loro Associazioni
PATS	Post-stroke Antihypertensive Treatment Study
PCKD	Polycystic kidney disease
PD	Pharmacodynamics
PEACE	Prevention of Events with Angiotensin Converting Enzyme Inhibition
PEAR	Pharmacogenomics Evaluation of Antihypertensive Responses
PG	Pharmacogenomics
PICOS	Population Intervention Comparison Outcome Study
PICXEL	Perindopril/Indapamide Combination more effective than Enalapril in Reducing Blood Pressure and Left Ventricular Mass
PK	Pharmacokinetics
POS	Chromosomal position
PP	Per-protocol
PRA	Plasma-renin activity
PRESERVE	Prospective Randomized Enalapril Study Evaluating Regression of Ventricular Enlargement
PRESMA	Preferred reporting items for systematic reviews and meta-analyses
PROBE	Prospective, randomised, open trial with blinded endpoint
PROGRESS	Perindopril Protection Against Recurrent Stroke Study
PTCD3	Pentatricopeptide repeat domain 3
PVD	Peripheral vascular disease
PWV	Pulse wave velocity
RAAS	Renin–angiotensin–aldosterone system
RACE	Ramipril Cardioprotective Evaluation
RCT	Randomised controlled trial
RE	Random effect model
REF	Reference
REGAAL	Losartan Left Ventricular Hypertrophy regression
REIN-2	Renoprotection in Patients with Non-Diabetic Chronic Renal Disease
RENAAL	Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan
RF	Renal failure
SAKURA	Study of Assessment for Kidney Function by Urinary Microalbumin in Randomized Trial
SBP	Systolic blood pressure
SCOPE	Study on Cognition and Prognosis in the Elderly
SD	Standard deviation
SE	Standard error
Ser	Serine
SELECT	Systolic Evaluation of Lotrel Efficacy and Comparative Therapies
SHELL	Systolic Hypertension in the Elderly Long-term Lacidipine

SILVHIA	Swedish Irbesartan Left Ventricular Hypertrophy Investigation versus Atenolol
SNP	Single nucleotide polymorphism
SNTG1	Syntrophin gamma 1
Syst-China	Systolic Hypertension in China
Syst-Eur	Systolic Hypertension in Europe
T	Thymine
T2DM	Type 2 diabetes mellitus
TEST	Tenormin after Stroke and Transient Ischaemic Attack
Thr	Threonine
TIA	Transient ischaemic attack
TOMHS	Treatment of Mild Hypertension Study
TRANSCEND	Telmisartan Randomised Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease
Trp	Tryptophan
UKPDS	United Kingdom Prospective Diabetes Study
VA	Veterans Administration
Val	Valine
VALUE	Valsartan Antihypertensive Long-term Use Evaluation
VHAS	Verapamil in Hypertension and Atherosclerosis Study
WHO	World health organization
WMD	Weighted mean difference
YOR	Yoruba in Nigeria
β1-ARs	Beta 1-adrenergic receptors

1 Introduction

1.1 Cardiovascular disease

Cardiovascular disease (CVD) comprises of a group of disorders of the heart and blood vessels, including hypertension (HTN), coronary heart disease (CHD) and cerebrovascular disease, as well as renal disease. CVD has major public health importance with a high prevalence throughout the world. This was emphasized by the Global Burden of Disease Study (GBD[1997])[1], which analysed data from 47 countries between 1950 and 1990 to estimate the leading causes of mortality and disability worldwide (1;2).

According to the World Health Organisation (WHO), HTN currently kills nine million people every year and is responsible for at least 45% of the deaths due to CHD and 51% of the deaths due to stroke (3).Therefore, HTN is one of the most important indications for drug therapy in CVD. It is estimated that the total number of adults with HTN will increase by more than 60% to 1.56 billion by 2025 (4).

Decreasing blood pressure (BP) levels to recommended targets is crucial to improving the CV prognosis in the HTN population. The reduction of CHD mortality, observed in a number of countries, has, at least in part, been associated with improved medical treatment and control of risk factors, mainly with regards to systolic BP (SBP) and total cholesterol (5).For instance, the International Verapamil SR-Trandolapril Study (INVEST [2003]) showed that hypertensive patients with CHD and a higher proportion of visits in which BP control was attained had a 42% decrease in the risk of myocardial infarction (MI) and a 50% reduction in the risk of stroke (6). Accordingly, the identification and characterisation of mechanisms contributing to the pathogenesis of HTN is vital for the future treatment and prevention of CVD.

[1] The numbers next to the study represent the study's publication year.

1.2 Human HTN

BP is a quantitative trait that is highly variable, both between and within individuals (7). It refers to the pressure exerted by circulating blood on the walls of blood vessels, and is mainly determined by cardiac output and peripheral vascular resistance. Cardiac output — the volume of blood pumped by the heart per minute (ml/min) — depends on the heart rate (HR) and stroke volume. The former is the number of heart beats per minute, while the latter is the volume of blood pumped out of the heart with each beat. Peripheral vascular resistance, the resistance to the flow of blood in peripheral arterial vessels, depends on functional and anatomic changes in the small arteries (lumen diameter 100–400 μm) and arterioles.

Guyton was the first person to suggest a primary role for the kidney in the development of HTN as noted in his seminal paper (8), persistently high BP or HTN is characterised by a disturbance of renal function that subsequently leads to an increase in sodium ion (Na^+) reabsorption. Therefore, there is an accumulation of Na^+ in the body, stimulating a marked expansion of extracellular volume and, consequently, cardiac output. When cardiac output rises, it increases blood flow to almost all body tissues. Consequently, an auto-regulatory mechanism for local control of blood flow causes an instant adjustment in the blood vessel diameter, re-establishing sufficient tissue perfusion. Insufficient autoregulation then increases peripheral vascular resistance and BP. The price of this biological adaptation is HTN.

1.2.1 Causation and epidemiology

BP is controlled by a complex network of physiological pathways, comprising vascular, neural, endocrine and renal mechanisms that act together to preserve continuous BP control. About 5% of patients with HTN have an underlying cause for their high BP, such as renal disease, constrictive vessel disease or monogenic disease. Although the other 95% have essential or primary HTN in which there is no underlying identifiable cause for the high BP, a genetic tendency caused by the cumulative effects of various lifestyle factors (e.g. high salt intake, low levels of physical activity and increasing obesity) over many years is a likely explanation.

Whilst the aetiology of HTN in unknown in the majority of individuals with HTN, studies have focused on the classifying the environmental and genetic (as mentioned below, **Section 1.4.1**) components in the causation of HTN to understand the molecular pathogenesis of the condition.

Many environmental factors elevate BP, including obesity, high dietary sodium intake, excess alcohol consumption, smoking, lack of physical exercise, low potassium intake, low calcium intake and psychological stress (9). Two variables that have been studied a great detail are salt intake and obesity. For example, the Intenational Study of Salt and Blood Pressure (INTERSALT [1989]) was a large, prospective epidemiological study involving 52 centres from 32 countries. The study identified a strong link between SBP and urinary Na^+ excretion, which was independent of any other risk factors for HTN (10). Positive associations have also been documented between body mass index (BMI) and BP in both cross-sectional and prospective studies, with the odds of progression to HTN increase by 20–30% for every 5% gain in body weight (11).

Environmental factors also have an important link with the genetic component. For example, alcohol intake is, clearly, mainly determined by consumption. However, individuals who inherit a variant of aldehyde dehydrogenase 2 (ALDH2), which is common among Japanese population, experience a more extreme negative response to alcohol and therefore consume less on average (12). The relationship between salt intake and BP is mediated by a person's salt sensitivity, which is partly genetically determined, as the change in SBP from a high to low sodium diet was significantly greater in patients' 460 tryptophan (Trp) variant of the alpha-adducin (ADD1) polymorphism (13).

1.2.2 Measurements and diagnosis

BP is measured in millimetres of mercury (mmHg) and is expressed in two terms: systolic, which represents the highest pressure in each cardiac cycle and is related to cardiac output; and diastolic, which represents the lowest pressure in each cardiac cycle and is related to systemic vascular resistance. According to the National Institute for Clinical Excellence (NICE), HTN is a chronic medical condition defined currently using the thresholds of SBP >=140 mm Hg and/or

diastolic BP (DBP)>=90 mm Hg; however, there is no definitive cut-off point above which a diagnosis of HTN is confirmed and below which it is excluded (14).As shown in **Table 1.1**, according to a number of guidelines, such as NICE in the United Kingdom (14), the European Society of Hypertension (ESH) / European Society of Cardiology (ESC) in Europe (15) and the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC) in the United States(16), BP measurements can be taken:

- At home (using home blood pressure monitoring (HBPM))
- In the clinic/office (using a sphygmomanometer)
- Over 24 hours (using ambulatory blood pressure monitoring (ABPM))

Table 1.1 Guidelines for definitions of HTN according to the measurement techniques.

NICE-United Kingdom	
Clinic/Office	SBP ≥140 mmHg and/or DBP ≥90 mmHg
ABPM (Day-time)	SBP ≥135 mmHg and/or DBP ≥85 mmHg
HBPM	SBP ≥135 mmHg and/or DBP ≥85 mmHg
ESH/ESC-Europe	
Clinic/office	SBP ≥140 mmHg and/or DBP ≥90 mmHg
ABPM	
Day-time	SBP ≥135 mmHg and/or DBP ≥85 mmHg
Night-time	SBP ≥120 mmHg and/or DBP ≥70 mmHg
24-hour	SBP ≥130 mmHg and/or DBP ≥80 mmHg
HBPM	SBP ≥135 mmHg and/or DBP ≥85 mmHg
JNC-United States	
Clinic/Office	SBP ≥140 mmHg and/or DBP ≥90 mmHg
ABPM	
Day-time	SBP ≥135 mmHg and/or DBP ≥85 mmHg
Night-time	SBP ≥120 mmHg and/or DBP ≥75 mmHg

Diagnoses of HTN are based on the measurement of BP, which is classically performed non-invasively in a clinic or office using a sphygmomanometer via a cuff around the upper arm, with the person relaxed and seated, and their arm outstretched and supported. The BP readings should be taken manually in a standardised way (most clinical studies use Korotkoff I and V, from the first sound heard to the complete disappearance of sounds). However, in a clinic or office, BP is usually higher compared to ABPM or HBPM; 15-20% of patients with stage I HTN may only have elevated BP levels in the presence of a healthcare worker, due to anxiety induced by the clinical setting; this phenomenon is referred to as 'white coat HTN' (17).

The NICE guidelines recommend that all patients suspected of having HTN should undertake ABPM, ensuring that the device is validated and a suitable cuff size for

the person's arm is used (14). However, ESH/ESC recommend that only those with grade I HTN and a low/moderate CV risk undertake ABPM or HBPM, in order to exclude white coat HTN (15). ABPM and HBPM may have greater prognostic value for the risk of CV events than clinic/office BP measurements; additionally, ABPM is associated with a doubling of BP control rates in comparison to clinic/office measurements (15;18;19).

HBPM offers more extensive data than office BP measurement can provide, is less expensive, is widely available and convenient, and has been shown to improve patient compliance with treatment and BP control. Therefore, HBPM can be used as a substitute for ABPM when the latter is not accessible or is not acceptable to the patient. It can also be used for monitoring treated patients between office visits and subsequently improving long-term medication adherence (20). For example, home and office BP were compared in Pressioni Arteriose Monitorate e Loro Associazioni's (PAMELA[1997]) study. It was found that SBP and DBP were significantly lower at home than in the office by 9.5 mmHg and 4.9 mmHg, respectively ($P < 0.01$) (21).

1.2.3 Management approaches

HTN management has improved significantly, due to increased awareness of the health risks associated with HTN, improved HTN management offered by primary care practitioners and the availability of effective treatment options. BP-lowering agents have been shown practically to be effective in decreasing mortality risk for stroke, MI and heart failure (HF) by 35-40%, 20-25% and >50% respectively (22). A meta-analysis of 1 million adults from 61 prospective studies showed that decreasing SBP by 20 mm Hg reduces CV risk by 50%, and, for every 2 mm Hg decrease in mean SBP, there is a lowering of mortality risk from CHD and stroke, by 7% and 10% respectively (23). HTN management can be accomplished by two main approaches: non-pharmacological (lifestyle interventions) and pharmacological.

1.2.3.1 Non-pharmacological approach

When a patient is suspected of having HTN, non-pharmacological measures are a crucial step that should be tried first (16). Lifestyle modifications are generally

useful in reducing a variety of CVD risk factors (including HTN) and promoting good health; therefore, they can be used either as a definitive treatment or as an adjunct to drug therapy. A practical, comprehensive approach for hypertensive patients includes weight loss for the overweight patient, regular physical activity, moderate alcohol consumption, dietary modification (such as reducing Na^+ and fat and increasing calcium, potassium and fibres) and quitting smoking (16).In general, modifying one's lifestyle effectively lowers BP and might be more worthwhile than the initial choice of BP-lowering agent in patients with stage 1 or 2 HTN (24).

In PREMIER[2003], investigators compared the effect of three interventions: comprehensive lifestyle modifications, incorporating the JNC-7 recommendations, behavioural modification without Dietary Approaches to Stop Hypertension (DASH) [2] ('established' group), 'established plus DASH' group and an 'advice-only' group. Results showed superior mean reductions in SBP/DBP in the established group by -10.5/-5.5 mmHg, compared with the advice-only group at -6.6/-3.8 mmHg, with the greatest reductions seen when DASH was also incorporated (-11.1/-6.4 mmHg)(25). However, the anticipated BP target is not always achieved as BP can continue to increase; to address this, BP-lowering agents need to be introduced.

1.2.3.2 Pharmacological approach: BP-lowering agents

Patients are commonly treated with one or more of the following BP-lowering therapies: angiotensin converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), calcium channel blockers (CCBs), diuretics (DIs) or beta-blockers (BBs). In general, ACEI hampers the formation of angiotensin II and aldosterone, which leads to a reduction in vascular tone and extracellular fluid volume and, consequently, a lowering of BP. ARBs and CCBs act as vasodilators to widen resistance arteries, reducing peripheral resistance. DIs increase water and salt excretion, thereby reducing extracellular fluid and blood volume, as well as BP. BBs decrease cardiac output and, therefore, BP. **Table 1.2,** outlines the BP-lowering treatments for patients with comorbid conditions.

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2 DASH is a diet rich in fruits, vegetables, and lowfat dairy products with a reduced content of dietary cholesterol as well as saturated and total fat. It is rich in potassium and calcium content.

Table 1.2 BP-lowering therapy for patients with comorbid conditions (adapted from Carretero and Oparil, 2000) (26) .

Condition	BP-lowering agents
Isolated systolic hypertention(ISH)	DIs or CCBs
Heart Failure	ACEIs, DIs, or BBs
Myocardial Infarction	BBs or ACEIs
Angina	BBs or CCBs
Atrial tachycardia and fibrillation	BBs or CCBs
Diabetes Mellitus	ACEIs or CCBs
Hyperthyroidism	BBs
Osteoporosis	Thiazide DIs
Essential tremor	BBs
Migraine	BBs or CCBs
Renal insufficiency (except for renal HTN)	ACEIs

According to the recommendations of a number of guidelines produced by NICE, ESH/ESC and JNC (14-16), the main BP-lowering agents for the initial management of HTN are ACEIs, ARBs, CCBs, DIs and BBs, as shown in **Table 1.3**.

Table 1.3 Guideline recommendations regarding monotherapy and combination HTN treatment.

Guidelines	Type of therapy	HTN therapy
NICE-United Kingdom	Monotherapy	CCBs are recommended for the initiation of treatment in Patients ≥55 years, blacks of African or Caribbean origin of any age. ACEI or ARB are recommended for the initiation of treatment in other patients aged <55 years
	Combination therapy	Recommended combinations as second-line treatment option: CCB-ACEI and CCB-ARB
ESH/ESC-Europe	Monotherapy	DIs, CCBs, ACEIs, ARBs, and BBs are recommended for the initiation and maintenance of treatment
	Combination therapy	Recommended combinations in pateints at high risk or with markedly high BP: CCB-ACEI, CCB-ARB and CCB-Thiazide-DI
JNC-United States	Monotherapy	Non-black patients: thiazide-DIs, CCBs, ACEI, or ARBs are recommended as initial treatment Black patients: thiazide-DI or CCBs are recommended as initial treatment
	Combination therapy	Up titration or combination with another class of agents recommended. ACEIs and ARBs are recommended for patients with CKD

Monotherapy has a solid place in the treatment algorithm of HTN, especially for grade 1 or mild HTN, as it allows for a determination of the drug's efficacy and tolerability, whereas one of the agents may be ineffective with combination therapy. However, when monotherapy is insufficient or less tolerated, finding an alternative that is more effective and/or better tolerated can be challenging and might erode patients' compliance and adherence. Escalating the dosage of a recommended monotherapy may be less effective for BP reduction than combining agents from different BP-lowering classes (27). However, the response to monotherapy with any of these agents is less than 50%, and despite the multiple initial therapies for HTN, less than half of hypertensive patients have their BP controlled to target and require additional BP-lowering agents (28).

Combination therapy allows a more rapid BP response in comparison to monotherapy and has a greater probability of achieving the target BP, and also may enhance patients' adherence (15). In addition, the combination of BP-lowering agents reduces incidences of major CV events (stroke and CHD) and may have greater CV benefits than when starting on monotherapy (29). For example, the Anglo-Scandinavian Cardiac Outcomes Trial — Blood Pressure Lowering Arm (ASCOT-BPLA ^{2005}) study showed that about nine out of ten patients required two or more BP-lowering agents to reduce BP to less than 140/90 mmHg (30). Consequently, most patients, and mainly those with high CV risk, will need combination therapy with two or more BP-lowering agents in order to achieve a controlled BP; recent guidelines also recommend that a two-drug combination therapy be considered a first-line alternative to monotherapy (15;16).

In addition, the combination of certain classes of BP-lowering agents has an additive effect, which allows earlier, larger and more sustained reductions in BP than up titration of monotherapy and a sequential add-on regimen (29). For instance, the Systolic Evaluation of Lotrel Efficacy and Comparative Therapies (SELECT ^{2005}) showed that CCB-amlodipine/ACEI-benazepril combination therapy was significantly more effective in reducing SBP and pulse pressure in patients with severe systolic HTN than either type of monotherapy ($p < 0.0001$) (31).

Similarly to the ACEI–CCB combination, ARB–CCB combinations have shown efficacy in reducing BP. The Nifedipine and Candesartan Combination (NICE-Combi ^{2005}) study showed that BP reduction was significantly greater in the CCB-

nifedipine/ARB-candesartan combination therapy group (12.1/8.7) than in the up-titrated candesartan monotherapy group (4.1/4.6, P< 0.0001). In addition, combination therapy was better for renal protection and also brought a significant decrease in urinary micro-albumin excretion levels, compared to either monotherapy (P< 0.05) (32). This evidence shows that combination therapy is more effective in reducing BP than high-dose monotherapy.

1.2.3.3 Control and resistance

Current control rates (SBP < 140 mm Hg and DBP < 90 mm Hg), though improved, are still far below the healthy population goal of 50% (33), which was originally set as the goal for the year 2000 and has since been extended. Despite the guidelines for the management of HTN, the attainment of ideal BP goals can be challenging for both physicians and patients. The former tend to base their HTN management plans on their own experiences with patients, as well as the recommendations of the HTN clinical guidelines. These are generally based on studies that were conducted on large populations with possibly unknown genetic variations, in which there was significant inter-individual variation in BP response to all classes of BP-lowering agents. Therefore, optimum BP control has been achieved only in a limited number of patients, despite the widespread availability of approved agents from several drug classes and with several mechanisms of action (34).

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT ^{2000}), which involved a large number of participants, including 47% female, 35% African American, 19% Hispanic, in addition to 36% with diabetes, about 34% of subjects managed to control their BP on an average of two BP-lowering agents after nearly five years of follow-up. In addition, about 50% needed three or more drugs to achieve adequate BP reduction (35).

According to NICE, resistant HTN is defined as BP that remains above 140/90 mmHg, despite the use of three BP lowering medications of different classes at the best tolerated doses, one of which must be a DI(14). A considerable number of patients fail to reach target BP ranges, despite lifestyle advice and standard medical therapy. The cross-sectional analysis of the Framingham Heart Study (FHS) also revealed that only 48% of HTN-treated patients were controlled to <

140/90 mm Hg, while < 40% of elderly patients (> 75 years of age) were at target BP (36).

For instance, less than 50% of hypertensive patients worldwide have their BP controlled, despite multiple BP-lowering agents, with the control rate at ~10% in the Middle East, 13% in Northern Europe, 20% in Southern Europe, 24% in Asia, 28% in North America and 31% in Latin America(28). Additionally, a recent analysis of national surveys in 2013 revealed that England had lower levels of HTN treatment (51%; USA 74%; Canada 80%) and control at < 140/90 mm Hg (27%; USA 53%; Canada 66%) than many other countries (37).

1.3 Clinical studies in BP-lowering agents: An overview

The clinical development of a new drug is usually associated with risk and uncertainty, with about 90% of human studies failing to achieve registration (38). A clinical study is any form of planned experimental study design that is designed to evaluate the effect of a new drug or intervention on clinical outcomes in humans. In general, clinical studies may be either pre-clinical studies (Phase 0), small clinical studies to investigate effect and safety (Phase I/II) or full-scale evaluation of the new treatment (Phase III), which includes randomised controlled trials (RCTs)(39).

In the main, the strength of RCTs is their superior ability to measure change over time from a treatment. They are often considered to be the 'gold standard' of clinical and epidemiological studies. This is because, if they are well-conducted, it is often possible to be fairly sure that the results are correct, at least for the type of patients who enrolled in the study. Consequently, they have an important role in determining the efficacy and safety of interventions. Treatment differences identified from cross-sectional observational studies, rather than RCTs, have methodological weaknesses, include confounding and cohort effects in addition to selection bias(39;40).

In addition, RCTs often share a number of principles, including: randomisation of subjects to receive one or other of the treatments under investigation, or to receive either treatment or placebo; blinding of all participants as to which group subjects are in; similarity of relevant demographics between group subjects (such as age and ethnic origin); dealing with dropouts and withdrawals (41).

1.3.1 Historical perspective

HTN therapy was, without a doubt, one of the main achievements of medicine in the second half of the twentieth century. This is not only because BP- lowering agents have been effectively developed, starting from the 1950s, but also because, in the same time window, the effects of drug-induced BP lowering have been tested thoroughly by means of the best evidence-providing approach, which is through large RCTs.

- In 1965, the first BP-lowering RCT was conducted by Wolff and Lindeman, involving patients with baseline DBP (93.3 mmHg); this was followed by a slightly larger one conducted by the Veterans Administration Cooperative Study Group on Antihypertensive Agents-I (VA-I [1967]), including patients with baseline DBP (115 through 129 mm Hg). Both studies compared the BP-lowering effects of hydralazine, hydrochlorothiazide and reserpine (42;43). Following this, RCTs comparing active BP-lowering drug treatments with placebo or, no drug treatment or less active treatment, were carried out in order to answer the question of whether drug-induced BP lowering is indeed beneficial.

- From 1965 to 1985, most of the placebo-controlled studies on BP-lowering agents were conducted, such as the Veterans Administration Cooperative Study Group on Antihypertensive Agents-II (VA-II [1970])(44), Oslo [1980](45) and the European Working Party on High Blood Pressure in the Elderly (EWPHE [1985])(46); the agents used in the active treatment arm were those agents commonly used at that time, such as thiazide-DI, BB, methyldopa, reserpine and hydralazine.

- From 1980, new classes of BP-lowering agents (such as CCB, ACEI and ARB) became increasingly used and studied as they proved their effectiveness in reducing the risk of HTN, such as in the Verapamil in Hypertension and Atherosclerosis Study (VHAS [1998]) (47), ALLHAT [2002] (48) and Diabetics Exposed to Telmisartan and Enalapril (DETAIL [2004]) (49).

1.3.2 Perspective challenge

In general, RCTs have shown that large numbers of people have HTN that is inadequately treated and are not achieving the goals set by the main clinical guidelines. However, in the past 20 years, there have been no studies reporting primary outcome data on the scale of ALLHAT [2002] (N=33,357) (48), the African American Study of Kidney Disease and Hypertension (AASK [2002]) (N=1,094) (50), ASCOT-BPLA [2005] (51) (N=19,257), Nordic Diltiazem (NORDIL [2000]) (N=10,881) (52) and other key studies that have marked clinical trial activity and informed guideline committees during the past two to three decades.

Regardless of the large number of RCTs that have studied BP-lowering agents, the study of BP response involves many challenges: differences in study designs, small sample sizes, short duration of follow-up and different methods for assessing drug exposures, as well as the fact that the ideal BP control rates seen in these studies have almost never been replicated in a community-based setting. Recent clinical studies have been designed to show that a BP-lowering agent is as good as, if not better than, an existing agent. However, in spite of the large number of RCTs on BP-lowering agents, some issues of practical importance in the management of HTN have not been investigated, or examined according to diagnostic criteria or definitions that are scarcely applicable today.

However, RCTs are typically time-consuming, and large sample sizes are often needed to ensure sufficient statistical heft. Evidence from RCTs has shown the benefit of BP-lowering agents in reducing adverse health outcomes in hypertensive patients. Consequently, clinical guidelines are at the intersection between research evidence and clinical actions that can improve patient outcomes.

Pharmacogenomics (PG) of HTN aims to identify potential genetic biomarkers to predict anti-HTN agent responses and adverse drug outcomes, allowing physicians to identify patients who are expected to either benefit or suffer harm from the treatments, so that they can use alternative pharmacotherapy and avoid adverse drug reactions. By integrating PG with pharmacokinetics (PK) and pharmacodynamics (PD), superior predictive medical care and treatment can be assured and provided, leading to more effective BP control and improved prevention of CV morbidity and mortality (53).

1.4 Genetics and pharmacogenomics of HTN

1.4.1 Genetic component of HTN

The identification of genetic mechanisms in HTN is challenging, just like other complex diseases, due to the lack of identification of the specific genes involved and the extent to which specific genes contribute to the phenotypes, populations and environments. Despite this, the study of genetic variation implicates common and rare mutations that are involved in the genetic architecture of HTN.

Epidemiology and family aggregation studies have shown that genes play a significant role in determining susceptibility to HTN. The heritability of clinic SBP is around 15–40% and 15–30% for clinic DBP; whereas for ambulatory night-time SBP and DBP the heritabilities are 69% and 51% (54;55).The genetic component of HTN has been confirmed. First, the BP distribution among the general population follows normal distribution, which reflects the presence of many environmental and genetic factors. Second, the rare monogenic syndromes of HTN, which directly alter renal tubular electrolyte transport, influence BP levels (56). Third, studies conducted on adoption, twins and families have shown that correlations in BP are more significant between biological parents and children than between parents and adopted children, revealing the presence of a heritable component in HTN and identifying the strong genetic factor that influences BP levels and leads to HTN diseases (57;58).

Individuals who have one or two parents with HTN are about twice as likely to develop high BP phenotypes; in addition, BP is increasingly more correlated to identical twins (monozygotic) than non-identical twins (dizygotic) (59). The Montreal Adoption Study compared BP correlation between biological sibling pairs and adoptive sibling pairs (as well as parent-child correlations). SBP correlation coefficients were 0.38 and 0.16 for biological and adopted siblings respectively, and DBP coefficients 0.53 compared with 0.29 respectively(57).

1.4.2 The study of genetic architecture to identify genes of HTN

Single nucleotide polymorphism (SNP) is the most common form of DNA sequence variation, where a single nucleotide adenine (A), cytosine (C), guanine (G), thymine (T) is replaced by another; this occurs more frequently in non-coding regions of the genome. Consequently, patterns of polymorphisms that differ systematically between individuals with different disease states can be identified and the effects of risk-enhancing or protective alleles can be represented. Strategies to identify variants involved in the complex traits of essential HTN can be divided into two broad categories: linkage and association studies. These can be further subdivided into candidate gene analysis and genome-wide scans.

1.4.2.1 Linkage studies

Linkage studies search for genetic loci or traits in related individuals (such as family cohorts) where affected and unaffected family members are phenotyped and genotyped. If two loci are transmitted together from parent to offspring more often than expected under independent inheritance, they are considered to be linked. The genetic relationships between family members are statistically analysed (using methods such as parametric or non-parametric analysis) to find the genetic markers in linkage disequilibrium (LD). Parametric analysis is so-called as it needs a specific assumption about the genetic model with defining multiple parameters; mode of inheritance, gene frequencies, and penetrance. Parametric analysis is frequently performed on Mendelian traits, in which the genetic model can be easily specified (60).

For HTN, parametric linkage analysis is unlikely, since there is not a simple disease model and mode of inheritance. Instead, non-parametric, (that is, assumption-free) linkage analysis is used. For example, the Medical Research Council British Genetics of Hypertension (BRIGHT [2003]) study was successful in identifying potential loci that modestly increase the risk of HTN after rigorous quality control, and analysed the genotypic data using non-parametric linkage. This study initially enrolled affected sibling pairs from 1599 families with severe HTN. The work identified a locus on chromosome (CHR) 6 that achieved genome-wide significance

(P= 0.042) and three more loci with suggestive significance on CHRs 2, 5 and 9 (P= 0.017) (61).

1.4.2.2 Association studies

Association studies are typically conducted in unrelated case-control samples (though it is poosible to conduct them on related individulas) through comparing the allele frequencies of a single marker or group of markers in candidate regions across the human genome. For qualitative traits, association analysis directly measures the statistical association between a disease (phenotype) and genetic marker (genotype) by comparing the allele frequencies of cases and controls. The goal is to find out whether a certain allele occurs in cases (compared with controls) more often than would be expected by chance. Quantitative traits, such as cholesterol and glucose, are measured for association using linear regression (62).

The least frequent allele of a SNP needs to be above 1% in a population to be effectively assessed by association studies (63). Consequently, such studies potentially have far greater power than linkage analysis for detecting variants with a modest effect on disease risk, given that the genetic marker is close enough to show strong LD with the functional variant. There are two types of association: direct and indirect. In the former, studies focus on the causal polymorphism of a phenotype (association between an identified functional variant and disease). Indirect association studies are more commonly performed (such as most genome wide association studies (GWAS)), as they require prior knowledge of the known function of the candidate regions involving the SNP numbers, which could be the causal variants themselves, or of LD with the causal polymorphisms (association between the disease and a marker locus that lies close to the disease locus and is in LD with it) (60;64).

1.4.2.3 Candidate gene studies

Candidate gene studies rely on a group of markers based on an a priori hypothesis about the role of a selected gene, or a group of pathway-related genes, on a phenotype. These studies suggest that several polymorphisms act together (along with environmental variables) to produce a CV phenotype.

To date, no candidate gene study has yet demonstrated a reproducible association with HTN; there are a number of possible reasons for this, which highlights the limitations of such studies. First, the choice of candidate genes may be incorrect. Second, the causative genes may be upstream or downstream from the genes studied. Third, the SNPs selected may offer incomplete coverage of all variants in the genes under study. Fourth, most studies are underpowered and problematic due to population stratification or phenotypic or locus heterogeneity. Finally, candidate gene studies depend on prior hypotheses about disease mechanisms, which prelude the discovery of genetic variants in earlier unknown pathways (60) .However, candidate gene studies do have an advantage over GWAS in that markers can be typed more densely. Consequently, the probability of detecting any true causal effect is improved, besides the probability that negative findings are truly negative.

1.4.3 GWAS

In recent years, there has been a great increase in the number of GWAS, which have become a standard method for disease gene discovery as well as a comprehensive approach that can be attempted to exploit the strength of association studies, even in the absence of convincing evidence about the causative variant locations or functions within candidate genes(60).

GWAS offers a large scale, hypothesis-free strategy based on SNP association mapping, which provides novel approaches for testing the hypothesis of 'common disease common variant' (CDCV) by using high-throughput genotyping technologies to assay hundreds of thousands of common SNPs and relate them to clinical conditions and measurable traits. This hypothesis states simply that common disorders are likely to be influenced by genetic variation that is also common in the population; in other words, one or a few predisposing alleles of relatively high frequency (60;63). However, there is insufficient empirical evidence to determine the validity of the CDCV hypothesis, and arguments for and against have been put forward. For GWAS it has been suggested that, as a rough guide, SNPs should meet a threshold of minor allele frequency (MAF) ≥ 1% or 2 % to be considered common (63).

However, the availability of SNP maps from haplotype map (HapMap) has led to a revolution in the examination of common diseases and traits, based on the CDCV hypothesis, using the GWAS approach. Those SNP maps provided a deeper understanding of the inter-individual genetic variations and population diversity, and reduced the cost of genotyping.For instance, the dense genotyping chips that are now offered cover hundreds of thousands of SNPs and offer ever greater coverage of the human genome (whether within or outside genes)(65).

Unfortunately, only a small number of GWAS on HTN and/or BP have been published, including studies whose main objective was not BP genetics (66). Several ethnicities have been examined, although most investigations have studied European origin because samples of European origin are more accessible and because the genetic analysis of African American individuals is more challenging. Incomplete accounting for admixture and African genomes have undergone a higher number of recombinations than European genomes. Two published studies on BP traits by the Cohorts for Heart and Aging Research in Genomic Epidemiology-Blood Pressure (CHARGE-BP) and Global Blood Pressure Genetics Consortium (Global-BP Gen) have identified an association that withstands correction for multiple testing ("genome-wide significance") within the study that can be replicated in an independent study. However, all of these variants have been found in individuals of European origin. Thus, comprehensive testing in other ethnic groups of the strongest associations is still needed (67;68).

1.4.3.1 Replication studies

The gold standard for validation of any genetic study is replication in further independent samples. The replication of GWAS findings is as important as that of candidate gene associations. Therefore, it should be conducted on an independent dataset drawn from the same population as the GWAS, in order to confirm the effect in the GWAS target population. When the latter is achieved, further populations may be sampled to determine if the SNP has an ethnic-specific effect (69).

Replication of a significant result in an additional population is sometimes referred to as generalisation, meaning that the genetic effect is of general relevance to multiple human populations. It is essential for the study to be well-powered in

order to detect false associated SNPs, where the null hypothesis is most likely true (that is, to confidently call the initial GWAS result a false positive.The National Cancer Institute and the National Human Genome Research Institute in the United States (NCI-NHGRI [2007]) produced a summary of their recommendations on the reporting of association studies, as well as criteria for replication, such as that replication studies should have adequate sample sizes in order to detect the effect of the possible allele (70). Often, the effects identified in an initial GWAS suffer from 'winner's curse,' which is a bias whereby genetic effect size estimates are overestimated in initial discovery studies of disease-predisposing variants (71). Therefore, replication samples should, if possible, be larger to account for the over-estimation of effect size.

1.4.3.2 Post GWAS functional studies and clinical utility

Post-GWAS analyses are needed in order to identify the truly functional variants that are responsible for the observed risk-differences, and to unravel the mechanisms causing their effects. Post-GWAS analyses involve a detailed genetic epidemiological analysis of the associated locus, bio-informatic calculations of functionality, and *in vitro* and *in vivo* experimental confirmation of the molecular mechanisms for the causal variants and their target genes. Epidemiological studies need dense SNP genotyping in large sample sizes to analyse the effects of less common candidate variants and to separate adjacent genetic variants that are frequently correlated and that make it difficult to recognise the truly causal variants.

Furthermore, to translate GWAS findings for clinical settings, a biomarker or a diagnostic test is important. A biomarker is a characteristic that is independently measured and assessed as an indicator of normal biologic processes, pathogenic processes, or pharmacological responses to a medical intervention (72). A PG biomarker is any molecular "barcode" detected via analysis of messenger ribonucleic acid (mRNA), deoxyribonucleic acid (DNA), protein or circulating cells that might be used to stratify patients for treatment advantage within clinical studies, to predict patient outcomes and/or observe responses to therapy (73). A PG biomarker can be used in a wide range of clinical studies; for patient selection, the result of a PG biomarker assay can decide whether a patient is suitable for treatment with a specific drug, or the most efficient dose for the patient, or the

patient's susceptibility to side effects, or the course and efficiency end-point of a treatment (74) .

1.4.4 PG of BP response to BP-lowering agents: An overview

In BP responses, BP-lowering agents were the first CV treatments for which there was a significant detection of clinical variation based on ethnicity. For instance, blacks generally respond well to DI or CCB, whereas whites respond well to all the drug classes. More specifically, the drug responses for DI and CCB were superior in blacks, while in whites, ACEI and BB were better (75). Given that different pathways influence HTN in divergent ethnic groups, there is a role for PG and personalised therapy that is targeted to certain pathways, based on ethnicity. Identification of patient characteristics (such as age, sex and BMI) that are associated with BP response to each BP-lowering class could increase the control rate, improve the 'trial-and-error' approach and reduce the CV risks of HTN (76).

In the main, data on predictors of BP response were generated from four clinical studies: the Genetic Epidemiology of Responses to Antihypertensives (GERA and GERA2 ^{2002}) studies (77); the Genetics of Drug Responsiveness in Essential Hypertension Study (GENRES ^{2007}) (78); and the Pharmacogenomics Evaluation of Antihypertensive Responses (PEAR ^{2009}) study (79). For the most part, PG studies of BP-lowering agents have used the candidate gene approach, which focuses on genetic variations that can impact BP-lowering agent PK or PD mechanisms. In line with this, the first GWAS of a BP-lowering drug to be published was based on an analysis of BP response to hydrochlorothiazide in the GERA^{2002} study.

As shown in the **Figure 1.1** below, BB suppress renin secretion and are effective only in individuals who have either a predominantly sympathetic cause for their BP or if their RAAS is activated. While CCBs tend to increase renin secretion and their effect is more prominent when the RAAS is suppressed. Thus opposite direction of effect shown by a SNP for BB and CCB may indicate that that SNP has a specific role for either BB or CCB.

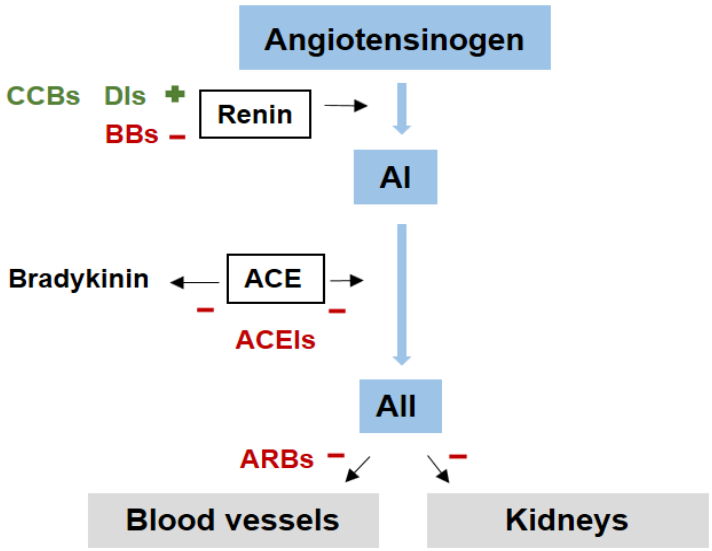


Figure 1.1 Drugs acting on the RAAS.
Drugs which suppress the system are shown in red, those which activate the system are in green.

1.4.4.1 ACEIs and ARBs

ACEIs and ARBs are inhibitors of the renin–angiotensin–aldosterone system (RAAS). While the former inhibit the conversion of angiotensin to angiotensin II and prevent the breakdown of bradykinin, the latter block the angiotensin II receptors(80). The candidate genes identified for PG associations in BP response to ACEI and ARBs are those in the RAAS, which plays an essential role in regulating BP and sodium homoeostasis. Genes encoding the components of RAAS include angiotensin-converting enzyme (ACE), angiotensinogen (AGT) and angiotensinogen II type-1 receptor (AGTR1), in addition to renin.

The ACE gene encodes ACE, and has been comprehensively studied for its effects on ACEI response. There is evidence of an association between the ACE insertion (I) and (D) deletion polymorphism and plasma ACE activity, with an increased level of activity in those possessing the D allele (81). According to its association with ACE concentrations, different studies have tested the contribution of I/D polymorphism to the inter-patient variability in ACEI response.

For example, the reduction in SBP was significantly greater in patients carrying the DD compared to II or ID genotypes (5.6 +/- 3.1 vs. 3.1 +/- 1.1 or 3.6 +/- 2.2,

respectively (P < 0.05)). In addition, the reduction in DBP was also significantly greater in DD hypertensives compared with II or ID (8.9 +/- 6 vs. 5.5 +/- 3.4 or 5.8 +/- 4, respectively (P < 0.05)) (82). The reduction of both SBP and DBP in the DD genotype was significantly greater than in the II genotype (10.13 +/- 4.91 vs 5.37 +/- 2.79, P <.01; 7.47 +/- 3.50 vs 4.71 +/- 2.40, P <.05, respectively) and no significant association of I/D polymorphism with essential HTN was found (83). Similarly, a sub-study of ALLHAT [2002], called Genetics of Hypertension-Associated Treatments (GenHAT [2002]), tested the association of various outcomes in ALLHAT [2002] with the I/D polymorphism in 37,939 patients. However, no association was found between this polymorphism and BP-lowering agents in the study (including lisinopril, amlodipine and chlorthalidone), nor with any of the study outcomes, either when considered in combination or stratified by drug therapy (84).

AGT encodes pre-angiotensinogen, which is expressed in the liver and is cleaved by the enzyme renin in response to lowered BP. The substitution of a threonine (Thr) for a methionine (Met) (SNP: rs6990) has been shown to be functional, with higher plasma AGT levels identified in individuals with the Thr/Thr genotype compared to those with the Met/Met genotype (85). For example, the reductions in both SBP and DBP after six weeks of treatment of the patients carrying the Thr/Thr genotype (SBP = 26 mm Hg, DBP = 14.83 mm Hg) were greater than in the groups carrying Met/ Thr (SBP = 3.0 mm Hg, DBP = 6.2 mm Hg) and Met/Met genotypes (SBP = 1.2 mm Hg, DBP = 0.10 mm Hg), suggesting that the Thr allele may be a possible genetic marker for HTN (86).

AGTR1 encodes the type I angiotensin II receptor, which is thought to mediate the CV effects of angiotensin II. A number of clinical studies have suggested that AT1R is involved in BP regulation and modulation of the effect of angiotensin II in relation to HTN. The main polymorphism studied was A1166C most studies showed no association with BP response to the RAAS blockade. For instance, the INVEST genetic sub-study (INVEST-GENES [2007]) showed that although race was associated with diastolic BP response, as DBP decrease was significantly smaller in Hispanics and blacks than whites (P= 0.0032 and P= 0.0069, respectively), the difference is likely not to be clinically significant and AGTR1 genotype was not associated with BP response (87). Similarly, Ohasama's [2004] study on hypertensive Japanese patients showed no difference among AT1R genotypes, although the AC and CC

genotypes were more common in hypertensives than in normotensives. This study proposed that the A1166C polymorphism is not a major genetic predisposing factor for HTN in the Japanese (88).

1.4.4.2 CCBs

CCBs inhibit the function of the calcium channel, preventing the calcium influx within the peripheral vascular smooth muscle cells and causing peripheral vasodilatation. Similarly, they act on cardiac myocytes, producing negative inotropic and chronotrophic effects. The PG of many CCBs has been studied in a range of clinical researches in relation to common genetic polymorphisms within calcium voltage-dependent channels subunit alpha1 C and subunit beta 2 (CACNA1C and CACNB2) and the calcium-activated potassium channel subunit beta-1 (KCNMB1). However, the PG studies of CCBs were mainly based on an analysis of INVEST-GENES [2007](89-91).

INVEST-GENES [2007] showed that there is no evidence of the association of CACNA1C, CACNB2 SNPs and BP responses to after-verapamil monotherapy, although there were significant differences in long-term CV outcome by genotype between them (89;90). KCNMB1 has two common non-synonymous polymorphisms: the substitution of a glutamate (Glu) for a lysine (Lys) and of a valine (Val) for a leucine (Leu), Glu65Lys (rs11739136) and Val110Leu (rs2301149), respectively. For instance, INVEST-GENES [2007] tested the association of these two nonsynonymous SNPs with BP response in hypertensive patients with CHD after verapamil monotherapy. The study stated that the SBP response did not differ with the KCNMB1 genotype, although, Lys65 variant carriers achieved BP control earlier than in Glu65Glu individuals (1.47 versus 2.83 months, P= 0.01) (91).

1.4.4.3 Thiazide-DIs

The PG of many thiazide-DI has been studied in many clinical studies in relation to common genetic polymorphisms within ADD1; the neural precursor cell expressed a developmentally down-regulated 4-like gene (NEDD4L).

The ADD1 gene encodes for a cytoskeletal protein called alpha-adducin, which plays a significant role in signal transduction and renal Na^+ transport. Therefore, it also has an important role in regulating sodium reabsorption. The glycine (Gly)

460Trp polymorphism in the ADD1 gene has been tested in many candidate gene studies. Patients who were carriers of the 460Trp allele had a lower base plasma-renin activity (PRA) as well as a greater BP-lowering response to Hydrochlorothiazide treatment, compared to Gly/Gly homozygotes (mean arterial BP decrease of 15.9 versus 7.4 mm Hg (p = 0.001) (92).

A population-based case-control study showed a lower risk of the combined outcome of MI and stroke with thiazide-DI, based on the Gly460Trp genotype (93); however, INVEST-GENES [2007] did not replicate this finding, instead showing that the effect of thiazide-DI on the risk of CV outcomes did not vary by Gly460Trp genotype (94). The ADD1 gene remains an interesting candidate and, together with NEDD4L, reveals a significant association with BP response to thiazide-DI, whereas neither gene alone shows such an association (95).

NEDD4L is an important determinant of sodium reabsorption in the distal nephron. It encodes an ubiquitin ligase that regulates the cell surface expression of the epithelial sodium channel (ENaC). For example, in the NORDIL [2000] study, where patients were randomised to diltiazem, versus conventional BP-lowering agents, mainly DI and/or BB, rs4149601 G allele carriers were shown to have a superior BP response (SBP/SBP: −19.5/−15.4 mm Hg) than patients with the AA genotype when treated with a thiazide DI/BB. However, no differences in response to CCB-diltiazem by genotype were identified (96).

The association of the G allele of rs4149601 with the BP response to thiazide-DI was also tested in the PEAR [2009] study. The study showed that with hydrochlorothiazide, there was a superior BP reduction for GG over GA and AA (SBP: −12.4 mm Hg, −10.2 mm Hg and −7.4 mm Hg; DBP: −5.5 mm Hg, −5.0 mm Hg and −2.2 mm Hg, respectively). Despite this, there was no evidence of such an association in the atenolol-treated patients (97).

1.4.4.4 BBs

The most convincing PG association for BP response to BB is that of adrenoceptor beta 1 (ADRB1), which was shown to be associated with BP response and long-term CV outcomes. ADRB1 genes encode the beta 1-adrenergic receptors (β1-ARs), which are the main myocardial targets for many BB medications and competitively

inhibit the agonist binding to ß1-ARs and stop catecholamine-stimulated receptor signalling. They include two non-synonymous polymorphisms, arginine (Arg) 389Gly and serine (Ser) 49Gly.

There is some evidence suggested that the Ser49Gly polymorphism alone does not significantly influence BP response, although when considered in combination with the Arg389Gly polymorphism, it can be more informative than Arg389Gly alone (98;99). Therefore, the most commonly studied is the Arg389Gly polymorphism, on which the majority of studies show a significant association with BP-lowering response to BBs. Two independent studies have shown an association between treatment-related hypertensive outcomes (such as MI and stroke) and ADRB1 polymorphisms (100;101).

With regard to BB, Arg389Gly and Ser49Gly are important determinants of BP-lowering response to metoprolol, as they can be used to predict the DBP response to Metoprolol in patients with HTN (98). Administration of BB-bisoprolol to healthy Arg 389-homozygous participants was associated with greater response in basal PRA, DBP and HR compared to homozygous Gly389 participants (102). On the other hand, Gly389 has been associated with decreased SBP and DBP in a large genetic study evaluating 30 regions that code for known BP-lowering agent targets (103).

1.5 Aims and Objectives

The previous chapter has outlined the pharmacological and pharmacogenetic approaches for HTN management and control, highlighting gaps in the current understanding of the effects of BP-lowering agents. These gaps raise a number of research questions to be answered through the specific aims of this thesis:

To systematically review the main BP-lowering agents, including ACEIs, ARB, CCBs, DIs and BBs in RCTs. This review has main objective; to identify the drug specific effect of BP-lowering agents on BP responses.

To identify SNPs associated with the BP-lowering responses of CCBs and BBs on NORDIL^{2000} subjects using GWAS.

2 Materials and Methods

2.1 Systematic review

This section summarises the strategies applied in systematically reviewing the main BP-lowering agents in RCTs (eligibility and exclusion criteria, search methods for identification of studies, data collection, software and meta-analysis) to identify the drug-specific effect of BP-lowering agents on BP responses.

The criteria for considering and excluding studies for this review have been determined according to the Population Intervention Comparison Outcome Study (PICOS) design framework (104), which grouped search terms into thematic groups in order to identify medical literature for systematic reviewing. The standard search strategy of the BP-lowering agents review, with supplementary terms, was used to identify the relevant works.

2.1.1 Eligibility criteria

2.1.1.1 Population

The population was evaluated according to three criteria: [1] Definition of disease of interest: persistently high BP or HTN, (as defined earlier, **Section 1.2.2**). As well, according to NICE, ISH defined as baseline SBP of 140 mm Hg or higher and DBP of less than 90 mm Hg)(14). [2] Participant characteristics: men and women (non-pregnant women), aged 18 years and over, who had a baseline resting SBP of 140 mm Hg or higher and/or DBP of at least 90 mm Hg, measured in a standard procedure for the duration of the study. Participants could be either previously treated with BP-lowering agents or untreated. [3] Healthcare setting[3]: participants with HTN, or who had (with HTN) any of following risk factors that require primary or secondary care setting. Primary care setting: smoking and obesity with body BMI of ≥ 30 kg/m2) (105). Secondary care setting: type 2 diabetes mellitus (T2DM), mild to moderate chronic kidney diseases (CKD): glomerular filtration rate (GFR), 30-89 mL/min per 173m2 (106), or history of CHD,

[3] Thresholds in health care setting were defined according NICE guidelines.

left ventricular hypertrophy (LVH) secondary to HTN, peripheral vascular diseases (PVD) or cerebrovascular events (CVE).

2.1.1.2 Interventions and comparators

Interventions and comparators were evaluated using three criteria: [1] Interventions: the BP-lowering agents ACEI, ARB, CCB, DI and BB were included in different doses and sub-classes as monotherapy or combination therapy in a stepped-care approach. [2] Comparators: a placebo or another BP-lowering agent (ACEI, ARB, CCB, DI or BB) was included in different doses and sub-classes as monotherapy or combination therapy in a stepped-care approach. In addition, drug doses should have been mentioned in both the intervention and the comparator treatment arms or, at least, in the intervention treatment arm. [3] Co-interventions: protocol for the continuation or discontinuation of background BP-lowering therapies before randomisation had to be the same in both arms. In addition, supplemental drugs from other classes were allowed as part of the stepped therapy. However, the addition of supplemental drugs after randomisation had to be pre-specified and follow the same protocol in both arms.

2.1.1.3 Outcome measures

Outcome measures were evaluated by five criteria: [1] Definition of outcome: clinic/office mean BP response, including delta, single or repeated BP measures. [2] Measurement protocol: mean BP response measured using a standard technique at least twice, with the patient resting for at least one minute. [3] Measurement duration: BP response measured for at least three months of active treatment, with all subsequent BP measurements recorded. [4] Primary outcomes: change from baseline of trough SBP and DBP for at least three months of active treatment was measured, if available at more than one time within the accepted window of three months or more. [5] Secondary outcomes: standard deviation (SD) of the change in BP compared with a placebo or other BP-lowering agents.

2.1.1.4 Study design

Study design was evaluated using three criteria: [1] Study design: single- or multi-centre RCTs. [2] Study sample size: RCTs that randomised at least 100 participants. However, in studies that were not limited to participants with HTN,

> 70% of participants should have had a resting SBP of at least 140 mm Hg or a DBP of at least 90 mm Hg or both, as defined above. [3] Study duration: RCTs that followed the participants for at least 12 months of active treatment.

2.1.2 Exclusion criteria

The population was excluded following the criteria mentioned earlier: [1] Participant characteristics: men and women (non-pregnant women) aged less than 18 years. Participants with resistant HTN, (as defined earlier 'Control and resistance, **Section 1.2.3.3**). Participants with HTN; however, baseline BP was not specified. [2] Healthcare setting: participants who had (with HTN) any of following risk factors that require tertiary care setting :kidney diseases including polycystic kidney disease (PCKD), glomerulonephritis, severe CKD: GFR, 15-29 mL/min per 173m2 , renal failure (RF): GFR, < 15mL/min per 173m2 or on dialysis and kidney transplant (106). Heart diseases including cardiac arrhythmia, HF: preserved ejection fraction (HFpEF) or reduced ejection fraction (HFrEF, < 40 %) and heart transplant (107). Hospitalised participants, due to high risk (accelerated/malignant) of HTN.

Interventions and comparators were excluded following the criteria mentioned earlier: [1] Interventions: BP-lowering drugs other than ACEI, ARB, CCB, DI or BB. In addition, the same drug within the same class of BP-lowering was compared to itself, using a different drug combination or different doses. [2] Comparators: BP-lowering agents were compared to non-pharmacological lifestyle changes or approaches, or compared according to different BP treatment goals. [3] Co-interventions: non-pre-specified protocol for dis/or continuation of background BP-lowering drugs before randomisation, as well as non-pre-specified protocol for supplemental drugs after randomisation.

Outcome measures were excluded following the criteria mentioned earlier: [1] Definition of outcome: Home or self-measurement mean BP response, as well as when clinic/office mean BP response was not specified. [2] Measurement protocol: mean BP response using non-auscultatory or oscillometric method, including pulse wave velocity (PWV) or ABPM, as well as when BP measurement protocol was not specified. [3] Measurement duration: mean BP response measured for less than three months of active treatment, as well as when duration of mean BP response

was not specified. [4] Outcomes: change from baseline of trough SBP and DBP for less than three months of active treatment was measured.

Study designs were excluded following the criteria mentioned earlier: [1] Study design: all studies where the unit of randomization is not at the individual level, including observational studies (case control, cross-sectional and cohort studies) and interventional studies (controlled clinical trials (CCTs)). Subgroup or ancillary studies. Crossover studies without a washout period. [2] Study sample size: RCTs that randomised less than 100 participants. Studies that included non hypertensives, either where there was < 70% hypertensives or the % of hypertensives was not specified. [3] Study duration: RCTs that followed participants for less than 12 months of active treatment.

2.1.3 Search methods for identification of studies

2.1.3.1 Electronic searches

The search was applied to four databases, including the Medical Literature Analysis and Retrieval System Online (MEDLINE (OVID), 1995-2015), the Erpta Medica Database (EMBASE (OVID), 1995-2015), the Cochrane Central Register of Controlled Trials (CENTRAL, 1995-2015) and the Web of Science (1995-2015). The Cochrane Database of Systematic Reviews (CDSR) and the Database of Abstracts of Reviews of Effects (DARE) in the Cochrane Library were searched for previous reviews and meta-analyses until 15 October 2015. The last search was run on 26 November 2015. No language restriction was used .The detailed search strategy for each of these databases is shown in appendix **Table 6.1, Table 6.2, Table 6.3 and Table 6.4** respectively.

The literature search in the current review spanned the last 20 years as internationally recognised major medical journals, such as the Journal of the American Medical Association (AMA) (108) and the British Medical Journal (BMJ)(109), have been increasingly interested in publishing studies that report on the results of RCTs in parallel with the drug regulatory bodies like the Food and Drug Administration (FDA) (110) requiring RCT evidence for efficacy and safety before approval in the last two decades.

2.1.3.2 Searching other resources

The reference lists of papers (both primary studies and reviews) were screened for any additional potentially eligible studies.

Overall, 48 relevant reviews were screened (ordered by review ID):

Abuissa [2005] (111)
Andraws [2007] (115)
Angeli [2004] (119)
Baguet [2007] (123)
Bakris [2014] (127)
Bangalore [2011] (131)
Bell [2010] (135)
Briasoulis [2014] (139)
Chen [2010] (143)
Chen [2013] (147)
de Leeuw [2002] (151)
Diao [2012] (155)
Doulton [2005] (112)
Ghamami [2014] (116)
Gillespie [2005] (120)
Goeres [2014] (124)
Grossman [2000] (128)
Heran [2010] (132)
Hsu [2001] (136)
Kang [2004] (140)
Khan [2006] (144)
Kronish [2011] (148)
Kuyper [2014] (152)
Li [2014] (156)
Li [2014] (113)
Lindholm [2005] (117)
Ma [2010] (121)
Mukete [2015] (125)
Nakao [2012] (129)
Neal [2000] (133)
Pahor [2000] (137)
Pasty [2003] (141)
Peters [2014] (145)
Sipahi [2012] (149)
Staessen [2001] (153)
Takagi [2014] (157)
Tsuchiya [2015] (114)
Turnbull [2008] (118)
Van Vark [2012] (122)
Vejakama [2012] (126)
Wang [2006] (130)
Wiysonge [2012] (134)
Wright [2009] (138)
Wu [2013] (142)
Xu [2012] (146)
Zanchetti [2015] (150)
Zhang [2014] (154)
Zou [2011] (158)

2.1.4 Data collection

2.1.4.1 Selection of studies

The author (Safaa Mohemmed Alsanosi) conducted the Initial screening (including titles and abstracts) of potentially eligible article. Two independent reviewers (Mohammed Abdulbasit Alsieni and Aishah Binti Che Roos) were given a random sample of 150 studies and asked to independently evaluate whether the studies would be included or excluded after they had been given the pre-specified PICOS framework. The reviewers disagreed on about five studies, which was due to the misunderstanding of certain criteria, on which they required further details. A meeting was arranged to clarify the problematic criteria and thoroughly explain each stage of the following process. As a result, reviewers agreed to exclude the five problematic studies.

2.1.4.2 Assessment of risk of bias

Mohammed and Aishah independently assessed the risk of bias for all included studies, using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) framework (including methodology checklist and flow-diagram)

(41). Any disagreements were resolved by discussion (between Safaa, Mohammed and Aishah) or by involving a third reviewer (Sandosh Padmanabhan).

The risk of bias was measured for each study through assessing seven specific domains: [1] Random sequence generation, [2] Allocation concealment, [3] Blinding of participants and personnel, [4] Blinding of outcome assessment, [5] Incomplete outcome data, [6] Selective outcome reporting and [7] Other issues.

- To check for publication bias, a funnel plot was used to estimate the intervention effect from the included studies against some measure of each study's size. Intervention (BP-lowering agents) was measured as mean differences. A funnel plot was used only when there were at least ten studies included in the meta-analysis; with fewer studies, the test's power is low in distinguishing chance from real asymmetry.The effect estimates were plotted on the horizontal scale, and the measures of the study size were put on the vertical axis. The effect estimates from the small studies would scatter more widely at the bottom of the graph, with the spread narrowing among the larger studies. In the absence of bias, the plot should approximately resemble a symmetrical (inverted) funnel(159).

Each potential source of bias was graded as high, low or unclear, and provide a quote from the study report together with a justification for our judgement in the 'Risk of bias' tables (as mentioned below, **Section 4.2.1**). The 'Risk of bias' judgements were summarised across different studies for each of the domains listed.

2.1.5 Data extraction

The data collection form was designed after taking into consideration how much information should be collected. All data from each eligible study was entered independently by reviewers (Mohammed and Aishah) into a standardised spreadsheet (Microsoft Excel 2010) and collected according to the PICOS framework: [1] population, [2] intervention and comparators, [3] outcome measures and [4] study design.

The extracted data from each study was assigned according to PICOs, as intended for the population: [1] Overall number (N), [2] Baseline: mean SBP and mean DBP, [3] N of randomised patients in each treatment arm, [4] % of participants with HTN and [5] Type of participants with HTN: previously treated with BP-lowering agents or untreated.

For the intervention and comparators: [1] Placebo run in period, [2] Washout period, [3] Class of BP-lowering agent, [4] Type of BP-lowering agent, [5] Doses of BP-lowering agent, [6] Duration of treatment and [7] Supplemental agents.

For the outcome measures: [1] BP measurement protocol: position, machine and process, [2] Mean SBP response, [3] SD of mean SBP response, [4] Mean DBP response, [5] SD of mean DBP response, [6] Duration of mean BP response and [7] Type of outcomes analysis: intention-to-treat (ITT) or per-protocol (PP) analysis. ITT analysis included all patients as originally allocated after randomisation, including those who deviated from the protocol (due to noncompliance, withdrawal or anything that occurred after randomisation). PP analysis included only those patients who completed the treatment originally allocated, excluding patients who deviated from the protocol.

For study types: [1] Study acronym, [2] Study full name, [3] Publication year, [4] Study overall duration, [5] Study design and [6] Primary and secondary outcome measures.

BP-lowering RCTs have been defined as all those in which [1] Any BP–lowering agents were compared with the placebo or another BP–lowering agent with the intention of investigating the BP differences between studies, defined as intentional BP-lowering RCTs. To expand the body of evidence, [2] Non-intentional BP-lowering RCTs were also included: that is, those studies in which BP-lowering agents were compared with the placebo or other BP–lowering agents, although the studies were not designed to investigate the effects of BP differences.

For studies with more than two intervention groups (multi-arm studies), only the directly relevant arms were included. When studies with various relevant arms were identified, the groups were combined into a single pairwise comparison and included the disaggregated data in the corresponding subgroup category. If the

study was comparing different BP-lowering agents and a number of them had many doses (e.g., the study had four treatment arms, nebivolol 5mg vs nebivolol 10 mg vs nebivolol 20mg vs amlodipine 10mg), the highest dose was considered (e.g., nebivolol 20mg vs amlodipine 10mg).

If the study was comparing different BP-lowering agents and a number of them belong to the same class with different doses (e.g., the study had four treatment arms, losartan: 100 mg vs olmesartan: 40 mg vs valsartan 320 mg vs amlodipine 10mg), the highest dose was considered (e.g., valsartan 320 mg vs amlodipine 10mg). In addition, if the study was a crossover study, BP-lowering agents should be randomized to one of the four sequences: two active treatment periods, separated by placebo wash-out periods.

2.1.5.1 Dealing with missing data

The position of the patient during BP measurement may alter the BP-lowering effect. However, in order not to lose valuable data, if only one position was reported, data from that position was extracted. When BP measurement data was available for more than one position, data was imputed in accordance with the following order of preference: [1] sitting and [2] supine.

SD of BP change at the end of the study was used if available. If this value was not reported at the end of the study: [1] SD of the change at other time points during treatment was imputed. [2] If SD of the change was not available at all, then the value imputed was SD of baseline SBP and DBP. [3] In cases where these values were also missing, SD of the change from other studies with the closest sample size was imputed.

If data was presented numerically (in tables or text) and graphically (in figures), the numeric data was imputed because of possible measurement error when estimating from graphs. However, if the data was only presented graphically, measurements were imputed and calculated approximately from graphs. All numeric calculations and extractions from graphs or figures were confirmed by reviewers (Mohammed and Aishah) .If relevant data were missing; authors were contacted. Though, not all of them responded.

2.1.5.2 Measures of treatment effect

BP response was documented in three ways, based on the type of data presented: [1] BP-delta, where the difference between mean BP readings was presented (such as -2.3 mmHg). [2] BP-single measure, where only one mean BP reading was presented (such as 120 mmHg). [3] BP-repeated measures, where a number of mean BP readings was presented (such as 120, 160 and 140 mmHg).

2.1.6 Software

2.1.6.1 Cochrane Review Manager 5.3

Cochrane Review Manager 5.3 (RevMan) software (160) is an open-source software for formulating and maintaining Cochrane reviews, including protocols and full reviews. It can be installed on computers without the need for system administrator privileges. RevMan is most useful when the review question is already formulated, as it allows the researchers to prepare the text, form tables showing the characteristics of studies and the comparisons in the review and add study data.

A number of features implemented by RevMan include standard statistical models (such as risk ratio, odds ratio (OR) and so on), meta-analysis (such as calculating weighted mean difference (WMD), testing for fixed (FE) and random (RE) effects model and so on), heterogeneity and sensitivity analysis. It can present the data entered graphically (such as in a forest plot, funnel plot and so on) and allows the visualisation of publication-quality plots. In addition, standard analytical software, such as IBM SPSS Statistics 19 and Microsoft EXCEL 2010, was used for data sorting, visualisation and basic statistical runs.

2.1.7 Meta-analysis

Data was processed in accordance with the Cochrane Handbook for Systematic Reviews of Interventions (159); data synthesis and analyses were performed using the RevMan software.

2.1.7.1 Data synthesis

Study participants were analysed in the groups to which they were randomised, regardless of which or how much treatment they actually received. Data for BP reduction was combined using the WMD method, which measures the total difference between the mean values in two groups in a clinical study. It evaluates the amount by which the studied treatments change the outcome from the usual, compared with the control. A P-value of < 0.05 was considered statistically significant for all comparisons.

For delta and single measure, BP response was calculated by subtracting the baseline value at randomisation from the value reported at the end of the trial or at the last time point during treatment. For repeated measures, the area under the curve (AUC) was used to plot BP readings against time after drug randomisation. The area was usefully determined by the trapezoidal rule, where the data points are connected by straight line segments, perpendiculars are drawn of each data point from the X axis and the sum of the areas of the triangles and trapezoids is computed (161).

$$AUC = \frac{Y0+Y1}{2}(X1 - X0)$$

- Y0 = first BP reading
- Y1 = second BP reading
- X1 = time of first BP reading
- X0 = time of second BP reading

2.1.7.2 Assessment of heterogeneity

Heterogeneity, which signifies variability among studies in a systematic review, was explored qualitatively (by comparing the characteristics of included studies) and quantitatively (using the chi-squared test of heterogeneity and inconsistency (I^2) statistic) (162). This review considered P <0.05 from the Chi 2 test as statistically significant for heterogeneity.

In the absence of significant statistically heterogeneity between studies (P > 0.05), meta-analysis was performed using an FE model, which offered a result that could be viewed as a typical intervention effect from the included studies in the analysis. An assumption was made that the true effect of intervention had the

same value in every study, in order to calculate a confidence interval for an FE meta-analysis. This assumption suggested that the observed differences between study results were due to chance and that there was no statistical heterogeneity. I^2 describes the % of total variation across studies that is due to heterogeneity rather than chance .To quantify I^2, 60% of the variability, which represented moderate heterogeneity, was considered in effect estimates. Thresholds for the interpretation of I^2 were as follows:

- 0-40%: might not be important.
- 30-60%: represents moderate heterogeneity.
- 50-90%: represents substantial heterogeneity.
- 75-100%: considerable heterogeneity.

However, when there was significant heterogeneity between study results, the RE model was used. This model offered an assumption that the estimated effects in the included studies were not equal, but did follow a certain distribution. The model showed the lack of knowledge of the reasons for different intervention effects, through considering the differences as if they were random. The types of heterogeneity were explored in stages:

- Step 1: methodological heterogeneity (such as variability in study design and risk of bias considered).
- Step 2: clinical heterogeneity (such as variability in the participants, interventions and outcomes studied).
- Step 3: statistical heterogeneity (such as variability in the intervention effects being evaluated in the different studies; this is a consequence of clinical or methodological differences, or both, among the studies).

When there was significant statistical heterogeneity between study results, sensitivity analysis was conducted through repeating the analysis, substituting alternate decisions if any were arbitrary or unclear, and the cause of heterogeneity was investigated with reference to the characteristics of the studies included in the meta-analysis.

2.2 Genome-wide Study

This section summarises the strategies applied to GWAS the NORDIL [2000] subjects (including, study population, genotyping, software, quality control, survival analysis, and standardised regression coefficient and replication studies) in order to identify SNPs associated with the BP-lowering responses of CCBs and BBs.

2.2.1 Study population

NORDIL[2000] was a prospective, randomised, open blinded endpoint (PROBE), multicentre study (163;164). It was conducted in both Norway and Sweden to compare the effects of diltiazem, a non-dihydropyridine CCB, versus conventional BP-lowering agents, mainly DI and/or BB. If the BP goal was not achieved, other BP-lowering agents were added. Recruitment started in September 1992 in 1032 health centres in Norway and Sweden. The primary endpoints considered were CV mortality, defined as MI, stroke, sudden death and other fatal CVDs, as well as CV morbidity, defined as MI and stroke. Secondary endpoints were total mortality and development or deterioration of CHD, congestive heart failure (CHF), atrial fibrillation (AF), transient ischemic attack (TIA), T2DM and RF.

The participants were hypertensive patients aged between 50 and 69 years, with an untreated DBP of at least 100 mmHg during the one-week washout period without BP-lowering agents. Individuals were both previously treated and untreated. The researchers enrolled 10,881 patients who had DBP of 100 mmHg or higher. Participants were randomly allocated to receive diltiazem (N= 5,410), DI or BB, or both (N = 5,471). Between the two groups, just over 51% of individuals were female and the mean age was 60. At baseline, mean SBP was 173.4 mmHg and mean DBP was 105.7 mmHg. During the mean follow-up period of 53 months, this decreased to 154.9/88.6 mmHg in the diltiazem group and 151.7/88.7 mmHg in the DI/BB group. The study showed that diltiazem was as effective as treatment based on BB-DI in preventing the combined primary endpoint of all stroke, MI, and other CV death. For the current study, Padmanabhan, S., and Dominiczak, A., have a collaboration to analyse NORDIL[2000] pateints and data was available for 5,280 Swedish patients.

2.2.2 Ethical considerations

All studies were approved by institutional ethics review committees at the relevant organizations. All participants provided informed written consent.

2.2.3 Genotyping

The NORDIL^{2000}-GWAS samples were genotyped using Illumina 550K Single and Illumina 610 Quad V1 BeadChip (165). DNA samples were available for 4,039 Swedish NORDIL^{2000} patients and successfully genotyped. In total, 500,915 SNPs common to both the Single and Quad chips, were included in the analysis. Genotyping was performed by Lee, W.K., Di Blasio, A.M., Laing, S., and Gentilini, D., as described in Padmanabhan et al. paper (166). Independent SNPs from replication cohorts; ASCOT-BPLA ^{2005}, GenHat^{2002}, GENRES ^{2007}, INVEST ^{2003} and PEAR ^{2009} were genotyped using Illumina Golden Gate Genotyping Assay and undertaken by investigators from each cohort (165).

2.2.4 Software

For computational efficiency, GWAS analyses were performed on a remote server via the open-source Telnet/SSH client PuTTY (http://www.chiark. greenend.org.uk/~sgtatham/putty/) and files were managed remotely using WinSCP (http://winscp.net/eng/index.php), an open-source SFTP, FTP and SCP client for Windows. Standard analytical software, such as IBM SPSS Statistics 19 and Microsoft EXCEL 2010, was used for data sorting, visualisation and basic statistical runs.

2.2.4.1 Quanto

Quanto (167) is a program computes sample sizes or powers for association studies of genes, gene-environment interactions and gene-gene interactions. To calculate sample size, alpha value (level of significance) needs to be determined. Alpha is incorrectly rejecting the null hypothesis (H0) (false positive). The graphical user interface makes it possible for users to simply change the model and inspect the results without having to change input files and rerun the program for every model. The results of each session are stored to a log file, which can be printed

or saved to a file for review at a later date. In addition, users can create a text file of the log that can be imported into other documents.

2.2.4.2 PLINK

PLINK (168;169) is an open-source and command-line-based tool set for whole genome association analysis. It can manage large genome-wide datasets in a computationally effective manner and run several analyses on parallel processors to reduce computational time. Among its features are basic data management (including data reading, merging, extracting and so on), standard summary statistics (such as rate of missingness, MAF, Hardy-Weinberg Equilibrium (HWE) and so on) and meta-analysis.

PLINK output results are stored as plain text files, of which there are several options for extensions, depending on the content of the results. Results files are often large; the genome-wide outputs may be uploaded to other applications (such as R) as a consequence.

2.2.4.3 R

R (170;171) is a well-developed, simple and effective programming language that includes user-defined functions and input-output facilities. It is an open-source software for flexible statistical analysis toolkits, such as data manipulation (transforming, merging and so on), standard statistical models (regression, analysis of variance (ANOVA) and so on), time-series analysis and clustering. Graphics/data visualisation and publication-quality plots can be formed through R (including mathematical codes and formulae).

Data analysis is performed by writing functions and scripts, rather than by pointing and clicking. Writing scripts makes it easy to programme a sequence of tasks that can be integrated into other processes. R has open interfaces that integrate easily with other applications and systems, and more than 2000 add-on ‘packages’ extending the R language in several domains are available for free download.

2.2.4.4 NORDIL Navigator

NORDIL Navigator is a closed-source software for genome association analysis. It is used to identify BP response associations between SNPs/genes and three BP-lowering agents: CCB, DI and BB, through implying SNP ID and selecting plot type (such as regional and chromosomal).

The Navigator provides, for each implication of SNP, an output results table including: [1] BP phenotype (such as SBP or DBP). [2] CHR number. [3] SNP chromosomal position (POS). [4] Major allele (A1) such as A, T, C or G. [5] Effect allele frequency, which represents the fraction of all CHRs in the GWAS population that carries that allele (0.1 to 0.99). [6] Standardised regression coefficient or beta, (see 'Association analysis of BP response using linear regression', **Section 3.2.5.1**). [7] Standard error (SE), which provides an estimate of the precision of a parameter (such as a mean, proportion and OR) to make inferences about data from a sample to some relevant population. [8] Statistical level of significance P-value, which measures probability of rejecting H0 when it is true; that is, no difference exists between BP-lowering agents .The GWAS Navigator allows plotting data (such as in a scattered plot) and visualise and download graphs. Output results are stored as EXCEL files and subsequently uploaded to other applications (such as SPSS).

2.2.5 Quality control

The NORDIL^{2000}-GWAS dataset that are analysed had already been subject to quality control. Nevertheless the following basic quality control steps were applied: checking for excessive missingness in both subjects and SNPs, exclusion of SNPs with excessively low MAF, exclusion of SNPs very deviated from HWE and cryptic relatedness. The quality control was performed using PLINK. The thresholds used for these quality control steps were as reported in Wellcome Trust Case Control Consortium (63;172):

- Rate of missingness, representing the number of called genotypes divided by the total number of genotypes scanned, was examined. PLINK reports missingness rate per individual and per marker in two output files; IMISS and LMISS respectively. Samples and SNPs with missingness rate of (>0.05) were removed.

- SNPs with MAF (<0.01) were removed.
- Each SNP was tested to see whether its genotypes were in HWE. Those with a P-value $<5\times1^{-6}$ were removed.

The subsequent quality control works best under an assumption of no LD among SNPs. So SNPs were pruned according to LD to produce dataset for a pruned SNP .Cryptic relatedness between individuals was estimated from GWAS data. Pairwise Identity by State (IBS) was calculated, from this identity by descent (IBD). Pairs of individuals whose estimated IBD indicated they were 3nd degree relatives or closer (plink output file PI_HAT>0.125) were identified.

2.2.5.1 Analysis to detect population outliers

Population structure was investigated using the NORDIL^{2000}data merged with a HapMap dataset (release 23, 270 individuals, 3.96 million SNPs) consisting of Utah residents with Northern and Western European ancestry (CEU), Chinese in Beijing (CHB) and Japanese in Tokyo (JPT) and Yoruba in Nigeria (YOR) samples. The SNP set for the merged dataset were restricted to the Nordil^{2000} LD pruned SNP set. Subsequently, multidimensional scaling (MDS) was plotted to provide a visual representation of any substructure, rather than clustering participants into groups. The first two components were plotted against each other to check similarities and differences between samples.

2.2.6 Statistical analysis

2.2.6.1 Association analysis of BP response using linear regression

Using PLINK software, standardised regression coefficient or beta, is the estimate resulting from a regression analysis that have been standardized (the variances of dependent and independent variables are the same). It was used in order to signify how the BP reacted to changes from BP-lowering agents (CCBs or BBs) for each copy of the effect allele, after adjusting for all other covariates.

Using Beta, SNPs were divided into the concordant and discordant and compared to their BP response/change under CCBs or BBs.The reason for studying discordance in the directionality of effect to CCB and BB is because this would prioritise a discordant SNP to be more specific for either BB or CCB.

For each copy of the effect allele (as mentioned above, **Figure 1.1**), SNPs that showed a positive BP change indicated that BP lowering agents and BP response were directly related (that is, as the value of one variable went up, the value of the other also tended to do so) and were considered to be concordant SNPs, labelled as 0. Conversely, SNPs that showed a negative BP change indicated that BP-lowering agents and BP response were inversely related (that is, as the value of one variable went up, the value of the other tended to go down) and were considered to be discordant SNPs, labelled as 1.

2.2.6.2 Survival analysis

Using R software, survival analysis refers to analysing the time to occurrence of death. In the context of this thesis survival analysis was used to model time-to-event data through assessing the effects of BP-lowering agents (CCBs or BBs) by measuring the number of NORDIL^{2000} subjects who survived or were saved after that treatment, over a period of time.

This implicited techniques that were required to compare the risks for death or an event associated with different therapy groups. Survival analysis included a sequence of statistical analytical methods that represented the time spent between a given exposure and the outcome of a certain event. Kaplan–Meier (KM), log-rank and cox-proportional hazards model were used to carry out the survival analysis.

2.2.6.3 KM survival analysis

KM test involves computing of probabilities of occurrence of event at a certain point of time and multiplying these successive probabilities by any earlier computed probabilities to get the final estimate. It measures the fraction of NORDIL^{2000} subjects living for a particular amount of time after receiving BP-lowering agents (CCBs or BBs).

KM survival curves measure the probability of surviving in a given length of time while considering time in many small intervals.They were used to estimate the curve from the observed survival times without assuming an underlying probability distribution and to determine whether the different categories of baseline predictor variable are statistically equivalent.

The log-rank test is a large- sample chi-square test where the test statistic provides an overall comparison of the KM survival curves being compared. It takes the whole follow-up period into account in the analysis and test the hypothesis that there is no difference between populations being studied in the survival probability at any given time point in follow up. It is recommended to present the survival plots as cumulative incidence (CV mortality) data displaying the proportion of patients with events increasing over time (173). This approach was followed for presentation of KM survival curves:

- Cumulative incidence, which measures the disease frequency or rate during a period of time, was used as the vertical axis. It measures the probability that a certain event (such as CV mortality) has happened before a given time.

- Survival time, which measures the follow-up time from a defined starting point to the occurrence of a given event, was on the horizontal axis. Start and endpoints had to be clearly defined, along with censored observations to measure survival time.

2.2.6.4 Cox-proportional hazards model

Since the KM method and the log-rank test can only study the effect of one factor at a time , Cox-proportional hazards model was set to predict the probability that CV mortality occurred at a given time for given values of the predictor variables (covariates) (174). The hazard was the probability of experiencing CV mortality, assuming that patients had survived up to a given point in time, or the risk of death at that moment. Cox model does not assume knowledge of absolute risk and only estimates relative risk. An additional advantage of Cox model over the KM-method is that it can accommodate both discrete and continuous measures of event times.

The Cox's method is a 'semi-parametric' approach and no specific type of distribution is assumed for survival. Although, there are some strong basic assumptions made on the effect of exposure variable on survival. The main assumptions are (174;175): [1] The hazard rate of an individual at time is proportional to the hazard rate at any other given time point in the follow-up period and [2] The exposure variable of interests and other covariates contribute linearly to the natural log of the hazard ratio .

- A number of parameters were used: [1] The drug interventions, including BP-lowering agents (CCBs or BBs). [2] The phenotype was delta BP changes after drug randomisation. [3] Covariates, other than the main exposure of interest (CV mortality), which were possibly predictive of the outcome under study, were adjusted. Adjusted covariates were age, sex, BMI, smoking, cholesterol, fasting glucose, T2DM, DBP at randomisation (DBP-1) and SNP.

2.2.6.5 Power calculations

In the NORDIL[2000] cohort, the SD of BP response was 16 and 18 mmHg for SBP and DBP, respectively. At alpha of 0.001, we would have >80% power to detect effect sizes of delta (Δ) 2% change in SBP (~3mmHg) and Δ1% change in DBP (~1.8mmHg) with 6000 subjects for different MAFs, as shown in **Figure 2.1.** For the long-term adverse outcome phenotype with 5,000 samples (assuming 300 incident adverse events), at alpha of 0.05, we will have > 80% power to detect interaction ORs of 2.3, 1.9, 1.8 or 1.7 or greater for SNPs with MAF of 5%, 10%, 15% or 25%, respectively.

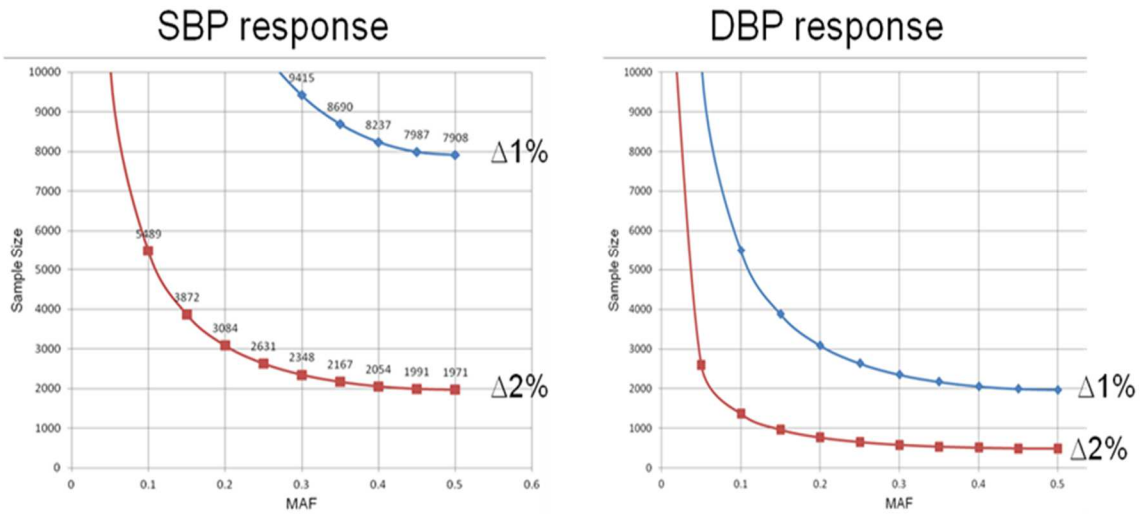


Figure 2.1 Sample size calculation for different MAFs.

2.2.7 Replication studies

To provide convincing statistical evidence for association, increase effect estimation and rule out associations due to biases, 286 independent SNPs from the NORDIL [2000] study were replicated, based on the interests of five collaborative

RCTs; ASCOT-BPLA [2005], GenHat[2002], GENRES [2007], INVEST [2003] and PEAR [2009],(characteristics of excluded studies are described in **Section 3.2.6.1**).

Subsequently, all replicated SNPs were checked through NORDIL Navigator in order to carry out a GWAS review for interesting signals of any significant associations with CCB and BB agents in relation to SBP or DBP changes. To determine the significant associations, the level of statistical significance ($P<1x10^{-5}$)[4] was used to maximise inclusiveness (include as much independent SNPs as possible).

[4] Level of statistical significance of ($P<1x10^{-5}$) was considered after discussion with supervisor.

2.2.7.1 Characteristics of replication studies (ordered by study ID)

ASCOT-BPLA [2005] (51)
Study design :multicentre, randomised controlled, double-blind study **Study duration :** 72 months
Participants N: 19,257 **Participants type :** hypertensives (baseline BP: 164/95 mmHg)
BP –lowering agents : CCB - amlodipine: 5 to 10 mg OD or BB - atenolol: 50 to 100 mg OD
SNP replicated :253 SNPs

GenHat[2002](176)
Study design : ancillary to ALLHAT **Study duration :** 57 months
Participants N: 33,357 **Participants type :** hypertensives (baseline BP: 146/84 mmHg)
BP –lowering agents : ACEI - lisinopril: 10 to 40 mg OD, CCB - amlodipine: 2.5 to 10 mg OD, or DI - chlorthalidone: 12.5 to 25 mg OD
SNP replicated : only 38 SNPs , for monotherapy (CCB amlodipine)

GENRES [2007] (78)
Study design : single-centre, randomised controlled, crossover, double-blind trial **Study duration :** 8 months
Participants N: 208 **Participants type :** hypertensives (baseline BP: 153/100 mmHg)
BP –lowering agents : ARB – losartan: 50 mg OD, CCB - amlodipine: 5 mg OD, DI - hydrochlorothiazide: 25 mg OD or BB - bisoprolol: 50 mg OD
SNP replicated :248 SNPS

INVEST [2003] (177)
Study design : multicentre, randomised controlled, open blinded endpoint study **Study duration :31** months
Participants N: 22,576 **Participants type :** hypertensives (baseline BP: 149.5/86.3 mmHg)
BP –lowering agents :CCB - verapamil: 240 mg OD or BB - atenolol: 50 mg OD
SNP replicated :245 SNPs

PEAR [2009] (79)
Study design : multicentre, randomised controlled, double-blind study **Study duration :** 9 weeks
Participants N: 800 **Participants type :** hypertensives (baseline BP: 138.5/87mmHg)
BP –lowering agents : DI - hydrochlorothiazide: 12.5 mg OD , BB - atenolol: 50 mg OD or their combination
SNP replicated : 164 SNPs for monotherapy (BB atenolol)

3 Systematic review

This chapter summarises the results of systematically reviewing the main BP-lowering agents in RCTs (literature searching, risk of bias in included studies and studies and effect of intervention) to identify the drug-specific effect of BP-lowering agents on BP responses.

3.1 Results of the search

Literature searching resulted in identification of 10,577 publications through multiple sources. After excluding duplicates, there were 5,568 records identified. The results of the search strategy and the review of the publications is summarised in the PRISMA flow diagram (**Figure 3.1**).

As shown in **Figure 3.1**, 184 were identified as potentially eligible studies, from which 102 RCTs were excluded after screening the full texts, (see 'Description of excluded studies', **Section 3.1.1**).

In the end, 82 RCTs, with a total of 197,684 participants were included for quantitative synthesis.

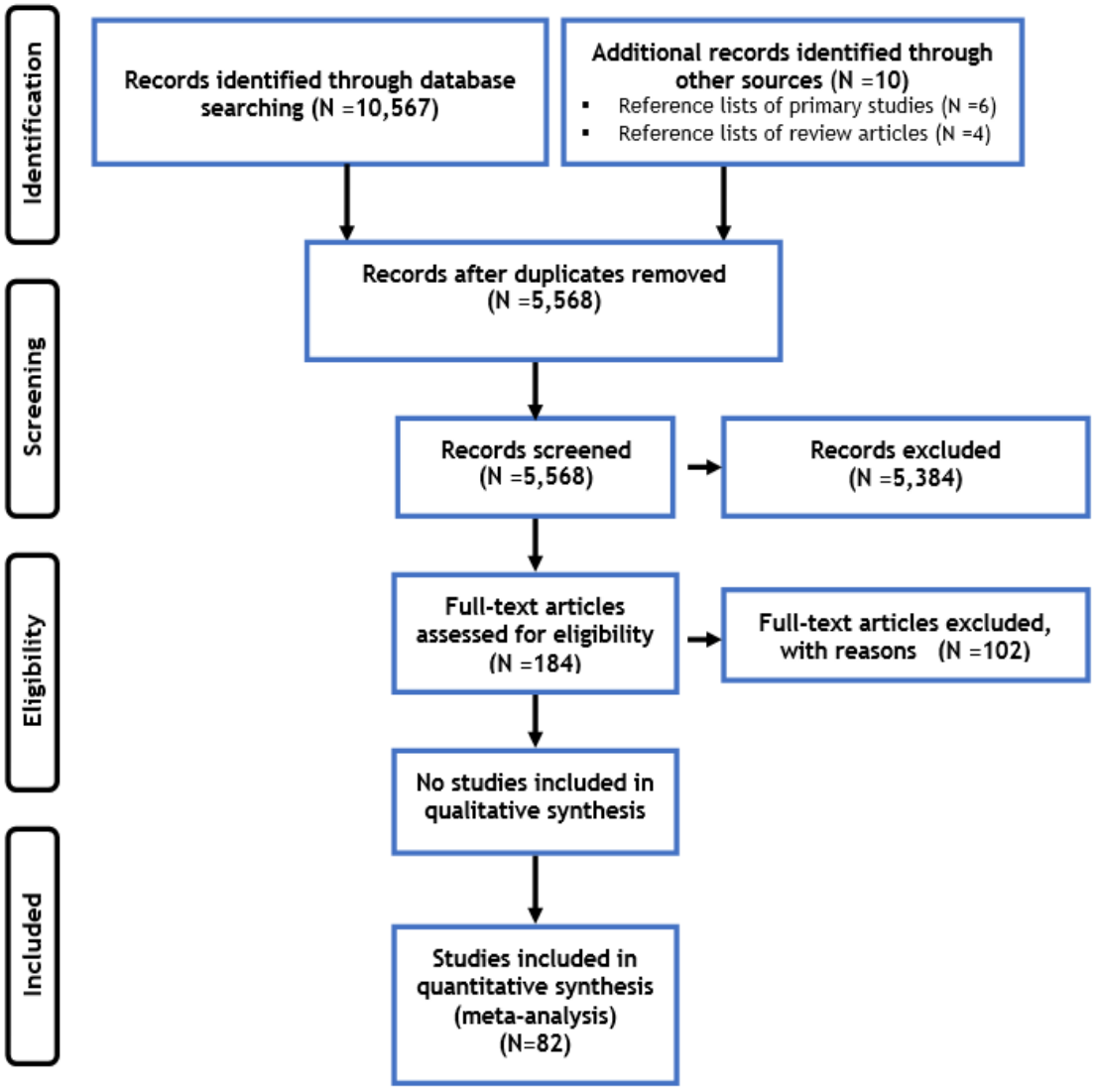


Figure 3.1 PRISMA study flow diagram.

3.1.1 Description of excluded studies

Overall, 102 RCTs were excluded after screening the full texts, (see 'Characteristics of excluded studies', **Section 4.1.1.1**). In nine studies (Bagatin [1998]; Chan [1995]; Elliott [2001]; Giordano [1996]; Kumar [2014]; Ostergren [1996]; STUMPE [1998]; Thulin [1999]; Townsend [1995]) participants had HTN; however, baseline BP was not specified.

Protocol for dis/or continuation of background BP-lowering drugs before randomisation was not pre-specified in ten studies (Cushman [2002]; Koylan [2005]; KHS[2009]; Lee [2008]; Leonetti [2005]; NOAAH [2014]; Ohma [2000]; ORIENT [2011]; RENAAL [2001]; SAKURA [2013]), whereas protocol for supplemental drugs after randomisation was not pre-specified in 14 studies (ANBP [2003]; CAPPP [1999]; COLM [2009]; Conlin [1998]; DIME [2014]; E-COST [2005]; Gerritsen [1998]; GLANT [1995]; Khan [2013]; NEBIS [2003]; Ono [2008]; Ren [2006]; SCOPE [2003]; Syst-China [1998]).

Mean BP response was not specified in only TRANSCEND [2008], whereas measurement protocol was not specified in 26 studies (AAA [2009]; Agabiti Rosei [2005]; Barnett [2004]; Bittar [1997]; Bulpitt [1999]; Chung [2009]; Crepaldi [1995]; CVIP [2004]; Flack [2001]; Fodor [1997]; Fonarow [2009]; Franke [1997]; Gavras [1999]; Grimm [2002]; Hansson [1996]; Himmelmann[1996]; Hu[1999]; Karch [1997]; Marazzi [1996]; Metelitsa [1996]; Neldam [2001]; PICXEL [2005]; Poisson [1996]; Schoenberger [1995]; Testa [1998]; Weiss [2005]). Both mean and duration of BP response were not specified in three studies (Dahlöf [2005]; HANE [1997]; TEST [1995]), while duration of mean BP response was not specified in four studies (Alici [2009]; Aurell [1997]; Elliott [1999]; Pessina [2001]).

In four crossover studies (Cifková [2000]; De Rosa [2000]; Konoshita [2010]; Puig [2007]) there was no washout period. In total, 31 studies included non hypertensives; 16 studies (ACTION [2005]; ADVANCE [2007]; APSIS [2006]; BENDECT [2004]; CAMELOT [2004]; DEMAND [2011]; DIABHYCAR [2004]; DIRECT-2 [2008] ;DREAM [2008]; HOPE [2000]; MARVAL [2002]; NICOLE [2003]; ONTARGET [2008]; PEACE [2004]; PROGRESS[2001]; REIN-2 [2005]) had < 70% hypertensives, and 15 studies (Bouhanick[1996] ; Cağlar [2011]; CARTER [2007]; Derosa [2011]; Fogari [2012] ; Fogari [2008]; GEMINI [2004]; Hayoz [2012]; Kim [2014]; Lin [2005]; Liu [2005]; LIVE [2000]; Millar-Craig [2003]; Toto [2008]; Wald [2008]) not specified the % of hypertensives .

3.1.1.1 Characteristics of excluded studies (ordered by study ID)

Study [5]	Reason for exclusion
AAA [2009] (178)	Measurement protocol of BP response not specified
ACTION [2005] (179)	Study included < 70% hypertensives (52%)
ADVANCE [2007] (180)	Study included < 70% hypertensives (59%)
Agabiti Rosei [2005] (181)	Measurement protocol of BP response not specified
Alici [2009] (182)	Duration of BP response not specified
ANBP [2003] (183)	No pre-specified protocol for interventional or supplemental drugs after randomisation. Patients randomly assigned to Enalapril or Hydrochlorothiazide as initial therapy (agent and dose); choice was made by the family physician.
APSIS [2006] (184)	Study included < 70% hypertensives (27%)
Aurell [1997] (185)	Duration of BP response not specified
Bagatin [1998] (186)	Participants with HTN; however, baseline BP not specified
Barnett [2004] (49)	Measurement protocol of BP response not specified
BENDECT [2004] (187)	Study included < 70% hypertensives (57%)
Bittar [1997] (188)	Measurement protocol of BP response not specified
Bouhanick[1996](189)	Study included hypertensives; however, % of hypertensives not specified
Bulpitt [1999] (190)	Measurement protocol of BP response not specified
Cağlar [2011] (191)	Study included hypertensives; however, % of hypertensives not specified
CAMELOT [2004] (192)	Study included < 70% hypertensives (60%)
CAPPP [1999] (193)	No pre-specified protocol for interventional or supplemental drugs after randomisation. Patients randomly assigned to Captopril or conventional BP-lowering agents BB and DI.
CARTER [2007] (194)	Study included hypertensives; however, % of hypertensives not specified
Chan [1995] (195)	Participants with HTN; however, baseline BP not specified
Chung [2009] (196)	Measurement protocol of BP response not specified
Cifková [2000] (197)	Crossover studies without a wash-out period
COLM [2009] (198)	No pre-specified protocol for interventional or supplemental drugs after randomisation. Patients randomly assigned to CCB (Azelnidipine and Amlodipine) and thiazides.
Conlin [1998] (199)	No pre-specified protocol for interventional or supplemental drugs after randomisation. Patients randomly assigned to Losartan +/- HCTZ or Nifedipine.
Crepaldi [1995] (200)	Measurement protocol of BP response not specified
Cushman [2002] (201)	No pre-specified protocol for dis/or continuation of background BP-lowering drugs before randomisation. Patients previously treated with BP-lowering agents (discontinued if necessary).
CVIP [2004] (202)	Measurement protocol of BP response not specified
Dahlöf [2005] (203)	Mean and duration of BP response not specified
De Rosa [2000] (204)	Crossover studies without a wash-out period
DEMAND [2011] (205)	Study included < 70% hypertensives (44.2%)
Derosa [2011] (206)	Study included hypertensives; however, % of hypertensives not specified
DIABHYCAR [2004] (207)	Study included < 70% hypertensives (56%)
DIME [2014] (208)	No pre-specified protocol for interventional or supplemental drugs after randomisation. Patients randomly assigned to receive DI or any other BP-lowering agents.
DIRECT-2 [2008] (209)	Study included < 70% hypertensives (62%)
DREAM [2008] (210)	Study included < 70% hypertensives (43.5%)
E-COST [2005] (211)	No pre-specified protocol for interventional or supplemental drugs after randomisation. Patients randomly assigned to ARB candesartan or conventional BP-lowering agents other than ACEI or ARBs.
Elliott [1999] (212)	Duration of BP response not specified
Elliott [2001] (213)	Participants with HTN; however, baseline BP not specified
Flack [2001] (214)	Measurement protocol of BP response not specified
Fodor [1997] (215)	Measurement protocol of BP response not specified

[5] For studies acronyms (see 'list of abbreviations', Acronyms and symbols)

Fogari [2012] (216)	Study included hypertensives; however, % of hypertensives not specified
Fogari [2008] (217)	Study included hypertensives; however, % of hypertensives not specified
Fonarow [2009] (218)	Measurement protocol of BP response not specified
Franke [1997] (219)	Measurement protocol of BP response not specified
Gavras [1999] (220)	Measurement protocol of BP response not specified
GEMINI [2004] (221)	Study included hypertensives; however, % of hypertensives not specified
Gerritsen [1998] (222)	No pre-specified protocol for interventional or supplemental drugs after randomisation. Patient received active drugs as 'escape medication' in addition to the study medication if necessary.
Giordano [1996] (223)	Participants with HTN; however, baseline BP not specified
GLANT [1995] (224)	No pre-specified protocol for interventional or supplemental drugs after randomisation. Patients randomly assigned to an ACEI or any kind of commercially available CCB could be used in this study.
Grimm [2002] (225)	Measurement protocol of BP response not specified
HANE [1997] (226)	Mean and duration of BP response not specified
Hansson [1996] (227)	Measurement protocol of BP response not specified
Hayoz [2012] (228)	Study included hypertensives; however, % of hypertensives not specified
Himmelmann[1996] (229)	Measurement protocol of BP response not specified
HOPE [2000] (230)	Study included < 70% hypertensives (46.9%)
Hu[1999] (231)	Measurement protocol of BP response not specified
Karch [1997] (232)	Measurement protocol of BP response not specified
Khan [2013] (233)	No pre-specified protocol for interventional or supplemental drugs after randomisation. Patients randomly assigned to CCB and non-selective BB.
Kim [2014] (234)	Study included hypertensives; however, % of hypertensives not specified
Konoshita [2010] (235)	Crossover studies without a wash-out period
Koylan [2005] (236)	No pre-specified protocol for dis/or continuation of background BP-lowering drugs before randomisation. Patients previously treated with BP-lowering agents.
Kumar [2014] (237)	Participants with HTN; however, baseline BP not specified
KHS[2009] (238)	No pre-specified protocol for dis/or continuation of background BP-lowering drugs before randomisation. Patients previously treated with BP-lowering agents other than ARB.
Lee [2008] (239)	No pre-specified protocol for dis/or continuation of background BP-lowering drugs before randomisation. Patients previously treated with ARB (Valsartan).
Leonetti [2005] (240)	No pre-specified protocol for dis/or continuation of background BP-lowering drugs before randomisation. Patients previously treated with BP-lowering agents (down titrated when applicable).
Lin [2005] (241)	Study included hypertensives; however, % of hypertensives not specified
Liu [2005] (242)	Study included hypertensives; however, % of hypertensives not specified
LIVE [2000] (243)	Study included hypertensives; however, % of hypertensives not specified
Marazzi [1996] (244)	Measurement protocol of BP response not specified
MARVAL [2002] (245)	Study included < 70% hypertensives (65%)
Metelitsa [1996] (246)	Measurement protocol of BP response not specified
Millar-Craig [2003] (247)	Study included hypertensives; however, % of hypertensives not specified
NEBIS [2003] (248)	No pre-specified protocol for interventional or supplemental drugs after randomisation. Concomitant therapy was permitted at any time, apart from DI, ACEI, and CCB.
Neldam [2001] (249)	Measurement protocol of BP response not specified
NICOLE [2003] (250)	Study included < 70% hypertensives (40%)
NOAAH [2014] (251)	No pre-specified protocol for dis/or continuation of background BP-lowering drugs before randomisation. Patients previously treated with BP-lowering agents.
Ohma [2000] (252)	No pre-specified protocol for dis/or continuation of background BP-lowering drugs before randomisation. Patients previously treated with BP-lowering agents.
Ono [2008] (253)	No pre-specified protocol for interventional or supplemental drugs after randomisation. Patients randomly assigned to ARB (Candesartan) group or a non-ARB group.
ONTARGET [2008] (254)	Study included < 70% hypertensives (68.7%)

ORIENT [2011] (255)	No pre-specified protocol for dis/or continuation of background BP-lowering drugs before randomisation. Patients previously treated with ACEI.
Ostergren [1996] (256)	Participants with HTN; however, baseline BP not specified
PEACE [2004] (257)	Study included < 70% hypertensives (45.5%)
Pessina [2001] (258)	Duration of BP response not specified
PICXEL [2005] (259)	Measurement protocol of BP response not specified
Poisson [1996] (260)	Measurement protocol of BP response not specified
PROGRESS [2001] (261)	Study included < 70% hypertensives (48%)
Puig [2007] (262)	Crossover studies without a wash-out period
REIN-2 [2005] (263)	Study included < 70% hypertensives (60%)
Ren [2006] (264)	No pre-specified protocol for interventional or supplemental drugs after randomisation. Patients randomly assigned to (Enalapril +/- Spirolactone) and BP-lowering agents not affecting RAAS (CCB and BB).
RENAAL [2001] (265)	No pre-specified protocol for dis/or continuation of background BP-lowering drugs before randomisation. Patients previously treated with BP-lowering agents (continued to receive).
SAKURA [2013] (266)	No pre-specified protocol for dis/or continuation of background BP-lowering drugs before randomisation. Patients previously treated with ACEI and ARB.
Schoenberger [1995] (267)	Measurement protocol of BP response not specified
SCOPE [2003] (268)	No pre-specified protocol for interventional or supplemental drugs after randomisation. Concomitant therapy was permitted, apart from (ACEI and ARB); however, concomitant therapy was extensively used in the Placebo group.
STUMPE [1998] (269)	Participants with HTN; however, baseline BP not specified
Syst-China [1998] (270)	No pre-specified protocol for interventional or supplemental drugs after randomisation. Patients randomly assigned to Nitrendipine, with the addition of Captopril or Hydrochlorothiazide, or both.
TEST [1995] (271)	Mean and duration of BP response not specified
Testa [1998] (272)	Measurement protocol of BP response not specified
Thulin [1999] (273)	Participants with HTN; however, baseline BP not specified
Toto [2008] (274)	Study included hypertensives; however, % of hypertensives not specified
Townsend [1995] (275)	Participants with HTN; however, baseline BP not specified
TRANSCEND [2008] (276)	Mean BP response not specified
Wald [2008] (277)	Study included hypertensives; however, % of hypertensives not specified
Weiss [2005] (278)	Measurement protocol of BP response not specified

3.1.2 Description of included studies

The literature search, which followed PRISMA statement recommendations, led to the identification of 82 studies (see 'Characteristics of included studies, **Section 4.1.2.1**) with a total of 197,684 participants, who were followed up for a median of 6 months.

BP-lowering strategies: 13 studies (ALPINE [2003]; Bremner [1997]; CROSS [2003]; FACET [1998]; Farsang [2007]; Holsgreve [2003]; HYVET [2008]; INVEST [2003]; Narkiewicz [2007]; PATS [1995]; SYST-EUR [1997]; UKPDS [1998]; VHAS [1998]) with 41,886 participants were on intentional BP-lowering, while the remaining 69 (155,798 participants) studies were classified as non-intentional BP-lowering studies.

Study design related characteristics: participants in the majority of studies had a placebo run-in period of at least one week before receiving BP-lowering agents. Additionally, in 19 studies (BLACK [2001]; Cushman [1998]; ELLE [2003]; ELVERA [2004]; FACET [1998]; Fogari [2008]; Grassi [2003]; Hoegholm [1995]; HYVET–P [2003]; IDNT [2001]; LAARS [2002]; LOTHAR [2006]; Mallion [2007]; Mounier-Vehier [1998]; NICS-EH [1999]; NORDIL [2000]; RACE [1995]; SHELL [2003]; Wu [2004]), participants had a washout period of at least one week before being administered the agents. In contrast, in 16 studies, participants did not have any placebo run-in or washout period (AASK [2002]; ACCOMPLISH [2008]; ALLHAT [2002]; CASE-J [2008]; CONVINCE [2003]; Derosa [2014]; DETAIL [2004]; Freytag [2001]; INVEST [2003]; JMIC-B [2004]; McInnes [2000]; Narkiewicz [2007]; Nilsson [2007]; UKPDS [1998]; VALUE [2004]; Yang [2015]).

Definition of HTN: Patients in 66 studies had a baseline resting BP of 140/90 mm Hg or higher. However, 16 studies (ACCOMPLISH [2008]; ALLHAT [2002]; Benetos [2000]; BLACK [2001]; CONVINCE [2003]; DETAIL [2004]; IDNT [2001]; INVEST [2003]; JMIC-B [2004]; MAISH [2007]; Mallion [2007]; Ruilope [2001]; SHELL [2003]; SYST-EUR [1997]; VALUE [2004]; Volpe [2003]) included patients with ISH. In addition, while almost all studies were conducted entirely on hypertensives, only five included more than 70% hypertensives (CONVINCE [2003] (80%); DETAIL [2004] (81%); IDNT [2001] (76%); NICS-EH [1999] (> 70 %); PATS [1995] (84%)).

BP measurement: all studies followed well-defined protocols and standardised techniques of BP measurement for the duration of the study (at least twice, with

the patient resting for at least one minute). A number of studies mentioned the guidelines that were followed to measure BP: American Society of Hypertension (ASH) (Alcocer [1995]; Freytag [2001]), American Heart Association (AHA) (Papademetriou [1997]; Volpe [2003]), British Hypertension Society (BHS) (Holsgreve [2003]; SYST-EUR [1997]), JNC (ALLHAT [2002]; BLACK [2001]; INVEST [2003]), Japanese Society of Hypertension (JSH) (CASE-J [2008]) and WHO (Black [1997]; Bremner [1997]; Hegner [1997]; Radauceanu [2004]).

In 75 studies BP was measured in a sitting position; seven teams measured it in a supine position (Alcocer [1995]; Benetos [2000]; Chanudet [2008]; Freytag [2001]; James [2002]; Mallion [2000]; NORDIL [2000]), and in one study (JMIC-B [2004]) both sitting and supine BP measurements were taken.

Presence of co-morbidity: 56 included studies enrolled hypertensive patients without other comorbid conditions. However, in 26 studies participants had at least one comorbidity (AASK [2002]; ACCOMPLISH [2008]; ALLHAT [2002]; ASCOT-BPLA [2005]; CASE-J [2008]; CONVINCE [2003]; CROSS [2003]; DETAIL [2004]; ELSA [2002]; FACET [1998]; Holsgreve[2003]; IDNT [2001]; INSIGHT [2000]; INVEST [2003]; JMIC-B [2004]; LAARS [2002]; LIFE [2002]; Luque [2005]; Mancia [2000]; MIDAS [1996]; Papademetriou [1997]; PATS [1995]; RACE [1995]; REGAAL [2002]; UKPDS [1998]; VALUE [2004]).

T2DM was the most common comorbidity in 12 studies (ACCOMPLISH [2008]; ASCOT-BPLA [2005]; CASE-J [2008]; CONVINCE [2003]; DETAIL [2004]; ELSA [2002]; FACET [1998]; Holsgreve[2003]; IDNT [2001]; Luque [2005]; Mancia[2000]; VALUE [2004]), while CHD was the main comorbidity in nine studies (ACCOMPLISH [2008]; ALLHAT [2002]; ASCOT-BPLA [2005]; CASE-J [2008]; CONVINCE [2003]; ELSA [2002]; INSIGHT [2000]; INVEST [2003]; JMIC-B [2004]) . CKD was the main comorbidity in six studies (AASK [2002]; ACCOMPLISH [2008]; ASCOT-BPLA [2005]; CASE-J [2008]; INSIGHT [2000]; VALUE [2004]).

Treatment status: 15 studies included previously treated hypertensives (ACCOMPLISH [2008]; ALLHAT [2002]; Bremner [1997]; Cushman [1998]; DETAIL [2004]; ELSA [2002]; FACET [1998]; HYVET [2008]; INSIGHT [2000]; JMIC-B [2004]; MIDAS [1996]; PATS [1995]; SHELL [2003]; SYST-EUR [1997]; VHAS [1998]). However, only five studies included previously untreated hypertensives (Derosa [2014]; ELVERA [2004]; Freytag [2001]; Holsgreve[2003]; Mallion [2007]), whereas the remaining 62 included both previously treated and untreated patients.

Treatment strategy: monotherapy was used as the first line of approach in the majority of studies, whereas combination therapy was used in one of the treatment arms in seven studies (ACCOMPLISH [2008]; ASCOT-BPLA [2005]; Cremonesi [2002]; Holsgreve[2003]; McInnes [2000]; Pareek [2010]; Stimpel [1997]) and in both treatment arms in eight studies (Benetos [2000]; Chanudet [2001]; CONVINCE [2003]; INSIGHT [2000]; Mallion [2000]; NORDIL [2000]; Os [1997]; Waeber [1999]).

BP–lowering agents: In total 36,410 participants were randomised to ACEI, 20,705 to ARB, 73,987 to CCB, 56,727 to DI and 43,617 to BB, as shown in **Table 4.1.**

ACEI was used in 37 studies (AASK [2002]; ACCOMPLISH [2008]; Alcocer [1995]; ALLHAT [2002]; ASCOT-BPLA [2005]; Black [1997]; Bremner [1997]; Chanudet [2001]; Cremonesi [2002]; Cushman [1998]; Derosa [2014]; DETAIL [2004]; ELVERA [2004]; FACET [1998]; Farsang [2007]; Holsgreve [2003]; HYVET–P [2003]; JMIC-B [2004]; Luque [2005]; Mallion [2000]; Mallion [2011]; Mancia [2000]; MAPAVEL [2002]; McInnes [2000]; Mimran [1998]; Mroczek [1996]; Narkiewicz [2007]; Nilsson [2007]; Os [1997]; PRESERVE [2001]; RACE [1995]; Ruilope [2001]; Stimpel [1997]; UKPDS [1998]; Waeber [1999]; Wu [2004]; Yang [2015]).

As regards ACEI sub-classes, seven dicarboxylate-containing agents (benazepril, delapril, enalapril, lisinopril, moexipril, perindopril and ramipril), two sulfhydryl-containing agents (captopril and zofenopril) and one phosphonate-containing agent (fosinopril) were used in the studies. Of these, enalapril (31.1%) was the most commonly used as it has been compared to other BP-lowering agents in 12 studies (Alcocer [1995]; Cushman [1998]; Derosa [2014]; DETAIL [2004]; JMIC-B [2004]; Luque [2005]; Mancia[2000]; MAPAVEL [2002]; Mimran [1998]; Os [1997]; PRESERVE [2001]; Ruilope [2001]), and to Placebo in Cushman [1998].

ARB was used in 34 studies (ALPINE [2003]; Black [1997]; Bremner [1997]; CASE-J [2008]; Chanudet [2001]; CROSS [2003]; Derosa [2013]; DETAIL [2004]; Fogari [2008]; Freytag [2001]; Giles [2007]; Guthrie [1998]; Hanefeld [2001]; Hegner [1997]; IDNT [2001]; James [2002]; LAARS [2002]; LIFE [2002]; LOTHAR [2006]; Mallion [2007]; Mallion [2011]; MAPAVEL [2002]; McInnes [2000]; Mimran [1998]; Narkiewicz [2007]; Oparil [1998]; Pareek [2010]; Radauceanu [2004]; REGAAL [2002]; REZALT [2009]; Ruilope [2001]; VALUE [2004]; Volpe [2003]; Wu [2004]). In total, seven ARB agents (candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan and valsartan) were used, with losartan (30.8%) the most commonly used as it has been compared to other BP-lowering agents in 12 studies (Chanudet [2001]; Giles [2007];

James [2002]; LAARS [2002]; LIFE [2002]; LOTHAR [2006]; Narkiewicz [2007]; Oparil[1998]; Pareek [2010]; REGAAL[2002]; Volpe [2003] ; Wu [2004])

CCB was used in 46 studies (AASK [2002] ; ACCOMPLISH [2008]; ALLHAT [2002]; ASCOT-BPLA [2005]; Benetos [2000]; BLACK [2001]; CASE-J [2008]; CONVINCE [2003]; Cushman [1998]; Derosa [2013]; Derosa [2014]; ELLE [2003]; ELSA [2002]; ELVERA [2004]; FACET [1998]; Farsang [2007]; Hoegholm [1995]; Holsgreve [2003]; IDNT [2001]; INSIGHT [2000]; INVEST [2003]; James [2002]; JMIC-B [2004]; LOTHAR [2006]; Luque [2005]; MAISH [2007]; Mallion [2007]; Mancia [2000]; MIDAS [1996] ; Mounier-Vehier [1998]; NICS-EH [1999]; NORDIL [2000]; Papademetriou [1997]; Pareek [2010]; PRESERVE [2001]; Radauceanu [2004]; REZALT [2009]; SHELL [2003]; SYST-EUR [1997]; VALUE [2004]; VHAS [1998]; Volpe [2003] ; Waeber [1999]; Wu [2004]; Yang [2015]; Zanchetti [2001]).

As regards CCB sub-classes, ten dihydropyridines (DHP) agents (amlodipine, azelnidipine, felodipine, isradipine, lacidipine, lercanidipine, manidipine, nicardipine, nifedipine and nitrendipine) and two non-dihydropyridines (non-DHP) agents (verapamil and diltiazem) were used. Of them all, amlodipine (38.5%) was the most commonly used as it has been compared to other BP-lowering agents in 21 studies (AASK [2002] ; ACCOMPLISH [2008]; ALLHAT [2002]; ASCOT-BPLA [2005]; Benetos [2000]; CASE-J [2008]; Derosa [2013]; ELVERA [2004]; FACET [1998]; Farsang [2007]; Hoegholm [1995]; IDNT [2001]; LOTHAR [2006]; MAISH [2007]; Mounier-Vehier [1998]; Pareek [2010]; Radauceanu [2004]; VALUE [2004]; Volpe [2003] ; Wu [2004]; Zanchetti [2001]) and to Placebo in IDNT [2001].

DI was used in 26 studies (ACCOMPLISH [2008]; ALLHAT [2002]; ALPINE [2003]; Benetos [2000]; Chanudet [2001]; CONVINCE [2003]; Cremonesi [2002]; CROSS [2003]; Fogari [2008]; Hegner [1997]; Holsgreve [2003]; HYVET [2008]; HYVET–P [2003]; INSIGHT [2000]; Mallion [2000]; McInnes [2000]; MIDAS [1996]; Mroczek [1996]; NICS-EH [1999]; NORDIL [2000]; Os [1997]; Papademetriou [1997]; PATS [1995]; SHELL [2003]; Stimpel [1997]; VHAS [1998]).

For DI sub-classes, three thiazide DIs (bendroflumethiazide, hydrochlorothiazide and trichlormethiazide), two thiazide-like DIs (chlorthalidone and indapamide) and one potassium-sparing DI (amiloride) were used. Chlorthalidone (30%) was the most commonly used DI as it has been compared to other BP-lowering agents in four studies (ALLHAT [2002]; Holsgreve[2003]; SHELL [2003]; VHAS [1998]).

BB was used in 22 studies (AASK [2002]; ASCOT-BPLA [2005]; Benetos [2000]; CONVINCE [2003]; ELSA [2002]; Freytag [2001]; Grassi [2003]; Greathouse [2010]; Holsgreve[2003]; INVEST [2003]; LAARS [2002]; LIFE [2002]; Mallion [2000]; Nilsson [2007]; NORDIL [2000]; Os [1997]; Pareek [2010]; RACE [1995]; REGAAL [2002]; Stimpel [1997]; UKPDS [1998]; Waeber [1999]).Looking at BB sub-classes, four beta-1 selective agents (atenolol, bisoprolol, metoprolol and nebivolol) were used; Atenolol (64%) was the most commonly used as it has been compared to other BP-lowering agents in 15 studies (ASCOT-BPLA [2005]; CONVINCE [2003]; ELSA [2002]; Freytag [2001]; Grassi [2003]; Holsgreve[2003]; INVEST [2003]; LAARS [2002]; LIFE [2002]; Mallion [2000]; Nilsson [2007]; Os [1997]; RACE[1995]; REGAAL[2002]; UKPDS [1998]).

In addition, 8,728 participants were randomised to a placebo (6.6%), which was used in one of the treatment arms of 13 studies (Black [1997]; BLACK [2001]; Cushman [1998]; Giles [2007]; Grethouse [2010]; Guthrie [1998]; Hanefeld [2001]; HYVET [2008]; IDNT [2001]; Mroczek [1996]; PATS [1995]; SYST-EUR [1997]; Waeber [1999]).

Table 3.1 Summary of BP-lowering agents used in the review.
The table shows that CCBs are the choice for first-line mono-therapy or second-line combination therapy recommended by most of the existing BP guidelines as well as the current review (as mentioned above, Table 1.3). DIs and BBs are still prescribed; thiazide DIs are the most commonly prescribed DIs, whereas BBs are no longer commonly prescribed as first-line BP-lowering agents. [Red highlights] indicate the highest N or %.

BP-lowering class	ACEI		ARB		CCB		DI		BB	
Guideline recommendations										
NICE- United Kingdom	1st line monotherapy 2nd line combination + CCB		1st line monotherapy 2nd line combination + CCB		1st line monotherapy 2nd line combination + ACEI or ARB					
ESH/ESC- Europe	1st line monotherapy 2nd line combination + CCB		1st line monotherapy 2nd line combination + CCB		1st line monotherapy 2nd line combination + ACEI ,ARB or DI		1st line monotherapy 2nd line combination Thiazide + CCB		1st line Monotherapy	
JNC- United States	1st line monotherapy 2nd line combination + CCB		1st line monotherapy 2nd line combination + CCB		1st line Monotherapy 2nd line combination + ACEI ,ARB or DI		1st line monotherapy Thiazide 2nd line combination Thiazide + CCB			
Current systematic review										
N of RCTs	37		34		46		26		22	
N of patients	36410		20705		73987		56727		43617	
% of patients	23.20%		21.20%		27.30%		8.10%		13.60%	
BP-lowering sub-class	**Dicarboxylate-containing**		**AT1receptor antagonists**		**DHP**		**Thiazide**		**Beta-1 selective**	
	Benazepril	8.90%	Candesartan	7.70%	Amlodipine	38.50%	Bendroflumethiazide	10.00%	Atenolol	64.00%
	Delapril	4.40%	Eprosartan	2.60%	Azelnidipine	2.00%	Hydrochlorothiazide	20.00%	Bisoprolol	8.00%
	Enalapril	31.10%	Irbesartan	12.80%	Felodipine	7.70%	Trichlormethiazide	10.00%	Metoprolol	20.00%
	Lisinopril	15.60%	Losartan	30.80%	Isradipine	3.80%	**Thiazide-like**		Nebivolol	8.00%
	Moexipril	6.70%	Olmesartan	17.90%	Lacidipine	3.80%	Chlorthalidone	30.00%		
	Perindopril	13.30%	Telmisartan	10.30%	Lercanidipine	7.70%	Indapamide	20.00%		
	Ramipril	4.40%	Valsartan	17.90%	Manidipine	7.70%	**Potassium-sparing**			
	Sulfhydryl-containing				Nicardipine	2.00%	Amiloride	10.00%		
	Captopril	2.20%			Nifedipine	9.60%				
	Zofenopril	6.70%			Nitrendipine	3.80%				
	Phosphonate-containing				**Non-DHP**					
	Fosinopril	6.70%			Verapamil	9.60%				
					Diltiazem	3.80%				

SD of BP change at the end of the study was used in 46 studies (Alcocer [1995]; ALLHAT [2002]; ALPINE [2003]; ASCOT-BPLA [2005]; Benetos [2000]; BLACK [2001]; Chanudet [2001]; Derosa [2013]; Derosa [2014]; ELLE [2003]; ELVERA [2004]; FACET [1998]; Farsang [2007]; Freytag [2001]; Fogari [2008]; Grassi [2003]; Grethouse [2010]; Hanefeld [2001]; Hegner [1997]; Hoegholm [1995]; Holsgreve [2003]; HYVET [2008]; INSIGHT [2000]; James [2002]; LIFE [2002]; Luque [2005]; MAISH [2007]; Mallion [2000]; MAPAVEL [2002]; Mcinnes [2000]; Mallion [2007]; MIDAS [1996] ; Mounier-Vehier [1998]; Narkiewicz [2007]; Nilsson [2007]; Os [1997]; Pareek [2010]; PRESERVE [2001]; Papademetriou [1997]; Radauceanu [2004]; UKPDS [1998]; VHAS [1998]; VALUE [2004]; Volpe [2003]; Wu [2004]; Yang [2015]).

Subsequently, SD of the change at each time point during treatment was used in 8 studies (AASK [2002]; CASE-J [2008]; LOTHAR [2006]; NICS-EH [1999]; NORDIL [2000]; PATS [1995]; REGAAL[2002]; SYST-EUR [1997]). Thereafter, SD of baseline SBP and DBP was imputed in 26 studies (ACCOMPLISH [2008]; Black [1997]; Bremner [1997]; CONVINCE [2003]; Cremonesi [2002]; CROSS [2003]; DETAIL [2004]; ELSA [2002]; Giles [2007]; Guthrie [1998]; HYVET–P [2003]; IDNT [2001]; INVEST [2003]; JMIC-B [2004]; LAARS [2002]; Mallion [2011]; Mancia [2000]; Mimran [1998]; Mroczek [1996]; Oparil [1998]; RACE [1995]; REZALT [2009]; Ruilope [2001]; SHELL [2003]; Waeber [1999]; Zanchetti [2001]). Finally, SD of the change from other studies with the closest sample size was implicated in two studies (Cushman [1998], imputed from MIDAS [1996] and Stimpel [1997], imputed from BLACK [2001]).

3.1.2.1 Characteristics of included studies (ordered by study ID)

AASK [2002](279-281)
Multicentre, randomised controlled, double-blind study **Mean duration of follow-up:** 49 months
Participants N: 1,094 **Mean baseline BP:** seated 150/96 mmHg **Method for BP measurement:** 3 consecutive BP readings were measured using a Hawksley random zero sphygmomanometer after at least 5 minutes of rest with the mean of the last 2 readings recorded **Hypertensive patients (%):** 100% **Type of hypertensive patients:** previously treated and untreated **Other co-morbid conditions:** mild to moderate CKD
Pre-intervention: placebo run-in period: no; wash-out period: no **Intervention:** ACEI - ramipril: 2.5 to 10 mg once daily (OD) or CCB - amlodipine: 5 to 10 mg OD, or BB - metoprolol: 50 to 200 mg OD **Co-intervention:** if BP goal was not achieved, other BP-lowering agents were added consecutively (furosemide, doxazosin, clonidine, and hydralazine or minoxidil)
Primary outcomes: GFR and other renal outcomes; all CV events, including CV deaths and hospitalisations for MI, strokes, HF, and revascularisation procedures; other hospitalised CV events

ACCOMPLISH [2004](282;283)
Multicentre, randomised controlled, double-blind study **Mean duration of follow-up:** 36 months
Participants N: 11,506 **Mean baseline BP:** seated 145.3/80 mmHg **Method for BP measurement:** BP measurements were recorded as the average of 3 readings taken at 2-minute intervals after the patient had remained in a seated position for 5 minutes **Hypertensive patients (%):** 100% **Type of hypertensive patients:** previously treated **Other co-morbid conditions:** history of CHD, CVE, mild to moderate CKD, PVD, LVH, or T2DM
Pre-intervention: placebo run-in period: no; wash-out period: no **Intervention:** ACEI + CCB - benazepril + amlodipine: 20 mg OD + 5 mg OD or ACEI + DI - benazepril + hydrochlorothiazide: 20 mg OD + 12.5 mg OD **Co-intervention:** if BP goal was not achieved, other BP-lowering agents were added (excluding any CCBs, ACEIs, ARBs, and thiazide DI but including BBs, alpha-blockers, clonidine, and spironolactone)
Primary outcomes: composite of death from CV causes, non-fatal MI, non-fatal stroke, hospitalisation for angina, resuscitation after sudden cardiac arrest, and coronary revascularisation

Alcocer [1995](284)
Multicentre, randomised controlled, double-blind study **Mean duration of follow-up:** 3 months
Participants N: 161 **Mean baseline BP:** supine 163/100.5 mmHg **Method for BP measurement:** according to ASH recommendations **Hypertensive patients (%):** 100% **Type of hypertensive patients:** previously treated and untreated **Other co-morbid conditions:** no
Pre-intervention: placebo run-in period: 4 weeks; wash-out period: no **Intervention:** ACEI - enalapril: 10 to 20 mg OD or ACEI - perindopril: 4 to 8 mg OD **Co-intervention:** if BP goal was not achieved, another BP-lowering agent was added (hydrochlorothiazide)
Primary outcomes: drug efficacy and safety

ALLHAT [2002](48;285)
Multicentre, randomised controlled, double-blind study **Mean duration of follow-up:** 57 months
Participants N: 33,357 **Mean baseline BP:** seated 146/84 mmHg

Method for BP measurement: according to JNC V guidelines for HTN **Hypertensive patients (%):** 100% **Type of hypertensive patients:** previously treated **Other co-morbid conditions:** at least 1 additional risk factor for CHD events
Pre-intervention: placebo run-in period: no; wash-out period: no **Intervention:** ACEI - lisinopril: 10 to 40 mg OD, CCB - amlodipine: 2.5 to 10 mg OD, or DI - Chlorthalidone: 12.5 to 25 mg OD **Co-intervention:** if BP goal was not achieved, other open-labelled BP-lowering agents were added consecutively (atenolol, reserpine, clonidine, or hydralazine)
Primary outcomes: fatal CHD or non-fatal MI combined **Secondary outcomes:** all-cause mortality, stroke, combined CHD, and combined CVD

ALPINE [2003](286); **Antihypertensive Treatment and Lipid Profile in a North of Sweden Efficacy evaluation**
Single-centre, randomised controlled, double-blind study **Mean duration of follow-up:** 12 months
Participants N: 393 **Mean baseline BP:** seated 154.8/96.9 mmHg **Method for BP measurement:** mean of 2 measurements in a standard way at least 2 times with the patient resting for at least 1 minute. **Hypertensive patients (%):** 100% **Type of hypertensive patients:** previously treated and untreated **Other co-morbid conditions**: no
Pre-intervention: placebo run-in period: 4 weeks; wash-out period: no **Intervention:** ARB - candesartan: 16 mg OD or DI - hydrochlorothiazide: 25 mg OD **Co-intervention:** if BP goal was not achieved, other BP-lowering agents were added (felodipine was added to the candesartan group and Atenolol was added to the hydrochlorothiazide group)
Primary outcomes: glucose and lipoprotein metabolism, electrolytes, BP, and subjective symptoms

ASCOT-BPLA [2005](51;287)
Multicentre, randomised controlled, double-blind study **Mean duration of follow-up:** 72 months
Participants N: 19,257 **Mean baseline BP:** seated 164/95 mmHg **Method for BP measurement**: BP was measured in a standard way on at least 2 occasions. BP was measured 3 times, after 5 minutes of rest in the sitting position. A semi-automated device was used, and the mean of the last 2 readings was used. **Hypertensive patients (%):** 100% **Type of hypertensive patients:** previously treated and untreated **Other co-morbid conditions:** at least 3 other CV risk factors (male sex; age 55 years or older; smoking; history of CHD, CVE, mild to moderate CKD, PVD, LVH; hyperlipidaemia, or T2DM)
Pre-intervention: placebo run-in period: 2 to 8 weeks; wash-out period: no **Intervention**: CCB + ACEI – amlodipine + perindopril: 5 to 10 mg OD + 4-8 mg OD or BB + DI – atenolol + bendroflumethiazide : 50 to 100 mg OD + 1.25-2.5Mg OD **Co-intervention:** no other BP-lowering agents were added
Primary outcomes: non-fatal MI + fatal CHD **Secondary outcomes:** all-cause mortality, total stroke, primary end point minus silent MI, all coronary events, total CV events and procedures, CV mortality, and non-fatal and fatal HF **Tertiary outcomes:** silent MI, unstable angina, chronic stable angina, PVD, life-threatening arrhythmias, development of T2DM , development of RF

Benetos [2000](288)
Multicentre, randomised controlled, double-blind study **Mean duration of follow-up:** 3 months
Participants N: 164 **Mean baseline BP:** supine 171.6/95.6 mmHg **Method for BP measurement:** 3 measurements were obtained with a manual mercury sphygmomanometer at 1-minute intervals after a 5-minute rest. The mean of the last 2 values was used. **Hypertensive patients (%):** 100% **Type of hypertensive patients**: previously treated and untreated

Other co-morbid conditions: no
Pre-intervention: placebo run-in period: 2 to 4 weeks; wash-out period: no **Intervention:** CCB - amlodipine: 5 mg OD or BB + DI - bisoprolol + hydrochlorothiazide: 2.5 mg OD + 6.25 mg OD **Co-intervention:** no other BP-lowering agents were added
Primary outcomes: drug efficacy and safety, and quality of life

Black [1997](289)
Multicentre, randomised controlled, double-blind study **Mean duration of follow-up:** 3 months
Participants N: 734 **Mean baseline BP:** seated 154/101.1 mmHg **Method for BP measurement:** according to WHO guidelines **Hypertensive patients (%):** 100% **Type of hypertensive patients:** previously treated and untreated **Other co-morbid conditions**: no
Pre-intervention: placebo run-in period: 2 to 4 weeks**;** wash-out period: no **Intervention:** ACEI - lisinopril: 10 to 20 mg OD, ARB - valsartan: 80 to 160 mg OD, or P - placebo **Co-intervention:** no other BP-lowering agents were added
Primary outcomes: drug efficacy, tolerability, and safety

Black [2001](290)
Multicentre, randomised controlled, double-blind study **Mean duration of follow-up:** 13 months
Participants N: 171 **Mean baseline BP**: seated 149/83 mmHg **Method for BP measurement:** according to JNC guidelines for HTN **Hypertensive patients (%)**: 100% **Type of hypertensive patients:** previously treated and untreated **Other co-morbid conditions**: no
Pre-intervention: placebo run-in period: 4 weeks; wash-out period: ≤ 8 weeks **Intervention:** CCB - felodipine: 2.5 to 5 mg OD or P - placebo **Co-intervention:** no other BP-lowering agents were added
Primary outcomes: drug efficacy and safety, LVM, and quality of life

Bremner [1997](291)
Multicentre, randomised controlled, double-blind study **Mean duration of follow-up:** 13 months
Participants N: 501 **Mean baseline BP:** seated 172/102 mmHg **Method for BP measurement:** according to WHO guidelines **Hypertensive patients (%):** 100% **Type of hypertensive patients:** previously treated **Other co-morbid conditions:** no
Pre-intervention: placebo run-in period: 2 weeks**;** wash-out period: no **Intervention:** ACEI - lisinopril: 2.5 to 20 mg OD or ARB - valsartan: 40 to 80 mg OD **Co-intervention:** if BP goal was not achieved, another BP-lowering agent was added (hydrochlorothiazide)
Primary outcomes: total mortality (death due to all causes) and BP

CASE-J [2008](292;293); Candesartan Antihypertensive Survival Evaluation in Japan
Multicentre, randomised controlled, open-label study **Mean duration of follow-up:** 48 months
Participants N: 4,728 **Mean baseline BP:** seated 162.8/91.7 mmHg **Method for BP measurement:** according to JSH guidelines **Hypertensive patients (%):** 100% **Type of hypertensive patients:** previously treated and untreated **Other co-morbid conditions:** at least 1 CV risk factor (history of CHD, CVE, mild to moderate CKD, PVD, LVH, or T2DM)
Pre-intervention: placebo run-in period: no**;** wash-out period: no **Intervention:** ARB - candesartan: 4 to 12 mg OD or CBB - amlodipine: 2.5 to 10 mg OD

Co-intervention: no other BP-lowering agents were added
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

Chanudet [2001](294)
Multicentre, randomised controlled, double-blind study **Mean duration of follow-up:** 3 months
Participants N: 277 **Mean baseline BP:** supine 165.5/98.2 mmHg **Method for BP measurement:** 3 consecutive measurements were taken and the third was considered. The SBP value corresponded to phase I and the DBP value to phase V of the Korotkoff sounds. The BP value recorded for the study was measured after 5 minutes of rest. **Hypertensive patients** (%): 100% **Type of hypertensive patients:** previously treated and untreated **Other co-morbid conditions:** no
Pre-intervention: placebo run-in period: 2 weeks; wash-out period: no **Intervention:** ACEI + DI - perindopril + indapamide: 2 mg OD + 0.625 to 1.25 mg OD or ARB - losartan: 50 mg OD **Co-intervention:** no other BP-lowering agents were added
Primary outcomes: drug efficacy and tolerability

CONVINCE [2003](295;296); Controlled Onset Verapamil Investigation of Cardiovascular End Points
Multicentre, randomised controlled, double-blind study **Mean duration of follow-up:** 36 months
Participants N: 16,602 **Mean baseline BP:** seated 150.1/86.8 mmHg **Method for BP measurement:** BP was measured in a standard way on at least 2 occasions with the patient resting for at least 1 minute. **Hypertensive patients (%)**: 80% **Type of hypertensive patients:** previously treated and untreated **Other co-morbid conditions:** at least 1 CV risk factor (smoking; obesity; hyperlipidaemia; or history of CHD, CVE, PVD, LVH, or T2DM)
Pre-intervention: placebo run-in period: no**;** wash-out period: no **Intervention:** CBB - verapamil: 180 mg OD or BB/DI - atenolol or hydrochlorothiazide: 50 mg OD or 12.5 mg OD **Co-intervention:** if BP goal was not achieved, other BP-lowering agents were added as step 2 (hydrochlorothiazide and atenolol). Any additional open-labelled BP-lowering agents (except a non-DHP CCB, thiazide DI, or BB) could be added as a step 3 if needed.
Primary outcomes: first occurrence of stroke, MI, or CV disease-related death

Cremonesi [2002](297)
Multicentre, randomised controlled, open-label study **Mean duration of follow-up:** 3 months
Participants N: 171 **Mean baseline BP:** seated 160.3/101.3 mmHg **Method for BP measurement:** 3 measurements, with standard mercury sphygmomanometry, were taken at 3-minute intervals after 5 minutes of sitting **Hypertensive patients (%):** 100% **Type of hypertensive patients:** previously treated and untreated **Other co-morbid conditions:** no
Pre-intervention: placebo run-in period: 2 weeks**;** wash-out period: no **Intervention:** ACEI + DI - delapril + indapamide: 30 mg OD + 2.5 mg OD or ACEI + DI - fosinopril + hydrochlorothiazide: 20 mg OD + 12.5 mg OD **Co-intervention:** no other BP-lowering agents were added
Primary outcomes: drug efficacy and safety

CROSS [2003](298); Candesartan Role on Obesity and on Sympathetic System
Multicentre, randomised controlled, double-blind study

Mean duration of follow-up: 3 months
Participants N: 176 **Mean baseline BP:** seated 146.1/98.6 mmHg **Method for BP measurement:** measurements were made by taking the I and the V Korotkoff sounds as indicative of SBP and DBP values, respectively. The mean of 3 consecutive measurements was taken with the patient resting for at least 1 minute. **Hypertensive patients (%):** 100% **Type of hypertensive patients:** previously treated and untreated **Other co-morbid conditions:** obesity
Pre-intervention: placebo run-in period: 2 weeks**;** wash-out period: no **Intervention:** ARB - candesartan: 8 to 16 mg OD or DI - hydrochlorothiazide: 25 to 50 mg OD **Co-intervention:** no other BP-lowering agents were added
Primary outcomes: drug efficacy on BP, insulin sensitivity, and sympathetic drive

Cushman [1998](299)
Multicentre, randomised controlled, double-blind study **Mean duration of follow-up:** 3 months
Participants N: 891 **Mean baseline BP:** seated 154.2/101.7 mmHg **Method for BP measurement:** BP measurements were obtained in triplicate with a standard mercury sphygmomanometer and patient resting for at least 1 minute. Korotkoff phases I and V were used for SBP and DBP, respectively. **Hypertensive patients (%):** 100% **Type of hypertensive patients:** previously treated **Other co-morbid conditions:** no
Pre-intervention: placebo run-in period: 4 weeks; wash-out period: 1 week **Intervention:** ACEI - enalapril: 5 mg OD, CCB - diltiazem: 120 or 180 mg OD, or P - placebo **Co-intervention:** no other BP-lowering agents were added
Primary outcomes: drug efficacy and safety

Derosa [2013](300)
Multicentre, randomised controlled, double-blind study **Mean duration of follow-up:** 12 months
Participants N: 276 **Mean baseline BP:** seated 148.8/98.6 mmHg **Method for BP measurement:** BP measurements were obtained using a standard mercury sphygmomanometer (Korotkoff I and V). 3 successive BP readings were obtained at 1-minute intervals, and the mean of the 3 readings was calculated. **Hypertensive patients (%):** 100% **Type of hypertensive patients:** previously treated and untreated **Other co-morbid conditions:** no
Pre-intervention: placebo run-in period: 2 weeks; wash-out period: no **Intervention:** ARB – olmesartan: 20 mg OD or CCB – amlodipine: 10 mg OD **Co-intervention:** no other BP-lowering agents were added
Primary outcomes: drug efficacy

Derosa [2014](301)
Single-centre, randomised controlled, double-blind study **Mean duration of follow-up**: 24 months
Participants N: 345 **Mean baseline BP:** seated 153.8/97.3 mmHg **Method for BP measurement:** BP measurements were obtained using a standard mercury sphygmomanometer (Korotkoff I and V). 3 successive BP readings were obtained at 1-minute intervals, and the mean of the 3 readings was calculated. **Hypertensive patients (%):** 100% **Type of hypertensive patients:** previously untreated **Other co-morbid conditions:** no
Pre-intervention: placebo run-in period: no; wash-out period: no **Intervention:** ACEI – Enalapril: 20 mg OD or CCB – Lercanidipine: 10 mg OD **Co-intervention:** no other BP-lowering agents were added
Primary outcomes: Biomarkers in CV risk stratification

DETAIL [2004](302)
Multicentre, randomised controlled, double-blind study **Mean duration of follow-up:** 60 months
Participants N: 250 **Mean baseline BP:** seated 158/87 mmHg **Method for BP measurement:** BP response measured using a standard technique at least 3 times with the patient resting for at least 1 minute. **Hypertensive patients (%):** 81% **Type of hypertensive patients:** previously treated **Other co-morbid conditions:** T2DM
Pre-intervention: placebo run-in period: no; wash-out period: no **Intervention:** ACEI – enalapril: 10 to 20 mg OD or ARB – telmisartan: 40 to 80 mg OD **Co-intervention:** if BP goal was not achieved, other BP-lowering agents were added consecutively (excluding ACEI and ARB)
Primary outcomes: Total mortality: death from all causes. CV events: MI, HF, CVE

ELLE [2003](303)**; Elderly and Lercanidipine**
Multicentre, randomised controlled, double-blind study **Mean duration of follow-up:** 6 months
Participants N: 324 **Mean baseline BP:** seated 167.2/97.5 mmHg **Method for BP measurement:** BP was measured twice at 3-minute intervals using the auscultatory method. Korotkoff phases I and V were used to identify SBP and DBP, respectively. **Hypertensive patients (%):** 100% **Type of hypertensive patients:** previously treated and untreated **Other co-morbid conditions:** no
Pre-intervention: placebo run-in period: 2 weeks; wash-out period: 1 week **Intervention:** CCB – lacidipine: 2 to 4 mg OD, CCB – lercanidipine: 5 to 10 mg OD, or CCB – nifedipine: 30 to 60 mg OD **Co-intervention:** no other BP-lowering agents were added
Primary outcomes: drug efficacy and safety

ELSA [2002](304-306)**; European Lacidipine Study on Atherosclerosis**
Multicentre, randomised controlled, double-blind study **Mean duration of follow-up**: 48 months
Participants N: 2,334 **Mean baseline BP:** seated 163.5/101.3 mmHg **Method for BP measurement:** 3 measurements of BP were taken by a mercury manometer after the patients had been seated for at least 5 minutes. The average of these 3 measurements was used. **Hypertensive patients (%):** 100% **Type of hypertensive patients:** previously treated **Other co-morbid conditions:** smoking, CHD, hyperlipidaemia, or T2DM
Pre-intervention: placebo run-in period: 4 weeks**;** wash-out period: no **Intervention:** CCB – lacidipine: 4 to 6 mg OD or BB – atenolol: 50 to 100 mg OD **Co-intervention:** if BP goal was not achieved, another open-labelled BP-lowering agent was added (hydrochlorothiazide)
Primary outcomes: change in mean maximum Intima media thickness (IMT), plaque number, fatal and non-fatal CV events, total mortality

ELVERA [2004](307;308); **Effects of Amlodipine and Lisinopril on Left Ventricular Mass and Diastolic Function (E/A Ratio)**
Multicentre, randomised controlled, double-blind study **Mean duration of follow-up:** 24 months
Participants N: 166 **Mean baseline BP:** seated 175/92.5 mmHg **Method for BP measurement:** 4 BP measurements were derived from several measurements made on 3 occasions. SBP and DBP were recorded at Korotkoff phase I and V to the nearest 2 mmHg. **Hypertensive patients (%):** 100% **Type of hypertensive patients:** previously untreated **Other co-morbid conditions:** no

Pre-intervention: placebo run-in period: 2 weeks; wash-out period: 8 weeks **Intervention:** ACEI – lisinopril: 10 to 20 mg OD or CCB – amlodipine: 5 to 10 mg OD **Co-intervention:** no other BP-lowering agents were added
Primary outcomes: the change from baseline of the combined mean maximum far wall IMT of carotid and femoral arteries

FACET [1998] (309); **Fosinopril Versus Amlodipine Cardiovascular Events Randomized**
Single-centre, randomised controlled, open-label study **Mean duration of follow-up:** 41 months
Participants N: 380 **Mean baseline BP:** seated 170/95 mmHg **Method for BP measurement:** BP was measured in a standard way on at least 2 consecutive visits with the patient resting for at least 1 minute. **Hypertensive patients (%):** 100% **Type of hypertensive patients:** previously treated **Other co-morbid conditions:** T2DM
Pre-intervention: placebo run-in period: no; wash-out period: 2 weeks **Intervention:** ACEI – fosinopril: 20 mg OD or CCB – amlodipine: 10 mg OD **Co-intervention:** if BP goal was not achieved, the other study drug was added at full dose
Primary outcomes: serum lipids and diabetes control, CV events, BP control, and renal function status

Farsang [2007](310)
Multicentre, randomised controlled, double-blind study **Mean duration of follow-up:** 3 months
Participants N: 303 **Mean baseline BP:** seated 160/101.1 mmHg **Method for BP measurement:** BP readings were taken by a standard mercury sphygmomanometer after 10 minutes of rest. Korotkoff I and V were taken as the SBP and DBP readings, respectively. **Hypertensive patients (%):** 100% **Type of hypertensive patients:** previously treated and untreated **Other co-morbid conditions:** no
Pre-intervention: placebo run-in period: 2 weeks; wash-out period: no **Intervention:** ACEI - zofenopril: 30 to 60 mg OD or CCB - amlodipine: 5 to 10 mg OD **Co-intervention:** no other BP-lowering agents were added
Primary outcomes: BP control and response rate

Fogari [2008](311)
Multicentre, randomised controlled, open blinded endpoint study **Mean duration of follow-up:** 4 months
Participants N: 126 **Mean baseline BP:** seated 170.3/103.9 mmHg **Method for BP measurement:** 3 measurements were taken using a standard mercury sphygmomanometer at 2-minute intervals after the patient had been seated for 10 minutes **Hypertensive patients (%):** 100% **Type of hypertensive patients:** previously treated and untreated **Other co-morbid conditions:** no
Pre-intervention: placebo run-in period: no; wash-out period: 2 weeks **Intervention:** ARB + DI – olmesartan + hydrochlorothiazide: 20 mg OD + 12.5 mg OD or ARB + DI - telmisartan + hydrochlorothiazide: 80 mg OD + 12.5 mg OD **Co-intervention:** no other BP-lowering agents were added
Primary outcomes: drug efficacy

Freytag [2001](312)
Multicentre, randomised controlled, double-blind study **Mean duration of follow-up:** 7 months
Participants N: 533 **Mean baseline BP:** supine 165.8/101.8 mmHg **Method for BP measurement:** according to ASH recommendations **Hypertensive patients (%):** 100% **Type of hypertensive patients:** previously untreated **Other co-morbid conditions**: no

Pre-intervention: placebo run-in period: no; wash-out period: no **Intervention:** ARB - telmisartan: 40 to 80 mg OD or BB - atenolol: 50 to 100 mg OD **Co-intervention:** if BP goal was not achieved, another open-labelled BP-lowering agent was added (hydrochlorothiazide)
Primary outcomes: drug efficacy and tolerability

Giles [2007](313)
Multicentre, randomised controlled, double-blind study **Mean duration of follow-up:** 3 months
Participants N: 723 **Mean baseline BP:** seated 154.6/103.4 mmHg **Method for BP measurement:** BP was determined in triplicate taken at 1-minute intervals after the patients had been sitting in the examination room for 5 minutes **Hypertensive patients (%):** 100% **Type of hypertensive patients**: previously treated and untreated **Other co-morbid conditions:** no
Pre-intervention: placebo run-in period: 4 weeks; wash-out period: no **Intervention:** ARB – losartan: 50 to 100 mg OD, ARB – olmesartan: 20 to 40 mg OD, ARB – valsartan: 80 to 320 mg OD, or P - placebo **Co-intervention:** no other BP-lowering agents were added
Primary outcomes: drug efficacy and tolerability

Grassi [2003](314)
Multicentre, randomised controlled, double-blind study **Mean duration of follow-up:** 3 months
Participants N: 205 **Mean baseline BP:** seated 156.2/100.4 mmHg **Method for BP measurement:** BP was measured by a standard mercury sphygmomanometer using I and V Korotkoff phases to identify SBP and DBP values, respectively. 3 measurements (spaced by 1 to 3-minute intervals) were taken after 5 minutes in the sitting position. **Hypertensive patients (%):** 100% **Type of hypertensive patients:** previously treated and untreated **Other co-morbid conditions:** no
Pre-intervention: placebo run-in period: 4 weeks; wash-out period: 10 days **Intervention:** CCB – nebivolol: 5 mg OD or BB – atenolol: 100 mg OD **Co-intervention:** if BP goal was not achieved, another open-labelled BP-lowering agent was added (hydrochlorothiazide)
Primary outcomes: drug efficacy and tolerability

Greathouse [2010](315)
Multicentre, randomised controlled, double-blind study **Mean duration of follow-up:** 3 months
Participants N: 811 **Mean baseline BP:** seated 151.3/99 mmHg **Method for BP measurement:** BP was measured in a standard way. All measurements were taken in triplicate at 2-minute intervals, and the mean value was calculated. **Hypertensive patients (%):** 100% **Type of hypertensive patients:** previously treated and untreated **Other co-morbid conditions:** no
Pre-intervention: placebo run-in period: 4 to 6 weeks; wash-out period: no **Intervention:** BB – nebivolol: 5 or 10 or 20 mg OD or P - placebo **Co-intervention**: no other BP-lowering agents were added
Primary outcomes: drug efficacy and safety

Guthrie [1998](316)
Multicentre, randomised controlled, double-blind study **Mean duration of follow-up:** 3 months
Participants N: 319 **Mean baseline BP:** seated 148.2/100 mmHg **Method for BP measurement:** BP was measured with a standard mercury sphygmomanometer. Measurements were made in the seated position (after remaining at rest for 5 to 10 minutes) and in the standing position (after standing for 2 minutes). The mean of 3 readings was taken.

Hypertensive patients (%): 100% **Type of hypertensive patients**: previously treated and untreated **Other co-morbid conditions:** no
Pre-intervention: placebo run-in period: 4 to 5 weeks; wash-out period: no **Intervention:** ARB – irbesartan: 75 to 150 or 150 to 300 mg OD or P - placebo **Co-intervention**: no other BP-lowering agents were added
Primary outcomes: drug efficacy and tolerability

Hanefeld [2001](317)
Multicentre, randomised controlled, double-blind study **Mean duration of follow-up:** 3 months
Participants N: 123 **Mean baseline BP:** seated 165.5/97.9 mmHg **Method for BP measurement:** BP was measured after the patient had rested in a sitting position for at least 3 minutes. The mean of 3 measurements was calculated. **Hypertensive patients (%):** 100% **Type of hypertensive patients:** previously treated and untreated **Other co-morbid conditions:** no
Pre-intervention: placebo run-in period: 3 weeks; wash-out period: no **Intervention:** ARB – valsartan: 80 mg OD or P - placebo **Co-intervention:** no other BP-lowering agents were added
Primary outcomes: drug efficacy and safety

Hegner [1997](318)
Multicentre, randomised controlled, double-blind study **Mean duration of follow-up**: 3 months
Participants N: 167 **Mean baseline BP:** seated 165.7/103.4 mmHg **Method for BP measurement:** according to WHO guidelines **Hypertensive patients (%):** 100% **Type of hypertensive patients:** previously treated and untreated **Other co-morbid conditions:** no
Pre-intervention: placebo run-in period: 2 weeks; wash-out period: no **Intervention:** ARB – valsartan: 80 mg OD or DI – hydrochlorothiazide: 25 mg OD **Co-intervention:** if BP goal was not achieved, another open-labelled BP-lowering agent was added (Atenolol)
Primary outcomes: drug efficacy and safety

Hoegholm [1995](319)
Multicentre, randomised controlled, double-blind study **Mean duration of follow-up**: 4 months
Participants N: 118 **Mean baseline BP:** seated 170.3/105 mmHg **Method for BP measurement:** BP was measured after 3 and 5 minutes of rest with a standard sphygmomanometer, and the mean of the 2 measurements was used **Hypertensive patients (%):** 100% **Type of hypertensive patients**: previously treated and untreated **Other co-morbid conditions:** no
Pre-intervention: placebo run-in period: 4 weeks; wash-out period: 4 weeks **Intervention:** CCB – amlodipine: 5 to 10 mg OD or CCB – felodipine: 5 to 20 mg OD **Co-intervention:** no other BP-lowering agents were added
Primary outcomes: drug efficacy and safety

Holzgreve [2003](320)
Multicentre, randomised controlled, double-blind study **Mean duration of follow-up:** 5 months
Participants N: 463 **Mean baseline BP:** seated 168.1/95.5 mmHg **Method for BP measurement:** according to the BHS recommendations **Hypertensive patients (%):** 100% **Type of hypertensive patients:** previously untreated **Other co-morbid conditions:** T2DM

Pre-intervention: placebo run-in period: 2 weeks; wash-out period: no **Intervention:** BB + DI - atenolol + chlorthalidone: 50 to 100 mg OD + 12.5 to 25 mg OD or CCB + ACEI - verapamil + trandolapril: 180 mg OD + 1 to 2 mg OD **Co-intervention:** no other BP-lowering agents were added
Primary outcome: HbA1c after 20 weeks of active treatment **Secondary outcome:** measures were the change in sitting SBP and DBP, the proportions of patients achieving normal BP or responding to BP-lowering agents

HYVET [2008](321;322); Hypertension in the Very Elderly Trial
Multicentre, randomised controlled, double-blind study **Mean duration of follow-up:** 25 months
Participants N: 3,845 **Mean baseline BP:** seated 173.0/90.8 mmHg **Method for BP measurement:** 2 BP measurements were taken during each of 2 visits, 1 month apart, after the patient had been seated for 5 minutes .The BP measurements were recorded with the use of either a mercury sphygmomanometer or a validated automated device, but by the end of the trial, a validated automated device was used. **Hypertensive patients (%):** 100% **Type of hypertensive patients:** previously treated **Other co-morbid conditions:** no
Pre-intervention: placebo run-in period: ≥8 weeks; wash-out period: no **Intervention**: DI – indapamide: 1.5 mg OD or P - placebo **Co-intervention:** if BP goal was not achieved, another BP-lowering agent was added (perindopril)
Primary outcomes: total stroke, total CHD, total mortality, total CV events

HYVET pilot [2003](323); Hypertension in the Very Elderly Trial- pilot
Multicentre, randomised controlled, open-label study **Mean duration of follow-up:** 13 months
Participants N: 1,283 **Mean baseline BP:** seated 181.5/99.6 mmHg **Method for BP measurement:** 2 readings of sitting BP were taken after the patient had rested for 5 minutes. The measurements were repeated 1 month later. The DBP value corresponded to Korotkoff phase V. **Hypertensive patients (%):** 100% **Type of hypertensive patients:** previously treated and untreated **Other co-morbid conditions:** no
Pre-intervention: placebo run-in period: no; wash-out period: ≥ 4 weeks **Intervention:** ACEI – lisinopril: 2.5 mg OD or DI – bendroflumethiazide: 2.5 to 5 mg OD **Co-intervention:** if BP goal was not achieved, another BP-lowering agent was added (diltiazem)
Primary outcomes: total stroke, total mortality, CV mortality, cardiac mortality, SBP and DBP

IDNT [2001](324-326); Irbesartan Diabetic Nephropathy Trial
Multicentre, randomised controlled, double-blind study **Mean duration of follow-up:** 30 months
Participants N: 1,715 **Mean baseline BP:** seated 159/87 mmHg **Method for BP measurement:** BP was measured in a standard way on at least 2 occasions with the patient resting for at least 1 minute. **Hypertensive patients (%):** 76% **Type of hypertensive patients:** previously treated and untreated **Other co-morbid conditions:** T2DM
Pre-intervention: placebo run-in period: no; wash-out period: 10 days **Intervention:** ARB – irbesartan: 300 mg OD or CCB – amlodipine: 10 mg OD or P - placebo **Co-intervention:** if BP goal was not achieved, other open BP-lowering agents were added (excluding ACEI, ARB, and CCB)
Primary outcomes: renal outcomes **Secondary outcomes:** the composite of fatal or non-fatal CVS events, adverse events

INSIGHT [2000](327); International Nifedipine GITS Study Intervention as a Goal in Hypertension Treatment
Multicentre, randomised controlled, double-blind study **Mean duration of follow-up:** 48 months

Participants N: 6,575 **Mean baseline BP:** seated 173.0/99 mmHg **Method for BP measurement:** BP was measured in a standard way on at least 2 occasions, 3 times after the patient had rested for 5 minutes **Hypertensive patients (%):** 100% **Type of hypertensive patients:** previously treated **Other co-morbid conditions:** history of at least 1 CV risk factor (smoking, hyperlipidaemia, history of CHD, LVH, mild to moderate CKD, or PVD)
Pre-intervention: placebo run-in period: 2 to 4 weeks**;** wash-out period: no **Intervention:** CCB – nifedipine: 30 mg OD or DI - amiloride + hydrochlorothiazide: 2.5 mg OD + 25 g OD **Co-intervention:** if BP goal was not achieved, other BP-lowering agents were added (including atenolol and enalapril, excluding CCBs and DIs)
Primary outcomes: CV death, MI, HF, or stroke

INVEST [2003](177;328)
Multicentre, randomised controlled, open blinded endpoint study **Mean duration of follow-up:** 31 months
Participants N: 22,576 **Mean baseline BP:** seated 149.5/86.3 mmHg **Method for BP measurement:** according to JNC guidelines for HTN **Hypertensive patients (%)**: 100% **Type of hypertensive patients:** previously treated and untreated **Other co-morbid conditions:** clinical evidence of CHD
Pre-intervention: placebo run-in period: no; wash-out period: no **Intervention:** CCB - verapamil: 240 mg OD or BB - atenolol: 50 mg OD **Co-intervention:** if BP goal was not achieved, other BP-lowering agents were added (including trandolapril and hydrochlorothiazide)
Primary outcomes: the first occurrence of death from any cause, non-fatal MI, or non-fatal stroke **Secondary outcomes:** all-cause death, non-fatal MI, non-fatal stroke, CV death, angina, CV hospitalisations, BP control, cancer, Alzheimer's disease, Parkinson's disease, gastro-intestinal bleeding

James [2002](329)
Single-centre, randomised controlled, double-blind study **Mean duration of follow-up:** 4 months
Participants N: 465 **Mean baseline BP:** supine 165.3/102.3 mmHg **Method for BP measurement:** BP was measured using a standard mercury sphygmomanometer at least 2 times after the patient had been in a supine position for at least 5 minutes. **Hypertensive patients (%):** 100% **Type of hypertensive patients:** previously treated and untreated **Other co-morbid conditions:** no
Pre-intervention: placebo run-in period: 4 weeks; wash-out period: no **Intervention:** ARB – losartan: 50 to 100 mg OD or CCB – lercanidipine: 10 to 20 mg OD **Co-intervention:** no other BP-lowering agents were added
Primary outcomes: drug efficacy and tolerability

JMIC-B [2004](330)**; Japan Multicenter Investigation for Cardiovascular Diseases-B**
Multicentre, randomised controlled, open blinded endpoint study **Mean duration of follow-up:** 36 months
Participants N: 1,836 **Mean baseline BP:** seated/supine 146/82 mmHg **Method for BP measurement:** BP was measured 3 times, and the average of the last 2 readings was calculated. Measurement was done with the patient in the sitting or supine position (whichever had been decided upon initially). **Hypertensive patients (%):** 100% **Type of hypertensive patients:** previously treated **Other co-morbid conditions:** clinical evidence or history of CHD
Pre-intervention: placebo run-in period: no; wash-out period: no

Intervention: ACEI - enalapril, imidapril, or lisinopril: 5 to 10 mg OD, 5 to 10 mg OD, or 10 to 20 mg OD, or CCB – nifedipine: 10 to 20 mg Twice-daily (BID) **Co-intervention:** if BP goal was not achieved, other BP-lowering agents were added (alpha blockers, doxazosin, bunazosin, or prazosin)
Primary outcomes: Cardiac death, acute MI, hospitalisations for angina pectoris or HF, and coronary revascularisation

LAARS [2002](331); Losartan Vascular Regression Study
Multicentre, randomised controlled, double-blind study **Mean duration of follow-up:** 24 months
Participants N: 280 **Mean baseline BP:** seated 159.5/100.9 mmHg **Method for BP measurement:** several measurements were taken after 5 minutes of rest, and the mean of the last 3 sitting DBP measurements was calculated until each of the final 3 individual measurements did not deviate by > 5 mmHg from the calculated mean of the 3 measurements **Hypertensive patients (%):** 100% **Type of hypertensive patients**: previously treated and untreated **Other co-morbid conditions**: ultrasonographically proven thickening of the IMT of the common carotid artery
Pre-intervention: placebo run-in period: 2 weeks; wash-out period: 1 week **Intervention:** ARB – losartan: 50 to 100 mg OD or BB – atenolol: 50 to 100 mg OD **Co-intervention:** if BP goal was not achieved, another BP-lowering agent was added (including hydrochlorothiazide and open-labelled CCBs)
Primary outcomes: IMT of CCA

LIFE [2002](332;333); Losartan Interventionfor Endpoint Reduction in Hypertension
Multicentre, randomised controlled, double-blind study **Mean duration of follow-up:** 56 months
Participants N: 9,193 **Mean baseline BP:** seated 174.4/97.8 mmHg **Method for BP measurement:** BP was measured according to standardised procedures at least 2 times after subjects had been seated for 5 minutes **Hypertensive patients (%):** 100% **Type of hypertensive patients:** previously treated and untreated **Other co-morbid conditions:** history of LVH
Pre-intervention: placebo run-in period: 1 to 2 weeks; wash-out period: no **Intervention:** ARB – losartan: 50 to 100 mg OD; BB – atenolol: 50 to 100 mg OD **Co-intervention:** if BP goal was not achieved, another BP-lowering agent was added (including hydrochlorothiazide and excluding ACEIs, ARBs, and BB)
Primary Outcomes: CVD mortality and mortality (composite endpoint of CV death, MI and stroke) **Secondary Outcomes:** total mortality, angina pectoris or CHF requiring hospital admission

LOTHAR [2006](334); Amlodipino e Losartana no Tratamento da Hipertensão Arterial
Multicentre, randomised controlled, double-blind study **Mean duration of follow-up:** 3 months
Participants N: 198 **Mean baseline BP:** seated 156.3/99.7 mmHg **Method for BP measurement:** BP recorded represents the mean of 3 consecutive measurements obtained with a mercury sphygmomanometer following a 5-minute rest in the sitting position **Hypertensive patients (%):** 100% **Type of hypertensive patients:** previously treated and untreated **Other co-morbid conditions:** no
Pre-intervention: placebo run-in period: no; wash-out period: 3 weeks **Intervention:** ARB - losartan: 50 to 100 mg OD or CCB - amlodipine: 5 to 10 mg OD **Co-intervention:** no other BP-lowering agents were added
Primary outcomes: drug efficacy and tolerability, metabolic effects

Luque [2005](335)
Multicentre, randomised controlled, double-blind study **Mean duration of follow-up:** 6 months
Participants N: 111 **Mean baseline BP:** seated 163.5/97.5 mmHg

Method for BP measurement: Measurements were taken after the patient had rested for 10 minutes. SBP and DBP were measured with a mercury sphygmomanometer at the time of phase I and phase V Korotkoff sounds, respectively. **Hypertensive patients (%):** 100% **Type of hypertensive patients:** previously treated and untreated **Other co-morbid conditions:** T2DM
Pre-intervention: placebo run-in period: 3 weeks; wash-out period: no **Intervention:** ACEI – enalapril: 10 to 20 mg OD or CCB – manidipine: 10 to 20 mg OD **Co-intervention:** no other BP-lowering agents were added
Primary outcomes: drug efficacy and tolerability, and effect on metabolic risk factors

MAISH [2007] (336); Manidipine versus Amlodipine in Elderly Subjects with Isolated Systolic Hypertention
Multicentre, randomised controlled, double-blind study **Mean duration of follow-up:** 3 months
Participants N: 195 **Mean baseline BP:** seated 159.1/81.9 mmHg **Method for BP measurement:** 3 measurements, using a standard sphygmomanometer, were taken at 5-minute intervals after 10 minutes of rest in the sitting position. SBP and DBP values were taken at the time of phase I and phase V Korotkoff sounds, respectively. **Hypertensive patients (%):** 100% **Type of hypertensive patients:** previously treated and untreated **Other co-morbid conditions**: no
Pre-intervention: placebo run-in period: 2 weeks; wash-out period: no **Intervention:** CCB - amlodipine: 5 to 10 mg OD or CCB - manidipine: 10 to 20 mg OD **Co-intervention:** if BP goal was not achieved, another BP-lowering agent was added (chlortalidone)
Primary outcomes: drug efficacy and safety

Mallion [2000](337)
Multicentre, randomised controlled, double-blind study **Mean duration of follow-up:** 3 months
Participants N: 446 **Mean baseline BP:** supine 163.3/100.7 mmHg **Method for BP measurement:** BP was measured with a standard mercury sphygmomanometer (DBP = Korotkoff phase V) with 3 readings after 10 minutes of rest **Hypertensive patients (%):** 100% **Type of hypertensive patients:** previously treated and untreated **Other co-morbid conditions:** no
Pre-intervention: placebo run-in period: 4 weeks; wash-out period: no **Intervention:** ACEI + DI - perindopril + indapamide: 2 mg OD + 0.625 mg OD or BB - atenolol: 50 mg OD **Co-intervention:** no other BP-lowering agents were added
Primary outcomes: drug efficacy and safety

Mallion [2007](338)
Multicentre, randomised controlled, double-blind study **Mean duration of follow-up:** 6 months
Participants N: 382 **Mean baseline BP:** seated 107.7/82.5 mmHg **Method for BP measurement:** 3 measurements were taken using a standard sphygmomanometer at 5-minute intervals after 10 minutes of rest. SBP and DBP values were taken at the time of phase I and phase V Korotkoff sounds, respectively. **Hypertensive patients (%):** 100% **Type of hypertensive patients:** previously untreated **Other co-morbid conditions:** no
Pre-intervention: placebo run-in period: 2 weeks; wash-out period: 1 to 2 weeks **Intervention:** ARB – olmesartan: 20 to 40 mg OD or CCB – nitrendipine: 10 to 20 mg OD **Co-intervention:** if BP goal was not achieved, another BP-lowering agent was added (hydrochlorothiazide)
Primary outcomes: drug efficacy and safety

Mallion [2011](339)
Multicentre, randomised controlled, double-blind study **Mean duration of follow-up:** 3 months
Participants N: 351 **Mean baseline BP:** seated 160.5/94.5 mmHg **Method for BP measurement:** 3 measurements were taken using a standard sphygmomanometer at 2-minute intervals after 5 minutes of rest. SBP and DBP values were taken at the time of the phase I and phase V Korotkoff sounds, respectively. **Hypertensive patients (%):** 100% **Type of hypertensive patients:** previously treated and untreated **Other co-morbid conditions:** no
Pre-intervention: placebo run-in period: 2 weeks; wash-out period: no **Intervention:** ARB - olmesartan: 10 to 40 mg OD or ACEI - ramipril: 2.5 to 10 mg OD **Co-intervention:** no other BP-lowering agents were added
Primary outcomes: drug efficacy and safety

Mancia [2000](340)
Multicentre, randomised controlled, double-blind study **Mean duration of follow-up:** 6 months
Participants N: 101 **Mean baseline BP:** seated 160/99.5 mmHg **Method for BP measurement:** BP was measured twice at 3-minute intervals after 5 minutes of rest using a mercury sphygmomanometer. SBP and DBP values were taken at the time of phase I and phase V Korotkoff sounds, respectively. **Hypertensive patients (%):** 100% **Type of hypertensive patients:** previously treated and untreated **Other co-morbid conditions:** T2DM
Pre-intervention: placebo run-in period: 3 weeks; wash-out period: no **Intervention:** ACEI – Enalapril: 10 to 20 mg OD or CCB – Manidipine: 10 to 20 mg OD **Co-intervention:** no other BP-lowering agents were added
Primary outcomes: drug efficacy

MAPAVEL [2002](341)**; Monitorización Ambulatoria Presión Arterial aproVEL**
Multicentre, randomised controlled, double-blind study **Mean duration of follow-up:** 3 months
Participants N: 238 **Mean baseline BP:** seated 159.3/101.8 mmHg **Method for BP measurement:** BP measurements, using mercury sphygmomanometer, were taken after patient had rested for 10 minutes. Three successive readings were obtained at 3-minute intervals. DBP was recorded at the disappearance of the Korotkoff sounds (phase V). The mean of the 3 values was recorded. **Hypertensive patients (%):** 100% **Type of hypertensive patients:** previously treated and untreated **Other co-morbid conditions:** no
Pre-intervention: placebo run-in period: 3 weeks; wash-out period: no **Intervention:** ACEI – enalapril: 20 mg OD or ARB – irbesartan: 300 mg OD **Co-intervention:** no other BP-lowering agents were added
Primary outcomes: drug efficacy and safety

McInnes [2000](342)
Multicentre, randomised controlled, double-blind study **Mean duration of follow-up:** 6.2 months
Participants N: 355 **Mean baseline BP:** seated 165.3/102.4 mmHg **Method for BP measurement:** measurements were taken using a fully automated device. Sitting BP was recorded 3 times at least 2 minutes apart after the patient had rested for at least 5 minutes. **Hypertensive patients (%):** 100% **Type of hypertensive patients:** previously treated and untreated **Other co-morbid conditions:** no
Pre-intervention: placebo run-in period: no; wash-out period: no **Intervention:** ACEI + DI - lisinopril + hydrochlorothiazide: 10 mg OD + 12.5 mg OD or

ARB + DI - candesartan + hydrochlorothiazide: 8 mg OD + 12.5 mg OD **Co-intervention:** no other BP-lowering agents were added
Primary outcomes: drug efficacy and tolerability

MIDAS [1996](343); Multicenter Isradipine Diuretic Atherosclerosis Study
Multicentre, randomised controlled, double-blind study **Mean duration of follow-up:** 36 months
Participants N: 883 **Mean baseline BP:** seated 149.7/96.4 mmHg **Method for BP measurement:** BP was measured in a standard way on at least 2 occasions with the patient resting for at least 1 minute. **Hypertensive patients (%):** 100% **Type of hypertensive patients**: previously treated **Other co-morbid conditions:** hyperlipidaemia, ultrasonographically proven thickening of IMT of common carotid artery
Pre-intervention: placebo run-in period: 3 to 8 weeks; wash-out period: no **Intervention:** CCB – isradipine: 2.5 to 5.0 mg BID or DI – hydrochlorothiazide: 12.5 to 25 mg BID **Co-intervention**: if BP goal was not achieved, another open-labelled BP-lowering agent was added (enalapril)
Primary outcomes: mean maximum IMT and some other findings of carotid artery, and vascular events/procedures

Mimran [1998](344)
Multicentre, randomised controlled, double-blind study **Mean duration of follow-up:** 3 months
Participants N: 200 **Mean baseline BP:** seated 164.4/101.4 mmHg **Method for BP measurement:** BP was measured with a standard Mercury sphygmomanometer. The mean of 3 readings taken 1 minute apart was calculated. **Hypertensive patients (%):** 100% **Type of hypertensive patients:** previously treated and untreated **Other co-morbid conditions:** no
Pre-intervention: placebo run-in period: 4 to 5 weeks; wash-out period: no **Intervention:** ACEI – enalapril: 10 to 20 mg OD or ARB – irbesartan: 57 to 150 mg OD **Co-intervention**: no other BP-lowering agents were added
Primary outcomes: drug efficacy, safety, and tolerability

Mounier-Vehier [1998](345)
Multicentre, randomised controlled, open-label study **Mean duration of follow-up:** 3 months
Participants N: 103 **Mean baseline BP:** seated 166.1/101.9 mmHg **Method for BP measurement:** BP was measured using a conventional mercury sphygmomanometer. Two readings were taken and the higher of the 2 was recorded. The first reading was taken after 10 minutes of rest, and Korotkoff phase I and phase V sounds were used to determine the values of SBP and DBP, respectively. **Hypertensive patients (%):** 100% **Type of hypertensive patients:** previously treated and untreated **Other co-morbid conditions:** no
Pre-intervention: placebo run-in period: no; wash-out period: 2 weeks **Intervention:** CCB – amlodipine: 5 to 10 mg OD or CCB – nifedipine: 20 mg BID **Co-intervention:** no other BP-lowering agents were added
Primary outcomes: drug compliance and efficacy

Mroczek [1996](346;346)
Multicentre, randomised controlled, double-blind study **Mean duration of follow-up:** 3 months
Participants N: 200 **Mean baseline BP:** seated 153.6/101.5 mmHg **Method for BP measurement:** Korotkoff sounds I and V, using a calibrated Mercury sphygmomanometer, were recorded as the SBP and DBP, respectively. Three readings were taken 1 minute apart after the patient had been seated for a minimum of 5 minutes.

Hypertensive patients (%): 100% **Type of hypertensive patients:** previously treated and untreated **Other co-morbid conditions:** no
Pre-intervention: placebo run-in period: 4 weeks; wash-out period: no **Intervention:** ACEI – moexipril: 7.5 or 15 mg OD, DI – hydrochlorothiazide: 25 mg OD, or P - Placebo **Co-intervention:** no other BP-lowering agents were added
Primary outcomes: drug efficacy and safety

Narkiewicz [2007](347)
Multicentre, randomised controlled, double-blind study **Mean duration of follow-up:** 3 months
Participants N: 327 **Mean baseline BP:** seated 158/98.9 mmHg **Method for BP measurement:** BP readings were taken after 10 minutes of rest in a supine position. BP readings were obtained by standard mercury sphygmomanometry. The SBP corresponded to Korotkoff phase I and the DBP corresponded at Korotkoff phase V. **Hypertensive patients (%):** 100% **Type of hypertensive patients:** previously treated and untreated **Other co-morbid conditions:** no
Pre-intervention: placebo run-in period: no; wash-out period: no **Intervention:** ACEI – zofenopril: 30 to 60 mg OD or ARB – losartan: 50 to 100 mg OD **Co-intervention:** no other BP-lowering agents were added
Primary outcomes: drug efficacy and office BP

NICE-EH [1999](348); National Intervention Cooperative Study in Elderly Hypertensives
Multicentre, randomised controlled, double-blind study **Mean duration of follow-up:** 60 months
Participants N: 429 **Mean baseline BP:** seated 172.3/93.8 mmHg **Method for BP measurement:** BP was measured in a standard way on at least 2 occasions with the patient resting for at least 1 minute. **Hypertensive patients (%)**: >70% **Type of hypertensive patients:** previously treated and untreated **Other co-morbid conditions:** no
Pre-intervention: placebo run-in period: 4 weeks; wash-out period: 2 weeks **Intervention:** CCB – nicardipine: 20 mg SR OD or DI – trichlormethiazide: 2 mg OD **Co-intervention:** no other BP-lowering agents were added
Primary outcomes: CV complications

Nilsson [2007](349)
Multicentre, randomised controlled, double-blind study **Mean duration of follow-up:** 3 months
Participants N: 304 **Mean baseline BP:** seated 155.2/100.4 mmHg **Method for BP measurement:** BP readings were taken using a standard mercury sphygmomanometer with the patient resting for at least 1 minute. The SBP corresponded to Korotkoff phase I and the DBP corresponded at Korotkoff phase V. **Hypertensive patients (%):** 100% **Type of hypertensive patients:** previously treated and untreated **Other co-morbid conditions:** no
Pre-intervention: placebo run-in period: no; wash-out period: no **Intervention:** ACEI – zofenopril: 30 to 60 mg OD **or** BB – atenolol: 50 to 100 mg OD **Co-intervention:** no other BP-lowering agents were added
Primary outcomes: drug efficacy

NORDIL [2000](163;164)
Multicentre, randomised controlled, open blinded endpoint study **Mean duration of follow-up:** 53 months
Participants N: 10,881 **Mean baseline BP:** supine 173.4/105.7 mmHg

Method for BP measurement: BP was measured in a standard way on at least 2 occasions with the patient resting for at least 1 minute. **Hypertensive patients (%):** 100% **Type of hypertensive patients:** previously treated and untreated **Other co-morbid conditions:** no
Pre-intervention: placebo run-in period: no; wash-out period: 1 week **Intervention:** CCB – diltiazem: 180 to 360 mg OD or conventional BP-lowering agents (DI or BB) or both **Co-intervention:** if BP goal was not achieved, another BP-lowering agent was added
Primary outcomes: stroke, MI, and other CV death **Secondary endpoints:** total mortality and development or deterioration of CHD, CHF, AF, TIA, T2DM and RF.

Oparil [1998](350)
Multicentre, randomised controlled, double-blind study **Mean duration of follow-up:** 3 months
Participants N: 432 **Mean baseline BP:** seated 155/101 mmHg **Method for BP measurement:** BP was measured with a mercury sphygmomanometer after the patient had rested for 10 minutes. 3 measurements were taken at least 1 minute apart. **Hypertensive patients (%):** 100% **Type of hypertensive patients:** previously treated and untreated **Other co-morbid conditions:** no
Pre-intervention: placebo run-in period: 3 weeks; wash-out period: no **Intervention:** ARB - losartan: 50 to 100 mg OD or ARB - irbesartan: 150 to 300 mg OD **Co-intervention:** if BP goal was not achieved, another BP-lowering agent was added (hydrochlorothiazide)
Primary outcomes: drug efficacy, safety, and tolerability

Os [1997](351)
Multicentre, randomised controlled, triple-blind study **Mean duration of follow-up:** 3 months
Participants N: 374 **Mean baseline BP:** seated 159.5/102.6 mmHg **Method for BP measurement:** BP (Korotkoff phase V) was measured using a standard mercury sphygmomanometer after the patient rested in a sitting position for 5 minutes in triplicate with 1 minute between the measurements **Hypertensive patients (%):** 100% **Type of hypertensive patients:** previously treated and untreated **Other co-morbid conditions:** no
Pre-intervention: placebo run-in period: 4 weeks; wash-out period: no **Intervention:** ACEI + DI - enalapril + hydrochlorothiazide: 20 mg OD + 6 mg OD or BB – atenolol: 50 mg OD **Co-intervention:** no other BP-lowering agents were added
Primary outcomes: drug efficacy and tolerability

Papademetriou [1997](352)
Multicentre, randomised controlled, double-blind study **Mean duration of follow-up:** 6 months
Participants N: 159 **Mean baseline BP:** seated 159.5/101 mmHg **Method for BP measurement:** according to AHA guidelines **Hypertensive patients (%):** 100% **Type of hypertensive patients:** previously treated and untreated **Other co-morbid conditions:** LVH
Pre-intervention: placebo run-in period: 2 weeks; wash-out period: no **Intervention:** CCB – isradipine: 2.5 to 10 mg BID or DI – hydrochlorothiazide: 25 to 50 mg OD **Co-intervention:** no other BP-lowering agents were added
Primary outcomes: LVM and wall thickness

Pareek [2010](353)
Multicentre, randomised controlled, double-blind study

Mean duration of follow-up: 3 months
Participants N: 148 **Mean baseline BP:** seated 160.2/99.4 mmHg **Method for BP measurement**: BP measurements were taken after 10 minutes of rest in duplicate separated by 2 minutes, with the average measurement being taken **Hypertensive patients (%):** 100% **Type of hypertensive patients:** previously treated and untreated **Other co-morbid conditions:** no
Pre-intervention: Placebo run-in period: 1 week; wash-out period: no **Intervention:** ARB + CCB - losartan + amlodipine: 25 to 50 mg OD + 2.5 to 5 mg OD or BB + CCB - metoprolol + amlodipine: 25 to 50 mg OD + 2.5 to 5 mg OD **Co-intervention:** no other BP-lowering agents were added
Primary outcomes: drug efficacy and tolerability

PATS [1995](354); Post-stroke Antihypertensive Treatment Study
Multicentre, randomised controlled, double-blind study **Mean duration of follow-up:** 36 months
Participants N: 5,665 **Mean baseline BP**: seated 154/93 mmHg **Method for BP measurement**: BP (phase V DBP) was measured and repeated after a 5-minute rest in a sitting position. The mean of the 4 readings of sitting BP was taken as the baseline BP. **Hypertensive patients (%):** 84% **Type of hypertensive patients:** previously treated **Other co-morbid conditions**: history of CVE
Pre-intervention: Placebo run-in period: 2 weeks; wash-out period: no **Intervention:** DI – indapamide: 2.5 mg OD or P - placebo **Co-intervention:** no other BP-lowering agents were added
Primary outcomes: mortality, stroke, CHD, and BP

PRESERVE [2001](355); Prospective Randomized Enalapril Study Evaluating Regression of Ventricular Enlargement
Multicentre, randomised controlled, double-blind study **Mean duration of follow-up:** 12 months
Participants N: 303 **Mean baseline BP:** seated 171.5/97.9 mmHg **Method for BP measurement:** BP was measured in a standard way on at least 2 occasions with the patient resting for at least 1 minute. **Hypertensive patients (%):** 100% **Type of hypertensive patients:** previously treated and untreated **Other co-morbid conditions:** no
Pre-intervention: placebo run-in period: ≥1 weeks; wash-out period: no **Intervention:** ACEI – enalapril: 10 to 20 mg OD or CCB – nifedipine: 30 to 60 mg OD **Co-intervention**: if BP goal was not achieved, another BP-lowering agent was added (Hydrochlorothiazide and Atenolol)
Primary outcomes: LVH and diastolic filling in HTN

RACE [1995](356); Ramipril Cardioprotective Evaluation
Multicentre, randomised controlled, open blinded endpoint study **Mean duration of follow-up:** 6 months
Participants N: 193 **Mean baseline BP:** seated 163.7/103.2 mmHg **Method for BP measurement:** 3 BP measurements (Korotkoff phase V for DBP) were taken using a mercury sphygmomanometer after 10 minutes of sitting, and the average value was recorded **Hypertensive patients (%):** 100% **Type of hypertensive patients:** previously treated and untreated **Other co-morbid conditions**: LVH
Pre-intervention: placebo run-in period: 2 weeks; wash-out period: 4 weeks **Intervention:** ACEI – ramipril: 2.5 to 5 mg OD or BB – atenolol: 50 to 100 mg OD **Co-intervention:** if BP goal was not achieved, another BP-lowering agent was added (furosemide or hydrochlorothiazide)
Primary outcomes: LVM

Radauceanu [2004](357)
Multicentre, randomised controlled, double-blind study **Mean duration of follow-up:** 3 months
Participants N: 246 **Mean baseline BP:** seated 156.3/99 mmHg **Method for BP measurement**: according to WHO guidelines **Hypertensive patients (%):** 100% **Type of hypertensive patients:** previously treated and untreated **Other co-morbid conditions:** no
Pre-intervention: placebo run-in period: 4 weeks; wash-out period: no **Intervention:** ARB – valsartan: 40 to 80 mg OD or CCB – amlodipine: 5 to 10 mg OD **Co-intervention:** no other BP-lowering agents were added
Primary outcomes: drug efficacy and safety

REGAAL [2002](358); Losartan Left Ventricular Hypertrophy Regression
Multicentre, randomised controlled, double-blind study **Mean duration of follow-up:** 9 months
Participants N: 225 **Mean baseline BP:** seated 148.5/98.5 mmHg **Method for BP measurement:** SBP and DBP were measured using a standard mercury sphygmomanometer after 5 minutes of rest. The means of 3 consecutive measurements at 2 to 3-minute intervals were used. **Hypertensive patients (%):** 100% **Type of hypertensive patients:** previously treated and untreated **Other co-morbid conditions:** LVH
Pre-intervention: placebo run-in period: 2 to 4 weeks; wash-out period: no **Intervention:** ARB – losartan: 50 to 100 mg OD or BB – atenolol: 50 to 100 mg OD **Co-intervention:** if BP goal was not achieved, another BP-lowering agent was added (hydrochlorothiazide)
Primary outcomes: changes in LVM index and sitting BP after treatment

REZALT [2009](359)
Multicentre, randomised controlled, double-blind study **Mean duration of follow-up:** 3 months
Participants N: 867 **Mean baseline BP:** seated 154.2/97.3 mmHg **Method for BP measurement:** BP was measured using a mercury sphygmomanometer. BP was measured 3 times at 1 or 2-min intervals; the mean value of these 3 measurements was used. **Hypertensive patients (%):** 100% **Type of hypertensive patients:** previously treated and untreated **Other co-morbid conditions:** no
Pre-intervention: placebo run-in period: 4 weeks; wash-out period: no **Intervention:** ARB – olmesartan: 20 mg OD or CCB – azelnidipine: 16 mg OD **Co-intervention:** no other BP-lowering agents were added
Primary outcomes: drug efficacy and safety

Ruilope [2001](360)
Multicentre, randomised controlled, double-blind study **Mean duration of follow-up:** 3 months
Participants N: 334 **Mean baseline BP:** seated 175.5/74.5 mmHg **Method for BP measurement:** BP was measured using a mercury sphygmomanometer after the patient had been sitting for at least 5 minutes. BP was measured 3 times at intervals of approximately 2 minutes, and the readings were averaged. **Hypertensive patients (%):** 100% **Type of hypertensive patients:** previously treated and untreated **Other co-morbid conditions:** no
Pre-intervention: placebo run-in period: 3 to 4 weeks; wash-out period: no **Intervention:** ACEI – enalapril: 5 to 20 mg OD or ARB – eprosartan: 600 to 800 mg OD **Co-intervention**: no other BP-lowering agents were added
Primary outcomes: drug efficacy and safety

SHELL [2003](361); **Systolic Hypertension in the Elderly Long-term Lacidipine**
Multicentre, randomised controlled, double-blind study **Mean duration of follow-up:** 60 months
Participants N: 1,882 **Mean baseline BP:** seated 178.1/86.8 mmHg **Method for BP measurement:** BP values were based on the average of 3 sphygmomanometric measurements obtained after 5 minutes of rest. The SBP corresponded to Korotkoff phase I and the DBP corresponded at Korotkoff phase V. **Hypertensive patients (%):** 100% **Type of hypertensive patients:** previously treated **Other co-morbid conditions:** no
Pre-intervention: placebo run-in period: no; wash-out period: 15 days **Intervention:** CCB – lacidipine: 4 mg OD or DI – chlorthalidone: 12.5 mg OD **Co-intervention:** if BP goal was not achieved, another BP-lowering agent was added (fosinopril or any ACEIs)
Primary outcomes: composite of CV and CVE including stroke, sudden death, MI, and CHF

Stimpel [1997](362)
Single-centre, randomised controlled, double-blind study **Mean duration of follow-up:** 3 months
Participants N: 140 **Mean baseline BP:** seated 161.2/101.6 mmHg **Method for BP measurement:** the mean of 3 sitting readings taken 1 minute apart was used **Hypertensive patients (%)**: 100% **Type of hypertensive patients:** previously treated and untreated **Other co-morbid conditions:** no
Pre-intervention: placebo run-in period: 4 weeks; wash-out period: no **Intervention:** ACEI + DI - moexipril + hydrochlorothiazide: 7.5 mg OD + 12.5 mg OD or BB + DI - metoprolol + hydrochlorothiazide: 100 mg OD + 12.5 mg OD **Co-intervention:** no other BP-lowering agents were added
Primary outcomes: drug efficacy and safety

Syst-Eur [1997](363;364)**; Systolic Hypertension in Europe**
Multicentre, randomised controlled, triple-blind study **Mean duration of follow-up:** 29 months
Participants N: 4,695 **Mean baseline BP:** seated 173.8/85.5 mmHg **Method for BP measurement:** according to BHS guidelines **Hypertensive patients (%):** 100% **Type of hypertensive patients:** previously treated **Other co-morbid conditions:** no
Pre-intervention: placebo run-in period: 12 weeks; wash-out period: no **Intervention:** CCB – nitrendipine: 10 mg OD or BID, 20 mg BID, or P - placebo **Co-intervention:** if BP goal was not achieved, another BP-lowering agent was added (enalapril and hydrochlorothiazide)
Primary outcomes: mortality, stroke, CHD, CHF, and BP

UKPDS [1998](365;366)**; United Kingdom Prospective Diabetes Study**
Multicentre, randomised controlled, open-label study **Mean duration of follow-up:** 100 months
Participants N: 1,148 **Mean baseline BP:** seated 159/93 mmHg **Method for BP measurement:** BP was measured in a standard way at least 2 times with the patient resting for at least 5 minutes **Hypertensive patients (%):** 100% **Type of hypertensive patients:** previously treated and untreated **Other co-morbid conditions:** smoking
Pre-intervention: placebo run-in period: no; wash-out period: no **Intervention:** ACEI – captopril: 25 to 50 mg BID or BB – atenolol: 50 to 100 mg OD **Co-intervention:** if BP goal was not achieved, another BP-lowering agent was added (frusemide, nifedipine, methyldopa, or prazosin); if possible, ACEIs and BBs were avoided
Primary outcomes: mortality, stroke, CHD and CHF, SBP and DBP

Value [2004](367;368); **Valsartan Antihypertensive Long-term Use Evaluation**
Multicentre, randomised controlled, double-blind study **Mean duration of follow-up:** 50 months
Participants N: 15,245 **Mean baseline BP:** seated 154.6/87.5 mmHg **Method for BP measurement:** BP was recorded in a standard way at least 2 times after patients had been seated for 5 minutes **Hypertensive patients (%):** 100% **Type of hypertensive patients:** previously treated and untreated **Other co-morbid conditions:** smoking, hyperlipidaemia, T2DM, LVH, mild to moderate CKD
Pre-intervention: placebo run-in period: no; wash-out period: no **Intervention**: ARB – valsartan: 80 -160 mg OD or CCB – amlodipine: 5-10 mg OD **Co-intervention:** if BP goal was not achieved, another BP-lowering agent was added (excluding ARBs)
Primary outcomes: time to first CV event; incidence of MI, HF and stroke; all-cause mortality; and new-onset diabetes

VHAS [1998](47;369)
Multicentre, randomised controlled, double-blind study **Mean duration of follow-up:** 48 months
Participants N: 1,414 **Mean baseline BP:** seated 167.6/102.3 mmHg **Method for BP measurement:** BP measurements were obtained at each visit from the same arm using Korotkoff phases I and V for the SBP and DBP, respectively. Before the assessment the patient was asked to rest seated for a minimum of 10 minutes. **Hypertensive patients (%):** 100% **Type of hypertensive patients**: previously treated **Other co-morbid conditions**: no
Pre-intervention: placebo run-in period: 3 weeks; wash-out period: no **Intervention:** CCB – verapamil: 240 mg SR OD or DI – chlorthalidone: 25 mg OD **Co-intervention:** if BP goal was not achieved, another BP-lowering agent was added (including captopril)
Primary outcomes: BP reduction, heart rate, clinical safety, CV events, deaths, and IMT

Volpe [2003](370)
Multicentre, randomised controlled, open blinded endpoint study **Mean duration of follow-up:** 4.2 months
Participants N: 857 **Mean baseline BP:** seated 171.7/82.5 mmHg **Method for BP measurement:** according to AHA guidelines **Hypertensive patients (%):** 100% **Type of hypertensive patients:** previously treated and untreated **Other co-morbid conditions**: no
Pre-intervention: placebo run-in period: 4 weeks; wash-out period: no **Intervention:** ARB – losartan: 50 to 100 mg OD or CCB – amlodipine: 5 to 10 mg OD **Co-intervention:** if BP goal was not achieved, another BP-lowering agent was added (hydrochlorothiazide)
Primary outcomes: drug efficacy and tolerability

Waeber [1999](371)
Multicentre, randomised controlled, double-blind study **Mean duration of follow-up:** 3 months
Participants N: 946 **Mean baseline BP:** seated 157.6/101 mmHg **Method for BP measurement;** measurements were taken using a mercury sphygmomanometer in duplicate, with at least a 1-minute interval in between, to the nearest 2 mmHg. The mean of the 2 readings was then calculated. **Hypertensive patients (%):** 100% **Type of hypertensive patients:** previously treated and untreated **Other co-morbid conditions**: no

Pre-intervention: placebo run-in period: 4 weeks; wash-out period: no **Intervention:** ACEI – enalapril: 10 to 20 mg OD or CCB + BB - felodipine + metoprolol: 5 to 10 mg OD + 50 to 100 mg OD or P - placebo **Co-intervention:** no other BP-lowering agents were added
Primary outcomes: drug efficacy and tolerability

Wu [2004](372)
Multicentre, randomised controlled, open-label study **Mean duration of follow-up:** 3 months
Participants N: 121 **Mean baseline BP:** seated 153.2/99.2 mmHg **Method for BP measurement:** BP was measured using a mercury sphygmomanometer twice, 5 minutes apart, and then the average was recorded **Hypertensive patients (%):** 100% **Type of hypertensive patients:** previously treated and untreated **Other co-morbid conditions**: no
Pre-intervention: placebo run-in period: no; wash-out period: 2 weeks **Intervention:** ARB – losartan: 50 to 100 mg OD or CCB – amlodipine: 5 to 10 mg OD **Co-intervention:** no other BP-lowering agents were added
Primary outcomes: drug efficacy and tolerability

Yang [2015](373)
Single-centre, randomised controlled, open-label study **Mean duration of follow-up:** 3 months
Participants N: 180 **Mean baseline BP:** seated 170/101.5 mmHg **Method for BP measurement:** BP measurements were taken 3 times using a mercury sphygmomanometer after the patient had rested for at least 5 minutes **Hypertensive patients (%):** 100% **Type of hypertensive patients:** previously treated and untreated **Other co-morbid conditions**: no
Pre-intervention: placebo run-in period: no; wash-out period: no **Intervention:** ACEI – perindopril: 4 mg OD or CCB – lercanidipine: 10 mg OD **Co-intervention:** no other BP-lowering agents were added
Primary outcomes: drug efficacy and safety

Zanchetti [2001](374)
Multicentre, randomised controlled, double-blind study **Mean duration of follow-up:** 12 months
Participants N: 489 **Mean baseline BP:** seated 158.1/101.3 mmHg **Method for BP measurement**: 3 measurements were taken using a standard sphygmomanometer at 2-minute intervals after 5 minutes of rest. SBP and DBP values corresponded to the phase I and phase V Korotkoff sounds, respectively. **Hypertensive patients (%):** 100% **Type of hypertensive patients:** previously treated and untreated **Other co-morbid conditions**: no
Pre-intervention: placebo run-in period: 3 weeks; wash-out period: no **Intervention:** CCB – amlodipine: 5 to 10 mg OD or CCB – manidipine: 10 to 20 mg OD **Co-intervention:** if BP goal was not achieved, another BP-lowering agent was added (enalapril)
Primary outcomes: drug efficacy, tolerability, and quality of life

3.1.3 Discussion

This chapter described the protocol for identifying the studies that would be useful for a systematic review of antihypertensive BP response. Most of the included studies were non-intentional BP-lowering studies; therefore, not all the desired BP data were available from each study. The baseline BP represented in the pooled population covered a wide range, from mild to moderate HTN, with the mean BP ranging from 145.3/80 mmHg (ACCOMPLISH [2004]) to 181.5/99.6 mm Hg (HYVET pilot [2003]), patients with a severe HTN (SBP 180 mmHg or higher or DBP 110 mmHg or higher) were not included in the present analysis. Monotherapy was used as the first line of approach in the majority of studies, though most large key studies, such as ACCOMPLISH [2008]; ASCOT-BPLA [2005]; CONVINCE[2003]; INSIGHT [2000]; NORDIL [2000], used combination therapy as the first line of approach. Despite the fact that 82 studies with a large number of participants comparing several classes of first-line BP-lowering agents were included, the number of studies for each of the sub-classes was limited. Therefore, data were insufficient for some comparisons. This was particularly the case for the dicarboxylate-containing ACEIs included, rendering the evidence for the sulfhydryl and phosphonate-containing ACEIs inadequate. The CCBs included were DHPs, rendering the evidence for non-DHPs inadequate, while the DIs included were thiazide-like, rendering the evidence for thiazide and potassium sparing inadequate.

Randomisation results can be challenging in relatively small sample size clinical studies (N < 100), resulting in an unequal number of participants among groups (375). Although RCTs that randomised at least 100 participants were included, sample size was another apparent difference between older and more recent RCTs. Most 1990s studies recruited a smaller numbers of participants, such as Alcocer [1995]; Hegner [1997]; Mimran [1998]; Mroczek [1996], compared to more recent studies, which for the most part recruited larger numbers of participants, such as ALLHAT [2002]; ASCOT-BPLA [2005]; INVEST [2003]; NORDIL [2000].

Hypertensive patients usually attended the clinic every two to three months for follow-up and were seen by family medicine residents or senior family physicians (376). Therefore, in this review, BP response was measured for at least three months of active treatment and all subsequent BP measurements.

In general, imputation techniques include the formation of assumptions about unidentified statistics, and it is better to avoid using them as much as possible. However, SD imputation helps us to include more available studies and it could potentially improve the generalizeability of results. The simplest imputation is of a specific value borrowed from one or more other studies (such as Cushman [1998] imputed from MIDAS [1996] and Stimpel [1997] imputed from BLACK [2001]). Imputing SDs either from other studies in the same meta-analysis, or from studies in another meta-analysis, produced almost correct results in two case studies (377). In addition, if more than a few candidate SDs are available, review authors would have to decide which one to use.

3.1.3.1 HTN definition, measurement and co-morbidity

The review included RCTs in which BP-lowering agents were studied in cohorts of hypertensive patients, and, in a wider approach, in cohorts in which at least a consistent proportion of hypertensive patients were present (defined as > 70 %), regardless of other comorbidities. Overall, only five studies (CONVINCE [2003] (80%); DETAIL [2004] (81%); IDNT [2001] (76%); NICS-EH [1999] (> 70 %); PATS [1995] (84%)) included non-hypertensive patients, so the analysis mainly focused on hypertensive patients.

Accurate measurement of BP is essential to classify individuals, to determine BP – related risk and to guide management. The auscultatory or oscillometric techniques, with a trained observer and sphygmomanometer, continue to be the method of choice for measurement in the clinic, using the I and V phases of the Korotkoff sounds (378). Following standard protocols, including multiple measurements, relaxed environment and positioning of the patient, is a ground rule when it comes to measuring BP. One of the strengths of this review was that methods of measuring BP were reviewed in as much detail as possible in order to make certain that they adhered to standard practice.

BP measurement is most commonly made in either the sitting or the supine position, both of which yield different results. Almost all studies reviewed used the sitting position; the supine position appeared in only a few studies (Alcocer [1995]; Benetos [2000]; Chanudet [2008]; Freytag [2001]; James [2002]; Mallion [2000]; NORDIL [2000]), while JMIC-B [2004] alone made use of both postures. It is generally accepted that

DBP measured while sitting is higher than when measured supine (by ≈ 5 mm Hg), though there is less agreement about SBP. When the arm position is exactly adjusted so that the cuff is at the level of the right atrium in both positions, the SBP has been reported to be 8 mm Hg 95% CI [4,11] higher in the supine than in the upright position (379).

In the present review, the patients who enrolled included those with HTN and T2DM, CHD, CKD or other conditions. It was not possible to investigate the effect of these subgroup populations on the effect size due to the small number of studies in each subgroup.

Worldwide, an estimated 422 million adults are living with T2DM, according to the latest 2016 data from the WHO (380). T2DM and HTN are known to coexist in patients, as there is a strong correlation between exacerbation of both conditions and changing lifestyle factors. HTN affects about 70% of patients with T2DM and is about twice as common in persons with diabetes as in those without (381).

In the current review, T2DM was the most commonly recorded comorbidity, as it was identified in 12 studies (ACCOMPLISH [2008]; ASCOT-BPLA [2005]; CASE-J [2008]; CONVINCE [2003]; DETAIL [2004]; ELSA [2002]; FACET [1998]; Holsgreve [2003]; IDNT [2001]; Luque [2005]; Mancia[2000]; VALUE [2004]). HTN, in patients with T2DM, causes a major increase in the risk of vascular complications in kidneys (382), and together both conditions are predisposed to heightening the chance of contracting CKD. Worldwide, an estimated 200 million people have CKD and the burden of CKD continues to increase(383). CKD was identified in six studies (AASK [2002]; ACCOMPLISH [2008]; ASCOT-BPLA [2005]; CASE-J [2008]; INSIGHT [2000]; VALUE [2004]).

T2DM is an independent risk factor for CHD, and the risk is markedly increased when HTN is present (384). Worldwide, an estimated 7.4 million people died from CHD and the overlap between HTN and T2DM also considerably enhances the risk of suffering from CHD (385). CHD was identified in nine studies (ACCOMPLISH [2008]; ALLHAT [2002]; ASCOT-BPLA [2005]; CASE-J [2008]; CONVINCE [2003]; ELSA [2002]; INSIGHT [2000]; INVEST [2003]; JMIC-B [2004]).

3.1.3.2 Treatment status, strategy and agents

In general, due to increased population awareness and the availability of effective treatment options provided by general practitioners, for instance, individuals have become more conscious of their health status and once diagnosed, they have received treatments. Accordingly, only five studies (Derosa [2014]; ELVERA [2004]; Freytag [2001]; Holsgreve [2003]; Mallion [2007]) stated that untreated hypertensives were their study population, while the majority of studies included either previously treated patients or both treated and untreated participants. However, the levels of awareness of HTN remain low, with rates of adequate BP-lowering treatment and control lower still, as only 46.5% of participants with HTN were aware of the diagnosis and BP was controlled in 32.5% of those being treated (386).

The right choice of initial BP–lowering agents can quickly establish the benefits of BP control and increase drug adherence. In clinical practice, many factors contribute to inadequate BP control, the most important of which include: failure to prescribe lifestyle modifications, patient non-compliance, inadequate BP-lowering drug doses or inappropriate drug combinations; in addition, it is difficult to achieve adequate BP control with monotherapy in most patients, even when the dose is optimised (16).Physicians are often hesitant to increase the prescribed dosages or add another group of agents to the management plan. They rely excessively on the monotherapy approach, which usually leads to inadequate control of BP and failure to find the ideal dosage regimen for their patients. International guidelines provide a number of consistent recommendations on the choice of agent; for example, RAAS inhibitors and CCBs, which are used in both monotherapy and combination therapy, are emphasised favourably in the NICE (14), ESH/ESC (15), JNC (16) as well as Chinese Hypertension League (CHL) (387) guidelines.

Nevertheless, monotherapy was used as the first line of approach in the majority of studies in the current review; it is still the case that choosing an effective monotherapy, which can be continued as part of a preferred combination regimen, may be beneficial. For instance, the VALUE [2004] study demonstrated that a CCB (amlodipine)-based regimen yielded a more concrete BP reduction, especially in the early stages of treatment (SBP/DBP in the amlodipine group was 4.0/2.1 mm Hg lower than in the ARB (valsartan)-based regimens at 1 month and 3.6 /2.2 mm

Hg lower at 2 months), and was associated with a lower incidence of MI and stroke over the course of the study (mean follow-up of 50 months). However, both regimes were similar in terms of the primary outcome of composite cardiac mortality and morbidity (367).

In contrast, studies have shown that combination therapy provokes a superior BP response in comparison to the up titration of monotherapy. ESH/ESC guidelines reinforce the significance of initiating combination therapy in high-risk patients and those with markedly high baseline BP, with SBP/DBP > 15–20/> 10 mmHg above the target (15). Combination therapy was used in a number of studies (ACCOMPLISH [2008]; ASCOT-BPLA [2005]; Benetos [2000]; Chanudet [2001]; CONVINCE [2003]; Cremonesi [2002]; Holsgreve [2003]; INSIGHT [2000]; Mallion [2000]; McInnes [2000]; NORDIL [2000]; Os [1997]; Pareek [2010]; Stimpel [1997]; Waeber [1999]) as the first line of approach. For example, ACCOMPLISH [2008] was the only large study to directly compare RAAS blockade in combination with either a CCB or DI, and demonstrated the benefit of an amlodipine-benazepril combination over hydrochlorothiazide-benazepril regimen in reducing BP (mean difference between the two groups was 0.9 mm Hg systolic and 1.1 mm Hg diastolic (P<0.001 for both SBP and DBP) and CV events in high-risk patients with HTN (282).

ACEIs and ARBs, which were used in this review 23.2% and 21.2% of studies respectively, have been used in many clinical studies. ARBs were introduced after ACEs with the expected profile of having the benefits of ACEI but without causing a cough (388). A number of meta-analyses have been done to compare the clinical benefits of these two agents in blocking the RAAS system. These meta-analyses have created some arguments regarding the possible superiority of ACEIs over ARBs in reducing total CV mortality and on the effect of ARBs on the incidence of MI (389;390). However, in a more recent meta-analysis, RAAS blockade was associated with a significant reduction in total CV mortality over control treatments, whereas a significant decrease in all-cause mortality was only found in patients receiving an ACEI and not in those being administered an ARB; the difference between ARBs and ACEIs was statistically significant (P=0.03) (391).

In addition, the study ONTARGET[2008], which compared ACEI-ramipril to ARB-telmisartan in high CV risk patients of whom a large proportion were hypertensive,

found that there was no significant difference between the ACEI and the ARB in terms of total or CV mortality (254). However, the tolerability profile of ACEI therapy was an important determinant of the discontinuation rate in treated hypertensive patients. In spite of the above, data from recently published studies that have used ACEI as a first-line treatment, or included it in combination therapy, have shown the beneficial effect of ACEI therapy on the development and progression of macro- and microvascular complications in T2DM. A number of the studies went further in suggesting that ACEI-based BP-lowering regimens may be superior to non-ACEI-based treatments in decreasing the risk of macrovascular disease, such as the Appropriate Blood Pressure Control in Diabetes study, ABCD ^{1998} (392), the CAPPP ^{1999} (193) and FACET ^{1998} (309), or both micro- and macrovascular complications in T2DM, such HOPE ^{2000} (230).

Enalapril, which was used 31.10% in the review, was developed partly to overcome limitations of captopril (e.g. rash, taste disturbance and proteinuria) (393). However, when hypertensive patients were allocated at random to treatment with the ACEI-enalapril or the ARB-losartan, both approaches led to similar clinical BP reductions, although enalapril appeared to be more effective at peak (394). It significantly reduced BP, as it "normalised < 90 mm Hg' BP" in 88%, 50% and 25% of patients with mild DBP (90-104 mmHg), moderate DBP (105-120 mmHg) and severe DBP (> 120 mmHg) and HTN respectively. Comparison with BB-atenolol revealed an almost parallel efficacy of the two drugs, although enalapril produced a significantly greater reduction in SBP in patients with mild and moderate HTN (for all, $P < 0.01$) (395). Both treatments with the ARB-irbesartan and the ACEI-enalapril significantly lowered BP ($P < 0.05$), though there was no significant difference in efficacy between treatment groups. The incidence of cough in the enalapril and Irbesartan groups was 17% and 10% respectively (for all, $P > 0.05$) (344).

Losartan, which was used 30.8% of studies in the review, was the first selective ARB agent to be introduced (396).It has been shown to decrease SBP in patients with less severe ISH (SBP range 140-200 mmHg), compared with placebos, and in patients with more severe ISH (SBP range 160-205 mmHg), compared with Atenolol. In addition, losartan was highly effective and well tolerated in both studies (397;398).

CCBs, which were used 27.30% of studies in the review, constitute a class of structurally heterogeneous drugs (DHPs and non-DHPs). Although they share a common feature of inhibiting the cellular entry of calcium through voltage-dependent L- and T-type calcium channels, significant differences exist between various CCBs with regard to their binding sites and chemical structure. DHP-CCBs are the most frequently prescribed CCBs for HTN and the only class of BP-lowering agents with no compelling contraindications. However, they may not be preferred in patients with peripheral oedema or heart conditions (rapid heart rate, low ejection fraction) (15). Whereas non-DHPs (verapamil and diltiazem) may be used when patients suffer unacceptable side effects with DHP-CCBs, their evidence for use in HTN is almost nonexistent, so hereafter, only DHPs will be considered.

DHP-CCBs may well be the preferred drug class in many BP-lowering combination strategies in large RCTs (with ACEIs, ARBs and DIs) (15). For example, ASCOT-BPLA [2005] showed that a CCB–ACEI combination (amlodipine-based) lowered BP by an average of 2.7/1.9 mm Hg more than a BB–DI combination (atenolol-based) throughout the follow-up period. Significant reductions in a number of outcomes (all-cause mortality, nonfatal MI and new-onset T2DM) were noted with CCB–ACEI, compared to BB–DI. In addition, by the end of the study, only 15% and 9% of participants were taking amlodipine or atenolol monotherapy respectively, providing additional evidence for the inadequacy of monotherapy in BP control. In addition, there was a lower visit-to-visit BP variability with the CCB-ACEI combination as opposed to the BB-DI combination (399).

Amlodipine, which was used 38.5% of studies in the review, has been commonly used in many large clinical studies such as ALLHAT [2002], ASCOT-BPLA [2005] or VALUE [2004], and it was at least as effective, if not slightly superior, in lowering BP. Amlodipine was, at times, more effective in preventing target organ damage than BP-lowering strategies that were based on the use of DI, BB and RAAS inhibitors (48;51;367).

Since one of the main clinical side effects of the first and second generation DHP CCBs (including amlodipine) is the peripheral oedema, a number of studies have demonstrated a reduced incidence of peripheral oedema with the use of these new CCBs. For example, such occurrences can be reduced by almost 50% in patients who developed oedema with the CCB-amlodipine and were switched to

the CCB-lercanidipine (400). In the same way, peripheral oedema occurred in 19% of patients treated with amlodipine but only in 9% and 4% of patients receiving, respectively, lercanidipine and lacidipine (401). The incidence of leg oedema can be significantly decreased through combining the CCB with RAAS inhibitors. This strategy has recently led to the development of several fixed-dose combinations of amlodipine and RAAS inhibitors (402).

The argument on whether DIs are the first-choice drug, as recommended by the JNC-7 Report, or are just one of the first-choice agents, as recommended by the ESH-ESC guidelines, is mainly based on different analyses of RCTs and drug cost considerations(15;16). Clinical studies have clearly highlighted the advantage of DIs, either as a monotherapy or in combination with BB, in reducing CV morbidity and mortality; a benefit comparable to that accomplished with other BP-lowering agents, such as ACEIs and CCBs (403).

DIs, which were used 8.10% of studies in the review, can be subdivided into three subclasses: thiazide (e.g., hydrochlorothiazide), thiazide-like (chlorthalidone) and potassium sparing (e.g., spironolactone)[6]. DIs are an essential part of BP therapy, and their effectiveness remains unquestioned; however, they have negative effects on patients' metabolic profiles.

For instance, the data obtained with the DI-chlorthalidone to date indicates that the plateau of the dose-response BP-lowering curve is reached with a daily dose of 25 mg and that increasing the dosage does not improve the BP-lowering effect; however, it does increase the incidence of negative metabolic effects, mainly hypokalaemia (404). In addition, the DI- hydrochlorothiazide was associated with increased insulin resistance and the risk of gout. Hydrochlorothiazide also increases the hepatic triglycerides level (405;406).

ALPINE [2003] showed that treatment with hydrochlorothiazide is often associated with BB-atenolol-impaired glucose metabolism, while treatment with ARB-candesartan is often linked to CCB-felodipine and is neutral (286). In the same way, VALUE [2004], which showed a greater incidence of new onset T2DM in the CCB-

[6] Potassium-sparing DIs such as (spironolactone and triamterene) were not used in this review.

amlodipine arm, can be tentatively explained by the greater occurrence of hypokalaemia induced by the association of hydrochlorothiazide (367).

However, a meta-analysis of randomised studies, in which one arm was based on either hydrochlorothiazide or chlorthalidone, reported that the latter was more effective than the former in preventing CV events in hypertensive patients (407). In most countries, thiazide and thiazide-like DIs are the cheapest BP-lowering agents available and the backbone of BP-lowering pharmacotherapy. Consequently, DIs such as chlorthalidone, which was used 30% in the review, are less expensive than newer types of BP-lowering agents and are preferred in terms of cost minimisation (408).

BBs had been used for the management of HTN for several decades. Along with DIs, they were the mainstay of antihypertensive management for many years. BBs, which were used 13.60% in the review, has been questioned as a first-line therapy in the management of hypertensive patients in some guidelines, due to their lower ability to prevent stroke and other CV events, in addition to their adverse impacts on glucose metabolism(14;16).They have been subjected to comprehensive research and their performance was frequently compared with other BP-lowering agents .The review of the evidence provided confirms that there are convincing reasons to question the usefulness of certain BBs in treating HTN. However, evidence suggests that there are essential differences among BB classes (409). Overall, the answer to the question of BBs' effectiveness lies not in worldwide generalisations, but in assessing individual patients and specific BB agents.

Atenolol, which was used 64% of studies in the review, has been studied as a monotherapy or in comination with other agent in many clinical studies. For instance, a meta-analysis of clinical studies comparing the main BP-lowering agents (AECIs, ARBs, CCBs, DIs and BBs (mainly atenolol) showed that ARBs were superior to BBs in reducing all-cause mortality, HF and T2DM incidence; in addition, DIs were better than BBs in reducing all-cause mortality, MI, stroke and HF. BBs were also inferior to ACEIs and CCBs for all-cause mortality, MI and stroke (410). Another meta-analysis of RCTs that evaluated BBs, mainly atenolol, for HTN, showed that BB-associated reduction in heart rate increased the risk of CV events and death for hypertensive patients ($P < 0.0001$) (411). However, BB studies

included in these two meta-analyses were carried out mainly on atenolol, which may not be representative of all BBs.

Only 13 studies used a placebo in one of their treatment arms (Black [1997]; BLACK [2001]; Cushman [1998]; Giles [2007]; Grethouse [2010]; Guthrie [1998]; Hanefeld [2001]; HYVET [2008]; IDNT [2001]; Mroczek [1996]; PATS [1995]; SYST-EUR [1997]; Waeber [1999]). This could be explained by the fact that the use of placebos is nowadays considered unethical, due to the possibility of exposing participants to harm by receiving a placebo instead of an active treatment, since not receiving an active treatment can aggravate their conditions or even pose the risk of death (412).

In recent times, traditional placebo-controlled designs can be modified so as to study both the placebo response and the response to the active treatment, in order to avoid the event of some in-study patients being left untreated. This kind of study is called a crossover study, since patients in the study cross over, at predetermined time points, from the placebo to the treatment arm and vice versa. An alternative option is the ‘add on’ design, in which both groups receive the standard treatment as well as either the studied treatment or the placebo (413).

3.2 Risk of bias in included studies

While studies with a small sample were excluded from the review, the majority of those included were large and multicentre studies with standardised protocols. All these studies were stated to be RCTs, (see 'Methodological quality of included studies', **Section 3.2.1**)

As shown in **Figure 3.2**, all included studies reported randomisation, although most did not mention the sequence generation process or method of allocation concealment. In these studies, selection bias was considered to be unclear.

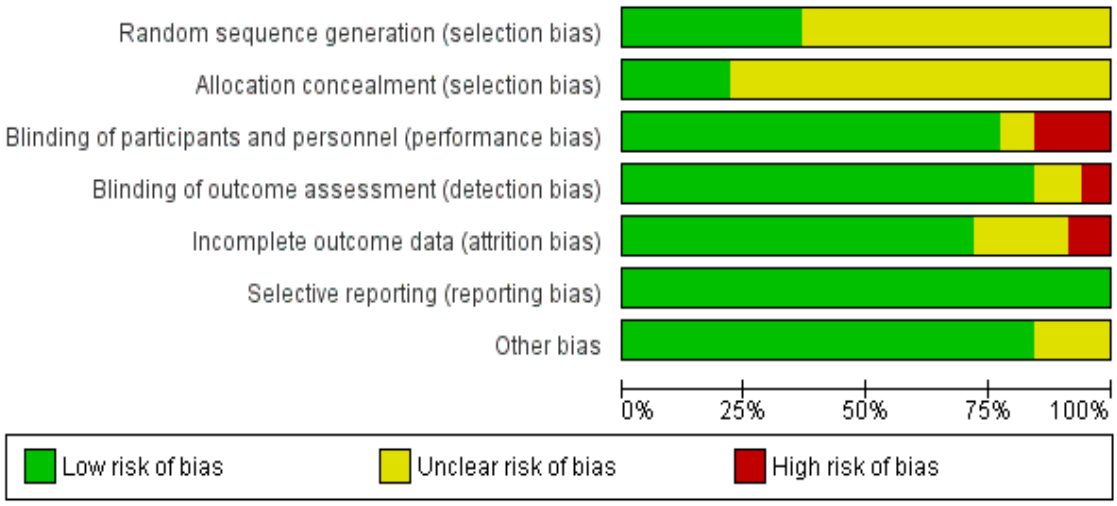


Figure 3.2 Risk of bias graph: review authors' judgements about each risk of bias item, presented as % across all included studies.

Random sequence generation was adequate in 30 studies (AASK [2002]; ACCOMPLISH [2008]; Alcocer [1995]; ALLHAT [2002]; ASCOT-BPLA [2005]; CASE-J [2008]; CONVINCE [2003]; Derosa [2013]; Derosa [2014]; ELSA [2002]; FACET [1998]; Fogari [2008]; Holsgreve [2003]; HYVET [2008]; HYVET–P [2003]; IDNT [2001]; INVEST [2003]; James [2002] ; JMIC-B [2004]; LAARS [2002]; LIFE [2002]; McInnes [2000]; MIDAS [1996] ; Mounier-Vehier [1998]; PATS [1995]; RACE [1995]; SHELL [2003]; SYST-EUR [1997]; UKPDS [1998]; VALUE [2004]) and unclear in the remaining 52 studies. Allocation concealment was adequate in 18 studies (ACCOMPLISH [2008]; ALLHAT [2002]; ASCOT-BPLA [2005]; CONVINCE [2003]; Derosa [2013]; Derosa [2014]; Fogari [2008]; HYVET [2008]; IDNT [2001]; INVEST [2003]; JMIC-B [2004]; LAARS [2002]; McInnes [2000]; Mounier-Vehier [1998]; PATS [1995]; RACE [1995]; SYST-EUR [1997]; UKPDS [1998]), whereas in the other 64 studies the information provided was insufficient to assess this aspect of bias risk and was considered unclear.

A computer-generated code for randomisation was used in 24 studies (ACCOMPLISH [2008]; ALLHAT [2002]; ASCOT-BPLA [2005]; CASE-J [2008]; Derosa [2013]; Derosa [2014]; ELSA [2002]; FACET [1998]; Fogari [2008]; Holsgreve [2003]; HYVET–P [2003]; IDNT [2001]; INVEST [2003]; James [2002]; JMIC-B [2004]; LAARS [2002]; LIFE [2002]; McInnes [2000]; Mounier-Vehier [1998]; PATS [1995]; RACE [1995]; SYST-EUR [1997]; UKPDS [1998]; VALUE [2004]). In addition, 12 studies (ACCOMPLISH [2008]; ALLHAT [2002]; ASCOT-BPLA [2005]; Derosa [2013]; Fogari [2008]; IDNT [2001]; INVEST [2003]; LAARS [2002]; McInnes [2000]; Mounier-Vehier [1998]; RACE [1995]; SYST-EUR [1997]) stated that their randomisation codes were concealed at the clinical studies centre, while two (CONVINCE [2003] and HYVET [2008]) used an Interactive Voice Response System (IVRS) for randomising, assigning and tracking blinded medication.

The majority of studies reported a double-blind design, and blinded active drugs were described as of identical appearance in some studies; however, it was still impossible to know the extent of blinding. Therefore, they were considered to have a low risk of performance bias. The method of blinding was not mentioned in six studies (LOTHAR [2006]; Pareek [2010]; SHELL [2003]; VHAS [1998]; Wu [2004]; Yang [2015]) and performance bias was considered unclear. There was a high risk of performance bias in 13 open-label studies (ASCOT-BPLA [2005]; CASE-J [2008]; CONVINCE [2003]; Cremonesi [2002]; FACET [1998]; Fogari [2008]; Holzgreve [2003]; HYVET [2008]; HYVET–P [2003]; INVEST [2003]; Mounier-Vehier [1998]; NORDIL [2000]; UKPDS [1998]).

An adequate blinding of outcome assessment was seen in most of the studies. However, it was unclear in eight studies (Bremner [1997]; DETAIL [2004]; LOTHAR [2006]; Pareek [2010]; SHELL [2003]; VHAS [1998]; Wu [2004]; Yang [2015]) whether blinding was broken prior to making the final decision to withdraw, as the method of binding was not described. In six studies (CASE-J [2008]; Cremonesi [2002]; FACET [1998]; HYVET–P [2003]; Mounier-Vehier [1998]; UKPDS [1998]) where drugs were administered as open label and outcome was not blindly assessed, a high risk of detection bias was considered. A PROBE design was instigated in five studies (ASCOT-BPLA [2005]; CASE-J [2008]; Fogari [2008]; INVEST [2003]; NORDIL [2000]); this differed from the typical double-blind method. In a PROBE study, outcomes are evaluated by a blinded endpoint committee to avoid detection bias.

In terms of incomplete outcome data, 33 studies (AASK [2002] ; Alcocer [1995]; Bremner [1997]; CASE-J [2008]; Cremonesi [2002]; Cushman [1998]; DETAIL [2004]; FACET [1998]; Farsang [2007]; Freytag [2001]; Holsgreve [2003]; HYVET [2008]; HYVET–P [2003]; IDNT [2001]; JMIC-B [2004]; LIFE [2002]; Luque [2005]; Mallion [2000]; Mallion [2011]; MIDAS [1996] ; Mroczek [1996]; Narkiewicz [2007]; Nilsson [2007]; NORDIL [2000]; PATS [1995]; PRESERVE [2001]; Radauceanu [2004]; REGAAL [2002]; REZALT [2009]; SHELL [2003]; SYST-EUR [1997]; VHAS [1998]; Yang [2015]) evidently accounted for all participants in each study arm, including those whose data was unavailable due to loss in follow-up, and they used ITT analysis. In these studies, the rate of discontinuation was generally low and equal between study arms.

In total, nine studies and their patients were excluded after randomisation as a result of poor documentation of informed consent (ALLHAT [2002]), data integrity concerns (ASCOT-BPLA [2005]; CONVINCE [2003]), missing outcome data (INVEST [2003]; Mounier-Vehier [1998]; UKPDS [1998]; Volpe [2003]) or misconduct (INSIGHT [2000]; VALUE [2004]), however, adequate information in reports helped to restore those participants to the right groups and ITT analysis was performed.Furthermore, 17 studies (ALPINE [2003]; Benetos [2000]; Black [1997]; CROSS [2003]; Derosa [2013]; ELSA [2002]; ELVERA [2004]; Giles [2007]; Grethouse [2010]; Guthrie [1998]; Hegner [1997]; MAISH [2007]; Mallion [2007]; McInnes [2000]; Ruilope [2001]; Stimpel [1997]; Zanchetti [2001]) evidently did not account for participants if they did not receive a specific minimum amount of the intended intervention, even though they did use “modified ITT” analysis, and therefore considered them to have a low risk of attrition bias.

Meanwhile, seven studies (Chanudet [2001]; ELLE [2003]; Grassi [2003]; Hanefeld [2001]; NICS-EH [1999]; Oparil [1998]; Pareek [2010]) did not evidently account for participants lost to follow-up, as they did use PP analysis, and therefore considered them to have a high risk of attrition bias. Added to this, 16 studies (ACCOMPLISH [2008]; BLACK [2001]; Derosa [2014]; Fogari [2008]; Hoegholm [1995]; James [2002]; LAARS [2002]; LOTHAR [2006]; Mancia[2000]; MAPAVEL [2002]; Mimran [1998]; Os [1997]; Papademetriou [1997]; RACE [1995]; Waeber [1999]; Wu [2004]) had an unclear risk of attrition bias, because it was uncertain whether the decision to withdraw participants for "uncontrolled BP" was pre-specified in the study's protocol, and the BP threshold for such withdrawal was also undefined.

For selective reporting, all studies reported all pre-specified outcomes, and therefore they have been judged as having a low risk of reporting bias. Other potential sources of bias came from the requirement to control high BP; a number of BP-lowering agents were added to randomly allocated treatment. Therefore, an unclear risk of this type of bias was judged for 13 studies (AASK [2002]; ACCOMPLISH [2008]; ALLHAT [2002]; CONVINCE [2003]; FACET [1998]; IDNT [2001]; INSIGHT [2000]; INVEST [2003]; LIFE [2002]; NORDIL [2000]; UKPDS [1998]; VALUE [2004]; VHAS [1998]).

Visual inspection of funnel plots for BP response (including delta, single measure and repeated measures), showed that almost all outliers were placebo controlled studies, as shown in appendix **Figure 6.1**, **Figure 6.2** and **Figure 6.3.** However, other Possible sources of asymmetry in funnel plots were identified (see 'Effect of intervention', **Section 4.3**) accordingly sensitivity analysis was carried out to exclude biased studies.

In the last part, according to the PRISMA summary assessment of the risk of bias, 48 of the studies (AASK [2002]; ACCOMPLISH [2008]; Alcocer [1995]; ALLHAT [2002]; ALPINE [2003]; ASCOT-BPLA [2005]; Benetos [2000]; Black [1997]; CROSS [2003]; Cushman [1998]; Derosa [2013]; Derosa [2014]; ELSA [2002]; ELVERA [2004]; Farsang [2007]; Freytag [2001]; Giles [2007]; Grethouse [2010]; Guthrie [1998]; Hegner [1997]; HYVET [2008]; IDNT [2001]; James [2002]; JMIC-B [2004]; LAARS [2002]; LIFE [2002]; Luque [2005]; MAISH [2007]; Mallion [2000]; Mallion [2007]; Mallion [2011]; McInnes [2000]; MIDAS [1996] ; Mroczek [1996]; Narkiewicz [2007]; Nilsson [2007]; PATS [1995]; PRESERVE [2001]; RACE [1995]; Radauceanu [2004]; REGAAL[2002]; REZALT [2009]; Ruilope [2001]; Stimpel [1997]; SYST-EUR [1997]; VALUE [2004]; Volpe [2003] ; Zanchetti [2001]) were rated as

high quality studies (that is, the majority of criteria were met, there was little or no risk of bias and the results were unlikely to be changed by further research).

Furthermore, 34 (BLACK [2001]; Bremner [1997]; CASE-J [2008]; Chanudet [2001]; CONVINCE [2003]; Cremonesi [2002]; DETAIL [2004]; ELLE [2003]; FACET [1998]; Fogari [2008]; Grassi [2003]; Hanefeld [2001]; Hoegholm [1995]; Holsgreve [2003]; HYVET–P [2003]; INSIGHT [2000]; INVEST [2003]; LOTHAR [2006]; Mancia [2000]; MAPAVEL [2002]; Mimran [1998]; Mounier-Vehier [1998]; NICS-EH [1999]; NORDIL [2000]; Oparil [1998]; Os [1997]; Papademetriou [1997]; Pareek [2010]; SHELL [2003]; UKPDS [1998]; VHAS [1998]; Waeber [1999]; Wu [2004]; Yang [2015]) were rated as acceptable quality studies (that is, most criteria were met, there were some flaws in the study, with an associated risk of bias, and conclusions may change in the light of further studies).

3.2.1 Methodological quality of included studies (ordered by study ID)

AASK [2002]		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	The randomisation was stratified by city using randomly permuted blocks
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not described
Blinding of participants and personnel (performance bias)	Low risk	Participants and personnel blinded
Blinding of outcome assessment (detection bias)	Low risk	Blind outcome assessment
Incomplete outcome data (attrition bias)	Low risk	Patients withdrawing from the study were accounted. ITT analysis was performed
Selective reporting (reporting bias)	Low risk	Outcomes listed in the methods section were all reported
Other bias	Unclear risk	A number of BP-lowering agents were added to randomly allocated treatment to control BP. The observed effects could equally have resulted from the different additional drugs

ACCOMPLISH [2004]		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomization scheme was generated by computer
Allocation concealment (selection bias)	Low risk	Central randomisation
Blinding of participants and personnel (performance bias)	Low risk	Participants and personnel blinded
Blinding of outcome assessment (detection bias)	Low risk	Blind outcome assessment
Incomplete outcome data (attrition bias)	Unclear risk	It is unclear whether an ITT or PP analysis was used
Selective reporting (reporting bias)	Low risk	Outcomes listed in the methods section were all reported
Other bias	Unclear risk	A number of BP-lowering agents were added to randomly allocated treatment to control BP. The observed effects could equally have resulted from the different additional drugs

Alcocer [1995]		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	The randomisation was stratified by centres using randomly permuted blocks
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not described
Blinding of participants and personnel (performance bias)	Low risk	Participants and personnel blinded

Blinding of outcome assessment (detection bias)	Low risk	Blind outcome assessment
Incomplete outcome data (attrition bias)	Low risk	Patients withdrawing from the study were accounted. ITT analysis was performed
Selective reporting (reporting bias)	Low risk	Outcomes listed in the methods section were all reported
Other bias	Low risk	No other possible bias was found

ALLHAT [2002]		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomization scheme was generated by computer
Allocation concealment (selection bias)	Low risk	Concealment scheme was implemented at the clinical trials centre and stratified by centre
Blinding of participants and personnel (performance bias)	Low risk	Participants and personnel blinded
Blinding of outcome assessment (detection bias)	Low risk	Blind outcome assessment
Incomplete outcome data (attrition bias)	Low risk	Two centres initially reported were excluded, due poor documentation of informed consent. ITT analysis was performed
Selective reporting (reporting bias)	Low risk	Outcomes listed in the methods section were all reported
Other bias	Unclear risk	A number of BP-lowering agents were added to randomly allocated treatment to control BP. The observed effects could equally have resulted from the different additional drugs

ALPINE [2003]		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation was not described
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not described
Blinding of participants and personnel (performance bias)	Low risk	Participants and personnel blinded
Blinding of outcome assessment (detection bias)	Low risk	Blind outcome assessment
Incomplete outcome data (attrition bias)	Low risk	Not indicated whether reasons for missing outcome data were similar across treatment groups. Modified ITT analysis was performed including all randomised patients who had completed the study and had taken at least one dose of study drug
Selective reporting (reporting bias)	Low risk	Outcomes listed in the methods section were all reported
Other bias	Low risk	No other possible bias was found

ASCOT-BPLA [2005]		
Bias	**Authors' judgement**	**Support for judgement**

Random sequence generation (selection bias)	Low risk	Randomization scheme was generated by computer
Allocation concealment (selection bias)	Low risk	Central randomisation
Blinding of participants and personnel (performance bias)	High risk	Study drugs were administered open-label
Blinding of outcome assessment (detection bias)	Low risk	A PROBE design was used.
Incomplete outcome data (attrition bias)	Low risk	Two centres with 85 patients initially reported were excluded, due data integrity concerns. ITT analysis was performed
Selective reporting (reporting bias)	Low risk	Outcomes listed in the methods section were all reported
Other bias	Low risk	No other possible bias was found

Benetos [2000]		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation was not described
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not described
Blinding of participants and personnel (performance bias)	Low risk	Participants and personnel blinded
Blinding of outcome assessment (detection bias)	Low risk	Blind outcome assessment
Incomplete outcome data (attrition bias)	Low risk	Not indicated whether reasons for missing outcome data were similar across treatment groups. Modified ITT analysis was performed including all randomly assigned patients who received at least one dose of the study medication, had one baseline BP measurement, and at least one subsequent BP measurement
Selective reporting (reporting bias)	Low risk	Outcomes listed in the methods section were all reported
Other bias	Low risk	No other possible bias was found

Black [1997]		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation was not described
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not described
Blinding of participants and personnel (performance bias)	Low risk	Participants and personnel blinded
Blinding of outcome assessment (detection bias)	Low risk	Blind outcome assessment
Incomplete outcome data (attrition bias)	Low risk	Not indicated whether reasons for missing outcome data were similar across treatment groups. Modified ITT analysis was performed including all randomised patients with a baseline

		measurement and at least one post treatment observation
Selective reporting (reporting bias)	Low risk	Outcomes listed in the methods section were all reported.
Other bias	Low risk	No other possible bias was found.

Black [2001]		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation was not described
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not described
Blinding of participants and personnel (performance bias)	Low risk	Participants and personnel blinded
Blinding of outcome assessment (detection bias)	Low risk	Blind outcome assessment
Incomplete outcome data (attrition bias)	Unclear risk	It is unclear whether an ITT or PP analysis was used
Selective reporting (reporting bias)	Low risk	Outcomes listed in the methods section were all reported
Other bias	Low risk	No other possible bias was found

Bremner [1997]		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation was not described
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not described
Blinding of participants and personnel (performance bias)	Low risk	Participants and personnel blinded
Blinding of outcome assessment (detection bias)	Unclear risk	It is unclear whether blinding was broken prior to making final decision to withdraw
Incomplete outcome data (attrition bias)	Low risk	Patients withdrawing from the study were accounted. ITT analysis was performed
Selective reporting (reporting bias)	Low risk	Outcomes listed in the methods section were all reported
Other bias	Low risk	No other possible bias was found

CASE-J [2008]		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomization scheme was generated by computer
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not described
Blinding of participants and personnel (performance bias)	High risk	Participants and personnel were not blinded
Blinding of outcome assessment (detection bias)	Low risk	A PROBE design was used.
Incomplete outcome data (attrition bias)	Low risk	Patients withdrawing from the study were accounted. ITT analysis was performed

Selective reporting (reporting bias)	Low risk	Outcomes listed in the methods section were all reported
Other bias	Low risk	No other possible bias was found

Chanudet [2001]		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation was not described
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not described
Blinding of participants and personnel (performance bias)	Low risk	Participants and personnel blinded
Blinding of outcome assessment (detection bias)	Low risk	Blind outcome assessment
Incomplete outcome data (attrition bias)	High risk	Data of withdrawn patients were not included. PP analyses was used
Selective reporting (reporting bias)	Low risk	Outcomes listed in the methods section were all reported
Other bias	Low risk	No other possible bias was found

CONVINCE [2003]		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	IVRS, for randomising, assigning, and tracking blinded medication was used
Allocation concealment (selection bias)	Low risk	IVRS, for randomising, assigning, and tracking blinded medication was used
Blinding of participants and personnel (performance bias)	High risk	A number of patients discontinued blinded medication (administered open-label)
Blinding of outcome assessment (detection bias)	Low risk	Blind outcome assessment
Incomplete outcome data (attrition bias)	Low risk	Participants from two centres with 126 patients were excluded, due to data integrity concerns. ITT analysis was performed
Selective reporting (reporting bias)	Low risk	Outcomes listed in the methods section were all reported
Other bias	Unclear risk	A number of BP-lowering agents were added to randomly allocated treatment to control BP. The observed effects could equally have resulted from the different additional drugs

Cremonesi [2002]		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation was not described
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not described
Blinding of participants and personnel (performance bias)	High risk	Participants and personnel were not blinded
Blinding of outcome assessment (detection bias)	High risk	Study drugs were administered open-label

Incomplete outcome data (attrition bias)	Low risk	Patients withdrawing from the study were accounted. ITT analysis was performed
Selective reporting (reporting bias)	Low risk	Outcomes listed in the methods section were all reported
Other bias	Low risk	No other possible bias was found

CROSS [2003]		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation was not described
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not described
Blinding of participants and personnel (performance bias)	Low risk	Participants and personnel blinded
Blinding of outcome assessment (detection bias)	Low risk	Blind outcome assessment
Incomplete outcome data (attrition bias)	Low risk	Not indicated whether reasons for missing outcome data were similar across treatment groups. Modified ITT analysis was performed including all patients allocated randomly to groups, provided that they had received at least one dose of the study medication and had post-baseline data
Selective reporting (reporting bias)	Low risk	Outcomes listed in the methods section were all reported.
Other bias	Low risk	No other possible bias was found

Cushman [1998]		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation was not described
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not described
Blinding of participants and personnel (performance bias)	Low risk	Participants and personnel blinded
Blinding of outcome assessment (detection bias)	Low risk	Blind outcome assessment
Incomplete outcome data (attrition bias)	Low risk	Patients withdrawing from the study were accounted. ITT analysis was performed
Selective reporting (reporting bias)	Low risk	Outcomes listed in the methods section were all reported
Other bias	Low risk	No other possible bias was found

Derosa [2013]		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomization scheme was generated by computer
Allocation concealment (selection bias)	Low risk	Central randomisation
Blinding of participants and personnel (performance bias)	Low risk	Participants and personnel blinded

Blinding of outcome assessment (detection bias)	Low risk	Blind outcome assessment
Incomplete outcome data (attrition bias)	Low risk	Not indicated whether reasons for missing outcome data were similar across treatment groups. Modified ITT analysis was performed including patients who had received at least one dose of study medication and had a subsequent efficacy observation
Selective reporting (reporting bias)	Low risk	Outcomes listed in the methods section were all reported
Other bias	Low risk	No other possible bias was found

Derosa [2014]		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomization scheme was generated by computer
Allocation concealment (selection bias)	Low risk	Allocation concealment was done with envelopes containing randomisation codes prepared by statisticians
Blinding of participants and personnel (performance bias)	Low risk	Participants and personnel blinded
Blinding of outcome assessment (detection bias)	Low risk	Blind outcome assessment
Incomplete outcome data (attrition bias)	Unclear risk	It is unclear whether an ITT or PP analysis was used
Selective reporting (reporting bias)	Low risk	Outcomes listed in the methods section were all reported
Other bias	Low risk	No other possible bias was found

DETAIL [2004]		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation was not described
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not described
Blinding of participants and personnel (performance bias)	Low risk	Participants and personnel blinded
Blinding of outcome assessment (detection bias)	Unclear risk	It is unclear whether blinding was broken prior to making final decision to withdraw
Incomplete outcome data (attrition bias)	Low risk	Patients withdrawing from the study were accounted. ITT analysis was performed
Selective reporting (reporting bias)	Low risk	Outcomes listed in the methods section were all reported
Other bias	Low risk	No other possible bias was found

ELLE [2003]		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation was not described
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not described

Blinding of participants and personnel (performance bias)	Low risk	Participants and personnel blinded
Blinding of outcome assessment (detection bias)	Low risk	Blind outcome assessment
Incomplete outcome data (attrition bias)	High risk	Data of withdrawn patients were not included. PP analyses was used
Selective reporting (reporting bias)	Low risk	Outcomes listed in the methods section were all reported
Other bias	Low risk	No other possible bias was found

ELSA [2002]		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomization scheme was generated by computer
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not described
Blinding of participants and personnel (performance bias)	Low risk	Participants and personnel blinded
Blinding of outcome assessment (detection bias)	Low risk	Blind outcome assessment
Incomplete outcome data (attrition bias)	Low risk	Not mentioned whether reasons for missing outcome data were similar between treatment groups. Modified ITT analysis was performed including all patients randomised to double blind medication who had the baseline ultrasound scan and at least one follow-up scan, including scans performed after withdrawal
Selective reporting (reporting bias)	Low risk	Outcomes listed in the methods section were all reported
Other bias	Low risk	No other possible bias was found

ELVERA [2004]		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation was not described
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not described
Blinding of participants and personnel (performance bias)	Low risk	Participants and personnel blinded
Blinding of outcome assessment (detection bias)	Low risk	Blind outcome assessment
Incomplete outcome data (attrition bias)	Low risk	Not indicated whether reasons for missing outcome data were similar across treatment groups. Modified ITT analysis was performed including patients for whom there were valid readings at baseline and at least one valid observation after 1 and 2 years
Selective reporting (reporting bias)	Low risk	Outcomes listed in the methods section were all reported
Other bias	Low risk	No other possible bias was found

FACET [1998]		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomization scheme was generated by computer
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not described
Blinding of participants and personnel (performance bias)	High risk	Study drugs were administered open-label
Blinding of outcome assessment (detection bias)	High risk	Outcome assessment not blinded
Incomplete outcome data (attrition bias)	Low risk	Patients withdrawing from the study were accounted. ITT analysis was performed
Selective reporting (reporting bias)	Low risk	Outcomes listed in the methods section were all reported
Other bias	Unclear risk	A number of BP-lowering agents were added to randomly allocated treatment to control BP. The observed effects could equally have resulted from the different additional drugs

Farsang [2007]		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation was not described
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not described
Blinding of participants and personnel (performance bias)	Low risk	Participants and personnel blinded
Blinding of outcome assessment (detection bias)	Low risk	Blind outcome assessment
Incomplete outcome data (attrition bias)	Low risk	Patients withdrawing from the study were accounted. ITT analysis was performed
Selective reporting (reporting bias)	Low risk	Outcomes listed in the methods section were all reported
Other bias	Low risk	No other possible bias was found

Fogari [2008]		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomization scheme was generated by computer
Allocation concealment (selection bias)	Low risk	Central randomisation
Blinding of participants and personnel (performance bias)	High risk	Study drugs were administered open-label
Blinding of outcome assessment (detection bias)	Low risk	A PROBE design was used.
Incomplete outcome data (attrition bias)	Unclear risk	It is unclear whether an ITT or PP analysis was used
Selective reporting (reporting bias)	Low risk	Outcomes listed in the methods section were all reported
Other bias	Low risk	No other possible bias was found

Freytag [2001]		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation was not described.
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not described.
Blinding of participants and personnel (performance bias)	Low risk	Participants and personnel blinded.
Blinding of outcome assessment (detection bias)	Low risk	Blind outcome assessment.
Incomplete outcome data (attrition bias)	Low risk	Patients withdrawing from the study were accounted. ITT analysis was performed.
Selective reporting (reporting bias)	Low risk	Outcomes listed in the methods section were all reported.
Other bias	Low risk	No other possible bias was found.

Giles [2007]		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation was not described
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not described
Blinding of participants and personnel (performance bias)	Low risk	Participants and personnel blinded
Blinding of outcome assessment (detection bias)	Low risk	Blind outcome assessment
Incomplete outcome data (attrition bias)	Low risk	Not indicated whether reasons for missing outcome data were similar across treatment groups. Modified ITT analysis was performed including patients who received at least 1 dose of study drug and had a baseline BP measurement and at least one post baseline BP assessment
Selective reporting (reporting bias)	Low risk	Outcomes listed in the methods section were all reported
Other bias	Low risk	No other possible bias was found

Grassi [2003]		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation was not described
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not described
Blinding of participants and personnel (performance bias)	Low risk	Participants and personnel blinded
Blinding of outcome assessment (detection bias)	Low risk	Blind outcome assessment
Incomplete outcome data (attrition bias)	High risk	Data of withdrawn patients were not included. PP analyses was used
Selective reporting (reporting bias)	Low risk	Outcomes listed in the methods section were all reported

Other bias	Low risk	No other possible bias was found

Greathouse [2010]		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation was not described
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not described
Blinding of participants and personnel (performance bias)	Low risk	Participants and personnel blinded
Blinding of outcome assessment (detection bias)	Low risk	Blind outcome assessment
Incomplete outcome data (attrition bias)	Low risk	Not indicated whether reasons for missing outcome data were similar across treatment groups. Modified ITT analysis was performed including all randomised patients who received at least one dose of study medication.
Selective reporting (reporting bias)	Low risk	Outcomes listed in the methods section were all reported
Other bias	Low risk	No other possible bias was found

Guthrie [1998]		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation was not described
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not described
Blinding of participants and personnel (performance bias)	Low risk	Participants and personnel blinded
Blinding of outcome assessment (detection bias)	Low risk	Blind outcome assessment
Incomplete outcome data (attrition bias)	Low risk	Not indicated whether reasons for missing outcome data were similar across treatment groups. Modified ITT analysis was performed including all randomised patients who had a baseline evaluation and at least one scheduled on-therapy evaluation
Selective reporting (reporting bias)	Low risk	Outcomes listed in the methods section were all reported
Other bias	Low risk	No other possible bias was found

Hanefeld [2001]		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation was not described
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not described
Blinding of participants and personnel (performance bias)	Low risk	Participants and personnel blinded

Blinding of outcome assessment (detection bias)	Low risk	Blind outcome assessment
Incomplete outcome data (attrition bias)	High risk	Data of withdrawn patients were not included. PP analyses was used
Selective reporting (reporting bias)	Low risk	Outcomes listed in the methods section were all reported
Other bias	Low risk	No other possible bias was found

Hegner [1997]		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation was not described
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not described
Blinding of participants and personnel (performance bias)	Low risk	Participants and personnel blinded
Blinding of outcome assessment (detection bias)	Low risk	Blind outcome assessment
Incomplete outcome data (attrition bias)	Low risk	Not indicated whether reasons for missing outcome data were similar across treatment groups. Modified ITT analysis was performed including all randomised patients who had a baseline measurement and at least one post-randomisation measurement for the variable to be analysed.
Selective reporting (reporting bias)	Low risk	Outcomes listed in the methods section were all reported
Other bias	Low risk	No other possible bias was found

Hoegholm [1995]		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation was not described
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not described
Blinding of participants and personnel (performance bias)	Low risk	Participants and personnel blinded
Blinding of outcome assessment (detection bias)	Low risk	Blind outcome assessment
Incomplete outcome data (attrition bias)	Unclear risk	It is unclear whether an ITT or PP analysis was used
Selective reporting (reporting bias)	Low risk	Outcomes listed in the methods section were all reported
Other bias	Low risk	No other possible bias was found

Holzgreve [2003]		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomization scheme was generated by computer
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was done with sealed envelopes containing the treatment was provided

		to the investigator for each random number: two of them were opened during the study
Blinding of participants and personnel (performance bias)	High risk	Two of study drugs were administered open-label
Blinding of outcome assessment (detection bias)	Low risk	Blind outcome assessment
Incomplete outcome data (attrition bias)	Low risk	Patients withdrawing from the study were accounted. ITT analysis was performed
Selective reporting (reporting bias)	Low risk	Outcomes listed in the methods section were all reported
Other bias	Low risk	No other possible bias was found.

HYVET [2008]		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	IVRS, for randomising, assigning, and tracking blinded medication was used
Allocation concealment (selection bias)	Low risk	IVRS, for randomising, assigning, and tracking blinded medication was used
Blinding of participants and personnel (performance bias)	High risk	Open follow-up was an option if patients used additional BP-lowering agent for more than 12 weeks
Blinding of outcome assessment (detection bias)	Low risk	Blind outcome assessment
Incomplete outcome data (attrition bias)	Low risk	Patients withdrawing from the study were accounted. ITT analysis was performed
Selective reporting (reporting bias)	Low risk	Outcomes listed in the methods section were all reported
Other bias	Low risk	No other possible bias was found.

HYVET pilot [2003]		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomization scheme was generated by computer
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not described
Blinding of participants and personnel (performance bias)	High risk	Study drugs were administered open-label
Blinding of outcome assessment (detection bias)	High risk	Outcome assessment not blinded
Incomplete outcome data (attrition bias)	Low risk	Patients withdrawing from the study were accounted. ITT analysis was performed
Selective reporting (reporting bias)	Low risk	Outcomes listed in the methods section were all reported
Other bias	Low risk	No other possible bias was found

IDNT [2001]		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomization scheme was generated by computer
Allocation concealment (selection bias)	Low risk	Randomization was blocked by centres

Blinding of participants and personnel (performance bias)	Low risk	Participants and personnel blinded
Blinding of outcome assessment (detection bias)	Low risk	Blind outcome assessment
Incomplete outcome data (attrition bias)	Low risk	Patients withdrawing from the study were accounted. ITT analysis was performed
Selective reporting (reporting bias)	Low risk	Outcomes listed in the methods section were all reported
Other bias	Unclear risk	A number of BP-lowering agents were added to randomly allocated treatment to control BP. The observed effects could equally have resulted from the different additional drugs

INSIGHT [2000]		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation was not described
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not described
Blinding of participants and personnel (performance bias)	Low risk	Participants and personnel blinded
Blinding of outcome assessment (detection bias)	Low risk	Blind outcome assessment
Incomplete outcome data (attrition bias)	Low risk	Analysis excluded 254 patients after randomisation from centres withdrawn due misconduct. ITT analysis was performed
Selective reporting (reporting bias)	Low risk	Outcomes listed in the methods section were all reported
Other bias	Un clear risk	A number of BP-lowering agents were added to randomly allocated treatment to control BP. The observed effects could equally have resulted from the different additional drugs

INVEST [2003]		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	An Internet-based management system automatically randomised each patient to a treatment strategy
Allocation concealment (selection bias)	Low risk	Central randomisation
Blinding of participants and personnel (performance bias)	High risk	Study drugs were administered open-label
Blinding of outcome assessment (detection bias)	Low risk	A PROBE design was used.
Incomplete outcome data (attrition bias)	Low risk	Not indicated whether reasons for missing outcome data were similar across treatment groups. ITT analysis was performed
Selective reporting (reporting bias)	Low risk	Outcomes listed in the methods section were all reported
Other bias	Unclear risk	A number of BP-lowering agents were added to randomly allocated treatment to control BP. The

		observed effects could equally have resulted from the different additional drugs

James [2002]		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomization scheme was generated by computer
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not described
Blinding of participants and personnel (performance bias)	Low risk	Participants and personnel blinded
Blinding of outcome assessment (detection bias)	Low risk	Blind outcome assessment
Incomplete outcome data (attrition bias)	Unclear risk	It is unclear whether an ITT or PP analysis was used
Selective reporting (reporting bias)	Low risk	Outcomes listed in the methods section were all reported
Other bias	Low risk	No other possible bias was found

JMIC-B [2004]		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomization scheme was generated by computer.
Allocation concealment (selection bias)	Low risk	Allocation concealment was done with sealed envelope method.
Blinding of participants and personnel (performance bias)	Low risk	Participants and personnel blinded.
Blinding of outcome assessment (detection bias)	Low risk	Blind outcome assessment.
Incomplete outcome data (attrition bias)	Low risk	Patients withdrawing from the study were accounted. ITT analysis was performed.
Selective reporting (reporting bias)	Low risk	Outcomes listed in the methods section were all reported.
Other bias	Low risk	No other possible bias was found

LAARS [2002]		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomization scheme was generated by computer
Allocation concealment (selection bias)	Low risk	Central randomisation
Blinding of participants and personnel (performance bias)	Low risk	Participants and personnel blinded
Blinding of outcome assessment (detection bias)	Low risk	Blind outcome assessment
Incomplete outcome data (attrition bias)	Unclear risk	It is unclear whether an ITT or PP analysis was used
Selective reporting (reporting bias)	Low risk	Outcomes listed in the methods section were all reported
Other bias	Low risk	No other possible bias was found

LIFE [2002]		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomization scheme was generated by computer
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not described
Blinding of participants and personnel (performance bias)	Low risk	Participants and personnel blinded
Blinding of outcome assessment (detection bias)	Low risk	Blind outcome assessment
Incomplete outcome data (attrition bias)	Low risk	Patients withdrawing from the study were accounted. ITT analysis was performed
Selective reporting (reporting bias)	Low risk	Outcomes listed in the methods section were all reported
Other bias	Unclear risk	A number of BP-lowering agents were added to randomly allocated treatment to control BP. The observed effects could equally have resulted from the different additional drugs

LOTHAR [2006]		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation was not described
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not described
Blinding of participants and personnel (performance bias)	Unclear risk	Method of blinding was not described
Blinding of outcome assessment (detection bias)	Unclear risk	Method of blinding was not described
Incomplete outcome data (attrition bias)	Low risk	It is unclear whether an ITT or PP analysis was used
Selective reporting (reporting bias)	Low risk	Outcomes listed in the methods section were all reported
Other bias	Low risk	No other possible bias was found

Luque [2005]		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation was not described
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not described
Blinding of participants and personnel (performance bias)	Low risk	Participants and personnel blinded
Blinding of outcome assessment (detection bias)	Low risk	Blind outcome assessment
Incomplete outcome data (attrition bias)	Low risk	Patients withdrawing from the study were accounted. ITT analysis was performed
Selective reporting (reporting bias)	Low risk	Outcomes listed in the methods section were all reported

Other bias	Low risk	No other possible bias was found

MAISH [2007]		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation was not described
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not described
Blinding of participants and personnel (performance bias)	Low risk	Participants and personnel blinded
Blinding of outcome assessment (detection bias)	Low risk	Blind outcome assessment
Incomplete outcome data (attrition bias)	Low risk	Not indicated whether reasons for missing outcome data were similar across treatment groups. Modified ITT analysis was performed including patients who received at least 1 dose of study drug and who had at least one visit after baseline
Selective reporting (reporting bias)	Low risk	Outcomes listed in the methods section were all reported
Other bias	Low risk	No other possible bias was found

Mallion [2000]		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation was not described
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not described
Blinding of participants and personnel (performance bias)	Low risk	Participants and personnel blinded
Blinding of outcome assessment (detection bias)	Low risk	Blind outcome assessment
Incomplete outcome data (attrition bias)	Low risk	Patients withdrawing from the study were accounted. ITT analysis was performed
Selective reporting (reporting bias)	Low risk	Outcomes listed in the methods section were all reported
Other bias	Low risk	No other possible bias was found

Mallion [2007]		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation was not described
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not described
Blinding of participants and personnel (performance bias)	Low risk	Participants and personnel blinded
Blinding of outcome assessment (detection bias)	Low risk	Blind outcome assessment
Incomplete outcome data (attrition bias)	Low risk	Not indicated whether reasons for missing outcome data were similar across treatment

		groups. Modified ITT was performed including randomised patients who received at least one dose of trial medication and with at least one post randomisation value for the primary efficacy variable
Selective reporting (reporting bias)	Low risk	Outcomes listed in the methods section were all reported
Other bias	Low risk	No other possible bias was found

Mallion [2011]		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation was not described
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not described
Blinding of participants and personnel (performance bias)	Low risk	Participants and personnel blinded
Blinding of outcome assessment (detection bias)	Low risk	Blind outcome assessment
Incomplete outcome data (attrition bias)	Low risk	Patients withdrawing from the study were accounted. ITT analysis was performed
Selective reporting (reporting bias)	Low risk	Outcomes listed in the methods section were all reported
Other bias	Low risk	No other possible bias was found

Mancia [2000]		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation was not described
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not described
Blinding of participants and personnel (performance bias)	Low risk	Participants and personnel blinded
Blinding of outcome assessment (detection bias)	Low risk	Blind outcome assessment
Incomplete outcome data (attrition bias)	Unclear risk	It is unclear whether an ITT or PP analysis was used
Selective reporting (reporting bias)	Low risk	Outcomes listed in the methods section were all reported
Other bias	Low risk	No other possible bias was found

MAPAVEL [2002]		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation was not described
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not described
Blinding of participants and personnel (performance bias)	Low risk	Participants and personnel blinded

Blinding of outcome assessment (detection bias)	Low risk	Blind outcome assessment
Incomplete outcome data (attrition bias)	Unclear risk	It is unclear whether an ITT or PP analysis was used
Selective reporting (reporting bias)	Low risk	Outcomes listed in the methods section were all reported
Other bias	Low risk	No other possible bias was found

McInnes [2000]		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomization scheme was generated by computer
Allocation concealment (selection bias)	Low risk	Central randomisation
Blinding of participants and personnel (performance bias)	Low risk	Participants and personnel blinded
Blinding of outcome assessment (detection bias)	Low risk	Blind outcome assessment
Incomplete outcome data (attrition bias)	Low risk	Not indicated whether reasons for missing outcome data were similar across treatment groups. Modified ITT was performed including all patients who took at least one dose of double-blind medication and who had efficacy data available after randomisation
Selective reporting (reporting bias)	Low risk	Outcomes listed in the methods section were all reported
Other bias	Low risk	No other possible bias was found

MIDAS [1996]		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	The randomisation was stratified by clinic using randomly permuted blocks
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not described
Blinding of participants and personnel (performance bias)	Low risk	Participants and personnel blinded
Blinding of outcome assessment (detection bias)	Low risk	Blind outcome assessment
Incomplete outcome data (attrition bias)	Low risk	Patients withdrawing from the study were accounted. ITT analysis was performed
Selective reporting (reporting bias)	Low risk	Outcomes listed in the methods section were all reported
Other bias	Low risk	No other possible bias was found

Mimran [1998]		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation was not described.
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not described.

Blinding of participants and personnel (performance bias)	Low risk	Participants and personnel blinded.
Blinding of outcome assessment (detection bias)	Low risk	Blind outcome assessment.
Incomplete outcome data (attrition bias)	Unclear risk	It is unclear whether an ITT or PP analysis was used.
Selective reporting (reporting bias)	Low risk	Outcomes listed in the methods section were all reported.
Other bias	Low risk	No other possible bias was found.

Mounier-Vehier [1998]		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomization scheme was generated by computer.
Allocation concealment (selection bias)	Low risk	Central randomisation.
Blinding of participants and personnel (performance bias)	High risk	Participants and personnel were not blinded.
Blinding of outcome assessment (detection bias)	High risk	Study drugs were administered open-label.
Incomplete outcome data (attrition bias)	Low risk	Not indicated whether reasons for missing outcome data were similar across treatment groups. ITT analysis was performed excluding one patient whose DBP exceeded 120 mm Hg at the end of the washout period
Selective reporting (reporting bias)	Low risk	Outcomes listed in the methods section were all reported.
Other bias	Low risk	No other possible bias was found.

Mroczek [1996]		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation was not described
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not described
Blinding of participants and personnel (performance bias)	Low risk	Participants and personnel blinded
Blinding of outcome assessment (detection bias)	Low risk	Blind outcome assessment
Incomplete outcome data (attrition bias)	Low risk	Patients withdrawing from the study were accounted. ITT analysis was performed
Selective reporting (reporting bias)	Low risk	Outcomes listed in the methods section were all reported
Other bias	Low risk	No other possible bias was found

Narkiewicz [2007]		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation was not described

Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not described
Blinding of participants and personnel (performance bias)	Low risk	Participants and personnel blinded
Blinding of outcome assessment (detection bias)	Low risk	Blind outcome assessment
Incomplete outcome data (attrition bias)	Low risk	Patients withdrawing from the study were accounted. ITT analysis was performed
Selective reporting (reporting bias)	Low risk	Outcomes listed in the methods section were all reported
Other bias	Low risk	No other possible bias was found

NICE-EH [1999]		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation was not described
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not described
Blinding of participants and personnel (performance bias)	Low risk	Participants and personnel blinded
Blinding of outcome assessment (detection bias)	Low risk	Blind outcome assessment
Incomplete outcome data (attrition bias)	High risk	Data of withdrawn patients were not included. PP analyses was used
Selective reporting (reporting bias)	Low risk	Outcomes listed in the methods section were all reported
Other bias	Low risk	No other possible bias was found

Nilsson [2007]		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation was not described
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not described
Blinding of participants and personnel (performance bias)	Low risk	Participants and personnel blinded
Blinding of outcome assessment (detection bias)	Low risk	Blind outcome assessment
Incomplete outcome data (attrition bias)	Low risk	Patients withdrawing from the study were accounted. ITT analysis was performed.
Selective reporting (reporting bias)	Low risk	Outcomes listed in the methods section were all reported
Other bias	Low risk	No other possible bias was found

NORDIL [2000]		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation was not described
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not described

Blinding of participants and personnel (performance bias)	High risk	Study drugs were administered open-label
Blinding of outcome assessment (detection bias)	Low risk	A PROBE design was used.
Incomplete outcome data (attrition bias)	Low risk	Patients withdrawing from the study were accounted. ITT analysis was performed.
Selective reporting (reporting bias)	Low risk	Outcomes listed in the methods section were all reported
Other bias	Unclear risk	A number of BP-lowering agents were added to randomly allocated treatment to control BP. The observed effects could equally have resulted from the different additional drugs

Oparil [1998]		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation was not described
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not described
Blinding of participants and personnel (performance bias)	Low risk	Participants and personnel blinded
Blinding of outcome assessment (detection bias)	Low risk	Blind outcome assessment
Incomplete outcome data (attrition bias)	High risk	Data of withdrawn patients were not included. PP analyses was used
Selective reporting (reporting bias)	Low risk	Outcomes listed in the methods section were all reported
Other bias	Low risk	No other possible bias was found

Os [1997]		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation was not described
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not described
Blinding of participants and personnel (performance bias)	Low risk	Participants and personnel blinded
Blinding of outcome assessment (detection bias)	Low risk	Blind outcome assessment
Incomplete outcome data (attrition bias)	Unclear risk	It is unclear whether an ITT or PP analysis was used
Selective reporting (reporting bias)	Low risk	Outcomes listed in the methods section were all reported
Other bias	Low risk	No other possible bias was found

Papademetriou [1997]		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation was not described

Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not described
Blinding of participants and personnel (performance bias)	Low risk	Participants and personnel blinded
Blinding of outcome assessment (detection bias)	Low risk	Blind outcome assessment
Incomplete outcome data (attrition bias)	Unclear risk	It is unclear whether an ITT or PP analysis was used
Selective reporting (reporting bias)	Low risk	Outcomes listed in the methods section were all reported
Other bias	Low risk	No other possible bias was found

Pareek [2010]		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation was not described
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not described
Blinding of participants and personnel (performance bias)	Unclear risk	Method of blinding was not described
Blinding of outcome assessment (detection bias)	Unclear risk	Method of blinding was not described
Incomplete outcome data (attrition bias)	High risk	Data of withdrawn patients were not included. PP analyses was used
Selective reporting (reporting bias)	Low risk	Outcomes listed in the methods section were all reported
Other bias	Low risk	No other possible bias was found

PATS [1995]		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomization scheme was generated by computer
Allocation concealment (selection bias)	Low risk	Allocation concealment was done with sealed envelope supplied by the coordinating office
Blinding of participants and personnel (performance bias)	Low risk	Participants and personnel blinded
Blinding of outcome assessment (detection bias)	Low risk	Blind outcome assessment
Incomplete outcome data (attrition bias)	Low risk	Patients withdrawing from the study were accounted. ITT analysis was performed
Selective reporting (reporting bias)	Low risk	Outcomes listed in the methods section were all reported
Other bias	Low risk	No other possible bias was found

PRESERVE [2001]		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation was not described

Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not described
Blinding of participants and personnel (performance bias)	Low risk	Participants and personnel blinded
Blinding of outcome assessment (detection bias)	Low risk	Blind outcome assessment
Incomplete outcome data (attrition bias)	Low risk	Patients withdrawing from the study were accounted. ITT analysis was performed
Selective reporting (reporting bias)	Low risk	Outcomes listed in the methods section were all reported
Other bias	Low risk	No other possible bias was found

RACE [1995]		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomization scheme was generated by computer
Allocation concealment (selection bias)	Low risk	Central randomisation
Blinding of participants and personnel (performance bias)	Low risk	Participants and personnel blinded
Blinding of outcome assessment (detection bias)	Low risk	Blind outcome assessment
Incomplete outcome data (attrition bias)	Unclear risk	It is unclear whether an ITT or PP analysis was used
Selective reporting (reporting bias)	Low risk	Outcomes listed in the methods section were all reported
Other bias	Low risk	No other possible bias was found

Radauceanu [2004]		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation was not described
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not described
Blinding of participants and personnel (performance bias)	Low risk	Participants and personnel blinded
Blinding of outcome assessment (detection bias)	Low risk	Blind outcome assessment
Incomplete outcome data (attrition bias)	Low risk	Patients withdrawing from the study were accounted. ITT analysis was performed
Selective reporting (reporting bias)	Low risk	Outcomes listed in the methods section were all reported
Other bias	Low risk	No other possible bias was found

REGAAL [2002]		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation was not described
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not described

Blinding of participants and personnel (performance bias)	Low risk	Participants and personnel blinded
Blinding of outcome assessment (detection bias)	Low risk	Blind outcome assessment
Incomplete outcome data (attrition bias)	Low risk	Patients withdrawing from the study were accounted. ITT analysis was performed
Selective reporting (reporting bias)	Low risk	Outcomes listed in the methods section were all reported
Other bias	Low risk	No other possible bias was found

REZALT [2009]		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation was not described
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not described
Blinding of participants and personnel (performance bias)	Low risk	Participants and personnel blinded
Blinding of outcome assessment (detection bias)	Low risk	Blind outcome assessment
Incomplete outcome data (attrition bias)	Low risk	Patients withdrawing from the study were accounted. ITT analysis was performed
Selective reporting (reporting bias)	Low risk	Outcomes listed in the methods section were all reported
Other bias	Low risk	No other possible bias was found

Ruilope [2001]		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation was not described.
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not described.
Blinding of participants and personnel (performance bias)	Low risk	Participants and personnel blinded.
Blinding of outcome assessment (detection bias)	Low risk	Blind outcome assessment.
Incomplete outcome data (attrition bias)	Low risk	Not indicated whether reasons for missing outcome data were similar across treatment groups. Modified ITT analysis was performed including all randomised subjects with at least one valid on-therapy BP measurement
Selective reporting (reporting bias)	Low risk	Outcomes listed in the methods section were all reported.
Other bias	Low risk	No other possible bias was found.

SHELL [2003]		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomization was made by BETA trial centre, using a sequentially based criterion

Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not described
Blinding of participants and personnel (performance bias)	Unclear risk	Method of blinding was not described
Blinding of outcome assessment (detection bias)	Unclear risk	Method of blinding was not described
Incomplete outcome data (attrition bias)	Low risk	Patients withdrawing from the study were accounted. ITT analysis was performed
Selective reporting (reporting bias)	Low risk	Outcomes listed in the methods section were all reported.
Other bias	Low risk	No other potential bias was found

Stimpel [1997]		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation was not described
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not described
Blinding of participants and personnel (performance bias)	Low risk	Participants and personnel blinded
Blinding of outcome assessment (detection bias)	Low risk	Blind outcome assessment
Incomplete outcome data (attrition bias)	Low risk	Not indicated whether reasons for missing outcome data were similar across treatment groups. Modified ITT analysis was performed including all randomised patients who had at least one baseline BP reading and one post baseline reading
Selective reporting (reporting bias)	Low risk	Outcomes listed in the methods section were all reported
Other bias	Low risk	No other possible bias was found

Syst-Eur [1997]		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomization scheme was generated by computer.
Allocation concealment (selection bias)	Low risk	Concealment scheme was implemented at the clinical trials centre and stratified by centre, sex and pervious cardiovascular complications
Blinding of participants and personnel (performance bias)	Low risk	Participants and personnel blinded
Blinding of outcome assessment (detection bias)	Low risk	Blind outcome assessment
Incomplete outcome data (attrition bias)	Low risk	Patients withdrawing from the study were accounted. ITT analysis was performed
Selective reporting (reporting bias)	Low risk	Outcomes listed in the methods section were all reported
Other bias	Low risk	No other possible bias was found

UKPDS [1998]

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization scheme was generated by computer
Allocation concealment (selection bias)	Low risk	Allocation concealment was done with opaque, sealed envelopes with a check maintained on numerical sequence, until dates of opening and results
Blinding of participants and personnel (performance bias)	High risk	Study drugs were administered open-label
Blinding of outcome assessment (detection bias)	High risk	Outcome assessment not blinded
Incomplete outcome data (attrition bias)	Low risk	Not mentioned whether reasons for missing outcome data were similar between treatment groups. ITT analysis was performed
Selective reporting (reporting bias)	Low risk	Outcomes listed in the methods section were all reported
Other bias	Unclear risk	A number of BP-lowering agents were added to randomly allocated treatment to control BP. The observed effects could equally have resulted from the different additional drugs

Value [2004]		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomization scheme was generated by computer
Allocation concealment (selection bias)	Unclear risk	Method of concealment was not described
Blinding of participants and personnel (performance bias)	Low risk	Participants and personnel blinded
Blinding of outcome assessment (detection bias)	Low risk	Blind outcome assessment
Incomplete outcome data (attrition bias)	Low risk	68 patients in 9 centres were excluded after randomisation due misconduct. ITT analysis was performed
Selective reporting (reporting bias)	Low risk	Outcomes listed in the methods section were all reported
Other bias	Unclear risk	A number of BP-lowering agents were added to randomly allocated treatment to control BP. The observed effects could equally have resulted from the different additional drugs

VHAS [1998]		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation was not described
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not described
Blinding of participants and personnel (performance bias)	Unclear risk	Method of blinding was not described
Blinding of outcome assessment (detection bias)	Unclear risk	Method of blinding was not described

Incomplete outcome data (attrition bias)	Low risk	Patients withdrawing from the study were accounted. ITT analysis was performed
Selective reporting (reporting bias)	Low risk	Outcomes listed in the methods section were all reported
Other bias	Unclear risk	A number of BP-lowering agents were added to randomly allocated treatment to control BP. The observed effects could equally have resulted from the different additional drugs

Volpe [2003]		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation was not described
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not described
Blinding of participants and personnel (performance bias)	Low risk	Participants and personnel blinded.
Blinding of outcome assessment (detection bias)	Low risk	Blind outcome assessment
Incomplete outcome data (attrition bias)	Low risk	Not indicated whether reasons for missing outcome data were similar across treatment groups. ITT analysis was performed including population with any missing post-randomisation measurements estimated by carrying forward previous post- randomisation measurements
Selective reporting (reporting bias)	Low risk	Outcomes listed in the methods section were all reported.
Other bias	Low risk	No other possible bias was found

Waeber [1999]		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation was not described
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not described
Blinding of participants and personnel (performance bias)	Low risk	Participants and personnel blinded
Blinding of outcome assessment (detection bias)	Low risk	Blind outcome assessment
Incomplete outcome data (attrition bias)	Unclear risk	It is unclear whether an ITT or PP analysis was used
Selective reporting (reporting bias)	Low risk	Outcomes listed in the methods section were all reported
Other bias	Low risk	No other possible bias was found

Wu [2004]		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation was not described
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not described

Blinding of participants and personnel (performance bias)	Unclear risk	Method of blinding was not described
Blinding of outcome assessment (detection bias)	Unclear risk	Method of blinding was not described
Incomplete outcome data (attrition bias)	Unclear risk	It is unclear whether an ITT or PP analysis was used
Selective reporting (reporting bias)	Low risk	Outcomes listed in the methods section were all reported
Other bias	Low risk	No other possible bias was found

Yang [2015]		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation was not described
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not described.
Blinding of participants and personnel (performance bias)	Unclear risk	Method of blinding was not described
Blinding of outcome assessment (detection bias)	Unclear risk	Method of blinding was not described
Incomplete outcome data (attrition bias)	Low risk	Patients withdrawing from the study were accounted. ITT analysis was performed
Selective reporting (reporting bias)	Low risk	Outcomes listed in the methods section were all reported.
Other bias	Low risk	No other possible bias was found.

Zanchetti [2001]		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation was not described
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not described
Blinding of participants and personnel (performance bias)	Low risk	Participants and personnel blinded
Blinding of outcome assessment (detection bias)	Low risk	Blind outcome assessment
Incomplete outcome data (attrition bias)	Low risk	Not indicated whether reasons for missing outcome data were similar across treatment groups. Modified ITT analysis was performed including all randomly assigned patients who received at least one dose of the treatment drug and who had at least one visit after baseline
Selective reporting (reporting bias)	Low risk	Outcomes listed in the methods section were all reported.
Other bias	Low risk	No other possible bias was found

3.2.2 Discussion

In a systematic review of published studies, there are multiple sources of biases that may lead to erroneous results and rigorous efforts required to protect against this. All included studies stated that they were RCTs; however, most studies did not address how treatment randomization occurred or how allocation of treatment was concealed, and, therefore, had an unclear risk of selection bias. All included studies also stated that they were double-blinded studies, but again, most did not describe how double blinding was ensured throughout the studies. Most of the studies were assessed as having a low risk of performance and detection bias. All efforts were made to reduce the risk of attrition bias by reporting all randomized participants in the analysis (ITT population) as much as possible. All of the studies had a low risk for reporting bias. One potential unclear source of bias was present in 13 of the 82 studies; mainly because a number of BP-lowering agents were added to randomly allocated treatment to control high BP. The overall quality was rated to be acceptable to high. Whereas 48 studies were rated to be high quality studies (as the majority of criteria were met and there was little or no risk of bias), 34 studies were rated as acceptable quality studies (as most criteria were met and there were some flaws in the study).

RCTs are considered the gold standard for demonstrating treatment efficacy. The main goal of comparative clinical studies is to provide comparisons of treatments with maximum precision and validity. This is the critical component of clinical studies, since it helps remove the effect of extraneous variables (such as age and previous injury) and reduces the bias associated with treatment assignment (414). Generally, biases are often assumed and acknowledged in observational studies, and the statistical analysis and subsequent interpretation try to take those biases into account. However, studies labelled as randomised are frequently assumed to be free of bias, and it is common that inadequate reporting masks the deficiencies they might have. Therefore, researchers should ensure both adequate sequence generation and reliable allocation concealment in randomisation schemes. An error in either factor could compromise randomisation, leading to incorrect results (415).

Randomisation is the process of assigning participants to treatment and control groups, assuming that each participant has an equal chance of being assigned to

any group and it depends mainly on two measures. Firstly, an allocation sequence that is appropriate to prevent selection bias must be generated (e.g. using a computer algorithm). Secondly, this sequence must be concealed from investigators enrolling patients (416). Proper randomisation, also known as allocation concealment, ensures no *a priori* knowledge of group assignment, as researchers are unaware of which group patients are allocated to at the time they enter the study. Knowledge of group assignment creates a level of possible selection bias that may affect the data. However, it is not uncommon for an adequate (i.e. randomized) allocation sequence to be inadequately concealed.

Since all included studies were stated as being RCTs, a high risk of selection bias (sequence generation and allocation concealment) was excluded. Adequate (that is, described in sufficient detail) random sequencing and allocation concealment was conducted in 30 and 18 studies respectively. However, 11 meta-analyses that involved 127 RCTs on the efficacy of interventions showed that studies with inadequate or unclear randomisation had a tendency to overestimate treatment effects by up to 40%, compared with those that used proper randomisation, and the outcome of the study can be negatively influenced by this (417). Consequently, an unclear risk of selection bias is still possible some studies.

The risk posed by prior knowledge of the allocated interventions on the part of participants and personnel in study is referred to as performance bias, which can be reduced by blinding of the above parties. However, some review authors confuse allocation concealment with blinding of allocated interventions. Allocation concealment aims to avoid selection bias in intervention assignment through protecting the allocation sequence before and until assignment, and can always be effectively implemented in spite of the study subject. On the other hand, blinding aims to avoid performance and detection bias through protecting the sequence after assignment, and cannot always be implemented (e.g. in studies comparing surgical with medical treatments)(416). In general, a patient or researcher who expects the effect of a particular intervention could intentionally observe or detect an improved treatment effect. The common term “double-blinded” refers to complete avoidance of performance bias through blinding both participants and personnel.

When the outcome can possibly be affected by patient or investigator's expectations, then blinding is important. Blinding is of three types - single blind: when the patient is blind, double blind: when the patient and the investigator are blind, and triple blind: when the patient, investigator and data clean-up people are blind (39). Bias may as well be introduced at some stage in the statistical analysis of the study through the selective use and reporting of statistical tests. This may be unintentionally made by investigators keen to observe a positive result, however the consequences are weighty (418).

In the current review, the majority of studies had a low risk for bias, as they described all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received and providing any information relating to whether the intended blinding was effective. Effective blinding can also ensure that the compared groups have a similar amount of care and additional treatment, as well as diagnostic investigations. However, blinding is not always possible in many situations, for various reasons. For instance, it is generally impossible to blind people to whether or not major surgery had been undertaken (159) .

In total, 13 open-label studies (ASCOT-BPLA [2005]; CASE-J [2008]; CONVINCE [2003]; Cremonesi [2002]; FACET [1998]; Fogari [2008]; Holsgreve [2003]; HYVET [2008]; HYVET-P [2003]; INVEST [2003]; Mounier-Vehier [1998]; NORDIL [2000]; UKPDS [1998]) were considered to be at high risk of performance bias due to knowledge of the allocated interventions on the part of participants and personnel throughout the study. However, open-label studies are still few and the PROBE design was used in a number of them, such as ASCOT-BPLA [2005]; CASE-J [2008]; Fogari [2008]; INVEST [2003]; NORDIL [2000]. The PROBE design was compared to the classical double-blind design, and has a lower cost and is more similar to standard clinical practice (419). Since the review is on BP response and the primary outcome is based on repeat measurements which (in this review) followed well-defined protocols and standardised techniques in all included studies, there was no difference between the two types of studies in this regard.

Regardless of careful concern of methods to blind individuals in clinical studies, situations will always happen when some or all groups of individuals cannot

ethically be blinded. Researchers have to understand this reality and consider other approaches to reduce bias when blinding is not possible. For instance, when patients or clinicians cannot be blinded, researchers should ensure that the two (or more) allocation groups are, apart from the intervention, treated as equally as possible. This might involve providing a standard care for patients (e.g., co-interventions, follow-up frequency and complications management) (418). On the other hand, researchers may decide to use an expertise-based study design, in which patients are randomly assigned to different clinicians that each performs one intervention.

Detection bias refers to the risk of how the evaluation of the outcome may impose a bias on effects. If bias is introduced during a study because of differential treatment of groups or biased assessment of outcomes, no analytical techniques can correct for this limitation. Therefore, researchers must interpret the results from un-blinded studies with caution as blinding of outcome assessors reduces detection bias (159) . Outcome assessors or investigators, who are aware of the real treatment, could intentionally change their assessment. An adequate blinding of outcome assessment was applied in most of the studies in this review by means of describing all measures used, if any, to blind outcome assessors from knowledge of which intervention a participant received and providing any information relating to whether the intended blinding was effective.

Nonetheless, it was unclear in eight studies (Bremner [1997]; DETAIL [2004]; LOTHAR [2006]; Pareek [2010]; SHELL [2003]; VHAS [1998]; Wu [2004]; Yang [2015]) whether blinding was broken prior to making the final decision to withdraw, as the method of binding was not described in sufficient detail. Detection bias was seen in a number of studies (CASE-J [2008]; Cremonesi [2002]; FACET [1998]; HYVET-P [2003]; Mounier-Vehier [1998]; UKPDS [1998]) where drugs were administered under an open label and outcome was not blindly assessed. Although open-label studies are still relatively rare, detection bias, due to outcome assessors' knowledge of the allocated interventions, may be present in these studies.

According Cochrane recommendations for systematic reviews of interventions, an acceptable overall drop-out rate is considered to be 20% or less of participants who were randomised or allocated into each group (159). While it is easier to assess whether a drop-out rate goes above 20%, there is no guarantee that results

from a study with a drop-out rate of less than 20% are at low risk of bias (420). Low total drop-out rates are often expected in shorter studies ,however high total drop-out rates might be acceptable for studies of longer duration (159).

Missing outcome data, due to attrition (drop-out) during the study or exclusions from the analysis, increase the risk that the observed effect estimate is biased. In most cases, attrition can happen if participants are withdrawn from the study, lost to follow-up, non-compliers or unavailable for other reasons. Some participants may be excluded from analysis when they were later found to be ineligible or PP analysis is performed (included only if they received the intended intervention in accordance with the protocol). The intention to exclude such participants should be specified before the outcome data are seen, although, some exclusions of participants may be justified and not be considered as leading to missing outcome data (421;422). Although omitting some participants from reports of analyses, in spite of outcome data being available, is justified in some cases, it is usually still advised to avoid it as much as possible. Ideally, investigators would have no exclusions after randomisation and use an ITT analysis, as all participants enrolled should be analysed as part of the original group they were assigned to.

An ITT analysis is often recommended as the least biased way to measure intervention effects in randomized studies. It includes keeping participants in the intervention groups to which they were randomized, in spite of the intervention they actually received, measure outcome data on all participants, and include all randomized participants in the analysis. The first principle can often be applied. Though, the second is often impossible due to attrition beyond the control of the researchers. In consequence, the third principle of including all participants can only be followed by making assumptions about the missing values (imputations) (423). Consequently, a small number of studies can perform a true ITT analysis without making imputations, mainly when there is extended follow-up. Therefore, in this systematic review, the risk of attrition bias was avoided by performing an ITT analysis including a description of the completeness of outcome data for each main outcome, incorporating attrition and exclusions from the analysis.

In practice, researchers can describe an analysis as ITT even when some outcome data are missing.The term “ITT” does not have a clear and consistent definition, and it is used inconsistently in study reports. For instance, review authors might also encounter analyses described as “modified ITT” such as ALPINE [2003]; Benetos [2000]; Black [1997]; CROSS [2003]; Derosa [2013]; ELSA [2002]; ELVERA [2004]; Giles [2007]; Grethouse [2010]; Guthrie [1998]; Hegner [1997]; MAISH [2007]; Mallion [2007]; McInnes [2000]; Ruilope [2001]; Stimpel [1997]; Zanchetti [2001]), which usually means that participants were excluded if they did not receive a specific minimum amount of the intended intervention (e.g. who did not receive at least one dose of study medication and from whom at least one post-baseline BP measurement) .This term is as well used in a variety of ways so review authors should always look for information about exactly who was included (424).

As a general observation, analyses with statistically significant differences between intervention groups are more likely to be reported than non-significant differences. However, all studies in this systematic review reported pre-specified outcomes listed in the methods section, therefore the reporting bias (defined as systematic differences between reported and unreported findings) was avoided.

Many patients require more than one BP-lowering agent to achieve their BP goal (AASK [2002]; ACCOMPLISH [2008]; ALLHAT [2002]; CONVINCE [2003]; FACET [1998]; IDNT [2001]; INSIGHT [2000]; INVEST [2003]; LIFE [2002]; NORDIL [2000]; UKPDS [1998]; VALUE [2004]; VHAS [1998]). The observed effects could equally have resulted from the different additional drugs. If this was not balanced between groups, it would lead to a risk of performance bias and the results may have been confounded; however, they were assumed to reflect the effect of the first drug. In addition, the results of this review are less likely to be affected, given that only 13 studies used additional BP-lowering agents.

In most cases, smaller numbers of participants was the problem with older studies, and the researchers tried to overcome this problem with new and larger studies, since a study with low statistical power has a smaller chance of detecting a true effect, based on the likelihood that a statistically significant result reflects a true effect. Consequently, the effect size will be overestimated, the results will be less reproducible and there is also an ethical dimension, as unreliable researches are ineffective and wasteful (425).

Funnel plot of the studies effect estimates against sample size, can be used assess the validity of meta-analyses. It is based on the theory that the precision in estimating the underlying treatment effect will increase as the sample size of included studies increases. Funnel plots have been interpreted in different ways by different observers and the value of them has not been systematically examined, and symmetry (or asymmetry) has generally been defined informally, through visual inspection (426;427).

Funnel plot asymmetry was found in (38%) journal meta-analyses and (13%) Cochrane reviews (426). Therefore, critical examination for the presence of publication and related biases has to become an important part of meta-analytic studies as well as systematic reviews. However, when there is evidence of small-study effects, publication bias should be considered as only one of a number of possible explanations such as data irregularities (such as poor methodological quality or inadequate analysis), true heterogeneity (such as intensity of intervention or differences in underlying risk) or chance (426). In the review, almost all the outlier were placebo controlled studies where the intensity of intervention might differ considerably. In most cases, funnel plot and tests for funnel plot asymmetry, might alert review authors to a problem which needs considering, although they do not provide a solution to this problem.

3.3 Effect of intervention

3.3.1 Delta-BP response

For the delta -BP response, 56 studies were included in the analysis (ordered by study ID):

AASK 2002	ELSA 2002	JMIC-B 2004	Oparil 1998
Alcocer 1995	FACET 1998	LAARS 2002	Os 1997
ALLHAT 2002	Farsang 2007	LIFE 2002	Papademetriou 1997
ALPINE 2003	Freytag 2001	MAISH 2007	Pareek 2010
ASCOT-BPLA 2005	Giles 2007	Mallion 2000	PRESERVE 2001
Benetos 2000	Grassi 2003	Mallion 2007	REZALT 2009
Black 1997	Greathouse 2010	Mallion 2011	Ruilope 2001
Black 2001	Guthrie 1998	Mancia 2000	Stimpel 1997
Bremner 1997	Hanefeld 2001	MAPAVEL 2002	Syst-Eur 1997
Chanudet 2001	Hegner 1997	Mimran 1998	UKPDS 1998
CONVINCE 2003	Hoegholm 1995	Mroczek 1996	Value 2004
Cremonesi 2002	HYVET 2008	NICE-EH 1999	Volpe 2003
DETAIL 2004	HYVET pilot 2003	Nilsson 2007	Waeber 1999
ELLE 2003	INVEST 2003	NORDIL 2000	Wu 2004

3.3.1.1 BP response for ACEI-delta

During a total of 56,431 person-years of follow-up, using the WMD method and FE model, the mean SBP reduction of ACEI was 1.98 mmHg, 95% CI 1 [1.81, 2.15] less than ARB, 1.43 mmHg, 95% CI [1.00, 1.85] less than CCB, 0.50 mmHg, 95% CI [0.15, 0.85] less than DI. SBP reduction was -0.99 mmHg, 95% CI [-1.50, -0.48] more than BB and -6.27 mmHg, 95% CI - [-8.06, -4.49] more than the placebo. However, there was no significant difference between ACEIs (P = 0.18), as shown in **Figure 3.3.**

For DBP, as shown in **Figure 3.4**, the mean DBP reduction of ACEI was 0.76 mm Hg, 95% CI [0.52, 1.01]. DBP reduction of ACEI was -0.52 mmHg, 95% CI [-0.67, -0.36] more than ARB, -0.83 mmHg 95% CI [-1.03, -0.63] more than DI, -0.95 mm Hg 95% CI [-1.21, -0.69] more than BB and -3.55 mmHg 95% CI [-4.09, -3.00] more than the placebo. However, there was no significant difference between ACEIs (P = 0.14).

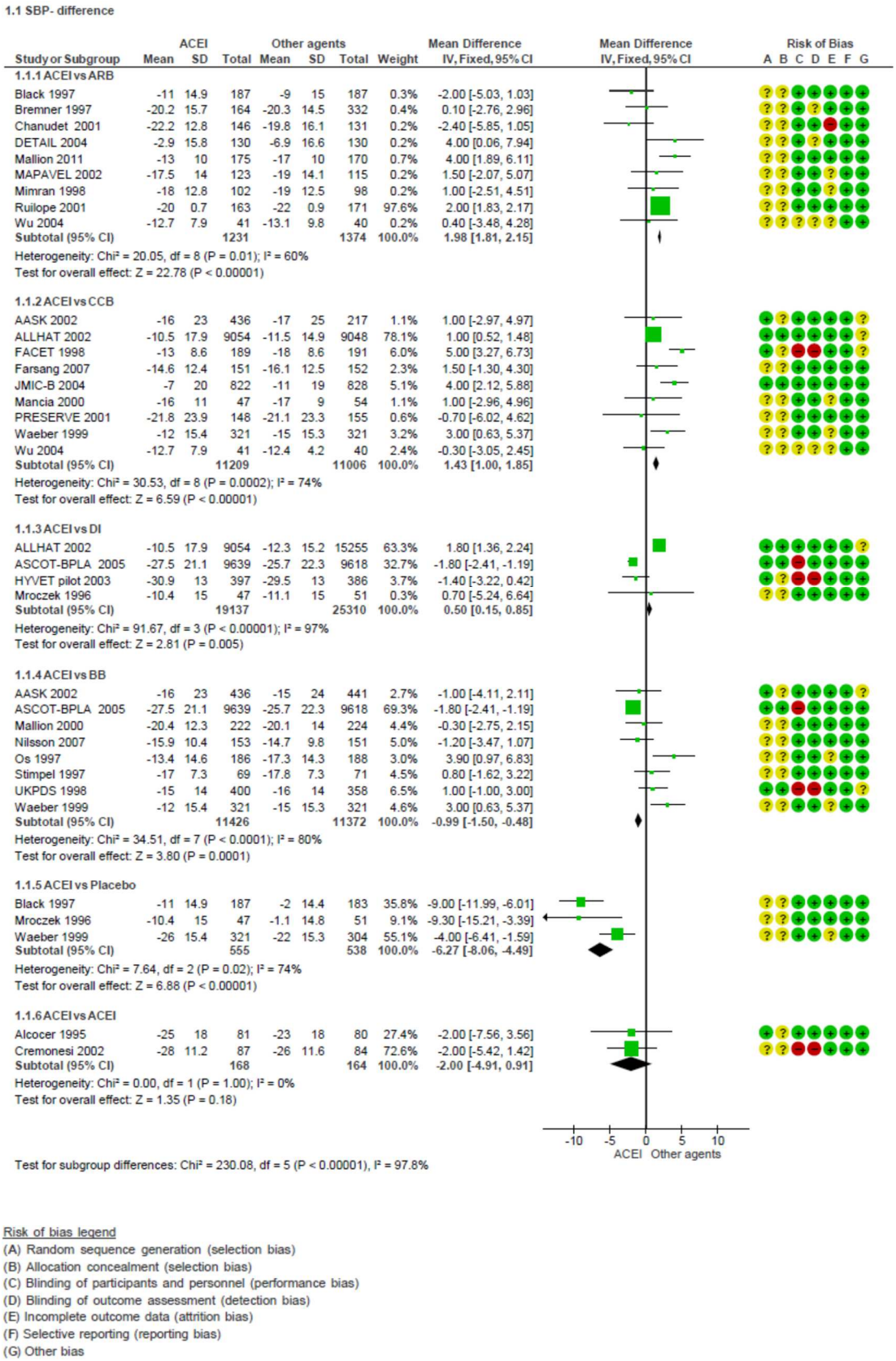


Figure 3.3 Forest plot of comparison of ACEI vs other agents: BP-delta, outcome [FE model]: SBP reduction. Net change in clinic/office SBP for ACEI versus other agents, both in diagrammatic and numerical format (mmHg, 95% CI) .The overall effect represents the pooled estimate of mean net change in SBP response.

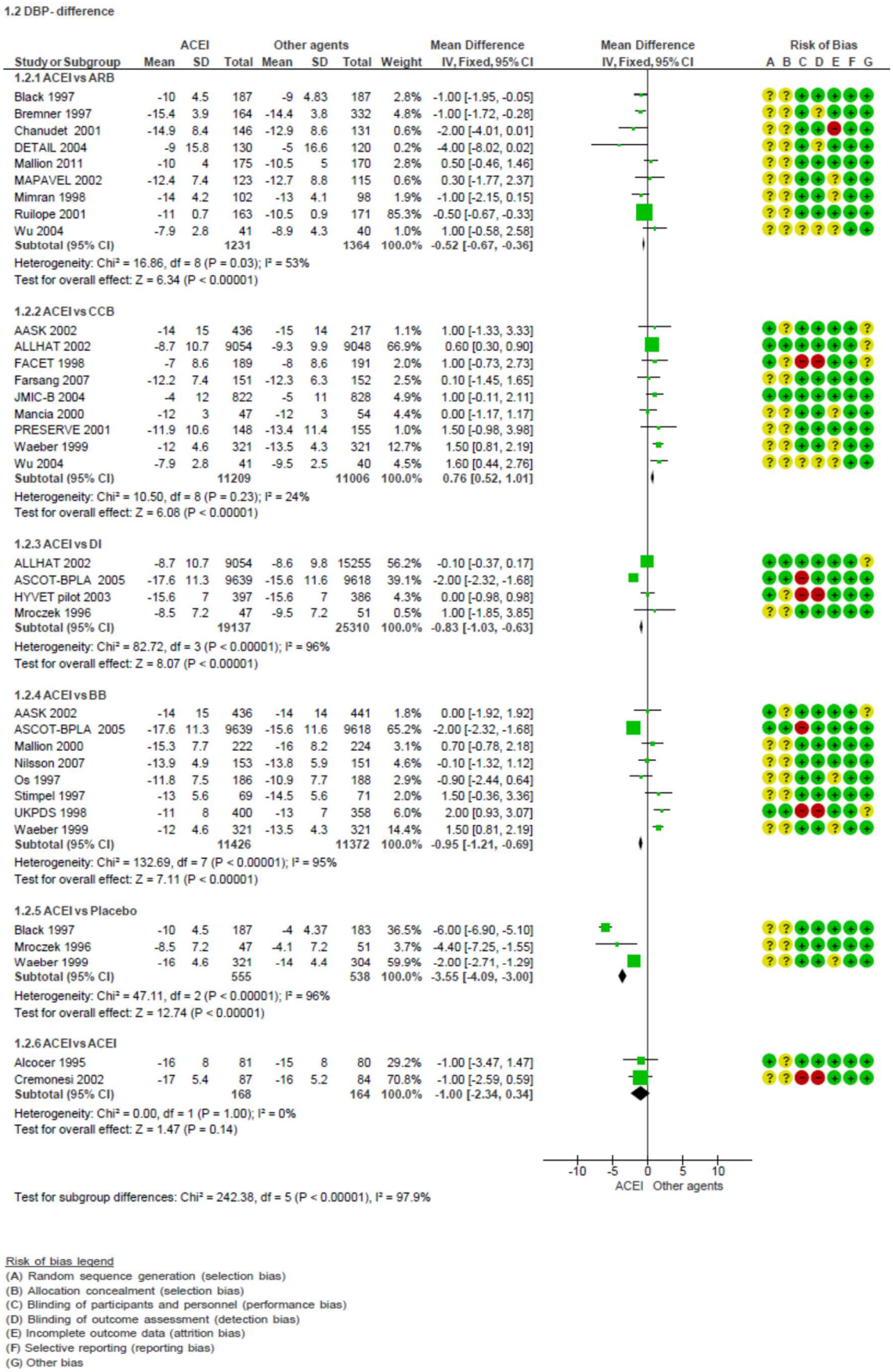


Figure 3.4 Forest plot of comparison of ACEI vs other agents: BP-delta, outcome [FE model]: DBP reduction. Net change in clinic/office DBP for ACEI versus other agents, both in diagrammatic and numerical format (mmHg, 95% CI) .The overall effect represents the pooled estimate of mean net change in DBP response.

Heterogeneity was seen of an I^2 value of 74% for the nine studies comparing SBP reduction respectively, with ACEIs vs CCBs. Using the RE model, mean differences were shown for both SBP and DBP of 2.06, 95% CI [0.66, 3.47] and 0.87, 95% CI [0.49, 1.25] respectively, as shown in **Figure 3.5** and **Figure 3.6**.The observed statistical heterogeneity was most likely due to the methodological diversity of the FACET [1998] study, drugs were administered under open labels. Sensitivity analyses, without the FACET [1998] study, resulted in homogeneously mean differences for both SBP and DBP of 1.20, 95% CI [0.76, 1.63] and 0.76, 95% CI [0.51, 1.00] respectively, as shown in **Figure 3.7** and **Figure 3.8.**

Heterogeneity was observed at an I^2 value of 97% and 96% for the four studies comparing ACEIs vs DIs. Using the RE model, mean differences were shown for both SBP and DBP of -0.29, 95% CI [-2.91, 2.33] and -0.50, 95% CI [-1.87, 0.87] respectively. The observed statistical heterogeneity was most likely due the methodological diversity of the ASCOT-BPLA [2005] and HYVET–P [2003] studies, as drugs were administered under open labels in both the studies, might have contributed the observed heterogeneity. Sensitivity analyses, without these studies, resulted in resulted in homogeneous mean differences for both SBP and DBP of 1.79, 95% CI [1.35, 2.23] and -0.09, 95% CI [-0.36, 0.18], respectively.

Heterogeneity was noticed to the tune of an I^2 value of 80 % and 95% for the eight studies comparing SBP and DBP reduction respectively, with ACEIs vs BBs. Using the RE model, mean differences were observed for both SBP and DBP of 0.43, 95% CI [-1.13, 1.98] and 0.32, 95% CI [-1.16, 1.80] respectively. The observed statistical heterogeneity was most likely due to the methodological diversity of the ASCOT-BPLA [2005] and UKPDS [1998] studies, as drugs were given under open labels. Sensitivity analyses, without these studies, resulted in homogeneous mean differences for both SBP and DBP of 0.79, 95% CI [-0.24, 1.83] and 0.82, 95% CI [0.34, 0.31] respectively.

Heterogeneity was also flagged up with an I^2 value of 74% and 96% for the three studies comparing SBP and DBP reduction respectively, with ACEIs vs placebo. Using the RE model, mean differences were highlighted for both SBP and DBP of -7.06, 95% CI [-10.96, -3.16] and -4.10, 95% CI [-7.23, -0.98] respectively. The observed statistical heterogeneity was most likely due the clinical diversity of the

Waeber [1999] study, as one of its intervention arms was a combination treatment. Sensitivity analyses, without this study, resulted in homogeneous mean differences for both SBP and DBP of -9.06, 95% CI [-11.73, -6.40] and -5.85, 95% CI [-6.72, -4.99] respectively.

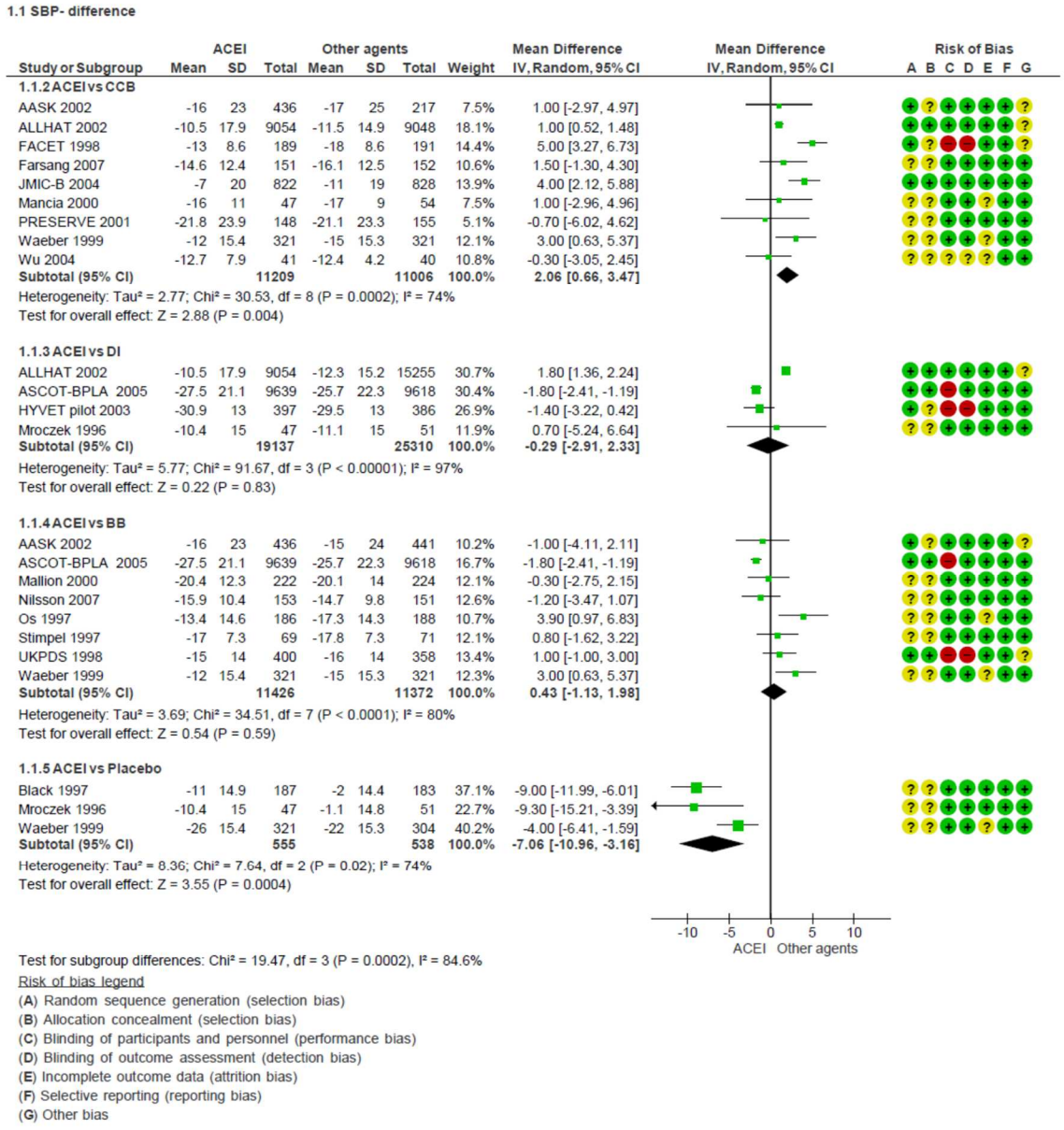


Figure 3.5 Forest plot of comparison of ACEI vs other agents: BP-delta, outcome [RE model]: SBP reduction. Net change in clinic/office SBP for ACEI versus other agents, both in diagrammatic and numerical format (mmHg, 95% CI) .The overall effect represents the pooled estimate of mean net change in SBP response.

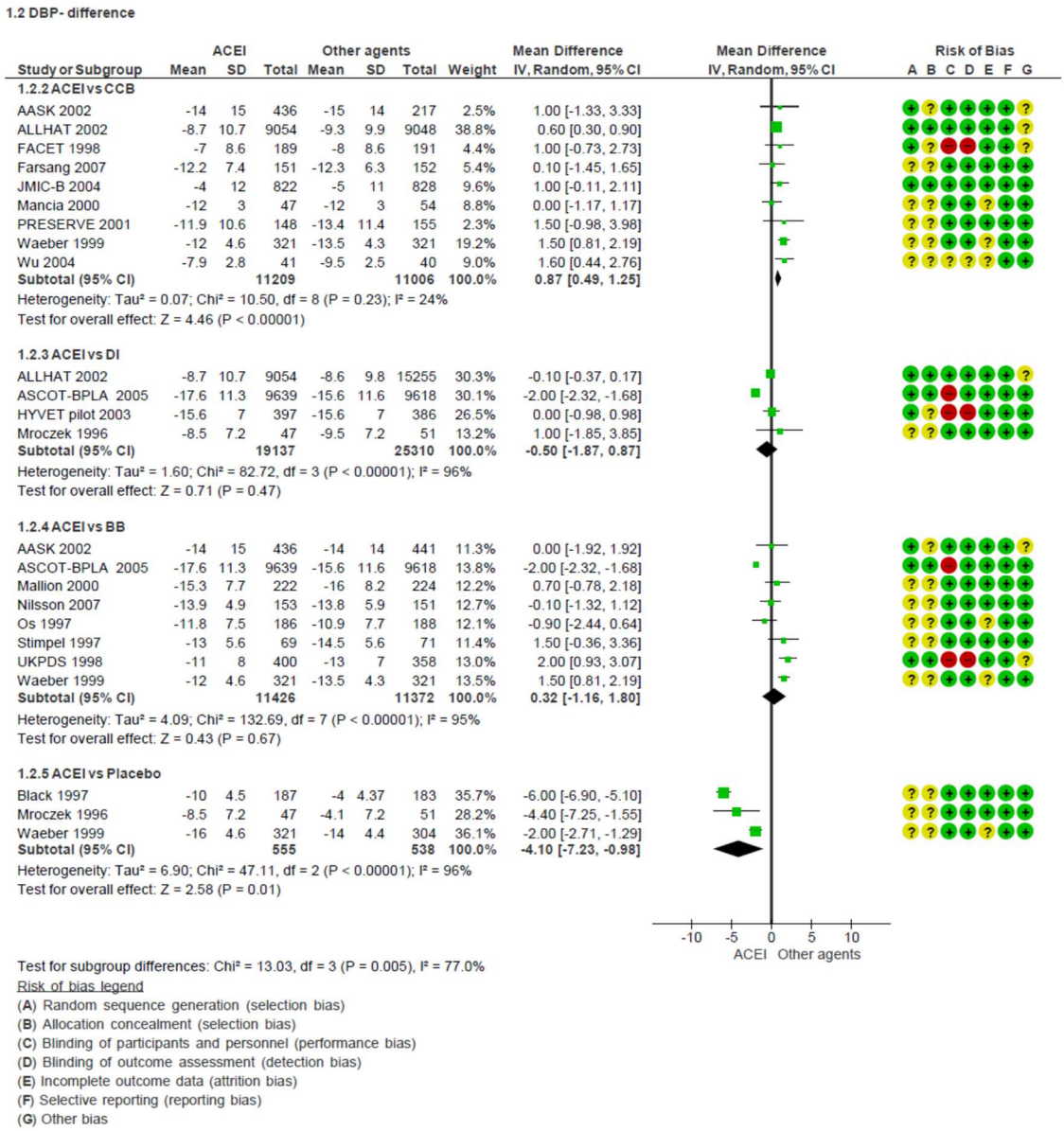


Figure 3.6 Forest plot of comparison of ACEI vs other agents: BP-delta, outcome [RE model]: DBP reduction. Net change in clinic/office DBP for ACEI versus other agents, both in diagrammatic and numerical format (mmHg, 95% CI) .The overall effect represents the pooled estimate of mean net change in DBP response.

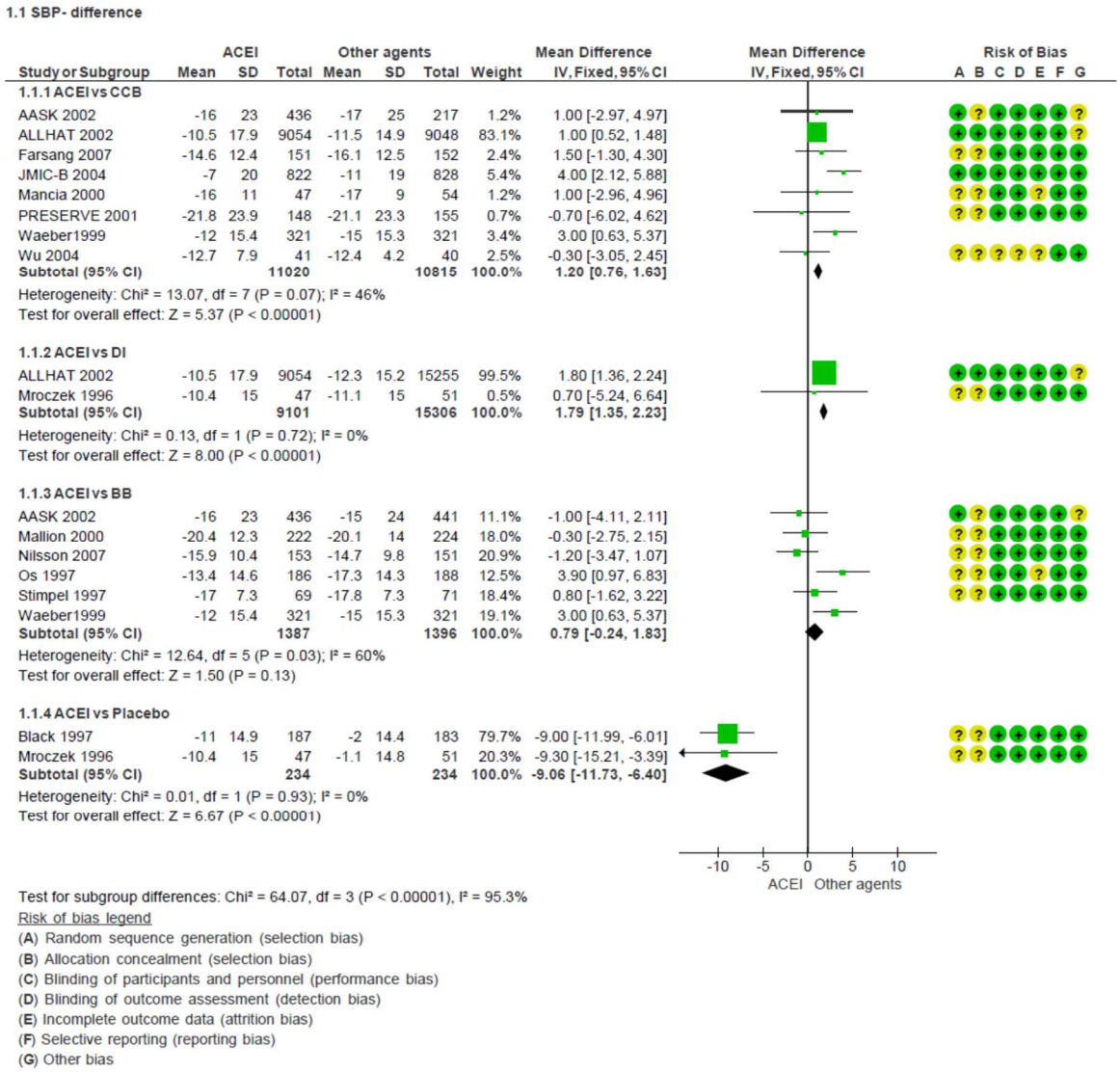


Figure 3.7 Forest plot of comparison of ACEI vs other agents: BP-delta, outcome [sensitivity analysis]: SBP reduction. Net change in clinic/office SBP for ACEI versus other agents, both in diagrammatic and numerical format (mmHg, 95% CI) .The overall effect represents the pooled estimate of mean net change in SBP response.

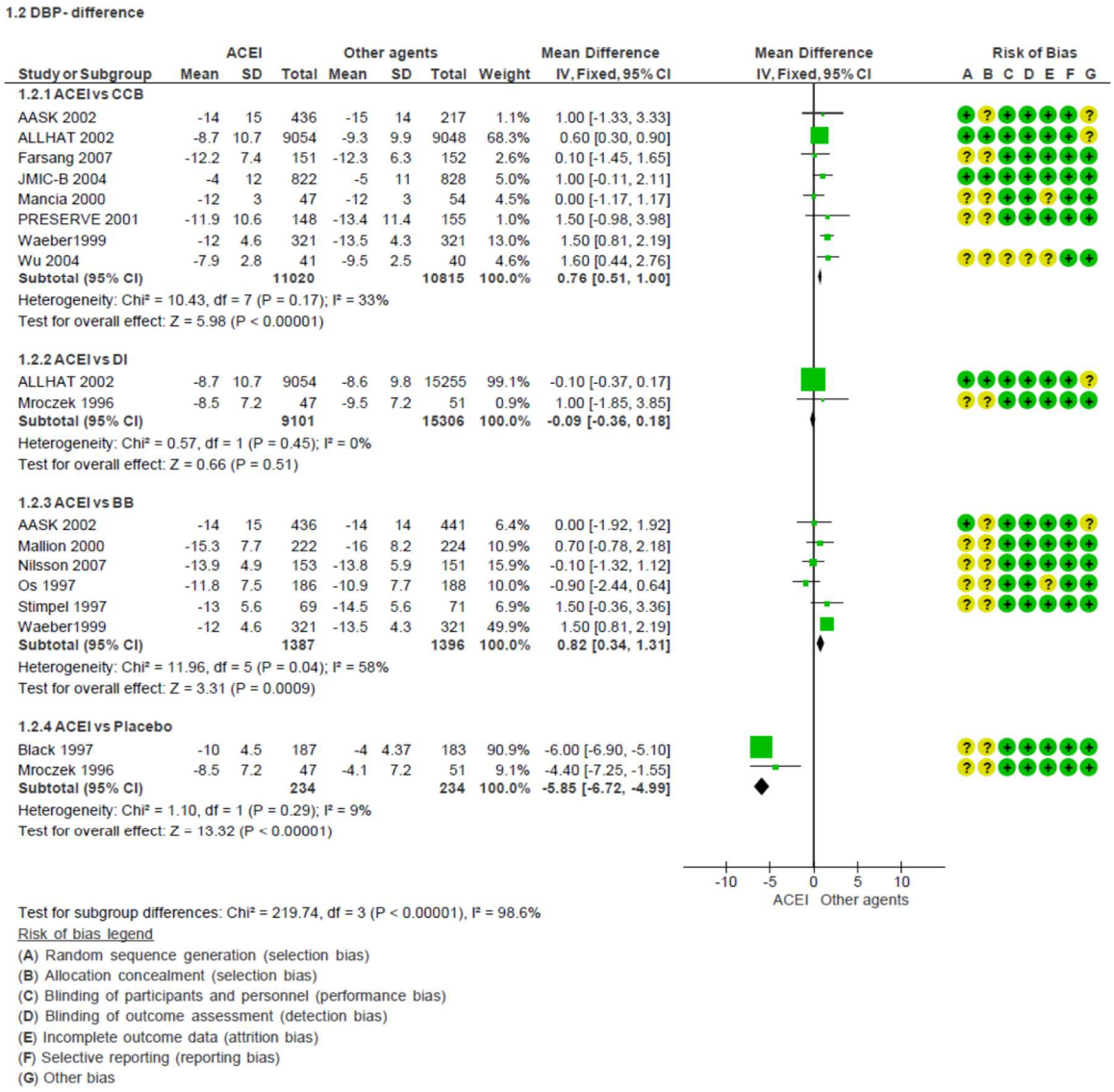


Figure 3.8 Forest plot of comparison of ACEI vs other agents: BP-delta, outcome [sensitivity analysis]: DBP reduction. Net change in clinic/office DBP for ACEI versus other agents, both in diagrammatic and numerical format (mmHg, 95% CI) .The overall effect represents the pooled estimate of mean net change in DBP response.

3.3.1.2 BP response to ARBs-delta

During a total of 27,900 person-years of follow-up, using the WMD method and FE model, the mean SBP reduction with ARBs was 1.92 mmHg, 95% CI [1.57, 2.26] less than that of CCBs. SBP reduction was -1.98 mmHg, 95% CI [-2.15, -1.81] more than ACEIs, -1.16 mmHg, 95% CI [-1.88, -0.44] more than BBs, -9.60 mmHg, 95% CI [-11.24, -7.96] more than the placebo and -2.12 mmHg, 95% CI [-3.88, -0.35] more than another ARB. However, there was no significant difference between ARBs and DIs (P = 0.05), as shown in **Figure 3.9.**

For DBP, as shown in **Figure 3.10**, the mean DBP reduction with ARBs was 0.52 mmHg, 95% CI [0.36, 0.67] less than ACEIs and 1.53 mmHg, 95% CI [1.34, 1.73] less than CCBs. For DBP, the mean reduction with ARBs was -6.13 mmHg, 95% CI [-6.62, -5.65] more than the placebo and -1.57 mmHg, 95% CI [-2.07, -1.07] more than another ARB. However, there was no significant difference between ARBs and DIs (P = 0.70) or between ARBs and BBs (P = 0.46).

Heterogeneity was also observed at an I^2 value of 69% and 85% for the five studies comparing SBP and DBP reduction respectively, with ARBs vs CCBs. Using the RE model, mean differences were shown for both SBP and DBP of 0.82, 95% CI [-0.58, 2.21] and 0.55, 95% CI [-0.48, 1.59] respectively, as shown in **Figure 3.11.**The observed statistical heterogeneity was most likely due to the methodological diversity of the VALUE [2004] study, as a number of BP-lowering agents were added to randomly allocated treatment to control BP. Sensitivity analyses, without this study, resulted in homogeneous mean differences for both SBP and DBP of 0.16, 95% CI [-0.96, 1.28] and 0.25, 95% CI 0.25 [-0.33, 0.83] respectively, as shown in **Figure 3.12.**

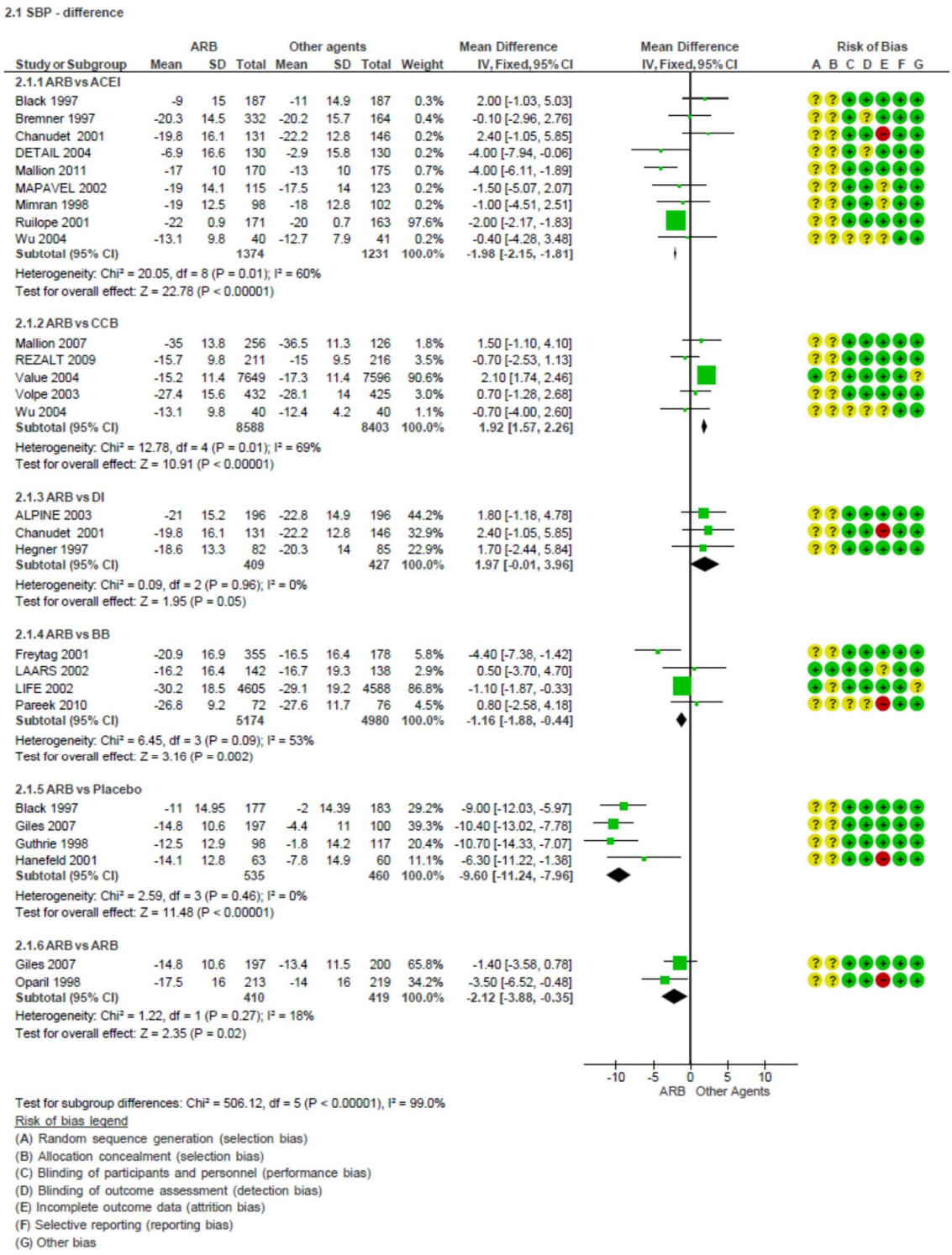


Figure 3.9 Forest plot of comparison of ARBs vs other agents: BP-delta, outcome [FE model]: SBP reduction. Net change in clinic/office SBP for ARBs versus other agents, both in diagrammatic and numerical format (mmHg, 95% CI) .The overall effect represents the pooled estimate of mean net change in SBP response.

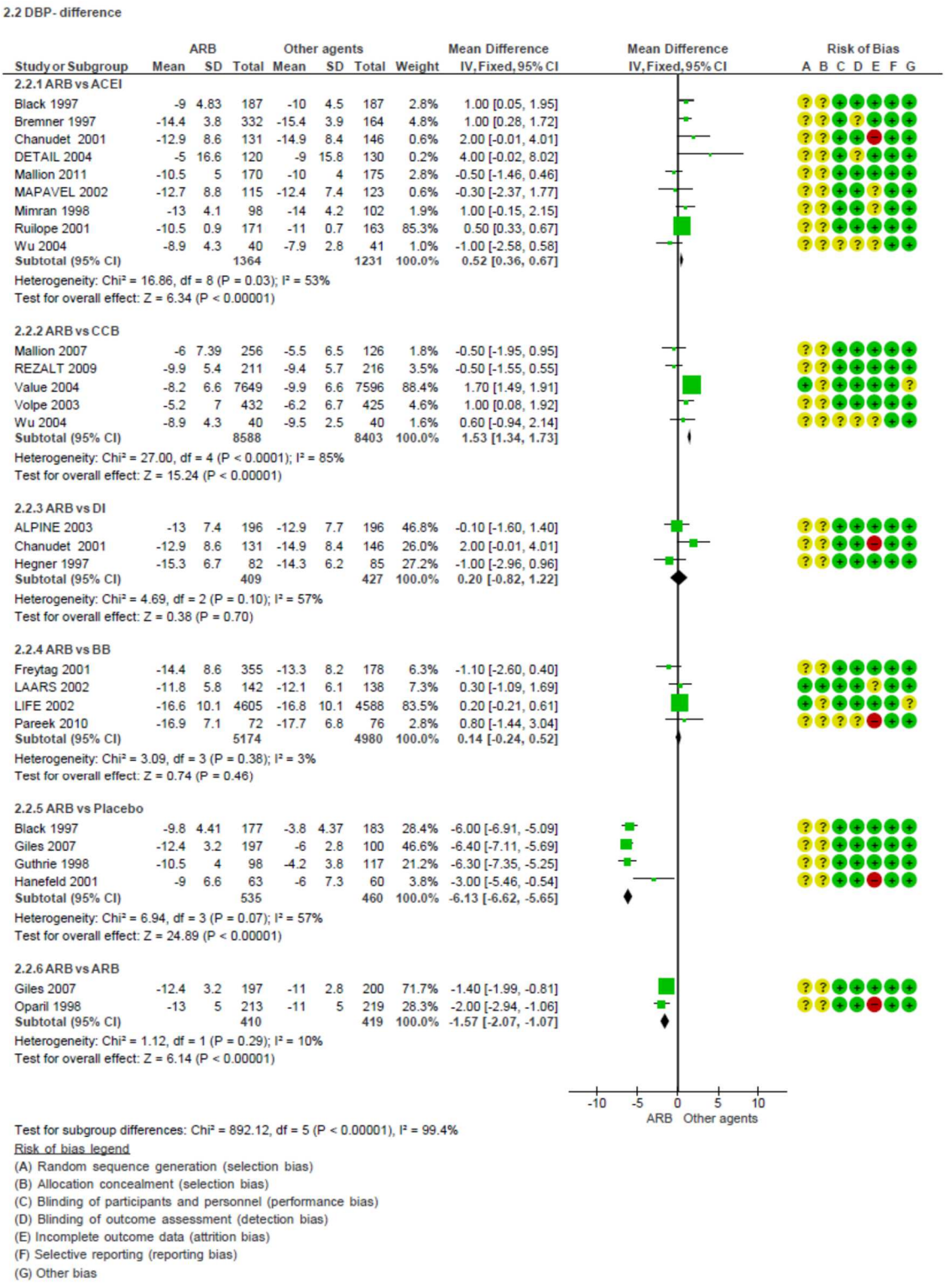


Figure 3.10 Forest plot of comparison of ARBs vs other agents: BP-delta, outcome [FE model]: DBP reduction. Net change in clinic/office DBP for ARBs versus other agents, both in diagrammatic and numerical format (mmHg, 95% CI) .The overall effect represents the pooled estimate of mean net change in DBP response.

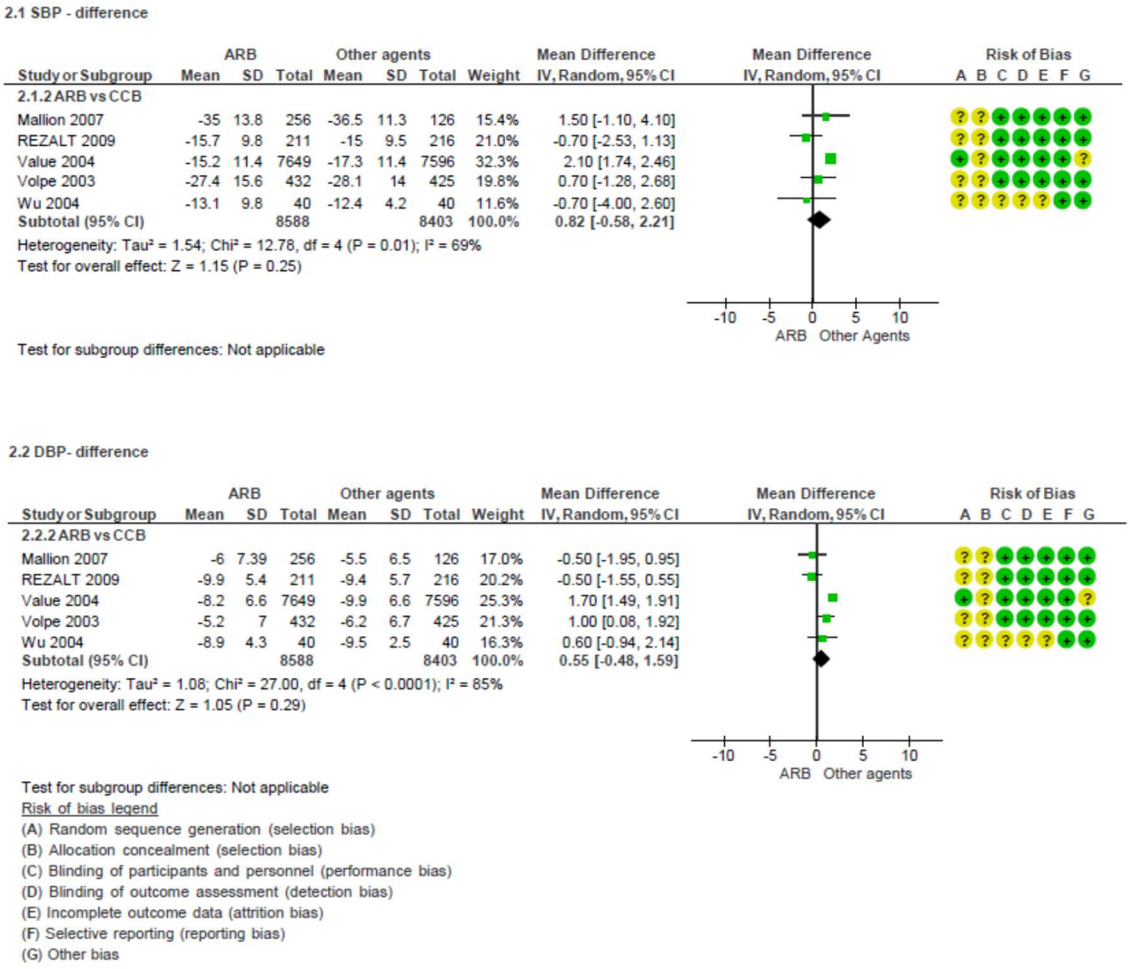


Figure 3.11 Forest plot of comparison of ARBs vs other agents: BP-delta, outcome [RE model]: BP reduction. Net change in clinic/office BP for ARBs versus other agents, both in diagrammatic and numerical format (mmHg, 95% CI) .The overall effect represents the pooled estimate of mean net change in BP response.

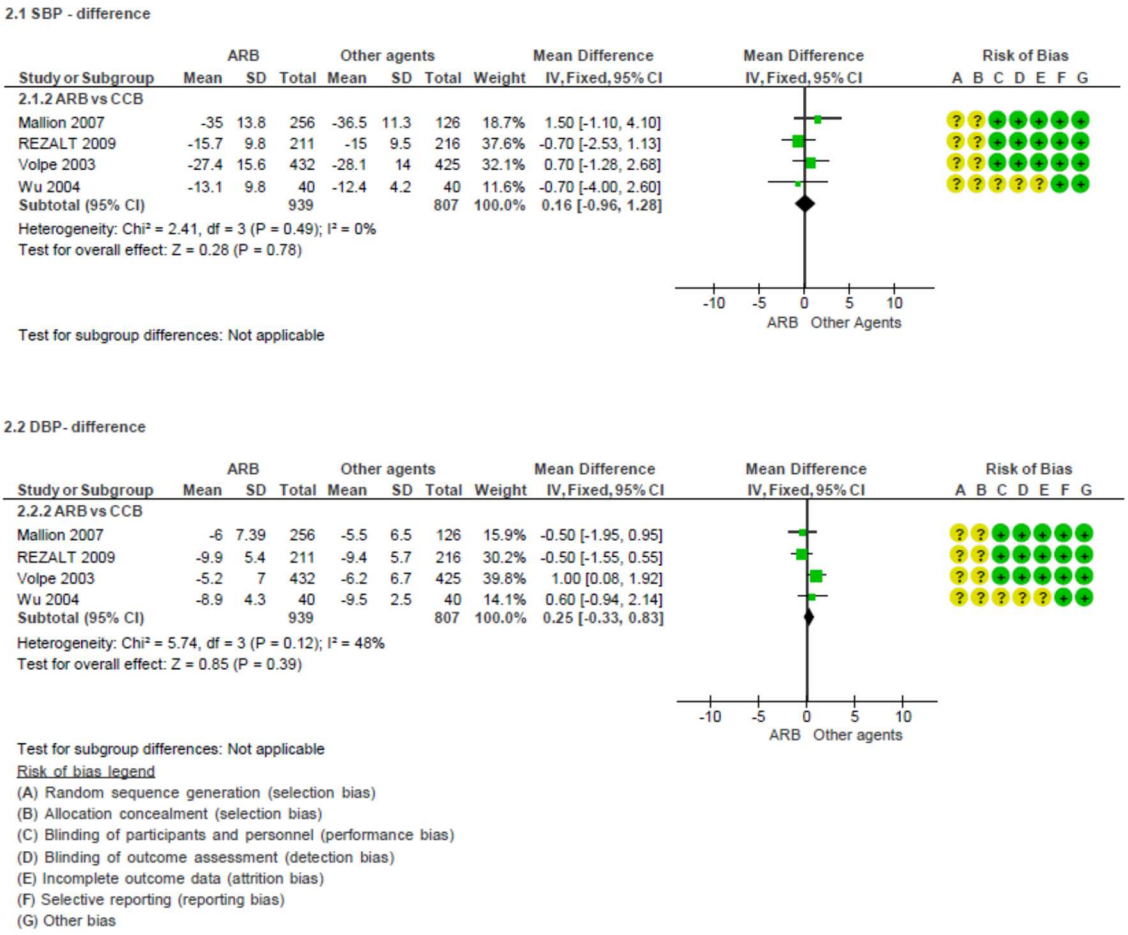


Figure 3.12 Forest plot of comparison of ARBs vs other agents: BP-delta, outcome [sensitivity analysis]: BP reduction. Net change in clinic/office BP for ARBs versus other agents, both in diagrammatic and numerical format (mmHg, 95% CI) .The overall effect represents the pooled estimate of mean net change in BP response.

3.3.1.3 BP response to CCBs-delta

During a total of 207,289 person-years of follow-up, using the WMD method and FE model, the mean SBP reduction from CCBs was 0.48 mmHg, 95% CI [0.24, 0.73] less than DI. SBP reduction was -1.43 mmHg, 95% CI [-1.85, -1.00] more than ACEIs, -1.92 mmHg, 95% CI [-2.26, -1.57] more than ARBs and -9.88 mmHg, 95% CI [-10.56, -9.20] more than the placebo. However, there was no significant difference between CCBs and BBs (P = 0.13) or between CCBs (P = 0.23), as shown in **Figure 3.13.**

For DBP, as shown in **Figure 3.14**, the mean DBP reduction under CCBs was -0.76 mmHg, 95% CI [-1.01, -0.52] more than ACEIs, -1.53 mmHg, 95% CI [-1.73, -1.34] more than ARBs, -0.76 mmHg, 95%CI [-0.90, -0.62] more than DIs, -0.50 mmHg, 95% CI [-0.64, -0.36] more than BBs and -4.64 mmHg, 95% CI [-4.96, -4.31] more than the placebo. However, there was no significant difference between CCBs (P = 0.64).

Heterogeneity was seen at an I^2 value of 95% and 93% for the seven studies comparing SBP and DBP reduction respectively, with CCBs vs DIs. Using the RE model, mean differences were shown for both SBP and DBP of 0.82, 95% CI [-0.62, 2.27] and -0.49, 95% CI [-1.18, 0.21] respectively, as shown in **Figure 3.15.** The observed statistical heterogeneity was most likely due to the methodological diversity of the ASCOT-BPLA [2005], CONVINCE [2003] and NORDIL [2000] studies, as drugs were administered under open labels. Sensitivity analyses, without these studies, resulted in homogeneously mean differences for both SBP and DBP of 0.82, 95% CI [0.44, 1.21] and -0.63, 95% CI [-0.89, -0.38] respectively, as shown in **Figure 3.16.**

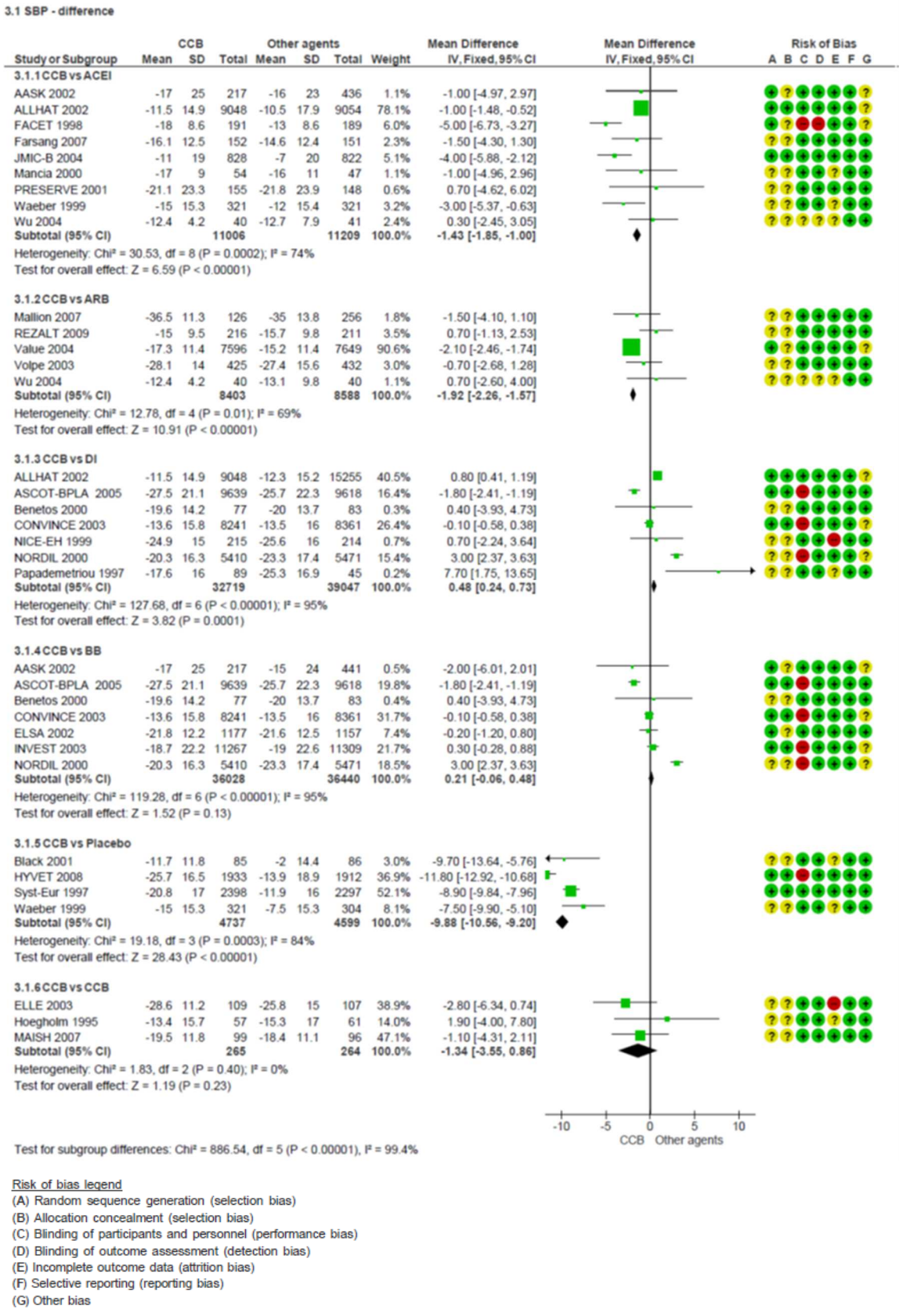


Figure 3.13 Forest plot of comparison of CCB vs other agents: BP-delta, outcome [FE model]: SBP reduction. Net change in clinic/office SBP for CCBs versus other agents, both in diagrammatic and numerical format (mmHg, 95% CI) .The overall effect represents the pooled estimate of mean net change in SBP response.

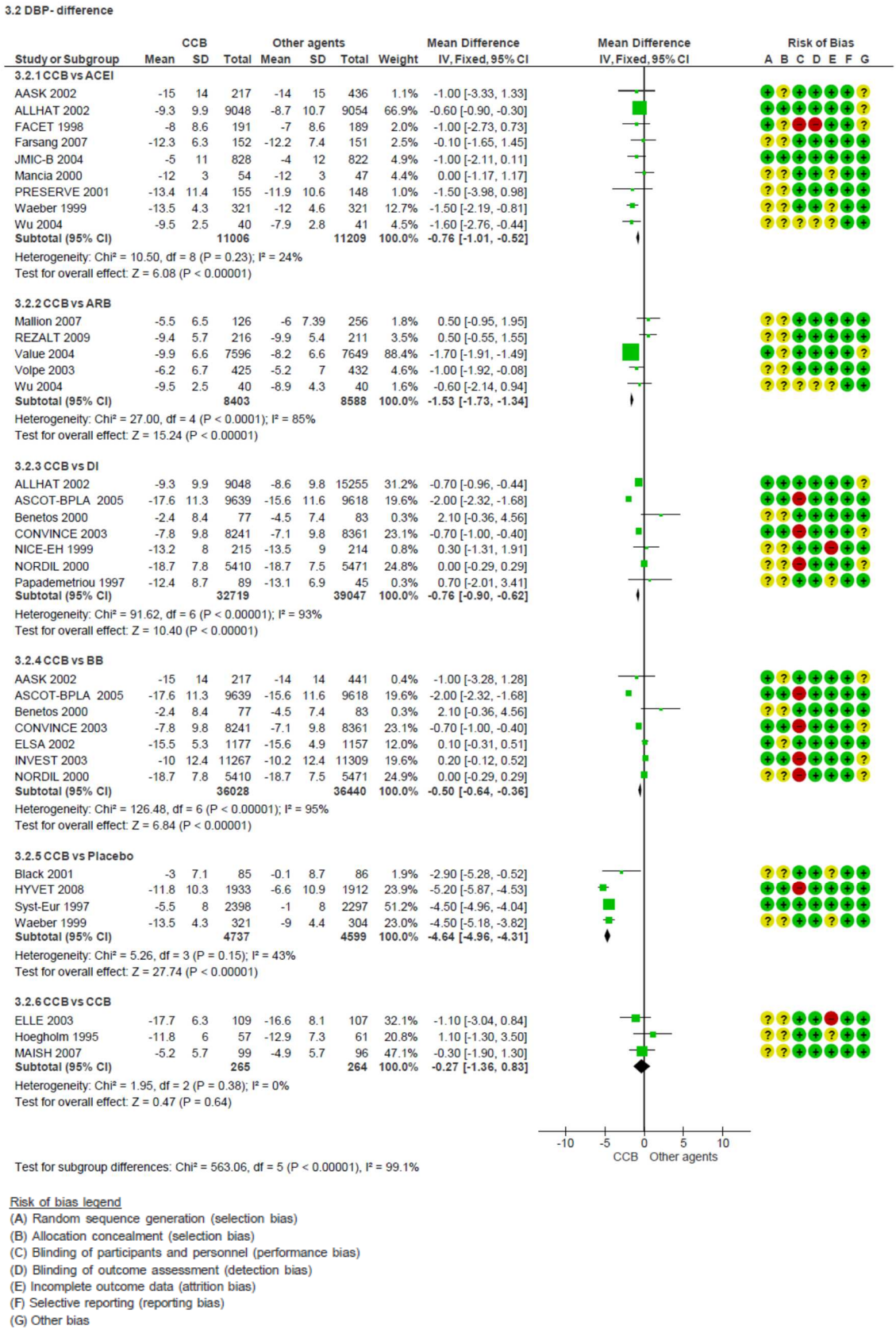


Figure 3.14 Forest plot of comparison of CCB vs other agents: BP-delta, outcome [FE model]: DBP reduction. Net change in clinic/office DBP for CCBs versus other agents, both in diagrammatic and numerical format (mmHg, 95% CI) .The overall effect represents the pooled estimate of mean net change in DBP response.

Heterogeneity was also observed of an I^2 value of 95% and 95% for the seven studies comparing SBP and DBP reduction respectively, with CCBs vs BBs. Using the RE model, mean differences were shown for both SBP and DBP of 0.09, 95% CI [-1.31, 1.49] and -0.36, 95% CI [-1.11, 0.39] respectively. The observed statistical heterogeneity was most likely due the methodological diversity of ASCOT-BPLA [2005], INVEST [2003], CONVINCE [2003] and NORDIL [2000] studies, as drugs were administered under open labels. Sensitivity analyses, without these studies, resulted in homogeneously mean differences for both SBP and DBP of-0.27, 95% CI [-1.22, 0.68] and 0.12, 95% CI [-0.28, 0.52] respectively.

Heterogeneity was also noticed at an I^2 value of 84% for the four studies comparing SBP reduction respectively, with CCBs vs the placebo. Using the RE model, mean differences were shown for both SBP and DBP of -9.58, 95% CI [-11.65, -7.51] and -4.64, 95% CI [-5.12, -4.15] respectively. The observed statistical heterogeneity was most likely due the methodological diversity of the HYVET [2008] study, as drugs were administered under open labels. Sensitivity analyses, without this study, resulted in homogeneously mean differences for both SBP and DBP of-8.76, 95% CI [-9.62, -7.90] and -4.46, 95% CI [-4.84, -4.08] respectively.

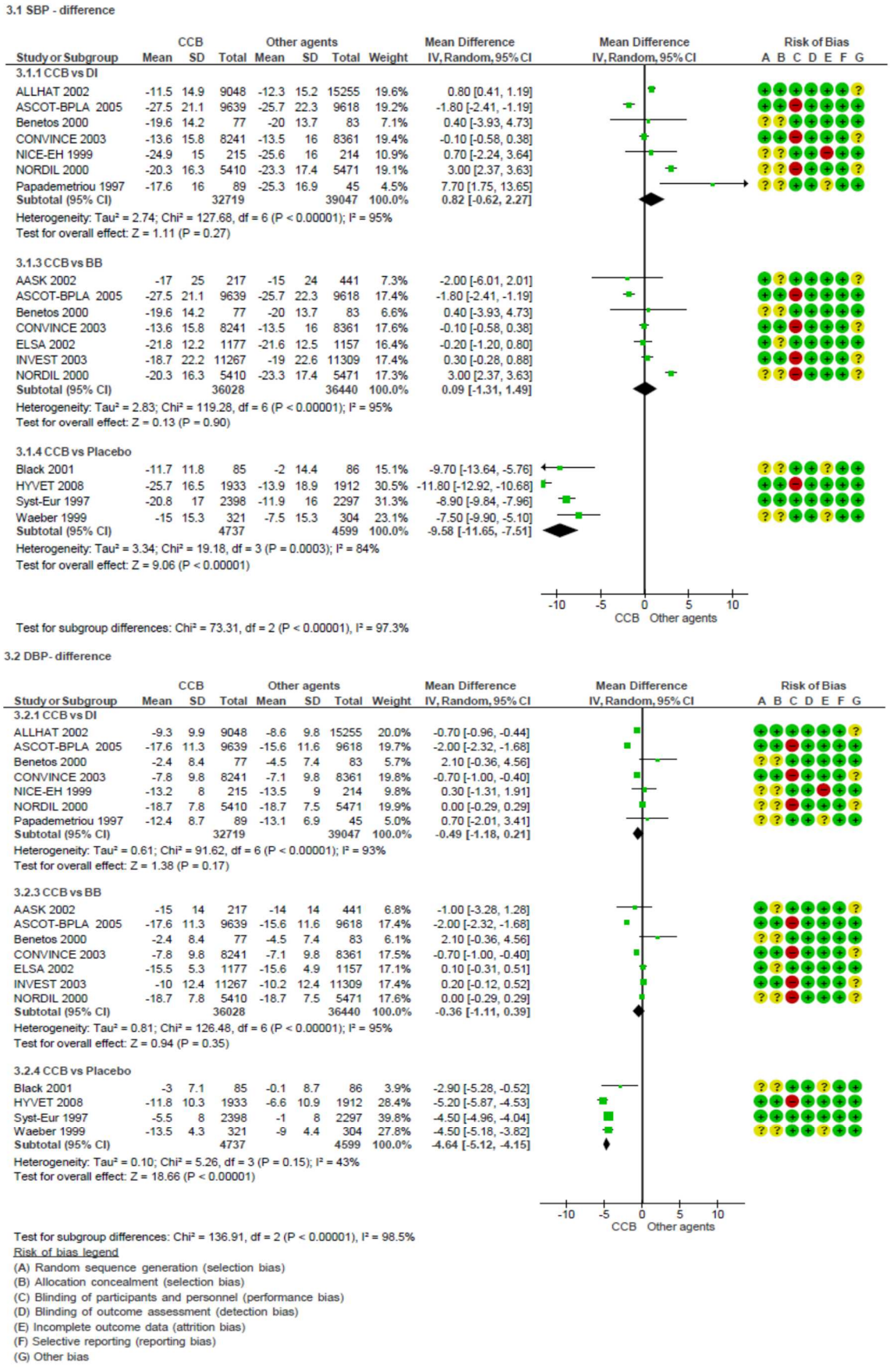


Figure 3.15 Forest plot of comparison of CCBs vs other agents: BP-delta, outcome [RE model]: BP reduction. Net change in clinic/office BP for CCBs versus other agents, both in diagrammatic and numerical format (mmHg, 95% CI) .The overall effect represents the pooled estimate of mean net change in BP response.

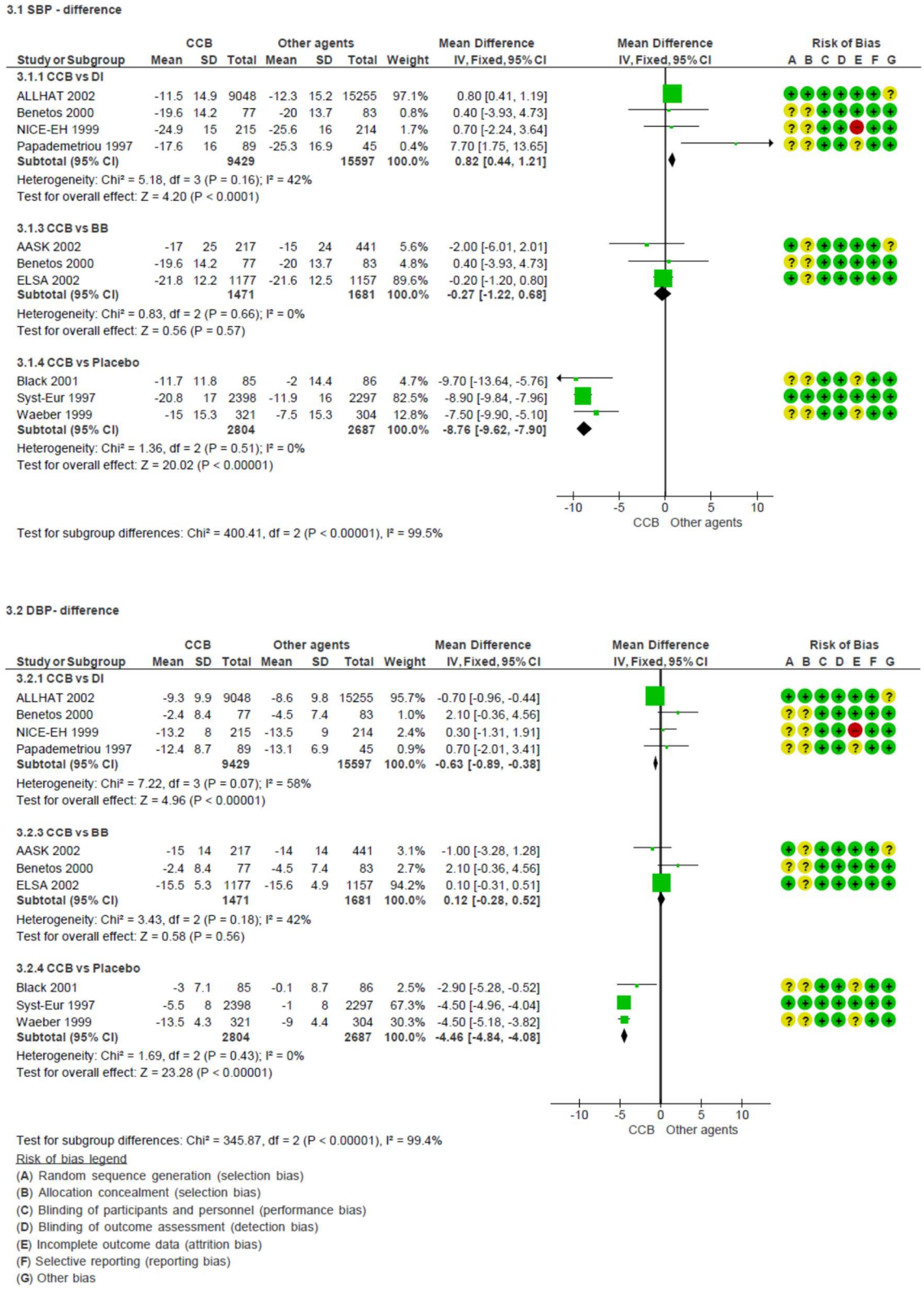


Figure 3.16 Forest plot of comparison of CCBs vs other agents: BP-delta, outcome [sensitivity analysis]: BP reduction. Net change in clinic/office BP for CCBs versus other agents, both in diagrammatic and numerical format (mmHg, 95% CI) .The overall effect represents the pooled estimate of mean net change in BP response.

3.3.1.4 BP response to DIs-delta

During a total of 108,399 person-years of follow-up, using the WMD method and FE model, the mean SBP reduction with DIs was -0.50 mmHg, 95% CI [-0.85, -0.15] more than ACEIs, -0.48 mmHg, 95% CI [-0.73, -0.24] more than CCBs and -10.00 mmHg, 95% CI [-15.78, -4.22] more than the placebo. However, there was no significant difference between DIs and ARBs (P = 0.05), between DIs and BBs (P = 0.14) or between DIs (P = 0.25), as shown in **Figure 3.17.**

For DBP, as shown in **Figure 3.18**, the mean DBP reduction under DIs was 0.83 mmHg, 95% CI [0.63, 1.03] less than ACEIs and 0.76 mmHg, 95% CI [0.62, 0.90] less than CCBs. For DBP, the mean reduction with DIs was -5.40 mmHg, 95% CI [-8.19, -2.61] more than the placebo. However, there was no significant difference between DIs and ARBs (P = 0.70), between DIs and BBs (P = 0.90) or between DIs (P = 0.22).

Heterogeneity was also in evidence to an I^2 value of 79% for the two studies comparing SBP reduction respectively, with DIs vs BBs. Using the RE model, mean differences were shown for both SBP and DBP of 1.72, 95% CI [-2.39, 5.83] and -0.08, 95% CI [-1.65, 1.48] respectively, as shown in **Figure 3.19**. The observed statistical heterogeneity was most likely due the clinical diversity of the Mallion [2000] study, as BP was measured in the supine position.

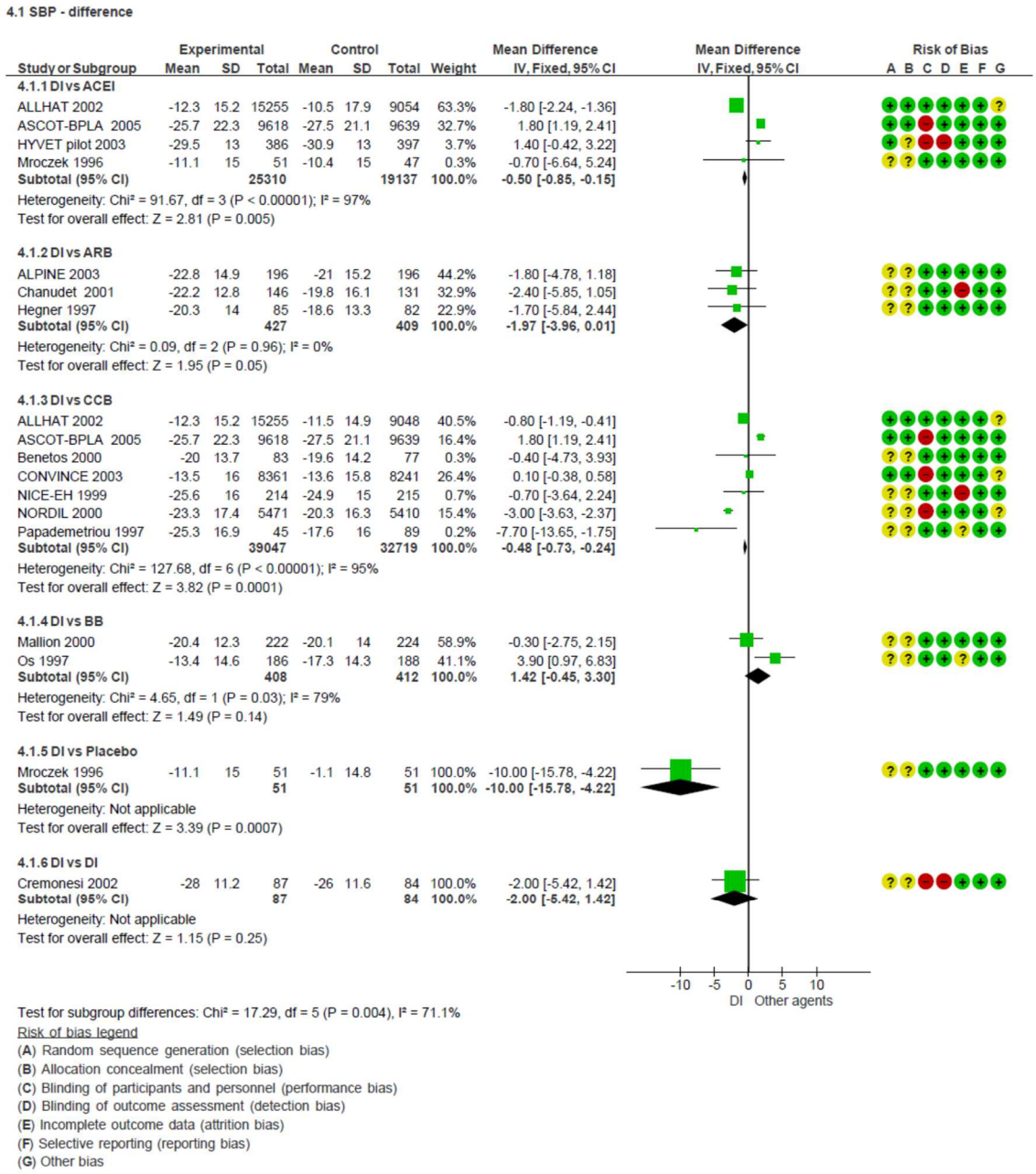


Figure 3.17 Forest plot of comparison of DIs vs other agents: BP-delta, outcome [FE model]: SBP reduction. Net change in clinic/office SBP for DIs versus other agents, both in diagrammatic and numerical format (mmHg, 95% CI) .The overall effect represents the pooled estimate of mean net change in SBP response.

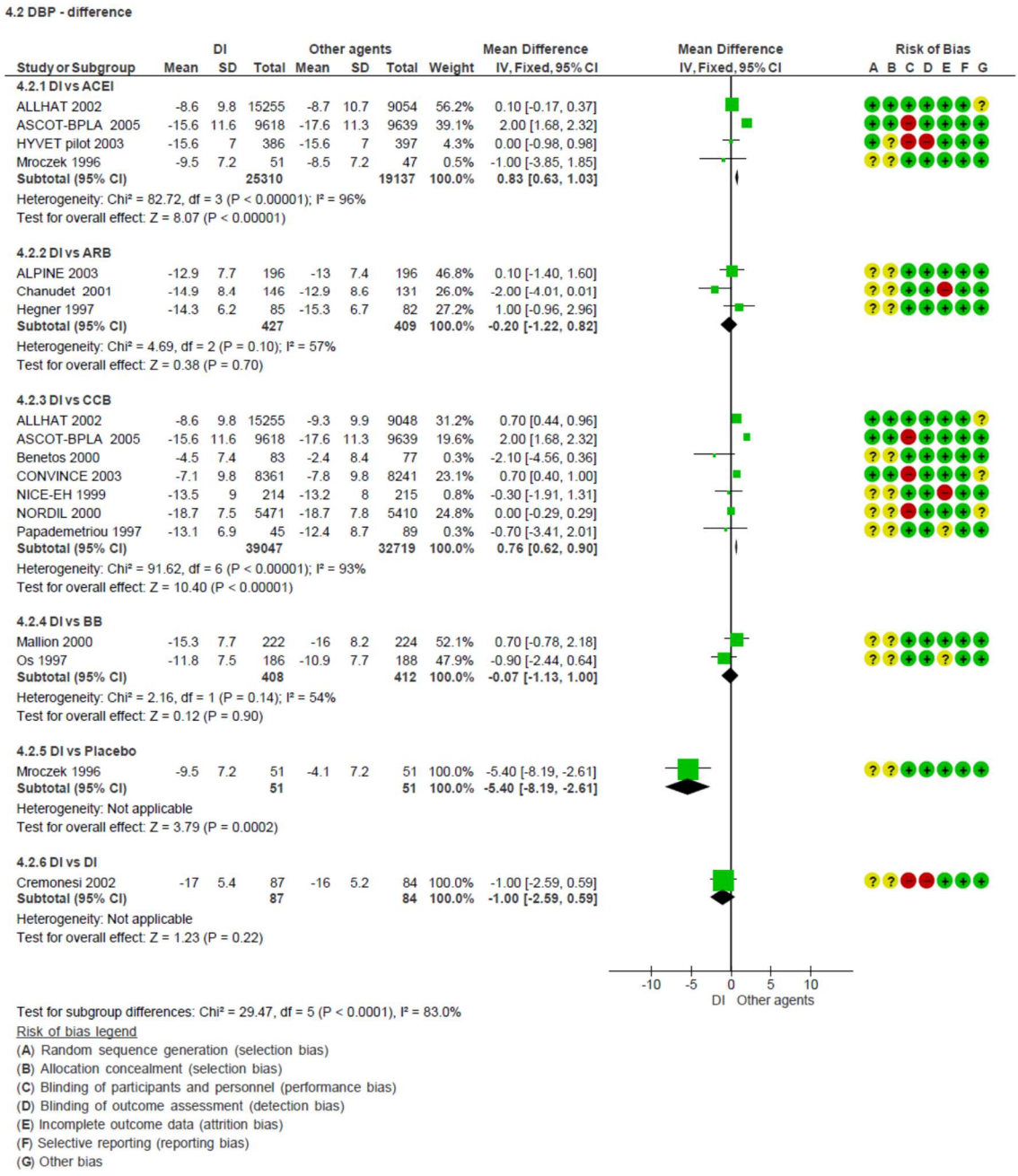


Figure 3.18 Forest plot of comparison of DIs vs other agents: BP-delta, outcome [FE model]: DBP reduction. Net change in clinic/office DBP for DIs versus other agents, both in diagrammatic and numerical format (mmHg, 95% CI) .The overall effect represents the pooled estimate of mean net change in DBP response.

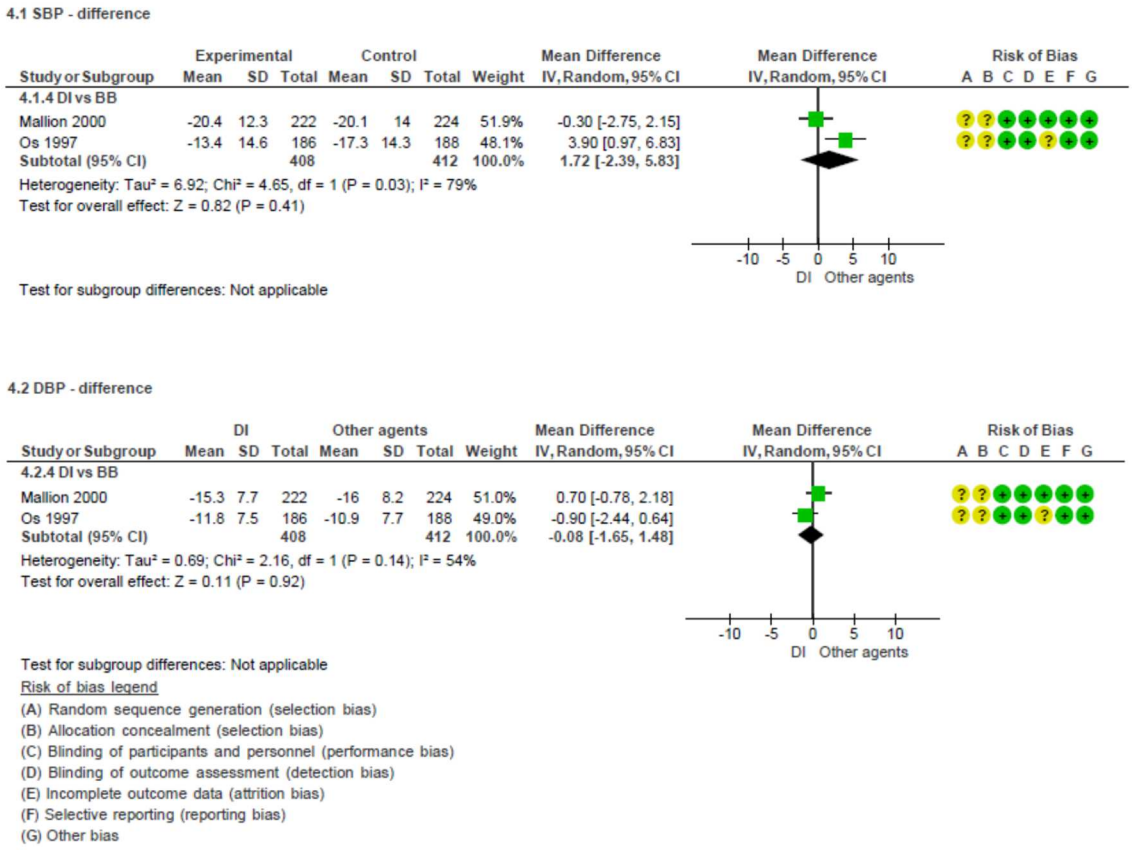


Figure 3.19 Forest plot of comparison of DIs vs other agents: BP-delta, outcome [RE model]: BP reduction. Net change in clinic/office BP for DIs versus other agents, both in diagrammatic and numerical format (mmHg, 95% CI) .The overall effect represents the pooled estimate of mean net change in BP response.

3.3.1.5 BP response to BBs-delta

During a total of 109,415 person-years of follow-up, using the WMD method and FE model, the mean SBP reduction under BBs was 0.99 mmHg CI [0.48, 1.50] less than ACEIs and 1.16 mmHg CI [0.44, 1.88] less than ARBs. SBP reduction was -7.24 mmHg, 95% CI [-9.22, -5.27] more than the placebo. However, there was no significant difference between BBs and CCBs (P = 0.13), between BBs and DIs (P = 0.14) or between BBs (P = 0.63), as shown in **Figure 3.20.**

For DBP, as shown in **Figure 3.21**, the mean DBP reduction under BBs was 0.95 mmHg, 95% CI [0.69, 1.21] less than ACEIs and 0.50 mmHg, 95% CI [0.36, 0.64] less than CCBs. For DBP, the mean reduction under BBs was -4.53 mmHg, 95%CI [-5.18, -3.88] more than the placebo. However, there was no significant difference between BBs and ARBs (P = 0.46), between BBs and DIs (P = 0.90) or between BBs (P = 0.85).

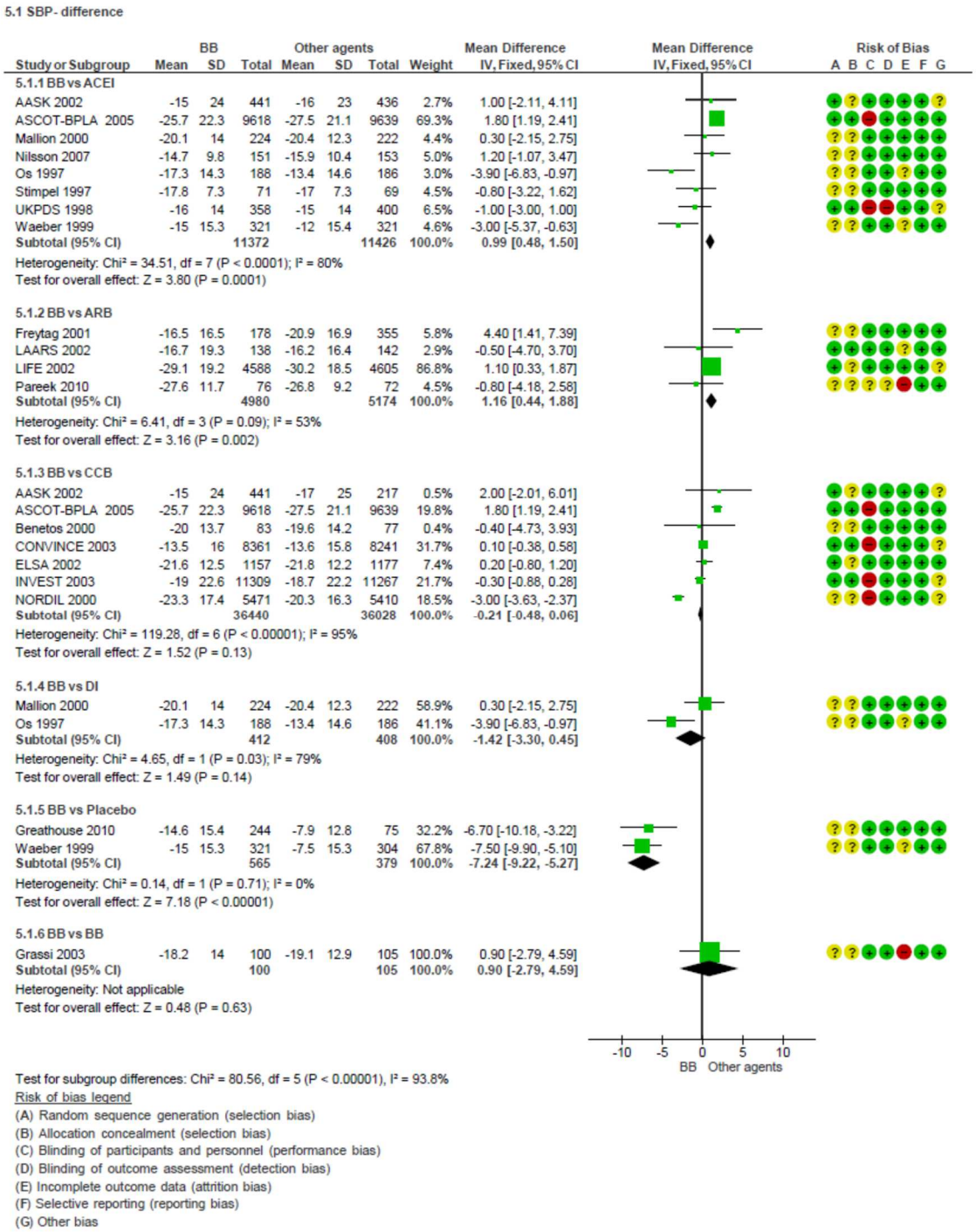


Figure 3.20 Forest plot of comparison of BBs vs other agents: BP-delta, outcome [FE model]: SBP reduction. Net change in clinic/office SBP for BBs versus other agents, both in diagrammatic and numerical format (mmHg, 95% CI) .The overall effect represents the pooled estimate of mean net change in SBP response.

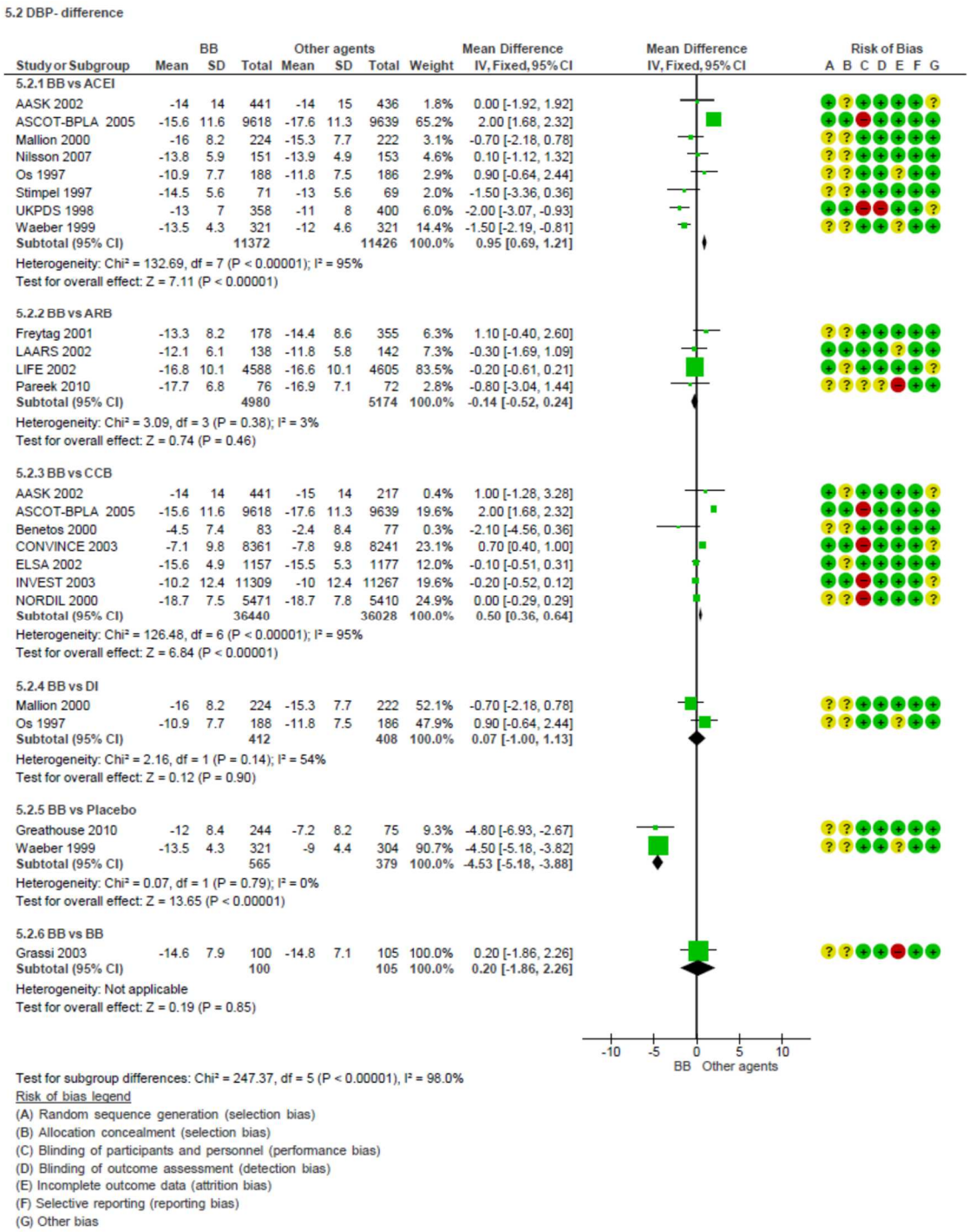


Figure 3.21 Forest plot of comparison of BBs vs other agents: BP-delta, outcome [FE model]: DBP reduction. Net change in clinic/office DBP for BBs versus other agents, both in diagrammatic and numerical format (mmHg, 95% CI) .The overall effect represents the pooled estimate of mean net change in DBP response.

3.3.2 Single measure-BP response

For single measure-BP response, 37 studies were included in the analysis (ordered by study ID):

AASK [2002]	Farsang [2007]	Luque [2005]	Radauceanu [2004]
Benetos [2000]	Fogari [2008]	McInnes [2000]	REGAAL [2002]
CASE-J [2008]	Grassi [2003]	MIDAS [1996]	Value [2004]
Chanudet [2001]	Hegner [1997]	Mounier-Vehier [1998]	VHAS [1998]
CROSS [2003]	Hoegholm [1995]	Narkiewicz [2007]	Volpe [2003]
Cushman [1998]	Holzgreve [2003]	NICE-EH [1999]	Wu [2004]
Derosa [2013]	James [2002]	Nilsson [2007]	Yang [2015]
Derosa [2014]	JMIC-B [2004]	Os [1997]	
ELLE [2003]	LIFE [2002]	PATS [1995]	
ELVERA [2004]	LOTHAR [2006]	RACE [1995]	

3.3.2.1 BP response to ACEIs-single measure

During a total of 8974 person-years of follow-up, using the WMD method and FE model, the mean SBP reduction under ACEIs was 1.17 mmHg, 95% CI [0.20, 2.14] less than CCBs and 5.20 mmHg, 95% CI [2.08, 8.32] less than DIs. SBP reduction with ACEIs was -7.10 mmHg, 95% CI [-10.99, -3.21] more than the placebo. However, there was no significant difference between ACEIs and ARBs (P = 0.19) or between ACEIs and BBs (P = 0.87), as shown in **Figure 3.22.**

For DBP, as shown in **Figure 3.23**, the mean DBP reduction under ACEIs was 1.29 mmHg, 95% CI [0.74, 1.84] less than CCBs and 2.20 mmHg, 95% CI [0.56, 3.84] less than DIs. DBP reduction with ACEIs was -1.83 mmHg, 95% CI [-2.78, -0.89] more than ARBs and -2.40 mmHg, 95% CI [-3.54, -1.26] more than the placebo. However, there was no significant difference between ACEIs and BBs (P = 0.12).

Heterogeneity was seen to an I^2 value of 76% and 80% for the five studies comparing SBP and DBP reduction respectively, with ACEIs vs BBs. Using the RE model, mean differences were shown for both SBP and DBP of -0.11, 95% CI [-2.94, 2.71] and -0.23, 95% CI [-1.76, 1.30] respectively, as shown **in Figure 3.24.**The observed statistical heterogeneity was most likely due to the methodological diversity of the Holzgreve [2003] study, as drugs were administered under open labels. Sensitivity analyses, without this study, resulted in homogeneous mean

differences for both SBP and DBP of of -1.40, 95% CI [-2.93, 0.14] and -1.09, 95% CI [-1.84, -0.35] respectively, as shown in **Figure 3.25.**

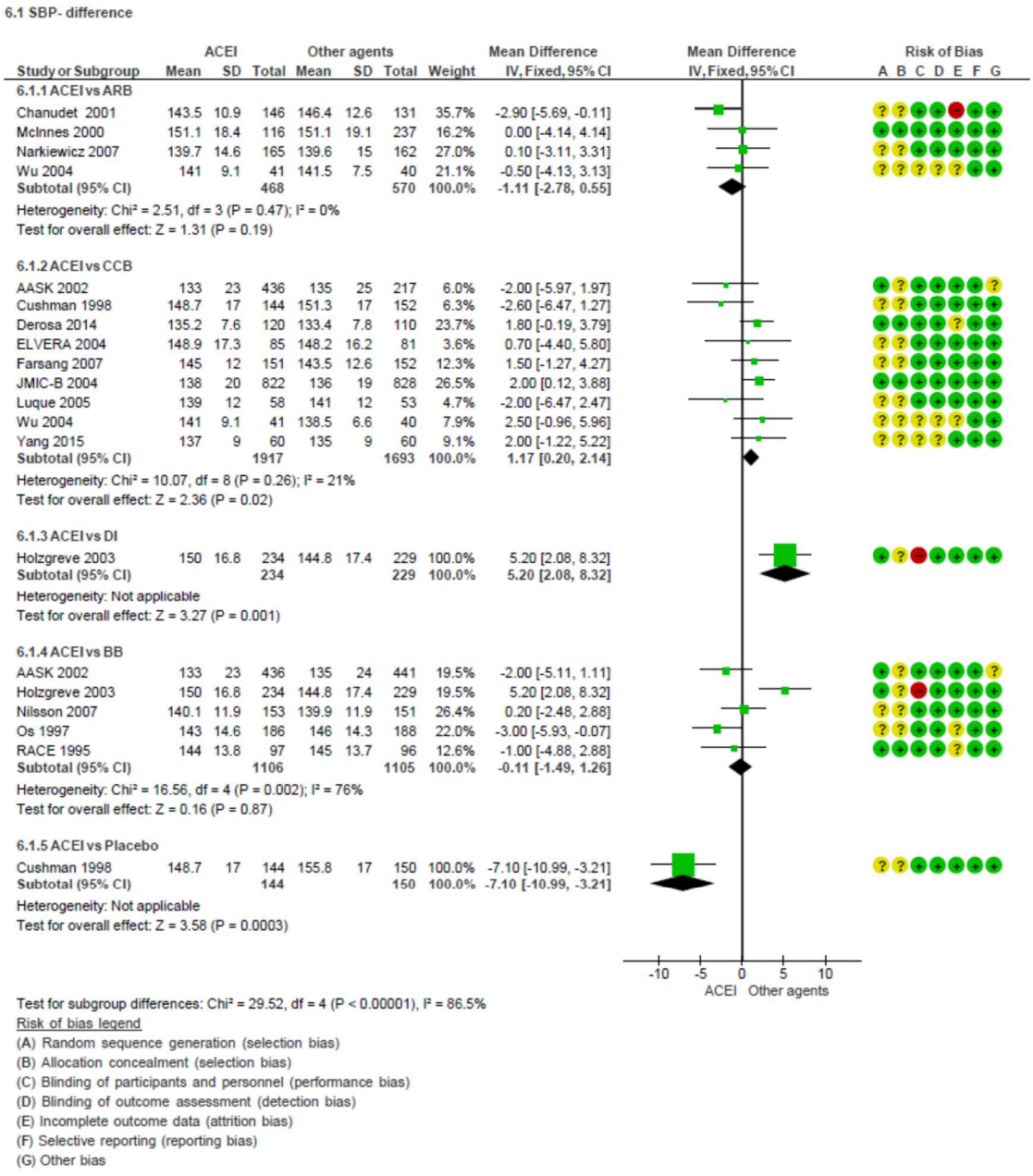


Figure 3.22 Forest plot of comparison of ACEIs vs other agents: BP-single measure, outcome [FE model]: SBP reduction. Net change in clinic/office SBP for ACEIs versus other agents, both in diagrammatic and numerical format (mmHg, 95% CI) .The overall effect represents the pooled estimate of mean net change in SBP response.

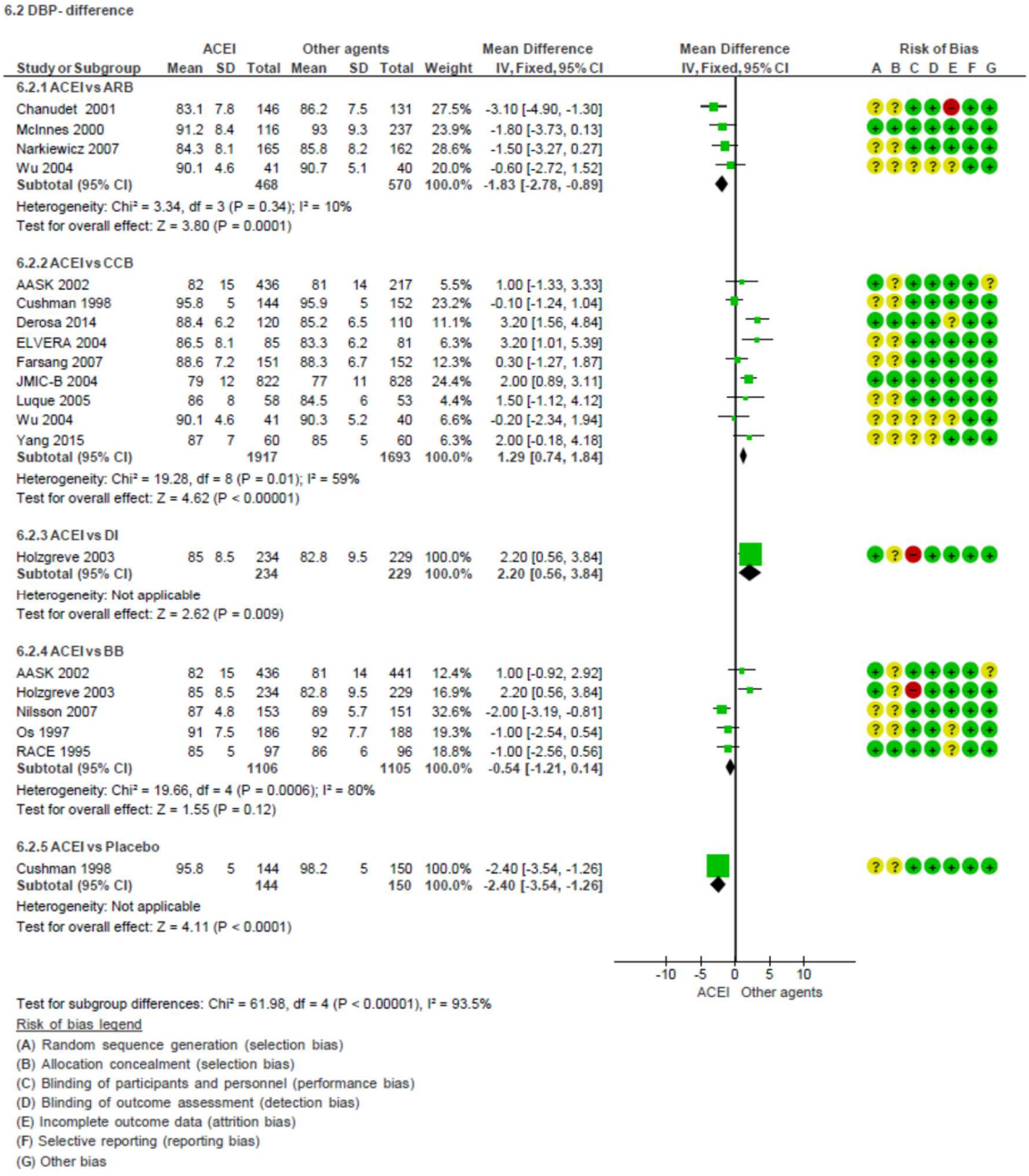


Figure 3.23 Forest plot of comparison of ACEIs vs other agents: BP-single measure, outcome [FE model]: DBP reduction. Net change in clinic/office DBP for ACEIs versus other agents, both in diagrammatic and numerical format (mmHg, 95% CI) .The overall effect represents the pooled estimate of mean net change in DBP response.

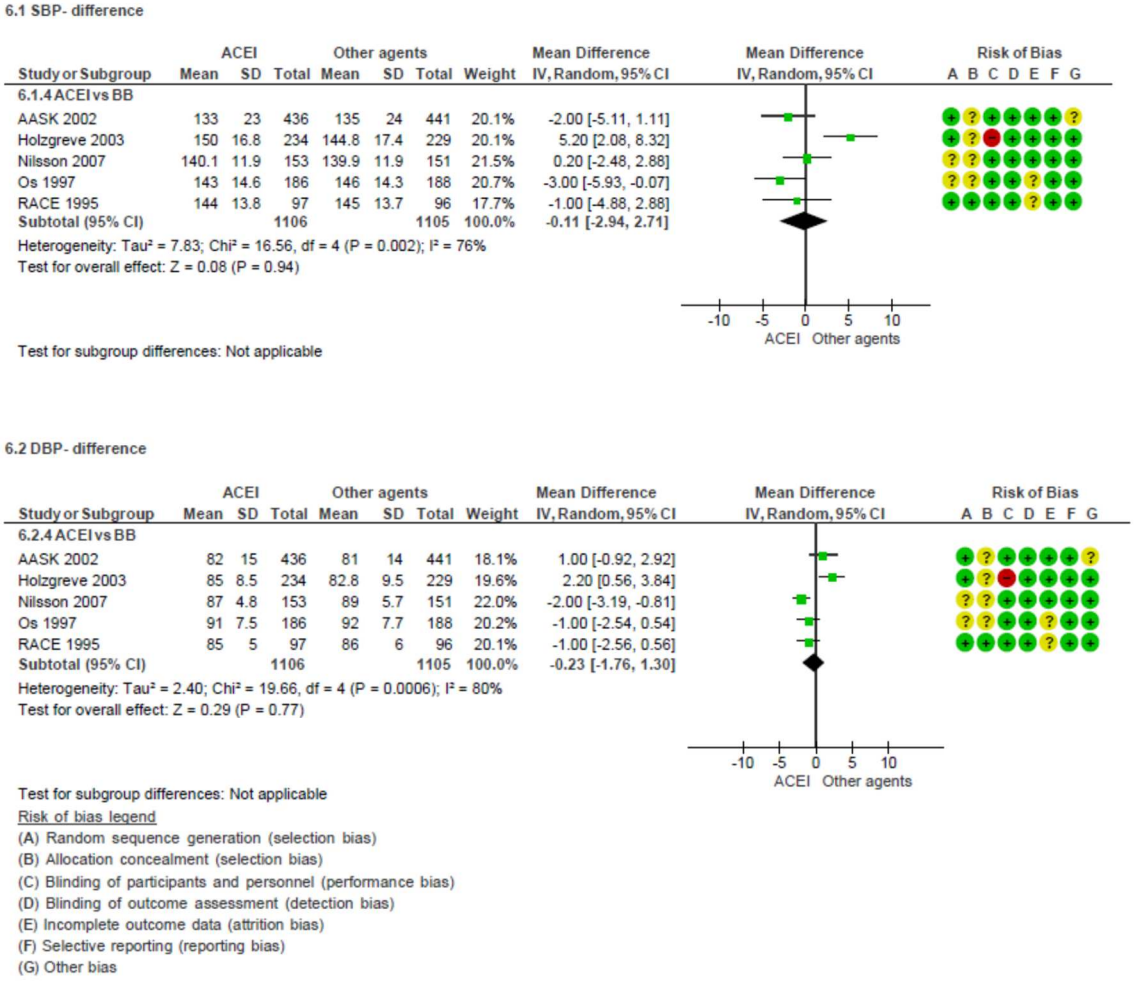


Figure 3.24 Forest plot of comparison of ACEIs vs other agents: BP-single measure, outcome [RE model]: BP reduction. Net change in clinic/office BP for ACEIs versus other agents, both in diagrammatic and numerical format (mmHg, 95% CI) .The overall effect represents the pooled estimate of mean net change in BP response.

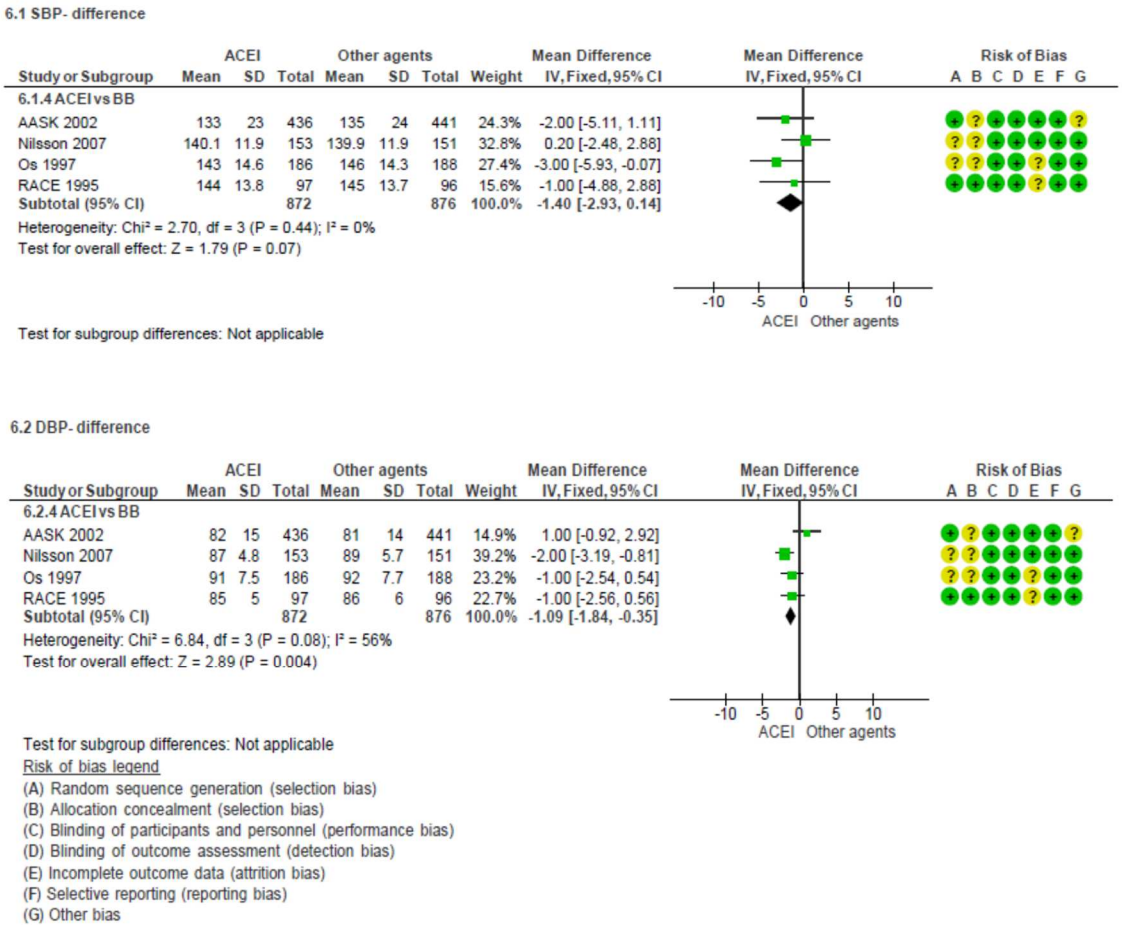


Figure 3.25 Forest plot of comparison of ACEIs vs other agents: BP-single measure, outcome [sensitivity analysis]: BP reduction. Net change in clinic/office BP for ACEIs versus other agents, both in diagrammatic and numerical format (mmHg, 95% CI) .The overall effect represents the pooled estimate of mean net change in BP response.

3.3.2.2 BP response to ARBs-single measure

During a total of 29,927 person-years of follow-up, using the WMD method and FE model, the mean SBP reduction under ARBs was 1.67 mmHg, 95% CI [1.30, 2.04] less than CCBs. SBP reduction was -1.26 mmHg, 95% CI [-2.02, -0.51] more than BBs and -5.20 mmHg, 95% CI [-7.38, -3.02] more than another ARB. However, there was no significant difference between ARBs and ACEIs (P = 0.19) or between ARBs and DIs (P = 0.06), as shown in **Figure 3.26.**

For DBP, as shown in **Figure 3.27**, the mean DBP reduction with ARBs was 1.83 mmHg, 95% CI [0.89, 2.78] less than ACEIs, 1.10 mmHg, 95% CI [0.87, 1.33] less than CCBs, 1.37 mmHg, 95% CI [0.48, 2.27] less than DIs and 0.44 mmHg, 95% CI [0.03, 0.85] less than BBs. For DBP, the mean reduction under ARBs was -3.20 mm Hg, 95% CI [-4.95, -1.45] more than another ARB.

Heterogeneity was seen at an I^2 value of 74% for the eight studies comparing SBP reduction respectively, with ARBs vs CCBs. Using the RE model, mean differences were shown for both SBP and DBP of 1.40, 95% CI [0.34, 2.45] and 1.10, 95% CI [0.61, 1.60] respectively, as shown in **Figure 3.28.** The observed statistical heterogeneity was most likely due to the clinical diversity of the James [2002] study, as BP was measured in the supine position). Sensitivity analyses, without this study, resulted in homogeneously mean differences for both SBP and DBP of 1.77, 95% CI [1.40, 2.14] and 1.12, 95% CI [0.88, 1.35] respectively, as shown in **Figure 3.29.**

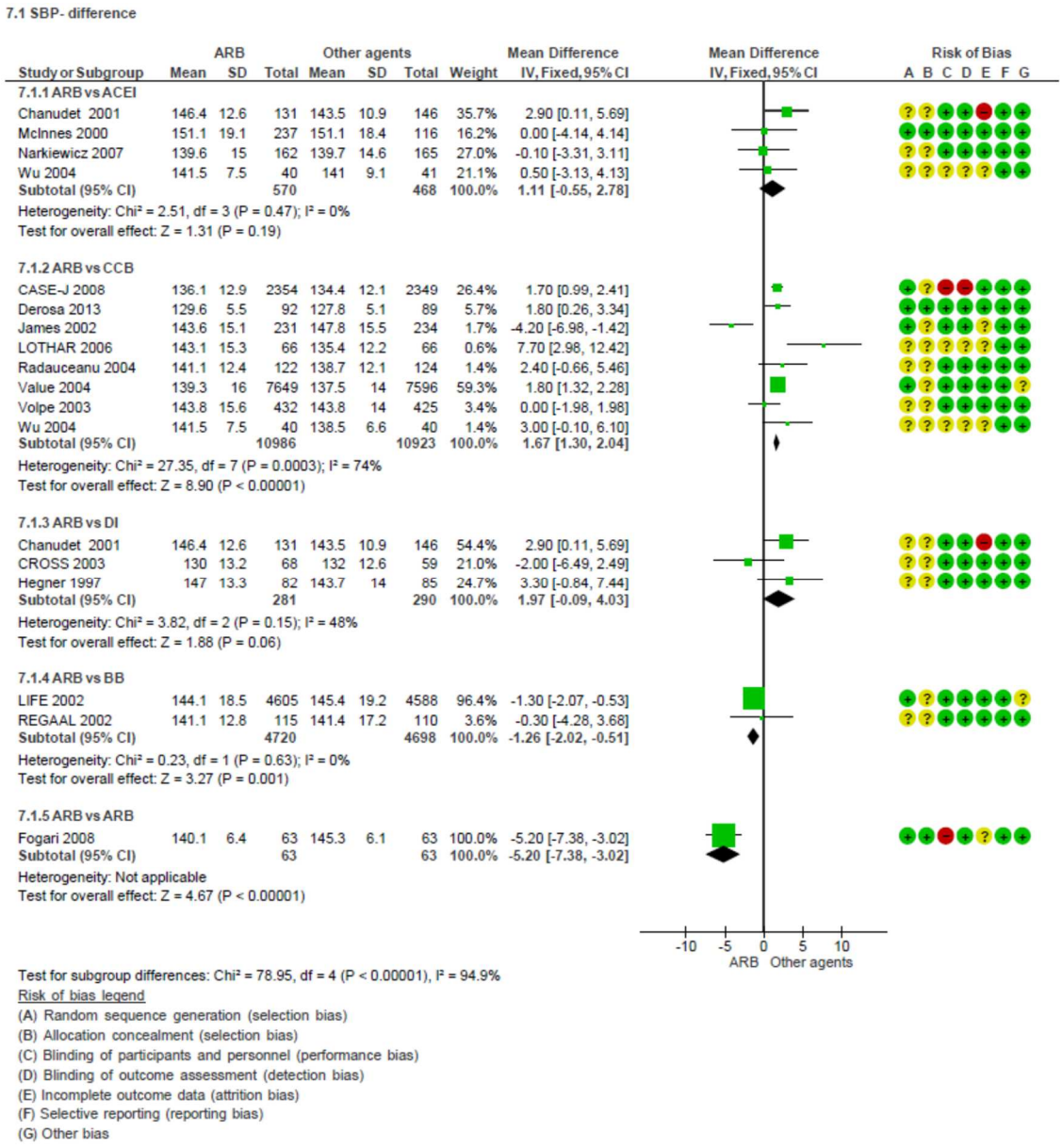


Figure 3.26 Forest plot of comparison of ARBs vs other agents: BP-single measure, outcome [FE model]: SBP reduction. Net change in clinic/office SBP for ARBs versus other agents, both in diagrammatic and numerical format (mmHg, 95% CI) .The overall effect represents the pooled estimate of mean net change in SBP response.

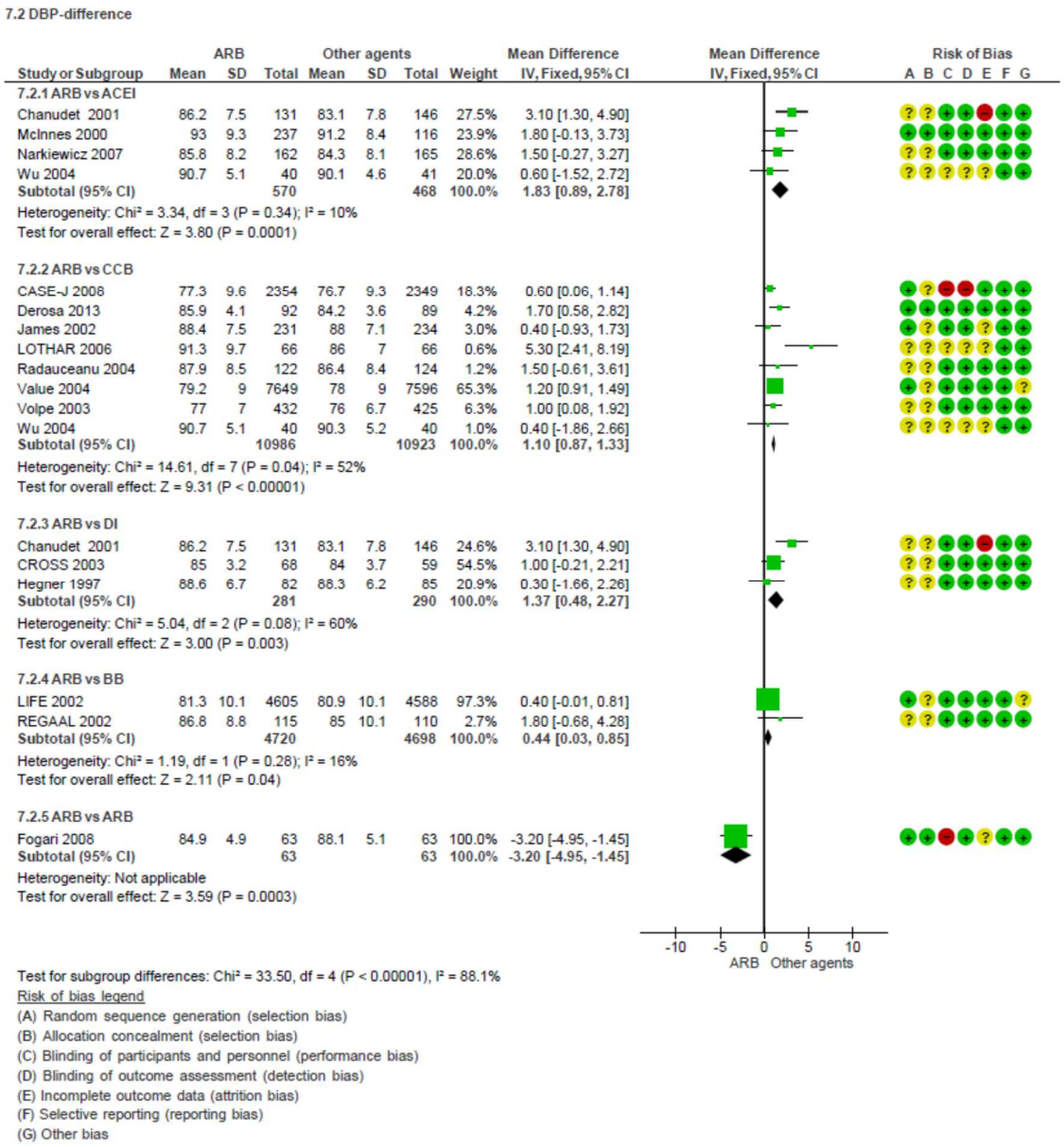


Figure 3.27 Forest plot of comparison of ARBs vs other agents: BP-single measure, outcome [FE model]: DBP reduction. Net change in clinic/office DBP for ARBs versus other agents, both in diagrammatic and numerical format (mmHg, 95% CI) .The overall effect represents the pooled estimate of mean net change in DBP response.

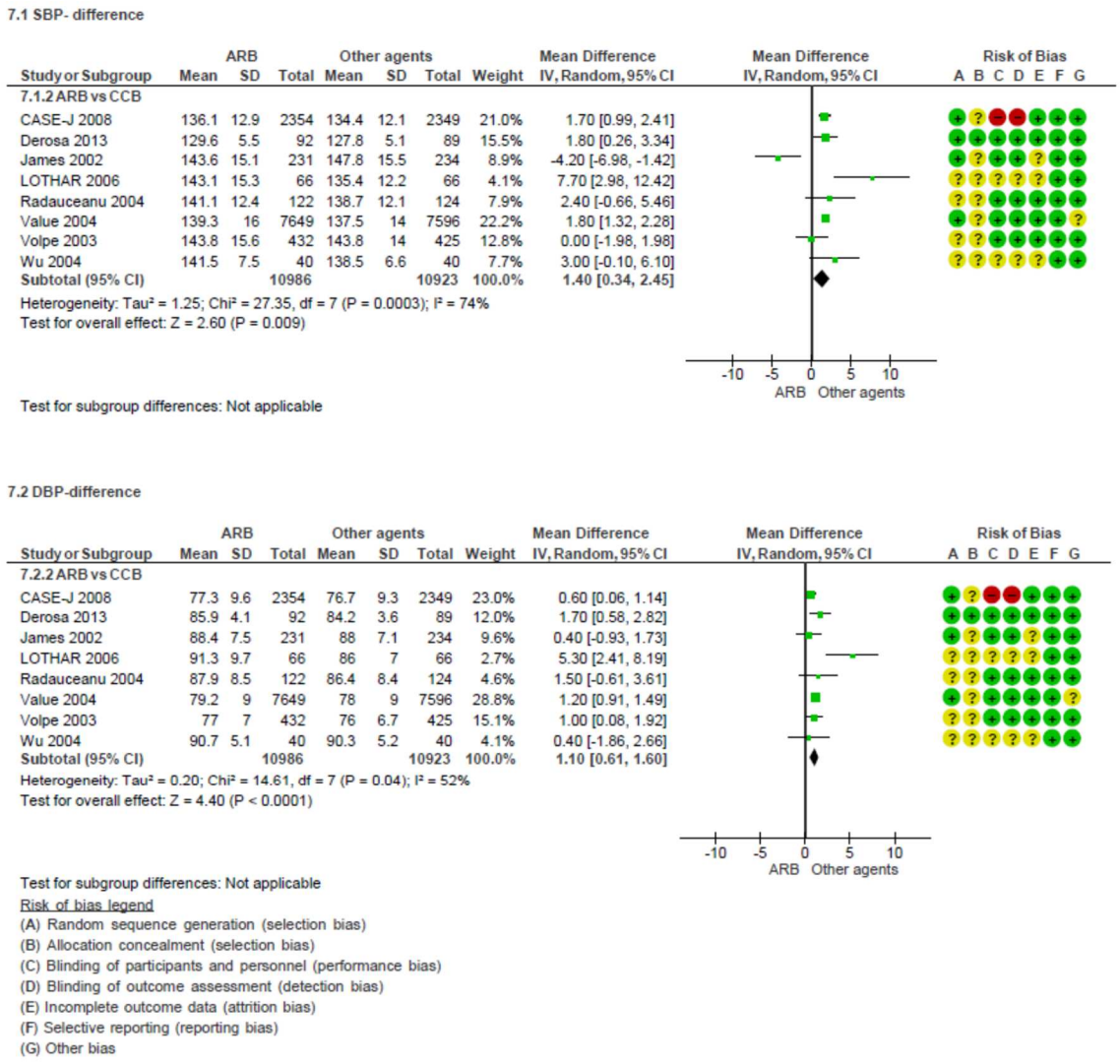


Figure 3.28 Forest plot of comparison of ARBs vs other agents: BP-single measure, outcome [RE model]: BP reduction. Net change in clinic/office BP for ARBs versus other agents, both in diagrammatic and numerical format (mmHg, 95% CI) .The overall effect represents the pooled estimate of mean net change in BP response.

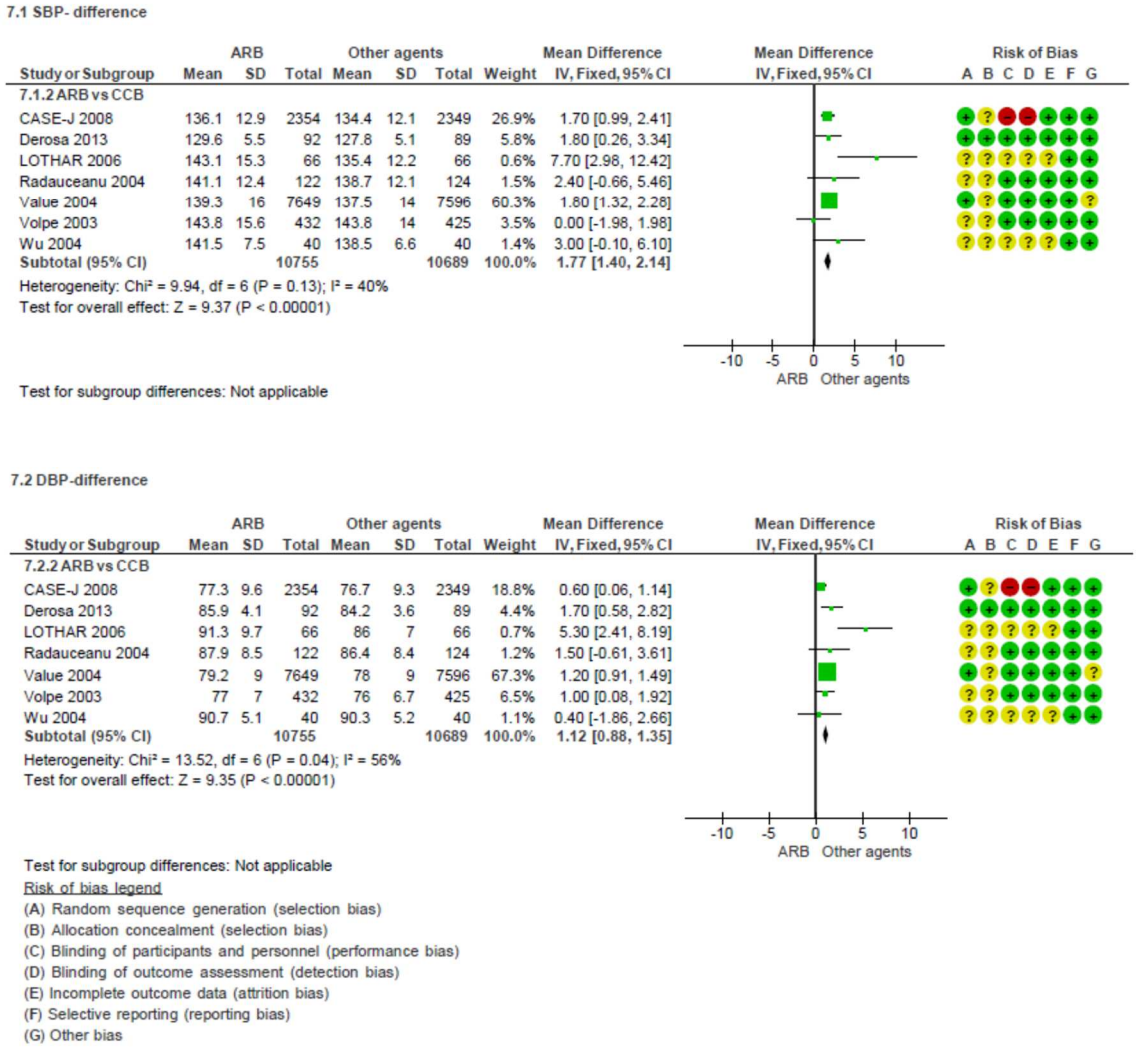


Figure 3.29 Forest plot of comparison of ARBs vs other agents: BP-single measure, outcome [sensitivity analysis]: BP reduction. Net change in clinic/office BP for ARBs versus other agents, both in diagrammatic and numerical format (mmHg, 95% CI) .The overall effect represents the pooled estimate of mean net change in BP response.

3.3.2.3 BP response to CCBs-single measure

During a total of 48,795 person-years of follow-up, using the WMD method and FE model, the mean SBP reduction with CCBs was 2.69 mmHg, 95% CI [1.35, 4.02] less than DIs. SBP reduction was -1.17 mmHg, 95% CI [-2.14, -0.20] more than ACEIs, -1.67 mmHg, 95% CI [-2.04, -1.30] more than ARBs and -4.50 mmHg, 95% CI [-8.33, -0.67] more than the placebo. However, there was no significant difference between CCB and BB (P=0.81) or between CCBs (P = 0.95), as shown in **Figure 3.30.**

For DBP, as shown in **Figure 3.31**, the mean DBP reduction under CCBs was 0.94 mmHg, 95% CI [0.10, 1.78] less than DIs and 1.27 mmHg, 95% CI [0.11, 2.44] less than BBs. For DBP, the mean reduction with CCBs was -1.29 mmHg, 95% CI [-1.84, -0.74] more than ACEIs, -1.10 mmHg, 95% CI [-1.33, -0.87] more than ARBs and -2.30 mmHg, 95% CI [-3.43, -1.17] more than the placebo. However, there was no significant difference between CCBs (P = 0.73).

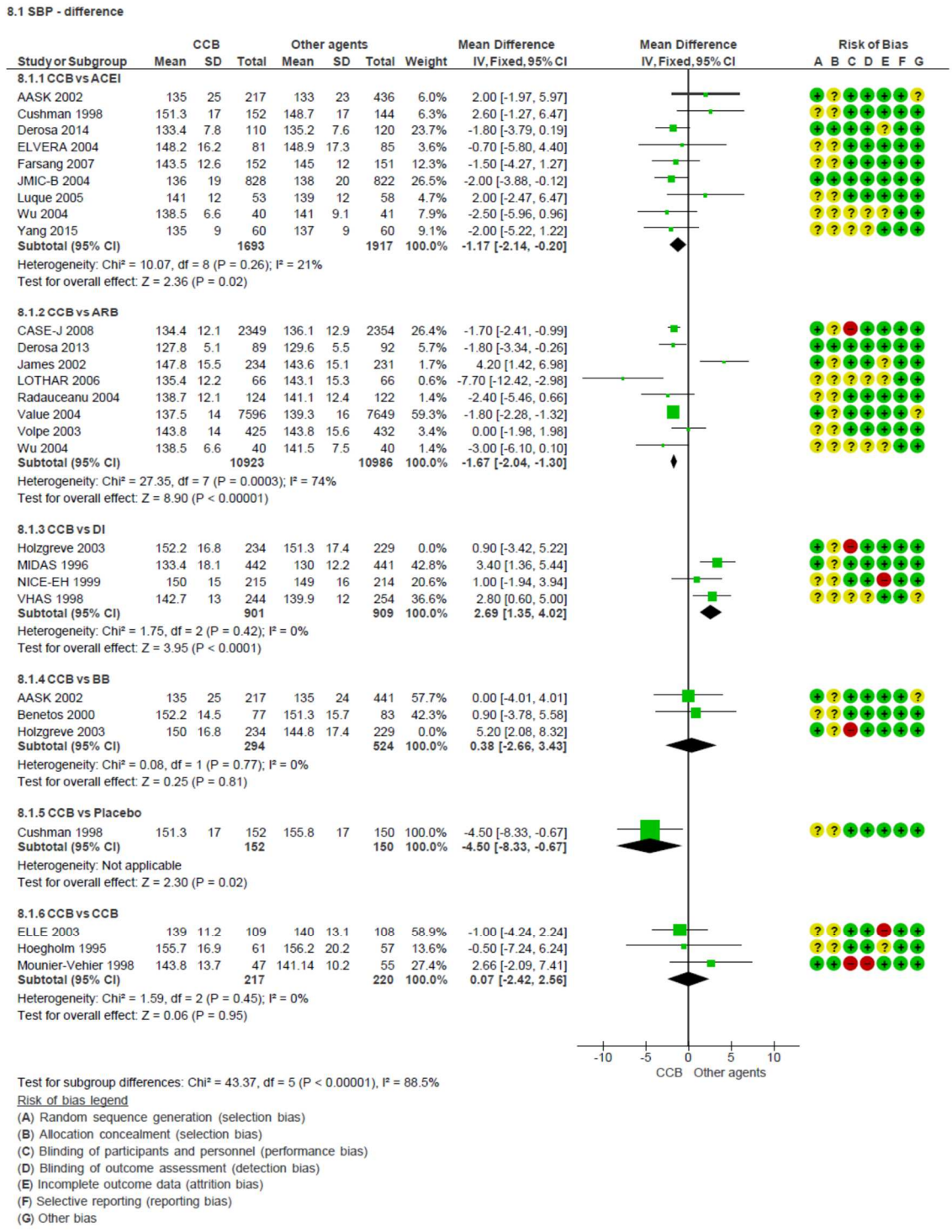


Figure 3.30 Forest plot of comparison of CCBs vs other agents: BP-single measure, outcome [FE model]: SBP reduction. Net change in clinic/office SBP for CCBs versus other agents, both in diagrammatic and numerical format (mmHg, 95% CI) .The overall effect represents the pooled estimate of mean net change in SBP response.

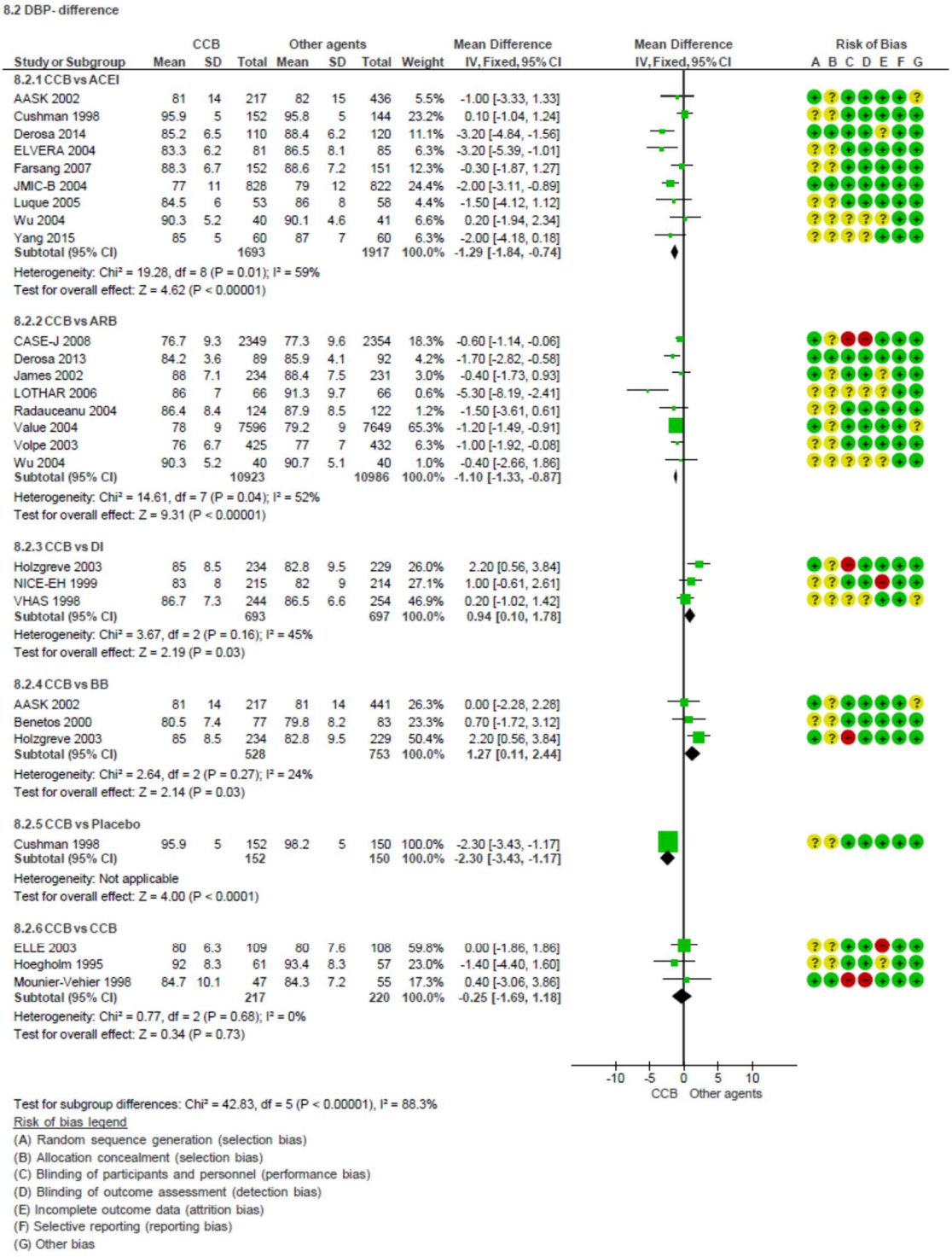


Figure 3.31 Forest plot of comparison of CCBs vs other agents: BP-single measure, outcome [FE model]: DBP reduction. Net change in clinic/office DBP for CCBs versus other agents, both in diagrammatic and numerical format (mmHg, 95% CI) .The overall effect represents the pooled estimate of mean net change in DBP response.

3.3.2.4 BP response to DIs-single measure

During a total of 16,833 person-years of follow-up, using the WMD method and FE model, the mean SBP reduction with DIs was -5.20 mmHg, 95% CI [-8.32, -2.08] more than ACEIs, -2.41 mmHg, 95% CI [-3.63, -1.19] more than CCBs, -3.00 mmHg, 95% CI [-5.93, -0.07] more than BBs and -6.20 mmHg, 95% CI [-7.14, -5.26] more than the placebo. However, there was no significant difference between DIs and ARBs (P = 0.06), as shown in **Figure 3.32.**

For DBP, as shown by **Figure 3.33**,the mean DBP reduction under DIs was –2.20 mmHg, 95% CI [-3.84, -0.56] more than ACEIs, –1.37 mmHg, 95% CI [-2.27, -0.48] more than ARBs, -0.94 mmHg, 95% CI [-1.78, -0.10] more than CCBs and -2.90 mm Hg, 95% CI [-3.39, -2.41] more than the placebo and -2.42 mmHg. However, there was no significant difference between DIs and BBs (P = 0.20).

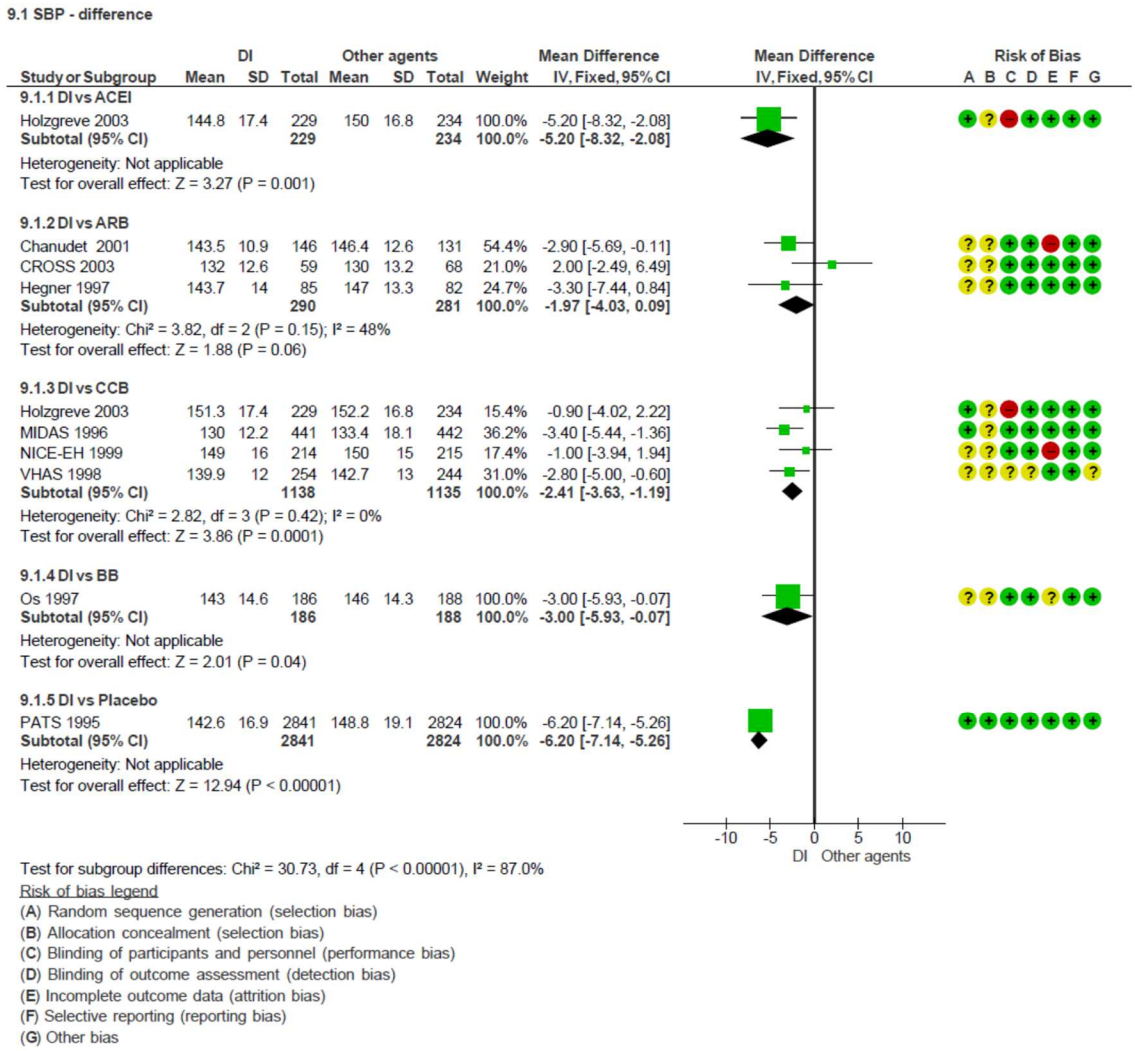


Figure 3.32 Forest plot of comparison of DIs vs other agents: BP-single measure, outcome [FE model]: SBP reduction. Net change in clinic/office SBP for DIs versus other agents, both in diagrammatic and numerical format (mmHg, 95% CI) .The overall effect represents the pooled estimate of mean net change in SBP response.

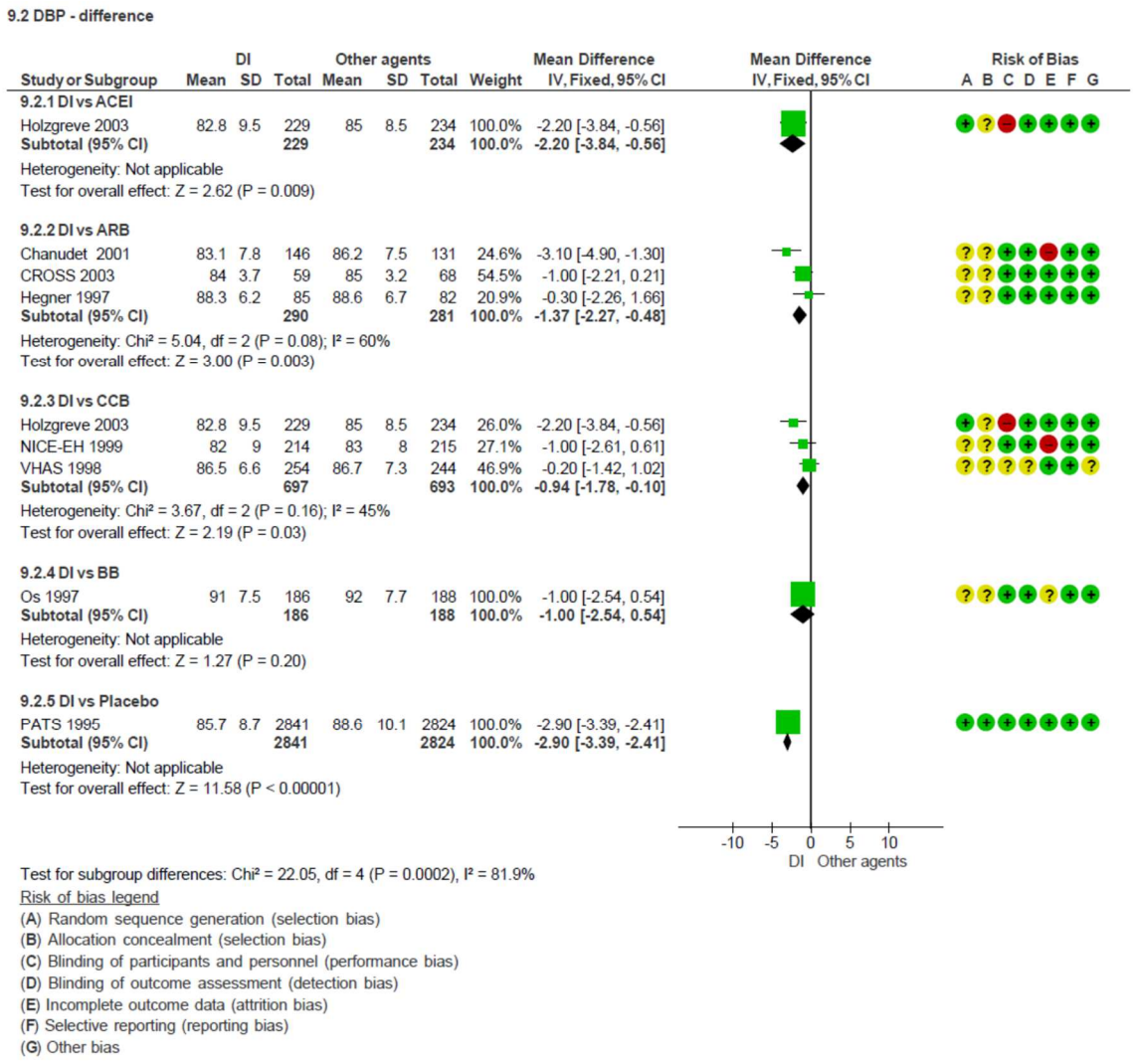


Figure 3.33 Forest plot of comparison of DIs vs other agents: BP-single measure, outcome [FE model]: DBP reduction. Net change in clinic/office DBP for DIs versus other agents, both in diagrammatic and numerical format (mmHg, 95% CI) .The overall effect represents the pooled estimate of mean net change in DBP response.

3.3.2.5 BP response to BBs-single measure

During a total of 19,422 person-years of follow-up, using the WMD method and FE model, the mean SBP reduction with BBs was 1.26 mmHg, 95% CI [0.51, 2.02] less than ARBs and 3.00 mmHg, 95% CI [0.07, 5.93] less than DIs. SBP reduction was -2.73 mmHg, 95% CI [-4.91, -0.56] more than CCBs. However, there was no significant difference between BBs and ACEIs (P = 0.87) or between BBs (P = 0.52), as shown in **Figure 3.34.**

For DBP, as shown by **Figure 3.35**, the mean reduction under BBs was -0.44 mmHg, 95% CI [-0.85, -0.03] more than ARBs and -1.27 mmHg, 95% CI [-2.44, -0.11] more than CCBs. However, there was no significant difference between BBs and ACEIs (P = 0.12), between BBs and DIs (P = 0.20) or between BBs (P = 0.78).

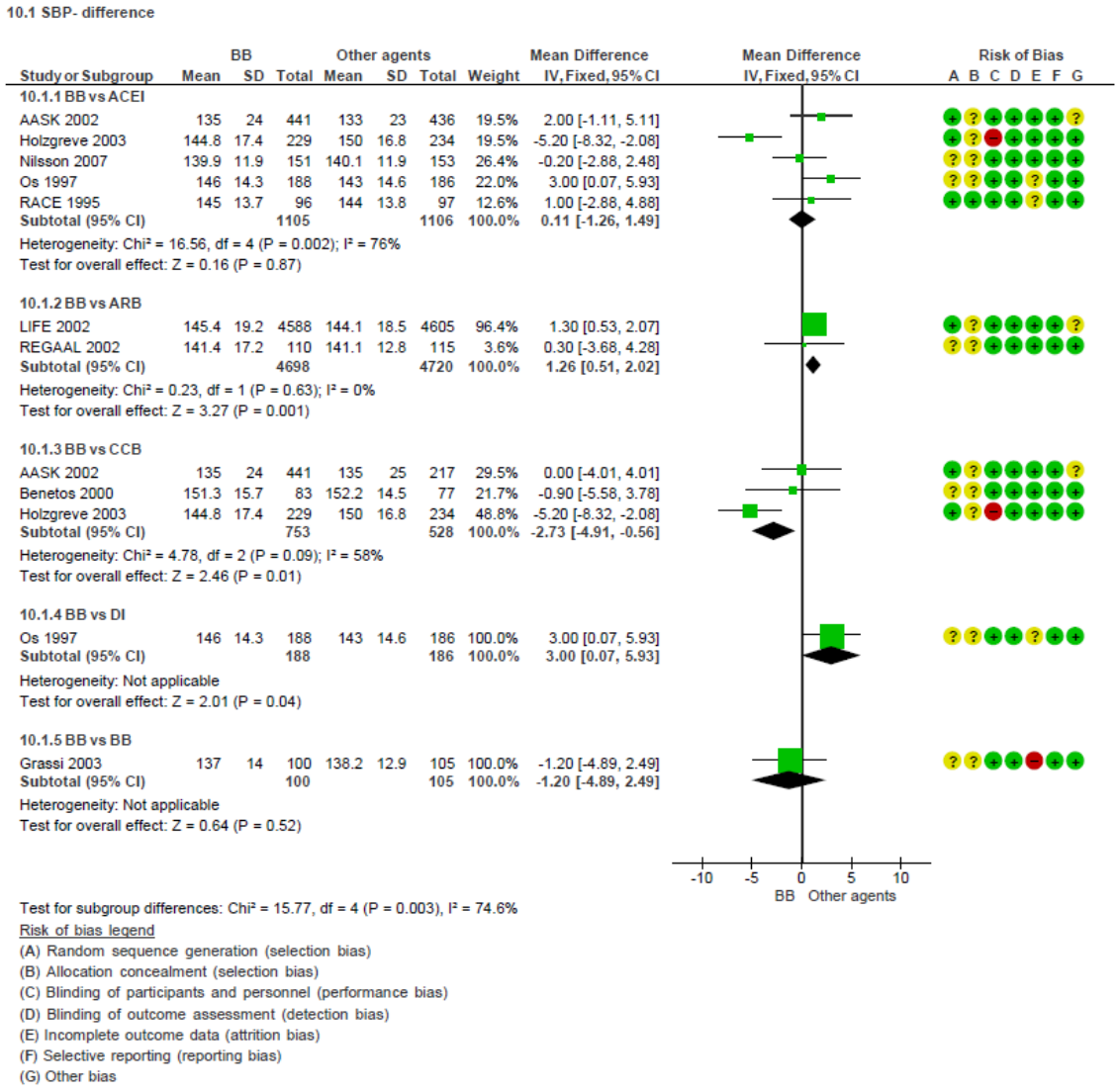


Figure 3.34 Forest plot of comparison of BBs vs other agents: BP-single measure, outcome [FE model]: SBP reduction. Net change in clinic/office SBP for BBs versus other agents, both in diagrammatic and numerical format (mmHg, 95% CI) .The overall effect represents the pooled estimate of mean net change in SBP response.

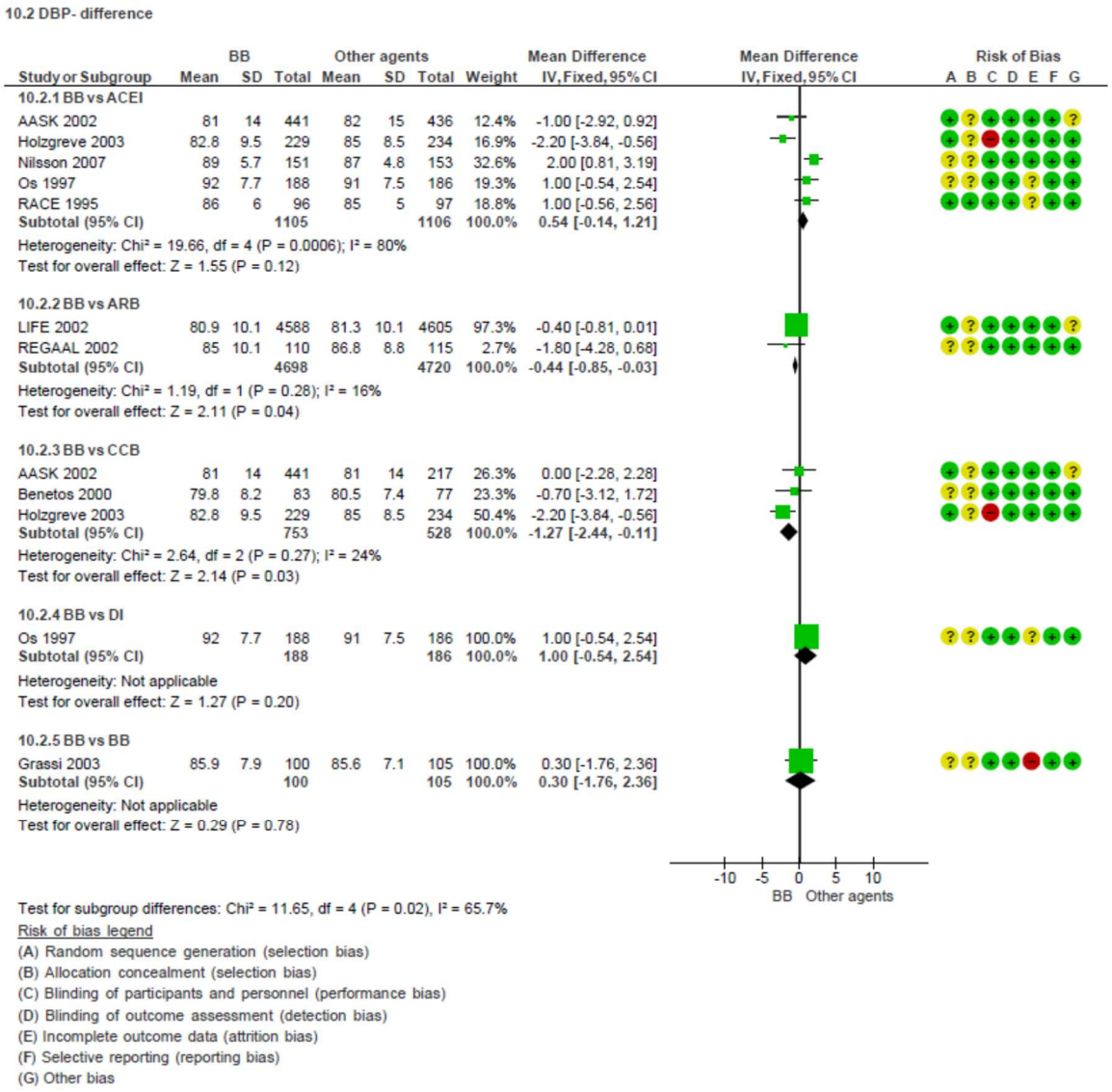


Figure 3.35 Forest plot of comparison of BBs vs other agents: BP-single measure, outcome [FE model]: DBP reduction. Net change in clinic/office DBP for BBs versus other agents, both in diagrammatic and numerical format (mmHg, 95% CI) .The overall effect represents the pooled estimate of mean net change in DBP response.

3.3.3 Repeated measures-BP response

For repeated measures –BP response, 20 studies were included in the analysis (ordered by study ID):

ACCOMPLISH [2004]	HYVET [2008]	LIFE [2002]	SHELL [2003]
ALLHAT [2002]	IDNT [2001]	NICE-EH [1999]	Syst-Eur [1997]
CASE-J [2008]	INSIGHT [2000]	NORDIL [2000]	UKPDS [1998]
Derosa [2014]	INVEST [2003]	PATS [1995]	Value [2004]
DETAIL [2004]	JMIC-B [2004]	REGAAL [2002]	Zanchetti [2001]

3.3.3.1 BP response to ACEIs-repeated measures

During a total of 35,188 person-years of follow-up, using the WMD method and FE model, the mean SBP reduction with ACEIs was 1.09 mmHg, 95% CI [0.64, 1.54] less than CCBs and 2.00 mmHg, 95% CI [1.56, 2.44] less than DIs. However, there was no significant difference between ACEIs and ARBs (P = 0.53) or between ACEIs and BBs (P = 0.12), as shown in **Figure 3.36.**

For DBP, the mean reduction under ACEIs was 1.01 mmHg, 95% CI [0.73, 1.30] less than CCBs. However, there was no significant difference between ACEIs and ARBs (P = 0.45), between ACEIs and DIs (P = 0.15) or between ACEIs and BBs (P = 0.71).

Heterogeneity was observed to an I^2 value of 90% for the three studies comparing DBP reduction with ACEIs vs CCBs. Using the RE model, mean differences for both SBP and DBP were shown of1.09, 95% CI [0.64, 1.54] and 2.19, 95% CI [0.42, 3.96] respectively, as shown in **Figure 3.37.** The observed statistical heterogeneity was most likely due the methodological diversity of the ALLHAT [2002] study, as a number of BP-lowering agents were added to randomly allocated treatment to control BP. Sensitivity analyses, without this study, resulted in homogeneously mean differences for both SBP and DBP of 1.81, 95% CI [0.44, 3.17] and 2.99, 95% CI [2.07, 3.91] respectively, as shown in **Figure 3.38.**

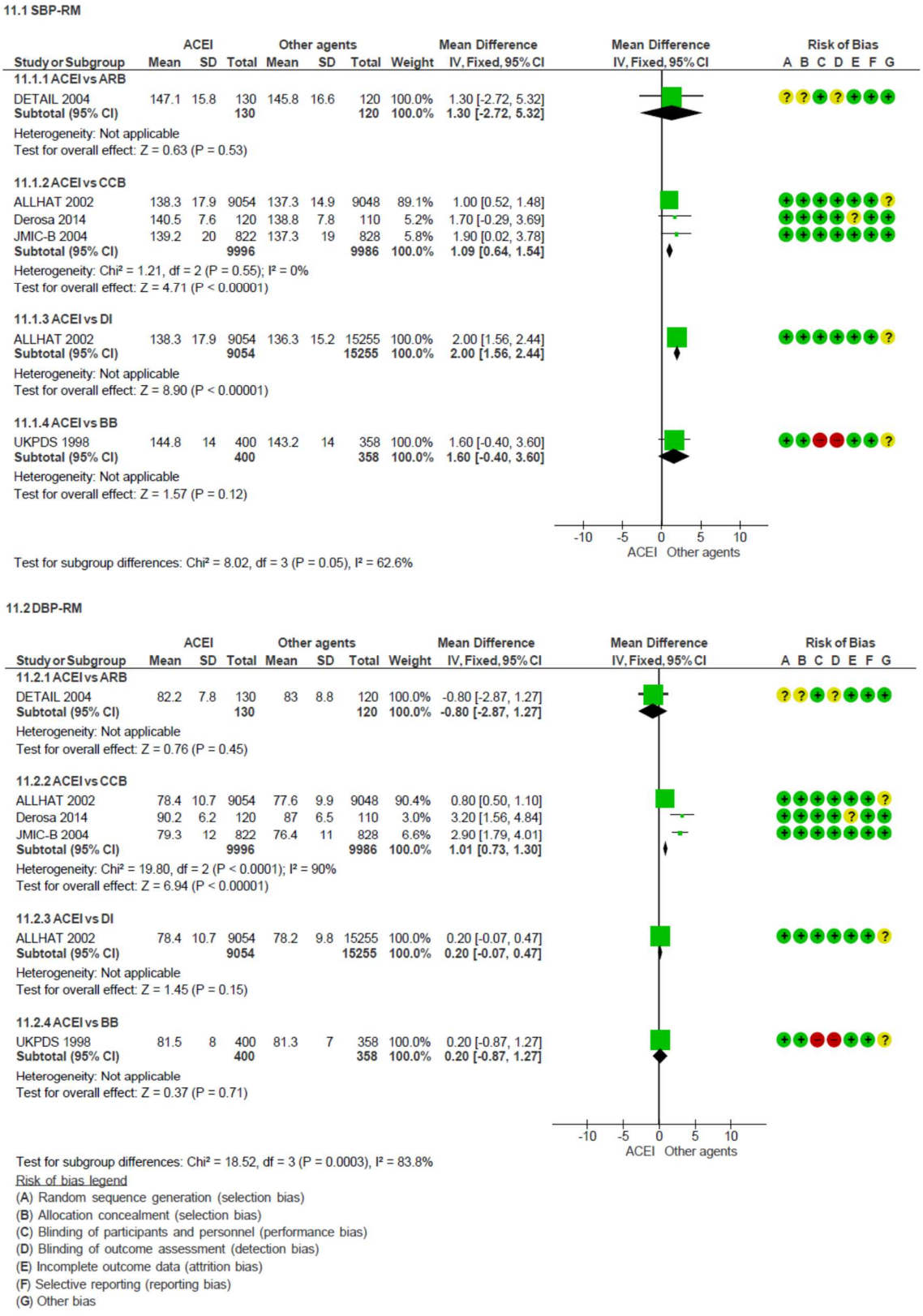


Figure 3.36 Forest plot of comparison of ACEIs vs other agents: BP-repeated measures, outcome [FE model]: BP reduction. Net change in clinic/office BP for ACEIs versus other agents, both in diagrammatic and numerical format (mmHg, 95% CI) .The overall effect represents the pooled estimate of mean net change in BP response.

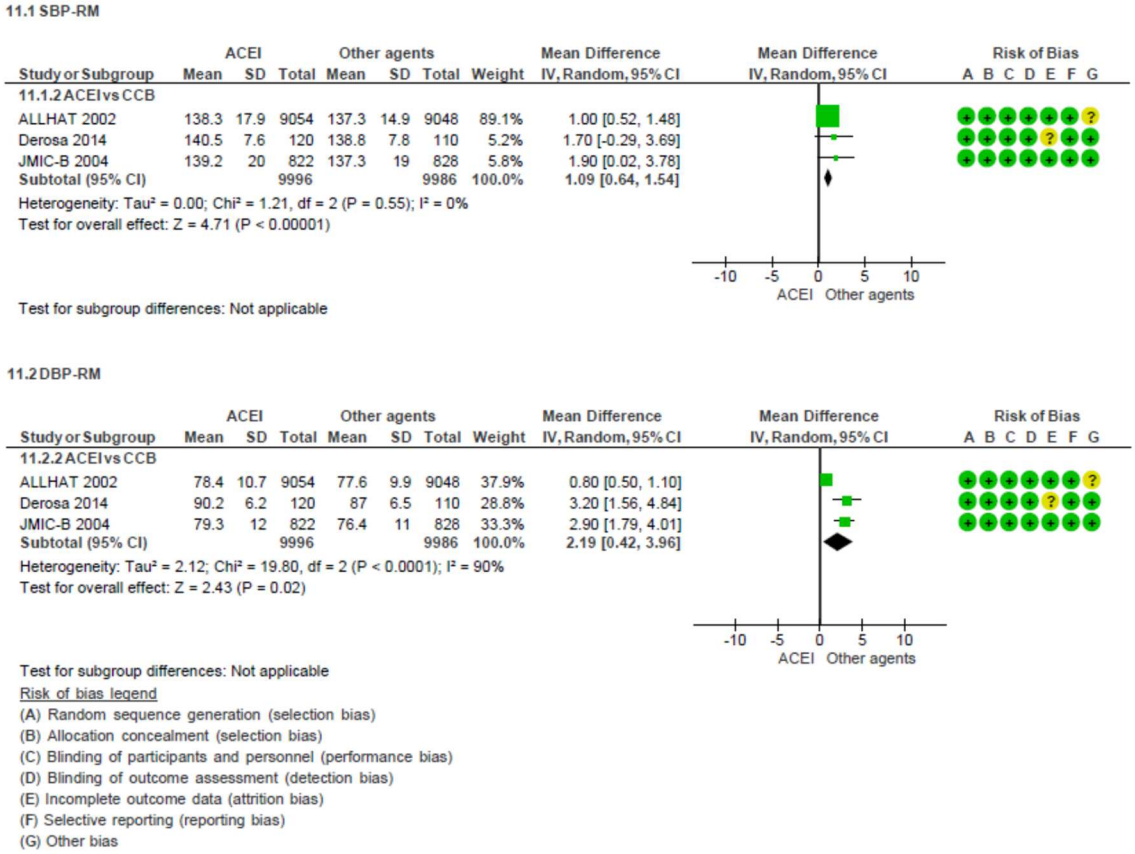


Figure 3.37 Forest plot of comparison of ACEIs vs other agents: BP-repeated measures, outcome [RE model]: BP reduction. Net change in clinic/office BP for ACEIs versus other agents, both in diagrammatic and numerical format (mmHg, 95% CI) .The overall effect represents the pooled estimate of mean net change in BP response.

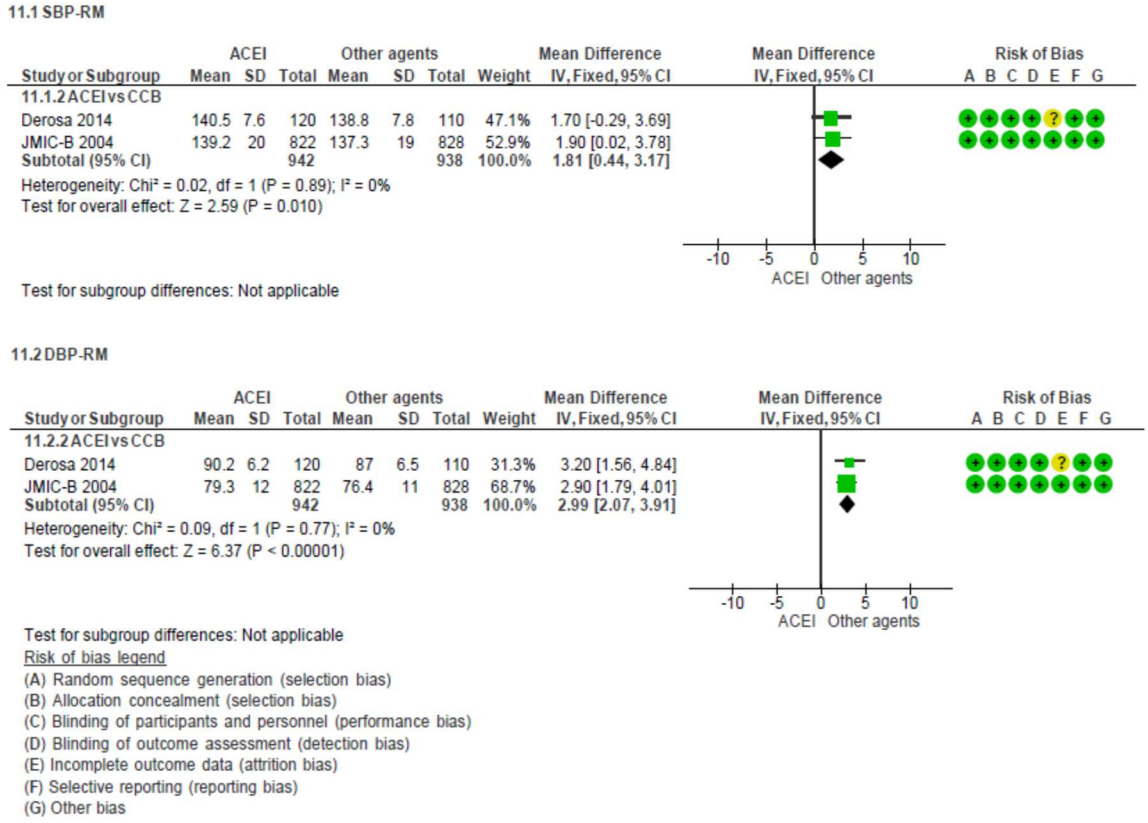


Figure 3.38 Forest plot of comparison of ACEIs vs other agents: BP-repeated measures, outcome [sensitivity analysis]: BP reduction. Net change in clinic/office BP for ACEIs versus other agents, both in diagrammatic and numerical format (mmHg, 95% CI) .The overall effect represents the pooled estimate of mean net change in BP response.

3.3.3.2 BP response to ARBs-repeated measures

During a total of 27,222 person-years of follow-up, using the WMD method and FE model, the mean SBP reduction with ARBs was 1.43 mmHg, 95% CI [1.04, 1.82] less than CCBs. SBP reduction was -0.99 mmHg, 95% CI [-1.75, -0.23] more than ACEIs. However, there was no significant difference between ARBs and ACEIs (P = 0.53) or between ARBs and the placebo (P = 0.15), as shown in **Figure 3.39.**

For DBP, the mean reduction with ARBs was 0.88 mm Hg, 95% CI [0.63, 1.13] less than CCBs and 0.90 mmHg, 95% CI [0.49, 1.31] less than BBs. However, there was no significant difference between ARBs and ACEIs (P = 0.45) or between ARBs and the placebo (P = 0.05).

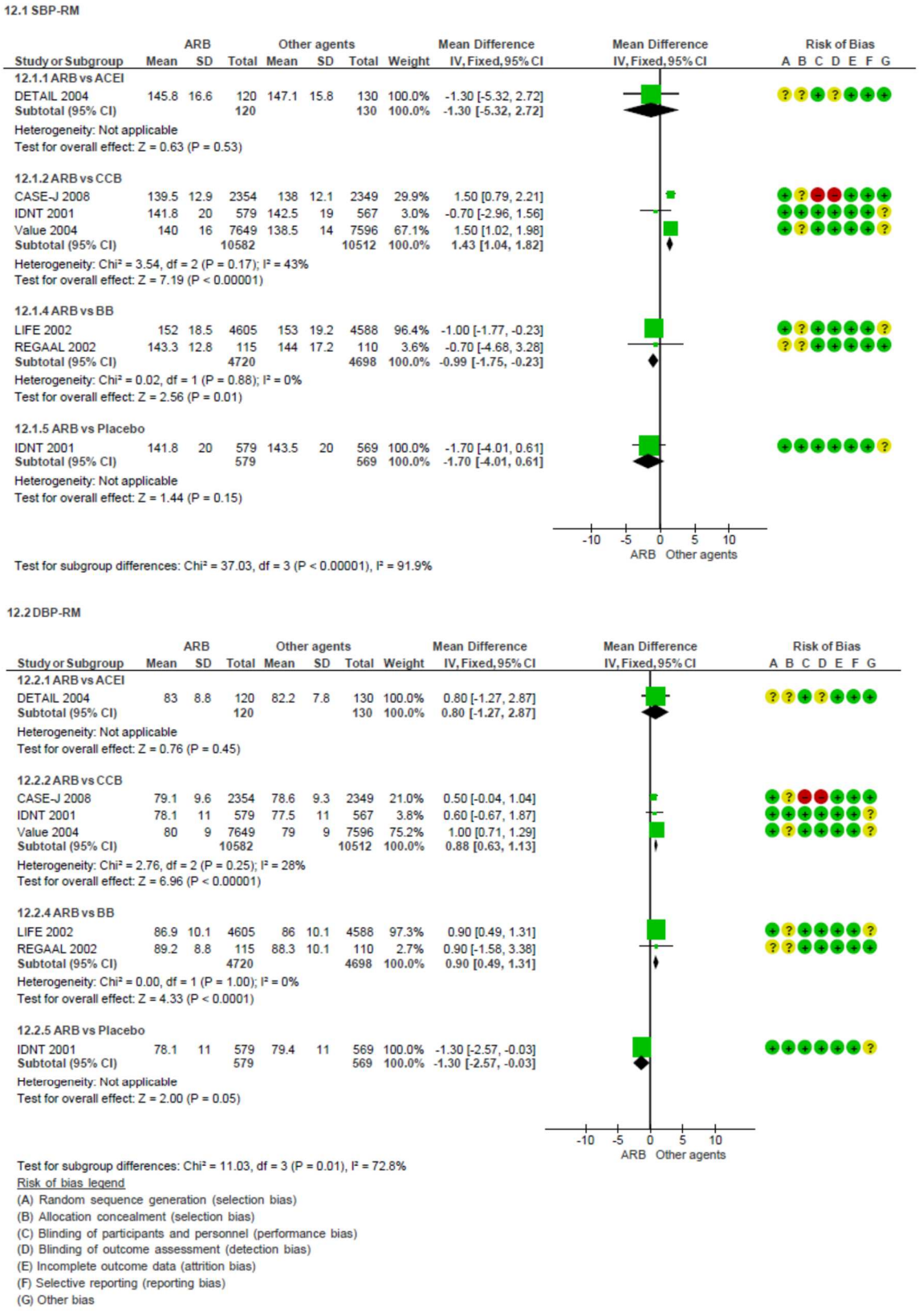


Figure 3.39 Forest plot of comparison of ARBs vs other agents: BP-repeated measures, outcome [FE model]: BP reduction. Net change in clinic/office BP for ARBs versus other agents, both in diagrammatic and numerical format (mmHg, 95% CI) .The overall effect represents the pooled estimate of mean net change in BP response.

3.3.3.3 BP response to CCBs-repeated measures

During a total of 117,259 person-years of follow-up, using the WMD method and FE model, the mean SBP reduction under CCBs was 0.97 mmHg, 95% CI [0.71, 1.24] less than DIs and 1.43 mmHg, 95% CI [1.00, 1.85] less than BBs. SBP reduction was -1.09 mmHg, 95% CI [-1.54, -0.64] more than ACEIs, -1.43 mm Hg, 95% CI [-1.82, -1.04] more than ARBs and -8.04 mmHg, 95% CI [-8.73, -7.35] more than the placebo. However, there was no significant difference between CCBs (P = 0.80), as shown in **Figure 3.40.**

For DBP, as shown in **Figure 3.41**, the mean DBP reduction with CCBs was -1.01 mmHg, 95% CI [-1.30, -0.73] more than ACEIs, -0.88 mmHg, 95% CI [-1.13, -0.63] more than ARBs, -0.37 mmHg, 95% CI [-0.52, -0.21] more than DIs and -4.66 mmHg, 95% CI [-5.03, -4.30] more than the placebo. However, there was no significant difference between CCBs and BBs (P = 0.13) or between CCBs (P = 1.00).

Heterogeneity was also observed to an I^2 value of 93% and 77% for the six studies comparing SBP and DBP reduction respectively, with CBBs vs DIs. Using the RE model, mean differences were shown for both SBP and DBP of 0.84, 95% CI [-0.31, 1.98] and -0.35, 95% CI [-0.71, 0.00] respectively, as shown in **Figure 3.42 .**The observed statistical heterogeneity was most likely due the clinical diversity of the ACCOMPLISH [2004] and NORDIL [2000] studies, as randomisation started with two interventional BP-lowering agents in either one or both treatment arms. Sensitivity analyses, without these studies, resulted in homogeneously mean differences for both SBP and DBP of 0.84, 95% CI [0.51, 1.16] and -0.46, 95% CI [-0.66, -0.25] respectively, as shown in **Figure 3.43.**

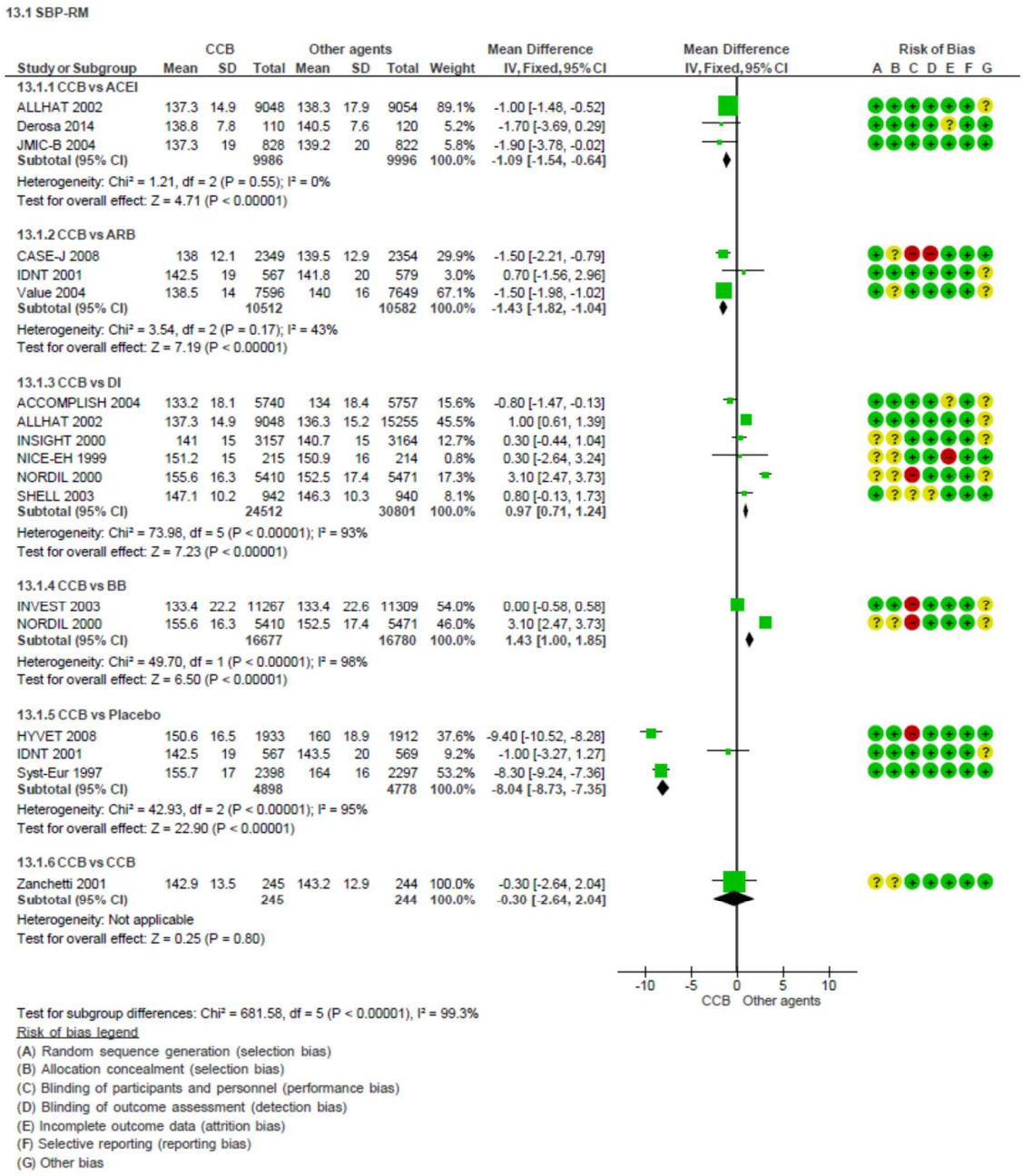


Figure 3.40 Forest plot of comparison of CCBs vs other agents: BP-repeated measures, outcome [FE model]: SBP reduction. Net change in clinic/office SBP for CCBs versus other agents, both in diagrammatic and numerical format (mmHg, 95% CI) .The overall effect represents the pooled estimate of mean net change in SBP response.

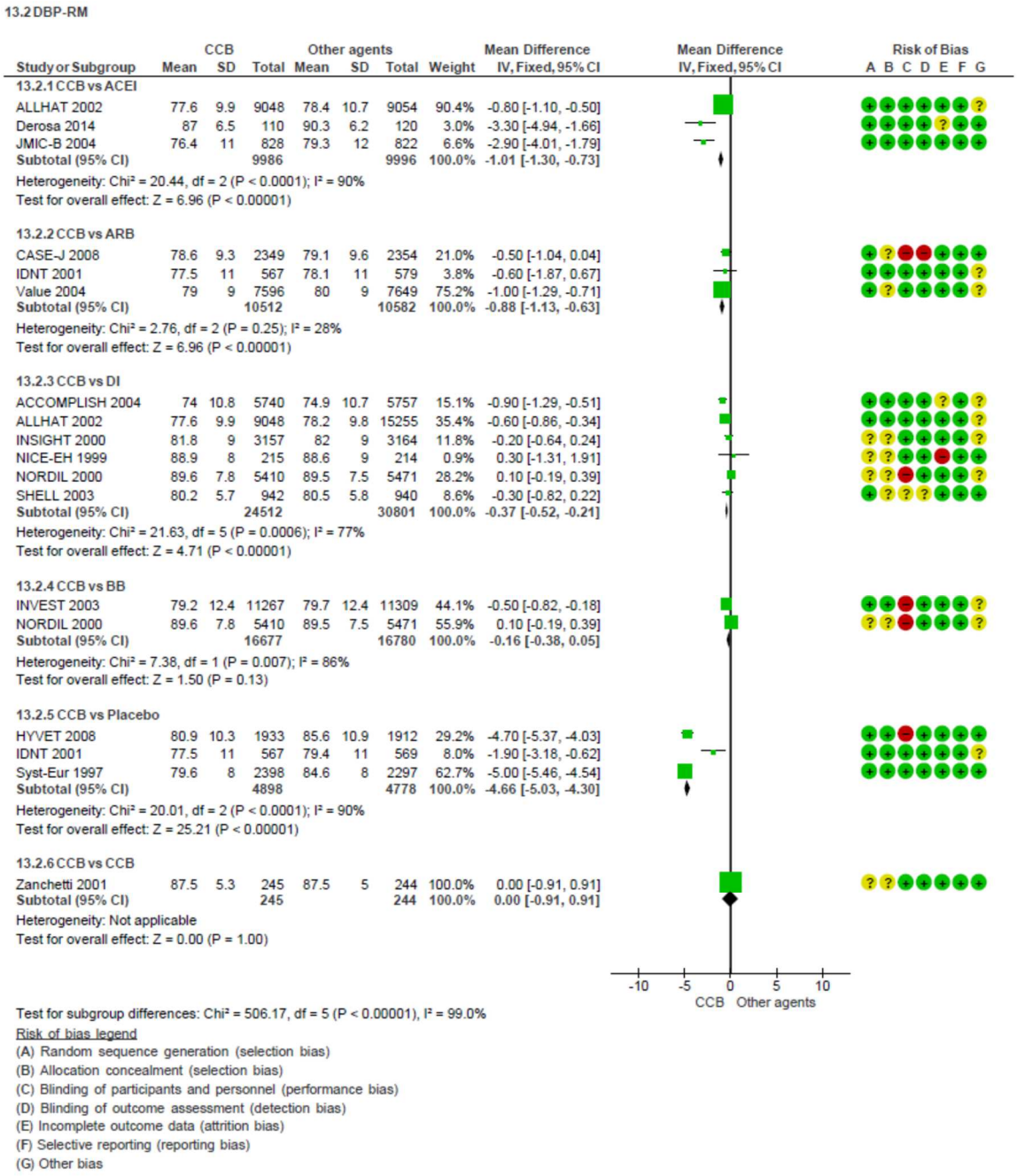


Figure 3.41 Forest plot of comparison of CCBs vs other agents: BP-repeated measures, outcome [FE model]: DBP reduction. Net change in clinic/office DBP for CCBs versus other agents, both in diagrammatic and numerical format (mmHg, 95% CI) .The overall effect represents the pooled estimate of mean net change in DBP response.

Heterogeneity was seen at an I^2 value of 98% and 86% for the two studies comparing SBP and DBP reduction respectively, with CBBs vs BBs. Using the RE model, mean differences were shown for both SBP and DBP of 1.55, 95% CI [-1.49, 4.59] and -0.20, 95% CI [-0.78, 0.39] respectively. The observed statistical heterogeneity was most likely due to the the clinical diversity of the NORDIL [2000] study, as BP was measured in the supine position.

Heterogeneity was also observed to an I^2 value of 95% and 90% for the three studies comparing SBP and DBP reduction respectively, with CBBs vs the placebo. Using the RE model, mean differences were shown for both SBP and DBP of -6.42, 95% CI [-9.91, -2.93] and -4.02, 95% CI [-5.35, -2.69] respectively. The observed statistical heterogeneity was most likely due to the methodological diversity of the IDNT [2001] study, as a number of BP-lowering agents were added to randomly allocated treatment to control BP. Sensitivity analyses, without this study, resulted in homogeneously mean differences for both SBP and DBP of -8.76, 95% CI [-9.48, -8.03] and -4.90, 95% CI [-5.28, -4.53] respectively.

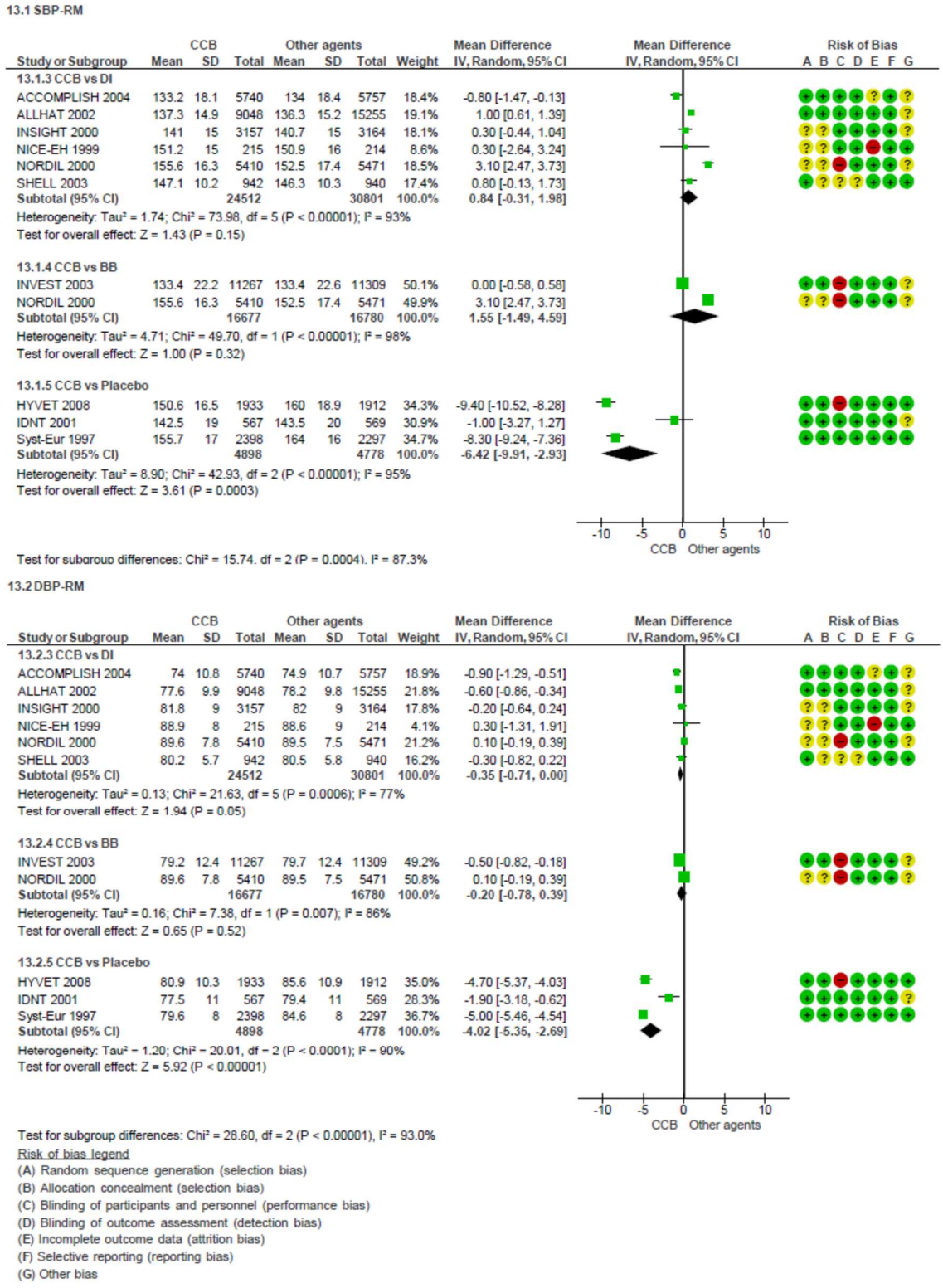


Figure 3.42 Forest plot of comparison of CCBs vs other agents: BP-repeated measures, outcome [RE model]: BP reduction. Net change in clinic/office BP for CCBs versus other agents, both in diagrammatic and numerical format (mmHg, 95% CI) .The overall effect represents the pooled estimate of mean net change in BP response.

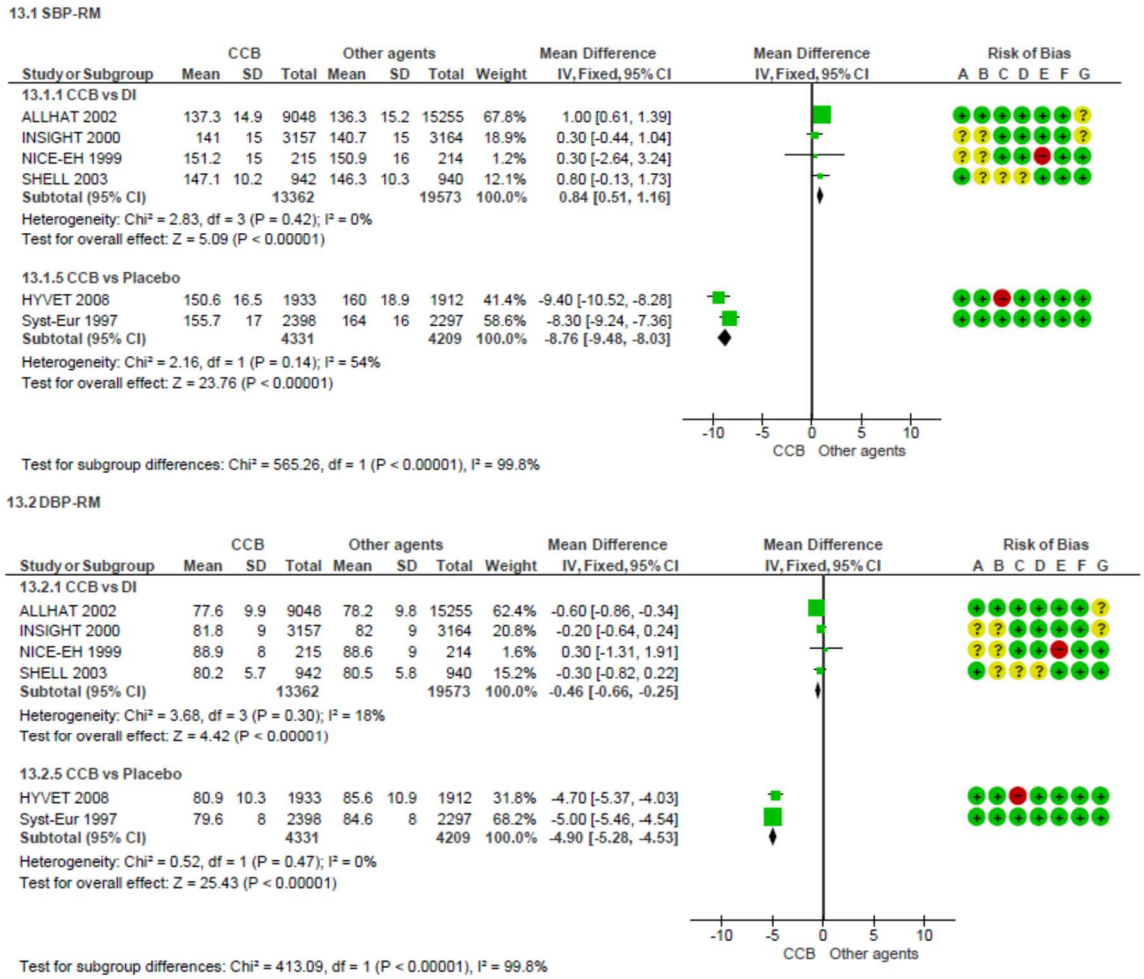


Figure 3.43 Forest plot of comparison of CCBs vs other agents: BP-repeated measures, outcome [sensitivity analysis]: BP reduction. Net change in clinic/office BP for CCBs versus other agents, both in diagrammatic and numerical format (mmHg, 95% CI) .The overall effect represents the pooled estimate of mean net change in BP response.

3.3.3.4 BP response to DIs-repeated measures

During a total of 85,624 person-years of follow-up, using the WMD method and FE model, the mean SBP reduction with DIs was -2.00 mmHg, 95% CI [-2.44, -1.56] more than ACEIs, -0.97 mmHg, 95% CI [-1.24, -0.71] more than CCBs and -4.40 mmHg, 95% CI [-5.34, -3.46] more than the placebo, as shown in **Figure 3.44.**

For DBP, the mean reduction under DIs was 0.37 mm Hg, 95% CI [0.21, 0.52] less than CCBs and -2.00 mmHg, 95% CI [-2.49, -1.51] more than the placebo. However, there was no significant difference between DIs and ACEIs (p = 0.15).

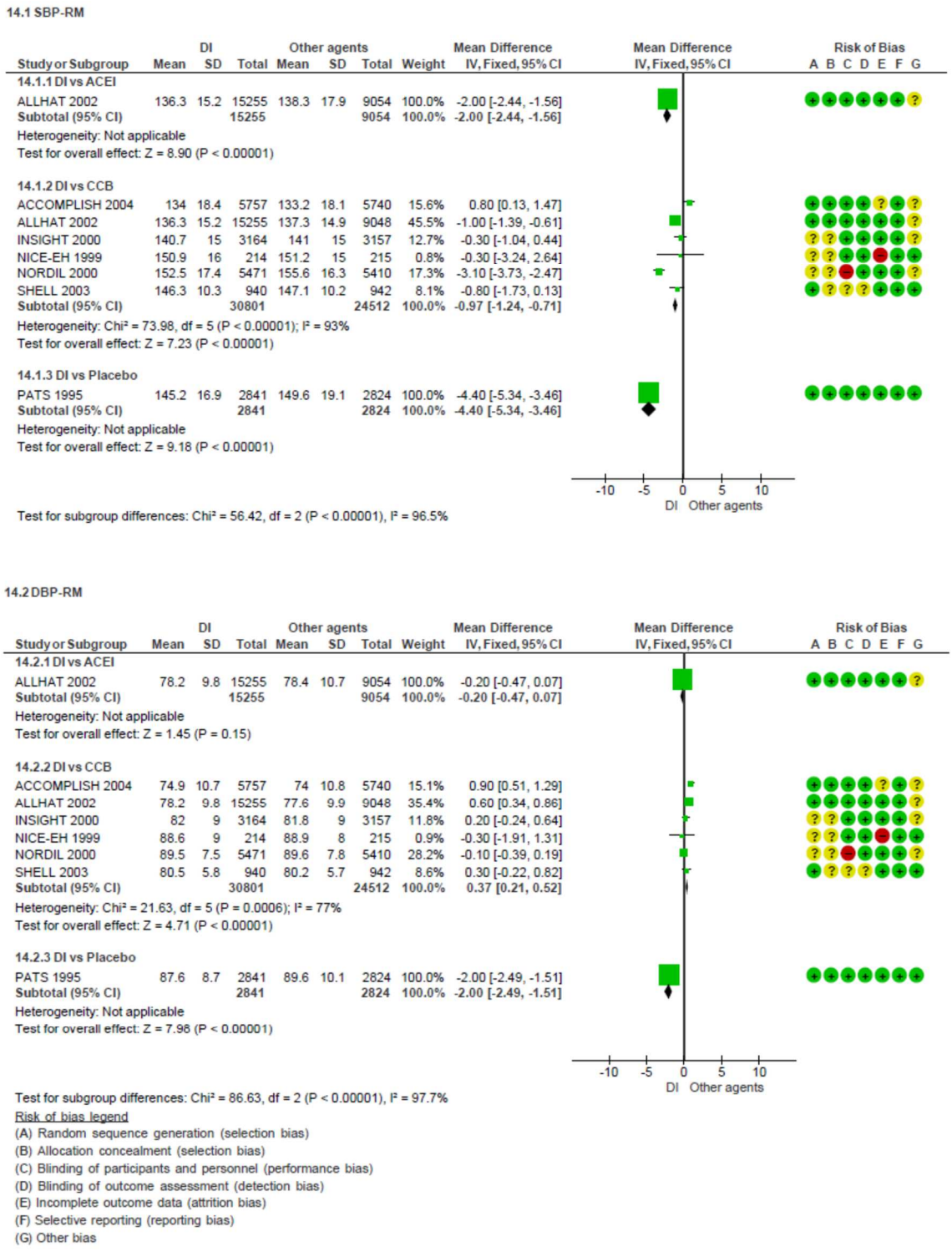


Figure 3.44 Forest plot of comparison of DIs vs other agents: BP-repeated measures, outcome [FE model]: BP reduction. Net change in clinic/office BP for DIs versus other agents, both in diagrammatic and numerical format (mmHg, 95% CI) .The overall effect represents the pooled estimate of mean net change in BP response.

3.3.3.5 BP response to BBs-repeated measures

During a total of 38,847 person-years of follow-up, using the WMD method and FE model, the mean SBP reduction with BBs was 0.99 mmHg, 95% CI [0.23, 1.75] less than ARBs and -1.43 mmHg, 95% CI [-1.85, -1.00] more than CCBs. However, there was no significant difference between BBs and ACEIs (P = 0.12), as shown in **Figure 3.45.**

For DBP, the mean reduction under BBs was -0.90 mmHg, 95% CI [-1.31, -0.49] more than ARBs. However, there was no significant difference between BBs and ACEIs (P = 0.71) or between BBs and CCBs (P = 0.13).

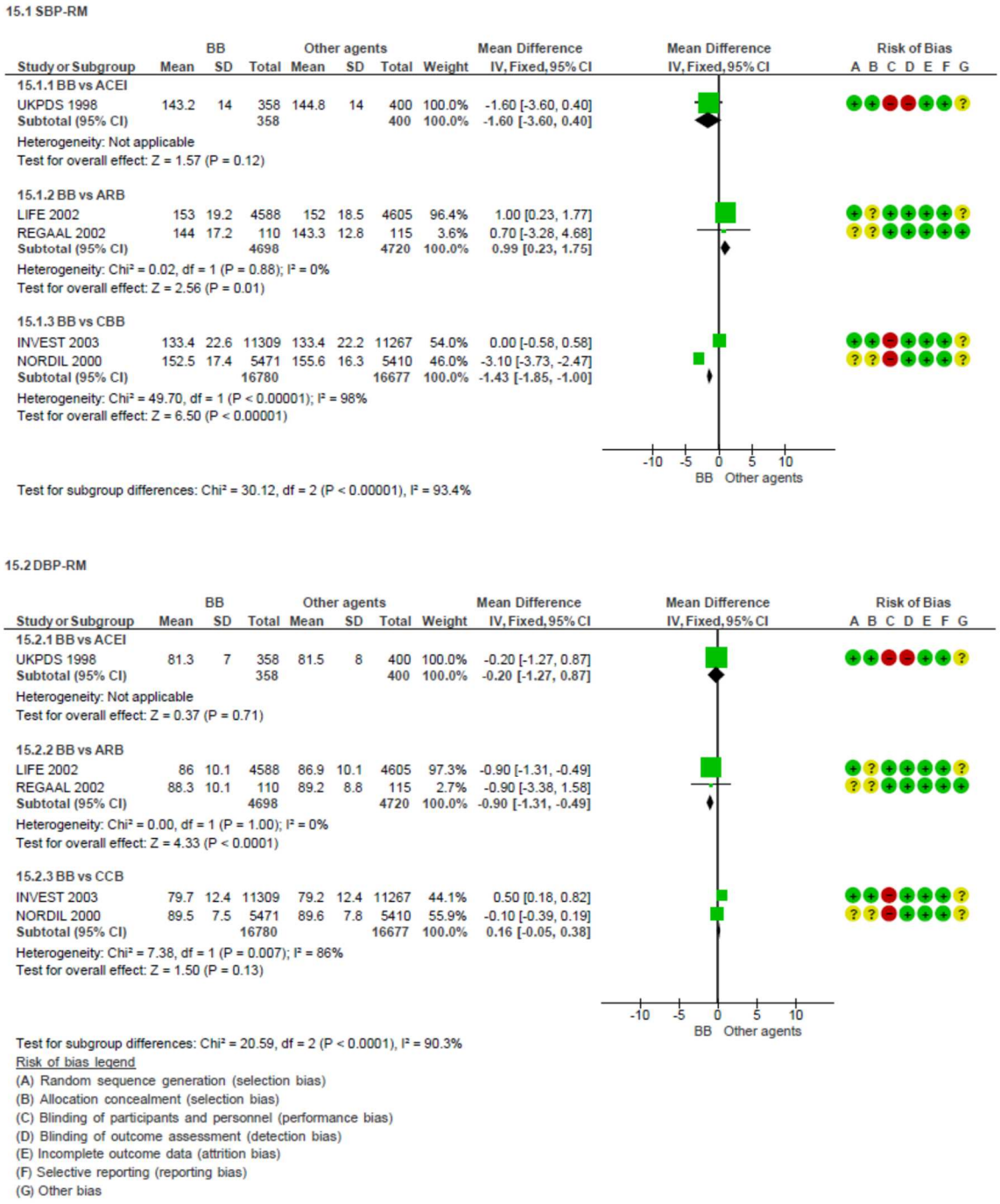


Figure 3.45 Forest plot of comparison of BBs vs other agents: BP-repeated measures, outcome [FE model]: BP reduction. Net change in clinic/office BP for BBs versus other agents, both in diagrammatic and numerical format (mmHg, 95% CI) .The overall effect represents the pooled estimate of mean net change in BP response.

3.3.1 Summary for BP responses

Table 3.2 Summary of ACEI-BP responses.
The table shows delta, single and repeated measures - BP response. Considering the level of statistical significance (P < 0.05) [White highlights] indicate significant statistical effect and [Grey highlights] indicate insignificant statistical effect.

ACEI	Studies N	Subjects N	SBP	I^2	Studies N	Subjects N	DBP	I^2
Delta-BP response [FE model]								
ACEI vs. ARB	9	2605	1.98	60%	9	2605	-0.52	53%
ACEI vs. CCB	9	22215	1.43	74%	9	22215	0.76	24%
ACEI vs. DI	4	44447	0.5	97%	4	44447	-0.83	96%
ACEI vs. BB	8	22798	-0.99	80%	8	22798	-0.95	95%
ACEI vs. Placebo	3	1093	-6.27	74%	3	1093	-3.55	96%
ACEI vs. ACEI	2	332	-2	0%	2	332	-1	0%
Delta-BP response [RE model]								
ACEI vs. CCB	9	22215	2.06	74%	9	22215	0.87	24%
ACEI vs. DI	4	44447	-0.29	97%	4	44447	-0.5	96%
ACEI vs. BB	8	22798	0.43	80%	8	22798	0.32	95%
ACEI vs. Placebo	3	1093	-7.06	74%	3	1093	-4.1	96%
Delta-BP response [sensitivity analysis]								
ACEI vs. CCB	8	21835	1.2	46%	8	21835	0.76	33%
ACEI vs. DI	2	24407	1.79	0%	2	24407	-0.09	0%
ACEI vs. BB	6	2783	0.79	60%	6	2783	0.82	58%
ACEI vs. Placebo	2	468	-9.06	0%	2	468	-5.85	9%
Single measure-BP response [FE model]								
ACEI vs. ARB	4	1038	-1.11	0%	4	1038	-1.83	10%
ACEI vs. CCB	9	3610	1.17	21%	9	3610	1.29	59%
ACEI vs. DI	1	463	5.2	-	1	463	2.2	-
ACEI vs. BB	5	2211	-0.11	76%	5	2211	-0.54	80%
ACEI vs. Placebo	1	290	-7.1	-	1	290	-2.4	-
Single measure-BP response [RE model]								
ACEI vs. BB	5	2211	-0.11	76%	5	2211	-0.23	80%
Single measure-BP response [sensitivity analysis]								
ACEI vs. BB	4	1748	-1.4	0%	4	1748	-1.09	56%
Repeated measures-BP response [FE model]								
ACEI vs. ARB	1	250	1.3	-	1	250	-0.8	-
ACEI vs. CCB	3	19982	1.09	0%	3	19982	1.01	90%
ACEI vs. DI	1	24309	2	-	1	24309	0.2	-
ACEI vs. BB	1	758	1.6	-	1	758	0.2	-
Repeated measures-BP response [RE model]								
ACEI vs. CCB	3	19982	1.09	0%	3	19982	2.19	90%
Repeated measures-BP response [sensitivity analysis]								
ACEI vs. CCB	2	1880	1.81	0%	2	1880	2.99	0%

As shown in **Table 3.2** :

ACEIs were superior to ARBs in lowering DBP (delta: -0.51 mmHg (P < 0.00001)), single measure: -1.83 mmHg (P = 0.0001) and repeated measures: -0.8 mmHg (P = 0.45).

ACEIs were “significantly” superior to the placebo in lowering both SBP and DBP: for SBP (delta: -9.06 mmHg (P < 0.00001) and single measure: -7.1 mmHg (P =

0.0003)) and for DBP (delta: -5.85 mmHg (P < 0.00001) and single measure: -2.4 mmHg (P < 0.0001)).

There was no significant BP variance between different agents within the same ACEI classes in BP response. For SBP/DBP (delta: -2.0 mmHg (P = 0.18)/-1.0 mmHg (P = 0.14)).

Table 3.3 Summary of ARB-BP responses.
The table shows delta, single and repeated measures - BP response .Considering the level of statistical significance (P < 0.05), [White highlights] indicate significant statistical effect, [Grey highlights] indicate insignificant statistical effect and [Red highlights] indicate significant statistical effect in all BP measures.

ARB	Studies N	Subjects N	SBP	I^2	Studies N	Subjects N	DBP	I^2
Delta-BP response [FE model]								
ARB vs. ACEI	9	2605	-1.98	60%	9	2605	0.52	53%
ARB vs. CCB	5	16991	1.92	69%	5	16991	1.53	85%
ARB vs. DI	3	836	1.97	0%	3	836	0.2	57%
ARB vs. BB	4	10154	-1.16	53%	4	10154	0.14	3%
ARB vs. Placebo	4	995	-9.6	0%	4	995	-6.13	57%
ARB vs. ARB	2	829	-2.12	18%	2	829	-1.57	10%
Delta-BP response [RE model]								
ARB vs. CCB	5	16991	0.82	69%	5	16991	0.55	85%
Delta-BP response [sensitivity analysis]								
ARB vs. CCB	4	1746	0.16	0%	4	1746	0.25	48%
Single measure-BP response [FE model]								
ARB vs. ACEI	4	1038	1.11	0%	4	1038	1.83	10%
ARB vs. CCB	8	21909	1.67	74%	8	21909	1.1	52%
ARB vs. DI	3	571	1.97	48%	3	571	1.37	60%
ARB vs. BB	2	9418	-1.26	0%	2	9418	0.44	16%
ARB vs. ARB	1	126	-5.2	-	1	126	-3.2	-
Single measure-BP response [RE model]								
ARB vs. CCB	8	21909	1.40	74%	8	21909	1.10	52%
Single measure-BP response [sensitivity analysis]								
ARB vs. CCB	7	21444	1.77	40%	7	21444	1.12	56%
Repeated measures-BP response [FE model]								
ARB vs. ACEI	1	250	-1.3	-	1	250	0.8	-
ARB vs. CCB	3	21094	1.43	43%	3	21094	0.88	28%
ARB vs. BB	2	9418	-0.99	0%	2	9418	0.9	0%
ARB vs. Placebo	1	1148	-1.7	-	1	1148	-1.3	-

As shown in **Table 3.3** :

ARBs were “significantly” superior to BBs in lowering SBP (delta: -1.16 mmHg (P = 0.002), single measure: -1.26 mmHg (P = 0.001), repeated measures: -0.99 mmHg (P = 0.01).

ARBs were superior to the placebo in lowering BP, both SBP and DBP. For SBP (delta: -9.6 mmHg (P < 0.00001) and repeated measures: -1.7 mmHg (P = 0.15)). For DBP (delta: -6.13 mmHg (P < 0.00001) and repeated measures: -1.3 mmHg (P = 0.05)).

There was a “significant” BP variance between different agents within same the ARB classes in BP response. For SBP (delta: -2.12 mmHg (P = 0.02) and single measure: -5.2 mmHg (P < 0.00001)). For DBP (delta: -1.57 mmHg (P < 0.00001) and single measure: -3.2 mmHg (P = 0.0003).

Table 3.4 Summary of CCB-BP responses.
The table shows delta, single and repeated measures - BP response .Considering the level of statistical significance (P < 0.05), [White highlights] indicate significant statistical effect, [Grey highlights] indicate insignificant statistical effect and [Red highlights] indicate significant statistical effect in all BP measures.

CCB	Studies N	Subjects N	SBP	I^2	Studies N	Subjects N	DBP	I^2
Delta-BP response [FE model]								
CCB vs. ACEI	9	22215	-1.43	74%	9	22215	-0.76	24%
CCB vs. ARB	5	16991	-1.92	69%	5	16991	-1.53	85%
CCB vs. DI	7	71766	0.48	95%	7	71766	-0.76	93%
CCB vs. BB	7	72468	0.21	95%	7	72468	-0.5	95%
CCB vs. Placebo	4	9336	-9.88	84%	4	9336	-4.64	43%
CCB vs. CCB	3	529	-1.34	0%	3	529	-0.27	0%
Delta-BP response [RE model]								
CCB vs. ACEI	9	22215	-2.06	74%	9	22215	-0.87	24%
CCB vs. ARB	5	16991	-0.82	69%	5	16991	-0.55	85%
CCB vs. DI	7	71766	0.82	95%	7	71766	-0.49	93%
CCB vs. BB	7	72468	0.09	95%	7	72468	-0.36	95%
CCB vs. Placebo	4	9336	-9.58	84%	4	9336	-4.64	43%
Delta-BP response [sensitivity analysis]								
CCB vs. ACEI	8	21835	-1.2	46%	8	21835	-0.76	33%
CCB vs. ARB	4	1746	-0.16	0%	4	1746	-0.25	48%
CCB vs. DI	4	25026	0.82	42%	4	25026	-0.63	58%
CCB vs. BB	3	3152	-0.27	0%	3	3152	0.12	42%
CCB vs. Placebo	3	5491	-8.76	0%	3	5491	-4.46	0%
Single measure-BP response [FE model]								
CCB vs. ACEI	9	3610	-1.17	21%	9	3610	-1.29	59%
CCB vs. ARB	8	21909	-1.67	74%	8	21909	-1.1	52%
CCB vs. DI	4	1810	2.69	0%	4	1810	0.94	45%
CCB vs. BB	3	818	2.73	58%	3	818	1.27	24%
CCB vs. Placebo	1	302	-4.5	-	1	302	-2.3	-
CCB vs. CCB	3	437	0.07	0%	3	437	-0.25	0%
Single measure-BP response [RE model]								
CCB vs. ARB	8	21909	-1.40	74%	8	21909	-1.10	52%
Single measure-BP response [sensitivity analysis]								
CCB vs. ARB	7	21444	-1.77	40%	7	21444	-1.12	56%
Repeated measures-BP response [FE model]								
CCB vs. ACEI	3	19982	-1.09	0%	3	19982	-1.01	90%
CCB vs. ARB	3	21094	-1.43	43%	3	21094	-0.88	28%
CCB vs. DI	6	55313	0.97	93%	6	55313	-0.37	77%
CCB vs. BB	2	33457	1.43	96%	2	33457	-0.16	86%
CCB vs. Placebo	3	9676	-8.04	95%	3	9676	-4.66	90%
CCB vs. CCB	1	489	-0.3	-	1	489	0	-
Repeated measures-BP response [RE model]								
CCB vs. ACEI	3	19982	-1.09	0%	3	19982	-2.19	90%
CCB vs. DI	6	55313	0.84	93%	6	55313	-0.35	77%
CCB vs. BB	2	33457	1.55	98%	2	33457	-0.20	86%
CCB vs. Placebo	3	9676	-6.42	95%	3	9676	-4.02	90%
Repeated measures-BP response [sensitivity analysis]								
CCB vs. ACEI	2	1880	-1.81	0%	2	1880	-2.99	0%
CCB vs. DI	4	32935	0.84	0%	4	32935	-0.46	18%
CCB vs. Placebo	2	8540	-8.76	54%	2	8540	-4.9	0%

As shown in **Table 3.4** :

CCBs were “significantly” superior to ACEIs in lowering BP, both SBP and DBP. For SBP (delta: -1.2 mmHg (P < 0.00001), single measure: -1.17 mmHg (P = 0.02), repeated measures: -1.81 mmHg (P = 0.010)). For DBP (delta: -0.76 mmHg (P < 0.00001), single measure: -1.29 mmHg (P < 0.00001), repeated measures: -2.99 mmHg (P < 0.00001)).

CCBs were also superior to ARBs in lowering BP, both SBP and DBP. For SBP (delta: -0.16 mmHg (P = 0.78), single measure: -1.77 mmHg (P < 0.00001), repeated measures: -1.43 mmHg (P < 0.00001)). For DBP (delta: -0.25 mmHg (P = 0.39), single measure: -1.12 mmHg (P < 0.00001), repeated measures: -0.88 mmHg (P < 0.00001)).

CCBs were “significantly” superior to the placebo in lowering BP, both SBP and DBP. For SBP (delta: -8.76 mmHg (P < 0.00001), single measure: -4.5 mmHg (P = 0.02), repeated measures: -8.76 mmHg (P < 0.00001)). For DBP (delta: -4.46 mmHg (P < 0.00001), single measure: -2.3 mmHg (P < 0.0001), repeated measures: -4.9 mmHg (P < 0.00001)).

There was no significant BP variance between different agents within the same CCB classes in BP response. For SBP (delta: -1.34 mmHg (P = 0.23), single measure: 0.07 mmHg (P = 0.95) and repeated measures: -0.3 mmHg (P = 0.80)). For DBP (delta: -0.27 mmHg (P = 0.64), single measure: -0.25 mmHg (P = 0.73) and repeated measures: 0 mmHg (P = 1.00).

Table 3.5 Summary of DI-BP responses.
The table shows delta, single and repeated measures - BP response .Considering the level of statistical significance (P < 0.05), [White highlights] indicate significant statistical effect, [Grey highlights] indicate insignificant statistical effect and [Red highlights] indicate significant statistical effect in all BP measures.

DI	Studies N	Subjects N	SBP	I^2	Studies N	Subjects N	DBP	I^2
Delta-BP response [FE model]								
DI vs. ACEI	4	44447	-0.5	97%	4	44447	0.83	96%
DI vs. ARB	3	836	-1.97	0%	3	836	-0.2	57%
DI vs. CCB	7	71766	-0.48	95%	7	71766	0.76	93%
DI vs. BB	2	820	1.42	79%	2	820	-0.07	54%
DI vs. Placebo	1	102	-10	-	1	102	-5.4	-
DI vs. DI	1	171	-2	-	1	171	-1	-
Delta-BP response [RE model]								
DI vs. ACEI	4	44447	0.29	97%	4	44447	0.5	96%
DI vs. CCB	7	71766	-0.82	0%	7	71766	0.49	0%
DI vs. BB	2	820	1.72	79%	2	820	-0.08	54%
Delta-BP response [sensitivity analysis]								
DI vs. ACEI	2	24407	-1.79	0%	2	24407	0.09	0%
DI vs. CCB	4	25026	-0.82	42%	4	25026	0.63	58%
Single measure-BP response [FE model]								
DI vs. ACEI	1	463	-5.2	-	1	463	-2.2	-
DI vs. ARB	3	571	-1.97	48%	3	571	-1.37	60%
DI vs. CCB	4	1810	-2.41	0%	4	1810	-0.94	45%
DI vs. BB	1	374	-3	-	1	374	-1	-
DI vs. Placebo	1	5665	-6.2	-	1	5665	-2.9	-
Repeated measures-BP response [FE model]								
DI vs. ACEI	1	24309	-2	-	1	24309	-0.2	-
DI vs. CCB	6	55313	-0.97	93%	6	55313	0.37	77%
DI vs. Placebo	1	5665	-4.4	-	1	5665	-2	-
Repeated measures-BP response [RE model]								
DI vs. CCB	6	55313	-0.84	93%	6	55313	0.35	77%
Repeated measures-BP response [sensitivity analysis]								
DI vs. CCB	4	32935	-0.84	0%	4	32935	0.46	18%

As shown in **Table 3.5** :

DIs were “significantly” superior to ACEIs in lowering SBP (delta: -1.79 mmHg (P < 0.00001), single measure: -5.2 mmHg (P = 0.001) and repeated measures: -2 mmHg (P < 0.00001)).

DIs were superior to ARBs in lowering BP, both SBP and DBP. For SBP (delta: -1.97 mm Hg (P = 0.05) and single measure: -1.97 mmHg (P = 0.06)). For DBP (delta: -0.2 mmHg (P = 0.70) and single measure: -1.37 mmHg (P = 0.003)).

DIs were “significantly” superior to CCBs in lowering SBP (delta: -0.82 mmHg (P < 0.0001), single measure: -2.41 mmHg (P < 0.0001) and repeated measures: -0.84 mmHg (P < 0.00001)).

DIs were “significantly” superior to the placebo in lowering BP, both SBP and DBP. For SBP (delta: -10 mmHg (P = 0.0007), single measure: -6.2 mmHg (P < 0.00001) and repeated measures: -4.4 mmHg (P < 0.00001)). For DBP (delta: -5.4 mmHg (P = 0.0002), single measure: -2.9 mmHg (P < 0.00001) and repeated measures: -2 mmHg (P < 0.00001)).

There was no significant BP variance between different agents within the same DI classes in delta BP response: SBP: -2 mmHg (P = 0.25) and DBP: -1 mmHg (P = 0.22).

Table 3.6 Summary of BB-BP responses.
The table shows Delta, single and repeated measures - BP response. Considering the level of statistical significance (P < 0.05), [White highlights] indicate significant statistical effect and [Grey highlights] indicate insignificant statistical effect.

BB	Studies N	Subjects N	SBP	I^2	Studies N	Subjects N	DBP	I^2
Delta-BP response [FE model]								
BB vs. ACEI	8	22798	0.99	80%	8	22798	0.95	95%
BB vs. ARB	4	10154	1.16	53%	4	10154	-0.14	3%
BB vs. CCB	7	72468	-0.21	95%	7	72468	0.5	95%
BB vs. DI	2	820	-1.42	79%	2	820	0.07	54%
BB vs. Placebo	2	944	-7.24	0%	2	944	-4.53	0%
BB vs. BB	1	205	0.9	-	1	205	0.2	-
Delta-BP response [RE model]								
BB vs. ACEI	8	22798	-0.43	80%	8	22798	-0.32	95%
BB vs. CCB	7	72468	-0.09	95%	7	72468	0.36	95%
Delta-BP response [sensitivity analysis]								
BB vs. ACEI	6	2783	-0.79	60%	6	2783	-0.82	58%
BB vs. CCB	3	3152	0.27	0%	3	3152	-0.12	42%
Single measure-BP response [FE model]								
BB vs. ACEI	5	2211	0.11	76%	5	2211	0.54	80%
BB vs. ARB	2	9418	1.26	0%	2	9418	-0.44	16%
BB vs. CCB	3	818	-2.73	58%	3	818	-1.27	24%
BB vs. DI	1	374	3	-	1	374	1	-
BB vs. BB	1	205	-1.2	-	1	205	0.3	-
Single measure-BP response [RE model]								
BB vs. ACEI	5	2211	0.11	76%	5	2211	0.23	80%
Single measure-BP response [sensitivity analysis]								
BB vs. ACEI	4	1748	1.4	0%	4	1748	1.09	56%
Repeated measures-BP response [FE model]								
BB vs. ACEI	1	758	-1.6	-	1	758	-0.2	-
BB vs. ARB	2	9418	0.99	0%	2	9418	-0.9	0%
BB vs. CCB	2	33457	-1.43	98%	2	33457	0.16	86%
Repeated measures-BP response [RE model]								
BB vs. CCB	2	33457	-1.55	98%	2	33457	0.20	86%

As shown in **Table 3.6** :

BBs were superior to ARBs in lowering DBP (delta: -0.14 mmHg (P = 0.46), single measure: -0.44 mmHg (P = 0.04), repeated measures: -0.9 mmHg (P < 0.0001)).

BBs were “significantly” superior to the placebo in lowering BP, both SBP and DBP (delta: -7.24 (P < 0.00001)/-4.53 mmHg (P < 0.00001)).

There was no significant BP variance between different agents within the same BB classes in BP response. For SBP (delta: 0.9 mmHg (P = 0.63) and single measure: -1.2 mmHg (P = 0.52)). For DBP (delta: 0.2 mmHg (P = 0.85) and single measure: 0.3 mmHg (P = 0.78)).

3.3.2 Discussion

After a systematic search and selection process according to the PRISMA protocol that included 82 RCTs assessing BP response (including delta, single and repeated measures) with 197,684 hypertensive patients, 56 studies were included in the analysis of delta BP response, 37 studies were included in the analysis of single-measure BP response and 20 studies were included in the analysis of repeated measures. The majority of the included studies, as mentioned before, were non-intentional BP-lowering studies; so, not all the desired BP response data were available from each study.The review found that CCBs were significantly superior to ACEIs in lowering both SBP and DBP (Chen [2010] (143)). DIs were significantly superior to ACEIs (Baguet[2007](123)) and CCBs (Chen[2010] (143), Baguet[2007](123) and Psaty[2003] (141)) in lowering SBP. ARBs were significantly superior to BBs in lowering SBP (BP response as an outcome; no reviews included or compared ARBs to BBs to our knowledge). CCBs (Wright[2009] (138)) and DIs (Wright[2009] (138) and Psaty[2003] (141)) were significantly superior to placebos in lowering both SBP and DBP.

In the majority of patients, reducing SBP has been much more difficult than lowering DBP. Whereas effective BP control can be achieved in most patients who are hypertensive, the majority of patients require two or more BP-lowering agents. In recent years, there has been a global improvement in BP control rates that has been largely attributed to the increased use of BP-lowering agents, such as monotherapy or combination therapy(33).

RAAS inhibitors play an important role in regulating BP. Both ACEIs and ARBs have been found to inhibit RAAS and effectively treat HTN. They have been found to have additional beneficial effects that may be independent of their BP-lowering properties (such as reducing the progression of nephropathy in T2DM and RF) (428;429). Furthermore, RAAS inhibitors are considered the class of choice for the treatment of HTN in obese patients due to their wide range of CV benefits (430).

In the review, ACEIs were superior to ARBs in lowering DBP[7]. Similarly, the candesartan and lisinopril microalbuminuria (CALM [2000]) study showed that for hypertensive patients with T2DM, ACEI-lisinopril is superior to ARB–candesartan in lowering BP; the mean SBP reductions were -15.7 mmHg and -12.4 mmHg, respectively, and the mean DBP reductions were -9.7 mmHg and -9.5 mmHg, respectively. However, there was no significant difference between the two treatments for SBP (P = 0.18) and DBP (P > 0.20) (431). Though, a large randomised study in hypertensive women to compare the BP-lowering efficacy and effects of ARB-candesartan and ACEI- enalapril showed that candesartan lowered seated BP by -17/-11 and -19/-11 mmHg after 6 and 12 weeks of treatment, respectively. This reduction was greater than with enalapril (-12/-8 and -13/-9 mmHg) (P < 0.01) (432).

ACEIs were significantly superior to the placebo in lowering BP, including both SBP and DBP. Similarly, the HOPE [2000] study showed that the mean BP was 135/76 mmHg in the ACEI-ramipril group and 138/78 mmHg in the placebo group after two years, and 136/76 mmHg and 139/77 mmHg respectively at the end of the study. In addition, treatment with ACEI-ramipril significantly reduced the rates of death from CV causes, MI, stroke, HF (P < 0.001) and complications related to T2DM (P = 0.03) compared to the placebo (230). Furthermore, ACEI-trandolapril significantly reduced 24-hour BP compared to the placebo; this reduction involved both daytime SBP/DBP (-9/-7.6 mmHg (P < 0.01)) and nighttime SBP/DBP (-5.3/-4.3 (P < 0.01)) (433).

There was no significant difference in BP response between different agents within the same ACEI class. ACEI-enalapril and lisinopril significantly lowered 24-hour BP (SBP/DBP: 127/81 and 124/78 mmHg respectively; P < 0.001). Whereas both daytime and nighttime BP were significantly reduced by both drugs, ACEI-lisinopril was more effective in lowering BP (P < 0.05) (434).

ARBs were significantly superior to BBs in lowering SBP. Similarly, LIFE [2002] showed that SBP at the last visit decreased by 30.2 and 29.1 mmHg in the ARB-losartan and BB-atenolol groups, respectively (treatment difference P = 0.017). DBP was

[7] No significant difference in repeated measures -BP response. This comparison included only one study (DETAIL[2004]).

reduced by 16.6 and 16.8 mmHg, respectively (P = 0.37). The LIFE [2002] results showed that ARB-losartan was superior to BB-atenolol in reducing the primary composite endpoints of CV morbidity and mortality, which were both significant (14·6%, P = 0.009) (435).

ARBs were superior to the placebo in lowering BP, including both SBP and DBP[8]. Similarly, RENAAL [2001] showed that ARB-losartan was superior to the placebo in lowering SBP/DBP by -2.0/-0.0 mmHg, but BP reduction was not significant (P = 0.59). Though CV morbidity and mortality was similar between the two interventions, the rate of first hospitalisation for HF was significantly lower with ARB-losartan (P = 0.005), and the level of proteinuria dropped by 35% with the same drug in comparison with the placebo (P < 0.001) (265). Furthermore, TRANSCEND [2008] showed that the mean BP was lower with ARB-telmisartan than it was with the placebo by -3.2/-1.3 mmHg at the end of the study. Of the secondary outcomes, a composite of CVS death, MI and/or stroke occurred in 384 (13.0%) patients on ARB-telmisartan compared to 440 (14.8%) on the placebo (P = 0.048) (276).

There was a significant difference in BP response between different agents within the same ARB class. Similarly, a meta-analysis of randomised studies of ARB therapy for BP reduction showed that telmisartan therapy was associated with a statistically significant difference in BP reduction relative to valsartan therapy in both the monotherapy and combination therapy groups (SBP/DBP: –2.04/–1.08 mmHg (P < 0.00001)) (436).

Among the drugs currently available as first-line treatments of HTN, DHP-CCBs continue to receive significant attention for their renowned BP-lowering efficacy and clear benefits in preventing CV complications and reducing associated mortality. Therefore, in the past few years, numerous large clinical studies, such as ALLHAT [2002] (48), VALUE [2004] (367), ASCOT-BPLA [2005] (51) and ACCOMPLISH [2004] (282), have confirmed clinical interest in a CCB-based therapy for the management of normal and high CV risk hypertensive patients. Meanwhile, a

[8] There was no significant difference in repeated measures -BP responses. This comparison included only one study (IDNT [2001]).

meta-analysis found that compared to ACEIs, BBs and DIs, CCBs were associated with a significantly higher risk of MI (OR = 1.26; P = 0.0003), HF (OR = 1.25; P = 0.005) and CV events (OR = 1.10; P = 0.02) (437). However, a larger meta-analysis including more subclasses of CCBs has cleared doubts regarding the increasing incidence of coronary events, and CCBs have been reported to show the lowest interindividual variation in SBP as opposed to other BP-lowering agents, which may be linked to a reduced risk of stroke (438).

CCBs were significantly superior to ACEIs in lowering BP, both SBP and DBP. Similarly, AASK [2002] showed that CCB–amlodipine was superior to ACEI-ramipril in lowering SBP/DBP by -2/-1 mmHg (48;50).On the other hand, Agabiti [2005] showed that ACEI-enalapril was superior to CCB-nifedipine in lowering SBP by -16.3 and -15.3 mmHg (P = 0.30) and DBP by -12.4 and -11.8 mmHg (P = 0.36), respectively (439).

Despite a similar BP reduction, ABCD [1998] showed a lower incidence of fatal and non-fatal MI in the ACEI-enalapril group (P = 0.001). Compared to CCB-nisoldipine, significantly more patients in the ACEI-enalapril group received a combination of drugs, including BBs (P = 0.03) and DIs (P = 0.02) (392). Furthermore, the ABCD [1998] (392), FACET [1998] (309) and MIDAS [1996] (343) studies showed the positive effects of ACEIs over CCBs on the development and progression of macro- and microvascular complications in T2DM and together may raise concern regarding the use of CCB in hypertensive patients with T2DM.

CCBs were superior to ARBs in lowering BP, including both SBP and DBP[9]. Similarly, the Morbidity and Mortality after Stroke, Eprosartan Compared with Nitrendipine for Secondary Prevention (MOSES [2005]) study, which was the first to compare ARB-eprosartan with CCB-nitrendipine in secondary-stroke prevention. The study showed that an early normotensive and superior BP reduction was achieved in CCB-nitrendipine of 132.7/80.2 mmHg over ARB-eprosartan (133.2/80.4 mmHg) but without any significant difference in BP values. However, cerebrovascular and CV events and non-CV deaths were significantly lower in the ARB-eprosartan group (P = 0.014) (440). In the VALUE [2004] study, there was no difference in fatal and

[9] There was no significant difference in delta BP responses. This comparison included only four studies with a relatively smaller N of participants.

nonfatal cardiac events at 4.2 years among patients randomised to CCB amlodipine or ARB valsartan. However, the amlodipine-based regimen was associated with more rapid control of HTN and fewer CV events during the first year of the study (367).

CCBs were significantly superior to the placebo in lowering BP, including both SBP and DBP, similar to the results of the ACTION [2004] study showing that CCB-nifedipine significantly reduced BP compared to the placebo by -14.6/-7.6 mmHg as opposed to -9.1/-4.5 mmHg ($P < 0.001$). CCB-nifedipine therapy showed a significant 13% reduction ($P < 0.05$) in the combined incidence of all-cause mortality: MI, angina, HF, stroke and peripheral revascularisation (179). However, BENEDICT [2004] showed that the average SBP/DBP was 141/82 mmHg in the CCB-verapamil group, 139/81 mmHg in the ACEI-trandolapril group and 142/83 mmHg in the placebo group. Compared to the placebo, BP reduction was significant ($P \leq 0.002$) for ACEI-trandolapril though not for CCB-verapamil (187).

There was no significant variance in BP response between different agents within the same CCB class. Similarly, a meta-analysis reporting comparative efficacy (changes in SBP and DBP), showed that CCB-manidipine and CCB-amlodipine were statistically equivalent: the effect size for DBP was -0.08 ($P = 0.22$) and for SBP was -0.01 ($P = 0.83$) (441). In addition, there were no statistically significant differences between CCB-nifedipine and CCB-amlodipine in their effects on SBP and DBP. The patients treated with nifedipine had a mean decrease in SBP of -18.8 mmHg and in DBP of -15.5 mmHg compared to amlodipine (-19.7 and -15.7 mmHg, respectively; $P = 0.55$) (442).

Multiple HTN treatment guidelines from various regions of the world recommend thiazide or thiazide-like DIs as a first-line treatment for patients with essential HTN (15;16;387). However, an analysis of clinical studies suggests that DI is less effective in lowering BP than RAAS blockers or CCBs and thus offers less CV protection than the latter options. In general, when a DI is used for the treatment of HTN, thiazide or thiazide-like DIs are mainly prescribed; however, the majority of large RCTs, such as ALLHAT [2002] or HYVET [2008], which demonstrate the CV benefit of DIs, have used thiazide-like DIs, such as chlorthalidone or indapamide, but not thiazide DI-hydrochlorothiazide (48;322).

DIs were significantly superior to ACEIs in lowering SBP. Similarly, the study Identification of the Determinants of the Efficacy of Arterial Blood Pressure Lowering drugs (IDEAL[2005]) showed that in middle-aged women, SBP reduction was superior with DI-indapamide at -11.5 mmHg compared to ACEI-perindopril at -8.3 mmHg (P = 0.001). However, the response in men was significantly smaller: -4.8 mmHg for DI-indapamide and -4.3 mmHg for ACEI-perindopril (P = 0.015). Although the SBP response to ACEI-perindopril reduced by 2 mmHg every 10 years in both sexes (P = 0.01), the response to DI-indapamide increased by 3 mmHg every 10 years of age in women (P = 0.02) (443).

The Treatment of Mild Hypertension Study (TOMHS [1993]) indicated the superiority of DI-chlorthalidone over ACEI-enalapril in lowering SBP (a change based on all follow-up BP measurements): -17.7 mmHg and -14.7 mmHg, respectively (P < 0.01) (444). Furthermore, ANBP2 [2003] showed the superiority of DI- hydrochlorothiazide compared to ACEI-enalapril in SBP reduction by -22/-9 mmHg with DIs and -20/-9 mmHg with ACEIs at year 1 and by -24/-10 mmHg with DIs and -23/-10 mmHg ACEIs at year 2 but with no significant difference. There was a borderline superiority of ACEI-enalapril compared to hydrochlorothiazide-based therapy in terms of CV event MI (P = 0.04) (445).

DIs were superior to ARBs in lowering BP, including both SBP and DBP[10]. BP decreased by -16.3/-12.0 mmHg in patients treated with ARB-candesartan and by -18.8/-11.4 mmHg in patients treated with DI- hydrochlorothiazide. However, the difference between treatments in favour of ARB-candesartan was not statistically significant (P > 0.20). Although the profile of adverse events was generally similar in both treatment groups, hypokalaemia and hyperuricemia were not found in patients treated with ARB-candesartan but occurred in 8.1% and 6.5%, respectively, of patients treated with DI- hydrochlorothiazide (249).

DIs were significantly superior to CCBs in lowering SBP. Similarly, ALLHAT [2002] showed that after 5 years, SBP was significantly higher with CCB-amlodipine (P = 0.03) compared to DI-chlorthalidone, whereas DBP was significantly lower with

[10] There was no significant difference (apart from DBP single measures). This comparison included only four studies with a relatively smaller N of participants.

CCB-amlodipine (0.8 mmHg, P < 0.001). However, stroke, combined CHD and CVD and all-cause mortality were similar for CCB-amlodipine and DI-chlorthalidone, with the exception that the CCB-amlodipine group had a 38% higher risk of HF and a 35% higher risk of hospitalisation/fatal HF (all, P < 0.001), compared to the DI-chlorthalidone group (48).Therefore, DI-chlorthalidone has been effectively incomparable in preventing the CV complications of HTN and can be useful in achieving BP control, along with enhancing the BP-lowering efficacy of multidrug regimens.

Furthermore, CONVINCE[2003] showed that CCB-verapamil was also associated with an increased risk of HF when compared to BB-atenolol or DI-hydrochlorothiazide (1.5% vs. 1.2%, P = 0.05) (446). Despite a similar BP reduction, INSIGHT [2000] showed that CCB therapy decreased the risk of all-cause mortality in patients from vascular and nonvascular causes, with T2DM compared to those without T2DM (P = 0.03); it also decreased the incidence of new cases of T2DM compared to DI therapy (P = 0.02) (447). CCB-nifedipine monotherapy decreased DBP by -4.3 mmHg (P = 0.005) in comparison to DI-HCTZ, and a progressive decrease in the LVM index was observed with CCB-nifedipine monotherapy (P = 0.03) (448).

DIs were significantly superior to the placebo in lowering BP, including both SBP and DBP. Similarly, the Medical Research Council trial of treatment of mild hypertension in older adults (MRCO [1992]) (449) and Oslo [1980](45) showed the superiority of DI-HCTZ over the placebo in lowering SBP and DBP: -16/-6 mmHg (P < 0.05) and -17/-10 mmHg (P < 0.01), respectively.

There was no significant variation in BP response between different agents within the same DI class[11]. SBP and DBP decreased similarly in patients with mild-to-moderate HTN and T2DM by 15% and 9%, respectively, with indapamide and by 17% and 10%, respectively, with hydrochlorothiazide (450). The data indicated a greater reduction of 24-hour mean SBP with chlorthalidone compared to hydrochlorothiazide (-12.4 mmHg versus -7.4 mmHg) and a reduction of 24-hour mean DBP with chlorthalidone compared to hydrochlorothiazide (-7.1 mmHg

[11] There was no significant difference in the delta BP response. This comparison included only one study (Cremonesi [2002]).

versus -5.1 mmHg). However, there was no statistical significance ((P = 0.05) and (P = 0.29), respectively). BP reduction was also not statistically significant for both: clinic SBP was -17.1 mmHg for hydrochlorothiazide and -10.8 mmHg for chlorthalidone (P= 0.84) and clinic DBP was -6.9 mmHg for hydrochlorothiazide versus -8.1 mmHg for chlorthalidone (P = 0.89) (451).

A number of international guidelines, including ESH/ESC (15) and CHL(387), still consider BB in their recommendations for HTN management. BBs are still preferred in hypertensive patients who have suffered from MI or other forms of CHDs and HF due to systolic dysfunction (452). The NICE guidelines recommend not using BBs as a first line of treatment for HTN, which has brought the BB group to the forefront of academic research (14), and JNC-7 found that BB-atenolol was lacking in protection against stroke (16).

An ASCOT-BPLA [2005] sub-study showed that BBs effectively lower brachial (arm) BP; however, they may be less effective in reducing central aortic pressure compared to other BP-lowering classes (for example, central aortic SBP was decreased by 4.3 mmHg with CCB-amlodipine compared to BB-atenolol (P < 0.0001))(453). Increased central aortic pressure has been associated with an increased risk of vascular events, particularly stroke (454). These results may at least explain the stroke risk associated with traditional BBs.

Another subgroup analysis of INVEST [2003] showed that the incidence of new-onset T2DM in the CCB-verapamil arm was significantly lower than in the BB-atenolol arm (6.2% vs. 7.3%, P < 0.05), as was the composite of death (12.0% vs. 13.4%, P < 0.05) (455). Consequently, BBs' clinical utility could still be in question due to their limited effectiveness in decreasing BP.

BBs were superior to ARBs in lowering DBP[12]. The study Swedish Irbesartan Left Ventricular Hypertrophy Investigation versus atenolol (SILVHIA [2001]) showed similar results, favouring BB-atenolol over ARB-irbesartan in reducing DBP; they attained -2.1 mmHg and –1.1 mmHg reductions at 12 and 24 weeks, respectively. However, there was no significant difference (for all, P > 0.001). LVM was reduced more

[12] There was no significant difference in the delta BP response. This comparison included only four studies with a relatively smaller N of participants.

extensively in the irbesartan group than in the BB-atenolol group (P = 0.024) (456). Furthermore, CVIP [2004] results showed that even though BBs were slightly superior to ARBs in reducing DBP toward the end of the study by -1.1 mmHg, there was no significant difference (P > 0.05) (202).

BBs were significantly superior to the placebo in lowering BP, including both SBP and DBP. Similarly, the Medical Research Council Trial of Treatment of Mild Hypertension (MRC [1985]) (449;457) and MRCO [1992] (449;457) showed the superiority of BBs over the placebo: propranolol by -9.5/-5.0 mmHg and atenolol by -13.0/-7.0 mmHg, respectively (for all, P < 0.05).

There was no significant discrepancy in BP response between different agents within the same BB class. Similarly, GEMINI[2004] showed that both carvedilol and metoprolol reduced BP; however, there was no significant difference between the two agents for SBP (P = 0.21) and DBP (P = 0.53). However, BB-carvedilol showed better metabolic effects in all races and both genders (221). Another study showed that both the BB atenolol and bisoprolol drugs significantly lowered BP compared to baseline (all, P < 0.5); however, SBP and DBP changes were not different between the two drugs (SBP (P = 0.55) and DBP (P = 0.37)) (458).

4 Genome-wide Study

This chapter summarises the results of NORDIL 2000 – GWAS subjects (including, demographics, quality control, GWAS and specificity of BP response , survival analysis, and replication studies) in order to identify SNPs associated with the BP-lowering responses of CCBs and BBs.

4.1.1 Demographics

The demographics of the NORDIL^{2000} population on CCBs and BBs are presented in the **Table 4.1**.

Table 4.1 Demographics of the NORDIL^{2000} population.

	CCB Arm	BB Arm
N	2018	2021
Male :Female %	50.1:49.9	49.6:50.4
Mean (SD)		
Age	60.2 (6.6)	60 (6.6)
BMI	28 (4.4)	28.3 (4.4)
SBP-baseline	173.8 (16.7)	173.3 (16.7)
DBP-baseline	104.3 (5.3)	104.2 (5.4)
% delta SBP	-9.6 (8.7)	-10.9 (9.2)
% delta DBP	-13.9 (7.5)	-13.7 (7.9)

4.1.2 Quality control

The NORDIL^{2000} data contains 4,039 samples and 500,915 SNPs. Following quality check for low MAF, HWE, and/or high rate of missingness: no SNPs had missingness rate of <0.95, no SNPs had MAF <0.01 and only 10 SNPs fail HWE at significant threshold of ($P< 5\times1^{-6}$) and were therefore removed. The IBS pairwise distance matrix was calculated. MDS was performed on this matrix as a data reduction measure. The first two MDS components were plotted against each other, as shown in **Figure 4.1.**

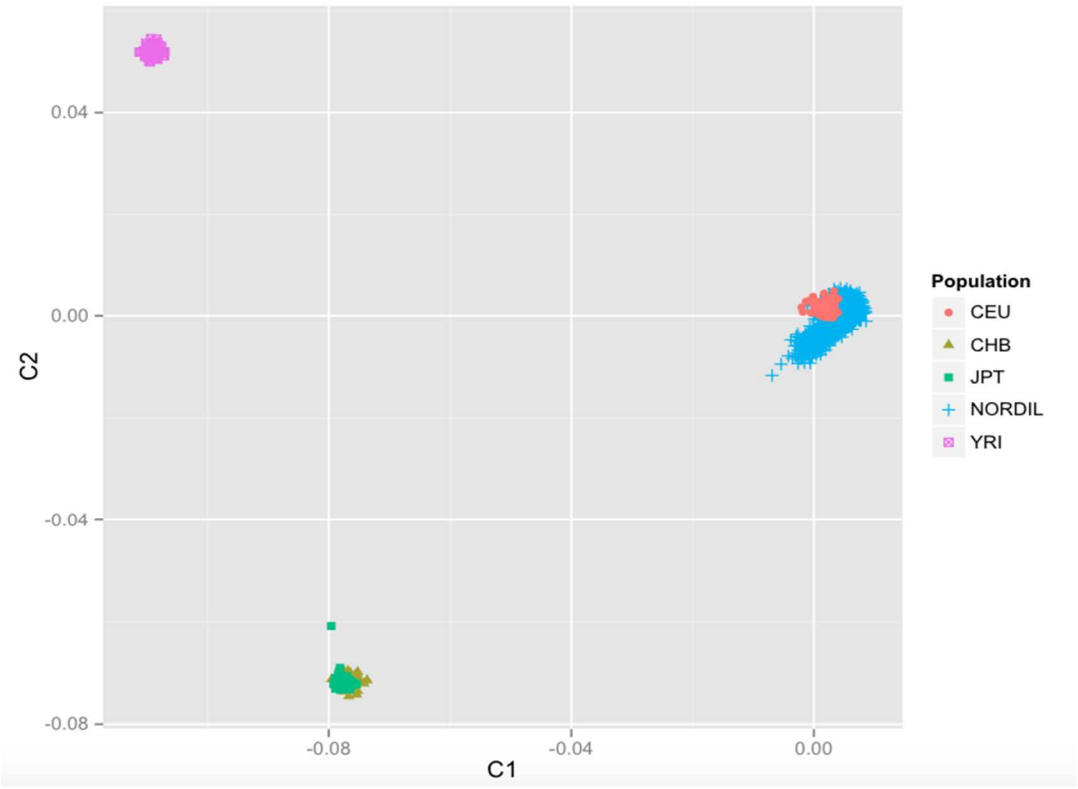


Figure 4.1 MDS plot of first two components for HapMap samples and NORDIL^{2000} samples. The plot confirmed the NORDIL^{2000}samples as being of European descent and did not reveal any outlier individuals .CEU= Utah residents with Northern and Western European ancestry. CHB= Chinese in Beijing.JPT= Japanese in Tokyo. NORDIL= European in Norway and Sweden. YOR=Yoruba in Nigeria.

4.1.1 GWAS of BP response

Association analysis using linear regression (under an additive genetic model) was performed on the change from baseline of SBP and DBP at six months post-randomisation. Analysis was performed in the BB arm (N=2021) and CCB arm (N=2018) and in the subset who were on monotherapy at 6 months- CCB (N= 1,639) or BB (N= 1,070). As shown in **Table 4.2**, 51 SNPs reached a significant threshold of ($P<1X10^{-5}$). However, no SNP achieved a genome wide significant threshold of ($P<5x10^{-8}$).

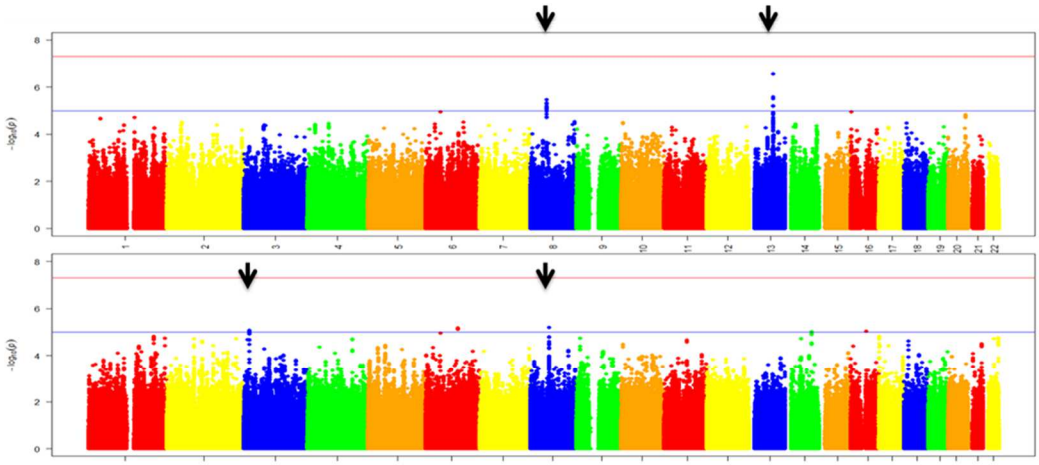
Figure 4.2 shows the manhattan plot for BP response to BB monotherapy in the NORDIL^{2000} cohort. There was no evidence for genomic inflation (λ=1) and no SNP achieved a genome wide significant threshold of $p<5x10^{-8}$. The top signals are indicated by arrows and the underlying genes presented in the table below.

Figure 4.3 shows the manhattan plot for BP response to CCB monotherapy in the NORDIL^{2000} cohort. The top signals are indicated by arrows and the underlying genes presented in the table belo

Table 4.2 Top GWAS-NORDIL^{2000} SNPs considering level of statistical significance 1X10^{-5}. [Red highlights] indicate SNPs presented in the manhattan plot below.

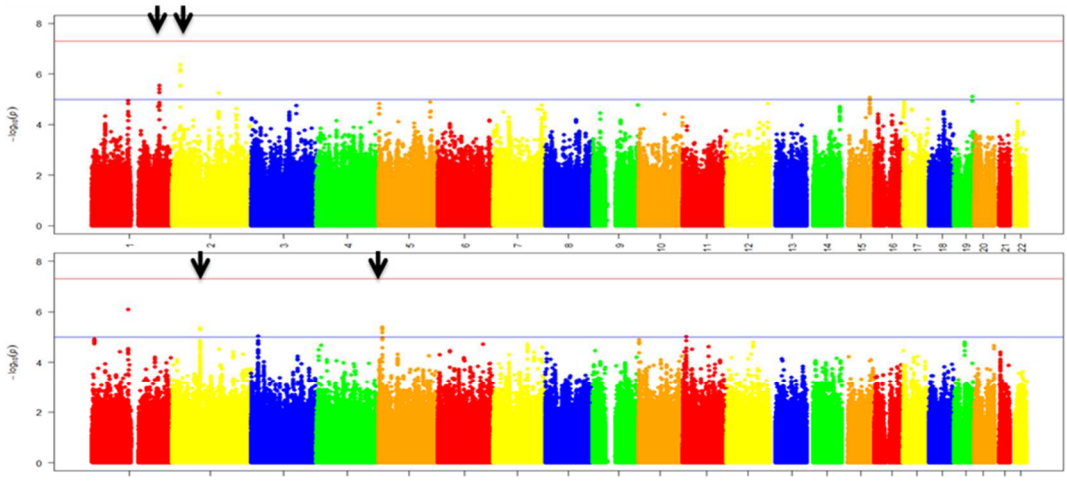
CHR	SNP	POS	A1	BETA	SE	P
13	rs12866529	75835110	A	-4.50	0.87	3.36E-07
2	rs7583409	25344560	G	-2.40	0.54	4.01E-07
6	rs12663184	30409579	T	5.08	1.05	1.40E-06
11	rs1502447	29206734	C	-1.30	0.27	2.33E-06
11	rs1502448	29207021	A	-1.30	0.27	2.33E-06
17	rs216195	2149917	C	2.55	0.54	2.71E-06
1	rs7548027	38864643	C	3.19	0.65	2.94E-06
5	rs1664786	53317468	T	1.76	0.38	3.24E-06
11	rs575929	78565913	G	-1.36	0.29	3.80E-06
16	rs8061566	26704144	A	-2.25	0.49	3.96E-06
5	rs1664789	53318406	C	1.75	0.38	3.98E-06
3	rs9830122	16102226	C	-1.76	0.38	4.07E-06
10	rs1914525	125535626	A	-2.50	0.54	4.17E-06
5	rs2062400	154574494	C	-1.87	0.40	3.93E-06
2	rs4907206	96924640	T	-1.65	0.36	4.47E-06
7	rs1406603	147570218	T	2.55	0.55	4.70E-06
1	rs4970609	38865036	G	2.44	0.54	5.85E-06
1	rs4970610	38865078	T	2.44	0.54	5.85E-06
1	rs594856	38880584	C	2.44	0.54	5.85E-06
2	rs4907203	96920270	T	-1.61	0.35	6.12E-06
18	rs605902	46699496	T	3.88	0.85	6.21E-06
18	rs625566	46668924	T	3.88	0.85	6.21E-06
19	rs8104633	56937927	T	-2.67	0.59	6.21E-06
12	rs2363877	6162722	G	1.27	0.28	6.84E-06
11	rs7480026	11945018	A	3.38	0.75	7.08E-06
14	rs2144067	101022159	T	-2.23	0.50	7.72E-06
13	rs17066095	75801978	C	-7.60	1.69	2.56E-06
8	rs17072101	4877059	G	0.52	0.96	4.61E-06
8	rs1810195	23537855	C	2.98	0.73	6.20E-06
3	rs10865738	16108387	C	-1.77	0.38	8.54E-06
6	rs7752482	148633692	G	2.32	0.52	9.27E-06
17	rs216182	2119813	G	2.42	0.54	9.51E-06
14	rs7147183	45528446	G	1.22	0.28	1.06E-05
14	rs8017812	84165788	A	1.83	0.41	1.07E-05
13	rs9585548	100368236	A	-1.23	0.28	1.09E-05
14	rs7141196	84175762	G	1.82	0.41	1.20E-05
9	rs1778982	137303859	T	2.23	0.51	1.26E-05
12	rs2363880	6172270	A	1.23	0.28	1.27E-05
14	rs8017871	45495969	G	1.21	0.28	1.30E-05
13	rs9565263	75842776	A	-3.61	0.82	1.30E-05
9	rs1981047	22163499	G	4.33	0.99	1.31E-05
2	rs749581	86301742	A	-1.86	0.43	1.36E-05
12	rs2363878	6163236	A	1.23	0.28	1.42E-05
1	rs6421774	204153436	C	2.76	0.63	1.43E-05
6	rs9403095	139985440	A	-1.68	0.39	1.54E-05
14	rs10148201	101029334	C	-2.14	0.49	1.55E-05
14	rs4411445	83929459	T	3.16	0.73	1.69E-05
4	rs2321559	141954857	G	-1.85	0.43	1.76E-05
7	rs1534702	147567736	T	2.48	0.58	1.82E-05
6	rs7766818	46825413	C	-2.10	0.49	1.87E-05
10	rs666595	6268232	T	-3.12	0.73	1.90E-05

CHR= chromosome. SNP= single nucleotide polymorphism. POS= chromosomal position. A1= major allele. SE =standard error. P= P value.



SNP	Position	Nearest gene	Effect allele freq	Beta (s.e.)	P	BP response
I	3p24	GALNTL2	0.36	1.5 (0.3)	8.5×10^{-06}	DBP
II	8q11.2	SNTG1	0.23	2.04 (0.4)	4.6×10^{-06}	SBP
III	8q12	FAM110B	0.55	1.49 (0.3)	6.2×10^{-06}	DBP
IV	13q22	Intergenic	0.96	-4.31 (0.9)	2.5×10^{-06}	SBP
V	13q22	Intergenic	0.19	2.45 (0.5)	3×10^{-07}	SBP

Figure 4.2 Manhattan plot of –log10 transformed P values against genomic position for BP response to BB monotherapy in the NORDIL[2000].
Red line indicates $P=5 \times 10^{-8}$ and blue line indicates $P=5 \times 10^{-7}$.**GALNT2**= polypeptide N-acetylgalactosaminyltransferase 2 (possibly influence triglyceride levels, and involved in T2DM). **SNTG1**= syntrophin gamma 1 (involved in idiopathic scoliosis). **FAM110B**= family with sequence similarity 110 member B (possibly involved in tumor progression).



SNP	Position	Nearest gene	Effect allele freq	Beta (s.e.)	P	BP response
VI	1q32	Intergenic	0.11	1.99 (0.4)	2.9×10^{-06}	SBP
VII	2p23	DNMT3A	0.31	1.43 (0.3)	4×10^{-07}	SBP
VIII	2p11.2	PTCD3	0.18	1.47 (0.3)	4.4×10^{-06}	DBP
IX	5p15.2	CTNND2	0.08	2.13 (0.5)	3.9×10^{-06}	DBP

Figure 4.3 Manhattan plot of –log10 transformed P values against genomic position for BP response to CCBmonotherapy in the NORDIL[2000].
Red line indicates $P=5\times10^{-8}$ and blue line indicates $P=5\times10^{-7}$.**DNMT3A** =DNA (Cytosine-5-)-methyltransferase 3 Alpha (possibly involved in cerebellar ataxia, deafness, and narcolepsy). **PTCD3**= pentatricopeptide repeat domain 3 (involved in mitochondrial translation). **CTNND2**=catenin delta 2 (involved in brain and eye development and cancer formation).

4.1.2 Specificity of BP response by studying discordant effect of SNPs to BB and CCB

The differential effects of SNP genoptype on BP response was studied in order to identify SNPS with directionally opposite BP responses to BB and CCB, as shown in **Table 4.3** and **Table 4.4**. The top discordant signals included five SNPs for SBP on BB arm, seven SNPs for DBP on BB arm, 12 SNPs for SBP on CCB arm and nine SNPs for DBP on CCB arm. The reason for conducting this analysis was to determine SNPs that show specific response to either BB or CCB and as they reflect different BP regulatory pathways. The **Figure 4.4** below depicts the top discordant signals identified in this study.

Table 4.3 Top discordant SNPs considering level of statistical significance 1X10^{-5} [SBP].
[Red highlights] indicate SNPs presented in the figure of top discordant signals below.

				BB				CCB			
CHR	SNP	POS	A1	N	BETA	SE	P	N	BETA	SE	P
13	rs12866529	75835110	A	970	-4.50	0.87	3.36E-07	1500	0.14	0.62	0.8269
6	rs12663184	30409579	T	971	5.08	1.05	1.40E-06	1500	-0.35	0.79	0.6611
13	rs17066095	75801978	C	971	-7.60	1.69	2.56E-06	1498	1.24	1.18	0.2924
8	rs17072101	4877059	G	971	0.52	0.96	4.61E-06	1499	-1.64	0.70	0.01936
13	rs9565263	75842776	A	971	-3.61	0.82	1.30E-05	1500	0.25	0.57	0.6629
2	rs7583409	25344560	G	971	0.82	0.73	0.2634	1500	-2.40	0.54	4.01E-07
17	rs216195	2149917	C	963	-1.48	0.72	0.04124	1489	2.55	0.54	2.71E-06
1	rs7548027	38864643	C	971	-0.77	0.88	0.3773	1500	3.19	0.65	2.94E-06
16	rs8061566	26704144	A	968	1.11	0.71	0.1199	1499	-2.25	0.49	3.96E-06
1	rs594856	38880584	C	971	-1.08	0.75	0.1476	1500	2.44	0.54	5.85E-06
1	rs4970609	38865036	G	971	-1.05	0.75	0.1587	1500	2.44	0.54	5.85E-06
1	rs4970610	38865078	T	971	-1.05	0.75	0.1587	1500	2.44	0.54	5.85E-06
19	rs8104633	56937927	T	968	1.39	0.80	0.08277	1498	-2.67	0.59	6.21E-06
17	rs216182	2119813	G	971	-1.34	0.74	0.06782	1499	2.42	0.54	9.51E-06
9	rs1981047	22163499	G	971	-0.82	1.36	0.5487	1500	4.33	0.99	1.31E-05
1	rs6421774	204153436	C	971	-0.57	0.81	0.4864	1499	2.76	0.63	1.43E-05
7	rs1534702	147567736	T	970	-0.09	0.77	0.9031	1495	2.48	0.58	1.82E-05

CHR= chromosome. SNP= single nucleotide polymorphism. POS= chromosomal position. A1= major allele. SE =standard error. P= P value.

Table 4.4 Top discordant SNPs considering level of statistical significance 1X10^{-5} [DBP].
[Red highlights] indicate SNPs presented in the figure of top discordant signals below.

				BB				CCB			
CHR	**SNP**	**POS**	**A1**	**N**	**BETA**	**SE**	**P**	**N**	**BETA**	**SE**	**P**
10	rs1914525	125535626	A	970	-2.50	0.54	4.17E-06	1500	0.32	0.40	0.4236
8	rs1810195	23537855	C	971	2.98	0.73	6.20E-06	1500	-0.90	0.54	0.09667
3	rs10865738	16108387	C	971	-1.77	0.38	8.54E-06	1499	0.02	0.29	0.9382
6	rs7752482	148633692	G	971	2.32	0.52	9.27E-06	1500	-0.25	0.40	0.5435
14	rs8017812	84165788	A	971	1.83	0.41	1.07E-05	1500	-0.26	0.30	0.3922
14	rs7141196	84175762	G	971	1.82	0.41	1.20E-05	1500	-0.26	0.30	0.3816
14	rs4411445	83929459	T	971	3.16	0.73	1.69E-05	1499	-0.50	0.55	0.3681
5	rs2062400	154574494	C	970	-1.10	0.52	0.0344	1499	-1.87	0.40	3.93E-06
2	rs4907206	96924640	T	971	0.57	0.47	0.2219	1499	-1.65	0.36	4.47E-06
2	rs4907203	96920270	T	971	0.61	0.46	0.182	1500	-1.61	0.35	6.12E-06
12	rs2363877	6162722	G	971	-0.46	0.37	0.2162	1497	1.27	0.28	6.84E-06
11	rs7480026	11945018	A	971	-0.66	0.98	0.4969	1500	3.38	0.75	7.08E-06
12	rs2363880	6172270	A	970	-0.57	0.37	0.1285	1499	1.23	0.28	1.27E-05
2	rs749581	86301742	A	971	0.22	0.61	0.7234	1500	-1.86	0.43	1.36E-05
12	rs2363878	6163236	A	970	-0.44	0.37	0.2344	1500	1.23	0.28	1.42E-05

CHR= chromosome. SNP= single nucleotide polymorphism. POS= chromosomal position. A1= major allele. SE =standard error. P= P value.

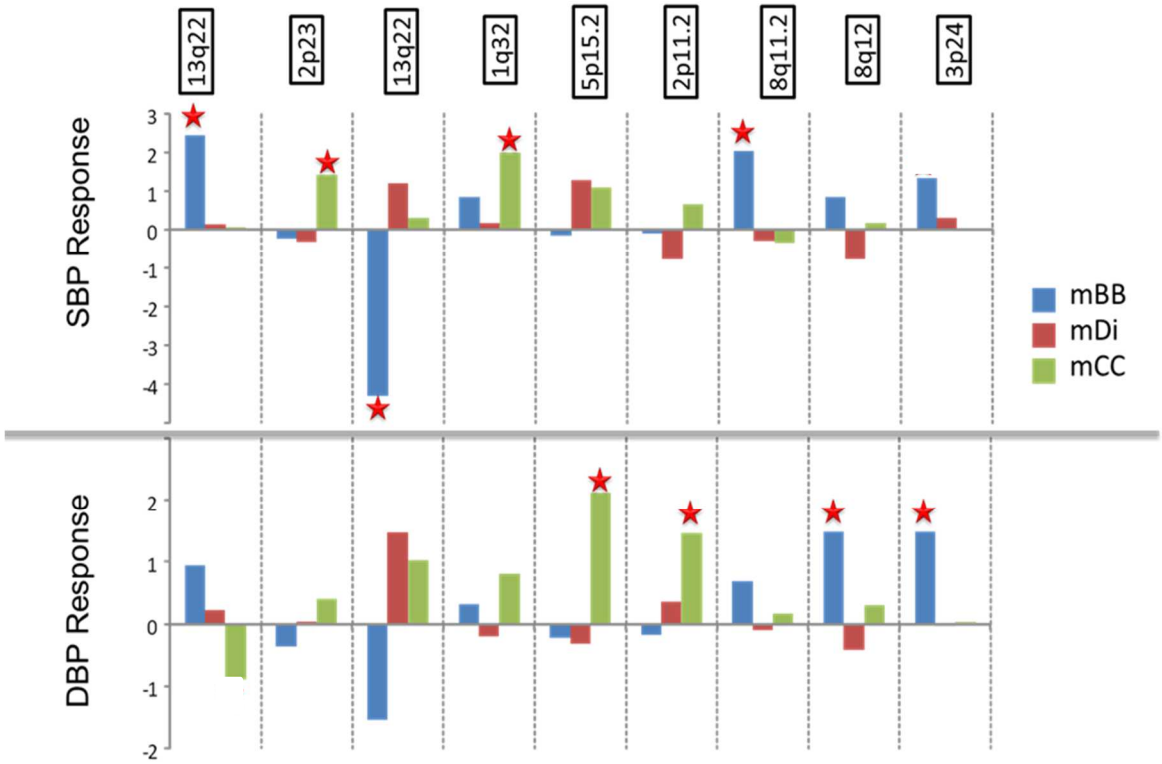


Figure 4.4 Top discordant signals identified in NORDIL[2000].
Y-axis represents BP response (delta BP changes before and after drug randomisation). X-axis represents drug groups. Red stars represent top discordant SNPs considering level of statistical significance $1X10_{-5}$.mBB= beta blocker monotherapy. mDi= diuretic monotherapy. mCC= calcium channel blocker monotherapy.

4.1.3 Survival Analysis

The 32 SNPs showing specific effects on BP response were taken forward for survival analysis. The results are presented in **Table** 4.5.

As shown in **Figure 4.5,** taking into consideration the SNP treatment and genotype, rs12866529, rs7548027, rs1914525 and rs4907206 in CHR 13, 1, 10 and 2 respectively, showed that CCB-0 has a greater subject survival rate than BBD-1, and it took longer for CCB-0 subjects to experience death compared to BBD-1. Therefore, AA subjects should continue to receive CCBs, as they have lower mortality rates.

Table 4.5 Survival analysis for top SNP showing specific effects on BP response[13].

SNP	CHR	POS	A1	KM_N	KM_events	Logrank_P	BBD.0_REF	BBD.1_beta	BBD.1_SE	BBD.1_P	CCB.0_beta	CCB.0_SE	CCB.0_P	CCB.1_beta	CCB.1_SE	CCB.1_P
rs10865738	3	16108387	C	3658	130	0.37	1	0.34	0.28	0.22	0.37	0.30	0.21	0.18	0.28	0.53
rs12663184	6	30409579	T	3659	130	0.95	1	0.03	0.31	0.93	0.05	0.20	0.82	0.01	0.30	0.98
rs12866529	13	75835110	A	3658	130	0.82	1	-0.15	0.27	0.58	0.03	0.21	0.88	-0.12	0.27	0.65
rs1534702	7	147567736	T	3651	130	0.10	1	0.21	0.25	0.40	0.33	0.23	0.16	-0.17	0.28	0.53
rs17066095	13	75801978	C	3656	130	0.57	1	-0.54	0.59	0.36	-0.04	0.18	0.84	0.32	0.38	0.40
rs17072101	8	4877059	G	3658	130	0.12	1	0.17	0.27	0.54	-0.08	0.22	0.71	0.43	0.25	0.09
rs1914525	10	125535626	A	3658	130	0.54	1	-0.43	0.32	0.18	-0.11	0.20	0.58	0.06	0.28	0.83
rs1981047	9	22163499	G	3658	130	0.04	1	0.90	0.30	0.00	0.18	0.20	0.35	0.18	0.38	0.63
rs216182	17	2119813	G	3658	130	0.81	1	0.21	0.25	0.42	0.17	0.25	0.50	0.10	0.26	0.69
rs216195	17	2149917	C	3636	129	0.63	1	0.25	0.26	0.33	0.27	0.26	0.30	0.10	0.26	0.71
rs2363877	12	6162722	G	3656	130	0.71	1	-0.26	0.27	0.35	-0.18	0.33	0.57	-0.13	0.27	0.61
rs2363878	12	6163236	A	3658	130	0.71	1	-0.26	0.27	0.35	-0.18	0.33	0.57	-0.14	0.27	0.61
rs2363880	12	6172270	A	3657	130	0.71	1	-0.25	0.27	0.35	-0.16	0.33	0.62	-0.14	0.27	0.60
rs4411445	14	83929459	T	3657	130	0.73	1	-0.19	0.43	0.66	-0.05	0.19	0.81	0.37	0.33	0.26
rs4907203	2	96920270	T	3659	130	0.54	1	0.16	0.26	0.54	0.19	0.22	0.40	-0.11	0.28	0.70
rs4907206	2	96924640	T	3657	130	0.65	1	0.16	0.26	0.54	0.16	0.22	0.47	-0.06	0.28	0.82
rs4970609	1	38865036	G	3659	130	0.13	1	0.02	0.26	0.93	0.26	0.25	0.28	-0.22	0.27	0.42
rs4970610	1	38865078	T	3659	130	0.13	1	0.02	0.26	0.93	0.26	0.25	0.28	-0.22	0.27	0.42
rs594856	1	38880584	C	3659	130	0.13	1	0.02	0.26	0.93	0.26	0.25	0.28	-0.22	0.27	0.42
rs6421774	1	204153436	C	3658	130	0.11	1	-0.15	0.26	0.57	-0.24	0.24	0.32	0.23	0.23	0.33
rs7141196	14	84175762	G	3659	130	0.77	1	-0.18	0.26	0.49	-0.16	0.25	0.53	0.05	0.24	0.83
rs7480026	11	11945018	A	3659	130	0.35	1	0.46	0.43	0.29	0.01	0.19	0.98	0.71	0.38	0.06
rs749581	2	86301742	A	3659	130	0.02	1	0.13	0.30	0.67	-0.15	0.21	0.48	0.61	0.25	0.02
rs7548027	1	38864643	C	3659	130	0.55	1	-0.26	0.28	0.35	0.03	0.21	0.87	-0.26	0.28	0.35
rs7583409	2	25344560	G	3659	130	0.93	1	0.06	0.26	0.81	0.10	0.26	0.68	0.03	0.26	0.92
rs7752482	6	148633692	G	3659	130	0.38	1	-0.51	0.32	0.11	-0.14	0.20	0.48	0.04	0.26	0.88
rs8017812	14	84165788	A	3659	130	0.77	1	-0.18	0.26	0.49	-0.16	0.25	0.52	0.05	0.24	0.83
rs8061566	16	26704144	A	3654	130	0.89	1	-0.14	0.26	0.60	0.00	0.30	0.99	-0.09	0.26	0.73
rs8104633	19	56937927	T	3650	129	0.56	1	0.28	0.26	0.27	0.27	0.24	0.26	0.05	0.26	0.86
rs9565263	13	75842776	A	3659	130	0.75	1	0.07	0.26	0.80	0.17	0.23	0.46	-0.11	0.27	0.68
rs1810195	8	23537855	C	3659	130	0.77	1	-0.43	0.43	0.32	-0.05	0.19	0.81	0.15	0.34	0.67
rs2062400	5	154574494	C	3657	130	0.93	1	-0.05	0.29	0.86	-0.02	0.21	0.94	0.11	0.27	0.69

SNP= single nucleotide polymorphism. CHR= chromosome. POS= chromosomal position. A1= major allele. P= P value. SE =standard error. BBD= Beta-blocker + Diuretic. BBD-0= major homozygous subjects (AA) on BB. REF= reference. BBD-1= heterozygous (AB) and minor homozygous (BB) subjects on CCB. CCB-0= major homozygous subjects (AA) on CCB. CCB-1= Heterozygous (AB) and minor homozygous (BB) subjects on CCB.

[13] Two places after the decimal point are presented.

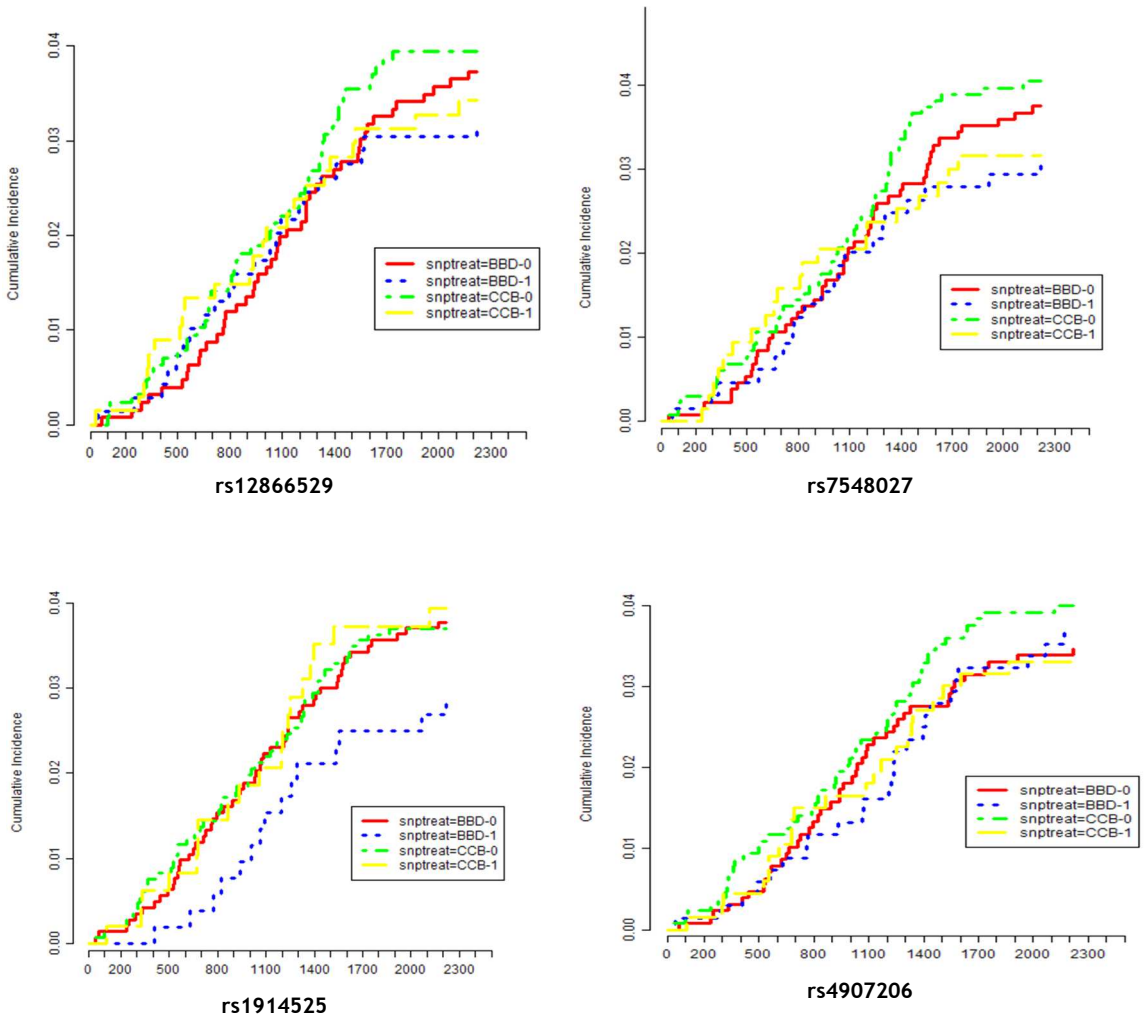


Figure 4.5 Examples for KM survival curves.
Y – Axis represents the cumulative incidence (probability of CV mortality).X- axis represents the survival time (follow-up time) .CCB-0 (green line) has a greater subject survival rate than BBD-1 (blue line), and it took longer for CCB-0 subjects to experience death compared to BBD-1.

4.1.4 Replication studies

In total, 286 replication SNPs have been genotyped as listed below. The **Table 4.6**, **Table 4.7**, **Table 4.8** and **Table 4.9** show the top 35 SNPs for SBP and DBP responses on BB arm and CCB arm. SNPs reached a significant threshold of ($P<1X10^{-5}$) include 11 SNPs for SBP on BB arm, 22 SNPs for DBP on BB arm, 23 SNPs for SBP on CCB arm, and 18 SNPs for DBP on CCB arm. Still, no SNP achieved a genome wide significant threshold of ($P<5x10^{-8}$).

rs10017978	rs11192911	rs13017029	rs1859541	rs350233	rs5755497	rs7598787
rs10043459	rs11215000	rs13039894	rs1885615	rs350234	rs575929	rs7632303
rs10050254	rs11215456	rs13085295	rs1899745	rs3761707	rs595696	rs7635750
rs10052034	rs11242092	rs13136923	rs1911338	rs3780040	rs6000342	rs7661835
rs10078498	rs1149361	rs13172360	rs1927777	rs3791958	rs6002626	rs7766818
rs1007904	rs11603334	rs13358400	rs2000894	rs3791970	rs6005062	rs7845960
rs10083582	rs11641984	rs13428812	rs2078288	rs3827761	rs6025134	rs7859610
rs10092564	rs11657636	rs1351833	rs2121914	rs3845563	rs6031755	rs7898561
rs10148201	rs11659880	rs1437349	rs216195	rs3966269	rs6091130	rs7932891
rs10224181	rs11672811	rs1469488	rs2171412	rs4149818	rs6109157	rs7950069
rs1040172	rs11683361	rs1483809	rs2236624	rs4149826	rs6127271	rs7988744
rs10507855	rs11785117	rs1492097	rs2239081	rs4237021	rs6421774	rs7989612
rs1072892	rs11803446	rs1492100	rs2254705	rs4243096	rs6442578	rs8024058
rs10756066	rs11829673	rs1552224	rs2293728	rs4260062	rs6450352	rs8026643
rs10774047	rs11856526	rs158857	rs2299166	rs4262947	rs6464161	rs8040531
rs10780347	rs11880103	rs158869	rs2320070	rs4279621	rs6532574	rs8048758
rs10800533	rs11906158	rs161338	rs2372781	rs4299163	rs6559174	rs8055597
rs10800559	rs11918950	rs1621170	rs2381700	rs4448317	rs666628	rs8077194
rs10815746	rs12047788	rs1664234	rs239349	rs4458034	rs6677933	rs8096764
rs10822065	rs12047943	rs16968814	rs2427113	rs4465961	rs6796129	rs8104633
rs10828545	rs12101908	rs16968841	rs2457975	rs4473232	rs6830263	rs831078
rs10828779	rs12122460	rs17024226	rs2494493	rs4474684	rs6840127	rs831080
rs10865738	rs12169559	rs17024235	rs2501357	rs4535404	rs6901073	rs839549
rs10886462	rs12170542	rs17024573	rs2501363	rs4590355	rs6978142	rs840709
rs10886616	rs12217685	rs17061550	rs2528892	rs4632107	rs7072554	rs847282
rs10902656	rs12244635	rs17062859	rs2528893	rs4640984	rs7081137	rs882000
rs10903802	rs12305488	rs17123869	rs2712339	rs4658576	rs7142452	rs883429
rs10940486	rs12440303	rs17123900	rs2712355	rs467368	rs7209564	rs885724
rs10957336	rs12583878	rs17137390	rs27154	rs4700590	rs7213347	rs908551
rs11052234	rs12587920	rs17253343	rs2727594	rs471677	rs7213426	rs9293641
rs11052254	rs12599751	rs17258240	rs2798298	rs4737483	rs7213756	rs9573846
rs1105586	rs12609158	rs17260280	rs285669	rs4748472	rs732796	rs9608491
rs11072435	rs12625987	rs1732325	rs2903018	rs4856154	rs7444019	rs9661153
rs11073738	rs12783377	rs17378294	rs3088038	rs4885403	rs745019	rs967689
rs11075052	rs12784928	rs17512637	rs310576	rs4925249	rs7478426	rs9685492
rs11102321	rs12866529	rs17540484	rs3113608	rs4970516	rs751500	rs979744
rs11115840	rs12868782	rs17621805	rs3113609	rs4975679	rs7551986	rs9829202
rs11115842	rs12874580	rs17663669	rs324644	rs4975681	rs7552738	rs9870990
rs11128778	rs12878303	rs17718834	rs324649	rs509572	rs757200	rs998232
rs11163182	rs12957255	rs1778982	rs345192	rs520210	rs7581217	rs9993133
rs11190308	rs12976102	rs17828175	rs345194	rs522907	rs7583409	

Table 4.6 Top 35 SNPs in NORDIL[2000] and replication studies [BB-SBP].

					NORDIL			GENRES			ASCOT			INVEST			PEAR		
PHENO	DRUG	CHR	POS	SNP	BETA	SE	P	BETA	SE	P	BETA	SE	P	BETA	SE	P	BETA	SE	P
SBP	BB	13	75835110	rs12866529	-2.44	0.47	3E-07	0.22	1.56	1.2683	-0.42	0.95	0.65	1.56	1.53	0.3119	-1.51	1.14	0.1873
SBP	BB	13	75834767	rs9573846	2.45	0.48	3E-07	0.22	-1.57	1.2719	-0.40	0.94	0.67	1.56	1.53	0.3119			
SBP	BB	13	75776984	rs12583878	-4.35	0.93	3.2E-06	0.47	2.05	2.8356	-2.39	1.87	0.20	2.04	2.46	0.4071			
SBP	BB	8	51603877	rs310576	2.43	0.52	3.4E-06	0.51	-0.95	1.4409	0.10	1.03	0.92	1.37	1.60	0.3943			
SBP	BB	8	51550648	rs11785117	2.04	0.45	4.6E-06										-0.33	1.13	0.7707
SBP	BB	6	46825413	rs7766818	2.14	0.49	0.000011	0.60	0.74	1.431	0.66	0.97	0.49	-0.92	1.52	0.545			
SBP	BB	16	891046	rs4474684	-1.74	0.40	1.13E-05	0.73	-0.38	1.0925	-0.01	0.76	0.98	-0.54	1.20	0.6515	-0.30	0.98	0.7613
SBP	BB	16	890923	rs4262947	1.73	0.39	1.14E-05	0.74	0.36	1.0953	-0.01	0.75	0.98	-0.41	1.22	0.736	-0.30	0.98	0.7613
SBP	BB	20	54760829	rs11906158	-1.90	0.44	0.000015	0.68	-0.50	1.1955	0.58	0.82	0.48	-0.95	1.29	0.4596			
SBP	BB	20	54761343	rs6025134	1.86	0.43	1.54E-05	0.73	0.40	1.1631	0.60	0.80	0.46	-1.23	1.27	0.3349	-1.51	0.95	0.117
SBP	BB	13	75930558	rs12874580	2.01	0.47	0.000019	0.31	-1.30	1.2863	0.15	0.91	0.87	1.33	1.50	0.3767			
SBP	BB	13	75927898	rs12868782	2.00	0.47	2.07E-05	0.30	-1.33	1.2854	0.15	0.91	0.87	1.38	1.66	0.409			
SBP	BB	1	38690397	rs882000	1.55	0.37	2.11E-05	0.08	-1.71	0.98223	-0.73	0.78	0.35	1.72	1.08	0.1139			
SBP	BB	13	75912002	rs4885403	1.95	0.46	2.57E-05	0.27	-1.43	1.3048	0.04	0.90	0.97	1.33	1.50	0.3767	-2.06	1.72	0.2339
SBP	BB	13	75907453	rs10507855	1.95	0.46	2.75E-05	0.27	-1.43	1.3048	0.04	0.90	0.97	1.33	1.50	0.3767	-2.06	1.72	0.2339
SBP	BB	8	140745634	rs3780040	1.71	0.41	2.96E-05	0.71	0.40	1.0556	-1.31	0.82	0.11	-0.11	1.40	0.9376	-0.44	0.92	0.6341
SBP	BB	8	140740112	rs885724	-1.66	0.40	3.54E-05												
SBP	BB	13	76023588	rs285669	1.58	0.39	4.09E-05	0.93	-0.10	1.0427	0.25	0.75	0.74	2.76	1.20	0.02252	-0.70	1.03	0.4967
SBP	BB	3	68414852	rs751500	-6.17	1.51	4.29E-05	0.62	-2.69	5.4384	-1.70	3.75	0.65	-2.40	4.87	0.6229			
SBP	BB	6	46827535	rs6901073	2.01	0.51	9.12E-05	0.73	0.50	1.4367	0.56	1.00	0.58	-0.77	1.59	0.629			
SBP	BB	8	6520900	rs6559174	3.82	0.98	9.79E-05	0.37	-3.22	3.5569	3.30	1.73	0.06	-1.52	2.40	0.5281	0.14	0.86	0.8715
SBP	BB	11	64840067	rs4149818	-2.62	0.69	0.000156	0.29	-1.68	1.5815	0.78	1.62	0.63	-3.44	3.23	0.2882	-1.77	3.33	0.5954
SBP	BB	18	13532326	rs11659880	-1.44	0.38	0.000159										-2.00	0.87	0.02324
SBP	BB	18	13533725	rs1149361	-1.52	0.40	0.000166	0.93	0.09	1.1376	-0.55	0.79	0.49	0.53	1.13	0.6416			
SBP	BB	1	240165038	rs3845563	1.38	0.37	0.000171										-0.27	0.97	0.7824
SBP	BB	16	63881879	rs16968841	6.27	1.69	0.000204	0.09	5.20	3.0948	4.35	2.86	0.13	4.45	4.45	0.3189	0.85	1.32	0.5205
SBP	BB	11	64842121	rs4149826	2.60	0.70	0.000204										-1.77	3.33	0.5954
SBP	BB	1	81202249	rs12122460	2.81	0.77	0.00025	0.71	-0.49	1.312	-0.45	1.63	0.78	2.48	1.93	0.201			
SBP	BB	3	16108387	rs10865738	-1.35	0.38	0.000327	0.82	0.23	1.0318	0.59	0.77	0.45	1.34	1.18	0.2562	-2.26	0.81	0.006354
SBP	BB	1	240169131	rs4658576	-1.44	0.41	0.000364				-1.87	2.41	0.44	-0.05	1.10	0.9608			
SBP	BB	8	6519822	rs7845960	-3.23	0.91	0.000375	0.51	2.87	4.3383	3.49	1.78	0.05	-1.29	2.46	0.6019			
SBP	BB	3	16088035	rs11128778	1.35	0.38	0.000389	0.91	-0.12	1.0649	0.52	0.77	0.50	1.11	1.21	0.3596			
SBP	BB	3	16095771	rs7632303	-1.35	0.38	0.000393	0.91	0.12	1.0649	0.55	0.77	0.48	1.11	1.21	0.3596			
SBP	BB	3	16087011	rs9870990	1.34	0.38	0.000397	0.91	-0.12	1.0649	-0.55	0.77	0.48	1.05	1.25	0.4047			
SBP	BB	3	16084764	rs6442578	1.34	0.38	0.000407	0.91	-0.12	1.0628	0.52	0.77	0.50	1.14	1.21	0.3463			

PHENO=phenotype. CHR= chromosome. POS= chromosomal position. SNP= single nucleotide polymorphism. SE =standard error. P= P value.

Table 4.7 Top 35 SNPs in NORDIL[2000] and replication studies [BB-DBP].

					NORDIL			GENRES			ASCOT			INVEST			PEAR		
PHENO	DRUG	CHR	POS	SNP	BETA	SE	P	BETA	SE	P	BETA	SE	P	BETA	SE	P	BETA	SE	P
DBP	BB	8	59041340	rs4737483	1.49	0.33	6.2E-06	0.64	0.33	0.7201	-0.08	0.33	0.801039	-1.85	1.19	0.1216			
DBP	BB	8	59040943	rs4237021	1.49	0.33	6.4E-06	0.57	0.41	0.72528	0.05	0.33	0.880076	-1.26	1.24	0.3108	-1.46	0.94	0.1239
DBP	BB	6	101787218	rs17061550	4.20	0.94	7.5E-06	0.53	-0.92	1.4735	0.85	1.04	0.412376	0.21	3.81	0.9565			
DBP	BB	3	16088035	rs11128778	1.50	0.34	8.5E-06	0.42	0.57	0.69987	0.59	0.36	0.102094	-1.09	1.30	0.4031			
DBP	BB	3	16087011	rs9870990	1.50	0.34	8.5E-06	0.42	0.57	0.69987	-0.54	0.37	0.139817	-1.13	1.35	0.4034			
DBP	BB	3	16084764	rs6442578	1.49	0.34	8.7E-06	0.42	0.57	0.69847	0.60	0.36	0.101879	-1.04	1.30	0.426			
DBP	BB	14	84171029	rs12587920	1.62	0.37	9.5E-06	0.23	0.89	0.74138	0.78	0.38	0.038668	0.11	1.32	0.9355			
DBP	BB	14	84170479	rs2372781	1.62	0.37	9.5E-06	0.23	0.89	0.74135	0.76	0.38	0.04383	-0.42	1.31	0.7492			
DBP	BB	1	109285290	rs839549	1.54	0.35	9.5E-06	0.13	1.12	0.73372	0.55	0.36	0.128842	-1.99	1.32	0.1332			
DBP	BB	3	16095771	rs7632303	-1.49	0.34	1.04E-05	0.42	-0.57	0.69987	0.61	0.36	0.095098	-1.09	1.30	0.4031			
DBP	BB	6	46825413	rs7766818	1.90	0.43	1.08E-05	0.90	-0.12	0.94248	0.57	0.46	0.211703	0.14	1.64	0.9314			
DBP	BB	14	84183319	rs17258240	-1.60	0.36	1.13E-05	0.41	-0.63	0.75658	0.81	0.40	0.040815	0.67	1.43	0.642			
DBP	BB	17	1854963	rs4473232	-1.46	0.34	0.000015	0.79	-0.18	0.69189	-0.55	0.37	0.141492	-3.65	1.33	0.006697	2.34	1.14	0.04162
DBP	BB	1	206499848	rs1664234	-1.42	0.33	1.54E-05	0.82	-0.15	0.64435	-0.34	0.34	0.31574	-0.15	1.22	0.9006			
DBP	BB	17	1862784	rs4458034	-1.45	0.34	1.72E-05	0.75	-0.23	0.69595	-0.55	0.37	0.12979	-3.23	1.31	0.01492			
DBP	BB	1	240165038	rs3845563	1.39	0.32	1.81E-05										-0.36	0.94	0.7005
DBP	BB	22	47334980	rs12169559	-2.39	0.56	1.83E-05	0.82	0.27	1.1512	2.79	0.91	0.002168	-0.78	2.15	0.7163			
DBP	BB	9	10599930	rs979744	-1.73	0.40	1.83E-05	0.33	0.78	0.80955	-0.07	0.42	0.868598	1.06	1.41	0.4554			
DBP	BB	22	33730285	rs5755497	2.36	0.55	1.89E-05	0.33	-0.94	0.96854	-0.41	0.74	0.579619	0.56	2.00	0.7811	-0.43	0.89	0.6321
DBP	BB	14	50937357	rs17123869	-1.55	0.36	1.92E-05	0.05	-1.49	0.73956	-0.16	0.41	0.700999	1.49	1.49	0.3158	1.21	1.53	0.4308
DBP	BB	2	218431141	rs3791958	3.07	0.72	1.92E-05	0.84	-0.36	1.7716	-1.39	0.98	0.157442	-1.56	2.09	0.458			
DBP	BB	4	141943027	rs2171412	-1.67	0.39	1.99E-05	0.63	0.33	0.67129	0.12	0.41	0.772842	-1.43	1.46	0.3291	-0.89	0.77	0.2524
DBP	BB	4	141942528	rs4535404	-1.67	0.39	2.03E-05										-2.38	1.00	0.0181
DBP	BB	3	16108387	rs10865738	-1.42	0.33	2.16E-05	0.37	-0.61	0.67796	0.60	0.36	0.099557	-0.70	1.27	0.5838	-2.43	0.79	0.00235
DBP	BB	11	72110746	rs1552224	1.73	0.41	2.18E-05	0.16	1.14	0.80233	0.64	0.46	0.163887	-3.06	1.76	0.08388	0.82	2.78	0.7697
DBP	BB	18	13533725	rs1149361	-1.51	0.36	2.44E-05	0.97	0.03	0.74882	-0.24	0.37	0.513102	-1.37	1.21	0.2597			
DBP	BB	2	111469920	rs3761707	-1.36	0.32	2.61E-05	0.38	-0.61	0.69133	-0.54	0.33	0.105447	-0.23	1.19	0.8467	0.05	0.84	0.9508
DBP	BB	11	72110633	rs11603334	-1.72	0.41	2.63E-05	0.16	-1.14	0.80233	0.64	0.46	0.163941	-3.15	1.78	0.07775	2.71	2.46	0.2731
DBP	BB	14	83874773	rs7142452	-2.66	0.64	3.13E-05	0.18	-1.67	1.2525	0.37	0.78	0.636657	0.77	2.81	0.7839			
DBP	BB	18	13532326	rs11659880	-1.39	0.34	3.54E-05										-1.59	0.85	0.0642
DBP	BB	1	240169131	rs4658576	-1.48	0.36	3.71E-05				-1.49	1.14	0.191604	0.31	1.19	0.7939			
DBP	BB	1	158076864	rs2494493	2.37	0.58	3.96E-05	0.98	-0.02	0.99416	0.33	0.58	0.573387	0.35	2.04	0.8655	-1.00	0.86	0.2488
DBP	BB	1	158078722	rs2501363	2.39	0.58	4.01E-05	0.97	-0.03	0.99806	0.25	0.60	0.67228	0.26	2.05	0.8973	0.90	0.88	0.3071
DBP	BB	1	158081468	rs2501357	-2.39	0.59	4.32E-05	0.96	0.05	0.99821	0.24	0.60	0.683273	0.14	2.05	0.9444	0.68	0.91	0.4592
DBP	BB	9	10585208	rs10756066	-1.49	0.37	5.13E-05	0.09	1.31	0.75683	-0.24	0.40	0.550347	0.35	1.47	0.8136	1.75	0.93	0.06083

PHENO=phenotype. CHR= chromosome. POS= chromosomal position. SNP= single nucleotide polymorphism. SE =standard error. P= P value.

Table 4.8 Top 35 SNPs in NORDIL[2000] and replication studies [CCB-SBP].

					NORDIL			GENRES			ASCOT			INVEST			GenHat		
PHENO	DRUG	CHR	POS	SNP	BETA	SE	P	BETA	SE	P	BETA	SE	P	BETA	SE	P	BETA	SE	P
SBP	CCB	2	25344560	rs7583409	1.43	0.28	4E-07										-0.55		0.7942
SBP	CCB	2	25345971	rs13428812	1.41	0.28	7E-07	0.38	-0.86	0.98333	-0.46	0.54	0.395596	0.84	1.31	0.5238	-1.19		0.5292
SBP	CCB	1	207148885	rs12047788	1.99	0.43	2.9E-06	0.36	1.79	1.9676	-0.26	0.83	0.749665	-3.02	2.28	0.1875	-2.41		0.6157
SBP	CCB	1	207149385	rs12047943	1.99	0.43	2.9E-06	0.36	1.79	1.968	-0.26	0.83	0.750445	-2.92	2.27	0.2003			
SBP	CCB	2	142201688	rs13017029	-1.22	0.27	5.6E-06	0.57	-0.61	1.0729	-0.57	0.51	0.263905	0.00	1.20	0.9994			
SBP	CCB	19	56935739	rs11672811	-1.42	0.32	7.9E-06	0.87	-0.18	1.1512	-1.41	0.61	0.022389	-0.40	1.45	0.7816			
SBP	CCB	15	86153787	rs8026643	1.47	0.33	8.5E-06	0.41	0.92	1.1153	0.88	0.60	0.144836	-0.08	1.29	0.953	2.61		0.1593
SBP	CCB	15	86167979	rs4243096	-1.50	0.34	0.000009	0.38	-0.98	1.1117	0.95	0.64	0.138458	-2.28	1.57	0.1484	2.52		0.1827
SBP	CCB	1	111940179	rs9661153	-1.82	0.42	1.11E-05	0.01	-4.13	1.68	0.65	0.75	0.382723	0.63	1.81	0.727	1.95		0.3606
SBP	CCB	19	56937927	rs8104633	1.35	0.31	1.19E-05												
SBP	CCB	5	158462574	rs17718834	1.72	0.39	1.27E-05	0.21	1.19	0.94645	1.12	0.85	0.186747	0.71	2.14	0.7414	8.89		0.2879
SBP	CCB	17	2149917	rs216195	1.25	0.29	1.31E-05												
SBP	CCB	15	86134435	rs10083582	-1.43	0.33	1.46E-05	0.34	-1.05	1.1034	0.77	0.60	0.200783	-2.88	1.56	0.06576			
SBP	CCB	12	127206133	rs12305488	2.52	0.58	1.47E-05	0.60	1.28	2.4522	0.40	1.09	0.713784	-1.43	2.26	0.5257	-2.06		0.3417
SBP	CCB	22	23166024	rs2236624	1.26	0.29	1.48E-05	0.44	0.77	0.99177	0.53	0.58	0.355716	1.63	1.39	0.243	2.38		0.4714
SBP	CCB	1	112022239	rs7551986	2.05	0.47	1.49E-05	0.54	1.50	2.4194	0.53	0.89	0.549622	0.18	2.23	0.9343			
SBP	CCB	12	127205455	rs11829673	-2.50	0.58	0.000015	0.59	-1.30	2.4421	0.53	1.06	0.618494	-1.43	2.26	0.5257			
SBP	CCB	5	1691716	rs4975681	1.24	0.29	1.51E-05										-1.95		0.4355
SBP	CCB	17	2100007	rs7213347	-1.24	0.29	1.55E-05	0.20	1.30	1.0031	-0.06	0.53	0.914126	1.92	1.36	0.1606			
SBP	CCB	7	147582248	rs4590355	-1.27	0.30	1.68E-05	0.65	0.59	1.3137	-0.73	0.56	0.192855	-2.58	1.66	0.1214	-3.47		0.07581
SBP	CCB	9	137303859	rs1778982	1.15	0.27	1.71E-05	0.05	-1.91	0.96716	-0.25	0.49	0.613733	-1.13	1.31	0.3877	-0.60		0.8034
SBP	CCB	1	204153436	rs6421774	-1.42	0.33	1.95E-05	0.01	3.10	1.2191	-0.42	0.60	0.484842	-2.20	1.30	0.09151	0.06		0.9769
SBP	CCB	14	101029334	rs10148201	1.12	0.26	1.96E-05	0.08	-1.80	1.0316	0.27	0.55	0.617694	-1.10	1.09	0.3162	3.49		0.08271
SBP	CCB	2	25378448	rs7581217	1.31	0.31	0.00002												
SBP	CCB	14	101025658	rs1007904	-1.12	0.26	2.17E-05	0.69	0.36	0.92367	0.21	0.53	0.696344	-1.10	1.09	0.3149			
SBP	CCB	5	1688899	rs4975679	1.19	0.28	2.22E-05				-0.01	0.55	0.98532	-0.77	1.66	0.6445			
SBP	CCB	17	2114983	rs7209564	1.23	0.29	2.22E-05												
SBP	CCB	15	86144240	rs11073738	1.34	0.32	2.31E-05	0.37	0.99	1.0988	0.86	0.59	0.141583	-3.73	1.48	0.01229			
SBP	CCB	7	136704198	rs161338	-1.16	0.27	2.42E-05	0.23	1.18	0.97497	0.51	0.58	0.376459	0.62	1.17	0.5987	-0.36		0.8887
SBP	CCB	7	147589814	rs4640984	-1.23	0.29	2.56E-05	0.82	-0.30	1.3747	-0.62	0.55	0.259427	-1.24	1.38	0.371			
SBP	CCB	17	26808089	rs7213426	2.58	0.62	2.71E-05	0.93	-0.23	2.4767	2.15	1.96	0.271905	-1.59	2.52	0.5277			
SBP	CCB	5	16536310	rs17540484	-2.96	0.71	2.73E-05	0.83	0.53	2.3939	1.40	1.65	0.397129	-1.34	3.03	0.6602	5.13		0.6958
SBP	CCB	18	45907135	rs2457975	-1.13	0.27	3.08E-05	0.22	1.19	0.97442	-0.45	0.49	0.367328	-0.14	1.29	0.9139			
SBP	CCB	5	158537089	rs17663669	-1.62	0.39	3.17E-05	0.29	-0.96	0.91345	1.17	0.81	0.14982	0.95	2.03	0.6424			
SBP	CCB	15	86130534	rs11856526	-1.30	0.31	3.31E-05	0.33	-1.07	1.1069	0.76	0.60	0.205619	-2.85	1.54	0.06668			

PHENO=phenotype. CHR= chromosome. POS= chromosomal position. SNP= single nucleotide polymorphism. SE =standard error. P= P value.

Table 4.9 Top 35 SNPs in NORDIL^{2000} and replication studies [CCB-DBP].

					NORDIL			GENRES			ASCOT			INVEST			GenHat		
PHENO	DRUG	CHR	POS	SNP	BETA	SE	P	BETA	SE	P	BETA	SE	P	BETA	SE	P	BETA	SE	P
DBP	CCB	1	111940179	rs9661153	-1.92	0.39	8E-07	0.15	-1.59	1.0888	0.55	0.41	0.1812289	0.65	1.95	0.7388	£1.57		0.1754
DBP	CCB	5	119818078	rs13358400	5.64	1.19	1.9E-06	0.34	-3.11	3.2444	-0.03	1.38	0.9798594	-10.26	12.05	0.3955	-£0.88		0.8796
DBP	CCB	5	11705756	rs13172360	2.13	0.46	3.9E-06	0.78	0.23	0.8227	0.87	0.67	0.1944851	2.26	2.74	0.4103			
DBP	CCB	5	11708830	rs2727594	-2.11	0.46	4.1E-06										£0.74		0.4516
DBP	CCB	2	86219224	rs3088038	1.47	0.32	4.4E-06	0.17	-1.15	0.83362	0.12	0.36	0.7320555	-2.11	1.52	0.1669			
DBP	CCB	2	86219395	rs7598787	1.48	0.32	4.4E-06	0.17	-1.15	0.83195	0.12	0.36	0.7316126	-1.74	1.54	0.2595	£1.05		0.3119
DBP	CCB	3	21038062	rs4465961	1.12	0.25	9.2E-06	0.67	0.26	0.6122	0.01	0.29	0.9742929	-0.43	1.36	0.7497			
DBP	CCB	11	10878088	rs7932891	1.21	0.27	9.4E-06	0.78	0.19	0.66534	0.00	0.33	0.9912189	-0.96	1.38	0.4847	-£0.96		0.4143
DBP	CCB	1	8165074	rs2078288	4.65	1.06	0.000012	0.11	-9.74	5.9869	-0.38	1.08	0.7266141	5.30	3.05	0.08346	£1.30		0.2061
DBP	CCB	1	8161565	rs11803446	4.66	1.07	1.25E-05	0.11	-9.60	5.9615	-0.41	1.08	0.7031113	5.24	2.80	0.06258			
DBP	CCB	10	1080988	rs7072554	-1.27	0.29	1.26E-05	0.03	1.71	0.80659	0.61	0.31	0.0532993	-0.13	1.63	0.9368	£2.30		0.05894
DBP	CCB	11	11821492	rs17378294	-3.81	0.88	1.39E-05	0.63	-1.73	3.5952	0.10	0.78	0.9022696	1.11	2.95	0.7062	-£14.13		0.1555
DBP	CCB	10	1073617	rs12784928	-1.26	0.29	1.57E-05	0.04	1.71	0.80731	0.62	0.32	0.0507236	0.62	1.58	0.6941			
DBP	CCB	19	34347126	rs2903018	-1.13	0.26	1.57E-05				0.20	0.29	0.5024061	-1.37	1.41	0.3318	£1.96		0.2163
DBP	CCB	12	82352058	rs11115840	6.13	1.42	1.58E-05				2.19	1.15	0.0559905	-10.07	6.04	0.09689	£4.31		0.2031
DBP	CCB	12	82353007	rs11115842	6.13	1.42	1.58E-05												
DBP	CCB	19	34345238	rs12976102	-1.13	0.26	1.59E-05	0.37	-0.57	0.63261	0.12	0.30	0.683037	-1.13	1.43	0.4306			
DBP	CCB	7	105388039	rs2528893	1.19	0.28	1.89E-05	0.31	0.70	0.68867	0.54	0.33	0.1006894	0.65	1.38	0.6363	-£3.89		0.00393
DBP	CCB	4	15589552	rs6830263	1.10	0.26	2.08E-05										-£0.43		0.6884
DBP	CCB	20	59468906	rs2427113	-1.23	0.29	2.19E-05												
DBP	CCB	11	78556382	rs17828175	1.13	0.27	2.44E-05												
DBP	CCB	7	151011519	rs6464161	-1.07	0.25	2.45E-05												
DBP	CCB	7	105388751	rs2528892	-1.14	0.27	2.56E-05	0.23	-0.79	0.65556	0.52	0.33	0.1076344	0.65	1.38	0.6363			
DBP	CCB	11	4905894	rs17253343	4.34	1.04	2.83E-05	0.83	0.49	2.2923	0.43	1.45	0.7683601	5.21	4.78	0.2767			
DBP	CCB	1	112005284	rs11102321	-1.97	0.47	2.84E-05	0.35	-1.35	1.4521	0.76	0.51	0.1353695	1.22	2.60	0.6389			
DBP	CCB	20	59490675	rs4925249	1.14	0.27	2.89E-05	0.85	-0.14	0.71149	-0.01	0.36	0.9706652	0.11	1.36	0.9337			
DBP	CCB	4	7186156	rs10017978	1.10	0.26	3.14E-05	0.71	0.22	0.60559	-0.04	0.30	0.8888023	0.88	1.37	0.5241			
DBP	CCB	17	2045089	rs7213756	-1.10	0.26	3.46E-05	0.68	0.27	0.6606	-0.60	0.29	0.039911	0.87	1.31	0.5074			
DBP	CCB	11	4908534	rs840709	-1.14	0.28	0.000038							2.35	1.40	0.09363			
DBP	CCB	1	111940531	rs6677933	1.26	0.31	0.000044	0.74	0.29	0.86445	0.41	0.35	0.2368596	0.05	1.55	0.9742			
DBP	CCB	1	112022239	rs7551986	1.80	0.44	4.54E-05	0.86	0.28	1.555	0.57	0.49	0.2487773	2.13	2.39	0.3738			
DBP	CCB	11	78565913	rs575929	-1.05	0.26	5.71E-05	0.89	-0.09	0.6328	-0.46	0.28	0.0964524	1.72	1.32	0.1936			
DBP	CCB	11	10885446	rs522907	-1.02	0.26	6.61E-05	0.80	-0.16	0.63459	-0.11	0.29	0.7015688	-1.08	1.31	0.4092			
DBP	CCB	10	68011335	rs1072892	-1.01	0.26	7.84E-05	0.96	0.03	0.58179	0.09	0.27	0.7548489	1.00	1.22	0.4158			
DBP	CCB	7	151009438	rs6978142	0.97	0.25	9.81E-05	0.36	0.60	0.65063	0.06	0.29	0.8416263	0.29	1.40	0.8379			

PHENO=phenotype. CHR= chromosome. POS= chromosomal position. SNP= single nucleotide polymorphism. SE =standard error. P= P value.

4.1.5 Discussion

PG, may represent a useful tool in the future to select antihypertensive therapy with the greatest efficacy, based on individual's genetic profile. This study performed the largest PG genome-wide meta-analysis of BP response to monotherapy with BB and CCB. In total, 51 SNPs showed a significant ($P<1X10^{-5}$) association with BP response. However, no SNP achieved a genome-wide significance of ($P<5x10^{-8}$) even after replication. This may just be a reflection of lack of statistical power or phenotypic heterogeneity. In order to prioritise the most plausible signals for further study two analytic methods were applied – [1] identify directionally discordant signals between SNP and BP response for BB and CCB and [2] confirm the validity of a SNP BP response by analysing the SNP effect on mortality. This strategy allows selecting the right SNPs for further study, because this reflects not just specificity of response, but also indicates a greater potential use in personalised therapy, if they were validated and functional. SNPs which in contrast show similar response to drugs from multiple classes are of limited value in personalisation of therapy. The rationale for studying directionally opposite association with BP response stems from the "ABCD" (ACEI/ARB, BB, CCB and DI) algorithm that HTN can be broadly classified as "high renin" or "low renin" based on the vasoconstriction-volume (renin/sodium) model of HTN(459-461).

In general, the biggest challenge to successfully carrying out a GWAS is attaining good, clean genotype data, given that the practical utility of genetic predictors will ultimately depend upon the quality of the original data. The missingness rate is a good indicator of marker quality. The missingness threshold should be determined based on a goal whereby a balance, which minimises the number of samples dropped and maximises genotyping efficiency, is attained (462).

It is essential to filter SNPs based on MAF, as statistical power is extremely low for rare SNPs. However, SNPs with MAF greater than 0.01 might account for a high % of the genetic differences between individuals. As a result, these common variants might contribute significantly to those common diseases in which susceptibility alleles might not be under intense negative selection. Therefore, there are likely to be hundreds of common and rare variants contributing to the familial clustering of HTN (60). Checking HWE is also an important step in quality control markers within GWAS data. Departure from this equilibrium can indicate

potential genotyping errors, population stratification or even actual association with the trait under study (63).

IBD and population structure procedures work best under an assumption of no LD among SNPs, because quality control steps can take a long time if performed on the full dataset. In addition, the relatedness of the pair of individuals within families would be overrepresented, and the samples might no longer be a reasonable reflection of allele frequencies in the population (as, 3rd degree relatives (PI_HAT>0.125) were identified). Population structure was used to decrease the dimensionality of the data while retaining most of the variation in the dataset. By using few components, each sample can be represented by relatively few values instead of thousands of variables (172;462).

In the main, a significant P value indicates that the evidence is strong enough to reject H0, assuming that there is no difference between the NORDIL^{2000} subjects under investigation. The P value depends on the difference that exists between the study groups, the sample size and SD, which represents the variability (scatter) of the NORDIL^{2000} data, considering the level of statistical significance ($1X10^{-5}$); the smaller (that is, more significant) the P value, the larger the difference between the study groups, the smaller the SD or the larger the sample size. Conversely, a non-significant P value does not indicate that H0 is true. Large P values could be simply due to small sample sizes or highly scattered data (for example, large SD). A non-significant P value merely indicates that the evidence is not strong enough to reject H0 (463).

Survival analysis is concerned with the time from treatment until death; still, it is applicable to certain areas other than mortality. In clinical studies, an intervention's effect is assessed by measuring the number of subjects who survived following that intervention over a period of time. However, this can be affected by a number of subject-related situations, known as censored observations, such as subjects who were uncooperative or fell out of contact during the study, who did not experience the event before the end of the study or who would have experienced the event if the study continued (464). In most cases, KM makes suitable allocations for those censored observations and makes use of the information about those subjects, up to the point when they are censored. Therefore, a KM test is one of the simplest ways to compute survival

over time, regardless of all subject- or situation-related difficulties. In addition, it applies to both small and larger samples, and time is divided not into periods of fixed length, but periods of variable duration (465). Consequently, KM could play a significant role in providing evidence-based data on the survival time of NORDIL^{2000} subjects.

A log-rank test was used to test the probability of an event occurring at any time point and was the same for each population; it tests the difference between survival times of CCB- and BB-treated groups of NORDIL^{2000} patients, and does not allow other covariates, such as age, sex or BMI, to be taken into account. The Cox proportional hazard model was used to study the probability that the event of interest occurred at a given time for certain values of the predictor variables; it tests the difference between survival times of CCB- and BB-treated groups of NORDIL^{2000} patients, allowing for other covariates to be taken into account (464;465).In multiple linear regression analysis, the outcome is continuous. Therefore, a positive beta indicates that the outcome value (such as BP response) increases when independent variables (such as BP-lowering agents) increase. For instance, for discordant SBP-SNPs, rs12866529 showed a negative effect (-4.495 beta) on BB and a positive effect on CCB (0.1361 beta), whereas rs12663184 showed a positive effect (5.077 beta) on BB and a negative effect on CCB (-0.3452 beta).

Replication across multiple, well-powered, independent samples is the gold standard for reliability of genetic associations. In this study, it was possible to replicate the top signals in multiple cohorts for BP response but not for outcomes. The main reason for the difficulties in finding a genome-wide significant signal is likely due to the differences in the study and BP measurement characteristics of each replication cohort. Although there are several genes with convincing data for both BP response and treatment-related outcomes, further replication and functional studies are needed, mainly those identified through GWAS.

Replication studies, such as ASCOT-BPLA ^{2005}, GenHat ^{2002}, GENRES ^{2007}, INVEST ^{2003} and PEAR ^{2009}, are vital to ensuring that a genotype-phenotype association observed through NORDIL^{2000}-GWAS represents a convincing association, in order to provide a reliable statistical association and rule out a chance finding or an artefact due to uncontrolled biases.The purpose of replication is to improve effect

estimation, requiring that replication studies use the same phenotype definition used in the initial study, which also helps avoid false positives due to data dredging. Consequently, testing and validation of statistical hypotheses of potentially identifiable SNPs and clinical outcomes linked to these SNPs must be carried out to define how these data can be integrated into patient care, in order to further clarify their role in HTN PG and their mechanisms of action (466;467).

The definite data of a replicated association represents only the start of the process toward identifying the causal genetic variant and the biologically relevant causal pathways. Several recent replicated associations point to genes in unpredicted positions of the genome or to regulatory regions between genes. Thus, these will lead to a better understanding of the pathological processes in disease causation (70).Failure to replicate the association signals in populations with different ancestries does not always make the initial findings invalid, as the differences in LD, defined as the non-random association of alleles in adjacent loci, create patterns across different populations that can be used to shorten the region of interest for further functional analysis (69). A marker that is not in strong LD with a causal variant might be identified in a study. Testing it within a different population can cause false rejection of the association; however, testing other markers in the same region can reveal another association signal.

Therefore, in order to search for other variants associated with the phenotype, a significant factor to consider in a replication study is the differentiation between tests of the same SNPs as in the original study—those in strong LD with the reported SNP and others in the reported region. New SNPs should be clearly rationalised by separating them from the others (i.e., earlier tested SNPs). If the new SNPs are selected on the basis of LD patterns across populations with original SNPs, then the different patterns should be empirically confirmed in the two populations (i.e., original and replication populations)(70).

5 General discussion and prospects

For the most part, the choice of BP-lowering agents should be based on a number of considerations, as follows. First, the efficacy of decreasing BP, besides tolerability (including metabolic effects) must be individually evaluated in each patient. Second, the presence of related clinical conditions with compelling indications; sub-clinical target organ damage and other associated clinical conditions (but not related to HTN) can highlight the choice of certain BP-lowering agents. Third, a combination of two or more drugs is needed in the majority of hypertensive patients in order to achieve their desired BP (16;468).

5.1 Systematic review

RCTs gained increasing recognition during the course of the twentieth century as the best approach to the assessment of healthcare and prevention alternatives. However, the included studies have many differences in terms of designs and methods, baseline and goal BP, and study populations and drugs; therefore, trying to attain a coherent conclusion from their data may be a challenge. Systematic reviews, like other types of research, are certainly based on subjective judgements. The assessments were, however, conducted by at least two reviewers and the majority of included studies were labelled as high quality, making misjudgements less likely, but still possible.

5.1.1 Strengths of the review

Other research groups have conducted meta-analyses on BP–lowering agents, a number of which have studied BP response as an outcome. The current review has the potential to contribute important dimensions to BP response measures. First, many reviewers have mainly considered delta BP response (Chen[2010] (143), Wright[2009] (138) and Zanchetti[2015](150)), whereas this review classified BP response into delta, single and repeated measures. Second, this review was strict in terms of BP measurement techniques as it only included studies that followed standard protocols for measuring BP response and described these protocols clearly in their methodology sections in order to guarantee high-quality BP data. Third, this review had no language restrictions, meaning that non-English studies were translated, reviewed and included if they fit the inclusion criteria for this review.

In total, seven studies in languages other than English were screened and excluded after the translation of their abstracts, as they did not fit the inclusion criteria: three Chinese studies (one was cross-sectional, and the other two observed participants for less than three months of active treatment), two Russian studies (one randomised less than 100 participants, and the other enrolled HF participants), and two French studies (one observed participants for less than three months of active treatment, and the other enrolled participants who self-measured the mean BP response).

5.1.2 Limitations of the review

Since, more than one BP-lowering agent is required to achieve BP targets (15;16), the sequential administration of additional drugs following the first-line drug may have resulted in confounding as BP responses are presumed to reflect the effect of the first drug. This is possibly the major weakness of the review, and explains why other reviews (Wright [1999];(469)) and (Wright[2000];(470)) restricted their systematic reviews to studies where confounding supplementary BP-lowering agents were administered to less than half of patients.

The limited number of studies providing BP repeated measures data might be another limitation, as the majority of studies present mainly a baseline reading and mean BP response towards the end of the study (as a delta or single measure). Apart from ALLHAT [2002,] Derosa [2014], NORDIL [2000] and PATS [1995], all repeated measures data were extracted from supplementary graphs or figures. Although the extractions from the graphs or figures were confirmed by reviewers, it is still preferable to present BP readings numerically.

To maximise inclusiveness, two assumptions were made: [1] the equi-effectiveness of all approved doses of BP-lowering agents within either class, with respect to BP response; and [2] the equi-effectiveness of a background BP-lowering agent if the same protocol was followed in both arms. However, it is unknown whether the same background treatment regimen would unequally affect the BP response through the unequal drug. However, the subgroup analyses necessary to test these assumptions adequately would have been underpowered. Another limitation was in those with HTN and T2DM, CHD, CKD or concomitant

conditions as it was not possible to investigate the effect of these subgroup populations on the effect size (lacked the performance of subgroup analyses).

5.1.3 Agreements and disagreements with other studies or reviews

We believe this is the first review of its kind.

5.1.4 Implication for research

Systematic reviews of RCTs comparing different drugs provide evidence of the choices of BP-lowering medication. However, direct comparative studies are lacking in relation to many of the competing drug sub-classes. As the current review did not focus on comparing different BP-lowering sub-classes and their effects on BP response, new RCTs comparing BP-lowering sub-classes would be useful to determine whether it is appropriate to combine such sub-classes. As some of the included BP-lowering agents are heterogeneous groups of drugs that can be sub-classified into classes (such as CCBs, DHPs and non-DHPs), the different classes have various binding sites and mechanisms and could therefore evoke diverse BP responses.

Because the majority of clinical studies reported the difference in BP response towards the end of the study, further RCTs reporting all types of BP measures are required, especially for repeated measures. These studies should avoid confounding factors as much as possible, such as considering the number of background/secondary drugs and drug dosages.

Better-designed RCTs are required to study the BP response to the main BP-lowering agents, especially for patients with co-morbidities, such as T2DM, CHD and CKD. These studies should consider BP control goals and adherence. It is important that all relevant outcomes are well defined and reported. Furthermore, studies investigating BP response over 24 hours (ABPM) are required and should accurately record the time of drug intake. They should also report the BP data with zero hour being the time of drug intake, and they should be required to report the SD for each hourly measurement.

5.1.5 Implication for practice

This review has two main implications: [1], BP response measurements in clinical studies, mainly RCTs, can be used to guide physicians to the expected BP reduction for each BP-lowering agent. Consequently, they can set their management plans in terms of the likely duration to achieve the target BP and the need for using additional BP-lowering agents besides first-line agents. [2], using more than one BP-lowering agent (as combination therapy) should be emphasized more than it is at present for the initial treatment of hypertensive patients because the classic "up titration" of monotherapy titrated at a time to reduce BP is mostly inadequate. The review supports JNC 7 and ESH/ESC guidelines in acknowledging the value of combination therapy and suggesting that a two-drug combination is more likely to achieve target BP in hypertensive patients. Consequently, combination therapy makes more sense for high-risk patients such as T2DM and CKD who need aggressive BP targets because achieving these targets reduces events.

5.2 Genome-wide Study

There is major interest in identifying genes that influence the PK and PD determinants of BP response, because these mechanisms may play the predominant role in determining interindividual variation in BP responses to antihypertensive drugs now in common use. However, thre are major challenges in using identical phenotype criteria should be used in both GWAS and replication studies , as using different phenotype definitions can cause a misinterpretation of results, accordingly, replication of a GWAS result should be assumed to be the replication of a specific statistical model; a given SNP predicts a specific phenotype effect (70). However, there are some situations in which there are inadequate participant numbers for replication, such as rare diseases. Therefore, meta-analysis of genome-wide datasets provides a strategy that increases power over that of individual studies, as well as potentially being more cost-effective than replication (471).

The integration of results in the clinical situation will determine which SNPs/genes have adequate evidence to be clinically functional. Nowadays, a single SNP chip would be most useful as a means of stratifying patients to the best BP-lowering

treatment option; accordingly, only a single test would be ordered (88). However, there are many new discoveries every year, and the level of evidence differs according to the BP-lowering agent class. There are still many unanswered questions in HTN PG, and several regions of the genome have yet to be investigated.Further studies will include exhaustive sequencing of the candidate interval, genotyping of variants in multiple population samples, testing for association, and functional studies and investigation of interactions with other genes or environmental factors. Identification of these validated gene variants should help us to understand the disease biology; however, their applicability to clinical practice and public health will depend on whether they can improve diagnosis, prevention or treatment strategies (73). The overall goal is to increase the understanding of HTN causation and its consequences, and to apply this knowledge to developing better-quality treatments and risk assessment strategies that will have a major positive impact on public health.

5.3 Future work

The plan is first to publish the results of the systemic review highlighting the fact that not all BP–lowering agents are equal in reducing BP. CCBs should be the choice for first-line mono-therapy or second-line combination therapy, as in most of the existing BP guidelines. Next, the drug-specific effects of BP-lowering agents on BP over 24 hours (ABPM) will be identified and compared with the findings of the current review. The studies reporting ABPM have already been screened (their records are available, so this review only needed to be updated to include studies after 2015) and excluded, as this review focuses on office and clinic BP pressure taken as delta, single and repeated measurements.

For the genome-wide study, the plan is first to publish the GWAS results highlighting the fact that only a small number of the GWAS studies on HTN and/or BP have been published; the current study is the largest PG genome-wide meta-analysis of BP response to mono-therapy with BB and CCB. A number of SNPs achieved significance ($P < 5 \times 10^{-7}$), but no SNP achieved genome-wide significance ($P < 5 \times 10^{-8}$), even after replication. Then, the SNPs associated with BP-lowering responses will be identified in subjects using the GWAS approach in a new study with higher statistical power and lower phenotypic heterogeneity.

6 Appendix

Table 6.1 Search strategy for MEDLINE (OVID): searched on 3 April 2015.
"MP" indicates multi-purpose search terms in the title, original title, abstract, subject heading, name of substance and registry word fields; "tw" indicates that the term is a text word meaning the 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 word; "?" indicates the retrieval of documents with British and 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.

#	Searches
1	antihypertensive agents.mp.
2	calcium channel blockers.mp.
3	(calcium adj2 (inhibit$ or blockader?)).tw.
4	angiotensin receptor antagonists.mp.
5	(angiotensin adj2 (inhibit$ or blockader?)).tw.
6	adrenergic beta-antagonists.mp.
7	(beta adj2 (inhibit$ or blockader?)).tw.
8	ace inhibitors.mp.
9	diuretics.mp.
10	or/1-9
11	hypertension/
12	hypertens$.tw.
13	(blood adj pressure).tw.
14	or/11-13
15	10 and 14
16	randomized controlled trial.pt.
17	controlled clinical trial.pt.
18	randomized.ab.
19	placebo.tw.
20	drug therapy.tw.
21	randomly.ab.
22	trial.ab.
23	or/16-22
24	animals/ not (humans/ and animals/)
25	23 not 24
26	15 and 25
27	limit 26 to (yr="1965 - 2015" and "all adult (19 plus years)")

Table 6.2 Search strategy for EMBASE (OVID): searched on 15 June 2015.
"MP" indicates multi-purpose search terms in the title, original title, abstract, subject heading, name of substance and registry word fields; "tw" indicates that the term is a text word, meaning the title and abstract; "Ab" indicates all searchable words from the abstract; "sh" indicates all searchable words in the subject heading field; "hw" indicates all searchable words in the heading word field; "/" indicates that it is a Medical Subject Heading (MeSH) term; "$" indicates all possible suffix variations of the root word; "?" indicates the retrieval of documents with British and 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.

#	Searches
1	antihypertensive agents.mp.
2	calcium channel blockers.mp.
3	(calcium adj2 (inhibit$ or blockader?)).tw.
4	angiotensin receptor antagonists.mp.
5	(angiotensin adj2 (inhibit$ or blockader?)).tw.
6	adrenergic beta-antagonists.mp.
7	(beta adj2 (inhibit$ or blockader?)).tw.
8	ace inhibitors.mp.
9	diuretics.mp.
10	or/1-9
11	hypertension/
12	hypertens$.tw.
13	(blood adj pressure).tw.
14	or/11-13
15	randomized controlled trial/
16	Clinical Trial/
17	crossover procedure/
18	double-blind procedure/
19	(doubl$ adj blind$).tw.
20	(clin$ adj25 trial$).tw.
21	placebo$.tw.
22	random$.tw.
23	(meta?analys$ or systematic review$).tw.
24	(crossover$ or cross-over$).tw.
25	or/15-24
26	(animal$ not human$).sh,hw.
27	25 not 26
28	10 and 14 and 27
29	limit 28 to (yr="1996 - 2015" and adult <18 to 64 years>)

Table 6.3 Search strategy for CENTRAL: searched on 20 August 2015.

"MP" indicates multi-purpose search terms in the title, original title, abstract, subject heading, name of substance and registry word fields; "tw" indicates that the term is a text word, meaning the title and abstract; "$" indicates all possible suffix variations of the root word; "?" indicates the retrieval of documents with British and 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.

#	Searches
1	antihypertensive agents.mp.
2	calcium channel blockers.mp.
3	(calcium adj2 (inhibit$ or blockader?)).tw.
4	angiotensin receptor antagonists.mp.
5	(angiotensin adj2 (inhibit$ or blockader?)).tw.
6	adrenergic beta-antagonists.mp.
7	(beta adj2 (inhibit$ or blockader?)).tw.
8	ace inhibitors.mp.
9	diuretics.mp.
10	or/1-9
11	Hypertension.mp.
12	hypertens$.tw.
13	(blood adj pressure).tw.
14	or/11-13
15	10 and 14
16	Publication Year from 1995 to 2015, in Cochrane Reviews (Reviews and Protocols), with Hypertension Group

Table 6.4 Search strategy for Web of Science: searched on 28 September 2015.
"TS" indicates all searchable words in the topic subject; "TI" indicates all searchable words in the title; "*" indicates any group of characters, including no character; "" indicates a search for the exact phrase appearing between the quotation marks; "$" indicates all possible suffix variations of the root word; "?" indicates the retrieval of documents with British and American word variants; "adj" indicates a search for two terms where they appear adjacent to one another.

#	Searches
1	TS="antihypertensive agents"
2	TS="calcium channel blockers"
3	TS="calcium inhibit*"
4	TS="calcium block*"
5	TS="angiotensin receptor antagonists"
6	TS="angiotensin inhibit*"
7	TS="angiotensin block*"
8	TS=(adrenergic beta antagonists)
9	TS="beta inhibit*"
10	TS="beta block*"
11	TS="ace inhibitors"
12	TS="diuretics"
13	#12 OR #11 OR #10 OR #9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1
14	TS="hypertension"
15	TI="hypertens*"
16	TS=(*blood adj pressure*)
17	#16 OR #15 OR #14
18	#13 and #17
19	TI="randomized controlled trial"
20	TI="controlled clinical trial"
21	TS="Randomized"
22	TS="Placebo"
23	TI="drug therapy"
24	TS="Randomly"
25	TI="Trial"
26	#25 OR #24 OR #23 OR #22 OR #21 OR #20 OR #19
27	TS=(animals/ not (humans/ and animals/))
28	#26 NOT #27
29	#18 and #28
30	limit to Publication Year from 1995 to 2015 with Meeting abstract

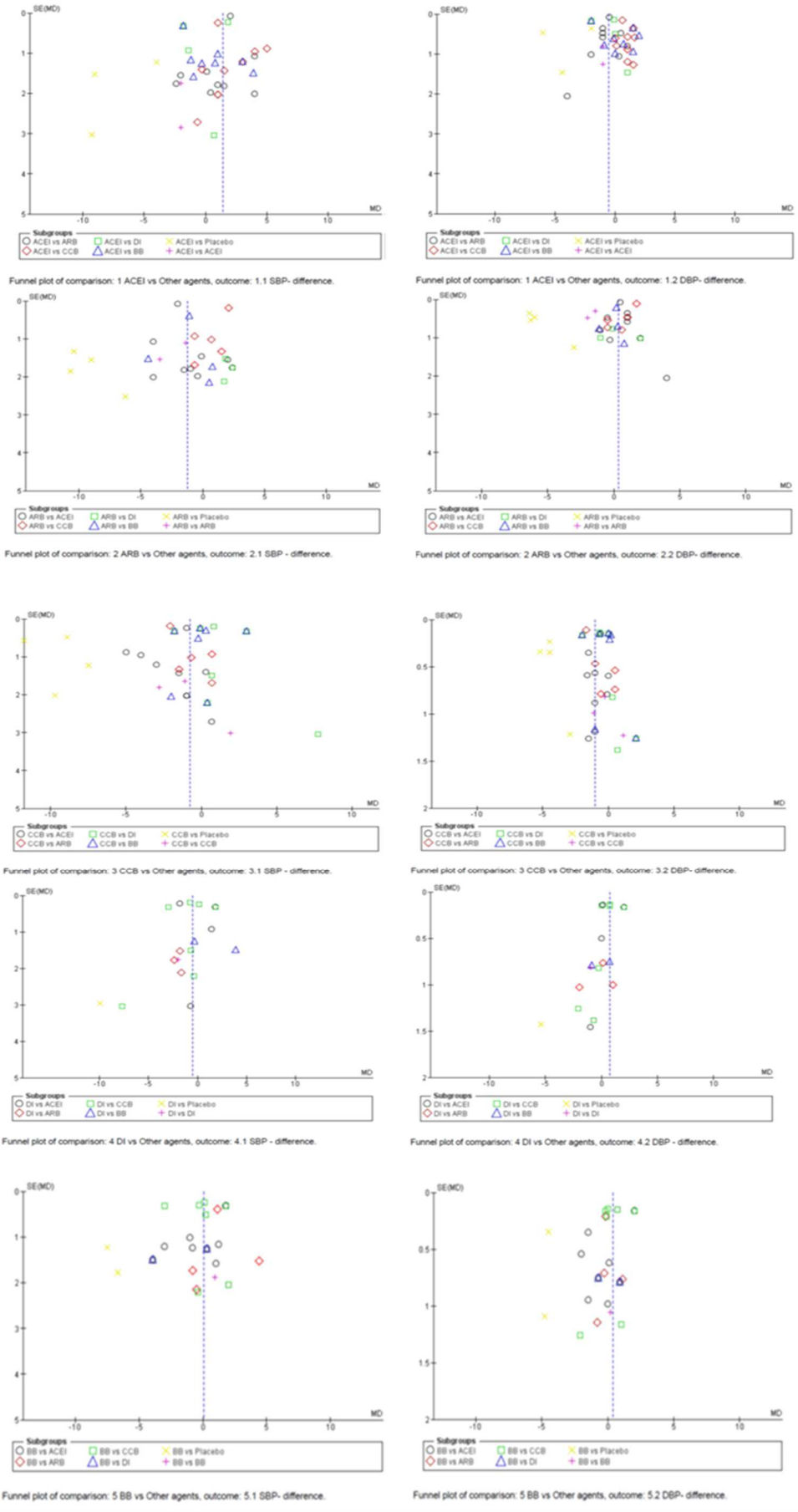


Figure 6.1 Funnel plot of comparison of BP-lowering agents: outcome: delta - BP response.

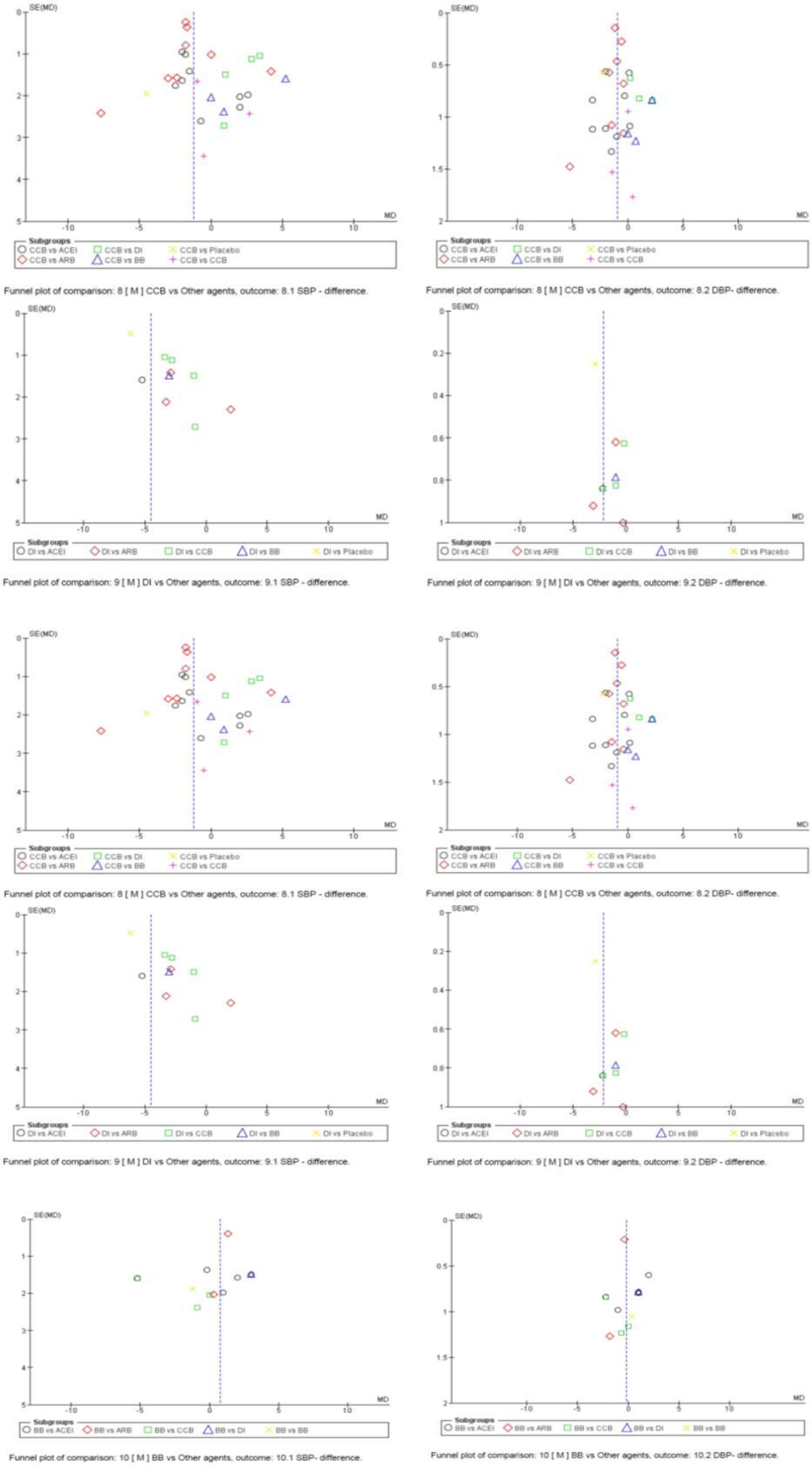
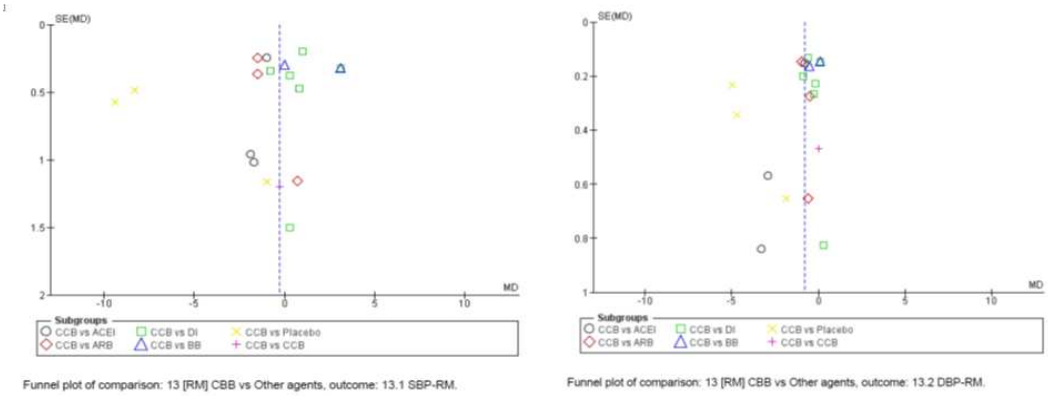


Figure 6.2 Funnel plot of comparison of BP-lowering agents: outcome: single measure - BP response.



Funnel plot of comparison: 13 [RM] CBB vs Other agents, outcome: 13.1 SBP-RM.

Funnel plot of comparison: 13 [RM] CBB vs Other agents, outcome: 13.2 DBP-RM.

Figure 6.3 Funnel plot of comparison of CCB vs other agents: outcome: repeated measures - BP response.

Funnel plot was only used to visually inspect CCB comparison as other comparison include less than 10 studies.

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