Management of Blood Pressure in Atrial Fibrillation, Heart Failure and Multimorbidity

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Abstract

Background
Elevated blood pressure is one of the major preventable causes of premature morbidity and mortality worldwide. Although pharmacological BP lowering has been demonstrated to prevent major cardiovascular events in the general population, its effects on less common outcomes, such as atrial fibrillation, and in specific populations, including patients with atrial fibrillation, heart failure and multimorbidity, remain poorly understood.

Aims
This thesis aimed to investigate the effects of blood pressure lowering on new-onset atrial fibrillation; to investigate the effects of blood pressure lowering on cardiovascular outcomes in patients with atrial fibrillation and cardiometabolic multimorbidity; and to investigate the effects of drugs with blood pressure lowering properties on blood pressure and clinical outcomes in patients with heart failure.

Methods
Four studies were conducted to address the aforementioned aims. Analyses for the first three studies relied on data from the Blood Pressure Lowering Treatment Trialists' Collaboration, which included individual participant data for fifty blood pressure lowering randomised controlled trials. The last study involved a systematic review and aggregate data meta-analysis of randomised controlled trials of drugs with blood pressure lowering properties in heart failure.

Results
The first study demonstrated that, in a relatively low-risk population, pharmacological blood pressure lowering, irrespective of its intensity, did not reduce the risk of new-onset atrial fibrillation (hazard ratio 1.01, 95% confidence interval 0.95 to 1.07 per each 5-mmHg reduction in systolic blood pressure). The second study found that blood pressure lowering reduced the risk of major cardiovascular events similarly in individuals with and without atrial fibrillation (hazard ratio for major cardiovascular events 0.91 (95% confidence interval 0.83 to 1.00) and 0.91 (95% confidence interval 0.88 to 0.93), respectively, for each 5-mmHg reduction in systolic blood pressure). The third study demonstrated that blood pressure lowering reduced the risk of major cardiovascular events by about 10%, irrespective of the number or pattern of cardiometabolic diseases at baseline (hazard ratio 0.90 (95% confidence interval 0.88 to 0.92) per each 5-mmHg reduction in systolic blood pressure). The fourth study showed that treatment with drugs with blood pressure lowering properties resulted in a small (about 2 mmHg), but significant, decrease in systolic blood pressure in patients with heart failure, with no evidence that treatment effects depended on the degree of blood pressure lowering or on baseline blood pressure.

Conclusions
This thesis improved our understanding of the efficacy and safety of blood pressure lowering, thus providing the much-needed evidence to inform therapeutic guidelines and clinical practice worldwide. This will ultimately reduce the burden of morbidity and mortality attributable to hypertension and conserve scarce healthcare resources that are struggling to meet the needs of our ageing and multimorbid population.

Acknowledgements

orandum est ut sit mens sana in corpore sano.
fortem posce animum mortis terrore carentem,
qui spatium vitae extremum inter munera ponat
naturae, qui ferre queat quoscumque labores,
nesciat irasci, cupiat nihil et potiores
Herculis aerumnas credat saevosque labores
et venere et cenis et pluma Sardanapalli.
monstro quod ipse tibi possis dare; semita certe
tranquillae per virtutem patet unica vitae.

In Satire X, Roman poet Juvenal (10.356-64)

English translation:
You should pray for a healthy mind in a healthy body.
Ask for a stout heart that has no fear of death,
and deems length of days the least of Nature's gifts
that can endure any kind of toil,
that knows neither wrath nor desire and thinks
the woes and hard labours of Hercules better than
the loves and banquets and downy cushions of Sardanapalus.
What I commend to you, you can give to yourself;
For assuredly, the only road to a life of peace is virtue.

From the very first day, I and all those close to me knew that the greatest threat to my DPhil was my ill health. I was determined, though, that I would not be defeated, and I would strive to succeed, even if I had to put more effort and sacrifice into it than most. I had to fight against the limitations imposed by my disease and find suitable alternatives when my disability prevented me from doing what I wanted to do (e.g., attend courses and/or conferences that required travelling far and overnight stays). Although I am pleased with what I achieved, not only due to my thesis but also because my health is much better than at the ouset of this journey, nothing would have been possible without the extraordinary help of those who looked after me during this time. The aphorism

"*Mens sana in corpore sano*" remains as true today as many centuries ago. Therefore, I want to thank all those who contributed to maintain and improve my mental and physical health throughout my DPhil.

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Publications

Publications contributing to DPhil thesis

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Contents

List of tables

List of figures

List of abbreviations

ACEI	Angiotensin converting enzyme inhibitor
AF	Atrial fibrillation
ARB	Aldosterone receptor blocker
BB	Beta-blocker
BMI	Body mass index
BP	Blood pressure
BPHFTC	Blood Pressure in Heart Failure Trialists' Collaboration
BPLTTC	Blood Pressure Lowering Treatment Trialists' Collaboration
CCB	Calcium channel blocker
CI	Confidence interval
DBP	Diastolic blood pressure
Diu	Diuretic
HF	Heart failure
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
HR	Hazard ratio
HTN	Hypertension
IPD	Individual participant data
IQI	Interquartile interval
LVEF	Left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
NICE	National Institute for Health and Care Excellence
OR	Odds ratio
RAAS	Renin angiotensin aldosterone system
RCT	Randomised controlled trial
RR	Risk ratio or relative risk
SBP	Systolic blood pressure
SD	Standard deviation

Chapter 1 Introduction

Motivation

High blood pressure (BP) is one of the major preventable causes of premature morbidity and mortality worldwide and in the UK.[1,2] Meta-analyses of randomised controlled trials (RCTs) have shown that overall BP lowering treatment significantly reduces the risk of fatal and non-fatal cardiovascular events irrespective of drug class and baseline BP.[3-5] However, the effect of BP lowering treatment on less common outcomes, such as atrial fibrillation (AF), remains unclear. In addition, evidence is missing on the effects of BP lowering in certain populations with common chronic conditions, such as AF, heart failure (HF) and multimorbidity. First, whether BP lowering treatment reduces the risk of stroke and other adverse cardiovascular events in patients with established AF similarly to the general population is unknown. Second, treatment with drugs with BP lowering properties improves prognosis in HF, but the contribution of BP reduction to treatment effects and the potential harmful effects of further BP reduction in patients with HF and low baseline BP are controversial. Third, BP management in patients with multimorbidity is complex due to the potential for disease-treatment and treatment-treatment interactions, and thus the efficacy of BP lowering in those patients remains poorly understood. This uncertainty translates into inconsistency in clinical guidelines and unwanted variation in clinical practice. Therefore, I set out to generate the much-needed evidence to improve management of high BP, which remains the leading risk factor for cardiovascular disease in the UK and across the globe.[2]

Aims

This doctoral thesis aims to investigate key questions related to BP management using individual participant data (IPD) meta-analyses of RCTs to ultimately reduce the burden of cardiovascular disease attributable to high BP.

To this end, my research addresses the following four objectives:

1. To investigate the effects of BP lowering treatment on the risk of new-onset AF;
2. To compare the effects of BP lowering treatment on major cardiovascular events in patients with and without AF;
3. To investigate the effect of BP lowering treatment on major cardiovascular events in patients with cardiometabolic multimorbidity;
4. To investigate whether drugs with BP lowering properties reduce BP in patients with HF, and whether BP mediates their effects on clinical outcomes.

Structure

To achieve those goals, I took a stepwise approach. First, I performed an in-depth literature review to understand what evidence was available on BP management, and to identify specific gaps in knowledge that were important to address. This review and the research questions that emerged from it are summarised in Chapter 2. Second, I had to become familiar with how the Blood Pressure Lowering Trialists' Collaboration (BPLTTC) was developed and how it was structured, because these data were available to me, and were likely to be the best source of answers to my research questions. An overview of the BPLTTC

is provided in Chapter 3. Third, I had to learn about the methodology I was going to use, particularly IPD meta-analyses of RCTs. Chapter 4 presents a detailed description of the merits and pitfalls of meta-analyses in general and IPD meta-analyses in particular. It also discusses the pros and cons of the methodology I adopted to address my research questions, including time-to-event analysis, cluster analysis and multiple imputation.

Having developed a solid foundation of knowledge and skills, I then completed three IPD meta-analyses and one systematic review and aggregate data meta-analysis. Chapter 5 presents the effects of BP lowering treatment on risk of new-onset AF. Chapter 6 focuses on the effects of BP lowering treatment in patients with AF. Chapter 7 presents the effects of BP lowering treatment in patients with cardiometabolic multimorbidity. Finally, Chapter 8 describes the effects of drugs with BP lowering properties in patients with HF. A synthesis of the main conclusions and a discussion of the overall implications for clinical practice and future research appear in Chapter 9. Finally, Chapter 10 provides a brief description of other relevant works in which I assumed a leading role during my DPhil, but that are not part of my thesis.

Chapter 2 Background

High blood pressure – the silent killer in the UK and across the globe

High BP is a major public health concern, affecting approximately 1 in 4 adults, which equates to about 1.13 billion people worldwide.[6] Recent projections suggest that this may rise to over 1.5 billion people by 2025 fuelled by population ageing and the increasing prevalence of lifestyle risk factors.[7] In fact, compelling evidence supports the causal association between unhealthy dietary patterns, such as excessive salt and saturated fat intake, and physical inactivity with increased risk of elevated BP, which may be at least partially mediated by overweight and obesity.[8,9]

Over the last decades, the geographical distribution of the burden of high BP has shifted due to globalisation and economic development.[10] Although systolic blood pressure (SBP) has been declining slightly since 1980 in women and men in high-income countries, opposite trends have been observed in low and middle-income countries, which currently bear the brunt of the high BP epidemic.[11] Indeed, it is estimated that two-thirds of the global population with hypertension live in low and middle-income countries,[12] which underpins their double burden of infectious and non-communicable diseases.[13] This may partially explain why, despite marked advances in diagnosis and treatment, the burden of disability-adjusted life-years attributable to high BP has risen by 40% since 1990.[14] Therefore, high BP currently represents a heavy toll in all regions of the world, with which weak health systems are struggling to cope.[15]

In the UK, it is estimated that about 28% of the adult population, which is equivalent to around 12 million people, suffer from hypertension,[16] as defined by contemporary guidelines.[17] The prevalence of hypertension is slightly higher in men than in women and it has remained relatively stable since 2012 in both sexes (**Figure 2.1**). In addition, hypertension represents a heavy healthcare burden. It is estimated that the clinical management of hypertension accounts for 12% of visits to primary care and up to £2.1 billion of healthcare expenditure, the bulk of which is due to BP lowering drugs, which are one of the most widely prescribed drugs in the National Health Service.[18]

The rising prevalence of high BP is a matter of serious concern because it is the main risk factor for the global burden of disease, accounting for 10.4 million deaths per year.[2] Indeed, most of the burden of cardiovascular disease, which remains the leading cause of death worldwide in both sexes, is attributable to elevated BP.[13] In the UK, high BP is the third biggest risk factor for disease after tobacco smoking and poor diet, and it is the largest single known risk factor for cardiovascular disease and related disability.[1] In addition, high BP is one of the leading causes of chronic kidney disease and vascular dementia,[19,20] which themselves account for substantial mortality and morbidity in the elderly.[21,22] Considering the sheer scale of the burden of disease and healthcare costs accounted for by high BP, there is a pressing need to manage it effectively.

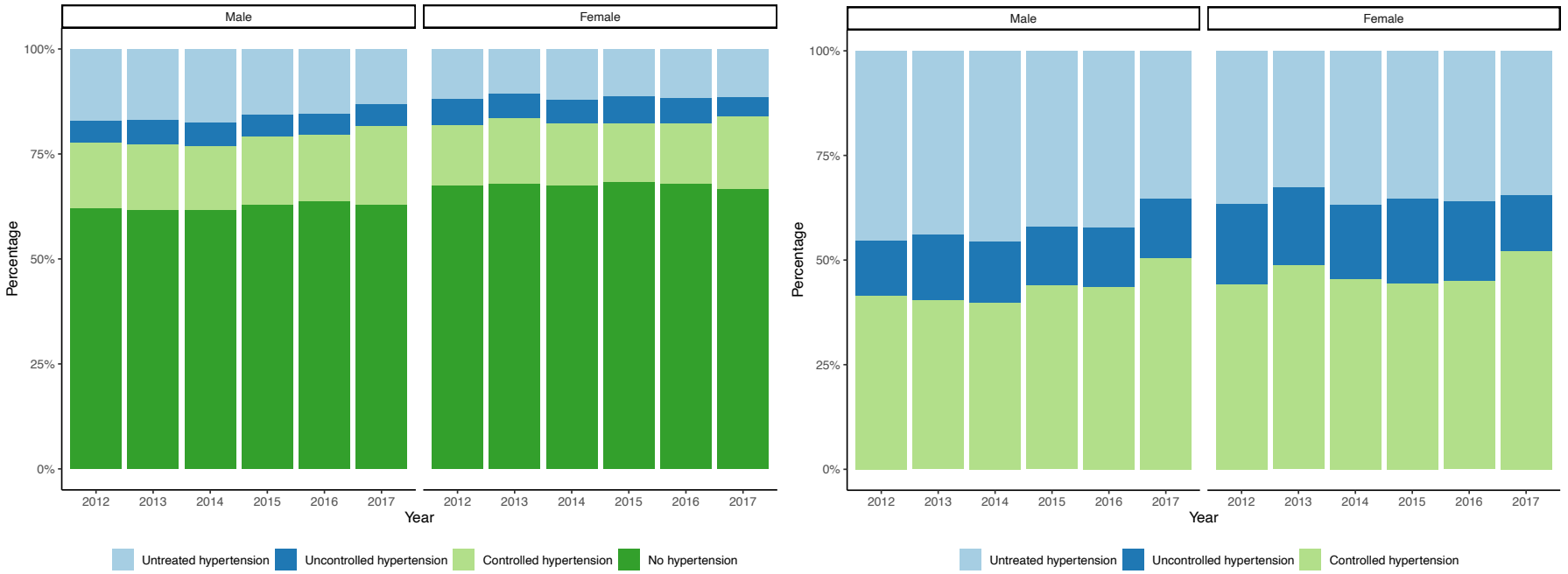

Figure 2.1 Prevalence, treatment and control of hypertension by sex in England between 2012 and 2017

Hypertension was defined as a systolic/diastolic blood pressure ≥ 140/90 mmHg, doctor-diagnosed hypertension or the use of antihypertensive medication. The control of hypertension was defined as systolic/diastolic blood pressure < 140/90 mmHg. Estimates are age-standardised to the English standard population in 2017. The left plot displays the percentages for the entire population; the right plot displays the percentages of treatment and control within the hypertensive population. Data from the Health Survey for England.[23]

However, operationalising the definition of hypertension and establishing treatment thresholds and targets have long been a matter of heated debate among the academic and clinical communities. BP is normally distributed in the population and there is no natural cut-off point above which a higher BP increases risk and below which it does not (**Figure 2.2**). This may explain why the definition of hypertension has traditionally been based on an arbitrary threshold of SBP and diastolic BP (DBP), which has changed over the years and differs among contemporary guidelines (**Table 2.1**).[24,25] Although the dichotomic definition of hypertension is widely adopted in both academic and clinical settings, it has been challenged by epidemiological studies showing that there is a continuous log-linear association between SBP and cardiovascular risk down to a SBP of 115 mmHg,[26] or even 90 mmHg in individuals without diabetes, dyslipidaemia and smoking at baseline.[27] This graded association seems to exist across large and diverse population groups, irrespective of sex, age, ethnicity and pre-existing cardiovascular disease.[28-31] In the absence of a clear epidemiological or biophysiological definition of hypertension, diagnosis has been framed by pharmacological evidence showing that above an certain threshold the benefits of treatment outweigh the harms.

Besides the difficulty in reaching a consensus on the definition of hypertension, the ideal method of measuring BP itself has become increasingly controversial, partially due to technological advances that paved the way for remote and continuous BP monitoring devices.[32-34] Indeed, evidence suggests that ambulatory and home-based BP monitoring are better than isolated office-based BP measurements at predicting cardiovascular risk and at diagnosing hypertension, particularly in the case of masked or white-coat hypertension.[35-37] Nonetheless, home-based and ambulatory BP monitoring are costly and not routinely

available in clinical practice.[38] Therefore, current guidelines for diagnosis of hypertension recommend preferring those methods rather than repeated office BP measurements only "if logistically and economically feasible".[39,40]

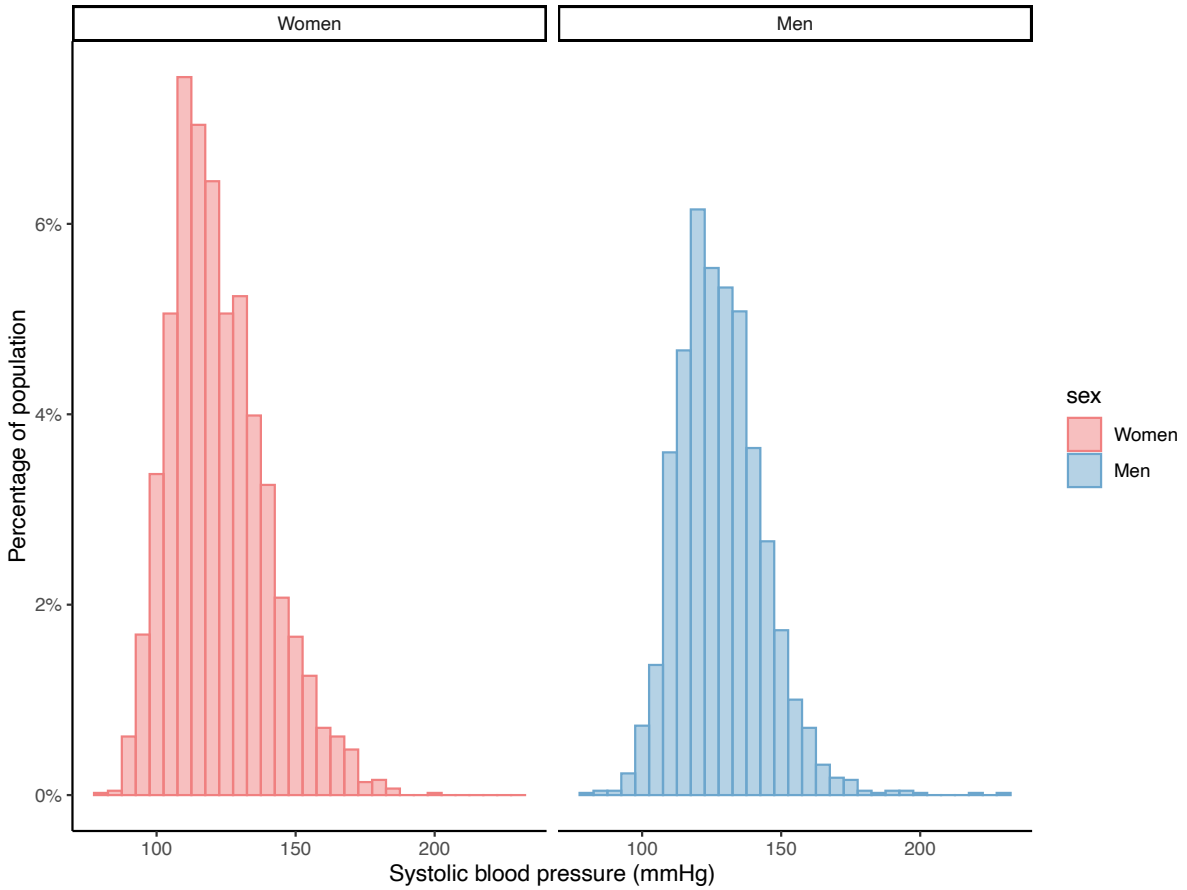

Figure 2.2 Distribution of systolic blood pressure in 2017 in England stratified by sex

The plots display the distribution of systolic blood pressure (in mmHg) in non-institutionalised adults (over 16-year-olds) in England in 2017. Data from the Health Survey for England.[23]

Table 2.1: Classification of office blood pressure and definitions of hypertension grade

Category	Systolic BP (mmHg)		Diastolic BP (mmHg)
European Society of Cardiology and European Society of Hypertension (2018)[39]			
Optimal	<120	And	<80
Normal BP	120 – 129	And/or	80 – 84
High normal BP	130 – 139	And/or	85 – 89
Grade 1 hypertension	140 – 159	And/or	90 – 99
Grade 2 hypertension	160 – 179	And/or	100 – 109
Grade 3 hypertension	≥ 180	And/or	≥ 110
Isolated systolic hypertension	≥ 140	And	< 90
American College of Cardiology and American Heart Association (2017)[41]			
Normal blood pressure	120	And	80
Elevated blood pressure	120 – 129	And	80 – 84
Stage 1 hypertension	130 – 139	Or	80 – 89
Stage 2 hypertension	≥ 140	Or	≥ 90
National Institute for Health and Care Excellence (2019)[17]			
Normal	< 140	And	< 90
Stage 1 hypertension	140 – 159	And/or	90 – 99
Stage 2 hypertension	160 – 179	And/or	100 – 119
Stage 3 hypertension	≥ 180	Or	≥ 120
International Society of Hypertension (2020)[40]			
Normal blood pressure	< 130	And	< 85
High normal blood pressure	130 – 139	And/or	85 – 89
Stage 1 hypertension	140 – 159	And/or	90 – 99
Stage 2 hypertension	≥ 160	And/or	≥ 100

Blood pressure (BP) category is defined according to seated clinic blood pressure and by the highest level of blood pressure, whether systolic or diastolic.

In stark contrast with cholesterol guidelines, which have long recommended treatment based on predicted cardiovascular risk,[42] hypertension guidelines relied solely on isolated BP thresholds to guide treatment initiation until recently. Indeed, the latest hypertension guidelines issued by the European Society of Cardiology represented a paradigm shift by incorporating overall cardiovascular risk in treatment recommendations,[39] and the recent International Society of Hypertension guidelines followed suit.[40] This was an acknowledgement that a dichotomic categorisation into hypertensive and non-hypertensive patients without taking into account concurrent cardiovascular risk factors results in substantially unaddressed cardiovascular risk.[43] In fact, evidence had been accruing on the importance of holistic cardiovascular risk assessment to guide BP lowering treatment. First, large epidemiological studies suggested that elevated BP, even below conventional treatment thresholds, was associated with an increased risk of cardiovascular events.[44,45] Then, randomised evidence demonstrated that a BP lowering strategy based on predicted cardiovascular risk was more effective than one based on BP levels alone across a range of thresholds, particularly for primary prevention.[46] However, the lowest level of cardiovascular risk that would merit BP lowering therapy is yet to be established.

However, concerns have been raised about the population impact of widening treatment eligibility to individuals who have high cardiovascular risk, even if not meeting previous treatment thresholds.[47] The implications are manifold. First, there are potentially psychological harms associated with labelling someone who is asymptomatic as “ill”, which has detrimental consequences for both the individual and society overall.[48,49] Second, drug-related health expenditure is expected to substantially increase.[50,51] Third, the burden of

managing a significantly larger number of patients with hypertension presents a major challenge to already stretched healthcare systems.[52,53] On the other hand, moving away from arbitrary cut-offs to a tailored treatment strategy informed by overall cardiovascular risk appears to be more cost-effective.[54] For instance, a modelling study in the USA estimated that a risk-based approach would prevent 900,000 more cardiovascular events, save 2.8 million more quality-adjusted life-years, and use 6% fewer medications compared with a treat-to-target approach in a representative sample of the population.[55] Therefore, a personalised BP treatment strategy based on overall cardiovascular risk would not only benefit individuals but also the health system. However, our understanding of general and hypertension-specific modifiers of cardiovascular risk,[56,57] as well as of the baseline level of cardiovascular risk that predicts treatment benefits, remains limited.[58] Therefore, individually tailored BP treatment is yet to be fully implemented into routine clinical practice.

Despite the ongoing uncertainties about fine-tuning pharmacological BP lowering in the general population, its broad efficacy and safety have been convincingly demonstrated over the years. Meta-analyses of RCTs in the general population have shown that BP lowering treatment significantly reduces the risk of fatal and non-fatal cardiovascular events irrespective of drug class and baseline BP down to a SBP threshold of 140 mmHg.[5,59] The most recent aggregate data meta-analysis showed that every 10-mmHg reduction in SBP resulted in a 17% reduction for coronary heart disease, a 27% reduction for stroke, a 28% reduction for HF, and a 13% reduction in all-cause mortality.[5] However, reliable evidence is scant for some sub-populations, which have typically been underrepresented in RCTs, such as the elderly and patients with concomitant diseases, including AF and HF. Evidence is also lacking

for individuals with high-normal BP (i.e., 130-139 mmHg), because those were rarely included in RCTs.

In addition, the ideal BP targets for primary and secondary prevention remain a matter of heated debate. Based on the most up-to-date evidence from RCTs,[60,61] contemporary guidelines state that the primary goal should be to reduce BP to below 140/90 mmHg, but a lower target of 130/80 mmHg should be pursued in all patients if tolerated, irrespective of age or pre-existing diseases.[17,39,40] For patients younger than 65 years, a more aggressive target of SBP between 120 and 129 mmHg is recommended. However, concerns about potential harms of excessive BP lowering underpin the recommendations for a more conservative target of SBP in the range of 130 to 139 mmHg in those aged over 65 years.[62,63] In fact, evidence supporting the principle of "the lower the better" is sparse in certain subgroups of patients, such as the very elderly (over 80-year-olds), and those with frailty and concurrent diseases, such as diabetes and chronic kidney disease.[64]

Notwithstanding the robust evidence supporting the efficacy of BP lowering treatment, real-world data shows that treatment and control of high BP remain suboptimal across the globe. Although hypertension awareness, treatment and control have improved substantially in high-income countries for the last few decades, overall less than two-thirds of the patients diagnosed with hypertension are prescribed BP lowering treatment, and of those only 20% tend to achieve BP control according to contemporary guidelines.[65] Furthermore, there is wide variation in BP control across countries from as low as 29% in Japan to as high as 58% in Germany. In the UK, my own analysis of data from the Health Survey for England revealed

that there was a modest improvement in BP treatment from 64% to 66% for women and from 55% to 65% for men between 2012 and 2017 (**Figure 2.1**).[23] Likewise, BP control increased from 44% to 52% in women and from 41% to 50% in men over the same period. However, those figures remain unacceptably low and far off from the ambitious goal set by Public Health England of treating to target 80% of the patients with hypertension by 2029.[66]

Treatment and control of hypertension are even worse in low and middle-income countries, where lack of access to essential medicines further compounds the problem. For instance, in China, population-based studies showed that only 30-40% of the patients with hypertension were on treatment and only 7-15% had their BP controlled in 2015-2017.[67,68] On the other hand, in India, only 10% of rural and 20% of urban hypertensive patients had their BP under control in 2013, with these stark differences between rural and urban settings reflecting longstanding inequalities in access to essential healthcare.[69] If medication shortages are largely a problem of low-income countries, patient compliance is a problem shared by high, middle and low-income countries alike. The underlying reasons are manifold, including side-effects, complex treatment regimens, the asymptomatic nature of raised BP, and lack of awareness on the risks incurred by uncontrolled hypertension.[70] A comprehensive, multipronged approach involving both healthcare professionals and patients is thus required to improve BP control and mitigate the detrimental impact of high BP on population health and societal welfare.[71]

Summary

- High BP is the leading risk factor for cardiovascular disease worldwide and hence it accounts for a heavy burden of disease and healthcare across the globe.
- Although the efficacy and safety of pharmacological BP lowering in the general population are well-established, there are key gaps in contemporary knowledge regarding holistic cardiovascular risk assessment, and appropriate treatment thresholds and targets, particularly in certain high-risk populations, such as patients with pre-existing diseases (e.g., AF or HF) and the elderly.
- There is a largely untapped potential to reduce the burden of cardiovascular diseases by improving BP treatment and control worldwide.

Blood pressure and risk of atrial fibrillation – evidence and gaps

AF is the most common sustained cardiac arrhythmia, with a lifetime risk of about 1 in 4 in over 40-year-olds.[72] The incidence of AF increases dramatically with age and it is higher in men than in women.[73] Despite marked variations between countries, epidemiological evidence shows that its incidence and prevalence are on the rise across the globe, due to the steady increase in life expectancy in most countries.[74-76] Indeed, it is estimated that age-

adjusted prevalence of AF quadrupled from 13.7 to 49.4 cases per 1000 person-years in women and from 20.4 to 96.2 cases per 1000 person-years in men over the last fifty years in the USA.[76] In Europe, the prevalence of AF increased from 1.7% in women and 1.3% in men at the age of 55-59 years, to 16.1% in women and 24.2% in men, for those over 85 years old.[77] Furthermore, it isestimated that by 2060 the prevalence of AF will be 1.3 to 1.8 million in the UK and about 18 million in Europe.[78,79] In addition, AF is putting a strain on healthcare systems worldwide. In the UK, a survey revealed that the costs of managing AF increased from 0.6 to 1.2% (£350 million) of the total National Health Service budget in 1995 to 0.9 to 2.4% (£460 million) by 2000.[80] Similar figures have been reported in other high-income countries, with most of the costs of managing AF attributable to a growing number of hospitalisations,expensive drug prescriptions for novel oral anticoagulants, and dosing and monitoring of warfarin.[81,82]

Considering that AF represents a heavy health and care burden, there is a pressing need to curb this epidemic by implementing cost-effective preventive strategies. Modifiable risk factors for cardiovascular disease are obvious targets, because most of them have long been recognised as independent predictors of new-onset AF.[83] Among others, those risk factors include hypertension, congestive HF, coronary artery disease, valvular heart disease, tachycardia or other supraventricular arrhythmias, diabetes mellitus, obesity, smoking and alcohol.[84,85] HF is associated with a three-fold increase in the risk of developing AF, and hence it is the main risk factor for AF.[86] However, hypertension, which doubles the risk of developing AF, has the highest population attributable fraction due to its high prevalence.[87] Therefore, BP lowering appears to be a promising strategy to curtail the increase in AF incidence.

Despite consistent observational evidence on the association between cardiovascular risk factors and AF, effective preventive strategies are lacking. Indeed, pharmacological interventions that are known to reduce cardiovascular risk, such as statins and BP lowering drugs, have disappointingly failed to reduce the risk of new-onset AF.[88] Although population-based cohort studies suggested that BP lowering treatment with renin angiotensin aldosterone system (RAAS) inhibitors was associated with a lower risk of new-onset AF in comparison with other drug classes,[89] this has not been corroborated in the most recent and largest meta-analysis of RCTs.[90] The latter demonstrated that BP lowering reduced the risk of new-onset AF overall by 10%, with a risk reduction of 25% in patients with HF but a null effect in patients without HF, irrespective of the drug class used. Evidence regarding AF recurrence was inconclusive as the single trial that included patients with baseline AF showed no clear effect.[90] However, this aggregate data meta-analysis relied only on published reports, and it was unable to perform detailed time-to-event analyses, or to adequately explore heterogeneity of treatment effects.[91] The limited evidence currently available is acknowledged by contemporary AF guidelines, which do not clearly recommend BP lowering for primary prevention of AF and call for further research into the causes and mechanisms that underpin the development of AF in different patient groups.[92] Therefore, there is a key gap in knowledge related to the role of BP lowering for primary prevention of AF.

Summary

- High BP is associated with an increased risk of new-onset AF in observational studies.
- Randomised evidence is contradictory as to whether BP lowering reduces the risk of AF overall or only in certain subpopulations (e.g., HF).
- The potential role of BP lowering treatment for primary prevention of AF is yet to be established.

Blood pressure in patients with atrial fibrillation – evidence and gaps

Besides the dramatic rise in AF incidence and prevalence worldwide, at least partially due to population ageing, there has been a shift in the pattern of comorbidities associated with AF. Indeed, observational evidence suggests that AF is increasingly associated with cardiometabolic comorbidities, such as high BP, diabetes mellitus, and obesity, above and beyond what would be expected due to ageing itself.[79] Therefore, not only is the AF population expanding, but it is also becoming "sicker". This, in turn, increases even further the risk of fatal and non-fatal cardiovascular events,[93] which is already high in patients with AF.[94] Ageing, together with an increased burden of comorbidities, may explain, at least in part, the lack of substantial improvement in AF prognosis despite major advances in pharmacological and interventional treatment.[95]

The mainstay of AF treatment has long been anticoagulation for stroke prevention, combined with a strategy of rate or rhythm control.[92] However, evidence demonstrated that most deaths in anticoagulated patients with AF are due to cardiovascular causes other than stroke, thus emphasising the need to identify interventions, besides effective anticoagulation, to further reduce mortality in the AF population.[96] In this regard, high BP appears as a promising therapeutic target, as it is estimated to affect 60 to 80% of the patients with permanent AF.[97]

Furthermore, high BP is the single most important risk factor for stroke.[98,99] However, whether BP lowering can mitigate the increased risk of cardiovascular events in patients with AF remains unclear. Indeed, evidence from a population-based cohort study, which showed that BP control in patients undergoing antihypertensive treatment was associated with a lower risk of major cardiovascular events, has not been confirmed in RCTs.[100] The only randomised trial in patients with AF reported that an angiotensin receptor blocker (ARB) did not reduce cardiovascular events,[101] and larger randomised trials in the general hypertensive population have been underpowered to perform subgroup analysis for AF at baseline. The dearth of robust evidence to inform clinical decision making is recognised by AF guidelines, which emphasise that "good BP control should form an integral part of the management of AF", but do not issue specific guidance on BP management in AF.[102] There is thus a pressing need to clarify whether BP lowering can effectively reduce the risk of cardiovascular events and hence improve prognosis in the rapidly growing population of patients with AF.

Summary

- Patients with AF have a higher risk of cardiovascular events than the general population.
- Cardiovascular events other than stroke account for most of the burden of morbidity and mortality in adequately anticoagulated patients with AF.
- Randomised evidence on whether BP lowering prevents cardiovascular events in patients with AF remains limited.

Blood pressure in patients with multimorbidity – evidence and gaps

Multimorbidity is defined as the coexistence of two or more chronic conditions, where each must be a non-communicable disease, a mental health disorder, or an infectious disease of long duration.[103] A key difference between multimorbidity and comorbidity is that there is no primary or index condition. In addition, multimorbidity is classified as concordant or discordant depending on whether the coexisting conditions share a common aetiology (e.g., coronary artery disease and cerebrovascular disease represent concordant multimorbidity, whilst diabetes mellitus and depression represent discordant multimorbidity).

Multimorbidity is rising across the globe, fuelled by a synergy of factors including population ageing, obesity, urbanisation, poor diets, climate change, and the growing burden of non-

communicable diseases (e.g., type 2 diabetes) and longstanding infectious diseases (e.g., tuberculosis), particularly in low and middle-income countries.[104] It is more common in the elderly, as diseases naturally accrue over time, as well as in women, perhaps due to longer life expectancy and increased exposure to the effects of poverty.[105] However, the absolute number of people with multimorbidity is larger in those younger than 65 years due to the age distribution of the population, particularly in areas of high deprivation.[106] In addition, there are marked contrasts in the patterns of multimorbidity related to socioeconomic context, age and sex.[105,107]

Multimorbidity is rapidly becoming the norm rather than the exception in our increasingly elderly population.[108] In the UK, it is estimated that the proportion of over 65-year-olds with two or more diseases will rise from 54% in 2015 to 68% by 2035.[109] The figures are even more striking for complex multimorbidity, defined as the co-occurrence of four or more diseases, which is predicted to increase from 9% in 2015 to 17% in 2025 in those over the age of 65 years. The forecast is made bleaker by the fact that future adults aged 65 to 74 years are more likely to have two or three diseases than in the past due to soaring rates of obesity and physical inactivity, which are risk factors for multiple diseases.

Besides the exponential rise in multimorbidity in the overall population, multimorbidity is also becoming increasingly common in patients with cardiovascular disease. In the UK, although the age/sex-standardised incidence of cardiovascular disease decreased by 34% between 2000 and 2014, the proportion of patients with cardiovascular disease who had five or more comorbidities increased by four-fold from 6% in 2000 to 24% in 2014, and the most common

comorbidity was hypertension.[110] In fact, despite variations in multimorbidity patterns across regions and populations, hypertension is consistently the most common disease in patients with multimorbidity.[111] As hypertension is the leading risk factor for cardiovascular disease, it is crucial to control BP in multimorbid patients.

However, evidence on BP management in the context of multimorbidity is sparse. This is mainly due to the fact that such patients have typically been excluded or underrepresented in RCTs, at least in part because they do not fit into the contemporary paradigm of single disease treatment.[112] In the absence of robust evidence from RCTs, the debate about BP lowering treatment in patients with multimorbidity has been heavily influenced by observational studies, which have suggested that lower BP may be associated with an increased risk of cardiovascular and non-cardiovascular events.[113] However, because such non-randomised studies have limited ability to distinguish cause from effect, the balance of harms and benefits of BP lowering treatment in multimorbid patients remains unclear.

Furthermore, the recent paradigm change in treatment guidelines, from a narrow focus on arbitrary BP thresholds to a more comprehensive approach based on overall cardiovascular risk,[114] rendered vast numbers of patients with cardiometabolic conditions eligible for treatment, even if their BP was below previously recommended treatment thresholds.[47] However, the benefits of such therapeutic strategy for patients with cardiometabolic multimorbidity remain uncertain as the value of risk-based decision making has not been convincingly demonstrated in patients with diabetes or established cardiovascular disease.[46] This may explain why guidelines vary little in treatment recommendations according to risk

or concomitant diseases. In addition, expanding the reach of antihypertensive treatment raises concerns about medication burden and safety, because patients with multimorbidity by definition have several concurrent diseases. As the interaction between those diseases and their respective treatments remains poorly understood, there is a serious risk of adverse drug-drug and drug-disease interactions.[115]

The uncertainties related to BP management in patients with multimorbidity are illustrated by both national[17,116] and international guidelines.[39,41,117] The most recent hypertension guidelines issued by the National Institute for Health and Care Excellence (NICE) acknowledged the lack of evidence in multimorbid patients and recommended using "clinical judgement when making treatment decisions particularly in people with (…) multimorbidity".[17] The NICE multimorbidity guidelines went even further and recommended research into deprescribing preventative treatments including antihypertensive drugs as "it is plausible that harms outweigh benefits in some people with multimorbidity (for example, because of higher rates of adverse events in older, frailer people prescribed multiple regular medicines, or because the expected benefit from continuing a preventive medicine is reduced when there is limited life expectancy or high risk of death from other morbidities)".[116] International guidelines and professional societies likewise summarised the evidence currently available and identified key gaps regarding management of BP in patients with multimorbidity. For instance, the recently published hypertension guidelines published by the European Society of Cardiology emphasised the need for "more outcome studies of the optimal treatment target for patients at different levels of baseline cardiovascular risk and with different comorbidities, including diabetes and chronic kidney disease".[39]

This dearth of evidence has important clinical implications because longstanding treatment paradigms that have focused on single diseases are now unable to meet the needs of the rapidly growing population with multimorbidity.[118] Inconsistent guidelines that leave much room for clinical judgement ultimately contribute to undesirable variation in clinical practice. This is well demonstrated by conflicting reports on whether multimorbidity is associated with better[119,120] or worse[121,122] BP control. Although management of BP in patients with multimorbidity likely requires an individually tailored approach based on holistic patient assessment, treatment decisions should be informed by high-quality randomised evidence, which is currently missing. Filling this gap in contemporary knowledge is key to tackle the burden of high BP in patients with multimorbidity, and hence avoid premature morbidity and mortality attributable to cardiovascular disease in those patients.

Summary

- Multimorbidity is on the rise across the globe, not only in prevalence but also in complexity.
- Hypertension is the most common condition in patients with multimorbidity.
- Evidence on the effects of BP lowering in patients with multimorbidity is scarce.
- Lack of consistent treatment recommendations results in unwarranted variation in clinical practice.
- There is an unmet need for evidence to inform BP lowering treatment in the context of multimorbidity.

Blood pressure in patients with heart failure – evidence and gaps

HF affects an estimated 1-2% of the population, which equates to about 26 million people worldwide.[123] Both incidence and prevalence are higher in men than in women and rise sharply with age, with an average age at diagnosis of 77 years.[124] From a global perspective, HF has been declared a pandemic as prevalence is on the rise in all continents.[125-129] The burden of HF is expected to markedly increase in the near future as evidence is emerging on the high prevalence of HF in heavily populated countries in South East Asia.[130] In the UK, although improvements in HF prevention have resulted in a modest decrease in incidence over the past few years, prevalence increased by 23% between 2002 and 2014, mainly due to population growth and ageing.[124] In consequence, the current burden of HF is estimated to be similar to that of the four most common causes of cancer combined. In addition, patients with HF tend to present with an increasing number of comorbidities, which adds further complexity and costs to their management. As a result of demographic trends and a substantial expansion of the treatment armamentarium,[131] the healthcare expenditure on HF has been steeply rising, with the bulk of the costs attributable to hospitalisations, particularly at the end of life.[132,133]

High BP is the leading risk factor for developing HF,[2] and it is estimated that antecedent hypertension (defined as BP above 140/90 mmHg) is present in 75% of patients with chronic HF.[134] However, the prevalence of hypertension as a comorbidity in patients with established HF seems to vary widely across Europe, with estimates ranging from 25 to 70% in different regions.[135] Elevated BP is more common in HF with preserved ejection fraction than in HF with

reduced ejection fraction, with a prevalence of up to 90% in the former.[136-138] Nonetheless, the poorly understood association between BP and clinical outcomes in HF creates a challenge for managing BP in this population. Contrary to the well-established log-linear association between SBP and cardiovascular events in the general population,[26] observational studies have reported a J-shaped relationship between SBP and all-cause and cardiovascular mortality in patients with HF, in particular among those with HF with reduced ejection fraction.[139-141] This "paradoxical" association has raised the question as to whether low SBP itself might be harmful or whether it is simply a marker of poorer health. Proponents of the former hypothesis have argued that in observational analyses patients with SBP below 110 mmHg had an increased risk of HF hospitalisation even though they were on maximum guideline-recommended medical therapy,[142] and that in some analyses the associations were present despite no evidence for more advanced HF or greater burden of known comorbidities among those with low BP.[143] On the other hand, low BP may be a surrogate marker for more severe heart dysfunction and lower cardiac output, which may be the actual causes of the adverse clinical outcomes, rather than BP itself.[144,145] This hypothesis is supported by trials of cardiac devices, in which resynchronisation therapy significantly increased BP and reduced mortality and HF hospitalisation.[146] Furthermore, the relative risk reduction was larger in patients with low baseline BP, in whom device-induced improvement in cardiac function resulted in an increase in BP. The associations between BP and clinical outcomes in patients with HF with preserved ejection fraction are even more uncertain, with conflicting reports from observational studies on whether low SBP and/or DBP carry an adverse prognosis.[147,148]

Clinical trials are ideally suited to investigate the causal nature of the association between BP and cardiovascular outcomes in patients with HF. However, in such patients, there is no compelling evidence from clinical trials on this question. Meta-analyses of hypertension trials in patients without HF have shown that decreasing BP significantly reduces the risk of fatal and non-fatal cardiovascular outcomes, with no effect heterogeneity across a broad range of baseline BP categories.[3,59] However, the extent to which those findings are applicable to HF patients is uncertain, because meta-analyses of antihypertensive drugs have typically excluded HF trials, even when they tested the effect of drugs with BP lowering properties. This exclusion has been justified by the absence of BP reduction in some trials despite improved clinical outcomes,[149-153] and no or harmful effects of some drugs (e.g. calcium channel blockers (CCB), alpha-blockers) on cardiovascular risk in patients with HF, despite their known BP lowering properties in the general population.[154-156] Therefore, randomised evidence is scant on whether BP reduction has a negative, neutral or positive impact on clinical outcomes in patients with HF, and whether there is heterogeneity in treatment effects between subgroups of patients with HF (e.g., according to baseline BP,[157-159] left ventricular ejection fraction,[160-162] or common comorbidities[163-165]). Although the main mechanisms of action of guideline-recommended drugs in HF are assumed to be related to neurohumoral modulation with BP lowering seen as an inevitable by-product, it is important to understand whether the observed J-shaped relationship between BP and clinical outcomes in patients with HF is causal and/or modifiable by BP lowering treatment.

The complexity of BP management in patients with HF is further exacerbated by the well-recognised diversity and complexity of the HF syndrome. In an attempt to create more

homogenous HF groups, a binary classification based on left ventricular ejection fraction has been historically used with separation of patients into HF with reduced and preserved ejection fraction. This classification has been recently superseded by the addition of a third category of HF with mid-range ejection fraction defined as left ventricular ejection fraction in the range of 40-49%,[166,167] with ejection fractions below or above that range classified as HF with reduced or preserved ejection fraction, respectively.[92] Although the diversity of the HF syndrome seems consensual, the appropriateness of patient classification into categories based on arbitrary cut-offs of left ventricular ejection fraction has been questioned,[168] and it has been argued that HF with reduced and preserved ejection fraction represent similar processes along one disease continuum, rather than distinct disease entities.[169-171] Regardless of the ongoing controversy, the classification based on left ventricular ejection fraction is clinically useful because it distinguishes between populations that differ on underlying aetiologies, demographics, comorbidities and, most importantly, on response to treatment,[160,161] including BP lowering drugs.[162] Indeed, there is evidence suggesting that the effect of BP on clinical outcomes varies along the spectrum of left ventricular ejection fraction[172] as does the effect of drugs with BP lowering properties.[173] Therefore, despite its limitations, this binary classification endures as the mainstay in research and in clinical practice and it is also adopted by contemporary HF guidelines.[92]

The ongoing controversy on BP management in HF is reflected on hypertension[39] and HF guidelines,[92] which state that "BP control is an element of the holistic management of patients with HF", but acknowledge that there have been no trials in the HF population purposefully comparing different BP lowering drugs or treatment goals. Therefore,

recommendations have been extrapolated from evidence in other high-risk populations, in whom intensive BP reduction showed greater protection from cardiovascular events, albeit with a potential increase in side effects.[174,175] Overall, HF and hypertension guidelines recommend titration of drugs that have compelling indications for management of HF and also reduce BP to attain a BP reduction consistent with a target of 130/80 mmHg, as in patients without HF. However, the ideal BP target in HF is yet to be established as the more intensive target, in comparison to the conventional 140/90 mmHg, has not been tested in RCTs in the HF population.[39,117] The recommendations are thus tempered with caution to acknowledge the uncertainty regarding the extrapolation of evidence from hypertensive patients in the general population to patients with HF, who are substantially different from them. On one hand, the normal distribution of BP in HF patients is typically shifted to the left compared to that of the general population, and thus it is unclear whether further treatment-induced BP reduction in those patients actually happens or influences clinical outcomes.[176,177] On the other hand, clinical outcomes for which the protective effect of BP lowering has been demonstrated in the general population may be less relevant in patients with HF, in whom atherosclerotic events, such as stroke and myocardial infarction, are relatively less common.[178-182]

Lack of clear guidelines and reliable evidence creates a dilemma for clinicians, who have to strike the balance between prescribing life-saving treatment with drugs that may reduce BP, and the potentially harmful effects of low BP itself in the HF population. Uncertainty ultimately results in unwarranted variation in clinical practice, and often inadequate treatment decisions. Indeed, concerns about deleterious BP reduction underpin clinicians'

reluctance to prescribe and up-titrate guideline-recommended drugs in patients with low baseline BP.[183,184] Paradoxically, those patients in whom the absolute risk reduction achieved by treatment is larger, because of their higher baseline cardiovascular risk, are the least likely to be adequately treated.[144,159,176,185,186] In addition, concerns about potential deterioration in renal function due to impaired renal perfusion underpin poor compliance with RAAS inhibitors.[187,188] Therefore, there is a pressing need to clarify whether there is heterogeneity in treatment effects, not only regarding efficacy but also safety, in important subgroups within the HF population, such as patients with low baseline BP, renal impairment, different New York Heart Association functional classes, and reduced or preserved ejection fraction.

Summary

- Both high and low BP are common in patients with HF and both have been associated with a poor prognosis in observational studies.
- Randomised evidence on the effects of BP lowering in patients with HF is lacking as no trials have purposely investigated it.
- Although a J-shaped relationship between BP and clinical outcomes has been proposed in HF, whether it is causal and/or modifiable by BP lowering treatment remains unclear.
- Current management of BP in HF is guided by extrapolation from other patients with high cardiovascular risk, despite marked differences between them.
- Uncertainty and controversy result in unwanted variation in clinical practice as well as overzealous treatment that may harm those patients who had more to gain from treatment with drugs with BP lowering properties.

Chapter 3 Data source

This chapter describes the data source that I used for most of my research – the Blood Pressure Lowering Treatment Trialists' Collaboration.

The history of the Blood Pressure Lowering Treatment Trialists' Collaboration

The BPLTTC was created in 1995 as a consortium of large-scale RCTs of BP lowering drugs.[189,190] IPD were pooled from all participating RCTs that were able to provide them. The primary aim was to answer questions related to the effects of BP lowering that individual trials had been unable to reliably answer, due to lack of power or methodological issues.[191] For the past 25 years, the BPLTTC has amassed a huge amount of high-quality IPD. This allowed conducting several meta-analyses that compellingly demonstrated that BP lowering reduces the risk of major cardiovascular events, such as ischaemic heart disease, HF and stroke, overall and in subgroups of patients with common comorbidities.[192-195] Furthermore, the BPLTTC was instrumental in demonstrating that a BP management strategy based on overall cardiovascular risk was more effective than a strategy based on arbitrary BP thresholds, which resulted in a paradigm shift in hypertension guidelines and hence in clinical practice across the globe.[39] Therefore, evidence generated by the BPLTTC has had a major impact on contemporary BP management. **Table 3.1** summarises the main findings of the meta-analyses carried out by the BPLTTC thus far.

However, the relatively small size of the BPLTTC precluded addressing relevant questions related to BP management in specific populations and the effects of BP lowering on outcomes other than conventional cardiovascular events. Therefore, in 2014 the scope of the BPLTTC was extended to include more detailed baseline, follow-up and outcome data from existing trials. In addition, an updated systematic review identified further trials that were eligible for inclusion in the BPLTTC. The principal investigators of those trials were invited to share IPD and join the collaboration.

Table 3.1 Summary of the key findings of the meta-analyses carried out by the BPLTTC

Title	Aims	Main findings
Effects of blood pressure lowering on cardiovascular events, in the context of regression to the mean: a systematic review of randomised trials (Journal of hypertension, 2019)[196]	To assess the clinical relevance of regression to the mean for clinical trials and clinical practice in the context of BP lowering treatment.	Most mean BP change was due to regression to the mean rather than treatment. Overall, a BP reduction of 6/3 mmHg decreased ischaemic heart disease by 14% (95% CI 11 to 17%) and stroke by 18% (95% CI 15 to 22%), and these treatment effects occurred at follow-up BP levels much closer to the mean than baseline BP levels. Benefits were apparent in numerous high-risk patient groups with baseline mean SBP less than 140 mmHg. Therefore, clinical practice should focus on prompt, empirical treatment to maintain lower BP for those with high BP and/or high risk.
Blood pressure lowering treatment strategies based on cardiovascular risk versus blood pressure: a meta-analysis of individual participant data (PLOS Medicine, 2018)[46]	To compare outcomes from a BP lowering treatment strategy based on predicted cardiovascular risk with one based on SBP level.	A BP lowering treatment strategy based on predicted cardiovascular risk is more effective (i.e., it avoids a larger number of cardiovascular events for a given number of persons treated) than one based on BP levels alone across a range of thresholds. The benefits of a risk-based strategy were less clear in patients with diabetes mellitus or established cardiovascular disease. Therefore, cardiovascular risk assessment should guide treatment decisions in moderate- to high-risk individuals, particularly for primary prevention.

Effects of blood pressure lowering on cardiovascular risk according to baseline body mass index: a meta-analysis of randomised trials (Lancet, 2015)[197]	To compare the effects of BP lowering regimens on cardiovascular risk in groups of patients categorised by baseline body mass index.	There was no association between body mass index category and the risk reduction for a given fall in SBP. There was also no strong evidence that selection of a particular class of BP lowering drug would lead to substantially different outcomes for obese versus lean individuals.
Blood pressure lowering treatment based on cardiovascular risk: a meta-analysis of individual patient data (Lancet, 2014)[114]	To investigate whether the benefits of BP lowering drugs are proportional to baseline cardiovascular risk, to establish whether absolute risk could be used to inform treatment decisions for BP lowering therapy.	Lowering BP provides similar relative protection at all levels of baseline cardiovascular risk, but progressively greater absolute risk reductions as baseline risk increases. These results support the use of predicted baseline cardiovascular disease risk equations to inform BP lowering treatment decisions.
Blood pressure lowering and major cardiovascular events in people with and without chronic kidney disease: meta-analysis of randomised controlled trials (BMJ, 2013)[192]	To estimate the cardiovascular effects of lowering BP in people with chronic kidney disease.	Compared with placebo, BP lowering regimens reduced the risk of major cardiovascular events by about a sixth per 5 mmHg reduction in SBP in individuals with and without chronic disease. There was no evidence in favour of class-specific effects. Therefore, BP lowering is an effective strategy for preventing cardiovascular events among people with moderately reduced renal function, irrespective of the drug class used.

The effects of blood pressure reduction and of different blood pressure lowering regimens on major cardiovascular events according to baseline blood pressure: meta-analysis of randomised trials (Journal of hypertension, 2011)[3]	To compare the risk reductions achieved by different BP lowering regimens among individuals with different levels of baseline BP.	There was no evidence of differences in the proportionate risk reductions achieved with different BP lowering regimens across groups defined according to baseline SBP. This finding was broadly consistent for comparisons of different regimens, for DBP categories, and for commonly used BP thresholds. Therefore, the benefits of BP lowering seem independent of baseline BP values, which supports BP lowering in high-risk patients with and without hypertension.
Do men and women respond differently to blood pressure lowering treatment? Results of prospectively designed overviews of randomised trials (European Heart Journal, 2008)[198]	To quantify the effects of BP lowering treatment in each sex, and to determine if there are important differences in the proportional benefits of treatment between women and men.	Achieved BP reductions were comparable for women and men in every comparison made. All the BP lowering regimens provided broadly similar protection against major cardiovascular events in women and men. Therefore, differences in cardiovascular risk between sexes are unlikely to reflect differences in response to BP lowering treatment.
Effects of different regimens to lower blood pressure on major cardiovascular events in older and younger adults: meta-analysis of randomised trials (BMJ, 2008)[199]	To determine the relative risk reductions achieved with different regimens to lower BP in younger and older adults.	There was no evidence that the protection against major cardiovascular events afforded by different drug classes varied substantially with age.
Blood pressure-dependent and independent effects of agents that inhibit the renin-angiotensin system (Journal of hypertension, 2007)[200]	To evaluate the BP-dependent and independent effects of ACEIs and ARBs on major cardiovascular events.	Treatment with ACEIs and ARBs resulted in a comparable BP-dependent reduction in cardiovascular events, including coronary artery disease, stroke, and HF. In addition, for ACEIs, but not ARBs, there was evidence of BP-independent effects on the risk of major coronary artery disease events.

Effects of different blood pressure lowering regimens on major cardiovascular events in individuals with and without diabetes mellitus: results of prospectively designed overviews of randomised trials (Archives of internal medicine, 2005)[193]	To compare the effects on cardiovascular events and death of different BP lowering regimens in individuals with and without diabetes.	BP lowering reduced the risk of major cardiovascular events to a comparable extent in individuals with and without diabetes, irrespective of the drug class used. There was modest evidence that lower BP goals could result in larger reductions in major cardiovascular events in individuals with versus those without diabetes.
Effects of different blood-pressure lowering regimens on major cardiovascular events: results of prospectively designed overviews of randomised trials (Lancet, 2003)[195]	To estimate effects of strategies based on different drug classes or those targeting different BP goals, on the risks of major cardiovascular events and death.	Overall, treatment with any of the commonly used BP lowering drugs produced comparable reductions in the risk of major cardiovascular events. There was some evidence supporting additional benefits of certain drug classes on cause-specific outcomes. For every outcome other than HF, more intensive BP lowering resulted in proportionally larger reductions in the risk of major cardiovascular events.
Effects of ACE inhibitors, calcium antagonists, and other blood-pressure lowering drugs: results of prospectively designed overviews of randomised trials (Lancet, 2000)[194]	To investigate the effects of ACEIs, CCBs, and other BP lowering drugs on mortality and major cardiovascular morbidity in several populations of patients.	BP lowering regimens based on ACEIs or CCBs effectively prevent major cardiovascular events. There was little evidence that the risk reduction afforded by treatment varied according to the intensity of BP lowering or depending on the drug class used.

ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blocker; BP, blood pressure; CCB, calcium channel blocker; DBP, diastolic blood pressure; SBP, systolic blood pressure

The current Blood Pressure Lowering Treatment Trialists' Collaboration

A total of 50 trials, with over 350,000 participants were included in the latest iteration of the BPLTTC, which made it the largest international hypertension collaboration and, to my knowledge, the largest collaboration of IPD from RCTs currently available. A detailed description of the methods underpinning the most recent iteration of the BPLTTC is provided below and the protocol has been published elsewhere.[201]

Inclusion and exclusion criteria

Trials were eligible for inclusion in the BPLTTC if they met one of the following criteria:

- Randomisation of patients between a BP lowering agent and a placebo or other inactive control (placebo-controlled trials);
- Randomisation of patients between different BP lowering intensities and/or targets (more versus less intense treatment trials); or
- Randomisation of patients between different antihypertensive drugs, including combinations (drug class comparison trials).

In addition, to avoid small study bias, trials were required to have a minimum of 1,000 patient-years of follow-up in each randomly allocated trial arm.

Although no restrictions on publication date, setting or drugs were applied, trials that met the following criteria were excluded:

- Trials exclusively conducted in patients with HF or short-term interventions following acute myocardial infarction or other acute settings (e.g., acute stroke);

- Trials with non-pharmacological interventions of BP lowering without a drug comparison arm (e.g., trials of renal denervation);
- Trials without a clearly defined randomisation process.

Identification of trials

A systematic review was conducted to identify trials that were eligible for inclusion in the current BPLTTC. A broad search query was run on electronic bibliographic databases, including PubMed/Medline (NCBI, Bethesda, MD, USA), The Cochrane Central Register of Controlled Trials (The Cochrane Collaboration, London, UK) and the ClinicalTrials.gov website covering the periods between the 1st of January 1966 and the 1st of June 2018. Filters were applied to restrict the search to RCTs or their meta-analyses. No language restrictions were applied. This search based on electronic databases was complemented with hand-searches of reference lists of eligible studies, related meta-analyses, and clinical trial registries to identify further relevant studies. The protocol for the systematic review, including details of the methods and search strategy, was registered with PROSPERO[202] (CRD42018099283).

Records obtained from different sources were then screened, based on title and abstract. For studies that were potentially eligible, full manuscripts were retrieved and assessed for inclusion. Two independent reviewers performed study screening and selection in duplicate, with disagreements resolved by a third reviewer. **Figure 3.1** summarises the search strategy that underlies the BPLTTC.

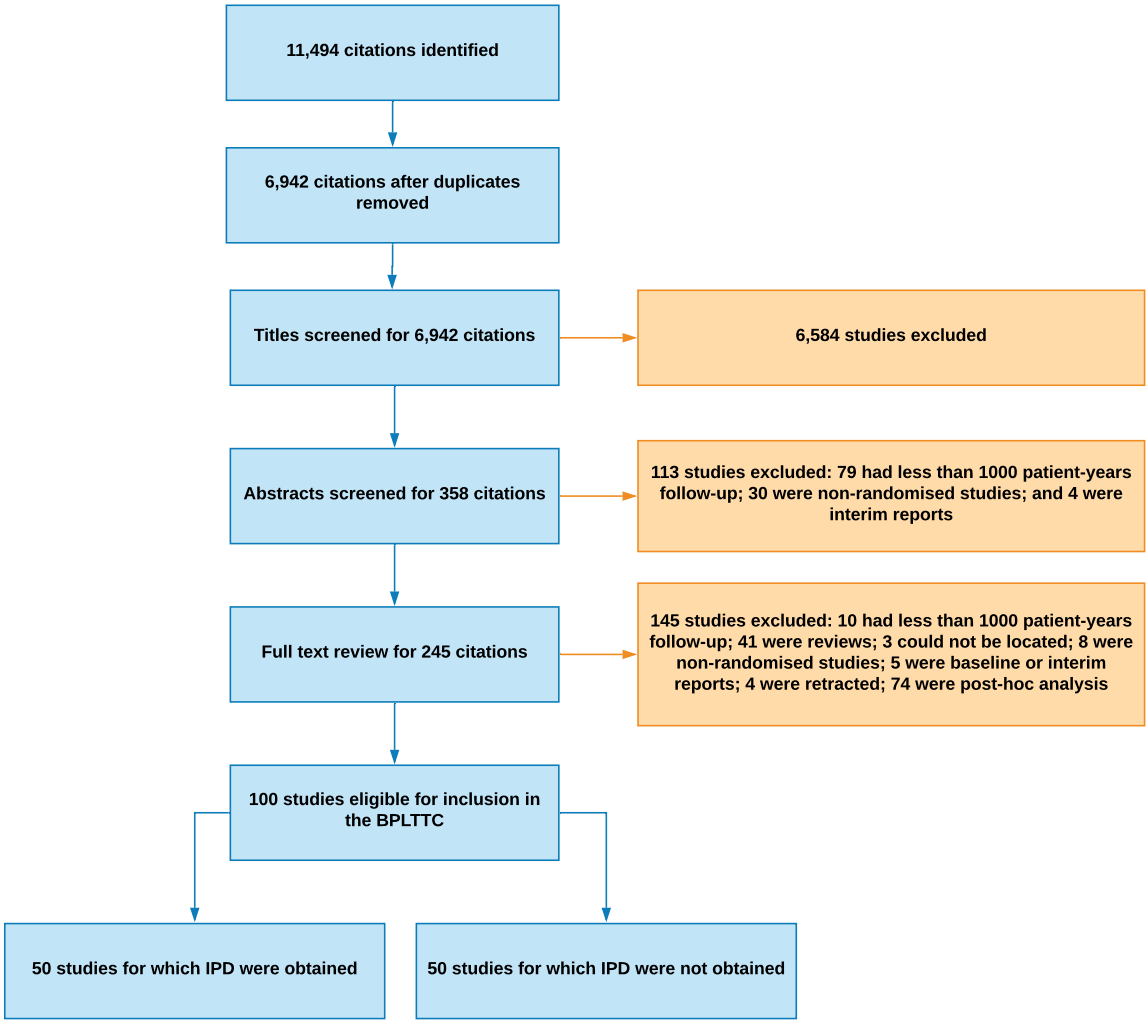

Figure 3.1 Flowchart illustrating the screening and selection of studies for inclusion in the Blood Pressure Lowering Treatment Trialists' Collaboration

Data collection, transfer and storage

For the final set of trials that complied with the aforementioned inclusion and exclusion criteria (**Table 3.2**), investigators were invited to join the BPLTTC and share IPD. In addition, all existing BPLTTC collaborators were asked to provide additional IPD. As of May 2020, the collaboration had acquired data from 50 trials with about 350,000 participants (**Table 3.3**). Despite ongoing efforts to gather IPD, there were 50 trials that could be potentially included in the BPLTTC for which IPD had not yet been obtained (**Figure 3.1**). Many of those trials were conducted many years ago and identification of the data guardian, or an electronic repository of the IPD, has proven challenging.

All data were transferred using a secure file transmission system, such as Oxford's Oxfile system. Data has been stored in a secure server in the University of Oxford in keeping with data protection regulations and data sharing agreements. Access to the data is restricted to those persons directly involved in the research, and data can be used exclusively for the purpose of the proposed study.

Table 3.2 List of eligible trials for the Blood Pressure Lowering Treatment Trialists' Collaboration[1]

Study name or author	Year	Participants
AASK (African American Study of Kidney Disease and Hypertension)[203]	**2006**	**1,094**
ABCD (Appropriate Blood Pressure Control in Diabetes Trial)[204]	**1998**	**1,900**
ACCOMPLISH (Avoiding Cardiovascular events through Combination therapy in Patients Living with Systolic Hypertension)[205]	2008	11,506
ACCORD (Action to Control Cardiovascular Risk in Diabetes)[206]	**2010**	**4,733**
ACTION (A Coronary Disease Trial Investigating Outcome with Nifedipine GITS)[207]	2004	7,665
ACTIVE I (Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events)[101]	**2011**	**9,016**
ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation)[208]	**2007**	**11,140**
ALLHAT (Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attacks Trial)[209]	**2002**	**42,418**
ALTITUDE (Aliskiren Trial in Type 2 Diabetes Using Cardiovascular and Renal Disease Endpoints)[210]	2012	8,561
ANBP (The Australian National Blood Pressure Study)[211]	**1980**	**3,427**
ANBP2 (Second Australian National Blood Pressure Study)[212]	**2003**	**6,083**
APSIS (Angina Prognosis Study in Stockholm)[213]	1996	809
ASCOT-BPLA (Anglo-Scandinavian Cardiac Outcomes Trial - Blood Pressure Lowering Arm)[213]	**2005**	**19,257**
ATTEMPT-CVD (A Trial of Telmisartan Prevention of Cardiovascular Diseases)[214]	2016	1,228
BBB (Behandla Blodtryck Battre)[215]	1994	2,127
BCAPS (β-Blocker Cholesterol lowering Asymptomatic Plaque Study)[216]	2001	793
BENEDICT (Bergamo Nephrologic Diabetes Complications Trial)[217]	**2004**	**1,808**
CAMELOT (The Comparison of Amlodipine vs Enalapril to Limit Occurrences of Thrombosis)[218]	**2004**	**3,327**
CAPPP (Captopril Prevention Project)[219]	**1999**	**10,985**
Cardio-Sis (CARDIOvascolari del Controllo della Pressione Arteriosa SIStolica)[220]	**2009**	**1,111**

CASE-J (Candesartan Antihypertensive Survival Evaluation in Japan)[221]	**2008**	**4,703**
CHIEF (Chinese Hypertension Intervention Efficacy study)[222]	2012	13,080
COLM (Combination of OLMesartan and calcium channel blocker or diuretic)[223]	**2014**	**5,141**
CONVINCE (Controlled Onset Verapamil Investigation of Cardiovascular End Points)[224]	**2003**	**16,476**
Coope J, et al[225]	1986	884
COPE (Combination Therapy of Hypertension to Prevent Cardiovascular Events)[226]	**2011**	**6,586**
DIABHYCAR (Non-insulin-dependent diabetes, hypertension, microalbuminuria or proteinuria, cardiovascular events, and ramipril)[227]	**2004**	**4,912**
DIME (Diuretics in the Management of Essential hypertension study)[228]	2014	1,130
DIRECT-Prevent 1 (Effect of candesartan on prevention)[229]	2008	1,421
DIRECT-Protect 1 (Effect of candesartan on progression)[229]	2008	1,905
DIRECT-Protect 2 (Effect of candesartan on progression and regression of retinopathy in type 2 diabetes)[230]	2011	1,905
DREAM (Diabetes REduction Assessment with ramipril and rosiglitazone Medication)[231]	2006	5,269
Dutch TIA Trial (Dutch Transient Ischemic Attack Trial)[232]	**1993**	**1,473**
E-COST (Efficacy of Candesartan on Outcome in Saitama Trial)[233]	**2005**	**2,048**
ELSA (Efficacy of Candesartan on Outcome in Saitama Trial)[234]	**2002**	**2,334**
EUROPA (European trial on reduction of cardiac events with perindopril in stable coronary artery)[235]	**2003**	**12,218**
EWPHE (European Working Party on High Blood Pressure in the Elderly)[236]	**1985**	**840**
FEVER (Felodipine Event Reduction Study)[237]	2005	9,711
HAPPHY (Heart Attack Primary Prevention in Hypertension Trial)[238]	1987	6,569
HDFP (Hypertension Detection and Follow Up Program)[239]	1979	10,940
HIJ-CREATE (Heart Institute of Japan Candesartan Randomized Trial for Evaluation in Coronary Heart Disease)[240]	**2009**	**2,049**
HOMED-BP (Hypertension Objective Treatment based on Measurement by Electrical Devices of Blood Pressure Study)[241]	**2012**	**3,518**

HOPE (Heart Outcomes Prevention Evaluation Study)[242]	**2000**	**9,297**
HOPE-3 (Heart Outcomes Prevention Evaluation-3)[243]	2016	12,705
HOT (Hypertension Optimal Treatment Study)[244]	1998	18,790
HYVET (Hypertension in the Very Elderly Trial)[245]	**2008**	**3,845**
IDNT (Irbesartan Diabetic Nephropathy Trial)[246]	**2001**	**2,861**
INSIGHT (International Nifedipine GITS Study: Intervention as a Goal for Hypertension Therapy)[247]	**2000**	**6,321**
INVEST (International Verapamil-Trandolapril Study)[248]	**2003**	**22,576**
IPPSH (International Prospective Primary Prevention Study in Hypertension) [249]	1985	6,357
JATOS (Japanese Trial to Assess Optimal Systolic Blood Pressure in Elderly Hypertensive Patients)[250]	2008	4,418
JMIC-B (Japan Multicenter Investigation for Cardiovascular Diseases-B)[251]	**2004**	**1,650**
LIFE (Losartan Intervention for Endpoint Reduction in Hypertension Study)[178]	**2002**	**9,193**
LIT (Lopressor Intervention Trial)[252]	1987	2,395
MIDAS (Multicenter Isradipine Diuretic Atherosclerosis Study)[253]	1996	883
MOSES (Morbidity and Mortality After Stroke, Eprosartan Compared With Nitrendipine for Secondary Prevention)[254]	**2005**	**1,352**
MRC-1 (Medical Research Council Treatment of Mild Hypertension)[255]	1985	26,054
MRC-2 (Medical Research Council Treatment of Hypertension in Older Adults)[256]	1992	6,579
Multicentre International Study[257]	1975	3,038
NAVIGATOR (Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research)[258]	2010	9,306
NICOLE (Nisoldipine in Coronary Artery Disease in Leuven Study)[259]	2001	819
NICS-EH (National Intervention Cooperative Study in Elderly Hypertensives)[260]	**1999**	**414**
NORDIL (Nordic Diltiazem Study) [261]	**2000**	**10,881**
ONTARGET (Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial)[262]	**2008**	**34,196**

OSCAR (OlmeSartan and calcium antagonists randomized study)[263]	2012	1,164
The Oslo Study[264]	1980	785
PART-2 (Prevention of Atherosclerosis with Ramipril Trial)[265]	**2000**	**617**
PATE-Hypertension (The Practitioner's Trial on the Efficacy of Antihypertensive Treatment in the Elderly with Hypertension)[266]	2000	1,748
PATS (Post-stroke Antihypertensive Treatment Study)[267]	2009	5,665
PEACE (Prevention of Events with Angiotensin Converting Enzyme Inhibition)[268]	**2004**	**8,290**
PHARAO (Prevention of hypertension with angiotensin-converting enzyme inhibitor ramipril in patients with high-normal blood pressure)[269]	2008	1,008
PREVEND IT (Prevention of Renal and Vascular Endstage Disease)[270]	**2004**	**864**
PREVENT (Prospective Randomized Evaluation of the Vascular Effects of Norvasc Trial)[271]	**2000**	**825**
PRoFESS (Prevention Regimen For Effectively Avoiding Second Strokes)[272]	2008	20,332
PROGRESS (Perindopril Protection Against Recurrent Stroke Study)[273]	**2001**	**6,105**
QUIET (Quinapril Ischaemic Event Trial)[274]	2001	1,750
RENAAL (Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan Study)[275]	2001	1,513
ROADMAP (Randomized Olmesartan And Diabetes Microalbuminuria Prevention Study)[276]	2011	4,447
SCOPE (Study on Cognition and Prognosis in the Elderly)[277]	2003	4,937
SHELL (Systolic Hypertension in the Elderly Long-term Lacidipine Trial)[278]	2003	1,882
SHEP (Systolic Hypertension in the Elderly Program)[279]	**1991**	**4,736**
SPRINT (Systolic Blood Pressure Intervention Trial)[280]	**2015**	**9,361**
SPS3 (Secondary Prevention of Small Subcortical Strokes)[281]	2013	3,020
STONE (Shanghai trial of nifedipine in the elderly)[282]	1996	1,632
STOP Hypertension (Swedish Trial in Old Patients with Hypertension)[283]	1991	1,627
STOP Hypertension-2 (Swedish Trial in Old Patients with Hypertension-2)[284]	**1999**	**13,228**

Sun M, et al[285]	1997	2,080
Syst-China (Systolic Hypertension in China) [282]	1988	2,394
Syst-Eur (Systolic Hypertension in Europe)[286]	**1997**	**4,695**
Taylor SH, et al[287]	1982	1,103
TEST (Ternormin after stroke and TIA)[288]	1995	720
TOMHS (Treatment of Mild Hypertension Study)[289]	1993	902
TRANSCEND (Telmisartan Randomised Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease)[290]	**2008**	**5,926**
TROPHY (Trial of Preventing Hypertension)[291]	2006	772
UKPDS (UK Prospective Diabetes Study)[292]	**1998**	**1,906**
VA NEPHRON-D (Veterans Affairs Nephropathy in Diabetes)[293]	2013	1,448
VALISH (Valsartan in Elderly Isolated Systolic Hypertension Study)[294]	**2010**	**3,079**
VALUE (Valsartan Antihypertensive Long-Term Use Evaluation)[179]	**2004**	**15,245**
VHAS (Verapamil in Hypertension and Atherosclerosis Study)[295]	**1997**	**1,414**
Wei Y, et al.[296]	2013	724

[1]Trials highlighted in bold are those for which IPD are available in the BPLTTC.

Table 3.3 Summary of the trials that provided individual participant data to the Blood Pressure Lowering Treatment Trialists' Collaboration

Placebo-controlled trials

Trial	Setting	Inclusion criteria	Exclusion criteria	Recruitment period	N (% of women)			Drug intervention	Additional treatment	Treatment goal	Follow-up (years)
					Total	Intervention	Placebo				
ACTIVE I	Multi-country	AF, ≥1 risk factor (age ≥75 years, on antihypertensive treatment, history of stroke, transient ischaemic attack or non-cerebrovascular embolism, left ventricular ejection fraction <45%, peripheral vascular disease, or age 55-74 years with either coronary artery disease or diabetes	Use of anticoagulation, peptic ulcer disease in past 6 months, history of intracerebral haemorrhage, thrombocytopaenia or mitral stenosis	Jun 2003 to May 2006	9016 (39)	4518 (39)	4498 (39)	ARB	None	None specified	4.1
ADVANCE	Multi-country	Age ≥55 years, type 2 diabetes (diagnosed aged ≥30 years), ≥1 major cardiovascular risk factor (microvascular disease, smoking, dyslipidaemia, microalbuminuria, type 2 diabetes for ≥10 years, age ≥65 years)	HbA1c target (≤6.5%), definite indication for long-term insulin therapy	Jul 2001 to Mar 2003	11140 (43)	5569 (42)	5571 (43)	ACEI and diuretics as fixed dose combination drug	At physician's discretion, but not thiazide diuretics, and only perindopril as ACEI allowed	None specified	4.2
ANBP	Australia	Age 30-69 years with mild hypertension (DBP 95-110 mmHg and SBP <200 mmHg)	Antihypertensive treatment in past 3 months, recent angina or myocardial infarction, stroke, hormone therapy, asthma, diabetes, gout, serious disease, tricyclic antidepressant	1973 to March 1979	3427 (37)	1721 (37)	1706 (36)	Diuretics	Methyldopa, propranolol, or pindolol, then hydralazine or clonidine	Reduce DBP to ≤90 mmHg (after two years, further reduced to 80 mmHg)	3.6
BENEDICT	Italy	Age ≥40 years, untreated SBP ≥130 and DBP ≥85 mmHg or needing treatment to attain below these levels, type 2 diabetes for <25 years, urinary albumin excretion rate <20 μg/min, serum creatinine ≤133 μmol/l	HbA1c ≥11%, nondiabetic renal disease	Around 2000 to 2003	1204 (48)	910 (47)	300 (50)	ACEI, CCB, both ACEI and CCB	Diuretics, doxazosin, prazosin, clonidine, methyldopa or β-blockers, minoxidil, or CCB	Reduce BP to 120/80 mmHg	3.1
CAMELOT	Multi-country (US, Canada, Europe)	Age 30-79 years, coronary artery stenosis >20% by angiography, DBP <100 mmHg	Left middle coronary artery obstruction >50%, HF	Apr 1999 to Apr 2002	1991 (26)	1336 (26)	655 (27)	CCB, ACEI	Allowed to continue β-blocker, α-blocker, diuretics	None specified	1.6
DIABHYCAR	Multi-country	Age ≥50 years, type 2 diabetes, urinary albumin excretion ≥20 mg/L in two consecutive urine samples	Serum creatinine >150 μmol/L, use of insulin, ACEI or ARB, HF, recent myocardial infarction, urinary tract infection	Feb 1995 to Apr 1998	4912 (30)	2443 (30)	2469 (30)	ACEI	Usual treatment	None specified	3.9
Dutch TIA Trial	The Netherlands	Transient ischaemic attack or non-disabling ischaemic stroke (Rankin Scale ≤3) in past 3 months	Cerebral ischaemia from identifiable causes other than arterial thrombosis or embolism	Feb 1986 to Mar 1989	1473 (36)	732 (34)	741 (38)	β-blocker	None specified	None specified	2.3

EUROPA	Multi-country (Europe)	Age ≥18 years, documented ischaemic heart disease	HF, hypotension, uncontrolled hypertension, renal insufficiency, serum potassium >5.5 mmol/L	Oct 1997 to Jun 2000	12218 (15)	6110 (14)	6108 (15)	ACEI	None specified	None specified	4.2
EWPHE	Multi-country	Age ≥60 years, BP 160-239/90-119 mmHg	Curable causes of high BP, retinopathy, HF, stroke, hepatitis/cirrhosis, gout, malignancy, diabetes requiring insulin treatment	From 1972	840 (70)	416 (69)	424 (71)	Diuretic	Methyldopa	Reduce BP but at unspecified levels	4.6
HOPE	Multi-country	Age ≥55 years, coronary artery disease, stroke, peripheral vascular disease or diabetes, plus ≥1 risk factor (hypertension, dyslipidaemia, smoking, or documented microalbuminuria)	HF, left ventricular ejection fraction <40%, using ACEI or Vitamin E, uncontrolled hypertension, nephropathy, or recent myocardial infarction or stroke	Dec 1993 to Jun 1995	9297 (27)	4646 (28)	4652 (26)	ACEI	None specified	None specified	4.5
HYVET	Multi-country	Age ≥80 years, sustained SBP ≥160 mmHg	Accelerated or secondary hypertension, recent haemorrhagic stroke, HF, serum creatinine >150 μmol/L, serum potassium <3.5 or >5.5 mmol/L, gout, and dementia	Feb 2001 to Oct 2007	3845 (60)	1913 (61)	1912 (60)	Diuretic	ACEI	Reduce BP to 150/80 mmHg	2.1
IDNT	USA	Age 30-70 years, type 2 diabetes, hypertension (BP ≥135/85 mmHg or taking antihypertensive drug), proteinuria, serum creatinine (μmol/l): 88 to 265 (women) or 106 to 265 (men)	None specified	Mar 1996 to Feb 1999	1715 (34)	1146 (36)	569 (29)	ARB and CCB	Others except ACEI, ARB and CCB	SBP <135 (10 mmHg lower if baseline value >145 mm Hg); DBP <85 mmHg	2.6
PART-2	New Zealand	Age ≤75 years, coronary artery disease, transient ischaemic attack or intermittent claudication within past 5 years	HF, serious nonvascular disease, SBP >160 mmHg, DBP >100 mmHg, DBP <100 mmHg during pre-randomisation run-in period	Not specified (published in 2000)	617 (18)	308 (18)	309 (18)	ACEI	None	None specified	4.6
PEACE	Multi-country (USA, Puerto Rico, Canada and Italy)	Aged ≥50 years, coronary artery disease	Unstable angina, severe valvular heart disease, recent/planned revascularisation, limited 5-year survival, serum creatinine >177 μmol/L, serum potassium >5.5 mmol/L	Nov 1996 to Jun 2000	8290 (18)	4158 (19)	4132 (17)	ACEI	None	None specified	4.7
PREVEND IT	The Netherlands	Microalbuminuria, BP <160/100 mmHg (no previous antihypertensive treatment), total cholesterol <8 mmol/L (no lipid lowering medication)	Creatinine clearance <60% of normal age-adjusted value	Apr 1998 to Jun 1999	864 (35)	433 (36)	431 (34)	ACEI	None	None specified	3.8
PREVENT	USA and Canada	Age 30-80 years, documented coronary artery disease, DBP <95 mmHg, cholesterol <325 mg/dL, fasting blood glucose <200 mg/dl	Contraindication for dihydropyridines, uncontrolled hypertension, diabetes and other major illness	Nov 1992 to Sep 1994	825 (20)	417 (20)	408 (20)	CCB	None	None specified	3.0
PROGRESS	Multi-country (Asia, Australasia and Europe)	Stroke or transient ischaemic attack in past 5 years	Indication or contraindication for ACEI	Jun 1995 to Nov 1997	6105 (30)	3051 (30)	3054 (30)	ACEI with/without diuretic	None	According to clinical criteria	3.9

SHEP	USA	Age ≥60 years, isolated systolic hypertension (BP 160-219/<90 mmHg, not on treatment)	Major cardiovascular disease, cancer, alcoholic liver disease, renal dysfunction, competing risk of SHEP primary endpoint or presence of medical management exclusions	Mar 1985 to Jan 1988	4714 (57)	2353 (56)	2361 (57)	Diuretic and β-blocker	None	If baseline SBP >180 mmHg: reduce to <160 mmHg; If baseline SBP 160-179 mmHg, reduce by 20 mmHg	5.0
Syst-Eur	Multi-country	Age ≥60 years, sitting SBP 160-219 mmHg, sitting DBP <95 mmHg, and standing SBP ≥140 mmHg	Secondary hypertension, retinal haemorrhage/papilloedema, HF, dissecting aortic aneurysm, serum creatinine ≥180 μmol/l, recent severe nosebleeds, stroke or myocardial infarction, dementia, disorders prohibiting standing position, any severe disease	Dec 1988 to Jan 1997	4695 (67)	2398 (67)	2297 (66)	CCB	Combined with or replaced by ACEI, diuretic, or both	Reduce sitting SBP by ≥20 mmHg to <150 mmHg	2.6
TRANSCEND	Multi-country	Intolerant to ACEI and with established coronary artery disease, peripheral vascular disease, cerebrovascular disease or diabetes with end-organ damage	HF, valvular/cardiac outflow tract obstruction, pericarditis, congenital heart disease, unexplained syncope, recent revascularisation, SBP >160 mmHg, heart transplantation, subarachnoid haemorrhage, significant renal stenosis, renal or hepatic dysfunction	Nov 2001 to May 2004	5926 (43)	2954 (43)	2972 (43)	ARB	None	None specified	4.9

More versus less intense treatment trials

Trial	**Setting**	**Inclusion criteria**	**Exclusion criteria**	**Recruitment period**	**N (% women)**			**Treatment goals**		**Treatment**	**Follow-up (years)**
					All	More intense	Less intense	More intense	Less intense		
AASK	USA	Age 18-70 years, Afro-American, hypertension, renal disease (estimated glomerular filtration rate 20-65 ml/min/1.73m^2)	DBP <95 mmHg, diabetes, urine protein:creatinine ratio >25, recent malignant hypertension, secondary hypertension, non-hypertensive chronic kidney disease, serious systemic disease, HF	Feb 1995 to Sep 1998	1094 (39)	540 (38)	554 (40)	Mean arterial pressure ≤92 mmHg	Mean arterial pressure 102-107 mmHg	1 of 3: β-blocker, ACEI, CCB; plus, furosemide, doxazosin, clonidine, and hydralazine or minoxidil sequentially	4.8

ABCD	USA	Age <75 years, type 2 diabetes, DBP ≥80 mmHg, not on antihypertensive treatment	Recent coronary artery disease, cerebrovascular disease, HF, renal disease	Mar 1991 to May 1993	950 (39)	474 (0.4)	476 (38)	DBP <75 mmHg for hypertensives (DBP ≥90 mmHg) or DBP reduction by 10 mmHg for normotensives	DBP 80-89 mmHg for hypertensives (DBP ≥90 mmHg) or no change for normotensives	Hypertensive group: CCB and ACEI; plus β-blocker, diuretic, or others but not CCB or ACEI; Normotensive group: CCB, ACEI or placebo	4.7
ACCORD	USA and Canada	Age ≥40y years with cardiovascular disease or ≥50 years with atherosclerosis, type 2 diabetes, HbA1c ≥7.5%, albuminuria, left ventricular hypertrophy or ≥2 cardiovascular risk factors; SBP 130-180 mmHg and taking ≤3 antihypertensive drugs, 24-hour protein excretion rate <1g	BMI ≥45 kg/m^2, serum creatinine ≥132.6 μmol/L and other serious illness	Jan to Jun 2001, then Jan 2003 to Oct 2005	4733 (48)	2362 (48)	2371 (48)	SBP <120 mmHg	SBP <140 mmHg	Drug classes available in clinical practice	4.7
Cardio-Sis	Italy	Age ≥55 years, SBP ≥150 mmHg, taking antihypertensive drug ≥12 weeks, ≥1 cardiovascular risk factor, prior transient ischaemic attack or stroke, coronary artery disease or peripheral artery disease	Fasting blood glucose ≥7 mmol/L, diabetes, serious conditions, renal disease, valvular heart disease, left ventricular hypertrophy, AF, substance misuse	Feb 2005 to Feb 2007	1111 (59)	558 (59)	553 (59)	SBP <130 mmHg	SBP <140 mmHg	Diuretic, ACEI, ARB, CCB, β -blocker, Clonidine	4.7
HOMED-BP	Japan	Self-measured SBP 135-179 mmHg or DBP 85-119 mmHg	None specified	May 2001 to Oct 2009	3518 (50)	1759 (50)	1759 (50)	SBP <120 mmHg and DBP <80 mmHg	BP 125-134/80-84 mmHg	ACEI, ARB or CCB; Diuretic; β-blocker; then other drug class (avoid reaching BP <110/65 mmHg)	4.9
SPRINT	USA and Puerto Rico	Age ≥50 years, SBP 130-180 mmHg, increased cardiovascular risk (clinical or subclinical cardiovascular disease other than stroke, chronic kidney disease, 10-year Framingham cardiovascular risk ≥15%	Diabetes or prior stroke	Nov 2010 to Mar 2013	9361 (36)	4678 (36)	4683 (35)	SBP <120 mmHg	SBP <140 mmHg	All major drug classes	3.0

UKPDS	UK	Age 25-65 years, newly diagnosed diabetes, and hypertension (untreated: SBP ≥160 mmHg and/or DBP ≥90 mmHg; treated: SBP ≥150 mmHg and/or DBP ≥85 mmHg)	Ketonuria, recent myocardial infarction, angina, HF, >1 major vascular episode, serum creatinine >15 μmol/L, retinopathy, malignant hypertension, severe concurrent illness	1987 to 1991	1906	758 (46)	390 (42)	BP <150/85 mmHg	BP <180/105 mmHg	ACEI and β-blocker for more intense arm; For both arms: diuretic, CCB, methyldopa then α-blocker	7.9
VALISH	Japan	Age 70 to 85 years, isolated hypertension (SBP >160 mmHg and DBP <90 mmHg)	Secondary or malignant hypertension, recent cerebrovascular disease or myocardial infarction, recent revascularisation, HF, valvular heart disease, serious arrhythmia, renal/liver dysfunction	Feb 2004 to Aug 2005	3079 (62)	1545 (62)	1534 (63)	SBP <140 mmHg	SBP ≥140 to <150 mmHg	ARB then other antihypertensive agents such as diuretics and CCB but no other ARB	2.6

Drug class comparison trials

Trial	Country	Inclusion criteria	Exclusion criteria	Recruitment period	N (% women)		Additional treatment	Treatment target	Follow-up (years)
ALLHAT	Multi-country	Age ≥55 years stage 1 or 2 hypertension plus ≥1 cardiovascular risk factor, or other atherosclerotic cardiovascular disease	HF	Feb 1994 to Jan 1998	All	42,418 (47)	Atenolol, clonidine or reserpine	BP <140/90 mmHg	4.8
					Diuretic	15,255 (47)			
					CCB	9048 (47)			
					ACEI	9054 (46)			
					α-blocker	9067 (46)			
ANBP2	Australia	Age 65-84 years, SBP ≥160 mmHg or DBP ≥90 mmHg (if SBP≥140 mmHg), no recent cardiovascular disease	Serious illness, plasma creatinine >221 μmol/L, malignant hypertension, dementia	April 1995 to Jun 1998	All	6083 (51)	β-blocker, CCB and α-blocker	Lower SBP by 20 mmHg to <160 mmHg (<140 mmHg if tolerated,) and DBP by 10 mmHg to <90 mmHg (<80 mmHg if tolerated)	4.1
					ACEI	3044 (50)			
					Diuretic	3039 (52)			
ASCOT-BPLA	Multi-country	Age 40-79 years, untreated SBP ≥160 or DBP ≥100 mmHg or treated SBP ≥140 or DBP ≥90 mmHg, ≥3 cardiovascular disease risk factors	Previous myocardial infarction, current treatment for angina, recent cerebrovascular disease, fasting triglycerides >4.5 mmol/L, HF, arrhythmia, haematological or biochemical abnormality at screening	Feb 1998 to May 2000	All	19,257 (23)	For CCB arm: ACEI; For β-blocker arm: diuretic	With diabetes: BP <140/90 mmHg; Without diabetes: BP <130/80 mmHg	5.3
					CCB	9639 (23)			
					β-blocker	9618 (23)			
CAPPP	Sweden and Finland	Age 25-66 years, DBP ≥100 mmHg on two occasions	Secondary hypertension, serum creatinine >150 μmol/L, condition requiring β-blocker treatment	Dec 1989 to Apr 1995	All	10,985 (47)	Diuretic and CCB if necessary	Supine DBP <90 mmHg	5.8
					ACEI	5492 (45)			
					Conventional: β-blocker and/or diuretic	5493 (48)			

CASE-J	Japan	Age 20-85 years, ≥1 high-risk factor, SBP ≥180 or DBP ≥110 mmHg, type 2 diabetes, angina pectoris, myocardial infarction, stroke, peripheral artery disease	BP ≥200/120 mmHg, type 1 diabetes, HF, ejection fraction <40%, AF, cancer	Sep 2001 to Jan 2003	All	4703 (45)	Allowed to continue background treatment (diuretic, α-blocker, β-blocker); any other treatment except ARB, CCB, ACEI	BP (mmHg) by age (years): <60 <130/85; 60-69 <140/90; 70-79 <150/90; ≥80 <160/90	3.1
					ARB	2354 (46)			
					CCB	2349 (43)			
COLM	Japan	Age 65-84 years, hypertension (treated BP ≥140/90 mmHg; untreated BP ≥160/100 mmHg), cardiovascular disease or cardiovascular risk factors	Secondary/malignant hypertension, recent major cardiovascular disease, revascularisation, angina pectoris, HF, AF, hepatic or renal dysfunction	Apr 2007 to Sep 2008	All	5141 (48)	β-blocker, α-blocker, ACEI	BP <140/90 mmHg	3.0
					ARB and CCB	2568 (48)			
					ARB and diuretic	2573 (48)			
CONVINCE	Multi-country	Age ≥55 years, hypertension, ≥1 cardiovascular risk factor	HF, dysrhythmia, secondary hypertension, recent myocardial infarction or stroke, renal disease, other serious disease, BP ≥190/110 mmHg without treatment	Sep 1996 to Dec 1998	All	16476 (55)	Additional treatment if necessary	BP <140/90 mmHg	2.8
					CCB	8179 (56)			
					β-blocker or diuretic	8297 (56)			
COPE	Japan	Age 40-85 years, BP ≥140/90 mmHg	SBP ≥200 or DBP ≥120 mmHg, secondary hypertension, diabetes, recent cardiovascular disease or revascularisation, HF, AF/flutter, hepatic or renal dysfunction, congenital or rheumatic heart disease, cancer	Jun 2003 to Nov 2006	All	3293 (49)	Additional treatment if necessary	BP <140/90 mmHg	3.6
					CCB/ARB	1110 (49)			
					CCB/β-blocker	1089 (49)			
					CCB/Diuretic	1094 (49)			
E-COST	Japan	Age 35-79 years, BP 140-180/90-110 mmHg	Diabetes, abnormal glycaemia, secondary hypertension, recent myocardial infarction or stroke, angina pectoris requiring β-blocker treatment, HF	Sept to Dec 1999	All	2048 (52)	Additional treatment but not ARB or ACEI	BP <140/90 mmHg	3.1
					ARB	1053 (56)			
					Conventional	995 (48)			
ELSA	Multi-country	Age 45-79 years, BP 150-210/95-115 mmHg	Recent myocardial infarction or stroke, type 2 diabetes	1994 to 1998	All	2334 (45)	Diuretic	DBP <95 mmHg	3.4
					CCB	1023 (46)			
					β-blocker	1012 (45)			
HIJ-CREATE	Japan	Age 20-80 years, coronary artery disease, and hypertension (BP ≥140/90 mmHg or on antihypertensive treatment)	Secondary hypertension, recent myocardial infarction or cerebrovascular disease, severe aortic stenosis, cardiomyopathy, serum creatinine >200 mg/L, serum potassium >5 mmol/L, hepatic dysfunction, malignancy	Jun 2001 to Apr 2004	All	2049 (20)	Any antihypertensive agents, excluding ACEI in the ARB arm	BP <130/85 mmHg	4.0
					ARB	1024 (18)			
					Non-ARB (including ACEI)	1025 (21)			
IDNT	USA	Age 30-70 years, type 2 diabetes, hypertension (BP ≥135/85 mmHg or on antihypertensive drug), proteinuria, serum creatinine of 88 to 265 μmol/L (women) or 106 to 265 μmol/L (men)	None specified	Mar 1996 to Feb 1999	All (except placebo)	1146 (36)	Others except ACEI, ARB and CCB	SBP <135 mmHg (10 mmHg lower if baseline value >145 mmHg); and DBP <85 mmHg	2.6
					ARB	579 (35)			
					CCB	567 (37)			

INSIGHT	Multi-country	Age 55-80 years, hypertension (SBP ≥150 or DBP ≥95 mmHg, or SBP ≥160 mmHg), ≥1 other risk factor	None specified	Sep 1994 to Jun 1996	All	6321 (54)	β-blocker or ACEI, then others except CCB or diuretic	SBP/DBP reduction by 20/10 mmHg or SBP/DBP <140/90 mmHg	2.8
					CCB	3157 (54)			
					Diuretic	3164 (53)			
INVEST	Multi-country	Age ≥50 years, documented coronary artery disease, essential hypertension requiring drug therapy	Patients taking β-blocker within two weeks of randomisation or for recent myocardial infarction	Jan 1998 to Feb 2003	All	22576 (52)	ACEI and/or diuretic	SBP/DBP <140/90 mmHg; <130/85 mmHg with diabetes or renal impairment	2.8
					CCB	11267 (52)			
					Non-CCB	11309 (52)			
JMIC-B	Japan	Age <75 years, hypertension (BP ≥160/≥95 mmHg or both SBP ≥150 and DBP ≥90 mmHg, or antihypertensive treatment), coronary artery disease	Myocardial infarction, unstable angina, DBP ≥120 mmHg, secondary hypertension, symptomatic cerebrovascular disease, HF, AF/arrhythmias, renal or hepatic dysfunction, uncontrollable diabetes and familial hypercholesterolaemia	Jan 1994 to Jul 1997	All	1650 (31)	α-blocker; nitrates or β-blocker for angina if needed	BP <150/90 mmHg	2.3
					CCB	828 (32)			
					ACEI	822 (30)			
LIFE	Multi-country	Age 55-80 years, hypertension (SBP 160-200 mmHg; DBP 95-115 mmHg), left ventricular hypertrophy	Secondary hypertension, recent myocardial infarction or stroke, angina pectoris requiring treatment, HF or left ejection fraction ≤40%	June 1995 to May 1997	All	9193 (54)	Diuretic and other antihypertensive treatment except ACEI, ARB and β-blocker	BP 140/90 mmHg	4.9
					ARB	4605 (54)			
					β-blocker	4588 (54)			
MOSES	Germany and Austria	Hypertension requiring treatment, transient ischaemic attack, ischaemic stroke or cerebral haemorrhage	Internal carotid artery occlusion or stenosis >70%, HF, age >85 years, on anticoagulant for cardiac arrythmia, high-grade aortic or mitral valve stenosis, unstable angina	Oct 1998 to Feb 2002	All	1352 (46)	Diuretic, β-blocker, α-blocker or centrally acting drugs; ACEI, ARB or CCB only if clinically necessary	BP <140/90 mmHg	**3.3**
					ARB	681 (46)			
					CCB	671 (45)			
NICS-EH	Japan	Age ≥60 years, SBP 160-220 mmHg and DBP <115 mmHg and no cardiovascular complications	None specified	Oct 1989 to Apr 1992	All	414 (67)	Titration but no additional treatment	BP response sufficient as determined by the investigator	3.2
					CCB	204 (60)			
					Diuretic	210 (74)			
NORDIL	Norway and Sweden	Age 50-74 years, untreated hypertension (DBP ≥100 mmHg on two occasions); if previously treated, DBP ≥100 mmHg on two consecutive visits	Age <50 or ≥70y, bradycardia, secondary hypertension, AF, recent stroke or myocardial infarction, HF	Oct 1992 to Oct 1999	All	10881 (51)	CCB group: ACEI, diuretic, α-blocker or any other if necessary; β-blocker group: ACEI or α-blocker or any other drug except CCB if necessary		4.2
					CCB	5410 (51)			
					β-blocker/Diuretic	5471 (51)			
ONTARGET	Multi-country	Coronary artery disease, peripheral artery disease, cerebrovascular disease or diabetes with end-organ damage	HF, pericarditis, congenital heart disease, unexplained syncope, planned revascularisation, uncontrolled hypertension, heart transplant, subarachnoid haemorrhage, renal artery disease, proteinuria, hepatic dysfunction, volume or sodium depletion, serious illness, secondary hypertension	Jan 2002 to Aug 2003	All	25620 (27)	None	None specified	4.8
					ACEI	8576 (27)			
					ARB	8542 (26)			
					ACEI and ARB	8502 (26)			

STOP HT-2	Sweden	Aged 70-84 years, SBP ≥180 mmHg and/or DBP ≥105 mmHg	Not specified	Sep 1992 to Dec 1998	All	6614 (67)		
					Conventional: β-blocker, diuretic or both	2213 (68)	Amiloride	BP <160/95 mmHg	4.5
					ACEI	2205 (66)	HCTZ	
					CCB	2196 (66)	β-blocker	
VALUE	Multi-country	Age ≥50 years, hypertension, cardiovascular disease, cardiovascular risk factors	Renal artery stenosis, recent myocardial infarction or stroke, severe hepatic disease or chronic renal failure, HF, on monotherapy with β-blocker for coronary artery disease and hypertension	Sep 1997 to Dec 1999	All	15,245 (42)	Diuretic, then other antihypertensive drugs except ARB (ACEI or CCB if clinically indicated other than for hypertension)	BP <140/90 mmHg	4.2
					ARB	7649 (42)			
					CCB	7596 (42)			
VHAS	Italy	Age 40-65 years, BP ≥160/95 mmHg	Secondary hypertension, recent stroke or transient ischaemic attack, coronary artery disease, peripheral artery disease, arrhythmias, HF, renal or hepatic dysfunction, hyperuricaemia, hypokalaemia, type 1 diabetes, familial dyslipidaemia, severe illness	Not specified (published in 1997)	All	1414 (51)	ACEI	Sitting DBP ≤90 mmHg; ≤95 mmHg if lowered by ≥10% from baseline values	1.7
					CCB	707 (50)			
					Diuretic	707 (52)			

ACEI, angiotensin converting enzyme inhibitor; AF, atrial fibrillation; ARB, aldosterone receptor blocker; BMI, body mass index; BP, blood pressure; CCB, calcium channel blocker; DBP, diastolic blood pressure; HCTZ, hydrochlorothiazide; HF, heart failure; SBP, systolic blood pressure

Data cleaning and harmonisation

The IPD that were obtained for each trial had to be cleaned and harmonised. Although data had been partially cleaned and harmonised prior to the start of my project, I had to complete the process before they were suitable to use in my analyses. Data harmonisation was particularly challenging for baseline variables and for outcomes, as those were not consistently and coherently reported in all trials, and data dictionaries were often unclear. Whenever there were discrepancies between the datasets that were shared with the collaboration and the information available in published articles, investigators were contacted for clarification. For missing data, investigators were also contacted to enquire about the possibility of providing those data. However, data were commonly unavailable, or investigators did not reply. In those circumstances, whenever possible, data were extracted from published reports or imputed using appropriate statistical methods as described in the chapters referring to individual studies (Chapters 5 and 7).

The most cumbersome data to harmonise were the adverse events because those were provided as lists of unstructured, free text notes. Although some trials had coded the adverse events, the coding system was specific for each trial and the lack of uniformity prevented merging codes provided by different trials. After an in-depth search for coding systems for adverse events in RCTs, I decided to use the Medical Dictionary for Regulatory Activities (MedDRA), which was developed by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use in 1990.[297] This rich and highly specific standardised medical terminology was created to facilitate sharing regulatory data related to

medicinal products among multiple stakeholders involved in pharmaceutical research worldwide. In addition to the original English master, there are approved translations of the MedDRA in several languages. However, each MedDRA term has an associated eight-digit numerical code that remains the same irrespective of the language. This simplifies coding in native language and hence increases the accuracy and precision of assigning codes, whilst at the same time ensuring easy data sharing internationally. In addition, the MedDRA subscription, which includes training and support, is available free of charge to academic institutions and government regulators. This allowed me to undertake some of the e-learning courses, which gave me an overview of the structure and scope of the MedDRA and equipped me with the skills required to code using the MedDRA browser. Finally, the MedDRA has the added advantage of offering standardised MedDRA queries, which are powerful tools to aid safety signal detection. This explains why the Food and Drug Administration endorsed the MedDRA as the coding system for adverse events in applications for marketing authorisation of medicinal products.[298] For all those reasons, I decided to use the MedDRA terminology to harmonise data related to adverse events in the BPLTTC.

From a technical perspective, the MedDRA follows a very logical structure, with five hierarchical levels arranged from very specific to very general. The Lowest Level Terms (about 70,000) are the most specific and reflect observations that may be reported in practice. The Preferred Terms sit at the next level and provide distinct descriptors (single medical concepts) for a symptom, sign, disease, diagnosis, investigation, or procedure. Each Lowest Level Term is linked to only one Preferred Term, but the latter can include several Lowest Level Terms (e.g., synonyms or lexical variants). Preferred Terms are grouped together into High Level

Terms according to their relatedness based on anatomy, pathology, physiology, or aetiology. High Level Terms that are related to each other, according to the aforementioned criteria, are grouped into High Level Group Terms. System Organ Classes, which are the most general terms, are groupings by aetiology, manifestation site or purpose. Each Lowest Level Term can be linked to several System Organ Classes, but only one is considered the primary System Organ Class to avoid double counting when analyses are run at the top level. This highly structured hierarchy allows analysing adverse events at different levels according to the intended degree of detail.

A total of ten trials provided data on adverse events, with free text lists that ranged from about 100 to over 10,000 distinct entries. I coded each entry manually using the Lowest Level Term descriptor that best matched the clinical record of the adverse event. I then applied the tool provided by the MedDRA browser to match the descriptor of the Lowest Level Term to the respective numeric code, and hence to the corresponding higher-level terms of the MedDRA hierarchy. **Figure 3.2** summarises the key steps in coding adverse events and provides two different examples of how I applied the terminology in practice.

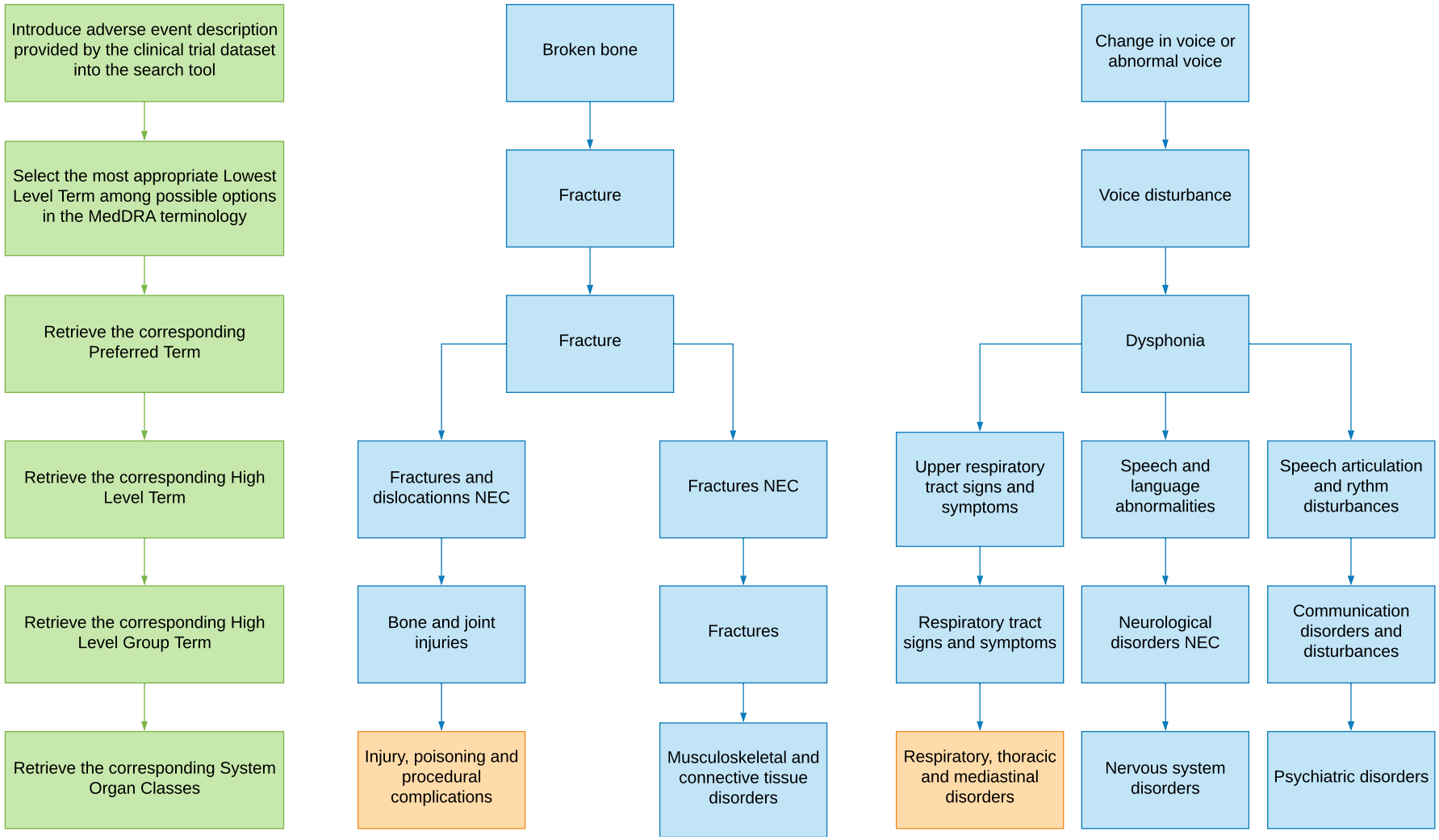

Figure 3.2 Application of the MedDRA hierarchy to code adverse events in the Blood Pressure Lowering Treatment Trialists' Collaboration

Highlighted in orange are the boxes corresponding to the primary system organ class to which each lowest level term would be allocated to.

Research governance and ethical considerations

As the BPLTTC does not have access to patient identifiable information, it is fully compliant with the Data Protection Act 1998 and the principles of the General Data Protection Regulation. Because the BPLTTC is hosted by the University of Oxford, it is also compliant with the institutional requirement for research governance and data management and security. The latest iteration of the BPLTTC was approved by the Oxford Central Ethics University Research Committee (OxTREC Reference: 545–14).

Chapter 4 Methods

This chapter discusses the theoretical underpinnings of the methodology I used to address my research questions, with a particular emphasis on IPD meta-analysis.

Many of the groups… are far too small to allow of any definite opinion being formed at all, having regard to the size of the probable error involved (Karl Pearson, 1904).[299]

Meta-analysis refers to the analysis of analyses. I use it to refer to the statistical analysis of a large collection of results from individual studies for the purpose of integrating findings. It connotes a rigorous alternative to the casual, narrative discussions of research studies which typify our attempts to make sense of the rapidly expanding literature (Gene Glass, 1976).[300]

Karl Pearson was probably the first to recognise that individual studies may fail to provide, by themselves, the evidence needed to make informed decisions. However, what we would nowadays call meta-analytic techniques were largely ignored in medicine for many years. It was only in 1976, that the psychologist Gene Glass coined the term "meta-analysis" to help make sense of the burgeoning literature that was rapidly becoming overwhelming in many medical fields. Since then, systematic reviews and meta-analysis have witnessed growing interest and development. This is well illustrated by the fact that a PubMed search for the word "meta-analysis" in the title or abstract resulted in 147,129 entries as of May 2020, thus reflecting the rapid increase in the number of published articles in the last decade (**Figure 4.1**). Over the years, the underlying methods and available software to aid implementation have substantially improved. In parallel, guidance on conduct and reporting of systematic reviews and meta-analysis has been published, and compliance with quality standards is now required by most peer-reviewed journals.[301-306]

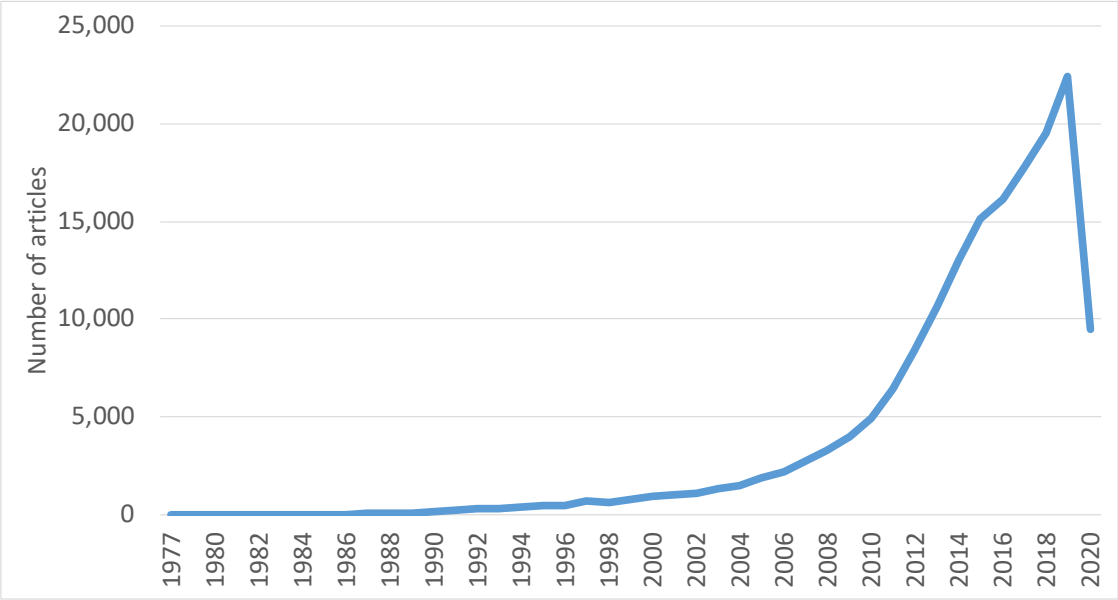

Figure 4.1 Cumulative number of articles found by searching for the term "meta-analysis" in the title or abstract of articles available on PubMed since inception until May 2020

Systematic reviews and meta-analysis

Systematic reviews are an objective and reliable way of synthesising evidence from multiple studies on the same subject.[306] They are distinguished from narrative reviews by the fact that they follow a well-defined sequence of steps. The first step is to define a clear research question. Once this is decided, the next step is to conduct a systematic literature review to identify all potential studies of interest using a thorough search strategy. To avoid missing studies, and the bias that could eventually result from this, it is recommended that the search strategy includes electronic databases, such as Medline and Cochrane, as well as consultation with experts and exploration of grey literature databases. After retrieving all the potentially relevant studies, carefully chosen selection criteria are applied to select which studies are appropriate for including in the analysis. The process of selection usually consists of a

stepwise approach, in which titles and abstracts are screened first, and then full reports are reviewed against inclusion and exclusion criteria that have been defined a priori. The last step involves analysing the final set of studies of interest in order to produce at least a qualitative summary of their findings. Whenever appropriate and feasible, systematic reviews culminate with a meta-analysis (from the Greek word “meta”, meaning “after” or “beyond”), which applies complex statistical modelling to combine the results of the individual studies in the form of a weighted average. Therefore, meta-analyses enhance the value of systematic reviews by providing a quantitative summary of their findings, which can be particularly relevant when there are conflicting results from small and/or underpowered studies.[306] The evidence thus generated is meant to be generalisable to a larger population, at least in terms of average to encompass random effects.

Individual participant data versus aggregate data meta-analysis

Systematic reviews are often based on aggregate data, which represent a summary of the IPD from each study, which can be extracted from published reports or obtained directly from authors. Problems arise when data are poorly reported (e.g., without decimals) or incompletely reported (e.g., without a measure of variability), not available, derived or presented differently across studies, or more likely to be reported if statistically significant (i.e., selective reporting).[307] In addition, when there is substantial heterogeneity, a weighted average may no longer be appropriate or, indeed, clinically meaningful. In these situations, exploring potential sources of heterogeneity, that is, identifying whether there is effect

modification across clinical subgroups, is critical. Furthermore, aggregate data is prone to cluster or ecological bias because study-level associations may not accurately represent subject-level associations, which cannot be accounted for in aggregate data meta-analysis.[307]

In this context, IPD meta-analysis emerged as a promising solution to overcome the limitations of aggregate data meta-analysis, and their merits are becoming more widely appreciated in different fields.[302,308-310] The advantages of IPD meta-analysis, in comparison with aggregate data meta-analysis, are summarised in **Table 4.1**, and among them there are some that deserve further ellaboration.[311] First, it is possible to investigate effect modification and adjust for potential confounders at both participant level and study level, thus avoiding the aforementioned cluster bias.[312] Second, access to raw IPD improves data quality to standardise definitions and analyses, to combine studies with different follow-up times, to analyse all outcomes (even those not commonly reported), and to obtain data for all participants.[313] Third, IPD enable handling missing data more appropriately, for instance by applying multiple imputation, thereby minimising the risk of bias and loss of power.[314] For all those reasons, IPD meta-analyses offer more robust effect estimates than aggregate data meta-analyses, particularly when effect sizes are small.[315] In addition, IPD meta-analysis typically rely on consortia of studies, and collaboration between investigators can lead to more complete identification of studies, as well as broader interpretation and endorsement of findings.

Table 4.1 Advantages of individual participant data meta-analysis[1]

Trial inclusion	Asking the IPD collaborative group (of trialists and other experts in the clinical field) to supplement the list of identified trials
	Clarify trial eligibility with trial investigators
Data quality	Include trials that are unpublished or not fully reported
	Include unreported data
	Check the integrity of trial IPD and resolve any queries with trial investigators
	Derive standardised outcome definitions across trials
	Derive standardised classifications of participant characteristics
	Ensure all trials use the same covariates, where appropriate
	Update follow-up of time-to-event outcomes beyond that reported
Risk of bias	Clarify trial design, conduct, and analysis methods with trial investigators
	Check risk of bias of trial IPD and obtain additional data if necessary
Analysis	Analyse all important outcomes
	Determine validity of analysis assumptions with IPD
	Derive measures of effect directly from the IPD
	Use a consistent unit of analysis for each trial
	Apply a consistent method of analysis for each trial
	Conduct more detailed analysis of time-to-event outcomes
	Investigate treatment modification at individual level and trial level
	Conduct more complex analyses not (usually) possible with aggregate data, such as multiple interactions or adjustment for confounding factors at individual level
	Use nonstandard models or measures of effect
	Use IPD for secondary clinical questions or surrogate outcomes
	Run sensitivity analyses using alternative methodology
Interpretation	Discuss the implications for clinical practice and research with a multidisciplinary team of collaborators, including trial investigators who supplied the data

[1]Adapted from Tierney et al.[316]

Despite the merits of IPD meta-analysis, the challenges of gathering, cleaning, and harmonising data cannot be overlooked.[317] Indeed, uncooperative investigators and incomplete or inconsistent raw data can hinder the success of such a resource-demanding project as an IPD meta-analysis. Therefore, when obtaining IPD is infeasible, methods that combine IPD with aggregate data can be used to include non-shared studies and hence provide an unbiased summary of the evidence available.[318] It is worth noting, though, that the aggregate data collected should be parameter estimates, with respective standard errors, rather than tabular data to allow for desired adjustments and to account for censoring. In addition, combining IPD and aggregate data is particularly important when the availability of IPD is related to study findings as this could result in selection bias.[306] Prospectively designed IPD meta-analyses have the potential to overcome some of the data-related challenges commonly faced by IPD meta-analyses.[319] Indeed, prospective meta-analyses select studies before their results are known, thus providing a unique opportunity for standardisation of data collection across trials, using the same instruments and the same definitions for all outcomes and subgroups, which in turn facilitates pooling data in meta-analyses.[306]

One stage versus two-stage approaches for individual participant data meta-analysis

IPD datasets have a two-level structure as participants are clustered in studies, which means that statistical models need to take into account the correlation between observations coming from the same study. This two-level structure of the data poses challenges to

traditional regression models and, over the past few decades, two alternative approaches have been proposed for summarising relative treatment effects – the one-stage and the two-stage approaches.[320] The relative merits and pitfalls of those two approaches are summarised in Table 4.2.

Table 4.2 Comparison between one and two-stage approaches for individual participant data meta-analysis

	One-stage approach	Two-stage approach
Usage	Less common	More common
Statistical modelling	Advanced expertise needed to develop one-stage models	More intuitive and simpler, as it is applied exactly as for aggregate data meta-analysis
Effect modification and interactions	More flexibility and power to investigate effect modification and treatment-covariate interactions; possibility to model individual and trial-level covariates in a single model; possibility to adjust for trial and individual-level variables (e.g., confounders)	Trial and individual-level heterogeneity is, by nature, investigated in different stages; less capability to investigate multiple interactions
Combination with aggregate data	Possible but complex	Relatively straightforward in the second stage provided outcome measures are consistent between studies
Individual studies	Estimates for individual studies are not generally provided. They could be but would not be the same as in reports of the individual trials.	Estimates for individual studies are reproduced and presented in a comparative fashion (through forest plots).
Heterogeneity	No standard method to characterise heterogeneity between studies	Heterogeneity can be assessed using methods typically applied in aggregate data meta-analysis

The most common and conceptually simpler of them is the so-called two-stage approach, which is in essence similar to aggregate data meta-analysis. In this approach, IPD are first analysed separately in each study, using identical methods, to produce study-specific estimates of relative treatment effect and possibly treatment-covariate interactions. The individual study estimates are then pooled in a second stage by calculating a weighted average, in which the weight of the estimates for the single parameters coming from the different studies are usually based on the inverse of their variances, because this gives the smallest possible variance for the pooled estimate.

Depending on the nature of the interventions and populations, it may be reasonable to assume that a single treatment effect is common to all studies, and hence differences between studies arise solely due to sampling variation. This is called a fixed effect meta-analysis[321] and its basic model can be specified as follows:

$$\hat{\beta}_j \sim \mathcal{N}(\beta_{IV}, V(\hat{\beta}_j))$$

Where $\hat{\beta}_j$ are the treatment effect estimates and $V(\hat{\beta}_j)$ the respective error variances for trial j = 1, …, J; and β_{IV} is the common treatment effect.[322] However, the assumption that trials share a common treatment effect is often unrealistic as there are multiple factors that can lead to heterogeneity between trials, including small sample bias, treatment-covariate interactions, selective drop-outs or competing risks, and differences in study design, case-mix or follow-up.[323-325]

Therefore, it is usually recommended to adopt a random effects model in two-stage meta-analyses, which can be specified as follows:

$$\hat{\beta}_j \sim \mathcal{N}(\beta_j, V(\hat{\beta}_j))$$

$$\beta_j \sim \mathcal{N}(\beta_{RE}, \tau^2)$$

In random effects models, $\hat{\beta}_j$ (i.e., treatment effect estimates) are allowed to vary due to sampling error within studies (reflected by $V(\hat{\beta}_j)$) and due to heterogeneity in the true treatment effects across studies (reflected by (τ^2)). The latter means that the actual effect within each study (β_j) is assumed as a random draw from a certain distribution and hence β_{RE} can be interpreted as the average effect across studies.[326]

As a result of assuming between-trial heterogeneity, the confidence intervals for treatment effect estimates are wider than in fixed effect meta-analysis, except when there is no between-trial heterogeneity, in which case the intervals are the same. The wider confidence intervals reflect the uncertainty about the extent to which the observed treatment effects represent the true treatment effects.[327-329] The between-trial heterogeneity or variance is represented by τ^2, and it can be estimated using several methods, including Restricted Maximum Likelihood estimation, which seems to outperform other methods.[330-333] However, when the outcome is rare, studies are small or less than ten in total, none of the currently available methods provides reliable estimates of heterogeneity.[334]

When between-study heterogeneity is non-trivial, it is appropriate to explore potential sources of heterogeneity, usually through subgroup analyses and/or meta-regression. These assess the relationship between, respectively, categorical and continuous study-level covariates and treatment effect estimates.[335] However, in most instances, it is of interest to investigate treatment-covariate interactions at participant level, rather than study level. Although participant-level interactions are preferably estimated directly using one-stage models, a two-stage approach can be used, in which interaction coefficients are initially estimated separately for each study and then combined using standard meta-analysis models.[323,336] However, this is a cumbersome process when interactions of several degrees of freedom are involved, that is, when either of the constituent terms has more than two levels.

The one-stage approach, albeit more complex and thus less commonly used than the two-stage approach, provides a more in-depth understanding of the data by estimating within-study and between-studies relationships simultaneously.[337] However, this raises the question as to how to account for clustering of participants within studies. Whilst in the two-stage approach, separate treatment effects are estimated for each trial, in the one-stage approach IPD from all studies are analysed concurrently using a single statistical model. Several methods can be adopted to account for clustering of participants within studies in one-stage models, including frailty models, marginal models, or stratified models.[310,338,339] A detailed description of each model is beyond the scope of my thesis, but it is worth noting that stratified models require fewer assumptions and are easier to implement than other models, and hence they are the preferred modelling approach for meta-analysis of adequately powered trials.[340]

One of the key advantages of the one-stage approach is that it provides more robust estimates of effect modification or treatment-covariate interactions than a two-stage approach even when few studies are available.[341,342] This is achieved by including an interaction term in the one-stage model.[343] To disentangle within-trial from between-trials heterogeneity, it is useful to centre covariates by their mean values within trials, so that the participant-level interaction is estimated within each trial.[344] In addition, if there are differences in follow-up time between trials and treatment effects vary over time, the overall treatment effect will be estimated with high heterogeneity, which can be addressed by modelling time-dependent treatment effects. The one-stage approach can simultaneously estimate heterogeneity in baseline rates between participants within different studies, heterogeneity of treatment effects, and their correlation by including a random trial effect and a random treatment-by-trial interaction in the model.[345]

Despite the marked differences between one and two-stage meta-analysis, it has been consistently shown that they lead to similar results when identical model assumptions and methods are applied, particularly when estimating single treatment effects.[337] Nevertheless, the objective of the analysis, the characteristics of the data or the resources available may render an approach more appropriate or perhaps more feasible than the other.[346,347] For instance, the two-stage approach is more intuitive, conceptually simpler and less statistically demanding than the one-stage approach, yet it provides reliable and robust estimates of treatment effects.[337] Altogether those reasons underpin its widespread implementation in the medical literature. However, the two-stage approach may lead to bias in pooled effects, standard errors, between-study heterogeneity, and correlation between random effects

when few studies or few participants (or events) per study are available, or when statistical models cannot fully account for differences in follow-up time or time between recurrent events. Although methods to mitigate those issues have been described,[347] a one-stage approach is usually preferred because it offers greater flexibility for making the required assumptions and greater power to detect treatment-covariate interactions.

The two-stage approach is, though, useful for exploratory and preliminary data analyses, which serve to inform the development of one-stage models. The two-stage approach is also advantageous when IPD are only available for a subset of studies, because treatment effects and respective standard errors obtained from published reports can be combined together with estimates derived directly from IPD in the second stage. However, this requires that treatment effects are estimated using the same modelling approach for studies that contribute with IPD and aggregate data.[348] Although it is possible to combine aggregate data with IPD using one-stage meta-analysis, more advanced and less well validated models are required.[349] Finally, two-stage approaches provide estimates for individual studies exactly as they were published, with heterogeneity displayed in forest plots. This allows readers and investigators to have a more detailed understanding of the contribution of individual studies to the pooled estimate, which is not possible with one-stage models. Therefore, the research question as well as the data and resources available may render one or two-stage approaches more feasible and appropriate.

Time-to-event analysis in individual participant data meta-analyses of intervention studies

Although IPD meta-analyses have been used in myriad contexts and settings, they are especially useful for modelling time-to-event outcomes in intervention studies (e.g., RCTs) for several reasons.[322] First, they can take into account censoring, thus overcoming potential issues raised by differences in follow-up times between trials. Second, they allow survival measures to be computed directly from the data disaggregated at individual level, irrespective of differences in the outcomes available in published trial reports. Third, they allow time-varying intervention effects and effect modification (e.g., treatment-covariate interactions) to be explored with greater detail and accuracy.

RCTs almost always have time-to-event outcomes, which should be analysed using statistical models that take into account the time ($T_{surv,i}$) elapsed until participant *i*, *i, …, n* developed the event of interest. The probability of participant *i* to remain free from the event of interest for at least t time is given by the function $S(t) = \Pr(T_{surv,i} > t)$. However, not all participants will be followed up until they develop the event of interest, which means that for some of them $T_{surv,i}$>$T_{cens,i}$, where $T_{cens,i}$ is the time when that participant was censored, for instance due to drop-out, death or end of the trial. Therefore, the event status, typically defined *E = 0* if censured or *E = 1* if the event of interest was observed for participant *i*, will be calculated for the observed event-free or survival time $T_i = \min(T_{surv,i}, T_{cens,i})$. Time-to-event outcomes or survival times can be analysed using a variety of regression models that account for censoring in general, and specifically right censoring that can affect randomised

trials, as described above.[350] The most widely implemented of those regression models is the Cox proportional hazards model. As the name implies, this model assumes that the ratio between the hazards of two individual remains constant over time, and violation of this assumption almost inevitably leads to bias. The Cox model is considered a semi-parametric model because it makes a parametric assumption regarding the effect of the predictors or covariates on the hazard function, but it makes no assumption about the nature of the hazard function $\lambda(t)$ itself (i.e., the baseline hazard is not specified).

Even in the context of RCTs, in which the distribution of covariates (i.e., potentially known and unknown confounders) is balanced between arms, other than due to the play of chance, the inclusion of treatment-covariate interactions in the Cox model should be considered. Indeed, the effect of an intervention may change over time as a result of the influence of covariates. For instance, if some covariate confers a higher risk for the outcome and the intervention is protective, it is expected that the proportion of patients with that baseline covariate will decline over time, and this decline will be faster in the control than in the intervention arm. Even if initially the distribution of the covariate was balanced between treatment arms, this will not hold true throughout follow-up. Therefore, the unadjusted treatment effect will tend towards the null (i.e., hazard ratio of one), thus violating the proportional hazards assumption. The unadjusted treatment effect represents the marginal intervention effect. The latter is the average intervention effect for the entire population across all time points, which means it depends on the duration of follow-up. The unadjusted treatment effect may not reflect the conditional treatment effect, that is, the effect of treatment in a patient with a certain profile of baseline covariates, which may be potential

treatment modifiers. Those variables need to be included in the model to estimate a conditional treatment effect. The choice between a marginal or a conditional model depends on the purpose of the analysis. Of note, two-stage models inherently lead to conditional treatment effect estimates, whilst one-stage models are more flexible as they allow estimating conditional and marginal treatment effects.[347,351]

The Cox regression model is the most widely used model for time-to-event analysis in intervention studies due to its good statistical properties, particularly the fact that the shape of the baseline hazard does not need to be specified to estimate hazard ratios for covariates. However, there are two instances in which Cox models are surpassed by other survival models. First, when the assumption of proportional hazards over time does not hold, when it is preferable to adopt models where proportionality occurs in another scale. Second, when the aim is to estimate absolute survival probabilities, it is necessary to define a distribution for the baseline hazard using a fully parametric model.[352]

Meta-analyses of IPD have inherently a hierarchical structure with patients clustered within trials. Initially, I tried to perform a random effects meta-analysis by fitting mixed-effects Cox regression models that accounted for heterogeneity across trials.[310,347,348] However, those models were not successfully implemented due to very small between-trial variances, which suggested that assuming a fixed treatment effect was likely reasonable. This was further supported by the low heterogeneity observed in two-stage meta-analysis models, which provided similar estimates irrespective of whether fixed effect or random effects were assumed. Nonetheless, due to differences in settings and patient populations, the trials

included in my meta-analyses were likely to have different baseline hazard functions. It was more appropriate to adopt a less restrictive assumption of proportional hazards within each trial, rather than an overall baseline hazard function as in classical Cox regression models. Therefore, I implemented Cox regression models stratified by trial, which accounted for censoring of time-to-event data and for clustering of subjects within trials by assuming different baseline hazards for each trial.[325]

In the meta-analyses that I carried out, and describe in detail in Chapters 5, 6 and 7, I used two stratified Cox regression models. Model (1) was the basic model, which included (i) a term for treatment arm (intervention versus comparator), (ii) a term for the difference in SBP reduction between arms aggregated at trial level, and (iii) an interaction term between treatment and difference in SBP reduction. The inclusion of terms (ii) and (iii) aimed to account for differences in intensity of SBP reduction across trials. This is important because the different intensities of SBP reduction are assumed to be the main drivers of heterogeneity of treatment effects across trials.[4]

Different methods have been used to standardise treatment effect estimates for the intensity of SBP reduction or cholesterol lowering in aggregate data and two-stage IPD meta-analyses, albeit not in previous BPLTTC meta-analyses.[5,353] However, in one-stage IPD meta-analysis, the most appropriate method is to include this standardisation as part of the main model, by using regression models adjusted for the intensity of SBP lowering. Moreover, this adjustment was performed using trial-level SBP reduction, calculated as the difference between intervention and control arms in the difference between SBP at approximately one-year and

SBP at baseline for each trial, to maintain the randomised nature of comparisons. The one-year time point was chosen because preliminary analysis showed that BP decreased linearly up to one year and then remained relatively stable afterwards in both trial arms. Although treatment effects are usually standardised by 10-mmHg reduction in SBP,[5,354] in my studies I standardised treatment effects by a more realistic 5-mmHg reduction in SBP, as this was closer to the average intensity of SBP lowering in the trials included in my meta-analyses. Whenever I wanted to investigate interactions between treatment and patient-level characteristics, for instance AF at baseline or number of cardiometabolic diseases at baseline, I included an additional interaction term in the model, as illustrated in model (2) below. A more detailed description of the actual application of those models is provided in the respective chapters.

In those stratified Cox models, for the i^{th} individual in the j^{th} trial ($i = 1 \dots n_j$, $j = 1 \dots j$), the hazard function at time *t* is estimated as follows:

$$\lambda_{ij}(t) = \lambda_{0j}(t)\exp\left(\beta_1\chi_{1ij} + \beta_2\chi_{2ij}\right) \quad (1)$$

$$\lambda_{ij}(t) = \lambda_{0j}(t)\exp\left(\beta_1\chi_{1ij} + \beta_2\chi_{2ij} + \beta_3\chi_{3ij}\right) \quad (2)$$

where λ_{0j} is the baseline hazard function in the j^{th} trial; the fixed parameter β_1 indicates the log hazard ratio of the event in intervention group relative to the control group, which is assumed to be identical across trials; the parameter β_2 represents the coefficient for the interaction between treatment arm and SBP reduction aggregated at trial level; and the parameter β_3 represents the coefficients for the interaction between treatment and

covariates that were investigated in different studies (e.g., AF at baseline, number of diseases at baseline).

Missing data in individual participant data meta-analyses

Types and mechanisms of missing data

Missing data are ubiquitous in clinical datasets, including electronic health records, registries of population-based cohorts, and clinical trial records. Therefore, missing data is an issue that affects IPD meta-analysis, in which, due to the hierarchical structure of the data, it can occur at two levels. First, there may be sporadically missing data, when data are missing at participant level because one or more variables are only partially reported in some of the studies.[355] Depending on the underlying mechanism, those missing data can be of three types: missing completely at random, when the probability of missingness is unrelated to observed and unobserved values; missing at random, when, given observed data, occurrence of missing values is independent of the actual values; and missing not at random, when given observed data, occurrence of missing values still depends on the actual values. Second, there is systematically missing data, when data are missing at study level because one or more variables have not been collected in some studies, perhaps due to financial constraints or different study designs. Therefore, taking into account the hierarchical structure of IPD datasets and the underlying mechanisms for missing data is critical to avoid biased results.

In my studies, I was confronted with both types of missing data. On one hand, baseline characteristics, such as sex, age or baseline diseases were sporadically missing for some patients in one or more trials. Considering the randomised nature of the trials, it seems reasonable to assume that data were missing completely at random or at least missing at random for those variables. On the other hand, some variables were systematically missing in one or more trials. This was often the case for AF at baseline, which resulted in the exclusion of a substantial proportion of the trials (twenty-eight out of fifty) from that meta-analysis. Likewise, data on history of cerebrovascular disease, ischaemic heart disease and diabetes mellitus were missing for the entire population of some trials because data collection for those variables was not part of the study design, or data were not shared with the collaboration.

Strategies to deal with missing data

The detrimental consequences of missing data cannot be overlooked. Not only do they cause loss of information, and hence can reduce statistical power, but they may also cause bias in parameter estimates and hence potentially lead to misleading inferences. In consequence, there has been increasing interest in finding methods to handle missing data. Simple imputation, which consists in replacing a missing value with a single value (e.g., mean, median or mode), emerged as an attractive approach to handle missing data, but it gave the same weight to observed and imputed data, thus leading to underestimation of standard errors.[356]

Multiple imputation was developed as an efficient, yet practical, alternative to overcome that limitation.[357] The elegantly simple idea behind it is the creation of *n* imputed datasets which together represent the expected distribution of missing data, given the observed data. Once those *n* datasets are created, a substantive model can be fitted to each of them and the results pooled together according to Rubin's rules, which are automatically applied in standard statistical software.[358]

Since Rubin's landmark paper, several methods of multiple imputation have been developed, each with its own advantages and disadvantages. Multiple imputation is a procedure in which a certain number of imputations are randomly drawn from a distribution conveniently derived from the data, taking into account the relationship between variables and the relationship of each variable with the missing patterns in the remaining ones.[356] As imputations are random, and not deterministic, a missing value may be replaced with a different value in each of the completed datasets, which means that each dataset is different. Therefore, an essential feature of multiple imputation is that the different imputations are stochastically independent. In addition, in order for Rubin's variance combination to hold precisely, the imputation model and the analysis model need to be congenial. This means that there should be one joint distribution for the data from which both the imputation and the substantive model can be derived by appropriate conditioning. Uncongenial models can be of two types:

1. The imputation model is simpler than the analysis model, in which case some variables present in the analysis model are not present in the imputation model. This should be

avoided because it invalidates Rubin's rules and can lead to inconsistent parameter estimates;

2. The imputation model is more complex than the analysis model, in which case some variables present in the imputation model are not used in the analysis model. This situation is not as problematic because there is at least one congenial imputation model nested within the more complex imputation model. Although Rubin's rules in this case can overestimate sampling variability of the multiple imputation estimators, this is typically preferable to losing auxiliary variables that can provide additional information to imputation of missing data.

In general, inference is valid with a finite number of imputations, and a relatively small number of imputations is often sufficient to obtain accurate estimates. However, this depends on the proportion of missing data and on the required precision of the estimates. In addition, multiple imputation provides valid results only when the hypothesis of missing at random holds. When data missing at random cannot be assumed, that is, when the probability of data being missing depends on the unobserved data, conditional on the observed data, multiple imputation is theoretically unsound. In practice, whether data is missing at random or not is difficult to ascertain due to the nature of the missing data. Nonetheless, even when it is impossible to confirm whether the assumptions needed for multiple imputation are valid, or those assumptions are actually not met, simulation studies suggest that multiple imputation still surpasses complete-case analysis or the use of missing data indicators.[359] An important consideration to bear in mind, though, is that multiple

imputation can reduce statistical power in comparison to complete-case analysis, because it appropriately accounts for the uncertainty associated with the imputation itself.

The aforementioned hierarchical structure of IPD datasets presents additional challenges to handle missing data. Simulation studies have shown that simple imputation produces biased estimates and seriously underestimates cluster level variances and overestimates individual level variances.[360] In contrast, multilevel multiple imputation provides valid point estimates and just slightly overestimated standard errors, in comparison to those obtained from complete data.[361] Furthermore, multiple imputation can handle both sporadically and systematically missing data by allowing for heterogeneity between studies.[362] There are several models, and associated algorithms, which can be used to impute missing data, including the joint multivariate normal model, fitted by Markov Chain Monte Carlo methodology.[363] The main advantage of this modelling approach is that it extends naturally to hierarchical data structures, such as those of IPD meta-analysis.[364] Joint multivariate normal models can be used for multilevel multiple imputation of both categorical and continuous variables in IPD datasets using appropriate statistical software.[364] I decided to use this model because it had shown to perform well in hierarchical data structures, and I was able to obtain valid estimates of the true values in simulation studies using my own data. The main challenges were the fact that it was not straightforward to implement it, and it was extremely slow for imputing categorical variables. Further details on how I actually implemented multilevel imputation models are provided in Chapters 5 and 7.

Cluster analysis

Cluster analysis is the process by which data objects are classified into homogeneous groups according to their characteristics in such a way that objects in the same cluster are very similar and objects in different clusters are quite distinct.[365] Data clustering is often confused with classification, in which objects are assigned to predefined classes. The key difference between the two is that in data clustering, the classes are not defined a priori but depend on the relationships that are identified between the individual data elements themselves.

Distances and similarities play an important role in cluster analysis and are in general reciprocal concepts.[366] Often, similarity measures and similarity coefficients are used to describe quantitatively how similar two data points or clusters are: the greater the similarity coefficient, the more alike and closer the two data elements are. Every clustering algorithm is based on an index of similarity (or dissimilarity) between data points.[367] If there is no measure of similarity or dissimilarity between pairs of data points, then no meaningful cluster analysis is possible.

In general, clustering algorithms can be categorised into hierarchical algorithms and partitional algorithms. Hierarchical algorithms can be further classified into divisive hierarchical algorithms and agglomerative hierarchical algorithms. In the former, the algorithm starts with one large cluster containing all data points in the dataset and gradually splits them into clusters; in the latter, the algorithm starts with many clusters each containing one data point and gradually merges them into larger clusters. However, hierarchical

clustering is infeasible in large datasets due to computational power. Therefore, partitioning algorithms, which create a one-level non-overlapping partition of the data points are more suitable for large datasets.[368] The k-means algorithm is probably the most widely partitional technique. The k-means algorithm requires the number of clusters, k, as input, which can be chosen randomly, using the output of a hierarchical clustering technique, or using other criteria. Once the initial clusters are defined, the centroid of each cluster is calculated. In the next iteration, the distance of each individual from the cluster centroids is calculated, and each individual is moved to the cluster whose centroid is closest. Then, cluster centroids are recalculated, and the same process is repeated until no individual is moved between clusters. The final solution thus depends on the initial centroids. In my study, I used hierarchical clustering to define the initial number of centroids and then ran the clustering algorithm to test possible options for the final number of clusters.

Cluster analysis has two important caveats.[369] The first is defining the ideal number of clusters. Ideally, the optimal clustering of individual data elements could be found by performing an exhaustive search of all possible partitions, which would involve repeating the clustering algorithm using different values of k and then comparing the results according to some criterion. However, this is not computationally feasible, particularly when using large datasets. Heuristic algorithms, such as k-means, provide a suitable alternative by restricting the search. Nonetheless, they are not guaranteed to reach the solution that maximises the compactness of the clusters (i.e., that minimises intra-cluster correlation) and simultaneously maximises the separation between distinct clusters. Those concepts are often illustrated

graphically by the so-called elbow method and average silhouette method, respectively, which can be used to determine the optimal number of clusters.[370,371]

The second is defining the variables to be included in the model. Striking the right balance between the number of variables and the number of individuals included in the analysis can be problematic. If the number of individuals is small relative to the number of variables, the variance associated with using many variables offsets the classification benefit accrued by including them in the analysis. There are several methods for choosing the best subset of variables.[368] However, most of them depend on distances, and these are modified by changing dimensionality, which hinders comparison between two clustering classifications based on different numbers of variables. In this scenario, a new criterion called CritCF has been recently developed to rank partitions, taking into account simultaneously the number of variables and the number of clusters.[372] Although it has been shown to provide valid results, it does not exhaustively test all possible combinations for the number of variables and clusters. Therefore, there is no guarantee that the global optimum is actually achieved. In any case, it seems the best criterion currently available and hence the combination of k and the set of variables that gives a higher CritCF tends to be chosen as the final model.

In my study, I defined the variables to be included in the clustering algorithm a priori because I was interested in clustering participants according to a specific and restricted set of baseline diseases. Therefore, the issue of defining the ideal number of variables to be included in the model did not apply to my study. Nevertheless, I still had to determine the ideal number of clusters, and the CritCF metric was instrumental in achieving that.

Chapter 5 Blood Pressure and Risk of Atrial Fibrillation

The broad theme of this chapter is the effect of BP lowering on the risk of AF. It describes the IPD meta-analysis of RCTs that I undertook to investigate whether BP lowering reduced the risk of developing AF.

An abstract of this research has been accepted for presentation at the European Society of Cardiology Congress in September 2020.

Abstract

Background and Aims

Although observational studies have suggested an association between elevated BP and increased risk of AF, randomised evidence on the effects of pharmacological BP lowering on the risk of AF remains limited. Therefore, this study aimed to investigate the effects of pharmacological BP lowering on the risk of new-onset AF overall and according to baseline risk for AF, baseline SBP and drug class.

Methods

IPD were extracted from trials with over 1,000 person-years of follow-up that had randomly assigned patients to different classes of BP lowering drugs, BP lowering drugs versus placebo, or more versus less intense BP lowering regimens. The effects of BP lowering on the risk of new-onset AF were estimated using one-stage IPD meta-analyses based on Cox proportional hazards models stratified by trial, assuming a fixed treatment effect. Participants were split into thirds of baseline risk for new-onset AF using an internally derived predictive model.

Results

Twenty-one trials were included with a total of 194,041 patients, in whom 6,357 new-onset AF events were recorded. The hazard ratio for new-onset AF was 1.01, 95% confidence interval [0.95 to 1.07] per each 5-mmHg reduction in SBP, and meta-regression suggested that treatment effects were similar irrespective of the intensity of SBP reduction. Overall, patients were at low risk for AF (median 2.3%, interquartile interval (IQI) [1.2% to 3.4%] at five years), and there was no evidence of heterogeneity in treatment effects across thirds of AF risk or across 10-mmHg strata of baseline SBP. There was also no clear evidence that

treatment effects differed between RAAS inhibitors and CCBs in comparison with placebo and/or standard treatment.

Conclusions

In this relatively low-risk population, pharmacological BP lowering, irrespective of its intensity or drug class used, did not reduce the risk of new-onset AF. Further research is warranted to better understand whether the same would hold true in high-risk populations, such as individuals with increased genetic susceptibility.

Background

AF is a major public health concern due to its growing incidence and prevalence in the ageing population[74] and its association with cardiovascular events.[373,374] Hypertension doubles the risk of developing AF[375] and accounts for more cases of AF than any other risk factor.[376] Although observational studies have demonstrated that elevated BP, even below the hypertensive range, is independently associated with incident AF,[377-381] whether BP lowering treatment can effectively reduce the risk of AF remains uncertain.

Population-based studies reported that BP control in patients with hypertension was associated with a lower risk of incident AF,[382] and the association was even greater for RAAS inhibitors, in comparison to other antihypertensive drug classes.[383] However, observational studies cannot accurately assess treatment effects due to the possibility of residual confounding. Randomised evidence is sparse, and thus far has not clearly supported the findings from observational studies.[384-388] Indeed, a meta-analysis of RCTs of RAAS inhibitors estimated an overall 18% risk reduction in new-onset AF, but this resulted from combining a 43% significant risk reduction in HF trials with a 6% non-significant risk reduction in antihypertensive trials.[389] A more recent and larger meta-analysis confirmed that BP lowering reduced the risk of new-onset AF overall by 10%, irrespective of the drug class used.[90] However, that overall risk reduction was driven by a 25% risk reduction in HF patients, as there was no significant effect in patients free from heart disease at baseline.

In addition, previous aggregate data meta-analyses lacked information on individual participants and, hence, were unable to explore modification of treatment effects by

important patient features, such as baseline BP, risk for AF or intensity of treatment. For instance, heterogeneity in treatment effects between trials might be partly explained by variations in trial-level risk for AF, but cluster bias cannot be excluded in aggregate data meta-analysis.[90] As evidence is accruing on the importance of investigating heterogeneity of treatment effects in RCTs, and their meta-analyses, it is crucial to explore how the balance of risks and benefits of treatment varies according to baseline risk for AF.[91]

Considering the conflicting and limited evidence currently available from both observational studies and RCTs, contemporary guidelines issued cautious recommendations about BP lowering for the prevention of new-onset and recurrent AF, emphasising the ongoing uncertainty and need for further evidence.[102] Therefore, I aimed to pool IPD from large RCTs of BP lowering treatment to investigate the effect of BP lowering treatment on the risk of new-onset AF overall and according to baseline risk for AF, baseline SBP and drug class.

Methods

Study design

I conducted an IPD meta-analysis of BP lowering RCTs that investigated treatment effects on the risk of new-onset AF according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses of IPD (PRISMA-IPD) guidelines.[302] I used data derived from the BPLTTC. A detailed description of the BPLTTC is provided in Chapter 3.[201]

For the purpose of this study, only trials that had collected information on AF as outcome were eligible for inclusion. Two types of trials were identified: (1) trials that reported AF as an adjudicated outcome, and (2) trials that reported AF as an adverse event. I excluded trials in which AF was not clearly reported as an outcome, or for which data regarding adverse events were not available. Trials for which IPD were not available in the BPLTTC were included only in supplementary two-stage meta-analyses. All data for baseline and follow-up variables were reported as per the definitions used in the primary trials.

Definition of outcomes

The primary outcome was incidence of new-onset AF reported as a pre-specified endpoint or detected as adverse event during follow-up (**Table 5.1**). AF events were detected by 12 lead electrocardiograms at baseline and then at scheduled visits during follow-up. Exploratory analyses for recurrent AF were also performed. Recurrent AF was defined as AF episodes recorded during follow-up in patients with a diagnosis of AF at baseline, irrespective of the rhythm in the electrocardiogram at baseline.

Table 5.1 Ascertainment of atrial fibrillation events in each of the included trials at baseline and during follow-up

Trial	Baseline	Follow-up	Type of event
ACCORD	12 lead ECG	12 lead ECGs every 2 years and close-out visit	Adjudicated endpoint
ADVANCE	12 lead ECG and medical history	12 lead ECG	Adjudicated endpoint and adverse event
ALLHAT	12 lead ECG	12 lead ECG every 6 months	Adjudicated endpoint
ASCOT	12 lead ECG and medical history	12 lead ECG	Adjudicated endpoint
BENEDICT	12 lead ECG	12 lead ECG	Adverse event
CAMELOT	12 lead ECG	Not reported	Adverse event
CAPPP	12 lead ECG	12 lead ECG	Adjudicated endpoint
CARDIO-SIS*	12 lead ECG	12 lead ECG yearly and at close-out visit	Adjudicated endpoint
COLM	12 lead ECG	12 lead ECG	Adverse event
COPE	12 lead ECG	12 lead ECG	Adverse event
DIABHYCAR	12 lead ECG	12 lead ECG	Adjudicated endpoint
EUROPA	12 lead ECG	12 lead ECG	Adverse event
EWPHE	12 lead ECG	12 lead ECG	Adjudicated endpoint
HIJCREATE	12 lead ECG	12 lead ECG	Adverse event
LIFE	12 lead ECG	12 lead ECG	Adjudicated endpoint
NORDIL	12 lead ECG	12 lead ECG	Adjudicated endpoint
ONTARGET	12 lead ECG	12 lead ECG every 6 months and at close-out visit	Adjudicated endpoint
SHEP	12 lead ECG	12 lead ECG yearly	Adjudicated endpoint
SPRINT*	12 lead ECG	12 lead ECGs every 2 years and close-out visit	Adjudicated endpoint
STOP HT-2	12 lead ECG	12 lead ECG	Adjudicated endpoint
SYSTEUR	12 lead ECG	12 lead ECG	Adjudicated endpoint
TRANSCEND	12 lead ECG	12 lead ECG every 6 months and at close-out visit	Adjudicated endpoint
VALUE	12 lead ECG	12 lead ECG yearly	Adjudicated endpoint

* The only data available were aggregated at trial level

Treatment comparisons

For the main analysis, intervention and control groups were compared. For placebo-controlled trials, the placebo arm was considered as the "comparator" and the active treatment was considered as the "intervention". For trials with two or more active treatment arms, the arm in which the achieved SBP reduction was greater was considered as the "intervention" and the other treatment arm(s) as the "comparator". This meant that intervention and control arms in this meta-analysis were not necessarily the same as those assigned by the original investigators in each trial. **Table 5.2** summarises the treatment comparisons considered in each trial and the difference in SBP reduction between trial arms.

Table 5.2 Treatment comparisons for primary analysis

Trial	Intervention	Comparator	SBP reduction (mmHg)
ACCORD	More intense treatment	Less intense treatment	12.4
ADVANCE	ACEI + Diuretic	Placebo	6.7
ALLHAT	ACEI or CCB	Diuretic	2.2
ASCOT	CCB + ACEI	BB + Diuretic	3.9
BENEDICT	ACEI or CCB or ACEI + CCB	Placebo	0.6
CAMELOT	ACEI or CCB	Placebo	7.3
CAPPP	ACEI	BB + Diuretic	1.3
CARDIO-SIS*	More intense treatment	Less intense treatment	4.7
COLM	ARB + CCB	ARB + Diuretic	0.3
COPE	CCB + ARB or CCB + BB	CCB + Diuretic	0.3
DIABHYCAR	ACEI	Placebo	2.1
EUROPA	ACEI	Placebo	4.9
EWPHE	Diuretic	Placebo	21.3
HIJCREATE	ARB	BB + Diuretic	1.0
LIFE	ARB	BB	1.1
NORDIL	CCB	BB + Diuretic	3.1
ONTARGET	ARB or ARB + ACEI	ACEI	1.9
SHEP	Diuretic + ACEI	Placebo	14.1
SPRINT*	More intense treatment	Less intense treatment	14.7
STOP HT-2	BB + Diuretic	ACEI or CCB	2.3
SYSTEUR	CCB	Placebo	9.4
TRANSCEND	ARB	Placebo	4.7
VALUE	ARB	CCB	2.4
Overall (mean)			3.6

* The only data available were aggregated at trial level

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta-blocker; CCB, calcium channel blocker; SBP, systolic blood pressure

Risk stratification

It was impossible to implement currently available risk scores for AF due to lack of data for certain variables in the BPLTTC dataset.[390-392] Therefore, I developed a new risk score that was specific to my study population. Participants were stratified to different levels of predicted risk for new-onset AF based on covariates and events recorded in the BPLTTC trials with data for the outcome AF. As I was interested in estimating the risk of new-onset AF, patients with a diagnosis of AF at baseline were excluded. I selected variables that had been identified as risk factors for incident AF and that were included in well-established AF risk scores.[390-392] Multilevel multiple imputation was used to impute missing baseline values for the covariates included in the model. I used a joint multivariate normal Bayesian model fitted by Markov Chain Monte Carlo analysis,[393] which assumed that the partially observed data followed a joint multivariate normal distribution.[394] All covariates were included as fixed effects, and trial was included as random intercept. The imputation model performed 2,000 burn-ins and generated five imputed datasets at least 1,000 iterations apart.

After imputation, unadjusted and multivariable analyses were performed using the imputed datasets, and model estimates were pooled using Rubin's rules.[395] Backward elimination, using a 0.1 significance threshold, was used to select the variables to remain in the final model. The predictive model was developed by fitting accelerated failure time models with frailty for trial, assuming a Weibull distribution for the baseline hazard and for the frailty term. The models were fitted to the entire population of the included trials (i.e., including both treatment arms), because internal whole trial models have been shown to be less sensitive

to bias introduced by overfitting, and to falsely identifying the existence of variability in treatment effect across the risk spectrum, in comparison to models based only on internal controls.[396] This predictive model (**Table 5.3**) was then used to estimate the risk for incident AF at five years, as this was close to the median follow-up of the included trials. The model had acceptable calibration (**Table 5.4**) and discrimination (c-statistic 0.80).[397] Participants were split into thirds of risk to estimate treatment effects, stratified by baseline risk for new-onset AF (**Figure 5.1**).

Table 5.3 Predictive model for atrial fibrillation

Simple factors	**Hazard ratio**	**Standard error**	**p-value**
Age	1.106	1.015	<0.001
Sex	0.226	1.372	<0.001
Systolic blood pressure (per 1 mmHg)	1.035	1.003	<0.001
Diastolic blood pressure (per 1 mmHg)	1.026	1.007	<0.001
Cerebrovascular disease	0.993	1.002	<0.001
Total cholesterol (per 1 mg/dL)	5.427	1.520	0.004
Body mass index (per 1 kg/m^2)	0.999	1.000	<0.001
Diabetes Mellitus	1.787	1.422	0.099
Interaction factors			
Age*Sex	1.016	1.004	<0.001
Age*Systolic blood pressure	1.000	1.000	0.010
Age*Cerebrovascular disease	0.984	1.005	0.003
Age*Diabetes Mellitus	0.984	1.005	0.001
Cerebrovascular disease * Total cholesterol	0.998	1.001	0.031
Total cholesterol * Diabetes Mellitus	1.002	1.001	0.003

Table 5.4 Actual versus predicted risk of new-onset atrial fibrillation at five years by tenths of risk

Risk tenths	Actual	Predicted
1	0.25	0.48
2	0.63	0.88
3	1.04	1.21
4	1.44	1.57
5	2.02	2.02
6	2.35	2.59
7	2.90	3.40
8	4.42	4.57
9	6.42	6.46
10	8.66	11.34

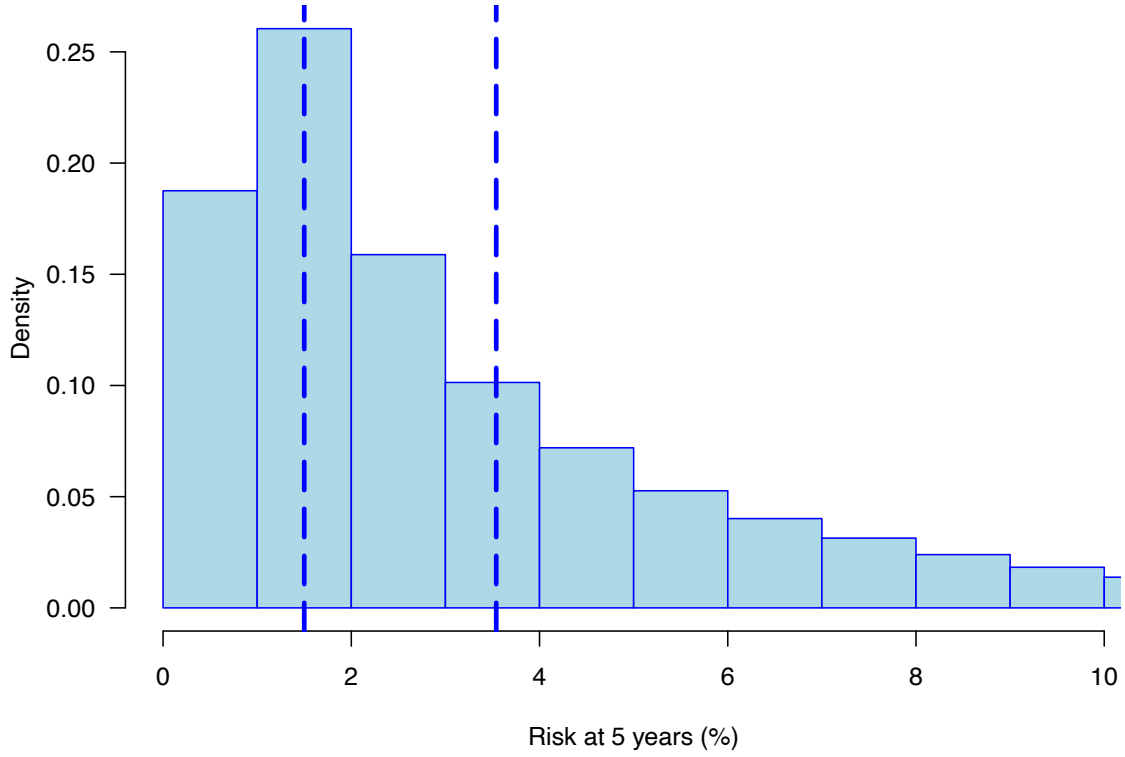

Figure 5.1 Distribution of risk for atrial fibrillation in the study population

Histogram displays the density distribution of the risk at five years for new-onset atrial fibrillation. The vertical lines represent the cut-off points used to stratify participants into thirds of risk.

Statistical analysis

My primary analyses aimed to address three questions:

1. Whether BP lowering treatment reduced the risk of new-onset AF overall;
2. Whether the effects of BP lowering treatment on AF varied according to baseline risk for AF or level of SBP;
3. Whether the effects of BP lowering treatment on AF varied by classes of BP lowering drugs.

Intention-to-treat analysis was adopted using the data provided by each trial, after internal quality checks had been carried out to ensure that data were accurate and transferred without error. To address my research questions, I used one-stage IPD meta-analysis models assuming a fixed treatment effect. For this, I implemented Cox proportional hazard models stratified by trial, after confirming that the proportional hazards assumption was not violated.[398] For questions (1) and (2), treatment effect estimates were standardised for a 5-mmHg reduction in SBP, in order to account for differences in intensity of BP lowering between trials. This was achieved by developing a meta-regression model with an interaction term for difference in SBP reduction and treatment (further details provided in Chapter 4).

Subgroup analyses were performed to investigate class-specific effects in trials that compared RAAS inhibitors or CCBs versus placebo and/or standard treatment (beta-blocker (BB) and/or diuretic). The number of trials and AF participants available for other drug class comparisons was insufficient to perform further subgroup analyses. Models for subgroup analysis

according to drug class were not standardised for BP lowering intensity in order to account for variations in BP lowering efficacy, tolerability, and BP-independent effects specific to different drug classes. Therefore, those models included only a simple term for treatment with a specific drug class.

Subgroup analyses were also performed for (1) AF status at baseline (i.e., for new-onset versus recurrent AF), (2) risk for new-onset AF at baseline (stratified into thirds of risk), and (3) baseline SBP (stratified into 10-mmHg categories). For those subgroup analyses, I used Cox regression models with additional terms for baseline AF status, risk for AF and SBP, and interactions between treatment, difference in SBP reduction and these potential moderators. These models described the effects of treatment on new-onset AF per unit of SBP lowering, for recurrent versus new-onset AF, each of the thirds of baseline risk for AF, or each 10-mmHg strata of baseline SBP. Wald tests were used to test for differences between subgroups. Hazard ratios (HR) with 95% confidence intervals (CI) were reported and results were presented using forest plots.

Supplementary sensitivity analyses were performed to (1) compare one-stage with two-stage approaches using both fixed effect and random effects models; (2) investigate the effect of including trials that reported AF as an adverse event rather than as an adjudicated endpoint; (3) assess the impact of including trials for which only aggregate data were available; (4) investigate whether standardisation for intensity of SBP reduction influenced treatment effect estimates; (5) investigate whether treatment effect was larger in trials in which the difference in SBP reduction between trial arms was equal or greater than 5 mmHg (i.e., to

further clarify whether treatment effects were related to the intensity of SBP reduction); and (6) assess the impact of standardising treatment effects by 5-mmHg reduction in SBP in subgroup analysis comparing different drug classes.

For the two-stage meta-analyses, Cox regression models were fitted for each trial. Then, the estimates from each trial were combined using fixed effect and random effects models with inverse variance weighting to calculate summary estimates with 95% confidence intervals. The analyses were standardised by 5-mmHg reduction in SBP using a method that had been applied in previous meta-analyses.[5,353] The log of the summary statistic of each trial was multiplied by 5/delta (and the variance by $(5/\text{delta})^2$), where delta was the difference between the mean SBP reduction in the intervention and control arms for each trial. Heterogeneity between studies was quantified using I^2 statistic (i.e., the percentage of total variation due to between-study differences) and Cochran's Q test with respective p-value. All p-values were calculated from two-tailed tests. Statistical analyses were performed using the packages "metafor", "lmer" and "survival" for R version 3.6.1.[399,400]

Results

A total of twenty-one trials provided data for the IPD meta-analyses (**Table 5.5**). Overall, those trials included 194,041 patients, in whom 6,357 new-onset and 516 recurrent AF events were recorded. IPD for two of the eligible trials were not available and thus those trials contributed only to sensitivity analysis combining IPD with aggregate data.[220,385] **Table 5.6** presents the baseline characteristics of the study population. The mean age of the participants was 65 years and 40% were female. The most common comorbidities were ischaemic heart disease (37.0%) and diabetes mellitus (34.8%). Mean baseline SBP and DBP were 154 mmHg (standard deviation (SD) 22) and 88 mmHg (SD 13), respectively. There were no patients with known HF at baseline.

Table 5.5 Baseline characteristics of the participants included in atrial fibrillation meta-analyses, stratified by trial

	ACCORD	ADVANCE	ALLHAT	ASCOT	BENEDICT		CAMELOT	CAPPP	COLM	COPE	DIABHYCAR
N	4733	11140	33357	19257	1209		1997	10985	5141	3293	4912
Age	62.73 (6.68)	65.77 (6.39)	66.88 (7.71)	63.00 (8.48)	62.34 (8.05)		57.67 (9.73)	52.06 (8.38)	73.62 (5.38)	63.65 (10.72)	65.05 (8.34)
Sex (Female)	2258 (47.7)	4735 (42.5)	15638 (46.9)	4515 (23.4)	570 (47.1)		526 (26.3)	5111 (46.5)	2488 (48.4)	1624 (49.3)	1480 (30.1)
SBP (mmHg)	139.00 (15.28)	145.02 (21.54)	146.27 (15.64)	164.01 (18.01)	150.89 (14.30)		129.08 (15.86)	160.72 (20.02)	157.99 (12.61)	153.91 (11.56)	145.43 (15.12)
DBP (mmHg)	75.79 (9.97)	80.65 (10.93)	84.02 (10.06)	94.65 (10.37)	87.48 (7.66)		77.48 (9.13)	98.95 (10.03)	86.97 (10.79)	88.80 (9.74)	82.28 (8.60)
AF	42 (0.9)	847 (7.6)	318 (1.0)	230 (1.2)	NA		NA	70 (0.6)	0 (0.0)	0 (0.0)	NA
IHD	4083 (86.3)	2380 (21.4)	8415 (25.4)	5284 (27.4)	NA		1857 (93.0)	201 (1.8)	563 (11.0)	109 (3.3)	739 (15.0)
CVD	307 (6.5)	1438 (12.9)	NA	2121 (11.0)	NA		81 (4.1)	160 (1.5)	751 (14.6)	126 (3.8)	NA
DM	4733 (100.0)	11140 (100.0)	12063 (36.2)	5145 (26.7)	NA		364 (18.2)	572 (5.2)	1362 (26.5)	466 (14.2)	4912 (100.0)
S Creat (mg/dL)	0.90 (0.23)	0.98 (0.29)	1.02 (0.30)	1.11 (0.19)	NN (NA)		1.03 (0.22)	0.98 (0.17)	0.80 (0.25)	0.75 (0.19)	1.01 (0.23)
Smoking	626 (13.2)	1550 (13.9)	7303 (36.7)	6277 (32.6)	146 (12.1)		528 (26.4)	2431 (22.1)	551 (10.8)	700 (21.3)	756 (15.4)
BMI (kg/m²)	32.15 (5.49)	28.34 (5.19)	29.78 (11.27)	28.72 (4.57)	29.08 (4.72)		29.77 (5.34)	27.85 (4.39)	24.27 (3.45)	24.55 (3.39)	29.18 (4.59)
	EUROPA	EWPHE	HIJCREATE	LIFE	NORDIL	ONTARGET	SHEP	STOP HT-2	SYSTEUR	TRANSCEND	VALUE
N	12218	840	2049	9193	10881	25620	4736	6614	4695	5926	15245
Age	60.70 (9.33)	71.77 (8.03)	65.30 (9.17)	67.62 (7.02)	59.90 (6.50)	67.04 (7.20)	71.62 (6.70)	76.03 (3.94)	69.74 (6.70)	67.48 (7.35)	67.23 (8.13)
Sex (Female)	1779 (14.6)	586 (69.8)	405 (19.8)	4963 (54.0)	5583 (51.4)	6831 (26.7)	2690 (56.8)	4416 (66.8)	3138 (66.8)	2547 (43.0)	6468 (42.4)
SBP (mmHg)	137.15 (15.46)	182.63 (16.48)	135.28 (18.00)	174.41 (14.28)	173.47 (17.62)	141.82 (17.41)	170.30 (9.40)	194.10 (15.29)	173.85 (9.96)	140.97 (16.63)	154.65 (18.99)
DBP (mmHg)	81.73 (8.21)	100.54 (7.10)	75.70 (11.89)	97.80 (8.86)	105.74 (5.30)	82.07 (10.40)	76.91 (8.30)	97.84 (10.02)	85.48 (5.87)	81.89 (10.13)	87.52 (10.79)
AF	NA	22 (2.6)	135 (6.6)	NA	101 (0.9)	846 (3.3)	0 (0.0)	313 (4.7)	246 (5.2)	205 (3.5)	398 (2.6)
IHD	12218 (100.0)	73 (8.7)	1745 (85.2)	1469 (16.0)	496 (4.6)	19102 (74.6)	232 (4.9)	647 (9.8)	164 (3.5)	4418 (74.6)	6981 (45.8)
CVD	222 (1.8)	63 (7.5)	205 (10.0)	401 (4.4)	271 (2.5)	5342 (20.9)	66 (1.4)	502 (7.6)	124 (2.6)	1302 (22.0)	3014 (19.8)
DM	NA	72 (8.6)	780 (38.1)	1195 (13.0)	727 (6.7)	9612 (37.5)	NA	719 (10.9)	449 (9.6)	2118 (35.8)	4823 (31.6)
S Creat (mg/dL)	1.07 (0.20)	1.01 (0.27)	0.91 (0.31)	0.98 (0.23)	0.98 (0.20)	1.08 (1.05)	NaN (NA)	1.01 (0.28)	0.99 (0.21)	1.07 (1.01)	1.14 (0.27)
Smoking	1862 (15.2)	143 (17.0)	509 (24.8)	1499 (16.3)	2442 (22.4)	3225 (12.6)	602 (100.0)	594 (9.0)	343 (7.3)	582 (9.9)	3664 (24.0)
BMI (kg/m²)	27.43 (3.50)	26.39 (4.53)	24.63 (2.99)	28.00 (4.78)	27.80 (4.34)	28.16 (4.77)	27.11 (4.79)	26.72 (4.00)	27.03 (4.10)	28.19 (4.82)	28.63 (5.04)

All categorical variables presented as N (%), and all continuous variables presented as mean (SD)

AF, atrial fibrillation; BMI, body mass index; BP, blood pressure; CVD, cerebrovascular disease; DBP, diastolic blood pressure; DM, diabetes mellitus; IHD, ischaemic heart disease; NA, not available; SBP, systolic blood pressure; S Creat, serum creatinine

Discrepancies between the data that were published for each trial and the data presented in this table may result from errors in the BPLTTC dataset, which are, though, unlikely to have influenced any analyses.

Table 5.6 Baseline characteristics of participants overall

	Overall	Comparator	Intervention
Number	194,019	95,144	98,875
Age (years)	65.28 (9.04)	65.37 (9.13)	65.20 (8.96)
Sex (Female)	78,333 (40.4)	39,383 (41.4)	38,950 (39.4)
Atrial fibrillation	3,773 (2.5)	1,802 (2.4)	1,971 (2.5)
Ischaemic heart disease	70,944 (37.8)	32,298 (35.0)	38,646 (40.5)
Cerebrovascular disease	16,430 (11.0)	7,400 (10.3)	9,030 (11.6)
Diabetes mellitus	62,937 (34.6)	30,187 (33.9)	32,750 (35.3)
Chronic kidney disease	13,043 (22.6)	6,689 (23.2)	6,354 (22.1)
Body mass index (kg/m²)	28.29 (6.41)	28.28 (7.44)	28.30 (5.23)
Total cholesterol (mg/dL)	216.82 (47.26)	218.70 (47.11)	215.03 (47.33)
Systolic blood pressure (mmHg)	153.98 (22.03)	155.01 (22.25)	152.98 (21.78)
Diastolic blood pressure (mmHg)	87.59 (12.54)	87.96 (12.59)	87.23 (12.48)
Pharmacological treatment			
Diuretic	20,853 (23.5)	9,227 (23.1)	11,626 (23.9)
Alpha-blocker	3,055 (4.2)	1,374 (4.2)	1,681 (4.1)
Beta-blocker	40,051 (41.0)	17,280 (38.8)	22,771 (42.8)
Angiotensin converting enzyme inhibitor	33,333 (37.6)	14,141 (35.4)	19,192 (39.5)
Angiotensin receptor blocker	6,406 (11.2)	3,288 (11.6)	3,118 (10.9)
Calcium channel blocker	33,869 (34.6)	15,925 (35.7)	17,944 (33.7)
Anticoagulant	2,262 (4.1)	922 (3.8)	1,340 (4.3)
Antiplatelet	37,528 (43.0)	15,313 (38.3)	22,215 (47.0)
Lipid lowering drug	39,921 (41.7)	17,356 (38.4)	22,565 (44.8)

All categorical variables are presented as N (%); all continuous variables are presented as mean (standard deviation).

Data presented in this table may not reflect data published by individual trials due to errors in the BPLTTC dataset, which are, however, unlikely to have influenced any analyses.

In placebo-controlled trials (nine trials), the difference in SBP reduction between arms was 6.6 (SD 3.2) mmHg, in drug-class comparisons (eleven trials) it was 2.2 (SD 0.9) mmHg, and in more versus less intensive BP lowering (one trial) it was 12.4 mmHg. Overall, the mean difference in SBP reduction between intervention and control arms was 3.6 (SD 3.1) mmHg.

There was no evidence that BP lowering treatment reduced the risk of new-onset AF (HR 1.01, 95% CI [0.95 to 1.07] per each 5-mmHg reduction in SBP) (**Figure 5.2**). This was supported by the meta-regression, which found no evidence that more intensive BP lowering would result in a significantly greater reduction in the risk of new-onset AF (**Figure 5.3**), and the fact that treatment estimates were similar without standardisation for intensity of SBP reduction (HR 1.00, 95% CI [0.95 to 1.05]).

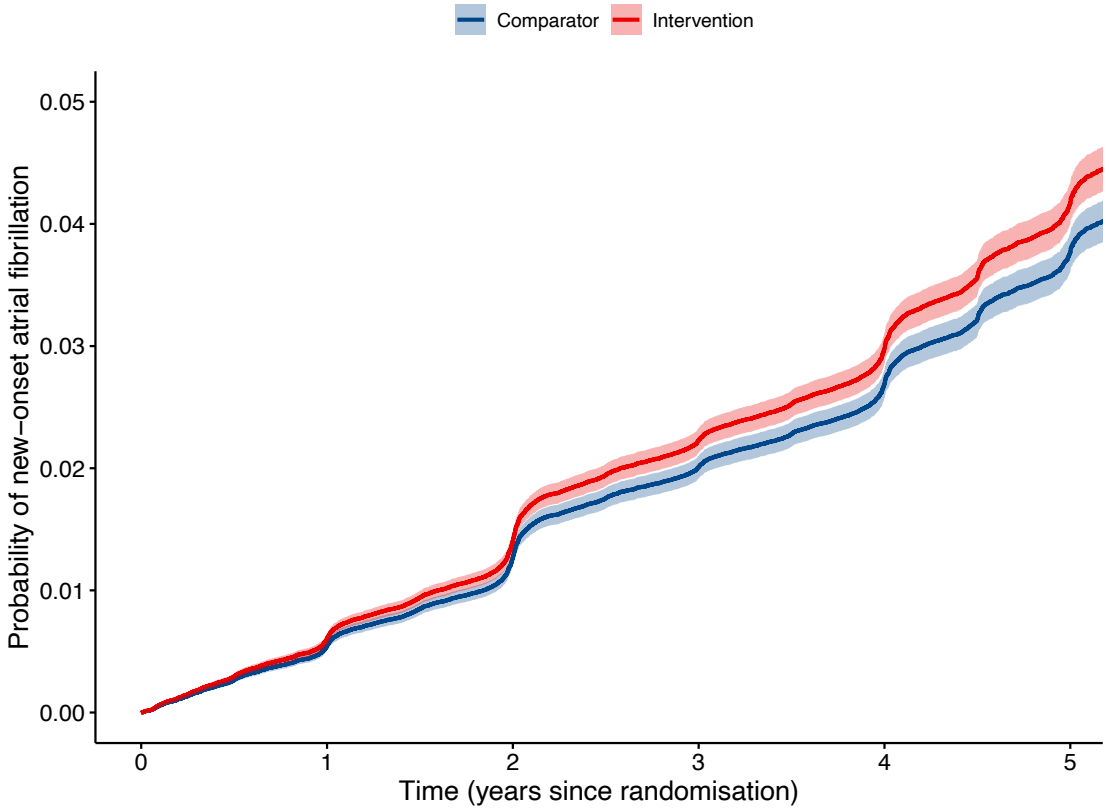

Figure 5.2 Cumulative event curves for new onset atrial fibrillation by treatment arm

Estimated probabilities of new-onset atrial fibrillation events are shown according to treatment arm (intervention versus comparator, as defined in treatment comparisons in the methods), standardised to 5-mmHg reduction in systolic blood pressure. The bands represent 95% confidence intervals.

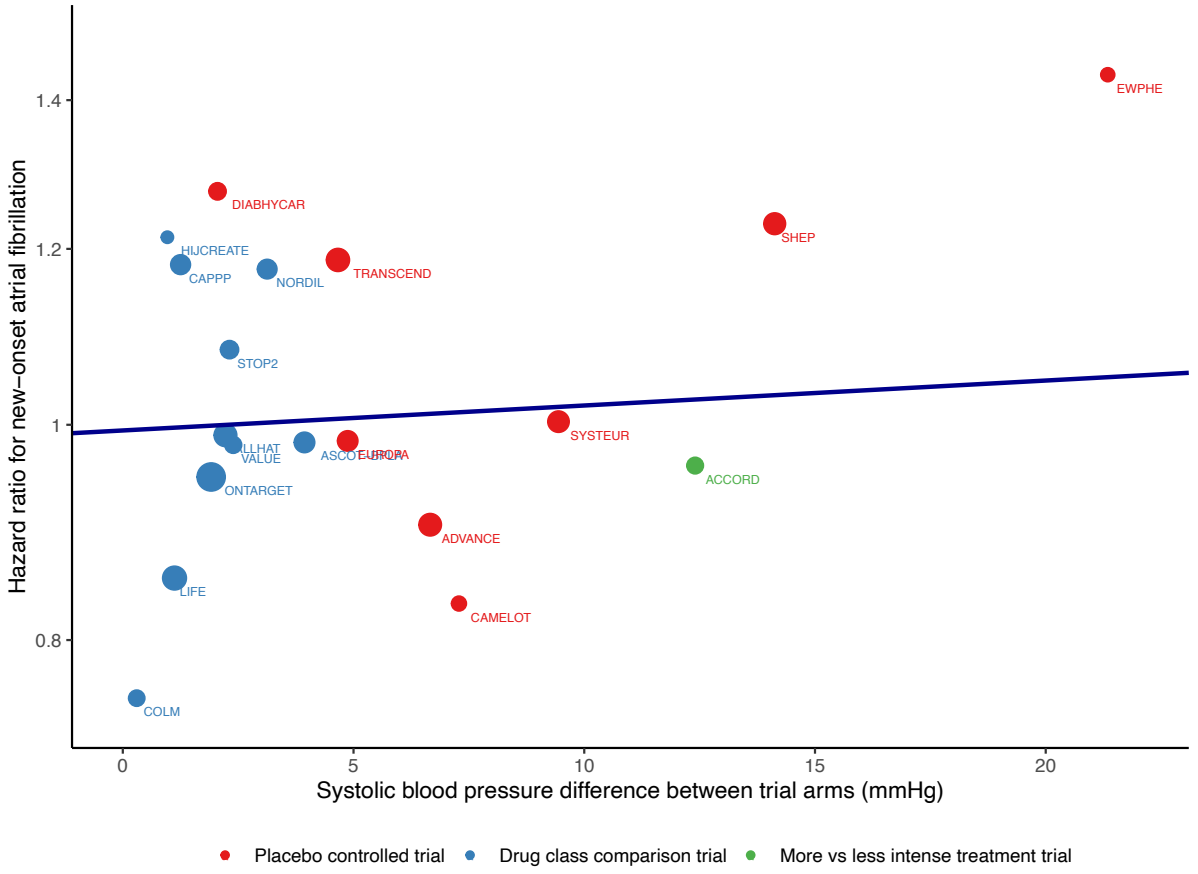

Figure 5.3 Hazard ratio for new-onset atrial fibrillation related to the one-year difference in systolic blood pressure reduction, aggregated at trial level

Risk of new-onset atrial fibrillation for all patients regressed against the systolic blood pressure difference between trial arms, plotted on the log scale (dark blue line). Circles represent the hazard ratio for each trial with the size inversely proportional to the respective standard error. Trials are coded by colour according to type of intervention: placebo-controlled trials (red), drug class comparison trials (blue), and more versus less intense treatment trials (green).

There was also no evidence that BP lowering treatment reduced the risk of recurrent AF (HR 0.97, 95% CI [0.81 to 1.17] per each 5-mmHg reduction in SBP) (Figure 5.4).

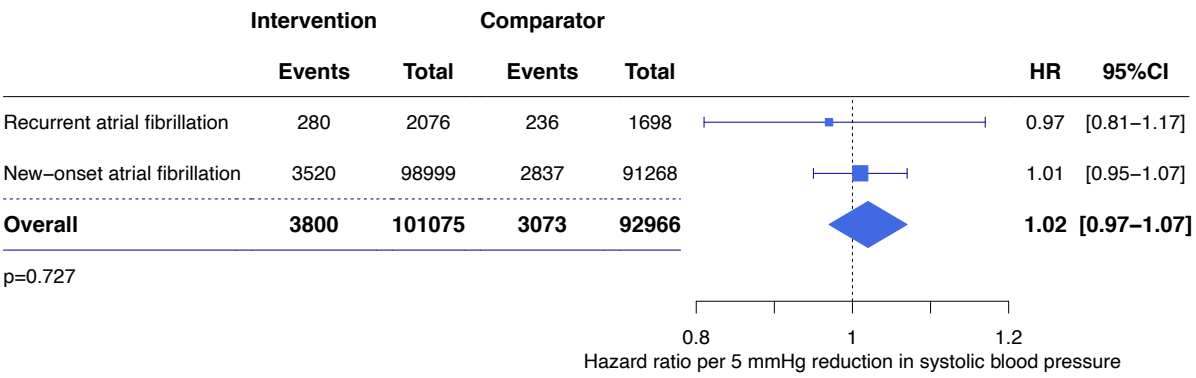

Figure 5.4 Effect of blood pressure lowering treatment on new onset versus recurrent atrial fibrillation

Forest plot displays the hazard ratios (HR) and 95% confidence intervals (CI) for new-onset, recurrent and overall atrial fibrillation standardized by 5-mmHg reduction in systolic blood pressure. P-value (0.727) for comparison between new-onset and recurrent atrial fibrillation.

The median baseline percentage risk for new-onset AF was estimated as 2.3%, IQI [1.2% to 3.4%] at 5 years. When patients were split into thirds of predicted risk for AF at five years, the median risks in the low, medium and high risk subgroups at five years were 0.9% IQI [0.6 to 1.2], 2.3 [1.8 to 2.8] and 6.0% [4.5 to 8.4], respectively. There was no evidence that BP lowering reduced the risk of new-onset AF in any of the risk strata (Figure 5.5). There was also no evidence of heterogeneity of treatment effects according to baseline SBP (Figure 5.5).

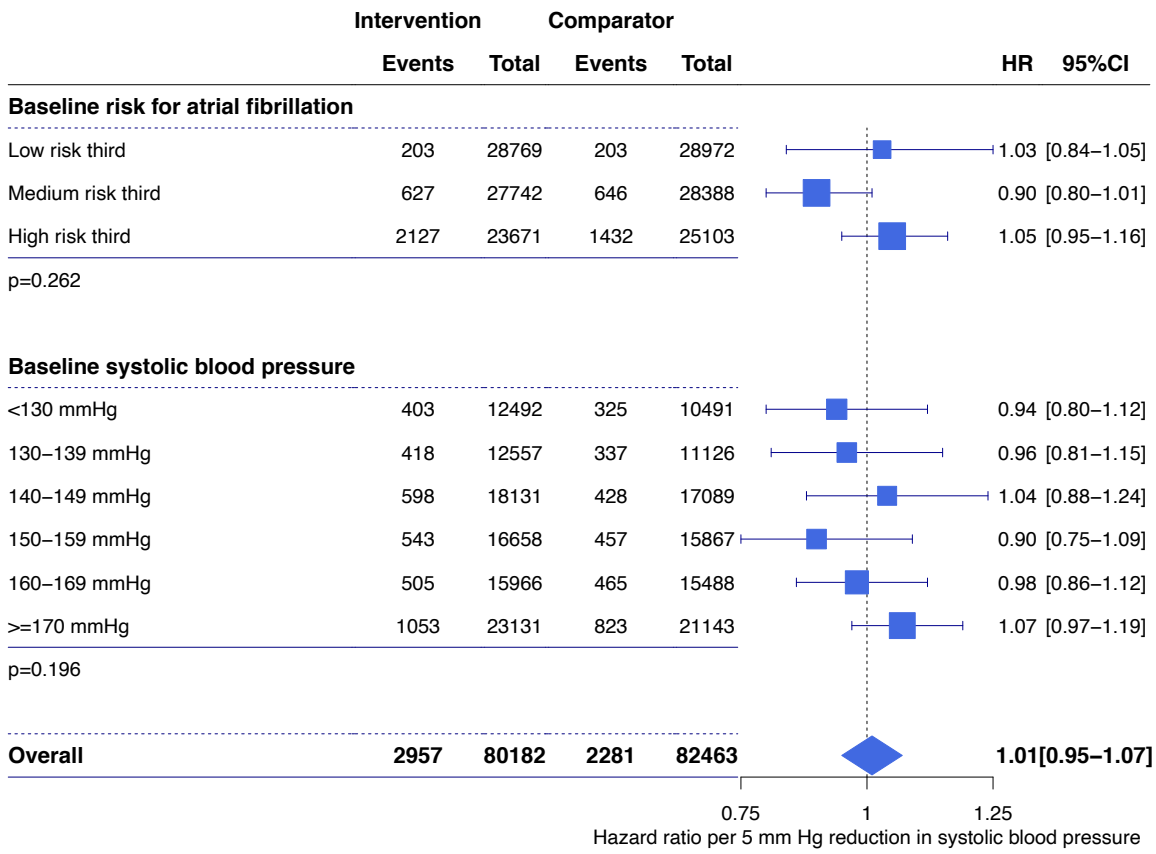

Figure 5.5 Effect of blood pressure lowering treatment on new-onset atrial fibrillation according to baseline risk for atrial fibrillation and baseline systolic blood pressure

Forest plot displays the hazard ratios (HR) and 95% confidence intervals (CI) for atrial fibrillation standardised by 5-mm Hg reduction in systolic blood pressure for each third of predicted risk for atrial fibrillation at five years and for each 10 mmHg strata of baseline systolic blood pressure. P value for test for linear trend.

A total of ten trials were included in the comparison of RAAS inhibitors versus placebo or standard treatment (i.e., BB and/or diuretic), including 75,094 patients (Table 5.7). A total of six trials were included in the comparison of CCBs versus placebo or standard treatment (i.e.,

BB and/or diuretic), including 45,437 patients. The small number of trials reporting other drug class comparisons precluded further subgroup analyses (Table 5.8). There was no clear evidence that any of the treatment regimens reduced the risk of new-onset AF, although confidence intervals were wide (Figure 5.6).

Table 5.7 Treatment comparisons for subgroup analyses by drug class

Trial	Intervention	Comparator	SBP reduction (mmHg)
Renin angiotensin aldosterone system inhibitors			
ALLHAT	ACEI	Diuretic	-3.0
BENEDICT	ACEI	Placebo	2.0
CAMELOT	ACEI	Placebo	7.4
CAPPP	ACEI	BB + Diuretic	-1.3
DIABHYCAR	ACEI	Placebo	2.1
EUROPA	ACEI	Placebo	4.9
HIJCREATE	ARB	BB + Diuretic	1.0
LIFE	ARB	BB	1.1
STOP HT-2	ACEI	BB + Diuretic	-2.0
TRANSCEND	ARB	Placebo	4.7
Calcium channel blockers			
ALLHAT	CCB	Diuretic	-1.4
BENEDICT	CCB	Placebo	-1.9
CAMELOT	CCB	Placebo	7.2
NORDIL	CCB	BB + Diuretic	-3.1
STOP HT-2	CCB	BB + Diuretic	-2.6
SYSTEUR	CCB	Placebo	9.4

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta-blocker; CCB, calcium channel blocker; SBP, systolic blood pressure

Table 5.8 Number of trials available for drug class comparisons

Drug classes		Number of trials
ACEI + Diuretic	Placebo	2
CCB + ACEI	BB + Diuretic	1
ACEI + CCB	Placebo	1
ARB + CCB	ARB + Diuretic	1
CCB + ARB	CCB + Diuretic	1
CCB + BB	CCB + Diuretic	1
Diuretic	Placebo	1
ARB + ACEI	ACEI	1
ARB + ACEI	ARB	1
ARB	CCB	1

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta-blocker; CCB, calcium channel blocker

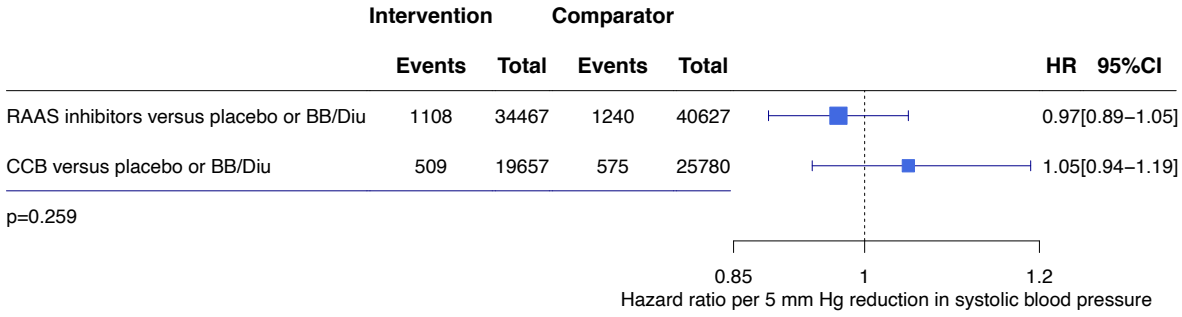

Figure 5.6 Effect of blood pressure lowering treatment on new-onset atrial fibrillation in subgroups of drug class

Forest plot displays the hazard ratios (HR) and 95% confidence intervals (CI) for new onset atrial fibrillation for renin angiotensin aldosterone system (RAAS) inhibitors and calcium channel blockers (CCB) in comparison with placebo or beta-blocker (BB) with or without diuretic (Diu). P value for test for difference between subgroups.

Inclusion of the two trials for which only aggregate data were available did not substantially change the treatment effect (HR 1.01, 95% CI [0.95 to 1.07] per 5-mmHg reduction in SBP), but increased heterogeneity (I^2 = 15%) (**Figure 5.7**). In addition, there was no evidence that the intensity of treatment-induced BP lowering was associated with the risk of new-onset AF, even after inclusion of those two trials (**Figure 5.8**). Using fixed effect or random effects two-stage meta-analyses provided similar results (HR 1.03, 95% CI [0.99 to 1.06] and HR 1.03, 95% CI [0.97 to 1.08] for fixed effect and random effects models, respectively) to the one-stage model (HR 1.01, 95% CI [0.95 to 1.07]), because there was little heterogeneity between trials (I^2 = 6.8% and I^2 = 9.5% for fixed effect and random effects models, respectively) (**Table 5.8**). Exclusion of trials (1) that reported AF as an adverse event instead of an adjudicated endpoint, or (2) that achieved a difference in SBP reduction between arms inferior to 5 mmHg did not have a substantial impact on treatment effect estimates.

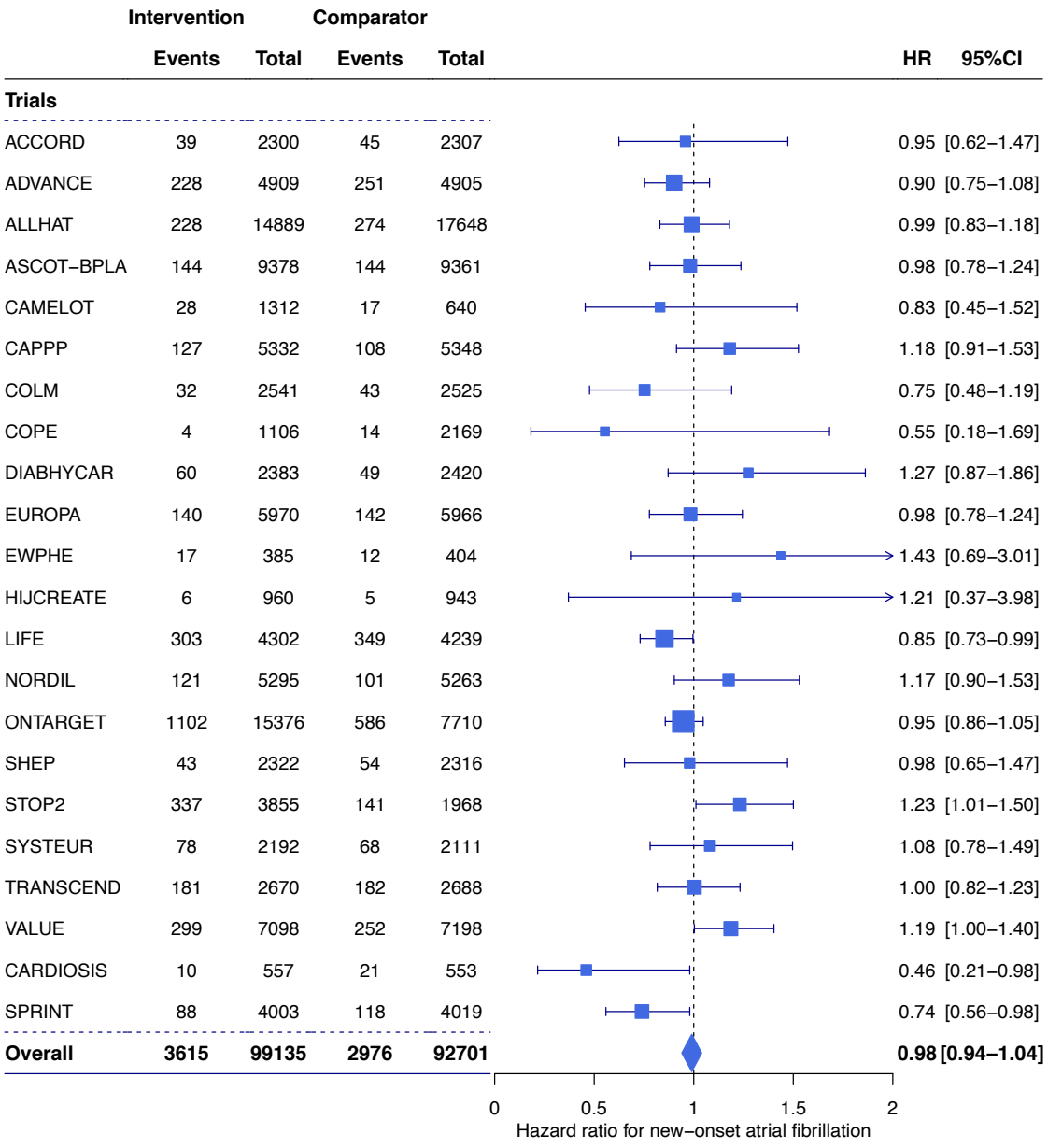

Figure 5.7 Effect of blood pressure lowering treatment on new-onset atrial fibrillation by trial, including trials for which only aggregate data were available

Forest plot displays the hazard ratios (HR) and 95% confidence intervals (CI) for new onset atrial fibrillation for each trial included in a two-stage fixed effect meta-analysis. This analysis includes the trials for which only aggregate data were available (CARDIOSIS and SPRINT) and it is not standardised by the intensity of systolic blood pressure lowering.

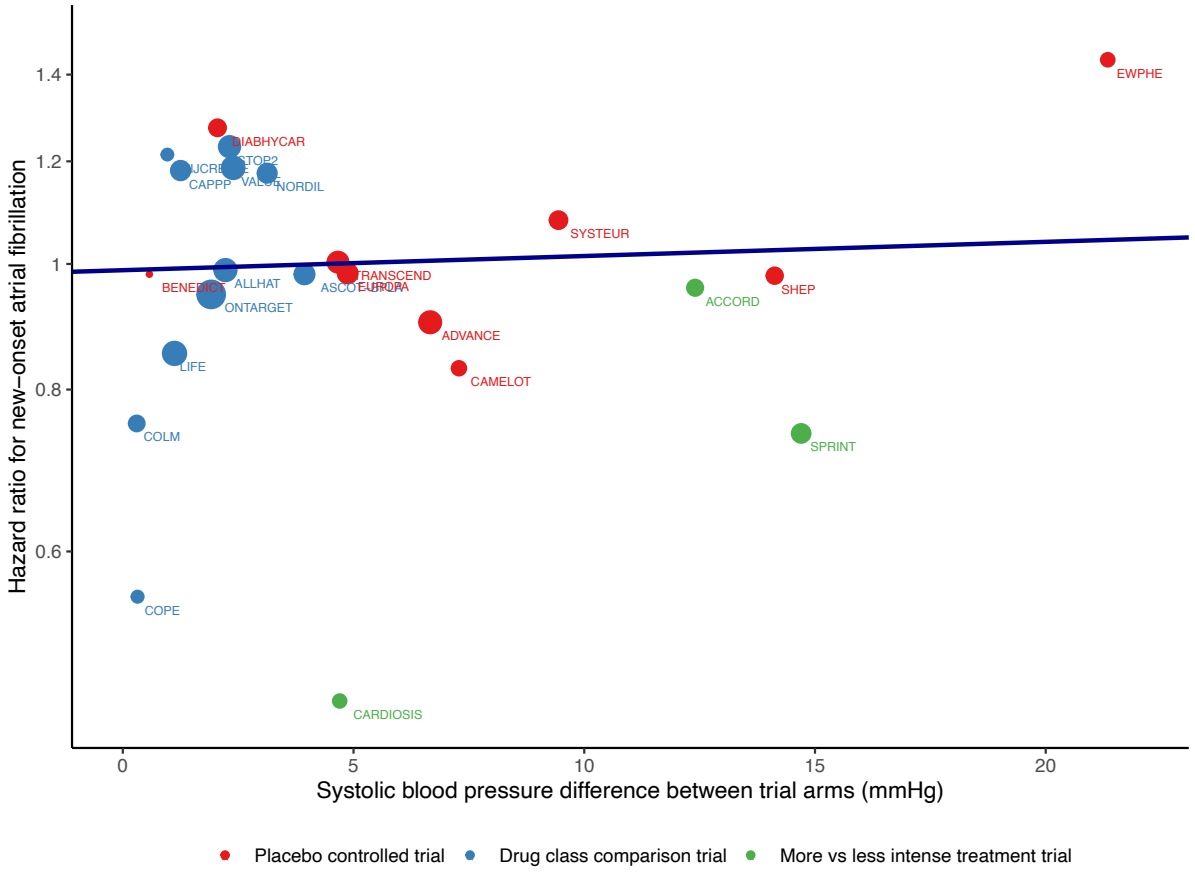

Figure 5.8 Hazard ratio of new-onset atrial fibrillation related to the one-year difference in blood pressure reduction

Risk of new-onset atrial fibrillation for all patients regressed against the systolic blood pressure difference between trial arms, plotted on the log scale (dark blue line). Circles represent the hazard ratio for each trial with the size inversely proportional to the respective standard error. Trials are coded by colour according to type of intervention: placebo-controlled trials (red), drug class comparison trials (blue) and more versus less intense treatment trials (green). Trials for which only aggregate data were available are also included (CARDIOSIS and SPRINT).

Table 5.9 Sensitivity analyses

One-stage meta-analysis excluding trials that reported atrial fibrillation as adverse event (14 trials)			
	Hazard ratio	95% Confidence Interval	
New-onset atrial fibrillation	1.03	[0.97 to 1.11]	
One-stage meta-analysis without standardisation for intensity of systolic blood pressure reduction (21 trials)			
	Hazard ratio	95% Confidence Interval	
New-onset atrial fibrillation	1.00	[0.95 to 1.05]	
One-stage meta-analysis including trials with systolic blood pressure reduction equal or greater than 5 mmHg (8 trials)			
	Hazard ratio	95% Confidence Interval	
New-onset atrial fibrillation	0.95	[0.84 to 1.07]	
One-stage meta-analysis stratified by drug class			
	Hazard ratio	95% Confidence Interval	
CCB versus placebo or BB/Diu	1.08	[0.89 to 1.31]	
RAAS-inhibitor versus placebo or BB/Diu	0.94	[0.82 to 1.08]	
Two-stage fixed effect meta-analysis (21 trials)			
	Hazard ratio	95% Confidence Interval	I^2
New-onset atrial fibrillation	1.03	[0.99 to 1.06]	6.8% (p = 0.37)
Two-stage random effects meta-analysis (21 trials)			
	Hazard ratio	95% Confidence Interval	I^2
New-onset atrial fibrillation	1.03	[0.97 to 1.08]	9.5% (p = 0.37)
Two-stage fixed effect meta-analysis including trials for which only aggregate data were available (23 trials)			
	Hazard ratio	95% Confidence Interval	I^2
New-onset atrial fibrillation	1.01	[0.95 to 1.07]	15% (p = 0.26)
Two-stage fixed effect meta-analysis including trials for which only aggregate data were available, without standardisation for intensity of systolic blood pressure reduction (23 trials)			
	Hazard ratio	95% Confidence Interval	I^2
New-onset atrial fibrillation	0.99	[0.94 to 1.04]	15% (p = 0.26)

All estimates are standardised by 5-mmHg reduction in systolic blood pressure, except when stated otherwise. P-value for Cochran's Q test. BB, beta-blocker; CCB, calcium channel blocker; Diu, diuretic; RAAS, renin angiotensin aldosterone system.

Discussion

This study found no evidence that pharmacological BP lowering reduced the risk of new-onset or recurrent AF across a range of BP lowering intensities in large-scale RCTs. In the relatively low-risk population included in those trials, there was also no evidence supporting heterogeneity of treatment effects according to predicted risk for AF, baseline SBP, or between therapeutic regimens based on RAAS inhibitors and CCBs.

Although observational studies have suggested an association between elevated BP and increased risk of AF,[381,401] evidence from RCTs on the preventative effect of BP lowering remains contradictory. Indeed, some of those trials failed to show a significant risk reduction in new-onset AF,[384,385,387,388] whilst others reported statistically significant risk reductions between 26% and 54%.[220,386,402] Although the potential lack of power of those post hoc studies cannot be overlooked, differences between populations, as well as in the inclusion and exclusion criteria applied in each study, most likely underpin the discrepant findings. For instance, two recent post hoc analyses of the Systolic Blood Pressure Intervention Trial reached different conclusions about the efficacy of BP lowering on prevention of new-onset AF. This may well be related to the fact that one of the studies included patients with paroxysmal AF, whilst the other excluded those patients with previous history of AF even if the baseline electrocardiogram was in sinus rhythm. As expected, the event rate was much higher in the former, as patients with paroxysmal AF are more likely to develop recurrent

AF.[403] This may explain why the study that included patients with paroxysmal AF reported that intense BP lowering significantly decreased the risk of AF. In contrast, in the study that excluded patients with paroxysmal AF, and hence included a population with an overall lower AF risk, BP lowering failed to significantly prevent new-onset AF.

On the other hand, it is possible that the conflicting results from RCTs are underpinned by the magnitude of the achieved BP reduction in each trial, but evidence in this regard is conflicting. Indeed, some trials that achieved large differences in BP reduction between trial arms reported a significant risk reduction in new-onset AF,[220,386] whilst others with similar BP reductions failed to show a significant risk reduction.[385] To fuel the controversy, another trial reported a significant risk reduction in new-onset AF, despite no difference in achieved BP between trial arms, which may be related to the fact that it only included patients with left ventricular hypertrophy.[402] By pooling the findings of all the aforementioned trials as well as other trials that had not published data on AF, my IPD meta-analysis arguably provides more robust evidence than individual trials. Therefore, it is reasonable to conclude that evidence hitherto available does not support that BP lowering reduces the risk of new-onset AF irrespective of the intensity of BP reduction. On the other hand, observational evidence suggested that a 20 mmHg increase in SBP was associated with a 21% increase in the risk of new-onset AF.[86] Therefore, a 3.6 mmHg reduction in SBP would be expected to result in an approximate 2% reduction in the risk of new-onset AF, which is within the 95% confidence interval of my treatment effect estimate. My study may thus have lacked power to detect a small risk reduction due to the small BP difference between trial arms.

Reassuringly, my findings are in keeping with a previous aggregate data meta-analysis,[90] which demonstrated that BP lowering treatment did not prevent new-onset AF in antihypertensive trials. However, my results contrast with that same meta-analysis because I found no evidence of effect modification by baseline risk for AF. More specifically, there was no evidence of a trend for greater treatment effects across thirds of predicted risk for AF in my IPD meta-analysis, whereas that previous aggregate data meta-analysis suggested that BP lowering only decreased the risk of AF at the higher end of the risk spectrum, for instance in patients with HF. This apparent discrepancy may be due to several reasons. First, the overall risk for new-onset AF was lower in my study population than in that meta-analysis, particularly because my population did not include patients with HF.[90] Indeed, the range of baseline risk for AF was 0.33 to 85% at five years (about 0.11 to 17% per year) in my population, whilst in that aggregate data meta-analysis the event rate ranged from 1.1 to 68% per year. Second, given the strong causal association between HF and AF, it is possible that the observed effect of BP lowering on new-onset AF may have been mediated by prevention of HF, which then reduced the risk of AF. This is corroborated by the null treatment effect in patients without HF at baseline in that aggregate data meta-analysis.

On the other hand, the lack of heterogeneity of treatment effects according to baseline risk for AF may be related to the limitations of the risk stratification itself. Clinical risk scores, such as the one I developed in my study population, are strongly influenced by age, which is coincidently a modifier of treatment effects.[404] The association between elevated BP and risk

of AF declines with age, thus suggesting that age may reduce the effect of BP lowering treatment on the risk of AF.[86] Polygenic risk scores offer a potential alternative to inform treatment decisions because they have better predictive ability and are independent of age.[405,406] Therefore, although my study suggested that BP lowering treatment did not reduce the risk of new-onset AF in a low-risk population, further research is warranted to investigate whether the same holds true in high-risk patients and whether polygenic risk scores can surpass clinical risk scores in identifying heterogeneity of treatment effects, which may eventually become possible using genetic data collected by some BP lowering trials.

My meta-analysis also did not support the existence of class-specific effects. Although contemporary guidelines[102] suggest that RAAS inhibitors may be superior to CCBs at preventing new-onset and/or recurrent AF,[402,407-409] no firm treatment recommendations are made, perhaps acknowledging the contradictory and low-quality evidence currently available. Even though my meta-analysis addressed some of the pitfalls of previous studies, the number of patients included in subgroup analyses by drug class was relatively small and data were insufficient to investigate all possible drug class comparisons. Therefore, further evidence is warranted to better clarify the existence of class-specific effects. Until then, guidelines should be updated to acknowledge the conflicting evidence currently available regarding the efficacy of RAAS inhibitors for primary prevention of AF.

Notwithstanding the null treatment effect, this study has important clinical implications. Indeed, it demonstrated that, contrary to the substantial risk reduction afforded by

pharmacological BP lowering for other major cardiovascular events (e.g., myocardial infarction and stroke), no risk reduction was evident for new-onset AF in patients with a low baseline risk, such as those included in BP lowering trials. Those findings should be interpreted in light of the two important subpopulations of patients with AF.[410] The first subpopulation and the largest is represented by patients who have concurrently high cardiovascular and AF risk, because well-established cardiovascular risk factors also increase the risk of new-onset AF (e.g., obesity, diabetes, dyslipidaemia, smoking). Those patients often have other compelling indications for BP lowering treatment regardless of their risk for new-onset AF, and hence risk stratification in those patients may not be warranted.

The second subpopulation is represented by patients who have high genetic predisposition for new-onset AF irrespective of the presence or absence of typical cardiovascular risk factors.[411] Nonetheless, even in those patients, a higher burden of clinical risk factors was associated with an increased risk of new-onset AF,[412] thus suggesting that cardiovascular risk factors interact with inherited susceptibility for AF. This has been further supported by a Mendelian randomisation study which showed that lifelong exposure to elevated BP was causally associated with an increased risk of incident AF, but only in individuals with high genetic susceptibility (unpublished results from my collaborative work described briefly in Chapter 10). Therefore, risk factor modification may contribute to reduce the risk of new-onset AF in genetically predisposed individuals, similarly to what has been demonstrated for coronary artery disease.[413] However, this has not been proven in RCTs. Therefore, further research is warranted to understand whether control of cardiovascular risk factors (e.g., BP,

diabetes, obesity, smoking) can prevent new-onset AF depending on genetically determined risk for AF.

This study includes the first IPD meta-analysis investigating the effect of BP lowering treatment on the risk of new-onset AF. Its main strengths are (1) the inclusion of a large number of incident AF events (over 6,300), due to unprecedented access to unpublished data from RCTs; and (2) the fact that it was able to estimate AF risk at individual level instead of relying on proxy measures (e.g., event rates) aggregated at trial level. Besides overcoming the limitations of previous observational studies and aggregate data meta-analyses of RCTs, this study achieved enough power to estimate treatment effects with narrow confidence intervals. The robustness of the main conclusions to sensitivity analyses, the minimal heterogeneity between trials and the consistency of the estimates provided by different methods (including when adding new studies lacking in IPD) further support the conclusions drawn.

However, some limitations deserve to be acknowledged. First, the number of trials reporting the outcome AF was relatively small considering the total number of trials included in the BPLTTC, which limited power to perform subgroup analyses for some drug classes. Second, I considered the outcome AF either as an adjudicated pre-specified endpoint or as a reported adverse event. Although adverse event reporting can be less accurate than adjudication of pre-defined endpoints, sensitivity analysis excluding trials that reported AF as adverse event did not have a material impact on pooled estimates. Third, it would have been interesting to

explore the effects of BP lowering treatment on AF across a broader range of baseline risk, but the population included in the eligible trials was overall at low risk for AF. Fourth, the SBP reduction achieved in the trials included in this study was small, since several head-to-head comparison trials achieved no, or minimal, SBP difference between arms. However, this is unlikely to have substantially influenced treatment estimates, because (1) there was minimal heterogeneity between trials; (2) meta-regression showed no correlation between the intensity of BP lowering and risk reduction afforded by treatment; and (3) sensitivity analysis including only trials that achieved a difference in SBP reduction between arms equal or greater than 5 mmHg yielded similar results to the main analysis. Finally, AF is typically asymptomatic and difficult to diagnose both clinically and by electrocardiogram, because AF episodes are often transient. Therefore, it is likely that some AF events failed to be detected and reported in all trials. However, in RCTs it is expected that misclassification would be non-differential and thus unlikely to bias treatment effect estimates.

Conclusion

In conclusion, this study showed that, in a relatively low-risk population, BP lowering treatment did not reduce the risk of new-onset AF irrespective of the intensity of BP reduction. Further research is warranted to investigate whether treatment effects are different in high-risk populations, such as patients with increased genetic susceptibility, and to clarify the existence of class-specific effects.

Chapter 6 Blood Pressure and Atrial Fibrillation at Baseline

This chapter focuses on the management of BP in the context of AF. It describes the IPD meta-analysis of RCTs that I conducted to compare the effects of BP lowering on cardiovascular outcomes between patients with and without AF at baseline. That is, unlike in Chapter 5, where AF is the studied outcome, here it is taken as a potential effect modifier.

An abstract of this research has been accepted for presentation at the European Society of Cardiology Congress in September 2020 and at the Joint Meeting of the European Society of Hypertension and International Society of Hypertension 2020, which has been postponed to 2021 due to the COVID-19 pandemic.

Abstract

Background and Aims

Randomised evidence on the efficacy of BP lowering treatment to reduce cardiovascular risk in patients with AF is limited. Therefore, this study aimed to investigate the effects of BP lowering in patients with and without AF at baseline.

Methods

IPD were extracted from all trials with over 1,000 person-years of follow-up that had randomly assigned patients to different classes of BP lowering drugs, BP lowering drugs versus placebo, or more versus less intensive BP lowering regimens. The effects of BP lowering treatment on a composite endpoint of major cardiovascular events (stroke, ischaemic heart disease or HF), according to AF status at baseline, were estimated using one-stage IPD meta-analyses based on Cox proportional hazards models stratified by trial, which assumed a fixed treatment effect.

Results

A total of twenty-two trials were included with 188,570 patients, of whom 13,266 (7%) had AF at baseline. Patients with AF had lower BP at baseline than patients without AF (143/84 mmHg, SD 21/12 mmHg versus 155/88 mmHg, SD 21/13 mmHg, respectively). Meta-regression showed that relative risk reductions were proportional to trial-level intensity of BP lowering, both in patients with and without AF. The hazard ratio for major cardiovascular events was 0.91 in patients with AF (95% confidence interval 0.83 to 1.00) and 0.91 in patients

without AF (95% confidence interval 0.88 to 0.93) for each 5-mmHg reduction in SBP, with no difference between subgroups (p = 0.91). Similar patterns were observed for individual components of the composite primary outcome. In patients with AF, there was no evidence that treatment effects varied according to baseline SBP or use of specific drug classes.

Conclusions

BP lowering treatment reduces the risk of major cardiovascular events similarly in individuals with and without AF. Guidelines should be updated to recommend pharmacological BP lowering for prevention of cardiovascular events in patients with AF.

Background

AF is the most common sustained cardiac arrhythmia and its incidence and prevalence are on the rise across the globe,[74,79] mainly due to population ageing and an increase in other cardiometabolic risk factors.[414] In observational studies, AF has been associated with an approximately 90% higher risk of a fatal vascular event, such as stroke, ischaemic heart disease, HF or vascular dementia, in comparison with patients without AF.[86] Even though the risk of stroke, in particular, can be mitigated by anticoagulation, the majority of deaths in contemporary anticoagulated AF patients are due to cardiovascular causes other than stroke, such as myocardial infarction and HF.[96,415] However, despite pharmacological interventions, such as anticoagulation and lipid lowering therapy, cardiovascular risk in patients with AF remains high.[102]

Although hypertension is the most common cardiovascular risk factor in patients with AF,[416,417] whether BP lowering reduces the risk of cardiovascular events in patients with AF remains uncertain. As BP lowering treatment significantly decreases cardiovascular risk in high-risk populations,[5] a similar effect could be expected in patients with pre-existing AF. However, the complex structural, neurohumoral and metabolic changes in the cardiovascular system that underpin the development and progression of AF may interfere with BP lowering treatment.[418] This uncertainty is further compounded by the fact that the only RCT specifically conducted in patients with AF failed to detect a risk reduction in cardiovascular events from

using an ARB.[101] Several other major BP lowering trials have included a small fraction of patients with pre-existing AF, but individually those trials have been underpowered to perform subgroup analysis according to AF status at baseline. Therefore, I sought to extract previously published and unpublished data to compare the effect of BP lowering treatment on fatal and non-fatal cardiovascular outcomes in patients with and without AF overall and by major drug classes.

Methods

Study design

I conducted an IPD meta-analysis of BP lowering RCTs that investigated treatment effects on cardiovascular outcomes by presence or absence of AF at randomisation according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses of IPD (PRISMA-IPD) guidelines.[302] This study relied on the resource provided by the BPLTTC. A detailed description of this collaboration and the dataset is provided in Chapter 3.

For the purpose of this study, I included only trials that had collected information on AF status at baseline, which was based on electrocardiogram at baseline and/or individual medical records. Three types of trials were identified: (1) trials that included both patients with and without AF at baseline; (2) trials that included only patients with AF at baseline; and (3) trials that excluded patients with AF at baseline. I excluded trials in which the presence of AF was

not explicitly assessed at baseline or in which AF status at baseline was not clear. All data for baseline and follow-up variables were reported as per the definitions used in the primary trials.

Definition of outcomes

The primary outcome was total major cardiovascular events, defined as the first occurrence of (1) fatal or non-fatal stroke; (2) fatal or non-fatal myocardial infarction or ischaemic heart disease; or (3) HF causing death or requiring hospitalisation. Secondary outcomes were the individual elements of the composite endpoint, as well as cardiovascular death and all-cause death.

Treatment comparisons

For the main analysis, intervention and control groups were compared. For placebo-controlled trials, the placebo arm was considered as the "comparator" and the active treatment was considered as the "intervention". For trials with two or more active treatment arms, the arm in which the BP reduction was greater was considered as "intervention" and the other treatment arm(s) as "comparator". This meant that intervention and control arms in this meta-analysis were not necessarily the same as those assigned by the original investigators in each trial. **Table 6.1** summarises the treatment comparisons considered in each trial and the respective difference in SBP reduction between trial arms.

Table 6.1 Difference in systolic blood pressure reduction between arms for each trial

Trial	Intervention	Comparator	SBP reduction (mmHg)
ACCORD	More intense treatment	Less intense treatment	12.4
ACTIVE-I	ARB	Placebo	2.6
ADVANCE	ACEI + Diuretic	Placebo	6.7
ALLHAT	Diuretic	ACEI or CCB	2.2
ASCOT	CCB + ACEI	BB + Diuretic	3.9
CAPPP	BB + Diuretic	ACEI	1.3
CARDIO-SIS	More intense treatment	Less intense treatment	4.7
CASE-J	ARB	CCB	2.3
COLM	ARB + CCB	ARB + Diuretic	0.3
COPE	CCB + ARB	CCB + Diuretic or CCB + BB	0.3
DUTCH-TIA	BB	Placebo	4.4
EWPHE	Diuretic	Placebo	21.3
HIJCREATE	ARB	BB + Diuretic	1.0
JMICB	CCB	ACEI	3.8
NORDIL	BB + Diuretic	CCB	3.1
ONTARGET	ARB + ACEI	ACEI or ARB	2.3
PROGRESS	ACEI + Diuretic	Placebo	8.2
SHEP	BB + Diuretic	Placebo	14.1
STOP HT-2	BB + Diuretic	ACEI or CCB	2.3
SYSTEUR	CCB	Placebo	9.4
TRANSCEND	ARB	Placebo	4.7
VALUE	CCB	ARB	2.4
Overall (mean)			3.7

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta-blocker; CCB, calcium channel blocker; SBP, systolic blood pressure

Statistical analysis

My primary analyses aimed to address four questions:

1. Whether AF status at baseline modified treatment effects;
2. Whether the associations between the intensity of BP reduction and outcomes were similar in those with and without AF at baseline;
3. Whether in patients with and without AF, treatment effects varied by classes of BP lowering drugs;
4. Whether in patients with AF, treatment effects varied according to baseline SBP.

Intention-to-treat analysis was adopted using the data provided by each trial, after my internal quality checks had been carried out to ensure that data were accurate and transferred without error. To address the research questions described above, I used a one-stage approach that applied a single statistical model to IPD from all trials simultaneously. I confirmed that the proportional hazards assumption was not violated, and then performed time-to-event meta-analyses by applying Cox proportional hazard models, stratified by trial, which assumed a fixed treatment effect.[398]

To account for the differences in intensity of BP lowering between trials, treatment effect estimates were standardised for a 5-mmHg reduction in SBP. This standardisation was applied to treatment estimates in patients with and without AF at baseline, by including an interaction term between difference in SBP reduction between arms and treatment in all one-stage models (further details provided in Chapter 4). Although measurement of BP in AF is

considered difficult, and the reliability of different methods and devices remains uncertain,[419,420] the difference in SBP reduction between treatment and control arms was similar within each trial for patients with and without AF at baseline. Therefore, the standardisation for the intensity of BP lowering was based on the difference in SBP reduction between treatment arms aggregated at trial level.

To investigate whether the association between the intensity of SBP reduction and cardiovascular outcomes was similar in those with and without AF at baseline, I used analytical and graphical representations of the Cox regression model with additional terms for AF status at baseline and interactions between treatment, difference in SBP and AF status at baseline. This model described treatment effects on primary and secondary outcomes per unit of SBP lowering, for each of the subgroups with and without AF at baseline. Finally, to assess whether treatment effects varied according to baseline SBP and drug class, I used models with additional terms for those potential moderators and interactions between treatment, difference in SBP and moderators.

Subgroup analyses were performed to investigate class-specific effects in trials that compared RAAS inhibitors or CCBs versus placebo and/or standard treatment (BB and/or diuretic) in patients with and without AF at baseline. The number of trials and AF participants available for other drug class comparisons was insufficient to perform further subgroup analyses. For patients with AF at baseline only, subgroup analysis was also performed according to baseline SBP considering it as a continuous variable and using a cut-off of 140 mmHg SBP, as this is the treatment threshold recommended by contemporary hypertension guidelines.[39] Wald tests

were used to test for differences between subgroups. Hazard ratios with 95% confidence intervals were reported and results were presented using forest plots with standardisation by 5-mmHg SBP difference between trial arms.

Supplementary sensitivity analyses were performed to (1) compare one-stage with two-stage approaches using fixed effect and random effects meta-analysis; and (2) investigate the effect of including trials that contributed to only one of the subgroups (i.e., either only included or excluded patients with baseline AF). For the two-stage meta-analyses, Cox regression models were fitted for each trial. Then, the estimates from each trial were combined using fixed effect and random effects models with inverse variance weighting to calculate summary estimates with 95% confidence intervals. The analyses were standardised by 5 mmHg reduction in SBP using a method that had been applied in similar studies.[5,353] The log of the summary statistic of each trial was multiplied by 5/delta (and the variance by $(5/delta)^2$), where delta was the difference between the mean SBP reduction in the intervention and control arms for each trial. Heterogeneity between studies was quantified using the I^2 statistic and evaluated using Cochran's Q test. All p-values were calculated from two-tailed tests. Statistical analyses were performed using the packages "metafor", "lmer" and "survival" for R version 3.6.1.[399,400]

Results

From the full BPLTTC database, twenty-eight trials (145,653 participants) were excluded because AF status at baseline was uncertain or unavailable. Twenty-two trials were eligible and provided data for the IPD meta-analyses (**Table 6.2**). Seven of those trials had previously published data about AF status at baseline. The twenty-two trials included 188,570 individuals, of whom 13,266 (7%) had AF at baseline. Seven trials explicitly excluded participants with AF at baseline (N = 13,170, 7% of the participants without AF at baseline) and one trial included only those with prevalent AF (N = 9,016, 67% of the participants with AF at baseline). The remaining fourteen trials included a mixed population of participants with and without AF at baseline (4,249 with AF and 153,198 without AF). All trials contributed data for all the outcomes of interest, with the exception of two trials that did not report the HF outcome[219,261] and one trial that did not report cardiovascular death.[220]

Patients with AF were older than those without AF (mean age 70 versus 65 years, respectively) (**Table 6.3**). A lower baseline SBP and DBP was evident in patients with AF, who were more commonly prescribed diuretics, angiotensin converting enzyme inhibitors (ACEIs), BBs and alpha-blockers: 143/84 mmHg (SD 21/12 mmHg) versus 155/88 mmHg (SD 21/13 mmHg) in patients without AF, respectively. : Cerebrovascular disease was more common in patients with AF, whilst ischaemic heart disease, diabetes mellitus and chronic kidney disease were more common in patients without AF. There were no patients with HF reported at baseline in either subgroup, as that was an exclusion criterion for the trials included in the BPLTTC.

Table 6.2 Baseline characteristics of the participants included in atrial fibrillation meta-analyses, stratified by trial

	ACCORD	ACTIVE	ADVANCE	ALLHAT	ASCOT	CAPPP	CARDIOSIS	CASEJ	COLM	COPE	Dutch TIA
N	4733	9016	11140	33357	19257	10985	1111	4703	5141	3293	1473
Age	62.73 (6.68)	70.11 (9.73)	65.77 (6.39)	66.88 (7.71)	63.00 (8.48)	52.06 (8.38)	66.99 (7.36)	63.85 (10.54)	73.62 (5.38)	63.65 (10.72)	64.43 (10.23)
Sex (Female)	2258 (47.7)	3542 (39.3)	4735 (42.5)	15638 (46.9)	4515 (23.4)	5111 (46.5)	653 (58.8)	2106 (44.8)	2488 (48.4)	1624 (49.3)	534 (36.3)
SBP (mmHg)	139.00 (15.28)	138.25 (17.40)	145.02 (21.54)	146.27 (15.64)	164.01 (18.01)	160.72 (20.02)	158.27 (8.50)	162.85 (14.18)	157.99 (12.61)	153.91 (11.56)	157.28 (24.59)
DBP (mmHg)	75.79 (9.97)	82.39 (11.30)	80.65 (10.93)	84.02 (10.06)	94.65 (10.37)	98.95 (10.03)	87.23 (8.08)	91.70 (11.19)	86.97 (10.79)	88.80 (9.74)	90.80 (11.96)
AF	42 (0.9)	9016 (100.0)	847 (7.6)	318 (1.0)	230 (1.2)	70 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
IHD	4083 (86.3)	2294 (25.4)	2380 (21.4)	8415 (25.4)	5284 (27.4)	201 (1.8)	128 (11.5)	596 (12.7)	563 (11.0)	109 (3.3)	138 (9.4)
CVD	307 (6.5)	1230 (13.6)	1438 (12.9)	NA	2121 (11.0)	160 (1.5)	91 (8.2)	473 (10.1)	751 (14.6)	126 (3.8)	1473 (100.0)
DM	4733 (100.0)	1785 (19.8)	11140 (100.0)	12063 (36.2)	5145 (26.7)	572 (5.2)	0 (0.0)	0 (0.0)	1362 (26.5)	466 (14.2)	79 (5.4)
S Creat (mg/dL)	0.90 (0.23)	1.09 (0.29)	0.98 (0.29)	1.02 (0.30)	1.11 (0.19)	0.98 (0.17)	0.94 (0.23)	0.90 (0.27)	0.80 (0.25)	0.75 (0.19)	1.03 (0.21)
Smoking	626 (13.2)	698 (7.7)	1550 (13.9)	7303 (36.7)	6277 (32.6)	2431 (22.1)	226 (20.3)	1025 (21.8)	551 (10.8)	700 (21.3)	693 (47.0)
BMI (kg/m²)	32.15 (5.49)	29.07 (5.77)	28.34 (5.19)	29.78 (11.27)	28.72 (4.57)	27.85 (4.39)	27.82 (4.18)	24.55 (3.66)	24.27 (3.45)	24.55 (3.39)	NA

	EWPHE	HIJCREATE	JMIC-B	NORDIL	ONTARGET	PROGRESS	SHEP	STOP HT-22	SYSTEUR	TRANSCEND	VALUE
N	840	2049	1650	10881	25620	6105	4736	6614	4695	5926	15245
Age	71.77 (8.03)	65.30 (9.17)	64.49 (8.51)	59.90 (6.50)	67.04 (7.20)	63.90 (9.55)	71.62 (6.70)	76.03 (3.94)	69.74 (6.70)	67.48 (7.35)	67.23 (8.13)
Sex (Female)	586 (69.8)	405 (19.8)	515 (31.2)	5583 (51.4)	6831 (26.7)	1852 (30.3)	2690 (56.8)	4416 (66.8)	3138 (66.8)	2547 (43.0)	6468 (42.4)
SBP (mmHg)	182.63 (16.48)	135.28 (18.00)	146.16 (19.39)	173.47 (17.62)	141.82 (17.41)	146.97 (19.01)	170.30 (9.40)	194.10 (15.29)	173.85 (9.96)	140.97 (16.63)	154.65 (18.99)
DBP (mmHg)	100.54 (7.10)	75.70 (11.89)	82.02 (11.74)	105.74 (5.30)	82.07 (10.40)	85.68 (10.83)	76.91 (8.30)	97.84 (10.02)	85.48 (5.87)	81.89 (10.13)	87.52 (10.79)
AF	22 (2.6)	135 (6.6)	0 (0.0)	101 (0.9)	846 (3.3)	476 (7.8)	0 (0.0)	313 (4.7)	246 (5.2)	205 (3.5)	398 (2.6)
IHD	73 (8.7)	1745 (85.2)	1650 (100.0)	496 (4.6)	19102 (74.6)	983 (16.1)	232 (4.9)	647 (9.8)	164 (3.5)	4418 (74.6)	6981 (45.8)
CVD	63 (7.5)	205 (10.0)	NA	271 (2.5)	5342 (20.9)	5124 (83.9)	66 (1.4)	502 (7.6)	124 (2.6)	1302 (22.0)	3014 (19.8)
DM	72 (8.6)	780 (38.1)	372 (22.5)	727 (6.7)	9612 (37.5)	761 (12.5)	NA	719 (10.9)	449 (9.6)	2118 (35.8)	4823 (31.6)
S Creat (mg/dL)	1.01 (0.27)	0.91 (0.31)	0.93 (0.37)	0.98 (0.20)	1.08 (1.05)	1.00 (0.26)	NaN (NA)	1.01 (0.28)	0.99 (0.21)	1.07 (1.01)	1.14 (0.27)
Smoking	143 (17.0)	509 (24.8)	563 (34.1)	2442 (22.4)	3225 (12.6)	1279 (21.0)	602 (100.0)	594 (9.0)	343 (7.3)	582 (9.9)	3664 (24.0)
BMI (kg/m²)	26.39 (4.53)	24.63 (2.99)	24.04 (2.94)	27.80 (4.34)	28.16 (4.77)	25.66 (3.78)	27.11 (4.79)	26.72 (4.00)	27.03 (4.10)	28.19 (4.82)	28.63 (5.04)

All categorical variables presented as N (%), and all continuous variables presented as mean (SD)

AF, atrial fibrillation; BMI, body mass index; BP, blood pressure; CVD, cerebrovascular disease; DBP, diastolic blood pressure; DM, diabetes mellitus; IHD, ischaemic heart disease; NA, not available; SBP, systolic blood pressure; S Creat, serum creatinine

Discrepancies between the data that were published for each trial and the data presented in this table may result from errors in the BPLTTC dataset, which are, though, unlikely to have influenced any analyses.

Table 6.3 Baseline characteristics of participants by atrial fibrillation status at baseline

	Atrial fibrillation	No atrial fibrillation	Total
Number	13,266	175,304	188,570
Age (years)	70.19 (9.12)	65.36 (9.05)	65.70 (9.14)
Sex (Female)	5,052 (38.1)	73,182 (41.7)	78,235 (41.5)
Ischaemic heart disease	3,923 (29.6)	56,759 (32.4)	60,682 (32.2)
Cerebrovascular disease	2,395 (18.5)	21,788 (15.5)	24,183 (15.7)
Diabetes mellitus	3,569 (26.9)	54,209 (32.2)	57,778 (31.8)
Chronic kidney disease	163 (20.3)	15,600 (25.4)	15,763 (25.3)
Smoking (current)	1,224 (9.3)	38,283 (24.3)	39,507 (23.1)
Body mass index (kg/m^2)	28.78 (5.60)	28.12 (9.67)	28.16 (9.44)
Total cholesterol (mmol/L)	5.3 (1.2)	5.6 (1.2)	5.6 (1.2)
Systolic blood pressure (mmHg)	142.8 (20.9)	154.6 (21.6)	153.82 (21.72)
Diastolic blood pressure (mmHg)	83.6 (11.7)	87.8 (12.6)	87.49 (12.58)
Pharmacological treatment			
Diuretic	6,082 (50.8)	19,196 (23.8)	25,278 (27.3)
Alpha-blocker	1,134 (10.7)	2,813 (4.4)	3,947 (5.2)
Beta-blocker	6,133 (51.3)	29,013 (36.0)	35,146 (38.0)
Angiotensin converting enzyme inhibitor	6,846 (59.6)	32,290 (44.0)	39,136 (46.1)
Angiotensin receptor blocker	568 (5.4)	6,420 (15.0)	6,988 (13.1)
Calcium channel blocker	3,557 (29.7)	29,566 (36.7)	33,123 (35.8)
Anticoagulant	4,418 (37.8)	1,823 (3.1)	6,241 (8.9)
Antiplatelet	6,443 (56.1)	35,539 (49.3)	41,982 (50.2)
Lipid lowering drug	3,742 (32.8)	31,100 (42.6)	34,842 (41.3)

All categorical variables are presented as N (% yes); all continuous variables are presented as mean (standard deviation).
Data presented in this table may not reflect data published by individual trials due to errors in the BPLTTC dataset, which are, however, unlikely to have influenced any analyses.

In placebo-controlled trials (eight trials), the difference in SBP reduction between arms was 7.2 (SD 3.9) mmHg, in drug comparison trials (twelve trials), it was 2.3 (SD 0.9) mmHg, and in more versus less intense BP lowering (two trials), it was 10.9 (SD 3.0) mmHg. Overall, the mean difference in SBP reduction between intervention and control arms was 3.7 (SD 3.2) mmHg, and that was similar in patients with and without AF (3.3 (SD 2.0) mmHg versus 3.7 (SD 3.3) mmHg for patients with and without AF, respectively).

Meta-regression showed that there was a log-linear association between the intensity of SBP lowering and the hazard ratio for major cardiovascular events, both in patients with and without AF at baseline (**Figure 6.1**).

Over a median follow up of 4.5 years (IQI 3.8 to 5.3), 3,674 (27.8%) and 21,380 (12.2%) patients with and without AF, respectively, developed a major cardiovascular event. This translates into a rate of major cardiovascular events of 73 and 28 per 1,000 patient-years for patients with and without AF, respectively (**Figure 6.2**).

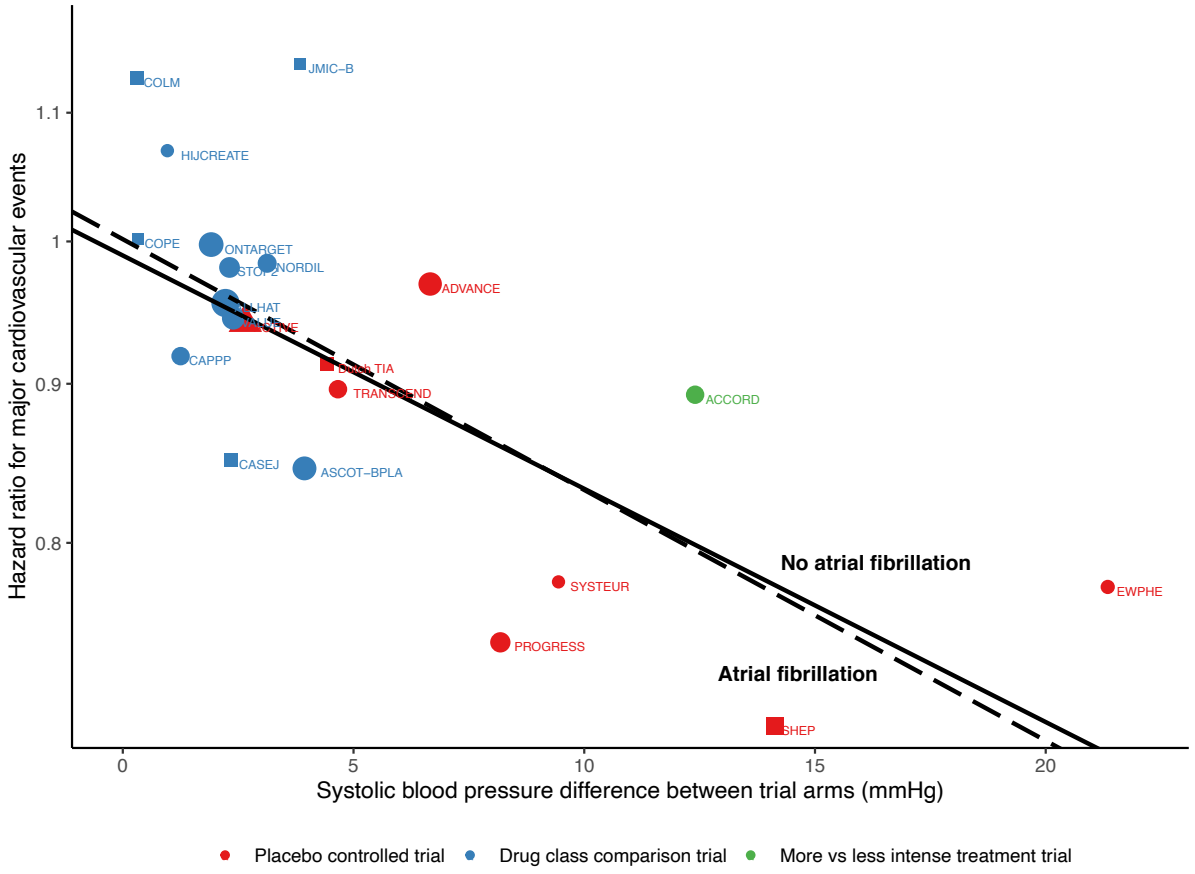

Figure 6.1 Hazard ratio for major cardiovascular events related to the one-year difference in systolic blood pressure reduction aggregated at trial level

Risk of major cardiovascular events, for patients with (dashed line) and without (solid line) atrial fibrillation at baseline, regressed against the systolic blood pressure difference between trial arms, plotted on the log scale. Shapes represent the hazard ratio for each trial with the size inversely proportional to the respective standard error. Trials are coded by shape according to the type of patients: atrial fibrillation only (triangle), no atrial fibrillation only (square), and mix of both (circles). Trials are also coded by colour according to type of intervention: placebo-controlled trials (red), drug class comparison trials (blue), and more versus less intense treatment trials (green). Systolic blood pressure difference between trial arms in mmHg.

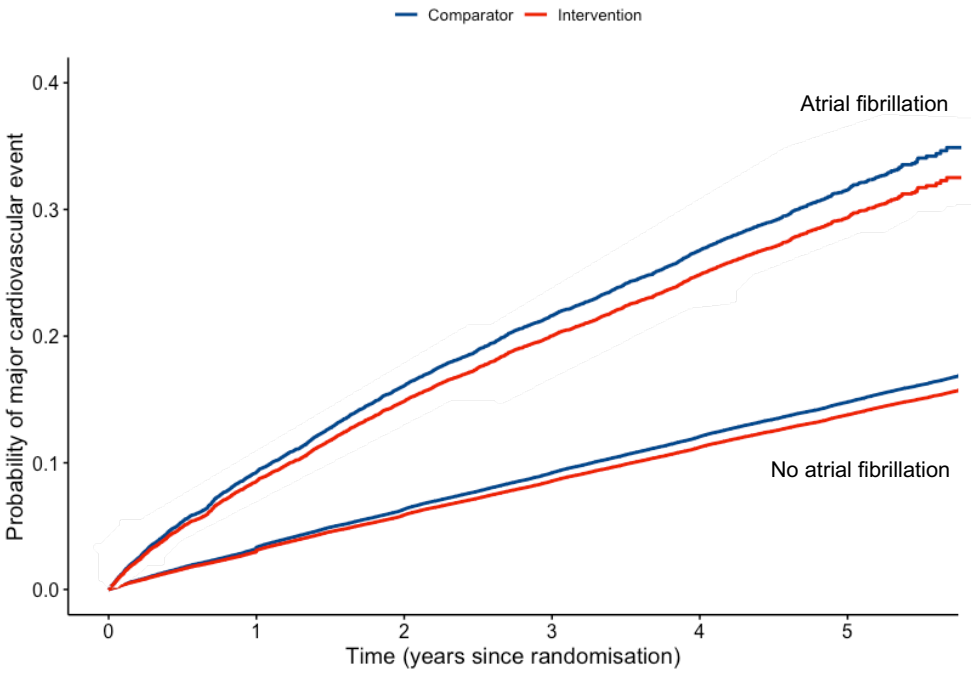

Figure 6.2 Cumulative event curves for the primary outcome (major cardiovascular events) by treatment arm, stratified by presence of atrial fibrillation at baseline

Estimated probabilities of major cardiovascular events (primary composite endpoint) according to treatment arm (intervention versus comparator as defined in treatment comparisons in the methods) are displayed for patients with atrial fibrillation (top) and without atrial fibrillation at baseline (bottom), standardised by 5-mmHg reduction in systolic blood pressure.

Each 5-mmHg decrease in SBP reduced the risk of major cardiovascular events by about 10% in patients with and without AF at baseline (HR 0.91, 95% CI [0.83 to 1.00] versus HR 0.91, 95% CI [0.88 to 0.93] for patients with and without AF at baseline, respectively) (**Figure 6.3**). Furthermore, there was no evidence that the risk reduction achieved by BP lowering treatment for any of the primary and secondary outcomes was different between patients with and without AF at baseline (**Figure 6.3**).

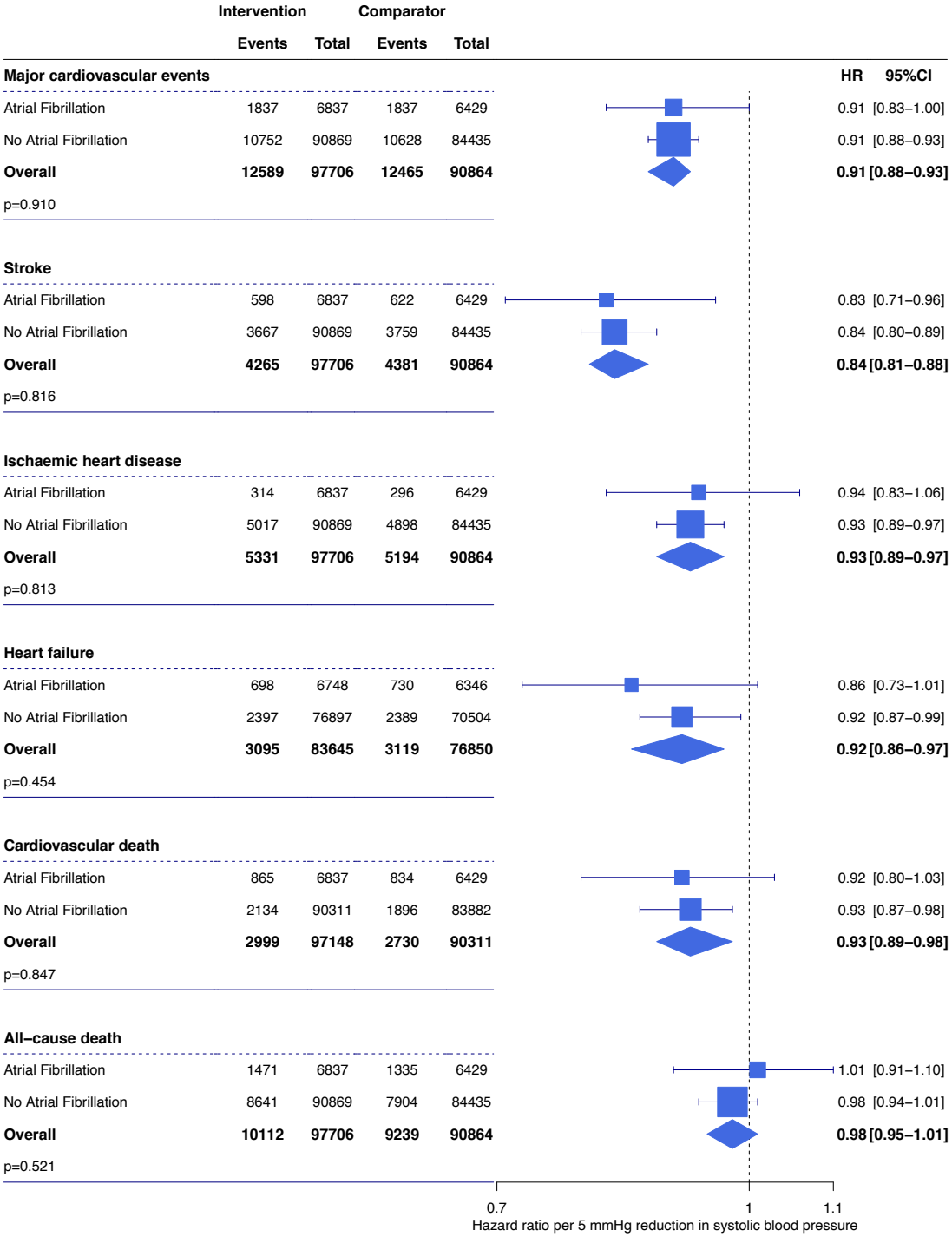

Figure 6.3 Effect of blood pressure lowering treatment on primary and secondary outcomes, stratified by presence of atrial fibrillation at baseline

Forest plot displays the hazard ratios (HR) and 95% confidence intervals (CI) for each outcome standardised by 5-mmHg reduction in systolic blood pressure. P-values for tests of difference between subgroups.

Subgroup analysis in patients with AF showed no evidence that the relative risk reduction in major cardiovascular events varied according to baseline SBP (test for linear trend p = 0.992). There was also no significant difference in treatment effects between patients with baseline SBP below and above 140 mmHg (p = 0.792) (**Figure 6.4**).

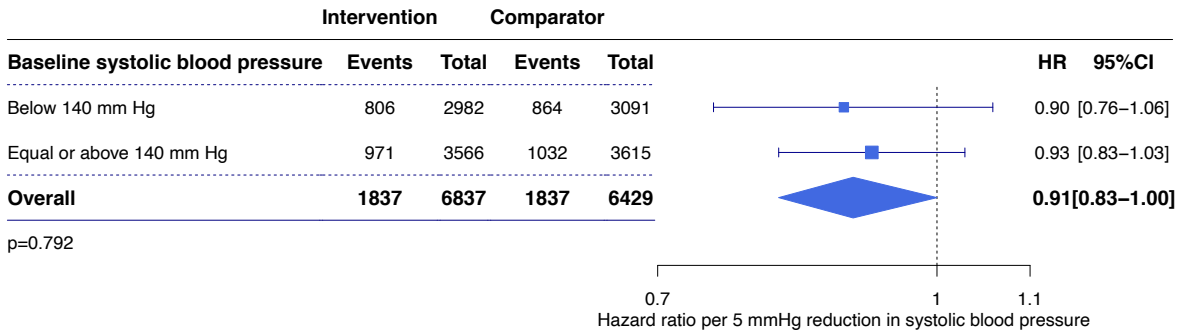

Figure 6.4 Effect of blood pressure lowering treatment on major cardiovascular events stratified by baseline systolic blood pressure in patients with atrial fibrillation

Forest plot displays the hazard ratios (HR) and 95% confidence intervals (CI) for major cardiovascular events in patients with atrial fibrillation, standardised by 5-mmHg reduction in systolic blood pressure, and stratified according to baseline systolic blood pressure (below versus equal or above 140 mmHg). P-value (0.792) for test of difference between subgroups.

Six trials were included in the comparison of RAAS inhibitors versus placebo or standard treatment (i.e., BB and/or diuretic), including 56,649 participants (**Table 6.4**). Four trials were included in the comparison of CCBs versus placebo or standard treatment (i.e., BB and/or diuretic), including 44,288 participants. The small number of trials reporting other drug class comparisons prevented further subgroup analyses (**Table 6.5**). There was no evidence that treatment effects were significantly different for regimens based on RAAS inhibitors or CCBs between patients with and without AF at baseline (p = 0.245 for RAAS inhibitors and p = 0.909 for CCBs) (**Figure 6.5**). However, the confidence intervals were wide due to the relatively small number of AF participants.

Table 6.4 Treatment comparisons for subgroup analyses by drug class

Trial	Intervention	Comparator	SBP reduction (mmHg)
Renin angiotensin aldosterone system inhibitors			
ACTIVE-I	ARB	Placebo	2.6
ALLHAT	ACEI	Diuretic	-3.0
CAPPP	ACEI	BB + Diuretic	-1.3
HIJCREATE	ARB	BB + Diuretic	1.0
STOP HT-2	ACEI	BB + Diuretic	-2.0
TRANSCEND	ARB	Placebo	4.7
Calcium channel blockers			
ALLHAT	CCB	Diuretic	-1.4
NORDIL	CCB	BB + Diuretic	-3.1
STOP HT-2	CCB	BB + Diuretic	-2.6
SYSTEUR	CCB	Placebo	9.4

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta-blocker; CCB, calcium channel blocker; SBP, systolic blood pressure

Table 6.5 Number of trials available for drug class comparisons

Drug classes		Number of trials
ARB + CCB	ARB + Diuretic	1
CCB+ACEI	BB + Diuretic	1
ACEI or ARB	BB + Diuretic	3
CCB	BB + Diuretic	2
ACEI or ARB	CCB	4 (only 2 trials of patients with atrial fibrillation)
ARB + CCB	CCB + BB	1
ARB + CCB	CCB + Diuretic	1
ACEI	Diuretic	1
CCB	Diuretic	1
ACEI or ARB	Placebo	2
ACEI + Diuretic	Placebo	2
Diu	Placebo	1
BB + Diuretic	Placebo	1
CCB	Placebo	1
BB	Placebo	1

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta-blocker; CCB, calcium channel blocker

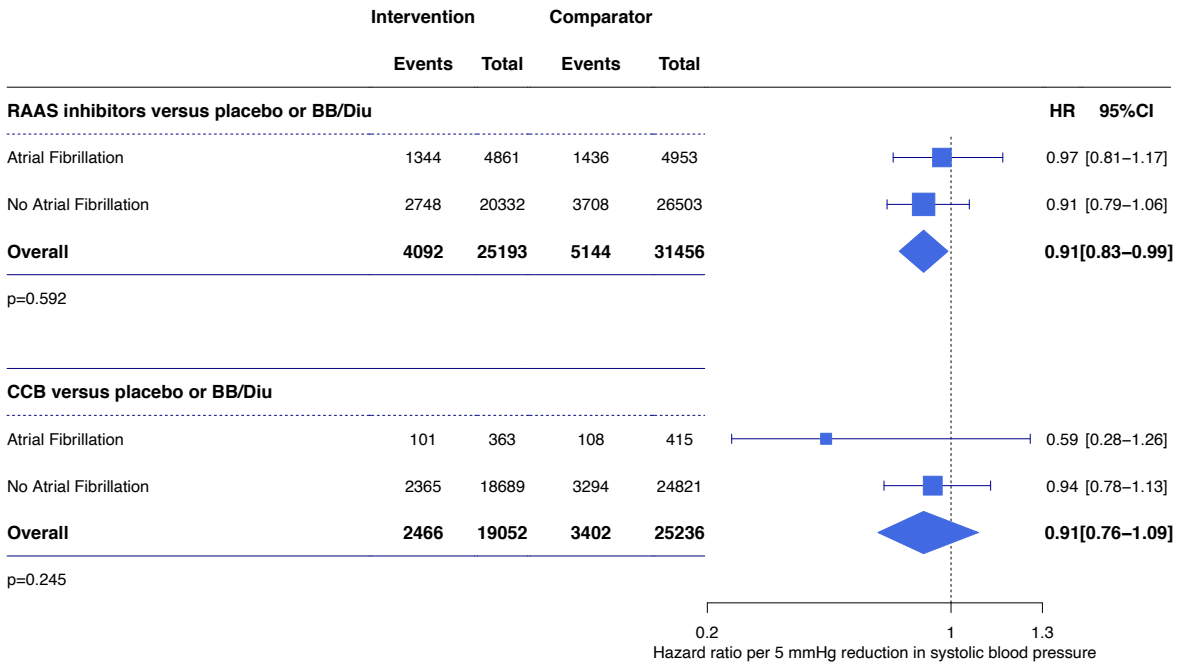

Figure 6.5 Effect of blood pressure lowering treatment on major cardiovascular events stratified by drug class in patients with and without atrial fibrillation

Forest plot displays the hazard ratios (HR) and 95% confidence intervals (CI) for major cardiovascular events standardized by 5-mmHg systolic blood pressure reduction for renin angiotensin aldosterone system (RAAS) inhibitors and calcium channel blockers (CCBs) in comparison with placebo or beta-blocker (BB) with or without diuretic (Diu). P-values for tests of difference between subgroups.

Sensitivity analysis using only trials that contributed to both subgroups, that is, the fourteen trials that included both participants with and without AF at baseline and thus allowed estimating the within-trial interaction between treatment and AF at baseline, showed broadly similar results to those from the main analyses. However, the smaller sample size meant that the confidence intervals were wider, particularly in patients with AF at baseline (Table 6.6). Sensitivity analysis using a two-stage approach yielded similar estimates to the one-stage approach overall and for subgroup analysis according to AF status at baseline (Figure 6.6). There were also no material differences between fixed effect and random effects models in the two-stage approach (Table 6.6).

Table 6.6 Sensitivity analyses for major cardiovascular events including only trials with a mix of patients with and without atrial fibrillation at baseline (N=14)

	Hazard ratio	95% Confidence interval
One-stage model using fixed effect meta-analysis		
Atrial fibrillation	0.94	[0.83 to 1.06]
No atrial fibrillation	0.91	[0.89 to 0.94]
All (test for difference between subgroups p = 0.68)	0.91	[0.89 to 0.94]
Two-stage model using fixed effect meta-analysis		
Atrial fibrillation (I^2 = 24%, p = 0.20)	0.94	[0.84 to 1.05]
No atrial fibrillation (I^2 = 28%, p = 0.15)	0.92	[0.89 to 0.94]
All (I^2 = 37%, p = 0.08)	0.92	[0.89 to 0.94]
Two-stage model using random effects meta-analysis		
Atrial fibrillation (I^2 = 19%, p = 0.20)	0.91	[0.79 to 1.06]
No atrial fibrillation (I^2 = 40%, p = 0.15)	0.91	[0.87 to 0.95]
All (I^2 = 45%, p = 0.08)	0.91	[0.87 to 0.95]

All models were standardised by 5-mmHg reduction in systolic blood pressure

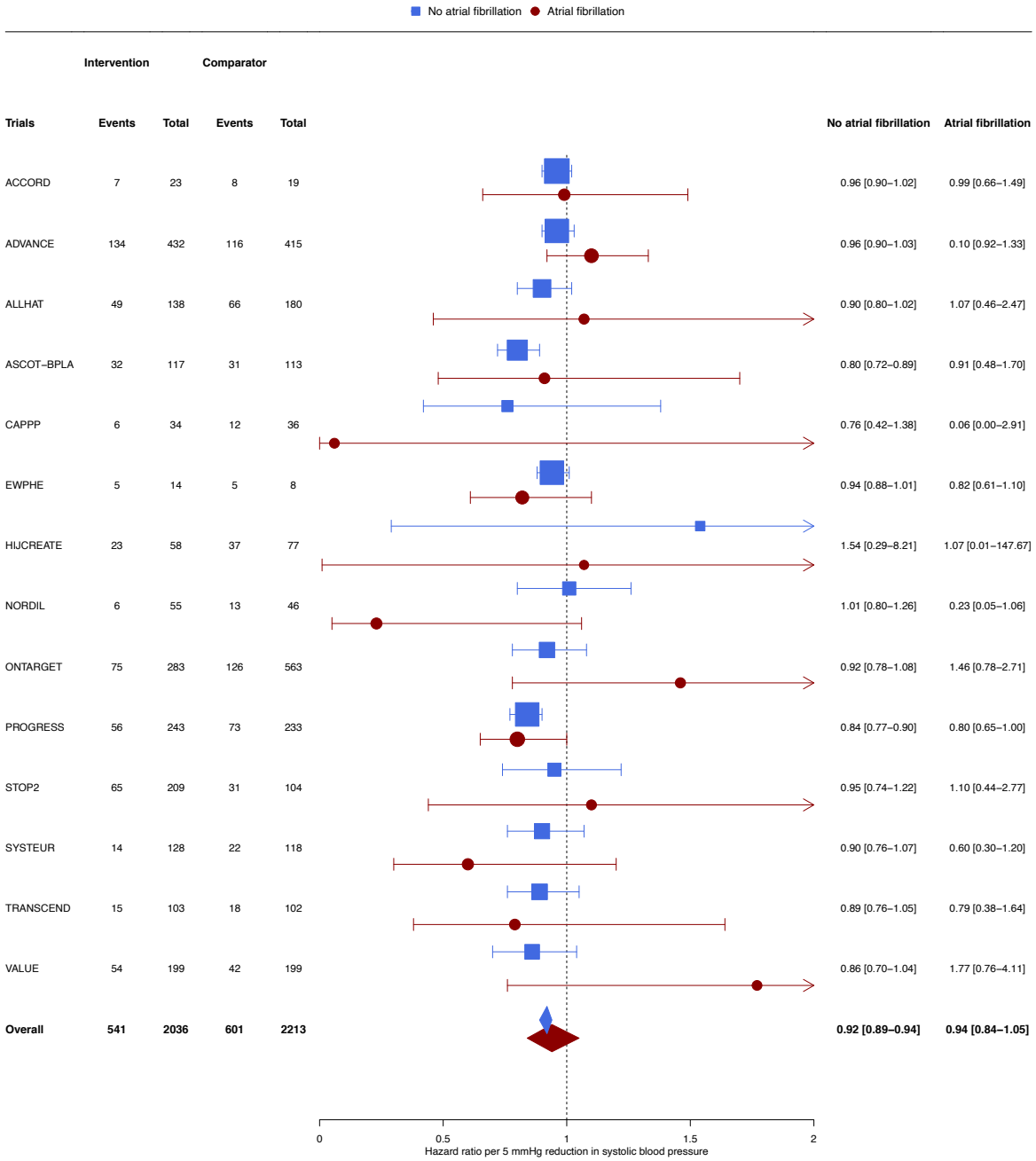

Figure 6.6 Effect of blood pressure lowering treatment on major cardiovascular events, stratified by presence of atrial fibrillation at baseline with separate estimates for each trial

Forest plot displays the hazard ratios and 95% confidence intervals for major cardiovascular events standardised by 5-mmHg reduction in systolic blood pressure in patients with and without atrial fibrillation at baseline.

Discussion

This study demonstrated that BP lowering treatment afforded a similar relative risk reduction in major cardiovascular events in patients with and without AF, with no evidence that treatment effects differed between those subgroups for any of the primary and secondary outcomes. Overall, each 5-mmHg reduction in SBP resulted in an approximately 10% lower risk of major cardiovascular events both in patients with and without AF at baseline. Furthermore, there was no evidence that, in patients with AF, the relative risk reduction varied depending on whether baseline SBP was above or below the conventional treatment threshold of 140 mmHg or according to the drug class used.

Although absolute risks are better estimated from population-based studies, the almost three-fold higher event rate that I observed in patients with AF at baseline compared with those without AF reflects their higher cardiovascular risk. This is in keeping with previous observational studies that reported that AF was associated with a two- to five-fold higher risk of major cardiovascular events in comparison with patients without AF.[86,421,422] Therefore, the similar relative risk reduction afforded by BP lowering treatment in patients with and without AF would translate into a larger absolute risk reduction in those with AF at baseline.

It is thus a paradox that much of the emphasis of AF-related research has been on anticoagulation for stroke prevention, and strategies for rate control or restoration of sinus rhythm, when the relative and absolute risk for cardiovascular events, such as HF and ischaemic heart disease, is greater than that of stroke in those patients.[422] The narrow focus on those two treatment pillars is failing to stem the tide of cardiovascular deaths in patients

with AF, thus suggesting that risk factors other than AF itself may be actually driving the increased cardiovascular risk.[423,424] Indeed, even with optimal anticoagulation and rate or rhythm control, the risk of stroke in patients with AF remains high (about 1.5% per year),[425] and this seems to result from associated risk factors rather than treatment failure.[426,427] Therefore, management of concurrent cardiovascular risk factors, among which high BP with an estimated prevalence of 70% is the most common, is a priority to improve cardiovascular outcomes and survival in the high-risk group of patients with AF.[428]

Although the most recent AF guidelines issued by the European Society of Cardiology state that "good BP control should form an integral part of the management of AF patients", randomised evidence has been lacking to support those recommendations.[102] This uncertainty underpins the cautious AF guidelines of the American College of Cardiology, which despite mentioning that "appropriate control of risk factors like hypertension substantially reduces stroke risk", make no specific recommendations about BP management in patient with AF.[417] In this context, my study provides compelling evidence that pharmacological BP lowering is an effective strategy to prevent cardiovascular events overall, and in particular to address the residual risk of stroke. Furthermore, my study suggested that patients with AF included in RCTs had a relatively low baseline SBP, with almost half of them not meeting the recommended threshold for treatment initiation of 140 mmHg.[39] However, stratified analyses according to baseline SBP demonstrated that the risk reduction afforded by BP reduction was similar above or below the 140 mmHg threshold. This is in keeping with the growing evidence that the association between BP and cardiovascular risk is continuous and hence treatment strategies based on risk rather than on arbitrary BP thresholds may be

more appropriate.[46,114] Nonetheless, even with intense BP lowering to under 120/80 mmHg, patients with AF remain at increased risk of cardiovascular events in comparison with those without AF (HR 1.88, 95% CI [1.32 to 2.70], p = 0.001).[388] This underscores the importance of a adopting a multipronged approach to manage cardiovascular risk in patients with AF.

On the other hand, hypertension guidelines recommend that drugs with shared rate and BP lowering properties (e.g., non-dihydropyridine CCBs and BBs) should be preferred in patients with AF and high BP.[39,41] However, those recommendations are based on the indication of those drugs for rate control as thus far whether pharmacological BP lowering decreased cardiovascular risk in patients with AF had not been demonstrated. In addition, the lack of evidence for class-specific effects, together with the log-linear association between the hazard ratio for major cardiovascular events and SBP reduction showed in my study, suggests that the intensity of BP lowering is more important than the specific drugs used to achieve it. Therefore, BP lowering seems an effective strategy to decrease the high cardiovascular risk of patients with AF, and whether certain drug classes have benefits above and beyond what would be expected for equivalent BP reduction is yet to be established.

The main strengths of this IPD meta-analysis are (1) the analysis of the effects of BP lowering treatment in a large number of patients with baseline AF included in RCTs, (2) the direct comparison of patients with and without AF, (3) the long follow-up time, and (4) the more than 20,000 major cardiovascular events reported during follow-up. Access to unpublished data regarding AF status at baseline increased the power to investigate the interaction between AF at baseline and BP lowering treatment. The robustness of the main conclusions

to sensitivity analyses and the consistency of the estimates provided by different methods further support the conclusions drawn. However, some limitations deserve to be acknowledged. The number of participants with AF was modest considering the total number of participants in the BPLTTC, because only a fraction of the trials reported AF at baseline and, among those, the rate of AF was relatively low. On the other hand, this meant that, even if a degree of misclassification was present due to omitted disclosure or the paroxysmal nature of the arrhythmia, a material impact on treatment effect estimates would be unlikely. Although it would have been interesting to compare the effects of other drug classes, particularly in head-to-head comparisons, data were insufficient to perform further subgroup analyses. Finally, concerns have been raised about the variability of BP measurement in patients with AF, which could have biased my estimates, but there was no evidence of this in my study population as the difference in SBP reduction between treatment and control arms was identical within each trial for patients with and without AF at baseline.[419] Therefore, this is unlikely to have biased my estimates of relative treatment effects, due to the randomised nature of the comparisons.

Conclusion

In conclusion, this study demonstrated that BP lowering treatment reduces the risk of major cardiovascular events in patients with AF to a similar extent to that of patients without AF, even when baseline BP is below recommended treatment thresholds. Owing to their higher absolute cardiovascular risk, treatment in patients with AF is likely to result in greater absolute risk reduction than in patients without AF. Guidelines should be updated to

recommend pharmacological BP lowering for prevention of cardiovascular events in patients with AF.

Chapter 7 Blood Pressure and Multimorbidity

This chapter focuses on the management of BP in the context of cardiometabolic multimorbidity. It describes the IPD meta-analysis of RCTs that I conducted (1) to describe common clusters and patterns of multimorbidity that can be identified in patients included in large trials of BP lowering treatment; and (2) to compare the effects of pharmacological BP lowering on cardiovascular outcomes in patients with different numbers and patterns of cardiometabolic diseases.

The chapter is organised into two sections. The first section comprises the main study that investigated the effects of BP lowering in patients with different numbers and patterns of diseases. The second section describes the cluster analysis that I explored as a novel tool to identify subgroups of patients with multimorbidity in RCTs. However, for reasons that are discussed in greater depth in the respective section, I decided to pursue the main analyses based on the number and patterns of diseases, rather than clusters. Therefore, the first section follows the structure of a scientific paper, as I aim to submit it to a journal in due course. The second section follows a less formal structure, which is in line with the exploratory nature of the analysis.

Effects of blood pressure lowering treatment on major cardiovascular events according to number and pattern of cardiometabolic diseases

Abstract

Background and Aims

Although multimorbidity has been rapidly growing in patients with high BP, evidence is lacking on the efficacy of BP lowering in those patients. Therefore, this study aimed to compare the effects of BP lowering treatment in patients with different numbers and patterns of cardiometabolic diseases.

Methods

IPD were extracted from all trials with over 1,000 person-years of follow-up that had randomly assigned patients to different classes of BP lowering drugs, BP lowering drugs versus placebo, or more versus less intensive BP lowering regimens. The effects of BP lowering treatment on a composite endpoint of major cardiovascular events (stroke, ischaemic heart disease or HF) were estimated using one-stage IPD meta-analyses based on Cox proportional hazards models stratified by trial, assuming a fixed treatment effect. Heterogeneity of treatment effects was investigated according to the number and pattern of cardiometabolic diseases at baseline, which comprised hypertension, ischaemic heart disease, cerebrovascular disease, chronic kidney disease, diabetes mellitus and obesity.

Results

A total of 48 trials were included with 330,460 patients, of whom 133,760 (40%) had cardiometabolic multimorbidity (i.e., two or more concurrent diseases) at baseline. BP lowering reduced the risk of major cardiovascular events by 10% (HR 0.90, 95% CI 0.88 to 0.92) per each 5-mmHg reduction in SBP, with no difference between subgroups based on the number of baseline diseases. There was also no evidence that treatment effects varied significantly according to the number of diseases for the individual components of the composite primary endpoint. Furthermore, meta-regression showed that relative risk reductions were proportional to trial-level intensity of SBP lowering, irrespective of the number of diseases. Among the most common multimorbidity patterns, there was no evidence that the relative reduction in major cardiovascular events differed from the approximately 10% achieved in patients with isolated hypertension.

Conclusions

BP lowering reduces the risk of major cardiovascular events to a similar extent regardless of the number of cardiometabolic diseases at baseline. However, patients with more diseases, who inherently have an increased cardiovascular risk, will benefit from a larger absolute risk reduction. Further randomised evidence is warranted to better understand how different multimorbidity patterns interact with BP treatment, particularly regarding non-cardiometabolic diseases.

Background

Multimorbidity is a growing epidemic worldwide, and it is strongly associated with population ageing.[105,108,109] Multimorbidity is also increasingly common in patients with cardiovascular disease, among whom hypertension is the most common disease.[110] As high BP is the leading modifiable risk factor for cardiovascular disease, adequate BP management in patients with cardiometabolic multimorbidity is crucial to reduce cardiovascular risk.

However, evidence on the efficacy of pharmacological BP lowering in patients with multimorbidity remains limited because they have typically been excluded or underrepresented in RCTs.[429,430] This underpins the contradictory and cautious recommendations regarding BP management in contemporary guidelines.[17,39,41,117] There is thus a pressing need for "more outcome studies of the optimal treatment target for patients at different levels of baseline cardiovascular risk and with different diseases, including diabetes and chronic kidney disease" (European Society of Cardiology, 2018).[39] Despite this lack of evidence, to my knowledge, not a single trial has reported treatment effects on cardiovascular outcomes according to multimorbidity status. Therefore, this study aimed to investigate whether the effects of BP lowering treatment on fatal and non-fatal cardiovascular outcomes varied according to the number and patterns of cardiometabolic diseases at baseline.

Methods

Study design

I conducted an IPD meta-analysis of BP lowering RCTs that investigated treatment effects on cardiovascular outcomes in patients with cardiometabolic multimorbidity according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses of IPD (PRISMA-IPD) guidelines.[302] The study relied on the dataset provided by the BPLTTC. A detailed description of the BPLTTC is provided in Chapter 3. In this study, I only included trials for which time-to-event data were available. I retrieved information about cardiometabolic multimorbidity at baseline for all trials that either published or included the variables of interest in the dataset provided to the collaboration.

Components of multimorbidity

I considered all diseases that were available at baseline in the BPLTTC dataset (**Table 7.1**). However, the proportion of missing data varied substantially among those baseline diseases, to the extent that some had been reported in less than half of the participants. I included in this study all the diseases for which less than 25% of the data were missing. Therefore, HF, anaemia and peripheral vascular disease were excluded, and the following cardiometabolic conditions were included: hypertension, ischaemic heart disease, cerebrovascular disease, chronic kidney disease, diabetes mellitus and obesity. Considering ischaemic heart disease, cerebrovascular disease, chronic kidney disease and diabetes mellitus as diseases is not

contentious, but the inclusion of hypertension and obesity is more controversial, as both can be considered as standalone diseases or as risk factors for other diseases.[431] Nonetheless, international medical associations and health organisations have consensually recognised obesity as a complex chronic disease,[432-435] and hypertension is included in about 85% of commonly used multimorbidity indices.[436] Furthermore, both are regarded as separate pathophysiological entities by the most recent revision of the International Statistical Classification of Diseases and Related Health Problems issued by the World Health Organisation,[437] and by the Quality and Outcomes Framework in England.[438] Therefore, I decided to include obesity and hypertension in the definition of multimorbidity, following the precedent of other studies.[105,110]

Participants were considered to have hypertension if they met one the following criteria: BP above 130/80 mmHg at baseline, use of antihypertensive medication at baseline, or previous diagnosis of hypertension.[41] Obesity was defined as body mass index (BMI) equal to, or above, 30 kg/m^2. Data for all other baseline diseases were directly extracted from each trial dataset, apart from chronic kidney disease. Whenever data regarding previous diagnosis of chronic kidney disease were missing, they were estimated using the glomerular filtration rate, calculated using serum creatinine values provided by each study. For this, the Cockcroft-Gault equation was used because the more recent CKD-EPI equation required data for race, which were not available for 20% of the participants. A cut-off of estimated glomerular filtration rate below 45 mL/min/1.73 m^2 was used to define chronic kidney disease.[439]

Table 7.1 Missing data for baseline diseases

Baseline disease	Number of trials with systematically missing data	Patient level missing data (N and %)[1]	Trial level missing data (N and %)[1]	Overall missing data (N and %)[2]
Hypertension	0	0	0	0
Ischaemic heart disease	1	187 (13.4%)	1,209 (86.6%)	1,396 (0.4%)
Cerebrovascular disease	8	196 (0.3%)	69,431 (99.7%)	69,431 (21%)
Chronic kidney disease	0	22,521 (100%)	0	22,521 (7%)
Diabetes mellitus	1	126 (1.0%)	12,218 (98.9%)	12,344 (4%)
Obesity	5	2,337 (3.8%)	58,176 (96.1%)	60,513 (18%)
Heart failure	47	0	314,499 (100%)	314,499 (95%)
Peripheral artery disease	28	0	192,005 (100%)	192,005 (58%)
Anaemia	1	15,245 (5.5%)	259,511 (94.5%)	274,756 (83%)
Total	48			330,460

[1] Percentages represent the percentage of missing data at patient and trial level

[2] Percentages represent the overall percentage of missing data for each variable

Handling of missing data

For all diseases, multilevel multiple imputation was used to deal with data missingness, due to the hierarchical structure of the data.[364] In the study population, systematic missing data was the most common type of missing data because some trials did not report certain baseline diseases (**Table 7.1**). Multilevel imputation was performed using a joint multivariate normal Bayesian model fitted by Markov Chain Monte Carlo analysis.[393] This method assumed that the partially observed data followed a joint multivariate normal distribution, and then a Gibbs sampler used the proper conditional distributions to update the parameters of the model and impute the missing data.[394] After imputation, Rubin's rules were used to analyse the imputed datasets and pool the resulting model estimates.[395] The missing data were imputed using information from the maximum number of predictors that the model could handle, whilst avoiding collinearity. The model included, as fixed effects, age, sex, baseline ischaemic heart disease, baseline cerebrovascular disease, baseline type 2 diabetes mellitus, weight, height, haemoglobin, SBP, DBP, total cholesterol, serum glucose, serum creatinine and randomisation arm. In addition, the matrix of the random effects included a random intercept for trial and a random slope for randomisation arm. Convergence was confirmed by looking at the trace plot for each imputed variable. Based on this, I used 2,000 burn-in iterations, and I selected five imputed datasets, spread at least 1,000 iterations apart.

Validation of the multiple imputation was done by removing one variable from a single trial at a time and then running the multiple imputation algorithm. I performed this twice (i.e., for two different trials) for each of the baseline diseases to confirm that the algorithm was

imputing the missing values accurately and that performance was consistent across trials. The percentage of agreement between the actual data and the imputed data for categorical variables varied between 90 and 92%. For instance, for diabetes mellitus, I deleted the data for the SPRINT trial and ran the multiple imputation algorithm. I then calculated the percentage of agreement between the true data as reported in the trial dataset and the imputed data generated by the algorithm, which was 91.3%. I then repeated the procedure for the VALUE trial and obtained a percentage of agreement of 90.2%, which meant that in 90.2% of the patients the presence and absence of diabetes was correctly determined by the algorithm. For continuous variables (i.e., weight, height and serum creatinine), I confirmed that there was an almost perfect overlap between the histograms of the actual and imputed data, and I also verified that the parameters of the distribution (IQI, median, mean and SD) matched up to one decimal place in the imputed and actual data.

Definition of multimorbidity

I used two complementary definitions of multimorbidity. First, I followed the standard definition based on disease counting, grouped here as one, two, three and four to six, to avoid small numbers of patients in the top categories. I also performed supplementary analysis for the primary outcome using all six categories. As 98% of the participants had hypertension at baseline, the category of one disease represented patients with isolated hypertension (i.e., patients with no additional disease), and the other categories represented patients with hypertension and one other disease, two other diseases and three or more other diseases. Hypertension is not the index disease because there is no temporal relationship between the

onset of hypertension and the other diseases, in which case it would have been more appropriate to talk about comorbidity, rather than multimorbidity. I adopted those labels to make it clear that, in each category, all patients had hypertension and a variable number of the other five cardiometabolic diseases. Therefore, all patients, other than those with isolated hypertension, met with the conventional definition of multimorbidity as the coexistence of two or more chronic diseases.[103]

Second, I stratified participants into multimorbidity patterns based on the cardiometabolic diseases included in this study. I investigated the thirty-two different combinations that were possible with the other five diseases, in addition to hypertension. Isolated hypertension was considered the reference category in all the analyses based on either numbers or patterns of diseases.

Definition of outcomes

The primary outcome was total cardiovascular events, defined as the first occurrence of (1) fatal or non-fatal stroke; (2) fatal or non-fatal myocardial infarction or ischaemic heart disease; or (3) HF causing death or requiring hospitalisation. Secondary outcomes were the individual elements of the composite endpoint, as well as cardiovascular death and all-cause death. All outcomes were as reported in the original trials.

Treatment comparisons

For the main analysis, intervention and control groups were compared. For placebo-controlled trials, the placebo arm was considered as the "comparator" and the active treatment was considered as the "intervention". For trials with two or more active treatment arms, the arm in which the BP reduction was greater was considered as "intervention" and the other treatment arm(s) as "comparator". For trials that compared different intensities of BP lowering, the more intense arm was considered as "intervention" and the less intense arm was considered as "comparator". Table 7.2 summarises the treatment comparisons considered in each trial and the respective difference in SBP reduction between trial arms.

Table 7.2 Difference in systolic blood pressure reduction between arms for each trial

Trial	Intervention	Comparator	SBP reduction (mmHg)
Placebo-controlled trials			6.1 (SD 3.5)
ACTIVE-I	ARB	Placebo	2.6
ADVANCE	ACEI + Diuretic	Placebo	6.7
ANBP	Diuretic	Placebo	9.7
BENEDICT	ACEI or CCB or ACEI + CCB	Placebo	0.6
CAMELOT	ACEI or CCB	Placebo	7.3
DIABHYCAR	ACEI	Placebo	2.1
EUROPA	ACEI	Placebo	4.9
EWPHE	Diuretic	Placebo	21.3
HOPE	ACEI	Placebo	3.2
HYVET	Diuretic	Placebo	12.0
PART2	ACEI	Placebo	5.9
PEACE	ACEI	Placebo	4.8
PREVENDIT	ACEI	Placebo	4.4
PREVENT	CCB	Placebo	5.8
PROGRESS	ACEI + Diuretic	Placebo	8.2
SHEP	BB + Diuretic	Placebo	14.1
SYSTEUR	CCB	Placebo	9.4
TRANSCEND	ARB	Placebo	4.7

Drug-class comparison trials			1.6 (SD 1.1)
ALLHAT	Diuretic	ACEI or CCB	2.2
ASCOT	CCB + ACEI	BB + Diuretic	3.9
ANBP2	Diuretic	ACEI	1.9
CAPPP	BB + Diuretic	ACEI	1.3
CASE-J	ARB	CCB	2.3
COLM	ARB + CCB	ARB + Diuretic	0.3
CONVINCE	CCB	BB + Diuretic	0.1
COPE	CCB + ARB	CCB + Diuretic or CCB + BB	0.3
ELSA	CCB	BB	2.2
HIJCREATE	ARB	BB + Diuretic	1.0
INSIGHT	Diuretic	CCB	0.3
INVEST	CCB	BB	0.3
MOSES	CCB	ARB	4.0
NICSEH	CCB	Diuretic	0.2
JMICB	CCB	ACEI	3.8
LIFE	ARB	BB	1.1
NORDIL	BB + Diuretic	CCB	3.1
ONTARGET	ARB and ACEI	ACEI or ARB	2.3
STOP HT-2	BB + Diuretic	ACEI or CCB	2.3
VALUE	CCB	ARB	2.4
VHAS	CCB	Diuretic	1.4
BP lowering intensity trials			10.1 (SD 5.1)
AASK	More intense treatment	Less intense treatment	12.8
ABCD	More intense treatment	Less intense treatment	11.2
ACCORD	More intense treatment	Less intense treatment	12.4
CARDIO-SIS	More intense treatment	Less intense treatment	4.7
HOMED-BP	More intense treatment	Less intense treatment	2.0
SPRINT	More intense treatment	Less intense treatment	14.7
UKPDS	More intense treatment	Less intense treatment	8.8
VALISH	More intense treatment	Less intense treatment	3.1
Overall			3.5 (SD 3.7)

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta-blocker; CCB, calcium channel blocker; SBP, systolic blood pressure

Statistical analysis

For both definitions of multimorbidity, I aimed to address two questions:

1. Whether the number or pattern of diseases at baseline modified treatment effects;
2. Whether the associations between the intensity of BP reduction and the primary outcome were similar across numbers of diseases and multimorbidity patterns.

Intention-to-treat analysis was adopted, after my internal quality checks had been carried out to ensure that data were accurate and transferred without error. To address the research questions described above, I used a one-stage approach that applied a single statistical model to IPD from all trials simultaneously. After confirming that the proportional hazards assumption was not violated, I performed time-to-event meta-analyses by applying Cox proportional hazard models stratified by trial, which assumed a fixed treatment effect.[398]

To account for differences in intensity of BP lowering between trials, treatment effect estimates were standardised for a 5-mmHg reduction in SBP. This standardisation was applied to treatment estimates by including an interaction term between difference in SBP reduction between arms and treatment (further details provided in Chapter 4).[398]

Furthermore, to assess whether the associations between the intensity of SBP lowering and cardiovascular outcomes were similar across categories of baseline diseases, I used analytical and graphical representations of the Cox regression model with additional terms for baseline diseases and interactions between treatment, difference in SBP and baseline diseases. This model described treatment effects on primary and secondary outcomes per unit of intensity

of SBP lowering, for each of the subgroups of baseline diseases. Wald tests were used to test for differences between subgroups. Hazard ratios with 95% confidence intervals were reported and results were presented using forest plots.

Supplementary sensitivity analyses were performed to (1) compare one-stage with two-stage approaches using fixed effect and random effects meta-analysis for the overall model; (2) compare the estimates based on the imputed dataset with complete-case analysis for analysis based on number of diseases; (3) investigate treatment-covariate interactions without standardisation for the intensity of SBP lowering for analysis based on the number of diseases. For the two-stage meta-analyses, Cox regression models were initially fitted to each trial. Then, the estimates from each trial were combined using fixed effect and random effects models with inverse variance weighting to calculate summary estimates with 95% confidence intervals. The analyses were standardised by 5 mmHg reduction in SBP using a method that had been applied in similar studies.[5,353] The log of the summary statistic of each trial was multiplied by 5/delta (and the variance by $(5/delta)^2$), where delta was the difference between the mean SBP reduction in the intervention and control arms for each trial. Heterogeneity between studies was quantified using I^2 statistic and Cochran's Q test. All p-values were calculated from two-tailed tests. Statistical analyses were performed using the packages "jomo", "mitml", "metafor", "lmer" and "survival" for R version 3.6.1.[394,399,400]

Results

From the full BPLTTC database, two trials (3,759 participants) were excluded due to lack of time-to-event data.[440,441] Forty-eight trials were eligible and provided data for the IPD meta-analyses (**Table 7.3**). The study population included a total of 330,460 participants, of whom 98% had hypertension at baseline. A total of 71,262 (22%) had isolated hypertension at baseline, 125,528 (38%) had hypertension and one disease, 95,536 (29%) had hypertension and two diseases, and 38,134 (12%) had hypertension and three or more diseases (**Table 7.4**).

The mean age overall was 66 (SD 9) years, which was also the mean age in participants with hypertension and up to three diseases. Overall, the mean baseline SBP/DBP was 153/87 mmHg. Participants with hypertension and two or more diseases tended to have lower baseline SBP/DBP, whilst those in the subgroup with isolated hypertension had higher baseline SBP/DBP. Ischaemic heart disease was the most common disease in participants with hypertension and one or two diseases, whilst diabetes was the most common disease in those with hypertension and three or more diseases. Most trials included a mixed population with isolated hypertension and up to three diseases, but only twelve trials included patients with hypertension and five diseases (**Table S7.1 in Appendix A**).

Table 7.3 Characteristics of participants included in this meta-analysis stratified by trial

	Age	Sex (Female)	SBP (mmHg)	DBP (mmHg)	IHD	CVD	DM	CKD	BMI (kg/m^2)	T Chol (mg/dL)
AASK	54.10 (10.67)	424 (38.8)	150.30 (23.85)	95.52 (14.21)	564 (51.6)	16 (1.5)	0 (0.0)	1094 (100.0)	30.57 (6.59)	211.70 (45.50)
ABCD	58.54 (8.34)	371 (39.1)	145.73 (17.74)	91.06 (8.43)	70 (7.4)	26 (2.7)	950 (100.0)	171 (18.0)	31.63 (5.83)	217.98 (54.23)
ACCORD	62.73 (6.68)	2258 (47.7)	139.00 (15.28)	75.79 (9.97)	650 (13.7)	307 (6.5)	4733 (100.0)	41 (0.9)	32.15 (5.49)	NA
ACTIVE	70.11 (9.73)	3542 (39.3)	138.25 (17.40)	82.39 (11.30)	2294 (25.4)	1230 (13.6)	1785 (19.8)	1269 (14.1)	29.07 (5.77)	NA
ADVANCE	65.77 (6.39)	4735 (42.5)	145.02 (21.54)	80.65 (10.93)	2380 (21.4)	1438 (12.9)	11140 (100.0)	597 (5.4)	28.34 (5.19)	200.96 (46.12)
ALLHAT	66.86 (7.69)	19841 (46.8)	146.28 (15.66)	84.00 (10.06)	5470 (12.9)	37328 (88.0)	15283 (36.0)	3057 (7.2)	29.50 (5.86)	215.87 (43.16)
ANBP	50.20 (8.95)	1257 (36.7)	157.42 (14.72)	100.45 (3.92)	16 (0.5)	0 (0.0)	0 (0.0)	240 (7.0)	26.66 (3.91)	230.87 (44.29)
ANBP2	72.80 (4.93)	3111 (51.1)	167.71 (12.60)	90.83 (8.12)	229 (3.8)	276 (4.5)	441 (7.2)	6 (0.1)	27.12 (4.22)	219.35 (39.48)
ASCOT-BPLA	63.00 (8.48)	4515 (23.4)	164.01 (18.01)	94.65 (10.37)	5284 (27.4)	2121 (11.0)	5145 (26.7)	12017 (62.4)	28.72 (4.57)	228.41 (41.61)
BENEDICT	62.34 (8.05)	570 (47.1)	150.89 (14.30)	87.48 (7.66)	1205 (99.7)	114 (9.4)	1209 (100.0)	0 (0.0)	29.08 (4.72)	210.13 (36.79)
CAMELOT	57.67 (9.73)	526 (26.3)	129.08 (15.86)	77.48 (9.13)	1857 (93.0)	81 (4.1)	364 (18.2)	25 (1.3)	29.77 (5.34)	182.49 (39.61)
CAPPP	52.06 (8.38)	5111 (46.5)	160.72 (20.02)	98.95 (10.03)	201 (1.8)	160 (1.5)	572 (5.2)	28 (0.3)	27.85 (4.39)	239.06 (45.39)
CARDIOSIS	66.99 (7.36)	653 (58.8)	158.27 (8.50)	87.23 (8.08)	128 (11.5)	91 (8.2)	0 (0.0)	0 (0.0)	27.82 (4.18)	216.41 (42.01)
CASEJ	63.85 (10.54)	2106 (44.8)	162.85 (14.18)	91.70 (11.19)	596 (12.7)	473 (10.1)	2018 (42.9)	2720 (57.8)	24.55 (3.66)	NA)
COLM	73.62 (5.38)	2488 (48.4)	157.99 (12.61)	86.97 (10.79)	563 (11.0)	751 (14.6)	1362 (26.5)	110 (2.1)	24.27 (3.45)	202.10 (37.73)
CONVINCE	65.62 (7.40)	9224 (56.0)	150.10 (15.95)	86.79 (9.83)	3820 (23.2)	1019 (6.2)	3244 (19.7)	0 (0.0)	NA	NA

COPE	63.65 (10.72)	1624 (49.3)	153.91 (11.56)	88.80 (9.74)	109 (3.3)	126 (3.8)	466 (14.2)	847 (25.7)	24.55 (3.39)	211.36 (36.26)
DIABHYCAR	65.05 (8.34)	1480 (30.1)	145.43 (15.12)	82.28 (8.60)	739 (15.0)	754 (15.4)	4912 (100.0)	231 (4.7)	29.18 (4.59)	NA
Dutch TIA	64.43 (10.23)	534 (36.3)	157.28 (24.59)	90.80 (11.96)	138 (9.4)	1473 (100.0)	79 (5.4)	92 (6.2)	NA	NA
ELSA	56.65 (7.56)	1065 (45.6)	159.53 (15.29)	98.18 (7.97)	305 (13.1)	0 (0.0)	98 (4.2)	163 (7.0)	27.22 (3.79)	225.39 (38.39)
EUROPA	60.70 (9.33)	1779 (14.6)	137.15 (15.46)	81.73 (8.21)	12218 (100.0)	222 (1.8)	5217 (42.7)	0 (0.0)	27.43 (3.50)	207.80 (40.57)
EWPHE	71.77 (8.03)	586 (69.8)	182.63 (16.48)	100.54 (7.10)	73 (8.7)	63 (7.5)	72 (8.6)	2 (0.2)	26.39 (4.53)	245.82 (51.90)
HIJCREATE	65.30 (9.17)	405 (19.8)	135.28 (18.00)	75.70 (11.89)	2049 (100.0)	205 (10.0)	780 (38.1)	3 (0.1)	24.63 (2.99)	192.98 (34.79)
HOMEDBP	59.60 (0.00)	1763 (50.1)	154.21 (17.50)	90.19 (12.18)	61 (1.7)	46 (1.3)	538 (15.3)	45 (1.3)	24.39 (3.46)	210.90 (35.40)
HOPE	66.41 (6.72)	2480 (26.7)	138.68 (19.64)	78.91 (10.58)	7477 (80.4)	8414 (90.5)	3577 (38.5)	517 (5.6)	27.72 (4.40)	NA
HYVET	83.60 (3.17)	2326 (60.5)	173.01 (8.53)	90.78 (8.50)	121 (3.1)	261 (6.8)	388 (10.1)	1745 (45.4)	24.70 (3.71)	204.64 (42.50)
INSIGHT	65.19 (6.54)	3392 (53.7)	172.53 (14.97)	98.78 (8.49)	671 (10.6)	1640 (25.9)	1302 (20.6)	458 (7.2)	28.16 (4.56)	NA
INVEST	66.19 (9.77)	11770 (52.1)	150.85 (19.53)	87.16 (11.94)	22576 (100.0)	1629 (7.2)	6400 (28.3)	424 (1.9)	NA	NA
JMIC-B	64.49 (8.50)	515 (31.2)	146.16 (19.39)	82.02 (11.74)	1650 (100.0)	639 (38.7)	372 (22.5)	191 (11.6)	24.04 (2.94)	200.74 (35.00)
LIFE	67.62 (7.02)	4963 (54.0)	174.41 (14.28)	97.80 (8.86)	1469 (16.0)	401 (4.4)	1195 (13.0)	512 (5.6)	28.00 (4.78)	233.61 (43.43)
MOSES	68.27 (9.91)	619 (45.8)	151.35 (18.37)	87.10 (10.15)	355 (26.3)	1352 (100.0)	498 (36.8)	72 (5.3)	27.52 (4.26)	NA
NICSEH	69.64 (6.54)	288 (67.1)	172.34 (12.07)	93.80 (10.30)	4 (0.9)	12 (2.8)	17 (4.0)	65 (15.2)	23.44 (3.15)	209.92 (38.34)
NORDIL	59.90 (6.50)	5588 (51.4)	173.47 (17.62)	105.74 (5.30)	496 (4.6)	271 (2.5)	727 (6.7)	31 (0.3)	27.80 (4.34)	248.34 (46.21)
ONTARGET	67.04 (7.20)	6831 (26.7)	141.82 (17.41)	82.07 (10.40)	19102 (74.6)	5344 (20.9)	9617 (37.5)	8695 (33.9)	28.16 (4.77)	190.62 (43.16)

PART2	60.51 (8.10)	114 (18.5)	133.04 (16.76)	79.23 (9.71)	420 (68.1)	62 (10.0)	51 (8.3)	14 (2.3)	26.79 (3.59)	236.47 (40.72)
PEACE	64.33 (8.19)	1494 (18.0)	133.42 (16.60)	77.74 (9.78)	8290 (100.0)	357 (4.3)	1380 (16.6)	525 (6.3)	NA	192.02 (38.92)
PREVENDIT	51.33 (11.81)	303 (35.1)	130.18 (17.64)	76.09 (9.73)	13 (1.5)	13 (1.5)	22 (2.5)	864 (100.0)	26.35 (4.35)	223.67 (39.99)
PREVENT	57.11 (9.57)	164 (19.9)	129.41 (17.20)	78.83 (9.09)	825 (100.0)	55 (6.7)	98 (11.9)	8 (1.0)	28.04 (4.76)	217.34 (38.56)
PROGRESS	63.90 (9.55)	1852 (30.3)	146.97 (19.01)	85.68 (10.83)	983 (16.1)	6105 (100.0)	761 (12.5)	472 (7.7)	25.66 (3.78)	NA
SHEP	71.62 (6.70)	2690 (56.8)	170.30 (9.40)	76.91 (8.30)	232 (4.9)	66 (1.4)	476 (10.1)	334 (7.1)	28.28 (43.13)	NA
SPRINT	67.92 (9.42)	3332 (35.6)	139.67 (15.58)	78.13 (11.94)	1877 (20.1)	0 (0.0)	0 (0.0)	2646 (28.3)	NA	190.11 (41.17)
STOP HT-22	76.03 (3.94)	4416 (66.8)	194.10 (15.29)	97.84 (10.02)	647 (9.8)	502 (7.6)	719 (10.9)	1118 (16.9)	26.72 (4.00)	249.38 (48.06)
SYSTEUR	69.74 (6.70)	3138 (66.8)	173.85 (9.96)	85.48 (5.87)	164 (3.5)	124 (2.6)	449 (9.6)	20 (0.4)	27.03 (4.10)	232.69 (46.45)
TRANSCEND	67.48 (7.35)	2547 (43.0)	140.97 (16.63)	81.89 (10.13)	4418 (74.6)	1302 (22.0)	2121 (35.8)	2155 (36.4)	28.19 (4.82)	196.28 (44.79)
UKPDS	56.41 (8.10)	511 (44.5)	158.66 (17.16)	93.04 (7.57)	15 (1.3)	20 (1.7)	1148 (100.0)	8 (0.7)	29.64 (5.46)	NA
VALISH	76.09 (4.08)	1924 (62.5)	169.24 (8.69)	81.64 (6.44)	194 (6.3)	202 (6.6)	399 (13.0)	1092 (35.5)	23.47 (3.40)	199.02 (33.88)
VALUE	67.23 (8.13)	6468 (42.4)	154.65 (18.99)	87.52 (10.79)	6981 (45.8)	3014 (19.8)	4823 (31.6)	1811 (11.9)	28.63 (5.04)	219.92 (45.61)
VHAS	54.19 (6.97)	722 (51.1)	168.95 (10.44)	102.24 (5.09)	0 (0.0)	0 (0.0)	108 (7.6)	48 (3.4)	27.11 (4.12)	223.63 (40.00)

All categorical variables are presented as N (%); all continuous variables are presented as mean (SD)

BMI, body mass index; CKD, chronic kidney disease; CVD, cerebrovascular disease; DBP, diastolic blood pressure; DM, diabetes mellitus; IHD, ischaemic heart disease; SBP, systolic blood pressure; T Chol, total cholesterol

Discrepancies between the data that were published for each trial and the data presented in this table may result from errors in the BPLTTC dataset, which are, though, unlikely to have influenced any analyses.

Table 7.4 Baseline characteristics of participants, stratified by number of diseases

	Isolated hypertension	Two diseases	Three diseases	Four or more diseases	Overall
Number	71,262	125,528	95,536	38,134	330,460
Age (years)	65 (10)	66 (10)	66 (9)	66 (8)	66 (9)
Sex (Female)	34,771 (48.8)	50,538 (40.3)	37,258 (39.0)	15,848 (41.6)	138,415 (41.9)
SBP (mmHg)	162.4 (20.0)	151.8 (21.7)	148.0 (20.2)	147.48 (19.38)	152.5 (21.4)
DBP (mmHg)	92.4 (12.0)	86.9 (12.2)	84.6 (11.7)	83.71 (11.52)	87.1 (12.3)
Ischaemic heart disease	0 (0.0)	45,176 (36.0)	48,930 (51.2)	25,893 (67.9)	119,999 (36.3)
Cerebrovascular disease	0 (0.0)	24,058 (19.2)	34,592 (36.2)	21,455 (56.3)	80,105 (24.2)
Diabetes mellitus	0 (0.0)	20,179 (16.1)	45,689 (47.8)	31,188 (81.8)	97,056 (29.4)
Chronic kidney disease	0 (0.0)	14,454 (11.5)	20,304 (21.3)	11,825 (31.0)	46,583 (14.1)
Obesity	0 (0.0)	21,661 (17.3)	41,557 (43.5)	28,192 (73.9)	91,410 (27.7)
Hypertension	69,811 (98.0)	121,421 (96.7)	93,492 (97.9)	37,646 (98.7)	322,370 (97.7)
Type of trial					
Placebo	13,295 (18.7)	36,003 (28.7)	30,018 (31.4)	12,116 (31.8)	91,432 (27.7)
Drug comparison	48,339 (67.8)	80,895 (64.4)	59,865 (62.7)	24,935 (65.4)	214,034 (64.8)
More vs less	9,628 (13.5)	8,630 (6.9)	5,653 (5.9)	1,083 (2.8)	24,994 (7.6)

All categorical variables are presented as N (%); all continuous variables are presented as mean (SD).

Data presented in this table may not reflect data published by individual trials due to errors in the BPLTTC dataset, which are, however, unlikely to have influenced any analyses.

In placebo-controlled trials (nineteen trials), the difference in SBP reduction between arms was 6.1 (SD 3.5) mmHg, in drug class comparisons (twenty-one trials) it was 1.6 (SD 1.1) mmHg, and in more versus less intensive BP lowering (eight trials), it was 10.1 (SD 5.1) mmHg (**Table 7.2**). Overall, the mean difference in SBP reduction between intervention and control arms was 3.5 (SD 3.7) mmHg. On average, the intensity of SBP lowering decreased as the number of baseline diseases increased. The mean difference in SBP reduction between trial arms was 4.1 (SD 4.8) mmHg, 3.5 (SD 3.7) mmHg, 3.3 (SD 3.1) mmHg and 2.9 (SD 2.4) mmHg for patients with isolated hypertension, and hypertension plus one, two or three or more diseases, respectively.

Over a median follow up of 4.1 years (IQI 3.1 to 5.0), 42,365 (13%) participants developed a major cardiovascular event, which equates to a rate of major cardiovascular events of 31 per 1,000 patient-years. However, the rate of major cardiovascular events increased in parallel with the number of baseline diseases, from 18 per 1,000 patient-years in those with isolated hypertension to 28 per 1,000 patient-years in those with hypertension and one disease, 37 per 1,000 patient-years in those with hypertension and two diseases, and 51 per 1,000 patient-years in those with hypertension and three or more diseases (**Figure 7.2**).

Treatment effects according to number of diseases

Each 5-mmHg reduction in SBP decreased the risk of major cardiovascular events by about 10% overall (HR 0.90, 95% CI [0.88 to 0.92]), and there was no evidence that the relative risk

reduction varied according to the number of baseline diseases (Figures 7.1). Even when participants were split into six categories, there was no evidence of significant differences in treatment effects according to the number of baseline diseases (Table 7.5). However, the smaller sample size when many diseases were included meant that the confidence intervals were wide, which explains why several categories were collapsed into a single subgroup of hypertension plus three or more diseases in the main analysis. Although BP lowering significantly decreased the risk of all secondary outcomes, the risk reduction was more marked for stroke (14%) and HF (12%), and smaller for ischaemic heart disease (9%), cardiovascular death (9%) and all-cause death (6%) (Figure 7.1). As for the primary outcome, the relative risk reduction afforded by BP lowering for all secondary outcomes was similar, irrespective of the number of baseline diseases.

Table 7.5 Hazard ratios for major cardiovascular events according to number of diseases at baseline, standardised by 5-mmHg reduction in systolic blood pressure

Major cardiovascular events	Number	Hazard ratio	95% Confidence interval
Isolated hypertension	7,162	0.89	[0.84 to 0.94]
Hypertension and one disease	125,528	0.87	[0.84 to 0.91]
Hypertension and two diseases	95,536	0.92	[0.89 to 0.96]
Hypertension and three diseases	34,131	0.90	[0.85 to 0.96]
Hypertension and four diseases	3,855	0.87	[0.72 to 1.05]
Hypertension and five diseases	148	1.59	[0.40 to 6.40]
Overall	330,460	0.90	[0.88 to 0.92]

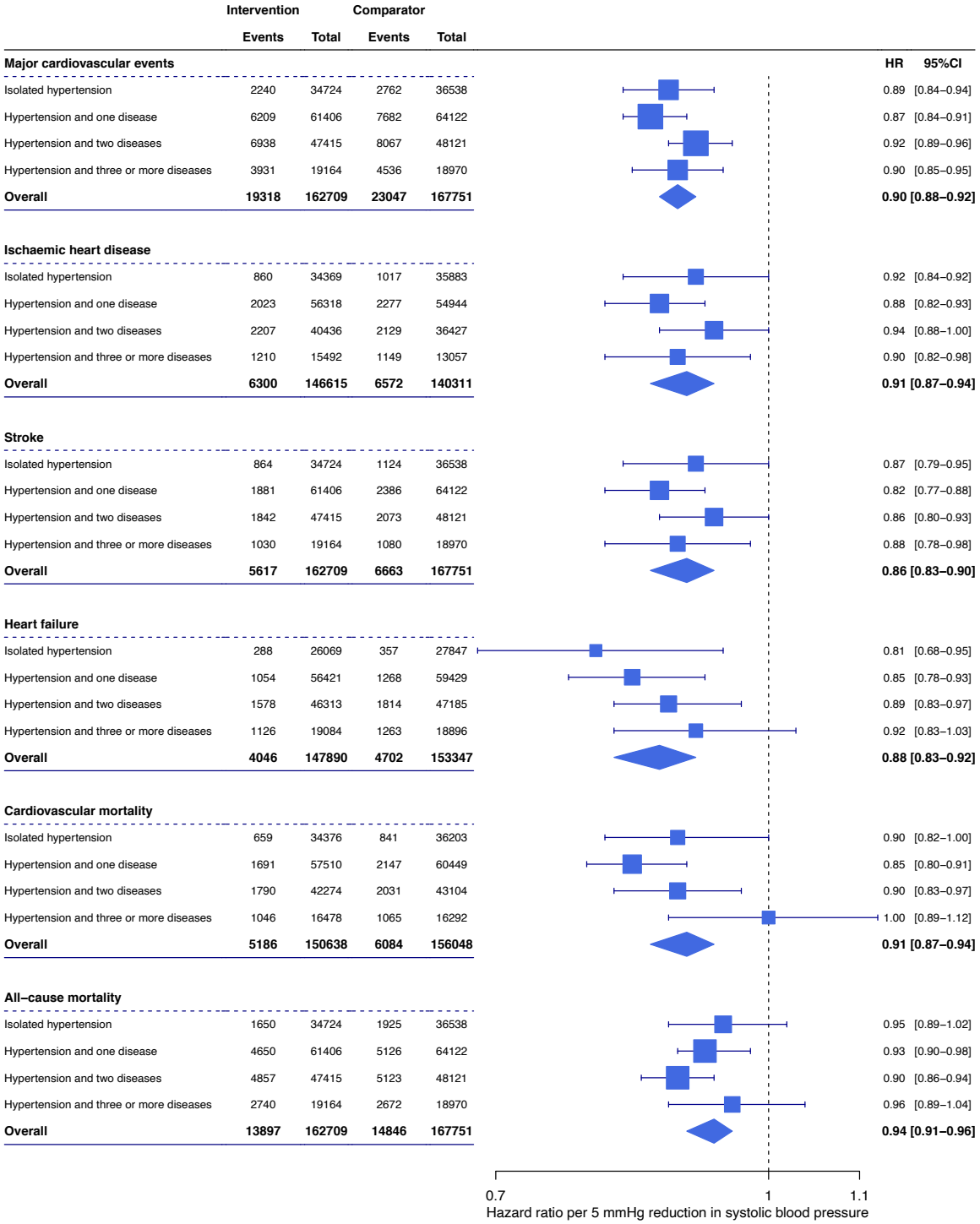

Figure 7.1 Effect of blood pressure lowering treatment on primary and secondary outcomes, stratified by number of diseases at baseline

Forest plot displays the hazard ratios (HR) and 95% confidence intervals (CI) for each outcome, fir intervention versus control arm, standardised by 5-mmHg reduction in systolic blood pressure.

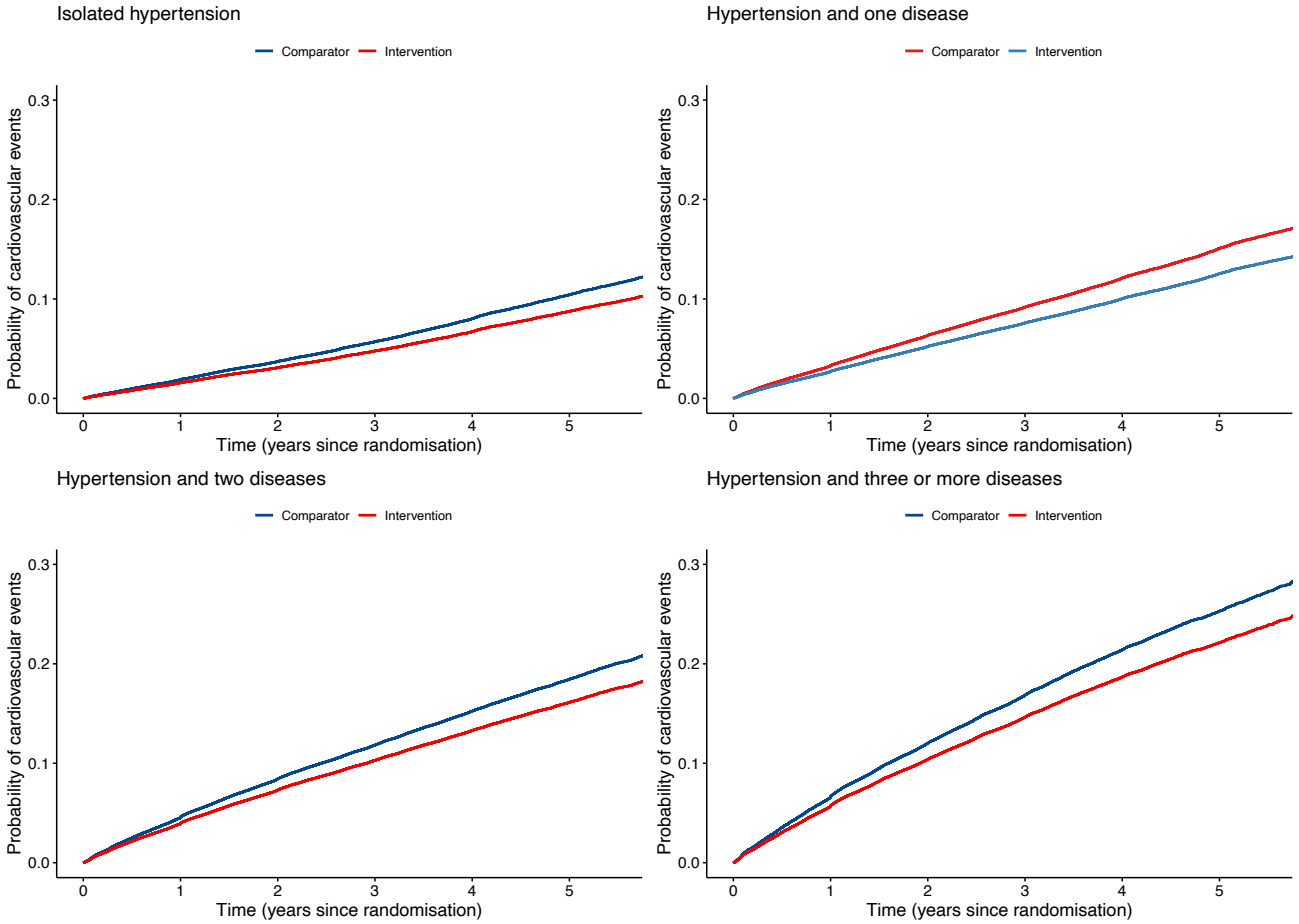

Figure 7.2 Cumulative event curves for major cardiovascular events for each randomised arm stratified by number of cardiometabolic diseases

Estimated probabilities of major cardiovascular events according to treatment arm (intervention versus comparator as defined in treatment comparisons), standardised by 5-mmHg reduction in systolic blood pressure, for patients with different numbers of cardiometabolic diseases at baseline.

There was a log-linear association between the intensity of SBP lowering and the reduction in the hazard ratio for major cardiovascular events for all subgroups based on number of diseases at baseline (Figure 7.3).

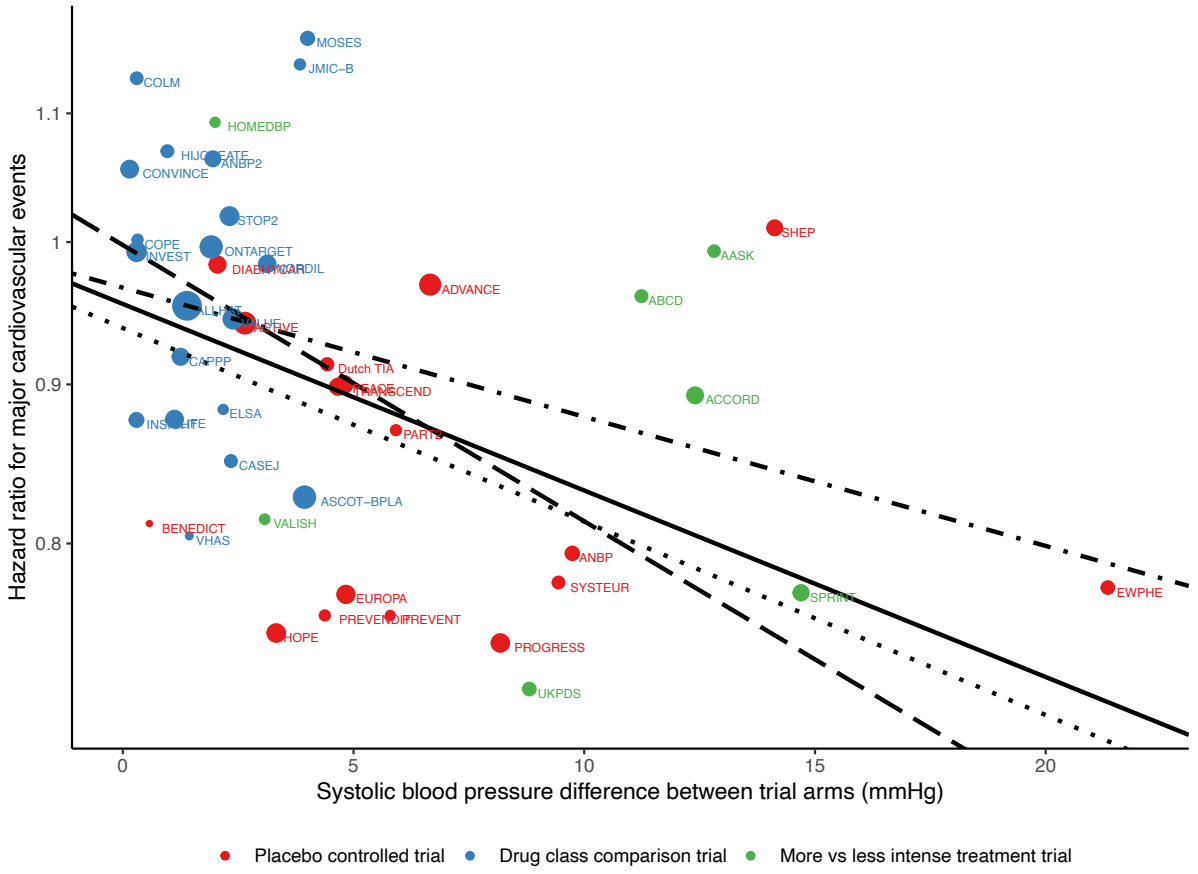

Figure 7.3 Hazard ratio of major cardiovascular events related to the one-year difference in systolic blood pressure reduction, aggregated at trial level

Risk of major cardiovascular events regressed against the difference in systolic blood pressure between trial arms, plotted on the log scale. Regression lines for participants with different categories of baseline diseases: isolated hypertension (solid line), hypertension and one disease (dotted line), hypertension and two diseases (dash-dotted line), and hypertension and three or more diseases (dashed line). Circles represent the hazard ratio for each trial with the size inversely proportional to the respective standard error. Trials are coded by colour according to type of intervention: placebo-controlled trials (red), drug class comparison trials (blue), and more versus less intense treatment trials (green).

Treatment effects according to multimorbidity patterns

The most common pattern was isolated hypertension, which was present in 71,262 (22%) patients. This was followed by multimorbidity patterns that combined hypertension with single diseases, namely ischaemic heart disease, cerebrovascular disease, obesity and diabetes (**Figure 7.4**). All multimorbidity patterns including five or more diseases were rare (less than 2,000 participants in each).

Overall, BP lowering reduced the risk of major cardiovascular events by approximately 10%, with no evidence that treatment effects were significantly different between patients with cardiometabolic multimorbidity and those with isolated hypertension (**Table 7.5**). Nor did any others differ from the reference group of isolated hypertension, with the exceptions of hypertension, ischaemic heart disease and diabetes ($p = 0.032$), and hypertension, diabetes and obesity ($p = 0.009$), in which the risk reduction in major cardiovascular events appeared to be lower than in patients with isolated hypertension. However, the confidence intervals for treatment effects were wide, reflecting the decline in the number of participants for the less common multimorbidity patterns.

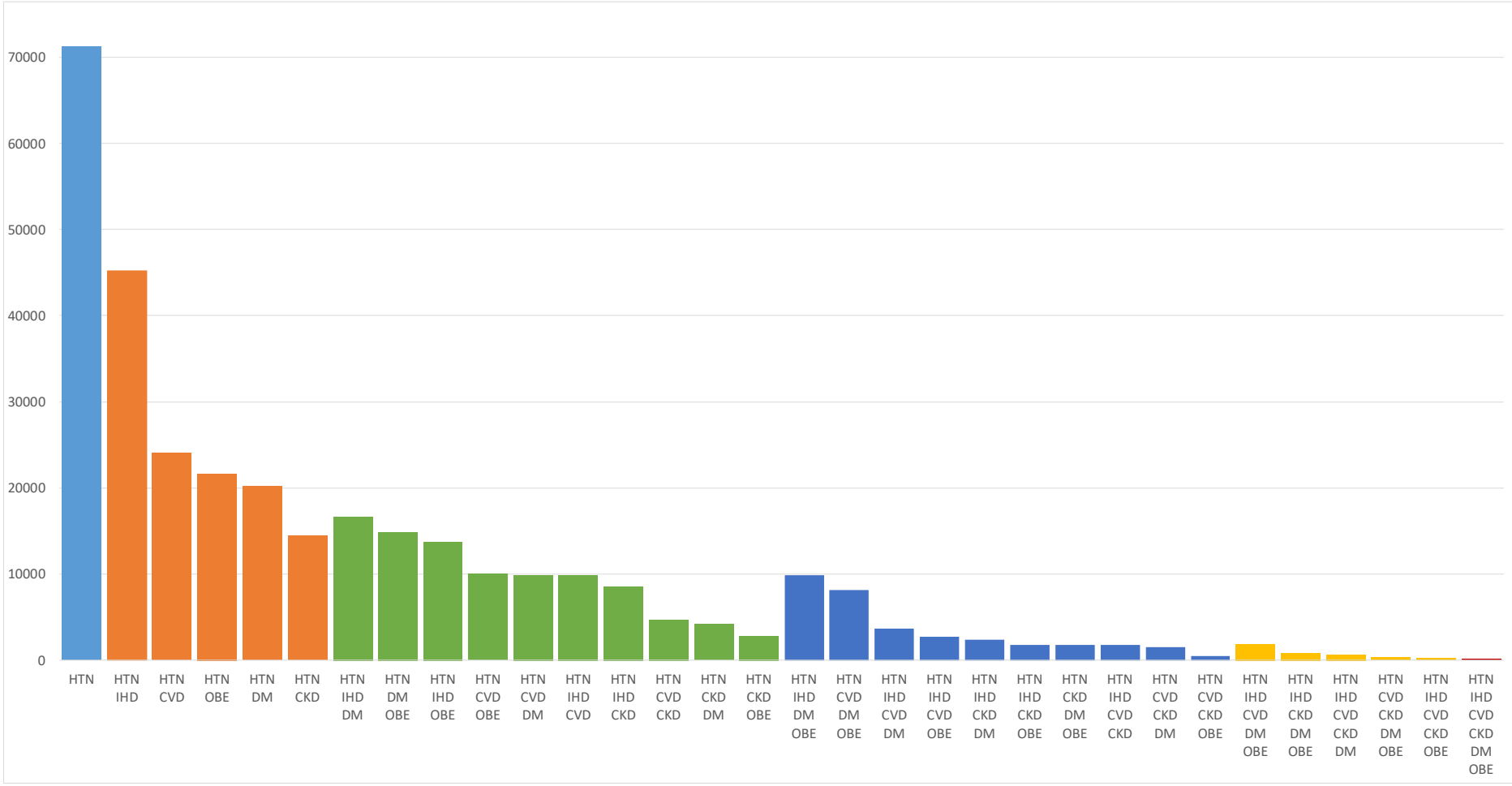

Figure 7.4 Distribution of multimorbidity patterns in the study population

Bars represent the absolute frequency of each disease pattern in the study population. CKD, chronic kidney disease; CVD, cerebrovascular disease; DM, diabetes mellitus; HTN, hypertension; IHD, ischaemic heary disease; OBE, obesity

Table 7.6 Hazard ratios for major cardiovascular events for each multimorbidity pattern, standardised by 5-mmHg reduction in systolic blood pressure

Baseline diseases	Number of events	Number of participants	Hazard ratio	95% Confidence interval	p-value[1]	Adjusted p-value[2]
HTN	5,002	71,262	0.89	[0.84 to 0.94]		
HTN IHD	4,093	45,176	0.85	[0.78 to 0.91]	0.314	1.000
HTN CVD	4,031	24,058	0.86	[0.79 to 0.93]	0.517	1.000
HTN OBE	1,670	21,661	0.88	[0.79 to 0.98]	0.864	1.000
HTN DM	2,470	20,179	0.89	[0.82 to 0.97]	0.921	1.000
HTN CKD	1,627	14,454	0.84	[0.76 to 0.93]	0.329	1.000
HTN IHD DM	2,427	16,708	1.01	[0.91 to 1.11]	0.032	1.000
HTN DM OBE	2,026	14,893	1.02	[0.94 to 1.12]	0.009	0.288
HTN IHD OBE	1,397	13,746	0.85	[0.73 to 0.98]	0.550	1.000
HTN CVD OBE	1,842	10,080	0.81	[0.65 to 1.00]	0.391	1.000
HTN CVD DM	2,182	9,904	0.89	[0.78 to 1.01]	0.998	1.000
HTN IHD CVD	2,026	9,901	0.87	[0.75 to 1.00]	0.737	1.000
HTN IHD CKD	1,080	8,575	0.94	[0.83 to 1.07]	0.402	1.000
HTN CVD CKD	1,097	4,707	0.85	[0.71 to 1.02]	0.642	1.000
HTN CKD DM	644	4,184	0.87	[0.74 to 1.04]	0.855	1.000
HTN CKD OBE	314	2838	0.77	[0.61 to 0.97]	0.241	1.000

HTN IHD DM OBE	1,569	9,905	0.91	[0.82 to 1.02]	0.686	1.000
HTN CVD DM OBE	2,012	8,140	0.84	[0.71 to 0.99]	0.489	1.000
HTN IHD CVD DM	1,029	3,652	0.91	[0.76 to 1.08]	0.824	1.000
HTN IHD CVD OBE	660	2716	0.98	[0.73 to 1.32]	0.509	1.000
HTN IHD CKD DM	520	2379	0.94	[0.72 to 1.23]	0.658	1.000
HTN IHD CKD OBE	223	1801	0.99	[0.75 to 1.30]	0.467	1.000
HTN CKD DM OBE	309	1767	0.98	[0.76 to 1.26]	0.465	1.000
HTN IHD CVD CKD	452	1749	0.89	[0.66 to 1.21]	0.978	1.000
HTN CVD CKD DM	459	1542	0.84	[0.61 to 1.15]	0.726	1.000
HTN CVD CKD OBE	110	480	0.84	[0.61 to 1.15]	0.726	1.000
HTN IHD CVD DM OBE	568	1896	0.9	[0.71 to 1.14]	0.932	1.000
HTN IHD CKD DM OBE	159	827	0.84	[0.50 to 1.42]	0.824	1.000
HTN IHD CVD CKD DM	200	620	0.84	[0.53 to 1.34]	0.823	1.000
HTN CVD CKD DM OBE	98	312	1.19	[0.45 to 3.11]	0.555	1.000
HTN IHD CVD CKD OBE	50	200	1.69	[0.45 to 6.37]	0.341	1.000
HTN IHD CVD CKD DM OBE	49	148	1.68	[0.35 to 7.95]	0.425	1.000
OVERALL	**42,365**	**330,460**	**0.90**	**[0.88 to 0.92]**		

[1] P-value for comparison between each disease pattern and the reference category (isolated hypertension)

[2] Adjusted p-value calculated using the Bonferroni correction to account for multiple comparisons

CKD, chronic kidney disease; CVD, cerebrovascular disease; DM, diabetes mellitus; HTN, hypertension; IHD, ischaemic heary disease; OBE, obesity

Additional sensitivity analyses

Sensitivity analysis using a two-stage approach yielded similar estimates to the one-stage approach, assuming a fixed treatment effect (HR 0.91, 95% CI [0.89 to 0.92] and HR 0.90, 95% CI [0.88 to 0.92] for the two-stage and one-stage approaches, respectively) (**Table 7.7**). Confidence intervals were slightly wider, though, when random effects were assumed in the two-stage meta-analysis (HR 0.91, 95% CI [0.86 to 0.93]), reflecting the moderate heterogeneity between trials (I^2 = 51%). Treatment estimates based on complete-case analysis were, overall, comparable to treatment estimates based on the imputed dataset, for the analysis stratified by number of cardiometabolic diseases at baseline (**Table 7.8**). However, the confidence intervals were wider due to the smaller sample size (total number of participants, 168,717). Removing the adjustment for the intensity of SBP reduction did not have a material impact on treatment effect estimates, overall (HR 0.91, 95% CI [0.90 to 0.94]) (**Table 7.9**). However, the risk reduction in the subgroups with three or more diseases were smaller reflecting the fact that the average BP reduction in those subgroups was also smaller, in comparison with the subgroups with one or two diseases.

Table 7.7 Sensitivity analyses for treatment effects on major cardiovascular events using two-stage meta-analysis

Two-stage meta-analysis	Hazard ratio	95% Confidence interval
Fixed effect model (I^2 = 45%, p < 0.001)	0.91	[0.89 to 0.92]
Random effects model (I^2 = 51%, p < 0.001)	0.89	[0.86 to 0.93]

Table 7.8 Sensitivity analyses for treatment effects on major cardiovascular events using complete-case analysis

Number of diseases	Number	Hazard ratio	95% Confidence interval
Isolated hypertension	46,418	0.90	[0.83 to 0.96]
Hypertension and one disease	62,537	0.86	[0.82 to 0.90]
Hypertension and two diseases	43,669	0.96	[0.91 to 1.00]
Hypertension and three or more diseases	16,093	0.90	[0.84 to 0.96]
Overall	168,717	0.91	[0.88 to 0.93]

Table 7.9 Sensitivity analyses for treatment effects on major cardiovascular events using one-stage model without adjustment for intensity of systolic blood pressure lowering

Number of diseases	Number	Hazard ratio	95% Confidence interval
Isolated hypertension	7,162	0.90	[0.85 to 0.95]
Hypertension and one disease	125,528	0.89	[0.83 to 0.95]
Hypertension and two diseases	95,536	0.94	[0.87 to 1.00]
Hypertension and three or more diseases	38,134	0.94	[0.88 to 1.00]
Overall	330,460	0.91	[0.90 to 0.94]

Discussion

This study demonstrated that BP lowering reduced the risk of major cardiovascular events by about 10%, with no evidence that the relative risk reduction varied according to the number of cardiometabolic diseases at baseline. Furthermore, the intensity of BP lowering seemed to be proportional to the relative risk reduction in major cardiovascular events across all numbers of baseline diseases. Treatment effects on major cardiovascular events were broadly

comparable between patients with the most common patterns of cardiometabolic multimorbidity and those with isolated hypertension.

To the best of my knowledge, this study is the first meta-analysis of RCTs to have investigated the effects of BP lowering treatment in patients with cardiometabolic multimorbidity. Previous aggregate data and IPD meta-analyses had shown that the effects of BP lowering treatment were consistent across different populations, irrespective of sex, age and established cardiometabolic disease.[114,193,198,199] However, those studies looked at the interaction between treatment and single diseases (e.g., diabetes mellitus, chronic kidney disease), whilst I investigated treatment effects in patients with concurrent cardiometabolic diseases.

My findings reassuringly demonstrated that even patients who meet the standard definition of multimorbidity (i.e., those who have two or more concomitant diseases)[103] benefit from a comparable relative risk reduction in cardiovascular events as do patients with isolated hypertension at baseline. The analysis based on multimorbidity patterns lent further support to the similar risk reduction afforded by BP lowering in patients with cardiometabolic multimorbidity, in comparison to those with isolated hypertension. In fact, there were no clinically relevant differences in the effects of BP lowering between multimorbidity patterns and isolated hypertension, and the two statistically significant differences most likely resulted from chance, since thirty-two different patterns were tested. However, no definite conclusions can be drawn, as the confidence intervals were wide, especially for the least common multimorbidity patterns.

Furthermore, my findings that the cardiovascular event rate rose in parallel with the number of cardiometabolic diseases are in keeping with previous observational studies showing that cardiometabolic multimorbidity was associated with an increased risk of cardiovascular events and death.[442-444] Indeed, a population-based cohort study reported that, at the age of 60 years, a history of any two of diabetes, ischaemic heart disease and stroke was associated with 12 years of reduced life expectancy, and a history of all three of these conditions was associated with 15 years of reduced life expectancy.[47] Considering that population-based studies are best suited to estimate absolute risks, it is reasonable to expect that BP lowering would benefit more patients with a higher burden of cardiometabolic diseases than those with isolated hypertension, in whom the absolute cardiovascular risk is lower. In addition, my findings suggest that BP lowering treatment would have similar effects for primary and secondary prevention, because the relative risk reduction was broadly comparable in patients with pre-existing ischaemic heart disease and cerebrovascular disease.

On the other hand, my findings are at odds with previous observational evidence, which suggested that lower BP was associated with an increased risk of cardiovascular and non-cardiovascular events in patients with multimorbidity.[113,445] Importantly, this association of low BP with both cardiovascular and non-cardiovascular events raises the question as to whether BP, in this case, reflects an overall poor health status.[446] This is supported by the fact that the U-shaped association between BP and mortality found by observational studies was not modified by antihypertensive treatment.[447] Moreover, observational studies cannot infer direction of causality, and the possibility of residual confounding cannot be excluded. By overcoming those pitfalls, my study reliably demonstrated that the relative risk reduction on

cardiovascular events was proportional to the intensity of BP lowering in patients with and without cardiometabolic multimorbidity. The slope of the association was even steeper in patients with hypertension plus three or more diseases, even though the latter group was older than were patients with fewer diseases. This is in line with previous findings that intensive BP lowering effectively prevents cardiovascular events in the high-risk elderly.[60,448] Nonetheless, to what extent those findings are transferrable to older patients with a greater burden of non-cardiometabolic multimorbidity and/or frailty remains uncertain.[449]

As multimorbidity is rapidly becoming the norm rather than the exception among patients with hypertension, and cardiometabolic diseases are the most common conditions in patients with hypertension worldwide, my study has important clinical implications.[105,108,450] First, it provides compelling evidence to support BP lowering in patients with high BP irrespective of the number and/or type of concomitant cardiometabolic diseases. Second, it demonstrates that patients with more diseases may benefit more, in absolute terms, from pharmacological BP lowering than patients who have isolated hypertension. In other words, this suggests that in those high-risk patients, the number needed to treat to prevent an equivalent number of cardiovascular events is smaller and hence BP lowering is more cost-effective from a population perspective. Therefore, my study argues against the overly cautious treatment recommendations in patients with multimorbidity. Paradoxically, the latter, who have more to gain from BP lowering, tend to be less intensely treated due to scepticism about the potential cardiovascular risk reduction to be achieved by treatment.[121,122] However, it is important to acknowledge that cautious BP lowering in patients with multimorbidity isbased on safety concerns, due to an increased risk of disease-disease and disease-drug interactions

in the context of concurrent diseases and polypharmacy.[451,452] This is even more important considering that multimorbidity is more common in the elderly, who are commonly vulnerable and frail. Further research is thus warranted to better understand how adverse events influence the risk-benefit balance of pharmacological BP lowering in patients with multimorbidity across the life span.

The main strengths of this study are (1) the large sample size, which allowed me to perform a comprehensive subgroup analysis that had not been possible in individual RCTs; (2) the access to unpublished data on baseline diseases and cardiovascular outcomes; (3) the access to IPD, which allowed me to harmonise the definitions of cardiometabolic diseases at baseline; (4) the reliance on RCTs to estimate treatment effects in patients with multimorbidity, whilst evidence hitherto available was extrapolated from observational studies that were prone to reverse causation and residual confounding; (5) the use of two complementary measures of multimorbidity, namely numbers of diseases and multimorbidity patterns. Indeed, although disease counting is a very crude measure of multimorbidity, it remains the most commonly used index of multimorbidity, and it is widely considered a proxy for greater risk for cardiovascular disease and mortality overall.[453] On the other hand, complementing this analysis with disease patterns offered a more in-depth assessment of multimorbidity.

However, there are also some limitations worth acknowledging. First, the definition of multimorbidity was constrained by lack of data on other potentially important diseases. Although a broader definition of multimorbidity would have been ideal, including preferably

non-cardiometabolic conditions, data were not available, because they were either not collected or such patients were excluded from the trials. Second, there was a substantial proportion of missing data. I decided to exclude baseline diseases for which the proportion of missing data was over 25% and use multiple imputation for the remaining diseases. Other than for the loss of potentially relevant data, this is unlikely to have biased my results because I validated the multiple imputation algorithm, and complete-case analysis confirmed the main findings of the analysis based on imputed data. Third, it is possible that patients with isolated hypertension at baseline had other diseases that were not recorded in trial datasets. If this happened, it might have increased their cardiovascular risk, which would dilute the effect of BP lowering treatment, and hence contribute to the lack of interaction between multimorbidity and treatment. However, I considered major cardiometabolic conditions that are well-established as the main drivers of cardiovascular risk. Fourth, although the accuracy and completeness of reporting baseline diseases in clinical trials tends to be better than routinely collected data, it is possible that misclassification may have ensued if data were self-reported or based on inaccurate medical records. However, the randomised nature of the trials means that this is unlikely to have significantly biased my results. Fifth, the analysis based on multimorbidity patterns was restricted by the small number of participants included in the less common patterns, that is, those with more diseases at baseline.

Finally, caution is needed when extrapolating my study findings to multimorbid patients in the community. The prevalence of multimorbidity in my study was 78%, which is identical to that reported by a large population-based study.[105] However, the percentages of patients with hypertension plus one, two and three or more diseases were slightly different, with a

lower number of diseases in patients included in RCTs when compared to those in the community (24%, 19% and 35% versus 38%, 29% and 12% for hypertension plus one, two or three diseases in the population-based study and my study, respectively).[105] Those differences most likely derive from the strict inclusion and exclusion criteria applied by each trial, which tended to select patients without complex multimorbidity. Therefore, although my study population is broadly representative of the population of hypertensive patients, those with a higher burden of multimorbidity are underrepresented, which adds uncertainty to extrapolation of my findings to them.

Conclusion

The risk reduction in major cardiovascular events achieved by BP lowering treatment seems broadly comparable irrespective of the number of cardiometabolic diseases at baseline. There was also no evidence that treatment effects varied across the most common patterns of cardiometabolic multimorbidity at baseline. Furthermore, considering that the absolute risk of cardiovascular events increased in parallel with the number of baseline diseases, it is expected that a similar relative risk reduction would translate into a larger absolute risk reduction in cardiovascular events in patients with more diseases. However, BP lowering in patients with cardiometabolic multimorbidity is complex, and individually tailored treatment is needed due to potential interactions between diseases and respective treatments. Further evidence is warranted to better understand the efficacy of BP lowering for primary and secondary cardiovascular prevention in patients with a broader range of cardiometabolic and non-cardiometabolic multimorbidity.

Cluster analysis

Background

Disease counting remains the most widely method of assessing multimorbidity, at least partly due to the conventional definition of multimorbidity as the presence of two or more diseases in the same individual.[103] Although the number of concurrent diseases seems to be directly correlated with poorer health outcomes and increased healthcare needs, disease counting is a crude measure that does not capture the full complexity of multimorbidity.[454,455] This is because it assumes that diseases are all equivalent, thus failing to account for non-random associations of diseases. To overcome the limitations inherent to that narrow perspective, whilst acknowledging that analyses including all possible combinations of diseases require very large numbers, and may be difficult to interpret, there has been growing interest in applying cluster analysis to study multimorbidity at population level.[456,457] The rationale behind cluster analysis in this setting is that identification of subgroups within large populations with specific combinations of coexisting diseases may facilitate the development of more targeted and likely more effective management strategies.[458]

Although cluster analysis has been increasingly used to identify common groups of chronic conditions among patients with multimorbidity, studies have been restricted to population-based cohorts.[459-462] Whether similar analyses can be conducted in the population of patients enrolled in BP lowering RCTs remains unknown, because individual trials were underpowered

to perform such analyses. It is thus unclear which meaningful subpopulations can be identified within BP lowering RCTs, and whether there is heterogeneity of treatment effects among them. Therefore, I aimed to identify clusters of patients with different multiple baseline cardiometabolic diseases (i.e., multimorbidity clusters) among the population included in the BPLTTC, and then to estimate whether there were significant differences in treatment effects between those clusters.

Methods

As hypertension was present almost universally in the study population, I performed cluster analysis taking into account the same baseline cardiometabolic diseases included in the previous section, apart from hypertension (i.e., ischaemic heart disease, cerebrovascular disease, chronic kidney disease, diabetes mellitus and obesity). This meant that in each cluster participants were considered to have hypertension by default, and then the clustering algorithm identified subgroups based on different combinations of the other five diseases. All diseases were considered as binary variables, with a value of 1 when the condition was present and 0 when it was absent.

I used partitional cluster analysis based on the k-means algorithm, after determining the initial number of clusters by hierarchical clustering, as this is required as input to the k-means algorithm.[368] I then selected the number of clusters with the highest value of CritCF.[372] Further details on the methodological concepts underlying cluster analysis are provided in Chapter 4. To integrate multiple imputation with cluster analysis, I first performed multiple imputation

to obtain five completed datasets, and then I run the clustering algorithm in each of the imputed datasets. I tested the performance of the clustering algorithm with four to eight clusters, and I selected seven clusters as this number of clusters was associated with the highest CritCF (0.54). Finally, I refit the cluster analysis for seven clusters to the five imputed datasets. Each participant was assigned to the most common cluster. This resulted in a categorical variable which represented the cluster membership of each participant. The cluster analysis was performed using the package "micluster" for R version 3.6.1.[369] All the other analyses related to estimating treatment effects adopted the same methods that I described for the main analyses in the previous section.

Results

The cluster algorithm split the study population into seven distinct clusters (**Table 7.10**). Although age and BP at baseline were not taken into account by the clustering algorithm, there was a clear segregation of those variables between clusters. For instance, the mean age in cluster 2 was 72 (SD 8) years, whilst in cluster 4 the mean age was 63 (SD 9) years. Likewise, the mean SBP at baseline was 160 (SD 21) mmHg and 145 (SD 20) mmHg in clusters 1 and 7, respectively. In addition, there were key differences in the prevalence of each of the five diseases between clusters. For instance, cluster 1 was characterised by an overall low prevalence of all diseases other than hypertension, whilst in cluster 2 most participants had diabetes and cerebrovascular disease, in cluster 4 most participants were obese, and in cluster 7 all participants had ischaemic heart disease. This demonstrates that the clustering

algorithm was able to identify patients with distinct features in the study population and group them together considering only five cardiometabolic diseases at baseline.

Each cluster was also characterised by a specific combination of disease patterns (**Figure 7.5 and Table S7.2 in Appendix A**). Cluster 1 was the cluster in which most of the participants had isolated hypertension at baseline (62%). Cluster 2 included mainly patients with the combination of cerebrovascular disease, diabetes and chronic kidney disease. In cluster 3, the most common multimorbidity patterns were the combination of diabetes and obesity with or without ischaemic heart disease. Cluster 4 included mostly patients with ischaemic heart disease plus obesity or isolated obesity. In cluster 5, the most frequent multimorbidity patterns were the combination of cerebrovascular disease and diabetes with or without obesity. In cluster 6, isolated cerebrovascular disease was by far the most common pattern, followed by the double combinations of cerebrovascular disease with chronic kidney disease, or diabetes, or obesity. Similarly, in cluster 7 isolated ischaemic heart disease was the most common pattern, followed by double combinations of ischaemic heart disease with any of the other four diseases.

There was no evidence that the clustering algorithm was simply splitting participants according to their trial of origin. On the contrary, clusters included variable proportions of participants from different trials (**Figure 7.6 and Table S7.3 in Appendix A**). The clustering algorithm also divided participants in clusters with distinct profiles of cardiovascular risk (**Figure 7.7**). Overall, the risk of major cardiovascular events was 23, 68, 38, 25, 57, 43 and 32 per 1,000 patient-years for clusters 1 to 7, respectively.

Table 7.10 Baseline characteristics, stratified by multimorbidity cluster

	Cluster 1	Cluster 2	Cluster 3	Cluster 4	Cluster 5	Cluster 6	Cluster 7
Number	112,867	1,751	33,871	43,744	17,382	35,149	85,696
Age	65.76 (10.24)	71.92 (8.16)	63.66 (7.83)	63.08 (9.31)	67.52 (7.88)	67.29 (8.79)	66.04 (9.01)
Sex (Female)	53,551 (47.4)	558 (31.9)	15,859 (46.8)	19,793 (45.2)	7,166 (41.2)	15,015 (42.7)	26,473 (30.9)
SBP (mmHg)	159.85 (20.88)	151.61 (19.50)	149.31 (19.52)	154.39 (22.03)	148.83 (19.35)	150.06 (19.11)	144.95 (20.39)
DBP (mmHg)	90.23 (12.40)	82.45 (11.07)	85.18 (11.39)	90.24 (12.59)	83.20 (11.15)	86.22 (11.00)	83.29 (11.69)
Ischaemic heart disease	0 (0.0)	0 (0.0)	11,529 (34.0)	17,006 (38.9)	5,768 (33.2)	0 (0.0)	85,696 (100.0)
Cerebrovascular disease	7,558 (6.7)	1,660 (94.8)	4,644 (13.7)	4,579 (10.5)	15,138 (87.1)	34,849 (99.1)	11,677 (13.6)
Diabetes mellitus	20,806 (18.4)	1,751 (100.0)	33,667 (99.4)	9 (0.0)	16,459 (94.7)	4,412 (12.6)	19,952 (23.3)
Chronic kidney disease	16,840 (14.9)	1,143 (65.3)	2,693 (8.0)	5,166 (11.8)	3,774 (21.7)	4,948 (14.1)	12,019 (14.0)
Obesity	938 (0.8)	13 (0.7)	31,509 (93.0)	41,397 (94.6)	6,047 (34.8)	8,954 (25.5)	2,552 (3.0)
Hypertension	109,996 (97.5)	1,740 (99.4)	33,330 (98.4)	43,051 (98.4)	17,089 (98.3)	34,685 (98.7)	82,479 (96.2)
Type of trial							
Placebo-controlled	24,768 (21.9)	417 (23.8)	10,858 (32.1)	11,247 (25.7)	5,076 (29.2)	9,350 (26.6)	29,716 (34.7)
Drug comparison	72,867 (64.6)	1,315 (75.1)	19,186 (56.6)	29,969 (68.5)	11,872 (68.3)	25,462 (72.4)	53,363 (62.3)
More vs less intense treatment	15,232 (13.5)	19 (1.1)	3,827 (11.3)	2,528 (5.8)	434 (2.5)	337 (1.0)	2,617 (3.1)
SBP difference between trial arms (mmHg)	4.20 (4.51)	2.54 (1.97)	3.71 (3.58)	3.52 (3.75)	2.92 (2.42)	2.99 (2.66)	2.89 (2.81)
Number of baseline diseases							
Isolated hypertension	70,006 (62.0)	0 (0.0)	3 (0.0)	1,243 (2.8)	0 (0.0)	10 (0.0)	0 (0.0)
Hypertension and one disease	39,600 (35.1)	53 (3.0)	1,568 (4.6)	21,746 (49.7)	353 (2.0)	17,710 (50.4)	44,498 (51.9)
Hypertension and two diseases	3,241 (2.9)	581 (33.2)	15,827 (46.7)	16,061 (36.7)	6,747 (38.8)	16,834 (47.9)	36,245 (42.3)
Hypertension and three diseases	20 (0.0)	1,116 (63.7)	15,078 (44.5)	4,487 (10.3)	7,931 (45.6)	595 (1.7)	4,904 (5.7)
Hypertension and four diseases	0 (0.0)	1 (0.1)	1,389 (4.1)	207 (0.5)	2,209 (12.7)	0 (0.0)	49 (0.1)
Hypertension and five diseases	0 (0.0)	0 (0.0)	6 (0.0)	0 (0.0)	142 (0.8)	0 (0.0)	0 (0.0)

All categorical variables are presented as N (%); all continuous variables are presented as mean (SD). DBP, diastolic blood pressure; SBP, systolic blood pressure
Data presented in this table may not reflect data published by individual trials due to errors in the BPLTTC dataset, which are, however, unlikely to have influenced any analyses.

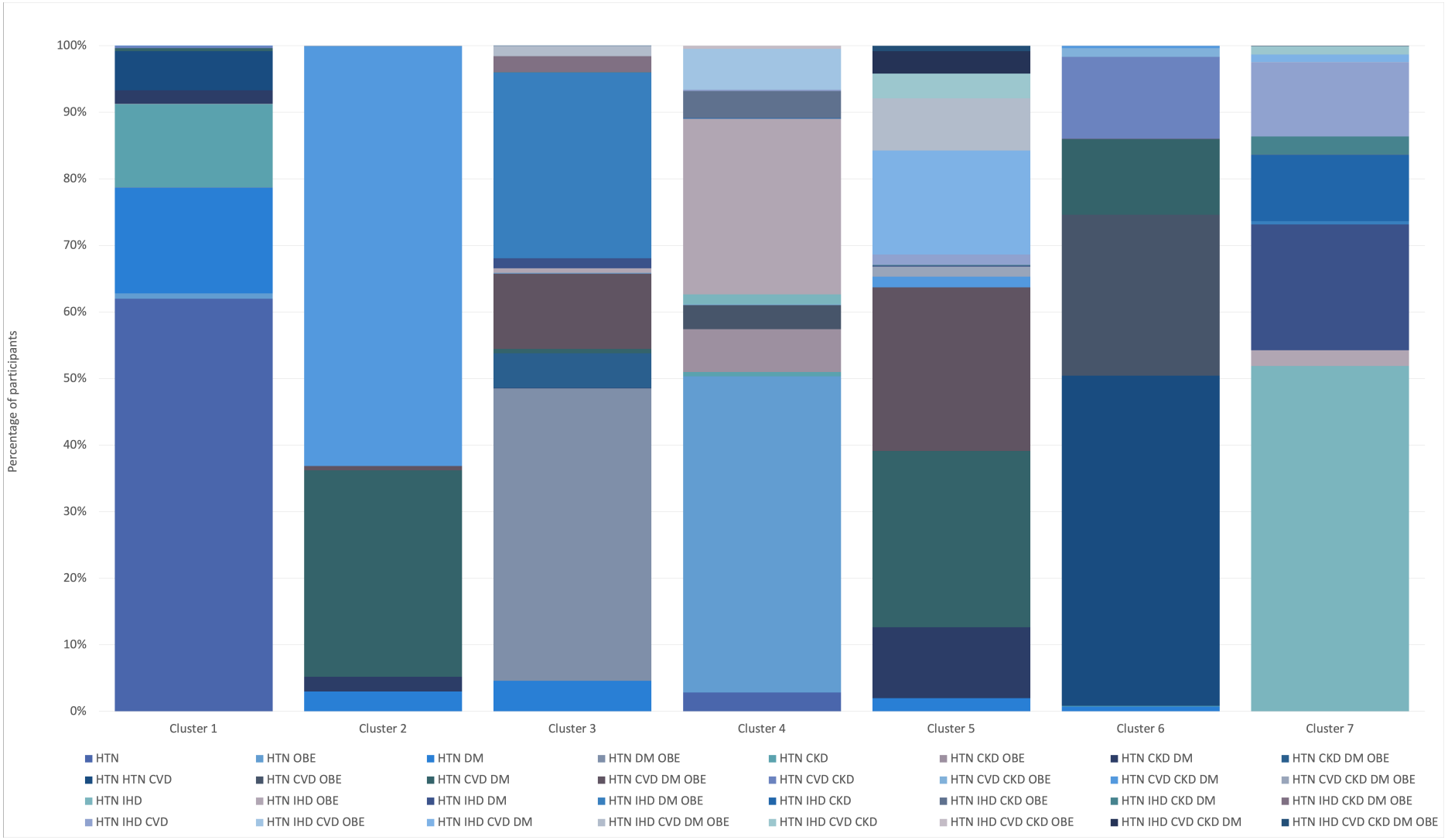

Figure 7.5 Distribution of multimorbidity patterns by cluster

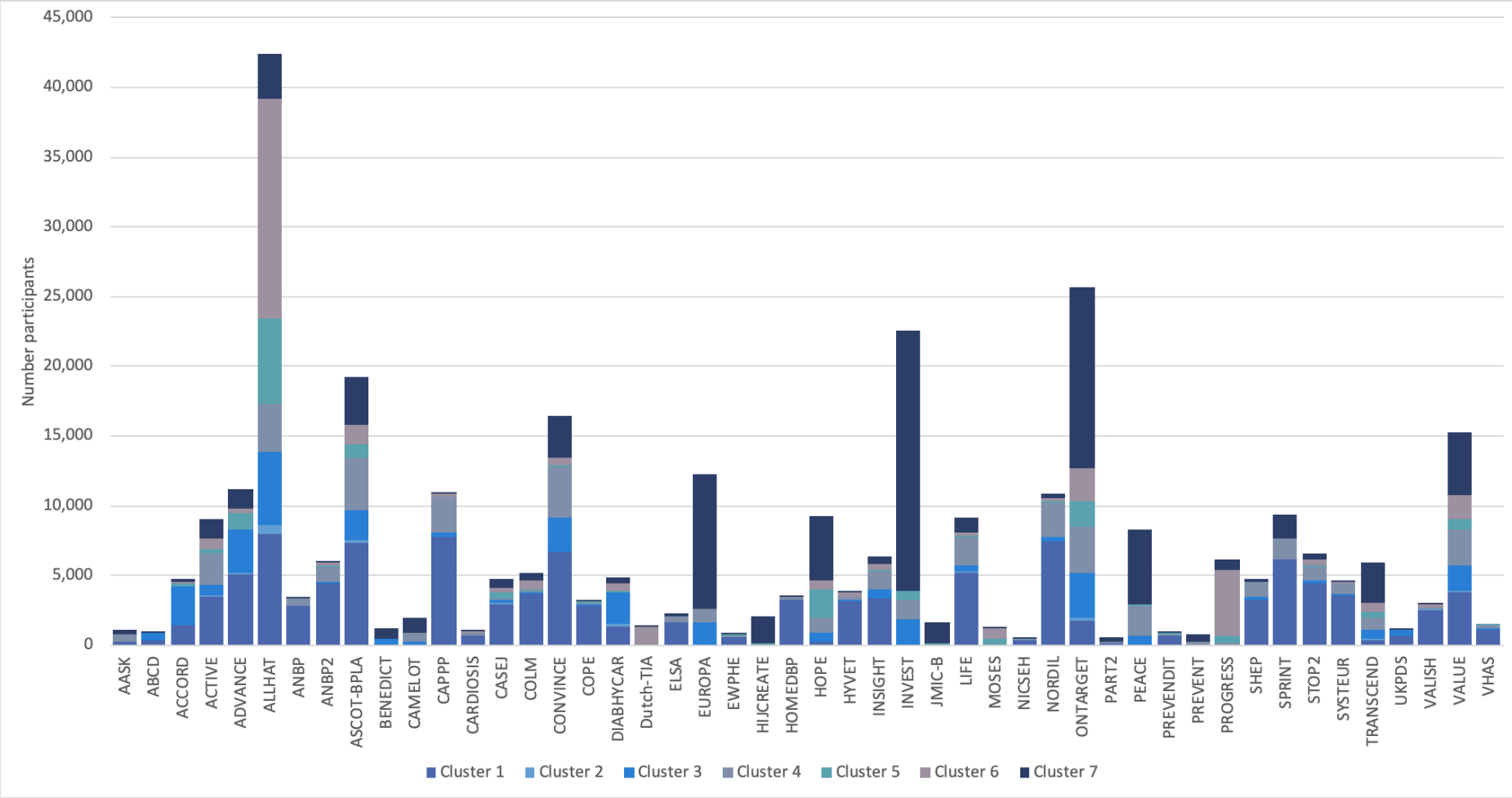

Figure 7.6 Distribution of clusters by trial

BP lowering treatment significantly reduced the risk of major cardiovascular events by about 10% in all clusters other than clusters 3 and 5 (**Table 7.11**). Considering cluster 1 as reference, as the vast majority of its participants had isolated hypertension and thus did not meet the diagnostic criteria for multimorbidity, there were only significant differences between clusters 3 and 5 and cluster 1.

The results for the secondary outcomes were broadly similar to those for the primary outcome, other than for all-cause death, in which no significant differences were found between clusters. Noteworthy, BP lowering resulted in a marked reduction in ischaemic heart disease in cluster 2, whose participants were typically elderly and had a greater burden of diabetes, cerebrovascular disease and chronic kidney disease. However, none of them had ischaemic heart disease at baseline, thus suggesting that in patients with such a multimorbidity profile, BP reduction may be particularly efficacious for primary prevention of ischaemic heart disease. On the other hand, there was no evidence that the efficacy of BP lowering as secondary prevention was larger than as primary prevention in patients with pre-existing ischaemic heart disease (cluster 7) and cerebrovascular disease (cluster 6).

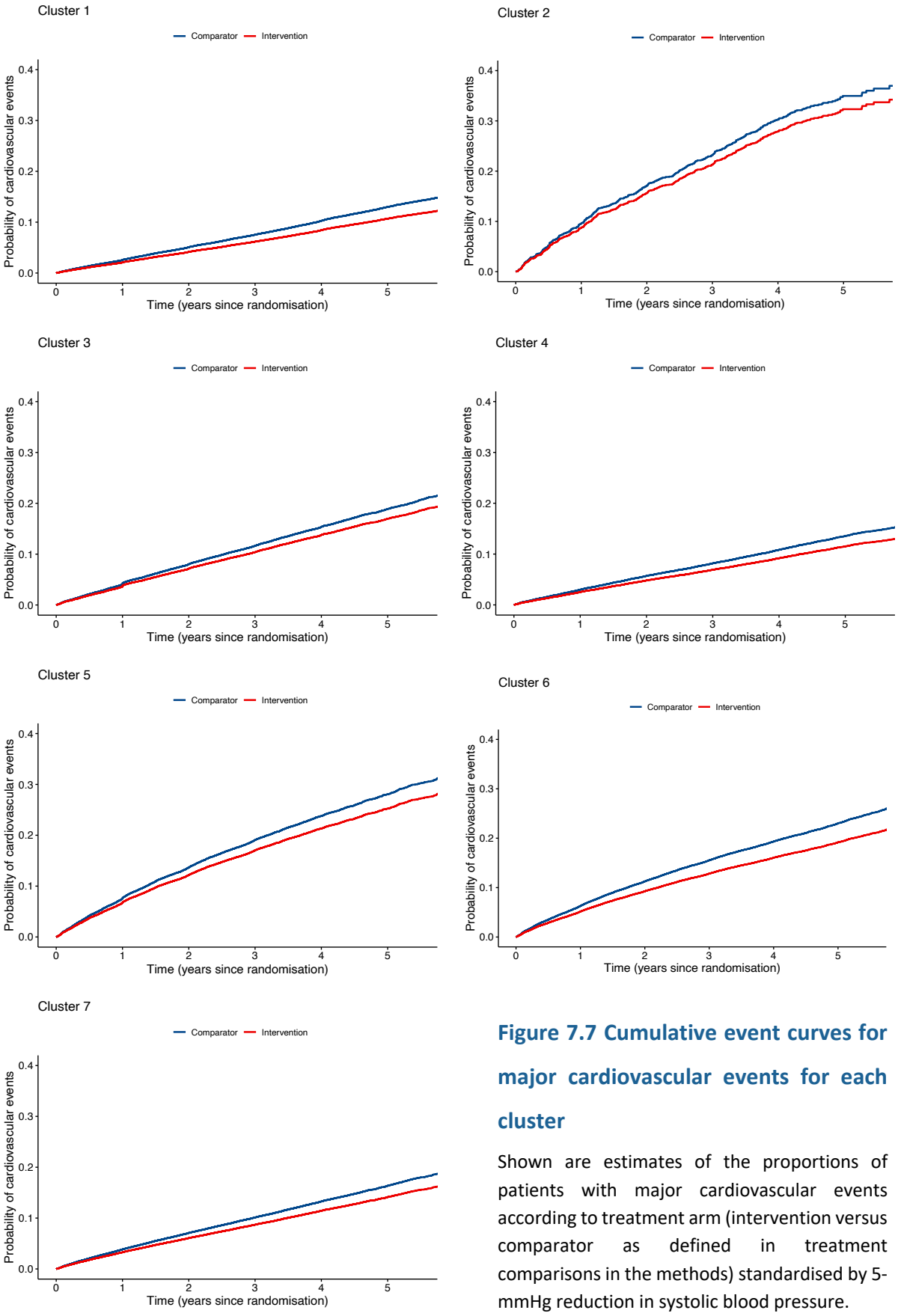

Figure 7.7 Cumulative event curves for major cardiovascular events for each cluster

Shown are estimates of the proportions of patients with major cardiovascular events according to treatment arm (intervention versus comparator as defined in treatment comparisons in the methods) standardised by 5-mmHg reduction in systolic blood pressure.

Table 7.11 Hazard ratios for primary and secondary outcomes overall and for multimorbidity clusters, standardised by 5-mmHg reduction in systolic blood pressure

Outcomes	Hazard ratio	95% Confidence interval	p-value[1]	Adjusted p-value[2]
Major cardiovascular events				
Cluster 1	0.88	[0.84 to 0.91]		
Cluster 2	0.94	[0.72 to 1.24]	0.616	1.000
Cluster 3	0.97	[0.92 to 1.03]	0.005	0.210
Cluster 4	0.90	[0.84 to 0.96]	0.628	1.000
Cluster 5	0.98	[0.91 to 1.07]	0.015	0.630
Cluster 6	0.86	[0.81 to 0.92]	0.576	1.000
Cluster 7	0.88	[0.84 to 0.93]	0.861	1.000
Overall	0.91	[0.89 to 0.93]		
Ischaemic heart disease				
Cluster 1	0.89	[0.83 to 0.96]		
Cluster 2	0.50	[0.29 to 0.87]	0.043	1.000
Cluster 3	0.99	[0.90 to 1.09]	0.093	1.000
Cluster 4	0.92	[0.83 to 1.03]	0.648	1.000
Cluster 5	0.93	[0.81 to 1.06]	0.650	1.000
Cluster 6	0.77	[0.67 to 0.90]	0.080	1.000
Cluster 7	0.92	[0.86 to 0.98]	0.601	1.000
Overall	0.91	[0.88 to 0.94]		
Stroke				
Cluster 1	0.84	[0.79 to 0.90]		
Cluster 2	0.88	[0.61 to 1.26]	0.823	1.000
Cluster 3	0.78	[0.68 to 0.89]	0.276	1.000
Cluster 4	0.85	[0.75 to 0.96]	0.931	1.000
Cluster 5	0.94	[0.81 to 1.08]	0.191	1.000
Cluster 6	0.86	[0.78 to 0.93]	0.793	1.000
Cluster 7	0.87	[0.79 to 0.96]	0.628	1.000
Overall	0.86	[0.83 to 0.90]		
Heart failure				
Cluster 1	0.81	[0.73 to 0.90]		
Cluster 2	0.69	[0.44 to 1.08]	0.487	1.000
Cluster 3	0.99	[0.88 to 1.10]	0.013	0.546

Cluster 4	0.86	[0.75 to 1.00]	0.518	1.000
Cluster 5	0.85	[0.71 to 1.01]	0.687	1.000
Cluster 6	0.92	[0.76 to 1.11]	0.277	1.000
Cluster 7	0.86	[0.77 to 0.95]	0.505	1.000
Overall	0.88	[0.83 to 0.92]		
Cardiovascular death				
Cluster 1	0.85	[0.79 to 0.91]		
Cluster 2	0.74	[0.46 to 1.20]	0.589	1.000
Cluster 3	0.99	[0.88 to 1.12]	0.031	1.000
Cluster 4	0.91	[0.81 to 1.03]	0.324	1.000
Cluster 5	1.10	[0.95 to 1.26]	0.002	0.084
Cluster 6	0.86	[0.77 to 0.96]	0.868	1.000
Cluster 7	0.90	[0.81 to 0.98]	0.397	1.000
Overall	0.91	[0.87 to 0.94]		
All-cause death				
Cluster 1	0.92	[0.88 to 0.96]		
Cluster 2	0.97	[0.71 to 1.31]	0.734	1.000
Cluster 3	0.94	[0.87 to 1.01]	0.642	1.000
Cluster 4	0.97	[0.89 to 1.05]	0.267	1.000
Cluster 5	0.99	[0.90 to 1.10]	0.151	1.000
Cluster 6	0.95	[0.88 to 1.02]	0.505	1.000
Cluster 7	0.92	[0.87 to 0.97]	0.992	1.000
Overall	0.94	[0.91 to 0.96]		

[1] P-value for significant differences between each cluster and cluster 1, which was considered the reference cluster

[2] Adjusted p-value calculated using to account for multiple comparisons

Discussion

This study has two key findings. First, it demonstrated that cluster analysis can successfully identify subgroups of participants in BP lowering trials, which have substantially different cardiometabolic disease profiles. Second, it suggested that there could be subtle, yet important, differences in the proportional effects of BP lowering between clusters of cardiometabolic diseases at baseline. Although this could have substantial implications for clinical practice, the difficulty in matching real-world patients with clusters precluded drawing definite conclusions and hence rendered applicability uncertain.

The first, and arguably the most relevant, finding of this study was the implementation of cluster analysis itself. The good performance of the cluster algorithm was demonstrated by the differences in the overall prevalence of diseases and in the distribution of the thirty-two patterns of disease among the seven clusters. In addition, a critical concern about the cluster analysis was whether it was simply splitting the patients according to the individual trials they were originally from. As the data had a two-level structure with participants naturally clustered within trials, it was possible that the clustering algorithm would define groups based on entire trials rather than individual participants. This would be justified by the greater similarity of participants within each trial than between trials. However, the clustering algorithm took into account the hierarchical structure of the data, and thus there was a variable mix of trials included in each cluster. Taken together, those findings showed that the cluster analysis performed well, which led me to the next step of investigating whether treatment effects varied across clusters.

The second finding of this study was that the relative risk reduction afforded by BP lowering treatment on major cardiovascular events was similar for clusters 1, 2, 4, 6 and 7, thus supporting my previous findings that the effects of BP lowering were broadly comparable across patterns of cardiometabolic multimorbidity. There were slight differences between clusters, which could be related to the specific profile of cardiometabolic diseases of the patients included in each cluster. Nonetheless, the confidence intervals were wide, reflecting the uncertainty in treatment effect estimations, and hence no firm conclusions can be drawn on whether there are clinically relevant differences in the effects of BP lowering between clusters. Indeed, the adjusted p-values did not support any significant differences between clusters 2 to 7 and cluster 1, which was considered as the reference cluster.

On the other hand, the subtle differences in treatment effects in secondary outcomes and risk of cardiovascular events among clusters raise some important hypotheses. First, it is plausible that patients in high-risk clusters, such as those in cluster 2, would reap greater absolute risk reduction for a similar relative risk reduction. Second, patients in the highest risk cluster were also substantially older, but still achieved similar risk reductions to those in younger clusters, which suggests that age should not be a deterrent to BP lowering treatment. Third, there was no evidence that the efficacy of BP lowering differed significantly for primary or secondary prevention of cerebrovascular disease and ischaemic heart disease. Although these ancillary findings do not provide definite answers, as they were not the primary purpose of this study, those are clinically relevant questions that warrant further investigation.

This cluster analysis has its merits. It is, to the best of my knowledge, the first successful attempt at characterising the population of patients included in large-scale hypertension trials

using cluster analysis. In addition, it demonstrated that the clustering algorithm was able to identify distinct groups of participants within the study population, which differed markedly in age, baseline BP, profile of diseases and risk of cardiovascular events. This, in turn, may explain why there were some subtle differences in treatment effects across clusters.

However, cluster analysis is by nature unsupervised, and hence often difficult to interpret. It is not clear why the cluster algorithm grouped certain multimorbidity patterns together. As a consequence, the clinical interpretation and practical implications of cluster analysis are uncertain. For instance, it would be impossible for a frontline clinician to allocate a patient with cerebrovascular disease and diabetes mellitus to a specific cluster, when patients with that combination of diseases were assigned to four different clusters by the algorithm. The logic behind the decisions made by the clustering algorithm is impossible to ascertain and hence to replicate in clinical practice. Therefore, the relevance of cluster analysis to investigate heterogeneity of treatment effects in the context of multimorbidity is debatable. In addition, lack of data meant that my cluster analysis was based on only five cardiometabolic diseases, whilst previous population-based cohort studies used a much larger and wider set of baseline diseases.[463] My study has thus highlighted the need for collecting more detailed data on baseline diseases in RCTs to better understand how treatment effects can be extrapolated to real-world populations, who are increasingly old and multimorbid. However, large-scale RCTs need to collect the minimum amount of data that is required to answer their research question reliably, and hence collecting more information is often not feasible and/or possible.

The limited applicability of the results of cluster analysis in clinical practice underpinned my decision to investigate the effects of BP lowering treatment in the context of multimorbidity using two other complementary approaches: numbers and patterns of cardiometabolic diseases. Therefore, those were the main analyses that I described in the previous section of this chapter and they serve as the basis for the paper that I intend to publish. The exploratory cluster analysis described in this section allowed me to delve deeper into the subject of multimorbidity in BP lowering trials, as well as to develop valuable skills, which warranted inclusion in my thesis. However, I do not intend to publish it due to its questionable applicability.

Conclusion

Cluster analysis can be successfully implemented to investigate multimorbidity in the setting of RCTs of BP lowering treatment. There may be slight differences in the effects of BP lowering across clusters of cardiometabolic multimorbidity, perhaps related to differences in disease patterns, age, baseline BP and overall cardiovascular risk. However, the translation of findings based on cluster analysis to individual patients is not straightforward, and hence its applicability to clinical practice is uncertain. Further research is warranted to address the hypotheses raised by this exploratory study.

Chapter 8 Blood Pressure and Heart Failure

This chapter describes the research stream on HF and BP. It is organised in two sections. The first describes the systematic review and aggregate data meta-analysis of RCTs that I conducted to summarise the evidence available on the effects of drugs with BP lowering properties in patients with HF. The second describes the steps I took and the progress I made to establish a new consortium of IPD from HF trials. This chapter did not use the resource provided by the BPLTTC, because the latter excluded trials conducted in patients with HF.

Part of this chapter was published in *The Journal of Hypertension* at https://journals.lww.com/jhypertension/Abstract/2019/07001/EFFECTS_OF_BLOOD_PRESSURE_LOWERING_DRUGS_IN_HEART.140.aspx. This publication benefitted from the input of several co-authors and my original DPhil supervisors as well as other contributions along the peer review process. I was responsible for designing the study, conducting the literature review, analysing the data, interpreting the results, and writing the manuscript.

An abstract of this research has also been presented at the 29th European Meeting on Hypertension and Cardiovascular Protection hosted by the European Society of Hypertension in June 2019, and at the European Society of Cardiology Congress in September 2019.

Effects of Blood Pressure Lowering Drugs in Heart Failure: a systematic review and meta-analysis of randomised clinical trials

Abstract

Background and Aims

There is ongoing controversy on whether a J-shaped association between BP and clinical outcomes exists in HF and whether it is modifiable by BP lowering treatment. Therefore, I aimed to combine evidence from all HF trials that investigated the effects of drugs with BP lowering properties to assess (1) the extent to which such drugs reduced BP in HF, (2) the association between the net change in BP between treatment arms and cause-specific outcomes, and (3) whether treatment effects varied according to baseline BP.

Methods

This systematic review and meta-analysis combined results from RCTs of drugs with BP lowering properties in patients with chronic HF with at least 300 patient-years of follow-up. The primary outcome was SBP change between trial arms. Secondary outcomes were HF hospitalisation, cardiovascular mortality, all-cause mortality and adverse events leading to treatment discontinuation. Random treatment effects were assumed in all meta-analyses.

Results

A total of 37 trials (91,950 HF patients) were included in this study. Overall, treatment with drugs with BP lowering properties significantly reduced SBP by 2.0 mmHg (95% CI [-2.9 to -1.1]). It also significantly reduced the risk of HF hospitalisation (RR 0.89, 95% CI [0.83 to 0.95])

and cardiovascular mortality (0.91, [0.85 to 0.97]), but not all-cause mortality (RR 1.00, 95% CI [0.91 to 1.10]). However, this came at the cost of a small increase in the risk of adverse events leading to treatment discontinuation (RR 1.21, 95% CI [1.06 to 1.37]). There was no strong evidence that the relative risk reduction afforded by treatment for all-cause mortality, cardiovascular mortality, HF hospitalisation and adverse events leading to treatment discontinuation was significantly different across categories of baseline BP. Meta-regression did not show significant associations between the intensity of BP reduction achieved in each trial and risk of the aforementioned clinical outcomes.

Conclusions

Treatment with drugs with BP lowering properties resulted in a small, but significant, decrease in SBP in patients with HF, with no evidence that the efficacy and safety depended on the intensity of BP lowering or on the baseline level of BP.

Background

In populations without known cardiovascular disease, epidemiological studies have shown a continuous log-linear positive association between BP and cardiovascular events with no evidence of a BP threshold below which the relationship changes.[26] By contrast, in patients with pre-existing cardiovascular disease, including those with HF, studies have typically shown a J-shaped relationship between SBP and all-cause and cardiovascular mortality.[464-466] However, the inability of such observational studies to draw causal conclusions means that it remains uncertain whether the increased risk of death associated with hypotension is a surrogate marker of disease severity, in particular for patients with HF and reduced ejection fraction, or whether lowering BP below 120 mmHg might cause more harm than good.[143]

Large RCTs, and subsequent meta-analyses, are ideally suited to investigate causal effects of BP lowering and hence to clarify the nature of the observed J-shaped relationship between BP and clinical outcomes in HF because they are, by definition, exempt from reverse causation or uncontrolled confounding. However, to date there have been no RCTs of BP lowering per se in patients with HF, and individual RCTs of drugs with BP lowering effects have reached somewhat discordant conclusions.[154,155,176,177,467,468] In addition, RCTs conducted in patients with HF were explicitly excluded from landmark meta-analyses that investigated the effects BP lowering treatment.[5,200,469] Those meta-analyses compellingly demonstrated that BP reduction prevented fatal and non-fatal cardiovascular events, and that this protective effect was proportional to the magnitude of BP lowering, thus suggesting that BP-dependent mechanisms partially underpinned those beneficial effects. However, to what extent those

findings are applicable to HF patients remains unclear. In the absence of reliable evidence, clinical practice guidelines have been making cautious recommendations about intensive BP reduction in HF. For instance, the 2018 European Society of Cardiology and European Society of Hypertension guidelines state that "it might be wise to avoid actively lowering BP to below 120/70 mmHg" in patients with HF.[39]

Therefore, I sought to take advantage of the fact that several licensed HF drugs have known BP lowering properties, to combine evidence from all HF RCTs that have investigated the effects of those drugs to assess (1) the extent to which such drugs lowered BP in HF patients, (2) the association between the net change in BP between treatment arms and cause-specific outcomes, and (3) whether treatment effects (including benefits and potential harms) varied according to baseline BP.

Methods

I conducted a systematic review and meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines of interventional studies[470] and The Cochrane Collaboration.[306] The protocol was registered with the PROSPERO[202] database of systematic reviews (CRD42018095395).

Literature Search

The bibliographic databases PubMed/Medline (NCBI, Bethesda, MD, USA), The Cochrane Central Register of Controlled Trials (The Cochrane Collaboration, London, UK) were searched from inception to December 2018 using terms related to HF and all drugs with known BP lowering properties (details in **Appendix C**). The search was restricted to RCTs or meta-analyses. No language restrictions were applied. This search was complemented with hand-search of reference lists of eligible studies and related meta-analyses, and search of trial registries (ClinicalTrials.gov website).

Inclusion and Exclusion Criteria

Trials conducted in patients with chronic ambulatory and symptomatic HF were included if they met one of the following criteria: (i) randomisation of patients to BP lowering drug(s) or placebo (or other inactive control comparator), or (ii) randomisation of patients to drugs with different intensities of BP lowering. Although included in the search query, trials on cardiac devices were excluded from this systematic review because they were not relevant to the study aims.

No restriction on publication date, setting, drugs or devices investigated was applied. Exclusion criteria were the following: (i) trials without a clearly defined comparison arm; (ii) trials conducted in patients hospitalised for acute HF either as first event or as decompensated chronic HF; (iii) trials conducted in patients with acute HF or reduced ejection

fraction in the context of myocardial infarction; (iv) trials conducted in patients with asymptomatic reduced ejection fraction, that is, trials that focused on prevention of HF. To minimise the risk of small-study effects, all studies were required to have a minimum of 300 patient-years of follow-up.

Outcomes

The primary outcome was the mean difference in SBP change between trial arms. Secondary clinical outcomes were (1) HF requiring hospitalisation; (2) cardiovascular mortality; (3) all-cause mortality, and (4) adverse events leading to treatment discontinuation. The latter was chosen because total, specific and serious adverse events were inconsistently reported and hence unsuitable for meta-analysis. All clinical outcomes were extracted from data reported by primary trials at the end of follow-up.

Screening and Selection of studies

I, and another investigator, independently screened titles and abstracts of all identified studies according to inclusion and exclusion criteria. Full-text articles were retrieved and reviewed in duplicate, with disagreements resolved by consensus. EndNote X8 software was used to manage references and organise screening. **Figure 8.1** summarises the stepwise approach followed during screening and selection of studies.

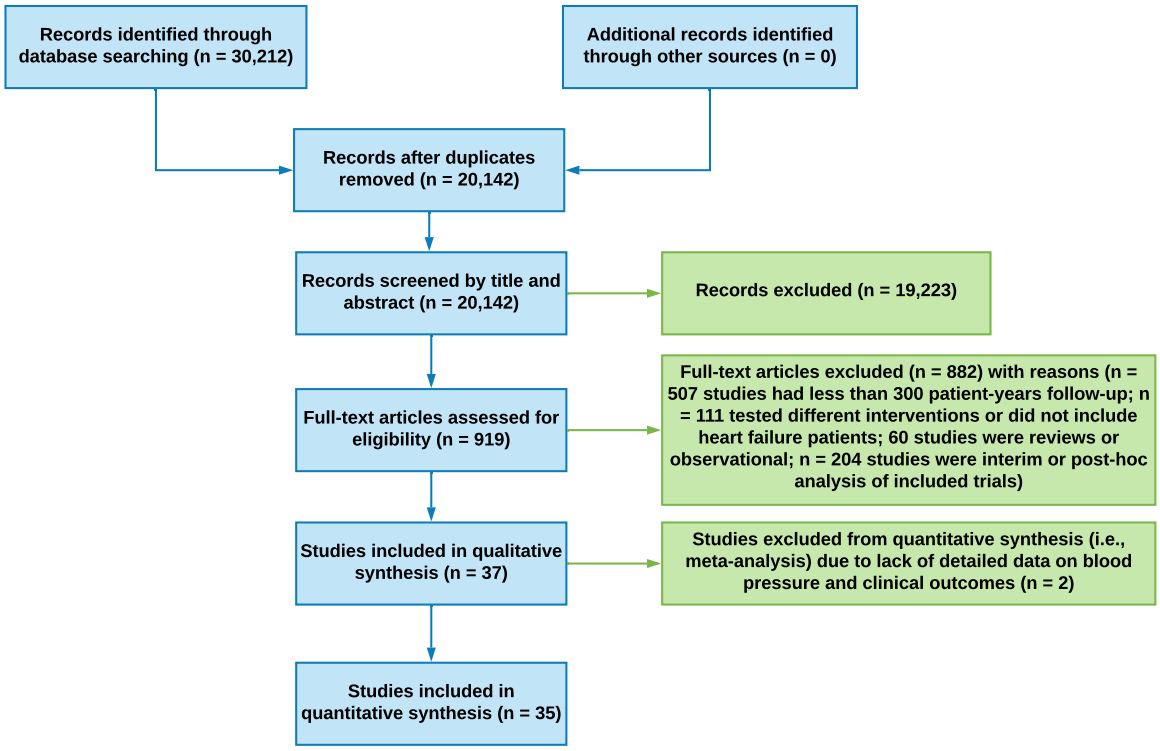

Figure 8.1 PRISMA Flow Diagram explaining in detail the process of screening and selection of relevant studies

Data Extraction

An electronic data abstraction form was used to record patient and study characteristics, including sample size, treatment comparisons, baseline BP, achieved BP, and mean BP reduction. Data were also collected for all available outcomes.

Risk of Bias Assessment

The methodological quality of eligible studies was assessed using the Cochrane risk of bias tool for interventional studies.[306] RCTs were classified as having a low, moderate, high or

unclear risk of the following: selection bias (randomisation and allocation concealment), performance bias (blinding of participants and investigators), detection bias (blinding of outcome adjudicators), attrition bias (differential loss to follow-up), and reporting bias (selective outcome reporting). Each trial was finally ascribed an overall risk of bias based on whether the risk of bias in each of the aforementioned domains could have led to material biases in the risk estimates.

Publication bias

Funnel plot asymmetry was used to detect whether there was publication bias by plotting treatment effect estimates against their respective standard errors. Egger's mixed-effects meta-regression model was used to assess whether there was significant funnel plot asymmetry.[471] The "fill and trim" method was applied to investigate whether adding fake studies that would improve the symmetry of the funnel plot would have a substantial impact on treatment effect estimates.[472]

Data analysis

A two-step approach was used to compare mean BP reduction between trial arms for all trials that reported BP values at baseline and at a second time point, either at the end of follow-up or at the end of drug up-titration, depending on what was available in trial reports. When multiple time points were available, achieved SBP at the end of drug up-titration (usually 6 to 8 weeks) was used, because this was the most commonly reported value when only a single

time point was available, and also because BP tended to remain stable after that. First, mean SBP change was calculated as the difference between mean achieved SBP and mean baseline SBP for each trial arm. Second, the difference in SBP change was computed as the SBP change in intervention group minus the BP change in the control group, so that a negative value represents a larger BP reduction in the intervention group. Some trials reported only the difference between the intervention and control groups, and I used that value, because it was impossible to compute the mean BP reduction in each trial arm.

Four trials had three arms, including three active treatment groups, and strategies were used to avoid double-counting of participants in each trial. For the ATMOSPHERE trial,[473] enalapril was compared with the combination of enalapril and aliskiren, and the aliskiren only group was excluded. For the J-CHF trial,[474] in which three different doses of carvedilol were compared against each other, low dose was compared with high dose and medium dose was excluded. For the RESOLVD trial,[475] which compared enalapril and candesartan isolated and combined, each drug was compared with the combination of both, with the participants in the latter arm split in equal parts. A similar approach was used for the CARMEN trial,[476] which compared carvedilol and enalapril isolated and combined. For the analysis stratified by study type, those two trials were included in the group of placebo-controlled trials, because the combined treatment was compared against each single drug plus placebo. The VACS trial[477] had three study arms including placebo, prazosin and isosorbide dinitrate-hydralazine, and hence each active treatment was compared with placebo, with the participants in the latter arm split in equal parts. For the remaining trials with two arms, the reference category was considered as (1) the placebo in placebo-controlled trials; (2) the standard of care in trials

with two different drug classes; and (3) the low dose in trials with different doses of the same drug.

For the analysis of the primary outcome (i.e., change in SBP), mean difference with 95%CI between SBP in the intervention arm and SBP in the control arm was computed for each trial. To investigate whether the effect of BP lowering drugs on SBP varied depending on the type of study, stratified analysis was performed considering placebo-controlled trials and trials comparing two active treatments. For clinical outcomes, relative risks (RRs) with 95% confidence intervals (CI) were computed from the number of events and total number of patients in each trial arm. To investigate whether the effect of BP lowering drugs on SBP and clinical outcomes varied depending on baseline SBP, trials were divided into five strata of mean baseline SBP aggregated at trial level (<120, 120–124, 125–129, 130–135, and ≥135 mmHg). Subgroup analysis was also performed for drug class, categorised as BB, RAAS inhibitor, and any other drug class. Only placebo-controlled trials were included in the latter analysis because trials comparing two active treatments did not fit into this categorisation.

Further subgroup analyses were performed according to left ventricular ejection fraction, hypertension at baseline, New York Heart Association functional class at baseline, age and duration of follow-up. For left ventricular ejection fraction, trials were divided into two categories using a cut-off of 30% for trial-level mean left ventricular ejection fraction. For hypertension, trials were split into two categories using a threshold of 50% for prevalence of baseline hypertension as defined in each trial; for functional class, trials were divided into two categories according to the class in which most of the patients were at baseline (class I/II

versus class III/IV); for follow-up duration, trials were split into two categories using a cut-off of 18 months, which was the median of the mean follow-up duration of the included trials; and for age, trials were split into two categories using a threshold of 65 years, as this was the median of the mean age aggregated at trial level.

Random effects meta-analysis, with inverse variance weighting, was used to calculate summary estimates with 95% CI for all outcomes, and Restricted Maximum Likelihood (REML) pooled estimators were chosen as they strike a good balance between unbiasedness and efficiency.[478] Heterogeneity between studies was estimated using the I^2 statistic, and the null hypothesis of no heterogeneity was tested using Cochran's Q test.

Meta-regression, using REML pooled estimators, was performed to investigate whether there was a correlation between the log of the relative risk (RR) for each clinical outcome and the change in SBP between study groups. The log RR for primary and secondary outcomes was regressed against the difference between the change in SBP in the intervention and control groups. All p-values were calculated from two-tailed tests. All analyses were performed using the "metafor" package for R version 3.2.1.[479]

Ethics and Confidentiality

This study involved secondary analysis of existing and anonymised data and it did not involve recruitment of patients or access to patient identifiable information.

Results

A total of thirty-seven trials (including 91,950 patients) of BP lowering drugs were identified as potentially eligible for investigation of at least one of the three study aims (**Table 8.1**). The trials were published between 1986 and 2017 and included participants from all five continents. The follow-up duration ranged from 10 to 56 months, with a mean of 29 months. The mean age of the patients across all trials was 65 years, and men were disproportionately represented in the populations included in those trials (**Table 8.2**). Indeed, twenty-three trials included 75% or more men, and only four trials included slightly more women than men.

Five trials had three study arms whilst the remaining had two study arms; eight trials tested BB against placebo; six tested ACEI/ARB against placebo; three trials tested mineralocorticoid receptor antagonist against placebo; three trials tested CCB against placebo; two trials compared BB with ACEI; seven trials compared different doses or drugs within the same class of BB or ACEI; three trials compared isosorbide dinitrate-hydralazine with placebo or alternative treatment; one trial tested ARB against standard treatment; and the remaining four trials studied aliskiren, omapatrilat, sacubitril-valsartan and bosentan. Four trials were conducted in patients with HF with preserved ejection fraction, thirty trials were conducted in patients with HF with reduced ejection fraction, and three trials included a variable proportion of patients with HF with preserved and reduced ejection fraction. J-CHF[474] did not report any of the primary or secondary outcomes considered in this meta-analysis and it was thus not included in any of the quantitative analyses. CIBIS II[480] did not report baseline or achieved BP and hence it was also not included in the quantitative analysis.

Table 8.1 Methodological characteristics of the included trials

Trial	Year	Blinding	Control	N centres/Location	FU	Control (N)	Intervention 1 (N)	Intervention 2 (N)	Baseline BP	Achieved BP	BP time
Placebo-controlled trials											
CIBIS[481]	1994	DB	PC	70/EU	23	Placebo (321)	Bisoprolol (320)		R	NR	NR
CIBIS II[480]	1999	DB	PC	274/EU	15	Placebo (1320)	Bisoprolol (1327)		NR	NR	NR
BEST[482]	2001	DB	PC	90/NA	24	Placebo (1354)	Bucindolol (1354)		R	PR	NR
COPERNICUS[483]	2002	DB	PC	334/NA, EU, AUS	11	Placebo (1133)	Carvedilol (1156)		R	PR	4
PEP-CHF[484]	2006	DB	PC	53/EU	26	Placebo (426)	Perindopril (420)		R	R	12
SENIORS[485]	2005	DB	PC	11/EU	21	Placebo (1061)	Nebivolol (1067)		R	R	4
SOLVD[486]	1991	DB	PC	23/NA, Belgium	48	Placebo (1284)	Enalapril (1285)		R	PR	NR
MERIT-HF[487]	1999	DB	PC	14/US, EU	18	Placebo (2001)	Metoprolol (1990)		R	R	6
Val-HeFT[488]	2001	DB	PC	302/US, EU, Africa	23	Placebo (2499)	Valsartan (2511)		R	PR	6
RALES[489]	1999	DB	PC	195/EU, NA, SA, Asia	24	Placebo (841)	Spironolactone (822)		R	NR	NR
A-HeFT[490]	2004	DB	PC	169/US	10	Placebo (532)	HZ-ISDN (518)		R	R	6
I-PRESERVE[491]	2008	DB	PC	293/EU, NA, SA, AUS, Africa	50	Placebo (2061)	Irbesartan (2067)		R	R	6
CHARM-Added[181]	2003	DB	PC	618/ NA, EU	41	Placebo (1272)	Candesartan (1276)		R	PR	NR
CHARM-Alternative[492]	2003	DB	PC	618/NA, EU	42	Placebo (1015)	Candesartan (1013)		R	PR	6
CHARM-Preserved[493]	2003	DB	PC	618/NA, EU	37	Placebo (1508)	Candesartan (1512)		R	PR	6
EMPHASIS-HF[494]	2011	DB	PC	278/US, EU, AUS	21	Placebo (1373)	Eplerenone (1364)		R	PR	NS
TOPCAT[495]	2014	DB	PC	233/NA, SA, Russia, Georgia	40	Placebo (1723)	Spironolactone (1722)		R	NR*	NR
PRAISE[496]	1996	DB	PC	105/NA	14	Placebo (582)	Amlodipine (571)		R	PR	3
PRAISE 2[497]	2013	DB	PC	105/NA	33	Placebo (827)	Amlodipine (827)		R	PR	3
ENABLE[498]	2017	DB	PC	151/EU, AUS, NA	18	Placebo (807)	Bosentan (804)		R	PR	78
MACH-1[154]	2001	DB	PC	NR/EU, NA, Israel	50	Placebo (1295)	Mibefradil (1295)		NR	NR	NR

PRECISE[499]	1996	DB	PC	NR/US	12	Placebo (398)	Carvedilol (626)		R	NR*	NR
VACS[477]	1986	DB	PC	US	28	Placebo (273)	HZN-ISDN (186)	Prazosin (183)	R	R	2
Drug comparison trials											
CIBIS III[500]	2005	OL	AT	128/EU, AUS and Tunisia	24	Bisoprolol (550)	Enalapril (550)		R	R	6
V-HeFT II[501]	1991	DB	AT	13/US	30	HZ-ISDN (401)	Enalapril (403)		R	R	4
ELITE I[502]	1997	DB	AT	125/US, SA, EU	11	Losartan (352)	Captopril (370)		R	NR	NR
ELITE II[503]	2000	DB	AT	289/NA, MC SA, EU	11	Losartan (1578)	Captopril (1574)		R	NR	NR
COMET[504]	2003	DB	AT	341/EU	58	Carvedilol (1511)	Metoprolol (1518)		R	PR	4
ATMOSPHERE[473]	2016	DB	AT	789/EU, NA, SA, Africa Asia	37	Enalapril (2336)	Aliskiren (2340)	Enalapril + Aliskiren (2340)	R	PR	4
PARADIGM-HF[505]	2014	DB	AT	1043/EU, America, Africa, Asia	27	Enalapril (4212)	Sacubitril/Valsartan (4187)		R	PR	8
OVERTURE[506]	2002	DB	AT	704/EU, America, Africa, Asia	15	Enalapril (2884)	Omapatrilat (2886)		R	PR	4
HEAAL[507]	2009	DB	AT	255/EU, America, Africa, Asia	56	Losartan 50 (1913)	Losartan 150 (1921)		R	R	6
ATLAS[508]	1999	DB	AT	287/EU, AUS, NA	46	Lisinopil LD (1596)	Lisinopril HD (1568)		R	PR	36
SUPPORT[151]	2015	OL	AT	17/Japan	53	Standard therapy (568)	Olmesartan (578)		R	NR*	12
CARMEN[476]	2004	DB	AT	65/EU	18	Carvedilol + Placebo (191)	Enalapril + Placebo (190)	Carvedilol + Enalapril (191)	R	R	8
J-CHF[474]	2012	DB	AT	Japan	36	Carvedilol LD (118)	Carvedilol MD (116)	Carvedilol HD (118)	R	NR	NR
RESOLVD[475]	2000	DB	PC	60/NA, Italy	11	Enalapril (109)	Candesartan (327)	Enalapril + Candesartan (332)	R	R	11

AT, active treatment; AUS, Australia; B, blinding; BP, blood pressure; BP time, months after randomisation when achieved BP was reported; C, type of control; Can, Canada; DB, double blind; EU, Europe; FU, follow-up duration in months; HD, high dose; HZ-ISDN, hydralazine and isosorbide dinitrate; LD, low dose; N, number; NA, North America; NR, not reported; NS, not specified**;** PC, placebo controlled; PR, partially-reported; R, reported; SA, South America; SB, single blind; US, United States of America

* This indicates that trial mentioned there was no difference in achieved blood pressure between study arms, but exact values were not reported.

Table 8.2 Baseline characteristics of the included trials

Trial	Sex (% male)	Age (years, mean)	HF type	NYHA I/II (%)	NYHA III/IV (%)	Ischaemic HF (%)	AF (%)	DM (%)	HTN (%)	LVEF (%, mean)	BMI (kg/m^2, mean)
CIBIS[481]	83	60	HFrEF	0	100	36	55	6	NR	25	NR
CIBIS II[480]	80	61	HFrEF	0	100	50	12	NR	NR	NR	NR
CIBIS III[500]	68	72	HFrEF	49	51	NR	NR	NR	66	29	NR
BEST[482]	78	60	HFrEF	0	100	58	27	11	NR	23	NR
COPERNICUS[483]	80	63	HFrEF	0	0	67	NR	NR	NR	20	NR
PEP-CHF[484]	45	76	HFpEF	75	25	NR	NR	NR	NR	65	NR
SENIORS[485]	43	76	Mix	59	41	NR	NR	NR	62	34	NR
V-HeFT II[501]	100	61	HFrEF	57	43	NR	NR	NR	47	29	NR
ELITE I[502]	67	74	HFrEF	65	35	68	NR	NR	59	30	NR
ELITE II[503]	70	71	HFrEF	52	48	79	NR	NR	49	31	NR
SOLVD[486]	80	61	HFrEF	68	32	71	18	NR	42	25	NR
MERIT-HF[487]	78	64	HFrEF	41	59	66	NR	NR	44	28	NR
Val-HeFT[488]	80	63	HFrEF	62	38	57	31	7	NR	27	NR
RALES[489]	73	65	HFrEF	0	100	55	4	NR	NR	25	NR
A-HeFT[490]	60	57	HFrEF	0	100	23	26	39	NR	24	NR
I-PRESERVE[491]	40	72	HFpEF	21	79	25	NR	64	89	60	NR
CHARM-Added[181]	78	64	HFrEF	24	76	63	26	7	48	28	NR
CHARM-Alternative[492]	68	67	HFrEF	48	52	69	20	7	50	30	NR
CHARM-Preserved[493]	60	67	HFpEF	61	39	56	9	23	65	54	NR

COMET[504]	80	62	HFrEF	48	52	52	44	18	37	26	NR
EMPHASIS-HF[494]	78	69	HFrEF	0	0	69	NR	NR	66	26	NR
TOPCAT[495]	49	69	HFpEF	67	33	NR	NR	NR	NA	56	NR
ATMOSPHERE[473]	79	63	HFrEF	64	36	56	NR	NR	62	28	27
PARADIGM-HF[505]	78	64	HFrEF	75	25	60	NR	NR	71	30	28
OVERTURE[506]	79	64	Mix	48	52	56	NR	NR	NR	24	NR
HEAAL[507]	71	66	HFrEF	69	31	64	NR	NR	60	33	27
PRAISE[496]	76	65	HFrEF	0	100	63	NR	NR	56	21	NR
PRAISE 2[497]	66	59	HFrEF	0	100	0	62	16	NR	21	NR
ATLAS[508]	80	64	HFrEF	0	84	NR	NR	NR	NR	23	NR
SUPPORT[151]	75	66	Mix	0	7	48	21	NR	NR	54	24
ENABLE[498]	74	67	HFrEF	0	100	69	NR	NR	NR	25	NR
MACH-1[154]	79	63	HFrEF	0	74	68	NR	NR	29	25	NR
PRECISE[499]	77	58	HFrEF	0	57	48	NR	NR	NR	23	NR
CARMEN[476]	81	62	HFrEF	7	29	68	NR	NR	32	NR	26
J-CHF[474]	89	60	HFrEF	0	17	29	NR	NR	NR	30	24
VACS[477]	100	58	HFrEF		0	44	NR	NR	40	30	NR
RESOLVD[475]	85	63	HFrEF	0	38	72	NR	NR	NR	28	NR

AF, atrial fibrillation; BMI, body mass index; BP, blood pressure; DM, diabetes mellitus; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HTN, hypertension; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association functional class; NR, not reported

Aim 1: Effect on blood pressure

Although baseline BP was reported in thirty-five trials, only twenty trials reported achieved BP in enough detail to be included in the meta-analysis, two of which contributed with two study arms.[476,509] Treatment with BP lowering drugs resulted in a significant 2.0 mmHg (95% CI [-2.9 to -1.1]) reduction in SBP when all trials were considered and 2.4 mmHg (95% CI [-3.2 to -1.5]) reduction in SBP when only placebo-controlled trials where included (**Figure 8.2**). However, there was significant heterogeneity between trials, which was largely driven by a single outlier, the MERIT-HF trial. There was no significant change in SBP amongst trials comparing two active treatments.

The heterogeneity on average SBP reduction amongst placebo-controlled trials was not explained by baseline SBP (p = 0.518) (**Figure 8.3 and Figure S8.1 in Appendix B**). There was also no evidence that heterogeneity was explained by other potential variables in subgroup analyses according to age (p = 0.634), left ventricular ejection fraction (p = 0.911), New York Heart Association functional class (p = 0.605), hypertension at baseline (p = 0.313), and duration of follow-up (p = 0.164). However, there was suggestive evidence for heterogeneity of treatment effects according to drug class, as RAAS inhibitors reduced SBP by 3.2 mmHg (95% CI [-4.0 to -2.4]), whilst BB appeared to have a neutral effect on SBP (**Figure 8.4A and Figure S8.2 in Appendix B**). However, there was no heterogeneity in sensitivity analysis excluding the outlier trial MERIT-HF (**Figure 8.4B**). Other drug classes were grouped together and achieved a SBP reduction of 2.4 mmHg (95% CI [-3.8 to -1.3]).

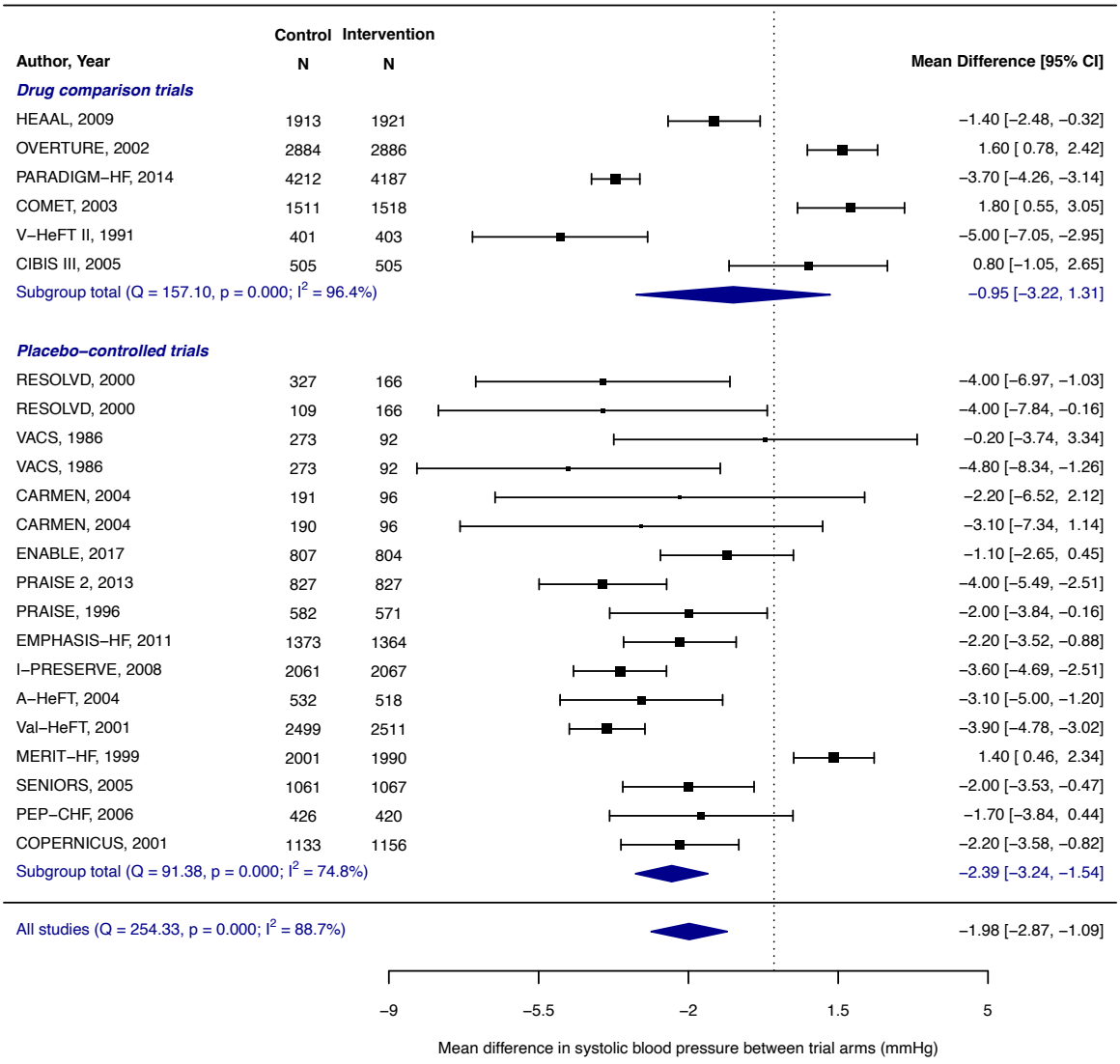

Figure 8.2 Meta-analysis of the effect of blood pressure lowering treatment in HF on the mean difference in systolic blood pressure, stratified by study type

Mean differences between the change in systolic blood pressure in the intervention arm versus the control arm are displayed for each trial and subgroup. Summary measures were calculated using random effects models with REML estimators. Negative values mean that the reduction in systolic blood pressure was greater in the intervention arm. Studies were separated into those that compared two active treatments and those that compared one active treatment with placebo.

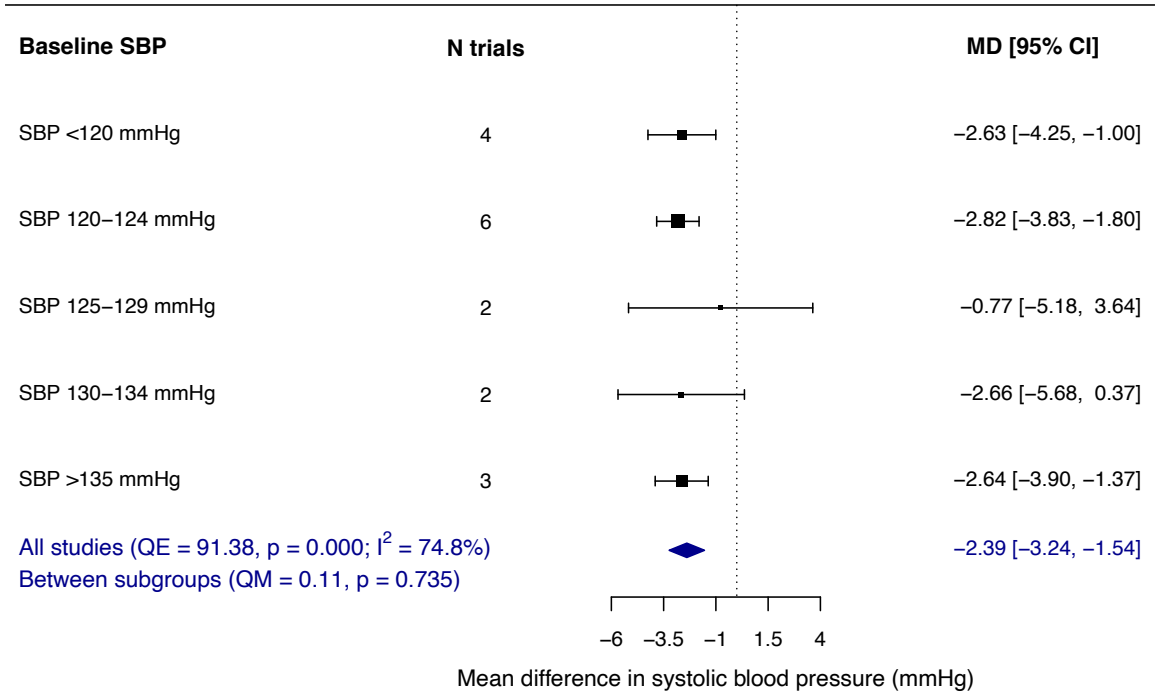

Figure 8.3 Meta-analysis of the effect of blood pressure lowering treatment on the mean difference in systolic blood pressure, stratified by baseline systolic blood pressure

Mean differences between the change in systolic blood pressure in the intervention arm versus the control arm are displayed for each strata of mean baseline systolic blood pressure aggregated at trial level. Summary measures were calculated using random effects models with REML estimators. Negative values mean that the reduction in systolic blood pressure was greater in the intervention arm. Only studies that compared active treatment with placebo were included.

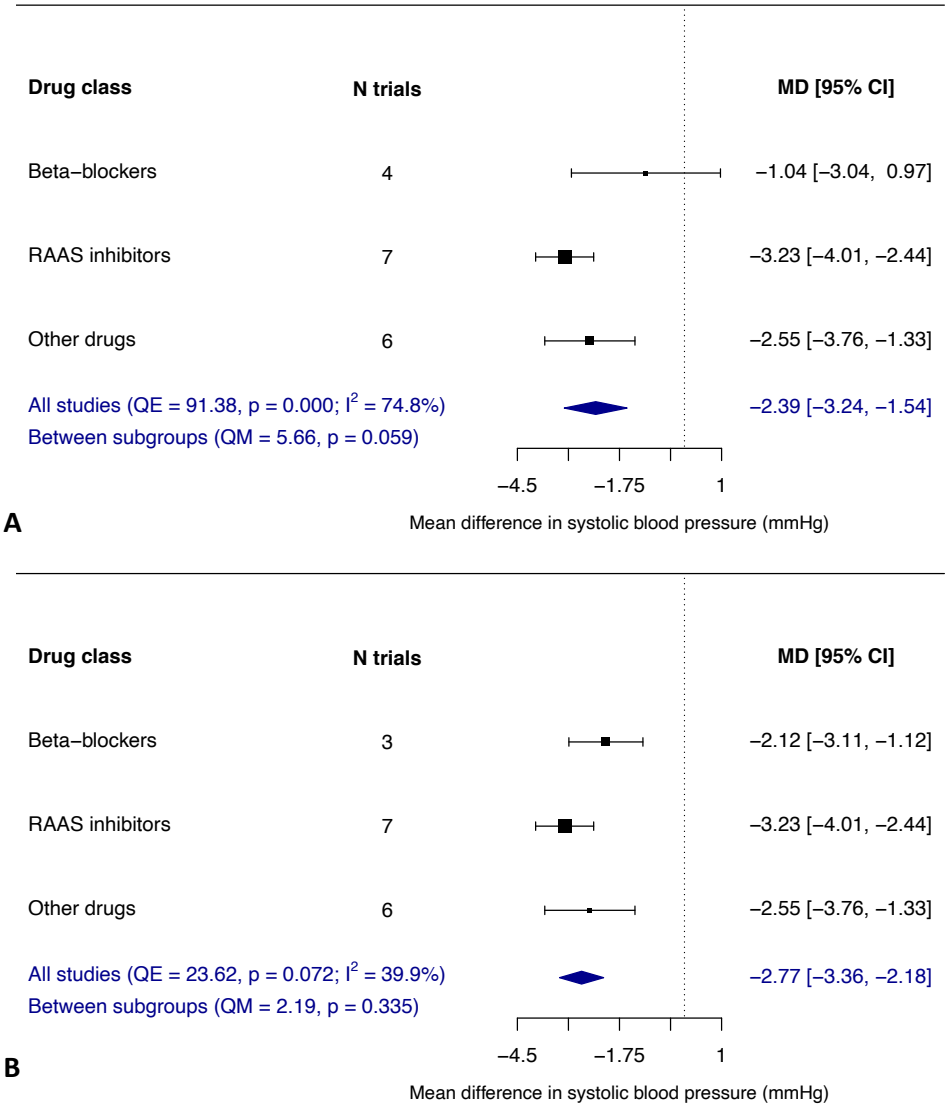

Figure 8.4 Meta-analysis of the effect of blood pressure lowering treatment on the mean difference in systolic blood pressure, stratified by drug class

Mean differences between the change in systolic blood pressure in the intervention arm versus the control arm are displayed for each drug class including (A) and excluding (B) the outlier trial MERIT-HF in the beta-blocker subgroup. Summary measures were calculated using random effects models with REML estimators. Negative values mean that the reduction in systolic blood pressure was greater in the intervention arm. Other drugs include calcium channel blockers, alpha-blockers, and hydralazine-isosorbide dinitrate. Only studies that compared active treatment with placebo were included. RAAS, renin angiotensin aldosterone system

Aim 2: Effect on clinical outcomes according to blood pressure change

Clinical outcomes were variably reported, with thirty-five trials reporting all-cause mortality, twenty-seven trials reporting cardiovascular mortality, twenty-six trials reporting HF hospitalisation, and twenty reporting adverse events leading to treatment discontinuation. Overall, there was no significant association between trial-level intensity of BP lowering and the risk of all-cause mortality, cardiovascular mortality, HF hospitalisation or adverse events leading to treatment discontinuation (**Figure 8.5**).

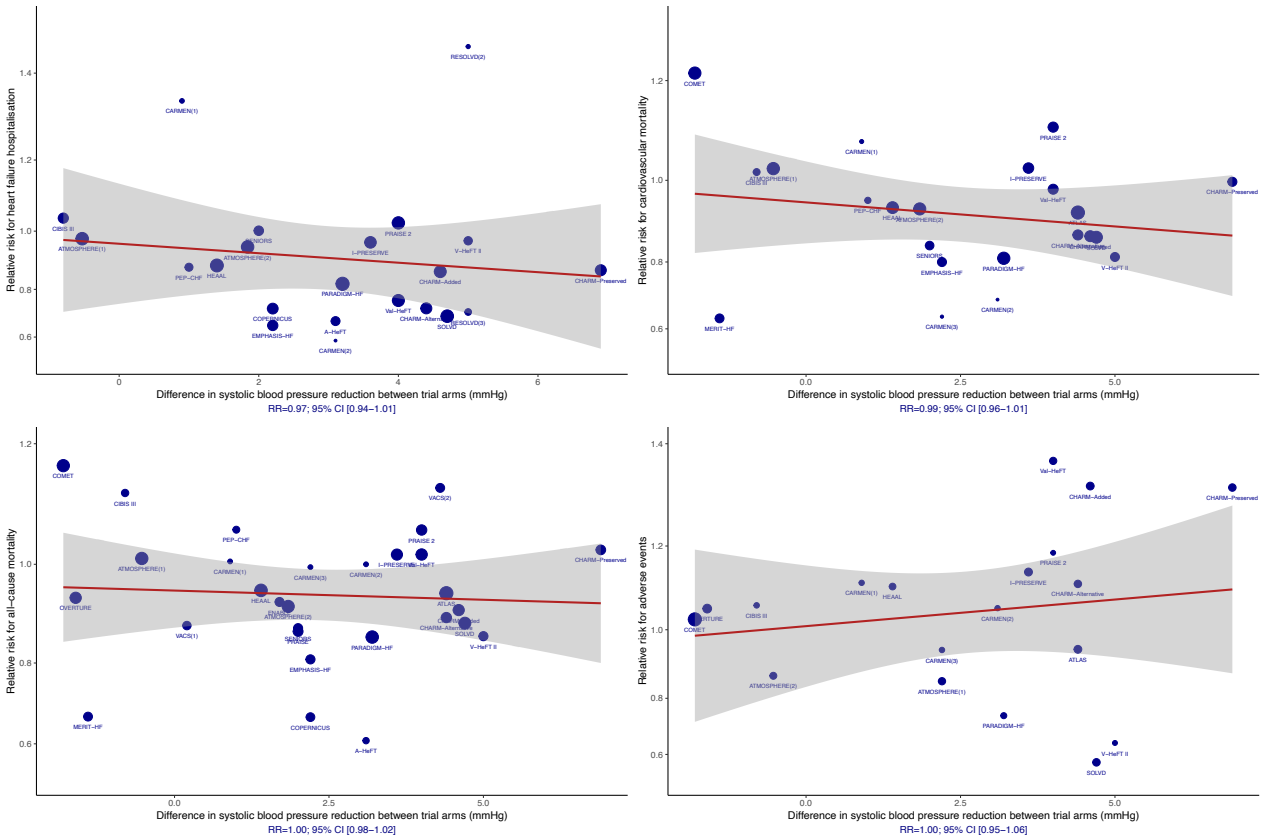

Figure 8.5 Meta-regression of the risk for all-cause mortality, cardiovascular mortality, heart failure hospitalisation and adverse events leading to treatment discontinuation according to the difference in systolic blood pressure between study groups

Log-risk ratios for each clinical outcome (all-cause mortality, cardiovascular mortality, heart failure hospitalisation and adverse events leading to treatment discontinuation) were regressed against the mean difference in systolic blood pressure reduction between the intervention and control arms in each trial (intervention arm minus control arm). A positive difference means that the reduction in systolic blood pressure was larger in the intervention arm.

Aim 3: Effect on clinical outcomes according to baseline blood pressure

Although not the main purpose of this analysis, treatment with drugs with BP lowering properties significantly decreased the relative risk of cardiovascular mortality and HF hospitalisation by about 10% (RR 0.89, 95% CI [0.83 to 0.95]) for HF hospitalisation and RR 0.91, 95% CI [0.85 to 0.97] for cardiovascular mortality), but there was no evidence that treatment influenced the risk of all-cause mortality (RR 1.00, 95% CI [0.91 to 1.10]). On the other hand, treatment with drugs with BP lowering properties resulted in an approximately 20% increase in the risk of adverse events leading to treatment discontinuation (RR 1.21, 95% CI (1.06 to 1.37)].

Mean baseline SBP aggregated at trial level ranged from 116 to 139 mmHg. There was no evidence of significant heterogeneity in treatment effects on all-cause mortality, cardiovascular mortality and HF hospitalisation across strata of mean baseline SBP (**Figure 8.6 and Figures S8.3-5 in Appendix B**). There was significant heterogeneity between SBP strata for adverse events leading to treatment discontinuation, which was driven by the lower relative risk of events in the category with SBP under 120 mmHg (**Figure 8.6 and Figure S8.6 in Appendix B**). However, heterogeneity was no longer present when sensitivity analysis was performed excluding that category, which included only one relatively small trial (**Figure 8.7**).

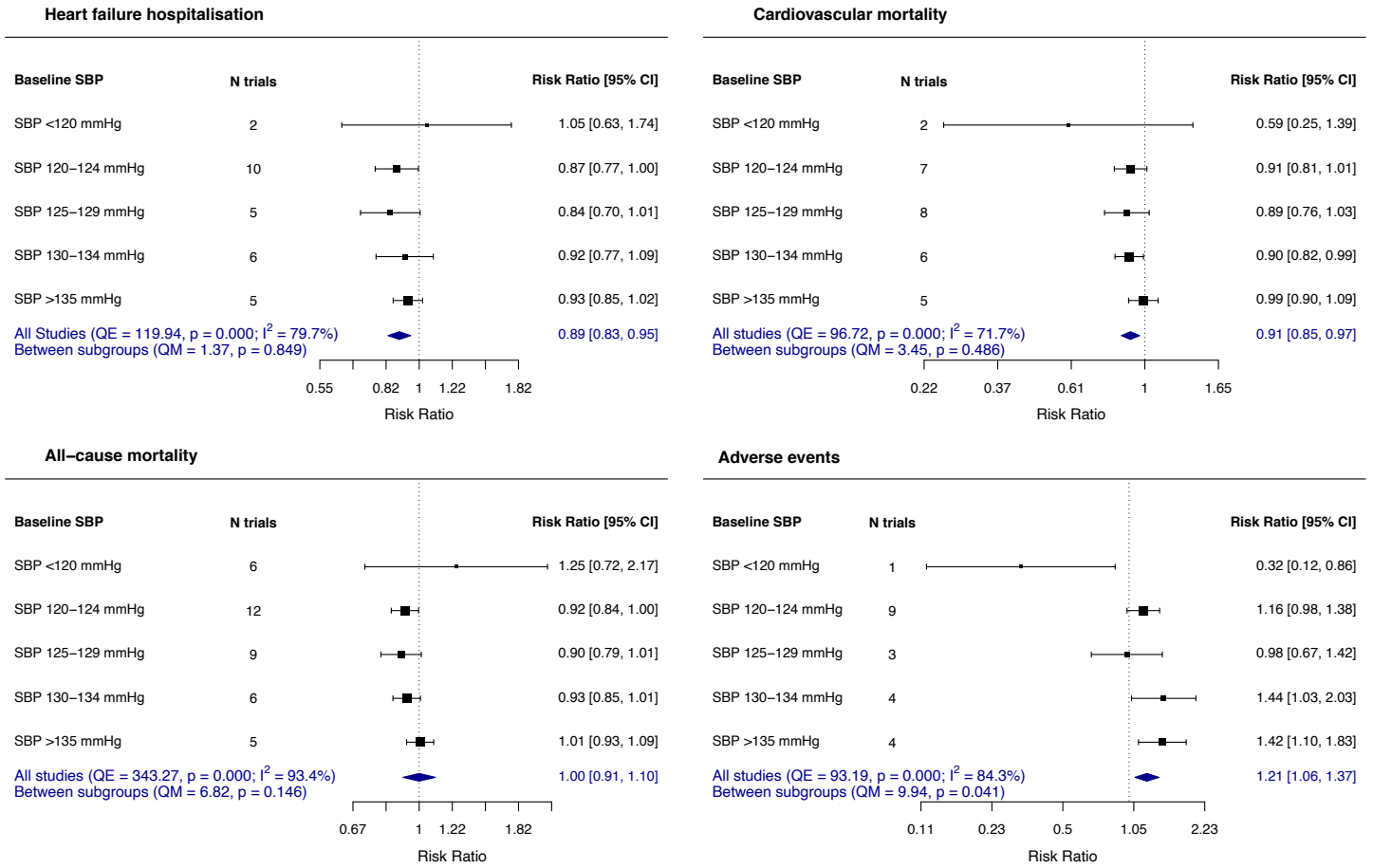

Figure 8.6 Meta-analysis of the effect of blood pressure lowering treatment on clinical outcomes stratified by baseline systolic blood pressure

Risk ratios and 95% confidence intervals are displayed for each clinical outcome (all-cause mortality, cardiovascular mortality, heart failure hospitalisation and adverse events leading to treatment discontinuation) for each strata of mean baseline systolic blood pressure aggregated at trial level. Summary measures were calculated using random effects models with REML estimators. SBP, systolic blood pressure

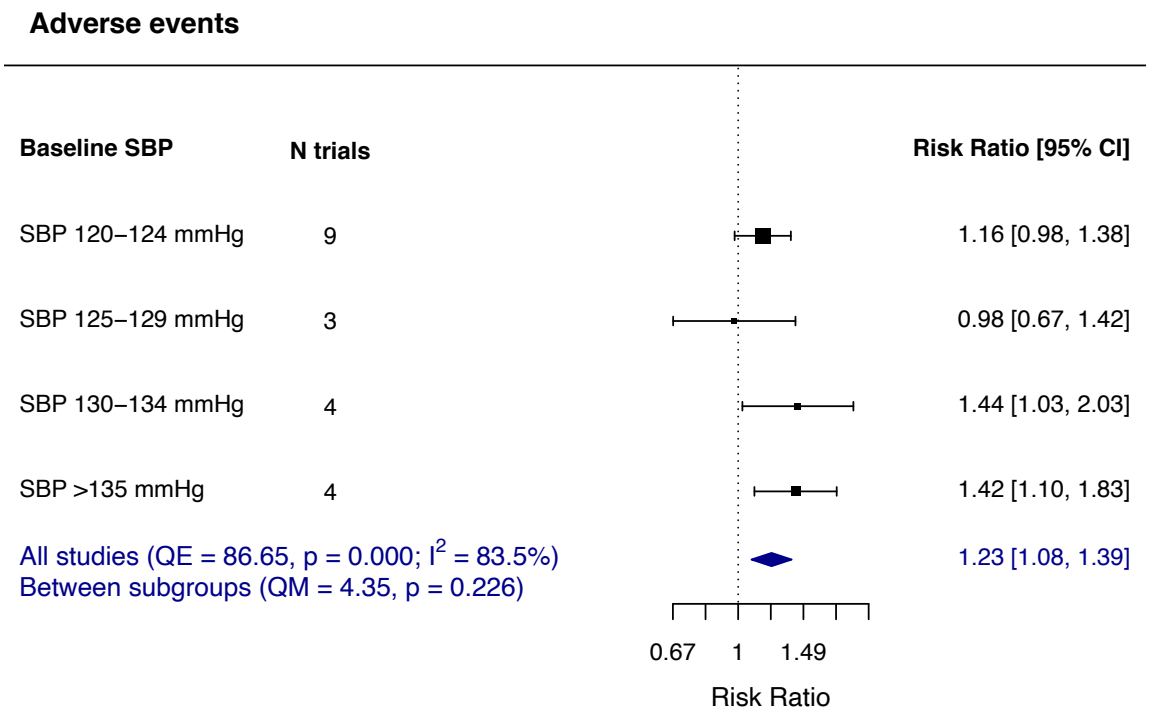

Figure 8.7 Meta-analysis of the effect of blood pressure lowering treatment on adverse events leading to treatment discontinuation stratified by baseline systolic blood pressure excluding the trial with systolic blood pressure below 120 mmHg

Risk ratios and 95% confidence intervals are displayed for adverse events leading to treatment discontinuation for each strata of mean baseline systolic blood pressure aggregated at trial level, excluding the lowest stratum (<120 mmHg), which included only a single trial. Summary measures were calculated using random effects models with REML estimators. SBP, systolic blood pressure

Risk of bias and publication bias

Thirty-three studies had a low risk of bias (**Table 8.3**). Two studies were considered to have an unclear risk of bias, because they did not provide information about randomisation method and allocation concealment,[495,502] and a further two were considered to have medium risk of bias because they were open-label.[151,500]

There was no evidence of significant publication bias according to Egger's test (p = 0.238; **Figure 8.8**). This was further corroborated by the "fill and trim" method, which demonstrated that the studies that were deemed to be lacking on the funnel plot would not result in a material difference to treatment effect estimates (mean difference in SBP reduction 1.67, 95% CI [-2.54 to -0.79]).

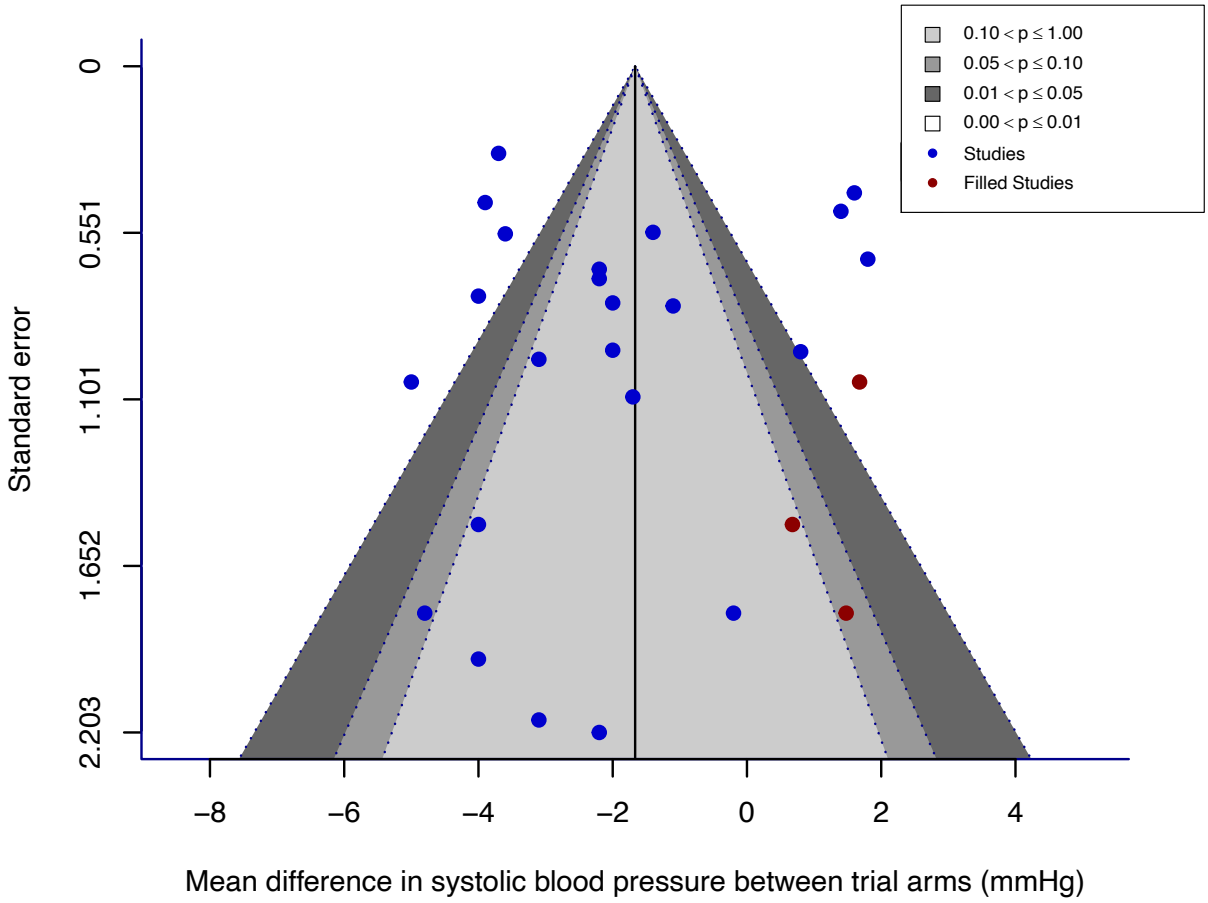

Figure 8.8 Funnel plot of the studies included in this aggregate data meta-analysis

Funnel plot of standard error by mean difference in systolic blood pressure between trial arms (in mmHg) for the studies included in the meta-analysis. Blue dots represent the actual estimates of the included studies and red dots represent the phantom studies that were added by the "fill and trim" method (see text for further details). Negative values mean that the reduction in systolic blood pressure was greater in the intervention arm.

Table 8.3 Risk of bias assessment for the studies included in the meta-analysis

Trial	Selection bias	Performance bias	Detection bias	Attrition bias	Reporting bias	Summary
CIBIS[481]	●	●	●	●	●	●
CIBIS II[480]	●	●	●	●	●	●
CIBIS III[500]	●	✖	●	●	●	❖
BEST[482]	●	●	●	●	●	●
COPERNICUS[483]	●	●	●	●	●	●
PEP-CHF[484]	●	●	●	●	●	●
SENIORS[485]	●	●	●	●	●	●
V-HeFT II[501]	●	●	●	●	●	●
ELITE I[502]	■	●	●	●	●	■
ELITE II[503]	●	●	●	●	●	●
SOLVD[486]	●	●	●	●	●	●
MERIT-HF[487]	●	●	●	●	●	●
Val-HeFT[488]	●	●	●	●	●	●
RALES[489]	■	●	●	●	●	■
A-HeFT[490]	●	●	●	●	●	●
I-PRESERVE[491]	●	●	●	●	●	●
CHARM-Added[181]	●	●	●	●	●	●
CHARM-Alternative[492]	●	●	●	●	●	●
CHARM-Preserved[493]	●	●	●	●	●	●
COMET[504]	●	●	●	●	●	●
EMPHASIS-HF[494]	●	●	●	●	●	●
TOPCAT[495]	●	●	●	●	●	●
ATMOSPHERE[473]	●	●	●	●	●	●
PARADIGM-HF[505]	●	●	●	●	●	●
OVERTURE[506]	●	●	●	●	●	●
HEAAL[507]	●	●	●	●	●	●
PRAISE[496]	●	●	●	●	●	●
PRAISE 2[497]	●	●	●	●	●	●
ATLAS[508]	●	●	●	●	●	●
SUPPORT[151]	●	✖	✖	●	●	❖
ENABLE[498]	●	●	●	●	●	●
MACH-1[154]	●	●	●	●	●	●
PRECISE[499]	●	●	●	●	●	●
CARMEN[476]	●	●	●	●	●	●
J-CHF[474]	●	●	●	●	●	●
VACS[477]	●	●	●	●	●	●
RESOLVD[475]	●	●	●	●	●	●

● Low risk of bias ❖ Medium risk of bias ✖ High risk of bias ■ Unclear risk of bias

Discussion

This systematic review and aggregate data meta-analysis demonstrated that treatment with drugs with BP lowering properties resulted in a small decrease (about 2 mmHg) in SBP, with no evidence of heterogeneity across strata of baseline SBP aggregated at trial level. Furthermore, treatment with those drugs achieved an approximate 10% reduction in the risk of HF hospitalisation and cardiovascular mortality with no evidence that it reduced the risk of all-cause mortality. However, it also led to an approximately 20% increase in adverse events leading to treatment discontinuation. There was no evidence that treatment effects on all-cause mortality, cardiovascular mortality and HF hospitalisation were significantly different across categories of baseline SBP. There was also no strong evidence for heterogeneity of effects on adverse events leading to treatment discontinuation by baseline SBP strata. However, published information was insufficient to thoroughly investigate treatment effects on BP as well as its association with a wider range of clinical outcomes. Meta-regression did not show significant associations between the intensity of BP reduction achieved in each trial and the risk of HF hospitalisation, cardiovascular mortality, all-cause mortality or adverse events leading to treatment discontinuation. There was substantial heterogeneity in all analyses, but data aggregated at trial level did not allow adequate exploration of sources of heterogeneity.

The longstanding controversy on whether drugs with BP lowering properties actually reduce BP in patients with HF remains far from being resolved. This meta-analysis suggested that there was a small decrease in SBP, which is consistent with findings in the general population

for a similar range of baseline SBP. Indeed, a landmark meta-analysis[510] that included 354 trials of antihypertensive drugs reported a reduction of 2 to 5 mmHg in SBP in patients with baseline SBP below 120 mmHg. Although my estimate of 2 mmHg is at the lower end of that range, this does not appear to be due to drug dosing because the doses used in HF trials were at least as high as the standard doses considered in the aforementioned meta-analysis. A more likely explanation is the fact that trials of drugs with BP lowering properties in HF patients allowed concomitant treatment in control arms with drugs that also had BP lowering properties, which may have diluted the BP lowering effect of the intervention. On the contrary, antihypertensive trials included in that previous meta-analysis compared specific drug classes against placebo, which magnified the BP lowering effect.[510]

Further analyses by type of drug suggested that RAAS inhibitors achieved the largest SBP reduction, whilst BBs had no significant impact on SBP. However, there were only four trials testing BBs, and sensitivity analysis suggested that the overall SBP change across BB trials was skewed by the heavy weight of the MERIT-HF trial, in which SBP increased in the metoprolol arm compared to the placebo arm.[511] Putting this outlier trial aside, my findings are in keeping with evidence in the general population, in which BBs tend to be, on average, less effective than other drug classes at reducing BP.[39]

In keeping with previous hypertension trials,[159,176] I found that the relative risk reduction afforded by drugs with BP lowering properties on clinical outcomes was broadly consistent across the spectrum of baseline SBP. This, together with previous evidence that patients in the lowest baseline BP stratum experience a greater absolute risk of cardiovascular events

and HF hospitalisation,[159,176,185,186] provides reassurance to clinicians and argues against overzealous treatment in that group of patients. Furthermore, the fact that the relative risk of adverse events leading to treatment discontinuation was similar across the range of baseline SBP was also in line with previous evidence. Indeed, a post hoc analysis of a landmark clinical trial showed that patients with the lowest baseline BP (SBP below 120 mmHg) had an increased risk of adverse events overall, and hypotension in particular, irrespective of the treatment arm they were allocated to.[143] This suggests that the higher incidence of adverse events and complications in those patients with low baseline BP is more likely to be related to the severity of the underlying illness than to the extent of treatment-induced BP reduction.

By lending further support to the safety of drugs with BP lowering properties in patients with HF regardless of baseline SBP, my study has important clinical implications. Concerns about potentially harmful consequences of further BP reduction in patients with HF, who already have low baseline BP, seem common causes of noncompliance with therapeutic recommendations.[512,513] Those concerns are based on the increased risk of HF hospitalisation and cardiovascular death associated with low BP in patients with HF. However, the higher absolute risk of poor outcomes in patients with low BP in comparison to those with BP within what is conventionally defined as the normal range, means that they experience a greater absolute risk reduction, given that the relative risk reduction is homogeneous across BP strata. It is thus paradoxical that patients who would reap the most benefit from treatment, in absolute terms, are the least likely to be titrated to the target doses that have been demonstrated to improve prognosis.[183,184,514] Furthermore, the absence of an association between treatment effects and intensity of BP reduction observed in my meta-regression is

in keeping with evidence suggesting that the main mechanisms of action of guideline-recommended drugs in HF are related to neurohumoral modulation, and thus independent of their BP lowering properties.[515,516] This underpins why, despite considerable uncertainty regarding BP management in HF, guidelines recommend titrating HF drugs, including new agents (e.g., combined neprilysin-angiotensin receptor antagonist),[516,517] according to tolerance, irrespective of achieved BP.[518]

Despite those reassuring findings, the question of the appropriate intensity or threshold of BP lowering in patients with chronic HF, in particular when baseline BP is low, could not be answered by my study, mainly because of missing information in published trial reports. In the absence of such direct evidence, guidelines and clinicians rely on contradictory evidence provided by individual studies, as well as on questionable extrapolation of findings from non-HF populations. Neither of those options is adequate to thoroughly understand how agents with BP lowering properties influence BP in patients with HF, and whether changes in BP have positive and/or negative consequences on clinical outcomes. Indeed, HF patients have several features that render extrapolation from the general population uncertain. On one hand, they tend to have a substantially lower BP and a higher burden of multimorbidity, which adds further complexity to treatment effects due to potential interactions.[176,177,519,520] On the other hand, outcomes that are strongly associated with high BP, such as stroke and myocardial infarction, tend to be less common in patients with HF, which may reduce the actual benefit of BP lowering.[178-181,521] In addition, observational studies in patients with HF have shown a strong interaction between BP and left ventricular function.[144,172] How such differences might impact on outcomes, when BP is intentionally or unintentionally reduced to very low levels,

remains unclear. Although stratified analyses have been attempted in individual trials, those were typically limited by lack of power to detect small, but clinically important, differences, particularly in subgroup analyses requiring more than one variable to test potential interactions.[157-159,175] Therefore, appropriately designed RCTs are needed.

The main limitations of this aggregate data meta-analysis relate to the lack of data on baseline and achieved BP in published trial reports, which may have reduced study power to detect important associations. The lack of relevant information from several trials could also have affected the validity of the overall conclusions. A related limitation is the fact that the procedure used to measure BP varied across trials, which may have contributed to the substantial heterogeneity in treatment effect estimates. However, this meta-analysis had limited ability to explore potential sources of heterogeneity because data were aggregated at trial level. Inconsistency in reporting clinical outcomes and adverse events also prevented analysing the impact of BP reduction on other clinical outcomes that could be potentially relevant, including myocardial infarction, stroke, AF and renal function. Indeed, the fact that only nine trials reported myocardial infarction and seven trials reported stroke precluded analysing the effects of treatment on those outcomes, which would be more likely to show a relationship with BP changes. Several of those limitations can be addressed in future collaborative work that seeks IPD from all relevant trials with collection of information on a range of baseline and follow-up information.

Conclusion

This systematic review and meta-analysis suggested that treatment with drugs with BP lowering properties, particularly with RAAS inhibitors, resulted in a small yet significant decrease in SBP in patients with HF irrespective of baseline SBP. In addition, there was no evidence that treatment effects on efficacy and safety outcomes varied according to the intensity of SBP lowering or along the range of baseline SBP, thus supporting the use of guideline-recommended treatment even in patients with low baseline BP. However, further research is warranted to better understand the potential mediating role of BP on a wider range of clinical outcomes in patients with HF.

Blood Pressure in Heart Failure Trialists' Collaboration: a new collaboration of individual participant data from randomised clinical trials in heart failure

Background

There are important gaps and contradictions in the currently available evidence regarding BP management in HF, which I described in great detail in previous sections (Chapter 2 and Chapter 8). However, my aggregate data meta-analysis[522] was unable to address those issues due to lack of data on baseline and achieved BP in published trial reports, as well as data on outcomes that could be more strongly influenced by BP reduction, such as myocardial infarction and stroke.[523] Finally, data aggregated at trial level are unable to thoroughly explore potential sources of heterogeneity of treatment effects in important subgroups of patients (e.g., according to left ventricular ejection fraction or functional class). Those limitations can be addressed by IPD meta-analyses, which pool data from all eligible trials. Although the BPLTTC offers an unparalleled resource of IPD from BP lowering trials, it explicitly excluded trials conducted in patients with HF. This important exclusion criterion rendered the BPLTTC unsuitable to unravel the controversies about BP and clinical outcomes in patients with HF. The relevance of the topic together with the inability to address it using published data that are currently available led me to instigate a new IPD collaboration – the Blood Pressure in Heart Failure Trialists' Collaboration (BPHFTC). This will include trials that investigated the effects of drugs with BP lowering properties in patients with HF, even if BP reduction was not

the main purpose of the trial. Herein, I describe the protocol for establishing the collaboration and conducting the first study using the IPD dataset.

Aims

The aims of this IPD meta-analysis are:

1. To investigate the effect of drugs with BP lowering properties on change in BP in patients with HF overall and stratified by drug class, baseline BP and left ventricular ejection fraction;
2. To investigate whether, and to what extent, treatment effects on clinical outcomes are related to the intensity of BP reduction achieved by each trial;
3. To investigate the effect of BP lowering drugs on efficacy and safety outcomes overall and stratified by drug class, baseline BP and left ventricular ejection fraction.

Methods

A systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines of interventional studies[470] and The Cochrane Collaboration.[306] The protocol was registered with the PROSPERO[202] database of systematic reviews (CRD42018095395). A detailed description of the underlying methods for this systematic review and meta-analysis is provided in the previous section and has also been published.[522]

Study design

The main analyses will be IPD meta-analyses of RCTs. Exploratory analyses will be performed combining IPD with data aggregated at trial level for those trials where IPD are not available.

Eligibility criteria

My systematic review and meta-analysis identified thirty-seven eligible trials, of which four were considered of no interest for this IPD meta-analysis because three of them investigated drugs that have not been approved for HF,[154,498,506] and one was aborted due to methodological issues.[475] An update of the systematic review after it had been published identified a further trial that was eligible for this study. Therefore, a total of thirty-four trials were eligible for inclusion. IPD were obtained for twenty-two of them and data aggregated at trial level will be used for the remaining twelve trials (**Table 8.4**).

Definition of outcomes

Primary outcomes will include:

1. Difference in change in SBP and DBP (i.e., difference, between randomised groups, in BP at six months (plus or minus two months) after randomisation minus baseline BP);
2. Major cardiovascular events – a composite endpoint, defined as first occurrence of (1) HF hospitalisation or death; (2) fatal or non-fatal stroke; or (3) fatal or non-fatal myocardial infarction;

3. A composite endpoint, defined as the first occurrence of HF hospitalisation or cardiovascular death.

Secondary outcomes will include the individual elements of the composite endpoints and:

- All-cause death;
- Decline in renal function – defined as end-stage renal disease, or a decrease of 40% or more in the estimated glomerular filtration rate from the value at randomisation, or a decrease in the estimated glomerular filtration rate of more than 30 ml per minute per 1.73 m^2, to less than 60 ml per minute per 1.73 m^2;[524]
- Adverse events leading to treatment discontinuation (or withdrawals due to adverse events).

All outcomes will be based on the definitions adopted by primary trials.

Treatment comparisons

For the main analyses, intervention and control groups will be compared. For placebo-controlled trials, the placebo arm will be considered as the "comparator" and the active treatment will be considered as the "intervention". For trials with two or more active treatment arms, the arm in which the BP reduction is higher will be considered as "intervention" and the other treatment arm(s) as "comparator". In addition to the main analysis across all trials, supplementary analyses will be carried out to investigate class-specific effects in trials that compared different treatment regimens with placebo or standard treatment. Separate analyses will be performed for ACEIs, ARBs, mineralocorticoid receptor antagonists, BBs and dihydropyridine CCBs.

Table 8.4 Trials eligible for inclusion in the heart failure collaboration and subsequent meta-analyses

Trial	Control (N)	Intervention 1 (N)	Intervention 2 (N)	Follow-up (months)
Trials with individual participant data available				
Placebo-controlled trials				
CIBIS[481]	Placebo (321)	Bisoprolol (320)		23
CIBIS II[480]	Placebo (1320)	Bisoprolol (1327)		15
BEST[482]	Placebo (1354)	Bucindolol (1354)		24
COPERNICUS[483]	Placebo (1133)	Carvedilol (1156)		11
PEP-CHF[484]	Placebo (426)	Perindopril (420)		26
SENIORS[485]	Placebo (1061)	Nebivolol (1067)		21
SOLVD[486]	Placebo (1284)	Enalapril (1285)		48
MERIT-HF[487]	Placebo (2001)	Metoprolol (1990)		18
Val-HeFT[488]	Placebo (2499)	Valsartan (2511)		23
RALES[489]	Placebo (841)	Spironolactone (822)		24
I-PRESERVE[491]	Placebo (2061)	Irbesartan (2067)		50
CHARM-Added[181]	Placebo (1272)	Candesartan (1276)		41
CHARM-Alternative[492]	Placebo (1015)	Candesartan (1013)		42
CHARM-Preserved[493]	Placebo (1508)	Candesartan (1512)		37
EMPHASIS-HF[494]	Placebo (1373)	Eplerenone (1364)		21
TOPCAT[495]	Placebo (1723)	Spironolactone (1722)		40
Drug comparison trials				
CIBIS III[500]	Bisoprolol (550)	Enalapril (550)		24
COMET[504]	Carvedilol (1511)	Metoprolol (1518)		58
ATMOSPHERE[473]	Enalapril (2336)	Aliskiren (2340)	Enalapril + Aliskiren (2340)	37

PARADIGM-HF[505]	Enalapril (4212)	Sacubitril/Valsartan (4187)		27
PARAGON-HF[525]	Valsartan (2419)	Sacubitril/Valsartan (2403)		35
ATLAS[508]	Lisinopil low dose (1596)	Lisinopril high dose (1568)		46
SUPPORT[151]	Standard therapy (568)	Olmesartan (578)		53
HEAAL[507]	Losartan 50 mg (1913)	Losartan 150 mg (1921)		56
Trials with aggregate data available				
Placebo-controlled trials				
PRECISE[499]	Placebo (398)	Carvedilol (626)		12
A-HeFT[490]	Placebo (532)	Hydralazine + Isosorbide dinitrate (528)		10
VACS[477]	Placebo (273)	Hydralazine + Isosorbide dinitrate (186)	Prazosin (183)	28
PRAISE 1[496]	Placebo (582)	Amlodipine (571)		14
PRAISE 2[497]	Placebo (827)	Amlodipine (827)		33
Drug comparison trials				
CARMEN[476]	Carvedilol + Placebo (191)	Enalapril + Placebo (190)	Carvedilol + Enalapril (191)	18
J-CHF[474]	Carvedilol low dose (118)	Carvedilol medium dose (116)	Carvedilol high dose (118)	36
V-HeFT II[501]	Hydralazine + Isosorbide dinitrate (401)	Enalapril (403)		30
ELITE I[502]	Losartan (352)	Captopril (370)		11
ELITE II[503]	Losartan (1578)	Captopril (1574)		11
Excluded trials				
MACH-1[154]	Placebo (1295)	Mibefradil (1295)		50
ENABLE[498]	Placebo (807)	Bosentan (804)		18
OVERTURE[506]	Enalapril (2884)	Omapatrilat (2886)		15
RESOLVD[475]	Enalapril (109)	Candesartan (327)	Enalapril + Candesartan (332)	11

Statistical analysis

Intention-to-treat analysis will be adopted using the data provided by each trial. For the IPD meta-analyses, a two-stage approach will be adopted (necessarily because IPD are unavailable for several trials). This means that the IPD will be first analysed separately in each trial and then the trial statistics will be combined in a standard meta-analysis.

SBP and DBP will be considered as continuous variables, and thus generalised linear models will be used to estimate the effect of treatment on the difference, between treatment arms, in SBP and DBP at six months (plus or minus two months) after randomisation minus baseline BP, adjusted for baseline SBP. The possibility of taking into account multiple measurements per patient over time using a mixed-effects model will be considered, depending on the data available. These models will include a random intercept for patient and a random slope for treatment.

In the first part of the two-step meta-analysis, the IPD from each trial will be analysed separately by fitting the following model:[348]

$$\gamma_{ij} = \phi_i + \beta_i \gamma_{0ij} + \theta_i \chi_{ij} + \varepsilon_{ij}$$

$$\varepsilon_{ij} \sim N\left(0, \sigma_i^2\right)$$

Where γ_{ij} denotes the SBP in the jth patient after treatment, ϕ_i is the fixed trial effect, $\beta_i \gamma_{0ij}$ is the adjustment for baseline SBP, χ_{ij} is coded 0/1 to denote control/treatment group, θ_i is

the underlying treatment effect in study *i*, and σ_i^2 is the residual variance of the responses in trial *i* after accounting for the treatment effect. From this model, the treatment effect estimate $\hat{\theta}_i$ and its variance $V(\widehat{\theta_i})$ can be calculated for each trial.

In the second part of the two-step approach, the $\hat{\theta}_i$ values and respective variances $V\left(\widehat{\theta_i}\right)$ will be combined using a standard random effects meta-analysis:[348]

$$\hat{\theta}_i = \theta_i + \varepsilon_i$$

$$\theta_i = \theta + u_i$$

$$u_i \sim N(0, \tau^2)$$

$$\varepsilon_i \sim N(0, V(\hat{\theta}_i))$$

In this model, $V\left(\hat{\theta}_i\right)$ estimates are assumed to be known, which is a common assumption in the meta-analysis field, and u_i denotes a random effect indicating that the treatment effect in the ith trial, θ_i, is normally distributed about a pooled treatment effect, θ, with between-study variance, τ^2. The pooled treatment effect estimate $\hat{\theta}$ will be a weighted average of the $\hat{\theta}_i$s, with trial weights equal to the inverse of $V\left(\hat{\theta}_i\right) + \tau^2$. As a sensitivity analysis, to convert the model into a fixed effect meta-analysis model, τ^2 will be set to zero.

All the other outcomes are binary and thus time-to-event analysis will be carried out, in a similar way, but using Cox regression models, which account for censoring. For the main analyses, random effects models with inverse variance weighting based on REML pooled estimators will be used. Again, fixed effect meta-analysis will be performed as a sensitivity

analysis. Hazard ratios with 95% confidence intervals will be reported and results will be presented using forest plots. Heterogeneity between studies will be quantified using the I^2 statistic and a test of the null hypothesis of no heterogeneity conducted using Cochran's Q test.

Meta-regression will be used to estimate how the log hazard ratio for each primary outcome varies as a function of the difference in SBP reduction between trial arms. The log hazard ratio for each outcome will be plotted against the difference in SBP reduction between trials arms, using a logarithmic scale. If the plot is clearly not linear, further models will be tried to establish the model that best fits the data. This will allow estimating the relative contribution of BP-dependent and independent mechanisms for the risk reduction in the primary outcomes. If a log-linear association is found between the intensity of SBP reduction and the risk reduction for clinical outcomes, the estimates of the hazard ratio for each outcome will be standardised by 5-mmHg reduction in SBP using meta-regression methods.

Subgroup analyses will be carried out for:

- Drug classes, as specified in treatment comparisons;
- Left ventricular ejection fraction, split into the following categories: < 30%, 30-39%, 40-49% and ≥ 50%;
- Baseline SBP, divided into the following categories: < 100 mmHg, 100-109 mmHg, 110-119 mmHg, 120-129 mmHg, 130-139 mmHg, 140-149 mmHg, 150-159 mmHg, ≥ 160 mmHg, although some categories may be combined depending on the distribution of baseline SBP in the population.

Wald tests will be used to test for differences between subgroups. All p-values will be calculated from two-tailed tests. Statistical analyses will be performed using the package "metafor" for R version 3.6.1.[479]

Ethical considerations

The proposal for this collaboration was reviewed by the Joint Research Office of the Clinical Trials and Research Governance Unit of the University of Oxford (letter in **Appendix D**). Ethical approval was waived in view of nature of this study, which relied on secondary data in de-identified form. No further regulatory input was considered necessary.

Discussion and conclusion

Although I managed to get access to IPD for most of the trials that were eligible for inclusion in the BPHFTC, data for some of the trials were out of reach because (1) data had been lost (e.g., the CARMEN trial), the sponsor was unwilling to provide data according to a reasonable data sharing agreement (e.g., PRAISE trials), or the sponsor and the Principal Investigator did not reply to my numerous e-mails (e.g., ELITE trials). In addition, for most of the trials, collaborators only agreed to share summary data for two-stage meta-analyses, which limited the ability to test for multiple interactions and explore outcome and follow-up data in greater depth.

Navigating the complexity of data sharing agreements and data protection regulations made me realise how challenging it is to establish a new trialists' collaboration. Despite the extraordinary benefits for all researchers involved of creating a large dataset of IPD to investigate key questions related to HF management, getting buy-in from all stakeholders proved difficult. Indeed, I came to the conclusion, together with my supervisors, that conducting this research would not be achievable within the timeframe of my DPhil. Therefore, efforts to establish the collaboration are ongoing, based on the work that I described in this chapter, and hopefully results will be available in the near future.

Chapter 9 Discussion and Conclusion

My thesis is arranged in three main sections. The first consists of the introduction, the background for my thesis, and the methods, including the data source and the key methodological approaches that I used in my research. The second comprises the four core chapters, in which I describe each of my studies. This section, the third and final, includes the discussion and conclusion, in which I will discuss the overall findings of my thesis and how they open avenues for further research. Specific discussion points for each of the core chapters are provided in their respective discussion sections.

Summary of main findings

In chapter 2, I described the results of a comprehensive literature review on the topic of high BP in general, as well as BP management in the context of AF, HF and multimorbidity. I discussed the evidence currently available on BP epidemiology, burden of disease and treatment, and I illustrated why improving BP management is a top public health priority. Finally, I identified the main gaps in contemporary evidence and described how they have a detrimental impact on population health and the sustainability of health services across the globe. Therefore, chapter 2 set the scene for the following chapters as it provided the background that was required to understand my research questions and my approach to address them.

Chapters 3 and 4 were the methods chapters. Chapter 3 focused on the data source that I used for most of my studies, the BPLTTC. It described how this collaboration of RCTs was set up and the underlying systematic review, alongside important data protection and ethical considerations. Chapter 4 provided the theoretical underpinnings of the key methods I used to address my research questions. It dissected the analytical approaches that I used in my research, particularly meta-analysis of aggregate data and IPD, one-stage versus two-stage IPD meta-analyses, time-to-event analysis in IPD meta-analysis, multiple imputation to deal with missing data, and cluster analysis. Chapter 4 also gave a general overview of the skills and knowledge I had to acquire in order to be able to complete my thesis. Understanding the methodological concepts and learning how to implement the related statistical models represented the bulk of the preliminary work for my thesis. Developing strong methodological foundations, based on both theory and evidence, was an essential requirement to complete my thesis and perhaps the greatest challenge for a medical doctor from a non-statistical background.

Chapter 5, the first of four core chapters, investigated the effects of BP lowering treatment on the risk of new-onset AF. This IPD meta-analysis, based on the BPLTTC, demonstrated that in a relatively low-risk population, BP lowering treatment did not reduce the risk of new-onset AF. There was also no evidence of heterogeneity of treatment effects according to baseline risk for AF, as estimated using an internally derived clinical risk score. Furthermore, there was no evidence in favour of class-specific effects, although the small number of trials included in subgroup analyses according to drug class precluded drawing definite conclusions.

Chapter 6 compared the effects of BP lowering treatment in patients with and without AF at baseline. This IPD meta-analysis, again based on the BPLTTC, found that BP lowering resulted in a similar relative risk reduction in major cardiovascular events in patients with and without AF at baseline, and that relative risk reduction seemed to be proportional to the intensity of BP lowering irrespective of AF status at baseline. There were also no differences in the relative risk reductions for secondary outcomes, such as stroke, myocardial infarction, HF and cardiovascular death. Furthermore, patients with AF appeared to benefit from a similar reduction in cardiovascular events irrespective of whether baseline SBP was above or below the conventional treatment threshold of 140 mmHg.

Chapter 7 investigated the effects of BP lowering treatment in patients with cardiometabolic multimorbidity in the BPLTTC. For the purpose of this study, six cardiometabolic diseases were considered at baseline: hypertension, ischaemic heart disease, cerebrovascular disease, chronic kidney disease, diabetes mellitus and obesity. The main finding of this study was that the risk reduction on major cardiovascular events was broadly comparable across groups defined according to the number of cardiometabolic diseases at baseline. There was also a log-linear relationship between the intensity of BP lowering and the risk reduction in major cardiovascular events, irrespective of the number of cardiometabolic diseases. In addition, the effects of BP lowering treatment were broadly consistent across multimorbidity patterns. Finally, although cluster analysis was able to identify subgroups of patients with different profiles of diseases and baseline cardiovascular risk, the application of those clusters to clinical practice was uncertain. Overall, this study highlighted the need for more in-depth data collection on baseline diseases to characterise patients included in RCTs. This will then enable

investigating to what extent evidence derived from RCTs can be extrapolated to multimorbid patients encountered in routine clinical practice.

Chapter 8 investigated the effects of drugs with BP lowering properties in patients with HF. As patients with HF were excluded from the BPLTTC, I adopted a different strategy to answer this research question, which was described in two sections. The first of those comprised the systematic review and aggregate data meta-analysis that I conducted to identify eligible trials and summarise the available evidence. It suggested that drugs with BP lowering properties, which are key components of guideline-recommended medical therapy for HF, achieved a small reduction in SBP of about 2 mmHg. Overall, treatment with those drugs reduced the risk of HF hospitalisation and cardiovascular death by approximately 10%, and it did not appear to reduce the risk of all-cause mortality. However, there was no evidence that treatment effects depended on the intensity of BP lowering, thus suggesting that mechanisms other than BP reduction itself underpin the beneficial effects of guideline-recommended drugs in HF. Furthermore, there was no evidence of heterogeneity of treatment effects according to baseline SBP. On the other hand, treatment with drugs with BP-lowering properties increased the risk of adverse events leading to treatment discontinuation by around 20%. However, this was not correlated to the intensity of BP lowering or baseline SBP, which reassuringly suggests that the small degree of treatment-induced BP lowering is safe. The second section described the progress I made in establishing a new trialists' collaboration that will gather IPD for trials of drugs with BP lowering properties in patients with HF to tackle the limitations of my aggregate data meta-analysis.

Strengths and limitations

Strengths

The main strengths of my thesis derive from the data source and methodology that I used to address my research questions. First, all my studies were based on RCTs, which are the gold standard to investigate treatment effects.[526] Indeed, observational studies, such as population-based cohort studies or studies based on electronic health records are unable to reliably assess the effect of a therapeutic intervention due to the possibility of residual confounding. Randomisation ensures that participants in trial arms are comparable with regards to all potential variables that may act as known or unknown confounders, other than due to the play of chance. This is critically important to attribute the observed benefits and harms to the intervention under study, and thus evidence from RCTs, at least when of large size, is generally regarded as of high quality and forms the basis of modern guidelines worldwide. Therefore, relying solely on RCTs significantly enhanced the value of my research.

Second, I adopted a methodological approach that maximised the information contained the data (e.g., by using Cox regression that took into account time of follow-up and censoring instead of logistic regression, and by using stratified models that accounted for clustering of participants within trials), and mitigated potential limitations (e.g., by using multilevel multiple imputation to handle missing data). This robust methodological approach allowed estimating treatment effects with rigour, whilst acknowledging the inherent uncertainty. Furthermore, it required me to acquire an in-depth understanding of advanced statistics and

to gain new skills that will be valuable for my future career as Public Health doctor and researcher.

In addition, using the BPLTTC for my research offered several advantages. First, the BPLTTC is a very large dataset of IPD from RCTs, including fifty trials and almost 350,000 participants. The benefits of such unprecedented sample size and diverse population in terms of statistical power cannot be underestimated. Second, I had access to published and unpublished data from landmark RCTs of BP lowering treatment, which included detailed baseline and follow-up variables (e.g., time-to-event outcomes). Once I had cleaned, harmonised and validated the data, this allowed me to investigate the effects of BP lowering on outcomes that are rarely available in published trial reports, such as AF, as well as to overcome selective reporting bias that can potentially affect RCTs.[527] Furthermore, detailed data on baseline diseases allowed me to pool data from different trials, and hence to investigate the effects of treatment on populations that are typically underrepresented in individual trials, such as patients with AF or multimorbidity.

Third, access to IPD offered me more flexibility to analyse the data. Instead of relying on summary measures aggregated at trial level, I could estimate treatment effects directly from IPD, which then enabled trying different models and select the one that best fitted the data. I successfully implemented stratified Cox models that accounted for censoring and for clustering of participants within trials and that assumed a fixed treatment effect. This assumption might be questionable, considering the diversity of populations, interventions and settings amongst the trials included in the BPLTTC. However, the main driver of the

heterogeneity between trials is most likely the intensity of BP lowering,[5,528] which was adjusted for in all models, and the results of the two-stage approach reassuringly demonstrated that assuming random treatment effects or a fixed treatment effect had no material impact on the pooled estimates. In addition, access to data disaggregated at patient level was essential to adequately adjust for the intensity of BP reduction in each trial using meta-regression. Although standardisation of treatment effects for BP lowering, as well as cholesterol lowering, had been done previously with a different method using a two-stage approach,[5,353] my studies were the first to report treatment effects adjusted for the intensity of BP reduction based on one-stage meta-regression models.

Fourth, data disaggregated at individual level allowed me to explore heterogeneity in treatment effects and treatment modification with more statistical power, and also to avoid ecological bias.[529] The latter affects aggregate data meta-analysis because trial-level associations may not reflect individual-level associations.[530] This enabled me, for instance, to investigate whether there was an individual-level interaction between BP lowering treatment and AF or multimorbidity at baseline.

Fifth, the BPLTTC included trials that spanned a long period of time and that were conducted in diverse geographical areas, health systems, and populations. Indeed, most of the trials were multicentric, with participants randomised in many countries across the globe. This contributed to the external validity of my research, which ultimately means that my findings are likely generalisable to the global population. The generalisability of my research is further supported by currently available evidence, which demonstrates that the effects of

pharmacological BP lowering are broadly comparable across populations worldwide, irrespective of age and sex.[198,199]

Limitations

Despite the unequivocal strengths of my thesis, there are also some limitations to be acknowledged. First, BP was measured in different ways across the RCTs, which may have caused random or systematic errors. Although guidelines clearly define a standard procedure to measure BP,[39,40] evidence suggests that there is substantial variability in the way BP is measured, even in the tightly controlled environment of RCTs.[531] Importantly, this introduces substantially variability to BP measurements,[532,533] which means there is a degree of uncertainty in the BP measurements used throughout my meta-analyses. However, considering the randomised nature of the comparisons, the impact on treatment effect estimates is unlikely to be significant.

Second, missing data is an issue in the BPLTTC dataset. In fact, missing data are omnipresent in records used for research purposes, including electronic health records, clinical trial databases and disease registries.[534] Missing data in the BPLTTC might have reduced the power to detect significant interactions and introduced bias in the results, as there was no guarantee that data were missing at random.[535,536] However, the characteristics of the missing data in the BPLTTC mean that their impact on my research findings is unlikely to be significant. Indeed, missing data in the BPLTTC were of two types: sporadic and systematic missing data. The former were relatively uncommon, in keeping with the more accurate data collection in

RCTs than in electronic health records that depend on routinely collected data.[537,538] Systematic missing data, that is, missing data for entire trials, were more frequent. However, those missing data are less prone to bias than missing data at the individual level, because it is impossible to ascertain whether the latter is random or related to other factors. When missing data are differential, that is, when they are related to the trial arm to which participants are randomised, bias may ensue in estimating treatment effects regardless of whether complete-case analysis or multiple imputation is adopted.[539] This limitation does not apply to systematic missing data, which can be imputed by drawing on the information provided by other trials in the IPD dataset. This, together with the fact that I applied a multilevel multiple imputation algorithm that I had extensively validated a priori, means that the missing data in the BPLTTC are unlikely to have substantially influenced my conclusions.

Third, cleaning and harmonising the data provided by each trial was rather complex. Among the main problems, it is worth mentioning the lack of consistency in reporting the outcomes of interest for my studies, the incongruencies in dates and times of events during follow-up, and the discrepant definitions used for baseline diseases. Harmonising the data was a lengthy and cumbersome process that required consulting published reports whenever the IPD and the data dictionaries were insufficient to harmonise the data. Although this may have introduced a degree of inaccuracy or misclassification in the data, it is unlikely that it had a substantial impact on treatment effect estimates due to the randomised nature of the comparisons.

Fourth, the BPLTTC did not include all trials that were potentially eligible for the collaboration, as only half of those agreed to share IPD. Therefore, the possibility of selection bias cannot be completely ruled out. However, twenty-one of the fifty trials for which IPD were inaccessible were published before 2000, because datasets had been lost or principal investigators were deceased. Considering the substantial improvements in BP lowering treatment and guidelines over the past 20 years, it is unlikely that those trials would reflect contemporary practice or indeed make a material difference to the overall findings. In addition, whenever possible, I took the necessary steps to mitigate the impact of potential selection bias. For instance, in the analysis that investigated the effects of BP lowering on the risk of new-onset AF, I performed a two-stage meta-analysis including trials for which only aggregate data were available. This sensitivity analysis reassuringly showed that excluding those trials from the main analysis had no meaningful impact on treatment effect estimates. The BPLTTC is an evolving dataset that is constantly being updated with additional data for trials that are already part of the collaboration (for example, genetic data is currently being sought and transferred for a subset of trials that collected it) as well as with new trials joining the collaboration. Therefore, further data are probably going to become available in the future and my studies may be updated accordingly.

In addition to data quality issues, the BPLTTC had another five potentially important caveats. First, the average follow-up duration of the RCTs included in the BPLTTC was about four years, which is a relatively short time, particularly to diagnose outcomes that are more protracted, such as AF. A longer follow-up would have enabled a more thorough assessment of the long-term benefits of pharmacological BP lowering. Second, the range of baseline BP was relatively

narrow and skewed towards high BP levels. This is at least partially explained by the fact that most trials had, as an inclusion criterion, the requirement for baseline BP to be above 140/90 mmHg. Therefore, subgroup analyses based on baseline BP were underpowered at the lower end of the BP spectrum. Third, the age range of the population was also skewed, with very few patients at the extremes of age, that is, below the age of 40 years and over the age of 80 years. Although those are the two groups in whom there is greater uncertainty regarding the benefits of BP lowering,[17] the generalisability of my findings to those patients is less clear because they were underrepresented in the BPLTTC. Fourth, data available for clinical outcomes was mostly restricted to cardiovascular events. As evidence is mounting on the wider benefits of BP lowering, it would have been interesting to investigate treatment effects on a broader range of outcomes, particularly dementia,[540] which has overtaken cardiovascular disease as the leading cause of death in the UK.[541]

Fifth, most of the included trials were conducted in high-income countries, mainly in Europe and North America, and populations from African and Asian descent were underrepresented in the BPLTTC. Indeed, among the patients for whom ethnicity was recorded (80% of the total population), there were 61% patients of Caucasian ethnicity, 10% of African ethnicity and 15% of Asian ethnicity. There is evidence of ethnic differences in cardiovascular risk (e.g., African Americans tend to have an earlier onset of hypertension,[542] whilst South East Asians have a particularly high risk for cardiometabolic conditions, such as diabetes),[543,544] and in response to pharmacological BP lowering (e.g., angioedema is about three times more likely to occur with ACEIs in patients of African ethnicity).[545] However, the effects of BP lowering in general appear to be generalisable to different ethnic groups.[546] Therefore, until more evidence

becomes available in African and Asian populations as well as in low and middle-income countries where the burden of hypertension is growing faster than elsewhere,[547] guideline-recommended treatment remains broadly similar, irrespective of ethnicity.[40] Nevertheless, caution is needed when extrapolating my findings to non-Caucasian populations as ethnic-specific nuances in BP management should not be overlooked.[548]

Besides the limitations associated with the data source, my thesis can be criticised by the way the intervention was defined in all studies. As there is robust evidence supporting that the main mechanism of action of BP lowering drugs is BP reduction itself,[5,549,550] I considered in my studies that the intervention arm was the one with the largest reduction in SBP, with the other arm(s) considered as comparator. This magnified the BP difference between trial arms and allowed treatment effects to be adjusted for the intensity of BP reduction, as this was the main source of between-trial heterogeneity. However, it is arguable that a more comprehensive methodological approach to tackle my research questions would have been to conduct network meta-analyses.[551] This would have enabled comparing different drug classes, even if they had not been compared directly in any of the trials,[528] and hence investigating the existence of class-specific effects, above and beyond BP lowering. However, as I discussed in Chapter 4, one-stage meta-analysis was the analytic approach that I decided to adopt, especially because I was interested in investigating treatment-covariate interactions, for which one-stage meta-analysis appear to be superior. Unfortunately the methodology behind one-stage network meta-analysis is still being developed and not yet at a stage where I could use it in this thesis.[552] Moreover, whether a strategy based on network meta-analyses would have had a material impact on the key findings of my thesis is

questionable. Indeed, a very recent network meta-analysis that pooled aggregate data from forty-six RCTs, twenty-six of which were also included in the BPLTTC, reported that different classes of antihypertensive agents afforded similar risk reductions in cardiovascular events, and thus the preference for a specific drug was of token importance.[528] This reinforced the prevailing hypothesis that BP lowering is the key underlying mechanism for the benefits of BP lowering drugs, and hence supported the appropriateness of my methodological approach.

Finally, the BPLTTC did not include trials conducted in patients with HF, which precluded answering my research question about the effects of BP lowering in that population. Therefore, I had to conduct an aggregate data meta-analysis and initiate a new trialists' collaboration to gather IPD that would complement the BPLTTC dataset. The strengths and limitations of that meta-analysis are carefully dissected in Chapter 8, but it is worth emphasising that the advantages of pooling evidence from large RCTs instead of observational studies are shared with the BPLTTC. The main limitations are intrinsic to the lack of data disaggregated at individual level (e.g., impossibility to test for multiple interactions, and cluster bias), which may become available once the HF trialists' collaboration is fully established. Although setting up this new collaboration could not be completed within the timeframe of my DPhil, this was expected considering that setting up such a collaboration is an intricate and time-consuming process. This is convincingly demonstrated by previous collaborations. Indeed, the Cholesterol Trialists' Collaboration was established in 1994, but it took over ten years for its first paper to be published in 2005; and even though the BPLTTC was faster, five years ensued between its creation in 1995 and its first publication in 2000.

Practical implications

Notwithstanding the aforementioned limitations, my thesis has important practical implications, which can be broadly divided into three key areas (1) clinical practice and health systems, (2) new avenues for future research, and (3) further development and implementation of methods for IPD meta-analysis.

Implications for clinical practice and health systems

Overall, my thesis added to the pool of evidence showing that pharmacological BP lowering effectively reduces cardiovascular risk across diverse populations, irrespective of baseline BP, drug class and pre-existing cardiometabolic conditions.[4,5,469] By analogy, my thesis also supported health policy targeting risk factors for high BP, such as dietary salt restriction.[8,553] Synergistic effects of pharmacological BP lowering at the individual level and health policy at the population level are likely required, if we are to reduce the burden of cardiovascular morbidity and mortality in a way that is universally effective and affordable. Each chapter of my thesis also has specific implications, as I discuss in detail below.

Prevention of new-onset atrial fibrillation

My research showed that BP lowering treatment did not reduce the risk of AF in relatively low-risk patients, which means that BP lowering is unlikely to be effective for primary prevention of AF in the general population. However, a targeted approach to high-risk

patients, particularly if based on genetic predisposition, may be beneficial, since BP seems to play a key role in the causal pathway leading to incident AF in genetically susceptible individuals (unpublished results, summarised in Chapter 10). Contemporary guidelines rely on observational evidence, suggesting that BP control may be associated with a lower risk of new-onset AF. However, my research, based on the best randomised evidence currently available, did not corroborate findings from observational studies, which may actually be due to confounding. Therefore, guidelines should be updated to acknowledge that there is currently conflicting evidence on whether BP lowering overall is effective for primary prevention of AF. It could still be that BP lowering may prevent new-onset AF in individuals who are at high risk for developing AF, such as those with increased genetic predisposition. However, until genetic risk scores are widely available and implemented in clinical practice, this is unlikely to have a significant impact on patient care. Publication and presentation of my results at international conferences is likely to influence guideline-writers. Ultimately, my research will improve healthcare efficiency by directing resources, such as BP lowering treatment, to patients who are more likely to benefit from them. This in turn will contribute to deterring the exponential rise in the prevalence of AF that has been forecasted for the coming years, thus reducing the hefty burden that it represents for healthcare systems worldwide.[78]

Treatment of patients with atrial fibrillation

My research showed that patients with AF benefit from BP lowering at least as much as patients without AF. Following publication of my results, a media campaign will be

undertaken to get this information into the wider scientific and lay communities. Contemporary guidelines are likely to be updated in line with my findings as there was thus far no compelling evidence that BP reduction could effectively decrease the risk of major cardiovascular events in patients with AF. Furthermore, my thesis demonstrated that patients with AF benefit from a larger absolute risk reduction for a similar relative risk reduction in cardiovascular events. This, together with the burgeoning prevalence of AF in our ageing population, means that, from a healthcare system perspective, BP lowering in patients with AF is more cost-effective than in the general population. Ultimately, my thesis emphasises that management of AF needs to shift from the present strategy focused on stroke prevention and rate or rhythm control to holistic or integrated patient care.[554] Prevention of cardiovascular events by addressing modifiable risk factors, such as high BP, will eventually improve prognosis of patients with AF. This will, in turn, save precious healthcare resources that are currently squandered treating avoidable morbidity and mortality secondary to cardiovascular events.

Treatment of patient with multimorbidity

My research showed that the benefits of BP lowering treatment were largely comparable, irrespective of the number and patterns of cardiometabolic diseases at baseline. It also suggested that more aggressive BP lowering resulted in larger reductions in cardiovascular events even in patients with multimorbidity. Those findings are important because the typical patient presenting to primary care with elevated BP has one or more concurrent diseases (about 78% have at least another chronic disease), the majority of which have a

cardiometabolic aetiology.[105,555] Those concurrent cardiometabolic conditions may influence the efficacy of BP lowering due to interactions between diseases and their respective treatments.[556]

On the other hand, my research challenged the current recommendation to consider deprescribing BP lowering treatment in patients with multimorbidity.[116] Since the risk of cardiovascular events increased in parallel with the number of diseases, the number needed to treat to prevent one cardiovascular event decreased as the number of diseases increased. This means that from societal and healthcare perspectives, it is more cost-effective to provide BP lowering treatment to patients with multimorbidity, in whom paradoxically guidelines recommend considering withholding treatment. Even though the extrapolation of my research to very old and/or frail patients is debatable,[557,558] lifestyle and dietary risk factors seem to be pushing the burden of multimorbidity to increasingly younger age groups, to whom my findings are most likely applicable.[103] Therefore, my research shows that there is a strong imperative to treat high BP and actually aim for intensive BP lowering in patients with cardiometabolic multimorbidity, provided they are not otherwise very old and frail. Following publication and presentation to the wider scientific community and policy makers, this much-needed evidence will likely inform clinical guidelines regarding BP treatment in multimorbid patients, which currently recommend using clinical judgement to make treatment decisions due to lack of data.[17,39] Evidence-based guidelines will eventually change clinical practice and avoid unwarranted variation in BP management in the rapidly growing population with multimorbidity. This will be beneficial for patients, healthcare systems and society overall.

My thesis showed that drugs with BP lowering properties resulted in a small reduction in BP in patients with HF, but this was not associated with treatment effects on efficacy and safety outcomes. Although my findings are unlikely to change contemporary guidelines, which already recommend those drugs as essential for management of patients with HF, they are likely to change clinical practice.[92] Indeed, recent evidence demonstrates that uptake of longstanding guideline recommendations remains unsatisfactorily low.[559] Furthermore, safety concerns have been shown to be key determinants of poor compliance with initiation and up-titration of guideline-recommended treatment. Therefore, by reassuring clinicians that guideline-recommended medical therapy is effective and safe, even in patients with low baseline BP, my research can improve HF care. This is even more paramount considering that high-risk patients are less likely to be treated to recommended targets, despite having more to gain from treatment in absolute terms.[143] Improving adherence to guideline-recommended medical therapy will benefit patients and healthcare systems alike. The former will gain from better disease prognosis, as those drugs have been shown to increase life expectancy and improve quality of life.[560] The latter will benefit from preventing HF complications and hospitalisations, which account for most of the healthcare burden attributable to HF worldwide.[561]

Implications for future research

Prevention of new-onset atrial fibrillation

Although my research suggested that BP lowering did not reduce the risk of new-onset AF in a population at a relatively low baseline risk for AF, further research is warranted to understand whether the same holds true in high-risk patients, for instance those with HF, paroxysmal AF, or increased genetic susceptibility. Indeed, evidence is emerging on the better ability of genetic risk scores to predict incident AF.[405,406] Genetic data available for some of the trials included in the BPLTTC may allow estimating treatment effects stratified by genetically determined risk in the future. Further research is also warranted to investigate the existence of class-specific effects, particularly for RAAS inhibitors, due to the conflicting results provided by observational and randomised studies.[90,389,562] It is crucial to understand whether BP lowering drugs can have benefits above and beyond BP reduction, for instance by modifying the arrhythmogenic substrate that initiates and perpetuates AF.[563]

Lack of evidence on recurrent AF also deserves investigation. Evidence is mounting on the influence of cardiovascular risk factors (e.g., overweight, smoking, alcohol) on rate and rhythm control and recurrence of AF.[564,565] This raises the hypothesis that adequate BP control may play a part in maintaining sinus rhythm following AF ablation or cardioversion. There is currently a pilot for a clinical trial investigating the effect of BP lowering on AF in patients with paroxysmal AF, which will shed light into this yet unanswered question.[566] Considering the difficulty in diagnosing AF, such a trial should preferably employ continuous

heart rate monitoring, using wearable devices (e.g. smartwatches)[567] that are promising to revolutionise remote monitoring and healthcare in general.[568] This would improve the capture of AF episodes that are most often asymptomatic and random, and thus likely to be missed by office-based electrocardiograms collected at fixed intervals during follow-up.

Treatment of patients with atrial fibrillation

Although my research showed that the relative risk reduction was similar in patients with and without AF at baseline, the confidence intervals were wide, reflecting the relatively small number of patients with AF included in the BPLTTC. In addition, the trials that contributed for this study covered a long time period and some of them were old. This raises the question as to whether the observed treatment effects are transferable to contemporary patients with AF, due to the marked advances in anticoagulation for stroke prophylaxis, and in drugs for rate and rhythm control over the last years.[102] However, this hypothesis is challenged by evidence showing that, despite those therapeutic improvements, prognosis remains bleak in patients with AF, and most deaths are attributable to cardiovascular diseases other than stroke.[96] Therefore, an adequately powered RCT in patients on state of the art treatment would ideally address the questions left unanswered by my research. At least one such trial is ongoing in China, which aims to evaluate whether intensive management of BP and cholesterol can safely prevent cardiovascular events in elderly patients with hypertension and AF.[569]

In addition, although, in the general population, the key determinant of the efficacy of BP lowering treatment is the intensity of BP reduction, irrespective of the drug class used, whether the same holds true in patients with AF is uncertain. As my subgroup analysis for drug class was only exploratory due to the small sample size, it would be important to test whether certain drug classes have added benefits in patients with AF, for instance by carrying out a network meta-analysis, if feasible,[570] or conducting a large RCT comparing different drug classes in patients with AF.

Treatment of patients with multimorbidity

Besides traditional cardiovascular outcomes that were considered in my research on the effects of BP lowering in patients with multimorbidity, it is paramount to investigate treatment effects on non-conventional, yet relevant, outcomes, such as cognitive function and patient important outcomes. Although the Systolic Blood Pressure Intervention Trial showed that patient reported outcomes, including quality of life and satisfaction with treatment, were similar between intensive and standard treatment arms, irrespective of the number of baseline diseases, evidence on how BP reduction influences outcomes that are important to multimorbid patients overall and for specific drug classes in particular is sparse.[571] This evidence is critical to weigh the pros and cons of pharmacological BP lowering and inform decision making at individual level, particularly in multimorbid patients in whom the risk-benefit balance remains poorly understood.

Even though my study demonstrated that BP lowering has similar benefits regardless of the number of cardiometabolic diseases at baseline, there were three important caveats, which need to be addressed by future research. First, the range of diseases was restricted to cardiometabolic conditions, which, despite being the most prevalent in population-based cohorts, represent only a small fraction of the long list of common diseases and hence do not reflect the variety of diseases typical of patients with multimorbidity.[110] Indeed, evidence shows that multimorbidity patterns are becoming increasingly complex, with the potential for significant disease-disease, disease-treatment and treatment-treatment interactions.[110] Evidence on the proportional effects of BP lowering in patients with non-cardiometabolic multimorbidity is not possible to generate from currently available RCTs because they either excluded patients with certain diseases (e.g., cancer, depression), or did not collect a detailed medical history at baseline. Therefore, future clinical trials should be (1) more flexible in their inclusion and exclusion criteria to reflect the broader spectrum of baseline multimorbidity in contemporary populations, and (2) more comprehensive in data collection regarding baseline characteristics. Within the confines of trials in BPLTTC, more in-depth analyses of multimorbidity could be done if all the data collected at baseline had been collated.

Second, it is uncertain whether my findings are applicable to frail and very old individuals, as those were underrepresented, or not represented at all, in my study population. Although there is substantial overlap between old age, multimorbidity and frailty, evidence is even scarcer in patients with frailty, which underpins the current recommendations to use clinical judgement to guide decision making about BP lowering in those patients.[17] The proper concept of frailty is a matter of heated debate with different definitions proposed by different

medical societies and expert panels in different contexts.[572] Nevertheless, it is clear that frailty is associated with a poor prognosis, and in consequence there is a pressing need to identify strategies that may improve quality of life and/or increase life expectancy in those patients. There is ongoing controversy though as to whether low BP in frail multimorbid patients is causally implicated in the increased risk of death or a marker of poor health overall,[573] with contradictory evidence suggesting that high adherence to BP lowering treatment is associated with a lower risk of all-cause death even in frail, elderly patients.[558] The yet unclear association between BP and clinical outcomes in this context underpins the cautious recommendation to consider deprescribing non-essential drugs, such as BP lowering agents, in elderly, frail and multimorbid patients.[574] Indeed, a recent RCT demonstrated that, among patients over the age of 80 years treated with multiple antihypertensive medications, a strategy of medication reduction, compared with usual care, was noninferior with regards to SBP control at twelve weeks.[575] However, the impact of such a strategy on long-term clinical outcomes is uncertain, thus emphasising the need for further research to identity multimorbid patients who may benefit from intensive BP reduction and those for whom a deprescribing strategy may be more appropriate.

Third, demonstrating that BP lowering can reduce cardiovascular risk in patients with multimorbidity immediately raises the question as to whether the reverse side of the coin is an increase in adverse events. Observational studies provide conflicting evidence on the association between pharmacological BP lowering and the risk of injurious falls.[430,576-578] However, randomised evidence to settle this controversy is missing. The BPLTTC may be able to partially answer this question by pooling the detailed data on adverse events, which is

available for a subset of the trials. Furthermore, it would be important to understand whether adverse events are related to the intensity of BP lowering and/or to off-target effects of antihypertensive agents, that are specific to certain drug classes. Nonetheless, concerns about whether the reduction in cardiovascular risk comes at the expense of an increase in adverse events in patients who are very old, frail and have non-cardiometabolic multimorbidity will persist because such patients have not been included in the BPLTTC. Therefore, further RCTs are warranted to clarify the balance of safety and efficacy of BP reduction in the context of multimorbidity, frailty and advanced age.

Treatment of patients with heart failure

My systematic review and aggregate data meta-analysis identified important gaps in our understanding of the relationship between BP and HF. However, those questions could not be answered with the evidence currently available in published RCTs for several reasons. First, data for baseline and follow-up BP measurements were erratic and incomplete, with few studies reporting mean values with respective standard errors. Second, outcomes that are strongly related to BP, such as stroke and myocardial infarction, were rarely reported, and there were also no data for outcomes that are especially relevant to patients with HF, such as renal function and AF. Third, in most trials data were not available to enable stratification of patients according to baseline characteristics, including diabetes, functional class or left ventricular ejection fraction. Fourth, aggregate data meta-analyses are inherently unable to adequately investigate treatment-covariate interactions at the patient level. Therefore, establishing a new trialists' collaboration to pool IPD from all RCTs of drugs with BP lowering

properties is crucial to enable investigating (1) the effects of those drugs on BP overall and for specific drug classes; (2) the effects of those drugs on a wide range of efficacy and safety outcomes, including conventional cardiovascular outcomes, as well as patient reported outcomes; (3) whether there is a correlation between the intensity of BP reduction and efficacy and safety outcomes.

Although I took the initial steps to establish this new IPD collaboration in HF (i.e., the BPHFTC), and actually gained access to twenty-four of the thirty-four eligible RCTs, it will take longer than the timeframe of my DPhil for the collaboration to come to fruition. Nevertheless, it is worth pursuing this collaboration in the future to clarify ongoing uncertainties about HF management, preferably including novel medicines that continue to be developed to tackle refractory HF.[579]

Implications for individual participant data meta-analysis

I conducted the first studies in the BPLTTC using one-stage IPD meta-analyses. This offered several advantages over the two-stage approaches that had been used in previous BPLTTC meta-analyses, as I have explained in previous sections. However, my methodological approach had some pitfalls that should be addressed in future research.

First, despite countless attempts to adjust model parameters, it was impossible to implement mixed-effects Cox regression models, which would have enabled assuming random treatment effects instead of a fixed treatment effect. As software is continuously being updated and improved, the possibility of implementing hierarchical Cox regression models with random intercept for trial and random slope for the effect of treatment by trial should be tested in the future, particularly in meta-analyses involving the BPLTTC.

Second, although BP lowering is assumed to be the main mechanism of action of the so-called antihypertensive drugs, it would be worth exploring whether certain drug classes offer additional advantages in certain populations (e.g., patients with multimorbidity or AF) or for specific outcomes (e.g., dementia, chronic kidney disease). For this purpose, network meta-analysis is the ideal methodology and it should be attempted in the BPLTTC in the future.[580,581]

Third, even though I demonstrated that cluster analysis can be successfully implemented in datasets of IPD from RCTs, further research is warranted to understand its full potential. Therefore, my research set the stage for future studies to explore cluster analysis in greater depth not only in hypertension but also in myriad contexts where it can identify clusters (i.e.,

subpopulations who share some characteristics) that may be of clinical relevance for diagnosis, management or prognosis.[582-585]

Fourth, the multilevel multiple imputation model that I developed provided valid and reliable estimates of the true values, but this is not always the case.[586,587] Although multilevel multiple imputation models have been shown to outperform complete-case analysis and methods that ignore the hierarchical structure of the data (i.e., between-study heterogeneity), they still have substantial limitations. First, multilevel models involve many parameters, particularly when random effects are assumed for all explanatory variables. On one hand, this means that some imputation models may run into convergence issues, leading to improper imputation, which may introduce bias in subsequent analyses. On the other hand, the estimation of those models requires substantial computational power and they may be infeasible without simplification. Second, methodological limitations and assumptions (e.g., covariance structure) may impair the performance of the models.[586] Third, multilevel regression models should only be implemented if data can be assumed to be missing at random and, hence, they should not be used when the probability of missingness depends on unmeasured variables. In this setting, machine learning based methods have recently emerged as a promising alternative to overcome the limitations of conventional multilevel imputation methods. Deep architectures are capable of automatically learning latent representations and complex inter-variable associations, which may improve the accuracy and reliability of data imputation.[588-590] Therefore, future research should investigate whether machine learning based methods can be used to impute missing data in the BPLTTC in particular, and more generally in datasets of IPD.

Conclusion

Overall, my thesis improved our understanding of the efficacy and safety of BP lowering in key areas where evidence was sparse. The evidence generated by my research will refine guideline-recommended treatment and inform clinical practice, thus improving BP management across the globe. This will ultimately reduce the burden of morbidity and mortality attributable to hypertension, the main risk factor for cardiovascular diseases, which remain the leading cause of death worldwide. Besides saving lives, better BP management will allow managing scarce healthcare resources more efficiently to enable meeting the needs of an ageing, and increasingly multimorbid, population. Above all, my research lends further support to the importance of "*imprecise medicine*", defined as "the indiscriminate use of effective treatments for a range of common diseases".[591] Despite the hype that nowadays surrounds "*precision medicine*", its relevance and impact remain largely unproven. In fact, although BP lowering treatment should be based on holistic patient assessment, and tailored to individual preferences and needs,[592] from a population perspective the benefits of BP reduction are broadly comparable irrespective of age, sex and pre-existing diseases. By extending the generalisability of the benefits of pharmacological BP lowering to populations in whom evidence was lacking, my research emphasises that health systems should invest in standardisation of care for high BP to improve the health of vast numbers of patients worldwide. Only with serious commitment and joint effort from governments, healthcare providers and patients will it be possible to stem the tide of ill health that is attributable to raised BP, and hence to extend healthy life expectancy in the UK and across the globe.

Chapter 10 Other works

This chapter describes other work that I took a leading part in during my DPhil, namely an observational study on sex differences in trends and levels of cardiovascular risk factors in England, and three Mendelian randomisation studies. Although not formally part of my DPhil thesis, those studies illustrate the breath and scope of the skills and knowledge that I acquired during my DPhil, which will certainly be valuable for my future career in Public Health. For reasons of parsimony, herein I provide the abstract for each of those studies as well as a brief description of my contribution as author.

Systolic blood pressure and risk of new-onset atrial fibrillation: a Mendelian randomisation study

Milad Nazarzadeh, Ana-Catarina Pinho-Gomes*, Zeinab Bidel, Dexter Canoy, Abbas Dehghan, Karl Smith Byrne, Derrick A Bennett, George Davey Smith, Kazem Rahimi*

* Joint first authors

Abstract

Background

Evidence on how to effectively prevent new-onset AF is limited, with observational and randomised studies providing conflicting results.[86,90] The recent finding that the effect of BP lowering treatment on new-onset AF varied according to trial-level baseline risk for AF[90] raised the hypothesis that the overall weak or insignificant treatment effects could be masking stronger effects in high-risk patients. Therefore, this study aimed to investigate whether lifelong exposure to elevated SBP was associated with incident AF, and to what extent that association was modulated by genetic susceptibility for AF.

Methods

Instruments for the instrumental variable-SBP association were selected single nucleotide polymorphisms with minor allele frequency above 0.01 that were independently and significantly associated with SBP at $p<5\times10^{-8}$ in a European population genome-wide association study.[593] A total of 130 single nucleotide polymorphisms with imputation quality above 0.9 were selected. Data for the corresponding summary statistics for the single

nucleotide polymorphism-AF association were retrieved from the largest and most recently published genome-wide association meta-analysis, which included a total of 60,620 AF cases and 970,216 controls of European ancestry.[594] To assess the SBP effect on AF according to genetic susceptibility for AF, one-sample Mendelian randomisation was applied to IPD from the UK Biobank.[595] Genetic susceptibility for AF was estimated by a genetic risk score based on variation in a total of 111 single nucleotide polymorphisms with minor allele frequency above 0.01, which were independently associated with AF at $p<5\times10^{-8}$ in the last published genome-wide association study in the European population.[594] A potential treatment effect with major BP lowering drug classes on AF risk was predicted through genetic variants in druggable genes that code proteins related to the function of each drug class. Estimated drug effects were compared with effects on incident coronary artery disease, for which direct trial evidence exists.

Results

A total of 329,237 UK Biobank participants were included, in whom 12,391 cases of AF were identified. Two-sample Mendelian randomisation demonstrated that genetically determined elevated SBP significantly increased the risk of new-onset AF (Odds ratio (OR) 1.17, 95% CI [1.10 to 1.24] per 10-mmHg increase in SBP). Furthermore, there was a graded relationship between SBP and risk of AF according to genetic susceptibility for AF. Indeed, there was no firm evidence of an effect in those with low genetic risk (OR 1.21, 95% CI [0.95 to 1.53]), whilst a strong effect was observed among those with high genetic predisposition for AF (OR 1.51, 95% CI [1.31 to 1.74]). The indirect comparison of predicted treatment effects using genetic proxies for three main drug classes (ACEIs, BBs and CCBs) suggested similar average effects for prevention of AF and coronary artery disease.

Conclusions

This study showed that the association between elevated BP and increased risk of AF is likely to be causal, with a more pronounced impact in individuals with high genetic susceptibility for AF. In the absence of clinical trials, this study provides another indication for BP lowering treatment, in particular among individuals with increased genetic predisposition for AF.

My contribution

I contributed in equal part to the conception and design of this study, interpretation of the data, and drafting and revising the manuscript.

Systolic blood pressure and risk of valvular heart disease: a Mendelian randomisation study

Milad Nazarzadeh, Ana-Catarina Pinho-Gomes, Karl Smith Byrne, Dexter Canoy, Francesca Raimondi, Jose Roberto Ayala Solares, Catherine M. Otto, Kazem Rahimi

Abstract

Background

Age-related valve degeneration, which typically presents as aortic stenosis or mitral regurgitation, is now the predominant cause of valve dysfunction in high-income countries due to population ageing.[596,597] Therefore, there is an unmet need to identify modifiable risk factors for heart valve disease in order to develop effective prevention and treatment strategies. Although observational studies suggested that elevated BP was associated with a greater risk of heart valve disease, those studies were prone to residual confounding. In the absence of randomised evidence, this study used Mendelian randomisation to investigate whether high SBP was causally associated with an increased risk of aortic stenosis, aortic regurgitation and mitral regurgitation.[598]

Methods

Participants were selected from the UK Biobank, a population-based cohort of 502,602 individuals aged 40 to 96 years at baseline, if they had valid genetic data and BP measurements.[599] SBP was measured during clinical assessment and instruments for the genetic effect of high BP were identified from variants that were independently associated

with SBP with minor allele frequency greater than 0.01. A total of 130 single nucleotide polymorphisms that have been shown to be associated with SBP in a genome-wide association meta-analysis involving 1 million participants of European ancestry were selected.[593] The main outcomes were incident aortic stenosis, aortic regurgitation, and mitral regurgitation, individually and combined. Cases were largely based on hospital records linked to the UK Biobank with International Classification of Diseases and Health Related Problems Tenth Revision codes. Instrumental variable analysis was performed by means of an adjusted two-stage predictor substitution method that used the genetic risk score as instrument variable.[600]

Results

A total of 329,237 participants were included, as they had valid genetic data and BP measurements. Of those, 177,741 (54%) were women, and mean age was 57 (SD 8) years. The prevalence of heart valve disease was 1.08% (3,570 individuals). Aortic stenosis (0.45%) and mitral regurgitation (0.53%) were more common than aortic regurgitation (0.19%). Each genetically associated 20-mmHg increment in SBP was associated with an increased risk of aortic stenosis (OR 3.26, 95% CI [1.50 to 7.10]), aortic regurgitation (OR 2.59, 95% CI [0.75 to 8.92]), and mitral regurgitation (OR 2.19, 95% CI [1.07 to 4.47]), with no evidence for heterogeneity by type of heart valve disease (p = 0.90). Sensitivity analyses confirmed the robustness of the association.

Conclusion

This study demonstrated that lifetime exposure to elevated SBP significantly increases the risk of heart valve disease. This association is likely to be causal, thus suggesting that BP

lowering treatment may be an affordable and effective strategy to prevent or retard the progression of heart valve disease.

My contribution

I contributed to the conception and design of this study. I shared, in equal part, the responsibility for interpreting the data and drafting and revising the manuscript.

This paper was published in *JAMA Cardiology* at https://jamanetwork.com/journals/jamacardiology/article-abstract/2737872.

Plasma lipids and risk of aortic valve stenosis: a Mendelian randomisation study

Milad Nazarzadeh , Ana-Catarina Pinho-Gomes, Zeinab Bidel, Abbas Dehghan, Dexter Canoy, Abdelaali Hassaine, Jose Roberto Ayala Solares, Gholamreza Salimi-Khorshidi, George Davey Smith, Catherine M Otto, Kazem Rahimi

Abstract

Background

Aortic valve stenosis is the most common degenerative heart valve disease and its prevalence is on the rise fuelled by population ageing.[596,597] Poor understanding of the underlying mechanisms and risk factors for initiation and progression of aortic stenosis has hindered the development of effective drugs for primary and secondary prevention. This underpins the conflicting evidence provided by observational studies and randomised trials on the association between lipid levels and aortic stenosis.[601-605] Therefore, we aimed to assess the causal association between genetically determined exposure to raised lipid levels and incidence of aortic stenosis.

Methods

Causality of association was assessed using a two-sample Mendelian randomisation framework through different statistical methods. We retrieved summary estimations of genetic variants that have been shown to be associated with plasma lipid levels in the Global Lipids Genetics Consortium, which included 188,577 participants, mostly of European

ancestry. Genetic variants associated with aortic stenosis, our primary outcome, were obtained from a total of 432,173 participants in the UK Biobank.[599,606] Secondary outcomes included aortic regurgitation and mitral regurgitation, which served as negative controls.

Results

The odds ratio for developing aortic stenosis per unit increase in lipid parameter was 1.52 (95% CI [1.22 to 1.90] per 0.98 mmol/L) for low-density lipoprotein cholesterol, 1.03 (95% CI [0.80 to 1.31] per 0.41 mmol/L) for high-density lipoprotein cholesterol, and 1.38 (95% CI [0.92 to 2.07] per 1 mmol/L) for triglycerides. There was no evidence of a causal association between any of the lipid parameters and aortic or mitral regurgitation.

Conclusion

This study showed that lifelong exposure to high low-density lipoprotein cholesterol increases the risk of symptomatic aortic stenosis, suggesting that cholesterol lowering treatment may be effective for prevention of aortic stenosis.

My contribution

I contributed to the conception and design of this study and interpretation of the data. I shared, in equal part, the responsibility for drafting and revising the manuscript.

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Sex differences in treatment and control of cardiovascular risk factors in England

Ana-Catarina Pinho-Gomes, Sanne Peters, Blake Thomson, Mark Woodward

Abstract

Background

About 6.1 million people in England have a diagnosis of cardiovascular disease.[607] Although death rates have been declining for the past decades, cardiovascular disease still accounts for about 1 in 4 deaths in England.[541] Compelling evidence demonstrates that control of major cardiovascular risk factors, such as high BP, high cholesterol, diabetes, smoking and overweight, is an effective preventative strategy.[608] Nevertheless, those risk factors remain poorly controlled across the globe,[609,610] with substantial differences between women and men.[611-613] In England, sex-specific data on the trends in prevalence, treatment and control of cardiovascular risk factors remains limited.[65,614] Understanding how the burden of cardiovascular risk factors has been evolving in women and men, and whether there are currently differences in risk factor control is critical to inform policy making and planning of healthcare delivery. Therefore, this study aimed to investigate sex differences in trends in major cardiovascular risk factors in England between 2012 and 2017, overall and stratified by age, history of cardiovascular disease, and level of social deprivation.

Methods

Data from the Health Survey for England[23,615] 2012 to 2017 on non-institutionalised English adults (aged over 16 years) were used to investigate sex-specific trends in prevalence, treatment and control of major cardiovascular risk factors: SBP and hypertension, haemoglobin A1C and diabetes, total and high-density lipoprotein cholesterol, BMI and smoking.

Results

Overall, 49,415 adults (51% women) were included. Trends in levels of cardiovascular risk factors were largely comparable between sexes over time, other than for high-density lipoprotein cholesterol and BMI. High-density lipoprotein cholesterol increased from 1.66 mmol/L to 1.81 mmol/L in women and from 1.34 mmol/L to 1.56 mmol/L in men between 2012 and 2017. BMI increased from 27.0 kg/m^2 to 27.8 kg/m^2 in women and from 27.3 kg/m^2 to 27.6 kg/m^2 in men during the same period. The proportion of individuals with neither hypertension, dyslipidaemia, obesity or smoking increased from 17% to 27% in women and from 14% to 21% in men between 2012 and 2017. The prevalence of hypertension and diabetes remained relatively stable in both sexes at about 24% in women and 26% in men for hypertension and 6% in women and 9% in men for diabetes. The prevalence of dyslipidaemia decreased from 66% to 48% in women and from 67% to 52% in men during the study period. Despite some improvement, treatment and control of hypertension, dyslipidaemia and diabetes mellitus remained suboptimal in both sexes. The proportions of controlled hypertension, diabetes and dyslipidaemia among those with each condition in 2017 were 50% versus 52% for hypertension, 19% versus 20% for diabetes, and 15% versus 24% for dyslipidaemia in women versus men, respectively.

Conclusions

Trends in major cardiovascular risk factors were broadly similar between the sexes in this nationally representative sample of the English adult population. Treatment and control of hypertension, diabetes mellitus, and dyslipidaemia improved over time, but remained suboptimal in both sexes. More intensive risk factor modification is needed as part of a renewed drive for further curbing cardiovascular disease in England.

My contribution

I led the conception and design of this study. I was responsible for acquiring the data, analysing and interpreting it. I also drafted and revised the manuscript with input from co-authors.

Table S7 1 Distribution of number of diseases by trial

	Isolated hypertension	Hypertension and one disease	Hypertension and two diseases	Hypertension and three diseases	Hypertension and four diseases	Hypertension and five diseases
AASK	0	255	588	251	0	0
ABCD	0	293	518	124	15	0
ACCORD	0	1,439	2,717	540	37	0
ACTIVE	2,439	3,945	1,994	547	87	4
ADVANCE	0	4,895	4,681	1,421	143	0
ALLHAT	1,001	14,262	18,052	8,540	552	11
ANBP	2,605	787	35	0	0	0
ANBP2	4,094	1,728	245	16	0	0
ASCOT-BPLA	1,833	7,541	6,604	2,853	410	16
BENEDICT	0	1	686	490	32	0
CAMELOT	60	965	733	223	16	0
CAPPP	7,500	3,078	387	19	1	0

CARDIOSIS	677	380	49	5	0	0
CASEJ	761	2,093	1,519	302	28	0
COLM	2,634	2,005	456	41	5	0
CONVINCE	6,554	6,814	2,683	395	30	0
COPE	1,931	1,053	257	45	7	0
DIABHYCAR	0	1,971	2,312	609	20	0
Dutch-TIA	0	1,040	367	61	5	0
ELSA	1,462	712	139	19	2	0
EUROPA	0	5,817	4,804	1,573	24	0
EWPHE	538	252	41	9	0	0
HIJCREATE	0	1,106	810	131	2	0
HOMEDBP	2,719	705	90	4	0	0
HOPE	6	710	4,833	3,037	700	11
HYVET	1,495	1,931	375	41	3	0
INSIGHT	2,082	2,761	1,252	217	9	0
INVEST	0	12,897	7,083	2,393	194	9
JMIC-B	0	676	721	236	17	0
LIFE	4,494	3,431	1,056	194	17	1
MOSES	0	508	501	279	59	5
NICSEH	326	98	5	0	0	0

NORDIL	7,118	3,184	535	39	5	0
ONTARGET	255	7,521	11,738	5,139	905	62
PART2	120	360	119	18	0	0
PEACE	0	3,781	3,570	883	56	0
PREVENDIT	0	679	174	11	0	0
PREVENT	0	498	265	56	6	0
PROGRESS	0	3,686	1,924	451	43	1
SHEP	2,728	1,714	284	10	0	0
SPRINT	4,694	3,746	886	35	0	0
STOP HT-22	3,235	2,573	706	90	8	2
SYSTEUR	3,236	1,254	190	14	1	0
TRANSCEND	68	1,717	2,631	1,236	251	23
UKPDS	0	662	472	14	0	0
VALISH	1,538	1,150	333	53	5	0
VALUE	2,029	6,527	5,061	1,465	160	3
VHAS	1,030	327	55	2	0	0

Table S7 2 Distribution of multimorbidity patterns by cluster

	Cluster 1	Cluster 2	Cluster 3	Cluster 4	Cluster 5	Cluster 6	Cluster 7
HTN	70006	0	3	1243	0	10	0
HTN IHD	0	0	0	675	3	0	44498
HTN CVD	6624	0	0	3	0	17431	0
HTN CKD	14146	0	0	288	0	20	0
HTN OBE	880	0	1	20780	0	0	0
HTN DM	17950	53	1567	0	350	259	0
HTN IHD CVD	0	0	0	81	273	0	9547
HTN IHD CKD	0	0	0	53	1	0	8521
HTN IHD DM	0	0	520	0	21	0	16167
HTN IHD OBE	0	0	200	11536	0	0	2010
HTN CVD CKD	372	0	0	0	0	4335	0
HTN CVD DM	538	543	224	0	4605	3994	0
HTN CVD OBE	4	0	0	1582	0	8494	0
HTN CKD DM	2274	38	14	0	1847	11	0
HTN CKD OBE	29	0	0	2809	0	0	0
HTN DM OBE	24	0	14869	0	0	0	0
HTN IHD CVD CKD	0	0	0	4	645	0	1100
HTN IHD CVD DM	0	0	0	0	2709	0	943
HTN IHD CVD OBE	0	0	0	2669	0	0	47
HTN IHD CKD DM	0	0	29	0	21	0	2329
HTN IHD CKD OBE	0	0	0	1781	0	0	20
HTN IHD DM OBE	0	0	9439	0	1	0	465
HTN CVD CKD DM	19	1104	5	0	279	135	0
HTN CVD CKD OBE	0	0	0	33	0	447	0
HTN CVD DM OBE	1	12	3838	0	4276	13	0
HTN CKD DM OBE	0	0	1767	0	0	0	0
HTN IHD CVD CKD DM	0	0	0	0	581	0	39
HTN IHD CVD CKD OBE	0	0	0	198	1	0	1
HTN IHD CVD DM OBE	0	0	517	9	1370	0	0
HTN IHD CKD DM OBE	0	0	818	0	0	0	9
HTN CVD CKD DM OBE	0	1	54	0	257	0	0
HTN IHD CVD CKD DM OBE	0	0	6	0	142	0	0

Table S7 3 Distribution of multimorbidity clusters by trial

	Cluster 1	Cluster 2	Cluster 3	Cluster 4	Cluster 5	Cluster 6	Cluster 7
AASK	248	0	0	509	0	18	319
ABCD	333	2	530	0	54	1	30
ACCORD	1448	2	2744	0	274	47	218
ACTIVE	3518	27	777	2272	285	740	1397
ADVANCE	5052	86	3154	0	1205	347	1296
ALLHAT	7971	665	5197	3498	6063	15816	3208
ANBP	2809	0	0	603	0	0	15
ANBP2	4386	0	110	1161	16	231	179
ASCOT-BPLA	7367	136	2222	3743	972	1368	3449
BENEDICT	1	0	431	0	35	0	742
CAMELOT	71	0	197	623	29	0	1077
CAPPP	7763	0	284	2644	12	139	143
CARDIOSIS	677	0	0	261	0	74	99
CASEJ	2968	79	188	134	466	326	542
COLM	3702	2	103	141	80	607	506
CONVINCE	6721	19	2411	3637	139	559	2990
COPE	2849	12	38	139	69	84	102
DIABHYCAR	1372	124	2269	0	107	588	452
Dutch-TIA	0	12	0	20	51	1290	100
ELSA	1613	0	41	449	2	0	229
EUROPA	0	0	1673	895	41	0	9609
EWPHE	581	0	19	128	8	46	58
HIJCREATE	0	0	43	46	86	0	1874
HOMEDBP	3208	1	58	150	15	32	54
HOPE	199	46	610	1061	2126	555	4700
HYVET	3145	18	39	246	73	222	102
INSIGHT	3339	39	654	1213	156	438	482
INVEST	0	0	1828	1435	610	0	18703
JMIC-B	0	0	12	29	60	0	1549
LIFE	5235	4	468	2066	97	252	1071
MOSES	0	12	0	27	378	788	147
NICSEH	400	0	2	10	1	12	4
NORDIL	7466	0	326	2487	23	227	352
ONTARGET	1724	292	3187	3297	1802	2425	12893
PART2	128	0	15	83	6	34	351
PEACE	0	0	667	2192	99	0	5332
PREVENDIT	688	0	5	142	9	11	9
PREVENT	0	0	39	190	9	0	587

PROGRESS	0	37	0	103	579	4722	664
SHEP	3301	1	147	1056	14	45	172
SPRINT	6124	0	0	1527	0	0	1710
STOP HT-22	4406	6	192	1045	79	390	496
SYSTEUR	3538	0	127	779	12	111	128
TRANSCEND	365	66	689	854	388	639	2925
UKPDS	650	0	466	0	13	12	7
VALISH	2544	14	29	81	78	153	180
VALUE	3834	49	1838	2523	757	1800	4444
VHAS	1123	0	42	245	4	0	0

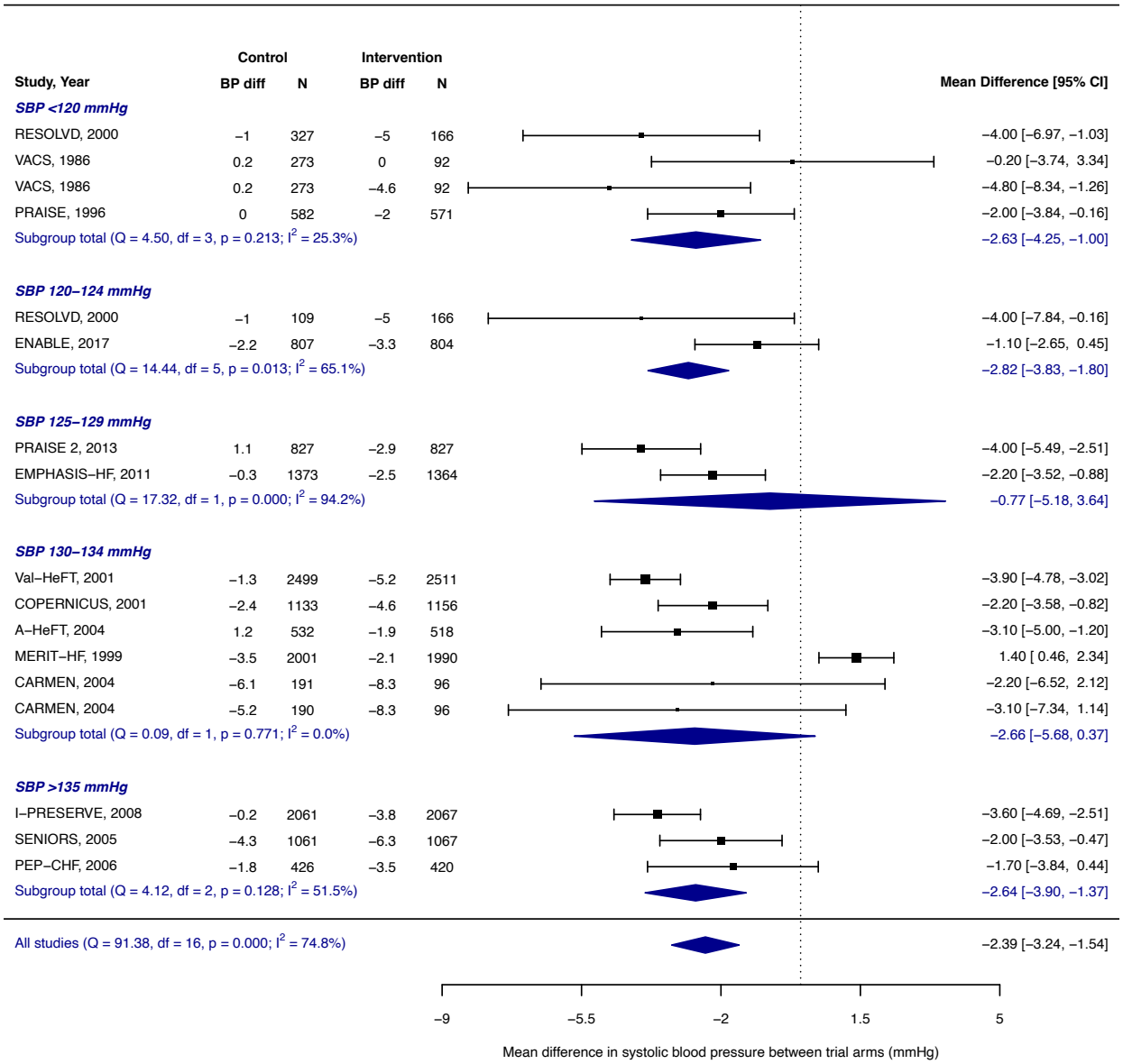

Figure S8. 1 Meta-analysis of the effect of blood pressure lowering treatment on the mean difference in systolic blood pressure, stratified by baseline systolic blood pressure, with estimates for individual trials

Mean differences between the change in systolic blood pressure in the intervention group versus the control group are displayed for each trial and each strata of mean baseline systolic blood pressure (SBP) aggregated at trial level. Summary measures were calculated using random effects models with REML estimators. Negative values mean that the reduction in systolic blood pressure was greater in the intervention group. Only studies that compared active treatment with placebo were included.

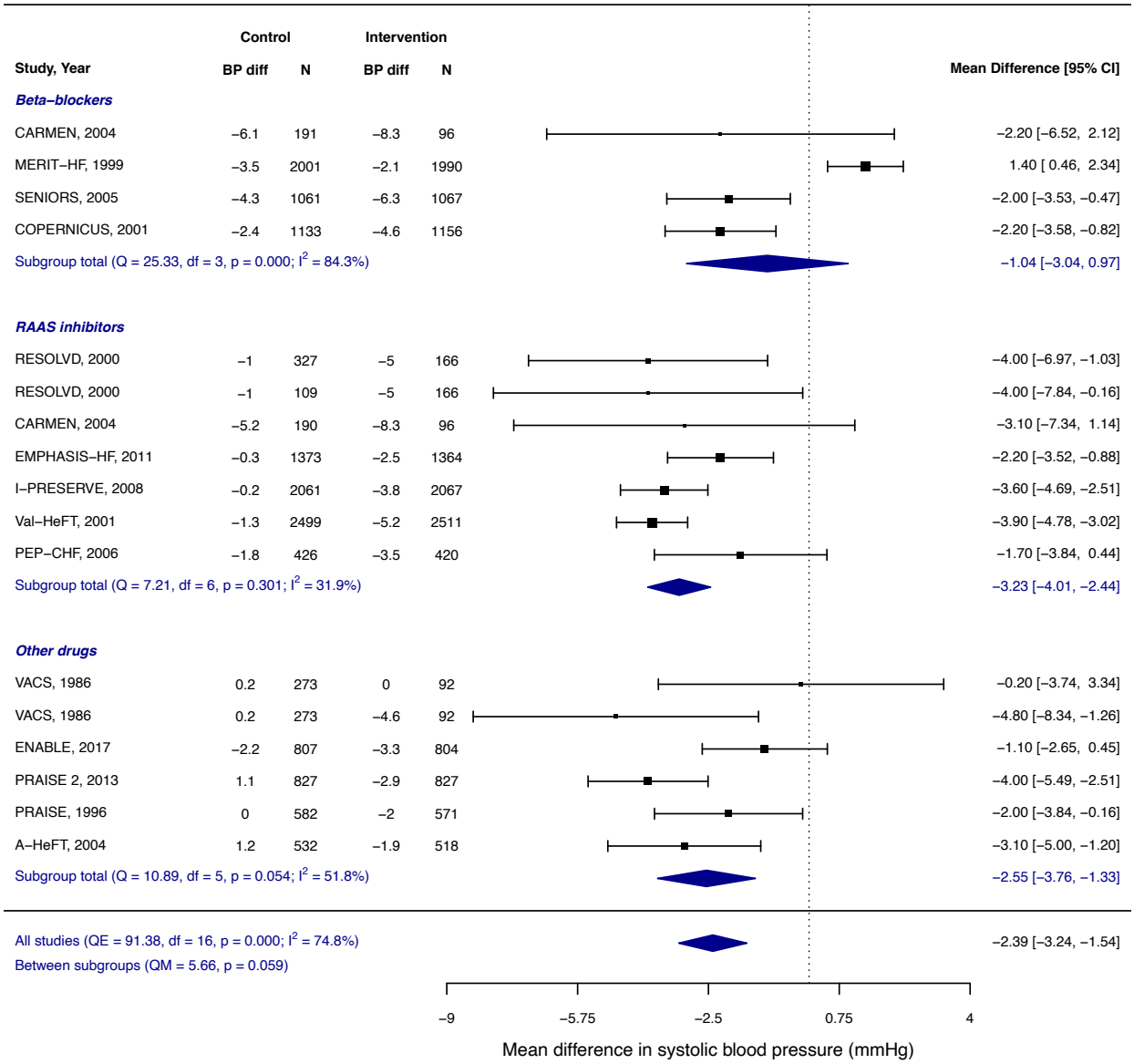

Figure S8. 2 Meta-analysis of the effect of blood pressure lowering treatment on the mean difference in systolic blood pressure, stratified by drug class, with estimates for individual trials

Mean differences between the change in systolic blood pressure (SBP) in the intervention group versus the control group are displayed for each trial and each drug class. Summary measures were calculated using random effects models with REML estimators. Negative values mean that the reduction in systolic blood pressure was greater in the intervention group. Other drugs include calcium channel blockers, alpha-blockers, and hydralazine-isosorbide dinitrate. Only studies that compared active treatment with placebo were included. BP diff, difference between achieved and baseline systolic blood pressure; RAAS, renin angiotensin aldosterone system

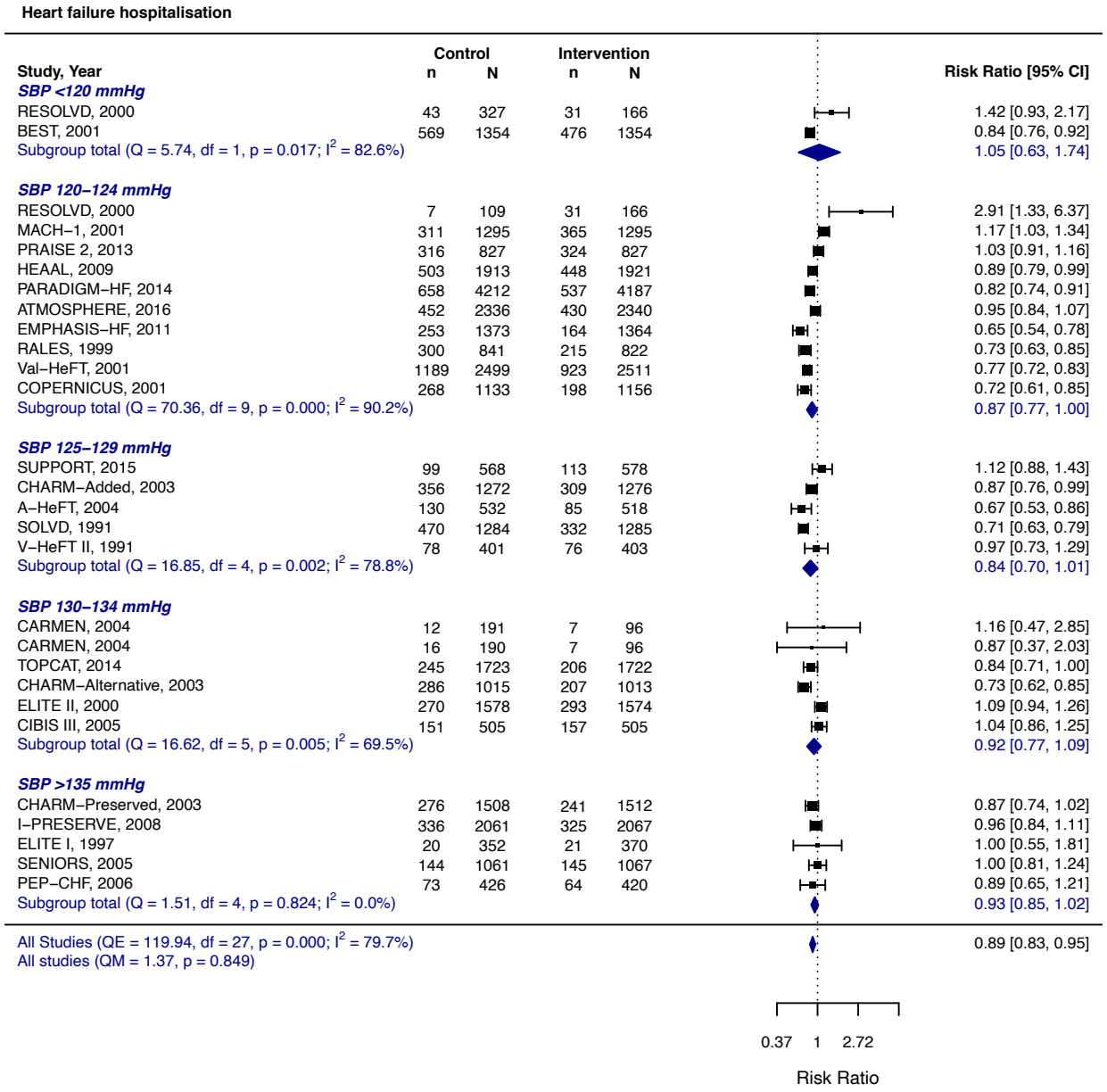

Figure S8. 3 Meta-analysis of the effect of blood pressure lowering treatment on heart failure hospitalisation stratified by baseline systolic blood pressure, with estimates for individual trials

Risk ratios and 95% confidence intervals (CI) are displayed for heart failure (HF) hospitalisation, for each trial and strata of mean baseline systolic blood pressure (SBP) aggregated at trial level. Summary measures were calculated using random effects models with REML estimators. n, number of events; N, total number of patients

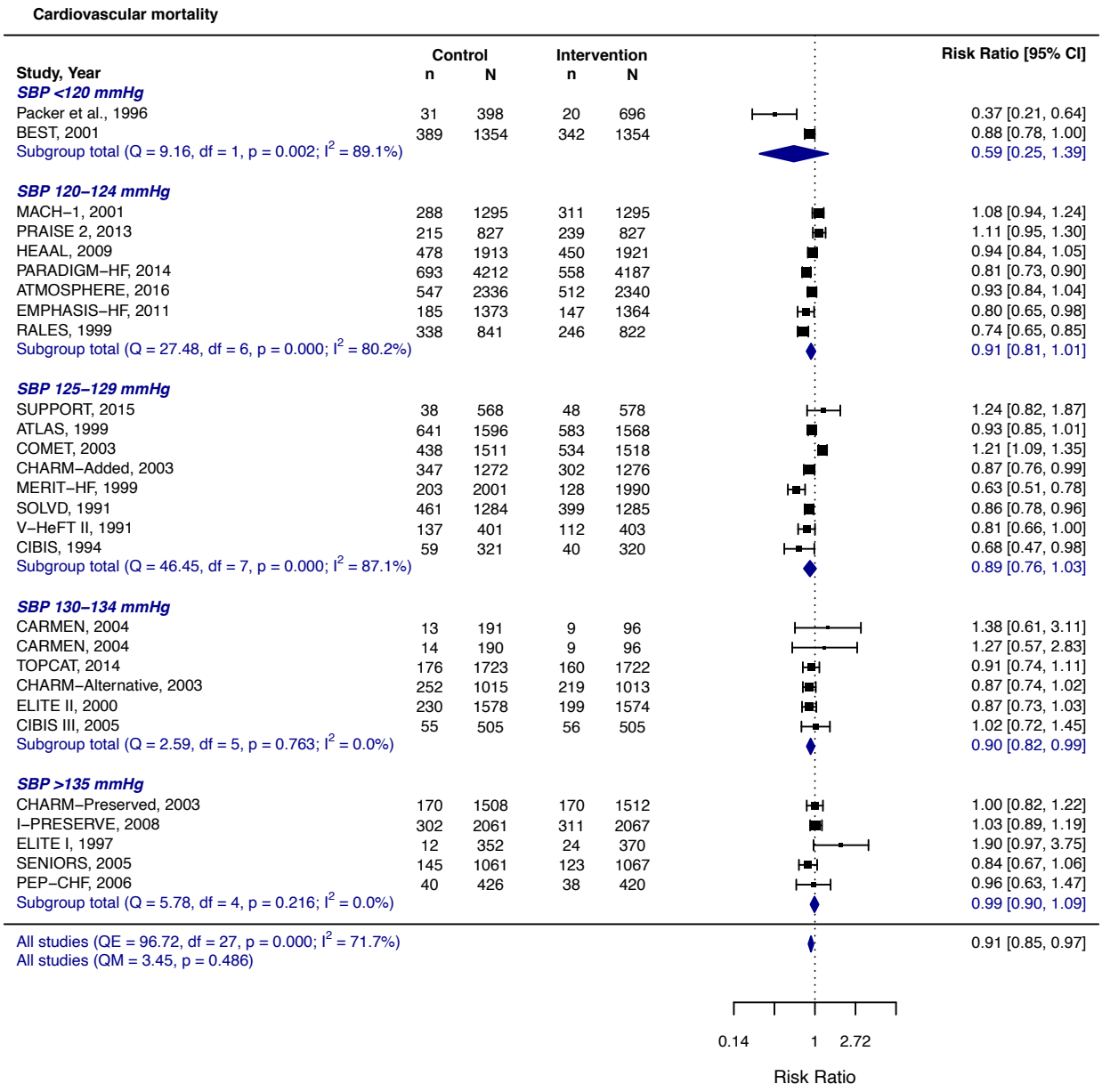

Figure S8. 4 Meta-analysis of the effect of blood pressure lowering treatment on cardiovascular mortality stratified by baseline systolic blood pressure, with estimates for individual trials

Risk ratios and 95% confidence intervals (CI) are displayed for cardiovascular mortality for each trial and strata of mean baseline systolic blood pressure (SBP) aggregated at trial level. Summary measures were calculated using random effects models with REML estimators. n, number of events; N, total number of patients

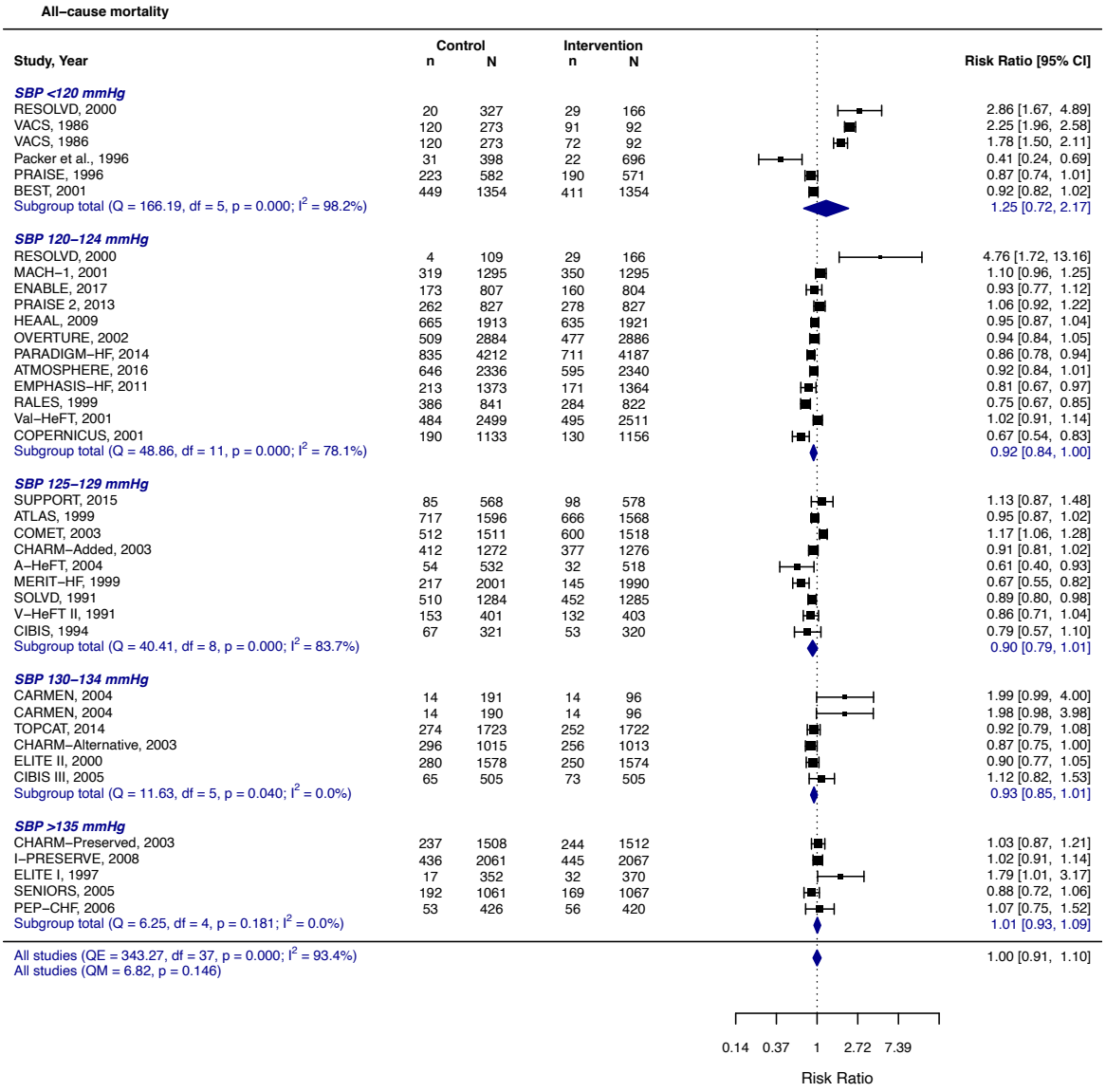

Figure S8. 5 Meta-analysis of the effect of blood pressure lowering treatment on all-cause mortality stratified by baseline systolic blood pressure, with estimates for individual trials

Risk ratios and 95% confidence intervals (CI) are displayed for all-cause mortality for each trial and strata of mean baseline systolic blood pressure (SBP) aggregated at trial level. Summary measures were calculated using random effects models with REML estimators. n, number of events; N, total number of patients

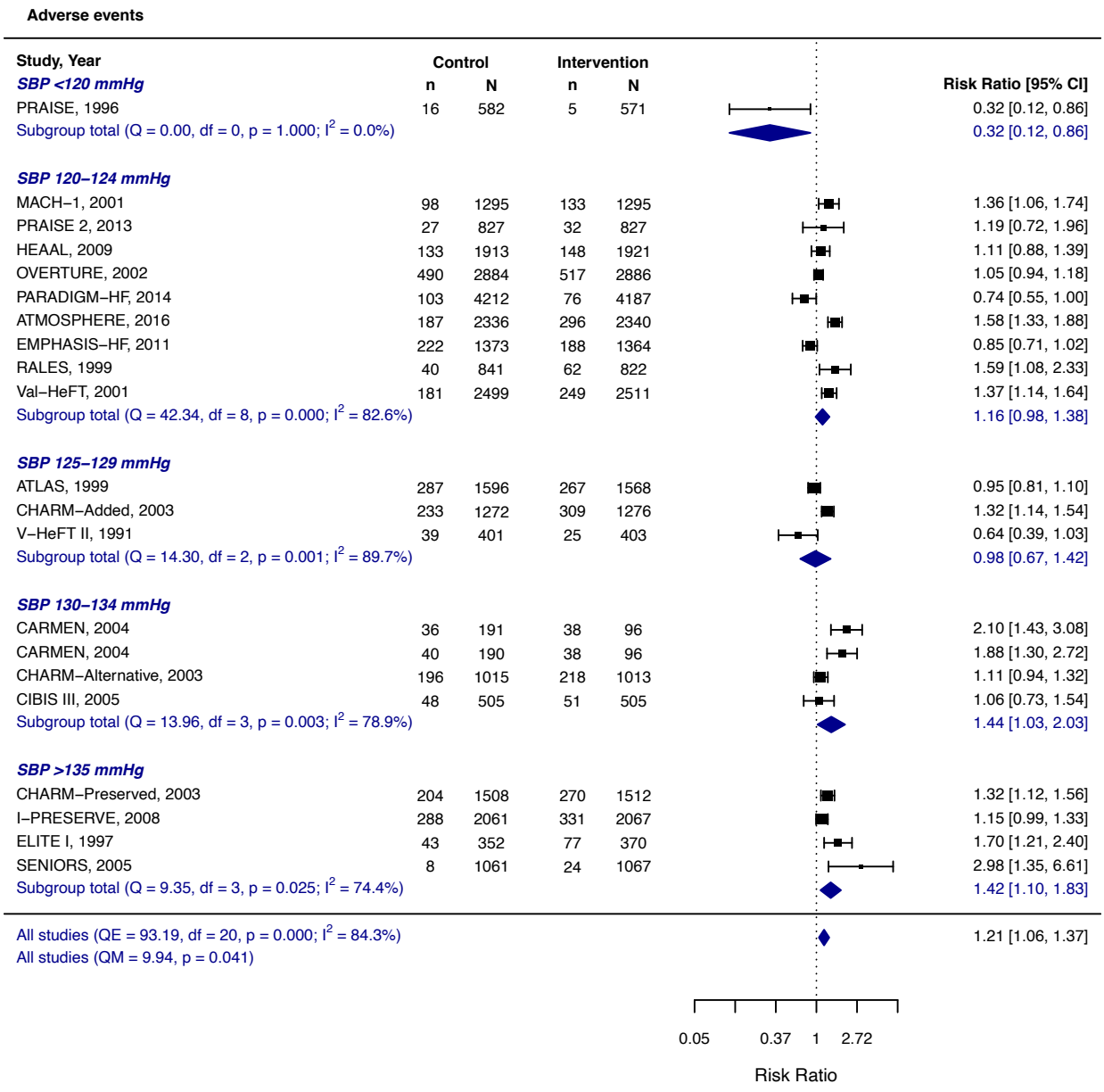

Figure S8. 6 Meta-analysis of the effect of blood pressure lowering treatment on adverse events leading to treatment discontinuation stratified by baseline systolic blood pressure, with estimates for individual trials

Risk ratios and 95% confidence intervals (CI) are displayed for adverse events leading to treatment discontinuation for each trial and strata of mean baseline systolic blood pressure (SBP) aggregated at trial-level. Summary measures were calculated using random effects models with REML estimators. n, number of events; N, total number of patients

Appendix C – Search strategy for systematic review

Medline

"Heart Failure"[Mesh]
"Cardiomyopathies"[Mesh]
(heart failure or cardiac failure or cardiac insufficiency or cardiomyopath*)[tw]
OR/ 1-3
(LCZ696 or LCZ 696 or LCZ-696 or sacubitril* or entresto)[tw]
"Angiotensin-Converting Enzyme Inhibitors"[Mesh]
(angiotensin converting enzyme inhibitor OR ACEI OR ACEI OR antagonist* OR inhibitor* benazepril OR captopril OR enalapril OR fosinopril OR imidapril OR lisinopril OR moexipril OR perindopril OR quinapril OR ramipril OR trandolapril OR zofenopril OR alacepril OR cilazapril OR spirapril OR delapril)[tw]
"Adrenergic beta-Antagonists"[Mesh]
(beta blocker* OR BB OR acebutolol OR atenolol OR betaxolol OR bisoprolol OR carvedilol OR labetalol OR metoprolol OR nadolol OR nebivolol OR penbutolol OR pindolol OR propranolol OR sotalol OR timolol)[tw]
"Mineralocorticoid Receptor Antagonists"[Mesh]
(aldosterone antagonist* OR mineralocorticoid-receptor antagonist OR MRA OR eplerenone OR spironolactone OR aldactone OR canrenoate potassium OR canrenoate OR canrenone OR canrenoic acid OR eplerenone)[tw]
"Angiotensin Receptor Antagonists"[Mesh]
(angiotensin receptor blocker* OR angiotensin receptor antagonist* OR ARB OR azilsartan OR candesartan OR eprosartan OR irbesartan OR losartan OR olmesartan OR telmisartan OR valsartan)[tw]
"Calcium Channel Blockers"[Mesh]
(calcium channel blocker* or amlodipine or diltiazem or felodipine or isradipine or lercanidipine or nicardipine or nifedipine or nisoldipine or verapamil or nitrendipine)[tw]
"Diuretics"[Mesh]
(thiazide* or hydrochlorothiazide or trichlormethiazide or chlorthalidone or indapamide or furosemide)[tw]
"Adrenergic alpha-Antagonists"[Mesh]
(doxazosin or indoramin or prazosin or terazosin or phenoxybenzamine or phentolamine)[tw]
(aliskiren or renin AND inhibitor*)[tw]
"Cardiac Resynchronization Therapy Devices"[Mesh]
(CRT or cardiac resynchronisation device or cardiac resynchronisation therapy)[tw]
OR/ 5-19
4 AND 23
(clinical[tiab] AND trial[tiab]) OR clinical trials as topic[MeSH] OR clinical trial[pt] OR random*[tiab] OR random allocation[MeSH] OR "therapeutic use" [Subheading]
24 AND 25

Cochrane Central Register of Controlled Trials (CENTRAL)

#1 MeSH descriptor: [Heart Failure] explode all trees
#2 MeSH descriptor: [Cardiomyopathies] explode all trees
#3 (heart failure or cardiac failure or cardiac insufficiency or cardiomyopath$):ti,ab,kw
#4 #1 or #2 or #3
#5 (LCZ696 or LCZ 696 or LCZ-696 or sacubitril$ or entresto):ti,ab,kw
#6 MeSH descriptor: [Angiotensin-Converting Enzyme Inhibitors] explode all trees
#7 (angiotensin converting enzyme inhibitor or ACEI or ACEI or antagonist$ or inhibitor$ benazepril or captopril or enalapril or fosinopril or imidapril or lisinopril or moexipril or perindopril or quinapril or ramipril or trandolapril or zofenopril or alacepril or cilazapril or spirapril or delapril):ti,ab,kw
#8 MeSH descriptor: [Adrenergic beta-Antagonists] explode all trees
#9 (beta blocker$ or BB or acebutolol or atenolol or betaxolol or bisoprolol or carvedilol or labetalol or metoprolol or nadolol or nebivolol or penbutolol or pindolol or propranolol or sotalol or timolol):ti,ab,kw
#10 MeSH descriptor: [Mineralocorticoid Receptor Antagonists] explode all trees
#11 (aldosterone antagonist$ or mineralocorticoid-receptor antagonist or MRA or eplerenone or spironolactone):ti,ab,kw
#12 MeSH descriptor: [Angiotensin Receptor Antagonists] explode all trees
#13 (angiotensin receptor blocker$ or angiotensin receptor antagonist$ or ARB or azilsartan or candesartan or eprosartan or irbesartan or losartan or olmesartan or telmisartan or valsartan):ti,ab,kw
#14 MeSH descriptor: [Calcium Channel Blockers] explode all trees
#15 (calcium channel blocker$ or amlodipine or diltiazem or felodipine or isradipine or lercanidipine or nicardipine or nifedipine or nisoldipine or verapamil or nitrendipine):ti,ab,kw
#16 MeSH descriptor: [Diuretics] explode all trees
#17 (thiazide$ or hydrochlorothiazide or trichlormethiazide or chlorthalidone or indapamide or furosemide):ti,ab,kw
#18 MeSH descriptor: [Adrenergic alpha-Antagonists] explode all trees
#19 (doxazosin or indoramin or prazosin or terazosin or phenoxybenzamine or phentolamine):ti,ab,kw
#20 (aliskiren or renin AND inhibitor*):ti,ab,kw
#21 MeSH descriptor: [Cardiac Resynchronization Therapy] explode all trees
#22 (CRT or cardiac resynchronisation device):ti,ab,kw
#23 (#5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22)
#24 #4 and #23
#25 #24

Appendix D – Ethical approval for the BPHFTC

Oxford University Hospitals NHS
NHS Foundation Trust

UNIVERSITY OF OXFORD

CTRG Clinical Trials and Research Governance

Joint Research Office
Boundary Brook House
Churchill Drive, Headington, Oxford OX3 7GB

20 December 2018

To whom it may concern

Ref: SCG 34

Efficacy and safety of drugs with blood pressure lowering properties in patients with heart failure

A proposal for the Blood Pressure in Heart Failure Trialists' Collaboration (BPHFTC)

This letter is to confirm that the study referenced above has been reviewed by the Joint Research Office study classification group.

Because the activity described will only use secondary research data in de-identified form, there is no further regulatory requirement for its sharing and research use.

This opinion can be reviewed by reference to the HRA's algorithm, available at http://www.hra-decisiontools.org.uk/research/ and attendant leaflet, *Defining Research,* or by reference to The Health Care Quality Improvement Partnership (HQIP)'s *Guide for Clinical Audit, Research and Service review.*

Should you require further information, please do not hesitate to contact me.

Sincerely,

Karen Melham

Dr Karen Melham
Senior Clinical Research Support Manager
Clinical Trials and Research Governance
University of Oxford

Copy to: Ms Jo Franklin, Research Governance Manager, OUH NHS Foundation Trust

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www.admin.ox.ac.uk/researchsupport/ctrg/; www.ouh.nhs.uk/researchers

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