Antihypertensive Drugs and Risk of Cancer: A Systematic Review and Meta-Analysis of Randomised Controlled Trials

by

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Thesis submitted in fulfilment of requirements for the degree of Doctor of Philosophy (PhD.) in the College of Medical, Veterinary, and Life Sciences of the University of Glasgow

May 2018

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Summary

Pharmacovigilance plays an important role in monitoring adverse drug reactions (ADRs) resulting from an intervention related to medicinal products. Due to the frequencies and potentially serious consequences, ADRs pose a considerable economic and clinical burden. Patients with an underlying risk factor or established cardiovascular disease (CVD) are usually on long-term treatment, thus it is important to monitor the efficacy and safety of drugs prescribed. Modern antihypertensive drugs have been showed to effectively reduce high blood pressure (BP) hence prevents the development or complications of CVD in high-risk patients. However, there is evidence from clinical trials and observational studies suggesting the association between antihypertensive drugs and risk of cancer. Furthermore, these observations are inconsistent and the majority of clinical trials were directed towards cardiovascular outcomes.

The thesis is divided into five main result chapters (4 to 8) based on the antihypertensive drug classes evaluated for risk of cancer in the systematic review and meta-analyses. Altogether, 90 randomised controlled trials (RCTs) enrolling 390,750 participants with an average follow-up of 3.5 years were included for qualitative and quantitative analysis.

Angiotensin converting enzyme inhibitor (ACEI) and risk of cancer: ACEI lowers BP through preventing the conversion of angiotensin 1 to angiotensin II by ACE in the renin-angiotensin system (RAS) pathway. In the present study, no significant association between ACEI and risk of cancer incidence or cancer-related death is reported. Factors such as tissue binding capacity, comparator used, clinical settings, age, and study duration do not affect the risk of cancer overall.

Angiotensin receptor blockers (ARB) and risk of cancer: In the RAS pathway, ARB acts directly on the angiotensin type 1 ($AT_{1)}$ receptor to inhibit downstream signalling which results in downregulation of sympathetic activity and lowering of BP. The present meta-analysis has reported no association between ARB use and risk of cancer incidents or cancer-related mortality. Subgroup assessment indicates that valsartan has a cancer protective effect, particularly against lung cancer. Patients' clinical settings, age, and study duration do not influence the risk of cancer in relation to ARB overall.

Calcium channel blockers (CCB) and risk of cancer: As a class, CCBs are potent vasodilators and are recommended for use as first or second-line drugs in treating hypertension. This study has reported a marginally increased risk of cancer incidents (P=0.06) but not cancer-related death overall in relation to CCB use. DHP-CCB is associated with a 9% increased risk for cancer compared to controls (P=0.05). A positive relationship is also observed with older patients and in patients with longer exposure to CCB. Therefore, a properly designed further research into the risk of a specific type of cancer with use of DHP CCB is warranted to detect a safety signal.

Beta-blockers (BB) and risk of cancer: Inhibition of stress mediators from activating beta-adrenoceptors has been proposed to be the underlying mechanism by which BB lower the risk of cancer. This study has found no evidence of an association between BB and the risk of cancer or cancer-related death. Factors such as cardioselectivity, treatment indication, age and study duration do not have an impact on cancer risk altogether.

Thiazide diuretics (TZ) and risk of cancer: TZ induces diuresis at the distal convoluted tubule and a great number of studies had attempted to link TZ and risk of renal cancer. No evidence of an association between TZ and the risk of cancer or cancer mortality is reported in the present study. Chemical structure differences, clinical settings, age, and study duration does not significantly influence the risk of cancer in relation to TZ use.

Strengths and limitation: The strengths of the systematic review and meta-analyses conducted in this thesis include; only RCTs were included, a comprehensive search strategy spanning over 60 years with no language restrictions, and a sufficiently large sample size of over 390,000 trial participants from various clinical settings with an average 3.5 years follow-up duration. Lack of individual-level data and non-standard reporting of cancer in RCTs are the main limitations.

Future recommendations: All RCT evaluating drug intervention should pre-identify cancer as one of the study outcomes as part of drug safety monitoring.

Table of Contents

Contents

List of Tables

List of Figures

Acknowledgement

Praise and gratitude belong to the Almighty God, the most compassionate and the most merciful, multiplied by his bounty upon me for He has granted me with health, perseverance, and strength during the quest for my doctorate.

I am deeply grateful to my principal supervisor, Prof Sandosh Padmanabhan, for his guidance, immense knowledge, and insightful comments. My thanks also extend to Dr Mayetri Gupta for her support and encouragement.

Many thanks to Prof John Petrie, Prof Colin Berry, and Prof Jacob George for sitting on my thesis defence committee as well as Ms Ruth Bennett for her kind assistance during the viva process.

Special thanks are due to Safaa Alsanosi for her guidance and contribution to the systematic review. I would also like to thank Mohammed A Alsieni, Mohammed Bazuhair, Alisha Aman and Tracy Ehima for helping me select and review the articles of which I could not have done it all by myself.

I would like to sincerely thank all the authors of clinical trials who have contributed data and information that is much needed for this thesis to be a success.

To my husband (Munzir Badron) and my princesses (Ikhlas and Inshirah), thank you for understanding and coping with my demanding academic commitments. Also, thanks to my parents for supporting me along this challenging journey.

Very special gratitude goes out to the Malaysian Ministry of Higher Education and the National Defence University of Malaysia for providing the funding for my study.

And finally, last but not least, I thank my fellow research colleagues for the stimulating discussions over coffee and for sharing their valuable knowledge.

Thanks for all your encouragement!

Author's Declaration

I declare that the work presented in this thesis, to the best of my knowledge and belief, represents my own work unless specified otherwise in the text. I was responsible for the analysis and interpretation of the results. The work represented in my thesis has not been previously submitted for any degree to the University of Glasgow or any other institutions.

Nur Aishah binti Che Roos

May 2018

List of Abbreviations, Acronyms and Symbols

=	Equal to
<	Greater than
>	Less than
≤	Less than or Equal to
≥	Greater than or Equal to
4C	Candesartan For Prevention Of Cardiovascular Events After Cypher Or Taxus Coronary Stenting
AASK	African American Study Of Kidney Disease And Hypertension
ABCD	Appropriate Blood Pressure Control In Diabetes
ABPM	Ambulatory Blood Pressure Monitoring
ACC/AHA	American College Of Cardiology/American Heart Association
ACE	Angiotensin converting enzyme
ACEI	Angiotensin converting enzyme inhibitors
ACTION	A Coronary Disease Trial Investigating Outcome With Nifedipine GITS
ACTIVE I	Atrial Fibrillation Clopidogrel Trial With Irbesartan For Prevention Of Vascular Events I
AF	Atrial fibrillation
AHT	Antihypertensive therapy
AIPRI	Angiotensin-Converting Enzyme Inhibition In Progressive Renal Insufficiency
AIRE	Acute Infarction Ramipril Efficacy
AIREX	Acute Infarction Ramipril Efficacy Extension Study
ALLHAT	Antihypertensive And Lipid-Lowering Treatment To Prevent Heart Attack Trial
ALPINE	Antihypertensive Treatment And Lipid Profile In A North Of Sweden Efficacy Evaluation
ANBP	Australian National Blood Pressure Study
ANTIPAF	Angiotensin II-Antagonist In Paroxysmal Atrial Fibrillation
ANZHF	Australia/New Zealand Heart Failure Research
APSI	Acebutolol Et Prévention Secondaire De l'Infarctus
APSIS	Angina Prognosis Study In Stockholm
ARB	Angiotensin receptor blockers
ASCOT-BPLA	Anglo-Scandinavian Cardiac Outcomes Trial- Blood Pressure Lowering Arms
ASIST	The Atenolol Silent Ischaemia Study
ATP	Adenosine Triphosphate
ATTEST	The Azilnidipine And Temocapril In Hypertensive Patients With Type 2 Diabetes Study
AVER	Amlodipine Versus Enalapril In Renal Failure
BB	Beta-Adrenergic Blockers
BENEDICT-B	Bergamo Nephrologic Diabetes Complications Trial-B
BEST	Beta-Blocker Evaluation Survival Trial
BHAT	Beta-Blocker Heart Attack Trial
BMI	Body Mass Index
BP	Blood pressure

Ca2+	Calcium ion
CABG	Coronary Artery Bypass Grafting
CAD	Coronary artery disease
CAMELOT	Comparison Of Amlodipine Versus Enalapril To Limit Occurrences Of Thrombosis
cAMP	Cyclic adenosine monophosphate
CAPPP	Captopril Prevention Project
CAPRICORN	Carvedilol Post- Infarct Survival Control In LV Dysfunction
CARMEN	Carvedilol And ACE-Inhibitor Remodelling Mild Heart Failure Evaluation Trial
CARP	Coronary Atherosclerosis Reduction Project
CASE-J	Candesartan Antihypertensive Survival Evaluation In Japan
CASE-J Ex	Candesartan Antihypertensive Survival Evaluation Extension Study
CATS	Captopril And Thrombolysis Study
CCB	Calcium channel blockers
CHARM-	Candesartan In Heart Failure: Assessment Of Reduction In Mortality And Morbidity
CHD	Coronary heart disease
CHF	Congestive heart failure
CI	Confidence interval
CIBIS	Cardiac Insufficiency Bisoprolol Study
CIOMS	Council For International Organizations Of Medical Sciences
CITAS	Cardiac Insufficiency Talinolol Study
CKD	Chronic kidney failure
CLEVER	Carvedilol Modified Release Formulation (Coreg) And Left Ventricular Mass Regression
COER	Controlled-Onset Extended-Release
CONSENSUS	Cooperative North Scandinavian Enalapril Survival Study
CONVINCE	Controlled Onset Verapamil Investigation Of Cardiovascular End Points
COOPERATE	Combination Treatment Of Angiotensin-II Receptor Blocker And Angiotensin-Converting-Enzyme Inhibitor In Non-Diabetic Renal Disease
COPERNICUS	Carvedilol Prospective Randomized Cumulative Survival
CORD	Comparison Of Recommended Doses Of ACE Inhibitors And Angiotensin II Receptor Blockers
CRIS	Calcium Antagonist Reinfarction Italian Study
CVD	Cardiovascular Disease
CVIP	Cardiovascular Irbesartan Project
DAG	Diacylglycerol
DALY	Disability-Adjusted Life Year
DAVIT II	Danish Verapamil Infarction Trial Ii
DCT	Distal convoluted tubule
DEMAND	Delapril And Manidipine For Nephroprotection In Diabetes
DETAIL	Diabetics Exposed To Telmisartan And Enalapril
DHP	Dihydropyridine
DIABHYCAR	Non-Insulin Dependent Diabetes, Hypertension, Microalbuminuria Or Proteinuria, Cardiovascular Events, And Ramipiril

DIAL	Diabete, Ipertensione, Albuminuria, Lercanidipina: Effect Of Lercanidipine Compared With Ramipril On Albumin Excretion Rate In Hypertensive Type 2
DIRECT	Diabetic Retinopathy Candesartan Trials
DREAM	Diabetes Reduction Assessment With Ramipril And Rosiglitazone Medication
Dutch TIA	Dutch Transient Ischaemic Attack
E-COST	Efficacy Of Candesartan On Outcome In Saitama Trial
EIS	European Infarction Study
ELSA	European Lacidipine Study On Atherosclerosis
EMA	European Medicines Agency
ENCORE II	Evaluation Of Nifedipine On Coronary Endothelial Function
ESH/ESC	European Society Of Hypertension/European Society Of Cardiology
ESPIRAL	Effect Of Antihypertensive Treatment On Progression Of Renal Insufficiency In Nondiabetic Patients
ESRD	End-stage renal disease
EUCLID	EURODIAB Controlled Trial Of Lisinopril In Insulin Dependent Diabetes
EUROPA	European Trial On Reduction Of Cardiac Events With Perindopril In Stable Coronary Artery Disease
EWPHE	European Working Party On High Blood Pressure In The Elderly
FACET	Fosinopril Amlodipine Cardiovascular Events Trial
FAMIS	Fosinopril In Acute Myocardial Infarction Study
FDA	Food And Drug Administration
FE	Fixed-Effects
FEVER	Felodipine Event Reduction
FOSIDIAL	Fosinopril In Dialysis
GISSI-3	Gruppo Italiano Per Lo Studio Della Soprawivenza Nell'infarto Miocardico 3
GISSI-AF	Gruppo Italiano Per Lo Studio Della Sopravvienza Nell'infarto Miocardico-Atrial Fibrillation
GLANT	Study Group Of Long-Term Antihypertensive Therapy
GPRD	General Practice Research Database
HANE	The Hydrochlorothiazide, Atenolol, Nitrendipine, Enalapril Study
HAPPHY	Heart Attack Primary Prevention In Hypertension
HBPM	Home Blood Pressure Monitoring
HCTZ	Hydrochlorothiazide
HDPAL	Hypertension In Hemodialysis Patients Treated With Atenolol Or Lisinopril
HEP	Treatment Of Hypertension In Elderly Patients In Primary Care
HF	Heart failure
HIJ-CREATE	Heart Institute Of Japan Candesartan Randomized Trial For Evaluation In Coronary Artery Disease
HOMED-BP	Hypertension Objective Treatment Based On Measurement By Electrical Devices Blood Pressure Trial
HOPE	Heart Outcomes Prevention Evaluation

HSCHG	Hypertension-Stroke Cooperative Study Group
HYVET	Hypertension In The Very Elderly Trial
HYVET-P	Hypertension In The Very Elderly Trial –Pilot Study
ICH	International Conference On Harmonisation
IDNT	Irbesartan Idiopathic Nephropathy Trial
IGT	Impaired glucose tolerance
IHD	Ischaemic heart disease
IMAGINE	Ischemia Management With Accupril Post– Bypass Graft Via Inhibition Of The Converting Enzyme
INNOVATION	Incipient To Overt: Angiotensin II-Blocker, Telmisartan, Investigation On Type 2 Diabetic Nephropathy
INSIGHT	International Nifedipine GITS Study Intervention As A Goal In Hypertension Treatment
INTACT	International Nifedipine Trial On Anti-Atherosclerotic Therapy
INTERMAP	International Population Study On Macronutrients And BP
INTERSALT	International Study Of Salt And Blood Pressure
INVEST	International Verapamil-Trandolapril Study
IP_3	Inositol Triphosphate
IPPPSH	International Prospective Primary Prevention Study In Hypertension
I-PRESERVE	Irbesartan In Patients With Heart Failure And Preserved Ejection Fraction
IRMA-2	Irbesartan In Patients With Type 2 Diabetes And Microalbuminuria -2
J- RHYTHM	Japanese Rhythm Management Trial For Atrial Fibrillation
JAMP	Japanese Acute Myocardial Infarction Prospective Study
J-DHF	Japanese Diastolic Heart Failure Study
J-ELAN	Japanese Study On The Effect Of Losartan And Amlodipine On Left Ventricular Diastolic Function In Patients With Mild-To-Moderate Hypertension
JMIC-B	Japan Multicenter Investigation For Cardiovascular Diseases-B
J-MIND	Japan Multicenter Investigation Of Antihypertensive Treatment For Nephropathy In Diabetics
JNC	Joint National Committee
LIFE	Losartan Intervention For Endpoint
LIT	Lopressor Intervention Trial
LIVE	Left Ventricular Hypertrophy Regression, Indapamide Versus Enalapril
LOMIR-MCT -IL	Lomir (Isradipine) Multicenter Study In Israel
LVH	Left Ventricular Hypertrophy
MACB	Metoprolol After Coronary Bypass
MACH-1	Mortality Assessment In Congestive Heart Failure Trial
MAOI	Monoamine Oxidase Inhibitor
MAPHY	Metoprolol Atherosclerosis Prevention In Hypertensives
MDC	Metoprolol In Dilated Cardiomyopathy
MDPT	Multicenter Diltiazem Post infarction Trial

MERIT-HF	Metoprolol CR/XL Randomised Intervention Trial In Congestive Heart Failure
MI	Myocardial infarct
MIAMI	Metoprolol In Acute Myocardial Infarction
MIDAS	Multicenter Isradipine Diuretic Atherosclerosis Study
MITEC	Media Intima Thickness Evaluation With Candesartan Cilexetil
MMSE	Mini Mental State Examination
MOSES	Morbidity And Mortality After Stroke, Eprosartan Compared With Nitrendipine For Secondary Prevention
MRC	Medical Research Council Trial Of Treatment For Mild Hypertension
MRCOA	Medical Research Council Trial Of Treatment Of Hypertension In Older Adults
NAVIGATOR	Nateglinide And Valsartan In Impaired Glucose Tolerance Outcomes Research
NESTOR	Natrilix SR Versus Enalapril Study In Hypertensive Type 2 Diabetics With Microalbuminuria
NHLBI	National Heart, Lung, And Blood Institute
NHS	Nagoya Heart Study
NICE	National Institute For Care And Health Excellence
NICOLE	Nisoldipine In Coronary Artery Disease In Leuven
NICS-EH	National Intervention Cooperative Study In Elderly Hypertensives Study Group
NIDDM	Non-Insulin Dependent Diabetes Mellitus
NORDIL	The Nordic Diltiazem Study
NYHA	New York Heart Association
OCTOPUS	Olmesartan Clinical Trial In Okinawan Patients Under OKIDS (Okinawan Dialysis Study)
OHA	Oral hypoglycaemic agent
OLIVUS	Impact Of Olmesartan On Progression Of Coronary Atherosclerosis: Evaluation By Intravascular Ultrasound
ONTARGET	Ongoing Telmisartan Alone And In Combination With Ramipiril Global Endpoint Trial
OPTIMAAL	Optimal Trial In Myocardial Infarction With The Angiotensin II Antagonist Losartan
OR	Odds ratio
ORIENT	Olmesartan Reducing Incidence Of End stage Renal Disease In Diabetic Nephropathy Trial
OSCAR	Olmesartan And Calcium Antagonists Randomized Study
Oslo	The Oslo Study
PARADIGM-HF	Prospective Comparison Of ARNI (Angiotensin Receptor-Neprilsyn Inhibitor) With ACEI To Determine Impact On Global Mortality And Morbidity In Heart Failure Trial
PART-2	Prevention Of Atherosclerosis With Ramipril
PAT	Propanolol Aneurysm Trial
PATS	Post-Stroke Antihypertensive Treatment Study
PCI	Percutaneous Coronary Intervention
PEACE	Prevention Of Events With Angiotensin Converting Enzyme Inhibition
PEP-CHF	Perindopril In Elderly People With Chronic Heart Failure

PHARAO	Prevention Of Hypertension With The Angiotensin Converting Enzyme Inhibitor Ramipiril In Patients With High-Normal Blood Pressure
PHYLLIS	Plaque Hypertension Lipid-Lowering Italian Study
PIP2	Phosphatidylinositol Biphosphate
POST	Prevention Of Syncope Trial
PRAISE	Prospective Randomized Amlodipine Survival Evaluation
PRAISE-2	Prospective Randomized Amlodipine Survival Evaluation
PREAMI	Perindopril And Remodelling In Elderly With Acute Myocardial Infarction
PRESERVE	Prospective Randomized Enalapril Study Evaluating Regression Of Ventricular Enlargement
PREVEND-IT	Prevention Of Renal And Vascular End-Stage Disease Intervention Trial
PREVENT	Prospective Randomized Evaluation Of The Vascular Effects Of Norvasc Trial
PREVER-treatment	Prevention Of Cardiovascular Events In Patients With Hypertension And Pre-Hypertension Study -Treatment
PROBE	Prospective, randomised open blinded-endpoint
PRoFESS	Prevention Regimen For Effectively Avoiding Second Strokes
PROGRESS	Perindopril Protection Against Recurrent Stroke Study
PROTECTS	Perindopril Regression Of Vascular Thickening European Community Trial
PTCA	Percutaneous Transluminal Coronary Angioplasty
PUTS	Perindopril Therapeutic Safety Study
PVD	Peripheral vascular disease
QUIET	Quinapril Ischaemic Event Trial
RASS	Renin Angiotensin System Study
RCC	Renal-cell carcinoma
RE	Random-effect
REIN	Ramipril Efficacy In Nephropathy
REIN-2	Ramipiril Efficacy In Nephropathy-2
RENAAL	Reduction Of Endpoints In NIDDM (Non-Insulin Dependent Diabetes Mellitus) With The Angiotensin II Antagonist Losartan
ROAD	Reno protection Of Optimal Antiproteinuric Doses
ROADMAP	Randomized Olmesartan And Diabetes Microalbuminuria Prevention
SAVE	Survival And Ventricular Enlargement
SCAT	Simvastatin/Enalapril Coronary Atherosclerosis Trial
SCOPE	Study On Cognition And Prognosis In The Elderly
SCR	Scottish Cancer Registry
SENIORS	Study Of The Effects Of Nebivolol Intervention On Outcomes And Rehospitalisation In Seniors With Heart Failure
SHELL	Systolic Hypertension In The Elderly: Lacidipine Long-Term Study
SHEP	Systolic Hypertension In The Elderly Programme
SHEP-PS	Systolic Hypertension In The Elderly Programme Pilot Study
SMT	Stockholm Metoprolol Trial
SOLVD-P	Studies Of Left Ventricular Dysfunction-Prevention

SOLVD-T	Studies Of Left Ventricular Dysfunction-Treatment
SPRINT	Secondary Prevention Reinfarction Israeli Nifedipine Trial
STAR-CAST	Short Treatment With Angiotensin Receptor Candesartan Surveyed By Telemedicine
STONE	Shanghai Trial Of Nifedipine In The Elderly
STOP-HTN2	Swedish Trial In Old Patients With Hypertension-2
Syst_Eur	Systolic Hypertension In Europe
Syst-China	Systolic Hypertension In China
T2DM	Type 2 diabetes mellitus
TAIM	Trial Of Antihypertensive Intervention And Management
TEST	Tenormin After Stroke And TIA (Transient Ischaemic Attack)
TIA	Transient Ischaemic Attack
TIBET	Total Ischaemic Burden European Trial
TOHMS	Treatment Of Mild Hypertension Study
TRACE	Trandolapril Cardiac Evaluation
TRANSCEND	The Telmisartan Randomised Assessment Study In ACE Intolerant Subjects With Cardiovascular Disease
TROPHY	Trial Of Preventing Hypertension
TZ	Thiazide diuretics
UKPDS	The United Kingdom Prospective Diabetes Study
USPHSH -	The United States Public Health Service Hospitals
VA COOP	Veteran Affairs Cooperative Study
VA NEPHRON-D	Veteran Affairs Nephropathy In Diabetes Trial
VAL-CARP	Valsartan Cardio-Renal Protection In Patients Undergoing Coronary Angiography Complicated With Chronic Renal Insufficiency
Val-HeFT	Valsartan Heart Failure Trial
VALIANT	Valsartan In Acute Myocardial Infarction
VALUE	Valsartan Antihypertensive Long-Term Use Evaluation
VART	Valsartan Amlodipine Randomized Trial
VERDI	Verapamil Versus Diuretic
VESPA	Verapamil Slow-Release For Prevention Of Cardiovascular Events After Angioplasty
VHAS	Verapamil In Hypertension And Atherosclerosis Study
VHeft II	Vasodilator-Heart Failure Trial Ii
V-HeFT III	Vasodilator Heart Failure Trial
Vs.	Versus
WHO	World Health Organization

1 Introduction

1.1 Pharmacovigilance

1.1.1 Definition for pharmacovigilance

The World Health Organization (WHO, 2002) defined pharmacovigilance as "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem". A similar definition is adopted by the International Council for Harmonisation (ICH) and Council for International Organizations of Medical Science (CIOMS) The field of drug safety monitoring also involves issues such as substandard medicine, medication error, lack of efficacy reports, abuse and misuse of drugs, adverse drug-substance interactions (e.g. chemicals, food, other medicine), and drug-related mortality assessment (WHO, 2002). Over the years, safety concerns have widened to include herbal products, traditional and complementary medicines, blood products, biologicals, medical devices, and vaccines. According to the WHO (2002), the main goals of pharmacovigilance are 1) to improve patient care, public health and safety with regards to use of medicines; 2) to contribute to assessment of drug safety and efficacy and 3) to support public health programmes by providing reliable and balanced information to the public.

1.2 Historical perspective of pharmacovigilance

The WHO Programme for International Drug Monitoring was initiated following a worldwide response to the infamous thalidomide disaster. The 16th World Health Assembly held in 1963 had called for a resolution (WHA 16.36)(WHO, 1963) to systematically collect information on serious adverse drug reactions (ADR) during drug development and post-marketing which subsequently led to the creation of WHO Pilot Research Project for International Drug Monitoring in 1968 (WHO, 2002). The rationale of this programme was to develop a system, applicable internationally, to identify rare ADR that could not be detected through clinical trials (Olsson, 1998). Following the pilot project in the United States (US), an international database (also known as VigiBase) was set up in Geneva in 1971 and subsequently moved to Uppsala in 1968, hence managed by UMC (Uppsala Monitoring Centre, 2017).

As of 2017, 125 countries are full members of the WHO Programme for International Drug Monitoring (Uppsala Monitoring Centre, 2017). Member States of this programme would collect, evaluate, and submit reports of suspected adverse drug reactions associated with medicinal products from individual case histories to VigiBase. These are known as individual case safety reports (ICSRs). UMC is responsible for validating this data judiciously and consequently disseminate the outcomes with member countries.

1.3 International collaboration and regulatory authorities

The following section describes the important organisations that play a key role in the global administration of pharmacovigilance.

1.3.1 The World Health Organization (WHO)

WHO is a United Nation (UN) agency that specialized in global public health. The WHO work in areas encompasses health system development; communicable and non-communicable diseases treatment and prevention; health promotion through life-course; preparedness, surveillance, and response during emergencies; and corporate services (WHO, 2017). The WHO Department of Essential Medicines and Health Products (EMP) in collaboration with the UMC promote pharmacovigilance at the country level. UMC is an independent, non-profit organization associated with WHO. Based in Sweden, UMC supports and coordinates the WHO Programme for International Drug Monitoring since 1978.

1.3.2 The International Council for Harmonization (ICH)

The ICH is a global organisation with the main goal is to produce, recommend and disseminate global standards for development and registration of medicines. Originally known as the International Conference on Harmonisation, this organisation was founded in 1990 bringing together regulatory agencies and industry associations of Europe, US, and Japan which are acknowledged as the founding regulatory members (ICH, 2017). In the first decade of its establishment, some of the important work undertaken included the Medical Dictionary for Regulatory Activities (MedRA) and the Common Technical Document (CTD). The new ICH association was established on 23rd October 2015 with attention directed towards extending the benefits of harmonisation beyond its founding regions. As

of June 2017, its members comprised regulatory authorities from Singapore, China, Brazil and Republic of Korea and industrial associations such as Biotechnology Innovation Organization (BIO), World Self-Medication Industry (WSMI), and International Generic and Biosimilar Medicines Association (IGBA) (ICH, 2017). The ICH members actively support adherence to ICH guidelines, appoint experts in Working Groups, and support the aims of the ICH association. Non-voting observers also included regulatory bodies from other countries such as Australia, India, Russia, and many others who may contribute input to the ICH activities.

1.3.3 The Council for International Organizations of Medical Science (CIOMS)

The CIOMS is an international, independent, non-profit organization established jointly by WHO and the United Nations Educational, Scientific and Cultural Organization (UNESCO) in 1949 (CIOMS, 2017). The main mission is to embolden and promote global biomedical scientific activities in conjunction with United Nation agencies by gathering representative of biomedical scientific community worldwide. One of the core activities of CIOMS includes the drug development and use programme which results in important works in pharmacovigilance (CIOMS, 2017). The first Working Group on pharmacovigilance was commissioned in 1986 which was known as the Working Group on International Reporting of Adverse Drug Reactions (CIOMS Working Group, 1987). Following the first work, several numbered and unnumbered Working Groups have been launched to address important topics in pharmacovigilance (CIOMS, 2017). Several CIOMS Working Group guidelines have served as a basis for several ICH guidelines. For example, the ICH E2 Clinical Safety Data Management-Definitions and standards for expedited reporting (ICH, 1994) was based on the CIOMS Working Group I and II reports (CIOMS, 2017).

1.3.4 Regulatory authorities in states member

Drug regulatory authorities play an important role in observing pharmacovigilance at the national or regional level. For example in the US, the Food and Drug Administration (FDA) is the agency responsible in ensuring the safety and effectiveness of human and veterinary drugs, vaccines, biological products and

medical devices intended for human uses apart from food products (FDA, 2018). The regulation set up by FDA extends to all 50 states in the US and other US territories and possessions including Columba, Puerto Rico, Guam, Virgin Islands, and American Samoa. In Europe, the European Medicines Agency (EMA) coordinates pharmacovigilance activities in 28 member states of the European Union (EU) as well as European Economic Area (EEA) (EMA, 2017). The main responsibilities of EMA are to facilitate development and access to medicines, evaluate an application for marketing authorisation, monitor the safety of medicines, and provide information to healthcare professionals and the public (EMA, 2017).

For the remaining non-EU European countries, pharmacovigilance is regulated by specific governmental agencies. For example, Swissmedic is the agency responsible for authorisation and oversight of medicinal products in Switzerland (Swissmedic, 2017). Likewise in Asia and the rest of the world, regulation and authorization of pharmaceutical products are managed by individual regulatory agencies specific to the country. In Japan, the regulatory framework for pharmaceutical products and medical devices is governed by the Pharmaceuticals and Medical Devices Agency (PMDA) which is supported by the Japan Ministry of Health, Labour and Welfare (MHLW) (Okada et al., 2015). These national centres vary in term of activities, source and funding with most are partly funded by ministries of health.

1.4 The importance of pharmacovigilance

Pharmacovigilance and all drug safety issues are relevant for all whose life is affected in any way by medical interventions. The wide range of stakeholders involved comprised policy makers, healthcare practitioners, pharmaceutical industries and scientists, health epidemiologist, health economist, health administrators, consumer groups, and patients among others (WHO, 2002). The main focus of pharmacovigilance concerned with only two outcomes and that is safety and efficacy (Siramshetty et al., 2016). Therefore, pharmacovigilance is important in ensuring patients' safety throughout the entire drug development cycle as well as when the drug is readily available in the market. Additionally, pharmacovigilance activities allow drug safety officials or related authorities to recommend that a drug development process be suspended or an approved drug

is pulled from the market whenever a concern arises. In a nutshell, pharmacovigilance is important in improving drug safety and the prevention of adverse events related to adverse drug reactions (ADR).

1.4.1 Definitions and terminologies associated with ADR

1.4.1.1 Side effect

According to the WHO International Drug Monitoring Programme, the side effect is defined as "any unintended effect of a pharmaceutical product occurring at doses normally used in man, which is related to the pharmacological properties of the drug" (Edwards and Biriell, 1994). This effect can be therapeutic or adverse. Occasionally, certain drugs or procedures are prescribed specifically for their side effect. In this situation, the effect is no longer known as a side effect but the intended effect. For instance, sildenafil which was originally intended for the treatment of hypertension and angina was subsequently found to be more effective in inducing an erection in men (Ghofrani et al., 2006). Following this discovery, sildenafil is currently used for the treatment of erectile dysfunction.

1.4.1.2 Adverse event

The WHO had defined an adverse event as "any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment" (EMA, 1995). Meanwhile, Aronson and Ferner (2005) proposed the definition of an adverse event as "any abnormal sign, symptom, laboratory test, a syndromic combination of such abnormalities, untoward or unplanned occurrence (e.g. an accident or unplanned pregnancy), or any unexpected deterioration in a concurrent illness." In the context of drug safety, an adverse event can be any unfavourable sign, symptom, or disease that patient experienced temporarily while taking a drug which may or may not be related to the treatment. All adverse drug effects are an adverse event, but not all adverse events are drug-induced. For example, hospital admission due to pneumonia whilst a patient is on drug therapy is identified as an adverse event but the event may or may not be caused by the drug intake.

1.4.1.3 Adverse drug reactions (ADRs)

According to WHO (1972), a drug is defined as any substance or product that is used or intended to be used to modify or explore physiological systems or pathological states for the benefit of the recipients. From a medical perspective, the term “drug” and “medicine” are often interchangeably used and they have a synonymous meaning. In clinical settings, drugs are usually prescribed either to help diagnose, treat, cure, or prevent disease or any abnormal conditions; to alleviate pain or suffering; or to control any physiological or pathological condition. Prescribers and patients expect the approved drug to be “safe and effective” in term of intended drug reactions; therefore, any unwanted, unintended, and toxic effects of drugs are termed “adverse drug reactions.”

An adverse drug reaction (ADR) is defined as “a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modifications of physiological function” (WHO, 1972). The WHO’s definition, however, was vague as it does not suggest the scale of reactions where inclusion of minor or insignificant reaction would defeat the surveillance system as they currently operate. Hence to overcome this ambiguity, a more recent definition was proposed by Edwards and Aronson (2000) : “An appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product.”

The terms “adverse reaction” and “adverse effect” are commonly used interchangeably. The differences between these two terms are distinguished by considering the emergence of ADR. An ADR arises from an interaction between an extrinsic component (e.g. a drug or metabolite, a contaminant) and an intrinsic factor (e.g. tissue protein such as a receptor, ion channel, or enzyme) which are distributed at the same site leading to an adverse outcome and subsequently adverse reaction (Aronson, 2013). An adverse effect is usually seen from the point of view of the drug. While ADRs are usually manifested as clinical signs or symptoms, adverse effects are usually detected by laboratory tests or clinical investigations such as gastrointestinal endoscopy or abdominal ultrasound

(Aronson, 2013). For example, prolonged treatment with glucocorticoid may lead to bone demineralisation also known as osteoporosis which is the adverse effect of therapy. The bone fracture caused by osteoporosis in patients taking glucocorticoid therapy is the adverse drug reaction.

However, abnormal laboratory tests unaccompanied by signs or symptoms are not ADR or adverse effect. This is known as markers of adverse effects.

1.4.1.4 Unexpected adverse drug reactions

According to the standard definitions recommended by ICH (1994), unexpected ADR is defined as "an adverse reaction, the nature or severity of which is not consistent with the applicable product information."

1.4.1.5 Serious adverse event or adverse drug reaction

It is important to clarify that the term 'serious' is not synonymous to 'severe.' Severity is us usually used to describe the intensity of a specific event such as mild, moderate, or severe (Aronson and Ferner, 2005). However, the event itself may not be relative to medical significant such as a severe headache or a severe cough. A serious event or reaction is usually associated with an occurrence which is life-threatening or where normal functioning of a patient is affected. Therefore, ICH (1994) had defined serious adverse event or ADR as" A serious adverse event (experience) or reaction is any untoward medical occurrence that at any dose:[1] results in death, or [2] is life threatening, or [3] requires inpatient hospitalisation or prolongation of existing hospitalisation, or [4] results in persistent or significant disability/incapacity, or [5] is a congenital anomaly/birth defect. As well as adding cancer to point [5], Aronson and Ferner (2005) had also put forward two additional serious adverse events or ADR: [6] requires medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure, or [7] is any medical event that would be regarded as serious if it had not responded to acute treatment.

1.4.2 Drugs withdrew after ADRs observed in patients with a long-term medical condition

In patients with chronic conditions such as diabetes and hypertension, treatments are generally life-long. Therefore, it is important to monitor the efficacy and safety of drug prescribed. Certain latent adverse reactions that were not detected during drug development and licensing could arise after decades of exposure such as cancer. Various events such as reported severe side effects or deaths, lack of efficacy, and regulatory or manufacturer' business issues could be the reason a drug is withdrawn from the market post-approval (Fung et al., 2001, Siramshetty et al., 2016). Drugs withdrawn due to ADR can be triggered by various sources of evidence including anecdotal reports, case reports, clinical trials, observational studies, systematic reviews, or animal studies (Lortie, 1986, Onakpoya et al., 2016). A systematic review of 462 medicinal products withdrawn showed that hepatotoxicity (18%) was the commonly reported ADR resulting in withdrawal and this was followed by immune-related reactions (17%), neurotoxicity (16%), cardiotoxicity (14%), carcinogenicity (13%), haematological toxicity (11%), and drug abuse and dependence (11%) (Onakpoya et al., 2016). Additionally, deaths contributed to 25% of reasons for drugs withdrawal. This review also demonstrated that drug withdrawals varied geographically with 43 (9.3%) products were withdrawn worldwide whereas the remaining 419 (90.7%) products were withdrawn in only one or two or more countries. The following sections describe the example of drugs used for chronic diseases which have been withdrawn from the market.

1.4.2.1 Antidepressants

Monoamine oxidase inhibitors (MAOIs) were the first class of antidepressant to be developed. It acts by elevating the level of norepinephrine, serotonin, and dopamine by inhibiting an enzyme known as monoamine oxidase. Phenoxypropazine and mebanazine belong to the MAOI class that was introduced to the market in the early 1960s. However, following reports of hepatotoxicity and drug interactions, both drugs were withdrawn from the UK market in 1966 and 1975 respectively (Onakpoya et al., 2016). Around the same period, scientists had hypothesized that serotonin deficiency may be the aetiological factors for depression (Cowen and Browning, 2015) hence the recommendation to use L-

tryptophan as an antidepressant and a natural hypnotic (Boman, 1988). This amino acid is a metabolic precursor to serotonin and was introduced into the market in 1963 (Onakpoya et al., 2016). However, L-tryptophan was discontinued worldwide after more than 20 years in the market following report of deaths associated with eosinophilia-myalgia syndrome (Onakpoya et al., 2016). Zimelidine was another antidepressant that was withdrawn worldwide. It was one of the first selective serotonin reuptake inhibitor (SSRI) to be marketed for use in depression in 1982 (Fagius et al., 1985, Onakpoya et al., 2016). Review of 13 case reports by the Swedish ADR committee had found that those receiving zimeldine had a 2.5 fold increased risk of developing Guillain-Barre syndrome (Fagius et al., 1985), a rare but serious autoimmune condition that leads to damage of the peripheral nervous system. These events had prompted the manufacturer to withdraw this drug from the market in 1983 (Onakpoya et al., 2016).

1.4.2.2 Oral hypoglycaemic agents (OHA)

Oral hypoglycaemic agents (OHA) or also known as anti-diabetic drugs also are used to treat type 2 diabetes mellitus (T2DM) by lowering blood glucose. The use of several OHA agents has been discontinued in a certain region or country due to ADR in the past decades. Biguanides are a class of OHA derived from a chemical compound known as guanidine which has hypoglycaemic properties but too toxic for clinical use (Quianzon and Cheikh, 2012). In the 1950s, three biguanides- phenformin, buformin, and metformin- were introduced for the treatment of T2DM (Quianzon and Cheikh, 2012). Despite their potency in lowering blood glucose (Geldermans et al., 1975), phenformin and buformin were discontinued in many countries due to severe metabolic acidosis and hepatotoxicity (Fung et al., 2001, Onakpoya et al., 2016).

Thiazolidinedione is another class of OHA which acts by activating the peroxisome proliferator-activated receptors gamma (PPARγ), a nuclear receptor. Troglitazone was the first thiazolidinedione to be approved for clinical use in 1997 (Onakpoya et al., 2016). However, its use has been discontinued in the same year it was introduced in several countries including the UK, US, Canada, and Switzerland due to reports of hepatotoxicity (Fung et al., 2001, Onakpoya et al., 2016). Another member of thiazolidinedione, rosiglitazone which was introduced in 1999, was withdrawn from the European market in 2011 after reports of increased risk of

heart attacks as demonstrated in the Rosiglitazone evaluated for cardiovascular (CV) outcomes in oral agent combination therapy for type 2 diabetes (RECORD) study (Nissen and Wolski, 2007). In the US, rosiglitazone prescription was restricted to those who have shown good control and those with poor blood glucose control despite treatment with other OHA after consultation with their healthcare provider (FDA, 2011b). However, these restrictions were removed in 2013 and prescription of rosiglitazone was considered safe for the treatment of T2DM in the US after re-assessment of safety data (FDA, 2015). Meanwhile, recent longitudinal studies have demonstrated a small risk of bladder cancer associated with the use of another member of this class known as pioglitazone (Lewis et al., 2011, Piccinni et al., 2011). Correspondingly, the EMA had recommended contraindications and caution to the prescription of this agent in clinical settings as well as initiating a region-wide review to investigate this safety signal (EMA, 2011).

1.4.2.3 Antihypertensive drugs

Antihypertensive agents are one of the commonest cardiovascular (CV) drugs prescribed for long term therapy. Over the years, certain antihypertensive drugs have been withdrawn from the market for various reasons. Nitrates have been around for a very long time and it has been assumed to be the first antihypertensive drug discovered in the early 20th century (Wallace and Ringer, 1909, Fye, 1986). Potassium nitrate or also known as saltpetre had demonstrated blood pressure (BP) lowering property in both human and animals (Reichert, 1880) by promoting nitric oxide synthesis hence causing a direct vasodilatory effect on the arteries. It was introduced into the market for the treatment of hypertension and ascites in 1901 (Onakpoya et al., 2016). However, its use has been discontinued in France, Egypt, and Venezuela effective in the 1980s due to potential carcinogenic risk observed in post-marketing surveillance (Onakpoya et al., 2016). Since the introduction of modern antihypertensive therapy, this particular agent has been rarely used.

Beta-adrenergic blockade has been considered as a possible treatment for hypertension in the early 1960s (Black and Stephenson, 1962). Practolol, a selective beta-blocker (BB), was one of the earliest of its class to be developed and introduced into the market in 1970 for treatment of hypertension, angina, and cardiac dysrhythmias (Onakpoya et al., 2016). Following reports of a serious

delayed idiosyncratic oculo-mucocutanous syndrome associated with the use of this drug (Anonymous, 1975a), practolol was withdrawn from multiple markets including the UK in 1975 (Onakpoya et al., 2016). Meanwhile, the marketing of a non-selective BB known as dilevalol introduced in 1986, was discontinued worldwide due to hepatotoxicity reports (Fung et al., 2001, Onakpoya et al., 2016). Nevertheless, there was no evidence to suggest that the other BB subclass is associated with risk of serious ADR. Alternatively, studies have linked BB therapy to increased risk of developing incident diabetes (Dahlöf et al., 2005, Elliott and Meyer, 2007).

Calcium channel blockers (CCB) have been showed to be more effective than BB in lowering the risk of CV mortality (Chen et al., 2010). Mibefradil, a non-selective calcium antagonist, was introduced in 1997 for the treatment of hypertension and chronic angina pectoris (Onakpoya et al., 2016). However, less than a year after its approval, this agent was pulled off from the market in 38 countries by its manufacturer (Roche) (Bradbury, 1998). Combination therapy with mibefradil and certain lipid-lowering agents such as statins or other drugs have been shown to be associated with rhabdomyolysis as well as suppression of the sinoatrial node that could result in fatality (Anonymous, 1998).

Above are just some examples of drugs intended for long-term therapy which use has been discontinued worldwide or certain countries. In summary, continuous post-marketing surveillance of drug safety is essential in the identification of adverse effects. Furthermore, the role of the pharmaceutical industry, academics, and regulatory authorities are undeniably important in the efforts of drug safety monitoring.

1.5 Cardiovascular disease and hypertension

1.5.1 Epidemiology of cardiovascular disease

Cardiovascular disease (CVD) is a term broadly used to describe disorders affecting the heart and blood vessels. This group of disorders includes coronary heart disease (CHD), cerebrovascular disease, peripheral arterial disease, rheumatic heart disease, deep vein thrombosis, and pulmonary embolism. According to the latest statistics from WHO, approximately 17.7 million people died from CVDs in

2015, representing 31.1% of deaths worldwide and an increment of 3.6% since the year 2000 (WHO, 2018b). Of these, CHD and stroke contributed the highest percentage of CVD mortality (15.5% and 11.1% respectively) consequently accounted for the top two cause of death worldwide. The most recent statistics from 2015 also showed CVD contributed 407.6 million disability-adjusted-life-years (DALY) in 7.3 billion people from 185 countries, representing 15% of total DALYs and also the highest for non-communicable disease (WHO, 2018b). DALY is a time-based measure combining time live with a disability and time lost due to premature mortality (Anand S. and Hanson K., 1997). More importantly, CHD and stroke were the two leading causes of DALYs worldwide with 160 countries had one of these conditions as the leading cause of DALYs in that particular year (GBD 2015 DALYs and HALE Collaborators, 2016).

In the United Kingdom (UK), CVD is the caused of more than 26% of all deaths and premature deaths. This condition is common in the north of England, central Scotland, and the south of Wales (British Heart Foundation, 2017). The cost of treating CVD in the UK is estimated to be approximately £9 billion annually (British Heart Foundation, 2017).

1.5.2 Risk factors for CVD

There are many risk factor associated with CVD and these attributes can be categorised into modifiable and non-modifiable risk factors. Modifiable risk factors include physical activity, cigarette smoking, dietary habit, socioeconomic status, hypertension, and obesity. Non-modifiable risk factors comprise age, gender, ethnicity, family history, and diabetes. Having one of these risk factors does not necessarily impose one to CVD, however, the presence of more risk factor will increase the likelihood. Apart from these classic clinical factors, recent research has also considered novel risk markers for developing CVD such as a lipid-related marker, c-reactive protein, micro-RNA (miRNA), N-terminal–proBNP, coronary artery calcium score and plaque burden (Thomas and Lip, 2017).

1.6 Hypertension

Blood pressure (BP) is the force that is exerted by the blood upon the wall of blood vessels, especially the arteries. The overall BP is maintained by cardiac output

(CO) and peripheral vascular resistance. Cardiac output (CO) - the amount of blood pumped by the heart through the circulatory system per minute (ml/min) - is determined by the heart rate (HR) and stroke volume (SV). HR is the number of heart beats per minute whereas SV is the amount of blood pumped from the ventricle per beat. Peripheral vascular resistance – the resistance to the flow of blood in peripheral arterial vessels – is conditional on the functional and anatomical changes in the arteries and arterioles such as vessel diameter, the tone of vascular musculature and blood viscosity. Arterial pressure control is greatly determined by serum sodium and renal function which are important in fluid balance mechanism (Guyton et al., 1984). If any changes should occur to either salt intake or kidney function, the exact pressure level to which the arterial pressure will be controlled would be altered accordingly. Autoregulatory responses for local blood flow will instinctively adjust the blood vessel diameter to re-establish optimal tissue perfusion. Failure of autoregulation results in increased peripheral vascular resistance and consequently elevated BP. High BP or also known as hypertension is a long-term medical condition in which the BP in the arteries is persistently elevated.

1.6.1 Causes of hypertension

A small number of patients have an underlying renal, adrenal or monogenic cause of elevated BP. However, the aetiology for high BP in the majority of patients remains unclear and no single identifiable cause is found and their condition is diagnosed as essential hypertension. There is growing evidence that the causes of hypertension are multifactorial meaning there are several factors when the effects are combined leads to the development of hypertension (Neutel and Smith, 1999). Complex interaction among multiple environmental factors and multiple gene factors at various combinations play a crucial role in determining the risk of developing hypertension. From the genetic aspect, development of hypertension is attributable by many genes or gene combinations (Padmanabhan et al., 2015). Currently, over 60 loci associated with BP or hypertension were discovered from genome-wide association studies (GWAS) and candidate gene studies (Zheng et al., 2015). Meanwhile, various environmental factors involving components of lifestyle such as poor diet, physical inactivity, alcohol consumption, and psychological stress also affect BP in the majority of people (Whelton et al., 2017).

1.6.2 Measurement and diagnosis of hypertension

In the clinic, BP is classically measured non-invasively using a sphygmomanometer with the patients' arm outstretched and supported. Measurement of BP at the upper arm is preferred and cuff and bladder dimensions should be adapted to the individual's arm circumference. BP is conventionally measured in millimetre mercury (mmHg) and every BP reading consist of two numbers: systolic pressure (SBP), which represents the maximum pressure during contraction of the ventricles; diastolic pressure (DBP) is the minimum pressure recorded just prior to the next contraction. **Table 1-1** summarizes the definition of hypertension according to methods of measurement in established scientific guidelines such as the National Institute for Health and Care Excellence (NICE, 2011), the European Society of Hypertension/ European Society of Cardiology (ESH/ESC) (Mancia et al., 2013b), and the Eighth Joint National Committee (JNC 8) guideline (James et al., 2014). Conventionally, hypertension is diagnosed when clinic BP is SBP 140 mmHg or higher and/or DBP 90 mmHg or higher according to many clinical guidelines. However, the recently published American College of Cardiology/ American Heart Association (ACC/AHA) guideline (Whelton et al., 2017) changed the definition of hypertension to SBP 130 mmHg or higher and/or DBP 80 mmHg or higher instead of SBP 140 and/or DBP 90 mmHg. This new definition would increase the proportion of people labelled as hypertensive especially in the US. In addition to clinic BP, most guidelines recommend monitoring of ambulatory BP (ABPM) or home BP monitoring (HBPM) as adjunct measurement and therefore should be used complementarily and not competitively in diagnosing hypertension. ABPM have a stronger predictive value for all-cause and CV mortality compared to office BP in a model that considered CV risk factors including age and sex (Banegas et al., 2018). Furthermore, routine and formal cardiology assessment should be carried out to detect target organ damage, to identify comorbidities (e.g. diabetes mellitus, dyslipidaemia) and to exclude secondary causes for hypertension (e.g. renal diseases, endocrine diseases, drugs).

Table 1-1: Guidelines for definitions of hypertension based on the measurement techniques.

NICE 2011- United Kingdom *	
Clinic	SBP ≥140 and/or DBP ≥90
ABPM (Daytime)	SBP ≥135 and/or DBP ≥85
HBPM	SBP ≥135 and/or DBP ≥85
ESH/ESC 2013 - Europe	
Clinic/Office	SBP ≥140 and/or DBP ≥90
ABPM	
Daytime	SBP ≥135 and/or DBP ≥85
Nightime	SBP ≥120 and/or DBP ≥70
24 –hour	SBP ≥130 and/or DBP ≥80
HBPM	SBP ≥135 and/or DBP ≥85
JNC 8 2014 -US †	
Clinic/office	SBP ≥140 and/or DBP ≥90
AHA/ACC 2017 – US	
Clinic/Office	SBP ≥130 and/or DBP ≥80
ABPM	SBP ≥130 and/or DBP ≥80
HBPM	SBP ≥130 and/or DBP ≥80
*Last updated November 2016 †Definition of hypertension was not addressed, but thresholds for pharmacologic treatment were defined. The current definition is based on the JNC 7 report.	

1.7 Global burden of hypertension

The current global burden of disease (GBD) estimates for hypertension is available for the year 2015 (WHO, 2018b) and the disease and injury outcomes caused by hypertension are measured as DALYs. Hypertension is an important public health problem and it was estimated that 7.8 million projected death (14% of total deaths) and 143 million DALYs were linked to hypertension (Forouzanfar et al., 2017). Deaths due to CVD attributed by hypertension was estimated at 41%, among which 40.1% were related to ischaemic heart disease (IHD), and 40.4% were related to cerebrovascular diseases (Forouzanfar et al., 2017). Overall, the GBD 2015 reported that high BP is the second and third leading risk factor for diseases in women and men respectively contributing to 7.8% and 9.2% of DALYs (GBD 2015 Risk Factors Collaborators, 2016). DALYs attributable to high BP is largely associated with CVD followed by diabetes mellitus, urogenital, blood, and endocrine disease.

Furthermore, the number of adults with hypertension is projected to rise to a total of 1.56 billion by the year 2025 (Kearney et al., 2005). Compared to economically developed countries, the prevalence of hypertension in the lower income countries is currently in excess of 5% at the rate of approximately 40% (WHO, 2018a) and this is predicted to increase in excess of 60% by 2025 (Kearney et al., 2005).

1.8 Hypertension management

Prospective Studies Collaboration (2002) reported that lowering BP can substantially decrease CV morbidity and mortality as well as all-cause mortality. A reduction of 20 mmHg of usual SBP (or 10 mmHg equivalent to usual DBP) is associated with more than double the difference in the stroke mortality rate and with twofold differences in the death rates from IHD and from other vascular causes in middle age individuals. A review of observational and randomised studies using antihypertensive therapy demonstrated that lowering of DBP by 5 mmHg reduce the risk of IHD by 21% and the risk of stroke by approximately 34% regardless of baseline BP level (Law et al., 2003). Therefore, striving for good BP control is important in all type of population to prevent CV complications. Management of hypertension can be achieved by non-pharmacological as well as pharmacological means.

1.8.1 Non-pharmacological treatment

A non-pharmacological intervention generally indicates lifestyle changes and this approach should be offered prior to initiating antihypertensive agents in a person undergoing assessment or periodical treatment for hypertension. Although appropriate lifestyle changes are the key to hypertension prevention, administration of BP lowering drugs should not be delayed in patients with high CVD risks. A practical and comprehensive lifestyle modification approach that have been shown to be effective in lowering BP in hypertensive patients are: [1] salt restriction, [2] moderation of alcohol consumption, [3] high consumption of vegetables, fruits, low-fat and other types of diet, [4] restriction of coffee and other caffeine-rich products consumption, [5] weight reduction and maintenance, [6] regular physical exercise, and [7] smoking cessation (NICE, 2011, Mancia et al., 2013b). In pre-hypertensive and Stage 1 hypertension patients, multiple lifestyle

modifications have been shown to improved BP control subsequently prevents the risk of chronic diseases (Elmer et al., 2006). Nevertheless, antihypertensive agent initiation is essential in situations where BP target is not achieved with lifestyle changes alone and especially in those with one or more risks of developing CV events.

1.8.2 Pharmacological therapy

There is unequivocal evidence from randomised controlled trials (RCTs) demonstrating the benefit of pharmacological BP reduction on the risk of major CV events and death. There are various classes of antihypertensive agents with new ones are being developed and tested by the pharmaceutical industry. However, agents that have been showed to reduce the risk of clinical events should be used preferably. The drug classes that are mainly prescribed in the primary care or hospital settings are angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), calcium channel blockers (CCB), diuretics, or beta blockers (BB). These drugs act at one or more anatomical sites of BP controls namely resistance arterioles, capacitance venules, the heart and kidney. Meta-analyses of RCTs using these five major antihypertensive classes had been shown to prevent CVD as compared to placebo (Law et al., 2009, Thomopoulos et al., 2015). Consistently, established clinical guidelines such as NICE, ESH/ESC, and JNC recommended ACEI, ARB, CCB, and thiazide diuretics (TZ) for the initial management of hypertension. Most guidelines do not recommend BB as first-line therapy unless indicated. The Losartan Intervention For Endpoint reduction in hypertension (LIFE) study randomised 9193 patients with essential hypertension to either ARB (losartan)-based or BB (atenolol)-based therapy (Dahlöf et al., 2002). The study participants were followed for at least four years to assess for a composite of CV events. Results showed that treatment with BB had a higher frequency of the primary composite endpoints of CV death, stroke, and myocardial infarction (MI) compared to treatment with ARB. Additionally, a recent systematic review and network meta-analysis of RCTs conducted in conjunction of the new ACC/AHA guidelines showed that BB was significantly less effective than TZ diuretics (Reboussin et al., 2017). The NICE guideline has recommended initial therapy with BB only in younger patients who are either intolerance or contraindicated to ACEI or ARB, pregnant, and in those with

evidence of increased sympathetic drive (NICE, 2011). Table 1-2 summarises the initial drug therapy as recommended by the respective guidelines.

Table 1-2: Guidelines recommendation for initial drug therapy

Guidelines	Recommended initial antihypertensive therapy
NICE 2011	ACEI or ARB for people age < 55 years.
	CCB for people age ≥ 55 years and black people of African or Caribbean origin of any age. Offer TZ diuretics if there is evidence of intolerance or heart failure (HF) or high risk of HF.
ESH/ESC 2013	ACEI, ARB, CCB, diuretics, or BB are recommended for initiation of treatment or maintenance
JNC-8 2014	TZ, CCB, ACEI or ARB, alone or in combination for non-black people.
	TZ or CCB, alone or in combination for black people.
ACC/AHA 2017	TZ, CCB, ACEI or ARB are recommended for initiation of treatment

Understanding the benefit of one antihypertensive agent versus another is important in determining the initial treatment for hypertension and in informing clinical decision. However, it is not uncommon for hypertension to co-exist with one or more chronic conditions, especially with increasing age. A retrospective observational study with a random sample of 86,100 patients age 20 years and older retrieved from the United Kingdom General Practice Research Database (GPRD) shown that hypertension commonly occurred with other conditions primarily CHD, CKD, and diabetes mellitus (Brilleman et al., 2013). Therefore, consideration of initial or maintenance of antihypertensive should also make allowance for the presence of comorbidities in the effort to achieve target BP control and at the same time promotes safe and effective pharmacotherapy. Table 1-3 outlines the recommended first-line therapy for hypertensive patients with comorbidities based on established guidelines.

Table 1-3: First line treatment in a patient with hypertension and comorbidities

Conditions	First-line antihypertensive treatment
Chronic kidney disease	ACEI or ARB
Type 1 diabetes	ACEI or ARB
Type 2 diabetes • Non-black • Black	 ACEI or ARB ACEI plus CCB/TZ or TZ
Heart failure	Patients already on ACEI/ARB plus BB should be given TZ
Ischaemic heart disease	BB and/or CCB
Atrial fibrillation	ACEI or ARB plus BB or non-dihydropyridine CCB
Peripheral artery disease	ACEI or CCB

Adapted from American Heart Association (2017), Cohen and Townsend (2017), Kennard and O'Shaughnessy (2016) and Mancia et al. (2013b).

The main objective of antihypertensive therapy is to attain and maintain goal of BP therapy. Data from the US showed that, of those treated for hypertension, only approximately 50% are under control (Go et al., 2014). If control is not achieved, the dose of the initial drug or add a second drug from the drug class recommended for initial therapy (See **Table 1-2**). Current recommendations by guidelines such as NICE and JNC-8 emphasize stepwise dose increase and addition of a second (and third or fourth) drug. For example, the Anglo-Scandinavian Cardiac Outcomes Trial- Blood Pressure Lowering Arm (ASCOT-BPLA) study demonstrated that nine out of ten patients required two or more antihypertensive agents to bring their BP down to less than 140/90 mmHg (Dahlöf et al., 2005).

A certain combination of antihypertensive drugs may exert an additive and protective effect. For example, the Systolic Evaluation of Lotrel Efficacy and Comparative Therapies (SELECT) study showed that CCB-amlodipine and ACEI-benazepril combination therapy was significantly more effective in lowering SBP and pulse pressure than either monotherapy ($p<0.001$) after eight weeks of treatment in a group of elderly patients with systolic hypertension (Neutel et al., 2005). Likewise, the Nifedipine and Candesartan Combination (NICE-Combi) Study demonstrated that CCB-nifedipine and ARB-candesartan combination therapy was superior to uptitrated ARB monotherapy in BP control ($p<0.0001$) and renal protection ($p<0.05$) after eight weeks of treatment in hypertensive patients (Hasebe et al., 2005). In addition, combination therapy has been showed to be

beneficial in lowering the risk of complications related to other conditions such as diabetes. The Action in Diabetes and Vascular disease: preterax and diamicron-MR Controlled Evaluation (ADVANCE) trial reported that ACEI-perindopril and TZ diuretic-indapamide combination had significantly reduced risks of major vascular complications including death compared to placebo in T2DM patients followed for an average of 4.3 years (Patel, 2007). Surrogate renal endpoint such as microalbuminuria which is associated with CV events was also greatly reduced with ACEI/diuretic combination therapy versus placebo. This evidence shows that combination therapy is more effective in lowering BP and the prevention of related complications.

However, a combination of two classes of renin-angiotensin system (RAS) blockers including ACEI and ARB is not recommended. In theory, a combination of ACEI and ARB should enhance RAS blockade. A dual blockade of the RAS pathway has been shown to be effective in lowering BP compared to either as monotherapy (Azizi et al., 2000, Mogensen et al., 2000, Stergiou et al., 2000). Despite the efficacy in BP reduction, there is evidence that the combination of ARB and ACEI is associated with increased risk of adverse events (The ONTARGET Investigators, 2008). A systematic review of 33 RCTs comparing dual RAS blockers with monotherapy with a mean duration of 52 weeks reported that dual therapy was associated with a 55% increased risk of hyperkalaemia ($p< 0.001$), a 66% increase in the risk of hypotension ($p< 0.001$), a 41% increase in the risk of renal failure ($p=0.01$), and a 72% increase in the risk of withdrawal from study due to adverse events ($p<0.001$) (Makani et al., 2013). All-cause mortality was significantly higher in the cohort without HF ($p=0.04$) whereas renal failure was significantly higher in the cohort with HF ($P<0.001$). Altogether, the risks of adverse effects outweigh the benefits of dual therapy hence not recommended in established clinical guidelines (NICE, 2011, James et al., 2014). The Systolic Blood Pressure Intervention Trial (SPRINT) reported that in patients >50 years and at high risk of CVD, but without prevalent diabetes or history of stroke, an intensive BP target of ≤120 mmHg was associated with lower rates of CV events and death compared to the standard target of 140 mmHg (The SPRINT Research Group, 2015)

1.9 Antihypertensive therapy (AHT) and risks of cancer: an overview

1.9.1 Historical perspective of AHT and risks of cancer

The association between antihypertensive therapy (AHT) and risks of malignancy has been made over more than half a century ago, prior to the advent of modern day hypertension treatment. Reserpine (isolated from *Rauwolfia serpentina*), used as a sedative and treatment for insanity for centuries in India (Moser, 2006), was first used in the US in late 1940. A clinical trial by Vakil (1949) showed that reserpine is very safe and effective in treating patients with benign hypertension. Despite its safety, reserpine was the first antihypertensive agent to be associated with increased cancer risk. The Boston Collaborative Drug Surveillance Programme (1974) has found that women exposed to reserpine have three times increased the risk of developing breast cancer. Following this discovery, two retrospective case-control studies also reported comparable findings around the same time. In Finland, 461 matched-pairs were assessed for risk of breast cancer in those exposed to reserpine and results showed a significant positive association between the two variables (Heinonen et al., 1974). Meanwhile, Armstrong et al. (1974) assessed 708 breast cancer cases and 1430 controls diagnosed with another type of cancer and reported a positive association between reserpine and breast cancer. Subsequent studies in the following years, however, found such an association was unlikely (Laska et al., 1975, Mack et al., 1975, O'Fallon et al., 1975). These revelations have since ignited disputes and numerous studies relating CV drugs as a precursor to malignant neoplasms.

Certain CV drugs have been implicated to either increase or decrease the risk of a certain type of malignancy. For example, aspirin was suggested to be protective of colorectal cancer. The Colorectal Adenoma/carcinoma Prevention Programme (CAPP2) trial was a large-scale trial assessing the antineoplastic effect of aspirin versus placebo in patients with major form of hereditary colorectal cancer and findings suggested lower rate of colorectal cancer incidence in those treated with long term high dose aspirin with (HR 0·4;P = 0.02) (Burn et al., 2011). In addition, studies showed that digoxin increases the risk of breast cancer. A large cohort study of postmenopausal women reported that long term use of digoxin was associated with 45% increased breast cancer risk among users versus non-user and

this relationship persistent even after adjustment for established breast cancer risk factors (Ahern et al., 2014). **Table 1-4** summarises the type of CV therapy commonly associated with a certain type of cancer. Many of these researches were designed using cohorts and population-based studies whereas associations hypothesized from a limited number of clinical trials were derived from the sub-study analysis. This subject remains controversial as no definitive conclusion can be made to this date.

Table 1-4: Cardiovascular drugs and risks of cancer

Cardiovascular drug	Cancer site	References
Increased risk		
Reserpine	Breast	(Armstrong et al., 1974, Boston Collaborative Drug Surveillance Programme, 1974, Heinonen et al., 1974, O'Fallon et al., 1975)
Digoxin	Breast	(Ahern et al., 2008, Biggar et al., 2011, Ahern et al., 2014)
Antihypertensive agents:		
ARB	Lung	(Hiatt et al., 1994, Pahor et al., 1996, Fitzpatrick et al., 1997, Sipahi et al., 2010, Bangalore et al., 2011, Li et al., 2014b, Ni et al., 2017)
CCB	Breast	
TZ	Kidney	
Decreased risk		
Aspirin	GI tract	(Rothwell et al., 2010, Burn et al., 2011)
Statin	Any	(Friis et al., 2005, Leung et al., 2013, Shi et al., 2014)

1.9.2 Antihypertensive drug class and risks of cancer

Over the last few decades, almost every antihypertensive drug class has been implicated with increased cancer risk. The following section described the relationship between major antihypertensive drug classes and risk for cancer. Details on the underlying mechanism of cancer are described in individual drug class chapters.

1.9.3 RAS inhibitors and cancer risk

There is evidence suggesting that several components in the renin-angiotensin-aldosterone system (RAS) pathway such as angiotensin II may be involved with carcinogenesis (Ager et al., 2008). Therefore, it was hypothesized that RAS inhibitors such as ACEI and ARB could reduce cancer risk. More about the RAS pathway and its component is described in 4 Section 4.1.1(page 148).

1.9.3.1 What is the evidence?

Earlier reviews highlighted a slightly higher incidence of malignancy in patients receiving ACEI compared to placebo in two RCTs (Felmeden and Lip, 2001, Grossman et al., 2001). The Study of Left Ventricular Dysfunction (SOLVD) trial which followed patients with congestive HF for 42.4 months reported an OR of 1.59, with 95% CI ranged between 0.90 to 2.82 (The SOLVD Investigators, 1992). In another RCT of patients with renal insufficiency followed for three years (Maschio et al., 1996), a slightly higher risk for cancer in patients receiving benazepril was observed than did those who received placebo (OR 1.52, 95%CI 0.45-5.42). In the more recent and larger-scale Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) enrolling 33,357 hypertensive patients with a CVD risk factor for eight years, the odds for cancer was 1.02 with 95% CI 0.93 to1.12 for ACEI when compared to the diuretic arm (The ALLHAT Collaborative Research Group, 2002).

Following these reports, subsequent trials using ARB have pre-specified cancer as one of their study outcomes. For example, the Losartan Intervention for Endpoint Reduction (LIFE) trial evaluated ARB-based versus BB-based therapy in 9,193 hypertensive patients found that the OR for cancer was 1.09 (95% CI 0.93-1.27) for those in the ARB treatment group (Dahlöf et al., 2002). In the Telmisartan Randomised Assessment Study in ACE Intolerants Subjects with Cardiovascular Disease (TRANSCEND) study, 5,926 patients were randomised to either ARB or placebo and were followed for approximately five years (The TRANSCEND Investigators, 2008). The risk for cancer in ARB users versus placebo showed a trend towards a positive relationship with OR 1.23 (95% CI 0.99-1.52).

Additionally, observational studies investigating the relationship between ACEI and risks of cancer have reported inconsistent outcomes. In a cohort study of 17,897 patients with high risk of CVD, Friis et al. (2001) reported a relative risk of 1.07 (95% CI 1.0-1.15) for overall cancer with use of ACEI. A similar relationship has also been reported by a larger study observing 149,417 cases and 597,668 controls over a five year period (Hallas et al., 2012). This study reported an OR of 1.17(95% CI 1.14-1.20) and 1.12(95% CI 1.06-1.18) for overall cancer risk among ACEI and ARB users respectively. In contrast, many epidemiological studies have found that ACEI exerts a protective effect against cancer. For example, a

retrospective cohort study of over five thousand hypertension patients based in Glasgow followed for over 15 years have found that ACEI users have a significantly lower risk for cancer incidence and fatal cancers compared to other antihypertensive users (Lever et al., 1998). In another study, Kedika et al. (2011) followed patients with adenomatous polyps (AP), a risk factor for colorectal cancer, for five years. The author reported that the risk for advance AP is 41% less likely in ACEI user compared to non-user, hence insinuating lower risk of colorectal cancer. Nevertheless, studies have also shown no evidence of overall or a specific type of malignancy with ACEI use. ACEI showed no significant effect on the risk of developing or protecting against breast cancer (Fryzek et al., 2006) and prostate cancer (Perron et al., 2004). Furthermore, two meta-analyses of RCTs, Bangalore et al. (2011) and Sipahi et al. (2011) demonstrated no significant association between ACEI and risks of cancer.

Meanwhile, a meta-analysis by Sipahi et al. (2010) suggested a small but significant increase in cancer risk associated with ARB. Pooling of results from nine RCTs enrolling 94,570 using ARB as one its treatment arm gave an RR of 1.08 (95% CI 1.01-1.15) for overall cancer risk among ARB user, with an increased occurrence of new lung cancer detected (RR 1·25, 1·05–1·49). Finding from this study ignited debate on the safety of ARB which led to a series of observational studies exploring the risk of cancer with ARB use. A preceding network meta-analysis had reported a weak association between ARB and cancer risk with multiple comparisons showed an OR of 1.12(95% CI 0.87-1.47) (Coleman et al., 2008). In a subsequently larger and more comprehensive systematic review and network meta-analysis of 70 RCTs enrolling 324,168 participants, Bangalore et al. (2011) found no significant relationship between ARB and cancer risk. Instead, the author reported an increased risk of cancer with ARB and ACEI combination. Around the same time, a meta-analysis of 15 RCTs enrolling 138,769 conducted by the ARB Trialist Collaboration found no significant association between ARB or ACEI/ARB combination and risk of overall or site-specific cancer (Teo, 2011).

Contrariwise, epidemiological studies have reported conflicting results. Several cohorts study reported no significant impact on cancer risk observed with ARB use. In a large nationwide Danish cohort study of new antihypertensive drug users followed for 2.5 years (Pasternak et al., 2011), use of ARB was not associated with risk of cancer overall with RR 0.99 (95% CI 0.95-1.03). A comparable result for

overall cancer (OR 1.03, 95% CI 0.99-1.06) was reported by a similarly designed study using the UK cohort followed for five years among new ARB users (Bhaskaran et al., 2012). Upon detail analysis, the increased risk was only observed for breast and prostate cancer. Additionally, the use of ARB is associated with increased breast cancer risk especially in pre-menopausal women (Gómez-Acebo et al., 2016). However, the number of cases and controls exposed to ARB were very small which potentially resulted in an unstable estimate.

A recent meta-analysis by Shen et al. (2016) evaluated 14 RCTs and 17 observational studies enrolling a total of nearly 4 million participants. Pooling of results from RCTs showed the use of ARB or ACEI did not have any impact on cancer risk whereas combined estimated from observational studies demonstrated a decreased risk (OR 0.82,95% CI 0.73-0.93). In another meta-analysis of observational studies, the result showed no evidence of an association between RAS inhibitors and breast cancer risk (Ni et al., 2017).

Overall, the risk of cancer related to RAS inhibitors is inconclusive. The evidence for an increased cancer risk or protective effect with ACEI use is insufficient with many of the studies refuting any link. An evaluation conducted by the US FDA (2011a) concluded that use of ARB is not associated with the potential risk of cancer. Nevertheless, further studies and data collection is needed to determine the active substances of the RAS blockers and the types of cancer that may be triggered, as well as to establish the exact relationship.

1.9.4 CCB and cancer risk

Calcium antagonist, particularly dihydropyridines (DHP), is effective in reducing severe CV events in the hypertensive elderly (Gong et al., 1996). Clinical studies have also demonstrated that CCB is as effective as other antihypertensive drug class in preventing CV outcomes in high risk patients (Black et al., 2003, Muramatsu et al., 2012).

1.9.4.1 What is the evidence?

In the 1990s, two studies reported a positive association between CCB and cancer. A cohort of 750 elderly hypertensive age 71 years or older were followed for five years (Pahor et al., 1996). These patients were cancer free at baseline and were

using ACEI, BB, or CCB. In comparison to BB and ACEI, results showed that CCB significantly increased overall cancer risk with excess risk among verapamil (RR 2.46, 95% CI 1.17-5.17) and nifedipine users (RR 2.34, 95% CI 1.09-5.03). In another study, postmenopausal women enrolled in the Cardiovascular Health Study (CHS) who were followed for five years have shown a significantly increased risk for breast cancer among CCB user versus non-user (Fitzpatrick et al., 1997). Similar observations have been reported by more recent studies. In a 12 year follow-up, Saltzman et al. (2013) observed a 1.6 fold increased risk (95% CI 1.0-2.5) for breast cancer in CCB user among 3,201 postmenopausal women. After stratification by formulation preparations, the increased risk was confined only to immediate release CCB (HR 2.4, 95% CI 1.3-4.5) whilst no significant association was observed with sustained release CCB. Meanwhile, Li et al. (2013) evaluated the risk of invasive breast cancer in 1,907 cases and 856 controls from a cohort of middle-age and elderly women. Results showed that long-term use of CCB for 10 years or more was associated with increased risk for both invasive ductal and lobular breast carcinoma. These relationships, however, did not vary substantially between DHP and non-DHP CCBs. Furthermore, the recent Spanish Multi Case-control (MCC) Study reported an increase in breast cancer risk associated with CCB use especially in women who are menopaused and overweight (Gómez-Acebo et al., 2016). Similar associations were also observed in those taking CCBs for five years or more and in several subtypes of breast cancer.

Contrariwise, many studies have found no significant association between CCB and cancer risk. In one of the earlier study, almost 18 thousand CCB users from the Danish prescription and health insurance database were followed for a duration of three years (Olsen et al., 1997). This study found no evidence of CCB affecting cancer risk overall or specific type of cancers. In a more recent and much larger study, Grimaldi-Bensouda et al. (2016) reported an adjusted HR of 0.88 (0.86 to 0.89) and 1.01 (0.98 to 1.04) for all cancer comparing CCB cohorts to non-CCB and another antihypertensive class cohort respectively. Additionally, several meta-analyses also reported consistent results. Grossman et al. (2002) evaluated the risk of cancer in meta-analyses of RCTs and observational studies. Pooling of eight RCTs showed an OR of 0.91 (0.80-1.04) indicating no significant relationship between CCB and cancer risk. Likewise, a meta-analysis of seven longitudinal studies showed a non-significant association. In a subsequent network meta-

analysis of RCTs by Coleman et al. (2008), 15 of the 27 included trials used CCB as one its treatment group. Results showed no evidence of excess cancer risk related to CCB use in both multiple comparison and pair-wise analysis. Compared to the previous studies, Bangalore et al. (2011) reported an increased cancer risk associated with CCB use (P = 0.02) in a meta-analysis of 22 RCTs with modest heterogeneity. Stratification by subclasses showed an OR of 1.06 (95% CI 1.01-1.12) and OR 1.02 (95% CI 0.90-1.15) for DHP- and non-DHP CCBs respectively suggesting DHP CCB may have an impact on cancer risk.

Two meta-analyses of observational studies demonstrated comparable results regarding CCB and breast cancer risk. A meta-analysis of 17 studies (nine cohorts, eight case-control) enrolling 149,607 showed an OR of 1.02 (95% CI 0.94-1.11) for overall cancer risk comparing CCB user and non-user (Li et al., 2014b). Long term use of CCB of ten years or longer has been showed to increase cancer risk by 1.7 fold but this estimation was derived from only two studies thus may not be accurate. No remarkable difference was observed between DHP- and non-DHP CCB with regard to breast cancer risk in comparison to the overall analysis. A more recent meta-analysis of 13 observational studies (seven cohorts, six case-control) showed an RR 1.07 (95% CI 0.99-1.16) (Ni et al., 2017). In their subgroup analysis, a meta-analysis of case-control studies showed a positive risk of breast cancer with RR 1.21(95% CI 1.08-1.35) whereas no significant association was observed with cohort studies. This observation could be the result of recall and selection bias commonly implicated with retrospective studies.

The conflicting results reported by these studies merit further investigation into the potential carcinogenicity risk of CCB and the specific type of cancer that may be influenced by its use.

1.9.5 BB and cancer risk

Although BB is no longer prescribed as first-line therapy in hypertension, its use remains as a standard of care for patients with CHD, especially after an MI episode (The CAPRICORN Investigators, 2001) and in patients with HF (Ponikowski et al., 2016). The number of studies linking BB and the risk of malignancy is very limited while most randomised trials primarily focused on cardioselective BB such as atenolol.

1.9.5.1 What is the evidence?

A randomised trial evaluating patients with MI, the Beta-blocker Heart Attack trial (BHAT) reported more patients in the propranolol group versus placebo were withdrawn for cancer although the exact rate was very little (0.2% versus 0.1% respectively) (Beta-blocker Heart Attack Trial Research Group, 1982). In a primary care setting where elderly hypertensive patients were recruited, Coope and Warrender (1986) observed a higher rate of cancer incidence in the atenolol group compared to control. They also recorded an excess of fatal lung cancers in the treatment group compared with control (OR 1.89, 95%CI 0.88-4.08). In the Medical Research Council's randomised trial of elderly with hypertension, patients allocated to atenolol had the highest number of cancer deaths compared to diuretic or placebo (MRC Working Party, 1992). A similar finding has been observed in the United Kingdom Prospective Diabetes Study (UKPDS) of diabetic hypertensive patients in which those receiving atenolol showed an increased rate of cancer-related mortality compared to those receiving captopril or placebo (OR 2.04, 95% CI 1.06-3.90) (UKPDS Investigators, 1998).

On the contrary, epidemiological studies showed an inconsistent association between BB and cancer risks. Most of the studies observed a decreased risk of cancer. In the prospective studies, one study has found an increased risk of breast cancer. In 3,201 elderly women followed for 12 years, Saltzman et al. (2013) reported that ever exposure to BB during the period of observation increased breast cancer risk with a hazard ratio (HR) of 1.1 (95% CI 0.7-1.7). Meanwhile, history of exposure to BB for 2 years prior to study increased breast cancer risk by 50% compared to those who were never exposed. However, the association estimated was not robust due to the small study size. In two larger studies enrolling approximately 50,000 patients from Denmark (Fryzek et al., 2006) and America (Wilson et al., 2016), results showed that BB did not affect the risk of breast cancer. In another case-control study of 1,736 breast cancer cases and 1,895 healthy controls (Gómez-Acebo et al., 2016), the OR for breast cancer was 1.11 (95% CI 0.75-1.63) in BB user. However, no significant association with breast cancer was observed after stratification by menopausal status and BMI.

Meanwhile, a cohort of 1,340 diabetic patients initiating insulin therapy observed significantly reduced the overall risk of cancer with RR 0.33 (Monami et al., 2013).

In a more general population, Chang et al. (2015) suggested that BB has a potential anti-cancer effect and is protective against a specific type of cancer including head and neck cancers, the gastrointestinal tract (GIT) cancers, and prostate cancer. A preceding retrospective study agreed and found that BB users among men had a significantly lower incidence of prostate cancer (Perron et al., 2004), hence suggesting its cancer prevention potential. Most of the retrospective studies have utilised prescription or healthcare database which were not designed to detect cancer. Additionally, these databases may have a limitation in providing the variables required to control for risk of cancer such as BMI, smoking status, dietary habit, and physical activity.

Three meta-analyses of RCTs demonstrated that BB does not influence the risk for cancers. A network meta-analysis of 27 RCTs enrolling 126,137 patients was comprised of 56 treatment arms (Coleman et al., 2008). Of these, only three trials used BB. Mixed-treatment comparison showed no difference in cancer risk between BB and control. None of the pairwise comparisons showed a significant association. A subsequent network meta-analysis included 70 trials comprising 324,168 participants and 148 comparator arms (Bangalore et al., 2011). Of these, only seven trials used BB and results of direct comparison between BB and controls showed a trend towards lower risk of cancer incidence overall (OR 0.94, 95%CI 0.88-1.00). A comparable result has been reported by a subsequent meta-analysis including nine RCTs although with a smaller number of participants (Monami et al., 2013). Recently published meta-analyses of observational studies focused on the risk of breast cancer. Ni et al. (2017) have reported a marginally increased risk of breast cancer risk with BB use (OR 1.0, 95% CI 0.96-1.09) from a combination of 7 retrospective studies and 4 prospective studies. It is important to interpret this result with caution because observational studies are naturally prone to the risk of bias.

Due to the limited number of available studies, it is difficult to determine whether BB does influent cancer risk with confidence. The likely mechanism by which BB may cause cancer is further discussed in **Chapter 7 Section 7.1.3 BB and cancer**.

1.9.6 Diuretics and cancer risk

Previous concerns have been about the metabolic problems associated with thiazides (TZ) use such as dyslipidaemia, insulin resistance and gout. However, these adverse effects have been shown to be mainly a dose-dependent effect. The possibility of diuretics promoting the development of cancer, particularly of the kidney, has been of concern since the 1980s.

1.9.6.1 What is the evidence?

Several prospective and retrospective studies had attempted to link diuretic use and cancer risk. Most of these studies had focused on diuretics as a whole and only the very small number of studies had looked into TZ specifically.

One of the earliest studies to suggest the possible relationship between diuretics and risk of cancer was from a small interview-based study of 160 cases of renal cell carcinoma (RCC) with age, race, sex-matched controls (Yu et al., 1986). This study found that diuretic use was associated with RCC especially in women. A consistent finding has been reported in a subsequent similarly designed but larger study of 495 cases and 697 controls (McLaughlin et al., 1988). In addition to the higher risk in women, this study also suggested that the risk for RCC is independent of high BP. In a prospective study of 192,133 Danish patients discharged from the hospital for hypertension, HF, or oedema, results showed that those exposed to diuretics had a greater increased risk for RCC and the risk was higher in women (Mellemgaard et al., 1992). Although utilisation of patients' discharge register could potentially reduce the risk of recall bias, this study failed to adjust for confounding factors such as smoking, and BMI thus could not clarify the observed association. Moreover, these studies did not distinguish the different type of diuretics used. Hiatt et al. (1994) have investigated the use of TZ and risk of RCC in 257 cases and an equal number of controls using patients data retrieved from a medical programme records. Multivariate analysis controlled for hypertension, smoking, BMI, and history of kidney infection showed a significantly elevated risk of RCC among women but not in men. In the same study population, Weinmann et al. (1994) evaluated the risk of RCC in a different type of diuretics including TZ, a loop diuretic, a potassium-sparing diuretic, and chlorthalidone in 206 cases and

292 controls. The investigators have reported that diuretics increased the risk of RCC in both genders and the association was not restricted to one class of diuretic.

Contrariwise, Chow et al. (1995) found that diuretics did not significantly affect the risk of RCC in a study of 691 cases and an equal number of controls. Instead, use of other unspecified antihypertensive medication was associated with two-fold excess risk. In the International Renal-cell Cancer study of 1732 cases and 2309 controls from Australia, US, and three European countries, results showed that there was no different in risk in diuretic user compared to another antihypertensive drug user after adjustment for hypertension (McLaughlin et al., 1995). However, long term diuretic use (more than 15 years) was associated with a 60% increased risk (RR 1.6, 95% CI 1.0-2.5). In keeping with much earlier studies, the finding of a meta-analysis of 13 observational studies (10 case-controls and 3 cohorts) by Grossman et al. (2002) also showed a positive association between diuretic use and risk of RCC overall and in both retrospective and prospective studies.

Another type of malignancies has also been evaluated but more literature or additional observation is required to confirm the reliability of the association. One of the most commonly studied types of cancer is breast cancer. In a multicentre cohort study of 3,198 elderly women followed for five years, no association was observed between diuretic use and risk of breast cancer after controlling for age, race, parity, age at menopause, and diabetes (Fitzpatrick et al., 1997). Conversely, a case-control study among elderly women found that diuretic use significantly elevated risk of breast cancer and the risk increased with increase duration (Largent et al., 2006). In a subsequent study of 114,549 women in the California Teachers Study cohort, ever use of diuretic did not have a significant impact on invasive breast cancer risk (Largent et al., 2010). However, the risk increased with the diuretic use of ten years or longer especially for the oestrogen-receptor positive subtype (RR 1.26, 95% CI 1.10-1.45). Like former studies, many of these studies did not report breast cancer risk specifically for TZ. By distinguishing the categories of diuretics, Coogan et al. (2008) found no significant association between TZ use and risk of breast cancer among 4,653 cases and 4,269 controls. A recent study reported a comparable result showing no significant association between diuretics and breast cancer risk in a multivariate analysis supporting the results of previous studies (Gómez-Acebo et al., 2016). Still, recall

bias and misclassification of exposure were likely as information was ascertained by self-report. Furthermore, a most recently published meta-analysis of 13 observational studies showed a trend towards a significantly positive association between diuretics and breast cancer risk with RR 1.05 (95% CI 0.99-1.12; P = 0.004). Nonetheless, the presence of substantial heterogeneity between the included studies renders a caution interpretation of this study conclusion. Also, the risk of bias with observational studies must be acknowledged and a causal role of diuretic in causing carcinogenicity cannot be automatically derived from these studies' conclusions.

A network meta-analysis of 70 RCTs enrolling 324,168 participants with 148 comparator arms has shown that TZ is not associated with the risk of cancer incidence overall (Bangalore et al., 2011). Multiple comparisons for TZ against other class of antihypertensive also showed no significant association to risk of cancer. Likewise, a meta-analysis of seven RCTs with data from 61,450 participants showed no significant association to risk of cancer mortality.

1.10 Summary of literature review and rationale for the present study

Pharmacovigilance activity is important in ensuring the efficacy and safety of medicinal-related products. Signals from epidemiological studies should be investigated and follow-up accordingly particularly of a serious or potentially serious nature such as malignancies. Recent epidemiological studies and meta-analyses have been critical in exploring whether there is a true relationship between antihypertensive drugs and cancer risk. On the basis of the results from these studies, the presence of an association for most antihypertensive drug class is very unlikely. Currently, there is no clear indication that antihypertensive therapy results in greater risk of malignancy. However, most antihypertensive drugs trials are directed towards CV outcomes hence evaluation of cancer risks is performed as a post-hoc analysis. It is likely that these factors contribute to the inconsistencies in the results observed. These inconsistencies raise a research question which forms the basis of the specific aims of this thesis.

1.11 Aim and objectives of the thesis

1.11.1 Aim

To investigate the association between exposure to major AHT drug classes and risks of cancer.

1.11.2 Objectives

1) To assess the relationship between exposure to RAS inhibitors and the risk of cancer and cancer-related death.

2) To assess the association between exposure to CCB and the risk of cancer and cancer-related death.

3) To evaluate the relationship between exposure to BB and the risk of cancer and cancer mortality.

4) To evaluate the association between TZ and the risk of cancer and cancer mortality.

2 Materials and Methods

2.1 Systematic review and meta-analysis

This section describes the strategies and methods applied to systematically review the five main classes of antihypertensive agents used in RCTs in order to identify the association between antihypertensive drugs and the risks of cancer. This systematic review has been written in accordance with the protocol set forth by the Cochrane guidelines on the effects of healthcare interventions (2011). The protocol for this review is registered with PROSPERO (ID: CRD42016039801).

2.1.1 Eligibility criteria

The criteria for considering and excluding studies for this review was conducted in accordance with the Population Intervention Comparison Outcome Study (PICOS) design framework (Santos et al., 2007). The PICOS strategy grouped search terms into thematic groups in order to identify medical literature for systematic reviewing. Standard search strategies of the antihypertensive agent's review, with supplementary terms, were used to identify the relevant works.

2.1.1.1 Population

Men and non-pregnant women aged 18 years and over who could be either previously treated with BP-lowering agents or untreated. All population receiving out-patient antihypertensive therapy as specified in the search strategy was included in this review.

Pregnant women, patients with existing cancers, pre-malignant cancers, benign tumours or high cancer risk (e.g. liver cirrhosis, hepatitis B or C, retrovirus infection, autoimmune disease, chronic inflammation etc.) ,organ transplant recipients, patients with underlying genetic disorders (e.g. Marfan’s syndrome, Down’s syndrome etc.) or studies with missing information about population characteristics or healthcare setting were excluded from this review.

2.1.1.2 Intervention and comparator

This review included adults who were treated with the five major classes of antihypertensive agents namely ACEI, ARB, BB, CCB, and TZ in different doses and

sub-classes as monotherapy whether in a stepped-care approach or not. As the primary pathway of action of ACEI and ARB was similar and the paucity of trials which used both ACEI and ARB combination after ONTARGET (The ONTARGET Investigators, 2008), for this review, the only combination allowed is ACEI plus ARB. The interventions of interest were compared against other classes of AHT (ACEI, ARB, CCB, BB, TZ) in different doses and sub-classes as monotherapy. Other comparators such as conventional BP lowering therapy (e.g., centrally-acting drugs, alpha-blockers, vasodilators, and another type of diuretics), placebo or no active treatment were also included. In addition, drug doses should be mentioned in both the intervention and the comparator arms or, at least, in the intervention arm. The intervention and comparator drugs must be administered orally and continue to be taken as outpatients if patients were hospitalized. Supplemental drugs from other classes were allowed as part of the stepped therapy which had to be pre-specified and follow the same protocol in both arms.

While treatment provider and trial participants are followed according to a stringent trial protocol, issues related to compliance or adherence reporting is not uncommon concerning long- and short-term studies. In a review of non-adherence to treatment protocol published in 100 randomised controlled trials, Dodd et al. (2012) demonstrated that only 25 trials were deemed to be adequate in term of treatment initiation and completeness report. Furthermore, ambiguous terms were often used in describing non-adherence to treatment which does not provide explicit information on the completeness of treatment.

Comparisons between drugs that belong to the same class were excluded. Combination of antihypertensive drugs classes, drugs other than the classes as listed in the search strategy, administration route other than oral (intravenous, intramuscular, intracoronary, intrathecal, sublingual, transdermal patch, ophthalmic solution), or studies with missing information about AHT class and dose in treatment arms were excluded. This review also excluded studies that used other pharmacological protocols (e.g. hormonal therapy, supplements, vitamins), or non-pharmacological approach (e.g. diet, lifestyle changes, exercise, surgical procedures).

2.1.1.3 Outcome

Studies included in this review should be able to report on cancer outcomes in term of the number of cancers and/or cancer-related deaths observed among participants on studied AHT compared with those who are on a different type of treatment, or placebo. Cancer outcomes include all malignancies regardless of type and site. The outcome of interest is defined as malignant neoplasms that comply with International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9CM 140.xx-208.xx) and/or International Classification of Diseases, Tenth Revision (ICD-10 C00-97).

Malignancies occurring specifically after transplantation and secondary cancers that have arisen after treatment of a primary malignancy were excluded in this review. In a few cases, insufficient data were found and authors of the studies were contacted for further information. Studies with insufficient information were excluded from this review and analysis.

2.1.1.4 Study design

Only randomised-controlled trials (RCTs) were included in this review which satisfied the following criteria: [1] parallel design with random allocation to treatment groups comparing the drugs as listed in the search strategy in humans, [2] randomised at least 100 participants per treatment arm, and [3] followed the study participants for at least 52 weeks or one year of active treatment. RCTs with the factorial design were allowed in this review.

This review excluded studies where the unit of randomisation was not at the individual level (cluster-randomized), when the same individual acts as control (cross-over studies), quasi-experimental designs where participants were not randomly allocated to study treatment, and all types of observational studies (cohorts, case control, cross-sectional, case-reports, editorials, commentaries, opinions). Clinical trials that randomized less than 100 participants per treatment arm and/ or followed participants for less than 52 weeks or one year of active treatment were also excluded. Studies that utilize human sample in a controlled environment outside of the human body (in vitro) were excluded. Any study design involving animals were ineligible.

2.1.1.5 Geographical context

This review included studies conducted in other countries as the five main classes of AHT are commonly prescribed worldwide. Therefore, there was no language restriction applied for this review.

2.1.2 Search strategy for identification of relevant studies

2.1.2.1 Electronic searches

The success of a systematic review depends on the ability to locate and retrieve the relevant literature. A thorough literature search of all available sources is crucial to ensure a complete and robust review. The Medical Literature Analysis and Retrieval System Online (MEDLINE (OVID)), the Excerpta Medica database (EMBASE (OVID)), and Cochrane Central Register of Controlled Trials (CENTRAL) were searched for published articles between 1950 and December 2015 (last search performed on 11th August 2016).

Search filters are commonly used as a strategy to identify the higher quality evidence from a considerable amount of literature indexed in the selected databases. Search filters also help in focusing the disease, type of studies and health care settings in question in order to achieve a manageable quantity of records (Beale et al., 2014). A comprehensive search for studies was sought using a combination of the keywords “antihypertensive”, ”angiotensin converting enzyme inhibitor”, “ACE inhibitors”, “angiotensin receptor blockers”, “angiotensin receptor antagonist”, “ beta adrenergic antagonist”, “beta blockers”, “calcium channel blockers”, “calcium channel antagonists”, “diuretics” , “thiazides”, “randomized controlled trial”, “randomized”, “randomly”, and “trial” in human beings. The Scottish Intercollegiate Guidelines Network or SIGN (Scottish Intercollegiate Guidelines Network, 2016) search filters were also applied to focus and assist with literature searches in this review. The SIGN search filters lay emphasize on specificity rather than sensitivity. The detailed search strategy is shown in Appendix (Page 313). The literature search in the current review spanned over the last 65 years as the first modern antihypertension (TZ) was introduced in the late 1950s (Freis et al., 1958, Freis, 1995, Moser and Feig, 2009). One of the main limitations of using data spanning a long period of time includes a change in rates on risk factors related to cancer.

For example, increasing age increases the risk of cancer and this is evident from the current prolonged life expectancy compared to the olden days. Moreover, cancer treatment discovery has led to a higher rate of cancer survivorsa . The increase in cancer incidence rates over time may be contributed by increased surveillance and detection implemented in study protocols.

2.1.3 Searching other resources

Clinical trial register such as www.ClinicalTrials.gov was searched for relevant study by drug names and/ or classes. ClinicalTrials.gov is an internet-based registry and results database of publicly and privately supported clinical studies of human participants conducted around the world. In addition, references from identified articles including reviews and meta-analyses were also reviewed to look for eligible trials. Authors were contacted via email for studies that did not report the outcome of interest. A second email was sent after one or two weeks of no response and whenever possible, other investigators were contacted in cases where the email address is not valid. The following reviews and meta-analyses were searched for eligible study:

Aung and Htay (2011) ; Bangalore et al. (2011); Chen et al. (2010) ; Ghamami et al. (2014); Heran et al. (2008a); Heran et al. (2008b);Hines and Murphy (2011); Li et al. (2014a); Monami et al. (2013); Musini et al. (2014); Perez et al. (2009); Teo (2011); Wiysonge et al. (2017); Wong et al. (2014); Wong and Wright (2014); Wong et al. (2016).

2.1.4 Managing references

Records or references yield from the chosen electronic databases were imported and collated into reference manager software in the form of a bibliographic library. The EndNote version X7 by Thomson Reuters Corporation was used to manage citations imported from the searched electronic databases in Research Information Systems, Incorporated (RIS) or endnote export (.enw) format. Duplicates (studies that appeared in more than one database) identified using EndNote X7 deduplication tool were removed and saved in a separate bibliographic library for safekeeping. Manual identification of duplicates was also carried out by scanning the references sorted by title. Following removal of duplicates, a

group for eligible references was created in the library for ease of full-text search. Only the main author (Nur Aishah Che Roos) of this review was responsible for the maintenance and amendment of the bibliographic library.

Subsequently, references from the bibliographic library were exported into Microsoft Excel (version 2013) spreadsheet for coding. Study inclusion or exclusion coding was performed according to the PICOS strategy as described previously in Section 2.1.1. A categorical coding stating "Yes" and "No" was used when considering references against the inclusion criteria.

2.1.5 Process for study selection and quality assessment

2.1.5.1 Screening of titles and/ or abstract

The primary author, Nur Aishah (NA), independently screened the titles and/or abstracts of studies against the predetermined inclusion criteria outlined above (Section 2.1.1). During the screening, the reasons and number of rejected articles were documented for record keeping purposes. The rejected references were classified into two categories; those that are clearly not relevant to the review question and those that address the topic of interest but fail on one or more criteria. When a definite decision could not be made based on the title and/or abstract alone, the full paper was obtained for detailed assessment against inclusion criteria.

The full text of potentially eligible studies was retrieved and independently assessed for eligibility by two reviewers, Safaa Alsanosi (SA) and Mohammed Alsieni (MA). SA has completed her Doctorate Degree in Cardiovascular Sciences at the University of Glasgow whereas MA has completed his Masters of Science in Clinical Pharmacology and is currently a doctorate candidate at the University of Glasgow.

2.1.5.2 Obtaining documents

The full-text articles were obtained from the University of Glasgow Library's print and online resources. Articles were also requested from ArticleReach Direct (ARD) for journal articles that were not held by the library. ARD is a consortium of academic libraries offering authorized users from participating institution's free

automated request for journal articles (ArticleReach Direct, 2017). Whenever necessary, the inter-library loan was requested and most of the articles were obtained from the British Library Document Supply Centre. An additional search was also conducted via the Internet using 'Google' search engine by typing the title of the article or name of the journal for full-text articles. The full-text search tool which is available on the EndNote toolbar was also utilised by highlighting the required references and clicking the search icon.

2.1.5.3 Risk of bias assessment

The methodological risk of bias of included studies was assessed and reported in accordance with the Cochrane Handbook (Higgins, 2011) which recommends the explicit reporting of the following individual elements for RCTs: [1] random sequence generation; [2] allocation sequence concealment; [3] blinding of participants and personnel; [4] blinding of outcome assessment; [5] completeness of outcome data; [6] selective outcome reporting; and [7] other sources of bias [source of funding]. Each domain was judged as being at high, low or unclear risk of bias as set out in the criteria provided by Higgins (2011) and a justification for judgement of each item was reported in the risk of bias table (See Chapter 3 Section 3.3.6, Page 119). Studies will be deemed to be at the highest risk of bias if they are scored as at high or unclear risk of bias for either the [1] sequence generation, [2] allocation concealment, [3] blinding of participants and personnel or [4] blinding of outcome assessment domains based on growing empirical evidence that these factors are particularly important potential sources of bias (Egger M, 2003, Higgins, 2011).

In all cases, two authors (MA and SA) independently assessed the risk of bias of included studies, with any disagreements resolved by discussion to reach consensus. Study authors were contacted for additional information about the included studies, or for clarification of the study methods as required.

2.1.6 Data extraction

Two reviewers (NA and SA) independently decided whether a trial was included. They also extracted and verified data entry from included studies. Discrepancies were resolved by discussion. Any uncertainty identified was resolved through

discussion with supervising author (Prof Sandosh Padmanabhan) where necessary. Missing data especially on cancer outcomes were requested from study authors by email though not all responded.

The data collection form was designed after taking into consideration how much information should be collected. A standardised Microsoft Excel 2010 worksheet was used to extract data from the included studies for assessment of study quality and evidence synthesis. The detail of the study quality assessment was described previously in Section 2.1.5.3. Information extracted for evidence synthesis was collected according to the PICOS framework: [1] population, [2] intervention and comparators, [3] outcome measures and [4] study design.

For the study population: [1] Overall number of study participants (N); [2] study population clinical settings; [3] N of randomised patients in each treatment arm; and [4] baseline characteristics (mean age in years, percentage of male, percentage of current smokers, percentage of participants with history of cancer).

For the study intervention and comparator: [1] Class of the drug; [2] the generic name of the drug; [3] Doses of the drug; [4] Duration of treatment; [5] Percentage of adherence to therapy; and [6] Supplemental agents.

For the outcome measures: [1] Cancer as a pre-specified outcome; [2] Number of incidence cancer and/ or cancer mortality in each treatment arm; [3] Cancer diagnosis adjudication; and [4] Source of cancer data (published or unpublished).

For study type: [1] Study acronym; [2] Study name; [3] First author's name; [4] Publication year; [5] Journal published;[6] Study duration (total, mean or median); and [7] Primary and secondary outcome measures.

For studies with multiple treatment arms (more than two intervention group), only the directly relevant treatment arms were included. If a study was comparing different AHT and a number of them had different doses (e.g., the study had four treatment arms, irbesartan 150mg vs irbesartan 300mg vs amlodipine 5mg vs amlodipine 10mg), cancer outcomes for the treatment arm were combined to corresponding AHT classes (e.g., ARB vs CCB). Similarly, if the study was comparing different AHT and a number of them belong to the same class with

different doses (e.g., the study had four treatment arms, irbesartan 150mg vs losartan 100mg vs olmesartan 40mg vs amlodipine 10mg), cancer outcomes for the treatment arm were combined to corresponding AHT classes (e.g., ARB vs CCB).

2.1.7 Meta-analysis

Data were processed in accordance with the Cochrane Handbook for Systematic Reviews of Interventions (Higgins, 2011); data synthesis and analyses were performed using the RevMan 5 software.

2.1.7.1 Meta-analysis software

RevMan 5 (Review Manager, 2014)is a software recommended for preparing and maintaining Cochrane Reviews developed by the Cochrane Collaboration Group. It was developed to facilitate literature reviews (both protocol and full review) and meta-analyses (Cochrane Community). It is available free for Cochrane author and academic use.

Analysis methods contained in Revman 5 includes Peto, Mantel-Haenszel, and inverse variance for meta-analysis. This software can be used to calculate ratios of effect measure (e.g. odds ratio, risk ratio, hazard ratio, ratio of means) expressed on a log-scale , 'difference' measure of effect (risk difference, differences in means) expressed on their natural scale (Deeks, 2010), heterogeneity and sensitivity analysis. For statistical models, both the fixed-effect (FE) model and random-effect (RE) model are included in the RevMan.

2.1.7.2 Fixed-effect (FE) model meta-analysis

The assumptions under the FE model is that there is only one true effect size that is shared by all the studies in the analysis and that differences in effect estimates observed are due to sampling error (Borenstein et al., 2010). The combined effect estimate generated from the FE meta-analysis reflects this one true effect size. The null hypothesis for this common effect is zero for a difference or one for a ratio (Borenstein et al., 2010). Distribution of points observed in the meta-analysis indicates sampling error and within-study error is reduced by assigning weights to each study in the analysis.

2.1.7.3 Random-effects (RE) model meta-analysis

Under the RE model, we assumed that different studies in the meta-analysis are estimating study-specific true effect (Borenstein et al., 2010). Therefore, the summary effect generated from the RE model estimates the mean of all the true effects. The null hypothesis for the summary is that the mean of these effects is 0.0 for a difference and 1.0 for the ratio (Borenstein et al., 2010). The RE model measures the mean of the distribution and thereby requires consideration of two sources of variance: 1) within study error, and 2) variation in the true effects across studies. Both sources of variance are minimized by assigning weight to each study.

For RE models, DerSimonian and Laird random-effects models are used. This is the most common RE model used in the majority of meta-analyses. Revman also allows presentation of analysis graphically such as analysis flow diagram, forest plots, funnel plots, and risk of bias graph and summary.

2.1.7.4 Data synthesis

Study participants were analysed in the group to which they were randomised, regardless of which or how much treatment they actually received. The aggregated data on cancer incidences and/ or cancer mortality obtained from included studies were treated as dichotomous variables and were presented in a 2x2 table giving the numbers of a participant who do or do not experience the event in each of the two groups as in **Table 2.1**. A traditional meta-analysis for individual drug classes was conducted using Revman 5 (version 5.3.5). The Mantel-Haenszel method was used in the estimation of odds ratio (OR) and confidence interval (CI) which have been shown to have better statistical properties when there are few events (Higgins, 2011). The value of 0.5 was added in the 2x2 cells in situations where no events occurred (corrected automatically by RevMan 5). In these analyses, an OR below 1 indicates lower odds in the treatment containing arm, whereas an OR above 1 indicates lower odds in the comparator. Heterogeneity was evaluated using the Q statistic for heterogeneity and I^2 statistics. Small p-values (< 0.05) and a large I^2 ratio (≥50%) signify evidence of heterogeneity and suggests study-specific OR should be reported instead of performing a meta-analysis. When homogeneity was not rejected, the Mantel-

Haenszel OR in an FE meta-analysis was reported. Publication bias was evaluated using funnel plot.

Table 2-1: Nomenclature for 2 x 2 table of events by treatment

	Events	Non-Events	
Treatment	A	B	n1
Control	C	D	n2

2.1.7.5 Heterogeneity assessment

Heterogeneity in a systematic review is defined as any kind of variability between included studies (Higgins, 2011). This variability may be due to clinical diversity (difference in participants, interventions, exposures or outcomes studied), and/ or methodological diversity (difference in study design and risk of bias). Statistical heterogeneity results when there is variability in the true treatment or risk factor effects as a consequence of clinical diversity, methodological diversity or both (Higgins and Thompson, 2002, Higgins, 2011).

Heterogeneity can be identified and measured by statistical tests. One of the common methods to assess heterogeneity is with Cochran's chi-square test or also known as the *Q*-statistic for heterogeneity (Higgins and Thompson, 2002). Q is defined as

$$Q = \sum_{i=1}^{k} Wi(Yi - M)^2,$$

where

- Wi is the study weight
- Yi is the study effect size
- M is the study effect
- K is the number of studies.

Q is a standardised measure indicating that it is not affected by the metric of the effect size index, but simply is the degrees of freedom (*df*),

$$df = k - 1,$$

where *k* is the number of studies.

Therefore, the excess variation attributed to differences in the true effects between studies is computed as $Q - df$.

It tests the null hypothesis that all included studies have the same effect on the population. This review considers a p-value of <0.05 as statistically significant for the presence of heterogeneity. It is noteworthy that the *Q*-statistic has a poor power especially in the availability of sparse data and excessive power of detecting clinically unimportant heterogeneity when there are many studies (Hardy and Thompson, 1998). To overcome this drawback, we also used I squared (I^2) statistics to quantify inconsistencies between studies.

According to Higgins (2011), I^2 statistics described the percentage of variability in the effect estimates that is due to heterogeneity rather than chance. It is computed as

$$I^2 = \left(\frac{Q - df}{Q}\right) \times 100\%$$

that is the ratio of excess dispersion to total dispersion.

The I^2 value ranges between 0% (indicate no observed heterogeneity) and a maximum of 100% (larger values indicate increasing heterogeneity). Tentatively, I^2 can be interpreted as follows (Higgins, 2011):

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

If there are very little variations between studies, the I^2 will be low and the FE model is more appropriate. The FE model assumes that there is one true effect size that underlies all the studies in the analysis and that all differences in

observed effects are due to sampling error (Borenstein et al., 2010). By way of explanation, the only difference between studies is their power to detect the outcome of interest.

Significant heterogeneity is typically considered if I^2 is 50% or more. It is worth noting that I^2 is not a measure of absolute heterogeneity and it does not provide information on the dispersion of true effects (Borenstein, 2009). It cannot reliably tell us which of two meta-analyses shows more heterogeneity in true effects. Therefore, I^2 should be used together with the observed effects to give the reviewers a sense of the true effects.

In the presence of statistically significant heterogeneity, one analytical approach is to incorporate it into a RE mode. The RE model does not fix heterogeneity, on the other hand, it allows for differences in the treatment effect from study to study (Riley et al., 2011) as it assumes that there is a distribution of true effect sizes. The RE model used the tau-squared (T^2) statistics to estimate between study variance from the observed effects. It is computed as

$$T^2 = \frac{Q - df}{C}$$

Where

$$C = \sum W_i - \frac{\sum W_i^2}{\sum W_i}$$

The T^2 estimates were used to assigned weights under the RE model, where the weight assigned to individual study is computed as

$$W_i^* = \frac{1}{V_{Yi}^*} = \frac{1}{V_{Yi} + T^2}$$

With V_Y^* is the sum of the within study variance (V_Y) and the between study variance (T^2).

Heterogeneity is further explored with reference to the characteristics of the studies included in the meta-analysis by performing sensitivity analysis through conducting subgroup analysis, repeating the analysis, and substituting alternate decisions if any were arbitrary or unclear.

2.1.7.6 Publication bias assessment

Publication bias is the failure to include all relevant trials because they were not published and hence, not accessible. Publication bias can be measured by comparing published and unpublished studies addressing the same question. In this review, publication bias was estimated visually by funnel plots. Funnel plots are primarily used as a visual tool in the exploration of publication and another type of bias in the meta-analysis (Sterne et al., 2006). A funnel plot is a simple scatter plot of the intervention effect estimates from individual studies against a measure of study size (Sterne et al., 2006, Higgins, 2011). The effect estimates of studies were plotted on the horizontal axis while the measure of a studies size was plotted on the vertical axis. Hence, results from small studies scattered at the bottom of the graph, with the spread narrowing among larger studies. Funnel plots were only used if there were at least ten studies included in the meta-analysis otherwise, the power of the tests is too low to differentiate chance and real asymmetry (Higgins, 2011). The plot approximately resembled a symmetrical inverted funnel in the absence of bias.

2.1.7.7 Sensitivity analysis

Sensitivity analyses were done by exclusion (when applicable) of trials in which the patients were also receiving other study treatment in a factorial designed RCT, rendering any attribution of cancer risk to one class of medication problematic. Additionally, the treatment effects were also assessed according to quality domains (concealed treatment allocation, blinding of patients and caregivers, blinded outcome assessment) and study sample size to explore the degree to which this systematic review was affected by changes in its methods or in the data used from individual studies.

2.1.7.8 Subgroup analysis

Subgroup analyses are typically undertaken to explore heterogeneity. In this review, subgroup analyses were conducted to explore the average effect of treatment when compared to control on the odds of cancer incidence considering [1] variant of intervention and comparators and [2] characteristic of the studies.

For variant of intervention and comparators subgroup analysis: [1] antihypertensive drug subclasses (e.g. DHP CCB and non-DHP CCB) [2] antihypertensive class vs placebo and antihypertensive class vs another antihypertensive class or active treatment.

For characteristic of studies subgroup analysis: [1] Mean age 65 years or older and mean age below 65, [2] Different health care settings (e.g., hypertension, a composite of CVD, and T2DM) and [3] duration of study (e.g., less than five years and five years or longer). The different type of clinical settings included hypertension, a composite of CVD (CHD, HF, arrhythmia, and stroke), and diabetes mellitus. High-risk hypertensive was defined as hypertension with one or more risk factor for CV events.

3 Antihypertensive therapy and risks of cancer: Systematic Review – Screening and Eligibility

3.1 Aim

This chapter described the systematic review search result (literature searching, excluded and included studies, and risk of bias in included studies) for RCTs studying the main antihypertensive agents to identify BP-lowering drug classes and risks of cancer as per protocol.

3.2 Results of the search

Literature searching resulted in 35 696 citations identified through multiple sources. After removal of duplicates, 27 235 records were screened for eligibility. The detail of the search strategy and review of the literature identified is summarized in the PRISMA study flow (**Figure 3.1**).

After removal of duplicates, 27, 235 citations and/or abstracts were screened for eligibility criteria. Just over 98% (26,772) of these were excluded based on title or abstract as pre-determined by this review PICOS criterion. The remaining 463 publications were assessed for eligibility and only 258 met the eligibility criteria. The 205 ineligible studies were excluded because less than 100 participants were enrolled per treatment arm and/ or follow-up of less than one year.

Finally, 90 RCTs enrolling 390,750 participants were included in this review and meta-analysis. Details of the excluded and included studies are described in **Section 3.2.1Description of excluded studies** and **Section 3.2.2 Description of included studies.**

Altogether, 26 studies in language other than English were screened and excluded after translation of their abstract or full-text as they did not meet the inclusion criteria: nine Russian studies (one was not a randomised study, one did not specify the duration of follow-up, two were observational studies, two had follow-up less than one year, three had no cancer outcomes), five French studies (four were non-RCTs and one had follow-up less than one year), five German studies (three were non-RCTs, one had used combined therapy, while the other one had enrolled less

than 100 participants per treatment arm), four Chinese studies (one was non-RCT, two had enrolled less than 100 participants per treatment arm, while the other had no cancer outcome), two Italian studies (both had follow-up less than 52 weeks), and one Portuguese study (enrolled less than 100 participants per treatment arm and had less than one year of follow-up).

3.2.1 Description of excluded studies

Overall, a total of 168 RCTs were excluded after a thorough screening of their full-text for eligibility.

Four studies (COOPERATE; JIKEI; KYOTO HEART; VART) were retracted due to ethical misconduct and unreliable data (Sawada, 2009, The Editors, 2009, Asayama et al., 2013, Takano et al., 2014). Different AHT class combination was used as an intervention in one study (HSCHG) and as a comparator in two studies (CLEVER; OSCAR).

One study (Tepel) reported overall cancer mortality but not according to AHT class. Meanwhile, cancer incidence was reported collectively the ATTEST study and not according to treatment group. Cancer events were not well-defined in two studies (Lund-Johansen; HDPAL) as they were reported as either malignant processes or cancer-related complications.

The majority of studies were excluded because of failure to report cancer outcomes. The reasons for exclusion for each trial are provided in **Table 3-1**.

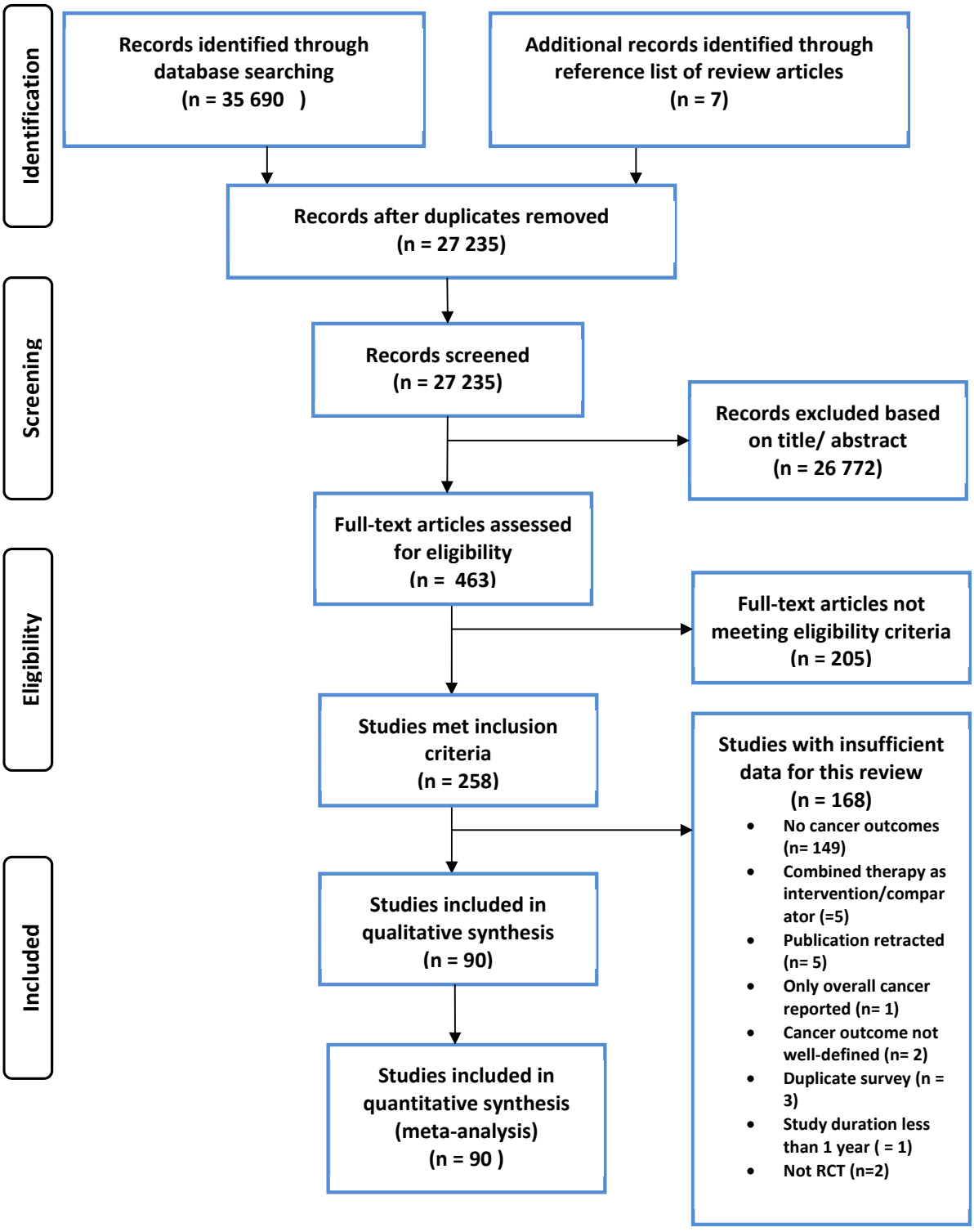


Figure 3-1 PRISMA Study flow diagram

Table 3-1: Reasons for exclusion of eligible RCTs (Ordered by study ID)

Study ID [1]	Reason for exclusion	Reference
4C	No data on cancer available	(Kondo et al., 2003)
AASK	No data on cancer available	(Wright Jr et al., 2002)
Aberg	No data on cancer available	(Aberg, 1995)
Agardh	No data on cancer available	(Agardh, 1996)
AIRE	No data on cancer available	(Cleland, 1997)
AIREX	No data on cancer available	(Hall, 1997)
ANBP-2	No data on cancer available	(Wing et al., 1997)
Andersen	No data on cancer available	(Andersen, 1979)
Andrews	No data on cancer available	(Andrews, 2000)
ANZHF	No data on cancer available	(Anonymous, 1997)
APSI	No data on cancer available	(Boissel, 1990)
Aronow	No data on cancer available	(Aronow, 1994)
ASSIST	No data on cancer available	(Pepine et al., 1994)
ATTEST	Reported cancer as an adverse drug reaction but did not specify to which treatment group.	(Katayama, 2008)
AVER	No data on cancer available	(Esnault et al., 2008)
Barber	No data on cancer available	(Barber, 1976)
Barnett	No data on cancer available	(Barnett, 2004)
BENEDICT	No data on cancer available	(Ruggenenti et al., 2004)
BENEDICT-B	No data on cancer available	(Ruggenenti et al., 2011)
BEST	No data on cancer available	(Eichhorn, 2001)
Beta-PRESERVE	No data on cancer available	(Zhou, 2010)
Bremner	No data on cancer available	(Bremner, 1997)
Breyer	No data on cancer available	(Breyer, 1996)
CAPPP	No data on cancer available	(Hansson et al., 1999)
CAPRICORN	No data on cancer available	(The CAPRICORN Investigators, 2001)
CARMEN	No data on cancer available	(Remme et al., 2004)
CARP	No data on cancer available	(Okada et al., 2011)
CASE-J	No data on cancer available	(Ogihara, 2008)
CATS	No data on cancer available	(Van Den Heuvel, 1997)
Cheng	No data on cancer available	(Cheng, 1997)
Chiariello	No data on cancer available	(Chiariello, 1991)
CIBIS	No data on cancer available	(Anonymous, 1994b)
CIBIS-II	No data on cancer available	(Anonymous, 1999)
Cice	No data on cancer available	(Cice, 2010)
CITAS	No data on cancer available	(Campeanu, 2001)
CLEVER	Combined drug classes were used as an active comparator (ACEI vs the combination of ACEI and BB	(Miller, 2010)
CONSENSUS	No data on cancer available	(Kjekshus, 1988)
Colluci	No data on cancer available	(Colucci et al., 1996)
COOPERATE	Publication retracted due to invalid data	(Nakao, 2003)
COPERNICUS	No data on cancer available	(Packer et al., 2002)
CORD	No data on cancer available	(Spinar, 2009)
COSMO-CKD	No data on cancer available	(Ando et al., 2014)
CRIS	No data on cancer available	(Rengo et al., 1996)
CVIP	No data on cancer available	(Schneider et al., 2004)
Daae	No data on cancer available	(Daae, 1998)
Derosa	No data on cancer available	(Derosa et al., 2014)
Derosa	No data on cancer available	(Derosa et al., 2011)
DETAIL	No data on cancer available	(Barnett, 2006)
DIAL	No data on cancer available	(Dalla Vestra, 2004)
DREAM	No data on cancer available	(The DREAM Trial Investigators, 2006)
DUTCH TIA	No data on cancer available	(Anonymous, 1993)
EIS	No data on cancer available	(Anonymous, 1984)
ELSA	No data on cancer available	(Zanchetti et al., 2002)
ENCORE II	No data on cancer available	(Luscher et al., 2009)
EUCLID	No data on cancer available	(Chaturvedi, 1997)
EUROPA	No data on cancer available	(Fox, 2003)
FAMIS	No data on cancer available	(Borghi, 1997)

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

Fogari	No data on cancer available	(Fogari et al., 2006)
Fogari	No data on cancer available	(Fogari et al., 2008)
Fogari	No data on cancer available	(Fogari et al., 2002)
Fogari	No data on cancer available	(Fogari et al., 2012a)
Fogari	Combined therapy (ARB or ACEI added on to CCB/TZ combination	(Fogari et al., 2012b)
FOSIDIAL	No data on cancer available	(Zannad, 2006)
GISSI-3	No data on cancer available	(Anonymous, 1994a)
GLANT	Not a randomized study.	(Matsuoka, 1995)
Goldman	No data on cancer available	(Goldman, 1980)
Goteborg Metoprolol Trial	No data on cancer available	(Herlitz, 1984)
HANE	No data on cancer available	(Philipp, 1997)
HAPPHY	No data on cancer available	(Wilhelmsen et al., 1987)
HDPAL	Reported cancer-related complications. No data on incident cancer and/ or cancer-related mortality was available.	(Agarwal et al., 2014)
HOMED-BP	No data on cancer available	(Noguchi et al., 2013)
HSCHG	Different drug class combination was used as an intervention (0.5 mg deserpidine combined with 5 mg methyclothiazide in each tablet).	(Hypertension-Stroke Cooperative Study Group, 1974)
HYVET	No data on cancer available	(Beckett et al., 2008)
HYVET-ex	No data on cancer available	(Beckett et al., 2012)
HYVET-P	No data on cancer available	(Bulpitt et al., 2003)
IMAGINE	No data on cancer available	(Rouleau et al., 2008)
INNOVATION	No data on cancer available	(Makino, 2007)
IPPPSH	No data on cancer available	(Anonymous, 1985)
JAMP	No data on cancer available	(Ueshima et al., 2004)
J-DHF	No data on cancer available	(Yamamoto et al., 2013)
J-ELAN	No data on cancer available	(Hori, 2006)
Jikei Heart	Publication retracted due to unreliable data and ethical misconduct (data were intentionally altered).	(Mochizuki et al., 2007)
JIMIC-B	No data on cancer available	(Yui et al., 2010)
J-MIND	No data on cancer available	(Baba et al., 2001)
J-RHYTHM 2	No data on cancer available	(Yamashita et al., 2011)
Keilich	No data on cancer available	(Keilich, 1997)
Kumar	No data on cancer available	(Kumar et al., 2015)
Kyoto Heart	Publication retracted due to unreliable data (critical problems existed with some of the data reported in this study)	(Sawada et al., 2009)
Lee	No data on cancer available	(Lee et al., 2011)
Lewis	No data on cancer available	(Lewis, 1993)
Lin	No data on cancer available	(Lin et al., 2013)
LIT	No data on cancer available	(LIT Research Group, 1987)
LIVE	No data on cancer available	(Gosse et al., 2000)
LOMIR-MCT-IL	No data on cancer available	(Yodfat, 1993)
Lund-Johansen	Reported malignant processes but no details were available.	(Lund-Johansen, 1981)
MACB	No data on cancer available	(Anonymous, 1995)
MACH-1	No data on cancer available	(Levine et al., 2000)
Maclean	No data on cancer available	(Maclean, 1993)
MDC	No data on cancer available	(Waagstein et al., 1993)
MDPT	No data on cancer available	(Anonymous, 1988)
MIAMI	No data on cancer available	(Herlitz, 1990)
MITEC	No data on cancer available	(Baguet, 2009)
MOSES	No data on cancer available	(Schrader et al., 2005)
NORDIL	No data on cancer available	(Hansson et al., 2000)
OLIVUS	No data on cancer available	(Hirohata et al., 2010)
OLIVUS-Ex	No data on cancer available	(Hirohata et al., 2012)
Olsson	No data on cancer available	(Olsson, 1986)
Olsson	Duplicate survey	(Olsson, 1984)
Omvik	No data on cancer available	(Omvik, 1993)
ORIENT	No data on cancer available	(Imai et al., 2011)
OSCAR	Combined drug classes used as an active comparator (ARB vs the combination of ARB and CCB)	(Kim-Mitsuyama et al., 2013)
Ott	Duplicate survey	(Ott, 2003)

Pacifico	No data on cancer available	(Pacifico, 1999)
Packer	No data on cancer available	(Packer, 1996)
Packer	No data on cancer	(Packer et al., 2001)
Pantoni	No data on cancer available	(Pantoni et al., 2005)
PART-2	No data on cancer available	(MacMahon et al., 2000)
PATS	No data on cancer available	(PATS Collaborating Group, 1995)
PEACE	No data on cancer available	(Braunwald et al., 2004)
Peng	No data on cancer available	(Peng et al., 2015)
PEP-CHF	No data on cancer available	(Cleland, 2006)
Perez-Stable	No data on cancer available	(Perez-Stable et al., 2000)
POST	No data on cancer available	(Sheldon et al., 2006)
PRAISE-2	No data on cancer available	(Packer et al., 2013)
PREAMI	No data on cancer available	(Ferrari, 2006)
PRESERVE	No data on cancer available	(Devereux, 2001)
PREVEND-IT	No data on cancer available	(Asselbergs, 2008)
PROGRESS	No data on cancer available	(PROGRESS Collaborative Group, 2001)
PROTECT	No data on cancer available	(Stumpe, 1995b)
PUTS	No data on cancer available	(Stumpe, 1993)
QUIET	No data on cancer available	(Pitt et al., 2001)
RASS	No data on cancer available	(Mauer et al., 2009)
REIN	No data on cancer available	(Ruggenenti, 2003)
ROAD	No data on cancer available	(Fan, 2007)
ROADMAP	No data on cancer available	(Haller et al., 2011)
Salathia	No data on cancer available	(Salathia, 1985)
Schmieder	No data on cancer available	(Schmieder et al., 2009)
SENIORS	No data on cancer available	(Flather et al., 2005)
Sever	No data on cancer available	(Sever, 1997)
Shaifali	No data on cancer available	(Shaifali et al., 2014)
Shanghai Study	No data on cancer available	(Shen, 1996)
STONE	Not RCT. The alternate allocation was used.	(Gong et al., 1996)
Stumpe	A study duration of less than 52 weeks (30 weeks)	(Stumpe, 1995a)
Shanghai Study	Duplicate publication of the Shanghai Study. (The same study population published in two different journals)	(Xu, 1998)
SHELL	No data on cancer available	(Malacco et al., 2003)
Shen	No data on cancer available	(Shen et al., 2012)
SHEP	No data on cancer available	(Kostis et al., 1997)
SHEP-PS	No data on cancer available	(Perry Jr et al., 1989)
Sjöland	No data on cancer available	(Sjoland, 1995)
STAR-CAST	No data on cancer available	(Sasamura et al., 2013)
TAIM	No data on cancer available	(Wylie-Rosett et al., 1993)
Talseth	No data on cancer available	(Talseth, 1990)
TEST	No data on cancer available	(Eriksson S., 1995)
Tepel	Cancer outcome reported not according to the drug class	(Tepel, 2008)
TIBET	No data on cancer available	(Fox, 1996)
TOHMS	No data on cancer available	(Neaton et al., 1993)
Trimarco	No data on cancer available	(Trimarco et al., 2012)
UK Lacidipine	No data on cancer available	(The UK Lacidipine Study Group, 1991)
USPHSH	Treatment arm comprised of HCTZ plus reserpine combination or hydralazine. The exact number of patients randomized to HCTZ plus reserpine not given	(Smith, 1977)
VA COOP	No data on cancer available	(Materson et al., 1993)
VA NEPHRON-D	No data on cancer available	(Fried et al., 2013)
VAL-CARP	No data on cancer available	(Ikeda, 2006)
VART	Publication retracted due to unreliable data and problems with management of conflict of interest	(Takano et al., 2014)
VESPA	No data on cancer available	(Bestehorn et al., 2004)
VHAS	No data on cancer available	(Rosei et al., 1997)
V-HeFT III	No data on cancer available	(Cohn et al., 1997)
Waters	No data on cancer available	(Waters et al., 1987)
Woo	No data on cancer available	(Woo et al., 2009)

3.2.2 Description of included studies

In accordance with the PRISMA statement recommendations, this review included 90 studies enrolling 390,750 participants with an average follow-up of 3.5 years. The characteristics of the study design, participants and interventions used of the included studies are summarised in **Section 3.2.2.1**. Additionally, selected characteristics of interest are tabulated in (Appendix).

Five studies (ACTIVE I; HOPE; NAVIGATOR; PRoFESS; SCAT) used partial or 2-by-2 factorial design while the rest of the included studies were of parallel design.

Geographical characteristics: Majority of the included studies were conducted in the western world which includes Europe, America, Australia, New Zealand, and Israel. 11 studies were conducted in Asia with nine studies (CASE-J Ex; E-COST; HIJ-CREATE; Kanamasa; NHS; NICS-EH; OCTOPUS; Otsuka; Suzuki) from Japan and two studies (FEVER; Syst-China) from China. All the studies were published in English.

Clinical settings: 21 studies enrolled hypertensive patients without co-morbidities (ALPINE; ANBP; E-COST; EWPHE; HEP; LIFE; MAPHY; MIDAS; MRC; MRCOA; NICS-EH; OSLO; PHYLLIS; PREVER-Treatment; SCOPE; SHEP; STOP-HTN2; Syst-China; Syst-Eur; VA COOP II; VERDI).

The remaining 69 included studies enrolled hypertensive and non-hypertensive patients with the presence of specific co-morbidities as an entry criterion. In seven studies, hypertensive participants with at least one risk factor for CVD were enrolled (ALLHAT; ASCOT-BPLA; CASE-J Ex; CONVINCE; FEVER; INSIGHT; VALUE). CHD was the most common comorbidity or illness in 18 studies (ACTION; APSIS; BHAT; CAMELOT; DAVIT II; HIJ-CREATE; INTACT; INVEST; Kanamasa; OPTIMAAL; Otsuka; Practolol Study; PREVENT; SCAT; SPRINT; SMT; TRACE; Wilcox). This was followed by HF in 13 studies (CHARM Added; CHARM Alternative; CHARM Preserved; I-PRESERVE; MERIT-HF; PARADIGM-HF; PRAISE; SAVE; SOLVD-P; SOLVD-T; Val-HeFT; VALIANT; V-HeFT II). Meanwhile, atrial fibrillation (AF) was the main comorbidity studied in three studies (ACTIVE I; ANTIPAF; GISSI-AF).

T2DM was the main health setting in 10 studies (DEMAND; DIABHYCAR; DIRECT-Protect 2; FACET; IDNT; IRMA-2; NHS; NESTOR; RENAAL; UKPDS). Participants with Type 1 DM and impaired glucose tolerance (IGT) were studied in three RCTs (DIRECT-Prevent; DIRECT-Protect I; NAVIGATOR).

CKD was the main health setting in five studies (AIPRI; ESPIRAL; OCTOPUS; REIN-2; Suzuki). Four studies (HOPE; ONTARGET; PAT; PRoFESS) investigate participants with vascular diseases (including stroke). Two studies (PHARAO; TROPHY) enrolled participants with pre-hypertension and one study (LaCroix) enrolled healthy adults.

Participants with baseline cancer: Eight studies (ACTION; CHARM Added; CHARM Alternative; CHARM Preserved; GISSI-AF; INVEST; Kanamasa; OCTOPUS) included participants with a history of cancer at baseline ranging from 0.4% to 7.5% of total study population. 17 studies (AIPRI; CASE-J Ex; EWPHE; HIJ-CREATE; INTACT; IRMA-2; LaCroix; MAPHY; MRCOA; OSLO; REIN-2; SHEP; SOLVD-T; SPRINT; TRACE; VA COOP II; VERDI) excluded patients with a history of malignancy. The remaining 63 included studies did not report a history of cancer at baseline.

Cancer pre-specified as an outcome: 14 studies (ALLHAT; CONVINCE; FACET; HEP; INVEST; Kanamasa; LIFE; MIDAS; MRC; MRCOA; ONTARGET; SCAT; TRANSCEND; UKPDS) pre-specified cancer as an outcome. However, the remaining 76 studies did not pre-specified cancer as a clinical end-point. Diagnosis of cancer or cancer-related deaths were centrally-adjudicated in 27 studies (ALLHAT; ASCOT-BPLA; BHAT; CONVINCE; FACET; HIJ-CREATE; IDNT; INSIGHT; INVEST; I-PRESERVE; LIFE; MAPHY; MIDAS; MRC; MRCOA; NHS; ONTARGET; OPTIMAAL; PARADIGM-HF; PAT; Practolol Study; PREVENT; SCOPE; SHEP; Syst-China; Syst-Eur; TRANSCEND) while four studies (FEVER; Otsuka; V-HeFT II; Wilcox) were site-reported by treating physicians. The remaining 59 studies did not report on the method of cancer diagnosis adjudication.

Source and type of cancer outcomes: 86 included studies have published cancer outcomes. Of these, cancer outcomes from 20 studies (ACTIVE 1; ALPINE; ASCOT-BPLA; CAMELOT; CHARM Added; CHARM Alternative; CHARM Preserved; DIRECT-Prevent; DIRECT-Protect 1; DIRECT-Protect 2; HOPE; IDNT; IRMA-2; NAVIGATOR; ONTARGET; PRoFESS; REIN-2; SCOPE; Val-HeFT; VALUE) were retrieved from

published systematic review and meta-analyses. Cancer outcomes were collectively reported for six studies (CHARM Added; CHARM Alternative; CHARM Preserved; DIRECT-Prevent; DIRECT-Protect 1; DIRECT-Protect 2) as CHARM Overall and DIRECT Overall. Conversely, cancer outcomes were unpublished in only four studies (DIABHYCAR; MERIT-HF; PARADIGM-HF; PREVER-Treatment) and the outcome of interest was provided by the study authors.

For type of cancer outcomes, 32 included studies (ACTIVE 1; ALLHAT; ALPINE; ANTIPAF; ASCOT-BPLA; CHARM Overall; CONVINCE; DEMAND; DIRECT Overall; FACET; GISSI-AF; HEP; I-PRESERVE; IRMA-2; Kanamasa; LIFE; NHS; NAVIGATOR; NICS-EH; OCTOPUS; ONTARGET; PHARAO; PREVER-Treatment; PRoFESS; RENAAL ; SCOPE; Syst-Eur ; TRANSCEND; VERDI) have reported both incident cancer and cancer-related deaths . 34 studies (ABCD; ACTION; AIPRI; BHAT; CAMELOT; CASE-J Ex; DAVIT II; ESPIRAL; EWPHE; FEVER; HIJ-CREATE; HOPE; INSIGHT; INVEST; LaCroix; MERIT-HF; MIDAS; NESTOR; NICOLE; PARADIGM-HF; PHYLLIS; PRAISE; PREVENT; SCAT; SOLVD-P; SOLVD-T; STOP-HTN2; TRACE; TROPHY; Val-HeFT; VALIANT; VALUE; VA COOP II) reported incident cancer alone and 24 studies (APSIS; ANBP; DIABHYCAR; E-COST; IDNT; INTACT; MAPHY; MRC; MRCOA; OPTIMAAL; OSLO; Otsuka; PAT; Practolol Study; REIN-2; SAVE; SHEP; SPRINT; SMT; Suzuki; Syst-China; UKPDS; V-HeFT II; Wilcox) only reported cancer-related deaths.

BP-lowering agents: Overall, 55,294 were randomised to ACEI, 86,558 to ARB, 40,115 to BB, 73, 627 to CCB, and 32, 534 to TZ, as shown in **Table 3.1**.
ACEI was used in 27 studies (ABCD; AIPRI; ALLHAT; CAMELOT; CHARM Added ; DEMAND; DIABHYCAR; ESPIRAL; FACET; HOPE; NESTOR ; ONTARGET; OPTIMAAL; Otsuka; PARADIGM-HF; PHARAO; PHYLLIS; SAVE; SCAT; SOLVD-P; SOLVD-T; STOP-HTN2; TRACE; UKPDS; Val-HeFT; VALIANT; V-HeFT II). The ACEI subclasses were further categorised into tissue ACEI and non-tissue ACEI. Four tissue ACEI (benazepril, quinapril, ramipril, and trandolapril) and five non-tissue ACEI (captopril, delapril, enalapril, fosinopril, and lisinopril) were used. However, two studies (CHARM Added; Val-HeFT) did not specify the ACEI subclass used. Among the ACEI subclasses, ramipril was mostly used as it was allocated to 31.3% of the patients randomised to the ACEI arm in four studies (DIABHYCAR; HOPE; ONTARGET; PHARAO).

ARB was used in 32 studies (ACTIVE I; ALPINE; ANTIPAF; CASE-J Ex; CHARM (Overall); DIRECT (Overall); E-COST; GISSI-AF; HIJ-CREATE; IDNT; I-PRESERVE; IRMA-2; LIFE; NHS; NAVIGATOR; OCTOPUS; ONTARGET; OPTIMAAL; PREVER-Treatment; PRoFESS; RENAAL; SCOPE; TRANSCEND; TROPHY; Val-HeFT; VALIANT; VALUE). Overall, six ARB subclasses (candesartan, irbesartan, losartan, olmesartan, telmisartan, and valsartan) were used in these studies. Of these, telmisartan was commonly used as it was allocated to 34.8% of the patients randomised to the ARB arm in three studies (ONTARGET; PRoFESS; TRANSCEND).

CCB was used in 30 studies (ABCD; ACTION; ALLHAT; APSIS: ASCOT-BPLA; CAMELOT; CASE-J Ex; CONVINCE; DAVIT II; ESPIRAL; FACET; FEVER; IDNT; INSIGHT; INTACT; INVEST; Kanamasa; MIDAS; NHS; NICOLE; NICS-EH; PRAISE; PREVENT; REIN-2; SPRINT; STOP-HTN2; Syst-China; Syst-Eur; VALUE; VERDI).

With regards to CCB subclasses, seven DHP agents (amlodipine, felodipine, isradipine, nicardipine, nifedipine, nisoldipine, and nitrendipine) and two non-DHP agents (diltiazem and verapamil) were used. Amlodipine was commonly used as it was allocated to almost half (42.5%) of the total patients randomised to the CCB arm in ten studies (ALLHAT; ASCOT-BPLA; CAMELOT; CASE-J Ex; FACET; IDNT; NHS; PRAISE; PREVENT; VALUE).

Diuretics were used in 18 studies (ALLHAT; ALPINE; ANBP; EWPHE; INSIGHT; La Croix; MAPHY; MIDAS; MRC; MRCOA; NESTOR; NICS-EH; OSLO; PHYLLIS; PREVER-Treatment; SHEP; VA COOP; VERDI).

For diuretics subclasses, four TZ (bendroflumethiazide, chlorothiazide, HCTZ, and trichloromethiazide) and two TZ-like diuretics (chlorthalidone and indapamide) were used. In between the diuretics, chlorthalidone was mostly used as it was allocated to more than half (55.2%) of the total participants randomised to the diuretics arm in three studies (ALLHAT; PREVER-Treatment; SHEP).

BB was used in 16 studies (APSIS; ASCOT-BPLA; BHAT; HEP; INVEST; LIFE; MAPHY; MERIT-HF; MRC; MRCOA; PAT; Practolol Study; SMT; UKPDS-38; VA COOP II; Wilcox). The BB subclasses included three cardioselective (atenolol, metoprolol, and practolol) and one non-cardioselective (propranolol). Atenolol was commonly

used as it was allocated to 68.1% of the total patients randomised to the BB arm in six studies (ASCOT-BPLA; HEP; INVEST; LIFE; MRCOA; UKPDS-38).

Treatment adherence: A total of 57 studies reported participants' adherence to study treatments ranging from 31% to 100% while the remaining 33 studies (ABCD; AIPRI; ANTIPAF; APSIS; CAMELOT; DEMAND; DIRECT (Overall); ESPIRAL; EWPHE; HIJ-CREATE; IDNT; INSIGHT; INTACT; Kanamasa; MAPHY; NHS; NICS-EH; OSLO; PHYLLIS; Practolol Study; PREVER-Treatment; REIN-2; SHEP; Suzuki Syst-China; Syst-Eur; TROPHY; Val-HeFT; VA COOP II; VERDI; Wilcox) did not provide any information on adherence.

Table 3-2: Summary of BP-lowering agents used in RCTs included in this systematic review.
Red highlights indicate the highest N or %.

AHT class	ACEI		ARB		CCB		Diuretics		BB	
N of RCTs	27		32		30		18		16	
N of participants	51,681		86,558		73, 627		32,534		40,115	
% of participants	13.18		22.09		18.78		8.3		10.24	
AHT subclasses	Tissue ACEI		AT-II receptor antagonists		DHP		Thiazide		Cardioselective	
	Benazepril	0.58%	Candesartan	16.07%	Amlodipine	42.94%	Bendroflumethiazide	13.21%	Atenolol	68.61%
	Quinapril	0.25%	Irbesartan	8.74%	Felodipine	9.78%	Chlorothiazide	5.29%	Metoprolol	10.37%
	Ramipril	31.29%	Losartan	9.73%	Isradipine	0.60%	Hydrochlorothiazide	24.8%	Practolol	3.80%
	Trandolapril	1.70%	Olmesartan	0.52%	Nicardipine	0.29%	Trichloromethiazide	0.65%	Non-cardioselective	
	Non-tissue ACEI		Telmisartan	34.83%	Nifedipine	12.42%	Thiazide-like		Propanolol	17.22%
	Captopril	17.72%	Valsartan	29.90%	Nisoldipine	0.87%	Chlorthalidone	55.18%		
	Delapril	0.25%	Non-specific		Nitrendipine	4.96%	Indapamide	0.87%		
	Enalapril	22.55%	ARB	0.21%	Non-DHP					
	Fosinopril	0.86%			Diltiazem	0.00				
	Lisinopril	17.52%			Verapamil	0.28				
	Non-specific									
	ACEI	7.29%								

3.2.2.1 Characteristics of included studies (ordered by study ID)

ABCD [2] **(1998) (Estacio et al., 1998)**
Design: Prospective, randomized, double-blind, parallel trial. **Mean duration of follow-up:** 5.6 years
Participants: 470 participants with NIDDM and hypertension **Age range:** 40-74 (mean: 57.5 yrs.) **Hypertensive patients (%):** 100 **Baseline cancer(%):** Not reported
Intervention: 2 treatment group **CCB**: nisoldipine 5-40mg/day vs **ACEI**: enalapril10-60mg/day **Co-intervention:** if BP goal was not achieved, other BP-lowering agents were added (Metoprolol and HCTZ)
Primary and secondary outcomes: 24-hour creatinine clearance, CV events, end-organ damage, urinary albumin excretion and LVH.
Funding Source: Bayer Pharmaceuticals

ACTION (2006);(Poole-Wilson et al., 2006)
Design: Prospective, randomized, double-blinded, parallel trial **Mean duration of follow-up:** 4.9 years
Participants: 7665 participants with treated stable symptomatic coronary artery disease (stable angina). **Age range :** 35-older (mean: 63.5yrs) **Hypertensive patients (%):** 52 **Baseline cancer(%):** 4.4
Intervention: 2 treatment group **CCB**: nifedipine GITS 60mg/day or **Placebo** **Co-intervention:** if BP goal was not achieved, other BP-lowering agents were added (except CCB)
Primary and secondary outcomes: Major CV event-free survival, combined endpoint for safety, any CV event; death, or procedure; and any vascular event or procedure.
Funding Source: Bayer Healthcare AG, Wuppertal, Germany

ACTIVE I (2011); (The ACTIVE I Investigators, 2011)
Design: Multicentre, partial factorial, randomized, double-blind, placebo-controlled trial **Mean duration of follow-up:** 4.1 years
Participants: 9016 participants with a history of a risk factor for stroke and permanent AF or had at least two episodes of intermittent AF in the last 6 months. **Age range:** 75-older (mean: 69.6 yrs.) **Hypertensive patients (%):** 88 **Baseline cancer(%):**Not reported
Intervention: 2 treatment group **ARB**: irbesartan 300mg/day vs **Placebo** **Co-intervention:** ACTIVE W: clopidogrel plus aspirin vs anticoagulants; ACTIVE A: clopidogrel vs placebo
Primary and secondary outcomes: First occurrence of stroke, MI, vascular death, and hospitalization for HF.
Funding Source: Bristol-Myers Squibb and Sanofi-Aventis[2]

AIPRI (1996);(Maschio et al., 1996)
Design: Prospective, randomized, double-blinded, parallel trial **Mean duration of follow-up:** 3 years
Participants: 583 patients with renal insufficiency caused by various disorders

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

Age range: 18-70 (mean: 51 yrs.) **Hypertensive patients (%):** 82 **Baseline cancer(%):** None
Intervention: 2 treatment group **ACEI**: Benazepril 10 mg/day vs **Placebo** **Co-intervention:** No other BP lowering agents were added
Primary and secondary outcomes: time from the initiation therapy to a doubling of the serum creatinine concentration or the need for dialysis; changes over time in the values for serum creatinine, urinary protein excretion, and diastolic pressure; adjustments in antihypertensive therapy
Funding Source: Boehringer Ingelheim, Bayer Schering Pharma and GSK

ALLHAT (2002) (The ALLHAT Collaborative Research Group, 2002)
Design: Prospective, randomized, double-blinded, parallel trial **Mean duration of follow-up:** 4.9 years
Participants: 33 357 hypertensive patients with at least one risk factor for CHD events. **Age range:** 55-older (mean: 67 yrs.) **Hypertensive patients (%):** 100 **Baseline cancer(%):** Not reported
Intervention: 3 treatment groups **ACEI**: Lisinopril 10-40 mg/day vs **CCB**: amlodipine 2.5-10 mg/day vs **TZ**: chlorthalidone 25 mg/day **Co-intervention:** if BP goal was not achieved, other BP-lowering agents were added consecutively (atenolol, reserpine, clonidine, or hydralazine)
Primary and secondary outcomes: fatal CHD or non-fatal MI combined, all-cause mortality, stroke, combined CHD, and combined CVD
Funding Source: Pfizer

ALPINE (2003) (Lindholm et al., 2003)
Design: Prospective, randomized, double-blinded, parallel trial **Mean duration of follow-up:** 1 year
Participants: 392 participants with hypertension. **Age range:** Not reported (mean: 55 yrs.) **Hypertensive patients (%):** 100 **Baseline cancer(%):** Not reported
Intervention: 2 treatment groups **ARB**: Candesartan cilexetil 16mg/day vs **TZ**: HCTZ 25mg/day **Co-intervention:** if BP goal was not achieved, other BP-lowering agents were added consecutively (felodipine was added to the candesartan group and Atenolol was added to the HCTZ group)
Primary and secondary outcomes: glucose and lipoprotein metabolism, electrolytes, BP, and subjective symptoms
Funding Source: Department of Public Health and Clinical Medicine, Umea˚ University, Sweden together with AstraZeneca R&D, Molndal, Sweden and Hassle Lakemedel AB, Sweden.

ANBP (1980);(The ANBP Study Commitee, 1980)
Design: Prospective, randomized, double-blinded, parallel trial **Mean duration of follow-up:** 4.1 years
Participants: 3427 participants with mild hypertension **Age range:** 30-69 (mean: 50.5 yrs.) **Hypertensive patients (%):** 100 **Baseline cancer (%):** Not reported
Intervention: 2 treatment groups **TZ**: Chlorothiazide 500mg - 1g/ day vs **Placebo**

Co-intervention: if BP goal was not achieved, other BP-lowering agents were added consecutively (methyldopa, propranolol, pindolol, hydralazine or clonidine).
Primary and secondary outcomes: Death from any cause, peripheral vascular events, TIA, MI, other IHD, HF, dissecting aneurysm of the aorta, retinal haemorrhages, hypertensive encephalopathy, and onset of renal failure.
Funding Source: National Health and Medical Research Council of Australia, the Life Insurance Medical Research Fund of Australia and New Zealand, the Victorian Government, the Clive and Vera Ramaciotti Foundations, and the Raine medical Research Foundation of Western Australia

ANTIPAF (2012)(Goette et al., 2012)
Design: Prospective, randomized, double-blinded, parallel trial **Mean duration of follow-up:** 1 year
Participants: 430 participants with paroxysmal AF. **Age range:** 18-older (mean: 61.5 yrs.) **Hypertensive patients (%):** 49 **Baseline cancer(%):** Not reported
Intervention: 2 treatment groups **ARB**: olmesartan 40mg/day vs **Placebo** **Co-intervention:** if BP goal was not achieved, other BP-lowering agents were added (diuretics, CCBs, and antiadrenergic agents.
Primary and secondary outcomes: Percentage of days with documented episodes of paroxysmal AF, time to the first occurrence of AF, number of hospitalizations for AF and stroke, quality of life.
Funding Source: German Ministry of Research and Education. Daiichi Sankyo Deutschland GmbH (Munich, Germany)

APSIS (1996);(Rehnqvist et al., 1996)
Design: Prospective, randomized, double-blinded, parallel trial **Median duration of follow-up:** 3.4 years
Participants: 809 patients with stable angina pectoris **Age range:** 70 or younger (mean: 59 yrs.) **Hypertensive patients (%):** 27 **Baseline cancer(%):** Not reported
Intervention: 2 treatment groups **BB**: metoprolol 25-200 mg/day vs **CCB**: verapamil 40-240 mg twice/day **Co-intervention:** No other BP lowering agents were added
Primary and secondary outcomes: Death, CV events, cerebrovascular events, peripheral vascular events, psychological variables reflecting the quality of life.
Funding Source: Swedish Heart Lung Foundation, the Swedish Research Medical Council, Knoll AG, Germany and Astra Hassle, Sweden.

ASCOT-BPLA (2005) (Dahlöf et al., 2005)
Design: Prospective, randomized, open-label, blinded-endpoint trial (PROBE) **Mean duration of follow-up:** 5.7 years
Participants: 19,257 participants with hypertension and had at least three other CV risk factors **Age range:** 40-79 (mean: 63 yrs.) **Hypertensive patients (%):** 100 **Baseline cancer(%):** Not reported
Intervention: 2 treatment groups **CCB**: 5-10mg/day with 4-8mg/day vs **BB**: 50-100mg/day atenolol **Co-intervention:** if BP goal was not achieved, other BP-lowering agents were added as required (perindopril was added to CCB-based therapy and bendroflumethiazide was added to BB-based therapy).

Primary and secondary outcomes: non-fatal MI and fatal CHD, all-cause mortality, total stroke, primary end point minus silent MI, all coronary events, total CV events and procedures, CV mortality, non-fatal and fatal HF, CHD, PVD, life-threatening arrhythmias, development of T2DM, development of renal impairment
Funding Source: Pfizer

BHAT (1982) (Anonymous, 1982)
Design: Prospective, randomized, double-blinded, parallel trial **Mean duration of follow-up:** 2.1 years
Participants: 3837 participants who had at least one documented MI **Age range:** 30-69 (mean: 54.8 yrs.) **Hypertensive patients (%):** 41 **Baseline cancer(%):** Not reported
Intervention: 2 treatment groups **BB**: Propanolol hydrochloride 180-240 mg/day vs **Placebo** **Co-intervention:** No other BP lowering agents were added
Primary and secondary outcomes: All-cause mortality, CHD mortality, sudden cardiac death, CHD mortality plus non-fatal MI.
Funding Source: National Heart, Lung, and Blood Institute (NHLBI)

CAMELOT (2004); (Nissen et al., 2004)
Design: Prospective, randomized, double-blinded, parallel trial **Mean duration of follow-up:** 2 years
Participants: 1997 participants with angiographically documented CAD and DBP 100 mm Hg **Age range:** 30-79 (mean: 57.7 yrs.) **Hypertensive patients (%):** 60.4 **Baseline cancer(%):** Not reported
Intervention: 3 treatment groups **CCB**: amlodipine 5mg/day + 1 tab placebo vs **ACEI**: enalapril 10mg/day + 1 tab placebo vs **Placebo** **Co-intervention:** No other BP lowering agents were added
Primary and secondary outcomes: Incidence of adverse CV events, the incidence of adverse events for enalapril treatment versus placebo and comparison of the amlodipine treatment group versus enalapril group, all-cause mortality and the incidence of revascularization in vessels that had undergone previous stent placement
Funding Source: Pfizer

CASE-J Ex (2011); (Ogihara et al., 2011)
Design: Prospective, randomized, open-label, blinded-endpoint trial (PROBE) **Mean duration of follow-up:** 4.5 years
Participants: 4703 with high-risk hypertension (at least one risk factor for CVD) **Age range:** 25-85 (mean: 63.9 yrs.) **Hypertensive patients (%):** 100 **Baseline cancer(%):** None
Intervention: 2 treatment groups **ARB**: Candesartan 4-12 mg/day vs **CCB**: Amlodipine 2.5- 10 mg/day **Co-intervention:** no other BP-lowering agents were added
Primary and secondary outcomes: Sudden death, cerebrovascular events, cardiac events, renal dysfunction, all deaths, left ventricular MI, the proportion of the subjects who withdrew from the allocated treatment **Extension study primary and secondary outcomes:** Fatal/non-fatal CV events, all-cause death, CV death, new-onset diabetes
Funding Source: Takeda Pharmaceutical and Pfizer Japan.

CHARM-Added (2003); (McMurray et al., 2003)
Design: Prospective, randomized, double-blinded, parallel trial **Median duration of follow-up:** 3.4 years
Participants: 2548 patients with NYHA class II-IV and left ventricular EF= 40% or lower, and who are being treated with ACEI. **Age range:** 18-older (mean: 64.1 yrs.) **Hypertensive patients (%):** 48 **Baseline cancer(%):** 6
Intervention: 2 treatment groups **ARB**: Candesartan 4-32mg/day vs **Placebo** **Co-intervention:** no other BP-lowering agents were added
Primary and secondary outcomes: All-cause and CV death, unplanned admission to hospital for the management of worsening CHF, non-fatal MI, non-fatal stroke, or coronary revascularization, development of new diabetes.
Funding Source: Astra-Zeneca

CHARM-Alternative (2003) (Granger et al., 2003)
Design: Prospective, randomized, double-blinded, parallel trial **Median duration of follow-up:** 2.8 years
Participants: 2028 patients with NYHA class II-IV and left ventricular EF= 40% or lower, and who are intolerance to ACEI. **Age range:** 18-older (mean: 67 yrs.) **Hypertensive patients (%):** 50 **Baseline cancer(%):** 6.6
Intervention: 2 treatment groups **ARB**: Candesartan 4-32mg/day or **Placebo** **Co-intervention:** no other BP-lowering agents were added
Primary and secondary outcomes: All-cause and CV death, unplanned admission to hospital for the management of worsening CHF, non-fatal MI, non-fatal stroke, or coronary revascularization, development of new diabetes.
Funding Source: Astra-Zeneca

CHARM-Preserved (2003); (Yusuf et al., 2003)
Design: Prospective, randomized, double-blinded, parallel trial **Median duration of follow-up:** 3.1 years
Participants: 3023 patients with NYHA functional class II–IV and had LVEF higher than 40% **Age range:** 18-older (mean: 67.2 yrs.) **Hypertensive patients (%):** 64 **Baseline cancer(%):** 7.5
Intervention: 2 treatment groups **ARB**: Candesartan 4-32mg/day vs **Placebo** **Co-intervention:** no other BP-lowering agents were added
Primary and secondary outcomes: All-cause and CV death, unplanned admission to hospital for the management of worsening CHF, non-fatal MI, non-fatal stroke, or coronary revascularization, development of new diabetes.
Funding Source: Astra-Zeneca

CONVINCE (2003) (Black et al., 2003)
Design: Prospective, randomized, double-blinded, parallel trial **Mean duration of follow-up:** 3 years
Participants: 16602 participants with hypertension and had 1 or more additional risk factors for CVD. **Age range: 55-older** (mean: 65.6 yrs.) **Hypertensive patients (%):** 100

Baseline cancer(%): Not reported
Intervention: 2 treatment groups **CCB**: COER verapamil 180 mg/day vs **non-CCB** :Atenolol 50 mg/day or HCTZ 12.5 mg/day **Co-intervention:** if BP goal was not achieved, other BP-lowering agents were added as step 2 (HCTZ and atenolol). Any additional open-labelled BP-lowering agents (except a non-DHP CCB, TZ, or BB) could be added as a step 3 if needed.
Primary and secondary outcomes: first occurrence of stroke, MI, or CV disease-related death, hospitalizations for CVD end-points, all-cause mortality, cancer, hospitalizations for bleeding (excluding haemorrhagic stroke), the incidence of primary end points occurring between 6 AM and noon.
Funding Source: G.D. Searle & Co and Pharmacia

DAVIT II (1999) (Sajadieh et al., 1999)
Design: Prospective, randomized, double-blinded, parallel trial **Mean duration of follow-up:** 1.3 years
Participants: 1775 patients with the diagnosis of acute MI (post MI 2 weeks) **Age range**: 76 or younger (mean: 60.7 years) **Hypertensive patients (%):** 14 **Baseline cancer(%):** Not reported
Intervention: 2 treatment groups **CCB**: verapamil 120 mg three times/day vs **Placebo** **Co-intervention:** no other BP-lowering agents were added
Primary and secondary outcomes: total mortality and first major event (i.e., death or reinfarction).
Funding Source: Knoll Aktiengesellschaft

DEMAND (2011) (Ruggenenti et al., 2011)
Design: Prospective, randomized, double-blinded, parallel trial **Median duration of follow-up:** 3.8 years
Participants: 380 participants with hypertension and T2DM (with albuminuria <200mg/min) **Age range**: 40-older (mean: 61.2 years) **Hypertensive patients (%):** 100 **Baseline cancer(%):** Not reported
Intervention: 3 treatment groups **CCB+ACEI**: manidipine 10 mg/day plus delapril 30mg/day vs **ACEI:** delapril 30 mg/day vs **Placebo** **Co-intervention:** Additional antihypertensive agents were allowed in the following steps: (1) HCTZ, indapamide, or furosemide (2) Β- or α-Β blockers; and (3) doxazosin, prazosin, clonidine hydrochloride or α-methyldopa. **Notes**: For this review, only the monotherapy arms were considered.
Primary and secondary outcomes: Rate of GFR decline, composite end-point of death from CV causes, sudden death; non-fatal MI or stroke; coronary revascularization; amputation; vascular surgery for peripheral atherosclerotic artery disease; new-onset, progression, or regression of retinopathy and peripheral neuropathy.
Funding Source: Independent academic trial

DIABHYCAR (2004) (Marre et al., 2004)
Design: Prospective, randomized, double-blinded, parallel trial **Median duration of follow-up:** 4 years
Participants: 4912 patients with T2DM who use oral antidiabetic drugs and have persistent microalbuminuria or proteinuria, and serum creatinine ≤ 150 µmol/l. **Age range**: 50-older (mean: 65.1 years) **Hypertensive patients (%):** 56 **Baseline cancer(%):** Not reported
Intervention: 2 treatment groups

ACEI: ramipiril 1.25mg/day vs **Placebo** **Co-intervention:** On top of usual treatment
Primary and secondary outcomes: incidence of CV death, fatal and non-fatal MI, stroke, HF, leading to hospital admission, and ESRF; all-cause death; any revascularisation procedure on coronary or other arterial vessels, transient neurological ischaemic episodes, doubling of the serum creatinine concentration, loss of vision in one eye, and amputation above the metatarsophalangeal joint.
Funding Source: Avantis (Paris) and the French Health Ministry

DIRECT-Prevent 1 (2008) (Chaturvedi et al., 2008)
Design: Prospective, randomized, double-blinded, parallel trial **Median duration of follow-up:** 4.7 years
Participants: 1421 participants with normotensive, normoalbuminuric type 1 diabetes without retinopathy **Age range**: 18-50 (mean: 29.7 years) **Hypertensive patients (%):** None **Baseline cancer(%):** Not reported
Intervention: 2 treatment groups **ARB**: candesartan 32 mg/day vs **Placebo** **Co-intervention**: no other BP-lowering agents were added
Primary and secondary outcomes: incidence and progression of retinopathy.
Funding Source: AstraZeneca and Takeda

DIRECT-Protect 1 (2008) (Chaturvedi et al., 2008)
Design: Prospective, randomized, double-blinded, parallel trial **Mean duration of follow-up:** 4.8 years
Participants: 1905 participants with normotensive, normoalbuminuric type 1 diabetes with retinopathy **Age range**: 18-55 (mean: 31.7 years) **Hypertensive patients (%):** None **Baseline cancer(%):** Not reported
Intervention: 2 treatment groups **ARB**: candesartan 32 mg/day vs **Placebo** **Co-intervention**: no other BP-lowering agents were added
Primary and secondary outcomes: incidence and progression of retinopathy.
Funding Source: AstraZeneca and Takeda

DIRECT-Protect 2 (2008) (Sjølie et al., 2008)
Design: Prospective, randomized, double-blinded, parallel trial **Mean duration of follow-up:** 4.7 years
Participants: 1905 participants with normoalbuminuric, normotensive, or treated hypertensive people with T2DM with mild to moderately severe retinopathy. **Age range**: 37-75 (mean: 56.9 years) **Hypertensive patients (%):** 62 **Baseline cancer(%):** Not reported
Intervention: 2 treatment groups ARB: candesartan 32 mg/day vs placebo **Co-intervention**: no other BP-lowering agents were added
Primary and secondary outcomes: incidence and progression of retinopathy.
Funding Source: AstraZeneca and Takeda

E-COST (2005) (Suzuki and Kanno, 2005)
Design: Prospective, randomized, open-label, parallel trial **Mean duration of follow-up:** 3.1 years
Participants: 2048 participants with essential hypertension **Age range**: 35-79 (mean: 67 years) **Hypertensive patients (%):** 100 **Baseline cancer(%):** Not reported
Intervention: 2 treatment groups **ARB**: candesartan 4-8mg/day vs **Control**: Conventional therapy **Co-intervention:** Other antihypertensive drugs were added as necessary (not specified)
Primary and secondary outcomes: Stroke, MI and CHF, which included fatal and non-fatal incidence
Funding Source: Not reported

ESPIRAL (2001) (Marin, 2001)
Design: Prospective, multicentre, randomized, open-label, parallel study **Mean duration of follow-up:** 3 years
Participants: 241 participants with hypertension and chronic renal failure. **Age range**: 24-74 (mean: 56 years) **Hypertensive patients (%):** 100 **Baseline cancer(%):** Not reported
Intervention: 2 treatment groups **ACEI**: fosinopril 10-30 mg/day vs **CCB**: nifedipine GITS 30-60 mg/day **Co-intervention:** Additional antihypertensive agents were allowed in the following steps: (1)Furosemide, (2) atenolol (3) doxazosin
Primary and secondary outcomes: Time elapsed until the serum creatinine values doubled, or the need to enter the dialysis programme; CV events, proteinuria evolution and serum creatinine values
Funding Source: Not reported

EWPHE (1985)(Amery et al., 1985)
Design: Prospective, multicentre, randomized, double-blinded, parallel trial **Mean duration of follow-up:** 4.7 years
Participants: 840 elderly participants with hypertension **Age range**: 60-older (mean: 72 years) **Hypertensive patients (%):** 100 **Baseline cancer(%):** None
Intervention: 2 treatment groups **TZ**: HCTZ 25 mg/day plus triamterene 50mg/day vs **Placebo** **Co-intervention:** if BP goal was not achieved, other BP-lowering agents were added (methyldopa).
Primary and secondary outcomes: Deaths; CV morbidity (non-fatal cerebral or subarachnoid haemorrhage, development of hypertensive retinopathy grade III or IV, dissecting, aneurysm, CHF)
Funding Source: Belgian National Research Foundation (NFWO) and through grants from Merck, Sharpe and Dohme, and Smith, Kline, and French.

FACET (1998) (Tatti et al., 1998)
Design: Prospective, randomized, open-label, blinded-endpoint trial (PROBE) **Mean duration of follow-up:** 2.9 years
Participants: 380 participants with hypertension and T2DM **Age range**: Not reported (mean: 63.1 years)

Hypertensive patients (%): 100 **Baseline cancer(%):** Not reported
Intervention: 2 treatment groups **ACEI**: fosinopril 20mg/day vs **CCB**: amlodipine 10 mg/day **Co-intervention:** If BP was not controlled on monotherapy, the other study drug was added at full dose (not specified).
Primary and secondary outcomes: Blood examination test; all-cause mortality; any major vascular events or procedure; cancer.
Funding Source: Bristol-Myers Squibb

FEVER (2005) (Liu et al., 2005)
Design: Prospective, multicentre, randomized, double-blinded, parallel trial **Mean duration of follow-up:** 3.3 years
Participants: 9711 Chinese participants with hypertension and one or two additional CV risk factors or disease **Age range**: 50-79 (mean: 61.5 years) **Hypertensive patients (%):** 100 **Baseline cancer(%):** Not reported
Intervention: 2 treatment groups **CCB**: Felodipine 5mg/day vs **Placebo** **Co-intervention:** Background therapy of HCTZ 12.5 mg/day throughout the trial in both treatment arms. If BP was not controlled, further 12.5 mg HCTZ dose given as open label was allowed and subsequently other AHT agents (except CCB).
Primary and secondary outcomes: Time to the first stroke; all CV events, cardiac events, all-cause death.
Funding Source: National Science and Technology Ministry, China and partly by Beijing Hypertension League Institute, and Shanxi Kangbao Pharmaceutical Company.

GISSI-AF (2009) (The GISSI-AF Investigators, 2009)
Design: Prospective, multicentre, randomized, double-blinded, parallel trial **Mean duration of follow-up:** 1 year
Participants: 1442 patients with AF. **Age range**: 40-older (mean: 68 years) **Hypertensive patients (%):** 85 **Baseline cancer(%):** 3.1
Intervention: 2 treatment groups **ARB**: valsartan 80-320mg/day vs **Placebo** **Co-intervention:** no other BP-lowering agents were added.
Primary and secondary outcomes: time to the first recurrence of AF; the proportion of patients who had more than one episode of AF over the 1-year follow-up period; total number of episodes of AF per patient, hospitalization for any reason and for a CV event, the composite of death and thromboembolic events, the number of patients in sinus rhythm at the time of each study visit, the duration of and ventricular rate at the first recurrence of AF, and a safety profile.
Funding Source: Novartis

HEP (1986) (Coope, 1986)
Design: Prospective, randomized, open-label, blinded-endpoint trial (PROBE) **Mean duration of follow-up:** 4.4 years
Participants: 884 elderly participants with hypertension **Age range**: 60-79 (mean: 68.8 years) **Hypertensive patients (%):** 100 **Baseline cancer(%):** Not reported
Intervention: 2 treatment groups

BB: 100mg/day atenolol vs **Control**: no treatment **Co-intervention:** Additional antihypertensive agents were allowed in the following steps: (2) bendrofluazide or (3) α-methyldopa.
Primary and secondary outcomes: Any CV events, clinical gout, T2DM, non-fatal cancer, vertigo and dizzy spells, all-cause death
Funding Source: Imperial Chemical Industries

HIJ-CREATE (2012) (Kasanuki et al., 2009, Sugiura et al., 2012)
Design: Prospective, randomized, open-label, blinded-endpoint trial (PROBE) **Median duration of follow-up:** 4.3 years
Participants: 2049 hypertensive participants with angiographically documented CAD **Age range**: 20-80 (mean: 64.8 years) **Hypertensive patients (%):** 100 **Baseline cancer(%):** None
Intervention: 2 treatment groups **ARB**: candesartan 4–12 mg/day vs **Control**: Non-ARB **Co-intervention:** Additional antihypertensive agents were allowed (exclude ACEI).
Primary and secondary outcomes: time to a first major adverse cardiac event, angioplasty, stenting or coronary artery bypass grafting; new onset diabetes.
Funding Source: Japan Research Promotion Society for CV Diseases

HOPE (2002) (The HOPE Study Investigators, 2000)
Design: Prospective, randomized, double-blind, two-by-two factorial, placebo-controlled trial **Mean duration of follow-up:** 5 years
Participants: High risk patients with CAD, stroke, peripheral vascular disease or diabetes plus at least one other CV risk factor **Age range**: 55-older (mean: 66 years) **Hypertensive patients (%):** 47 **Baseline cancer(%):** Not reported
Intervention: 2 treatment groups **ACEi**: 10 mg/day ramipiril vs **Placebo** **Co-intervention:** no other BP-lowering agents were added. **Notes:** Additional randomised treatment: Vitamin E 400 IU vs Placebo
Primary and secondary outcomes: Composite of MI, stroke or CV mortality, all-cause mortality, revascularization, hospitalization for CV morbidity and complications related to diabetes
Funding Source: Medical Research Council of Canada, Hoechst-Marion Roussel, AstraZeneca, King Pharmaceuticals, Natural Source Vitamin E Association and Negma, and the Heart and Stroke Foundation of Ontario research Chair.

I-PRESERVE (2010) (Zile et al., 2010)
Design: Prospective, multicentre, randomized, double-blinded, parallel trial **Mean duration of follow-up:** 4.1 years
Participants: 4128 participants with HF and preserved LVEF ≥ 45%. **Age range**: 60 – older (mean: 72 years) **Hypertensive patients (%):** 64 **Baseline cancer(%):** Not reported
Intervention: 2 treatment groups **ARB**: irbesartan 75-300mg/day vs **Placebo** **Co-intervention:** no other BP-lowering agents were added.
Primary and secondary outcomes: Time to first occurrence of the composite outcome of death or CV hospitalization, CV death; all-cause mortality, combined vascular endpoint, combined HF endpoint, HF mortality or hospitalizations; quality of life, change in NYHA functional class, change in patient global assessment of symptoms, N-terminal B-type natriuretic peptide levels in blood.

Funding Source: Bristol-Myers Squibb and Sanofi-Aventis

IDNT (2003) (Berl et al., 2003)
Design: Prospective, multicentre, randomized, double-blinded, parallel trial **Median duration of follow-up:** 2.6 years
Participants: 1715 participants (treatment, control) with hypertension and T2DM nephropathy **Age range**: 30-70 (mean: 59 years) **Hypertensive patients (%):** 100 **Baseline cancer(%):** Not reported
Intervention: 3 treatment groups **ARB**: Irbesartan 300mg/day vs **CCB**: Amlodipine 10 mg/day vs Placebo **Co-intervention:** if BP goal was not achieved, other open BP-lowering agents were added (excluding ACEI, ARB, and CCB).
Primary and secondary outcomes: time to a composite end-point of doubling of baseline serum creatinine, ESRD, and death; time to a composite end-point of fatal or non-fatal CV events
Funding Source: Bristol-Myers Squibb Pharmaceutical Research Institute and Sanofi-Synthelabo

INSIGHT (2000) (Brown et al., 2000)
Design: Prospective, multicentre, randomized, double-blinded, parallel trial **Median duration of follow-up:** 2.6 years
Participants: 6321 participants with hypertension and at least one additional CV risk factor **Age range**: 55-80 (mean: 65 years) **Hypertensive patients (%):** 100 **Baseline cancer(%):** Not reported
Intervention: 2 treatment groups **CCB**: nifedipine: 30 mg/day vs **TZ**: amiloride + HCTZ: 2.5 mg/day + 25 g/day **Co-intervention:** if BP goal was not achieved, other BP-lowering agents were added (including atenolol and enalapril, excluding CCBs and diuretics)
Primary and secondary outcomes: CV death, MI, HF, or stroke
Funding Source: Bayer AG.

INTACT (1990) (Lichtlen, 1987, Lichtlen, 1990)
Design: Prospective, multicentre, randomized, double-blinded, parallel trial **Mean duration of follow-up:** 3 years
Participants: 425 participants showing mild CAD on arteriography. **Age range**: 65 or younger (mean: 53.1years) **Hypertensive patients (%):** Not reported **Baseline cancer(%):** Not reported
Intervention: 2 treatment groups **CCB**: nifedipine 80 mg/day vs **Placebo** **Co-intervention:** no other BP-lowering agents were added.
Primary and secondary outcomes: Changes in pre-existing stenosis (percentage and diameter of progression or regression)
Funding Source: Not reported

INVEST (2003) (Pepine et al., 2003)
Design: Prospective, randomized, open-label, blinded-endpoint trial (PROBE) **Mean duration of follow-up:** 2.7 years
Participants: 22576 participants with hypertension and CAD patients. **Age range**: 50-older (mean: 66.1 years) **Hypertensive patients (%):** 47 **Baseline cancer(%):** Not reported

Intervention: 2 treatment groups **CCB**: Verapamil Sustained Release 240-360mg/day vs **BB**: Atenolol 50-100mg/day **Co-intervention:** if BP goal was not achieved, other BP-lowering agents were added (including trandolapril and HCTZ).
Primary and secondary outcomes: the first occurrence of death from any cause, non-fatal MI, or non-fatal stroke; 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
Funding Source: Abbot Laboratories

IRMA-2 (2001) (Parving et al., 2001)
Design: Prospective, multicentre, randomized, double-blinded, parallel trial **Median Mean duration of follow-up:** 2 years
Participants: 590 participants with hypertension, T2DM and microalbuminuria. **Age range**: 30-70 (mean: 58 years) **Hypertensive patients (%):** 100 **Baseline cancer(%):** None
Intervention: 3 treatment groups **ARB**: irbesartan 150mg/day vs **ARB**: irbesartan 300mg/day vs **Placebo** **Co-intervention**: if BP goal was not achieved, other BP-lowering agents were added (excluding DHPs and ACEI).
Primary and secondary outcomes: Time from the base-line visit to the first detection of overt nephropathy, changes in the level of albuminuria, changes in creatinine clearance, and the restoration of normoalbuminuria by the time of the last visit.
Funding Source: Sanofi–Synthelabo and Bristol-Myers Squibb

Kanamasa et al (1998); (Ishikawa et al., 1997, Kanamasa et al., 1999)
Design: Prospective, randomized, open-label, clinical trial **Mean duration of follow-up:** 2.2 years
Participants: 1054 patients with healed MI **Age range**: Not reported (mean: 60 years) **Hypertensive patients (%):** 46 **Baseline cancer(%):** 0.4
Intervention: 2 treatment groups **CCB**: nifedipine 10-30mg/day short-acting and short-acting diltiazem 30-90mg/day vs **Control**: Non-CCB **Co-intervention:** no other BP-lowering agents were added.
Primary and secondary outcomes: Cardiac death and nonfatal, recurrent MI, cancer
Funding Source: Not reported

LaCroix et al (2000); (LaCroix, 2000)
Design: Prospective, single centre, randomized, double-blinded, parallel trial **Mean duration of follow-up:** 3 years
Participants: 320 healthy, normotensive elderly participants **Age range**: 60-79 (mean: 68 years) **Hypertensive patients (%):** None **Baseline cancer(%):** None
Intervention: 3 treatment groups **TZ**: HCTZ12.5mg/day vs **TZ**: HCTZ 25mg/day vs **Placebo** **Co-intervention:** no other BP-lowering agents were added.
Primary and secondary outcomes: Change in bone mineral density at the total hip, spine, and total body.
Funding Source: Ciba-Geigy and the National Institute of Health

LIFE (2002) (Dahlöf et al., 1997, Dahlöf et al., 2002)
Design: Prospective, multicentre, randomized, double-blinded, parallel trial **Mean duration of follow-up:** 4.8 years
Participants: 9193 participants with essential hypertension and LVH **Age range**: 55–80 (mean: 67 years) **Hypertensive patients (%):** 100 **Baseline cancer(%):** Not reported
Intervention: 2 treatment groups **ARB**: losartan 50-100mg/day vs **BB**: atenolol 50-100mg/day **Co-intervention:** if BP goal was not achieved, other BP-lowering agents were added (HCTZ 12.5-25mg/day, excluding ARB, ACEI and BB).
Primary and secondary outcomes: CVD mortality and mortality, total mortality, angina pectoris or CHF requiring hospital admission
Funding Source: Merck

MAPHY (1988)(Wikstrand, 1988)
Design: Prospective, multicentre, randomized, double-blinded, parallel trial **Median Mean duration of follow-up:** 4.2 years
Participants: 3234 participants with essential hypertension. **Age range**: 40-64 (mean: 52.6 years) **Hypertensive patients (%):** 100 **Baseline cancer(%):** None
Intervention: 2 treatment groups **TZ**: HCTZ 50mg/day or bendroflumethiazide 5 mg/day vs **BB**: metoprolol 200 mg/day **Co-intervention:** if BP goal was not achieved, other BP-lowering agents were added (hydralazine, spironolactone, or others but not BB or TZ).
Primary and secondary outcomes: Total mortality, sudden cardiac death, pooled incidence of fatal and nonfatal coronary events, stroke.
Funding Source: Swedish National Association Against Heart and Chest Diseases (Stockholm) and the Astra Cardiovascular Research Laboratories (Molndal).
Notes: This multicentre study was a subset of the HAPPHY trial. The analysis takes into consideration only 1 of the 2 BBs (metoprolol).

MERIT-HF (1999) (MERIT-HF Study Group, 1999)
Design: Prospective, multicentre, randomized, double-blinded, parallel trial **Mean duration of follow-up:** 1 year
Participants: 3991 participants with chronic HF (ejection fraction 40% or less). **Age range**: 40-80 (mean:63.8 years) **Hypertensive patients (%):** 44 **Baseline cancer(%):** Not reported
Intervention: 2 treatment groups **BB**: metoprolol CR/XL 12.5-200mg/day vs **Placebo** **Co-intervention:** no other BP-lowering agents were added.
Primary and secondary outcomes: Total mortality, combined endpoint of all-cause mortality and all-cause hospitalization); Pooled incidence of cardiac death and nonfatal acute MI; the number of hospitalizations due to HF and other CV causes Other: (1)Combined endpoint of all-cause mortality, hospitalizations due to HF, and emergency department visits due to HF (time to the first event) (2) Tolerability, defined as overall discontinuation of treatment and discontinuation due to worsening of HF (3) NYHA functional status
Funding Source: Astra Hassle AB, Molndal

MIDAS (1996) (Borhani et al., 1996)
Design: Prospective, multicentre, randomized, double-blinded, parallel trial **Mean duration of follow-up:** 3 years
Participants: 883 participants with hypertension. **Age range**: 40 –older (mean: 58.5 years) **Hypertensive patients (%):** 100 **Baseline cancer(%):** Not reported
Intervention: 2 treatment groups **CCB**: isradipine 5-10 mg/day vs **TZ**: 25-50 mg/day HCTZ **Co-intervention:** if BP goal was not achieved, other BP-lowering agents were added (enalapril 2.5-10 mg twice/day).
Primary and secondary outcomes: the rate of progression in mean maximum intimal media thickness (IMT) of carotid focal points
Funding Source: Sandoz Pharmaceuticals

MRC (1985) (MRC Working Party, 1985)
Design: Prospective, multicentre, randomized, single-blinded, parallel trial **Mean duration of follow-up:** 4.9 years
Participants: 17 354 participants with hypertension. **Age range**: 35-64 (mean: 52 years) **Hypertensive patients (%):** 100 **Baseline cancer(%):** Not reported
Intervention: 3 treatment groups **BB**: 240 mg/day propranolol vs **TZ**: 10 mg/day bendrofluazide vs **Placebo** **Co-intervention:** if BP goal was not achieved, other BP-lowering agents were added (methyldopa)
Primary and secondary outcomes: Fatal or non-fatal stroke, coronary events, fatal and non-fatal MI, other CV events and death from other cause.
Funding Source: Imperial Chemical Industries Ltd and Merck Sharp and Dohme.

MRCOA (1992) (MRC Working Party, 1992)
Design: Prospective, multicentre, randomized, single-blinded, parallel trial **Mean duration of follow-up:** 5.8 years
Participants: 4396 participants with hypertension. **Age range**: 65-74 (mean: 70.3 years) **Hypertensive patients (%):** 100 **Baseline cancer(%):** None
Intervention: 3 treatment groups **BB**: 50 mg/day atenolol vs **TZ**: 50 mg/day HCTZ and 5 mg/day amiloride (single tablet) or 25 mg/day HCTZ and 2.5 mg/day amiloride vs **Placebo** **Co-intervention:** if BP goal was not achieved, other BP-lowering agents were added in the following steps- (1) nifedipine up to 20 mg/day or matching placebo and (2) other antihypertensive drugs).
Primary and secondary outcomes: Fatal or non-fatal stroke, coronary events, fatal and non-fatal MI, other CV events and death from other cause.
Funding Source: Merck, Sharp and Dohme, Imperial Chemical Industries, and Bayer

NHS (2012) (Muramatsu et al., 2012)
Design: Prospective, randomized, open-label, blinded-endpoint trial (PROBE) **Median Mean duration of follow-up:** 3.2 years
Participants: 1150 participants with hypertension and T2DM or IGT. **Age range**: 30-75 (mean: 63 years) **Hypertensive patients (%):** 100 **Baseline cancer(%):** Not reported
Intervention: 2 treatment groups

ARB: valsartan 80 -160mg/day vs **CCB**: amlodipine 5 -10mg/day **Co-intervention:** if BP goal was not achieved, other BP-lowering agents were added (diuretics, ß-blockers, or α-blockers could be added after 8 weeks as needed).
Primary and secondary outcomes: a composite of CV morbidity and mortality
Funding Source: Nagoya University Graduate School of Medicine

NAVIGATOR (2010) (The NAVIGATOR Study Group, 2010)
Design: Prospective, multicentre, randomized, double-blinded trial with a 2-by-2 factorial design. **Mean duration of follow-up:** 5 years
Participants: 9306 patients with impaired glucose tolerance and established CVD or CV risk factors **Age range**: 18-older (mean: 63.7 years) **Hypertensive patients (%):** 75 **Baseline cancer(%):** Not reported
Intervention: 2 treatment groups **ARB**: valsartan 80-160 mg/day vs **Placebo** **Co-intervention:** no other BP-lowering agents were added. **Notes:** Additional randomised treatment: nateglinide vs placebo
Primary and secondary outcomes: (1) incidence of T2DM, (2) a composite of death from CV causes, nonfatal MI, nonfatal stroke, hospitalization for HF, arterial revascularization, or hospitalization for unstable angina, (3) core CV outcome
Funding Source: Novartis Pharma

NESTOR (2004) (Marre, 2003, Marre, 2004)
Design: Prospective, multicentre, randomized, double-blinded, parallel trial **Mean duration of follow-up:** 1 year
Participants: 570 patients with T2DM and hypertension **Age range**: 35-80 (mean: 60 years) **Hypertensive patients (%):** 100 **Baseline cancer(%):** Not reported
Intervention: 2 treatment groups **TZ**: indapamide SR 1.5 mg/day vs **ACEI**: enalapril 10 mg/day **Co-intervention:** if BP goal was not achieved, other BP-lowering agents were added (amlodipine 5-10 mg/day and atenolol 50-100mg/day)
Primary and secondary outcomes: (1) Microalbuminuria (2) BP measurements and variability following treatment (3) Ambulatory BP measurements (4) Potential genetic markers for albuminuria and CV risk.
Funding Source: Institut de Recherches Internationales Servier

NICOLE (2003) (Dens et al., 2003)
Design: Prospective, single centre, randomized, double-blinded, parallel trial **Mean duration of follow-up:** 3 years
Participants: 826 participants with CAD who underwent successful single or multiple vessel PTCA **Age range**: 75 or younger (mean: 60 years) **Hypertensive patients (%):** 41 **Baseline cancer(%):** Not reported
Intervention: 2 treatment groups **CCB**: nisoldipine SR 20-40mg/day vs **Placebo** **Co-intervention:** no other BP-lowering agents were added.
Primary and secondary outcomes: (1) Angiographic: angiographic progression of non-dilated coronary arterial lesions (2) Clinical: CV events, including death, stroke, acute MI, repeat PTCA, PTCA of a new or progressive lesion, or coronary artery bypass grafting (CABG).
Funding Source: Bayer AG, Wuppertal, Germany

NICS-EH (1999) (NICS-EH Study Group, 1999)
Design: Prospective, randomized, double-blinded, parallel trial **Median Mean duration of follow-up:** 4.6 years **Notes:** In total, 15 participants were withdrawn, but the intention-to-treat analysis was not used
Participants: 429 elderly participants with hypertension and no history of CV complications. **Age range**: 60-older (mean: 69.8 years) **Hypertensive patients (%):** 100 **Baseline cancer(%):** Not reported
Intervention: 2 treatment groups **CCB**: nicardipine HCL SR 40 mg/day vs **TZ**: trichlormethiazide 2 mg/day **Co-intervention:** no other BP-lowering agents were added.
Primary and secondary outcomes: CV complications and other non-CV end-points
Funding Source: Not reported

OCTOPUS (2013) (Iseki et al., 2013)
Design: Multicentre, prospective, randomized, open-label, blinded-endpoint trial (PROBE) **Mean duration of follow-up:** 3.5 years
Participants: 469 participants with hypertension and ESRD **Age range**: 20-79 (mean: 59.5 years) **Hypertensive patients (%):** 100 **Baseline cancer(%):** 5.3
Intervention: 2 treatment groups **ARB**: Olmesartan 10-40mg/day vs **Control**: Non-ARB (excluding ACEI) **Co-intervention:** no other BP-lowering agents were added.
Primary and secondary outcomes: (1) All causes of death (2) CVD (3) HMBP to evaluate the relationship between CVD (4) Blood access troubles requiring an operation.
Funding Source: Own fund and donation

ONTARGET(2008) (The ONTARGET Investigators, 2008, Teo, 2011)
Design: Prospective, multicentre, randomized, double-blinded, parallel trial **Mean duration of follow-up:** 4.7 years
Participants: 25620 patients with coronary, peripheral, or cerebrovascular disease or diabetes with end-organ damage. **Age range**: 55 or older (mean: 66.4 years) **Hypertensive patients (%):** 69 **Baseline cancer(%):** Not reported
Intervention: 3 treatment groups **ARB**: 80mg/day telmisartan vs **ACEI**: 5-10mg/day ramipiril vs **ARB+ACEI**: 80mg/day telmisartan plus 5-10mg/day ramipiril **Co-intervention:** No information on further titration or background therapy
Primary and secondary outcomes: Death from CV causes, nonfatal MI, nonfatal stroke, hospitalization for congestive HF
Funding Source: Boehringer Ingelheim and the Heart and Stroke Foundation of Ontario

OPTIMAAL (2002) (Dickstein and Kjekshus, 2002)
Design: Prospective, multicentre, randomized, double-blinded, parallel trial **Mean duration of follow-up:** 2.7 years
Participants: 5477 participants with confirmed acute MI and HF **Age range**: 50 or older (mean: 67.4 years) **Hypertensive patients (%):** 36 **Baseline cancer(%):** Not reported
Intervention: 2 treatment groups

ARB: losartan 12.5-50 mg/day vs **ACEI**: captopril 37.5-150 mg/day **Co-intervention:** No information on further titration or background therapy
Primary and secondary outcomes: All-cause mortality
Funding Source: Merck, Sharp and Dohme Research Laboratories

OSLO (1980) (Helgeland, 1980)
Design: Prospective, randomized, parallel trial **Mean duration of follow-up:** 5.5 years
Participants: 785 men with hypertension **Age range**: 20-49 (mean: 45.3 years) **Hypertensive patients (%):** 100 **Baseline cancer(%):** None
Intervention: 2 treatment groups **TZ**: HCTZ 50 mg/day vs **Control**: No treatment **Co-intervention:** if BP goal was not achieved, other BP-lowering agents were added (methyldopa 500mg-1g/day or propranolol 80-320 mg/day).
Primary and secondary outcomes: CV events
Funding Source: Not reported

Otsuka *et al* (1982)
Design: Prospective, randomized, open, and non-placebo controlled trial **Mean duration of follow-up:** 4.8 years
Participants: 253 patients with coronary artery disease post PCI **Age range**: 18-79 (mean: 63 years) **Hypertensive patients (%):** 46 **Baseline cancer(%):** Not reported
Intervention: 2 treatment groups **ACEI**: 10-20 mg/day quinapril vs **Control**: Non-ACEi **Co-intervention:** no other BP-lowering agents were added. **Notes:** Aspirin and ticlopidine were administered as an adjunct pharmacologic therapy.
Primary and secondary outcomes: Death, MI, CVA and revascularization
Funding Source: Not reported

PARADIGM-HF (2014) (McMurray et al., 2014)
Design: Prospective, multicentre, randomized, double-blinded, parallel trial **Mean duration of follow-up:** 2.3 years
Participants: 8442 patients with class II, III, or IV HF and an ejection fraction of 40% or less **Age range**: 18-older (mean: 63.8 years) **Hypertensive patients (%):** 35 **Baseline cancer(%):** Not reported
Intervention: 2 treatment groups **ACEI**: enalapril 20 mg/day vs **Control**: LCZ696 400 mg/day (ArNi) **Co-intervention:** no other BP-lowering agents were added.
Primary and secondary outcomes: composite of death from CV causes or a first hospitalization for HF; the time to death from any cause, the change from baseline to 8 months in the clinical summary score on the Kansas City Cardiomyopathy Questionnaire (KCCQ), the time to a new onset of AF, and the time to the first occurrence of a decline in renal function
Funding Source: Novartis Pharmaceutical

PAT (2002) (The Propranolol Aneurysm Trial Investigators, 2002)
Design: Prospective, multicentre, randomized, double-blinded, parallel trial **Mean duration of follow-up:** 2.5 years
Participants: 548 patients with asymptomatic small abdominal aortic aneurysm

Age range: Not reported (mean: 68.9 years) **Hypertensive patients (%):** 36 **Baseline cancer(%):** Not reported **Notes**: 4 randomized patients were excluded from analysis as they did not meet the eligibility criteria.
Intervention: 2 treatment groups **BB**: propranolol 160-240 mg/day vs **Placebo** **Co-intervention:** no other BP-lowering agents were added.
Primary and secondary outcomes: the Growth rate of an aneurysm, mortality, elective resection of an aneurysm, reasons for permanent withdrawal from study medication, quality of life
Funding Source: Canadian Institute of Health Research

PHARAO (2008); (Lüders et al., 2008)
Design: Multicentre, prospective, randomized, open-label, blinded-endpoint trial (PROBE) **Mean duration of follow-up:** 3 years
Participants: 1008 participant with high-normal office BP **Age range**: 50-85 (mean: 62.3 years) **Hypertensive patients (%):** None **Baseline cancer(%):** Not reported
Intervention: 2 treatment groups **ACEI**: ramipiril 5 mg/day vs **Control** **Co-intervention:** no other BP-lowering agents were added. **Notes:** It was not reported whether participants in the control group were given alternative antihypertensive or no treatment.
Primary and secondary outcomes: development of hypertension, reduction in CVA events and CV events, overall mortality, reasons for admissions to hospital, the occurrence of pathological fasting glucose levels in serum/pathological HbA1c levels.
Funding Source: Sanofi Aventis Pharma GmbH

PHYLLIS (2004) (Zanchetti et al., 2004)
Design: Prospective, multicentre, randomized, double-blinded, parallel trial **Mean duration of follow-up:** 2.6 years
Participants: 508 patients with hypertension, hyperlipidaemia, and asymptomatic carotid atherosclerosis **Age range**: 45-70 (mean: 58.4 years) **Hypertensive patients (%):** 100 **Baseline cancer(%):** Not reported
Intervention: 4 treatment groups **TZ**: HCTZ 25 mg/QD plus placebo vs **ACEI**: Fosinopril 20 mg/QD plus placebo vs **TZ+Statin**: HCTZ 25 mg/QD plus pravastatin vs **ACEI+statin**: Fosinopril 20 mg/QD plus pravastatin **Co-intervention:** if BP goal was not achieved, other BP-lowering agents were added (Nifedipine GITS 30-60 mg/QD). **Notes:** For this review, only the TZ and ACEI arm were considered.
Primary and secondary outcomes: Rate of change in maximum intimal media thickness (IMT) of the coronary artery wall, changes in BP, changes in lipid level and other laboratory variables
Funding Source: Bristol-Myers Squibb and Menarini

Practolol Study (1975) (Anonymous, 1975b)
Design: Prospective, multicentre, randomized, double-blinded, parallel trial **Mean duration of follow-up:** 1.2 years
Participants: 3038 participants recovering from acute MI. **Age range**: 69 or younger (mean: 55 years) **Hypertensive patients (%):** Not reported **Baseline cancer(%):** Not reported

Intervention: 2 treatment groups **BB**: practolol 400 mg/day vs **Placebo** **Co-intervention:** No information on further titration or background therapy. Drugs considered to interact with beta-adrenoceptor antagonists were not permitted.
Primary and secondary outcomes: All-cause mortality, reinfarction, effects of treatment on BP, angina pectoris, and arrhythmia, causes of treatment withdrawal.
Funding Source: Not reported

PRAISE (1996) (Packer et al., 1996)
Design: Prospective, multicentre, randomized, double-blinded, parallel trial **Mean duration of follow-up:** 1.2 years
Participants: 1153 participants with severe chronic HF and ejection fractions of less than 30 percent. **Age range**: Not reported (mean: 64.7 years) **Hypertensive patients (%):** Not reported **Baseline cancer(%):** Not reported
Intervention: 2 treatment groups **CCB**: amlodipine 5-10mg/day vs **Placebo** **Co-intervention:** No information on further titration or background therapy.
Primary and secondary outcomes: Mortality from all causes and CV morbidity.
Funding Source: Pfizer Central Research

PREVENT(2000) (Pitt et al., 2000)
Design: Prospective, multicentre, randomized, double-blinded, parallel trial **Mean duration of follow-up:** 3 years
Participants: 825 participants with coronary artery disease. **Age range**: 30-80 (mean: 56.9 years) **Hypertensive patients (%):** Not reported **Baseline cancer(%):** Not reported
Intervention: 2 treatment groups **CCB**: amlodipine 20-40mg/day vs **Placebo** **Co-intervention:** No information on further titration or background therapy.
Primary and secondary outcomes: change in the mean minimal diameter of early atherosclerotic segments and reduction in the rate of coronary disease progression.
Funding Source: Pfizer, Inc./US Pharmaceuticals Group

PREVER-Treatment (2016) (Fuchs et al., 2016)
Design: Prospective, multicentre, randomized, double-blinded, parallel trial **Mean duration of follow-up:** 1.5 years
Participants: 655 participants with stage I hypertension and no current use of BP-lowering medication. **Age range**: 30-70 (mean: 54 years) **Hypertensive patients (%):** 100 **Baseline cancer(%):** Not reported
Intervention: 2 treatment groups **TZ**: chlorthalidone/amiloride 12.5/2.5 mg/day vs **ARB**: losartan 50 mg/day **Co-intervention:** if BP goal was not achieved, other BP-lowering agents were added in the following steps- (1) amlodipine up to 10 mg/day (2) propranolol up to 80 mg/day
Primary and secondary outcomes: mean BP between the two treatment groups, fatal and nonfatal major CV events.
Funding Source: Department of Science and Technology (DECIT), Health Ministry; National Council of Research (CNPq) and Agency for Funding of Studies and Projects (FINEP), Science and Technology Ministry; National Institute of Health Technology Assessment (IATS); and Funding of Incentive to Research (FIPE), Hospital de Clinicas de Porto Alegre, all in Brazil

PRoFESS (2008); (Yusuf et al., 2008)
Design: Prospective, randomized, double-blind, 2x2 factorial, placebo-controlled trial **Mean duration of follow-up:** 2.5 years
Participants: 20,332 patients with recent ischaemic stroke **Age range**: 50-older (mean: 66.2 years) **Hypertensive patients (%):** 74 **Baseline cancer(%):** Not reported
Intervention: 2 treatment groups **ARB**: telmisartan 80mg/day vs **Placebo** **Co-intervention:** No information on further titration or background therapy. **Notes:** Other randomized drugs included aspirin and dipyridamole extended release vs clopidogrel
Primary and secondary outcomes: Recurrent stroke of any type and total vascular events
Funding Source: Boehringer Ingelheim, with additional support from Bayer Schering Pharma and GlaxoSmithKline

REIN-2 (2005) (Ruggenenti et al.)
Design: Multicentre, prospective, randomized, open-label, blinded-endpoint trial (PROBE) **Mean duration of follow-up:** 1.6 years
Participants: 338 patients with non-diabetic proteinuric nephropathy with background ACEI treatment **Age range**: 18-70 (mean: 53.4 years) **Hypertensive patients (%):** Not reported **Baseline cancer(%):** None
Intervention: 2 treatment groups **Conventional BP control**: ramipiril 5 mg/day and concomitant antihypertensive therapy vs **Intensified BP control**: felodipine 5-10 mg/day and concomitant antihypertensive therapy **Co-intervention:** No information on other antihypertensive therapy. **Notes:** Combined therapy approach
Primary and secondary outcomes: Time to ESRD.
Funding Source: Aventis Pharma SA

RENAAL (2002) (Brenner et al., 2001)
Design: Prospective, multicentre, randomized, double-blinded, parallel trial **Mean duration of follow-up:** 3.4 years
Participants: 1513 patients with T2DM and nephropathy **Age range**: 31-70 (mean: 60 years) **Hypertensive patients (%):** 94 **Baseline cancer(%):** Not reported
Intervention: 2 treatment groups **ARB**: 50-100mg/day Losartan vs **Placebo** **Co-intervention:** Open-label conventional antihypertensive therapy excluding ARBs and ACEIs were given along with the randomized treatment.
Primary and secondary outcomes: composite of a doubling of the base-line serum creatinine concentration, ESRD, or death and composite of morbidity and mortality from CV causes, proteinuria, and the rate of progression of renal disease.
Funding Source: Merck and Company.

SAVE (1992) (Pfeffer et al., 1992)
Design: Prospective, multicentre, randomized, double-blinded, parallel trial **Mean duration of follow-up:** 3.5 years
Participants: 2231 patients with acute MI and left ventricular dysfunction (EF 40% or less) **Age range**: 21-80 (mean: 59.4 years)

Hypertensive patients (%): 43 **Baseline cancer(%):** Not reported
Intervention: 2 treatment groups **ACEI**: captopril 25-50 mg/TID vs **Placebo** **Co-intervention:** No information on further titration or background therapy.
Primary and secondary outcomes: CV mortality and morbidity, all-cause mortality, development of overt HF, hospitalization to treat congestive HF.
Funding Source: Bristol-Myers Squibb

SCAT (2000) (Teo et al., 2000)
Design: Prospective, randomized, double-blind, 2x2, placebo-controlled trial **Mean duration of follow-up:** 4 years
Participants: 460 patients with CAD and normal or mildly elevated cholesterol. **Age range**: 21-older (mean: 61 years) **Hypertensive patients (%):** 36 **Baseline cancer(%):** Not reported
Intervention: 2 treatment groups **ACEI**: Enalapril 2.5 -10 mg/ BID vs **Placebo** **Co-intervention:** no other BP-lowering agents were added. **Notes:** Other randomized drugs included simvastatin vs placebo.
Primary and secondary outcomes: Quantitative coronary angiography (QCA) measures and clinical events (death, MI, stroke, hospitalization for angina, revascularization, and cancer).
Funding Source: Merck Frost Canada and Company

SCOPE (2003) (Lithell et al., 2003)
Design: Prospective, multicentre, randomized, double-blinded, parallel trial **Mean duration of follow-up:** 3.7 years
Participants: 4964 elderly patients with hypertension and a Mini Mental State Examination (MMSE) test score >=24. **Age range**: 70–89 (mean: 76.4 years) **Hypertensive patients (%):** 100 **Baseline cancer(%):** Not reported
Intervention: 2 treatment groups **ARB**: candesartan 8 – 16 mg/day vs **Placebo** **Co-intervention:** Other antihypertensive drugs, except ACEI or AT1-receptor blockers, could be added later
Primary and secondary outcomes: Major CV events, CV death, non-fatal stroke, non-fatal MI, cognitive function measured by the MMSE and dementia.
Funding Source: AstraZeneca

SHEP (1991) (SHEP Cooperative Research Group, 1991)
Design: Prospective, multicentre, randomized, double-blinded, parallel trial **Mean duration of follow-up:** 5 years
Participants: 4736 elderly patients with systolic hypertension. **Age range**: 60-older (mean: 71.6 years) **Hypertensive patients (%):** 100 **Baseline cancer(%):** None
Intervention: 2 treatment groups **TZ**: chlorthalidone 12.5-25 mg/day vs **Placebo** **Co-intervention:** if BP goal was not achieved, other BP-lowering agents were added (atenolol 25-50 mg/day or reserpine 0.05-0.1 mg/day) **Notes:** Potassium supplements were given to all participants who had potassium serum level below 3.5 mmol/L

Primary and secondary outcomes: total stroke, sudden cardiac death, rapid cardiac death, fatal and non-fatal MI, left ventricular failure, other CV death, TIA, coronary artery therapeutic procedures and renal dysfunction.
Funding Source: National Heart, Lung, and Blood Institute and the National Institute on Ageing. Drugs were supplied by the Lemmon Co, Sellersville, Pa; Wyeth Laboratories, AH Robins Co, and Studart Pharmaceuticals

SOLVD-P (1992) (The SOLVD Investigators, 1992)
Design: Prospective, multicentre, randomized, double-blinded, parallel trial **Mean duration of follow-up:** 3.1 years
Participants: 4228 patients with severe congestive HF (LVEF < 35%, with no overt HF) **Age range**: Not reported (mean: 59.1 years) **Hypertensive patients (%):** 37 **Baseline cancer(%):** Not reported
Intervention: 2 treatment groups **ACEI**: enalapril 2.5 - 10 mg/BID vs **Placebo** **Co-intervention:** Patients were allowed to receive diuretics for hypertension, digoxin for current or past AF, and nitrates for angina.
Primary and secondary outcomes: overall mortality and morbidity, quality of life, changes in clinical and functional status, hospitalizations, adherence to study drug, side effects
Funding Source: National Heart, Lung, and Blood Institute and Merck, Sharp and Dohme

SOLVD-T (1991) (The SOLVD Investigators, 1991)
Design: Prospective, multicentre, randomized, double-blinded, parallel trial **Mean duration of follow-up:** 3.5 years
Participants: 2569 patients with severe congestive HF (LVEF < 35%, with overt HF) **Age range**: 80 or younger (mean: 60.9 years) **Hypertensive patients (%):** 42 **Baseline cancer(%):** None
Intervention: 2 treatment groups **ACEI**: enalapril 2.5 - 10 mg/BID vs **Placebo** **Co-intervention:** In patients with worsening symptoms of congestive HF, an increase in the dose of diuretics or the addition of vasodilators was recommended.
Primary and secondary outcomes: overall mortality and morbidity, quality of life of patients, changes in clinical and functional status, hospitalizations, adherence to study drug, side effects
Funding Source: National Heart, Lung, and Blood Institute and Merck, Sharp and Dohme

SPRINT (1988) (The Israeli SPRINT Study Group, 1988, Jonas et al., 1998)
Design: Prospective, multicentre, randomized, double-blinded, parallel trial **Mean duration of follow-up:** 5 year **Notes:** The primary study followed patients up to 1 year
Participants: 2127 survivors of acute MI **Age range**: 30-74 (mean: 57.5 years) **Hypertensive patients (%):** 27 **Baseline cancer(%):** None **Notes**: The primary trial reported 2276 patients underwent randomisation however baseline characteristics for only 2149 patients were reported as one study centre failed to supply complete baseline data. The current analysis used the total number of patients reported in the 5-year mortality follow-up.
Intervention: 2 treatment groups **CCB**: 30 mg/day nifedipine vs **Placebo** **Co-intervention:** No information on further titration or background therapy.
Primary and secondary outcomes: total mortality and non-fatal recurrent acute MI, CV events cardiac surgery.

Funding Source: Bayer AG

SMT (1985) (Olsson, 1985)
Design: Prospective, single, randomized, double-blinded, parallel trial **Mean duration of follow-up:** 3 years
Participants: 301 survivors of acute MI **Age range**: 70 or younger (mean: 59.7 years) **Hypertensive patients (%):** 26 **Baseline cancer(%):** Not reported
Intervention: 2 treatment groups **BB**: 100 mg/day metoprolol vs **Placebo** **Co-intervention:** No information on further titration or background therapy.
Primary and secondary outcomes: total mortality, non-fatal recurrent acute MI, other ischaemic manifestations.
Funding Source: Swedish National Association Against Heart and Chest Diseases and AB Hassle, Molndal, Sweden

STOP-HTN2 (2001) (Hansson et al., 1999, Lindholm et al., 2001)
Design: Prospective, randomized, open-label, blinded-endpoint trial (PROBE) **Mean duration of follow-up:** 5 years
Participants: 6614 elderly participants with hypertension **Age range**: 70-84 (mean: years) **Hypertensive patients (%):** 100 **Baseline cancer(%):** Not reported
Intervention: 3 treatment groups **ACEi** : enalapril 10mg/day or lisinopril 10mg/day vs **CCB**: felodipine 2.5mg/day or isradipine 2.5mg/day vs **Control**: Conventional therapy (atenolol 50 mg/day; metoprolol 100mg/day; pindolol 5mg/day or HCTZ+amiloride 25/2.5mg) **Co-intervention:** if BP goal was not achieved, other BP-lowering agents were added (Patients on BBs were given HCTZ; patients on HCTZ were given any of the BBs; patients on ACEI were given HCTZ 12.5-5.0 mg/day; patients on CCB were given any of the BBs).
Primary and secondary outcomes: Combined endpoint of fatal and non-fatal stroke, fatal MI, and other fatal CVD.
Funding Source: AstraZeneca, Merck Sharp and Dohme, and Sandoz (later Novartis)

Suzuki et al. (2008)
Design: Multicentre open-labelled randomized trial **Mean duration of follow-up:** 3 years
Participants: 366 patients with end-stage renal disease on haemodialysis **Age range**: 30-80 (mean: 59.6 years) **Hypertensive patients (%):** 93 **Baseline cancer(%):** Not reported
Intervention: 2 treatment groups **ARB**: losartan 50-100mg/day or candesartan 8-12mg/day or valsartan80-160mg/day vs **Control**: Non-ARB **Co-intervention:** No details on concomitant antihypertensive therapy allowed.
Primary and secondary outcomes: the development of fatal and nonfatal CV events, all-cause death
Funding Source: Own fund

Syst-China (1998)(Liu et al., 1998)
Design: Prospective, multicentre, randomized, double-blinded, parallel trial **Mean duration of follow-up:** 4 years

Participants: 2391 elderly patients with systolic hypertension **Age range**: 60 or older (mean: 66.5 years) **Hypertensive patients (%):** 100 **Baseline cancer(%):** Not reported
Intervention: 2 treatment groups **CCB**: nitrendipine 10-40mg/day vs **Placebo** **Co-intervention:** if BP goal was not achieved, other BP-lowering agents were added (captopril 12.5-50mg/day or HCTZ 12.5-50mg/day)
Primary and secondary outcomes: Death, stroke, retinal haemorrhage or exudates, MI, congestive HF, dissecting aortic aneurysm, renal insufficiency, and all other events.
Funding Source: State Planning Commission of the People's Republic of China. The study analysis was facilitated through a fellowship granted by Bayer AG, Wuppertal, Germany, to Dr Ji Guang Wang

Syst-Eur (1997) (Staessen et al., 1997)
Design: Prospective, multicentre, randomized, double-blinded, parallel trial **Mean duration of follow-up:** 2 years
Participants: 4695 elderly participants with isolated systolic hypertension **Age range**: 60 or older (mean: 70.3 years) **Hypertensive patients (%):** 100 **Baseline cancer(%):** Not reported
Intervention: 2 treatment groups **CCB**: 10-40 mg/day nitrendipine vs **Placebo** **Co-intervention:** if BP goal was not achieved, other BP-lowering agents were added (captopril 12.5-50mg/day or HCTZ 12.5-50mg/day)
Primary and secondary outcomes: stroke, MI, congestive HF, cardiac events, renal insufficiency.
Funding Source: European Union and Bayer AG, Wuppertal, Germany

TRACE (2005) (The TRACE Study Group, 1994, Kober, 1995, Buch et al., 2005)
Design: Prospective, multicentre, randomized, double-blinded, parallel trial **Mean duration of follow-up:** 5.6 years
Participants: 1749 participants with MI and left ventricular dysfunction (ejection fraction <= 35%) **Age range**: 18 or older (mean: 67.5 years) **Hypertensive patients (%):** 23 **Baseline cancer(%):** None
Intervention: 2 treatment groups ACEI: trandolapril 2-4 mg/day vs Placebo **Co-intervention:** No information on further titration or background therapy.
Primary and secondary outcomes: total mortality, CV mortality, sudden death, reinfarction, severe congestive HF, left ventricular function.
Funding Source: Roussel-Uclaf and Knoll

TRANSCEND (2008) (The TRANSCEND Investigators, 2008)
Design: Prospective, multicentre, randomized, double-blinded, parallel trial **Mean duration of follow-up:** 4.7 years
Participants: 5926 patients with a history of CVD or T2DM with end-organ damage intolerant to ACE inhibitors **Age range**: Not reported (mean: 66.9 years) **Hypertensive patients (%):** 76 **Baseline cancer(%):** 4.9
Intervention: 2 treatment groups **ARB**: 80mg/day telmisartan vs **Placebo** **Co-intervention:** No information on further titration or background therapy.

Primary and secondary outcomes: CV death, MI, stroke, hospitalisation for HF, new HF, development of T2DM, AF, cognitive decline or dementia, nephropathy, and revascularisation.
Funding Source: Boehringer Ingelheim.

TROPHY (2006) (Julius et al., 2006)
Design: Prospective, multicentre, randomized, double-blinded, parallel trial **Mean duration of follow-up:** 3.6 years
Participants: 809 participants with BP on study entry in the high-normal range (pre-hypertension) **Age range**: 30-65 (mean: 48.5 years) **Hypertensive patients (%):** None **Baseline cancer(%):** Not reported
Intervention: 2 treatment group **ARB**: 16 mg/day candesartan vs **Placebo** **Co-intervention:** no other BP-lowering agents were added.
Primary and secondary outcomes: Development of clinical hypertension.
Funding Source: AstraZeneca

UKPDS-38 (1998) (Anonymous, 1998, UKPDS Investigators, 1998)
Design: Prospective, multicentre, randomized, double-blinded, parallel trial **Mean duration of follow-up:** 9 years
Participants: 1148 hypertensive patients with T2DM **Age range**: Not reported (mean: 56.8 years) **Hypertensive patients (%):** 100 **Baseline cancer(%):** Not reported
Intervention: 3 treatment groups **ACEI**: Captopril 25- 50 mg/BID vs **BB**: Atenolol 50-100 mg/day vs **Control**: Non-ACEI/BB **Co-intervention:** if BP goal was not achieved, other BP-lowering agents were added in the following steps: (1) Frusemide 20 mg/day (max 40 mg/bid) (2) Nifedipine SR 10 mg (max 40 mg)/ bid (3) Methyldopa 250 mg (max 500 mg)/ bid (4) Prazosin 1 mg (max 5 mg) / TID
Primary and secondary outcomes: Time to occurrence of (1) first clinical end point related to diabetes (2) death related to diabetes (3) All-cause mortality. Macrovascular and microvascular complications.
Funding Source: MRC, British Diabetic Association, the Department of Health, the National Eye Institute, and the National Institutes of Health (USA), the British Heart Foundation, Novo-Nordisk, Bayer, Bristol Myers Squibb, Hoechst, Lilly, Lipha, and Farmitalia Carlo Erba.

VA COOP II (1982) (Anonymous, 1982)
Design: Prospective, multicentre, randomized, double-blinded, parallel trial **Mean duration of follow-up:** 1 year
Participants: 394 patients with mild to moderate hypertension **Age range**: 21-65 (mean: 50 years) **Hypertensive patients (%):** 100 **Baseline cancer(%):** None
Intervention: 2 treatment groups **BB**: 80-640 mg/day propranolol vs **TZ**: 50-200 mg/day HCTZ **Co-intervention:** no other BP-lowering agents were added
Primary and secondary outcomes: Treatment efficacy, and adverse effects.
Funding Source: Ayerst Laboratories Inc.

Val-HeFT (2001) (Cohn and Tognoni, 2001)
Design: Prospective, multicentre, randomized, double-blinded, parallel trial

Mean duration of follow-up: 1.9 years
Participants: 5010 patients with HF **Age range**: 18 or older (mean: 62.7 years) **Hypertensive patients (%):** 6.7 **Baseline cancer(%):** Not reported
Intervention: 2 treatment groups **ARB**: valsartan 80-320 mg/day vs **Placebo** **Co-intervention:** no other BP-lowering agents were added
Primary and secondary outcomes: mortality and morbidity, CV outcomes, NYHA functional class, quality-of-life scores, and signs and symptoms of HF.
Funding Source: Novartis Pharmaceuticals

VALIANT (2003) (Pfeffer et al., 2000, Pfeffer et al., 2003)
Design: Prospective, multicentre, randomized, double-blinded, parallel trial **Mean duration of follow-up:** 2.1 years
Participants: 14,703 patients with HF and/or left ventricular systolic dysfunction (LVSD) after MI. **Age range**: 18 or older (mean: 64.8 years) **Hypertensive patients (%):** 55 **Baseline cancer(%):** Not reported
Intervention: 3 treatment groups ACEI: captopril 150 mg/day vs ARB: valsartan 320 mg/day vs ACEI+ARB: 150/320 mg/day **Co-intervention:** no other BP-lowering agents were added
Primary and secondary outcomes: all-cause mortality, CV death, acute coronary syndromes (fatal and nonfatal), CV morbidity, revascularization procedures, CV procedures, hospitalization.
Funding Source: Novartis Pharmaceuticals

VALUE (2004) (Julius et al., 2004)
Design: Prospective, multicentre, randomized, double-blinded, parallel trial **Mean duration of follow-up:** 4.2 years
Participants: 15,245 participants with treated or untreated hypertension and a high risk of cardiac events **Age range**: 50 or older (mean: 67 years) **Hypertensive patients (%):** 92 **Baseline cancer(%):** Not reported
Intervention: 2 treatment groups **ARB**: Valsartan 80 - 160mg/day vs **CCB**: Amlodipine 5 - 10mg/day **Co-intervention:** if BP goal was not achieved, other BP-lowering agents were added (excluding ACEI)
Primary and secondary outcomes: Time to first cardiac event, Fatal and non-fatal MI, fatal and non-fatal HF, and fatal and non-fatal stroke, all-cause mortality, new-onset diabetes.
Funding Source: Novartis Pharma AG

VERDI (1989) (Holzgreve et al., 1989)
Design: Prospective, multicentre, randomized, double-blinded, parallel trial **Mean duration of follow-up:** 1 year
Participants: 369 untreated hypertensive patients **Age range**: 22-71 (mean: 50.5 years) **Hypertensive patients (%):** 100 **Baseline cancer(%):** None
Intervention: 2 treatment groups **TZ**: HCTZ 12.5-25mg/day vs **CCB**: sustained release verapamil 120-240mg/day **Co-intervention:** no other BP-lowering agents were added
Primary and secondary outcomes: BP determined with a device permitting automatic repeated measurements with printouts.

Funding Source: Knoll AG

V-HeFT II (1991) (Holzgreve et al., 1989, Cohn et al., 1991)
Design: Prospective, multicentre, randomized, double-blinded, parallel trial **Mean duration of follow-up:** 2.5 years
Participants: 804 men with chronic HF **Age range**: 18-75 (mean: 60.5 years) **Hypertensive patients (%):** 48 **Baseline cancer(%):** Not reported
Intervention: 2 treatment groups **ACEI**: enalapril 5-20 mg/day vs **Control**: hydralazine 37.5-300 mg/day plus isosorbide dinitrate 40-160 mg/day **Co-intervention:** No information on further titration or background therapy.
Primary and secondary outcomes: exercise tolerance, cardiothoracic ratios, measurement of ejection fraction, quality of life, all-cause death.
Funding Source: Cooperative Studies Program of the Medical Research Service, Department of Veterans Affair Central Office.

Wilcox et al. (1980)
Design: Prospective, randomized, double-blinded, parallel trial **Mean duration of follow-up:** 1 year
Participants: 388 patients with suspected MI. **Age range**: No age limit (average: 55 years) **Hypertensive patients (%):** Not reported **Baseline cancer(%):** Not reported
Intervention: 3 treatment groups **BB**: propranolol 120 mg/day vs **BB**: atenolol 100 mg/day vs **Placebo** **Co-intervention:** No information on further titration or background therapy.
Primary and secondary outcomes: Mortality at 6 weeks and one year.
Funding Source: Imperial Chemical Industries Limited.

3.2.3 Discussion

This chapter described the protocol for identification of studies that were used in a systematic review for antihypertensive drugs and risk of cancer. In addition to lowering elevated BP, antihypertensive drugs are also commonly used in treating other conditions such as congestive HF, cardiac dysrhythmia, and renal insufficiency. In this review, more than half (59%) of the included trials are non-intentional BP lowering studies where studied antihypertensive therapy was investigated for other indications and outcomes. The majority (76.7%) of the included RCTs of major antihypertensive drugs class enrolled patients with comorbidities especially heart diseases and metabolic disorder namely T2DM. High risk hypertensive, CHD, and HF contributed 42.2% of study participants in this review. These comorbidities are not unprecedented complications of hypertension as long-term elevated BP is known to cause alteration to arterial conductance and resistance, hence jeopardizing vital organ integrity.

3.2.3.1 Treatment strategy and agents

Established clinical guidelines (NICE, 2011, Mancia et al., 2013a, James et al., 2014) has outlined a common general principle on hypertension treatment initiation. Majority of the included study initiated treatment by monotherapy and added another drug (sometimes more than one) in a stepped care approach in some patients. Great detail on antihypertensive therapy strategy is described in 1, Section 1.8.2.

The RAS inhibitors, specifically ARB and ACEI, were used in 22.1% and 13.2% of participants enrolled in this review respectively. Both classes of drugs are amongst the widely used antihypertensive treatment and are generally well-tolerated. Equally, ACEIs and ARBs offers similar clinical benefits which includes BP lowering (LIFE, SCOPE, VALUE), alleviating CHF symptoms (CHARM Alternative, Val-HeFT, VALIANT), inhibition of diabetic renal disease (IDNT, RENAAL), and possibly preventing new onset of T2DM (Gillespie et al., 2005) and AF (Healey et al., 2005). However, one of the disadvantages commonly associated with ACEIs is chronic dry cough which is not dose-dependent (Yesil et al., 1994) and subsequently makes ARBs as the preferable alternative in patients who are ACEI-intolerant. Several meta-analyses have suggested that ACEIs is inferior in preventing stroke when compared to other classes (Blood Pressure Lowering Treatment Trialists' Collaboration, 2003, Law et al., 2009) while ARBs are inferior to ACEIs in reducing MI and CV deaths (Strauss and Hall, 2006, Strauss and Hall, 2017).

In this review, 31.3% of participants randomised to ACEI were given ramipril which makes it the most used ACEI. The HOPE study showed that when added to concomitant therapy, ramipril is beneficial on the primary combined endpoints of CV death, non-fatal MI, and non-fatal stroke (RR reductions 22%, $p<0.001$) as well as associated with lower rates of incident T2DM (RR 0.66, $p<0.001$) compared to placebo in patients with high CV risk. A comparable finding was reported for the ramipiril treatment arm in the ONTARGET study who recruited participants of similar characteristics. Conversely, similar protective effects against CV risk and diabetic nephropathy was not seen in patients with underlying T2DM (Marre, 2004). The DREAM trial also reported an insignificant reduction in incident diabetes in participants with IGT. The possible explanation could be due to the different characteristics of the study population, a lower dose of ramipiril used,

and shorter study duration. All the major studies have reported a higher rate of discontinuation or adverse effect due to dry cough in the ramipril treatment arm.

On the other hand, telmisartan was the most used ARB (34.8%) as it was studied in three large key RCTs (ONTARGET, PRoFESS, and TRANSCEND). It was approved by the US FDA in November 1998 (FDA, 1998) for the treatment of hypertension and as an alternative to ACEI. Among the Angiotensin II antagonists, telmisartan is the most lipophilic, thus shows excellent oral absorption and tissue penetration (Wienen et al., 2000). Trials comparing telmisartan and ramipril (ONTARGET, VALIANT) have demonstrated that telmisartan is not inferior to ramipril when used in patients with high CV risk. A parallel finding was also reported by Li et al. (2014a) in a meta-analysis of RCTs comparing ARB vs ACEI for primary hypertension.

CCBs is the second most used antihypertensive in this review with DHP-CCBs predominates over non-DHP CCBs. Amlodipine was used in ten major trials contributing to 42.9% of participants enrolled in this review. Major trials have shown that CCBs are at least equally effective if not superior (ALLHAT, VALUE) in lowering BP. However, several controlled trials (ABCD, FACET, and ALLHAT) have exhibited trends toward higher CV events with CCBs. On the contrary, large trials enrolling high-risk hypertensives (CAMELOT, INVEST, VALUE) have demonstrated that CCBs are as clinically effective as other drug classes in reducing major CV events. In addition, the combination of CCB and other drug class have proven beneficial in improving patients' outcomes.

The decision on which drug class is to be prescribed first is still controversial. In clinical practice, the management of hypertension varies greatly due to factors which included: patients' non-compliance and non-adherence; switching or addition of another drug; and difficulties to achieve adequate BP control with monotherapy even after the dose is optimised. Hence, dose titration plus additional drug treatment approach is not uncommon in more than 90% of RCTs included in this review and study drugs administered as second-line of therapy has been investigated in several key trials (ASCOT-BPLA, CONVINCE, FEVER). Data from ASCOT-BPLA have shown that amlodipine plus perindopril was more effective than atenolol plus bendroflumethiazide. The FEVER study has demonstrated that CCB added-on to diuretic was well-tolerated and was directed towards a lower

incidence of major CV events. Meanwhile, the combined therapy arm in the DEMAND study showed that delapril plus manidipine safely reduced CV risk and stabilized insulin sensitivity. However, not all drug combinations proved to be beneficial and most major scientific hypertension guidelines do not recommend initial treatment with combination therapy because of concern about the excessive reduction in BP, increased side effects, and the difficulty of attributing adverse events to one drug. Many clinical guidelines have discouraged the combination of two different RAAS blockers. Two large key trials (ONTARGET and VALIANT) have suggested that ARB plus ACEI combinations had no increase in benefit but was associated with more adverse effects namely ESRD and stroke. Quite the opposite, the CHARM-Added and Val-HeFT trials have demonstrated that combined ARB and ACEI therapy was superior to placebo in reducing hospitalizations for HF. These differences in findings were probably due to the different patient's characteristics where patients studied in the CHARM-Added and Val-HeFT had symptomatic HF on ACEI therapy and variable doses of ACEI was used although there was no attempt to titrate the ACEI to the maximum dose.

3.2.3.2 Cancer reporting in clinical trials

Monitoring for adverse or unwanted effects is routinely conducted during phase II and phase III of clinical trials. The FDA (1995), EMA (1995) and ICH (1994) have outlined a guideline on reporting serious adverse event or ADR. According to the guidelines, cancer or malignancy is classified as a serious ADR because it requires hospitalisations and results in persistent or significant disability or capacity. Moreover, the carcinogenic study is recommended for any pharmaceutical product whose clinical use is continuous for at least six months (ICH Expert Working Group, 1995).

All included trials in this review lasted at least one year with the longest mean duration of follow-up was nine years (APSIS, UKPDS-38). An extensive period of study follow-up is essential for cancer detection because most human malignancies grow at a slow and steady rate for a long period of time during the clinically measurable phase. A study on human malignant tumour kinetics by Friberg and Mattson (1997) has found that a cancerous tumour has consumed more than half of its lifespan when it became detectable by the diagnostic method. For example, an approximate size 10 μmeter in diameter breast tumour with an

average doubling time of 280 days took more than eighteen years to produce a detectable tumour with a 2 mm diameter (Friberg and Mattson, 1997); where the lowest level of detection by mammography is stated to be 2.1 mm (Spratt et al., 1986). Though, different tumour types vary in term of growth rate and detection methods.

Of the included studies, only 14.4% has pre-specified cancer as a clinical endpoint. There was no difference in term of the year these studies were carried out as it was fairly ranged between the 1990s to the 2000s and it is of interest to note that these trials compared new AHT against older agents (BB or TZ) or placebo. TZ has been used as a reference group in many observational studies because it has not been convincingly linked to the risk of any cancer. It is also likely that these trials predefined cancer as one of their outcome of interest due to the increasing numbers of literature attempting to tie AHT to the risk of cancers.

Almost all the included studies (97.7%) published cancer outcomes where cancer incidence was reported as a serious adverse effect in safety analysis, the reason for treatment discontinuation or cause of deaths. Conversely, the main reason for 92% of the excluded studies is no cancer outcome reported or available. Although unpublished data were received from the remaining trials, the list is neither extensive nor complete and is probably biased because of selective data sharing.

3.2.3.3 Limitations

One limitation of this review is it is restricted to published trials and it is possible that smaller trials are missing. The grey literature was not searched due to the sheer volume of citations identified from electronic databases and time constraint. Searching for grey literature can be time-consuming because they are not usually included in the bibliographic database. Although data from the grey literature may be used to overcome publication bias, the quality of information is variable. However, this review is unlikely to miss any RCTs based on the extensive search strategy that has been implemented. Additionally, a different type of cancer incidence is more common in a certain part of the world. This factor could be contributed by the different ecological, environmental, genetic and socioeconomic variables. The inclusion of trial such as the FEVER and NHS study which enrolled only Chinese and Japanese participants respectively may not

reflect the true risk associated with antihypertensive treatment. For example, cancer of the nasopharynx, oesophagus, stomach and liver shows higher incidence rate in China than in the USA (Wang et al., 2012).

3.3 Risk of bias in included studies

The method used in the assessment of the risk of bias across all studies were described in Chapter 2, Section 2.1.5.3 (page 63). All included studies were stated to be RCTs (See 'Methodological quality of included studies', **Section 3.3.6**). The risk of bias is summarized in **Figure 3.2** presented as percentages across all included studies. Another bias is defined as the source of funding.

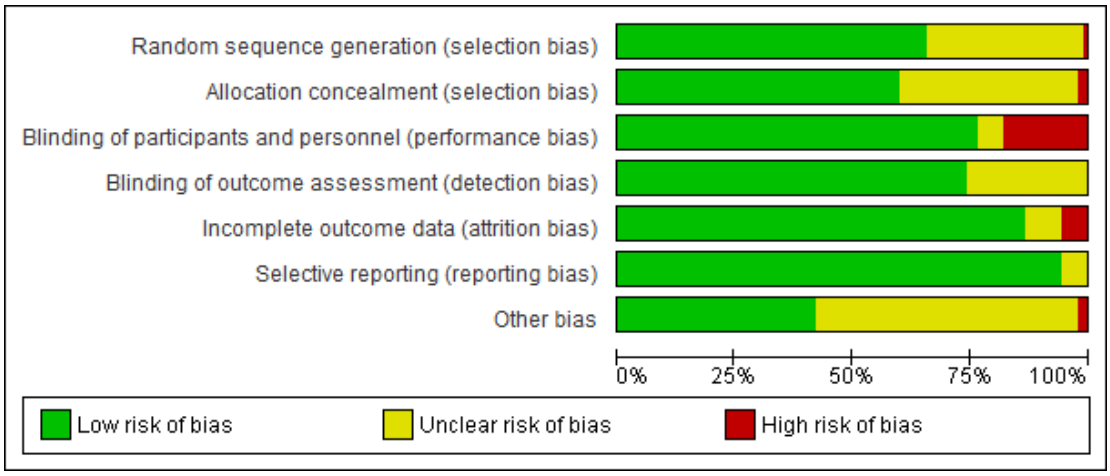


Figure 3-2: Risk of bias graph.
Review authors' judgements about each risk of bias item presented as percentages across all included studies.

3.3.1 Randomisation and allocation

Random sequence generation method was reported adequately in 59 (65.6%) of the included studies. We judged 30 (33.3%) included studies (ABCD; AIPRI; ALPINE; APSIS; ANBP; ESPIRAL; EWPHE; HOPE; INSIGHT; INTACT; IRMA-2; Kanamasa; MAPHY; NICOLE; NICS-EH; OCTOPUS; OSLO; Practolol Study; PRAISE; PREVENT; RENAAL; SCAT; SMT; STOP-HTN2; Suzuki; Syst-China; Val-HeFT; VA COOP II; VERDI; Wilcox) as unclear risk of bias as the method of randomisation was not reported. One study (E-COST) was judged reporting of the random sequence generation as high risk of bias.

The allocation domain was adequate in 54 (60%) of the included studies. The allocation concealment method was not reported in the remaining 34 studies (ABCD; AIPRI; ALPINE; APSIS; ANBP; CAMELOT; DAVIT II; ESPIRAL; EWPHE; FACET; HIJ-CREATE; INSIGHT; INTACT; IRMA-2; MAPHY; MIDAS; MRC; MRCOA; NICOLE; NICS-EH; OCTOPUS; OSLO; Otsuka; PRAISE; PREVENT; RENAAL; SCAT; SPRINT; SMT; STOP-HTN2; Suzuki; Syst-China; Val-HeFT; VA COOP) and was judged as unclear risk of bias. Two studies (E-COST; Kanamasa) were deemed as high risk of bias due to inadequate allocation concealment method.

3.3.2 Blinding

More than half (68 studies) of the included trials reported blinding of both participants and personnel where the active or study drugs and the placebo or control drugs were usually described as externally indistinguishable. Hence, these studies were considered to have a low risk of performance bias. However, there was a high risk of performance bias in 20 open-label studies (ASCOT-BPLA; CASE-J Ex; E-COST; ESPIRAL; FACET; HEP; HIJ-CREATE; INVEST; Kanamasa; MAPHY; NHS; OCTOPUS; OSLO; Otsuka; PHARAO; REIN-2; STOP-HTN2; Suzuki ; UKPDS-38; V-HeFT II) as both participants and personnel were aware of the assigned treatment. The risk of performance bias was unclear in two single-blind studies (MRC; MRCOA) where the treatment assignments were known to the doctors and nurses but not to the participants.

Blinding of outcome assessment was deemed adequate in more than half (73%) of included studies. Prospective, randomized, open-label, blinded-endpoint (PROBE) design was implemented in 14 of these studies (ASCOT-BPLA; CASE-J Ex; FACET; HEP; HIJ-CREATE; INVEST; NHS; OCTOPUS; OSLO; PHARAO; REIN-2; STOP-HTN2; UKPDS-38; V-HeFT II). The PROBE design was used mainly to avoid the introduction of bias in open-label clinical trials. Though, the risk of detection bias was unclear in 24 studies (AIPRI; ALLHAT; ANTIPAF; APSIS; ASCOT-BPLA; E-COST; ESPIRAL; GISSI-AF; INTACT; Kanamasa; LaCroix; MAPHY; NESTOR; NICOLE; Otsuka; Practolol Study; SAVE; SCAT; SPRINT; Suzuki; TROPHY; VA COOP II; VERDI; Wilcox) as blinding of outcome assessment was not described .

3.3.3 Incomplete outcome data

Eleven studies (ALPINE; DEMAND; MERIT-HF; NESTOR; OSLO; Otsuka; PHARAO; PRAISE; PREVENT; STOP-HTN2; Suzuki) have complete outcome data and no participant was lost to follow-up. The loss to follow-up was negligible in 57 studies where the attrition rate was between 0.02% and 15% (less than 20%). In these studies, the rate of discontinuation was generally low and equal between study arms. Four trials were judged to have high risk of bias for the following reasons: [1] high attrition rate of 19% (MRC) and 25% (MRCOA), [2] data of withdrawn participants were not included and per protocol analysis was used (NICS-EH), and [3] data presented in the study did not represented all randomized participants as one of the study centre failed to supply complete data and reason for failure was not stated (SPRINT).

The remaining 21 studies (ABCD; ACTION; AIPRI; ANTIPAF; APSIS; DAVIT II; ESPIRAL; IDNT; Kanamasa; MAPHY; MIDAS; PHYLLIS; Practolol Study; SCAT; SHEP; SMT; TROPHY; VA COOP II; VERDI; V-HeFT II; Wilcox) evidently accounted for all participants in each study arm, although participants loss to follow-up was not reported, and intention-to-treat (ITT) analysis was performed. Therefore, we judged these studies to be at low risk of attrition bias. Four studies (E-COST; HEP; INTACT; Val-HeFT) were judged to have an unclear risk of bias due to inadequate description of outcome data.

3.3.4 Selective reporting

Overall, 85 of the included studies (94%) reported outcomes as stated in the methodology section or the respective study protocols where available. Only five studies were judged to have an unclear risk of reporting bias. Four of these studies (HEP; VA COOP II; V-HeFT II; Wilcox) did not pre-specify study outcomes in the method section and we had no access to the respective study protocols. One study (VALIANT) failed to report revascularization procedures outcome as pre-specified in its method section.

3.3.5 Other potential sources of bias

3.3.5.1 Source of funding

Source of funding for each individual study was considered as a potential source of bias. In total, 72 studies have received various forms of support and sponsorship (e.g. financial, drugs provision, data analysis) from the pharmaceutical industries. Six studies (ANBP; BHAT; HIJ-CREATE; PAT; PREVER-Treatment; V-HeFT II) were supported by governmental bodies' research grant and/ or non-profit organizations such as the National Institute of Health, National Medical Council, NHBLI, Heart and Stroke Foundation etc. Four studies (DEMAND; NHS; OCTOPUS; Suzuki) were independent academic research while the remaining eight studies (E-COST; ESPIRAL; INTACT; Kanamasa; NICS-EH; OSLO; Otsuka; Practolol Study) have inadequate information on the funding source.

More than half of the included studies (57%) were judged to have an unclear risk of bias as the role and extend of sponsors' involvement was inadequately reported. In 37 of the included studies (ACTION; ACTIVE I; ALLHAT; ANBP; ASCOT-BPLA; DAVIT II; DEMAND; DIRECT (Overall); GISSI-AF; HIJ-CREATE; HOPE; I-PRESERVE ; INVEST; IRMA-2; LaCroix; LIFE; MRCOA; NHS; OCTOPUS; OPTIMAAL; PAT; PHARAO; PREVER-Treatment; REIN-2; SAVE; SCOPE; SHEP; SOLVD-P; SOLVD-T; Suzuki; Syst-China ; Syst-Eur; TRACE; TRANSCEND; UKPDS-38; VALIANT; V-HeFT II), the risk of bias was judged to be low as the respective study sponsors were not directly involved in the planning of studies, collection, analysis, and interpretation of data. Conversely, two studies (TROPHY; Val-HeFT) were judged to have a high risk of bias because the sponsors were directly involved in organizing, data collection and analysis of the clinical trials.

Overall, 50 of the included studies (55.6%) were judged to be at high risk of bias whereas the remaining 40 studies (ACTION; ACTIVE I; ASCOT-BPLA; BHAT; CASE-J Ex; CHARM (Overall); CONVINCE; DEMAND; DIABHYCAR; DIRECT (Overall); FEVER; HEP; IDNT; INVEST; I-PRESERVE ; MERIT-HF; NHS; NAVIGATOR; ONTARGET; OPTIMAAL; PARADIGM-HF; PAT; PHYLLIS; PREVER-Treatment; PRoFESS; REIN-2; SCOPE; SHEP; SOLVD-P; SOLVD-T; Syst-Eur; TRACE; UKPDS-38; VALIANT; VALUE; V-HeFT II) were deemed to be at low risk of bias (See **Chapter 2, Section 2.1.4.3).**

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

ABCD		
Bias [3]	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear risk	The method was not described
Allocation concealment	Unclear risk	The method was not described
Blinding of participants and personnel	Low risk	Participants and personnel were blinded
Blinding of outcome assessment	Low risk	Blind outcome assessment
Incomplete outcome data	Low risk	Missing data were unlikely to have an impact on the results of the trial
Selective reporting	Low risk	Outcomes listed in the methods were all reported
Other bias	Unclear risk	Sponsor's role or involvement was not reported.

ACTION		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low risk	Randomisation was blocked and stratified by centre.
Allocation concealment	Low risk	The chair of the safety monitoring committee prepared the random allocation list.
Blinding of participants and personnel	Low risk	Participants and personnel were blinded
Blinding of outcome assessment	Low risk	Blind outcome assessment
Incomplete outcome data	Low risk	Missing data were unlikely to have an impact on the results of the trial
Selective reporting	Low risk	Outcomes listed in the methods were all reported
Other bias	Low risk	Role of sponsor restricted to study medication supply and on-site monitoring.

ACTIVE I		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low risk	Central randomisation service through an automated voice response system (AreS)
Allocation concealment	Low risk	Allocated through AreS.
Blinding of participants and personnel	Low risk	Participants and personnel were blinded
Blinding of outcome assessment	Low risk	Blinded outcome assessment
Incomplete outcome data	Low risk	Missing data were unlikely to have an impact on the results of the trial
Selective reporting	Low risk	Outcomes listed in the methods were all reported
Other bias	Low risk	Sponsors had no direct role in the collection, analysis, or interpretation of study data

[3] The six domains assess the risk of bias in each individual studies for: [1] Random sequence generation and allocation concealment method assess for risk of selection bias; [2] Blinding of participants and personnel assess the risk of performance bias; [3] Blinding of outcome assessment assess for risk of detection bias; [4] Incomplete outcome data assess for risk of attrition bias; [5] Selective reporting of outcome assess for risk of reporting bias; and [6] Other bias assess the risk of source of funding bias.

AIPRI		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear risk	Randomisation was balanced for disease severity at each centre. The exact method of randomisation was not described.
Allocation concealment	Unclear risk	The method was not described
Blinding of participants and personnel	Low risk	Participants and personnel were blinded
Blinding of outcome assessment	Unclear risk	A quality-control and end-point–evaluation committee confirmed all the diagnoses and all the instances in which end points were reached. It was not stated whether they were blinded.
Incomplete outcome data	Low risk	Missing data were unlikely to have an impact on the results of the trial
Selective reporting	Low risk	Outcomes listed in the methods were all reported
Other bias	Unclear risk	Sponsor's role or involvement was not described

ALLHAT		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low risk	Stratified by the centre and blocked in random block sizes of 5 or 9
Allocation concealment	Low risk	Generated by a computer, implemented at the clinical trials centre
Blinding of participants and personnel	Low risk	Participants and personnel were blinded
Blinding of outcome assessment	Unclear risk	Not described.
Incomplete outcome data	Low risk	Two sites and their patients originally reported were excluded, which might impact on the results, although it was because of their poor documentation of informed consent. But an ITT analysis was performed
Selective reporting	Low risk	Outcomes listed in the methods were all reported
Other bias	Low risk	Industrial sponsors had no direct role in the collection, analysis, or interpretation of study data.

ALPINE		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear risk	The method was not described
Allocation concealment	Unclear risk	The method was not described
Blinding of participants and personnel	Low risk	Participants and personnel were blinded
Blinding of outcome assessment	Low risk	Blind outcome assessment
Incomplete outcome data	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	Low risk	Outcomes listed in the methods were all reported
Other bias	Unclear risk	Role of the sponsor was not described

ANBP		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear risk	Stratified by age and sex. The exact method of randomisation was not described
Allocation concealment	Unclear risk	The method was not described
Blinding of participants and personnel	Low risk	Participants and personnel were blinded
Blinding of outcome assessment	Low risk	Blind outcome assessment
Incomplete outcome data	Low risk	3931 were randomized but 504 participants were not given study medication as their BP fell before tablets were due and never again reached the threshold to qualify them to start tablets. Therefore, the trial population was made up of 3427 patients. All randomized patients were reported or analysed in the group to which they were allocated by randomisation. Lost to follow-up: 0.2%
Selective reporting	Low risk	Outcomes listed in the methods were all reported
Other bias	Low risk	Sponsored by government bodies or non-profit organizations

ANTIPAF		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low risk	Used internet-based e-Trial Management System (XTrial™).
Allocation concealment	Low risk	Used internet-based e-Trial Management System (XTrial™).
Blinding of participants and personnel	Low risk	Participants and personnel were blinded
Blinding of outcome assessment	Unclear risk	Not described.
Incomplete outcome data	Low risk	Missing data were unlikely to have an impact on the results of the trial
Selective reporting	Low risk	Outcomes listed in the methods were all reported
Other bias	Unclear risk	Role of the sponsor was not described.

APSIS		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear risk	The method was not described
Allocation concealment	Unclear risk	The method was not described
Blinding of participants and personnel	Low risk	Participants and personnel were blinded
Blinding of outcome assessment	Unclear risk	Not described.
Incomplete outcome data	Low risk	Missing data were unlikely to have an impact on the results of the trial
Selective reporting	Low risk	Outcomes listed in the methods were all reported
Other bias	Unclear risk	Role of the sponsor was not described.

ASCOT-BPLA		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low risk	Computer generated optimum allocation
Allocation concealment	Low risk	Computer generated optimum allocation
Blinding of participants and personnel	High risk	Study drugs were administered open-label
Blinding of outcome assessment	Low risk	Blind outcome assessment
Incomplete outcome data	Low risk	Two centres with 85 patients were excluded after randomisation, but missing data were equal between the treatment groups, and an ITT analysis was performed
Selective reporting	Low risk	Outcomes listed in the methods were all reported
Other bias	Low risk	Sponsors had no direct role in the collection, analysis, or interpretation of study data

BHAT		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low risk	Stratified by clinical centre and was carried out in a block fashion (groups size of 4,6, and 8)
Allocation concealment	Low risk	Central allocation. The assignment made by the Coordinating Centre and transmitted to the Clinical Centre by telephone
Blinding of participants and personnel	Low risk	Participants and personnel were blinded
Blinding of outcome assessment	Low risk	Blind outcome assessment
Incomplete outcome data	Low risk	Missing data were unlikely to have an impact on the results of the trial
Selective reporting	Low risk	Outcomes listed in the methods were all reported
Other bias	Unclear risk	Role of the sponsor was not described

CAMELOT		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low risk	The randomisation code was generated using a block size of 6.
Allocation concealment	Unclear risk	The method was not described
Blinding of participants and personnel	Low risk	Participants and personnel were blinded
Blinding of outcome assessment	Low risk	Blind outcome assessment
Incomplete outcome data	Low risk	Missing data were unlikely to have an impact on the results of the trial
Selective reporting	Low risk	Outcomes listed in the methods were all reported
Other bias	Unclear risk	Sponsor participated in discussions regarding study design and protocol development and provided logistic support.

CASE-J Ex		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low risk	Computer-generated lists of permutation blocks stratified by 9 regional blocks and complication of T2DM
Allocation concealment	Low risk	The allocation results were immediately transmitted to the collaborating physicians through the Internet and/or facsimile.
Blinding of participants and personnel	High risk	Study drugs were administered open-label
Blinding of outcome assessment	Low risk	Blind outcome assessment
Incomplete outcome data	Low risk	Missing data were unlikely to have an impact on the results of the trial
Selective reporting	Low risk	Outcomes listed in the methods were all reported
Other bias	Unclear risk	Role of the sponsor was not described

CHARM Overall		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low risk	Stratified by site and component trial, and provided through a coordinating telephone centre
Allocation concealment	Low risk	Computer generated assignment and provided through a coordinating telephone centre. The assignment code was held at an independent centre and by the data safety monitoring board.
Blinding of participants and personnel	Low risk	Participants and personnel were blinded
Blinding of outcome assessment	Low risk	Blind outcome assessment
Incomplete outcome data	Low risk	Missing data were unlikely to have an impact on the results of the trial
Selective reporting	Low risk	Outcomes listed in the methods were all reported
Other bias	Unclear risk	The sponsor of the study managed the data, and their representatives were involved in the data analysis and data interpretation.

CONVINCE		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low risk	The Interactive Voice Response System (IVRS) was used
Allocation concealment	Low risk	Allocation via a trans-telephonic interactive voice response system
Blinding of participants and personnel	Low risk	Participants and personnel were blinded
Blinding of outcome assessment	Low risk	Blind outcome assessment
Incomplete outcome data	Low risk	Participants from 2 sites (n=126; 62 randomized to COER verapamil) were excluded because of data integrity concerns, and its impact on results was unclear, but ITT analysis was performed in this systematic review
Selective reporting	Low risk	Outcomes listed in the methods were all reported

Other bias	Unclear risk	Sponsor participated in designing and monitoring of the study. All analyses were carried out independent of the sponsor.

DAVIT II		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low risk	Permutation blocks of 10 at each centre.
Allocation concealment	Unclear risk	The method was not described
Blinding of participants and personnel	Low risk	Participants and personnel were blinded
Blinding of outcome assessment	Low risk	Blind outcome assessment
Incomplete outcome data	Low risk	Missing data were unlikely to have an impact on the results of the trial
Selective reporting	Low risk	Outcomes listed in the methods were all reported
Other bias	Low risk	Role of sponsor restricted to study drug supply.

DEMAND		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low risk	Block of 6 patients assigned to each therapy with a 1:1:1 ratio.
Allocation concealment	Low risk	Computer-generated and randomisation numbers were blindly assigned
Blinding of participants and personnel	Low risk	Participants and personnel blinded
Blinding of outcome assessment	Low risk	Blind outcome assessment
Incomplete outcome data	Low risk	No patients were lost to follow-up
Selective reporting	Low risk	Outcomes listed in the methods were all reported
Other bias	Low risk	Independent academic trial

DIABHYCAR		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low risk	Stratified by centre and balanced by blocks of two treatments, using a computer generated random number list.
Allocation concealment	Low risk	Centralised allocation.
Blinding of participants and personnel	Low risk	Participants and personnel blinded
Blinding of outcome assessment	Low risk	Blind outcome assessment
Incomplete outcome data	Low risk	Missing data were unlikely to have an impact on the results of the trial.
Selective reporting	Low risk	Outcomes listed in the methods were all reported
Other bias	Unclear risk	Partly sponsored by a pharmaceutical company

DIRECT Overall		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low risk	Random assignment was done centrally, using an interactive voice-response system
Allocation concealment	Low risk	Central allocation

Blinding of participants and personnel	Low risk	Participants and personnel blinded
Blinding of outcome assessment	Low risk	Blind outcome assessment
Incomplete outcome data	Low risk	Missing data were unlikely to have an impact on the results of the trial
Selective reporting	Low risk	Outcomes listed in the methods were all reported
Other bias	Low risk	Sponsors did the statistical analysis, validated by an independent statistician.

E-COST		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation	High risk	The envelope method. The names of subjects were written on slips of paper, and the physician randomly placed the slips of paper into envelopes representing the different group assignments.
Allocation concealment	High risk	Inadequate.
Blinding of participants and personnel	High risk	Study drugs were administered open-label
Blinding of outcome assessment	Unclear risk	Not described.
Incomplete outcome data	Unclear risk	All randomized patients were reported or analysed in the group to which they were allocated by randomisation. However, the details on numbers and reasons for withdrawal and loss to follow-up were not reported.
Selective reporting	Low risk	Outcomes listed in the methods were all reported
Other bias	Unclear risk	Funding source not reported

ESPIRAL		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear risk	The method was not described.
Allocation concealment	Unclear risk	The method was not described.
Blinding of participants and personnel	High risk	Study drugs were administered open-label
Blinding of outcome assessment	Unclear risk	Not described
Incomplete outcome data	Low risk	Missing data were unlikely to have an impact on the results of the trial
Selective reporting	Low risk	Outcomes listed in the methods were all reported
Other bias	Unclear risk	Funding source not reported

EWPHE		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear risk	The method was not described.
Allocation concealment	Unclear risk	The method was not described.
Blinding of participants and personnel	Low risk	Participants and personnel blinded
Blinding of outcome assessment	Low risk	Blind outcome assessment
Incomplete outcome data	Low risk	Missing data were unlikely to have an impact on the results of the trial
Selective reporting	Low risk	Outcomes listed in the methods were all reported

Other bias	Unclear risk	Supported by a grant from pharmaceutical companies who prepared active and placebo tablets. Yearly meetings were sponsored by a pharmaceutical company.

FACET		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low risk	Computer generated randomisation list.
Allocation concealment	Unclear risk	The method was not described.
Blinding of participants and personnel	Low risk	Participants and personnel blinded
Blinding of outcome assessment	Low risk	Blind outcome assessment
Incomplete outcome data	Low risk	Missing data were unlikely to have an impact on the results of the trial
Selective reporting	Low risk	Outcomes listed in the methods were all reported
Other bias	Unclear risk	Role of the sponsor was not described

FEVER		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low risk	Computer-generated randomisation list.
Allocation concealment	Low risk	Allocation by phone or fax after verified eligibility.
Blinding of participants and personnel	Low risk	Participants and personnel blinded
Blinding of outcome assessment	Low risk	Blind outcome assessment
Incomplete outcome data	Low risk	Missing data were unlikely to have an impact on the results of the trial
Selective reporting	Low risk	Outcomes listed in the methods were all reported
Other bias	Unclear risk	Partly sponsored by a pharmaceutical company

GISSI-AF		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low risk	Computer-generated randomisation list.
Allocation concealment	Low risk	By means of a computerized, telephone randomisation system, with the group assignments concealed
Blinding of participants and personnel	Low risk	Participants and personnel blinded
Blinding of outcome assessment	Unclear risk	An independent end-point committee adjudicated all reports of primary end points, deaths, and hospitalizations. Not described whether they were blinded to assigned treatment or not.
Incomplete outcome data	Low risk	Missing data were unlikely to have an impact on the results of the trial
Selective reporting	Low risk	Outcomes listed in the methods were all reported
Other bias	Low risk	The sponsor had no role in the design or conduct of the trial.

HEP		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low risk	Prepared by a random number tables
Allocation concealment	Low risk	By opening an opaque envelope supplied in sequence supplied by the trial instructor
Blinding of participants and personnel	Unclear risk	Not described
Blinding of outcome assessment	Low risk	Blind outcome assessment
Incomplete outcome data	Unclear risk	Not indicated whether reasons for missing outcome data were similar across treatment groups
Selective reporting	Unclear risk	No access to the protocol
Other bias	Unclear risk	Role of the sponsor was not described

HIJ-CREATE		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low risk	Computer-generated randomisation list.
Allocation concealment	Unclear risk	The method was not described.
Blinding of participants and personnel	High risk	Study drugs were administered open-label
Blinding of outcome assessment	Low risk	Blind outcome assessment
Incomplete outcome data	Low risk	Missing data were unlikely to have an impact on the results of the trial
Selective reporting	Low risk	Outcomes listed in the methods were all reported
Other bias	Low risk	The sponsor played no role in the study design, data collection, data analysis, data interpretation, or writing of the report.

HOPE		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear risk	Central randomisation (2 x 2 factorial design), no description of the random sequence generation
Allocation concealment	Low risk	Central allocation
Blinding of participants and personnel	Low risk	Participants and personnel blinded
Blinding of outcome assessment	Low risk	Blind outcome assessment
Incomplete outcome data	Low risk	Missing data were unlikely to have an impact on the results of the trial
Selective reporting	Low risk	Outcomes listed in the methods were all reported
Other bias	Low risk	Sponsored by government bodies or non-profit organizations

I-PRESERVE		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low risk	Automated, central randomisation system permuted block and stratified by site and by use of ACE inhibitors at baseline.

Allocation concealment	Low risk	Via an interactive voice-response system.
Blinding of participants and personnel	Low risk	Participants and personnel blinded
Blinding of outcome assessment	Low risk	Blind outcome assessment
Incomplete outcome data	Low risk	Missing data were unlikely to have an impact on the results of the trial
Selective reporting	Low risk	Outcomes listed in the methods were all reported
Other bias	Low risk	The sponsor collected the trial data which were then analysed independently of the sponsor.

IDNT		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low risk	Computer-generated randomisation list.
Allocation concealment	Low risk	To minimize any centre effect, randomisation was blocked by the centre
Blinding of participants and personnel	Low risk	Participants and personnel blinded
Blinding of outcome assessment	Low risk	Blind outcome assessment
Incomplete outcome data	Low risk	Missing data were unlikely to have an impact on the results of the trial
Selective reporting	Low risk	Outcomes listed in the methods were all reported
Other bias	Unclear risk	Role of the sponsor was not described

INSIGHT		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear risk	The method was not described.
Allocation concealment	Unclear risk	The method was not described.
Blinding of participants and personnel	Low risk	Participants and personnel blinded
Blinding of outcome assessment	Low risk	Blind outcome assessment
Incomplete outcome data	Low risk	254 patients (132 and 122 patients in each group) were excluded after randomisation from centres withdrawn for misconduct, and they were not included in the analysis
Selective reporting	Low risk	Outcomes listed in the methods were all reported
Other bias	Unclear risk	Role of the sponsor was not described

INTACT		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear risk	The method was not described.
Allocation concealment	Unclear risk	The method was not described.
Blinding of participants and personnel	Low risk	Participants and personnel blinded
Blinding of outcome assessment	Unclear risk	Blinding of outcome assessment was not described

Incomplete outcome data	Unclear risk	77 patients were excluded from the final report as they had no or slight study deviations and completed the study. The final analysis only included 348 patients who underwent a second angiogram.
Selective reporting	Low risk	Outcomes listed in the methods were all reported
Other bias	Unclear risk	Source of funding not reported.

INVEST		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low risk	An Internet-based management system was used.
Allocation concealment	Low risk	Central allocation.
Blinding of participants and personnel	High risk	Study drugs were administered open-label
Blinding of outcome assessment	Low risk	Blind outcome assessment
Incomplete outcome data	Low risk	Missing data were equal between the treatment groups, and an intention-to-treat analysis was performed
Selective reporting	Low risk	Outcomes listed in the methods were all reported
Other bias	Low risk	Sponsor provided financial support for all study medications. The sponsors have played no role in editorial or data management.

IRMA-2		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear risk	The method was not described.
Allocation concealment	Unclear risk	The method was not described.
Blinding of participants and personnel	Low risk	Participants and personnel blinded
Blinding of outcome assessment	Low risk	Blind outcome assessment
Incomplete outcome data	Low risk	Missing data were unlikely to have an impact on the results of the trial.
Selective reporting	Low risk	Outcomes listed in the methods were all reported
Other bias	Low risk	The steering committee included two nonvoting members from the sponsoring company who oversaw the study design, the conduct of the trial, and the management and analysis of the data

Kanamasa		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear risk	Determined according to the fifth digit of their hospital identification number.
Allocation concealment	High risk	Inadequate. Allocation based on the odd number or even number
Blinding of participants and personnel	High risk	Study drugs were administered open-label
Blinding of outcome assessment	Unclear risk	Blinding of outcome assessment was not described

Incomplete outcome data	Low risk	Missing data were unlikely to have an impact on the results of the trial
Selective reporting	Low risk	Outcomes listed in the methods were all reported
Other bias	Unclear risk	Source of funding not reported.

LaCroix		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low risk	A complete randomized list was prepared with study identifiers stratified by sex and used equal allocation with blocking size of nine
Allocation concealment	Low risk	The blocking size was known only to the statistician. A complete randomized list was prepared with study identifiers indicated and each vial of medication was labelled by pharmacy staff.
Blinding of participants and personnel	Low risk	Participants and personnel blinded
Blinding of outcome assessment	Unclear risk	Study statistician and data monitoring committee saw unblinded data but none had any contact with study participants.
Incomplete outcome data	Low risk	Missing data were unlikely to have an impact on the results of the trial
Selective reporting	Low risk	Outcomes listed in the methods were all reported
Other bias	Low risk	Financially sponsored by government and study tablets were sponsored by a pharmaceutical company.

LIFE		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low risk	Computer-generated allocation sequence
Allocation concealment	Low risk	Adequate. Central allocation.
Blinding of participants and personnel	Low risk	Participants and personnel blinded
Blinding of outcome assessment	Low risk	Blind outcome assessment
Incomplete outcome data	Low risk	Missing data were unlikely to have an impact on the results of the trial
Selective reporting	Low risk	Outcomes listed in the methods were all reported
Other bias	Low risk	Study data are in the sponsor's database who provided the study steering committee with free access to all data. Data interpretation and analysis, paper writing and publication was independent of the sponsor.

MAPHY		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear risk	The method was not described.
Allocation concealment	Unclear risk	The method was not described.
Blinding of participants and personnel	High risk	Study drugs were administered open-label
Blinding of outcome assessment	Unclear risk	Not described

Incomplete outcome data	Low risk	Missing data were unlikely to have an impact on the results of the trial
Selective reporting	Low risk	Outcomes listed in the methods were all reported
Other bias	Unclear risk	Partly sponsored by a pharmaceutical company

MERIT-HF		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low risk	Computer generated randomisation list.
Allocation concealment	Low risk	Allocation by the interactive voice recording system.
Blinding of participants and personnel	Low risk	Participants and personnel blinded
Blinding of outcome assessment	Low risk	Blind outcome assessment
Incomplete outcome data	Low risk	No patients were lost to follow-up
Selective reporting	Low risk	Outcomes listed in the methods were all reported
Other bias	Unclear risk	Role of the sponsor was not described

MIDAS		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low risk	The randomisation process was stratified and blocked by clinic
Allocation concealment	Unclear risk	The method was not described.
Blinding of participants and personnel	Low risk	Participants and personnel blinded
Blinding of outcome assessment	Low risk	Blind outcome assessment
Incomplete outcome data	Low risk	Missing data were unlikely to have an impact on the results of the trial
Selective reporting	Low risk	Outcomes listed in the methods were all reported
Other bias	Unclear risk	Role of the sponsor was not described

MRC		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low risk	Randomisation was in a stratified block of eight within each sex and clinic
Allocation concealment	Unclear risk	The method was not described.
Blinding of participants and personnel	Unclear risk	Single blind
Blinding of outcome assessment	Low risk	Blind outcome assessment
Incomplete outcome data	High risk	All randomized patients were reported or analysed in the group to which they were allocated by randomisation. Lost to follow-up: 19%
Selective reporting	Low risk	Outcomes listed in the methods were all reported
Other bias	Unclear risk	Role of the sponsor was not described

MRCOA		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low risk	Randomisation was in a stratified block of eight within each sex and clinic
Allocation concealment	Unclear risk	The method was not described.
Blinding of participants and personnel	Unclear risk	Single blind
Blinding of outcome assessment	Low risk	Blind outcome assessment
Incomplete outcome data	High risk	All randomized patients were reported or analysed in the group to which they were allocated by randomisation. Lost to follow-up: 25%
Selective reporting	Low risk	Outcomes listed in the methods were all reported
Other bias	Low risk	Study drugs supplied by sponsor

NAVIGATOR		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low risk	Computer generated stratified according to centre, with a block size of eight within each centre.
Allocation concealment	Low risk	Central allocation.
Blinding of participants and personnel	Low risk	Participants and personnel blinded
Blinding of outcome assessment	Low risk	Blind outcome assessment
Incomplete outcome data	Low risk	212 patients were excluded after randomisation because of protocol deficiencies at the site and they were not included in the final analysis. ITT analysis was performed.
Selective reporting	Low risk	Outcomes listed in the methods were all reported
Other bias	Unclear risk	Data were collected, managed, and analysed by the sponsor, with oversight from the executive committee, and the analyses were replicated by an independent academic statistician.

NESTOR		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low risk	Computer generated
Allocation concealment	Low risk	Central allocation
Blinding of participants and personnel	Low risk	Participants and personnel blinded
Blinding of outcome assessment	Unclear risk	Not described
Incomplete outcome data	Low risk	No patients were lost to follow-up
Selective reporting	Low risk	Outcomes listed in the methods were all reported
Other bias	Unclear risk	Role of the sponsor was not described

NHS		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low risk	Minimization method with five factors of baseline characteristics.
Allocation concealment	Low risk	Automatically performed by a host computer system
Blinding of participants and personnel	High risk	Study drugs were administered open-label
Blinding of outcome assessment	Low risk	Blind outcome assessment
Incomplete outcome data	Low risk	Missing data were unlikely to have an impact on the results of the trial
Selective reporting	Low risk	Outcomes listed in the methods were all reported
Other bias	Low risk	Independent academic study

NICOLE		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear risk	The method was not described.
Allocation concealment	Unclear risk	The method was not described.
Blinding of participants and personnel	Low risk	Participants and personnel blinded
Blinding of outcome assessment	Unclear risk	Not described
Incomplete outcome data	Low risk	Seven patients were excluded from the ITT population as they did not take any study tablet.
Selective reporting	Low risk	Outcomes listed in the methods were all reported
Other bias	Unclear risk	Role of the sponsor was not described

NICS-EH		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear risk	The method was not described.
Allocation concealment	Unclear risk	The method was not described.
Blinding of participants and personnel	Low risk	It was stated as double-dummy, but details was not described
Blinding of outcome assessment	Low risk	Blind outcome assessment
Incomplete outcome data	High risk	Data of withdrawn patients were not included. PP analyses were used
Selective reporting	Low risk	Outcomes listed in the methods were all reported
Other bias	Unclear risk	Status of study funding not reported

OCTOPUS		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear risk	The method was not described.
Allocation concealment	Unclear risk	The method was not described.
Blinding of participants and personnel	High risk	Study drugs were administered open-label
Blinding of outcome assessment	Low risk	Blind outcome assessment

Incomplete outcome data	Low risk	Missing data were unlikely to have an impact on the results of the trial
Selective reporting	Low risk	Outcomes listed in the methods were all reported
Other bias	Low risk	The study was supported by own fund and donation

ONTARGET		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low risk	Stratified according to the site with the use of permuted blocks
Allocation concealment	Low risk	Central automated telephone service
Blinding of participants and personnel	Low risk	Participants and personnel blinded
Blinding of outcome assessment	Low risk	Blind outcome assessment
Incomplete outcome data	Low risk	Missing data were unlikely to have an impact on the results of the trial
Selective reporting	Low risk	Outcomes listed in the methods were all reported
Other bias	Unclear risk	Partly sponsored by a pharmaceutical company

OPTIMAAL		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low risk	Block randomisation was used at each centre
Allocation concealment	Low risk	Computer generated allocation
Blinding of participants and personnel	Low risk	Participants and personnel blinded
Blinding of outcome assessment	Low risk	Blind outcome assessment
Incomplete outcome data	Low risk	Missing data were unlikely to have an impact on the results of the trial
Selective reporting	Low risk	Outcomes listed in the methods were all reported
Other bias	Low risk	The sponsor provided data management assistance and two non-voting members of the steering committee. The scientific conduct of the study and manuscript preparation was independent of the sponsor.

OSLO		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear risk	Randomisation performed by a "random number table". However, the table was not adjusted for the actual numbers, which is the reason for the difference between groups.
Allocation concealment	Unclear risk	The method was not described.
Blinding of participants and personnel	Unclear risk	No description of whether drug administration was performed open or blinded.
Blinding of outcome assessment	Low risk	Blind outcome assessment
Incomplete outcome data	Low risk	No patients were lost to follow-up
Selective reporting	Low risk	Outcomes listed in the methods were all reported
Other bias	Unclear risk	Source of funding not reported

Otsuka		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low risk	Minimization method controlling for the following four factors.
Allocation concealment	Unclear risk	The method was not described.
Blinding of participants and personnel	High risk	Study drugs were administered open-label
Blinding of outcome assessment	Unclear risk	Not described
Incomplete outcome data	Low risk	No patients were lost to follow-up
Selective reporting	Low risk	Outcomes listed in the methods were all reported
Other bias	Unclear risk	Source of funding not reported

PARADIGM-HF		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low risk	The randomisation list was produced by the IVRS.
Allocation concealment	Low risk	Interactive voice response system
Blinding of participants and personnel	Low risk	Participants and personnel blinded
Blinding of outcome assessment	Low risk	Blind outcome assessment
Incomplete outcome data	Low risk	Missing data were unlikely to have an impact on the results of the trial
Selective reporting	Low risk	Outcomes listed in the methods were all reported
Other bias	Unclear risk	Role of the sponsor was not described

PAT		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low risk	Computer-generated randomisation list
Allocation concealment	Low risk	Centrally allocation
Blinding of participants and personnel	Low risk	Participants and personnel blinded
Blinding of outcome assessment	Low risk	Blind outcome assessment
Incomplete outcome data	Low risk	4 patients were excluded from analysis as they were randomized in error and did not meet eligibility criteria. An ITT analysis was performed.
Selective reporting	Low risk	Outcomes listed in the methods were all reported
Other bias	Low risk	Sponsored by a government body

PHARAO		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low risk	Computer-generated randomisation list.
Allocation concealment	Low risk	Central allocation
Blinding of participants and personnel	High risk	Study drugs were administered open-label
Blinding of outcome assessment	Low risk	Blind outcome assessment

Incomplete outcome data	Low risk	No patients were lost to follow-up
Selective reporting	Low risk	Outcomes listed in the methods were all reported
Other bias	Low risk	The study was conducted independently of all sponsors

PHYLLIS		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low risk	Computer-generated in a block size of 4
Allocation concealment	Low risk	Central allocation
Blinding of participants and personnel	Low risk	Participants and personnel blinded
Blinding of outcome assessment	Low risk	Blind outcome assessment
Incomplete outcome data	Low risk	Missing data were unlikely to have an impact on the results of the trial
Selective reporting	Low risk	Outcomes listed in the methods were all reported
Other bias	Unclear risk	Role of the sponsor was not described

Practolol Study		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear risk	Randomized code of numbers was used. The exact method was not described.
Allocation concealment	Low risk	Sealed envelope and sequentially numbered containers
Blinding of participants and personnel	Low risk	Participants and personnel blinded
Blinding of outcome assessment	Unclear risk	Not described
Incomplete outcome data	Low risk	Patients information or data collection were incomplete as a few physicians had not finally reviewed all patients by the cut-off date. Missing data were unlikely to alter the results and conclusion
Selective reporting	Low risk	Outcomes listed in the methods were all reported
Other bias	Unclear risk	Source of funding not reported

PRAISE		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear risk	The exact method was not described.
Allocation concealment	Unclear risk	The method was not described.
Blinding of participants and personnel	Low risk	Participants and personnel blinded
Blinding of outcome assessment	Low risk	Blind outcome assessment
Incomplete outcome data	Low risk	No patients were lost to follow-up
Selective reporting	Low risk	Outcomes listed in the methods were all reported
Other bias	Unclear risk	Source of funding not reported

PREVENT		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear risk	The exact method was not described.
Allocation concealment	Unclear risk	The method was not described.
Blinding of participants and personnel	Low risk	Participants and personnel blinded
Blinding of outcome assessment	Low risk	Blind outcome assessment
Incomplete outcome data	Low risk	No patients were lost to follow-up
Selective reporting	Low risk	Outcomes listed in the methods were all reported
Other bias	Unclear risk	Source of funding not reported

PREVER-Treatment		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low risk	Computer-generated list.
Allocation concealment	Low risk	Via a 24-h web-based automated system.
Blinding of participants and personnel	Low risk	Participants and personnel blinded
Blinding of outcome assessment	Low risk	Blind outcome assessment
Incomplete outcome data	Unclear risk	Withdrawals were not included in the analysis. No indication of ITT analysis performed.
Selective reporting	Low risk	Outcomes listed in the methods were all reported
Other bias	Low risk	The sponsors had no participation in the design and conduct of the study, preparation and approval of the manuscript.

PRoFESS		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low risk	Central telephone randomisation system.
Allocation concealment	Low risk	Central allocation.
Blinding of participants and personnel	Low risk	Participants and personnel blinded
Blinding of outcome assessment	Low risk	Blind outcome assessment
Incomplete outcome data	Low risk	Missing data were unlikely to have an impact on the results of the trial
Selective reporting	Low risk	Outcomes listed in the methods were all reported
Other bias	Unclear risk	The trial was sponsored by pharmaceutical companies and was designed by the steering committee, which included representatives of the sponsor

REIN-2		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low risk	Minimisation method
Allocation concealment	Low risk	Central allocation
Blinding of participants and personnel	High risk	Study drugs were administered open-label

Blinding of outcome assessment	Low risk	Blind outcome assessment
Incomplete outcome data	Low risk	3 patients were excluded from analysis post-randomisation as they never took the study tablet. ITT analysis was performed.
Selective reporting	Low risk	Outcomes listed in the methods were all reported
Other bias	Low risk	The sponsors had no participation in the design and conduct of the study, preparation and approval of the manuscript.

RENAAL		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear risk	The method was not described.
Allocation concealment	Unclear risk	The method was not described.
Blinding of participants and personnel	Low risk	Participants and personnel blinded
Blinding of outcome assessment	Low risk	Blind outcome assessment
Incomplete outcome data	Low risk	Missing data were unlikely to have an impact on the results of the trial
Selective reporting	Low risk	Outcomes listed in the methods were all reported
Other bias	Unclear risk	Role of the sponsor was not described

SAVE		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low risk	Computer-generated stratified according to centre
Allocation concealment	Low risk	Central allocation
Blinding of participants and personnel	Low risk	Participants and personnel blinded
Blinding of outcome assessment	Unclear risk	Not described
Incomplete outcome data	Low risk	Missing data were unlikely to have an impact on the results of the trial
Selective reporting	Low risk	Outcomes listed in the methods were all reported
Other bias	Low risk	The sponsor was not involved in the acquisition or management of data and did not have access to unblinded information.

SCAT		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear risk	The method was not described.
Allocation concealment	Unclear risk	The method was not described.
Blinding of participants and personnel	Low risk	Participants and personnel blinded
Blinding of outcome assessment	Unclear risk	Not described
Incomplete outcome data	Low risk	Missing data were unlikely to have an impact on the results of the trial
Selective reporting	Low risk	Outcomes listed in the methods were all reported
Other bias	Unclear risk	Role of the sponsor was not described

SCOPE		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low risk	Computer-generated randomisation schedule
Allocation concealment	Low risk	Central allocation.
Blinding of participants and personnel	Low risk	Participants and personnel blinded
Blinding of outcome assessment	Low risk	Blind outcome assessment
Incomplete outcome data	Low risk	Missing data were unlikely to have an impact on the results of the trial
Selective reporting	Low risk	Outcomes listed in the methods were all reported
Other bias	Low risk	The study data were entered in the sponsor's database. The Executive and Steering Committees had full-access to all data and were free to suggest analyses, interpret results, and write paper independently of the sponsor

SHEP		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low risk	Randomisation stratified by clinical centre and by antihypertensive status at initial contact. The exact method was not described.
Allocation concealment	Low risk	Central allocation
Blinding of participants and personnel	Low risk	Participants and personnel blinded
Blinding of outcome assessment	Low risk	Blind outcome assessment
Incomplete outcome data	Low risk	Missing data were unlikely to have an impact on the results of the trial
Selective reporting	Low risk	Outcomes listed in the methods were all reported
Other bias	Low risk	Financially sponsored by government and study tablets were sponsored by pharmaceutical companies.

SOLVD-P		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low risk	Computer-generated randomisation
Allocation concealment	Low risk	Central allocation
Blinding of participants and personnel	Low risk	Participants and personnel blinded
Blinding of outcome assessment	Low risk	Blind outcome assessment
Incomplete outcome data	Low risk	Missing data were unlikely to have an impact on the results of the trial
Selective reporting	Low risk	Outcomes listed in the methods were all reported
Other bias	Low risk	The study was conducted independently of all sponsors

SOLVD-T		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low risk	Computer-generated randomisation

Allocation concealment	Low risk	Central allocation
Blinding of participants and personnel	Low risk	Participants and personnel blinded
Blinding of outcome assessment	Low risk	Blind outcome assessment
Incomplete outcome data	Low risk	Missing data were unlikely to have an impact on the results of the trial
Selective reporting	Low risk	Outcomes listed in the methods were all reported
Other bias	Low risk	The study was conducted independently of all sponsors

SPRINT		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low risk	Block size of six divided randomly into triplet according to the intervention arm
Allocation concealment	Unclear risk	The method was not described.
Blinding of participants and personnel	Low risk	Participants and personnel blinded
Blinding of outcome assessment	Unclear risk	Blinding of outcome assessment was not described
Incomplete outcome data	High risk	Data presented in the study did not represent all randomized participants as one of the study centres failed to supply complete baseline data (n= 127). Reason for failure not stated.
Selective reporting	Low risk	Outcomes listed in the methods were all reported
Other bias	Unclear risk	Role of the sponsor was not described

SMT		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear risk	Stratified according to the type of ventricular arrhythmias, age, and estimated infarct size. The method was not reported
Allocation concealment	Unclear risk	The method was not described.
Blinding of participants and personnel	Low risk	Participants and personnel blinded
Blinding of outcome assessment	Low risk	Blind outcome assessment
Incomplete outcome data	Low risk	Missing data were unlikely to have an impact on the results of the trial
Selective reporting	Low risk	Outcomes listed in the methods were all reported
Other bias	Unclear risk	Partly sponsored by the pharmaceutical company

STOP-HTN2		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear risk	The method was not described.
Allocation concealment	Unclear risk	The method was not described.
Blinding of participants and personnel	High risk	Study drugs were administered open-label
Blinding of outcome assessment	Low risk	Blind outcome assessment
Incomplete outcome data	Low risk	No patients were lost to follow-up
Selective reporting	Low risk	Outcomes listed in the methods were all reported

Other bias	Unclear risk	Role of the sponsor was not described

Suzuki		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear risk	Dynamic allocation method after stratification by sex, age, SBP, and diabetes
Allocation concealment	Unclear risk	The method was not described.
Blinding of participants and personnel	High risk	Study drugs were administered open-label
Blinding of outcome assessment	Unclear risk	Not described
Incomplete outcome data	Low risk	No patients were lost to follow-up
Selective reporting	Low risk	Outcomes listed in the methods were all reported
Other bias	Low risk	The study was supported by own fund

Syst-China		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear risk	Stratification by centre, sex, and previous CV complications. The exact method was not described.
Allocation concealment	Unclear risk	Each clinical centre received supplies of the three active study drugs, all labelled 'A', and the three matching placebos, all labelled 'B. The first patient of each of the four strata was always assigned to type 'A' medication.
Blinding of participants and personnel	Low risk	Participants and personnel blinded
Blinding of outcome assessment	Low risk	Blind outcome assessment
Incomplete outcome data	Low risk	Missing data were unlikely to have an impact on the results of the trial
Selective reporting	Low risk	Outcomes listed in the methods were all reported
Other bias	Low risk	The study was conducted independently of all sponsors

Syst-Eur		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low risk	Computer-generated scheme
Allocation concealment	Low risk	Central allocation
Blinding of participants and personnel	Low risk	Participants and personnel blinded
Blinding of outcome assessment	Low risk	Blind outcome assessment
Incomplete outcome data	Low risk	Missing data were unlikely to have an impact on the results of the trial
Selective reporting	Low risk	Outcomes listed in the methods were all reported
Other bias	Low risk	The study was conducted independently of all sponsors

TRACE		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low risk	Computer-generated assignment scheme
Allocation concealment	Low risk	Computer-generated using separate randomisation lists at each centre
Blinding of participants and personnel	Low risk	Participants and personnel blinded
Blinding of outcome assessment	Low risk	Blind outcome assessment
Incomplete outcome data	Low risk	Missing data were unlikely to have an impact on the results of the trial
Selective reporting	Low risk	Outcomes listed in the methods were all reported
Other bias	Low risk	The study was conducted independently of all sponsors

TRANSCEND		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low risk	Randomisation was stratified according to the site with the use of permuted blocks.
Allocation concealment	Low risk	Via a computerized voice-activated telephone call
Blinding of participants and personnel	Low risk	Participants and personnel blinded
Blinding of outcome assessment	Low risk	Blind outcome assessment
Incomplete outcome data	Low risk	Missing data were unlikely to have an impact on the results of the trial
Selective reporting	Low risk	Outcomes listed in the methods were all reported
Other bias	Low risk	The study was conducted independently of all sponsors

TROPHY		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low risk	Automated randomisation system according to study sites in blocks of four
Allocation concealment	Low risk	Automated randomisation system
Blinding of participants and personnel	Low risk	Participants and personnel blinded
Blinding of outcome assessment	Unclear risk	Blinding of outcome assessment was not described
Incomplete outcome data	Low risk	One centre (n=24 participants) were excluded from the study post-randomisation because of inadequate record keeping. Of those included in the safety population, data on BP were not available for 13 participants. However, missing values were imputed by using the last-observation-carried-forward method
Selective reporting	Low risk	Outcomes listed in the methods were all reported
Other bias	High risk	The sponsor provided funding and organized the study.

UKPDS-38		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low risk	Stratified for those with or without previous treatment for hypertension was performed by the coordinating centre
Allocation concealment	Low risk	Sealed opaque envelopes were used
Blinding of participants and personnel	High risk	Study drugs were administered open-label
Blinding of outcome assessment	Low risk	Blind outcome assessment
Incomplete outcome data	Low risk	Missing data were unlikely to have an impact on the results of the trial
Selective reporting	Low risk	Outcomes listed in the methods were all reported
Other bias	Low risk	The study was conducted independently of all sponsors

VA COOP II		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear risk	The method was not described.
Allocation concealment	Unclear risk	The method was not described.
Blinding of participants and personnel	Low risk	Participants and personnel blinded
Blinding of outcome assessment	Unclear risk	Not described
Incomplete outcome data	Low risk	Only patients who entered the long term treatment phase were included in this review. All withdrawals were accounted.
Selective reporting	Unclear risk	Outcomes were not pre-specified in the method section and no access to study protocol.
Other bias	Unclear risk	Role of the sponsor was not described

Val-HeFT		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear risk	Stratified according to whether or not they were receiving BB as background therapy. The exact method was not described.
Allocation concealment	Unclear risk	The method was not described.
Blinding of participants and personnel	Low risk	Participants and personnel blinded
Blinding of outcome assessment	Low risk	Blind outcome assessment
Incomplete outcome data	Unclear risk	Missing outcome data i.e. total hospitalisations. All randomised patients who discontinued prematurely included in the analysis
Selective reporting	Low risk	Outcomes listed in the methods were all reported
Other bias	High risk	Site monitoring, data collection, and data analysis were performed by Novartis Pharmaceuticals.

VALIANT		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low risk	Automated randomisation scheme
Allocation concealment	Low risk	Allocated via IVRS
Blinding of participants and personnel	Low risk	Participants and personnel blinded
Blinding of outcome assessment	Low risk	Blind outcome assessment
Incomplete outcome data	Unclear risk	Information from 105 patients at one site was censored before un-blinding because of adequate informed consent process could not be ensured. Study medications were not administered to 77 patients. It was not indicated whether ITT analysis was performed.
Selective reporting	Unclear risk	Not all outcomes listed in the method section were reported i.e. Revascularization procedures
Other bias	Low risk	The study was conducted independently of all sponsors

VALUE		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low risk	Computer-generated randomisation scheme
Allocation concealment	Low risk	Central allocation
Blinding of participants and personnel	Low risk	Participants and personnel blinded
Blinding of outcome assessment	Low risk	Blind outcome assessment
Incomplete outcome data	Unclear risk	68 patients in 9 centres were excluded after randomisation because of good clinical practice deficiencies and they were not included in intention-to-treat analyses, which might lead some bias
Selective reporting	Low risk	Outcomes listed in the methods were all reported
Other bias	Unclear risk	Role of the sponsor was not described

VERDI		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear risk	The method was not described.
Allocation concealment	Low risk	Central allocation.
Blinding of participants and personnel	Low risk	Participants and personnel blinded
Blinding of outcome assessment	Unclear risk	Not described
Incomplete outcome data	Low risk	Missing data were unlikely to have an impact on the results of the trial
Selective reporting	Low risk	Outcomes listed in the methods were all reported
Other bias	Unclear risk	Role of the sponsor was not described

V-HeFT II		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low risk	Used a randomized six-subject permuted-block stratified according to the medical centre and patients' participation/non-participation in V-HeFT I
Allocation concealment	Low risk	Central allocation
Blinding of participants and personnel	Low risk	Participants and personnel blinded
Blinding of outcome assessment	Low risk	Blind outcome assessment
Incomplete outcome data	Low risk	Missing data were unlikely to have an impact on the results of the trial
Selective reporting	Unclear risk	Outcomes were not pre-specified in the method section and no access to study protocol.
Other bias	Low risk	Supported by a government body

Wilcox		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear risk	The method was not described.
Allocation concealment	Low risk	Predetermined randomized code for each hospital
Blinding of participants and personnel	Low risk	Participants and personnel blinded
Blinding of outcome assessment	Unclear risk	Blinding of outcome assessment was not described
Incomplete outcome data	Low risk	Missing data were unlikely to have an impact on the results of the trial
Selective reporting	Unclear risk	Outcomes were not pre-specified in the method section and no access to study protocol.
Other bias	Unclear risk	Role of the sponsor was not described

3.4 Discussion

According to the hierarchy of study designs to assess the effects of interventions, RCT is acknowledged as the gold standard. Although all the included studies are RCTs, the method of conduct differs greatly between individual studies; consequently the variable quality of studies. More than half (60%) of the included studies were published after the establishment of the Consolidated Standards of Reporting Trials (CONSORT) statement. The CONSORT statement was first published in 1996 (Begg et al., 1996) and was revised in 2001 (Moher et al., 2001) with the latest update published in 2010 (Schulz et al., 2010). It provides guidance for reporting of RCTs, though it emphasizes more on individually randomised, two groups, parallel trials. Despite the improvement in the reporting quality of RCTs,

many studies in this review remain inadequately reported and this may introduce bias leading to underestimation or overestimation of the true intervention effect.

Selection bias refers to systematic differences between the baseline characteristics of the individuals, groups or data that are compared (Higgins, 2011) hence not representing the intended study population. Approximately 40% of the included studies have a dubious risk of selection bias as they have inadequate or failed to report the method used for the random allocation process. Of these studies, 68.4% were published prior to 2000. Random allocation consists of two steps: [1] random sequence generation, and [2] allocation concealment. When done correctly in a large enough sample, the random allocation is effective in reducing the risk of bias. The studies were judged as unclear or high risk of selection bias when one or both steps were not reported.

The optimal strategy to minimize the likelihood of differential treatment or assessments of outcomes is to blind as many individuals as possible in a trial. Performance bias refers to systematic differences between groups in the care that is provided, or in exposure to factors other than the interventions of interest (Higgins, 2011). Performance bias may occur when the person delivering and receiving the treatments being compared are aware of which participants received which treatment. Detection bias refers to systematic differences between groups in how outcomes are determined (Higgins, 2011) and the risk for this type of bias can be reduced by blinding the outcome assessors. Simply over half of the included studies (57%) were adequately blinded to reduce the risk of both performance and detection bias. Some of the studies utilized the PROBE design which offers advantages such as lower cost and greater similarity to the standard clinical practice compared to the classical double-blind design. A meta-analysis comparing the double-blind placebo-controlled and the PROBE design in hypertension trial has found that the result was statistically equivalent (Smith et al., 2003).

Attrition bias refers to systematic differences between groups in withdrawals from a study (Higgins, 2011). Attrition bias may be introduced from the exclusion of participants from analysis or results. Ideally, an intention-to-treat (ITT) analysis is preferable as it included all randomized participants regardless of status at the end of a study follow-up. The ITT approach is considered as the gold standard because it preserved randomisation (Fergusson et al., 2002, Glasser and Howard,

2006), limits from arbitrary inferences, focuses on greater accountability, limit type I error and allows for greater generalisability (Fergusson et al., 2002). The overall attrition rate from all the included studies in this review ranged from 0.02% to 25%. The trials judged with high attrition bias tend to be older trials and has a longer duration of follow-up. Majority of included studies reported outcome as described in the method section or study protocols where available. Only a few studies were judged as unclear risk of reporting bias and the access to protocol was not available. Some of these studies were published more than 20 years ago and receiving a response from authors are very unlikely.

Another factor considered as a potential source of bias was the source of funding for each included studies. Majority of the included studies (80%) received assistance in the form of financial support, trial organization or simply study drugs provision from pharmaceutical industries and most of these trials were conducted in Europe and North America. Industry-sponsored studies in this review showed a slight preference for comparing study drugs against a placebo (56.9%) than against similarly effective drugs (43.1%). However, only half (50%) of the industry-supported study explicitly reported the role of the sponsor during the trials. One of the main reasons for concern in industry-funded trials is that the quality of study sponsored by profit-making firms may be poor. Dieppe et al. (1999) had found that 88% of pharmaceutical-sponsored studies reported a significant beneficial effect of the intervention tested compared to only 69% of studies with other or unknown source of funding. Studies of poor quality could overestimate therapeutic benefit by about 34% (Moher, 1999). Another reason is that the industry only sponsors studies that will produce positive results. This situation could subject a potential problem as when new drugs are approved for marketing but the sponsors have failed to disclose all of their potential benefits or risks. Furthermore, withholding the publication of unfavourable result contributes to the risk of publication bias.

4 Association between angiotensin-converting enzyme inhibitors (ACEI) and risks of cancers

4.1 Introduction

4.1.1 The renin-angiotensin system (RAS)

The renin-angiotensin system (RAS) plays an important role in CV homeostasis by regulating blood volume and systemic vascular resistance, hence influence cardiac output and arterial pressure. **Figure 4-1** depicts the classical RAS pathway and its inhibitory agents that are useful in controlling elevated BP. When renal blood flow is reduced, juxtaglomerular cells in the kidney convert prorenin into renin and secrete it into the circulation. Angiotensinogen, the primary hormone in the RAS and the only known substrate for renin, is catalytically cleaved to produce angiotensin I in the event of low BP (Sparks et al., 2014). Subsequently, angiotensin-converting enzyme (ACE) cleaves two amino acids from the C-terminus of the inactive angiotensin I converting it into the vasoactive peptide angiotensin II. Angiotensin II is the main effector molecule of the RAS pathway and its biological effect is mediated by the angiotensin II (AT) receptors, which is further categorised into AT receptor type 1 (AT_1) and AT receptor type 2 (AT_2). Most of the effects classically related to the function of RAS are mediated by the AT_1 including smooth muscle cell contraction, renal tubular sodium reabsorption, the release of aldosterone from the renal adrenal glomerulosa, and the release of antidiuretic hormone (ADH) from the posterior pituitary (Sparks et al., 2014).

In addition to angiotensin I, bradykinin is also one of the most important active substrates for ACE. Bradykinin is a potent vasodilator and its activation is also important in inflammatory reactions (Hornig et al., 1997, Golias et al., 2007). Bradykinin exerts its vasodilatory effect by acting on a specific endothelial B_2 receptor leading to the release of prostacyclin, nitric oxide (NO) and endothelium-derived hyperpolarizing factor (EDHF) (Hornig et al., 1997). In the kinin-bradykinin system, the ACE degrades bradykinin into inactive bradykinin components. Thus, it has been suggested that inhibition of the RAS pathway enhanced the vasodilatory effect of kinin-bradykinin cascade which consequently assists in lowering BP.

Characterization of the RAS was concluded in the 1950s with the identification of angiotensinogen, angiotensin I and II, and ACE (Skeggs et al., 1956). Apart from its BP regulatory function, inappropriate activation of RAS has many deleterious effects including vasoconstriction, cell proliferation, inflammatory responses, oxidative stress, prothrombotic effects, and increased insulin resistance (Tomiyama et al., 1994, Brown et al., 1998, Lévy, 2004).

4.1.2 Pharmacokinetics of ACEI

Table 4-1: summarises the pharmacologic characteristics of the various ACEI. All the ACEI shares the same basic structure, however, they can be categorised based on their functional binding group: sulphydryl, carboxyl, or phosphinyl. Of the three groups, carboxyl-containing ACEI tends to be more potent due to the better strength of binding to the zinc-ligand. Only captopril and lisinopril do not require activation through hepatic metabolism to form its active metabolite. The ability of ACEI to bind to tissue ACE is considerably variable. The relative potency and ability to bind tissue ACE of ACE inhibitors is: quinaprilat = benazeprilat > ramiprilat > perindoprilat > lisinopril > enalapril > fosinopril > captopril (Konermann et al., 1998, Lala and McLaughlin, 2008). Fosinopril has the greatest lipophilicity thus longer half-life while lisinopril has the least for both variables. Most of the ACEI are eliminated via the kidney and only a few are excreted through the liver or faeces. The ACE inhibitors are generally well tolerated, with hypotension, cough, and hyperkalaemia being the most frequently reported adverse effects for the entire class.

4.1.3 Mechanism of action

Figure 4-1demonstrates the classical RAS pathway and the site for RAS inhibitors. ACEI acts mainly by inhibiting the converting enzyme that hydrolyses angiotensin I to angiotensin II, hence depleting the agonist for angiotensin II receptors. At the same time, inhibition of the ACE also generates excess bradykinin which is a potent vasodilator. Meanwhile, blockade of the angiotensin II receptors specifically at the AT_1 by ARB results in the dilatation of vasculature preferentially in the vital organs namely the heart, kidney, and brain (Timmermans, 1993). Unlike ACEI, ARBs have no effect on bradykinin metabolism and they are selective blockers of angiotensin effects. Inhibition of the RAS results in reduce arterial

pressure thereby reduce preload and afterload on the heart. Furthermore, blockade of the AT_1 receptors and aldosterone secretion from the zona glomerulosa of the adrenal cortex promotes renal excretion of sodium and water. In the same time, sympathetic activity is down-regulated through blockade of angiotensin II effects on the sympathetic nerve.

4.1.4 ACEI and cancer risk

There is evidence suggesting several components of RAS, particularly expressed in tissues, may be involved in carcinogenesis (Ager et al., 2008). Angiotensin II is important in regulating tissue angiogenesis, proliferation, apoptosis, and inflammation (Deshayes and Nahmias, 2005) which is primarily induced by AT_1 receptors. Inhibition of ACE prevents generation of angiotensin II and downstream signalling activated via AT_1 receptors; hence reduce angiogenesis and cell proliferation. However, there is some evidence that signalling via AT_2 receptors can also be pro-angiogenic (Sarlos et al., 2003) and pro-inflammatory (Wolf et al., 2002). Several experimental studies have shown that modulation of the RAS pathway by ACEI conferred antineoplastic effects. In-vitro studies of captopril have shown to inhibit cancer cell growth in pancreatic ductal cancer cells (Reddy et al., 1995), ductal breast carcinoma (Small et al., 1997), and human neuroblastoma (Chen et al., 1991) by modulation of mitosis and gene expression. In a study using a murine model of hepatocellular carcinoma, perindopril had significantly inhibited tumour development and angiogenesis independent of AT1 receptor blockade (Yoshiji et al., 2001). This observation was also accompanied by the suppression of vascular endothelial growth factor (VEGF), a potent angiogenic factor.

Furthermore, the metabolism of angiotensin I form heptapeptide angiotensin (1-7) by endopeptidases such as neprilysin, prolyl endopeptidase, and thimet oligopeptidase. Angiotensin (1-7) is a biologically active peptide hormone with a vasodilator, antiproliferative, and antithrombotic properties (Ferrario, 2005). Administration of ACEI, in one way, could promote conversion of angiotensin I to angiotensin (1-7) via an alternative pathway. An in-vivo experiment by Soto—Pantoja and colleague (2009) has observed reduced tumour angiogenesis in athymic mice bearing human lung cancer xenografts that were administered angiotensin (1-7). In addition, tumour growth was significantly reduced in treated

mice compared to control. Therefore, the purported underlying mechanism by which ACEI may be protective of carcinogenesis is by reducing angiogenesis and cellular proliferation. Evidence of ACEI and the risk of cancer from epidemiological studies are described in Chapter 1 Section 1.9.3 (page 45).

This chapter aims to systematically review and report the meta-analysis of RCTs using ACEI as one of its treatment and its association with risks of cancer.

Table 4-1: Summary of pharmacologic characteristics of various ACEI

Group type	Generic name	Active metabolite	% of inhibition of tissue ACE	Protein-bound fraction (%)	Elimination half-life (h)	Excretion
Suphyhydryl-containing	Captopril	None	NA	25-30	_	Urine (>95%)
Dicarboxylate-containing	Enalapril	Enalaprilat	2.3	20-89	1.3	Urine
	Benazepril	Benazeprilat	27	97	1.5-2	Urine (88%), bile (11-12%)
	Lisinopril	None	6	0	_	Urine (100%)
	Ramipril	Ramiprilat	11	73	9-18	Urine (60%)
	Quinapril	Quinaprilat	33	97	2	Urine (61-96%)
	Perindopril	Perindoprilat	17	60	3-10	Urine (75%)
	Trandolapril	Trandolaprilat	NA	65-94	6-10	Faeces (66%), Urine (33%)
Phosphinyl-containing	Fosinopril	Fosinoprilat	NA	≥ 95	12	Faeces (50%), Urine (50%)

Abbreviations: ACE, angiotensin-converting enzyme, NA, not available.

Data adapted from (Konermann et al., 1998, Lala and McLaughlin, 2008, Saha et al., 2008)

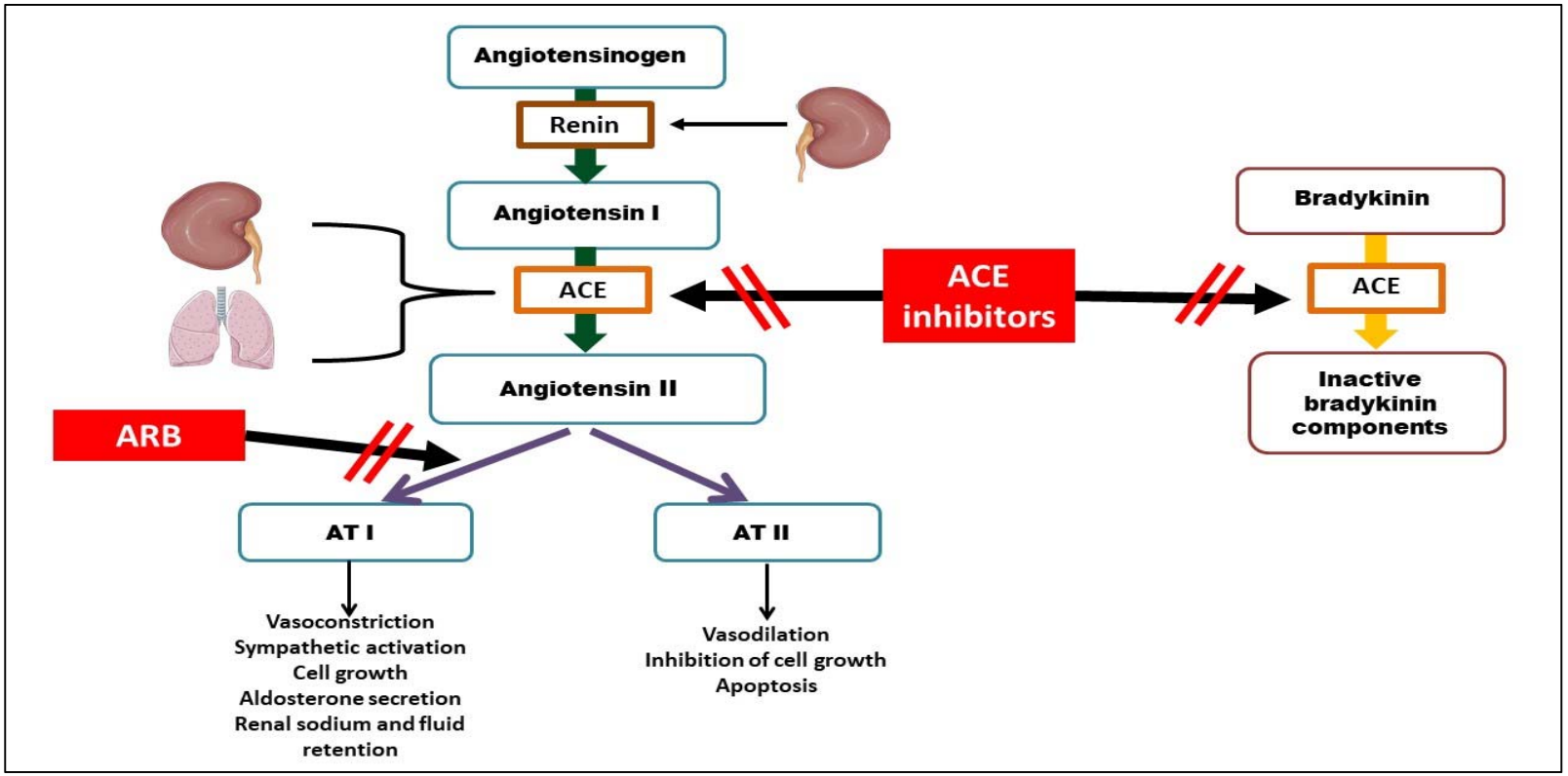


Figure 4-1 The renin-angiotensin system (RAS).
RAS are executed through high affinity binding of angiotensin II to specific angiotensin receptors. These receptors belong to the large family of G-protein coupled receptors (GPCRs) and can be separated into two pharmacological classes, AT1 and AT2, each with distinct functions linked to specific intra-cellular signaling pathways. Inappropriate activation of the RAS may lead to deleterious effects. Two pharmacological agents, ACEI and ARB, are the main inhibitors of this pathway and they act by 1) preventing the conversion of angiotensin I to angiotensin II, 2) generation of bradykinin, and 3) blockade of the angiotensin II type 1 (AT1) receptors, hence inhibiting downstream signalling. ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; AT, angiotensin II receptor.

4.2 Methodology

4.2.1 Systematic review

Full descriptions of the methods used for this systematic review and meta-analysis have been described previously in Chapter 2, Section 2.1 (page 57).

Data for four studies were extracted from the ARB Trialists Collaboration meta-analysis (Teo, 2011) because of availability of data either as individual data (ONTARGET) or tabulated data (CHARM-Added 2003, Val-HeFT, VALIANT) on cancer outcomes. Data for PARADIGM-HF was supplied by the primary author (Professor John J.V. McMurray of the University of Glasgow). Data for the remaining studies were either published in the primary study or in post-hoc analyses.

4.2.2 Meta-analysis

For data synthesis, see Chapter 2 Section 2.1.7.4 (page 66).

Sensitivity analyses were done by exclusion of trials with: [1] factorial design; [2] poor methodological quality; and [3] small sample size with the number of total participants less than 1000.

For incident cancer, the following subgroups category were conducted: [1] subclass; [2] comparator; [3] clinical setting; [4] mean age; and [5] duration of follow-up

4.3 Results

Overall, the search has identified 27 eligible ACEI trials enrolling 135,037 participants with an average follow-up of 3.6 years (range 1 to 9 years). The average patients' age across all studies is 64 years old.

The searching and identification process of trials was summarised in Figure 3-1 (Page 74). I have excluded 63 studies from the total of 90 included RCTs from the main systematic review primarily because they do not consist of an ACEI treatment arm. The full characteristics and risk of bias of studies included in this review have

been described previously (See Chapter 3, Section 3.2.2.1 and Section 3.3.6. correspondingly).

Majority of the studies were published in the 21st century with the latest study published in 2014. Three studies (ALLHAT, ONTARGET, and VALIANT) enrolled more than 10,000 total participants, thus contributed the most number of participants in this review. Majority of the studies have recruited patients with underlying risk factors for or existing CVD including hypertension, T2DM, CHD, and HF. The AIPRI trial recruited patients with chronic renal insufficiency caused by various diseases which may not be of CV origin. Meanwhile, the PHARAO trial enrolled participants with high-normal BP (SBP less than 140 mmHg and DBP less than 90 mmHg) who were not on any antihypertensive treatment.

Overall, approximately 38.3% of patients across all studies were randomised to treatment with ACEI. Of these, just over half of the patients (52.4%) were assigned to tissue ACEI. The ACEI treatment arm in the STOP-HTN2 study consisted of both tissue- (enalapril) and non-tissue ACEI (Lisinopril). Only two studies (CHARM-Added and Val-HeFT) did not fall into either category as the type of ACEI used was not specified.

Most of the included RCTs compared ACEI to active controls including ARB, BB, CCB, TZ, and conventional antihypertensive therapy. One study (PARADIGM-HF) has compared ACEI to a new drug class, an angiotensin II receptor blocker neprilysin inhibitor (ARNI), which is a novel drug for treatment of HF that is likely to be a useful antihypertensive drug. Ten trials compared ACEI to placebo as either one of or the only comparator arm. Meanwhile, three studies contained a combination therapy as one of its treatment group. Two studies (ONTARGET, and VALIANT) randomised patients to ACEI, ARB and ARB plus ACEI. These trials were regarded as ACEI monotherapy versus ARB monotherapy and ACEI plus ARB combination. The DEMAND study has randomised patients to ACEI, ACEI plus CCB combination, and placebo. Only data from the ACEI monotherapy and placebo treatment arm were considered in this review and meta-analysis.

Furthermore, the CHARM-Added trial investigated the use of ARB versus placebo in HF patients already receiving an ACEI. Similarly, the Val-HeFT trial which tested the strategy of ARB versus placebo, more than 90% of patients were receiving

background ACEI therapy in both groups. Therefore, these two trials were regarded as a trial of ACEI versus ARB plus ACEI.

All the included studies implemented a double-blind design except for five studies. Two studies (ESPIRAL and Otsuka) were conducted as open-label while the remaining three studies (FACET, PHARAO, and STOP-HTN2) have only the outcome assessors blinded. A great number of studies consisted of two parallel treatment group. Seven studies have three treatment groups while two studies have implemented a 2-by-2 factorial design.

All the studies were followed for at least one year with the UKPDS-38 study followed the longest. The mean age for patients across all studies is over 50 years. Almost all of the included studies have majority male participants except for the PHYLLIS study with an excess of ten percent female participants. Conversely, the V-HeFT II study consists of male-only patients. The reporting of current smokers is inconsistent across studies, though only one study (SAVE) reported more than 50% of patients were current smokers.

The selected characteristics of interest extracted from the 27 included studies are summarised in Table A-3 (Page 321). The reporting of all these variables was inconsistent across all studies.

In the CHARM-Added study, patients with baseline cancer (6% of total participants) were allowed to participate in the trial whereas patients with cancer or malignancy were excluded in the AIPRI, SOLVD-T, and TRACE trials. Majority of the trials did not pre-specified cancer as an outcome and the adjudication of cancer diagnosis varies across studies. Only seven studies had malignancy either centrally or site-adjudicated. Likewise, the rate of adherence to treatment was not reported consistently across trials. The loss to follow-up ranged from 0 to 3.2%.

4.4 ACEI and risks of incident cancer

4.4.1 Overall

Altogether, 21 RCTs were eligibly fulfilling all criteria for the comparison between ACEI and other agents for incident cancer. Data were available from 117, 560

(97.5%) of the 120,602 patients who were enrolled in the 21 studies. **Figure** 4-2 shows the meta-analysis of ACEI and risk of cancer incidence in a fixed-effect (FE) model. According to randomised allocation, cancer incidence was 5.87% in patients assigned to the ARB group versus 6.32% assigned to non-ACEI treatment. The meta-analysis result was mainly influenced by data from the ALLHAT and ONTARGET trials with the most weight assigned to these studies at 31.7% and 27.1% respectively. Majority of the remaining studies were assigned a weight of less than five percent. A fairly equal number of studies has reported an OR of either more or less than 1 with 95% CI overlapping 1. From the forest plot, CIs for all the studies crossed the line of no effect indicating a lack of statistical significance at the study level. Consequently, the combined OR was 0.99 with 95% CI between 0.94 and 1.05 (P-value = 0.82). The diamond that represents the pooled effect estimates is narrow and it overlaps the line of no effect indicating the absence of statistical significance at the meta-analysis level.

In the random effects (RE) model depicted in **Figure 4-3,** slightly more weight was assigned to the ALLHAT (32.1%) while weight for the ONTARGET study reduced by 1.2%. The combined effect estimates yielded an OR 1.00 (95% CI 0.95-1.05; P = 0.85) coming close to the FE model.

Assessment of heterogeneity in both FE and RE model showed a chi-square P-value of 0.58 and I^2 statistics of 0% indicating no statistical differences between studies.

Visual inspection of the funnel plot (**Appendix** Figure A-1) shows fairly equal distribution of studies on both sides of the diagram. No outlier was detected.

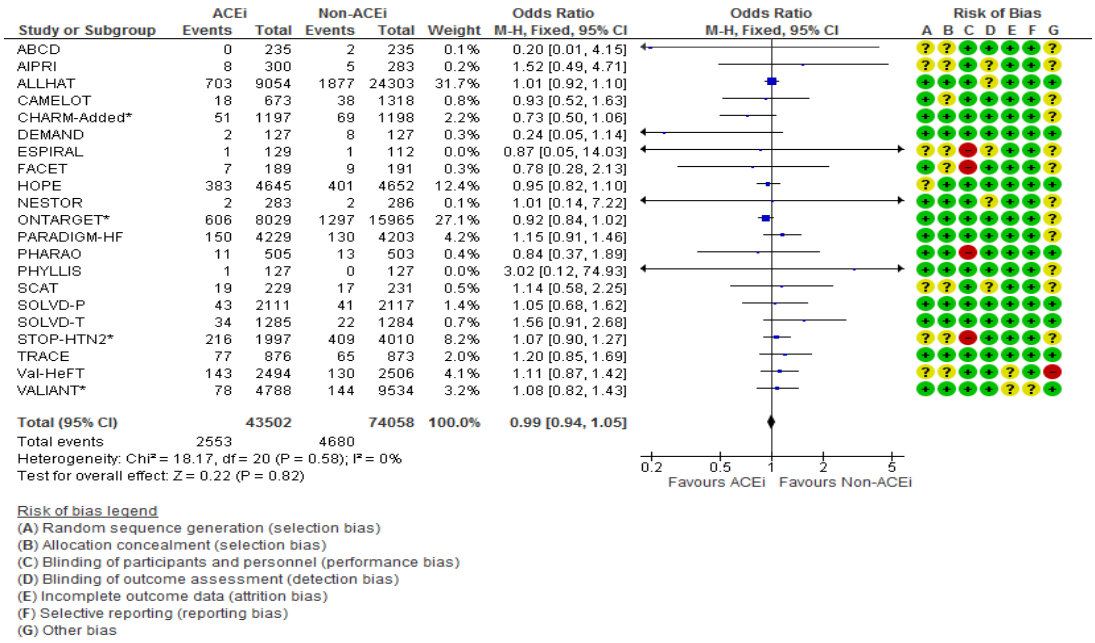


Figure 4-2 Forest plot of incident cancers by ACEI vs. non-ACEI controls [FE model]. Odds ratios and 95% confidence interval overall and in 21 trials. The overall effect represents the pooled estimate of odds for incident cancers.*Included were patients with no history of cancer or active cancer at baseline.

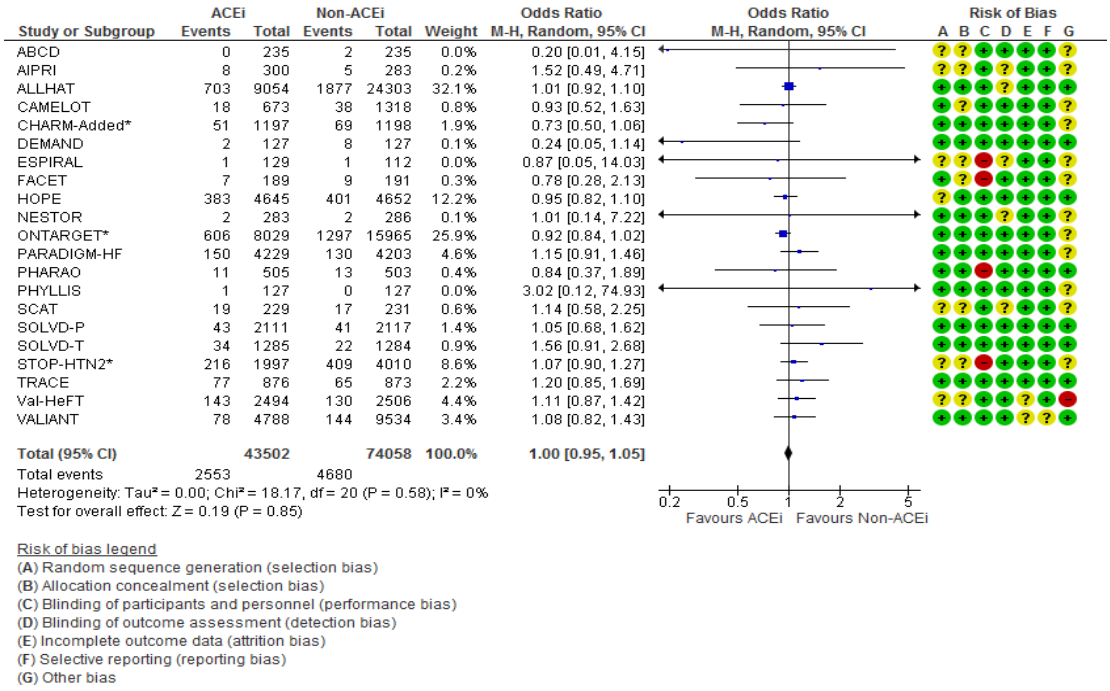


Figure 4-3 Forest plot of incident cancers by ACEI vs non-ACEI controls [RE model]. Odds ratios and 95% confidence interval, overall and in 21 trials The overall effect represents the pooled estimate of odds for incident cancers.* Included were patients with no history of cancer or active cancer at baseline.

4.4.2 Sensitivity analyses

Exclusion of two trials (HOPE and SCAT) with factorial design did not affect the risk of cancer with OR 1.00 (95% CI 0.95-1.06; **Figure 4-4**) and P-value of 0.98. Likewise, this result is mainly influenced by the ALLHAT and ONTARGET trial. Chi-square test for heterogeneity yields a P-value of 0.48 and I^2 statistics is observed at 0% indicating low heterogeneity between studies. **Figure 4-5** shows the meta-analysis results after exclusion of eight trials with small sample sizes. Similarly, no difference was observed after exclusion of these trials giving an OR of 1.00 (95% CI 0.95-1.05; P-value = 0.87). Assessment of heterogeneity showed a chi-square test P-value of 0.41 and an I^2 statistics of 4% indicating a statistically insignificant difference between studies. The trivial heterogeneity observed is most likely due to clinical and methodological diversity of the PARADIGM-HF (a non-conventional comparator was used) and PHARAO (pre-hypertension participants) study.

Exclusion of twelve trials with poor methodological quality is shown in Figure 4-6 with OR 0.97, 95% CI 0.90-1.04 (P-value = 0.38). The direction of the combined effect estimates was largely influenced by ONTARGET study with 65.9% of the overall weight. Chi-square test for heterogeneity yields a P-value of 0.09 and I^2 statistics is observed at 42%. The moderate heterogeneity observed is most probably due to the methodological diversity of the CHARM-Added (patients in the ACEI treatment arm were originally randomised to placebo), DEMAND (a three arm parallel study containing a combination arm), ONTARGET (a three arm parallel study containing a combination arm), and PARADIGM-HF (a non-conventional comparator was used) study.

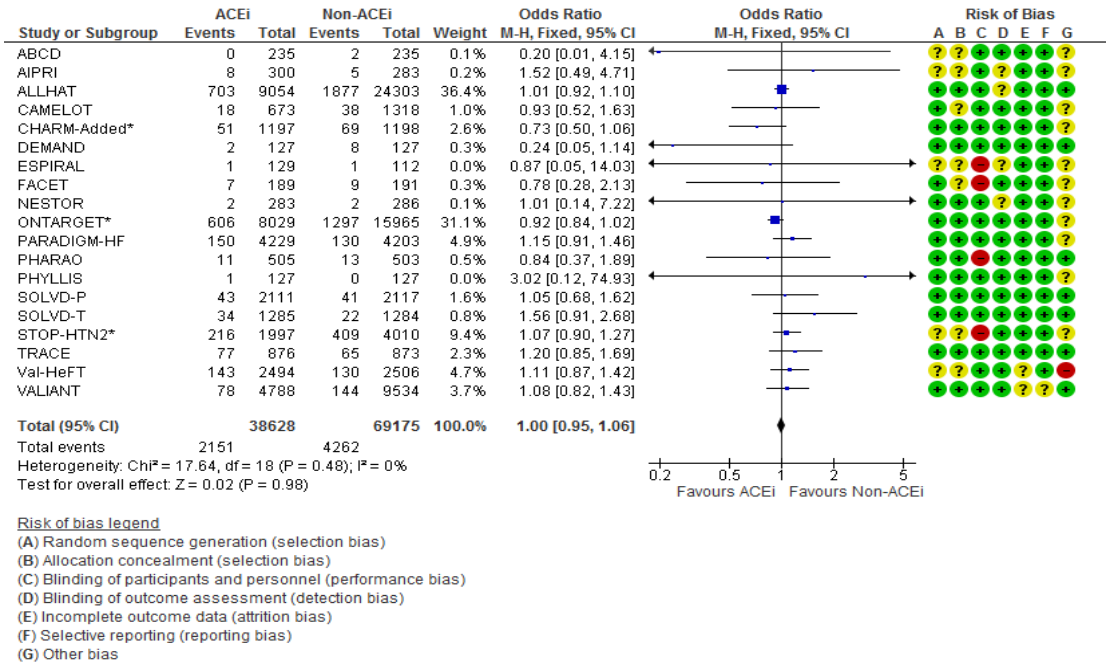


Figure 4-4 Forest plot of incident cancers by ACEI vs control [Sensitivity analysis: Exclusion of trials with factorial design].
The overall effect represents the pooled estimate of odds for incident cancers.* Included were patients with no history of cancer or active cancer at baseline.

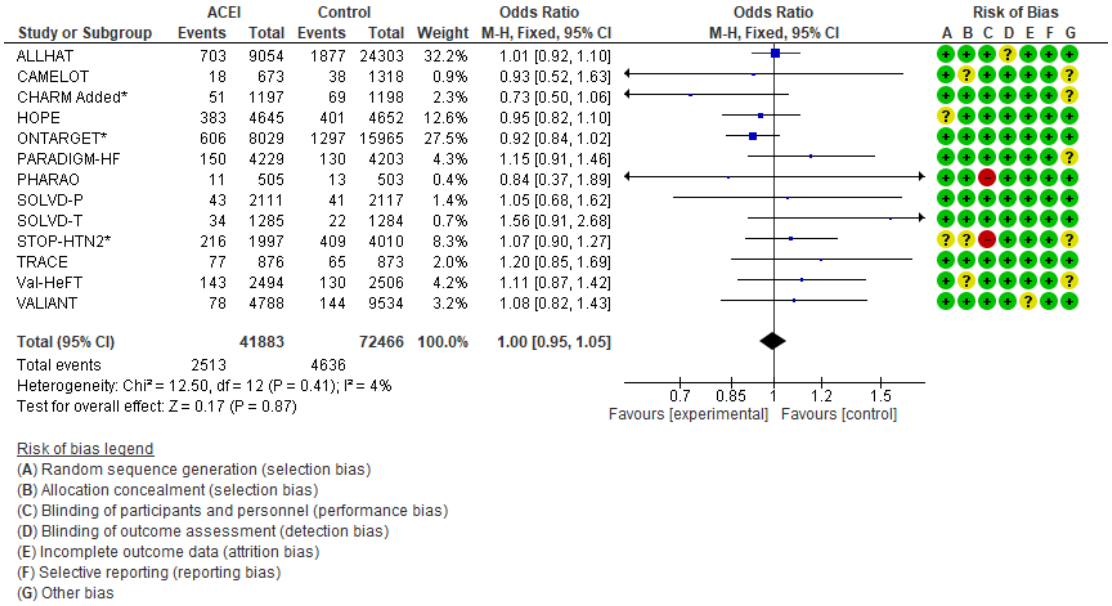


Figure 4-5 Forest plot of incident cancers by ACEI vs controls [Sensitivity analysis: Study size].
The overall effect represents the pooled estimate of odds for incident cancers. * Included were patients with no history of cancer or active cancer at baseline.

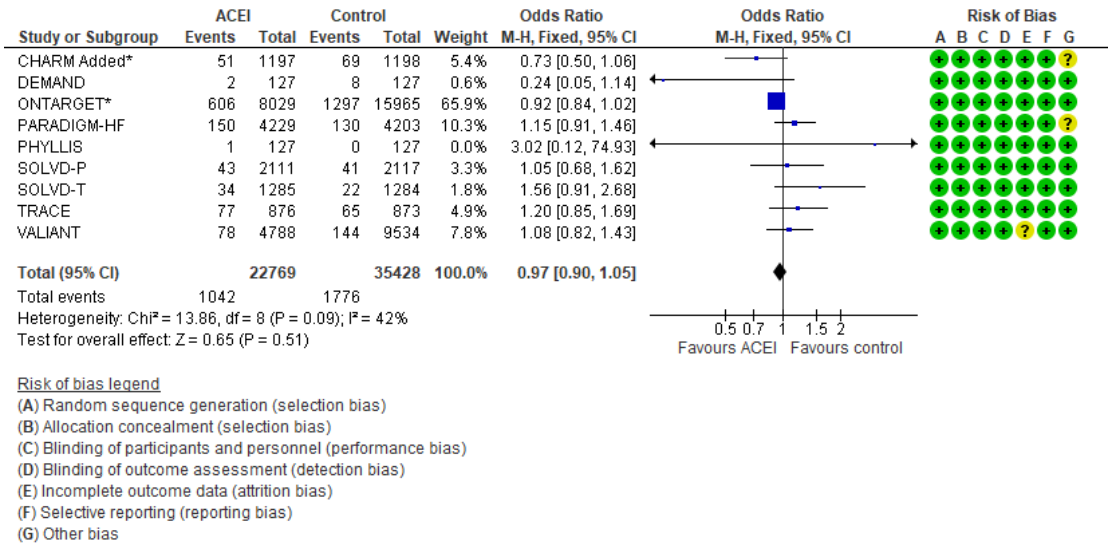


Figure 4-6: Forest plot of incident cancers by ACEI vs. controls [Sensitivity analysis: Methodological quality].
The overall effect represents the pooled estimate of odds for incident cancers. * Included were patients with no history of cancer or active cancer at baseline.

4.4.3 Subgroup analyses

Table 4-2 summarises the results of subgroup analyses performed for ACEI and cancer risk.

4.4.3.1 By subclasses: tissue ACEI and non-tissue ACEI

Only six RCTS enrolling 36,885 participants had used tissue ACEI as one of the study treatment. In this analysis, tissue ACEI included benazepril, delapril, and ramipiril whereas non-tissue ACEI comprised captopril, enalapril, and fosinopril. Cancer incidence was 7.51% in the tissue ACEI group versus 7.99% in the control group with OR 0.94 (95% CI 0.87-1.02). As shown in **Figure 4-7**, this analysis is mainly influenced by the ONTARGET study followed by the HOPE study, each assigned 63.9% and 29.3% of the overall weight respectively. The chi-square test P-value was 0.33 and the I^2 statistics of13%. The minimal heterogeneity observed is likely due to clinical and methodological diversity of the DEMAND (a three arm parallel study containing a combination arm) and ONTARGET (a three arm parallel study containing a combination arm) study.

For non-tissue ACEI, data were available from 13 RCTs with a total of 75,434 patients. Cancer incidence was 5.01% in the ACEI treatment group versus 5.63% in

the control group. The result of this study was greatly driven by the ALLHAT study carrying over 50% of the overall weight (**Figure 4-7**). The combined effect estimates resulted in OR 1.03 (95% CI 0.96-1.10). Assessment of heterogeneity showed a chi-square P-value of 0.70 and I^2 statistics at 0% indicating no statistical difference between studies.

4.4.3.2 By type of comparator

Overall, 12 RCTs compared ACEI to active controls with data available from 91,025 patients. Cancer incidence was 5.93% in the ACEI treatment group versus 6.45% in the active control group. Pooling of effect estimates from the 12 studies yields an OR of 0.99 (95% CI 0.93-1.05) with P-value = 0.77 (**Figure 4-8**). The ALLHAT and ONTARGET study has the biggest influence in this analysis as they carry 41.6% and 35.5% of the overall weight correspondingly. The chi-square test resulted in a P-value of 0.83 and the I^2 statistics of 0% indicating no statistical heterogeneity between studies.

Two RCTs have compared ACEI to ARB and data were available from 25,792 patients. Cancer incidence was 5.34% in the ACEI treatment group versus 5.56% in the ARB treatment group. Both included studies (ONTARGET and VALIANT) with OR less than 1 and their 95% CI overriding 1. Combined effect estimates resulted in OR 0.96 (95% CI 0.86-1.07; P-value = 0.42). This result was mainly influenced by the ONTARGET study as it carried the most weight overall at 87.4% (**Figure 4-8**). Assessment of heterogeneity showed a chi-square P-value of 0.95 and I^2 statistics is observed at 0% indicating no statistical difference between studies.

For comparison with ACEI and ARB combination, four RCTs were included with data available from 33,129 patients. Cancer incidence was 5.32% in the ACEI treatment group versus 5.48% in the combination treatment group with OR 0.97 (95% 0.88-1.07; P-value = 0.52). The ONTARGET study was assigned the heaviest weight of 73.2% overall and eventually had a major influence in the direction of the combined OR (**Figure 4-8**). The chi-square test resulted in a P-value of 0.03 and the I^2 statistics of 66% signifying evidence of a difference between studies. The observed heterogeneity observed is most likely due to methodological diversity of the Val-HeFT (ARB versus placebo study) and VALIANT (a three arm parallel study containing a combination arm) study.

Likewise, four RCTs used CCB as one of its randomised treatment with data available from 22,724 patients. Cancer incidence was 8.15% in the ACEI treatment group versus 8.16% in the CCB treatment group with OR 1.00 (95% CI 0.91-1.10; P-value = 0.98). This analysis was greatly influenced by the ALLHAT study which carries 76.9% of the overall weight (**Figure 4-8**). Three (ALLHAT, ESPIRAL, FACET) of the four included studies yields OR less than 1 with 95% CI overlapping 1. Assessment of heterogeneity showed a chi-square P-value of 0.94 and I^2 statistics is observed at 0% indicating no statistical difference between studies.

For placebo, data were available from 17,391 patients enrolled in six RCTs. Cancer incidence was 5.62% in the ACEI treatment group versus 5.68% in the placebo group with OR 0.99 and 95% CI ranging from 0.87 to 1.13 (P-value = 0.88). From **Figure 4-8**, it is clear that the HOPE study had influenced the direction of the pooled effect estimates with assigned study weight of 80.3% overall. Assessment of heterogeneity showed a chi-square P-value of 0.23 and I^2 statistics is observed at 28%. The observed moderate heterogeneity is most probably due to the methodological diversity of the DEMAND (a three arm parallel study containing a combination arm), HOPE (factorial design), and SCAT study (factorial design).

4.4.3.3 By population clinical settings

Data for patients with high-risk hypertension were available from 74,582 enrolled in nine RCTs. Cancer incidence was 7.78% in the ACEI treatment group versus 8.03% in the control group. Combined effect estimates resulted in OR 0.97 with 95% CI ranged between 0.92 and 1.03 (P-value = 0.34). Majority of the studies' OR lies on the left side of the plot favouring ACEI. Furthermore, the overall result was mainly driven by the ALLHAT study (39.6%) followed by the ONTARGET study (33.8%) as demonstrated by the weight assigned to each study (**Figure 4-9**). Assessment of heterogeneity showed a chi-square P-value of 0.48 and I^2 statistics is observed at 0% indicating no statistical difference between studies.

For patients with underlying T2DM, data were available from 1,673 patients enrolled in four RCTs. Cancer incidence was 1.32% in the ACEI treatment group versus 2.50% in the control group with OR 0.53 with a very wide 95% CI from 0.26-1.09 (P-value = 0.08). From **Figure 4-9**, the ORs for three of the four studies are located on the left side with the wide 95% CI depicted as a wide-edged diamond

in the forest plot. Moreover, this analysis was mainly driven by the FACET and DEMAND study as they carried the most weight overall (41.1% and 37.6% respectively). The chi-square test resulted in a P-value of 0.50 and the I^2 statistics of 0% signifying no statistical heterogeneity between studies.

Meanwhile, data for patients with underlying CKD were available from 824 patients enrolled in two RCTs (**Figure 4-9**). Cancer incidence was 2.10% in the ACEI treatment group versus 1.52% in the control treatment group with OR 1.41 and a very wide 95% CI from 0.50 to 3.99 (P-value = 0.52). The AIPRI study has a major influence in this analysis with an assigned weight of 82.5%. The chi-square test resulted in a P-value of 0.71 and the I^2 statistics of 0% signifying no statistical heterogeneity between studies.

For patients with established CVD which includes CHD with or without congestive HF, data were available from 41,146 patients enrolled in nine RCTs. Cancer incidence was 3.43% in the ACEI treatment group versus 2.82% in the control group. From **Figure 4-9**, the majority of the included studies' effect estimates lie on the right side of the forest plot favouring control. The combined effect estimates yield an OR 1.09 (95% CI 0.97-1.22) with a P-value of 0.16 for the overall effect. The chi-square test resulted in a P-value of 0.53 and the I^2 statistics of 0% signifying no statistical heterogeneity between studies.

4.4.3.4 By mean age groups

For studies with patients' mean age of 65 years or older, data were available from 74,404 enrolled in five RCTs. Cancer incidence was 8.07% in the ACEI treatment group versus 8.13% in the control group with OR 0.98 (95% CI 0.93-1.04; P-value = 0.51). The direction of this analysis was mainly influenced by the ALLHAT and ONTARGET study (**Figure 4-10**). The chi-square test resulted in a P-value of 0.40 and the I^2 statistics of 1%. The trivial difference between studies observed is most likely due to clinical and methodological diversity of the ONTARGET (a three arm parallel study containing a combination arm) and TRACE (post-MI patients) study.

On the other hand, data for studies with a younger mean age (< 65 years) were available from 43,156 patients enrolled in 16 RCTs. Cancer incidence was 3.01% in the ACEI treatment group versus 2.60% in the control group with combined OR

of 1.05 and a wide 95% CI ranging from 0.94 to 1.18 (P-value = 0.40; **Figure 4-10**). None of the studies had principally influenced this analysis because none of the individual study weight was more than 50%. Assessment of heterogeneity showed a chi-square P-value of 0.61 and I^2 statistics of 0% indicating no statistical difference between studies.

4.4.3.5 By duration of follow-up

Data for studies with mean patients' follow-up < 3 years were available from 30,948 patients enrolled in seven RCTs. Cancer incidence was 3.12% in the ACEI treatment group versus 2.49% in the control group. Combined effect estimates resulted in OR of 1.10 (95% CI 0.96-1.26; P-value = 0.18). The individual OR for the majority of the included study is more than 1 with the PARADIGM-HF, Val-HeFT, and VALIANT study heavily influenced the direction of this analysis (**Figure 4-11**). Assessment of heterogeneity showed a chi-square P-value of 0.97 and I^2 statistics is observed at 0% indicating no statistical difference between studies.

Meanwhile, studies with patients' mean follow-up duration of three years or longer were available from 86,612 patients enrolled in 14 RCTs. Cancer incidence was 7.01% in the ACEI group versus 7.56% in the control group. Combined effect estimates resulted in OR of 0.98 with 95% CI ranged between 0.93 and 1.03 (P-value = 0.45; **Figure 4-11**). None of the studies has principally influenced this analysis because all the studies were weighted less than 50%. The chi-square test resulted in a P-value of 0.34 and the I^2 statistics of 11%. The observed heterogeneity between studies is most likely due to clinical and methodological diversity of the DEMAND and ONTARGET study (a three arm parallel study containing a combination arm).

For studies with patients' mean follow-up duration of five years or longer, data were available from 17,523 patients enrolled in four RCTs. Cancer incidence was 8.72% in the ACEI group versus 8.98% in the control group with OR 1.01 (95% CI 0.91-1.13; P-value = 0.81). This analysis was mainly driven by the HOPE trial with an assigned weight of 54.7% (**Figure 4-11**). The chi-square test resulted in a P-value of 0.39 and the I^2 statistics of 1% indicating a small difference between studies was present.

Table 4-2 Angiotensin-converting enzyme inhibitors and risk of cancer: Subgroup analyses

Subgroup analysis		No. of study	No. of participants	Cancer incidence (%)		OR (95% CI)	P-value	I^2 (%)
				ACEI	Control			
Overall effect	FE model	21	117560	5.87	6.32	0.99 [0.94, 1.05]	0.82	0
Subclass	Tissue ACEI	6	36885	7.51	7.99	0.94 [0.87, 1.02]	0.14	13
	Non-tissue ACEI	13	75434	5.01	5.63	1.03 [0.96, 1.10]	0.46	0
Type of comparator	Active	12	91025	5.93	6.45	0.99 [0.93-1.05]	0.77	0
	ARB	2	25792	5.34	5.56	0.96 [0.86-1.07]	0.42	0
	ACEI plus ARB	4	33129	5.32	5.48	0.97 [0.88-1.07]	0.52	66
	CCB	4	22724	8.15	8.16	1.00 [0.91-1.10]	0.98	0
	Placebo	6	17391	5.62	5.68	0.99 [0.87-1.13]	0.88	28
Clinical setting	High-risk hypertension	9	74582	7.78	8.03	0.97 [0.92, 1.03]	0.34	0
	T2DM	4	1673	1.32	2.50	0.53 [0.26, 1.09]	0.08	0
	CKD	2	824	2.10	1.52	1.41 [0.50, 3.99]	0.52	0
	Established CVD	9	41146	3.43	2.82	1.09 [0.97, 1.22]	0.16	0
Mean age	≥ 65 years	5	74404	8.07	8.13	0.98 [0.93, 1.04]	0.51	1
	< 65 years	16	43156	3.01	2.60	1.05 [0.94, 1.18]	0.40	0
Duration of follow-up	< 3 year	7	30948	3.12	2.49	1.10 [0.96, 1.26]	0.18	0
	≥ 3 years	14	86612	7.01	7.56	0.98 [0.93, 1.03]	0.45	11
	≥ 5 years	4	17523	8.72	8.98	1.01 [0.91, 1.13]	0.81	1

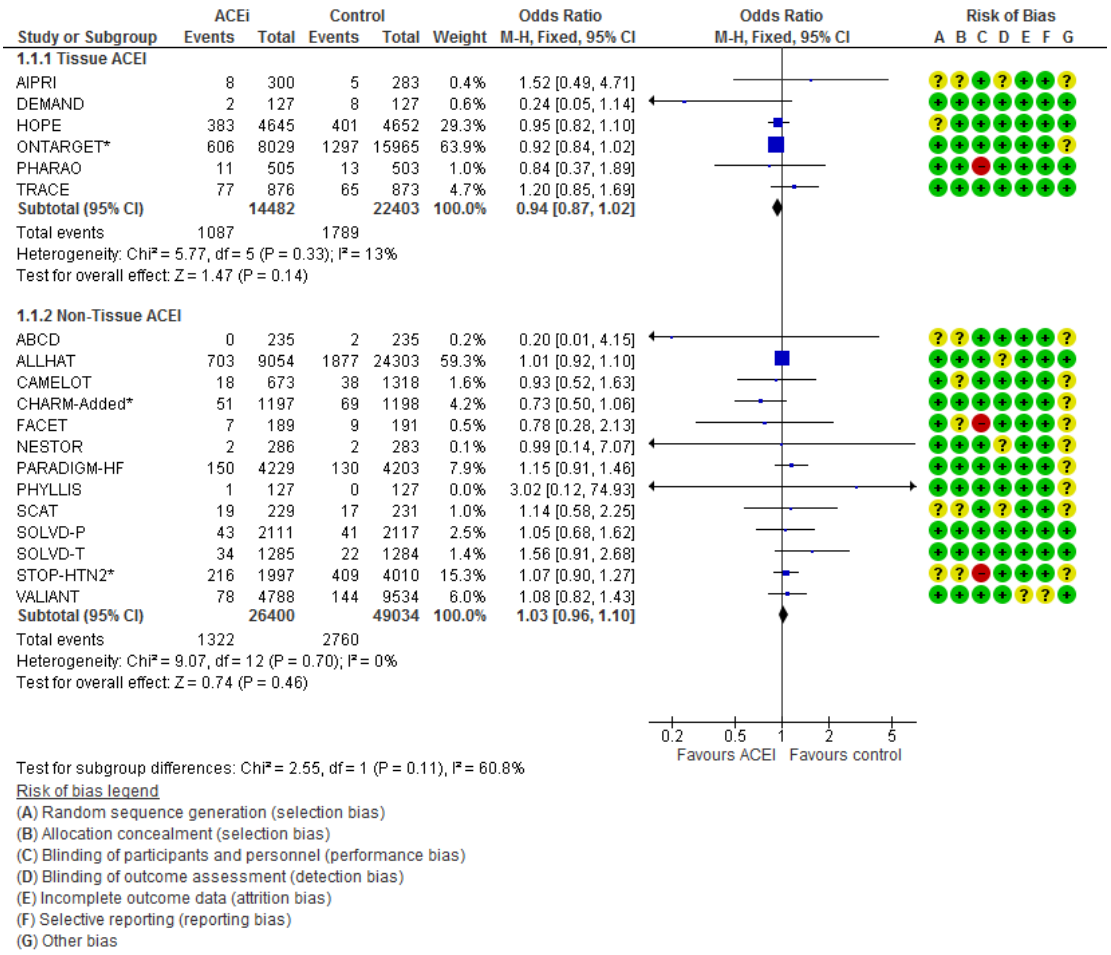


Figure 4-7: Forest plot of incident cancers by ACEI subclasses [FE model].
1) Tissue ACEI vs. controls in 6 trials; 2) Non-tissue ACEI vs. controls in 13 trials. The subtotal effect represents the pooled estimate of odds for incident cancers for each subclass. *Included were patients who were cancer free at baseline.

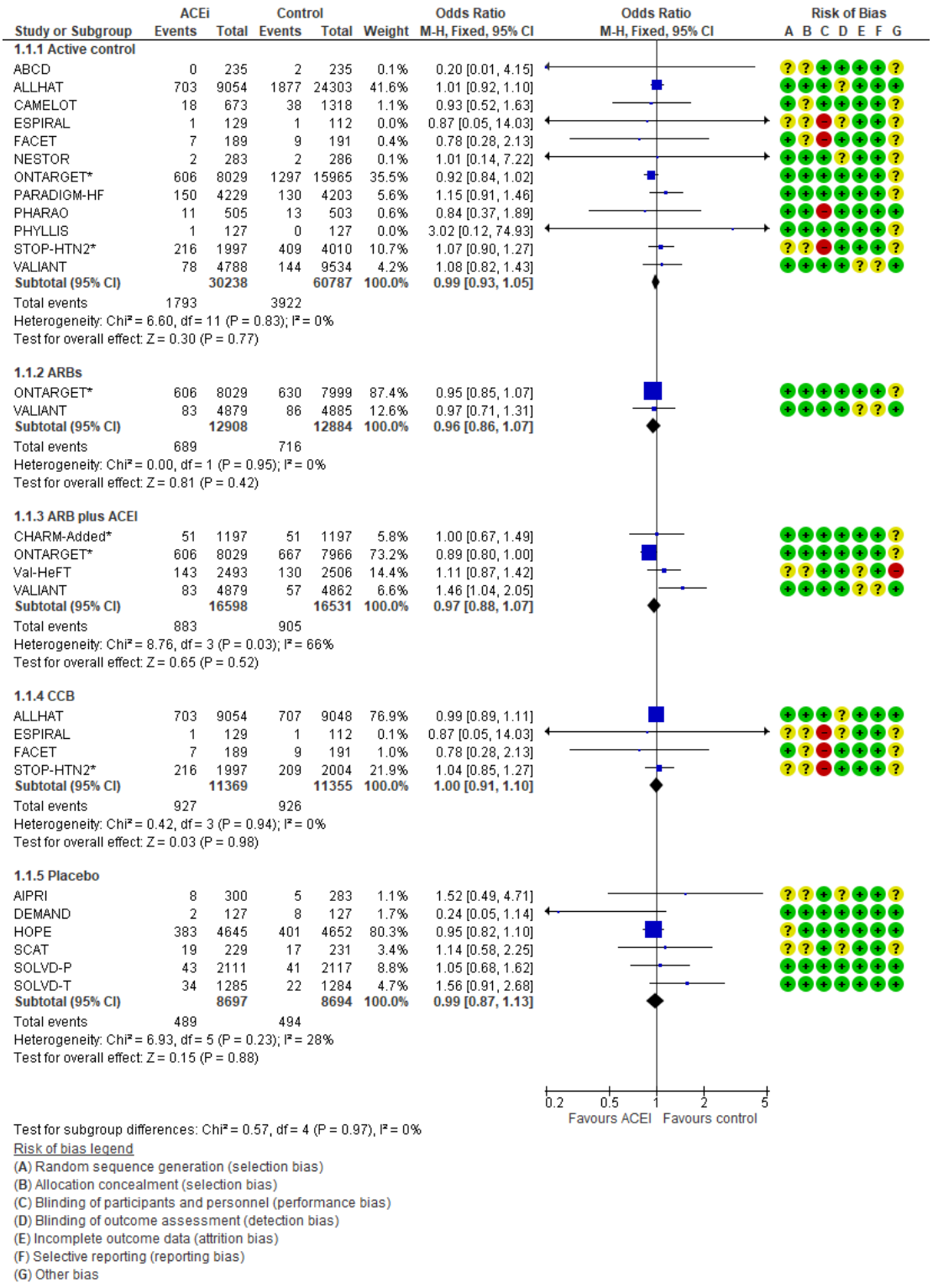


Figure 4-8: Forest plot of incident cancers by comparators [FE model].
1) Active controls; 2) ARBs; 3) ARB plus ACEI; 4) CCB and 5) Placebo. The subtotal effect represents the pooled estimate of odds for incident cancers for each comparator. *Included were patients who were cancer free at baseline.

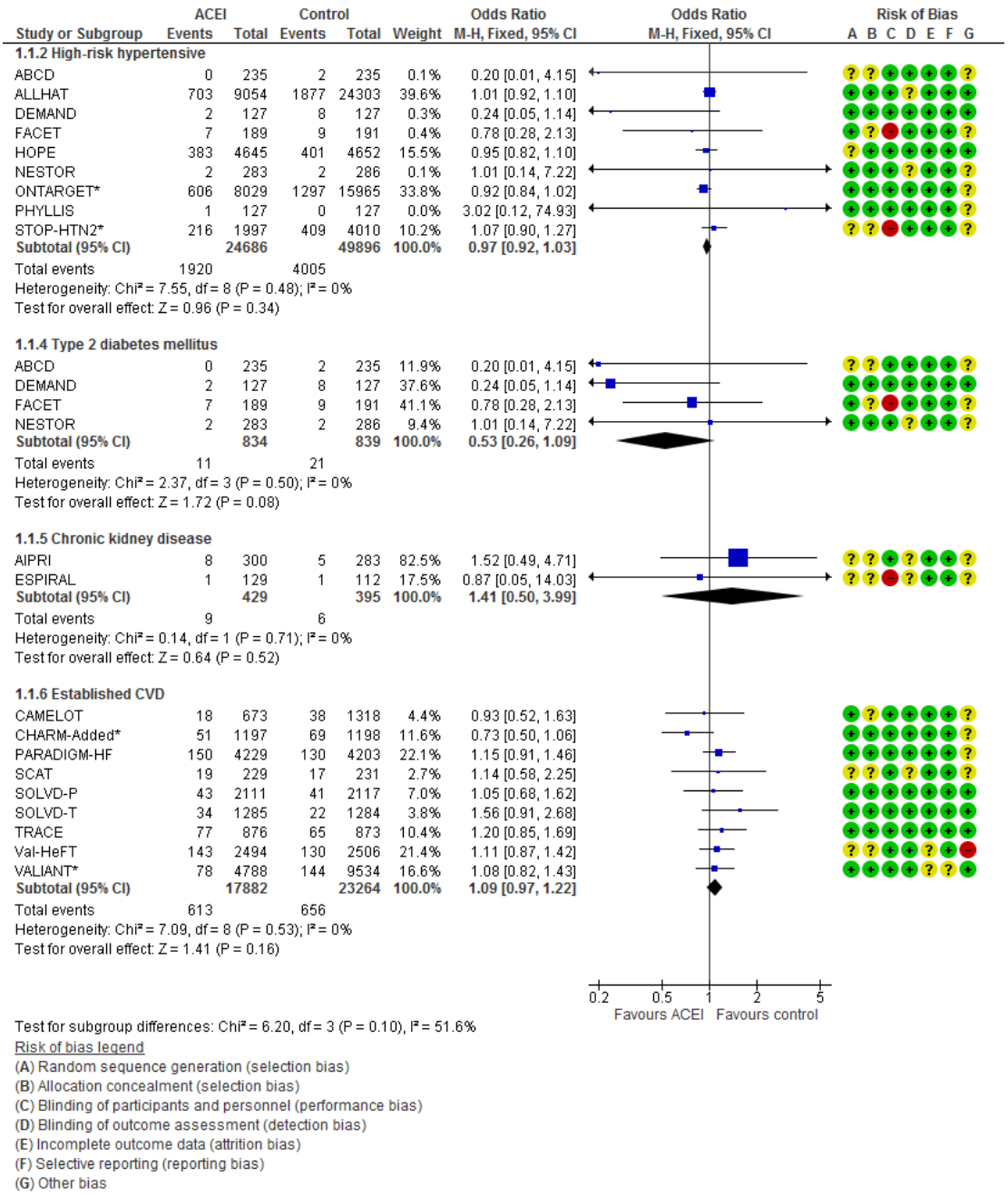


Figure 4-9: Forest plot of incident cancers by population clinical setting [FE model]. 1) High risk hypertension; 2) T2DM; 3) CKD; 4) Established CVD. The subtotal effect represents the pooled estimate of odds for incident cancers for each clinical setting. *Included were patients who were cancer free at baseline.

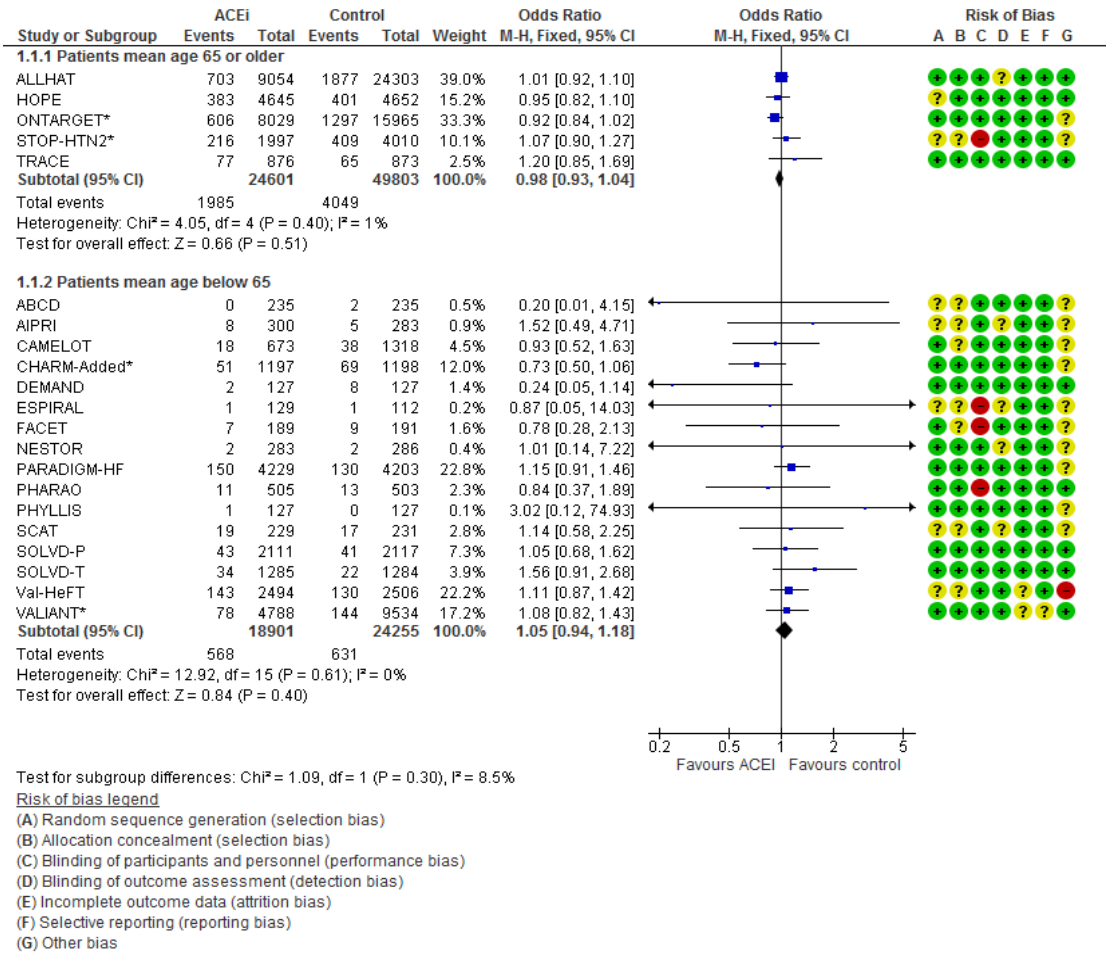


Figure 4-10: Forest plot of incident cancers by mean age [FE model].
1) ≥ 65 years; 2) < 65 years. The subtotal effect represents the pooled estimate of odds for incident cancers for each criterion. *Included were patients who were cancer free at baseline.

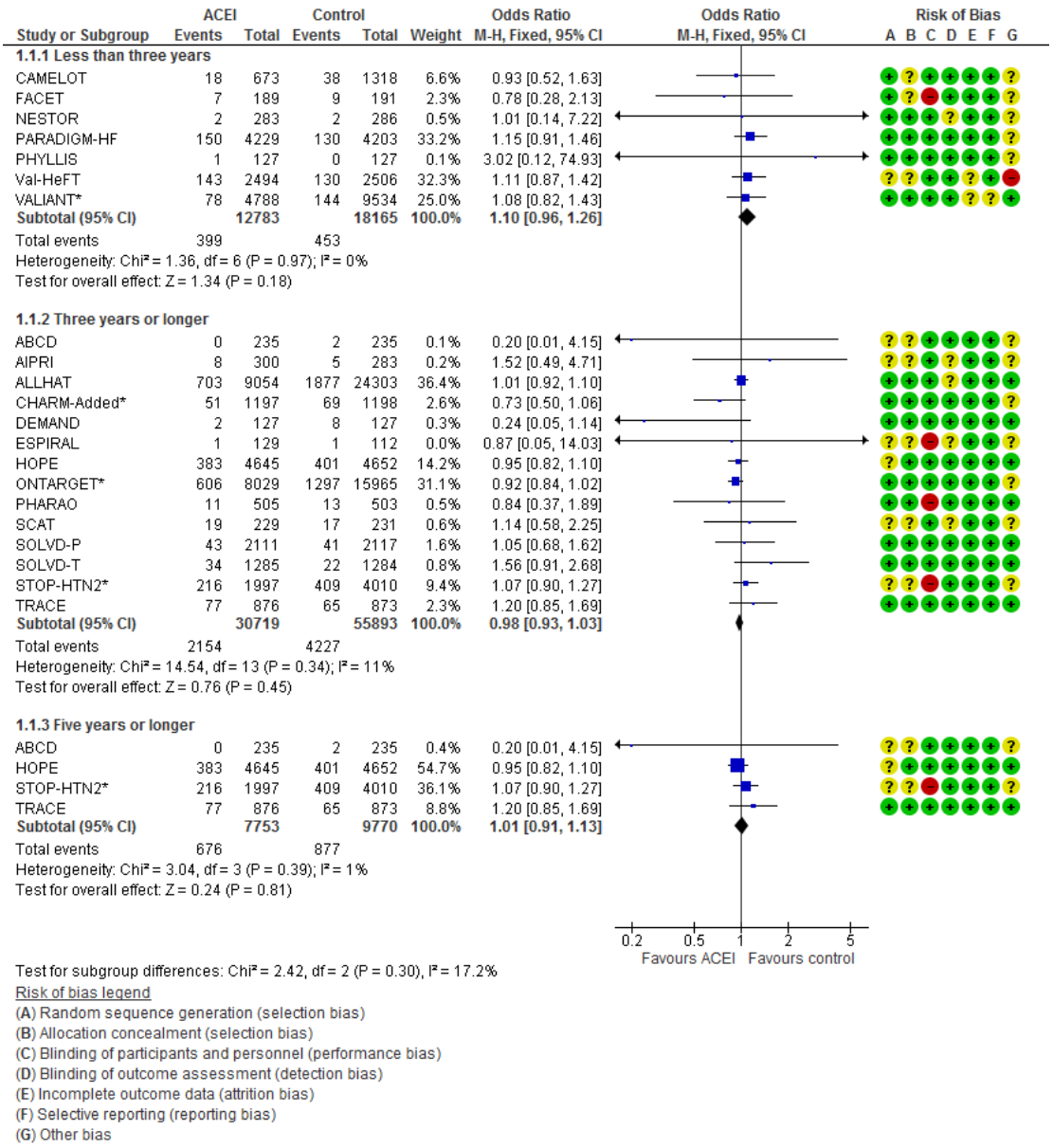


Figure 4-11: Forest plot of cancer incident by mean duration of follow-up [FE model]. 1) Follow-up < 3 years; 2) Follow-up ≥ 3 years; 3) Follow-up ≥5 years. The subtotal effect represents the pooled estimate of odds for cancer incidence for each criterion.

4.5 ACEI and risks of cancer-related death

Altogether, 14 RCTs were included for comparison between ACEI and other antihypertensive agents for risk of cancer-related death. Data on cancer-related death were available from 80,440 (99.7%) of 80,653 patients who were enrolled in the 14 studies. Figure 4-12 shows the meta-analysis of these studies in an FE model. According to the assigned treatment arm, cancer-related death was 1.96%

in the ACEI group versus 2.32% in the non-ACEI group, OR 0.97 with 95% CI 0.88 – 1.08 (P = 0.62).

The main analysis was mainly influenced by the ALLHAT study as it was assigned the most weight overall at 55.9% which is clearly depicted as the largest blue square in the forest plot. The weight assigned to the majority of the 13 remaining individual studies is less than 10%. Four studies recorded an OR more than 1 ranging from 1.01 to 3.00. On the other hand, seven studies observed an OR less than 1 ranging from 0.70 to 0.99 whereas three studies have OR equal to 1. The 95% CI for all the studies includes 1 which are displayed as CIs crossing the vertical line of no effect in the forest plot. Therefore, none of the individual studies is statistically significant at the study level. When the results of all the 14 studies were pooled together, the combined effect showed an OR of 0.97 with 95% CI ranged between 0.88 and 1.08 (P-value = 0.62) and the diamond that represents the combined effect estimate in the forest plot encroaches the line of no effect. This result indicates that no statistical significance is observed at the meta-analysis level.

Random effects (RE) model (Figure 4-13) shows an additional 1.3% weight was assigned to the ALLHAT study (57.2%). Similarly, the ALLHAT study carries the most weight overall giving an OR 0.98 and 95% CI 0.88 to1.08 (P = 0.67) which is comparable to the result of the FE model.

Assessment of heterogeneity in both FE and RE model showed a chi-square test P-value of 0.78 and I^2 statistics of 0%. These values indicate no evidence of statistically significant heterogeneity between the difference studies.

Appendix Figure A-2 shows the distribution of the 14 studies in a funnel plot. There is a missing study at the bottom right of the plot. No outlier is observed and the plot appears fairly symmetry.

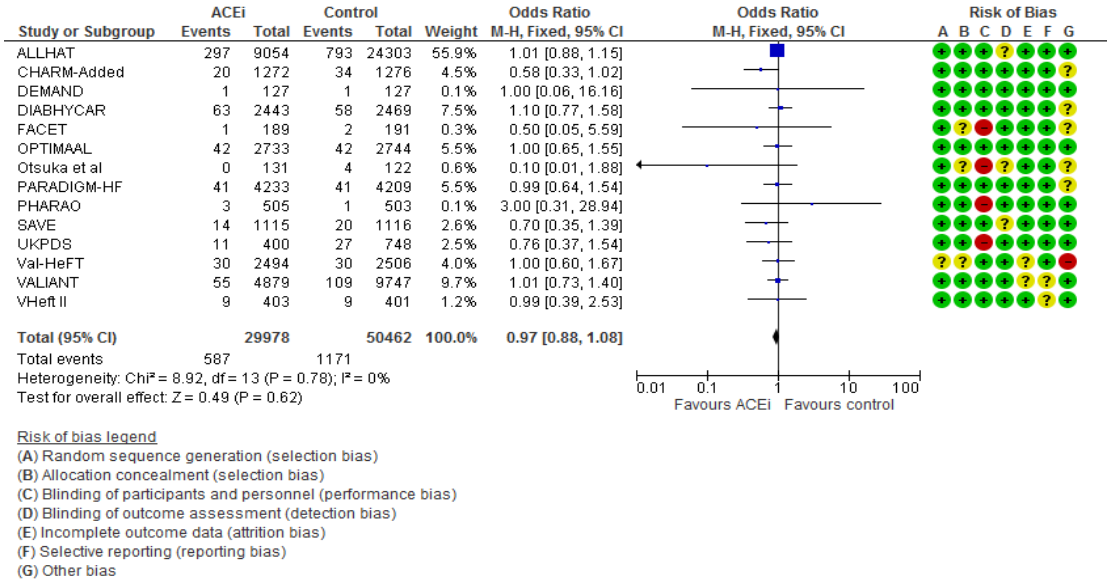


Figure 4-12: Forest plot of cancer-related deaths by ACEI versus non-ACEI controls [FE model].
Odds ratios and 95% confidence interval, overall and in 14 trials. The overall effect represents the pooled estimate of odds for cancer-related death.

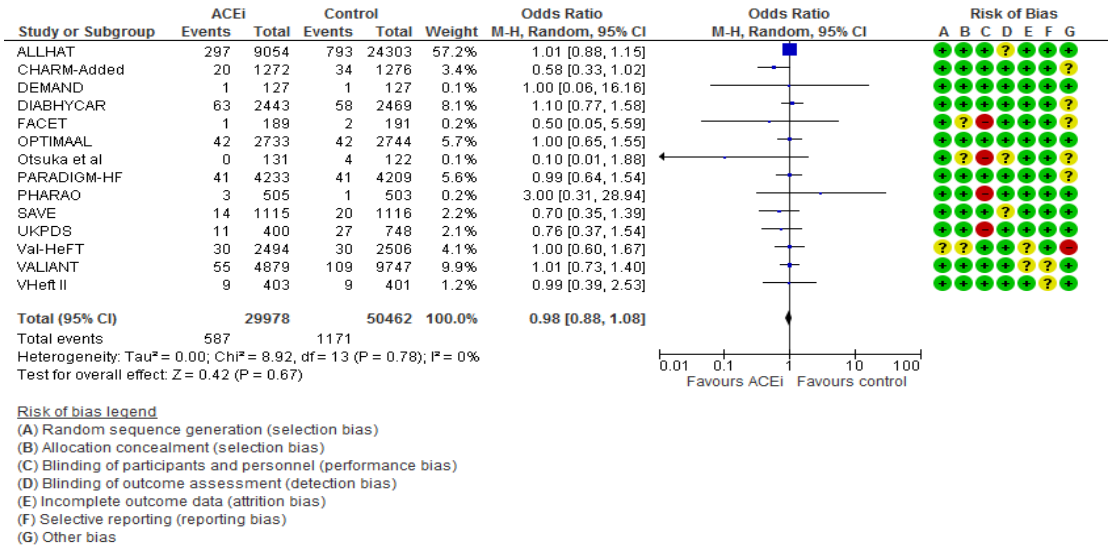


Figure 4-13: Forest plot of cancer-related deaths by ACEI vs non-ACEI controls [RE model].
Odds ratios and 95% confidence interval, overall and in 14 trials. The overall effect represents the pooled estimate of odds for cancer-related death.

4.6 Discussion

Results of this study have demonstrated no evidence of significant association of cancer incidence with use of ACEI (OR 0.99, 95% CI 0.94-1.05). This result is unlikely due to type II error because of the narrow 95% CI and lack of heterogeneity ratio. Sensitivity analyses also showed that the inclusion of studies with a different design, sizes, and quality did not affect the risk of cancer. Likewise, for cancer-related death, no increase in risk was observed with summary OR 0.97 (95% CI 0.88 – 1.08).

An earlier case report described the relationship between the use of ACEI and malignancy by induction of an autoimmune disease of the skin and mucous membrane known as pemphigus vegetans (Bastiaens et al., 1994). Review of three patients presented with pemphigus vegetans has shown that this condition was possibly induced by enalapril and was associated with lung cancer. This finding was consistent with a preceding report that had described a statistically increased in cancer incidence associated with pemphigus (Younus and Ahmed, 1990). In another case report of an elderly heterosexual man free of retrovirus infection, captopril was implicated with the development of a rare type of cancer identified as Kaposi's sarcoma (Puppin et al., 1990). It is believed that inhibition of the enzyme dipeptidylcarboxypeptidase by ACEI leading to rising kinin level was responsible for the various cutaneous reactions observed. Additionally, two RCTs reported increased cancer incidence associated with ACEI therapy. The SOLVD-T study has followed HF patients for an average 3.5 years and found that those receiving enalapril has a slightly higher incidence of cancer compared to placebo (OR 1.59,95% CI 0.90-2.82) (The SOLVD Investigators, 1991). In the AIPRI study, patients with renal insuffiency caused by various aetiology were followed for an average of three years (Maschio et al., 1996). The trial investigators reported higher cancer incidence in those randomised to benazepril treatment versus placebo (OR 1.52, 95% CI 0.49-4.71). In spite of that, assessment of different ACEI subclasses categorised into tissue and non-tissue ACEI in a subgroup analysis of the present study found no significant association to risk of cancer in comparison to non-ACEI controls. The varied ACEI effect may be related to differences in inhibition of tissue versus plasma ACE, thus may affect their clinical therapeutic effects. Erman et al. (1991) assessed the range of ACE activity in human serum and tissue samples and inhibition effects of short-term oral ramipiril. This study

reported that ACE activity in the renal cortex was >600 times that of the heart, > 500 times that of the veins, and >150 times that of the arteries. ACE activity in renal cortex and arteries were almost completely inhibited by ramipiril whereas ACE activity in the heart and veins was inhibited to a lesser extent. Meanwhile, a recent meta-analysis by Sun et al. (2016) assessed the efficacy and safety of different ACEI in HF patients. Although they have found that enalapril might be the best option considering factors associated with HF, it has the highest incidence of cough, gastrointestinal disturbance, and greater renal function deterioration. Lisinopril ranked the worst for both efficacy and safety profile as it did poorly in lowering both systolic and diastolic BP and was associated with the highest incidence of all-cause mortality. As for trandolapril and ramipiril, both had better efficacy and safety profile.

ACEIs are also associated to dry cough, which is a class phenomenon and attributed to an increase in bradykinin and/or other vasoactive peptides. In an experimental study using human lung carcinoma cell line and rat lung cancer model, Papp et al. (2002) demonstrated that angiotensin II mediated alveolar epithelial cells apoptosis via AT1 receptor. Based on this mechanism, several studies tried to link ACEI and lung cancer. A cohort study of 5207 hypertensive patients on antihypertensive therapy followed for up to ten years reported a significant reduction in lung cancer incidence amongst those on ACEI (Lever et al., 1998). However, this study was insufficiently powered to detect different types of cancer in subgroup analyses. In a much larger study, Friis et al. (2001) retrospectively observed cancer incidence among 17,897 patients on ACEI treatment with a 3.7 years follow-up. This study found no difference in lung cancer risk between ACEI users and other antihypertensive users (OR 1.0, 95% CI 0.7-1.03). A similar finding was reported in a post-hoc analysis of the STOP-HTN2 (Lindholm et al., 2001) trials where patients who were on ACEI did not have increased risk compared to CCB and conventional drugs. Then again, the STOP-HTN2 trial was not designed to detect cancers. Results from these studies disproved the hypothesis that ACEI is associated with increased lung cancer risk. Moreover, inhibition of ACE could lead to decreased production of angiotensin II and increased the formation of angiotensin (1-7) which can potentially prevent cancer development. Increase detection of lung cancer in patients on ACEI is likely due to increased screening for patients presenting with a chronic cough in clinical settings.

Apart from lung cancer, several studies have also investigated the relationship between ACEI and colorectal cancer (Lever et al., 1998, Kedika et al., 2011, Makar et al., 2014). Experimental studies suggested that ACEI used in conjunction with non-steroidal anti-inflammatory drugs (NSAIDs) is protective against colorectal cancer. Upregulation of cyclooxygenase-2 (COX-2) messenger ribonucleic acid (mRNA) was markedly increased in most human colorectal cancers (Eberhart et al., 1994); thus inhibition of COX-2 activity is thought to be one of the mechanisms by which NSAIDs exert its antineoplastic effects. However, the use of specific COX-2 inhibitors, as well as conventional NSAIDs, have side-effects such as gastric ulcers or CV complications in predisposed patients. In addition to COX-2, insulin-like growth factors type II (IGF-II) acting on IGF receptor type I (IGF-IR) is also implicated in the tumorigenesis of colorectal cancer (Manousos et al., 1999, Vigneri et al., 2015) In an in-vivo study using mouse and human colon cancer cells, Yasumaru et al. (2003) reported that concurrent use of NSAIDs and ACEI decreased IGF-IR expression level and had significantly reduced tumour growth. Interestingly, the use of either agent separately did not have a significant effect as compared to control.

The RAS pathway is blocked at different levels by ACEI and ARB. A meta-analysis of nine ARB trials enrolling total 94,579 participants by Sipahi et al. (2010) proposed increased malignancy risk associated with ARB. Contrariwise in a meta-analysis of 14 RCTs evaluating ACEI, Sipahi et al. (2011) reported that ACEI did not significantly influence the risk for cancer. Although ACEI acts in the same pathway as ARB, their mechanism of action is very different. However, the subgroup meta-analysis conducted in this review indicates that there is no difference in cancer risk between ACEI and ARB. Similarly, the risk of cancer between ACEI monotherapy and ACEI and ARB combination did not differ significantly. Then again, this observation should be interpreted with caution due to the limited number and variability of studies included in this analysis. Nevertheless, no significant difference is observed with other comparators.

The inhibition of ACE have proven to be safe and effective in controlling BP and preventing major CV outcomes in patients with hypertension, high risk or established CVD as demonstrated in clinical trials. The ABCD trial followed hypertensive patients with T2DM for an average of 5.6 years and found a lower incidence of fatal and non-fatal MI in those receiving ACEI versus CCB (Estacio et

al., 1998). In a similar clinical setting, Tatti et al. (1998) reported a lower risk of major CVD events in those randomised to ACEI versus CCB despite similar effects in biochemical parameters in hypertensive patients with T2DM followed for an average three years. In patients with established CVD or high risk for diabetes, treatment with ACEI was as effective as ARB (The ONTARGET Investigators, 2008). Treatment with ACEI also protects against the progression of renal insufficiency in patients with CKD (Maschio et al., 1996). Current clinical guidelines are recommending ACEI as one of the primary treatment for hypertension (NICE, 2011, Mancia et al., 2013a, James et al., 2014) and left ventricular dysfunction (Hunt et al., 2005, Swedberg et al., 2005, NICE, 2010). However, it is important to consider whether different clinical settings or disease severity have any impact on cancer risk. In a subgroup analysis, no significant increase in cancer risk was detected in a different population with different clinical settings. Owing to the limited number of study available, cancer risk observed in patients with T2DM or CKD is not conclusive with OR 0.53 (0.26-1.09) and OR 1.41 (0.50, 3.99) respectively. Additionally, no significant difference in cancer risk was observed in patients older versus younger than 65 years.

The relationship between ACEI therapy and risk of cancer-related death was assessed in this review. Cancer-related mortality differs from cancer incidence because cancer deaths inform us of the effect of ACEI on cancer progression hence survival in cancer patients. Results from the current study correspond to the results of previous systematic review and meta-analysis that shows ACEIs have no effect on cancer-related mortality (Bangalore et al., 2011, Sipahi et al., 2011, Teo, 2011). In a systematic review of ten studies (two interventional, eight observational) with total 4,178 patients with cancer of various type, use of ACEI or ARB have been showed to improve outcomes in term of recurrence, distant metastasis and overall survival rate in cancer patients (Mc Menamin et al., 2012). A recent and larger meta-analysis including 55 studies has reported that use of RAS blockers was associated with better outcomes in term of cancer progression and survival (Sun et al., 2017). Compared to non-user, RAS inhibitors significantly improved overall survival (HR 0.82, 95% CI 0.77–0.88), progression-free survival (HR 0.74, 95% CI 0.66–0.84) and cancer-free survival (HR 0.80, 95% CI 0.67–0.95). This study also found that overall cancer survival was influenced by the type of cancer and RAS inhibitors. Improvement of overall survival was only observed in

solid cancers but not cancers of the blood such as leukaemia and multiple myeloma. The underlying mechanism by which ACEI or RAS inhibitors affect the progression of solid cancer is still not clearly understood. However, it has been postulated that ACEI disrupts tumour angiogenesis by suppressing VEGF formation independent of the AT1 blockade (Yoshiji et al., 2001).

4.6.1 Strength and limitations

This review incorporates all data publicly available reported to date and this is the largest meta-analysis of RCTs observing ACEI and risk of cancer overall. Only RCTs were included thus decreasing the effects of confounding variables. An OR of 0.99 with a very narrow 95% CI obtained makes a false-negative result unlikely. The absence of statistical heterogeneity also supported the pooling of outcomes from all of the included studies.

Nevertheless, this review has several important limitations. Majority of the included trials were not designed to detect cancer outcomes as a primary outcome. Adjudication of the incidence of cancer was unknown and they are frequently reported as serious adverse events. Majority of the RCTs have a short average duration of follow-up ranging from one to nine years. Hence, the analyses only can rule out the effect on late preclinical stage cancers. The risk of site-specific cancer was not reported due to inadequate access to such data. Many trials were excluded from the analysis due to the lack of cancer outcome reporting. Therefore, this meta-analysis is subject to outcome reporting bias. Lastly, access to individual-patient data from the included RCTs was not available, thus it is not possible to perform a time-to event analysis. Additionally, it is possible to introduce ascertainment bias in this review during data collection. However, the risk of ascertainment bias is reduced by implementing independent data abstraction and quality review as well as sensitivity and subgroup analyses.

4.7 Conclusion

There is no evidence that ACEI significantly increases or decrease the risk of any cancer or cancer-related death. These data add to the growing body of evidence suggesting these agents do not affect the risks of cancer.

5 Association between angiotensin receptor blockers (ARB) and risks of cancer

5.1 Introduction

The RAS is described in more detail in **Chapter 4 Section 4.1.1.** ARBs is one of the earliest pharmacological inhibitors to target the RAS pathway in BP control. The characteristics of different ARB types are summarised in **Table 5-1.** Currently, only seven orally active ARB has been approved by the FDA for the treatment of hypertension. Among the ARBs, irbesartan has the best bioavailability with approximately 70% of the drug reaches circulation following oral administration, whereas eprosartan had the least oral bioavailability. The active metabolite for losartan, EXP 3174, when administered via the intravenous route is more potent and has a longer duration of action than the parent drug (Burnier and Brunner, 2000). However, the EXP 3174 has poor oral bioavailability, thus losartan is in the market. Meanwhile, candesartan is administered orally as a prodrug, candesartan cilexetil, which is rapidly converted to candesartan during absorption in the gastrointestinal tract. The remaining ARBs are either directly active and have no active metabolite. Telmisartan has the longest half-life allowing a once a day regime, while losartan has the shortest half-life of approximately two hours. All ARBs are highly bound to plasma protein and they are mainly excreted via the biliary system with a lesser fraction are excreted through the kidney. The mechanism of action for ARBs is described in **Chapter 4, Section 4.1.4** and **Figure 4-1**.

5.1.1 ARB and cancer risk

The underlying mechanism where blockade of angiotensin type 2 (AT_2) receptors by ARB leads to cancer formation is still unclear. As described earlier, angiotensin II is known to regulate angiogenesis thereby plays a role in carcinogenesis (See 4 Section 4.1.4(page 150). In an in-vivo study, sarcoma and fibrosarcoma cells were implanted in mice treated with candesartan, lisinopril, or control (Fujita et al., 2002). This experiment demonstrated that treatment with candesartan or lisinopril inhibited angiogenesis, growth, and metastasis of a tumor, hence suggesting that blockade of the AT_2 receptors may become a potential target in

tumor chemoprevention strategy. Evidence from epidemiological studies is discussed in Chapter 1, Section 1.9.3.1(page 46).

This chapter aims to systematically review and report the meta-analysis of RCTs using ARB as one of its treatment and its association with risks of cancer.

Table 5-1 Pharmacokinetics of angiotensin receptor blockers (ARB)

Drug name	Bioavailability	Active metabolite	Half-life (h)	Protein binding (%)	Elimination route
Losartan	33	EXP 3174	2	98.7	Bile (90%), renal (10%)
Valsartan	25	No	9	95	Bile (70%), renal (30%)
Irbesartan	70	No	11-15	90-95	Bile (80%), renal (20%)
Candesartan cilexetil	42	Candesartan	3-11	99.5	Bile (40%), renal (60%)
Telmisartan	43	No	24	> 99	Bile (99%), renal (1%)
Eprosartan	15	No	5-7	98	Bile (90%), renal (10%)
Olmesartan	29	No	14-16	> 99	Bile (90%), renal (10%)
Azilsartan					

Adapted from Brunner (2002), Burnier and Brunner (2000), and Brousil and Burke (2003).

5.2 Methodology

5.2.1 Systematic review

Full descriptions of the methods used have been described previously in Chapter 2 Section 2.1 (page 57).

Majority of the included trials have published cancer outcomes in their primary study or as a post-hoc analysis. In eleven trials (ALPINE, CHARM Overall, DIRECT Overall, IDNT, ONTARGET, TRANSCEND, and VALIANT), cancer outcomes were reported in two earlier meta-analyses (Bangalore et al., 2011, Teo, 2011). Cancer outcomes for the PREVER-Treatment study were supplied by the trial primary author (Dr Flávio D. Fuchs of Hospital de Clinicas de Porto Alegre, Brazil).

5.2.2 Meta-analysis

For data synthesis, see Chapter 2 Section 2.1.7.4 (page 66).

For incident cancer, sensitivity analyses were done by exclusion of trials with: [1] factorial design; [2] poor methodological quality; [3] small sample size with the number of total participants less than 1000; and [4] inclusion of patients with baseline cancer.

Additionally, the following subgroup analyses were performed: [1] by subclass;[2] by the comparator; [3] by clinical setting; [4] by mean age; and [5] by the duration of follow-up.

Furthermore, individual patient data for the four major valsartan trials (VALUE, Val-HeFT, VALIANT and NAVIGATOR) was provided by Novartis, a pharmaceutical company, through Professor John J.V. McMurray of the University of Glasgow. The analysis of these trials was designed and performed by the authors in conjunction with Statistics Collaborative Incorporated (SCI). They also reviewed these data to identify all cancers (except basal cell cancers) reported as adverse events or deaths.

Data from the four major valsartan trials were analysed for risk of fatal and non-fatal lung, breast and prostate cancer. Additionally, focus was given to the following treatment comparison: [1] valsartan vs. placebo, [2] valsartan vs. CCB, [3] valsartan vs. non-RAS blocker comparator, [4] valsartan plus ACEI vs ACEI alone (data from Val-HeFT and two of the three arms of VALIANT), [5] valsartan vs ACEI (data from two of the three arms of VALIANT), [6] valsartan plus ACEI ("more intense" RAS blockade) vs. either ACEI or ARB monotherapy ("less-intense" RAS blockade) using data from Val-HeFT and all three arms of VALIANT), and [8] valsartan monotherapy vs. any comparator (placebo, ACEI, or CCB).

The analysis for valsartan and risks of cancer, in particular, was conducted by SCI. Only within study OR estimates and 95% CIs were reported for comparison [1], [2], and [5]. The heterogeneity for the combined analyses [3, 4, and 6] was assessed using the Breslow-Day test (a chi-square test with one degree of freedom). The analysis was performed using R 2.9.2.

5.3 Results

The searching and identification process of trials was summarised in Figure 3-1(Page 74). Altogether, 63 studies were excluded from the total of 90 included RCTs from the main systematic review primarily because they do not consist of an ARB treatment arm. In total, 32 RCTs enrolling 160,063 participants with an average follow-up of 3.3 years (range 1 to 5 years) were included in the overall ARB cancer-risk meta-analysis. The average patients' age across all studies is 61.5 years old.

The characteristics and risk of bias of the 32 studies included in this review have been described previously (See Chapter 3, Section 3.2.2.1 and Section 3.3.6). All the included studies were published in the 21st century with the most recent study was published in 2016. Four trials (ONTARGET, PRoFESS, VALIANT, and VALUE) have enrolled more than 10,000 total participants consequently contributed the largest number of patients in this review. More than half of the total participants (65.2%) have underlying CVD such as AF, CHD, and HF. Meanwhile, the TROPHY study enrolled participants with BP within the high-normal range (SBP between 130-139 mmHg and DBP between 85-89 mmHg) who were never treated for hypertension.

Overall, over half (54.1%) of the total participants were assigned treatment with ARB and telmisartan was the most prescribed (34.8%) among another type of ARB. Whilst the majority of the study has used one type of ARB, Suzuki et al. (2008) have used candesartan, losartan and valsartan in its ARB treatment arm versus no ARB. Most of the included trials compared ARB to active controls including ACEI, BB, CCB, TZ, and conventional antihypertensive therapy. The CHARM-Added trial investigated the use of ARB versus placebo in HF patients already receiving an ACEI, hence was regarded as a trial of ARB versus ACEI. Two studies (ONTARGET and VALIANT) randomised patients to ACEI, ARB and ARB plus ACEI combination. In these studies, both the ARB monotherapy arm and combination arm were considered as the ARB treatment arm. Henceforth, these trials were regarded as ARB versus ACEI monotherapy.

In this review, CHARM Overall comprised three separate studies, CHARM-Added, CHARM-Alternative, and CHARM-Preserved. Similarly, cancer outcomes for

DIRECT-Prevent 1, DIRECT-Protect 1, and DIRECT-Protect 2 were collectively reported as DIRECT Overall.

All the included studies are randomised trials. Majority of the studies have implemented blinding to both trial personnel and patients in a parallel design. It is noteworthy that all the included Japanese trials have instigated either the PROBE design (CASE-J Ex, HIJ-CREATE, NHS, and OCTOPUS) or open label design (E-COST, Suzuki). Two trials applied a double-blind, two-by-two factorial design. In the NAVIGATOR study, patients with IGT and established CVD were randomised to valsartan or matching placebo and nateglinide or matching placebo in addition to lifestyle modification. Meanwhile, PRoFESS randomised stroke patients to telmisartan or placebo and aspirin-dipyridamole combination or clopidogrel. All the study participants were followed for at least one year with the longest follow-up was five years. The mean age for patients across all studies was over 50 years.

The selected characteristics of interest extracted from the 32 included studies are summarised in Table A-3 (page 321). The reporting of all these variables was inconsistent across all studies. Almost all of the included studies enrolled at least 50% or more male participants except for the SCOPE study with more than 60% of participants were made up of women. The reporting of current smokers is inconsistent across studies, yet none of the percentage reported was remarkable. Only six of the included studies (CHARM Overall, GISSI-AF, OCTOPUS, and TRANSCEND) have allowed participation of patients with baseline cancer whereas three studies (CASE-J Ex, HIJ-CREATE, and IRMA-2) reported exclusion of such patients. Most of the trials did not pre-specified cancer as an outcome. Eight studies have cancer outcomes adjudicated centrally whereas the remaining studies lacked such information. The loss to follow-up ranged between nil to 9.7% which was tolerable.

5.4 ARB and risk of incident cancer

5.4.1 Overall

For risk of incident cancer, 25 RCTs comparing ARB against active control or placebo were available. Data on cancer incidence were available from 148, 275 (97.4%) of the 152,172 patients who were enrolled in the 25 studies.

Figure 5-1 shows the meta-analysis of ACEI and risk of cancer incidence in a fixed-effect (FE) model. Altogether, cancer incidence was 5.78% in patients assigned to the ARB group versus 5.87% assigned to non-ARB treatment. This result was mainly influenced by the ONTARGET, VALUE and the NAVIGATOR study which carries 19%, 18.4%, and 11% of the overall weight correspondingly. The distribution of weight among the remaining 22 studies was less than 10% each.

More than 50% of the studies reported an OR more than 1 but their 95% CI includes 1. One study, DIRECT (Overall), generated an OR of 1.69 with 95% CI between 1.06 and 2.71 indicating 69% increased risk in the ARB treatment group. Meanwhile, two studies generated an OR less than 1 with 95% CI not crossing 1. The OCTOPUS and VALUE study yields an OR of 0.39 (95%CI 0.16, 0.96) and 0.84 (95% CI 0.75, 0.93) respectively. Apart from these four studies, CIs for all the studies crossed the line of no effect indicating a lack of statistical significance at the study level. Overall, the combined OR of all 25 studies yields an OR of OR 0.99 with 95% CI 0.95 – 1.04 (P = 0.79). The diamond that represents the pooled effect estimates is narrow and it impinges the line of no effect indicating the absence of statistical significance at the meta-analysis level.

In the random effects (RE) model (**Figure 5-2**), the weight assigned to both ONTARGET and VALUE study slightly reduced by approximately 6% each. The combined effect estimates yields an OR of 1.00 (95% CI 0.94-1.06; P = 0.96).

Assessment of heterogeneity in both FE and RE model showed a chi-square P-value of 0.09 and I^2 statistics of 28% indicating minimal differences between studies. The observed statistical heterogeneity is most likely due to clinical and methodological diversity of the OCTOPUS (PROBE design), ONTARGET (a three parallel arm study with a combination comparator arm), and VALUE (patients with high CVD risk).

Visual inspection of the funnel plot (Appendix Figure A-1) shows a missing study in the middle and left side of the plot. No outlier was detected.

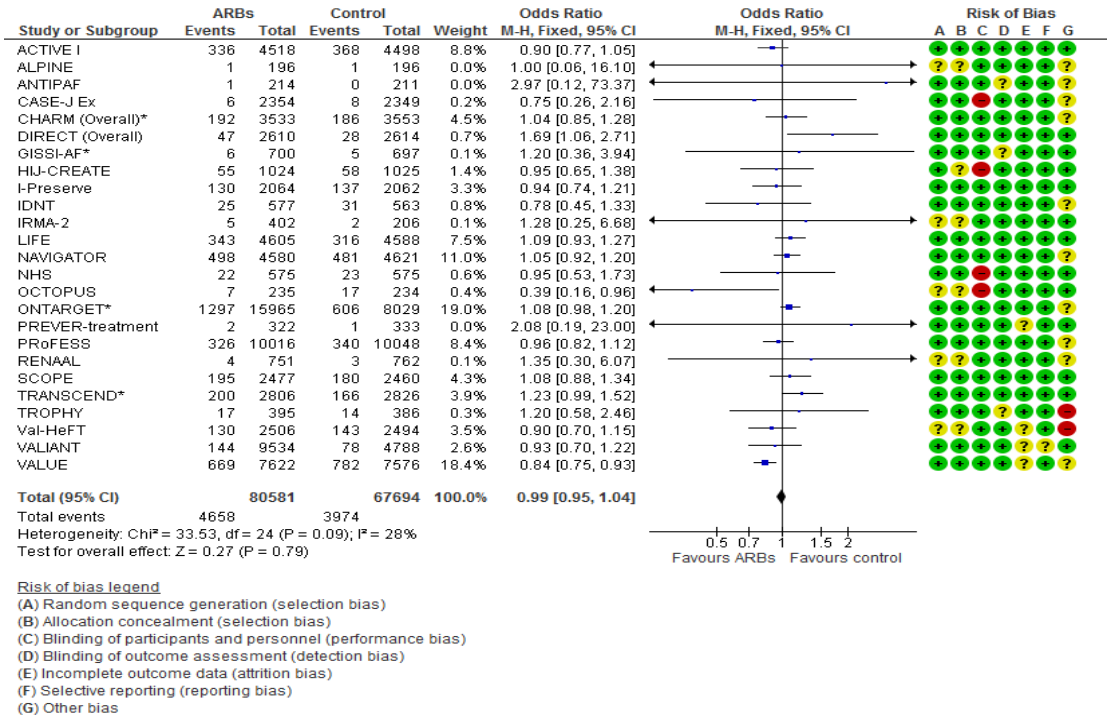


Figure 5-1: Forest plot of incident cancers by ARB vs non-ARB controls [FE model]. Odds ratios and 95% confidence interval, overall and in 25 trials. The overall effect represents the pooled estimate of odds for incident cancers. * Included were patients with no history of cancer or active cancer at baseline.

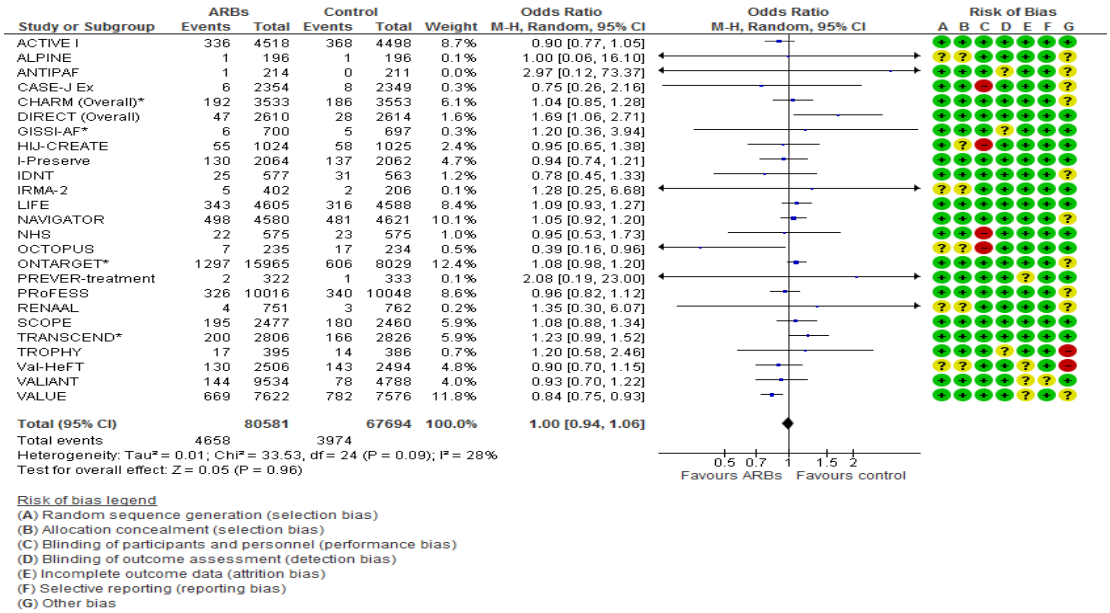


Figure 5-2: Forest plot of incident cancers by ARB vs. non-ARB controls [RE model]. Odds ratios and 95% confidence interval, overall and in 25 trials. The overall effect represents the pooled estimate of odds for incident cancers.* Included were patients with no history of cancer or active cancer at baseline.

5.4.2 Sensitivity analyses

Exclusion of two trials (NAVIGATOR and PRoFESS) with factorial design yields an OR of 0.99 (95% CI 0.94-1.04; **Figure 5-3**) and P-value of 0.68. Similar to the primary meta-analysis, this result is mainly influenced by the ONTARGET and VALUE trial. Chi-square test for heterogeneity yields a P-value of 0.07 and I^2 statistics is observed at 33% indicating a moderate variation across studies is due to heterogeneity rather than chance.

Figure 5-4 shows a meta-analysis after exclusion of six trials with small sample size. The ONTARGET, VALUE, and NAVIGATOR studies have greatly influenced the direction of this analysis as they carry the most weight overall (19.2%, 18.5%, and 11.1% respectively). Combined effect estimates show an OR of 1.00 with 95% CI ranged from 0.95 to 1.04. Assessment of heterogeneity showed a chi-square test P-value of 0.06 and I^2 statistics of 36% indicating the presence of moderate differences between studies. The moderate heterogeneity observed is most likely due to clinical and methodological diversity of the ONTARGET (a three parallel arm study with a combination comparator arm) and VALUE study (patients with high CVD risk).

Meanwhile, exclusion of nine trials considered as low methodological quality as shown in **Figure 5-5** yields an OR of 1.00 (95% CI 0.95-1.05). This result was mainly driven by the ONTARGET and VALUE study as they were assigned the highest weight proportion (20.3% and 19.5% respectively). Chi-square test for heterogeneity yields a P-value of 0.02 and I^2 statistics is observed at 46% indicating a substantial presence of heterogeneity. The heterogeneity observed is probably due to clinical and methodological diversity of the ACTIVE (patients with AF) and VALUE (patients with high CVD risk) study.

Furthermore, incorporation of patients with baseline cancer data in three trials (GISSI-AF, TRANSCEND and ONTARGET) resulted in OR 1.00 (95% CI 0.96-1.04; **Figure 5-6**). Similar to the primary analysis, the direction of this analysis was mainly driven by the ONTARGET and VALUE study. Assessment of heterogeneity showed a chi-square test P-value of 0.08 and I^2 statistics of 30% indicating the presence of moderate differences between studies. The moderate heterogeneity observed is most likely due to clinical and methodological diversity of the

ONTARGET (a three parallel arm study with a combination comparator arm) and VALUE (patients with high CVD risk) study.

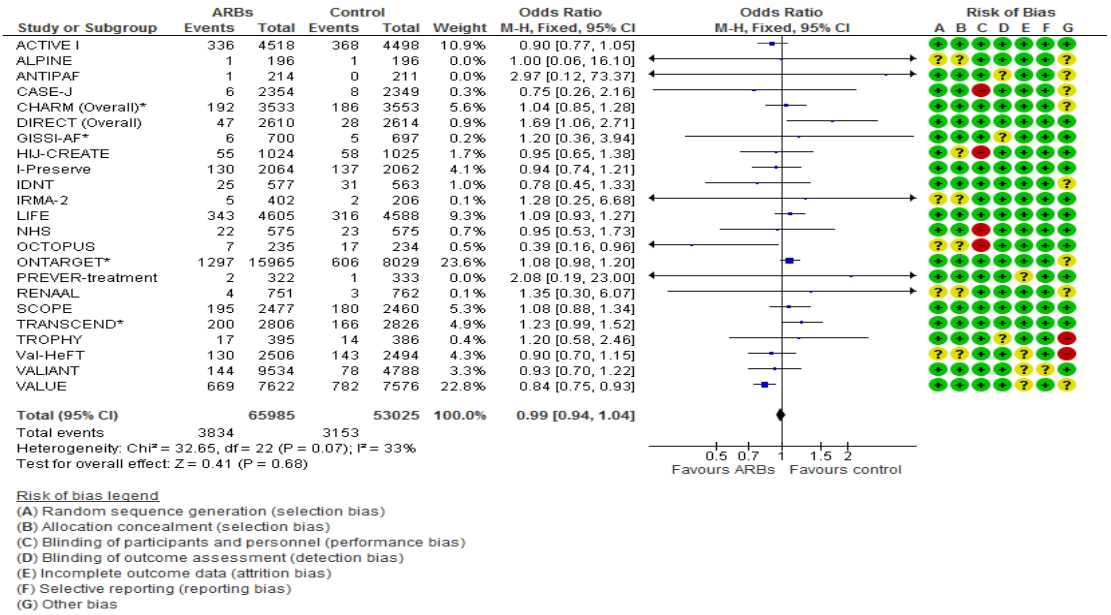


Figure 5-3: Forest plot of incident cancers by ARB vs controls [Sensitivity analysis: Exclusion of trials with factorial design.]
The overall effect represents the pooled estimate of odds for incident cancers. * Included were patients with no history of cancer or active cancer at baseline.

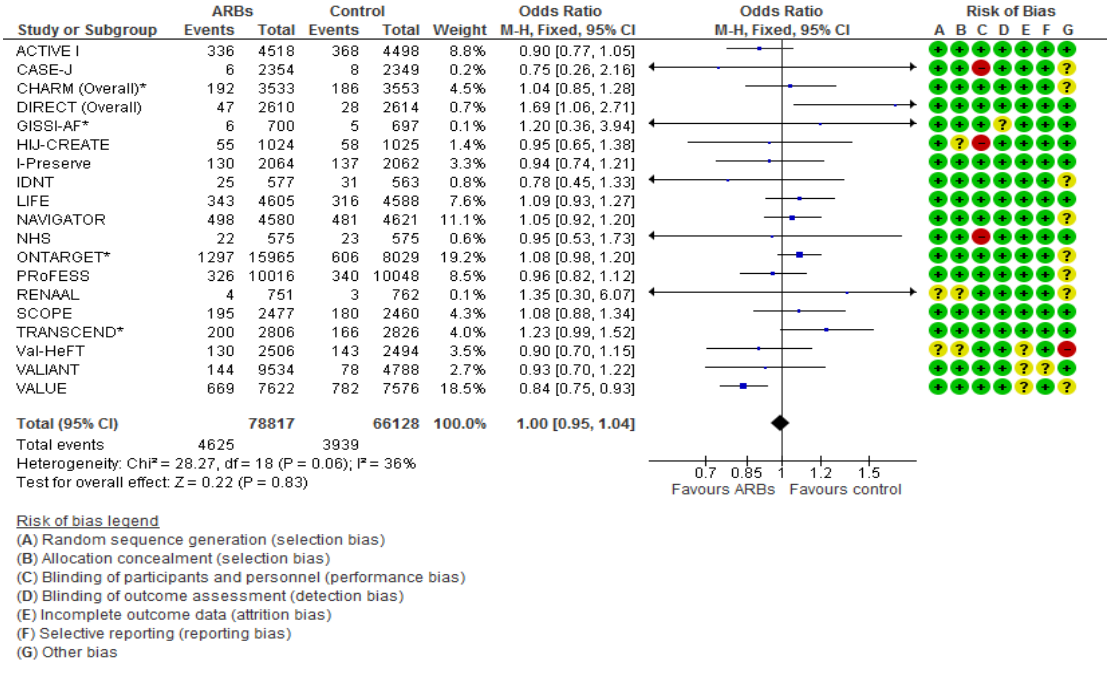


Figure 5-4: Forest plot of incident cancers by ARB vs controls [Sensitivity analysis: Study size].
The overall effect represents the pooled estimate of odds for incident cancers. * Included were patients with no history of cancer or active cancer at baseline.

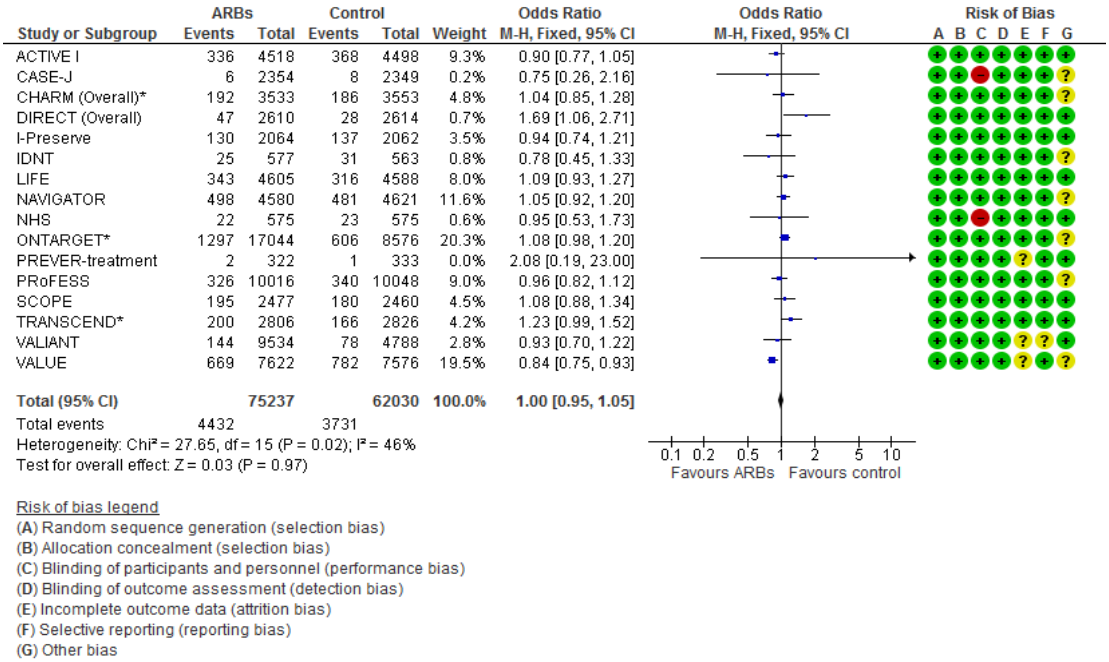


Figure 5-5: Forest plot of incident cancers by ARB vs controls [Sensitivity analysis: Methodological quality].
The overall effect represents the pooled estimate of odds for incident cancers. * Included were patients with no history of cancer or active cancer at baseline.

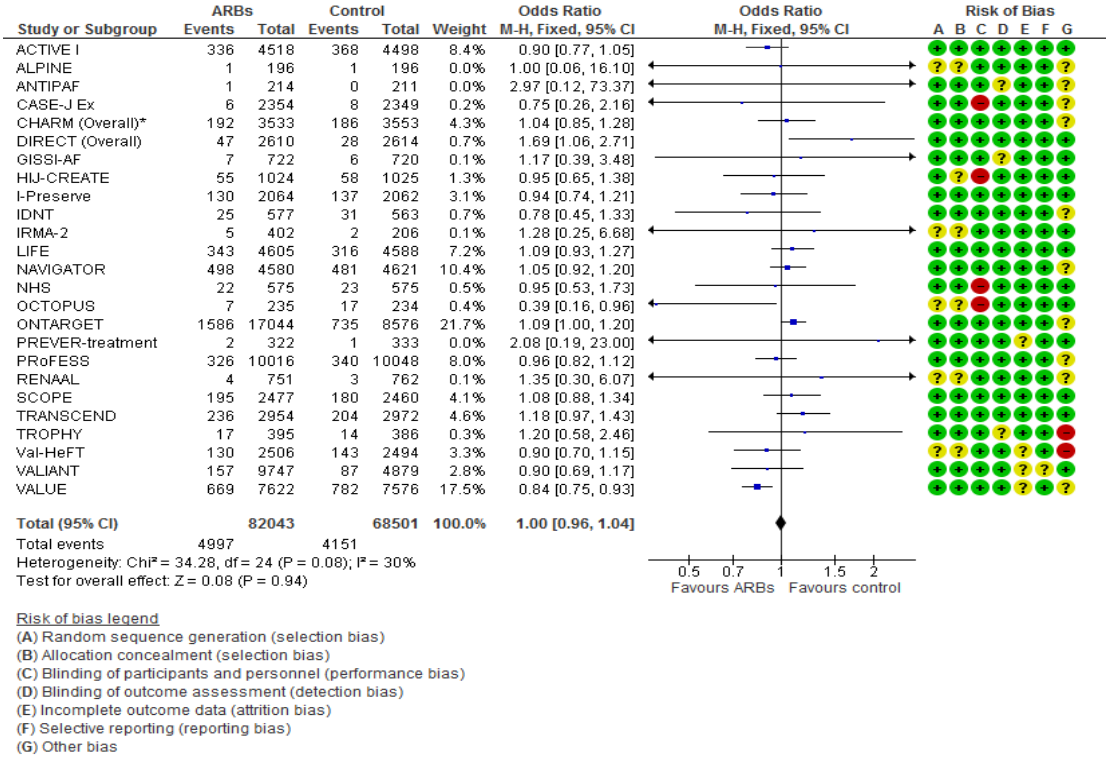


Figure 5-6: Forest plot of incident cancers by ARB vs controls [Sensitivity analysis: Inclusion of patients with baseline cancer].
The overall effect represents the pooled estimate of odds for incident cancers. * Included were patients with no history of cancer or active cancer at baseline.

5.4.3 Subgroup analyses

Table 5-2 summarises the results for subgroup analyses performed for ARB and cancer risk.

5.4.3.1 By subclasses

Figure 5-7 depicts the meta-analysis of ARB by subclasses. Three RCTs enrolling 49,690 participants have used telmisartan as one of the study treatment. Cancer incidence was 6.33% in the telmisartan group versus 5.32 % in the control group with OR 1.07 (95% CI 0.99, 1.16). This analysis was mainly influenced by the ONTARGET which was assigned 60.6% of the overall weight. The chi-square test resulted in a P-value of 0.17 and the I^2 statistics of 44%. The moderate heterogeneity observed is likely due to clinical and methodological diversity between the included trials.

For irbesartan, data were available from four RCTs with a total of 14,890 patients. Cancer incidence was 6.56% in the irbesartan treatment group versus 7.34% in the control group. The direction of this study was greatly driven by the ACTIVE I study which carries over 60% of the overall weight. The combined effect estimates resulted in OR 0.91 (95% CI 0.80, 1.03). Assessment of heterogeneity showed a chi-square P-value of 0.90 and I^2 statistics is observed at 0% indicating no statistical difference between studies.

Six RCTs enrolling 46,268 participants have used valsartan as one of the study treatment. Cancer incidence was 5.76% in the valsartan group versus 7.29% in the control group with OR 0.92 (95% CI 0.85, 0.99). This analysis was mainly influenced by the VALUE trial which was assigned 50.8% of the overall weight. The chi-square test resulted in a P-value of 0.22 and the I^2 statistics of 29%. The small heterogeneity observed is likely due to methodological diversity of the NAVIGATOR study (factorial design).

Seven RCTs enrolling 25,172 participants used candesartan as one of the study treatment. Cancer incidence was 4.08% in the candesartan group versus 3.78% in the control group with OR 1.08 (95% CI 0.95, 1.23). This analysis was mainly influenced by the CHARM (Overall) and SCOPE which was assigned 39.3% and 37.3%

of the overall weight correspondingly. The chi-square test resulted in a P-value of 0.59 and the I^2 statistics of 0% indicating no statistical difference between studies.

Three RCTs enrolling 11,361 participants used losartan as one of the study treatment. Cancer incidence was 6.15% in the losartan group versus 5.63% in the control group with OR 1.09 (95% CI 0.93, 1.28). This analysis was mainly driven by the LIFE study which was assigned 98.7% of the overall weight. The chi-square test resulted in a P-value of 0.84 and the I^2 statistics of 0% indicating no statistical difference between studies.

Lastly, two RCTs enrolling 894 participants used olmesartan as one of the study treatment. Cancer incidence was 1.78% in the olmesartan group versus 3.82% in the control group with OR 0.47 (95% CI 0.20, 1.08). This analysis was mainly governed by the OCTOPUS study which was assigned 97.1% of the overall weight. The chi-square test resulted in a P-value of 0.23 and the I^2 statistics of 30% indicating a moderate difference between studies.

5.4.3.2 By type of comparator

Figure 5-8 shows the meta-analysis of ARB by the different type of comparators. Altogether, 11 RCTs compared ARB to active controls with data available from 77,873 patients. Cancer incidence was 5.96% in the ARB treatment group versus 6.34% in the active control group. Pooling of effect estimates from the 11 studies yields an OR of 0.97 (95% CI 0.91, 1.03). The ONTARGET and VALUE study has the biggest influence in this analysis as they carry 34.9% and 33.7% of the overall weight correspondingly. The chi-square test resulted in a P-value of 0.03 and the I^2 statistics of 46% indicating remarkable heterogeneity between studies. The heterogeneity observed is likely due to methodological and clinical diversity of the ONTARGET and VALUE study.

Five RCTs compared ARB to ACEI and data were available from 42,403 patients. Cancer incidence was 5.23% in the ARB treatment group versus 5.26% in the ACEI treatment group. Combined effect estimates resulted in OR 1.06 (95% CI 0.97, 1.16). This result was mainly influenced by the ONTARGET study as it carries the most weight overall of 57%. Assessment of heterogeneity showed a chi-square P-

value of 0.96 and I^2 statistics is observed at 0% indicating no statistical difference between studies.

For comparison with ACEI and ARB combination, two RCTs were included with data available from 25,712 patients. Cancer incidence was 5.56% in the ARB treatment group versus 5.64% in the combination treatment group with OR 0.98 (95% CI 0.88, 1.10). The ONTARGET study was assigned the heaviest weight of 91.6% overall and eventually had a major influence in the direction of the combined OR. The chi-square test resulted in a P-value of 0.008 and the I^2 statistics of 86% suggesting evidence of statistically significant difference between studies. The observed heterogeneity observed is most likely due to the clinical diversity between the ONTARGET (CVD or T2DM patients with target organ damage) and VALIANT (heart failure patients post MI) study.

Three RCTs used CCB as one of their randomised treatment with data available from 21,051 patients. Cancer incidence was 6.61% in the ARB treatment group versus 7.74% in the CCB treatment group with OR 0.84 (95% CI 0.75, 0.93). This analysis was greatly influenced by the VALUE study which carries 96% of the overall weight. All the included RCTs have an OR less than 1 with 95% CI crossing 1 except the VALUE study. Assessment of heterogeneity showed a chi-square P-value of 0.89 and I^2 statistics is observed at 0% indicating no statistical difference between studies.

For placebo, data were available from 65,958 patients enrolled in 14 RCTs. Cancer incidence was 5.56% in the ARB treatment group versus 5.48% in the placebo group with OR 1.02 (95% CI 0.96, 1.09). The direction of the combined effect estimate was greatly driven by the NAVIGATOR and ACTIVE I study which was assigned 25.5% and 20.4% respectively. Assessment of heterogeneity showed a chi-square P-value of 0.43 and I^2 statistics is observed at 1%. The observed small heterogeneity is most probably due to the clinical diversity of the ACTIVE I (patients with AF) and TRANSCEND (patients with CVD or T2DM) study.

5.4.3.3 By population clinical settings

Figure 5-9 shows the meta-analysis of ARB by study population main clinical settings. Data for patients with underlying hypertension as the main clinical

setting were available from 40,494 enrolled in eleven RCTs. Cancer incidence was 6.52% in the ARB treatment group versus 7.06% in the control group. Combined effect estimates resulted in OR 0.92 (95% CI 0.86, 1.00). Majority of the studies' OR lies on the left side of the plot favouring ARB. The overall result was mainly influenced by the VALUE study which was assigned over 50% of the overall weight. Assessment of heterogeneity showed a chi-square P-value of 0.17 and I^2 statistics is observed at 29% indicating a moderate difference between studies. The heterogeneity observed is likely due to the clinical diversity of the VALUE (patients with high CVD risk) study.

Data for patients who were at high risk for CVD or with established CVD were available from 11 RCTs enrolling 111,375 patients. Cancer incidence was 5.88% in the ARB treatment group versus 6.05% in the control group. Combined effect estimates resulted in OR 0.99 (95% CI 0.94, 1.04). This analysis was mainly driven by the ONTARGET and VALUE study with an assigned weight of 24.9% and 24.1% respectively. The chi-square test resulted in a P-value of 0.04 and the I^2 statistics of 47% suggesting evidence of a substantial difference between studies. The observed heterogeneity observed is most likely due to methodological and clinical diversity of the ONTARGET (a three parallel arm study with a combination comparator arm) and VALUE (patients with high CVD risk) study.

Meanwhile, data for patients with AF were available from three RCTs with a total of 10,838 patients. Cancer incidence was 6.31% in the ARB treatment group versus 6.90% in the control group. Combined effect estimates resulted in OR 0.91 (95% CI 0.78, 1.06). This analysis was mainly driven by the ACTIVE I study which carries 98.4% of the overall weight. Heterogeneity assessment showed a chi-square P-value of 0.69 and the I^2 statistics of 0% indicating no statistical difference was present between these studies.

For patients with underlying T2DM, data were available from 4,411 patients enrolled in four RCTs. Cancer incidence was 2.43% in the ARB treatment group versus 2.80% in the control group with OR 0.90 (95% CI 0.62, 1.31). This analysis was mainly driven by the IDNT and NHS study as they carry the most weight overall (52% and 38.3% respectively). The chi-square test resulted in a P-value of 0.85 and the I^2 statistics of 0% signifying no statistical heterogeneity between studies.

Lastly, data for patients with underlying nephropathy or CKD were available from 3,122 patients enrolled in three RCTs. Cancer incidence was 2.30% in the ARB treatment group versus 3.27% in the control treatment group with OR 0.68 (95% CI 0.44, 1.06). The IDNT study has a major influence in this analysis with an assigned weight of 60.6%. The chi-square test resulted in a P-value of 0.29 and the I^2 statistics of 20% signifying minimal statistical heterogeneity between studies. The observed heterogeneity observed is most likely due to the methodological diversity of the OCTOPUS trial (a PROBE trial).

5.4.3.4 By mean age groups

Figure 5-10 shows the meta-analysis of ARB by study population mean age groups. For patients age 65 or older, data were available from 10 RCTs enrolling a total of 98,248 participants. Cancer incidence was 6.83% in the ARB treatment group versus 6.72% in the control group with OR 0.99 (95% CI 0.94-1.04). This analysis was mainly influenced by the ONTARGET and VALUE trial. The chi-square test resulted in a P-value of 0.01 and the I^2 statistics of 56% indicating a statistically significant difference was present between studies. The observed heterogeneity observed is most likely due to clinical diversity of the ONTARGET (a three parallel arm study with a combination comparator arm), VALUE (a CCB was used as a comparator) and TRANSCEND (patients with CVD or T2DM) trial.

Meanwhile, data for patients younger than 65 years were available from the 16 trials with 50,027 participants. Cancer incidence was 3.76% in the ARB treatment group versus 4.16% in the control group with OR 1.02 (95% CI 0.93-1.12). This analysis was mainly driven by the NAVIGATOR study which carries 47.8% of the overall weight. Heterogeneity assessment showed a chi-square P-value of 0.41 and the I^2 statistics of 4% indicating a minimal difference between studies. The observed heterogeneity observed is most likely due to clinical and methodological diversity of the CHARM Added (patients with background ACEI therapy) and OCTOPUS (homogenous patients with ESRD) trial.

5.4.3.5 By duration of follow-up

Figure 5-11 shows the meta-analysis of ARB by the mean duration of study follow-up. Ten RCTs were followed for three years or less with a total of 45,897 participants. Cancer incidence was 2.71% in the ARB treatment group versus 3.16%

in the control group with OR 0.95 (95% CI 0.85, 1.06). This analysis was mainly driven by the PRoFESS study which carries 50.4% of the overall weight. Heterogeneity assessment showed a chi-square P-value of 0.99 and the I^2 statistics of 0% indicating no statistical heterogeneity between studies.

The remaining 15 RCTs were followed-up for at least three years and data were available for 97,154 patients. Cancer incidence was 7.46% for ARB versus 7.40% for controls (OR 1.00, 95% CI 0.95-1.05). This analysis was mainly driven by the ONTARGET and VALUE study which carries 23% and 22.3% of the overall weight respectively. Heterogeneity assessment showed a chi-square P-value of 0.03 and the I^2 statistics of 45% indicating a statistically significant difference among studies. The observed heterogeneity observed is most likely due to clinical and methodological diversity of the VALUE (patients with high CVD risk) trial.

Table 5-2: Angiotensin receptor blockers and risk of cancer: Subgroup analyses

		No. of study	No. of participants	Cancer incidence (%)		OR (95% CI)	P-value	I^2 (%)
				ARB	Control			
Overall effect	FE model	25	148275	5.78	5.87	0.99(0.95, 1.04)	0.96	28
Subclass	Telmisartan	3	49690	6.33	5.32	1.07 (0.99, 1.16)	0.10	44
	Irbesartan	4	14890	6.56	7.34	0.91 (0.80, 1.03)	0.13	0
	Valsartan	6	46268	5.76	7.29	0.92 (0.85, 0.99)	0.02	29
	Candesartan	7	25172	4.08	3.78	1.08 (0.95, 1.23)	0.22	0
	Losartan	3	11361	6.15	5.63	1.09 (0.93, 1.28)	0.26	0
	Olmesartan	2	894	1.78	3.82	0.47 (0.20, 1.08)	0.07	30
Type of comparator	Active controls	11	77873	5.96	6.34	0.97 (0.91, 1.03)	0.26	49
	ACEI	5	42403	5.23	5.26	1.06 (0.97, 1.16)	0.19	0
	ARB+ACEI	2	25712	5.56	5.64	0.98 (0.88, 1.10)	0.76	86
	CCB	3	21051	6.61	7.74	0.84 (0.75, 0.93)	0.001	0
	Placebo	14	65958	5.56	5.48	1.02 (0.96, 1.09)	0.52	1
Clinical setting	Hypertension	11	40494	6.52	7.06	0.92 (0.86, 1.00)	0.05	29
	High risk CVD	11	111375	5.88	6.05	0.99 (0.94, 1.04)	0.62	47
	AF	3	10838	6.31	6.90	0.91 (0.78, 1.06)	0.22	0
	T2DM	4	4411	2.43	2.80	0.90 (0.62, 1.31)	0.57	0
	Nephropathy or CKD	3	3122	2.30	3.27	0.68 (0.44, 1.06)	0.09	20
Mean age	≥ 65 years	10	98248	6.83	6.72	0.99 (0.94, 1.04)	0.56	56
	< 65 years	16	50027	3.76	4.16	1.02 (0.93, 1.12)	0.62	4
Duration of follow-up	< 3 year	10	45897	2.71	3.16	0.95 (0.85, 1.06)	0.32	0
	≥ 3 years	15	97154	7.46	7.40	1.00 (0.95, 1.05)	0.93	45

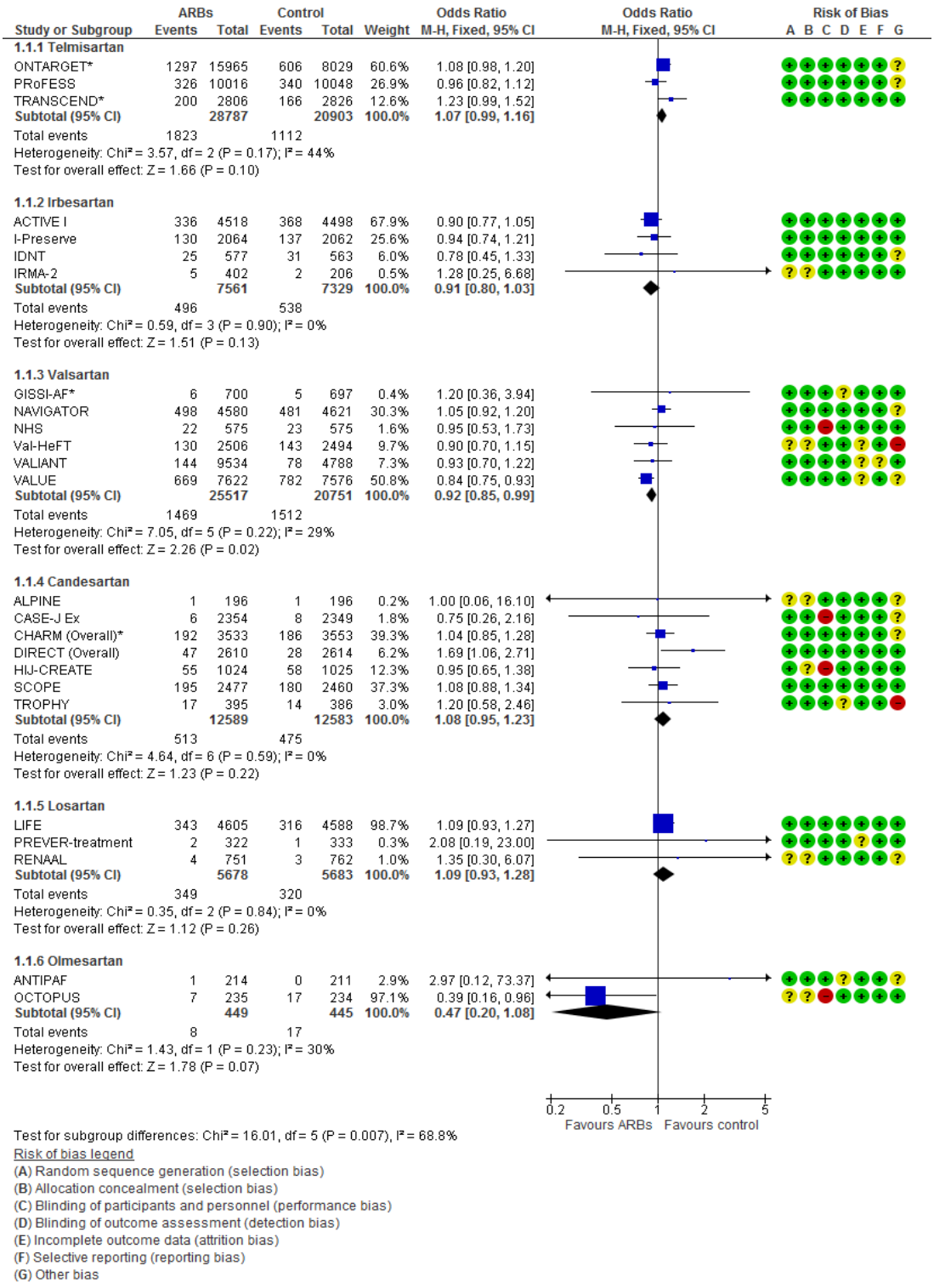


Figure 5-7: Forest plot of cancer incident by ARB subclasses [FE model].
1) Telmisartan; 2) Irbesartan; 3) Valsartan; 4) Candesartan; 5) Losartan; and 6) Olmesartan in 25 trials. The subtotal effect represents the pooled estimate of odds for incident cancers for each subclass. ** Included were patients with no history of cancer or active cancer at baseline.

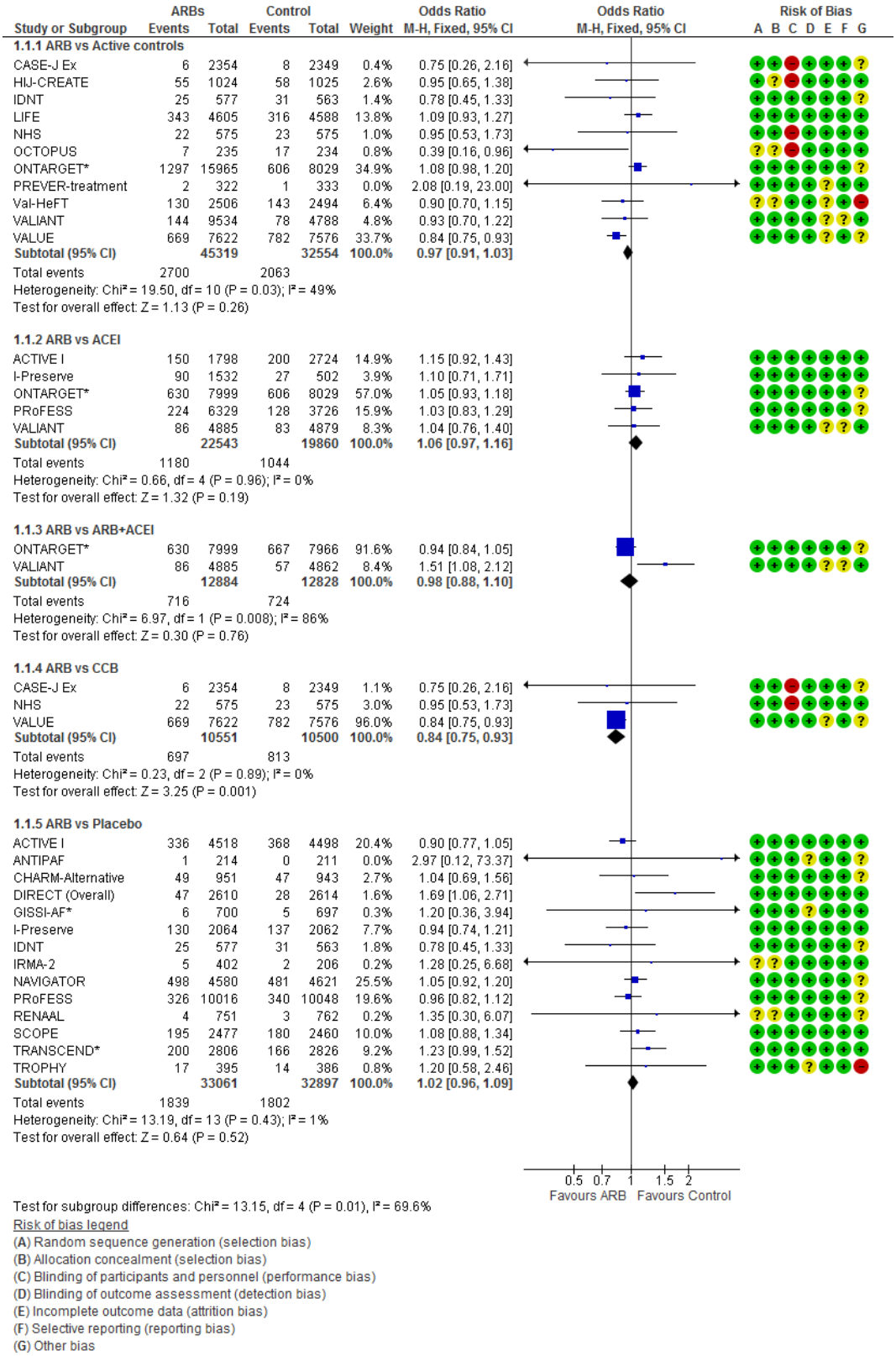


Figure 5-8: Forest plot of incident cancers by comparators [FE model].
1) Active controls; 2) ACEI; 3) ARB and ACEI combination; 4) CCB and 5) Placebo. The subtotal effect represents the pooled estimate of odds for incident cancers for each comparator. * Included were patients with no history of cancer or active cancer at baseline.

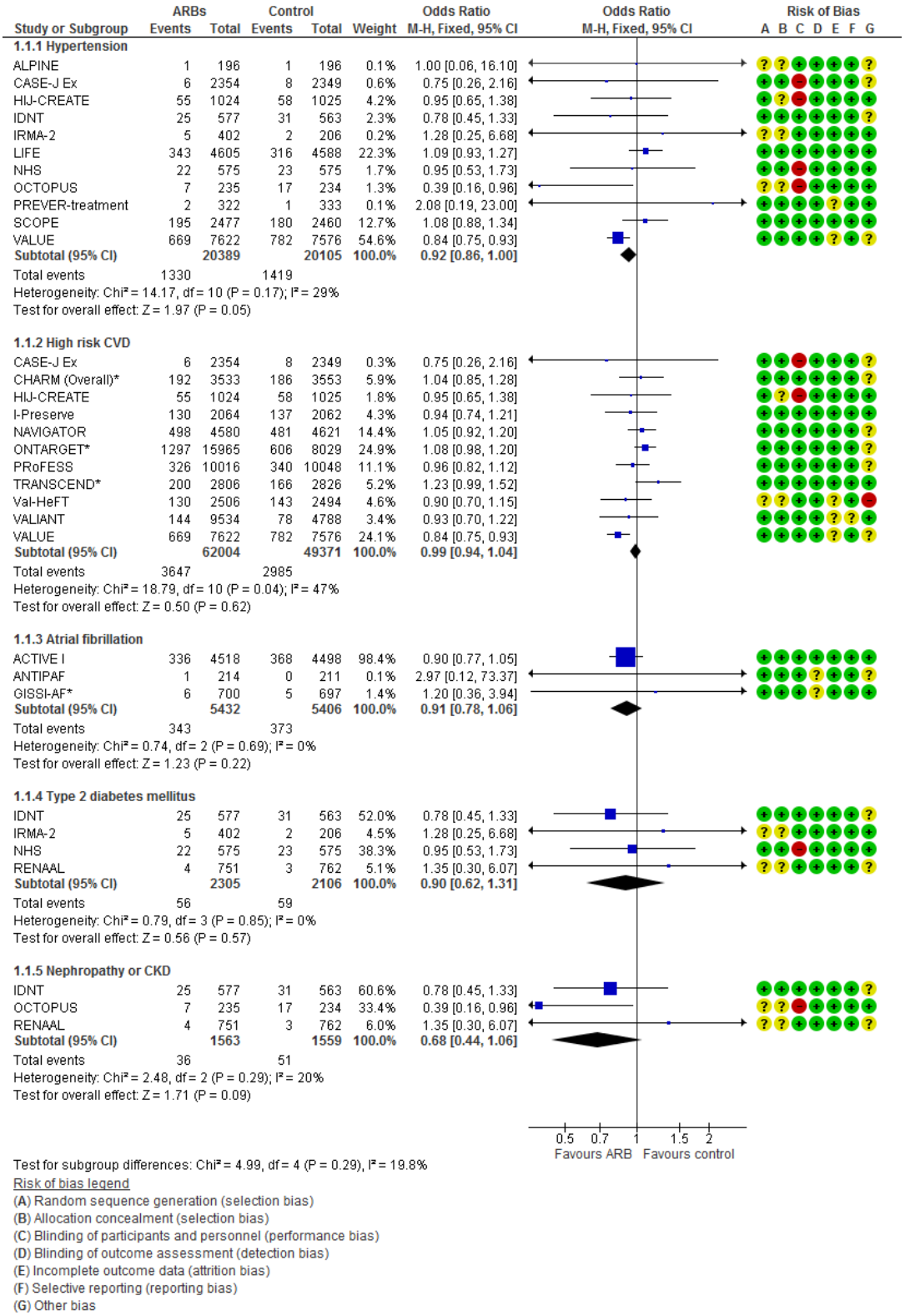


Figure 5-9: Forest plot of incident cancers population clinical setting [FE model].
1) Hypertension; 2) High risk or established CVD ; 3) Atrial fibrillation; 4) Type 2 diabetes mellitus; and 5) Nephropathy or CKD. The subtotal effect represents the pooled estimate of odds for incident cancers for each healthcare setting. * Included were patients with no history of cancer or active cancer at baseline.

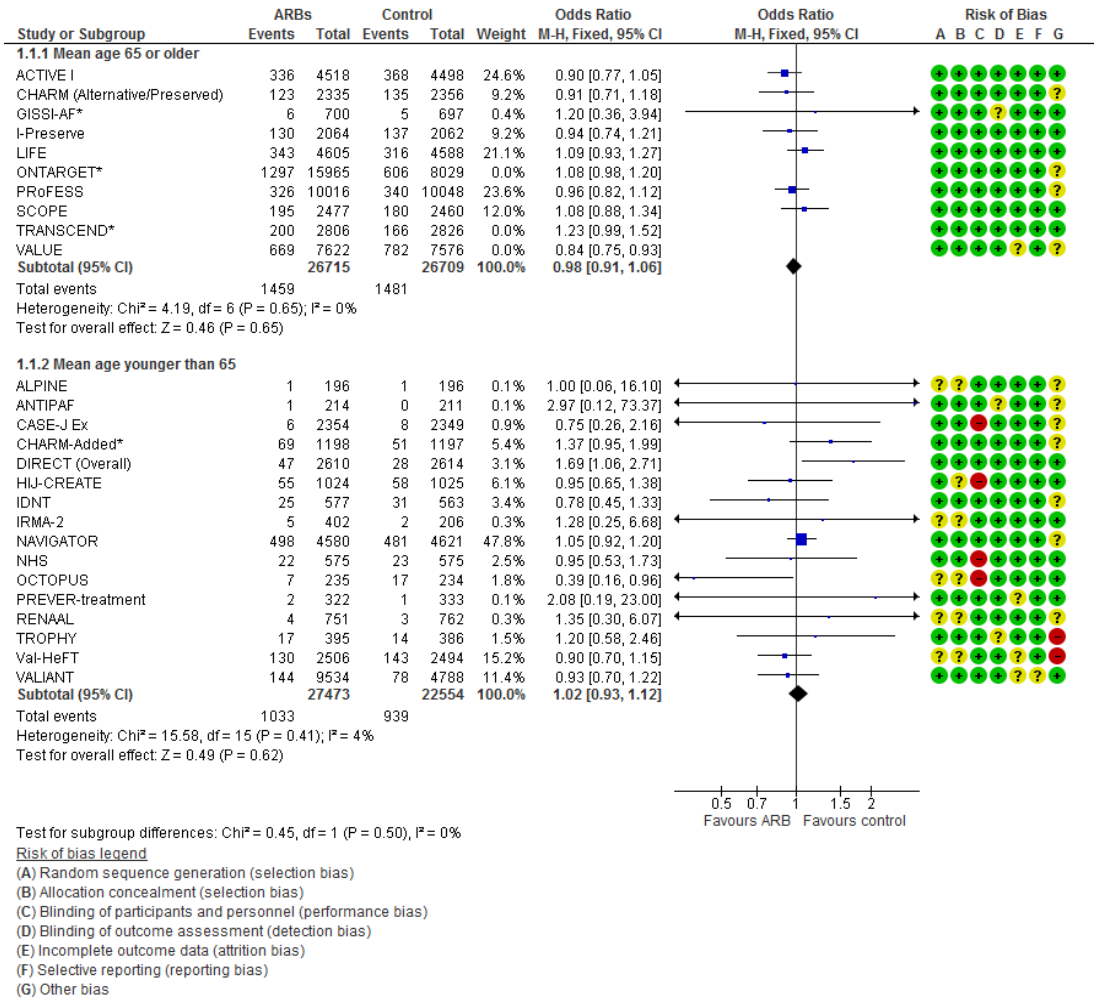


Figure 5-10: Forest plot of incident cancers by mean age [FE model].
1) ≥ 65 years; 2) < 65 years. The subtotal effect represents the pooled estimate of odds for incident cancers for each criterion. * Included were patients with no history of cancer or active cancer at baseline.

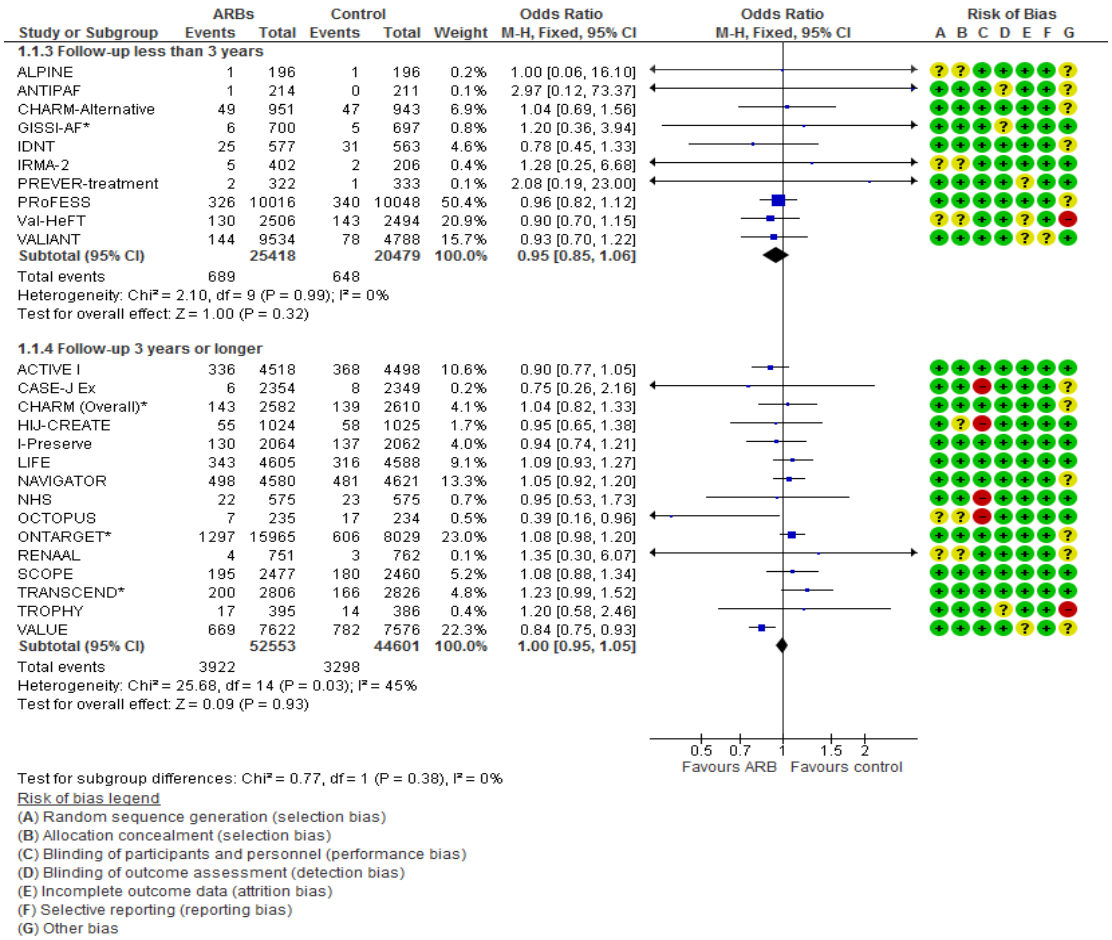


Figure 5-11 Forest plot of cancer incidence by study mean duration of follow-up [FE model]. 1) Follow-up < 3 years; 2) Follow-up ≥ 3 years; 3) Follow-up ≥ 5 years. The subtotal effect represents the pooled estimate of odds for cancer incidence for each criterion. * Included were patients with no history of cancer or active cancer at baseline *

5.5 ARB and risk of cancer-related death

Overall, 25 RCTs were included for comparison between ARB and other antihypertensive drug class for risk of cancer-related death. In total, data from 151,855 (98.23%) patients out of 154,588 patients were available for the analysis of ARB and risk of cancer mortality.

Figure 5-12 shows the meta-analysis of ARB and cancer-related mortality in an FE model. According to the assigned treatment arm, cancer-related death was 1.79% in the ARB group versus 1.71% in the non-ARB group. This analysis was mainly influenced by the ONTARGET and VALUE study as they carry the most weight overall (19.4% and 13.1% respectively). The remaining studies were assigned less

than 10% of the overall weight individually. Distribution of studies with OR more or less than 1 is fairly equal. One study, CHARM (Overall), yields an OR 1.47 with 95% CI ranged from1.05 to 2.05. Otherwise, the 95% CI for the rest of the studies includes 1 indicating a lack of statistical significance at the study level. Combination of the studies effect estimates yields an OR of 1.02 with 95% CI 0.94-1.10 (P = 0.59). From the forest plot, the summary effect is represented by a narrow diamond that overlaps the line of no effect suggesting a lack of statistical significance at the meta-analysis level.

Figure 5-13 shows the meta-analysis of ARB and cancer-related mortality in a RE model. In this analysis, the ONTARGET study was assigned an additional 0.5% (19.9%) whereas the weight assigned to the VALUE study was reduced by 0.2% (12.9%). Nevertheless, these two studies remain the biggest influence in the direction of this meta-analysis. The combined OR in this statistical model is comparable to the FE model analysis with OR 1.02 (95% CI 0.94-1.10).

Assessment of heterogeneity in both FE and RE model showed a chi-square test P-value of 0.94 and I^2 statistics of 0%. These values indicate no evidence of statistically significant heterogeneity between studies.

Figure A-2 **(**Appendix Page 324**)** shows the distribution of the 25 studies in a funnel plot. The dispersion of studies appears fairly symmetrical on both sides of the plot with no outlier observed.

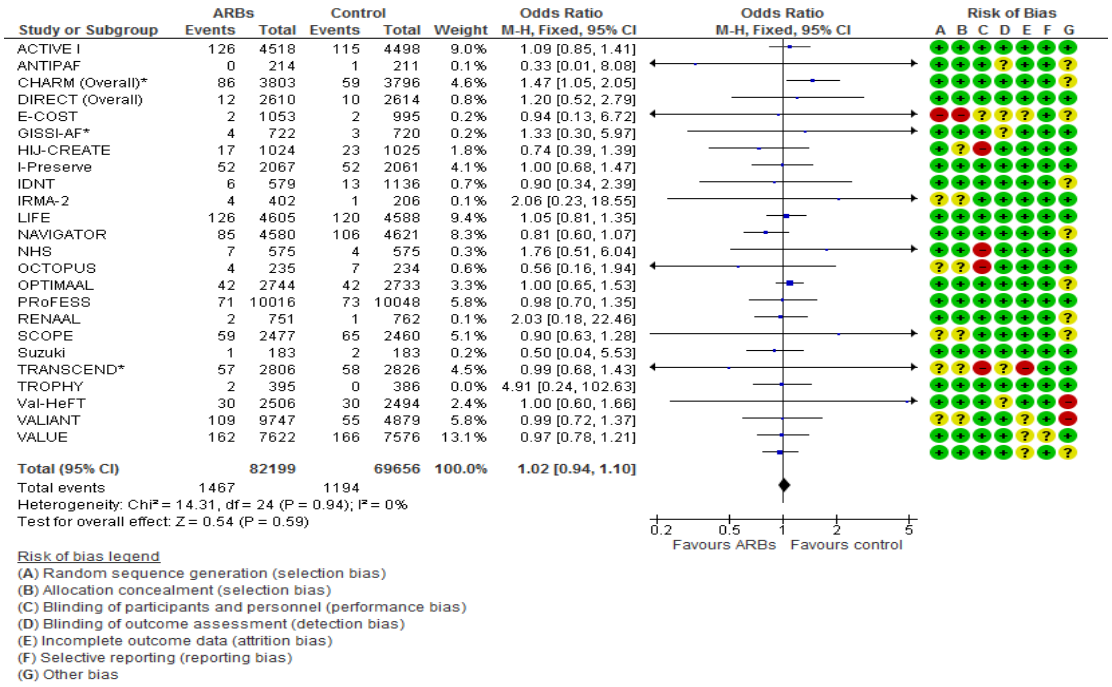


Figure 5-12: Forest plot of cancer-related deaths by ARB vs non-ARB controls [FE model]. Odds ratios and 95% confidence interval, overall and in 25 trials. The overall effect represents the pooled estimate of odds for cancer-related death. * Included were patients with no history of cancer or active cancer at baseline

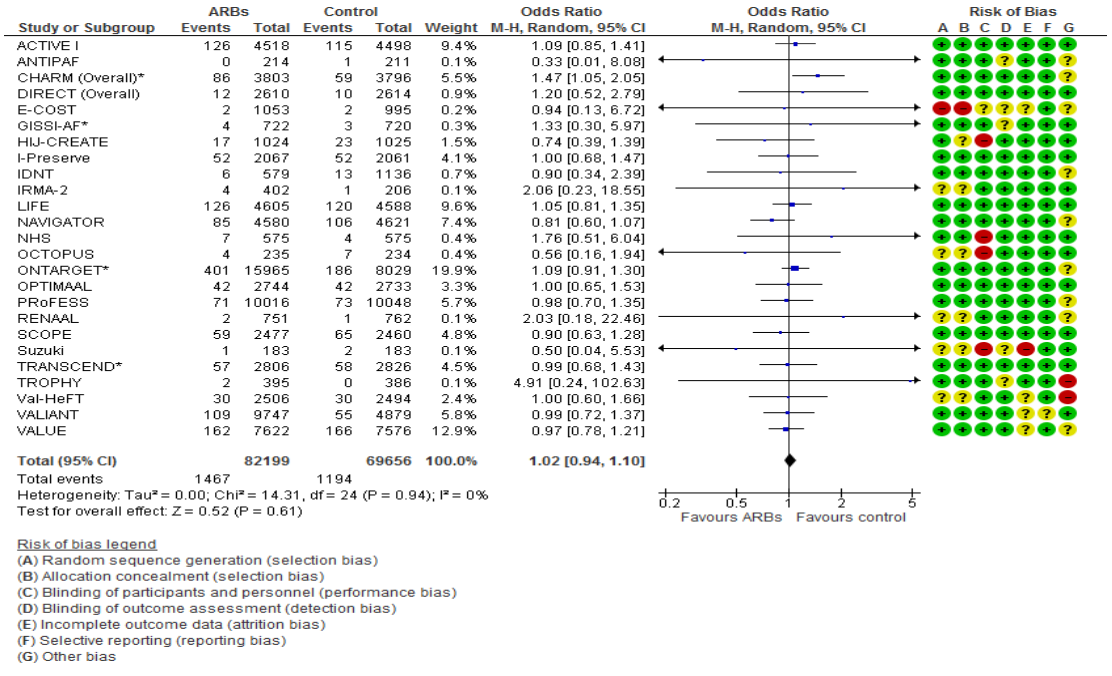


Figure 5-13: Forest plot of cancer-related deaths by ARB vs non-ARB controls [RE model]. Odds ratios, and 95% confidence interval, overall and in 25 trials The overall effect represents the pooled estimate of odds for cancer-related death. * Included were patients with no history of cancer or active cancer at baseline

5.6 Valsartan and risk of cancer

Figure 5-14 shows the meta-analysis of valsartan trials and risk of cancer. Altogether, six valsartan trials enrolling 41,947 participants with an average follow-up of 2.9 years (range 1-4.2) were included in the overall cancer risk meta-analysis. In this analysis, only the ARB monotherapy versus ACEI monotherapy arm in the VALIANT study was considered. Cancer incidence was 6.23% in the valsartan treatment group versus 6.66% in the control group. Three of the studies have OR less than 1 ranging from 0.85 to 0.95 whereas two studies have an OR more than 1. With the exception of the VALUE trial, the 95% CI for all the studies includes 1. The direction of this analysis was mainly driven by the VALUE study as it was assigned 51.2% of the overall weight. Pooling of OR from all the studies yields an OR of 0.93 (95% CI 0.86-1.00) and a P-value of 0.07. Heterogeneity assessment showed a chi-square P-value of 0.23 and the I^2 statistics of 28% indicating a minimal difference between studies. The observed heterogeneity observed is most likely due to the methodological diversity of the NAVIGATOR trial (the only study implementing factorial design in this meta-analysis). See Section 5.4.3.1, Figure 5-7 for analysis incorporating the ARB and ACEI combination arm into the ARB monotherapy arm in the VALIANT study.

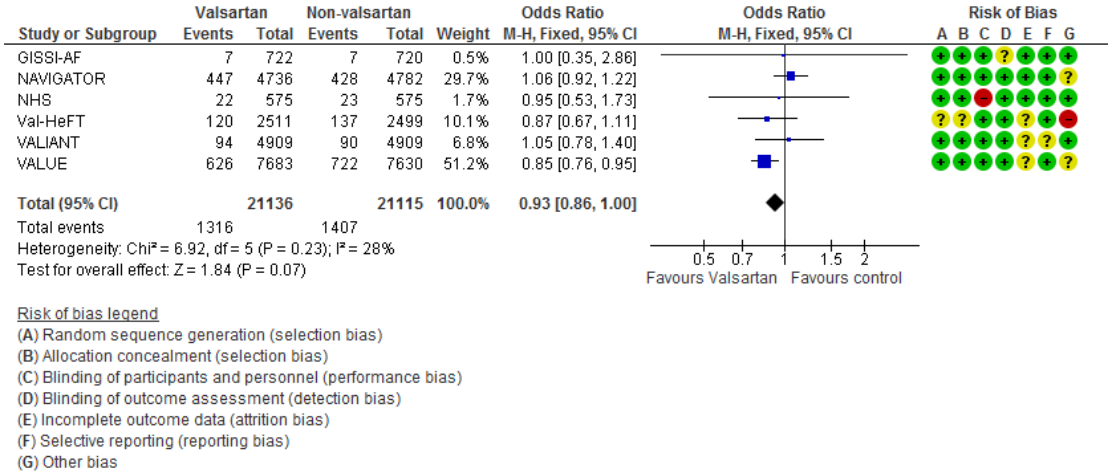


Figure 5-14: Forest plot of incident cancers by valsartan versus non-ARB controls [FE model].
Odds ratios and 95% confidence interval, overall and in six trials. The overall effect represents the pooled estimate of odds for incident cancers.

5.7 Valsartan and risk of specific cancer

The four RCTS with individual-patient data analysed included 44,544 patients of which 17,328 were assigned to valsartan monotherapy and 7,369 to combined valsartan and ACEI therapy.

5.7.1 Lung cancer

Figure 5-15 shows the meta-analysis of valsartan trials and lung cancer risk. Lung cancer cases were 0.61% in the valsartan group versus 0.95% in the control group. This analysis was mainly influenced by the VALUE and NAVIGATOR study as they carried 45.5% and 29.9% of the overall weight respectively. Three of the studies lie on the left side of the forest plot favouring valsartan. The 95% CI for two of the studies (VALIANT and VALUE) did not cross the line of no effect suggesting statistical significance at the study level. Combined effect estimates yield an OR of 0.73 (95% CI 0.59-0.90) with P-value of 0.004. The marginally wide diamond representing summary effect lies on the right side of the forest plot indicating significance at the meta-analysis level. Heterogeneity assessment showed a chi-square P-value of 0.17 and the I^2 statistics of 41% indicating a moderate difference between studies. The observed heterogeneity observed is most likely due to the clinical diversity of the Val-HeFT trial (over 90% of participants in both treatment and control arm received ACEI therapy).

5.7.2 Breast cancer

Data were available from 16,928 female participants across all four RCTs. **Figure 5-16** shows the meta-analysis of valsartan trials and breast cancer risk. Breast cancer cases were 1.33% in the valsartan group versus 1.52% in the control group. This analysis was mainly influenced by the VALUE and NAVIGATOR study as they carried 51.7% and 37.2% of the overall weight respectively. The 95% CI for all of the studies crosses the line of no effect suggesting a lack of statistical significance at the study level. Combined effect estimates yield an OR of 1.02 (95% CI 0.79-1.32). The marginally wide diamond representing summary effect lies on the line of no effect indicating lack of significance at the meta-analysis level. Heterogeneity assessment showed a chi-square P-value of 0.56 and the I^2 statistics of 0% suggesting no statistical difference between studies.

5.7.3 Prostate cancer

Data were available from 27,577 male participants across all four RCTs**. Figure 5-17** shows the meta-analysis of valsartan trials and prostate cancer risk. Prostate cancer cases were 1.64% in the valsartan group versus 2.04% in the control group. This analysis was mainly influenced by the VALUE and NAVIGATOR study as they carried 54.5% and 29.8% of the overall weight respectively. The 95% CI for all of the studies crosses the line of no effect suggesting a lack of statistical significance at the study level. Combined effect estimates yield an OR of 0.99 (95% CI 0.83-1.18). The narrow diamond representing summary OR lies marginally on the left of the line of no effect indicating lack of significance at the meta-analysis level. Heterogeneity assessment showed a chi-square P-value of 0.18 and the I^2 statistics of 39% suggesting a moderate difference between studies. The observed heterogeneity observed is most likely due to the clinical diversity of the Val-HeFT trial (over 90% of participants in both treatment and control arm received ACEI therapy.

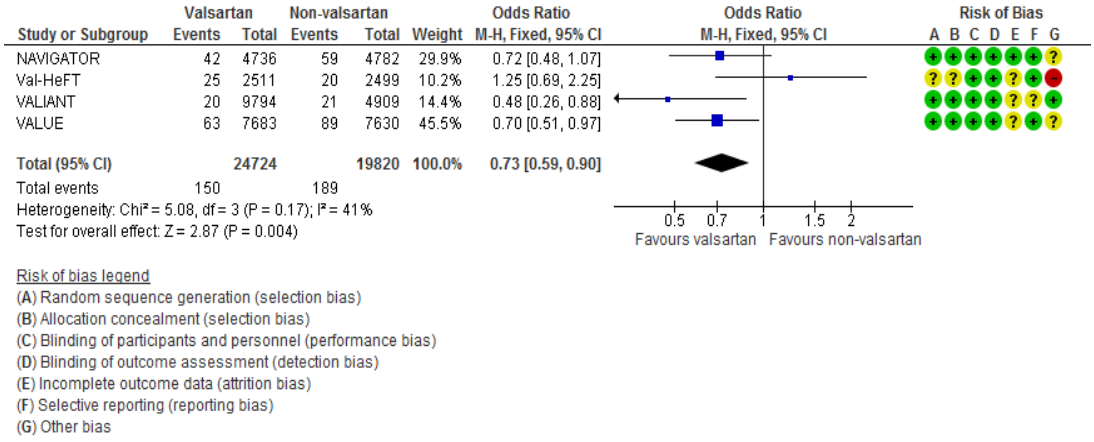


Figure 5-15: Forest plot of lung cancer incidence by valsartan vs. controls, overall and in four trials [FE model].
The overall effect represents the pooled estimate of odds for lung cancer incidence.

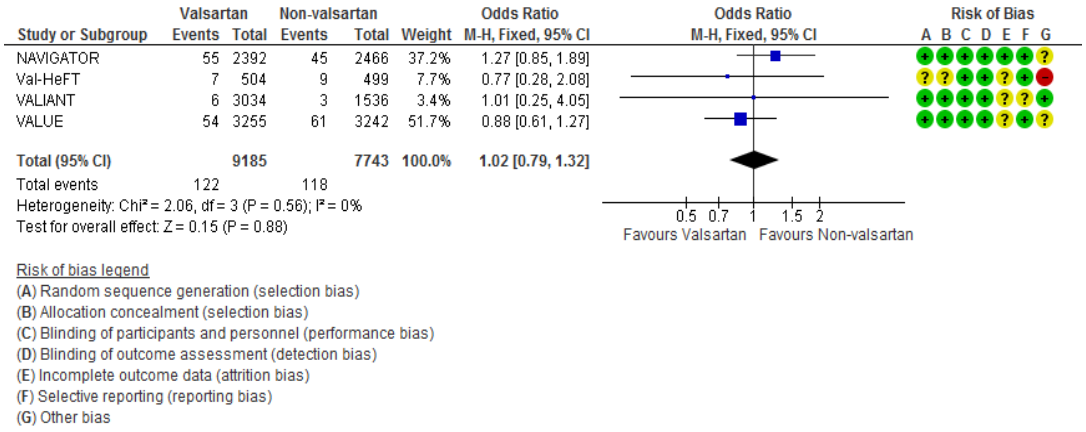


Figure 5-16 Forest plot of breast cancer incidence by valsartan vs. controls, overall and in four valsartan trials [FE model]
The overall effect represents the pooled estimate of odds for breast cancer incidence.

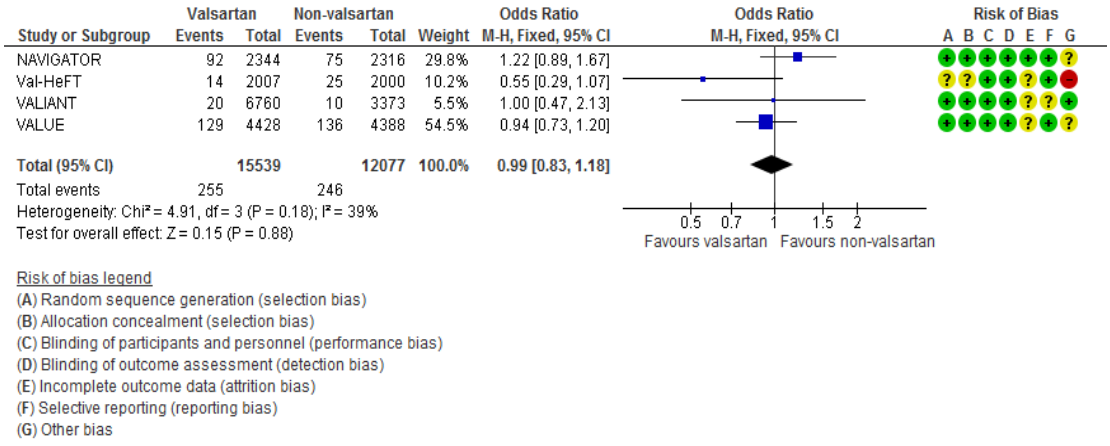


Figure 5-17 Forest plot of prostate cancer incidence by valsartan vs. controls, overall and in four valsartan trials [FE model].
The overall effect represents the pooled estimate of odds for prostate cancer incidence.

5.7.4 Valsartan trials and treatment comparison

The results of the comparisons described in the **Methods Section 5.2.2** are summarised in **Table 5-3** (single trial comparison) and **Table 5-4** (combined trial comparisons).

Table 5-3 shows treatment comparisons in individual valsartan trials for risk of any or certain type of common cancers including lung, breast, and prostate

cancer. For risk of any cancer, two trials have shown an OR of less than 1 with 95% CI excluding 1. The VALUE study compared valsartan to CCB and the measure of association has shown an OR of 0.85 (95% CI 0.76, 0.95). Meanwhile, the VALIANT study compared combined valsartan and ACEI therapy ("more intense) to ACEI monotherapy or either RAS blocker as monotherapy ("less intense"). The measure of association showed an OR of 0.68 (95% CI 0.49, 0.94) and OR of 0.66 (95% CI 0.49, 0.89) for the former and latter respectively. Likewise for lung cancer, the VALUE and VALIANT study have demonstrated statistical significance at study level with OR 0.70 (95%CI 0.51, 0.97) and OR 0.19 (95% CI 0.07, 0.56) respectively. The VALIANT study also showed an OR of less than 1 for "more intense" versus "less intense" therapy (OR 0.22, 95% CI 0.08, 0.61) for risk of lung cancer. Although most of the trials have shown a small OR for risk of any or certain type of cancers, they have a wide 955 CI spanning the null value of 1.

Table 5-4 showed an analysis of cancer in combined trials with a common comparator. A noteworthy association has been observed with the risk of any or lung cancer in certain trial combination. For non-RAS blocker comparator, combined estimates from the NAVIGATOR and VALUE trial showed a notable result for risk of lung cancer with OR 0.71 (95% CI 0.55, 0.91). Risk of any cancer was not reported due to evidence of heterogeneity. For comparison between ARB plus ACEI combination and ACEI monotherapy, the combined estimate from the Val-HeFT and VALIANT study showed an OR 0.79 (95% CI 0.65, 0.96) for risk of any cancer. The risk of lung cancer was not reported due to evidence of heterogeneity. Similarly, for "more intense" versus "less intense" comparison, the combined estimate from the Val-HeFT and VALIANT showed analogous association with an OR of 0.77 (95% CI 0.64, 0.93) for risk of any cancer. In addition, comparison with non-RAS blockers for risk of lung cancer was in favour of valsartan with OR 0.71 (0.56, 0.90). The common estimates for risk of breast and prostate cancer showed mixed direction with fairly wide 95% CI across all combined analyses.

Table 5-3: Number of cancers (any, lung, breast, prostate) in major valsartan trials.
Odds ratios (95% confidence intervals) for treatment comparisons

Comparison (for numbering, see methods)	Any cancer		Lung cancer		Breast cancer		Prostate cancer	
	A	B	A	B	A	B	A	B
1.Valsartan (A) vs. placebo (B)								
NAVIGATOR	447 1.06 (0.92, 1.22)	428	42 0.72 (0.48, 1.07)	59	55 1.27 (0.85, 1.89)	45	92 1.22 (0.89, 1.67)	75
2. Valsartan (A) vs. CCB (B)								
VALUE	626 0.85 (0.76, 0.95)	722	63 0.70 (0.51, 0.97)	89	54 0.88 (0.61, 1.27)	61	129 0.94 (0.73, 1.20)	136
4. Valsartan + ACEI (A) vs. ACEi (B)								
Val-HeFT	120 0.87 (0.67, 1.11)	137	25 1.25 (0.69, 2.25)	20	7 0.77 (0.28, 2.08)	9	14 0.55 (0.29, 1.07)	25
VALIANT	61 0.68 (0.49, 0.94)	90	4 0.19 (0.07, 0.56)	21	1 0.34 (0.04, 3.30)	3	8 0.79 (0.31, 2.02)	10
5. Valsartan (A) vs ACEi (B) VALIANT	94 1.05 (0.78, 1.40)	90	16 0.76 (0.40, 1.46)	21	5 1.66 (0.40, 6.96)	3	12 1.20 (0.52, 2.79)	10
6. Valsartan + ACEI (A) vs ACEI or ARB monotherapy(B)								
Val-HeFT	120 1.05 (0.78, 1.40)	137	25 0.76 (0.40, 1.46)	20	7 1.66 (0.40, 6.96)	9	14 0.55 (0.29, 1.07)	25
VALIANT	61 0.66 (0.49, 0.89)	184	4 0.22 (0.08, 0.61)	37	1 0.26 (0.03, 2.06)	8	8 0.72 (0.32, 1.62)	22

Table 5-4 Analyses of cancer in the combined trial

Comparison (for numbering, see methods)	Breslow-Day	P value	Combined OR (95% CI)
3. Valsartan monotherapy vs non-RAS blocker comparator			
NAVIGATOR + VALUE			
Any cancer	5.97	0.01	NR
Lung cancer	0.007	0.93	0.71 (0.55, 0.91)
Breast cancer	1.73	0.19	1.04 (0.08, 1.36)
Prostate cancer	1.71	0.19	1.04 (0.86, 1.26)
4. Valsartan + ACEi vs ACEi			
Val-HeFT + VALIANT			
Any cancer	1.36	0.24	0.79 (0.65, 0.96)
Lung cancer	10.27	0.001	NR
Breast cancer	0.42	0.52	0.66 (0.27, 1.62)
Prostate cancer	0.58	0.54	0.62 (0.37, 1.06)
6. Valsartan + ACEi vs ACEi or ARB monotherapy			
Val-HeFT + VALIANT			
Any cancer	1.86	0.17	0.77 (0.64, 0.93)
Lung cancer	9.44	0.002	NR
Breast cancer	0.92	0.34	0.58 (0.24, 1.38)
Prostate cancer	0.24	0.62	0.62 (0.37, 1.03)
7. Valsartan monotherapy vs. any non-ARB comparator			
NAVIGATOR, VALUE + VALIANT			
Any cancer	6.57	0.04	0.94 (0.86, 1.02)
Lung cancer	0.05	0.98	0.71 (0.56, 0.90)
Breast cancer	2.13	0.34	1.06 (0.81, 1.38)
Prostate cancer	1.82	0.40	1.05 (0.87, 1.26)

5.8 Discussion

As demonstrated in the current meta-analysis, there is no evidence to suggest that the use of ARB as a class increased the risk of either cancer incidence or cancer-related mortality. Fixed effect and random effects model evaluated relatively agree on the risk of cancer incidence with OR 0.99 (95% CI 0.95-1.04) and OR 1.00 (95% CI 0.94-1.06) correspondingly. The consistencies of summary estimates, narrow CI, and minimal heterogeneity between studies observed validates the present study hypothesis that ARB does not influence the risk of any cancer overall. Furthermore, sensitivity analyses assessing study size, methodological quality, and incorporation of patients with baseline cancer all showed a consistent association with the primary meta-analysis. Similarly, no significant association was observed between ARB use and risk of cancer-related death.

Evaluation of different ARB subtypes in a subgroup analysis has shown that valsartan has a significantly lower risk of cancer incidence (with OR 0.92 (95% CI 0.85, 0.99; P = 0.02). A comparable association was reported by Teo (2011) in a meta-analysis of 15 ARB trials. The author reported a significantly lower risk of cancer for patients randomised to valsartan in four RCTs with OR 0.92 (95% CI 0.85–0.99). Moreover, the assessment of individual patient data meta-analysis from the four major valsartan trials showed a significantly lower risk of lung cancer in those assigned to valsartan. Several studies have also reported evidence of lower lung cancer risk associated with ARB use. A systematic review and meta-analysis of eight observational studies enrolling 433,1054 participants showed decreased lung cancer risk associated with ARB with OR 0.81 (95% CI 0.69-0.54) (Zhang et al., 2015). Likewise, a recent study by Shen et al. (2016) has also found a similar relationship between RAS blockers including ARB and lung cancer in a meta-analysis of six observational studies (OR 0.85, 95% CI 0.75-0.87) and nine RCTs (OR 0.88, 95% CI 0.79-0.99). However, the exact risk of lung cancer with ARB was not seen in this review. A recent cohort study of over one million participants using data from the American Veteran Affairs (VA) register reported a hazard ratio (HR) 0.74 (95% CI 0.67-0.83, P< 0.0001) for lung cancer in patients taking ARB compared to non-ARB (Rao et al., 2013).

Conversely, there are studies that have demonstrated evidence of ARB associated with an increased risk of lung cancer. In a meta-analysis of nine RCTs enrolling 94,570 participants, Sipahi et al. (2010) reported an excess risk for lung cancer in patients randomised to ARB for at least three years with a relative-risk (RR) estimate of 1.25 (P-value =0.01). Although statistically significant, the CI was wide ranging from 1.05 to 1.49 suggesting high dispersion hence the conclusion is less certain. Moreover, most of the patients in the meta-analysis received telmisartan as the study drug. Nonetheless, given the limited data, the author also failed to assess the risk of cancer associated with specific ARBs. In another study, the Collaborative Transplant Study (CTS) which prospectively collects data on solid organ transplants reported increased risk of lung cancer in renal transplant recipients particularly in a subpopulation with history of smoking who received ACEI and ARB combinations (SIR 7.10, 95% CI 3.27-15.4, P-value<0.001) (Opelz and Döhler, 2011). Though, any cancer risk is readily observed in transplant recipients compared to the general population due to the immunosuppressive therapy they receive to prevent transplant rejection. Furthermore, the CTS observation is only applicable to ARB and ACEI combination therapy as they could not draw a particular influence of either class of agent. An experimental study demonstrated that apoptosis was induced in the alveolar epithelial cell of human lung carcinoma cell line and rat model by administration of purified angiotensin II (Papp et al., 2002). Administration of AT1 selective antagonist blocked angiotensin-induced apoptosis. This finding suggests the role of ARB in lung carcinogenesis as an evasion of apoptosis is one of the hallmarks of cancer.

The subgroup analyses also found no difference in the risk of cancer incidence between ARB and other antihypertensive drug classes or placebo except CCB. One subgroup analysis indicated that ARB has a significant cancer protective effect compared to CCB. A comparable observation is also seen in a single trial VALUE (**Table 5-3)**. The risk of any or lung cancer was significantly lower in those receiving ARB versus CCB. The difference in risk could possibly be explained by the different pathways in which these drugs are involved. The pro-tumorigenic effects of the RAS pathway are prevented by blockade of the AT1 receptor by ARB leading to decreased VEGF and other pro-angiogenic factors expression hence impairing angiogenesis and cellular proliferation (Chen et al., 2013). Meanwhile, the disruption of cellular apoptosis as a result of decreased or increased

intracellular calcium induced by CCB leading to an increased potential for tumour growth has been hypothesized (Mason, 1999). Nonetheless, this observation should be regarded as hypothesis-generating only and not as a conclusion to a test. As ARB and CCB are not primarily prescribed for cancer prevention and the trial (VALUE) was not powered for this endpoint, it is difficult to conclude definitively that valsartan is protective or amlodipine is harmful due to the study design with two parallel arms. Including a placebo control arm would allow the investigators to capture the value of non-specific therapeutic or harmful effects that are common to all antihypertensive drugs. Therefore, most analyses including trials without a placebo comparator presented in this thesis may not be able to describe the precise risk of cancer. Both classes of drugs have been recommended as first choice therapy for the treatment of hypertension by established clinical guidelines. A meta-analysis of nine RCTs evaluating ARB versus CCB in total 25,084 participants has shown that CCB is superior to ARB in reducing the incidence of stroke and MI overall (Wu et al., 2014). Nevertheless, the excellent safety and tolerability profile of ARB has improved the adherence to antihypertensive therapy and enhanced our ability to manage hypertension in those patients with sensitivities to other antihypertensive drug classes, including the ACE inhibitors.

In a meta-analysis of two RCTs, Bangalore et al. (2011) reported an increased risk with ARB and ACEI combination therapy versus control (OR 1.14, 95% CI 1.04-1.24). The authors had also conducted a trial sequential analysis which suggested firm evidence of at least 10% increase risk for cancer with combined RAS blockers. Around the same time, a meta-analysis of seven RCTs found no significant association between combined ARB/ACEI therapy versus ACEI monotherapy with OR 1.01 (95% CI 0.94-1.10) (Teo, 2011). On the contrary, this review has observed a significantly lower risk of any cancer and lung cancer in particular with combined RAS blockers (“more intense”) versus monotherapy (“less intense”) (Table 5-4, Comparison 4). However, this observation is only limited to valsartan. This finding is consistent with experimental evidence that angiotensin II may act as an oncogenic agent (George et al., 2010). Though, the use of multiple RAS blockers concurrently is no longer recommended in clinical practice (NICE, 2011). Dual ARB and ACEI therapy showed no mortality benefit and did demonstrate increased non-fatal adverse events. The ONTARGET study has shown that despite reducing progression of proteinuria, combined RAS blockers increased composite primary

renal outcome including dialysis, doubling of creatinine, and death (HR 1.09, 95% CI 1.09-1.84) (Mann et al., 2008). Whereas in the Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Endpoints (ALTITUTDE) trial, aliskiren versus placebo was added to a background therapy of either ACEI or ARB (Parving et al., 2012). This trial was prematurely terminated due to lack of benefit and increased risk of hyperkalaemia and hypotension.

Findings from this review are different than Sipahi et al. (2010) and are in-line with recent meta-analyses that have reported comparable results (Bangalore et al., 2011, Teo, 2011, Shen et al., 2016, Zhao et al., 2016). In spite of that, the search and analyses of the current study are more comprehensive as RCTs published after 2010 were included with the most recent data available from the PREVER-Treatment study. Also, individual-patient level data used in the ARB Trialists Collaboration (ATC) (Teo, 2011) for ACTIVE 1, ONTARGET, TRANSCEND, and PRoFESS were incorporated in the current meta-analyses. Cancer data for the ACTIVE I and DIRECT-Overall study were only available from the ATC meta-analysis. Furthermore, the data from JIKEI Heart Study (Mochizuki et al., 2007) and KYOTO Heart Study (Sawada et al., 2009) used in the Bangalore et al. (2011) meta-analysis were excluded because these studies were retracted from publication due to unreliable data and ethical misconduct. Thus, the result of the current meta-analysis is more precise in providing evidence for ARB and risk of cancer overall.

The RAS pathway was extensively studied for its role in haemodynamic regulation, hence the pathogenesis of hypertension. Discussion of the RAS pathway is commonly centred on angiotensin II and its receptors. Results of several experimental studies have recognised angiotensin II as a potent mitogen where it is involved in cellular proliferation (Stoll et al., 1995, Arafat et al., 2007), angiogenesis (Herr et al., 2008), inflammation and tissue remodelling (Suzuki et al., 2003). Angiotensin II signalling through an angiotensin-type-I receptor (AT-1R) facilitates cellular proliferation and angiogenesis while stimulation of angiotensin-type-II receptor (AT-2R) has anti-proliferative properties (George et al., 2010). Overexpression of AT-1R has been demonstrated in in-vitro studies of breast carcinoma cells (Herr et al., 2008, Rhodes et al., 2009), pancreatic adenocarcinoma cells (Arafat et al., 2007), hepatocarcinoma cells (Yoshiji et al., 2001), and renal cell carcinoma (Dolley-Hitze et al., 2010). Despite its anti-

proliferative effect, the AT-2R has been found to be overexpressed in several cancer-types such as astrocytomas (Arrieta et al., 2008) and lung tumours (Tamura et al., 2008). Thus, blockade of the RAS pathway suggests possible prevention and attenuation of cancer progression.

5.8.1 Strengths and limitations

In comparison to the previous meta-analysis, the search for this review was extended to include trials published after 2010 rendering this study to be the most comprehensive and largest meta-analysis of ARB and risk of overall cancer. This study has also incorporated all data publicly available to date and only RCTs were included ensuring minimal selection bias and effects of confounding variables. Furthermore, the utilization of individual-patient data from four major valsartan studies provided a more precise OR for the risk of lung cancer.

There are limitations to this study. Firstly, the majority of the RCTs were not designed to detect incident cancer and/ or cancer-related mortality a primary end-point. Apart from cancer-deaths, diagnosis of malignancy was variably adjudicated across the different studies. Second, only aggregate data reported as raw number (n/N) were available for most of the studies. Due to unavailability of individual-patient data, the time-to-event analysis was not conducted in this review. Availability of such information could better estimate the association of drug class studied to the occurrence of site-specific and overall cancer. Lastly, most of the studies were followed for an average short period of time ranging from one to five years. As cancer development is a slow process, the results could only reflect late-detected cancers.

5.8.2 Conclusion

In conclusion, ARB as an antihypertensive drug class does not influence the risk of cancer or cancer-related death overall. Valsartan, as a subclass, potentially have a protective effect against cancer, particularly lung cancer. Future studies investigating the prospect of valsartan use as a cancer-prevention in a high-risk population and as a targeted cancer therapy is warranted.

6 Association between calcium channel blockers (CCB) and risks of cancer

6.1 Introduction

The CCB, a drug class, exerts its effects through interaction with the voltage-gated calcium channels (VGCC) in the heart and in smooth muscle of the peripheral arterioles and arteries. The pharmacological and electrophysiological diversity of calcium channels arises primarily from the existence of multiple α1 subunits which determines the characteristics for the L-, P/Q-, N-, R-, and T-type VGCC (Bean and McDonough, 2001, Catterall et al., 2005, Ozawa et al., 2006). The CCBs used in CVD, namely hypertension, CHD, arrhythmias, and left ventricular dysfunction, inhibits mainly the L-type VGCC, although some of the CCB may possess other VGCC subtype blocking activity. Based on their chemical structures, CCBs are categorised into three subclasses: DHP, phenylalkylamines, and benzothiazepines. The phenylalkylamines and benzothiazepines CCBs are also collectively known as non-dihydropyridine CCB. Each of the CCB subclasses has its own particular binding site on the α1 subunit called the N, V, and D sites (Opie, 1997). The DHP or N site appeared to be on the calcium channel pore while the benzothiazepine or D site is located on the α1 subunit. The phenylalkylamines binding site or V site is located on the α1 subunit in the C-terminal chain region adjacent to S6 helix. The DHP CCBs are potent vasodilators but they have minimal effect on cardiac conduction or heart rate. Conversely, non-DHP CCBs slow atrioventricular node conduction and decrease sinoatrial node automaticity resulting in decreased heart rate. Both DHPs and non-DHPs are indicated for the treatment of hypertension and angina pectoris. Additionally, verapamil is also used to treat cardiac arrhythmias.

6.1.1 CCB and cancer

Apoptosis, a form of programmed cell death, regulates normal tissue mass and balances the production of growth and death factors that control mitosis and cell death. Earlier studies had demonstrated the crucial role of Ca^{2+} signalling where transient increase in cytosolic Ca^{2+} activates a cascade of events leading to cell death (Nicotera and Orrenius, 1998, Hajnóczky et al., 2003, Guo, 2009a) Disruption in apoptosis was proposed as one of the underlying cellular mechanism

by which CCB may promote carcinogenesis (Guo, 2009a). Connor and team (1988) had used a rat prostate gland model to study androgen-programmed cell death of the sexual accessory tissues following castration. Rats administered verapamil and nifedipine upon castration exhibited a significant delay in tissues regression compared to control. These findings were further corroborated in an in-vitro study by Escargueil-Blanc et al. (1997) using the human endothelial cell in a culture containing oxidised low-density lipoprotein (ox-LDL). The study demonstrated that in cultures treated with nifedipine or nisoldipine, increased Ca^{2+} concentration and deoxyribonucleic acid (DNA) fragmentation elicited by ox-LDL were inhibited.

On the contrary, several studies demonstrated cell death not repressed by CCBs. Leszczynski et al. (1994) induced apoptosis in isolated non-transformed vascular smooth muscle cells (SMC) of rats with a number of cell proliferation inhibitors. Cell cultures treated with verapamil demonstrated no effect of apoptosis prevention. In an in-vivo study (Balakumaran et al., 1996), the effect of different CCBs (diltiazem, verapamil, nifedipine, and nicardipine) versus saline on apoptosis was assessed using rat thymus. A common effect was seen across all four types of CCB and higher apoptotic index was observed in CCBs compared to control. Thus, the effects of CCBs on apoptosis remains inconsistent. Evidence from epidemiological studies is described in Chapter 1, Section 1.9.4 (page 48).

This chapter aims to systematically review and report the meta-analysis of RCTs using CCB as one of its treatment and its association with risks of cancer.

6.2 Methodology

6.2.1 Systematic review

Full descriptions of the methods used for this systematic review have been described previously in Chapter 2, Section 2.1(page 57).

Except for the ASCOT-BPLA (Dahlöf et al., 2005) and REIN-2 (Ruggenenti et al.) study, cancer outcomes for all of the studies included in this review were published and available publicly. Cancer data for the ASCOT-BPLA and REIN-2 trial were available from a published meta-analysis (Bangalore et al., 2011). In addition, the number of cancer-related mortality in the NHS study (Muramatsu et

al., 2012) was provided by one of the trial investigator (Dr Toyoaki Murohara of Nagoya University, Japan). Pre-existing cancers before randomisation were not included in the analyses in ACTION (Poole-Wilson et al., 2006), INVEST (Pepine et al., 2003) Kanamasa (1999) and STOP-HTN2 (Lindholm et al., 2001).

6.2.2 Meta-analysis

For data synthesis, see Chapter 2, Section 2.1.7.4 (page 66).

For CCB and risk of incident cancer, a sensitivity analysis was performed by firstly excluding the FEVER trial (Liu et al., 2005) because it is also considered as a CCB and TZ diuretic combination therapy versus TZ monotherapy. The FEVER study was designed to assess the effects on CV outcomes of adding a low dose CCB felodipine versus placebo in hypertensive patients whose BP had already been reduced by a low dose TZ diuretic which was continued throughout the trial. Exclusion of the CAMELOT trial was also investigated as this study is detected as an outlier from the primary meta-analysis and funnel plot. Trials with the following criteria were also excluded trials with the following criteria: [1] small sample size with the number of total participants less than 1000; [2] poor methodological quality. Association robustness was assessed by including participants with baseline cancer available from four trials (ACTION, INVEST, Kanamasa, and STOP-HTN2).

Additionally, subgroup analyses were also conducted on the following groups and treatment comparisons: [1] subclass; [2] comparator; [3] clinical setting; [4] mean age; and [5] duration of follow-up.

6.3 Results

A total of 60 trials were excluded from the 90 studies included in the primary systematic review mainly because they do not consist of CCB treatment arm. Details for reasons of exclusion and inclusion of studies are described in Chapter 3, Section 3.2.1. Overall, identified 30 RCTs enrolling 165,811 patients with an average follow-up of 3.5 years (range between 1 and 9.1 years) were identified in the search. The average age for patients is 61.9 years across all trials.

The full description of the studies' characteristics is described in Chapter 3, Section 3.2.2.1 whereas the methodological quality is described in Chapter 3,

Section 3.3.6. The oldest study was published in 1989 (VERDI) while the most recent study was published in 2011 (CASE-J Ex). The largest study was the ALLHAT trial with 33,357 participants enrolled and this was followed by INVEST and VALUE with 22,576 and 15,245 participants enrolled correspondingly. The majority (88.6%) of the patients were hypertensive with more than half of these patients (65.6%) had risk factors for CV events e.g. T2DM, history of CHD such as angina pectoris and myocardial infarct. The remaining participants were mostly patients with established CHD.

Across the 30 studies, only 44.4% of the total study population were randomised to the CCB treatment arm. Of these, the majority of the patients used DHP CCB (71.4%) while the rest used either verapamil (28.4%) or diltiazem (0.2%). Overall, 21 RCTs compared CCB to active controls which include RAS inhibitors such as ACEI or ARB, CCB, and TZ. Two of these trials, Kanamasa and REIN-2, did not specify the active control used and the comparators were only described as non-CCB and conventional antihypertensive therapy respectively. Meanwhile, 12 RCTs randomised patients to placebo.

All the included studies have a minimum duration of treatment at least one year with the longest mean follow-up was nine years. The mean or median age for the study participants was above 50 years across all 30 studies. However, two studies, STOP-HTN and Syst-Eur, recruited older patients with mean age above 70 years. Most of the studies recruited equal proportion or more than 50% males into each respective trial except for CONVINCE, INSIGHT, NICS-EH, and STOP-HTN2 (ranged between 33% and 46%). In the meantime, the proportion of active smokers was exceptionally high in two RCTs, INTACT and NICOLE (84% and 71.2% correspondingly).

Four trials implemented more than two parallel treatment arms. Kanamasa has randomised patients to two CCB treatment arms (nifedipine and diltiazem) and non-CCB. Apart from ACEI, three trial has compared CCB to one additional active control (ALLHAT, STOP-HTN2) or placebo (CAMELOT). In addition, most of the trials have implemented a double-blind design. Seven trials blinded only the study endpoint assessors (ASCOT-BPLA, CASE-J Ex, FACET, INVEST, NHS, REIN-2, and STOP-HTN2). Two trials, ESPIRAL and Kanamasa, used an open-label design.

Table A-3 shows the selected characteristics of interest extracted from individual trials. On a whole, only four studies (ACTION, INVEST, Kanamasa, STOP-HTN2) have reported recruitment of patients with baseline cancer whereas five studies (CSE-J Ex, INTACT, REIN-2, SPRINT, VERDI) excluded such patients from their study protocol. Only seven trials had pre-specified cancer as one of the study outcomes while the remaining trials were not designed to detect cancer. Cancer adjudication varied across all studies with only 11 studies centrally adjudicated cancer outcomes and one study (FEVER) used site reports for cancer diagnoses. Reporting of treatment adherence and attrition was inconsistent across studies. Treatment adherence was reported to be between moderate to good in 17 studies ranging from 55% to 96%. As for attrition rate, three studies (PRAISE, PREVENT, STOP-HTN2) have not loss any patients throughout the individual study period. Meanwhile, 17 studies reported the number of patient loss to follow-up at the rate between 0.3% and 10%. Cancer outcomes for all the studies were available publicly.

6.4 CCB and risks of incident cancer

6.4.1 Overall

As a whole, 25 trials were included and data were available for 142,841 (89.4%) of the total 159,798 patients enrolled. Cancer incidence was 5.66% in patients assigned to CCB versus 5.34% in patients assigned to control. In the FE model as shown in **Figure 6-1**, the ASCOT-BPLA was given the most weight at 23.8% overall and this was immediately followed by the ALLHAT and VALUE trials (18.8% and 17.3% respectively). The remaining weight was distributed variably between 22 studies. Three studies (ACTION, CAMELOT, VALUE) have shown a significantly increased odds for cancer with OR ranging between 1.20 and 4.39 and 95% CI not including 1. In the forest plot, the CIs for CAMELOT and VALUE clearly did not cross the line of no effect and lies on the right side of the plot whereas the 95% CI lower limit for the ACTION study almost encroaching 1. Although many of the remaining studies showed increased odds for cancer while only a few showed OR less than 1, the 95% CI of all the studies overlaps 1. The CI of these studies crossed the line of no effect indicating no statistical significance at the study level. Nonetheless, the combined OR was 1.08 with 95% CI between 1.03 and 1.13 (P-value = 0.0007) and

the diamond that represents the pooled effect estimates lies to the right side of the forest plot indicating a statistical significance at the meta-analysis level.

Figure 6-2 shows the RE model meta-analysis of the 25 trials included for the assessment of overall cancer risk. In this model, equal weight was assigned to ACTION, CAMELOT and VALUE at 11.4%, 11.0% and 11.0% correspondingly. The combined OR was 1.09 with 95% CI between 1.00 and 1.19 (P-value = 0.06). The diamond of pooled effect lies to the right side of the plot and is slightly wider with the left tips impinging the line of no effect showing a considerable trend towards significance.

Both the FE and RE model showed a considerable presence of heterogeneity. The Chi-square test for heterogeneity showed a P-value of 0.002 indicating statistical evidence for differences between studies. In addition, the I^2 statistic showed that 51% variations across the studies are due to heterogeneity rather than chance. The observed statistical heterogeneity is most likely due to the methodological and clinical diversity of the CAMELOT and FEVER studies. Sensitivity analyses, without these studies, resulted in a narrower 95% CI and a marked decreased in I^2 statistics across studies (See **Section 6.4.2.Sensitivity analyses**).

Finally, assessment of the funnel plot as shown in Appendix Figure A-1 (Page 323) demonstrated a fairly symmetrical distribution of studies at the top of the plot. However, small studies are missing on the left side of the funnel plot and there is an outlier on the top right. The outlier was identified as the CAMELOT study. The funnel plot asymmetry is most likely due to selective outcome reporting bias when located studies may not provide usable data for the outcome of interest.

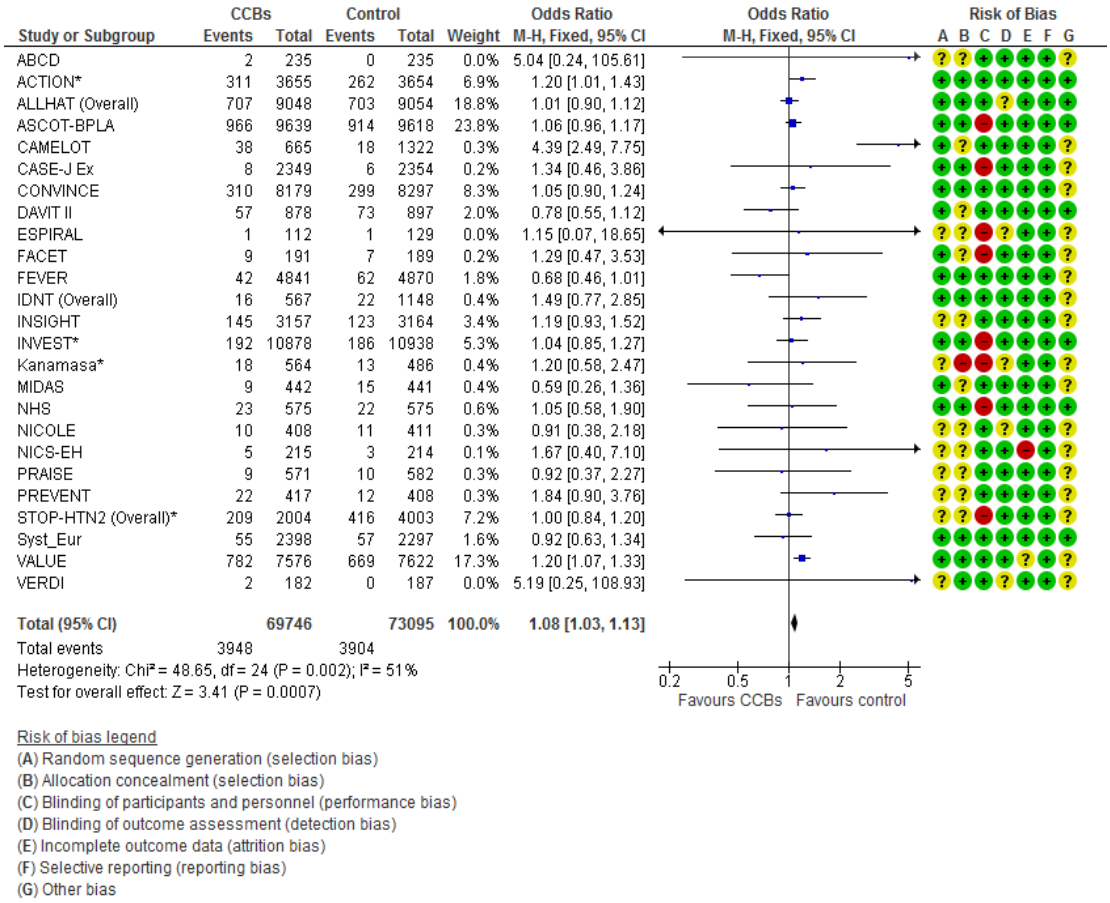


Figure 6-1: Forest plot of incident cancers by CCB vs non-CCB controls [FE model].
Odds ratios and 95% confidence interval, overall and in 25 trials. The overall effect represents the pooled estimate of odds for incident cancers. *Included were patients with no history of cancer or active cancer at baseline.

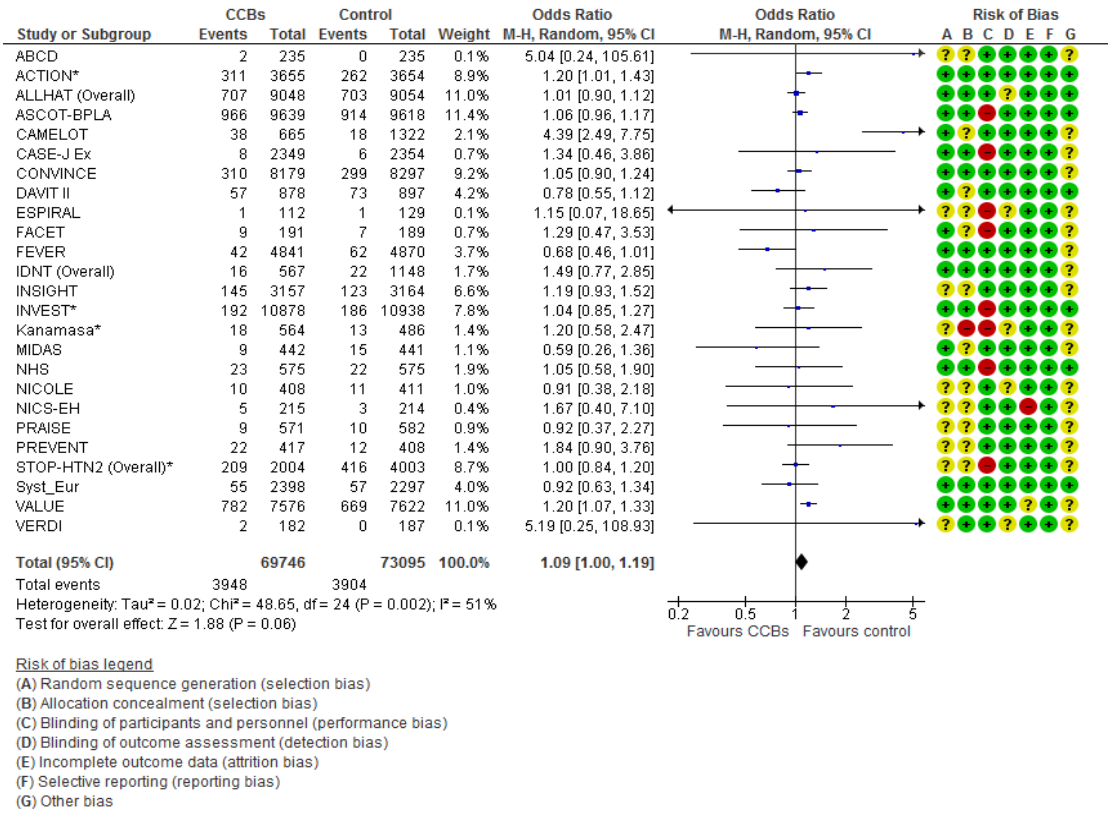


Figure 6-2: Forest plot of incident cancers by CCB vs non-CCB controls [RE model]. Odds ratios, and 95% confidence interval, overall and in 25 trials. The overall effect represents the pooled estimate of odds for incident cancers. *Included were patients with no history of cancer or active cancer at baseline.

6.4.2 Sensitivity analyses

Exclusion of the FEVER study from the overall analysis in an FE model generated an OR 1.09 (95% CI 1.04-1.14) with a P-value of 0.0002 (**Figure 6-3**). Weight distribution between studies is comparable to the primary result. Chi-square test for heterogeneity yields a P-value of 0.007 indicating statistical evidence for differences between studies. The I^2 statistics of 47% indicating a moderate amount of variation across studies is due to heterogeneity rather than chance. Meanwhile, the RE model yielded an OR of 1.11 with a wider 95% CI ranging from 1.02 to 1.21 (**Figure 6-4**).

Figure 6-5 shows the result of meta-analysis in an FE model after exclusion of the CAMELOT and FEVER study with an OR 1.08 (95% CI 1.03-1.13). Chi-square test for heterogeneity showed a P-value of 0.34 signifying no evidence of a difference

between studies. The I^2 test had markedly decreased with its value observed at 9% implying that the amount of variations across studies due to heterogeneity is trivial. The RE meta-analysis (**Figure 6-6**) yielded a similar pooled effect estimate as the FE model (OR 1.08, 95% CI 1.03-1.13).

Exclusion of eight studies with small sample size resulted in OR 1.08 (95% CI 1.03-1.13) with P-value of 0.001 (**Figure 6-7)**. This result was mainly driven by the ALLHAT, ASCOT-BPLA, and VALUE studies as they were assigned the most and comparable weight each (11.4%, 11.8%, and 11.4% respectively. The presence of heterogeneity is evidenced by the Chi-square P-value of 0.0004 and the I^2 statistics observed at 62%. The RE model showed an OR 1.09 with 95% CI between 0.99 and 1.19 (P-value = 0.09; **Figure 6-8**) which is slightly wider.

Exclusion of nineteen studies with high risk of bias left only six studies in the overall analysis (**Figure 6-9)**. The FE model analysis resulted in a combined OR of 1.10 (95% CI. 1.04-1.17; P-value = 0.002))The result was mainly influenced by the ALLHAT and VALUE trials as both trials carried equal weights and more than half of the weight combined for the overall meta-analysis. Test for heterogeneity yields a chi-square P-value of 0.17 and an I^2 of 36%. Meanwhile, RE model analysis showed an OR of 1.10 with slightly wider 95% CI between 1.01 and 1.21 (P-value = 0.03; **Figure 6-10**).

In the meantime, the inclusion of patients with baseline cancer into the FE meta-analysis yielded a combined effect estimate of OR 1.08, 95% CI 1.04-1.14 (P-value = 0.0006; **Figure 6-11**) which is comparable to the primary FE meta-analysis. Similarly, RE meta-analysis did not have any impact on the overall result as it gave a similar summary effect estimate and 95%CI to the main result (OR 1.09, 95% CI 1.00-1.19; **Figure 6-12**).

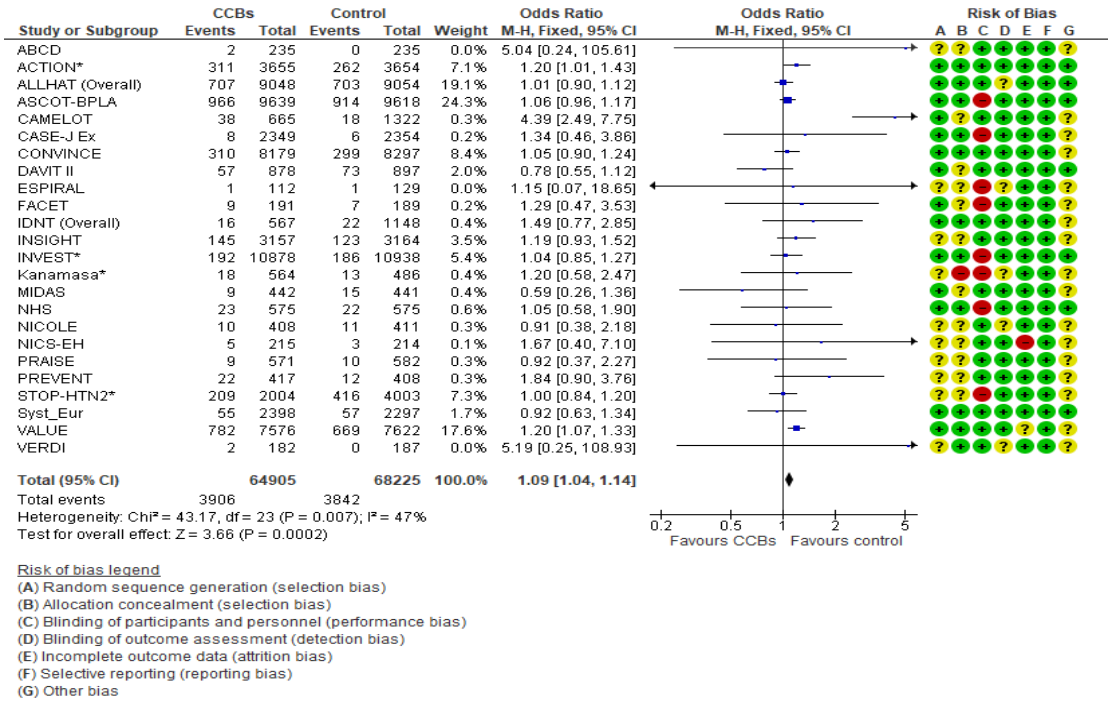


Figure 6-3: Forest plot of incident cancers by CCB vs controls [Sensitivity analysis: Exclusion of the FEVER trial, FE model].
The overall effect represents the pooled estimate of odds for incident cancers. *Included were patients with no history of cancer or active cancer at baseline

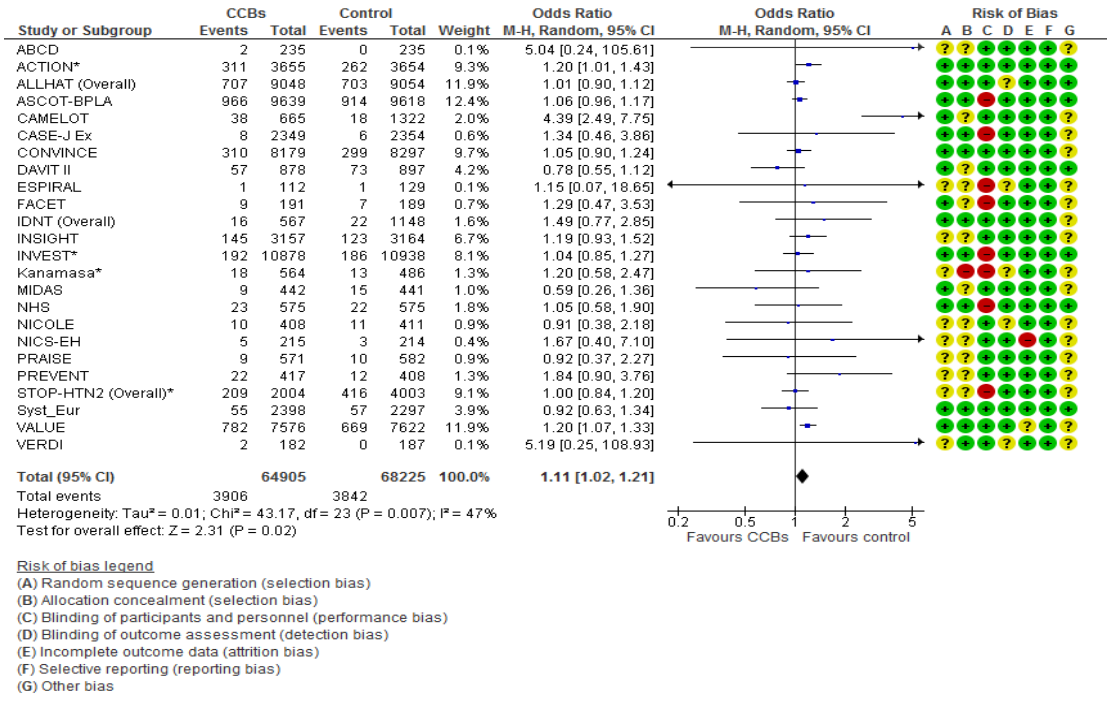


Figure 6-4: Forest plot of incident cancers by CCB vs controls [Sensitivity analysis: Exclusion of the FEVER trial, RE model].
The overall effect represents the pooled estimate of odds for incident cancers. *Included were patients with no history of cancer or active cancer at baseline.

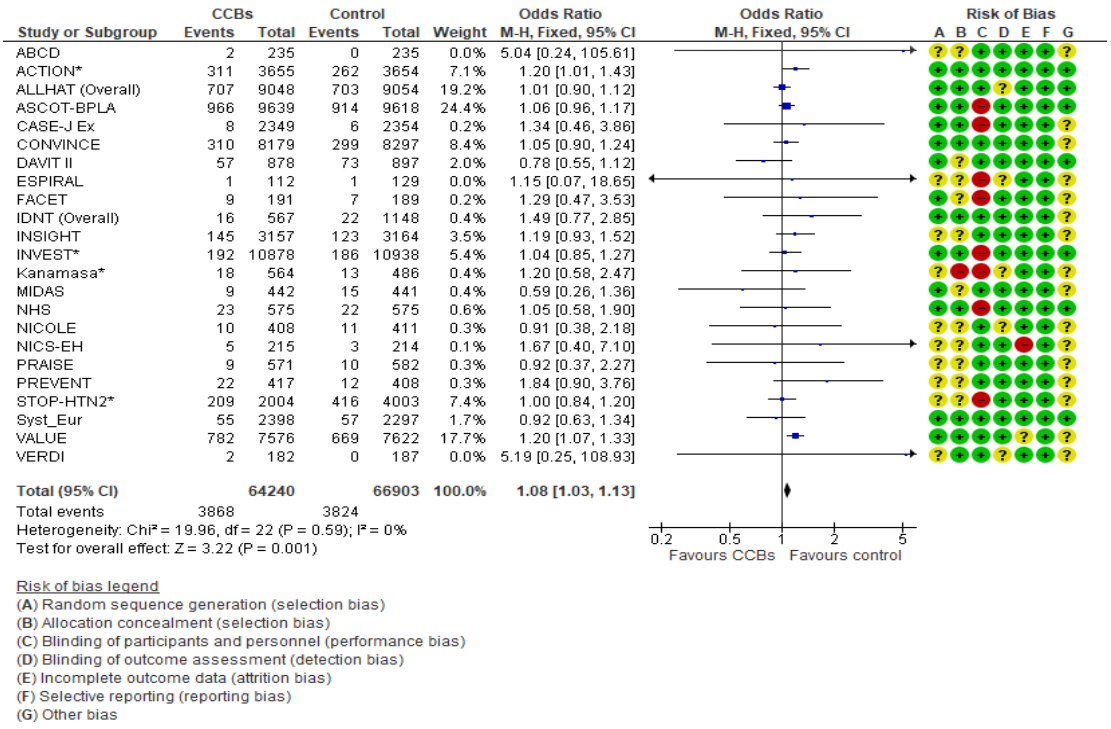


Figure 6-5: Forest plot of incident cancers by CCB) vs non-CCB controls [Sensitivity analysis: Exclusion of the CAMELOT and FEVER trial, FE model].
The overall effect represents the pooled estimate of odds for incident cancers. * Included were patients with no history of cancer or active cancer at baseline.

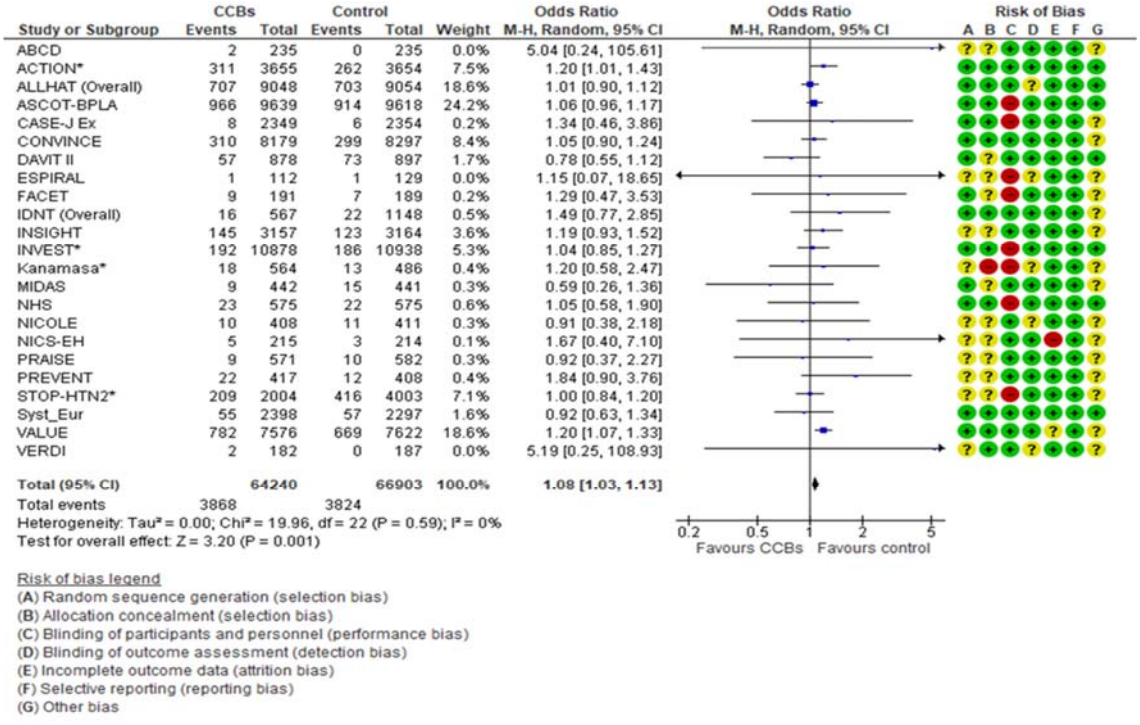


Figure 6-6: Forest plot of incident cancers by CCB) vs non-CCB controls [Sensitivity analysis: Exclusion of the CAMELOT and FEVER trial, RE model].
The overall effect represents the pooled estimate of odds for incident cancers. * Included were patients with no history of cancer or active cancer at baseline.

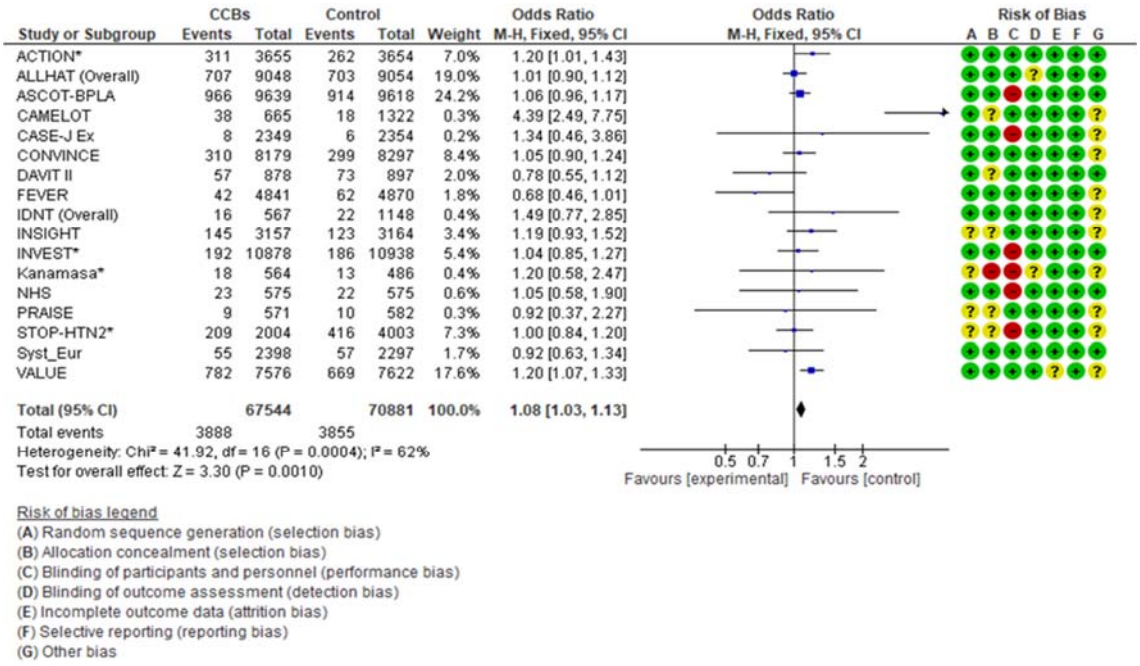


Figure 6-7: Forest plot of incident cancers by CCB vs. controls [Sensitivity analysis: Study size, FE model].
The overall effect represents the pooled estimate of odds for incident cancers*Included were patients with no history of cancer or active cancer at baseline.

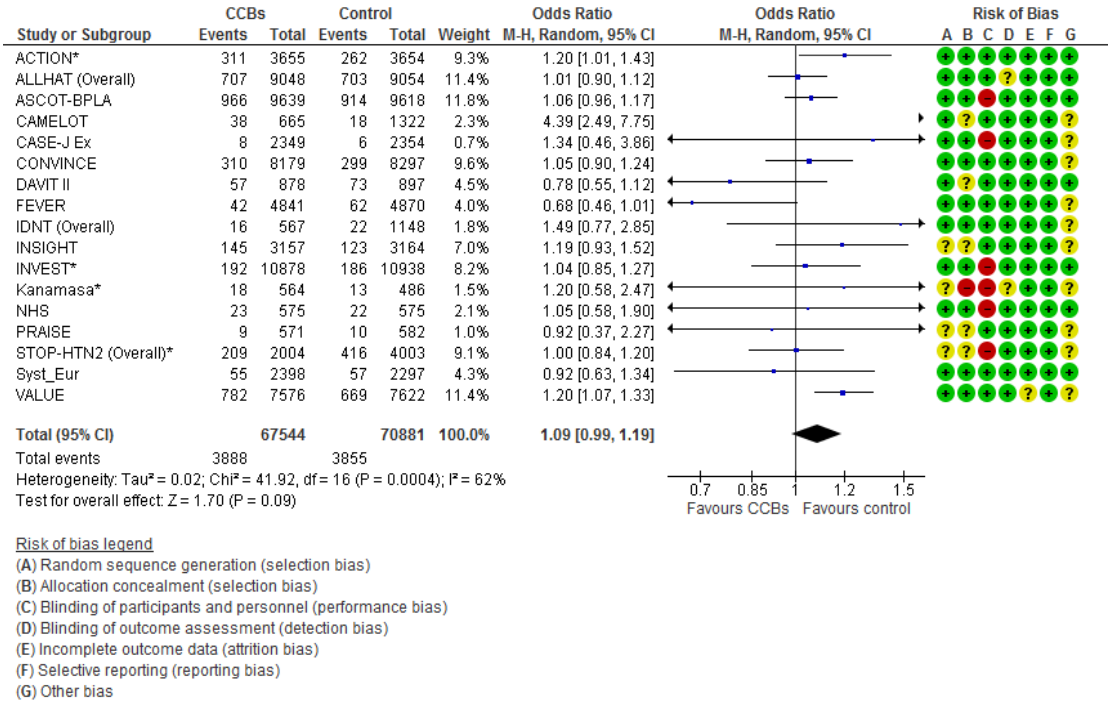


Figure 6-8: Forest plot of incident cancers by CCB vs. controls [Sensitivity analysis: Study size, RE model].
The overall effect represents the pooled estimate of odds for incident cancers*Included were patients with no history of cancer or active cancer at baseline.

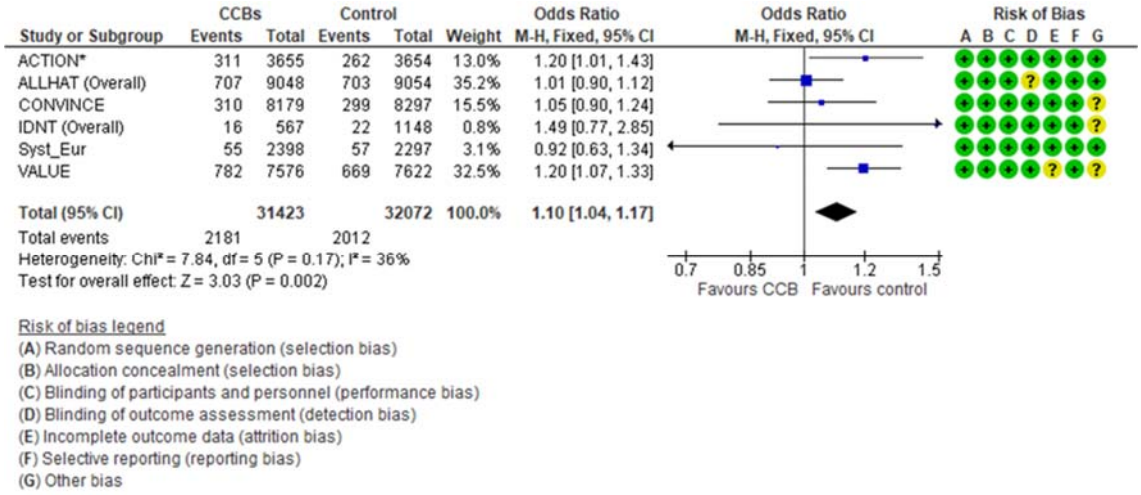


Figure 6-9: Forest plot of incident cancers by CCB vs. controls [Sensitivity analysis: Methodological quality, FE model].
The overall effect represents the pooled estimate of odds for incident cancers * Included were patients with no history of cancer or active cancer at baseline.

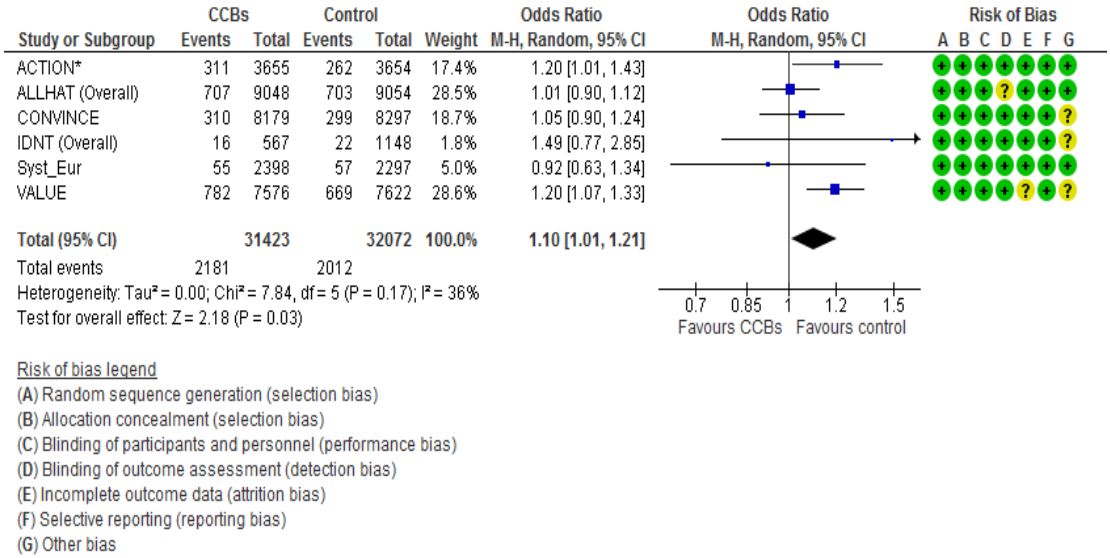


Figure 6-10: Forest plot of incident cancers by CCB vs. controls [Sensitivity analysis: Methodological quality, RE model].
The overall effect represents the pooled estimate of odds for incident cancers * Included were patients with no history of cancer or active cancer at baseline.

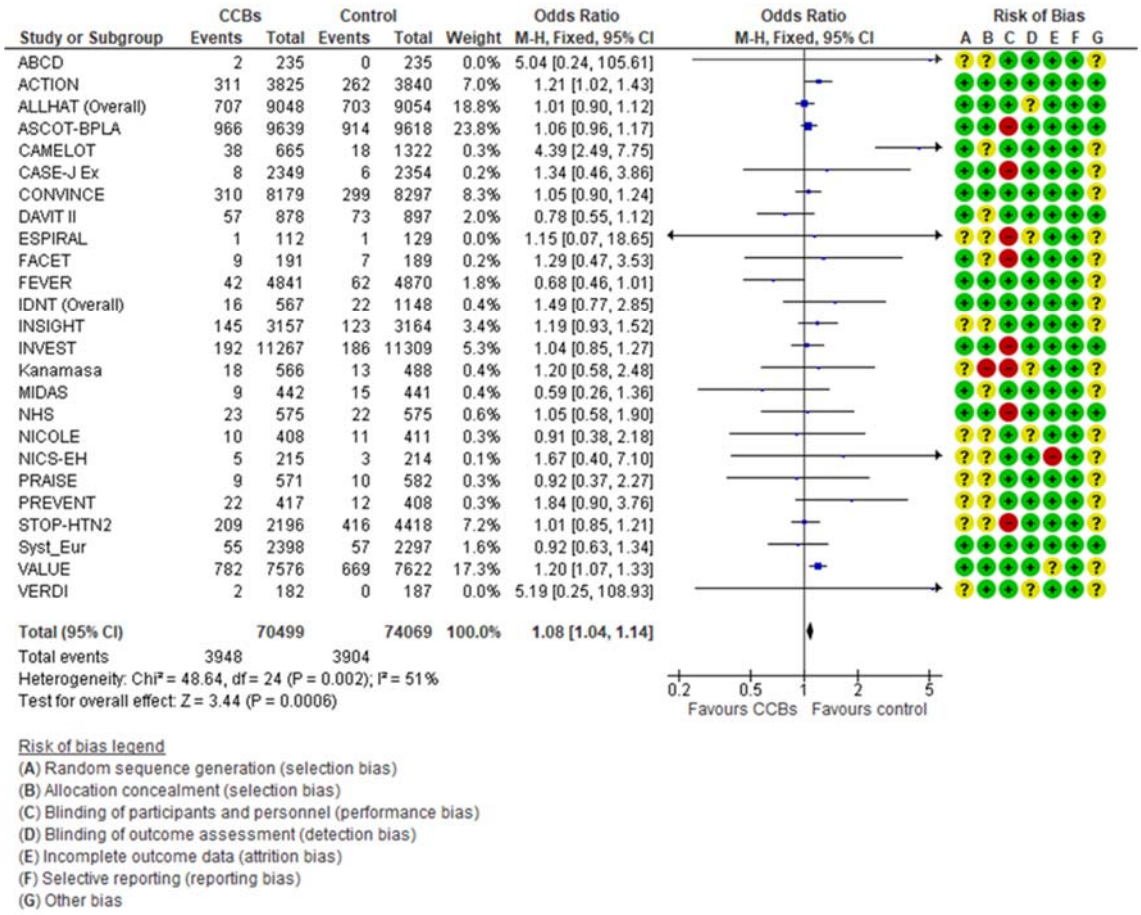


Figure 6-11: Forest plot of incident cancers by CCB vs. controls [Sensitivity analysis: Inclusion of patients with baseline cancer, FE model].
The overall effect represents the pooled estimate of odds for incident cancers

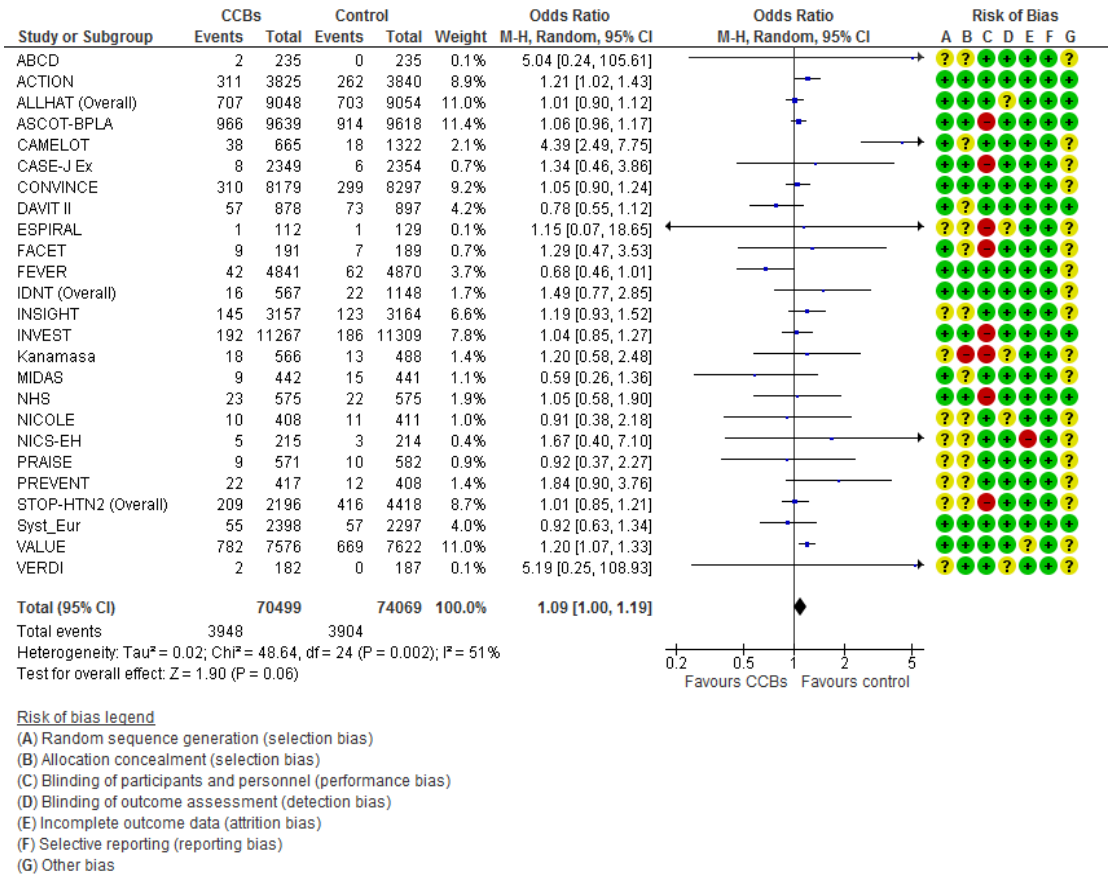


Figure 6-12: Forest plot of incident cancers by CCB vs. controls [Sensitivity analysis: Inclusion of patients with baseline cancer, RE model].
The overall effect represents the pooled estimate of odds for incident cancers

6.4.3 Subgroup analyses

Table 6-1 summarises the results for subgroup analyses that were carried out for CCB and cancer risk. Altogether, there are five subgroups analyses.

6.4.3.1 By subclass

Data for DHP CCB was available from 21 RCTs enrolling 118,173 patients. Cancer incidence was 6.47% in the DHP CCB treatment group versus 6.41% in the control group. The FE model estimates resulted in OR 1.08 (95% CI 1.03-1.13; P-value = 0.002; **Figure 6-13**).Meanwhile, the RE model (**Figure 6-14**) estimated an OR 1.11 with 95% CI between 1.00 and 1.23 and P-value of 0.05 at the edge of significance. The chi-square test resulted in a P-value of 0.001 and the I^2 statistics of 55% indicating a substantial amount of heterogeneity between studies. The statistical heterogeneity observed is likely due to the inclusion of the CAMELOT (an outlier) and the FEVER trial (methodological diversity) in the analysis.

For non-DHP CCB, data were available from five RCTs enrolling 40,861 patients. Cancer incidence was 2.80% in the non-DHP CCB treatment group versus 2.76% in the control group with OR 2.76 (95% CI 0.90-1.14; P-value = 0.81). Test for heterogeneity resulted in a chi-square P-value of 0.56 and an I^2 statistics of 0% signifying no observed heterogeneity. Both FE and RE meta-analysis agrees well with each other.

6.4.3.2 By type of comparator

Overall, 17 RCTs have compared CCB to active controls and data were available from 11,3998 patients. Cancer incidence was 6.09% in the CCB treatment group versus 5.84% in the non-CCB group. The summary effect estimate resulted in OR 1.08 (95% CI 1.02-1.13; P-value = 0.004). The combined effect estimate was mainly influenced by the ALLHAT, ASCOT-BPLA, and VALUE trials as they carried the heaviest weight overall (21.1%, 27.5%, and 21.1% respectively; **Figure 6-15**). Test for heterogeneity resulted in a chi-square P-value of 0.76 and I^2 statistics of 0% signifying no observed heterogeneity. The RE meta-analysis (**Figure 6-16)** agree well with the estimates derived from the FE model.

Eight studies have compared ACEI or ARB to CCB and data were available from 27,289 patients. Cancer incidence was 7.72% in the CCB treatment group versus 6.82% in the RAS inhibitors treatment group with OR 1.14 (95% CI 1.04-1.26; P-value = 0.004; **Figure 6-15**). The result of this analysis was greatly driven by the VALUE trial as it was given the heaviest weightage (73%). Test for heterogeneity resulted in a chi-square P-value of 0.67 and I^2 statistics of 0% signifying no observed heterogeneity. Pooled estimates from the RE model is (**Figure 6-16**) is in agreement with the FE model.

For placebo, data were available from eight studies enrolling 27,423 patients. Cancer incidence was 3.80% in the CCB treatment group versus 3.63% in the placebo group. The FE model (**Figure 6-15**) combined effect estimate resulted in OR 1.05 (95% CI 0.93-1.19; P-value 0.44). Meanwhile, the RE model yields a lower OR of 1.00 with wider 95% CI between 0.80 and 1.25 (P-value = 0.99). The chi-square test resulted in a P-value of 0.05 and the I^2 statistics of 49% indicating a considerable amount of heterogeneity between studies (**Figure 6-16**). The

statistical heterogeneity observed is likely due to methodological diversity of the FEVER (background TZ therapy) and DAVIT II (small study size) studies.

6.4.3.3 By population clinical setting

Data for patients with essential hypertension were available from five RCTs enrolling 12,383 patients. Cancer incidence was 4.34% in the CCB treatment group versus 6.88% in the control group (OR 0.98, 95% CI 0.84-1.15; P-value = 0.83; **Figure 6-17**). The combined effect estimate was mainly influenced by the STOP-HTN2 trial which with 76.8% of the overall weight. The RE meta-analysis (**Figure 6-18**) agree with the FE model estimates. Heterogeneity assessment shows a chi-square P-value of 0.51 and an I^2 statistics of 0% indicating no observed statistical heterogeneity.

For hypertensive patients with one or more risk factor CV events, data were available from 11 RCTs enrolling 102,213. Cancer incidence was 5.50% in the CCB treatment group versus 5.15% in the control group. The FE model (**Figure 6-17**) yields an OR 1.06 (95% CI 1.01-1.12) with a P-value of 0.03 whereas the RE model results in a combined effect estimate of OR 1.04 with a wider 95% CI 0.94-1.15 (P-value = 0.48; **Figure 6-18**). The result of this analysis was mainly influenced by the ALLHAT, ASCOT-BPLA, and VALUE studies which were assigned most of the overall weight. Heterogeneity test resulted in a chi-square P-value of 0.06 and I^2 statistics of 44%. The statistically moderate heterogeneity observed is most likely due to the methodological diversity of the CONVINCE (two comparators were used) and FEVER (background TZ therapy) trials.

Data from seven RCTs enrolling 35,581 patients were available to assess the risk of incident cancer in patients with underlying CHD such as angina pectoris and myocardial infarct. Cancer incidence was 3.71% in the CCB treatment group versus 3.17% in the control group with OR 1.17 (95% CI 1.04-1.31; P-value = 0.007; Figure 6-17). The RE meta-analysis (**Figure 6-18**) showed a higher summary OR with wider 95% CI (OR 1.31 (95% CI 0.95-1.80; P-value = 0.10). Significant differences between studies were observed with the I^2 test of 79% (chi-square P-value <0.0001). The heterogeneity observed is most likely contributed by methodological diversity of the CAMELOT (an outlier) trial.

As for patients with underlying T2DM, data were available from four studies enrolling 3,715 patients. Cancer incidence was 3.19% in the CCB treatment group versus 2.38% in the control group. The combined FE estimate resulted in OR 1.28 with 95% between 0.86 and 1.90 (P-value = 0.24; **Figure 6-17**). The RE meta-analysis result (OR 1.27, 95% CI 0.85-1.89; P-value = 0.24; Figure 6-18) to a certain extend agrees with the FE estimates. This analysis was primarily influenced by the NHS study which carries 45% of the overall weight. The chi-square test yields a P-value of 0.70 and the I^2 statistics of 0% indicating no observed statistical heterogeneity.

6.4.3.4 By mean age groups

For studies with patients' mean age of 65 years or older, data were available from eight RCTs enrolling 89,044 participants. Cancer incidence was 5.54% in the CCB treatment group versus 5.39% in the control group with OR 1.08 (95% CI 1.02 – 1.14; P-value = 0.01; **Figure 6-19**). The RE model (**Figure 6-20)** estimates fairly agree with the FE model estimates resulting in OR 1.08 (95% CI 1.01-1.15; P-value = 0.02). The summary effect estimate was primarily driven by the ALLHAT and VALUE trials in which both studies combined carries more than half of the overall weight (27.9% and 28% respectively; **Figure 6-20**). Heterogeneity assessment between the eight studies yields a chi-square test P-value of 0.38 and an I^2 statistics of 7% indicating no observed statistical heterogeneity.

Meanwhile, data for studies with patients' mean age younger than 65 years were available from 17 RCTs enrolling 53,797 participants. Cancer incidence was 5.87% in the CCB treatment group versus 5.26% in the control group (OR 1.09, 95% CI 1.02-1.18; P-value = 0.02). In this meta-analysis, the ASCOT-BPLA and ACTION trials carry the most weight overall with 62.7% and 18.3% correspondingly (**Figure 6-19**). Meanwhile, the RE meta-analysis resulted in a larger OR and wider 95% CI (OR1.16, 95% CI 0.95-1.41; P-value = 0.16; **Figure 6-20**). Heterogeneity assessment observed with chi-square test (P-value = 0.0005) and I^2 statistics (61%) suggests evidence of differences between studies. The heterogeneity observed was mainly contributed by methodological diversity of the CAMELOT and FEVER (background TZ therapy) trial.

6.4.3.5 By duration of follow-up

Three subgroups analyses were carried out to assess the impact of duration of study follow-up on cancer risk.

For studies with mean patients' follow-up less than three years, data were available from nine studies enrolling 34,940 participants. Cancer incidence was 2.34% in the CCB treatment group versus 2.14% in the control group with OR 1.11 (95% CI 0.96-1.28; P-value = 0.16; **Figure 6-21**). The RE model showed a larger OR of 1.27 and a wider 95% CI between 0.90 and 1.79 (P-value = 0.18; **Figure 6-22**). This meta-analysis was mainly influenced by the ASCOT-BPLA, ALLHAT, and VALUE study as they carry the most weight overall (20.3%,17.9%, and 18.0% respectively; **Figure 6-22**). Heterogeneity assessment observed with the chi-square test (P-value = 0.0003) and I^2 statistics (73%) suggests evidence of differences between studies. The heterogeneity observed was primarily contributed by the CAMELOT trial probably due to methodological and clinical diversity.

Data for studies with mean patients' follow-up three years or longer were available from 16 RCTs enrolling 107,901. Cancer incidence was 6.72% in the CCB treatment group versus 6.39% in the control group (OR 1.08, 95% CI 1.03-1.13; P-value = 0.002; **Figure 6-21**). The RE model estimates agree with the FE model to some extent (OR 1.08, 95% CI 1.01-1.15; P-value = 0.02; **Figure 6-22)**. Similarly, the ASCOT-BPLA, ALLHAT, and VALUE study had the biggest influence in this meta-analysis. Tests for heterogeneity resulted in a chi-square P-value of 0.21 and an I^2 statistics of 22% suggesting minimal differences between studies.

Additionally, the risk of cancer in trials followed for five years or longer was assessed. Data were available from three studies enrolling 25,734 patients. Cancer incidence was 9.91% in the CCB treatment group versus 9.60% in the control group with OR 1.05 (95% CI 0.97-1.14; P-value = 0.26). The RE meta-analysis fairly agree with the FE estimates (OR 1.05, 95% CI 0.96-1.14; P-value = 0.26). The ASCOT-BPLA study carried the most weight (77.2%) between the three studies hence had the biggest influence in this meta-analysis. Tests for heterogeneity results (chi-square P-value= 0.52 and I^2 = 0%) suggests no observed statistical heterogeneity between studies.

Table 6-1: Calcium channel blockers and risk of cancer: Subgroup analyses

Subgroup analysis		No. of study	No. of participants	Cancer incidence (%)		OR (95% CI)	P-value	I^2 (%)
				CCB	Control			
Overall effect	RE model	25	142,841	5.66	5.34	1.09 (1.00-1.19)	0.06	51
Subclass	DHP	21	118,173	6.47	6.41	1.11 (1.00-1.23)	0.05	55
	Non-DHP	5	40,861	2.80	2.76	1.01 (0.90-1.14)	0.81	0
Type of comparators	Active	17	11,3998	6.09	5.84	1.08 (1.02-1.13)	0.004	0
	RAS inhibitors	8	27,289	7.72	6.82	1.14 (1.04-1.25)	0.005	0
	Placebo	8	27,423	3.80	3.63	1.00 (0.80-1.25)	0.99	49
Clinical setting	Hypertension	5	12,383	5.34	6.88	0.98 (0.84-1.15)	0.81	0
	High-risk hypertensive	11	102,213	5.50	5.15	1.04 (0.94-1.15)	0.48	44
	CHD	7	35,581	3.71	3.17	1.31 (0.95-1.80)	0.10	79
	T2DM	4	3,715	3.19	2.38	1.27 (0.85-1.89)	0.24	0
Age	≥ 65 years	8	89,044	5.54	5.39	1.08 (1.01-1.15)	0.02	7
	< 65 years	17	53,797	5.87	5.26	1.16 (0.95-1.41)	0.16	61
Duration of follow-up	< 3 years	9	34,940	2.34	2.14	1.27 (0.90-1.79)	0.18	73
	≥ 3 years	16	107,901	6.72	6.39	1.08 (1.01-1.15)	0.02	22
	≥ 5 years	3	25,734	9.91	9.60	1.05 (0.96-1.14)	0.26	0

Abbreviations: CCB, calcium channel blockers; CHD, coronary heart disease; DHP, dihydropyridine; RAS, renin-angiotensin system; RE, random-effect; T2DM, type 2 diabetes mellitus; OR, odds ratio; CI; confidence interval.

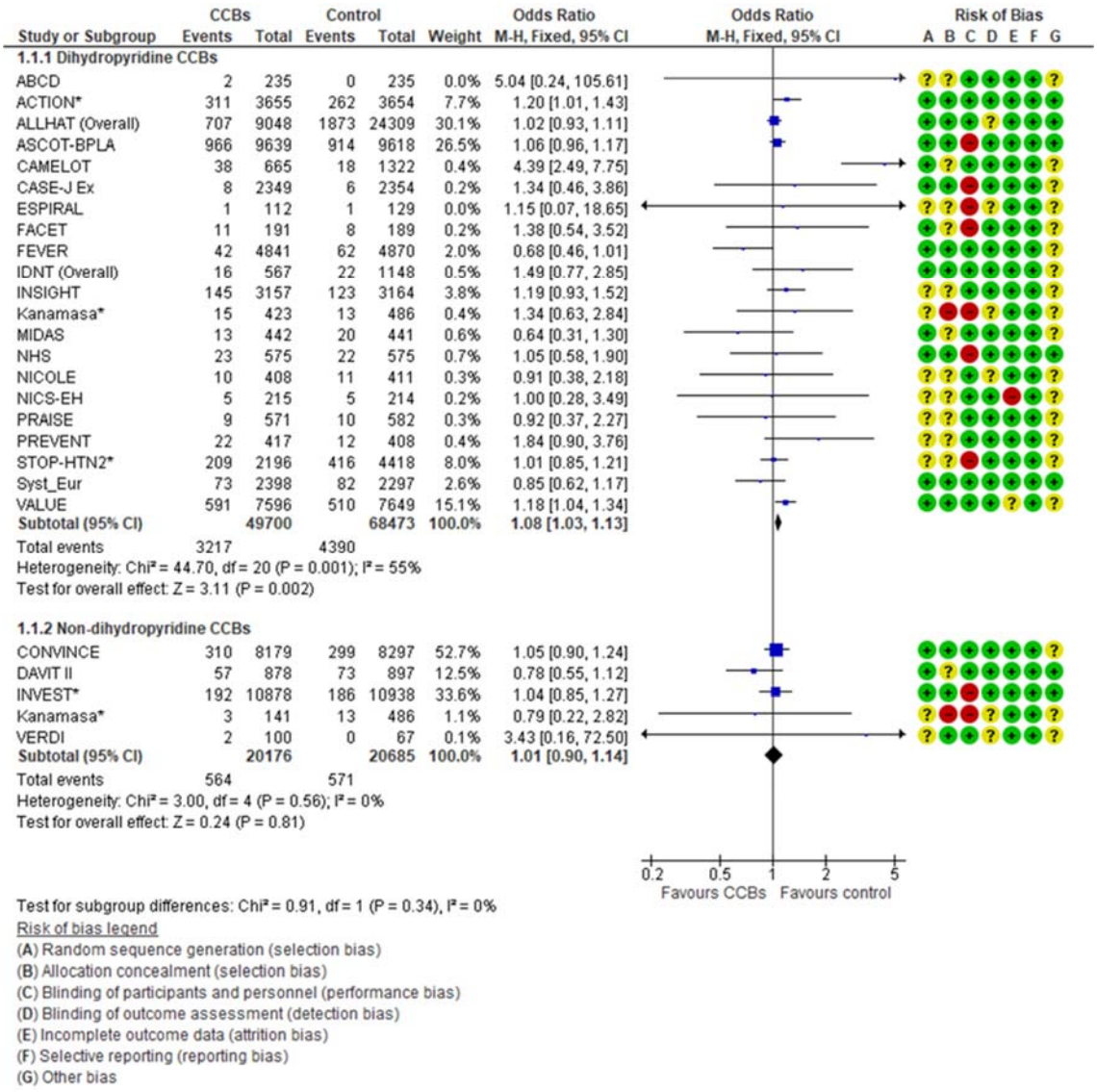


Figure 6-13: Forest plot of cancer incidence by CCB subclass [FE model].
1) DHP vs controls in 21 trials; 2) Non-DHP vs controls in 5 trials. The subtotal effect represents the pooled estimate of odds for cancer incidence for each subclass.* Included were patients with no history of cancer or active cancer at baseline.

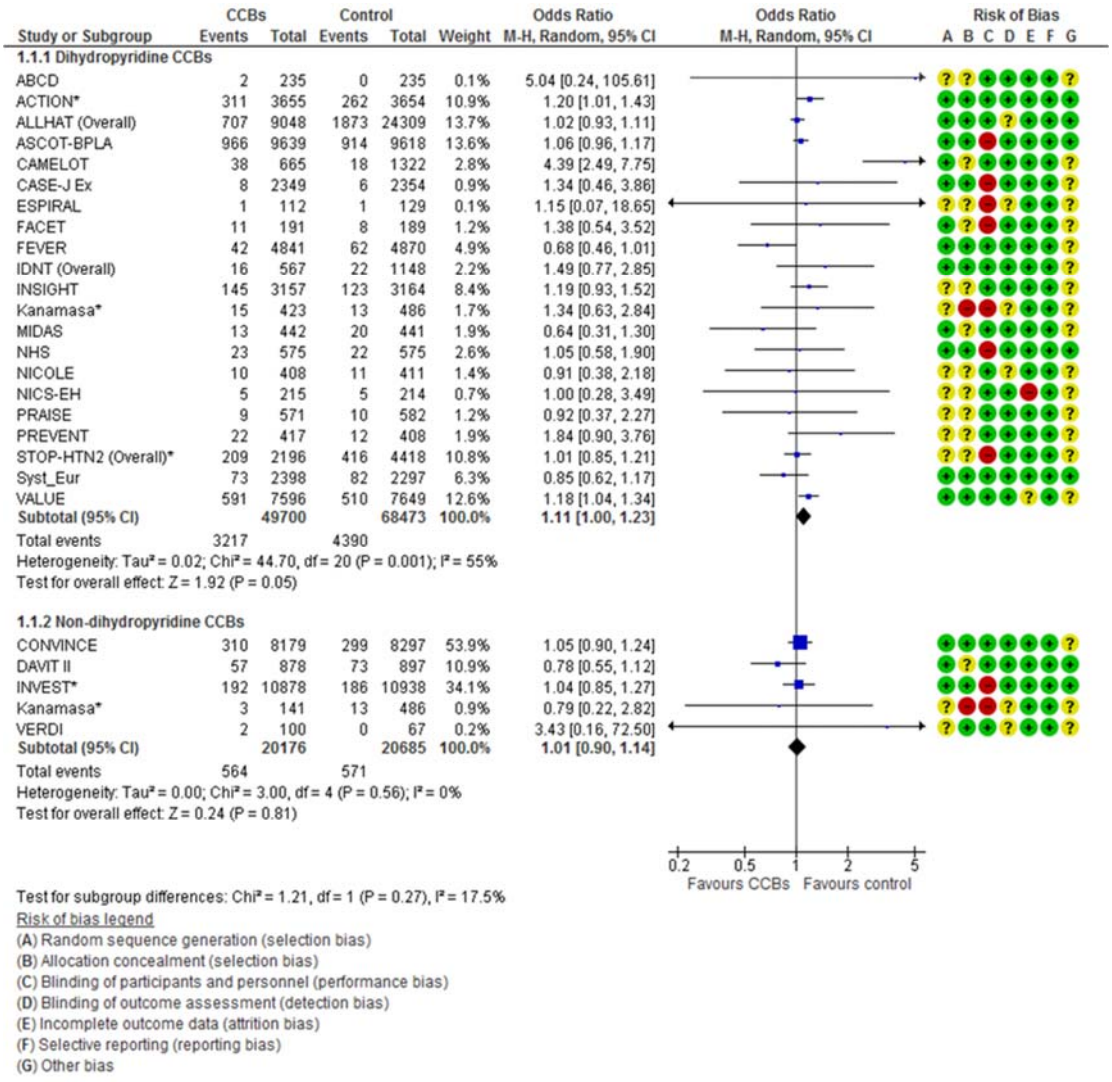


Figure 6-14: Forest plot of cancer incidence by CCB subclass [RE model].
1) DHP vs controls in 21 trials; 2) Non-DHP vs controls in 5 trials. The subtotal effect represents the pooled estimate of odds for cancer incidence for each subclass.* Included were patients with no history of cancer or active cancer at baseline.

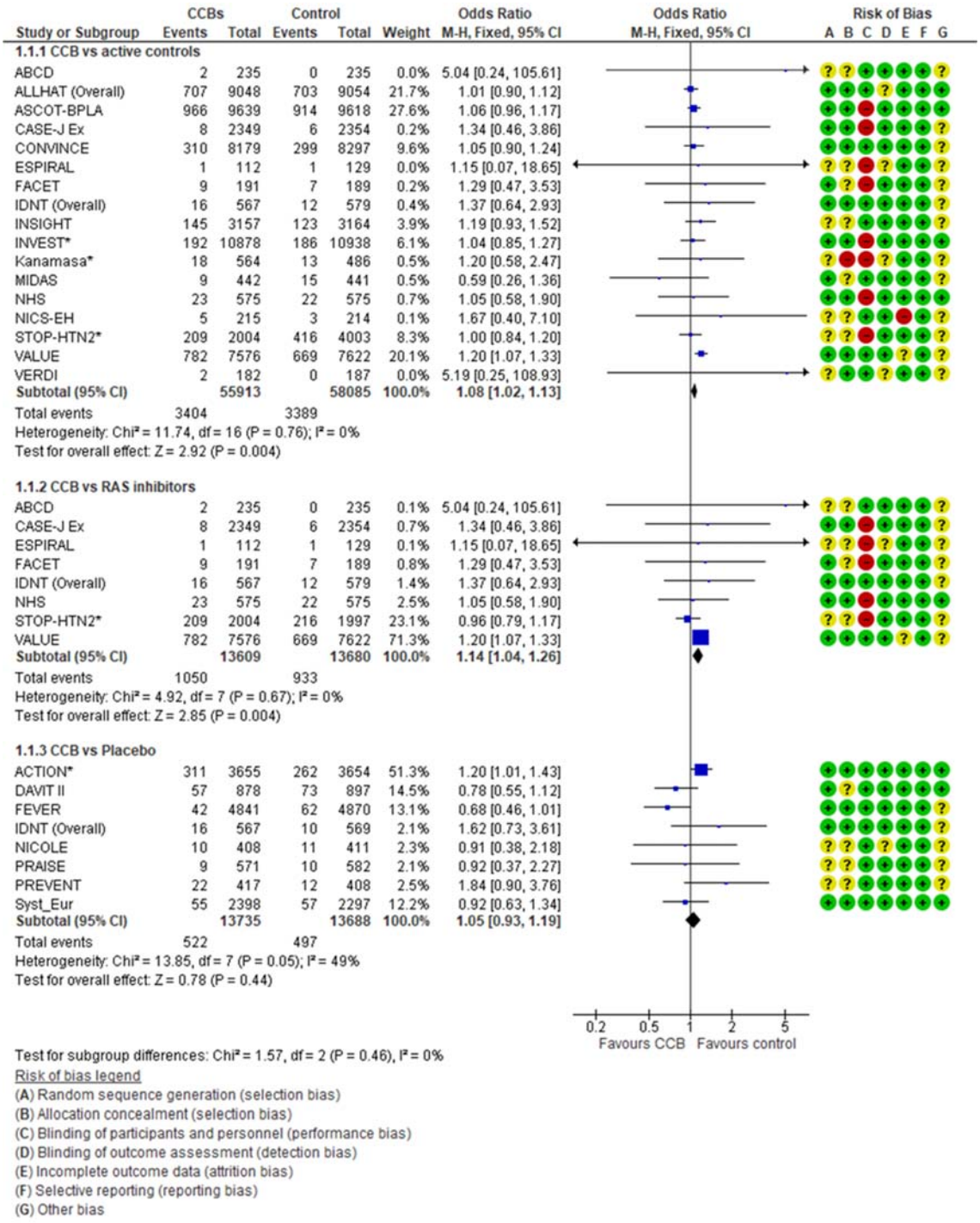


Figure 6-15: Forest plot of cancer incidence by comparators [FE model].
1) Active controls; 2) RAS inhibitors; 3) Placebo. The subtotal effect represents the pooled estimate of odds for cancer incidence for each comparator. * Included were patients with no history of cancer or active cancer at baseline.

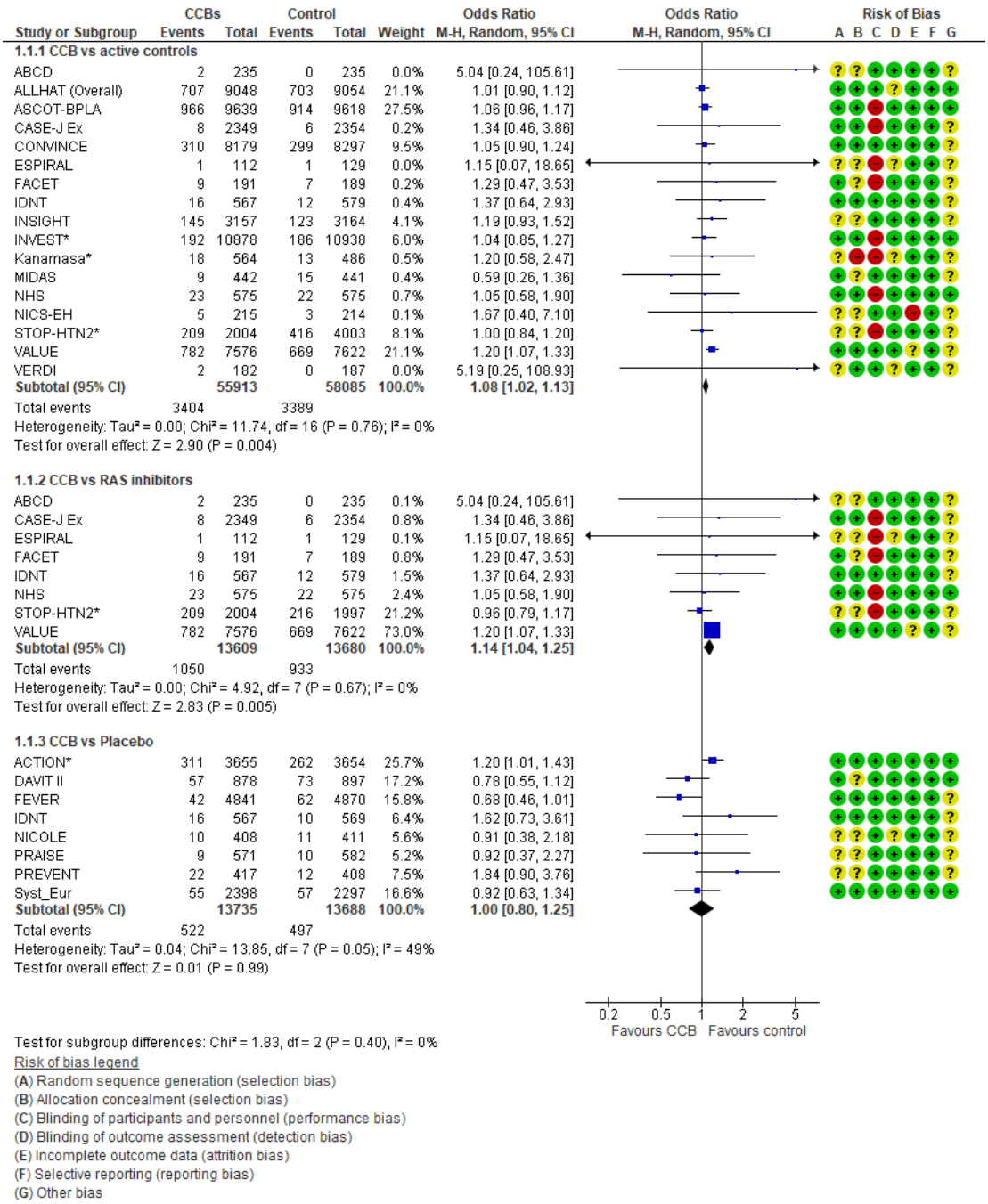


Figure 6-16: Forest plot of cancer incidence by comparators [RE model].
1) Active controls; 2) RAS inhibitors; 3) Placebo. The subtotal effect represents the pooled estimate of odds for cancer incidence for each comparator. * Included were patients with no history of cancer or active cancer at baseline.

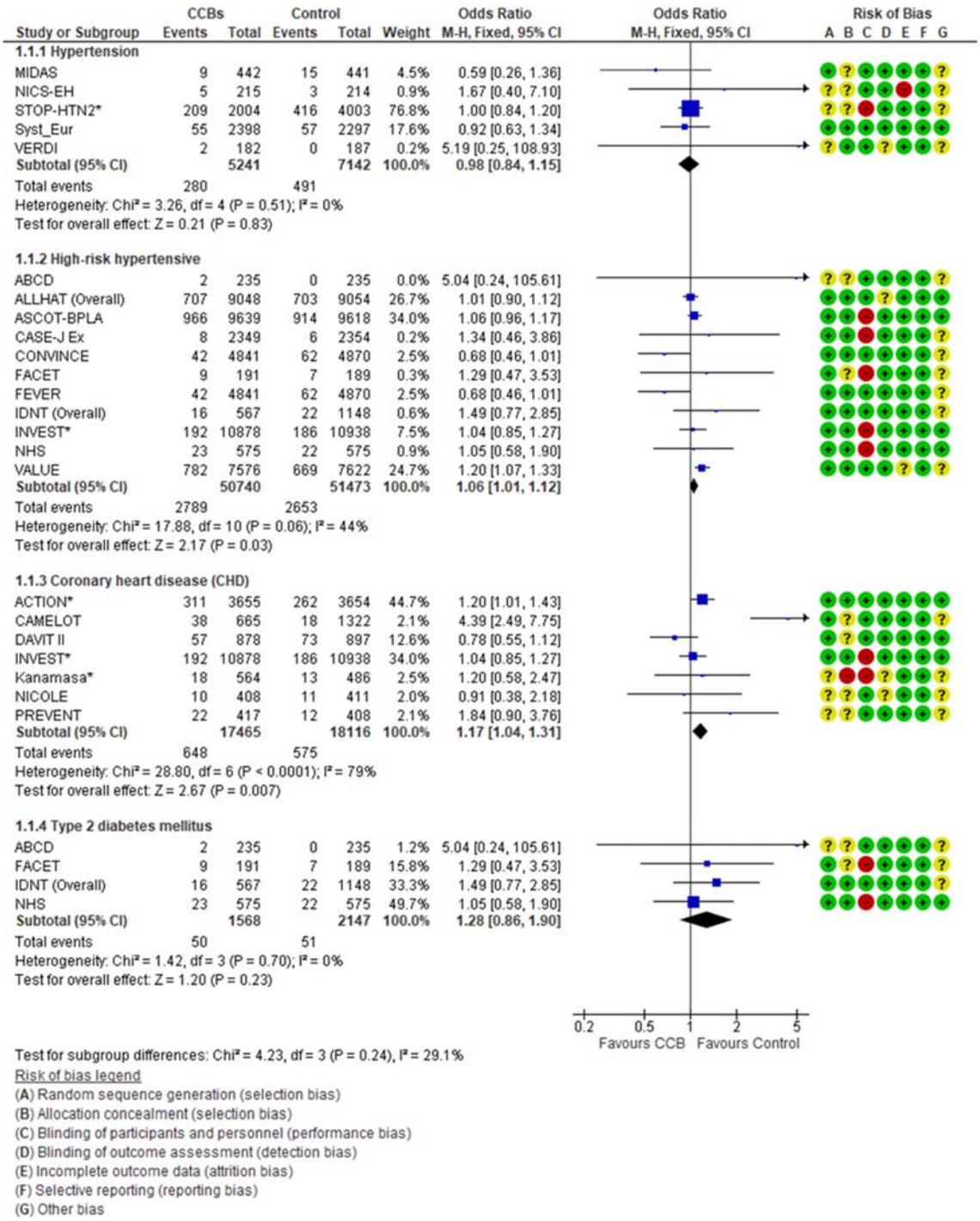


Figure 6-17: Forest plot of cancer incidence by clinical setting [FE model].
1) Hypertension; 2) High-risk hypertension; 3) Coronary heart disease; 4) Type 2 diabetes mellitus. The subtotal effect represents the pooled estimate of odds for cancer incidence for each clinical setting. * Included were patients with no history of cancer or active cancer at baseline.

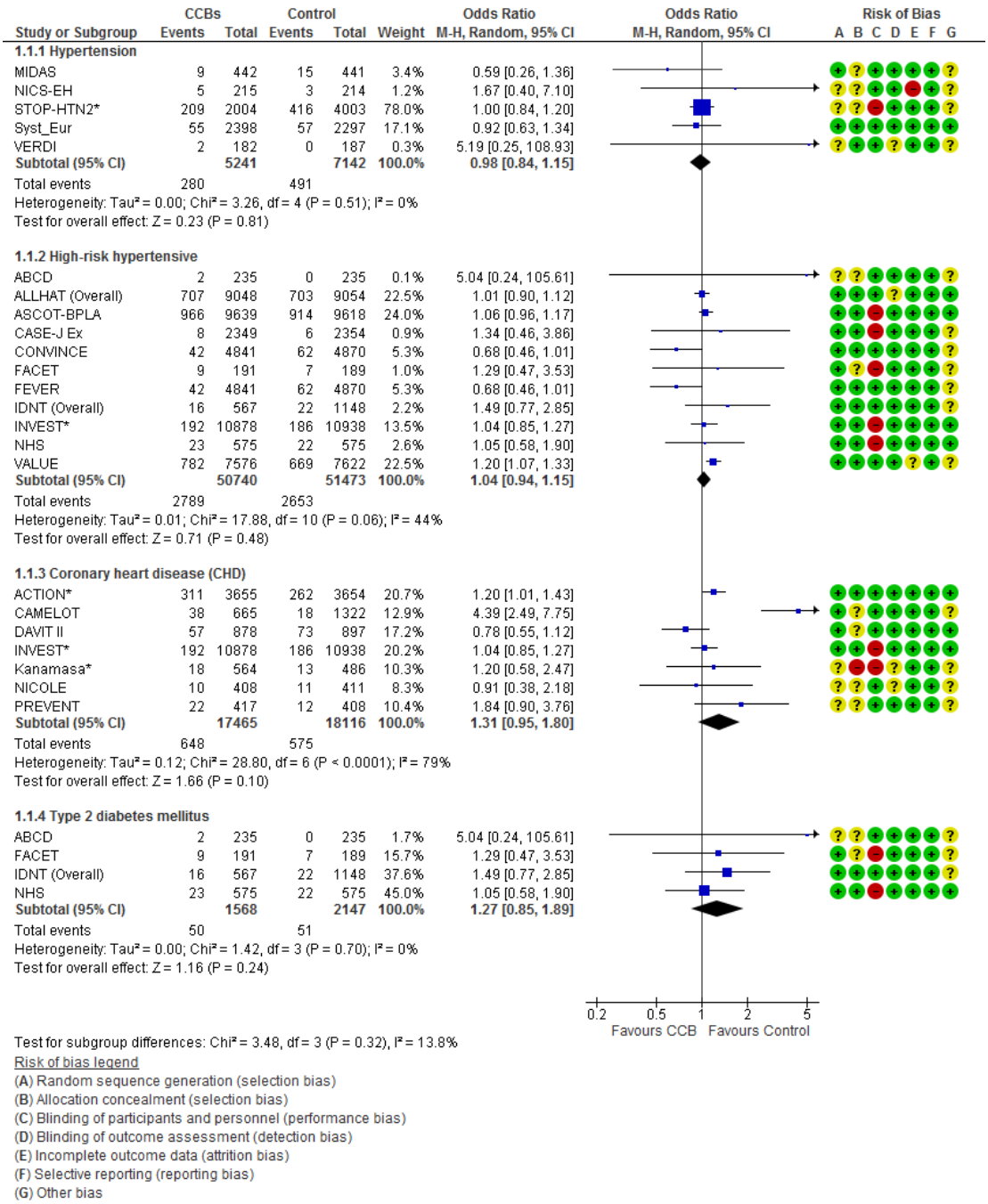


Figure 6-18: Forest plot of cancer incidence by clinical setting [RE model].
1) Hypertension; 2) High-risk hypertension; 3) Coronary heart disease; 4) Type 2 diabetes mellitus. The subtotal effect represents the pooled estimate of odds for cancer incidence for each clinical setting. * Included were patients with no history of cancer or active cancer at baseline.

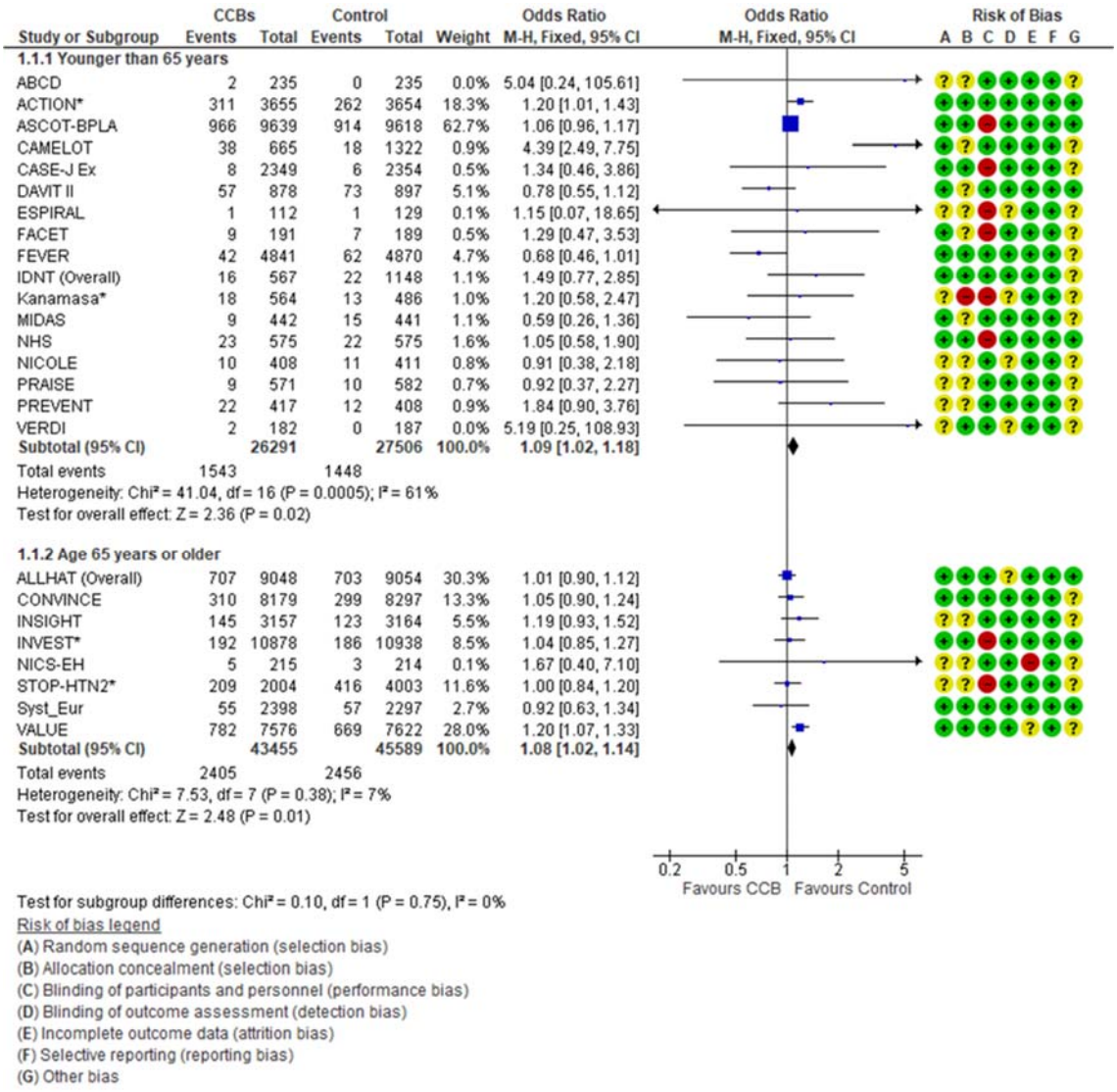


Figure 6-19: Forest plot of cancer incidence by mean age [FE model].
1) ≤ 65 years; 2) ≥ 65 years. The subtotal effect represents the pooled estimate of odds for cancer incidence for each criterion. * Included were patients with no history of cancer or active cancer at baseline.

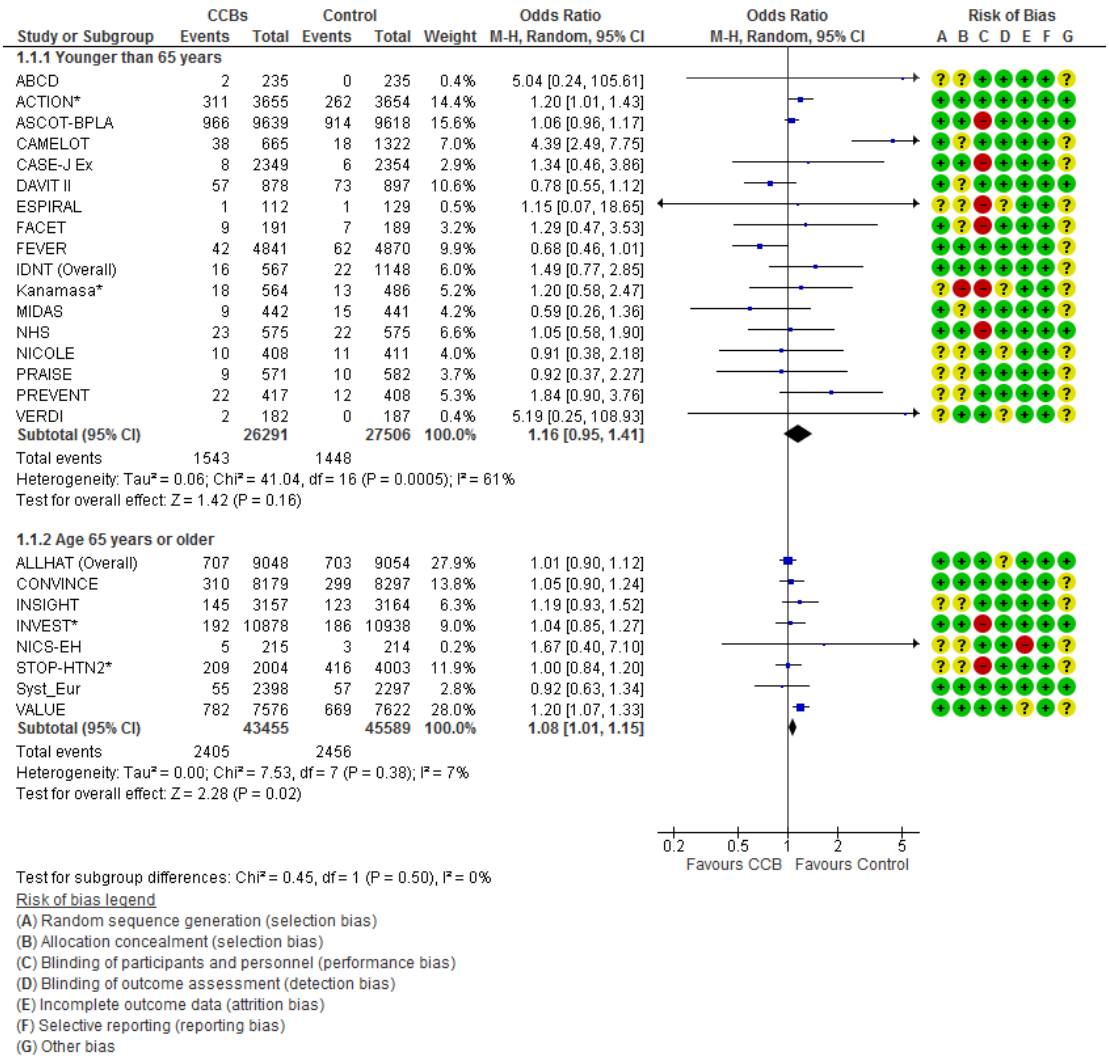


Figure 6-20: Forest plot of cancer incidence by mean age [RE model].
1) ≤ 65 years; 2) ≥ 65 years. The subtotal effect represents the pooled estimate of odds for cancer incidence for each criterion. * Included were patients with no history of cancer or active cancer at baseline.

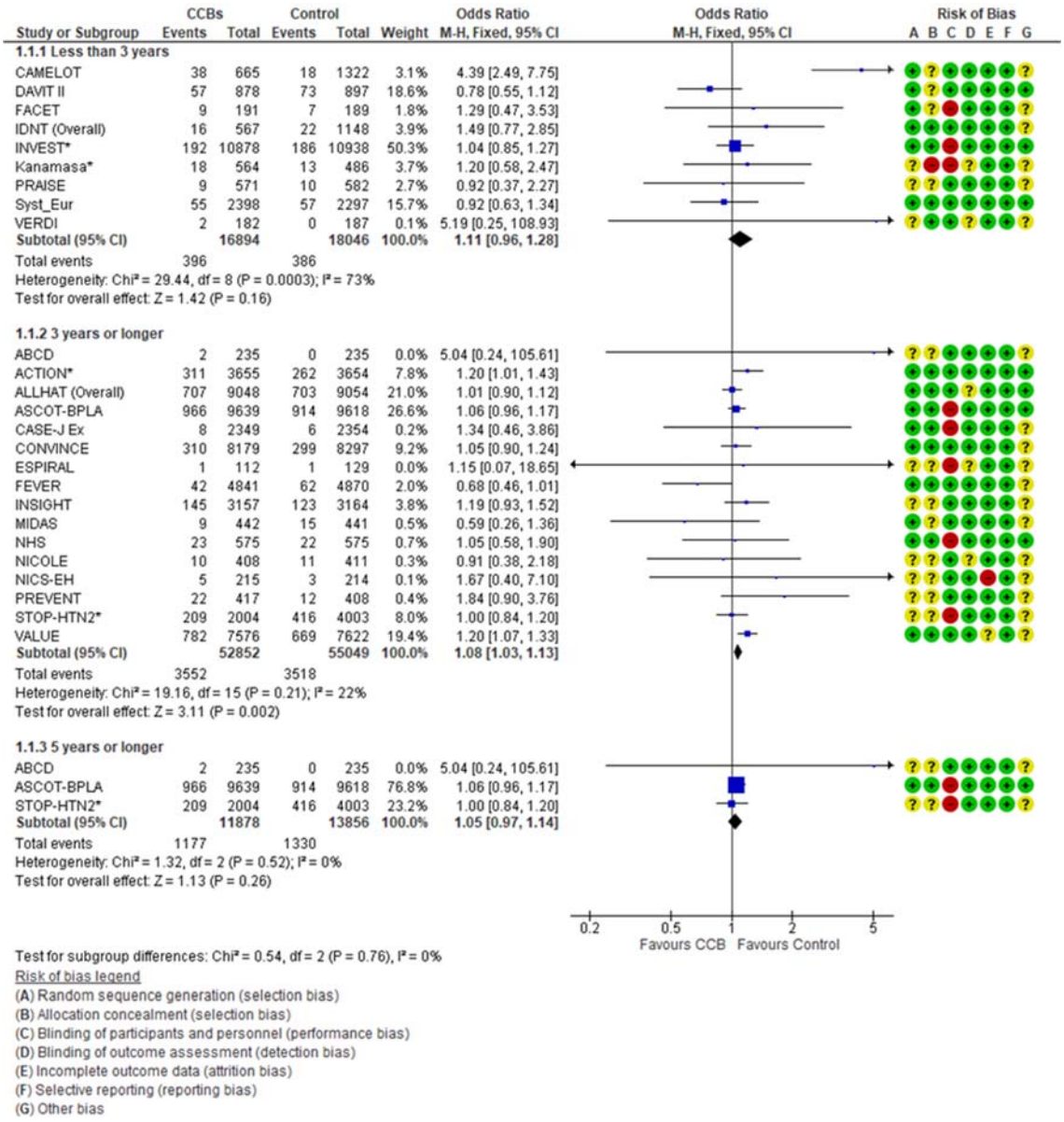


Figure 6-21: Forest plot of cancer incidence by study mean duration of follow-up [FE model].

1) Follow-up less < 3 years; 2) Follow-up ≥ 3 years 3) Follow-up ≥ 5 years. The subtotal effect represents the pooled estimate of odds for cancer incidence for each criterion. * Included were patients with no history of cancer or active cancer at baseline.

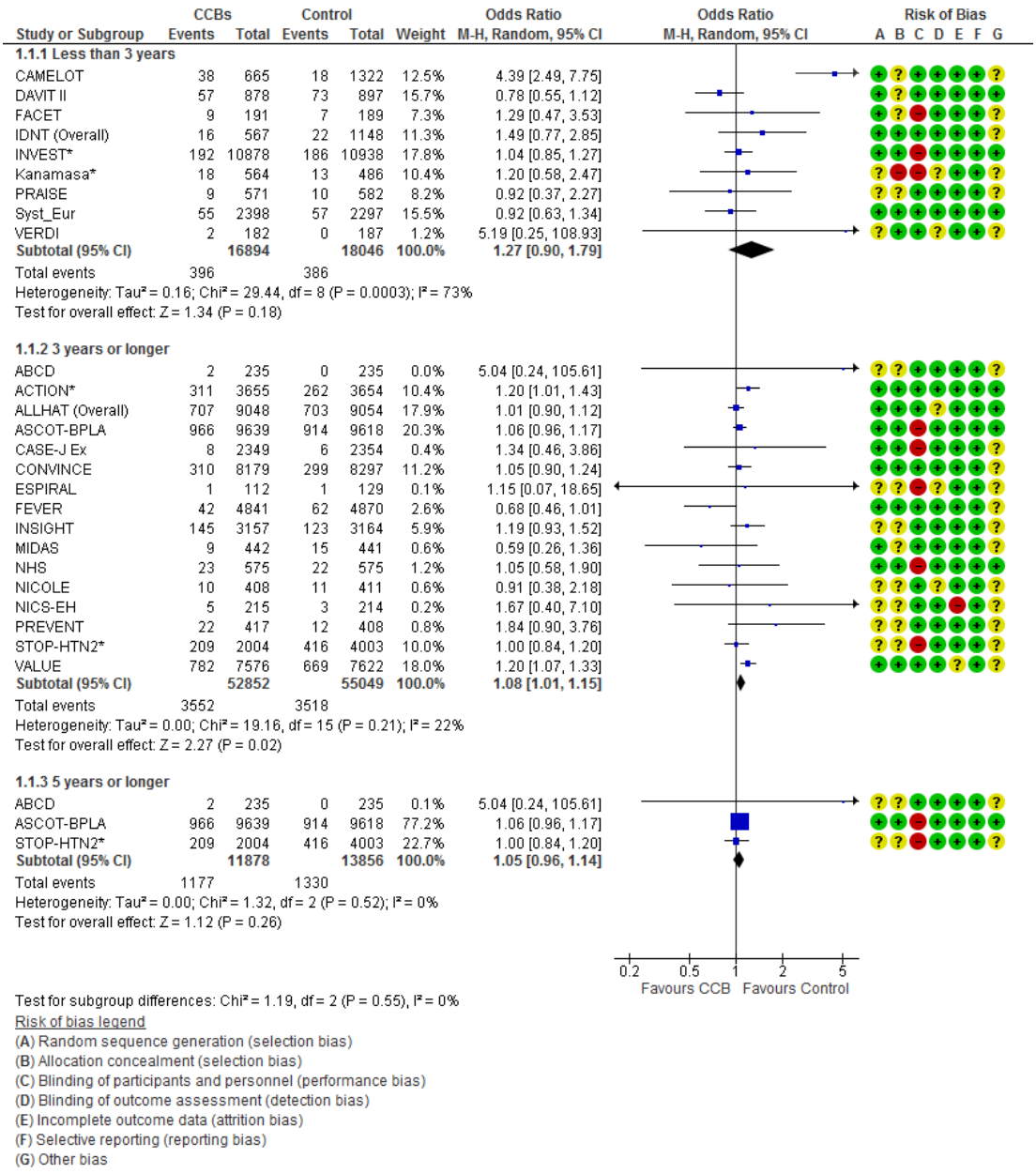


Figure 6-22: Forest plot of cancer incidence by study mean duration of follow-up [RE model].
1) Follow-up less < 3 years; 2) Follow-up ≥ 3 years 3) Follow-up ≥ 5 years. The subtotal effect represents the pooled estimate of odds for cancer incidence for each criterion. * Included were patients with no history of cancer or active cancer at baseline.

6.5 CCB and cancer-related death

Altogether, 15 trials were eligible and included in the meta-analysis of CCB and risk of cancer-related mortality. Data were available from 84,840 (99.2%) patients out of 85,535 patients enrolled in the fifteen studies. Based on randomised treatment allocation, cancer-related death was 2.23% in the CCB treatment group versus 2.64% in the control group.

In the FE model (**Figure 6-23)**, the ALLHAT study contributed the biggest influence in this meta-analysis as it was given almost half of the overall weight (45.9%). This is followed by the ASCOT-BPLA study carrying 33.1% of the overall weight assigned between the fifteen included trials. Five trials (APSIS, CONVINCE, FACET, IDNT, INTACT) have observed non-significant increased odds for cancer in the CCB treatment arm whereas the MIDAS study is the only trial that had observed no different in cancer odds between treatment and control (OR 1.00, 95% CI 0.29-3.47). All the remaining nine trials in the meta-analysis had recorded decreased OR for cancer in the CCB treatment arm. From the forest plot, the 95% CI of all the studies overlaps 1 as all the CIs cross the line of no effect indicating no statistical significance at the study level. The diamond representing the combined estimate was located to the left side of the forest plot with its right edge impinging the line of no effect indicating no statistical significance at 5% significance level. The combined effect estimate resulted in OR 0.95 with 95% CI between 0.86 and 1.04 (P-value = 0.25).

Figure 6-24 showed the result of this meta-analysis in a RE model. The weighting of all fifteen studies was comparable to the weighting assigned in the FE model. Additionally, both FE and RE meta-analysis agreed on the combined OR of 0.95 (95% CI 0.86-1.04).

The chi-square statistic for heterogeneity recorded a P-value of 0.59 indicating no statistical evidence for a difference between the fifteen included studies. Additionally, the I^2 statistics observed at the value of 0% suggests no statistical difference between the studies.

Furthermore, the funnel plot as shown in the Appendix Figure A-2 demonstrates missing study in the middle left and bottom right side of the plot. No outlier study detected lying outside the triangular region within which 95% of studies are expected to lie in the absence of both biases and heterogeneity. The funnel plot asymmetry is most likely due to selective outcome reporting bias when located studies may not provide usable data for the outcome of interest.

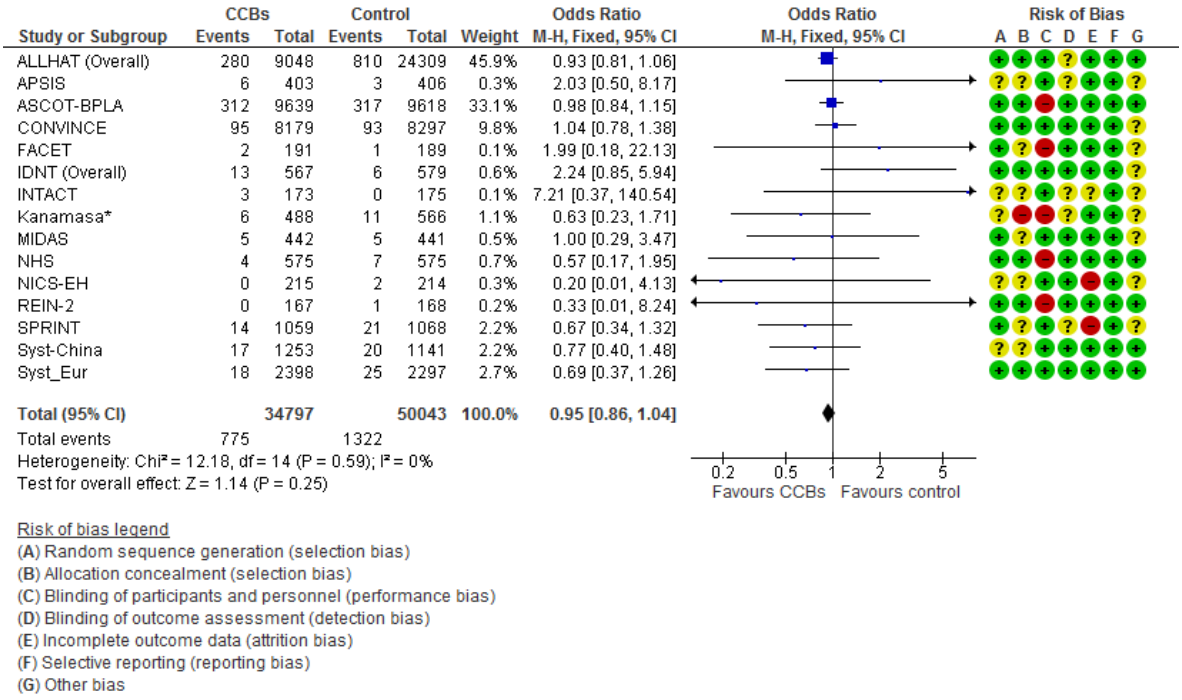


Figure 6-23: Forest plot of cancer-related death by CCB versus non-CCB controls [FE model]
Odds ratios and 95% confidence interval, overall and in 15 trials. The overall effect represents the pooled estimate of odds for cancer-related death.

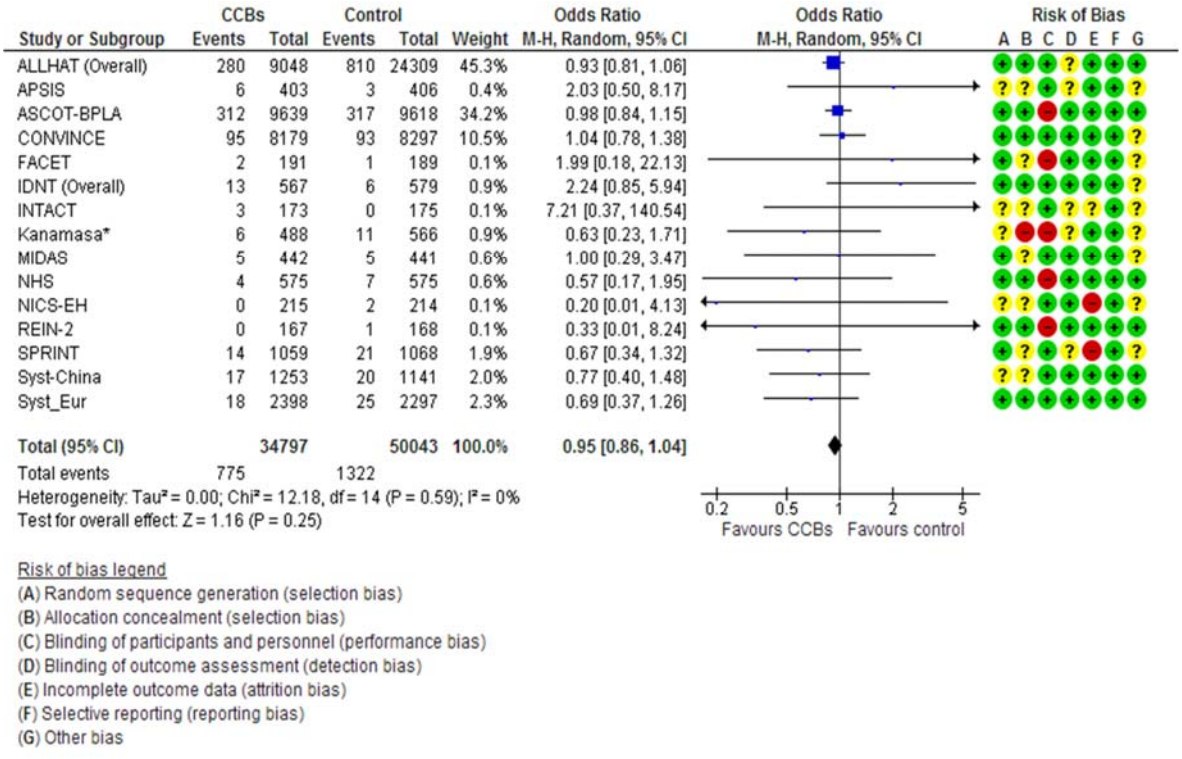


Figure 6-24: Forest plot of cancer-related death by CCB vs non-CCB controls [RE model].
Odds ratios and 95% confidence interval, overall and in 15 trials. The overall effect represents the pooled estimate of odds for cancer-related death.

6.6 Discussion

The results from the current study suggest marginally significant increased risks for cancer overall with use of CCB in both FE (OR 1.08, 95% CI 1.03-1.13) and RE model (OR 1.09, 95% CI 1.00-1.19). Both FE and RE meta-analyses were used in the remaining sensitivity and subgroup analyses because of the substantially high heterogeneity between studies as indicated by a significant chi-square test (P-value = 0.002) and I^2 index of 51%. Also, sensitivity analyses showed trends towards a positive association between CCB and cancer risk. However, this meta-analysis showed that CCBs have no impact on cancer-related death.

The association between CCB and cancer incidence from this study is similar to the most recent meta-analysis published by Bangalore et al. (2011). They have included 22 RCTs using CCB as one of its study drugs and reported a summary OR of 1.06 (95% CI 1.01-1.11) with a moderate index of heterogeneity observed (I^2 = 27.8%). Additionally, Bangalore and colleague have conducted a network meta-analysis including altogether 70 trials and 324,168 participants. Multiple indirect comparisons showed no significant relationship to risks of cancer when compared to other antihypertensive agents or controls, except for beta-blockers (OR 1.08, 95% CI 1.01-1.15). An identical network meta-analysis of 27 RCTs using major antihypertensive classes was applied by Coleman et al. (2008). Compared to Bangalore, this study has more relaxed inclusion criteria because they have included study with a shorter duration of follow-up (six months). The overall OR for CCB was reported as 0.95 (95% CI 0.79-1.13) with the remaining pairwise comparison demonstrated a lack of significant association between treatment and cancer. Nevertheless, network meta-analysis is more subject to erroneous conclusions than a routine meta-analysis and tends to only be valid for very similar studies. Besides, one of the included studies in the meta-analysis by Bangalore and colleagues was identified as non-RCT (Gong et al., 1996) and inaccurate cancer data was imputed for the MIDAS study. Both cancer incidence and cancer-related deaths from this study were used in the meta-analysis of CCB and cancer risk.

A review by Frishman (2007a) has outlined the differences between DHP and non-DHP CCBs in term of pharmacological effects which may translate into differences in clinical outcomes for certain conditions. Although both subclasses share a

common mechanism of action, DHP CCBs tend to be a more potent vasodilator whereas non-DHP CCBs has a marked negative inotropic effect. These differences in clinical effects also may contribute to the varying safety profile. Due to the DHP CCBs' potent peripheral vasculature vasodilatory effects, patients on these agents are more predisposed to experience a headache, facial flushing, and ankle oedema compared to non-DHP CCBs. Likewise, patients on non-DHP CCBs are more likely to experience atrioventricular (AV) conduction disturbances due to its negative chronotropic effects. Numerous literature published to date have shown interest in the potential risk of cancer with CCB use, but limited data were available for the difference in risk between DHP and non-DHP subclass. The subgroup analyses from the current review demonstrated a positive relationship between DHP CCBs and the risk of cancer with OR 1.11 (95% CI 1.00-1.23) at borderline significance (P-value = 0.05). However, a considerable disagreement between the FE model (OR 1.08 (95% CI 1.03-1.13; P-value = 0.002) and RE model estimates reflect the heterogeneity present between the studies, therefore pooling of studies is not recommended. Lack of significant difference was observed for non-DHP CCBs (OR 1.01, 95% CI 0.90-1.14). Bangalore and colleagues (2011) also observed a comparable association in their meta-analysis of 18 DHP and four non-DHP CCB trials. They reported an OR of 1.06 (95% CI 1.01-1.12) and OR 1.02, 95% CI 0.90-1.15) for the former and latter respectively. These findings support the hypothesis that, unlike DHP CCBs, non-DHP CCBs do not affect risks of cancer. This is also supported by a much earlier meta-analysis of 39 RCTs using verapamil published two decades ago (Dong et al., 1997). The authors have reported a lack of significant associations between verapamil and active treatment or placebo for cancer incidence and cancer deaths. However, this study exercised less strict inclusion criteria in which they allowed studies with 10 participants enrolled and lasted for at least seven days duration.

Additionally, when compared to the different type of comparators, the subgroup analysis from the current review showed increased risk of cancer for patients in the CCB group versus any active controls (OR 1.08, 95% CI 1.02-1.13; P-value = 0.004) and renin-angiotensin system (RAS) inhibitors (OR 1.14 95% CI 1.04-1.25; P-value 0.005). Majority of these studies used DHP CCBs as their study drug and all studies, except one, have shown trends toward a positive association with OR more than 1 which may have contributed to the significant increase in cancer risk.

In the RAS inhibitors subgroup, all the studies have used DHP CCB as a comparator. These results corroborate the other findings as discussed in the previous chapters (See Chapter 4, Section 4.6.5 and Chapter 5, Section 5, Section 5.6.2) where the comparison between ARB or ACEI versus CCB showed reduced or no difference respectively in risk for cancer in the RAS inhibitors group. Concern regarding cancer risk associated with antihypertensive agents particularly the ARB and CCB has been constant in recent years. A meta-analysis of nine RCTs by Sipahi et al. (2010) has sparked a controversy with the safety of ARB use. This study reported a moderate increased in new cancer incidence, especially lung cancer, in those using ARB. However, a subsequent meta-analysis of 15 major ARB trials (Teo, 2011) did not confirm this and has alternatively concluded that ARB treatment was not associated to the risk of any or specific cancer incidence as well as cancer deaths. The only hypothesis that could be drawn from this finding is that treatment with RAS inhibitors in general and ARB specifically in comparison to CCB is safer in term of cancer risk. Though still unclear, the cellular effect exerted by CCB mechanism of action may have some impact on cancer risk.

Conversely, a meta-analysis of 21 observational studies has shown a lack of association for both CCB subclasses (Ni et al., 2017). The authors investigated the use of major antihypertensive drug classes and risk of breast cancer and found no differences in either DHP or non-DHP CCB use. Alternatively, the authors suggested that prolonged use of ACEI or ARB therapy has a beneficial effect on breast cancer risk. However, this meta-analysis was limited by potential bias and confounders inherent in observational studies. A much earlier pre-clinical experimental study has assessed the carcinogenic potential of DHP CCBs in rodents for two years (Ahr et al., 1998). Groups of 50 male and 50 female rats each were treated with nifedipine, nisoldipine, nimodipine, or nitrendipine and were compared to control. The investigators have found no evidence for the carcinogenic potential of DHP CCBs.

Age has long been established as one of the risk factors for cancer with incidence rates increasing with age for most cancers. An American statistic in 2009 has shown that more than half of cancers occurred in adults aged 65 years or older (U.S. Cancer Statistics Working Group, 2017). Likewise in the UK, the peak age for cancer occurrence ranged between 65 to 75 years for both males and females between the year 2012 and 2014 (Cancer Research UK, 2017). A subgroup analysis

assessing age and risk of cancer has yielded a positive association in patients age 65 years or older (OR1.08 95% CI 1.01-1.15) which agrees to the aforementioned evidence. It has been suggested that some of the biologic mechanism in ageing may be involved in the pathogenesis of certain age-related diseases such as cancer. Some of the hallmarks for aging are also shared by cancer which includes genomic instability and epigenetic alteration (Collado et al., 2007, Hanahan and Weinberg, 2011, López-Otín et al., 2013). Aging is also commonly implicated in chronic diseases where stress and inflammation plays an important role. A subgroup analysis in this review has shown that different health settings do not significantly affect the risk of cancer. Although all the different subgroups showed trends toward increased cancer risk, lack of significance suggests the effect of CCBs are independent of patients' health background and illness severity.

Previous epidemiological studies have also linked prolong use of CCB to increased cancer risk. A population-based case-control study by Li et al. (2013) investigated the risk of breast cancer among females aged 55 to 74 in a tri-county metropolitan area. The investigators have found that long-term use of CCB for ten years or more was associated with increased risk for ductal and lobular breast carcinoma. Following this, a meta-analysis of 17 observational studies reported an OR of 1.71 (95% CI 1.01-2.42) for breast cancer in patients taking CCB for more than 10 years (Li et al., 2014b). In a subgroup analysis based on follow-up duration, studies with a follow-up of three years or longer have shown an increased risk for cancer (OR 1.08, 95% CI 1.01-1.15). This evidence suggests that CCB may exhibit a cumulative dose relationship with cancer. However, the association was not significant for studies followed for five years or longer. The most likely reason was due to only a few numbers of studies (n=3) were available. Two of the three included studies reported an OR more than 1 though their 95% CI crossing 1. Quite the contrary, a recently published study using the Women's Health Initiative cohort reported no association to cancer was observed when CCBs were considered by the duration of use, length of action, or drug class (Brasky et al., 2017). Yet, this study showed an elevated risk for triple-negative breast cancer (HR 1.60, 95% CI, 1.04–2.48) which warrants further consideration. The underlying mechanism by which CCB affects breast cancer development is not clear. It is possible that breast tissue is more prone to alteration in apoptotic activity than other tissues. Moreover, the growth and differentiation of mammary gland are independently modulated by

hormones such as oestrogen and progesterone thus suggests a feasible interaction between apoptosis and hormonal activity. Therefore, more related studies are required to clarify this hypothesis.

In another aspect, many studies have shown beneficial effects of CCBs in general when used in conjunction with standard chemotherapy in cancer patients. The notion that CCB increases antineoplastic sensitivity has been explored since the 1980s and has been solely focused on verapamil. In one of the earliest study, Tsuruo et al. (1981) used a mice model with leukaemia to assess the effect of verapamil when used concomitantly with antineoplastic agents. Verapamil has been showed to increased cytotoxicity of both vincristine and vinblastine by increasing cellular uptake and inhibiting the efflux of these agents from tumour cells. Subsequently, a review of in-vitro and in-vivo studies has reported the sensitivity of various types of tumour cells resistant towards several cytotoxic therapies including doxorubicin and thiotepa was augmented by verapamil (Simpson, 1985). Also, verapamil improves patients survival by reversing multidrug resistance (MDR) in patients with breast cancer (Timcheva and Todorov, 1996, Belpomme et al., 2000), and multiple myeloma (Salmon et al., 1991). In a recent experimental study, Chiu and team (2010) have assessed the efficacy of verapamil, diltiazem, and nifedipine to reverse vincristine- and doxetacel-induced resistance in human lung cancer lines. Verapamil was reported to only sensitize cell lines but has no effect on parent cancer cells. They also found that diltiazem and nifedipine also sensitize cell lines but with lower efficacy than verapamil. Hence, inhibition of calcium channels may provide a potential target in cancer chemotherapy.

6.6.1 Study strengths and limitations

The main strength of this review is that only RCTs were included and this study design is regarded as the gold standard for evaluating the effectiveness of an intervention. Apart from strong internal validity, RCTs also balances both measure and unmeasured confounders. To the best of found knowledge, this is the largest systematic review and meta-analysis of RCTs associating CCB and cancer risk. In addition, this systematic review search spans over a period of 60 years which eventually adds and updates the most recent review which was published in 2011 (Bangalore et al., 2011). Cancer outcomes data from the CASE-J Ex, NHS, and

INTACT were only incorporated in this meta-analysis of CCB trials and risk of cancer.

Nevertheless, this review has its limitations. Firstly, the majority of the studies included in this review were not designed to detect cancer incidence as one of their endpoints. The inclusion of patients with baseline cancer in the analysis is possible as not all studies stated whether such patients were excluded and this could lead to a spurious result. However, incorporating such patients in the meta-analysis where applicable did not significantly impact the summary effect as demonstrated in the sensitivity analysis. Then again, the diagnosis of malignancy was adjudicated variably across the different studies. Second, only aggregate data were available for all the studies. Therefore, time-to-event analyses were not performed. Additionally, the majority of the cancer outcomes available were limited to cancer incidence, not to the incidence of a different type of cancers.

The longest study follow-up was nine years with the majority of the studies follow-up lasted approximately five years or less. Therefore, the chance to detect a pro-cancer or anti-cancer effect of the study drug within this short period of time could be decreased. Additionally, the results of this study could only reflect late-detected cancers. Furthermore, this meta-analysis is limited to evaluation CCB as a drug class, not individual CCBs.

6.6.2 Conclusion

There is evidence suggesting that CCB use, particularly DHP CCB, is associated with an elevated risk for cancer as a whole. However, the disagreement between FE and RE meta-analyses suggests further evaluation of trials with minimal heterogeneity between studies where possible. Additionally, a properly designed further research into the risk of a specific type of cancer with the use of DHP CCB is warranted.

7 Association between beta-adrenergic blockers (BB) and risks of cancer

7.1 Introduction

The adrenergic nervous system (ANS) or also known as the sympathetic nervous system is mainly mediated by neurotransmitters released by adrenergic neurones known as epinephrine and norepinephrine (NE). These neurotransmitters are also collectively termed as catecholamines. The receptors these catecholamines stimulate are called adrenergic receptors or adrenoceptors. There are two distinct types of adrenoceptor classified as alpha (α)- and beta (β)-adrenergic receptors. Beta-adrenergic receptors (β-AR) exists as three distinct subtypes: β_1, β_2, and β_3 (Figure 7-1). Meanwhile, two α-adrenergic receptor major subtypes are α_1 and α_2. Both α- and β-adrenergic receptors belong to the G-protein-coupled receptor superfamily and utilize a variety of second messenger pathway to modulate cellular function. The β-AR are mostly involved in the relaxation of effector cells and dilatation of blood vessels. However, stimulation of β_1-adrenoceptor in the heart increases the force and rate of myocardial contractility causing the heart to beat faster while stimulation of β_1-AR in the kidney increases renin secretion from the juxtaglomerular cells. Once the β-AR has been described, blockade of this receptor became feasible.

In general, BB antagonises the effect of sympathetic nerve stimulation or action of catecholamines on the β-AR which is widely distributed all over the human body system. The β_1-AR are primarily distributed in the heart and kidney while the β_2-AR are predominant in other organs such as the lung, vascular smooth muscle, and skeletal muscles. BP lowering effect of BB involves the following mechanism (Rang, 2016):[1] reduction in cardiac output by blockade of the β1-AR located in the sino-atrial node and myocardium, [2] reduction of renin release from the juxtaglomerular cells by blockade of the β1-AR located in the kidney, and [3] reduction of sympathetic activity where blockade of the β-AR located in the central and peripheral nervous system inhibits the release of sympathetic neurotransmitters

Table 7-1 showed some of the properties possessed by individual BB which includes β1-blockade potency ratio, relative β_1-AR selectivity, and intrinsic

sympathomimetic activity (ISA). The ß1-blockade potency ratios are compared to propranolol which has a ratio of one. The BBs are further categorised into ß1-AR selective or cardioselective BB and ß1-AR non-selective or non-cardioselective BB, according to their abilities to antagonize sympathetic amines in low doses at some tissues than in other tissues. Furthermore, the BBs also differs in term of ISA which means some of the BB such as pindolol mimics the effect of catecholamines and may cause an increase in BP and heart rate. In general, cardioselective BBs antagonise the $ß_1$-AR in the heart at low doses but have less effect on $ß_2$-AR in the bronchial and vascular locations. At higher doses, cardioselective BB can block $ß_2$-AR causing bronchospasm in susceptible patients. However, cardioselective BB is safer in patients with bronchospastic diseases because the $ß_2$-adrenergic receptors can still be stimulated by $ß_2$-adrenergic agonist to facilitate bronchodilation.

7.1.1 BB and cancer

Previous studies have found that the use of BB is associated with a lower risk of cancer (Perron et al., 2004, Monami et al., 2013). The proposed underlying mechanism is related to the inhibition of stress mediators such as catecholamines from activating ß-AR signalling to inhibit cellular proliferation and cellular migration and invasion (Fitzgerald, 2009, Guo, 2009b). Sood and colleagues (2006) have conducted an in-vitro study using ovarian cancer cells that were exposed to increasing levels of epinephrine, NE, and cortisol. They reported that both catecholamines had significantly enhanced cell invasiveness. As for cortisol, although cell invasiveness significantly increased, the effect of cortisol was substantially smaller than that observed in catecholamines. This finding was further supported by another experimental study by Guo (2009b) using human pancreatic cell lines. The investigators demonstrated that both ß-AR subtypes were expressed in the human pancreatic cancer cells and cells pre-treated with NE displayed significant cellular invasion at an average ~2.5 fold increase compared to control. Guo and colleague also found that propranolol inhibits NE-mediated increase in matrix metalloproteinases (MMP) and vascular endothelial growth factor (VEGF) which are thought to play a role in cell proliferation, migration, differentiation, and angiogenesis (Duffy, 2000-2013, Rodríguez et al., 2010). Using a different cancer cell type, Liao (2010) evaluated the involvement of ß-AR, nuclear factor κB (NF-κB), MMP-2 and -9, VEGF, and cyclooxygenase-2 (COX-2) in modulating cell apoptosis and cell cycle arrest by propranolol in human

gastric adenocarcinoma cell lines. In addition to decrease production of pro-angiogenic and pro-proliferation cytokines, the author also found that pro-inflammatory cytokines (NF-κB and COX-2) were also reduced after treatment with propranolol. Propanolol also induced arrest of the resting and mitotic cell cycle in gastric cancer cells. Therefore, experimental studies discussed earlier have indicated that BB affects cancer development by inhibiting the ß-AR signalling pathway and subsequently decrease the release of pro-inflammatory, pro-angiogenic and pro-mitotic mediators. Evidence from observational studies is discussed in Chapter 1, Section 1.9.5 (page 50).

This chapter aims to systematically review and report the meta-analysis of RCTs using BB as one of its treatment and its association with risks of cancer.

Table 7-1 : Pharmacodynamic effects of β-adrenergic blocking drugs

	β_1 - Blockade Potency Ratio (Propanolol = 1.0)	Relative β_1 Selectivity	Intrinsic Sympathomimetic Activity (ISA)
Acebutolol	0.3	+	+
Atenolol	1.0	++	0
Betaxolol	1.0	++	0
Bisoprolol	10.0	++	0
Carteolol	10.0	0	+
Carvedilol*	10.0	0	0
Esmolol	0.02	++	0
Labetolol*	0.3	0	+
Metoprolol	1.0	++	0
Nadolol	1.0	0	0
Penbutolol	1.0	0	+
Pindolol	6.0	0	++
Propanolol	1.0	0	0
Sotalol	0.3	0	0
Timolol	6.0	0	0

+ indicates modest effect; ++, strong effect; 0, no effect.
* possess additional α_1-adrenergic blocking activity.
Adapted from Frishman and Saunders (2011).

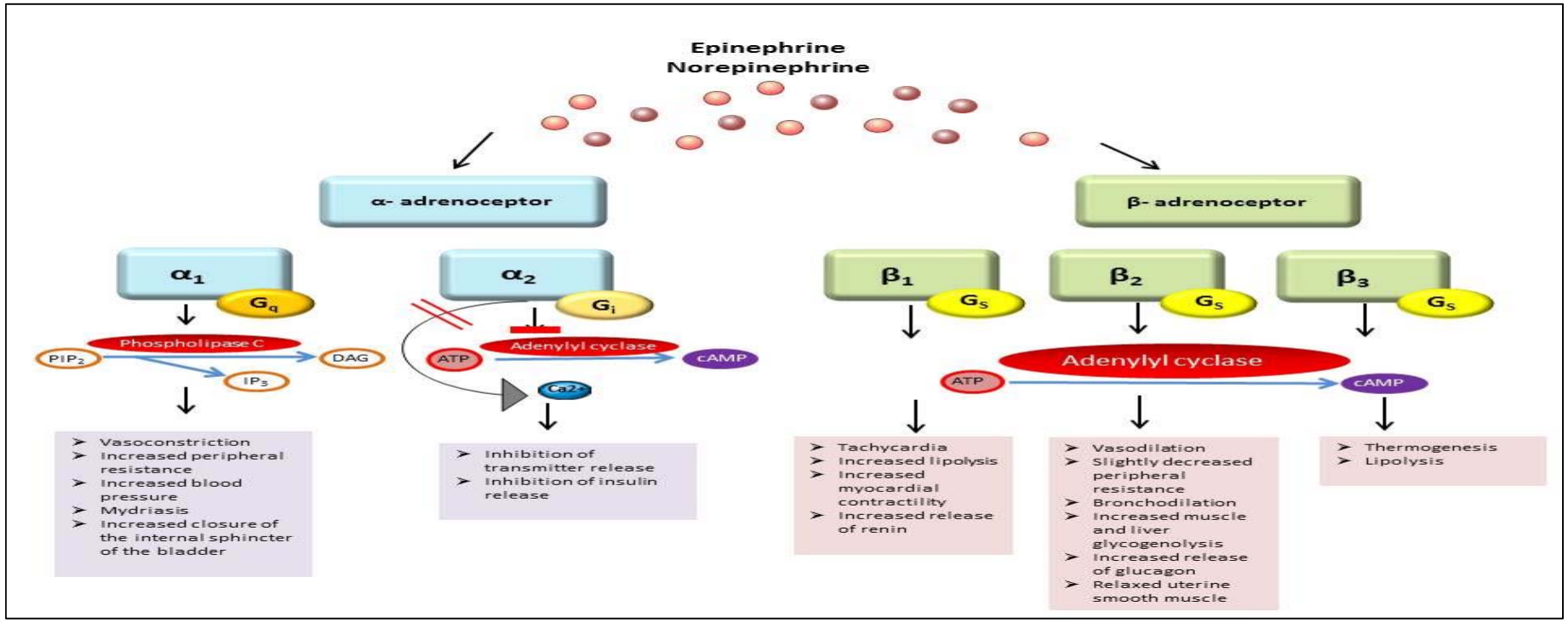


Figure 7-1 Adrenergic receptors.
β-adrenoceptors are coupled with the stimulatory G-protein subunit (Gs) that activates adenylyl cyclase when stimulated by cateholamines and leads to an increase in cAMP. Modified from Frishman (2007b).

7.2 Methodology

7.2.1 Systematic review

Full descriptions of the methods used have been described previously in Chapter 2, Section 2.1 (page 57).

Except for the MERIT-HF study (MERIT-HF Study Group, 1999), cancer outcomes for all of the included studies were published and available publicly. Cancer data for the MERIT-HF trial was provided by one of the trial investigator (Professor John Wikstrand of Wallenberg Laboratory for Cardiovascular Research, Sahlgrenska University Hospital, Göteborg University, Sweden). However, the cancer data provided comprised both benign and malignant neoplasms and were not specified whether these data were for fatal or non-fatal cancers. Therefore, all data were treated as incident cancer with only malignant data were included.

7.2.2 Meta-analysis

For data synthesis, see Chapter 2 Section 2.1.7.4 (page 66).

For BB and risk of incident cancer, sensitivity analyses were performed by excluding trials with the following criteria: [1] small sample size with the number of total participants less than 1000 which; [2] poor methodological quality; [3] studies with different add-on therapy protocol;and [4] studies with ambiguous cancer outcomes. With regard to BB and risk of cancer-related death, a sensitivity analysis was conducted by excluding the MRC (MRC Working Party, 1985) and MRCOA (MRC Working Party, 1992) due to high risk of attrition bias. Additionally, a sensitivity analysis was conducted by the inclusion of the CONVINCE (Black et al., 2003) and STOP-HTN2 (Lindholm et al., 2001) trials. These two studies randomised patients to either BB or diuretics as one treatment arm versus other antihypertensive agents and have reported cancer outcomes collectively.

Subgroup analyses were conducted on the following theme: [1] cardio-selectivity; [2] comparator; [3] clinical setting; [4] mean age; and [5] duration of follow-up.

7.3 Results

The searching and identification process of trials is summarised in Figure 3-1 (Page 74). Altogether, 74 of the 90 studies were excluded mainly because they do not consist of BB treatment arm.

In general, the search conducted has identified 16 studies enrolling 90,956 patients with an average follow-up of 3.9 years (range 1 to 9 years). The average age of participants across all trials is 60.5 years. The full description of the studies' characteristics is described in Chapter 3, Section 3.2.2.1 whereas the methodological quality is described in Chapter 3, Section 3.3.6. The oldest eligible study was published in 1975 while the latest was 2005. No difference In term of study size was observed between old or recent studies. The largest trial was INVEST (Pepine et al., 2003), followed by ASCOT-BPLA (Dahlöf et al., 2005) and MRC where these studies recruited more than 10,000 participants.

Overall, hypertensive patients accounted for the highest proportion (85.8%) of the population studied, followed by patients with underlying CVD (13.6%) comprising CHD and HF. All of the studies enrolled patients with mean age older than 50 years. Most of the included trials were males predominant with two studies, MAPHY (Wikstrand, 1988) and VA COOP II, enrolled only male participants. Also, the proportion of smokers was exceptionally high in the Practolol Study (Anonymous, 1975a) exceeding more than half of its study population. Most of the trials' participants were followed for less than five years except for APSIS (Rehnqvist et al., 1996), ASCOT-BPLA, MRCOA, and UKPDS-38 (UKPDS Investigators, 1998) with the longest duration of follow-up was nine years.

All of the included studies are RCTs that have used BB as one of its treatment arms. Majority of the eligible studies (75%) used cardioselective BB as one its treatment. The remaining RCTs used propranolol (four studies), a non-cardioselective BB whereas Wilcox (1980) used both BB subtypes for its BB treatment arm. Nine of the RCTs compared BB to active controls which include RAS inhibitors (ACEI or ARB), CCB, and TZ. The remaining studies compared BB to placebo or no treatment.

All of the eligible studies instigated two parallel treatment arms, except for three trials. These trials have an additional treatment arm where they also randomised participants to placebo (MRC and MRCOA) or another non-specified antihypertensive agent (UKPDS-38). Most of the included studies have implemented a double-blind design. Only two RCTs (MRC and MRCOA) were single-blinded whereas the remaining three studies (ASCOT-BPLA, HEP, and INVEST) used the PROBE design.

Table A-3 (Page 321) shows the selected characteristics of interest extracted from individual trials. Overall, only one study (INVEST) reported enrolment of patients with baseline cancer while three studies (MAPHY, MRCOA, and VA COOP II) have excluded such patients in their study protocol. Only four trials aimed to identify malignancy as one of their outcomes whereas most of the eligible studies were not designed to detect cancer as their primary or secondary endpoints. Report of cancer adjudication varied across studies with only one study (Wilcox) established cancer diagnosis from study site reports.

With regard to treatment adherence, the ASCOT-BPLA, LIFE (Dahlöf et al., 2002), and SMT (Olsson, 1985) have shown good adherence (80% or more) while the rest displayed moderate adherence (more than 50%). Furthermore, the reporting of loss to follow-up was not reported consistently across studies. However, it is important to note that the MRC and MRCOA trials have reported a considerably high rate of participants' loss to follow-up at 19% and 25% respectively.

According to the risk of bias assessment as described in the general method (see Chapter 2, Section 2.4.1.3), only seven of the included trials (ASCOT-BPLA, BHAT, INVEST, LIFE, MERIT-HF, PAT, and UKPDS-38) were deemed to have a low risk of bias.

7.4 BB and risks of incident cancer

7.4.1 Overall

In total, seven RCTs were eligible and data from 60,132 participants enrolled was available for BB and risk of cancer. Cancer incidence was 4.88% in patients assigned to BB versus 5.19% assigned to control. In the FE model as shown in **Figure**

7-2, the overall result was mainly driven by the ASCOT-BPLA study as it weighted the most at 60.6% followed by LIFE and INVEST at 23.0% and 13.1% respectively. Three studies showed an increased odds of cancer incidence with OR ranging from 1.03 to 2.01 and wide 95% CI traversing 1. On the other hand, VA COOP II showed a marked decrease in cancer incidence estimate with OR 0.16 and 95% CI 0.01 to 3.20.

Visually, the ASCOT-BPLA study's influence in the analysis was apparent as it was represented by the largest box which corresponds to its weight. The 95% CI of all the studies overlaps 1 as all the CI crossed the line of no effect indicating no statistical significance at the study level. Although the diamond representing the combined estimate was located to the left of the forest plot, the 95% CI of the overall effect estimate overlaps 1 indicating no statistical significance at 5% significance level.

Meanwhile, the RE model as shown in **Figure 7-3** depicted comparable individual studies' weightage and effect estimates. Both FE and RE models agree on the pooled effect estimate of OR 0.93 and 95% CI 0.87-1.01(P-value = 0.07) indicating no significant difference in odds of cancer between treatment and control group.

The chi-square statistic for heterogeneity recorded a P-value of 0.81 indicating no statistical evidence for a difference between the seven included studies. Additionally, the I^2 statistics observed at 0% suggests no heterogeneity.

Finally, assessment of the funnel plot (Appendix Figure A-1, Page 323**)** demonstrated missing studies in the upper- and mid-left area of non-significance indicating clear asymmetry.

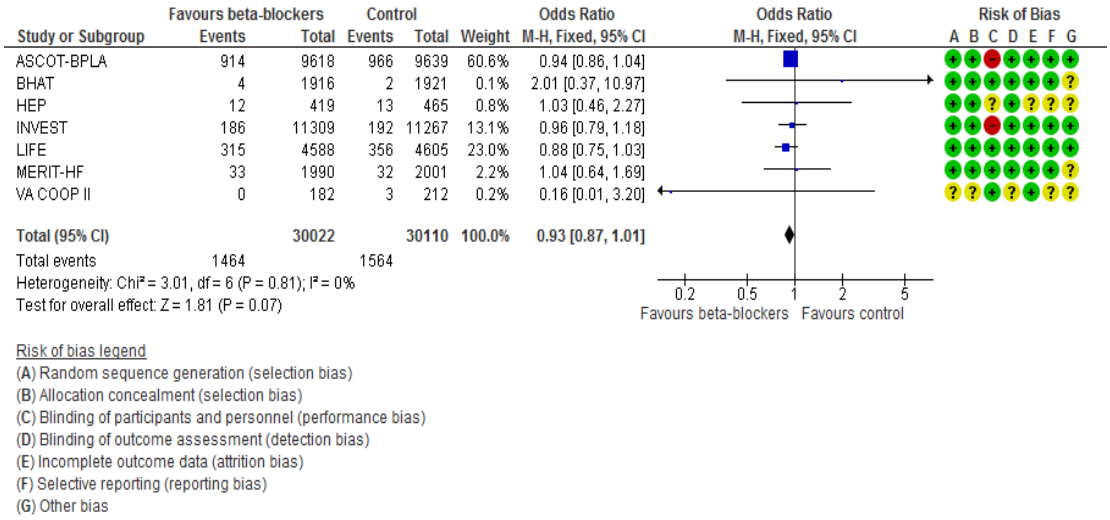


Figure 7-2: Forest plot of cancer incidence by BB vs non-BB controls [FE model].
Odds ratios, and 95% confidence interval, overall and in 7 trials. The overall effect represents the pooled estimate of odds for cancer incidence.

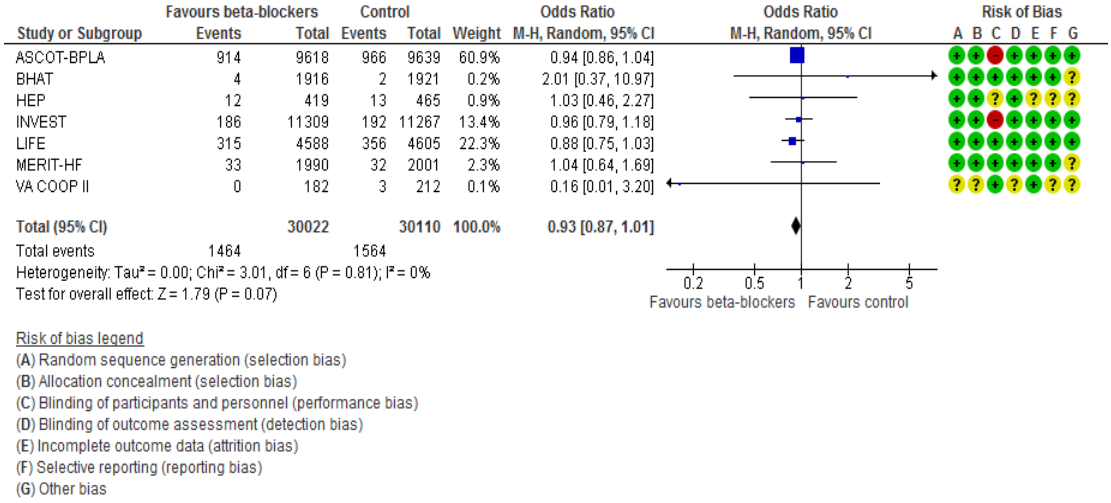


Figure 7-3: Forest plot of cancer incidence by BB vs non-BB controls [RE model].
Odds ratios, and 95% confidence interval, overall and in 7 BB trials, The overall effect represents the pooled estimate of odds for cancer incidence.

7.4.2 **Sensitivity analyses**

As shown in **Figure 7-4**, elimination of the MERIT-HF study from the analysis did not significantly affect the overall combined estimate with OR 0.93 and 95% CI 0.86-1.00 (P-value = 0.06). Similarly, exclusion of the HEP and VA COOP II trials with small sample size (N < 1000) resulted in OR of 0.93 with 95% CI 0.87-1.01 (P-value = 0.08, **Figure 7-5**).

Meanwhile, exclusion of four studies with inadequate blinding of personnel, patients and/or outcome assessors (ASCOT-BPLA, HEP, INVEST, and VA COOP II) slightly decrease the overall estimate giving an OR of 0.90 with marginally wider 95% CI between 0.77 to1.04. Exclusion of these studies left only three trials and the meta-analysis was largely driven by the LIFE study where it carries the most weight at 90.8% (**Figure 7-6**). Likewise, exclusion of studies with different add-on therapy (ASCOT-BPLA and INVEST) generated an OR of 0.90 with 95% CI 0.78 – 1.04 with most of the weightage given to the LIFE study at 87.2% (**Figure 7-7**).

Conversely, the inclusion of two trials with inadequate information on cancer outcomes for BB (CONVINCE and STOP-HTN2) increase the availability of data for cancer incidence (**Figure 7-8**). Cancer incidence was 4.84% in the BB treatment group versus 5.39% in the control group. The weight given to the ASCOT-BPLA study was reduced from 60.6% to 43.6% in the FE model. Nearly equal weight was given to the CONVINCE and LIFE studies (15.0% and 16.5% correspondingly) and 12.9% of the overall study weight was given to the STOP-HTN2 study. The two included studies, CONVINCE and STOP-HTN2, reported a decrease in odds for cancer incidence with OR 0.95 (95% CI 0.85-1.12) and OR 0.93 (95%CI 0.78-1.11) respectively.

Furthermore, the 95% CI for all the studies overlap 1 suggesting no statistical significance at the study level. However, the summary effect lies to the right side of the forest plot with its 95% CI impinging 1 (OR 0.94, 95% CI 0.88-1.00) and a P-value of 0.04 indicating the overall effect is statistically significant at the 5% significance level. Heterogeneity assessment by chi-square statistics yields a P-value of 0.93 while the I^2 statistics of 0%.

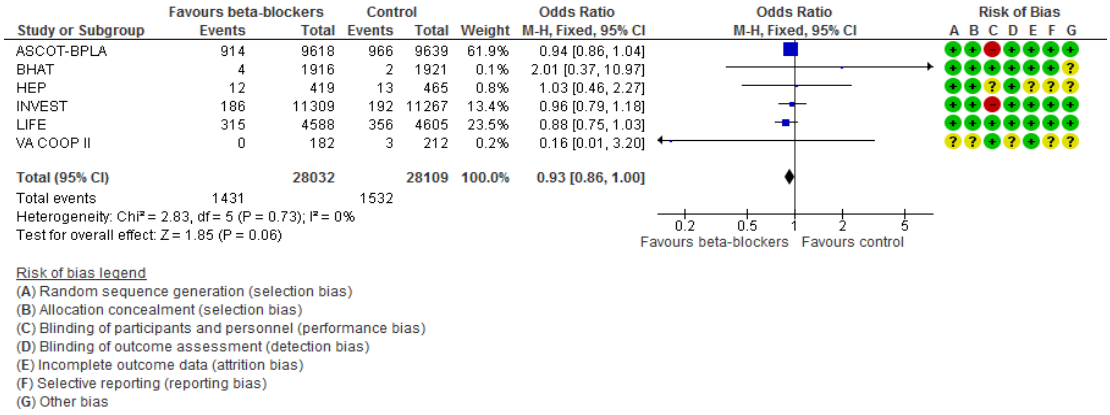


Figure 7-4: Forest plot of incident cancers by BB vs controls [Sensitivity analysis: Exclusion of study with ambiguous cancer outcome].
The overall effect represents the pooled estimate of odds for incident cancers.

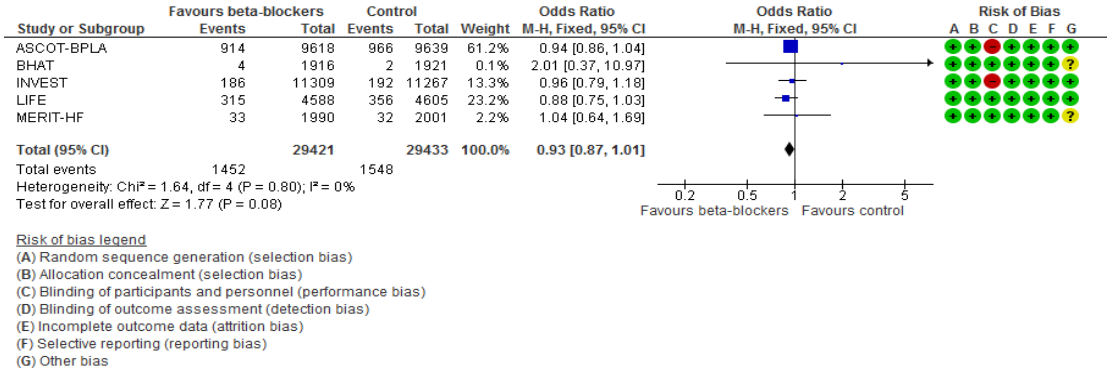


Figure 7-5 Forest plot of incident cancers by BB vs non-BB controls [Sensitivity analysis: Study size].
The overall effect represents the pooled estimate of odds for incident cancers.

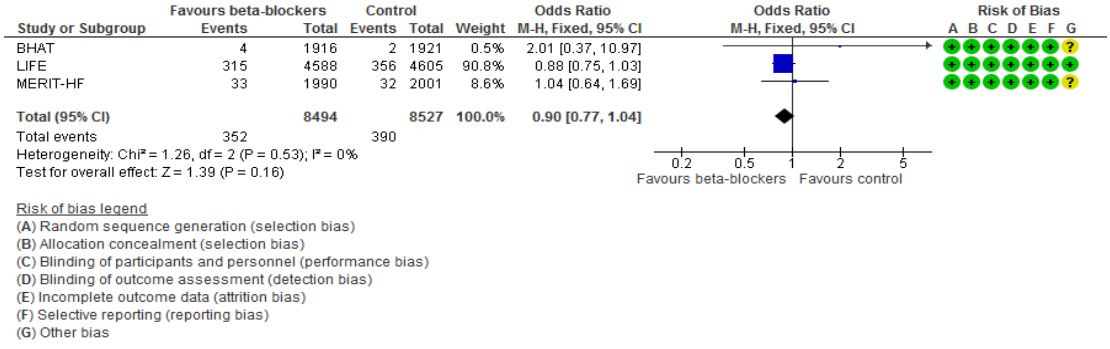


Figure 7-6: Forest plot of incident cancers by BB vs controls [Sensitivity analysis: Study design].
The overall effect represents the pooled estimate of odds for incident cancers.

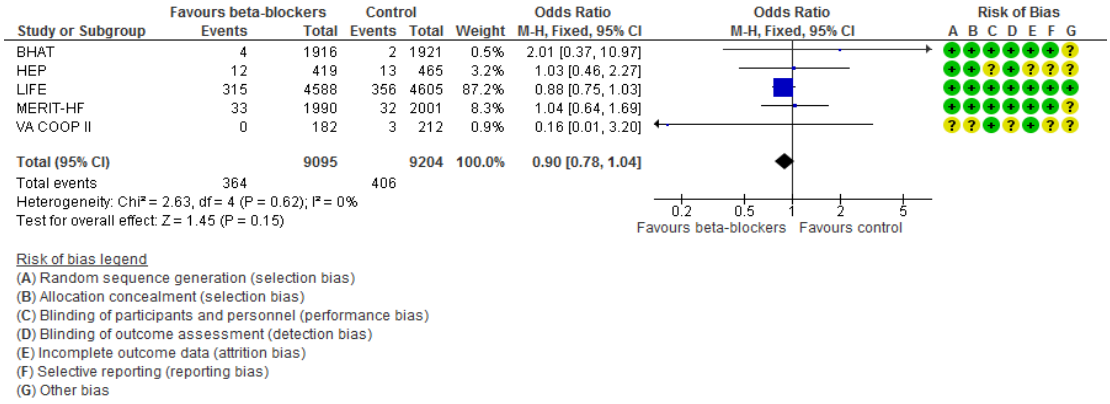


Figure 7-7: Forest plot of incident cancers by BB vs controls [Sensitivity analysis: Exclusion of studies with different add-on therapy protocol].
The overall effect represents the pooled estimate of odds for incident cancers.

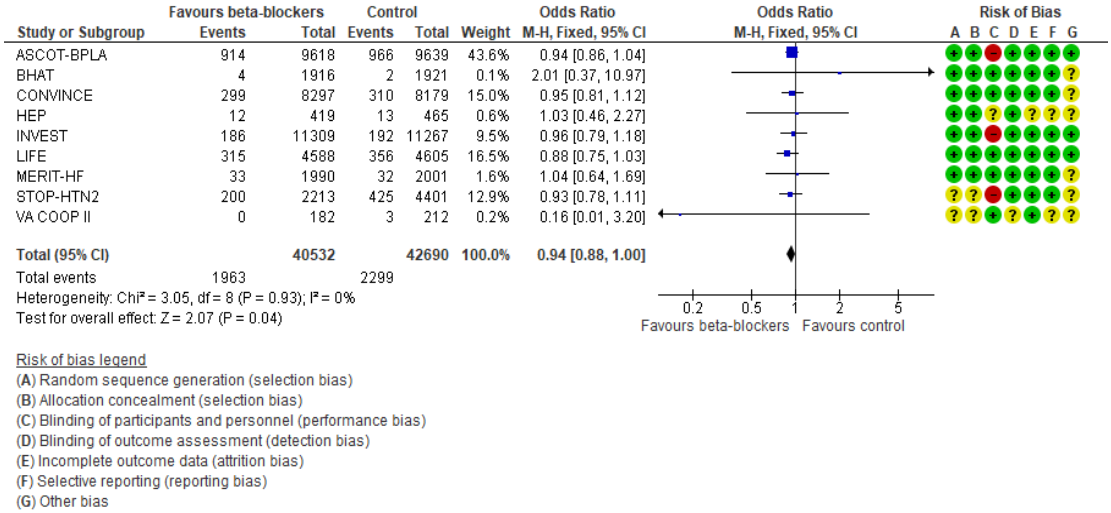


Figure 7-8: Forest plot of incident cancers by BB vs controls [Sensitivity analysis: Inclusion of the CONVINCE and STOP-HTN2 trials].
The overall effect represents the pooled estimate of odds for incident cancers.

7.4.3 Subgroup analyses

Table 7-2 summarises the results for subgroup analyses that were conducted for BB and the risk of cancer.

7.4.3.1 By receptor selectivity

Data for cardioselective BB was available from five RCTs enrolling 55,901 patients. Cancer incidence was 5.23% in the BB treatment group versus 5.57% in the control group. The combined effect estimate resulted in OR 0.93 with 95% CI 0.87-1.01

(P-value = 0.07). The I^2 test for heterogeneity of 0% indicates that all studies were evaluating the same effect.

On the other hand, only two RCTs (BHAT and VA COOP II) were available for non-cardioselective BB with the total number of participants was 4,231. Cancer incidence was 0.19% in the BB treatment group versus 0.23% in the control group, OR 0.87 with 95% CI 0.25-3.06 (P-value= 0.83). The test for heterogeneity was 53% suggesting moderate heterogeneity between studies (see Figure 7-9). Participants recruited in the BHAT study have the worst health condition (post-MI) compared to those in the VA COOP II study.

7.4.3.2 By type of comparator

As shown in Figure 7-10, data were available from four RCTs for comparison between BB and active controls which include ARB (LIFE), CCB (ASCOT-BPLA, INVEST), and TZ (VA COOP II) enrolling a total of 51,420 participants. Cancer incidence was 5.51% in the BB treatment group versus 5.90% in the active controls treatment group, OR 0.93 with 95% CI 0.86-1.00 (P-value = 0.06). At the study level, when compared to ARB, the OR for cancer incidence was 0.88 (95% CI 0.75-1.03). For the two studies that compared BB to CCB, the overall OR for cancer was 0.93 with 95% CI between 0.87 and 1.03. Meanwhile, comparison to TZ showed the OR for cancer was 0.16 (95% CI 0.01-3.20). The I^2 test for heterogeneity of 0% indicates that all studies were evaluating the same effect.

For comparison with placebo or no treatment, data were available from three RCTs (BHAT, HEP, and MERIT-HF) with a total number of 8,712 patients. Cancer incidence was 1.03% in the BB treatment group versus 1.07% in the control group. The combined OR gave an estimate of 1.08 with 95% CI 0.72-1.61 (P-value = 0.72). The I^2 test for heterogeneity of 0% indicates that all the studies were evaluating the same effect.

7.4.3.3 By population clinical setting

A total of five studies (ASCOT-BPLA, HEP, INVEST, LIFE, and VA COOP II) enrolled 52,304 participants with underlying hypertension. Cancer incidence was 5.46% in the BB treatment group versus 5.84% in the control group, OR 0.93 (95% CI 0.86-1.00; P-value = 0.06). The I^2 test for heterogeneity was measured at 0%.

As for patients with high CVD risk (ASCOT-BPLA) comprising CHD (BHAT and INVEST) and HF (MERIT-HF), data were available from 49,661 participants. Cancer incidence was 4.58% in the BB treatment group versus 4.80% in the control group (OR 0.95, 95% CI 0.87-1.04; P-value = 0.25). Likewise, the test for heterogeneity was assessed at 0% (See Figure 7-11).

7.4.3.4 By mean age groups

For studies with mean patients' age of 65 years old or older, data were available from 32,653 patients enrolled in three studies (HEP, INVEST, and LIFE). Cancer incidence was 3.14% in the BB treatment group versus 3.43% in the control group. The combined OR was observed at 0.91 with 95% CI ranged between 0.81 and 1.03 (P-value = 0.15; Figure 7-12). The I^2 test for heterogeneity was measured at 0%.

On the other hand, data for studies with mean patients' age younger than 65 years was available from four RCTs (ASCOT-BPLA, BHAT, MERIT-HF and VA COOP II) enrolling 27,479 patients. Cancer incidence was 6.94% in the BB treatment group versus 7.28% in the control group with OR 0.95 and 95% CI 0.86-1.04 (P-value = 0.24). Heterogeneity was observed at I^2 of 0%.

7.4.3.5 By duration of follow-up

For studies followed for three years or longer, data were available from three trials (ASCOT-BPLA, HEP, LIFE) with a total of 29,334 participants. Cancer incidence was 8.49% in the BB treatment group versus 9.08% in the control group yielding an OR of 0.93 with 95% CI ranged between 0.85 and 1.00 (P-value = 0.06). Heterogeneity was observed at I^2 of 0%.

Meanwhile, data for studies with follow-up less than three years was available from four RCTs (BHAT, INVEST, MERIT-HF, VA COOP II) enrolling 30, 798 participants. Cancer incidence was 1.45% in the BB treatment group versus 1.49% in the control group with OR 0.97 (95% CI 0.81-1.17; P-value = 0.77). Heterogeneity was observed at I^2 of 0% (see Figure 7-12).

Table 7-2 : Beta-blockers and risk of cancer: Subgroup analysis

Subgroup analysis		No. of study	No. of participants	Cancer incidence (%)		OR (95% CI)	P-value	I^2 (%)
				BB	Control			
Overall effect	FE model	7	60132	4.88	5.19	0.93 (0.87-1.01)	0.07	0
Receptor selectivity	Cardioselective	5	55901	5.23	5.57	0.93 (0.87-1.01)	0.07	0
	Non-cardioselective	2	4231	0.19	0.23	0.87 (0.25-3.06)	0.83	53
Type of comparators	Active	4	51420	5.51	5.9	0.93 (0.86-1.00)	0.06	0
	Placebo or no treatment	3	8712	1.13	1.07	1.08 (0.72, 1.61)	0.72	0
Clinical setting	Hypertension	5	52304	5.46	5.84	0.93 (0.86-1.00)	0.06	0
	High CVD risk	4	49661	4.58	4.8	0.95 (0.87-1.04)	0.25	0
Age	≥ 65 years	4	32653	3.14	3.43	0.91 (0.81-1.03)	0.15	0
	< 65 years	3	27479	6.94	7.28	0.95 (0.86-1.04)	0.24	0
Duration of follow-up	≥ 3 years	3	29334	8.49	9.08	0.93 (0.85-1.00)	0.06	0
	< 3 year	4	30798	1.45	1.49	0.97 (0.81-1.17)	0.77	0

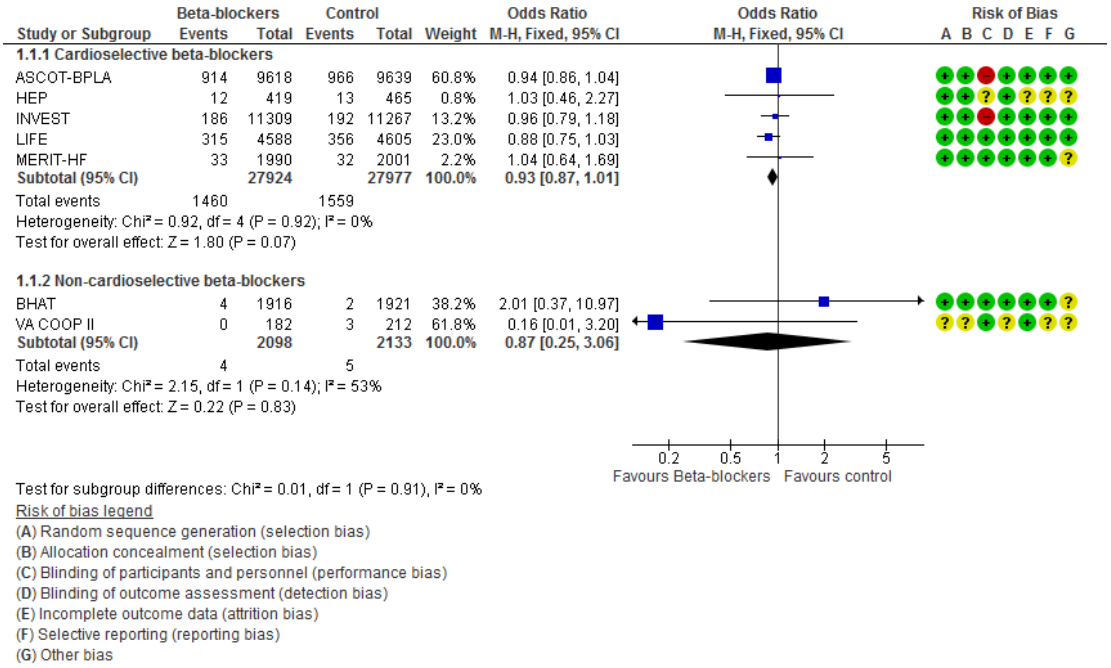


Figure 7-9: Forest plot of cancer incidence by BB receptor selectivity [FE model].
1) Cardioselective BB vs controls in 4 trials; 2) Non-cardioselective BB vs controls in 2 trials. The subtotal effect represents the pooled estimate of odds for cancer incidence for each subclass.

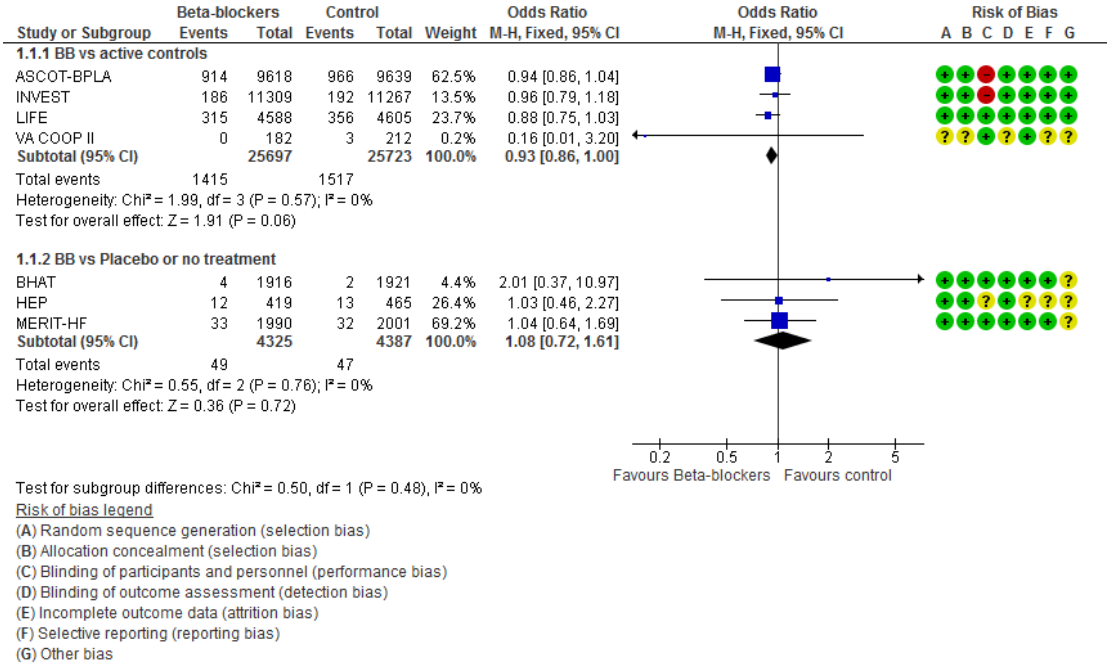


Figure 7-10: Forest plot of cancer incidence by comparators [FE model].
1) Active controls; 2) Placebo or no treatment. The subtotal effect represents the pooled estimate of odds for cancer incidence for each comparator.

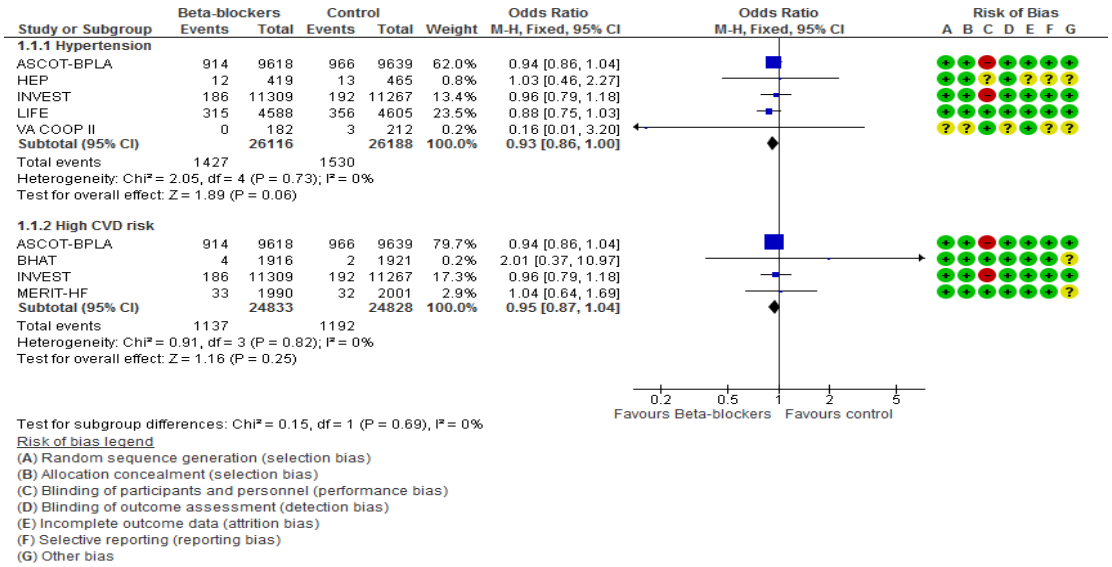


Figure 7-11: Forest plot of cancer incidence by clinical setting [FE model].
1) Hypertension; 2) High-risk CVD. The subtotal effect represents the pooled estimate of odds for cancer incidence for each clinical setting.

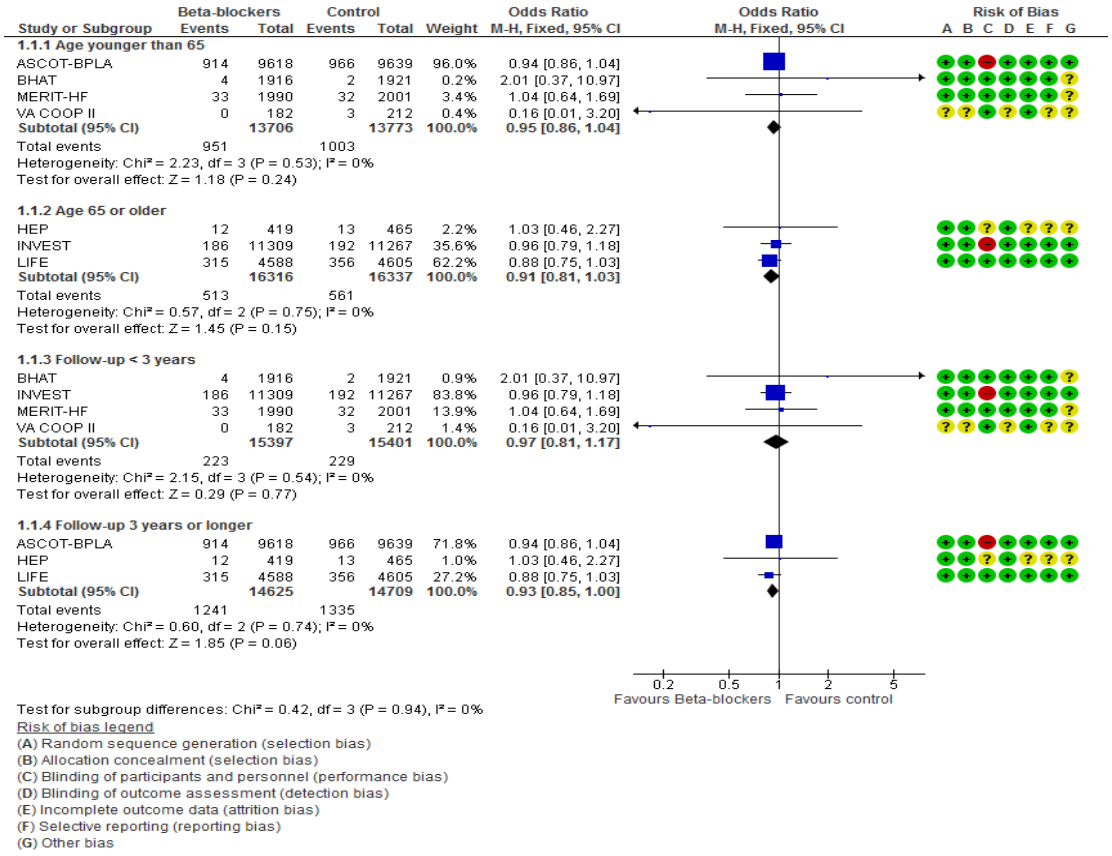


Figure 7-12: Forest plot of cancer incidence by Mean age and duration of follow-up [FE model].
1) Mean age ≥ 65 years; 2) Mean age < 65; 3) Follow-up ≥ 3 years ; 4) Follow-up < 3 years. The subtotal effect represents the pooled estimate of odds for cancer incidence for each criterion...

7.5 BB and cancer-related death

Overall, 12 RCTs were included in the meta-analysis of BB and its association to risk of cancer-related mortality. Data were available from 49,683 (82.6%) participants out of 60,160 patients enrolled in the 12 trials. Based on treatment assignment, cancer-related death was 2.41% in the BB treatment group versus 2.34% in the control group.

As shown in **Figure 7-13**, the meta-analysis was mainly influenced by the ASCOT-BPLA study as it carries the heaviest weight overall (53.9%) and this was followed by the LIFE study at 20.0%. Only the UKPDS-38 study showed a statistically significant increase in the odds for cancer with OR 2.04 and its 95% CI ranged between 1.06 and 3.90. Yet, the UKPDS-38 study did not have a huge influence on the overall pooled effect estimate as it only carries 2.1% of the overall weight. Also, three other studies with increased odds for cancer (ASCOT-BPLA, HEP, and MRCOA) were not statistically significant as their 95% CI crossed 1. Conversely, the APSIS study yielded the lowest effect estimate, OR 0.49 with 95% CI ranged between 0.12 and 1.98 and it only carries 1.1% of the overall weight. The study by Wilcox showed no statistical difference between the BB treatment group and control with OR equivalent to 1 and 95% CI ranged between 0.09 and 11.09.

From the forest plot, the point estimate and 95% CI for the UKPDS-38 study lies on the right side of the plot that favours the control group. Meanwhile, the 95% CI of the remaining studies overlaps 1 as all the CI crossed the line of no effect indicating no statistical significance at the study level. The diamond representing the combined estimate was located to the right side of the forest plot, but the 95% CI of the overall effect estimate overlaps the line of no effect indicating no statistical significance at 5% significance level. Based on the FE model, the overall pooled OR for BB and cancer-related death was 1.04 with 95% CI ranged between 0.93 and 1.17.

The chi-square statistic for heterogeneity recorded a P-value of 0.64 indicating no statistical evidence for a difference between the eligible studies 12. Additionally, the I^2 statistics observed at the value of 0% suggests no statistical difference between the studies.

In the RE model meta-analysis, as shown in **Figure 7-14**, the UKPDS-38 study was given slightly more weightage compared to the FE model (2.1% versus 3.2% respectively). The weight assigned to ASCOT-BPLA and LIFE has reduced by 0.5% and 0.7% respectively. The overall combined effect has marginally increased with OR 1.05 (95% CI 0.93-1.17; P-value = 0.46).

Heterogeneity test evaluated using chi-square test showed a P-value of 0.64 in both FE and RE model. Likewise, the I^2 statistics described the proportion of variances across studies that is due to heterogeneity was 0%. The Tau^2 indicated that Tau is equivalent to 0 which means that most of the true effects fall within 0.93 and 1.17.

The funnel plot as shown in Appendix Figure A-2 (Page 324) indicated missing studies in the middle and bottom right and left side of the plot. No outlier was detected. In general, the funnel plot appeared symmetrical.

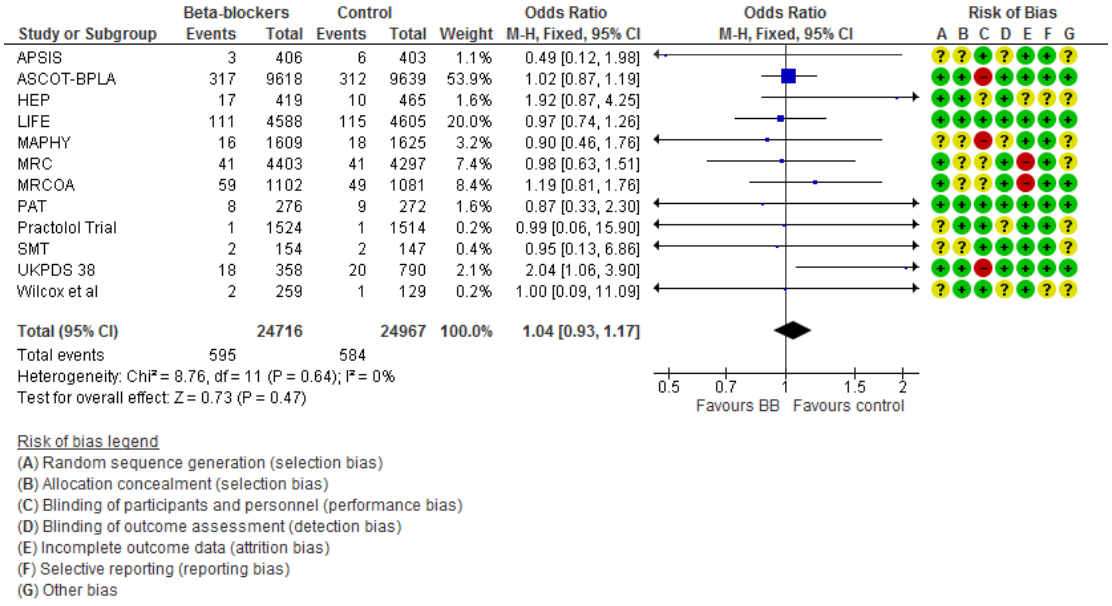


Figure 7-13 Forest plot of cancer-related death by BB vs non-BB controls [FE model].
Odds ratios, and 95% confidence interval, overall and in 12 trials. The overall effect represents the pooled estimate of odds for cancer-related death.

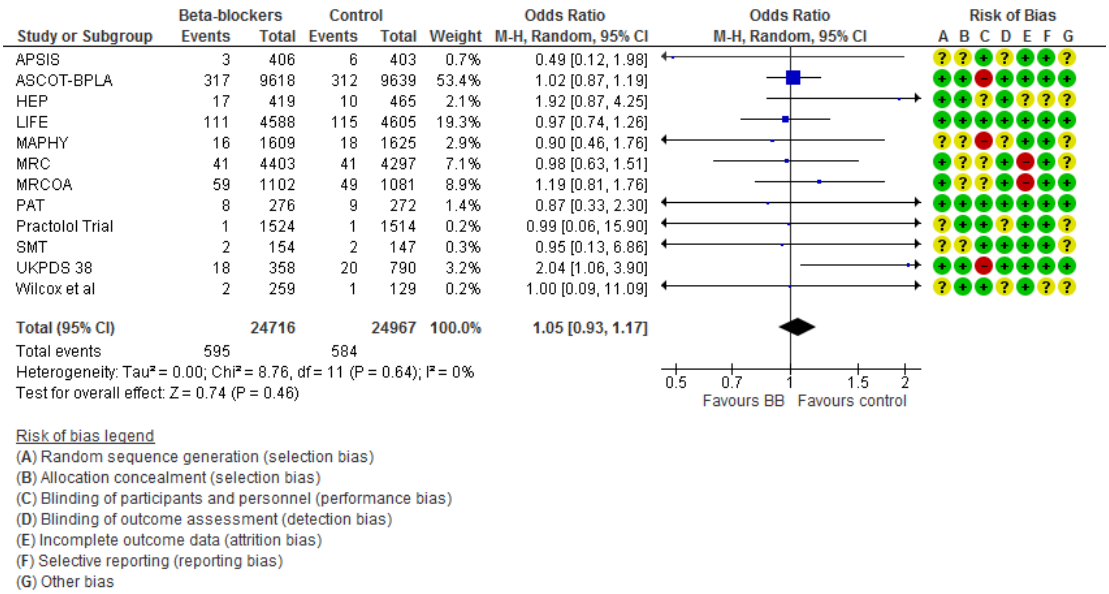


Figure 7-14 Forest plot of cancer-related death by BB versus non-BB controls [RE model]. Odds ratios, and 95% confidence interval, overall and in 12 trials The overall effect represents the pooled estimate of odds for cancer-related death.

7.6 Discussion

From the results, there is little evidence of significant association between BB use and cancer incidence although the summary effect is less than unity (OR 0.93, 95% CI 0.87-1.01). This is supported by the marginally wide 95% CI which contains 1 and a P-value of 0.07 just short of significance. Furthermore, both FE and RE meta-analysis agrees on the summary effect estimates.

Subgroup analyses performed showed BB has no significant effect on cancer when compared to active controls overall (OR 0.93, 95% CI 0.86-1.00) or placebo (OR 1.08, 95% CI 0.72, 1.61). Analysis at the study level has demonstrated that odds for cancer are less for BB when compared to ARB and CCB, the two drug classes that have been implicated with increased cancer risk in previous studies (Sipahi et al., 2010, Li et al., 2013). A meta-analysis of nine RCTs using ARBs by Sipahi et al. (2010) reported a significantly increased risk of new cancer occurrence in patients assigned to ARB (RR 1.08, 95% CI 1.01–1.15; p=0.016) with a specific concern to risk of lung cancer (RR 1·25, 1.05–1.49; p=0.01).

Common risk factors shared by CVD and cancer such as smoking, obesity, hyperglycaemia, hypertension, and hyperlipidaemia induced inflammation and this can lead to expression and release of pro-inflammatory mediators subsequently fostering proliferation, survival, and migration (Coussens and Werb, 2002, Libby, 2006). Especially hypertension, a well-established CVD risk factor, has been related to malignancy in previous studies. The most current study has reported that the risk of cancer increased correspondingly for every 10 mmHg BP increment (Stocks et al., 2012) To assess whether underlying CVD or hypertension affect the risk for cancer, a subgroup analysis was performed based on study population clinical settings. This subgroup analysis has found that the risk for cancer was independent of treatment indication where a comparable association was observed between the population with underlying hypertension (OR 0.93, 95% CI 0.86-1.00; P-value = 0.06) and high CVD risk (OR 0.95, 95% CI 0.87-1.04).

Overall, the current study's results corroborated the results of two recent meta-analyses (Bangalore et al. (2011), (Monami et al., 2013). In the most recent study, Monami et al. (2013) conducted a meta-analysis of RCTs using BB in addition to an observational study looking at the risk of cancer in T2DM on insulin. The eligibility criteria for this study were more relaxed because the authors have allowed the inclusion of studies with smaller sample sizes (n participants < 100). Their meta-analysis of nine RCTs concluded that BB was associated with a non-significant trend towards a reduced risk of cancer overall (OR 0.93, 95% CI 0.86-1.01; P-value = 0.07). In another study, Bangalore et al. (2011) have conducted a network meta-analysis of antihypertensive drugs and risk of cancer which includes BB. Their direct meta-analysis of seven BB trials yielded an OR of 0.94 with 95% CI ranged between 0.88 and 1.00 (P-value = 0.10). However, this meta-analysis included two studies, CONVINCE (Black et al., 2003) and STOP-HTN2 (Lindholm et al., 2001) that were excluded from the current review because of inadequate information on cancer outcomes for the BB treatment arm. Both studies have randomised patients to either BB or diuretics as one treatment arm versus other antihypertensive agents and reported cancer outcomes collectively. Incorporation of these data could introduce bias and may lead to a spurious result as the observed effects may have equally resulted from administration of either drug. This was demonstrated in the current study sensitivity analysis where inclusion of these two studies in the meta-analysis has shifted the combined treatment effect from non-significant to

statistically significant (OR 0.94, 95% CI 0.88-1.00; P-value = 0.04). Similar precaution was also taken in a much earlier network meta-analysis. The meta-analysis by Coleman et al. (2008) has assessed the impact of major antihypertensive medication classes on cancer incidence and reported no significant difference in risk of cancer in relation to BB with OR 1.00 (95% CI 0.78-1.32). Compared to the current study, the eligibility criteria for this meta-analysis was less strict because they allowed smaller studies (n participants < 100 per treatment arm) and shorter duration of patients' follow-up (minimum six months).

In addition, the effect of different BB receptor selectivity on the risk of cancer was evaluated. From the subgroup analysis, there is little evidence of an association when analyses were restricted to cardioselective BB (OR 0.93, 95% CI 0.87-1.01; P-value = 0.07) and non-cardioselective BB (OR 0.87, 95% CI 0.25-3.06) although the trend is toward a reduced risk of cancer in both subtypes. The only other meta-analysis that has considered BB receptor selectivity was by Bangalore et al. (2011). They have observed an OR of 0.15 (95% CI 0.02-1.50) from one non-cardioselective BB study whereas an OR of 0.94 (95% CI 0.88-1.00) for cardioselective BB, which is similar to the present study result. Many prior studies have not considered the different BB agents subtypes in analysis and this, may in part, have led to the continuous reporting of conflicting results.

Studies that have considered the effects of the different BB subtypes mainly looked at cancer patients' survival as their main outcome. One earlier study (Barron et al., 2011) conducted an observational study following 5,333 women with breast cancer between 2001 and 2006. The author observed significantly lower odds of terminal stage breast cancer (OR 0.24, 95% CI 0.07-0.85) and breast-cancer specific mortality (OR 0.19, 95% CI 0.06-0.60) in propranolol users compared to the non-BB user. Conversely, there was no difference in tumour spread or breast-cancer specific mortality in atenolol users compared to matched-controls. Quite recently, a study by Watkins et al. (2015) investigated the impact of selective and non-selective BB on survival in 1,425 medical records of women with ovarian cancer. The investigators found that those receiving non-selective BB had a median overall survival (OS) of 94.9 months versus 38 months for those receiving β_1-adrenoceptor selective agents (P-value < 0.001) and this effect was independent to the effect of the drug on hypertension. A similar result was reported in another study (Renz et al., 2017) looking at the survival of 595 patients

with post-pancreatic ductal adenocarcinoma resection. Renz and colleague reported the median OS of patients receiving BB was 40 months versus 23 months in non-BB user (P-value = 0.0007) and 21 months in those receiving cardioselective agents (P-value = 0.0396). They also found that microtumours treated with either non-selective BB or $ß_2$-adrenoceptor selective agents showed significantly lower residual metabolic activity (P-value = 0.032). Although the present study analysis for non-cardioselective BB resulted in a non-significant association and showed significantly high evidence of heterogeneity (I^2 = 53%), the effect magnitude and direction supports the outcome reported by both Watkins et al. (2015) and Renz et al. (2017). As for cancer-related death, only the MRC study used the non-selective BB and has shown a non-significant lower odds of cancer-related death (OR 0.98, 95% CI 0.63-1.51). However, the reverse outcome was reported by one previous analysis using an established UK primary care database (Shah et al., 2011) following 3,462 patients aged 40 to 85 with a new common cancer diagnosis for up to ten years. Compared with cancer patients receiving other antihypertensive therapy, this study found that users of BB overall experienced poorer survival with HR 1.21 (95% CI 0.94-1.55) for the non-selective BB. Still, findings from previous studies combined with the result from the present study suggest targeted therapy of the adrenergic beta-2 pathway could potentially be promising in the therapeutic strategy of cancer patients and merits further research.

Furthermore, the meta-analysis conducted in the present study also found no significant association between BB and the risk of overall cancer-related mortality with OR 1.04 (95% CI 0.93-1.17; P-value = 0.47). Results from the present study to a certain extent agree with the findings reported by Bangalore et al. (2011) where their meta-analysis of seven BB studies and cancer-related deaths have demonstrated an OR of 1.02 (95% CI 0.92-1.14; P-value = 0.51). Compared to this study, the present meta-analysis is larger and more precise because five additional studies were included and the CONVINCE study which does not contain adequate information on cancer outcomes for the BB treatment arm was excluded. Of the included studies in the analysis, only the MAPHY and MRCOA have reported the exclusion of patients with baseline cancer. For this reason, the treatment effect derived could not be determined if it was confounded by underlying cancer diagnosed prior to the study randomisation.

Nonetheless, the use of BB in cancer patients has been shown to reduce cancer-specific mortality in some studies. In one observational study(Botteri et al., 2013), treatment with BB showed significantly lower breast-cancer death in menopausal women with triple-negative breast cancer (TNBC). The researcher identified 800 patients operated between 2007 and 2008 with TNBC and found the risk of breast-cancer specific mortality favoured those on BB treatment with HR 0.42 (95% CI 0.18-0.97). Apart from breast cancer, BB use was also associated with a lower risk of prostate cancer-specific (Grytli et al., 2014), ovarian cancer-specific (Watkins et al., 2015), and melanoma –specific mortality (Wrobel and Le Gal, 2015).

On the contrary, a number of studies have found that BB use was not associated with improved survival for common cancers. Some of the studies (Shah et al., 2011) have been described earlier in this discussion. In another large United Kingdom (UK) study (Cardwell et al., 2014), a cohort of 6,339 prostate cancer patients identified from the UK Clinical Practice Research database (CPRD) was followed for an average follow-up of six years. The researchers found little evidence of a reduction in risk of prostate cancer-specific mortality in BB users compared to non-users (OR 0.94, 95% CI 0.81-1.09). Furthermore, this finding was supported by a recent systematic review and meta-analysis of 30 observational studies enrolling 88,026 cancer patients (Weberpals et al., 2016). The authors of this meta-analysis concluded that there was no significant clinical evidence associating BB use and survival. They have also proposed that the beneficial effect of BB on cancer survival might be based on immortal time bias (ITB) which refers to a period of follow-up during which, by design, the event or outcome of interest cannot take place (Lévesque et al., 2010). Most cohort studies are susceptible to ITB when they fail to account for appropriate follow-up time and treatment status in the design and analysis.

7.6.1 Strengths and limitations

The main strength of this review is that only RCTs were included where this study design is the gold standard for evaluating the effectiveness of the intervention. Additionally, only studies with cancer data for BB were incorporated for this meta-analysis, hence resulting in a more precise association for the drug class studied. Cancer outcomes from the BHAT and MERIT-HF study were only incorporated in

this review of BB trials. Also, a comprehensive search was conducted spanning a period of over 60 years.

The present review has a number of shortcomings. One limitation is that all of the RCTs were not designed to detect incident cancer and/ or cancer-related mortality as a primary end-point. Apart from cancer-deaths, diagnosis of malignancy was variably adjudicated across the different studies. Second, only aggregate data reported as raw number (n/N) were available for most of the studies. Due to the unavailability of individual-patient data, the time-to-event analysis was not performed. Availability of such information could better estimate the association of drug class studied to the occurrence of site-specific and overall cancer. Moreover, most of the studies were followed for an average short period of time ranging from one to five years. As cancer development is a slow process, the results from the present study could only reflect late-detected cancers. Also, the risk of cancer from this meta-analysis could not be inferred to individual BB as only atenolol, metoprolol, practolol, and propranolol were used in the included trials. Finally, the number of trials included in the meta-analysis for cancer incidence was too small (n= 7 for incident cancer). Although only five or more trials are all that is needed to give some confidence that the result is valid (Herbison et al., 2011), the conclusion drawn from these reviews is not possible to predict as estimates could still differ substantially following the addition of studies in the future.

7.6.2 Conclusion

BB use is not significantly associated with the risk of cancer or cancer-related death overall. Results from this review and meta-analysis add to the growing body of evidence suggesting this drug class does not affect the risk for malignancy. Finally, further research investigating the use of non-cardioselective BB as part of a treatment strategy for cancer therapy is warranted.

8 Association between Thiazide diuretics (TZ) and risks of cancer

8.1 Introduction

A diuretic is any substance that increases production of urine thereby promoting the removal of body salt, mainly sodium, and water. There are different types of diuretics and various diuretic agents are used in medicine for specific purposes. Prior to the advent of modern day's diuretics, only intravascular and intramuscular mercurial agents were available and effective, though their use was difficult and restricted. Understanding the mechanism of a renal tubular mechanism for acidifying the urine has led to the development of carbonic anhydrase inhibitor (Pitts, 1945). In the process of refining and producing a more potent carbonic anhydrase inhibitor, exploration of several key compounds and addition of a benzene ring to sulfonamide has resulted in chlorothiazide, a first for its class (Novello and Sprague, 1957, Beyer, 1982). Members of this drug class are derived from benzothiadiazine with a benzothiadiazine ring as a parent structure and are collectively termed as 'thiazide' diuretics. Drugs that act on the same co-transporter in the distal tubules of the kidney but do not have the chemical structure of a TZ are known as 'TZ-like' diuretics.

The pharmacokinetics of TZ varies between subclasses and individual drugs. The comparison between TZ-type and TZ-like diuretics are outlined in Table 8-1 **(page 280)**. Although these drugs are collectively known as TZ, significant differences in chemical structure exist. The only common structure between the two subclasses is the sulphonamide group (SO_2NH_2), the chemical compound that inhibits carbonic anhydrase activity. All TZs are absorbed orally and have a volume of distribution equal to or greater than total body weight. The oral bioavailability is relatively high and varies between individual TZ. All TZs are highly protein-bound, hence limit its filtration by the renal glomeruli and allow its delivery to secretory sites of the renal proximal tubular cells. Among the TZs, chlorthalidone has the longest elimination half-life of 50 to 60 hours. Most TZs are renally excreted except for indapamide which is metabolized by the liver and excreted via the biliary system.

In general, the main action of diuretics is to promote diuresis by the kidney which is achieved by altering how the kidney handles sodium. Different diuretic acts on a different segment of the renal tubular system. **Figure 8-1** depicts a unit of nephron with sites of action for major diuretic groups. The primary site of action for TZ is at the distal convoluted tubule (DCT) of the nephron. Inset is a molecular level depiction of TZ exerting its effect on the epithelial cells of the renal distal tubule. Approximately 10% of the filtered sodium chloride (NaCl) is reabsorbed in the distal tubule (Ives, 2012) and sodium (Na) returns into the circulation via the adenosine triphosphate (ATP)-activated sodium-potassium pump. Inhibition of the Na/Cl co-transporter (NCC) by TZ at the luminal side of the epithelial cells in the DCT prevents reabsorption of NaCl. The resulting low intracellular sodium (Na) in turn lowers intracellular calcium (Ca) mediated by the Na/Ca exchanger (NCX1). Low intracellular Ca subsequently enhanced the diffusion of Ca through calcium ion channels expressed on the luminal membrane and therefore increases Ca reabsorption. The hypocalciuric effect caused makes TZ useful in patients with kidney stones produced by hypercalciuria. Moreover, the unabsorbed NaCl is consequently delivered to the collecting duct where only 2-5% is reabsorbed by the kidney (Ives, 2012) while the remaining is excreted with excess water as urine.

8.1.1 TZ and cancer

One of the postulated mechanisms where TZ could alter the risk for cancer is that TZ, such as HCTZ, as a cyclic amide can be converted to a nitroso derivative in the stomach which is mutagenic (Andrews et al., 1984). An experimental study using rats have shown that rats treated with HCTZ developed chronic nephropathy and renal adenomas (Lijinsky and Reuber, 1987). Treatment with TZs has also been shown to alter the epithelial structure of the nephron distal tubule. Loffing et al. (1996) have demonstrated in an animal study where rats treated with TZ such as HCTZ or metolazone for three days provoked apoptosis and most of the DCT epithelial cells have thickened resembling a stratified epithelium. Findings from these experimental studies led to the speculation that the continuous bombardment of the DCT with TZ may lead to neoplastic changes and possibly give rise to renal cancer. For evidence from epidemiological studies, see Chapter 1, Section 1.9.6 (page 53).

This chapter aims to systematically review and report the meta-analysis of RCTs using TZ diuretic as one of its treatment and its association with risks of cancer.

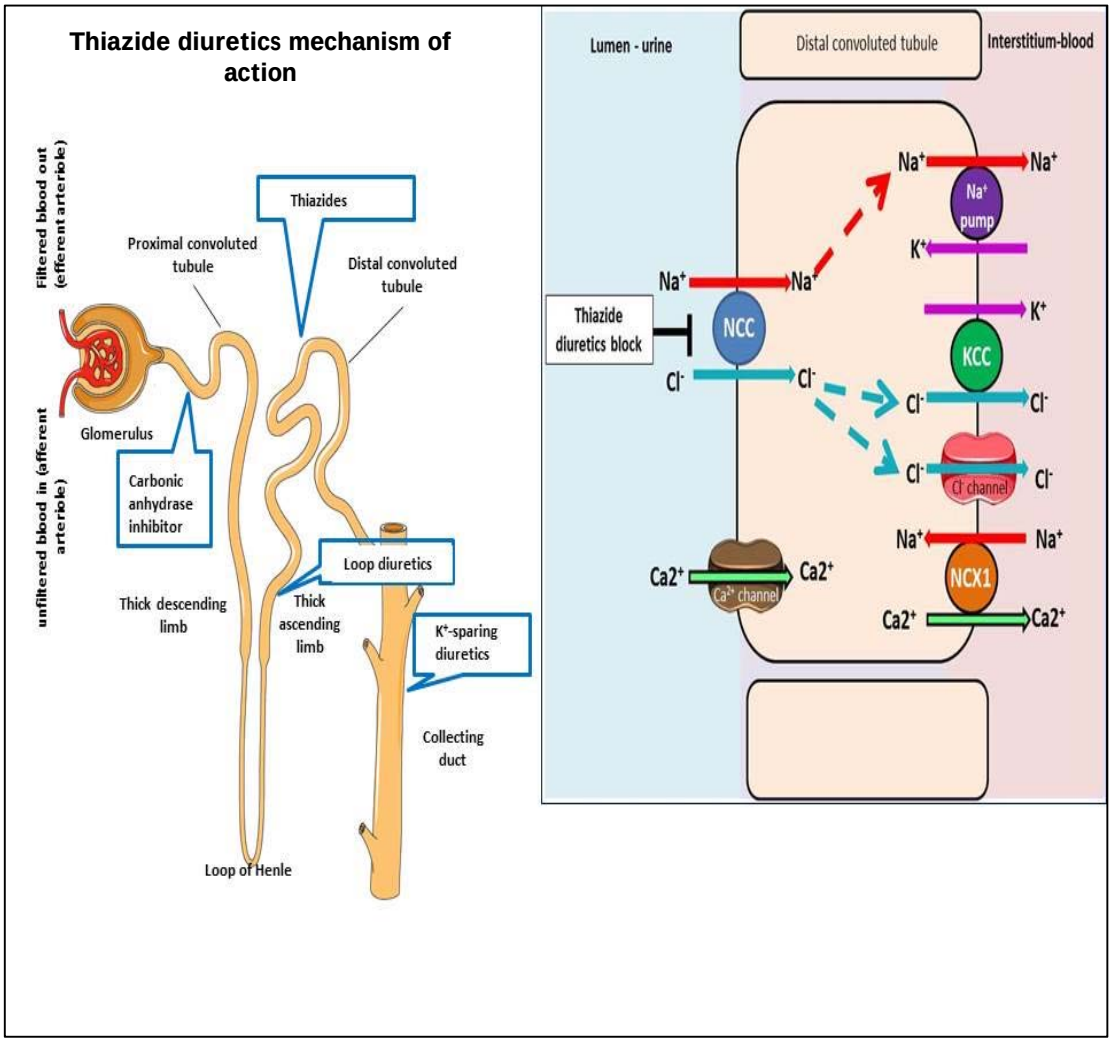


Figure 8-1 Site of diuretics action in the nephron.
TZ block the Na/Cl cotransporter that is selectively expressed in the distal convoluted tubule, inhibiting its ability to transport ions. The inhibition of Na transport in this segment results in greater delivery of sodium to the collecting duct. KCC, potassium chloride c-transporter; NCC, sodium chloride co-transporter; NCX1, sodium calcium exchanger 1. Modified from Ives (2012).

Table 8-1: Pharmacokinetic characteristics of thiazide diuretics

Diuretic	**Thiazide**			**Thiazide-like**		
Drug name	Chlorothiazide	HCTZ	Bendroflumethiazide	Chlorthalidone	Indapamide	Metolazone
Chemical compound	Benzothiadiazine derivative	Benzothiadiazine derivative	Benzothiadiazine derivative	Benzophenones derivative	Chlorosulphonamide derivative	Quinazoline derivative
Relative carbonic anhydrase inhibition*	++	+	0	+++	++	+
Oral bioavailability (%)	15-30	60-70	90	65	93	65
Volume of distribution (*litres per kilogram*)	1	2.5	1.0-1.5	3-13	25†	113†
Protein binding (%)	70	40	94	99	75	95
Half-life (*hour*)	1.5-2.5	9-10	9	50-60	14	8-14
Route of elimination	100% renal	95% renal	30% renal	65% renal	Hepatically metabolised	80% renal

* Plus signs indicates inhibition with greater number of plus signs reflecting increased inhibition. The zero indicates the inhibition constant of 0.

† The volumes of distribution for indapamide and metolazone are given for the total volume in litres. Data on litres per kilogram were not available.
Table adapted from Ernst and Moser (2009).

8.2 Methodology

8.2.1 Systematic review

Full descriptions of the methods used have been described previously in Chapter 2, Section 2.1. Except for the ALPINE (Lindholm et al., 2003) and PREVER-Treatment study (Fuchs et al., 2016), all cancer outcomes were published in the individual primary study or post-hoc analyses. Cancer data for the ALPINE study was retrieved from a meta-analysis published by Bangalore et al. (2011). Meanwhile, cancer input for the PREVER-Treatment study was provided by the study's primary author, Dr Flávio D. Fuchs of Hospital de Clinicas de Porto Alegre, Rio Grande do Sul, Brazil. Furthermore, the PHYLLIS study has four treatment arms consisted of TZ, ACEI, TZ plus statin, and ACEI plus statin. However, only the TZ and ACEI monotherapy were considered in this review.

8.2.2 Meta-analysis

For data synthesis, see Chapter 2, Section 2.1.7.4 (page 66).

Sensitivity analyses for TZ and risk of cancer were conducted by the exclusion of studies based on the following criteria: [1] small sample size with the number of total participants less than 1000, and [2] poor methodological quality. Additionally, the ALPINE study was excluded from the overall meta-analysis due to a different add-on therapy between the TZ diuretic treatment arm and control.

Subgroup analyses were also conducted on the following groups and treatment comparisons: [1] subclass; [2] comparator; [3] clinical setting; [4] mean age; and [5] duration of follow-up.

8.3 Results

The searching and identification process of trials is summarised in Figure 3-1 (page 74). From the 90 studies eligible for the systematic review, only 18 studies were included in the analysis for TZ. The 72 eligible studies excluded from this review were primarily because they do not consist of a TZ diuretic treatment arm.

As a whole, the search result has identified 18 studies enrolling 79,058 participants with an average follow-up of 3.4 years. The average age for patients across all trials is 59.5 years. The full characteristics and risk of bias of the 18 studies included in this review have been described previously (See Chapter 3, Section 3.2.2.1 and Section 3.3.6).

Majority of the studies were published in the1980s and 1990s with the oldest study, ANBP (The ANBP Study Commitee, 1980), published in 1980 whereas only five studies were published after the 20th century. The largest study is the ALLHAT trial enrolling 33,357 patients and all studies have recruited at least 300 participants in total. All studies, except one, recruited patients with underlying hypertension. The trial conducted by LaCroix (2000) has targeted healthy elderly men and women who were normotensive with baseline bone mineral density at the total hip that was within two standard deviations of the normal value for their age.

Overall, 41.2% of the participants across all the studies were randomised to TZ diuretic. Of these, slightly over half (56.1%) of the participants were assigned to TZ-like diuretics including chlorthalidone and indapamide. Majority of the studies have compared TZ to active controls such as RAS inhibitors, CCB, and BB. The remaining five studies compared TZ to either placebo or no treatment.

Most of the studies consist of two parallel treatment arms and only four studies consist of an additional one or two treatment arms. The ALLHAT study has compared TZ to ACEI and CCB whereas the MRC and MRCOA study has compared TZ to BB and placebo. Except for three studies, the majority of the studies have implemented the double-blind methods. Treatment assignment in both the MRC and MRCOA studies were single-blind while the OSLO study was open-label with blinded end-points assessors.

All the participants in the studies were followed for at least one year with the longest mean duration of follow-up was 5.8 years. The mean or median age of patients recruited into most of the studies is above 50 years except in the OSLO study whose patients were slightly younger with a mean age 45.3 years. Four studies, EWPHE, MRCOA, NICS-EH, and SHEP, were designed to investigate the effect of TZ in older patients with a mean or median age ranged between 69 and

72 years. Furthermore, the proportion of male and female participants was comparatively equally distributed across all studies except in seven studies where male (MAPHY, MIDAS, OSLO, VA COOP II) or female (EWPHE, LaCroix, NICS-EH) participants were predominant. The proportion of smokers ranged from small to moderate across all studies.

Table A-3 (Page 321) shows the selected characteristics of interest extracted from individual trials. The reporting of all these variables was inconsistent across all studies. None of the studies has reported the status of cancer patients' enrolment but eight studies have stated cancer or malignancy as their exclusion criteria from their protocol. Also, only four studies (ALLHAT, MIDAS, MRC, MRCOA) were designed to detect cancer incidence and/ or cancer-related deaths as one of their primary or secondary outcomes. The remaining 18 studies did not mention cancer incidents or cancer-related death as one of their primary or secondary endpoints. Method for arbitration of cancer diagnosis and other major adverse events were not described in many of the included studies. Only seven studies reported that cancer and/or cancer-related deaths were centrally adjudicated. Similarly, reporting of patients' adherence to study treatment was lacking in many except for eight studies. In these studies, patients' adherence was reported to be between good to excellent ranging from 65% to 100%. Most of the studies have reported the proportion of participants who were lost to follow-up. No patients were lost to follow-up in three studies (ALPINE, NESTOR, OSLO) while two studies, MRC and MRCOA have a high attrition rate of 19% and 25% respectively. Cancer outcomes were available publicly for all studies except for one.

8.4 TZ and risks of incident cancer

8.4.1 Overall

Altogether, 12 RCTs were included and data were available from 44,768 (99.4%) of the total 45,039 patients enrolled. Cancer incidence was 6.36% in the TZ treatment group versus 6.74% in the control group. In the FE model as shown in **Figure 8-2**, the ALLHAT study had the highest weight at 86.6% overall which is clearly indicated by the largest blue square in the forest plot. The weight assignment between the heaviest and the second heavy study is very wide with a difference of 76.5%. The remaining studies only carry a small portion of weight

each ranging from 0.1% to 1.5%. Only four studies (LaCroix, MIDAS, NESTOR, VA COOP II) had recorded an increased risk with OR more than 1, however, the 95% CI for these studies overlaps 1. The remaining studies recorded an OR equivalent or less than 1 with the 95% CI includes 1. Confidence intervals for all the studies crossed the line of no effect indicating a lack of statistical significance at the study level. As a result, the combined OR is 0.97 with 95% CI ranged between 0.90 and 1.05 (P-value = 0.43). The diamond that represents the pooled effect estimates impinges the line of no effect, hence indicating the absence of statistical significance at the meta-analysis level.

Figure 8-3 depicts the RE model meta-analysis of the 18 RCTs included in the assessment of cancer risk. Likewise, the ALLHAT study was given the heaviest weightage at 87.4% overall while the majority of the remaining studies carries a weight of less than 1%. The combined effect estimate yields an OR of 0.97 with 95% CI ranged between 0.90 and 1.05 (P-value = 0.43), unequivocally similar to the FE model.

Assessment of heterogeneity in both FE and RE model showed a chi-square P-value of 0.80 and an I^2 statistics of 0% indicating no statistical differences between studies.

Visual assessment of the funnel plot as shown in Appendix Figure A-1(Page 323) demonstrated missing studies on the middle right side of the plot but no outlier is detected. Overall, the funnel plot appears relatively symmetry on both sides of the plot indicating the risk of publication bias is unlikely.

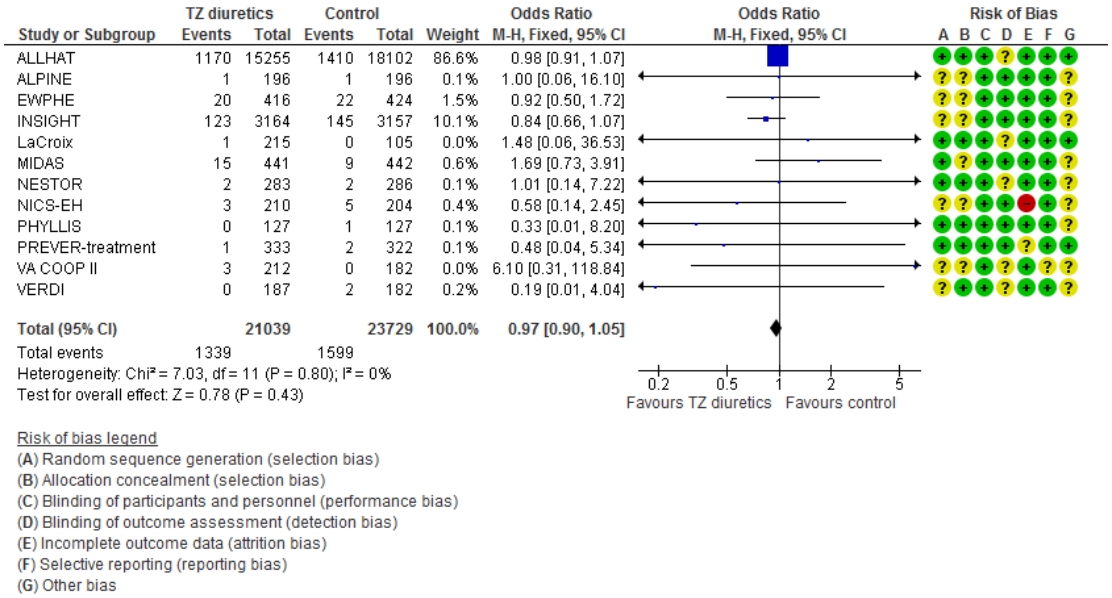


Figure 8-2: Forest plot of incident cancers by TZ vs non-TZ controls [FE model].
Odds ratios and 95% confidence interval, overall and in 18 trials. The overall effect represents the pooled estimate of odds for incident cancers.

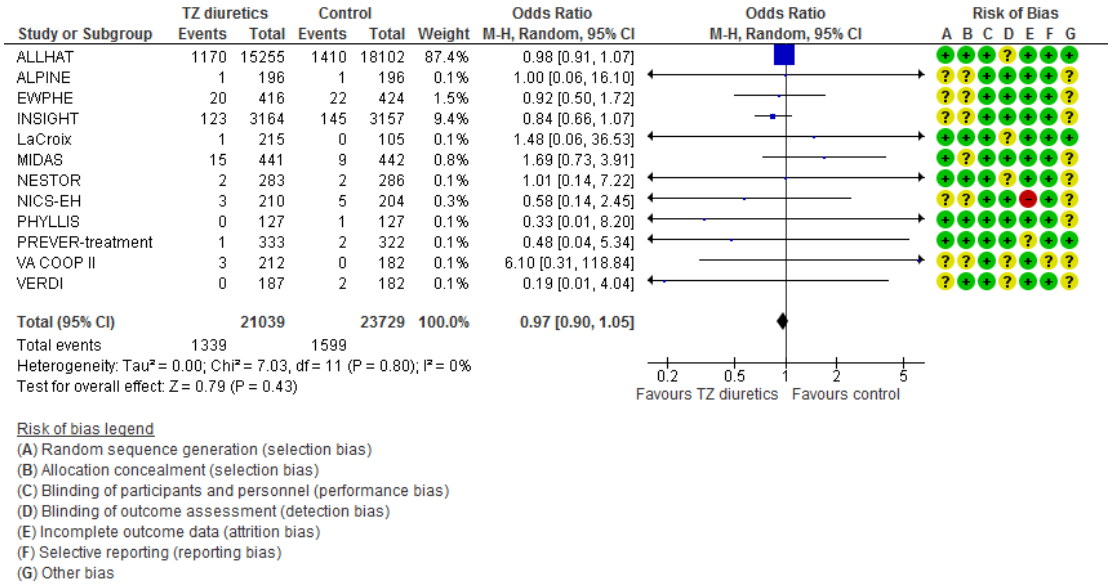


Figure 8-3: Forest plot of incident cancers by TZ vs non-TZ controls [RE model].
Odds ratios, and 95% confidence interval, overall and in 18 trials. The overall effect represents the pooled estimate of odds for incident cancers.

8.4.2 Sensitivity analysis

Exclusion of 16 studies enrolling less than total 1000 participants resulted in OR 0.97 with 95% CI ranged between 0.90 and 1.05 (P-value = 0.41; **Figure 8-4**). This result is largely driven by the ALLHAT study because it was assigned 89.5% of the overall weight. Chi-square test for heterogeneity yields a P-value of 0.23 and I^2 statistics is observed at 30% indicating low heterogeneity between studies. The heterogeneity observed is most likely due to the methodological diversity of the ALLHAT (a three-arm parallel study) and INSIGHT (used a different type of TZ drug) study.

Figure 8-5 shows the meta-analysis of five studies after exclusion of studies judged to be of low methodological quality. The combined effect estimates yield an OR of 0.98 with 95% CI ranged between 0.91 and 1.06 (P-value = 0.66). This result was mainly influenced by the ALLHAT study because it was assigned 99.5% of the overall weight. Assessment of heterogeneity showed a chi-square test P-value of 0.93 and I^2 statistics of 0% indicating a lack of statistical significance in differences between studies.

Finally, the exclusion of the ALPINE study from the overall-meta-analysis resulted in OR 0.97 with 95% CI ranged between 0.90 and 1.05 (P-value = 0.43; **Figure 8-6**). The weighting of the studies in this meta-analysis is comparable to the primary meta-analysis analysis with the ALLHAT study assigned the most weight (86.7%). Assessment of heterogeneity showed a chi-square test P-value of 0.72 and I^2 statistics of 0% indicating a lack of statistical significance in differences between studies.

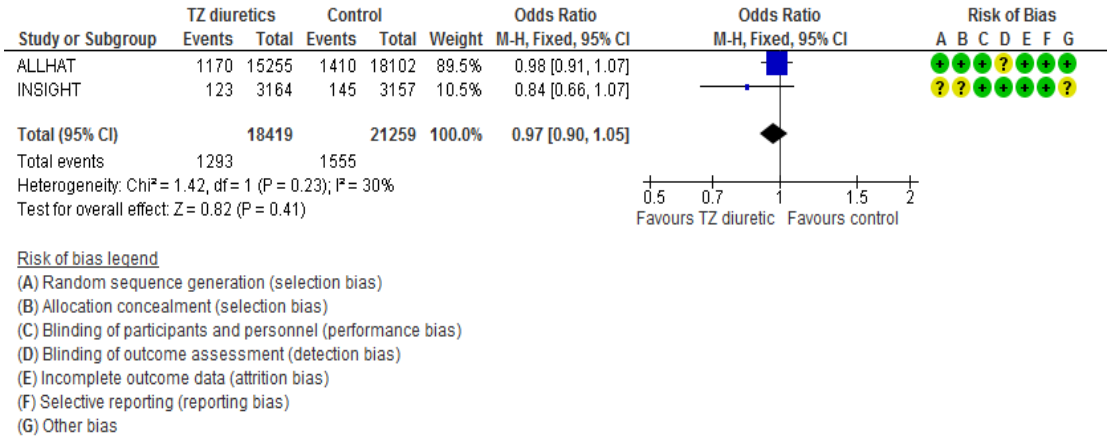


Figure 8-4 Forest plot of incident cancers by TZ vs controls [Sensitivity analysis: Study size].
The overall effect represents the pooled estimate of odds for incident cancers.

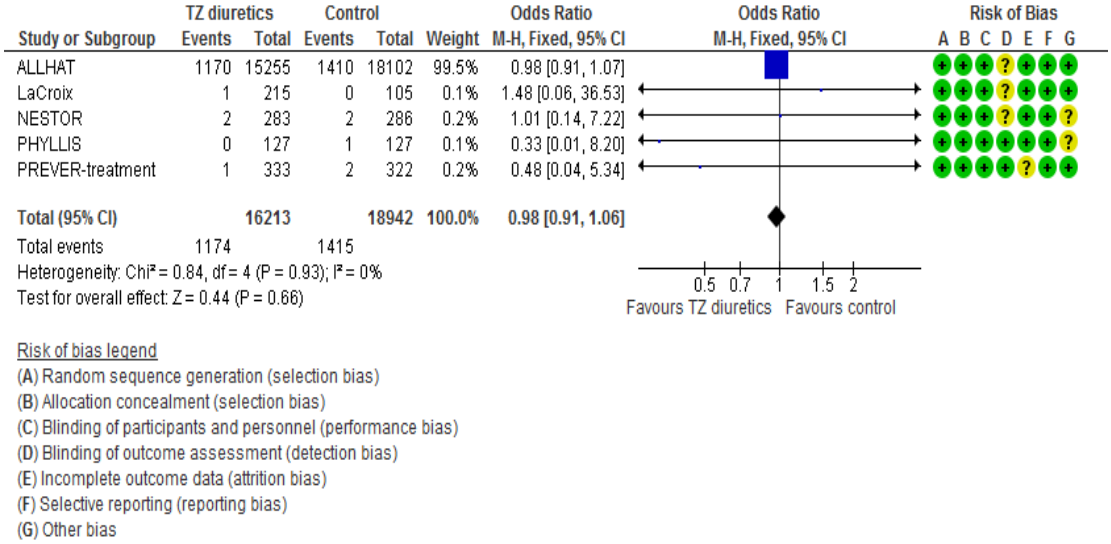


Figure 8-5 Forest plot of incident cancers by TZ vs controls [Sensitivity analysis: Methodological quality].
The overall effect represents the pooled estimate of odds for incident cancers.

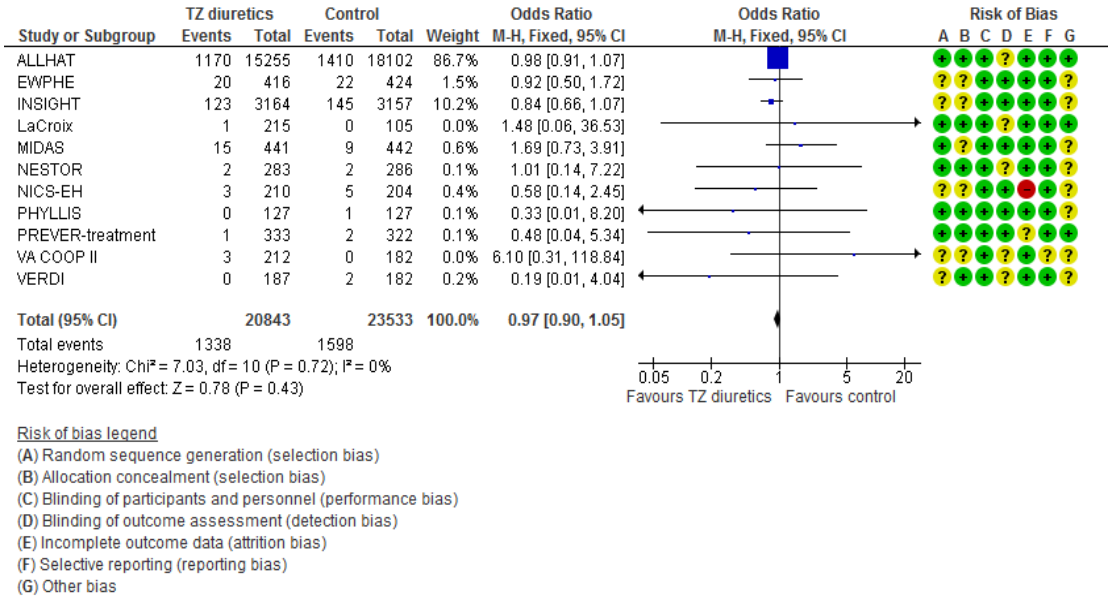


Figure 8-6 Forest plot of incident cancers by TZ vs controls [Sensitivity analysis: Exclusion of the ALPINE trial].
The overall effect represents the pooled estimate of odds for incident cancers.

8.4.3 Subgroup analyses

Table 8-2: summarises the results for subgroup analyses performed for TZ and cancer risk.

8.4.3.1 By Subclass

Data for TZ-type diuretics were available from nine RCTs with a total study population of 10,187. Cancer incidence was 3.21% in the TZ-type treatment groups versus 3.69% in the control group. The combined effect estimate resulted in OR 0.89 with a rather wide 95% CI ranging from 0.72 to1.10 (P-value = 0.28). As shown in **Figure 8-7**, the INSIGHT study has the biggest influence as it carries the heaviest weight overall (77.4%) and is depicted as the largest blue square in the forest plot. The chi-square test resulted in a P-value of 0.66 and the I^2 statistics of 0% indicates no statistical difference between studies.

For TZ-like diuretics, data were available from 34,581 patients enrolled in three RCTs. Cancer incidence was 7.39% in the TZ-like diuretics treatment group versus 7.56% in the control group with OR 0.98 (95% CI 0.91-1.07; P-value = 0.67). This result was largely driven by the ALLHAT study as it was assigned 99.7% of the overall weight (**Figure 8-7**). Assessment of heterogeneity showed a chi-square P-

value of 0.84 and I^2 statistics is observed at 0% indicating no statistical difference between studies.

8.4.3.2 By type of comparator

Altogether, ten RCTs have compared TZ to active controls with data available from 43,608 patients. Cancer incidence was 6.46% in the TZ-diuretics treatment group versus 6.79% in the active control group. Pooling of effect estimates from the ten studies yields an OR of 0.97 (95% CI 0.90-1.05) with P-value = 0.44 (**Figure 8-8**). The ALLHAT study had the biggest influence in this analysis as it carries 88% of the overall weight. The chi-square test resulted in a P-value of 0.64 and the I^2 statistics of 0% indicates no statistical heterogeneity between studies.

Five RCTs compared TZ to RAS inhibitors comprising ACEI and ARB and data were available from 26,179 patients. Cancer incidence was 7.25% in the TZ treatment group versus 7.10% in the RAS inhibitors treatment group. Combined effect estimates resulted in OR 0.98 (95% CI 0.89-1.08; P-value = 0.75). This result was mainly influenced by the ALLHAT study as it carries the most weight overall at 99.2% (**Figure 8-8)**. Assessment of heterogeneity showed a chi-square P-value of 0.75 and I^2 statistics observed at 0% indicating no statistical difference between studies.

Similarly, five RCTs have compared TZ to CCB with data available from 32,290 patients. Cancer incidence was 6.81% in the TZ treatment group versus 6.66% in the CCB treatment group with OR 0.96 (95% 0.88-1.05; P-value = 0.40). The ALLHAT study was assigned the heaviest weight of 84% overall and consequently has a major influence in the direction of the combined OR (**Figure 8-8**). The chi-square test resulted in a P-value of 0.33 and the I^2 statistics observed at 13% signifies low heterogeneity between studies. The observed heterogeneity is most likely due to methodological and clinical diversity of the MIDAS study (predominant male participants).

For placebo, data were available from 1,160 patients enrolled in two RCTs. Cancer incidence was 3.33% in the TZ treatment group versus 4.16% in the placebo group with OR 0.94 and a relatively wide 95% CI ranging from 0.51 to 1.73 (P-value = 0.84). From **Figure 8-8**, it is clear that the EWPHE study has influenced the

direction of the pooled effect estimates with assigned study weight of 96.9% overall. Assessment of heterogeneity showed a chi-square P-value of 0.78 and I^2 statistics observed at 0% indicates no statistical difference between studies.

8.4.3.3 By population health setting

Data for patients with uncomplicated hypertension were available from 3,947 enrolled in seven RCTs. Cancer incidence was 2.16% in the TZ treatment group versus 2.10% in the control group. The combined effect estimates resulted in OR 1.05 with a rather wide 95% CI ranged between 0.68 and 1.61 (P-value = 0.83). The overall result was mainly driven by the EWPHE study (51.2%) followed by the MIDAS study (21.4%) as demonstrated by the weight assigned to each study (**Figure 8-9**). Assessment of heterogeneity showed a chi-square P-value of 0.54 and I^2 statistics is observed at 0% indicates no statistical difference between studies.

For hypertensive patients with one or more risk factor for CV events, data were available from 40,902 patients enrolled in four RCTs. Cancer incidence was 6.81% in the TZ treatment group versus 7.13% in the control group with OR 0.97 (95% CI 0.90-1.04; P-value = 0.40). This analysis was mainly driven by the ALLHAT study as it carries the greatest weight of 89.2% overall. The chi-square test resulted in a P-value of 0.63 and the I^2 statistics of 0% signifies no statistical heterogeneity between studies.

8.4.3.4 By mean age groups

For studies with patients' mean age of 65 years or older, data were available from 41,252 enrolled in five RCTs. Cancer incidence was 6.84% in the TZ treatment group versus 7.19% in the control group. The pooled effect estimates resulted in OR 0.97 (95% CI 0.90-1.04; P-value = 0.38). The analysis was mainly influenced by the ALLHAT study as it was assigned the most weight of 87.8% overall (**Figure 8-10)**. The chi-square test resulted in a P-value of 0.73 and the I^2 statistics of 0% signifying no statistical heterogeneity between studies.

On the other hand, data for studies with younger mean age (< 65 years) were available from 3,516 patients enrolled in seven RCTs. Cancer incidence was 1.24% in the TZ treatment group versus 0.98% in the control group with combined OR of 1.26 and a wide 95% CI ranging from 0.68 to 2.32 (P-value = 0.47; **Figure 8-10**).

This result was mainly influenced by the MIDAS study which carries the most weight overall (47.6%). Assessment of heterogeneity showed a chi-square P-value of 0.63 and I^2 statistics observed at 0% indicates no statistical difference between studies.

8.4.3.5 By duration of follow-up

Data for studies with mean patients' follow-up three years or longer were available from 42,135 patients enrolled in six RCTs. Cancer incidence was 6.76% in the TZ treatment group versus 7.09% in the control group. Combined effect estimates resulted in OR of 0.97 (95% CI 0.90-1.05; P-value = 0.45). This analysis was mainly driven by the ALLHAT study which was assigned the greatest weight overall (87.2%; **Figure 8-11**). Assessment of heterogeneity showed a chi-square P-value of 0.59 and I^2 statistics observed at 0% indicates no statistical difference between studies.

Meanwhile, studies with patients' mean follow-up duration of less than three years were available from 2,633 patients enrolled in six RCTs. Cancer incidence was 0.52% in the TZ group versus 0.62% in the control group. Combined effect estimates resulted in OR of 0.86 with a very wide 95% CI ranged between 0.34 and 2.18 (P-value = 0.74; **Figure 8-11**). Weights were fairly distributed between studies with almost equivalent weight was assigned to the VERDI, PREVER-Treatment, and NESTOR study (26.5%, 21.2%, and 20.7% respectively). The chi-square test resulted in a P-value of 0.67 and the I^2 statistics of 0% signifies no statistical heterogeneity between studies.

Table 8-2: Thiazide diuretics and risk of cancer: Subgroup analyses

Subgroup analysis		No. of study	No. of participants	Cancer incidence (%)		OR (95% CI)	P-value	I^2 (%)
				TZ	Control			
Overall effect	FE model	12	44768	6.36	6.74	0.97 (0.90-1.05)	0.43	0
Subclass	TZ	9	10187	3.21	3.69	0.89 (0.72-1.10)	0.28	0
	TZ-like diuretics	3	34581	7.39	7.56	0.98 (0.91-1.07)	0.67	0
Type of comparator	Active	10	43608	6.46	6.79	0.97 (0.90-1.05)	0.44	0
	RAS inhibitors	5	26179	7.25	7.10	0.98 (0.89-1.08)	0.75	0
	CCB	5	32290	6.81	6.66	0.96 (0.88-1.05)	0.40	13
	Placebo	2	1160	3.33	4.16	0.94 (0.51-1.73)	0.84	0
Clinical setting	Hypertension	7	3947	2.16	2.10	1.05 (0.68-1.61)	0.83	0
	High- risk hypertensive	4	40902	6.81	7.13	0.97 (0.90-1.04)	0.40	0
Age	≥ 65 years	5	41252	6.84	7.19	0.97 (0.90-1.04)	0.38	0
	< 65 years	7	3516	1.24	0.98	1.26 (0.68-2.32)	0.47	0
Duration of follow-up	≥ 3 years	6	42135	6.76	7.09	0.97 (0.90-1.05)	0.45	0
	< 3 year	6	2633	0.52	0.62	0.86 (0.34-2.18)	0.74	0

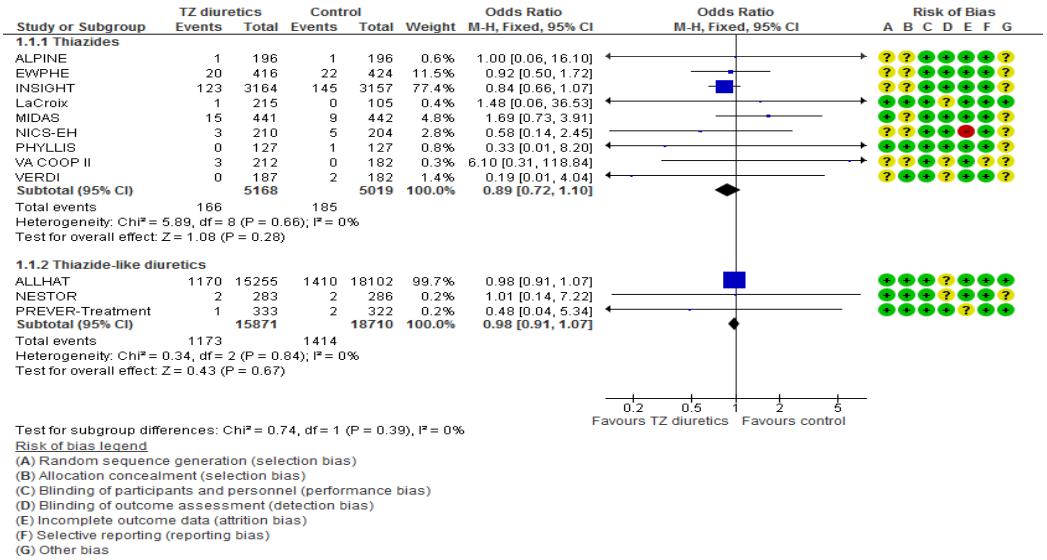


Figure 8-7: Forest plot of cancer incidence by TZ subclass [FE model].
1)TZ vs controls in 9 trials; 2) TZ-like vs controls in 3 trials The subtotal effect represents the pooled estimate of odds for cancer incidence for each subclass.

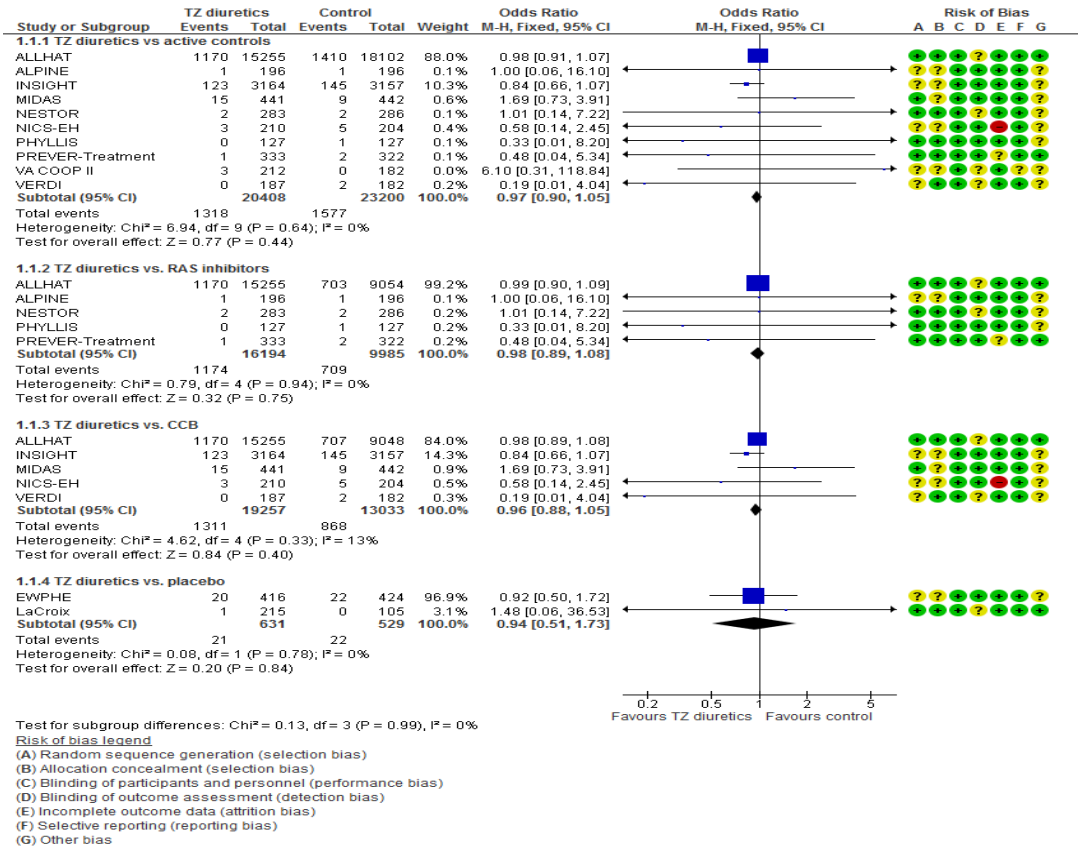


Figure 8-8: Forest plot of cancer incidence by comparators [FE model].
1) Active controls; 2) RAS inhibitors; 3) CCB; 4) Placebo. The subtotal effect represents the pooled estimate of odds for cancer incidence for each comparator.

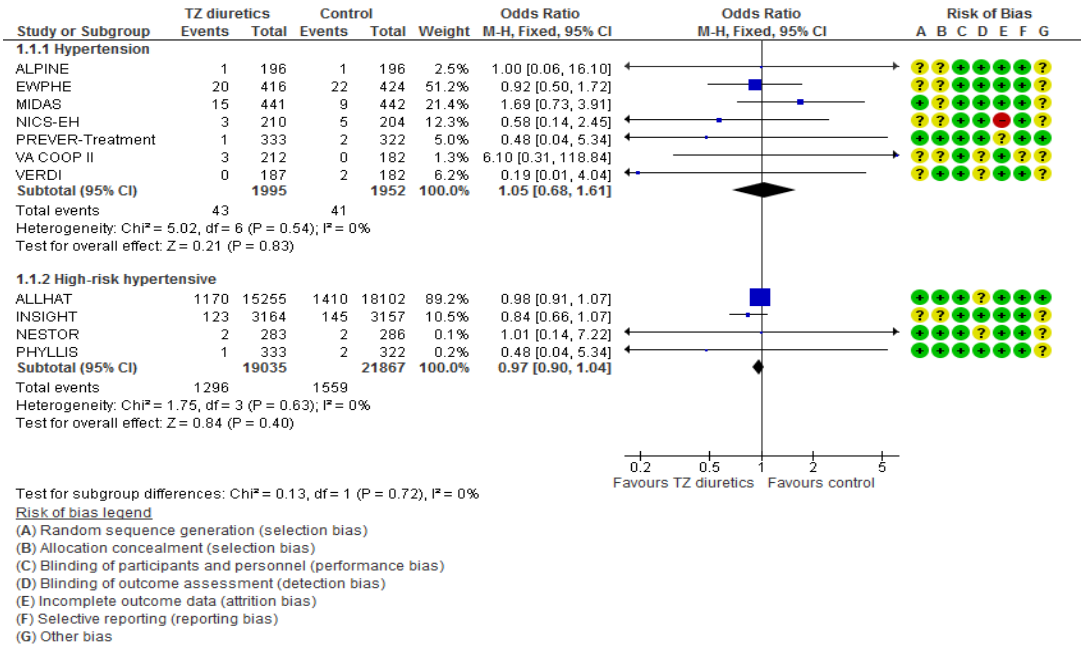


Figure 8-9: Forest plot of cancer incidence by clinical setting [FE model].
1) Hypertension; 2) High-risk hypertension. The subtotal effect represents the pooled estimate of odds for cancer incidence for each clinical setting.

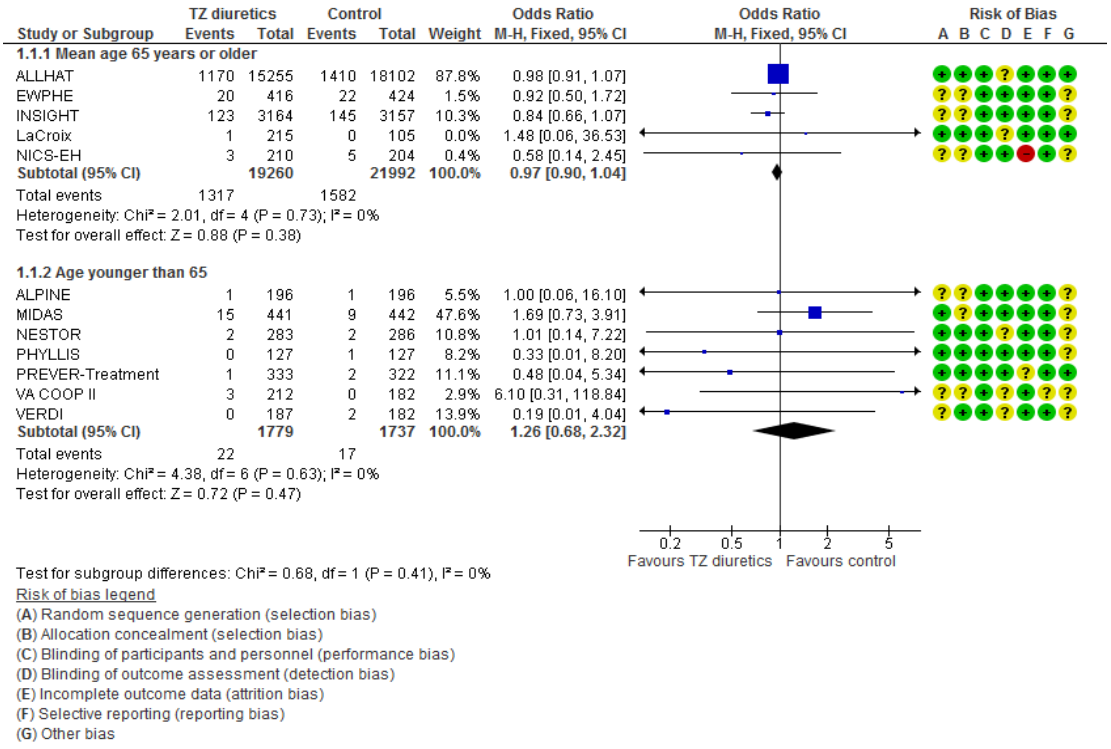


Figure 8-10: Forest plot of cancer incidence by study population's mean age [FE model].
1) Mean age ≥ 65 years; 2) Mean age < 65 years. The subtotal effect represents the pooled estimate of odds for cancer incidence for each criterion.

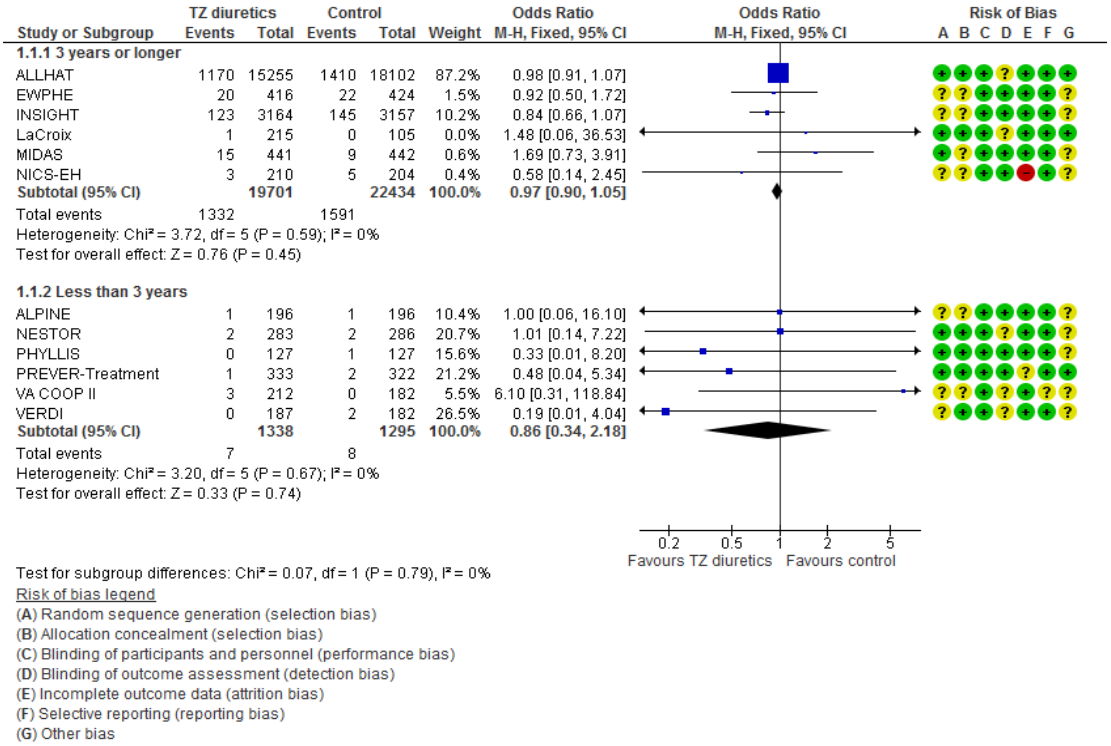


Figure 8-11: Forest plot of cancer incidence by study mean duration of follow-up [FE model].
1) Follow-up ≥ 3 years; 2) Follow-up < 3 years. The subtotal effect represents the pooled estimate of odds for cancer incidence for each criterion.

8.5 Thiazide diuretics and cancer-related death

Overall, 10 RCTs were included in the meta-analysis of TZ-diuretics and cancer-related death. Data were available from 69,241 (99.9%) patients out of total 69,256 patients enrolled in the ten studies. Based on randomly assigned therapy, cancer-related deaths were 2.58% in the TZ group versus 2.35% in the control group.

Figure 8-12 shows the meta-analysis 10 TZ-diuretic trials in an FE model. The main analysis was mainly influenced by the ALLHAT study as it was assigned the most weight overall at 67.4% which is clearly depicted as the largest blue square in the forest plot. This is followed by the SHEP, MRCOA, and MRC study which carry 10%, 9.8% and 8.5% of the overall weight correspondingly. Five studies have recorded an OR more than 1 ranging from 1.06 to 4.90. On the other hand, the five remaining studies observed an OR less than 1 ranging from 0.32 to 0.96. The 95% CI of all the studies includes 1 which is displayed as CI crossing the vertical

line of no effect in the forest plot. Therefore, none of the individual studies is statistically significant at the study level. When the results of all the ten studies were pooled together, the combined effect showed an OR of 1.03 with 95% CI ranged between 1.03 and 1.14 (P-value = 0.56) and the diamond that represents the combined effect estimate in the forest plot is located on the line of no effect. This result indicates that no statistical significance is observed at the meta-analysis level.

Figure 8-13 showed the meta-analysis of the ten studies in a RE model. In comparison to the FE model, an additional 1.2% weight was assigned to the ALLHAT study whereas the remaining 17 studies carry less than 10% weight individually. Nevertheless, both FE and RE model meta-analyses arrive at an identical combined OR of 1.03 (95% CI 0.93-1.14) and a relatively similar overall effect P-value of 0.57.

Assessment of heterogeneity in both FE and RE model showed a chi-square test P-value of 0.97 and I^2 statistics of 0%. These values indicate no evidence of statistically significant heterogeneity between the difference studies.

Evaluation of the funnel plot as shown in Appendix Figure A-2 (Page 324) demonstrates missing study on the right side of the plot. All the studies fall within the area of non-significance and no outlier is detected. Otherwise, the funnel plot appears fairly symmetrical indicating the presence of bias is unlikely.

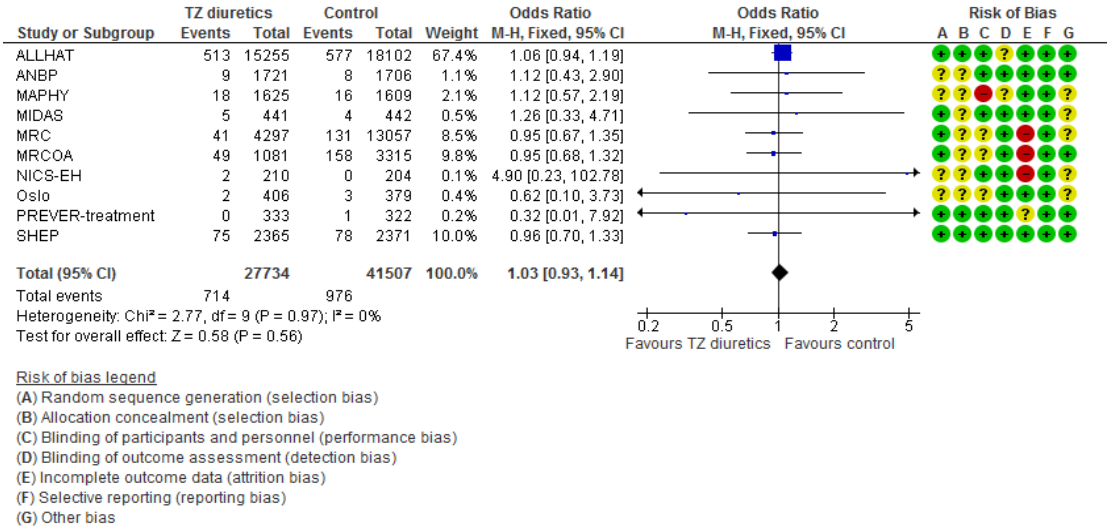


Figure 8-12 Forest plot of cancer-related death by TZ vs non-TZ controls [FE model]. Odds ratios, and 95% confidence interval, overall and in 10 trials The overall effect represents the pooled estimate of odds for cancer-related death.

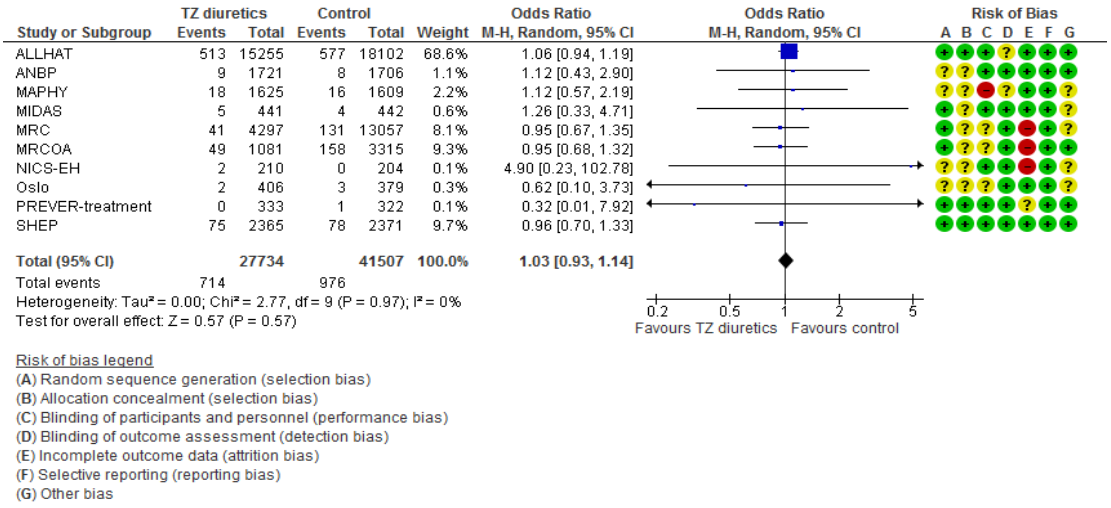


Figure 8-13 Forest plot of cancer-related death by TZ vs non-TZ controls [RE model]. Odds ratios, and 95% confidence interval, overall and in 10 trials The overall effect represents the pooled estimate of odds for cancer-related death.

8.5.1 **Sensitivity analysis**

Figure 8-14 shows the meta-analysis of eight studies after exclusion of the MRC and MRCOA. The combined effect estimates yield an OR of 1.05 with 95% CI ranged between 0.94 and 1.17 (P-value = 0.40). This result was mainly influenced by the ALLHAT study because it was assigned 82.5% of the overall weight. Assessment of heterogeneity showed a chi-square test P-value of 0.95 and I^2 statistics of 0% indicating a lack of statistical significance in differences between studies.

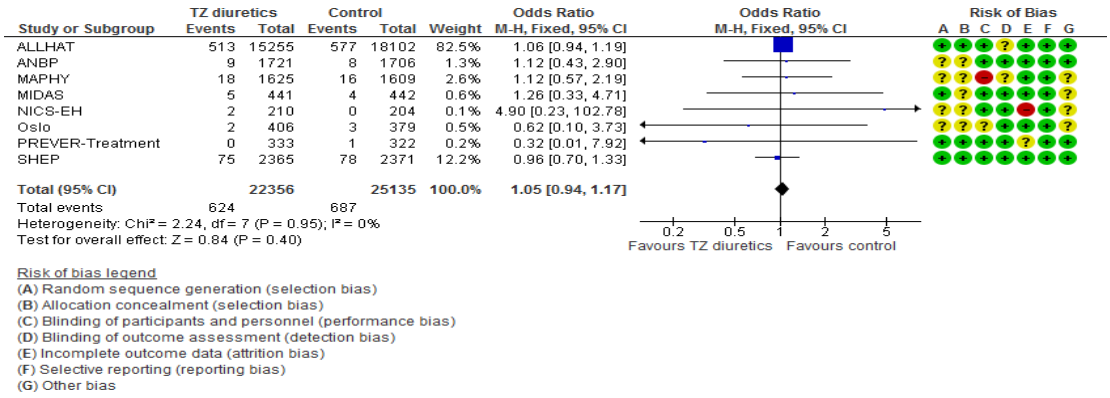


Figure 8-14 Forest plot of cancer-related death by TZ vs controls [Sensitivity analysis: Exclusion of trials with high attrition rate].
The overall effect represents the pooled estimate of odds for incident cancers

8.6 Discussion

The result of the present meta-analyses showed that TZ is not significantly associated with any cancer risk with OR 0.97 (95%CI 0.90-1.05; P-value = 0.43). The results of sensitivity analyses also suggest a similar direction to the combined effect estimates. Likewise, no significant association was seen between TZ and risks of cancer-related deaths (OR 1.03, 95% CI 0.93 and 1.14). The magnitude and direction of the association are comparable even after exclusion of the two trials with high attrition bias (MRC and MRCOA) with OR 1.05 (95% CI 0.94-1.17).

Consistently, both TZ and TZ-like diuretics showed decreased cancer risk although the association is not statistically significant with OR 0.89 (95% CI 0.72-1.10) and OR 0.98 (95% CI 0.91-1.07) respectively. Previous systematic reviews and meta-analyses of RCTs have not reported the risk for cancer between TZ and TZ-like diuretics (Coleman et al., 2008, Bangalore et al., 2011). Generally, both TZ and TZ-like diuretics are safe and well tolerated and their use is interchangeable. In practice, however, TZ-like diuretics such as chlorthalidone is preferred over HCTZ because the former is 1.5 to 2.0 times as potent and has a much longer duration of action than the latter. The main concern when prescribing diuretics would be electrolyte disturbance due to its mechanism of action at the distal tubules of the kidney. Blockade of the Na^+/Cl^- cotransporter at the distal tubule by TZ prevents reabsorption of Na+ which subsequently increases Na+ delivery to the collecting duct. Since Na^+ reabsorption is coupled to K^+ secretion in the collecting duct, TZ can lead to hypokalaemia by excessive secretion of potassium into the urine. Hyponatraemia is also a typical complication seen in TZ users especially in

elderlies and existing hypokalaemia (Fuisz et al., 1962, Chow et al., 2003). Additionally, studies have also reported lower insulin sensitivity following treatment with TZ (The ALLHAT Collaborative Research Group, 2002, Eriksson et al., 2008). A recent meta-analysis of 12 RCTs has assessed HCTZ and TZ-like diuretics (indapamide or chlorthalidone) effects on biochemical properties (Liang et al., 2017). The authors reported that the risk for hypokalaemia, hyponatraemia, or changes in serum glucose or total cholesterol is not different between the two TZ. Due to lack of head-to-head comparative trial between HCTZ and TZ-like diuretics, the authors have included data with a combination of diuretics and other antihypertensive class agents which could make an assessment of diuretics' attributes on metabolic effects challenging. Nonetheless, these negative metabolic disturbances only occur at high doses and can be minimized by shifting to a low-dose strategy (Sica et al., 2011).

Though insignificant, TZ to some extent appeared to have a protective effect against cancer incidence when compared to other antihypertensive agents or placebo. Subgroup analyses conducted in the present review have demonstrated an OR less than 1 with 95% CI overriding 1 for all comparisons using any active controls, RAS inhibitors, CCB or placebo (Table 8-2:). The most recent network meta-analysis of 70 RCTs with 148 comparator arms have reported an OR of 1.01, 0.99,0.96, and 0.95 for TZ in direct comparison to ARB, ACEI, CCB, and placebo correspondingly for cancer incidence (Bangalore et al., 2011). In an earlier network meta-analysis of 27 RCTs with 56 comparator arms assessing the odds for cancer in major antihypertensive class agents, the OR for diuretics was 0.94 (95% CI 0.73-1.19) with placebo or untreated control group as the referent comparison (Coleman et al., 2008). Despite this evidence, many earlier epidemiological studies demonstrated the opposite.

The most common malignancy to be associated with diuretics is the RCC. A retrospective cohort study by Yu et al. (1986) was one of the earliest studies to linked diuretics as one of the risk factors for RCC. The investigators assessed obesity, cigarette smoking, coffee consumption and diuretic use as a risk factor in 160 pairs of RCC cases and controls. They have found that diuretics use is a significant risk factor for RCC in female but not in men with RR of 4.5 (95% CI 1.6-14.5) and this relationship has remained even after controlling for hypertension (RR 4.0, 95% CI 1.3-12.5). Apart from diuretics, Yu and colleague also reported a

positive association with the other factors studied which are shared with another type of malignancy. This discovery had prompted a case-control study enrolling 495 RCC cases and 697 controls assessing the odds for RCC with the use of diuretics (McLaughlin et al., 1988). A consistent association was seen in females but just in those without hypertension (16 cases, 6 controls) with OR 5.3 (P value <0.01) and not in those with hypertension (OR 0.7). Consistently, a 518 RCC cases and 1,381 population-based controls study in Canada has also reported a significant increase in odds of RCC in women who used diuretics after adjusted for high BP with OR 2.3 (95% CI 1.3-4.0)(Kreiger et al., 1993). These studies, however, are likely to be subjected to recall bias as they have used the interview-questionnaire method. In addressing this problem, an all-women cohort study in the US used a medical-record database as a source of information on prescription diuretic use (Finkle et al., 1993). After adjusting for potential confounding factors, the investigators reported a significant association between RCC and diuretics (OR 2.9, 95% CI 1.7-4.7). All the same, none of these studies specified the type of diuretics investigated. In another historical case-control study, the risk of RCC was assessed in relation to the use of TZ (Hiatt et al., 1994). Hiatt and team had reported a significant excess risk in women ever having used TZ with OR 4.00 (95% CI 1.5-10.8) after adjusting for hypertension, body mass index (BMI), smoking, and kidney infection. Alternatively, they found that hypertension is not significantly linked to risk of RCC after adjustment to TZ therapy.

While kidney cancer is more common in men than women with a male: female ratio of around 17:10 (Cancer Research UK, 2016), the fact that most of these studies have documented that women are at higher risk of RCC than men suggests a specific cause. A cross-sectional study of the Netherland population from 1987 to 1995 reported that women used diuretic two to three times more than men (Klungel et al., 1998) possibly because women have a greater tendency for oedema than men. Another explanation could be related to the differences in the level of sex hormone present in both men and women. In an experimental study using the ovariectomized rat model, Verlander et al. (1998) demonstrated that oestrogen has an effect on TZ diuretic in the kidney. After comparing between ovariectomized and control rats, the authors concluded that the presence of oestrogen is necessary to maintain the complexity and density of TZ-sensitive NaCl cotransporter (TSC1) in the DCT. Unfortunately, due to a lack of individual-patient

data, the difference between gender in odds of RCC and other cancer types was not assessed in the present study.

Nevertheless, findings from these studies also suggest that the presence of high BP does not affect the risk of cancer which agrees with a subgroup analysis in the present study. Assessment of odds for cancer in hypertensive patients and in patients with higher risk for CV events showed a non-significant association with OR 1.05 (95% CI 0.68-1.61) and OR 0.97 (95% CI 0.90-1.04) respectively. The primary meta-analysis of TZ and odds of cancer incidence in the present review is not restricted to only patients with hypertension which render any association by indication unsupported.

More recent epidemiological studies have tried linking diuretics and risk of another cancer type. Li et al. (2003) conducted a population-based study assessing elderly women for risk of breast cancer in association to the use of antihypertensive medications. They found that together with immediate release CCBs, TZ and potassium-sparing diuretics modestly increased breast cancer risk with OR 1.4 (95% CI 1.1-1.8) and OR 1.6 (95% CI 1.2-2.1) correspondingly. In another population-based case-control study, Largent et al. (2006) assessed the risk of breast cancer in association with hypertension and diuretic use among middle-aged and elderly women using a cancer surveillance programme database. This study reported an increased risk for breast carcinoma in women ever treated for hypertension (OR 1.77, 95% CI 1.04-3.03) and in women who were exposed to diuretics irrespective of the indication (OR 1.79, 95% CI 1.07-3.03). In both studies, the cases reported more risk factor for breast cancer than controls such as family history of breast cancer, older age at first pregnancy, and menopause. Additionally, the results of these studies could only be inferred to older and menopausal women. A subsequent larger case-control study assessed breast cancer risk among women aged between 18 and 75 years using 30 years of data from hospital-based surveillance study (Coogan et al., 2008). On the contrary, this study found no significant association between breast cancer and TZ use regardless of the duration of exposure. The proposed mechanism by which TZ could affect breast cancer risk is by increasing insulin resistance as a result of TZ-induced hypokalaemia. Bruning et al. (1992) conducted a case-control study among 223 women aged between 38 to 75 years presenting with early stage breast cancer and 441 age-matched women with no cancer. A second control group

comprised patients with malignant lymphoma, melanoma, or uterine breast cancer. This study measured the level of non-fasting serum C-peptide, a 31-amino acid that is released simultaneously with insulin from the pancreatic beta cells following cleavage of proinsulin. The authors reported that post-menopausal and, to a lesser extent, pre-menopausal breast cancer patients have a higher serum level of C-peptide compared to controls indicating specificity for breast malignancy. However, a recent meta-analysis of 22 observational studies has found no differences between fasting insulin and fasting/non-fasting C-peptide levels in women with and without breast cancer (Hernandez et al., 2014).

Studies looking into the overall survival of cancer in relation to TZ diuretic are comparably limited. In a cohort study of 14,166 patients aged between 45 to 74 years with history of CHD and over 5.6 years follow-up, Tenenbaum et al. (2001) reported a significantly increased risk for colon cancer mortality in patients treated with diuretics (HR 3.7, 95% CI 1.7–8.3), while mortality difference for other cancer types were not observed. This association, however, was not specified to the type of diuretic and was only observed among non-aspirin user. This study was further limited by the lacked information on drug doses which is crucial in distinguishing the undesirable effect of the drug and those related to the degree of metabolic derangements. One mechanistic hypothesis linking TZ to colon cancer is that TZ diuretic such as HCTZ as a cyclic imide can be converted to a mutagenic N-nitroso derivative in the stomach (Andrews et al., 1984). In time, accumulation of these mutagenic compounds could potentially be carcinogenic in the gastrointestinal tract. In a more recent population-based cohort study using a cancer registry linked to a prescription database, Holmes et al. (2013) assessed the five major antihypertensive class and survival in patients with cancer. They reported a significantly increased mortality in colorectal (HR 1.28, 95% CI 1.15–1.42), lung (HR 1.10, 95% CI 1.01–1.19), and prostate cancer (HR 1.41, 95% CI 1.20–1.65) related to TZ diuretic when compared to non-user. Nonetheless, the indication for TZ in cancer patients may have been related to fluid retention problem rather than hypertension. For this reason, it is possible that patients taking TZ have additional comorbidities which may adversely affect survival.

8.6.1 Study strengths and limitations

To the best of author's knowledge, this is the largest meta-analysis of RCTs investigating the association between TZ and the risk of cancer. On that account, RCTs included also ensured internal validity by minimizing selection bias and confounding bias. Cancer outcomes from the ANBP, MAPHY, NESTOR, and PREVER-Treatment study which has never been incorporated in the most recent review available (Bangalore et al., 2011) was also included in the present study.

However, like any review, this study has a number of limitations. Firstly, the RCTs included in this review were not designed to detect cancer as one of their study endpoints. Accordingly, not all of the studies had mentioned whether patients with baseline cancer were enrolled in the trials leading to the possibility of an augmented association. However, the negative association observed in both cancer incidence and cancer-related death meta-analyses are reassuring. Secondly, only aggregate cancer data were available from the majority of the included studies thus limiting potential cancer-specific and time-to-event analysis. Also, the associations derived from this review are only applicable to TZ as a class and not as individual drugs.

The general impression remains that most human malignancies grow at a slow rate for long periods of time during the clinical and measurable phase. In this review, the longest study follow-up was 6.5 years with the majority of studies were followed for less than five years. For a tumour to be detectable clinically would require at least five years of observation based on the kinetics and growth rate of malignant cells (Friberg and Mattson, 1997). Moreover, the result of this review could only reflect late-detected cancers.

8.7 Conclusion

There is no evidence that use of TZ affects the risk of cancer or cancer-related death. Low dose TZ probably remain a good choice for initial treatment of hypertension in the elderly. Unless indicated, avoid starting treatment with TZ diuretic in younger and/or pre-menopausal women as there is evidence of higher risk for RCC in women compared to men.

9 General discussion and prospects

9.1 General overview

Hypertension accounts for around 5% of the current global disease burden because of increasing life-expectancy and concomitant factors such as obesity, physical inactivity, and high salt diet. Antihypertensive drugs are prescribed to help prevent detrimental outcomes of hypertension including stroke, CHD, and HF. There is a continuous relationship between BP and risk and this is reflected in the changing BP targets over time in hypertension treatment guidelines. The recent SPRINT trial has precipitated an update in hypertension guidelines by lowering target BP to 130 systolic. An important message from SPRINT was that it was possible to attain target BP in treated patients and this required on-average one extra drug in the intensive arm control. Whilst the use of antihypertensive drugs has increased, the shift to lower target BP will result in greater exposure to antihypertensive drugs for patients and for longer periods of time. Thus it is important to establish potential long-term adverse reactions of these commonly used drugs. The carcinogenic potential of antihypertensive drugs have been under scrutiny for a while and results have not been conclusive. It is on this background that this project was developed to determine through a comprehensive systematic review, the risk of cancer for all major antihypertensive drug classes. Most reviews of primary studies focused on the beneficial effect and clinical efficacy of antihypertensive drugs without adequately addressing adverse effects (Ernst and Pittler, 2001, Baguet et al., 2007, Fretheim et al., 2012). A balanced assessment of benefit and harm is crucial in assisting healthcare providers and patients in making an informed decision about its application. However, this can be difficult to achieve due to the massive amount of information generated from a great number of individual studies which may be biased, methodologically flawed, time and context dependent, and can be misinterpreted and misrepresented (Wilson and Petticrew, 2008). Hence, a systematic review of adverse effects within reviews of effectiveness could provide the much needed evidence to guide practitioners in decision-making.

9.1.1 Strengths of the review

The main strength of this review is described in each individual result chapter. Most of the studies included in this review have good methodological quality. To the best of author's knowledge, this is the largest, most comprehensive and updated systematic review and meta-analysis of RCTs of its kind. Additionally, this review has the potential to contribute important insight into the risk of cancer in relation to exposure to major antihypertensive drug classes in an indicated population. The comprehensive search strategy implemented allowed me to capture as many relevant citations and articles as possible. Secondly, the strict entry criteria ensure sufficiently large sample size which is necessary to produce results between different interventions that are significantly different. Finally, the inclusion of the population from various clinical health settings consequently increased external validity particularly in those who are indicated for the studied antihypertensive drug class. At the same time, stratified analyses were also performed to assess potential confounding by indication in a population with different health settings. This is important to obtain valid measures of the effects of antihypertensive agents on risks of cancer outcomes.

9.1.2 Limitations of the review

Most of the limitations described in the individual result chapters are associated with the included RCTs design weaknesses and the lack of individual-patient-level data which hinders the analysis of specific drug within a class in association to a specific type of cancer. This review is limited to the assessment of drug classes and as such, the potential of any of the individual drugs to alter the risk of cancer cannot be confirmed. Nonetheless, evaluation of subclasses for every drug class in subgroup analyses have demonstrated lack of significant association to risk of cancer except for CCB. This review also did not take into account the cumulative dose of drugs exposed to participants, therefore it is impossible to report whether exposure to a small or high cumulative dose of antihypertensive drugs could alter the risk for cancer. However, results from subgroup analyses conducted based on the duration of follow-up are comparable to the primary meta-analysis across all antihypertensive classes.

Meanwhile, a long duration of observation is essential to detect pro- or anti-cancer effect of interventions studied as most cancer has a long latency period. Latency period in this review is defined as the length of time between exposure to antihypertensive therapy and diagnosis of cancer. Most of the studies included were followed for an average short period of time ranging from one to five years. As cancer development is a slow process, this review could only reflect late-detected cancers. All the included studies also failed to describe the time interval between initiation of treatment and cancer diagnosis. Cancer incidence diagnosed in the early stage of studies may have developed long before exposure to the study intervention, thus the inclusion of these patients in the meta-analyses potentially lead to overestimation of effect. Despite this inadequacy, sensitivity analyses in this review have demonstrated that inclusion of patients with established cancer did not affect the result of the primary meta-analysis.

At the same time, the software used for this review is not built to run certain analysis such as meta-regression which can supplement and support the primary meta-analysis. Nevertheless, the subgroup analyses conducted is sufficient to assess moderator variables.

9.1.3 Comparison with other reviews

Appraisal of the literature has shown a number of studies similar to the present review where such studies either assessed all the major antihypertensive drug classes together or individually with regards to any or specific type of cancer. Only studies that are very similar to the present review are described and discussed in this section. Studies focusing on one class of antihypertensive agents were discussed in individual antihypertensive drug class chapters. Altogether, two reviews have been identified to have a comparable study objective, design, and outcome of the present study. Both studies have conducted a network meta-analysis, a complex method of combining both direct and indirect effect estimates concurrently. This approach enables observation of indirect comparisons constructed from two trials that contain one common treatment (e.g. comparison of treatment A versus C with trials comparing A versus B and B versus C) (Song et al., 2011). The validity for both meta-analysis and network meta-analysis is dependent upon the adequacy of the evidence and similarity of trials. The recently published PRISMA Extended Statement for reporting of systematic review requires

that all network meta-analyses are based on a systematic review (Hutton et al., 2015).

The first study to assess major antihypertensive drug classes and their impact on cancer incidence in RCTs was a network meta-analysis by Coleman et al. (2008). The reviewers have searched four electronic databases as well as trial references, reports and registries through June 2007. The Jadad score was used for quality assessment which evaluates randomisation, masking, and accountability of all participants (Jadad et al., 1996). No other restrictions were applied. This publication, however, did not supplement readers with the study flow chart describing the screening, eligibility, inclusion and exclusion of studies. Hence, it is difficult to determine the burden of the study selection process and to compare with the present review. Overall, 27 RCTs with a total of 126,137 patients enrolled were included in the final meta-analysis. Due to the relaxed inclusion criteria, study with less than one year treatment follow-up (Borghi and Ambrosioni) was also included in the network meta-analysis. Only results from multiple comparison and pairwise analysis were reported in which Coleman and team have consequently concluded that these drug classes are not associated with increased risk of cancer.

A much similar network meta-analysis was published by Bangalore et al. (2011). The objective of Bangalore and team was to assess the association of antihypertensive drug classes with the risk of cancer incidence and cancer-related death. In addition to electronic databases and trials reference list, they also reviewed grey literature and hand-searched the FDA database up to August 2010. Authors of studies were contacted for additional information as required. They also restricted the inclusion criteria to only trials with at least one year follow-up and enrolled a minimum of 100 patients. The study flow describing the process of trials selection presented in this review demonstrated that the authors have conducted the search discretely for each drug class. Methodological qualities of included trials were assessed in accordance with the Cochrane Collaboration risk of bias tool. Altogether, they included 70 RCTs enrolling 324,168 participants. Bangalore and team have analysed individual drug classes directly by also stratifying them according to subclasses. Apart from monotherapy, they also assessed ACEI and ARB combination on the risk of cancer. For the ONTARGET

study, cancer data for the ARB monotherapy treatment group had been compared to ACEI monotherapy and then to ACEI and ARB combination treatment groups in the same meta-analysis. Double-counting of the same study is an inappropriate method for combining patient outcome data (Senn, 2009) as this could introduce bias leading to inaccurate effect estimate. In keeping to the PRISMA guideline of reporting systematic review, the meta-analysis of cancer outcomes was conducted in an intention-to-treat manner for both direct and multiple comparisons. Apart from network meta-analysis, they also conducted trial sequential analysis (TSA) to assess for consistency of effect between the direct and multiple comparisons. TSA, similar to interim analyses, is a method that combined the sample sizes of all included trials for a meta-analysis with monitoring boundaries of statistical significance.

From direct comparisons, Bangalore reported a significant increase in odds of cancer incidence for CCB overall and DHP CCB in particular, but not for cancer deaths. Meta-analysis of two trials using ACEI and ARB combination as one of its treatment group in the FE model has shown a significant increased risk for cancer incidence, but not in the RE model. No significant association was observed with other class of antihypertensive drugs. Results from multiple comparisons were largely similar to the direct comparisons except they found no increased risk of cancer incidence with use of CCB in both FE and RE model. As for ARB and ACEI combinations, comparison with placebo, ARB or ACEI monotherapy, BB and TZ increased cancer risk only in the FE model. Meanwhile, results from the TSA suggested evidence for at least a 10% relative risk increase of cancer with ACEI and ARB combination.

In comparison to the Bangalore study, a similar search strategy was employed in the present review. Instead of PubMed, a search using Medline was performed because it enabled a more focused search. The ClinicalTrials.gov, a registry of clinical trials and is the largest of its kind, was also hand-searched for relevant trials. In addition, the search was extended up to December 2015. Due to the massive volume of citations generated from the three databases and time-constraint, the search for grey literature was not performed. Nonetheless, this search strategy did cover all the RCTs included in the Bangalore review and more. The literature searching was also performed collectively for all drug classes as this

method is more efficient in the process of study selection. Where possible, the primary or secondary author of the respective trials was contacted though not many have responded. The eligibility criteria for this review is stricter. A similar approach has been used in assessing the methodological quality of each included RCT. In comparison to Bangalore, an additional 20 RCTs were included in the present review in which 14 of the studies were published prior to 2010 and only nine studies were published after 2010 (the latest 2016). Seven studies (APRES, GISEN, GLANT, HSCSG, JIKEI, KYOTO Heart Study, and STONE) included in the Bangalore review were excluded from this study for reasons described in Chapter 3, Section 3.2.1 (page 73).

Unlike Bangalore, trials with two types of antihypertensive drug used in one group where the exact number of patients receiving the treatment and the number of cancer incidence according to drug class was not specifically stated were not incorporated in the meta-analysis of either class of drug. For example, the CONVINCE study randomised patients to verapamil in one group and atenolol or HCTZ in another group. Therefore, cancer data from this study was only included in the meta-analysis for CCB and risk of cancer, but not for BB or TZ. Whenever possible, patients with baseline cancer were excluded in the present study. Excluding these patients could introduce the risk of bias into the result as it was not an ITT analysis and the treatment groups may be unbalanced. However, sensitivity analyses performed by including these patients showed the measured effects did not differ.

9.2 Implication for research

It is recognized that safety must be monitored in all clinical trials; therefore a standardized formal procedure to identify adverse events and to conduct an interim analysis for safety reason should always be considered. Since many studies had attempted to implicate antihypertensive drugs to the risk of cancer, better designed RCTs with cancer pre-specified as one of the safety endpoint is warranted. Pre-identification of cancer as an outcome with careful monitoring can ensure early diagnosis and credibility of the results. Moreover, it is not uncommon for trials to not publish outcomes measured during clinical trials upon completion of the trial regardless of funding sources or the journals in which they are published (Jones et al., 2015). The presence of outcome reporting bias prevents

the classification of RCTs merely as either published or unpublished. Despite the availability of data from 390,750 trial participants in this review, it is difficult to determine the true effect of antihypertensive drugs, mainly CCBs, on the risk of cancer incidence. Preventing underestimation of the intervention effect on undesirable events such as cancer entails reporting of all serious adverse events especially in future long term clinical trials. Trials with adverse events collection deficiencies led to inadequate cancer ascertainment.

An individual participant data (IPD) meta-analysis use the same basic methodology as any traditionally conducted systematic review and meta-analysis. Moreover, this approach is preferred whenever possible as this method can improve the quality of both data and analyses, hence the reliability of the results. For this method to be successful, extensive collaboration between researchers is essential in ensuring the validity of trial data consequently avert outcome reporting bias.

9.3 Implication for practice

The implication for practice in this review can be described under two themes- the safety of antihypertensive agents and general drug safety.

9.3.1 Antihypertensive agents safety

Evidently, all the antihypertensive agents class are deemed to be effective in lowering BP thereby recommended as first or second-line therapy for hypertension by NICE, JNC 8, and ESH/ESC guidelines. This review supports the continuous use of ACEI, ARB, and BB as recommended by these established guidelines. Low dose TZ probably remain a good choice for initial treatment of hypertension in the elderly. Unless indicated, avoid starting treatment with TZ diuretic in younger and/or pre-menopausal women as there is evidence of higher risk for RCC in women compared to men. More importantly, this review found a significantly increased risk for cancer associated to use of DHP CCBs which merits further assessment. In the meantime, it is probably best to start with low dose CCB and followed by combination therapy with other antihypertensive class where indicated.

9.3.2 General drug safety

The current available ICH guidelines for carcinogenicity testing is only indicated for any pharmaceutical product whose expected clinical use is continuous for at least 6 months or if there is concern about their carcinogenic potential (EMA, 1996). For such agents, a two year carcinogenicity evaluation is undertaken using rodents. However, a call for revision to this guidance had been proposed quite recently to introduce better way to address the risk of cancer in human of small molecule pharmaceuticals and to define the conditions under which the two year rodent carcinogenicity studies add value to the assessment (EMA, 2016); negative predictions can be made when negative carcinogenic signals are present and vice versa. In doing so, use of animals, drug development resources and timelines to market authorization can be reduced without compromising patients' safety. Nonetheless, continuous pharmacovigilance is key in early identification of any adverse events that may cross the line of a drug's efficacy. Documentation of new cancer cases should take into consideration any medicinal substance exposure regardless of prescription status and duration of use.

9.4 Future works

Firstly, the plan is to conduct a network meta-analysis using data from the current review. Subsequently, I would like to conduct a trial sequential analysis (TSA) to evaluate the reliability of the association between CCB and cancer risk as observed in this study. Eventually, the results of this systematic review highlighting the risks of cancer associated with individual drug class will be published to add to the growing body of evidence. I have also identified the need for observational studies carefully adjusted for all potential confounders to assess cancer risk linked to CCBs. Future studies are recommended to focus on identifying the type and dose of CCB that may alter the risk for cancer and the type of cancer that CCB is likely to cause.

9.5 Conclusion

In summary, the present study found no evidence of increased risk of cancer or cancer-related mortality with the use of ACEI, ARB, BB, or TZ. However, increased risk of cancer with CCB use cannot be ruled out. Further study is warranted in verifying the risk of any cancer and specific type of cancer associated with CCB, particularly DHP-CCB.

Appendix

Table A-1:Keywords use for electronic database search.
MP indicates multi-purpose search terms in the title, original title, abstract, subject heading, the name of substance and registry word fields; “tw” indicates that the term is a text word meaning and title and abstract; “Pt.” Indicates publication types, such as reviews, clinical trials, directories, and letters; “Ab” indicates all searchable words from the abstract; “/” indicates that it is a Medical Subject Heading (MeSH) term; “$” indicates all possible suffix variations of the root words; “?” indicates the retrieval of documents with British or American word variants; “adj” plus a number between any two terms returns records that contain both terms within the specified number of words from each other.

	Keyword searches
1.	Ace inhibitors.mp.
2.	angiotensin converting enzyme inhibitors/
3.	(Benazepril or captopril or enalapril or cilazapril or delapril or fosinopril or imidapril or Lisinopril or moexipiril or perindopril or quinapril or ramipril or spirapril or temocapril or trandolapril or zofenopril).tw
4.	Or/1-3
5.	angiotensin receptor antagonists/
6.	angiotensin II receptor antagonist$.mp or Angiotensin Receptor antagonists/
7.	angiotensin II receptor blocker$.tw
8.	(abitesartan or azilsartan or candesartan or elisartan or embusartan or eprosartan or forasartan or irbesartan or losartan or milfasartan or olmesartan or saprisartan or tasosartan or telmisartan or valsartan or zolasartan).tw
9.	Or/ 5-8
10.	calcium channel blockers/
11.	(calcium adj2 (inhibit$ or block?)).tw.
12.	Calcium channel antagonis$.mp
13.	(Amlodipine or benidipine or diltiazem or felodipine or isradipine or manidipine or nicardipine or nifedipine or nisoldipine or nitrendipine or verapamil).tw
14.	Or/10-13
15.	adrenergic beta-antagonists.mp.
16.	(beta adj2 (inhibit$ or block?)).tw.
17.	Beta block$.mp
18.	Beta-receptor antagonist$.mp
19.	(Acebutolol or atenolol or bisoprolol or carvedilol or celiprolol or esmolol or labetolol or metoprolol or nadolol or nebivolol or propranolol or sotalol or timolol).tw
20.	Or/15-19
21.	Diuretics.mp
22.	thiazides.mp.
23.	(Chlorothiazide or hydrochlorothiazide or bendroflumethiazide or hydroflumethiazide or methylchlothiazide or polythiazide or trichlormethiazide or chlorthalidone or metolazone or indapamide).tw
24.	Or/21-23
25.	4 or 9 or 14 or 20 or 24
26.	randomized controlled trial.pt.
27.	controlled clinical trial.pt.
28.	randomized.ab.
29.	Drug therapy.tw.
30.	randomly.ab.
31.	trial.ti
32.	Or/26-31
33.	animals/ not (humans/ and animals/)
34.	32 not 33
35.	25 and 34
36.	limit 35 to (humans and yr.="1950 - 2015" and "all adult (19 plus years)" and humans and randomized controlled trial)

Table A-2 : Characteristics of included studies

Trial	Year	N	Cohort	Treatment	n	Control	n	Average follow-up (years)	Age (years)	Proportion male (%)	Trial design and methods
ABCD	1998	470	Normotension and HTN with type 2 DM	Enalapril	235	Nisoldipine	235	5.6	57.5 (8.3)	67.5	Parallel groups, double blind
ACTION	2004	7665	CAD	Nifedipine	3825	Placebo	3840	4.9 (1.1)	63.5 (9.3)	79.4	Parallel groups, double blind
ACTIVE I	2011	9016	AF plus one risk factor for stroke	Irbesartan	4518	Placebo	4498	4.1	69.6 (9.7)	60.7	Parallel groups, double blind
AIPRI	1996	583	CKD	Benazepril	300	Placebo	283	3*	51 (13)	72.2	Parallel groups, double blind
ALLHAT	2002	33357	HTN with at least 1 risk factor for CHD event	Lisinopril	9054	a) Chlorthalidone	15255	4.9 (1.4)	67	53	Parallel groups, double blind
						b) Amlodipine	9048				
ALPINE	2003	393	HTN	Candesartan	196	HCTZ	196	1	55 (9.5)	48	Parallel groups, double blind
ANBP	1980	3427	Mild HTN	Chlorothiazide	1721	Placebo	1706	4	50.5 (9)	63.3	Parallel groups, double blind
ANTIPAF	2011	430	AF	Olmesartan	214	Placebo	211	1	61.5 (10.7)	58.6	Parallel groups, double blind
APSIS	1996	809	CHD (stable angina pectoris)	Verapamil	403	Metoprolol	408	9.1*	59 (7)	69.5	Parallel groups, double blind
ASCOT-BPLA	2005	19257	HTN with at least 3 other CVD risk	Amlodipine	9639	Atenolol	9618	5.5	63 (8.5)	77	PROBE
BHAT	1982	3837	Post-MI	Propanolol	1916	Placebo	1921	2.1	54.8	85.5	Parallel groups, double blind
CAMELOT	2004	1991	Normotension with CAD	Enalapril	675	a) Amlodipine	665	2	57.7	72	Parallel groups, double blind
						b) Placebo	657				
CASE-J Ex	2011	4703	High risk HTN	Candesartan	2354	Amlodipine	2349	4.5 (1.9)	63.9	55.2	PROBE

CHARM Added	2003	2548	HF	Candesartan	1276	Placebo	1272	3.4*	64.1 (11)	78.7	Parallel groups, double blind
CHARM Alternative	2003	2028	HF	Candesartan	1013	Placebo	1015	2.8*	67 (11)	68.2	Parallel groups, double blind
CHARM Preserved	2003	3023	HF	Candesartan	1514	Placebo	1509	3.1*	67.2 (11.1)	59.9	Parallel groups, double blind
CONVINCE	2003	16602	HTN	Verapamil	8179	Atenolol	680	3 (2-4.25)	65.6(7.4)	44	Parallel groups, double blind
						HCTZ	7617				
DAVIT II	1999	1775	CHD post MI	Verapamil	878	Placebo	897	1.3	60.7 (9.2)	79.8	Parallel groups, double blind
DEMAND	2011	380	HTN with T2DM and albuminuria	Delapril	126	a) Delapril + manidipine	127	3.8 (3.1-4.7)*	61.2 (7.7)	66.9	Parallel groups, double blind
						b) Placebo	127				
DIABHYCAR	2004	4912	Type 2 DM with albuminuria	Ramipiril	2443	Placebo	2469	4 (3-6)*	65.1 (8.4)	70	Parallel groups, double blind
DIRECT-Prevent 1	2008	1421	T1DM without retinopathy	Candesartan	711	Placebo	710	4.7 (4.2-5.1)*	29.7	56.7	Parallel groups, double blind
DIRECT-Protect 1	2008	1905	T1DM with retinopathy	Candesartan	951	Placebo	954	4.8 (4.4-5.3)*	31.7 (7.75)	57.3	Parallel groups, double blind
DIRECT-Protect 2	2008	1905	T2DM with retinopathy	Candesartan	951	Placebo	954	4.7	56.9	49.8	Parallel groups, double blind
E-COST	2005	2048	HTN	Candesartan	1053	Conventional	995	3.1(0.4)	67	48	Parallel groups, open-label
ESPIRAL	2001	241	HTN with CKD	Nifedipine GITS	112	Fosinopril	129	3	56 (24-74)	59	Parallel groups, open-label
EWPHE	1991	840	Elderly with HTN	HCTZ plus Triamterene	416	Placebo	424		72 (8)	30.3	Parallel groups, double blind
FACET	1998	380	HTN with T2DM	Fosinopril	189	Amlodipine	191	2.9	63.1 (0.5)	60	PROBE

FEVER	2005	9711	HTN on thiazide therapy	Felodipine	4841	Placebo	4870	3.3 (1)	61.5 (7.2)	61	Parallel groups, double blind
GISSI-AF	2009	1442	AF	Valsartan	722	Placebo	720	1	68 (9.2)	62	Parallel groups, double blind
HEP	1896	884	HTN	Atenolol	419	Control	465	4.4	68.8 (5.2)	31	PROBE
HIJ-CREATE	2009	2049	HTN with CAD	Candesartan	1024	Non-ARB	1025	4.2 (3.5-4.9)	64.8 (9.2)	80.2	PROBE
HOPE	2000	9297	Patients high risk of cardiovascular events	Ramipiril	4645	Placebo	4652	5	66 (7)	73.3	Factorial, double-blind
IDNT	2003	1715	HTN with T2DM nephropathy	Amlodipine	567	Irbesartan	579	2.6	59(7.5)	66	Parallel groups, double blind
						Placebo	569				
INSIGHT	2000	6321	HTN	Nifedipine	3157	Co-amilozide	3164	4.5	65(6.5)	46.3	Parallel groups, double blind
INTACT	1990	348	Mild CHD	Nifedipine	173	Placebo	175	3	53.1 (7.6)	NR	Parallel groups, double blind
INVEST	2003	22576	HTN with CHD	Verapamil SR	11267	Atenolol	11309	2.7 (0-5.4)	66.1 (9.8)	48	PROBE
I-PRESERVE	2010	4128	HF with preserved EF	Irbesartan	2067	Placebo	2061	4.1	72(7)	60	Parallel groups, double blind
IRMA-2	2001	608	HTN with type 2 DM and microalbuminuria	Irbesartan	402	Placebo	206	2	58 (8)	69	Parallel groups, double blind
Kanamasa et al	1998	1054	CAD post MI	Nifedipine	425	Non-CCB	488	2.2 (2.3)	60 (11.5)	80	Parallel groups, open-label
				Diltiazem	141						
LaCroix	2000	320	Healthy adult	HCTZ	215	Placebo	105	3	68 (4.5)	36	Parallel groups, double blind
LIFE	2002	9193	HTN	Losartan	4605	Atenolol	4588	4.8 (0.9)	67 (7)	46	Parallel groups, double blind
MAPHY	1988	3234	HTN	HCTZ	1625	Metoprolol	1609	4.2*	52.6 (7)	100	Parallel groups, double blind

MERIT-HF	2001	3991	HF	Metoprolol	1990	Placebo	2001	1	63.8 (9.7)	77.5	Parallel groups, double blind
MIDAS	1996	883	HTN	Isradipine	442	HCTZ	441	3	58.5 (8.5)	78	Parallel groups, double blind
MRC	1985	17354	Mild HTN	Bendrofluazide	4297	Propranolol	4403	4.9	52 (8)	52.2	Parallel groups, single blind
						Placebo	8654				
MRC-OA	1992	4396	HTN	HCTZ plus amiloride	1081	Atenolol	1102	5.8	70.3	41.8	Parallel groups, single blind
						Placebo	2213				
NAVIGATOR	2010	9306	IGT with established CVD or CV risk factors	Valsartan	4631	Placebo	4675	5	63.7	50.6	Factorial 2-by-2, double-blind
NESTOR	2004	570	HTN with T2DM	Indapamide	283	Enalapril	286	1	60 (9.9)	64	Parallel groups, double blind
NHS	2012	1150	HTN with Type 2 DM or IGT	Valsartan	575	Amlodipine	575	3.2 (2.6-4.7)*	63 (8)	66	PROBE
NICOLE	2003	819	CHD underwent PCI	Nisoldipine	408	Placebo	411	3	60 ((9)	79	Parallel groups, double blind
NICS-EH	1999	429	Elderly HTN	Nicardipine	215	Trichlormethiazide	214	4.6*	69.8 (6.5)	33	Parallel groups, double blind
OCTOPUS	2013	469	HTN with ESRD	Olmesartan	235	Non-ARB	234	3.5	59.5 (12)	62	PROBE
ONTARGET	2008	25620	CVD or DM with end-organ damage	Telmisartan	8542	a) Ramipiril	8576	4.7	66.4 (7.2)	73	Parallel groups, double blind
						b) Telmisartan + ramipiril	8502				
OPTIMAAL	2002	5477	HF with CAD (MI)	Captopril	2733	Losartan	2744	2.7 (0.9)	67.4(9.8)	71.2	Parallel groups, double blind
OSLO	1980	785	HTN	HCTZ	406	No treatment	379	5.5 (5-6.5)	45.3 (2.9)	100	PROBE
Otsuka et al	2004	253	CAD post PCI	Quinapril	131	Control	122	4.8 (4.2-5.1)*	63	72	Parallel groups, open-label

PARADIGM-HF	2014	8442	HF with EF ≤ 40%	Enalapril	4229	LCZ696	4203	2.25	63.8(11.4)	78.2	Parallel groups, double blind
PAT	2002	548	Asymptomatic small AAA	Propanolol	276	Placebo	272	2.5 (1.1)	68.9 (7.9)	84	Parallel groups, double blind
PHARAO	2008	1008	Pre-HTN	Ramipiril	505	Non-ACEi	503	3	62.3 (8.1)	48	PROBE
PHYLLIS	2004	508	HTN with hypercholesterolaemia	Fosinopril	127	HCTZ	127		58.4 (6.7	40	Parallel groups, double blind
Practolol Study	1975	3038	Post-MI	Practolol	1524	Placebo	1514	1.2	55	86.5	Parallel groups, double blind
PRAISE	1996	1153	HF	Amlodipine	571	Placebo	582	1.2 (0.5-2.75)	64.7 (0.5)	76	Parallel groups, double blind
PREVENT	2000	825	CHD	Amlodipine	417	Placebo	408	3	56.9 (30-78)	80.1	Parallel groups, double blind
PREVER-Treatment	2016	655	HTN	Losartan	322	Chlorthalidone / amiloride	333	1.5	54	51	Parallel groups, double blind
PRoFESS	2008	20332	CVA	Telmisartan	10146	Placebo	10186	2.5 (1.5-4.3)	66.2 (8.6)	64	Factorial 2-by-2, double-blind
REIN 2	2005	335	CKD	Felodipine	167	Conventional AHT	168	1.6* (1-3)	53.4 (15.3)	74.9	PROBE
RENAAL	2001	1513	T2DM with nephropathy	Losartan	751	Placebo	762	3.4	60 (7)	63.2	Parallel groups, double blind
SAVE	1992	2231	HF with CAD (post-MI)	Captopril	1115	Placebo	1116	3.5 (0.8)	59.4	82.5	Parallel groups, double blind
SCAT	2000	460	CAD	Enalapril	229	Placebo	231	4	61 (10)	89.1	Factorial, double-blind
SCOPE	2003	4964	HTN with MMSE score ≥ 24	Candesartan	2477	Placebo	2460	3.7	76.4	35.5	Parallel groups, double blind
SHEP	1991	4736	Elderly with HTN	Chlorthalidone	2365	Placebo	2371	5	71.6 (6.7)	43	Parallel groups, double blind
SMT	1985	301	Post-MI	Metoprolol	154	Placebo	147	3	59.7 (7)	80.4	Parallel groups, double blind
SOLVD-P	1992	4228	HF with LVEF ≤ 35%	Enalapril	2111	Placebo	2117	3.1 (1.2-5.2)	59.1	88.6	Parallel groups, double blind

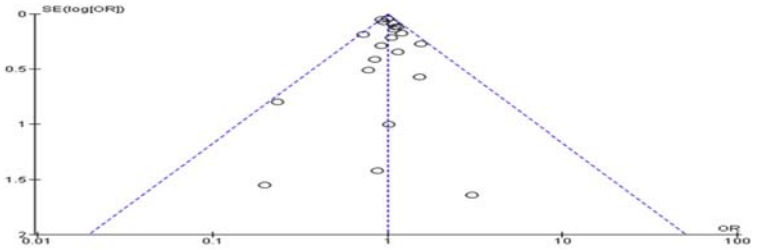
SOLVD-T	1991	2569	HF with LVEF ≤ 35%	Enalapril	1285	Placebo	1284	3.5 (1.2-5.2)	60.9	80.4	Parallel groups, double blind
SPRINT	1998	2127	CHD post-MI	Nifedipine	1059	Placebo	1068	5	57.5 (9)	85	Parallel groups, double blind
STOP-HTN2	1999	6614	HTN	Felodipine/ isradipine	2196	ACEI	2205	5	76	33.2	PROBE
						BB /TZ	2213				
Suzuki	2008	366	ESRD on dialysis	Valsartan/ Losartan/ Candesartan	183	Non-ARB	183	3	59.6(10)	59	Parallel groups, open-label
Syst-China	1998	2394	HTN	Nitrendipine	1253	Placebo	1141	4 (0.1-7.8)	66.5 (5.5)	64	Parallel groups, double blind
Syst-Eur	1997	4695	HTN	Nitrendipine	2398	Placebo	2297	2 (0.1-8.1)	70.3 (6.7)	33	Parallel groups, double blind
TRACE	2005	1749	HF with LVEF ≤ 35%	Trandolapril	876	Placebo	873	5.6	67.5	71.5	Parallel groups, double blind
TRANSCEND	2008	5926	CVD or DM with end-organ damage intolerant to ACEi	Telmisartan	2954	Placebo	2972	4.7 (4.25-5.3)	66.9(7.4)	57	Parallel groups, double blind
TROPHY	2006	772	Pre-HTN	Candesartan	391	Placebo	381	3.6 (1.1)	48.5 (8)	59.6	Parallel groups, double blind
UKPDS 38	1998	758	HTN with T2DM	Captopril	400	a) Atenolol	358	9	56 (8)	55	Parallel groups, double blind
						b) Conventional therapy	390				
VA COOP II	2004	394	HTN	Propanolol	182	HCTZ	212	1	50 (9.8)	100	Parallel groups, double blind
Val-HeFT	2001	5010	HF	Valsartan	2511	ACEI	2499	1.92 (0-3.2)	62.7 (11.1)	80	Parallel groups, double blind
VALIANT	2003	14703	HF or LVSD post MI	Valsartan	4909	a) Captopril	4909	2.1*	64.8	68.9	Parallel groups, double blind

						b) Valsartan + captopril	4885				
VALUE	2004	15245	HTN with high risk cardiac events	Valsartan	7649	Amlodipine	7596	4.2 (1.2)	67(8.2)	58	Parallel groups, double blind
VERDI	1989	167	HTN	Verapamil	182	HCTZ	187	1	50.5 (10.7)	54	Parallel groups, double blind
Vheft II	1991	804	HF	Enalapril	403	Hydralazine-isosorbide	401	2.5 (0.5-5.7)	60.5	100	Parallel groups, double blind
Wilcox et al	1980	388	Suspected MI	Propanolol	132	Placebo	129	1	NR	NR	Parallel groups, double blind
				Atenolol	127						

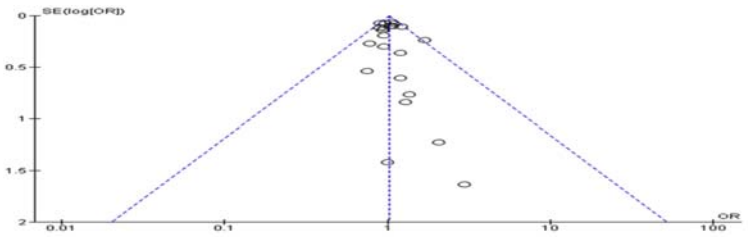
Table A-3: Selected characteristics of included trials

Trial	History of cancer	Cancer pre-specified as outcome	Adjudication	Data source	Men (%)	Current smoker (%)	Adherence (%)	Loss to follow-up (%)
ABCD	NR	No	NR	Published	67.5	NR	NR	NR
ACTION	4.4	No	NR	Published	79.4	17.7	79	NR
ACTIVE I	NR	No	NR	Published	60.7	7.7	70	0.4
AIPRI	0	No	NR	Published	72.2	NR	NR	NR
ALLHAT	NR	Yes	Central	Published	53	22	78	2.8
ALPINE	NR	No	NR	Published	48	13	100	0
ANBP	NR	No	NR	Published	63.3	25	64.7	2.6
ANTIPAF	NR	No	NR	Published	58.6	NR	NR	NR
APSIS	NR	No	NR	Published	69.5	22	NR	NR
ASCOT-BPLA	NR	No	Central	Published	77	33	81	0.3
BHAT	NR	No	Central	Published	85.5	57.2	60	0.3
CAMELOT	NR	No	NR	Published	72	26.5	NR	2.8
CASE-J Ex	0	No	NR	Published	55.2	21.8	96.3	10
CHARM Added	6	No	NR	Published	78.7	16.8	75	0.2
CHARM Alternative	6.6	No	NR	Published	68.2	13.6	77	0.1
CHARM Preserved	7.5	No	NR	NR	59.9	13.5	75	0.1
CONVINCE	NR	Yes	Central	Published	44	23	60.5	7
DAVIT II	NR	Yes	NR	Published	79.8	NR	87	NR
DEMAND	NR	No	NR	Published	66.9	10.2	NR	0
DIABHYCAR	NR	No	NR	Unpublished	70	15.4	59.3	3.2
DIRECT-Prevent 1	NR	No	NR	Unpublished	56.7	25.5	NR	1.3
DIRECT-Protect 1	NR	No	NR	Unpublished	57.3	26.4	NR	1.4
DIRECT-Protect 2	NR	No	NR	Unpublished	49.8	27	NR	1
E-COST	NR	No	NR	Published	48	NR	77	NR
ESPIRAL	NR	No	NR	Published	59	NR	NR	NR
EWPHE	0	No	NR	Published	30.3	NR	NR	15
FACET	NR	Yes	Central	Published	60	6	77	1
FEVER	NR	No	Site reported	Published	61	29	86	0.3
GISSI-AF	3.1	No	NR	Published	62	8.5	83.1	4.5
HEP	NR	No	NR	Published	31	24.5	70	NR
HIJ-CREATE	0	No	NR	Published	80.2	38	NR	0.4
HOPE	NR	No	NR	Published	73.3	14.2	78.8	0.1
IDNT	NR	No	Central	Published	66	17	79	0.5
INSIGHT	NR	No	Central	Published	46.3	28.4	NR	2.4
INTACT	0	No	NR	Published	NR	84	NR	NR
INVEST	3.4	Yes	Central	Published	48	12.4	79.5	2.5
I-PRESERVE	NR	No	Central	Published	60	NR	64	1.5
IRMA-2	0	No	NR	Published	69	18.6	85	0.5
Kanamasa	0.4	Yes	NR	Published	80	NR	NR	NR
LaCroix	0	No	NR	Published	36	7.5	82	1.6
LIFE	NR	Yes	Central	Published	46	16	82	0.1
MAPHY	No	No	Central	Published	100	2.1	NR	NR
MERIT-HF	NR	No	NR	Unpublished	77.5	14.5	79	0

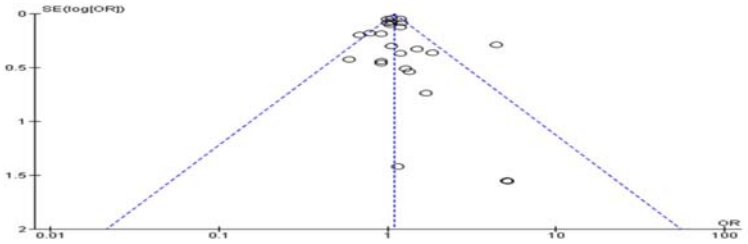
MIDAS	NR	Yes	Central	Published	78	20	55	NR
MRC	NR	Yes	Central	Published	52.2	28.8	68	19
MRCOA	0	Yes	Central	Published	41.8	18.2	69	25
NAVIGATOR	NR	No	NR	Published	50.6	11	74	9.7
NESTOR	NR	No	NR	Published	64	14	88	0
NHS	NR	No	Central	Published	66	18.3	NR	2.6
NICOLE	NR	No	NR	Published	79	71.2	75	2
NICS EH	NR	No	NR	Published	33	9.9	NR	NR
OCTOPUS	5.3	No	NR	Published	62	16.8	51	0.2
ONTARGET	NR	Yes	Central	Published	73	12.4	81.3	0.2
OPTIMAAL	NR	No	Central	Published	71.2	NR	82	0.02
OSLO	0	No	NR	Published	100	41.7	NR	0
Otsuka et al	NR	No	Site reported	Published	72	NR	31	0
PARADIGM-HF	NR	No	Central	Unpublished	78.2	NR	81.2	0.2
PAT	NR	No	Central	Published	84	34.7	65.3	1.1
PHARAO	NR	No	NR	Published	48	45.5	80	0
PHYLLIS	NR	No	NR	Published	40	16.2	NR	NR
Practolol Study	NR	No	Central	Published	86.5	70	NR	NR
PRAISE	NR	No	NR	Published	76	NR	90	0
PREVENT	NR	No	Central	Published	80.1	24.7	79	0
PREVER-Treatment	NR	No	NR	Unpublished	51	7.3	NR	3.1
PRoFESS	NR	No	NR	Published	64	21.2	68.3	0.6
REIN 2	0	No	NR	Published	74.9	NR	NR	2
RENAAL	NR	No	NR	Published	63.2	18.3	53.5	0.2
SAVE	NR	No	NR	Published	82.5	53	70	0.3
SCAT	NR	Yes	NR	Published	89.1	15	95	NR
SCOPE	NR	No	Central	Published	35.5	8.7	49	0.2
SHEP	0	No	Central	Published	43	12.7	NR	NR
SMT	NR	No	NR	Published	80.4	56.8	96.7	NR
SOLVD-P	NR	No	NR	Published	88.6	23.5	75	0.2
SOLVD-T	0	No	NR	Published	80.4	22.1	65	0.1
SPRINT	0	No	NR	Published	85	46.6	83	0.5
STOP-HTN2	NR	No	NR	Published	33.2	9	63.3	0
Suzuki	NR	No	NR	Published	59	22	NR	0
Syst-China	NR	No	Central	Published	64	31	NR	9.9
Syst-Eur	NR	No	Central	Published	33	7.3	NR	5
TRACE	0	No	NR	Published	71.5	74	63.5	0.3
TRANSCEND	4.9	Yes	Central	Published	57	9.8	81	0.3
TROPHY	NR	No	NR	Published	59.6	NR	NR	NR
UKPDS 38	NR	No	NR	Published	55	22.5	77	NR
VA COOP II	0	No	NR	Published	100	NR	NR	NR
Val-HeFT	NR	No	NR	Published	80	NR	NR	NR
VALIANT	NR	No	NR	Published	68.9	32	83	0.9
VALUE	NR	No	NR	Published	58	NR	74	0.6
VERDI	0	No	NR	Published	54	NR	NR	NR
VHeFT II	NR	No	Site-reported	Published	100	33	86	NR
Wilcox et al	NR	No	Site-reported	Published	NR	NR	NR	NR



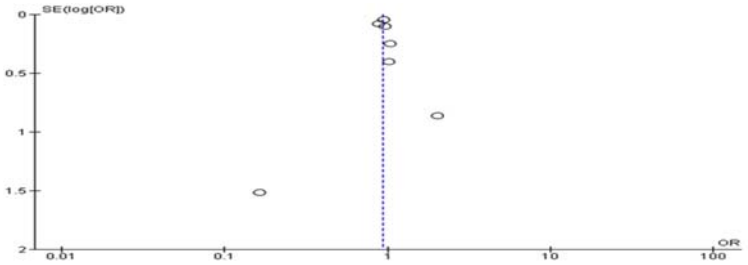
Funnel plot of comparison: ACEI vs. non-ACEI, outcome: 4-5 Incident cancers



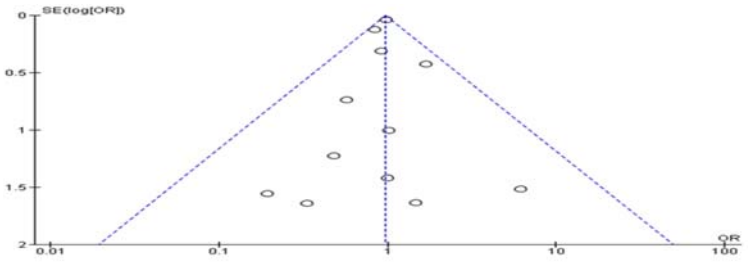
Funnel plot of comparison: ARB vs. non-ARB, outcome: 5-5 Incident cancers



Funnel plot of comparison: CCB vs. non-CCB, outcome: 6-4 Incident cancers

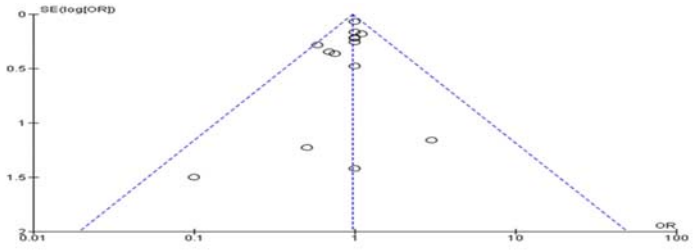


Funnel plot of comparison: BB vs. non-BB, outcome: 7-5 Incident cancers

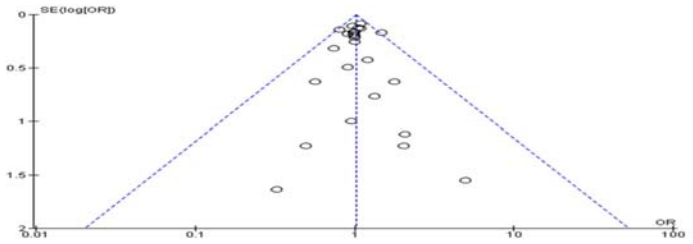


Funnel plot of comparison: TZ vs. non-TZ, outcome: 8-5 Incident cancers

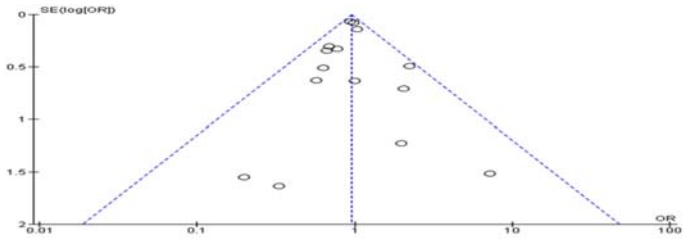
Figure A-1 Funnel plots of antihypertensive drug classes' comparison: outcome: Incident cancers



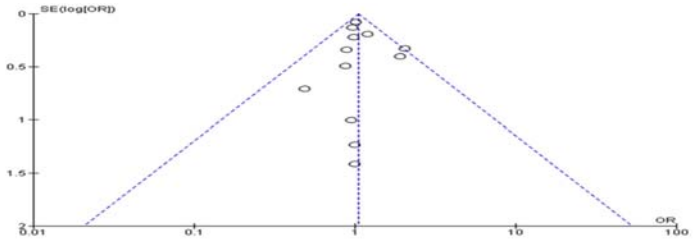
Funnel plot of comparison: ACEI vs. non-ACEI, outcome: 4-7 Cancer-related death



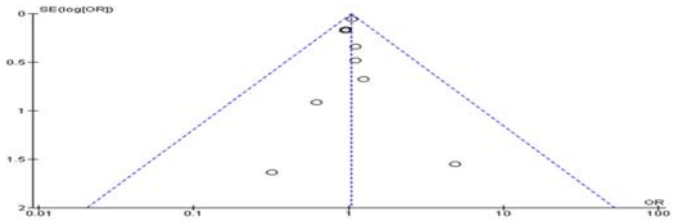
Funnel plot of comparison: ARB vs. non-ARB, outcome: 5-7 Cancer-related death



Funnel plot of comparison: CCB vs. non-CCB, outcome: 6-6 Cancer-related death



Funnel plot of comparison: BB vs. non-BB, outcome: 7-7 Cancer-related death



Funnel plot of comparison: TZ vs. non-TZ, outcome: 8-7 Cancer-related death

Figure A-2 Funnel plots of antihypertensive drug classes' comparison: outcome: Cancer-related deaths

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