



**Blood pressure, atrial fibrillation and diabetes: evidence
from observational and randomized analyses**

By

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*Thesis presented for the degree of Doctor of Philosophy in
Population Health at the University of Oxford*

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Abstract

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The subgroup-specific relationships between blood pressure (BP), risk of atrial fibrillation (AF) and risk of diabetes are unclear. These two chronic diseases have key epidemiologic and clinical similarities, are difficult to examine through traditional cohort studies, and are of high clinical and public health importance. Using observational analyses of electronic health records and meta-analyses of randomized trials, the relationships between blood pressure, atrial fibrillation and diabetes are investigated in this thesis. First, I show that blood pressure is modestly associated with risk of atrial fibrillation in a population free of cardiovascular disease [HR 1.21 95% confidence interval 1.19, 1.22 per 20 mm Hg higher systolic blood pressure (SBP)]. While a non-significant effect of BP lowering on AF in non-heart failure populations is observed in a meta-analysis of randomized trials, this randomized estimate is similar in magnitude to the observational association, suggesting that BP lowering may modestly lower the risk of AF. Second, I show that elevated BP is associated with a higher risk of incident diabetes (HR 1.76 CI 1.56, 1.98 per 20 mm Hg higher SBP), although the causality of this finding is unclear. Third, I demonstrate in both observational and randomized analyses that the relationship between blood pressure and cardiovascular events appears to be modified by achieved BP in type 2 diabetes, with attenuated proportional reductions at

achieved SBP less than 130 mm Hg. However, I also show that BP lowering to levels lower than those recommended in current guidelines (<130 mm Hg SBP) may lower the risk of stroke, renal disease and retinopathy. These findings are of clinical and public health importance, as they suggest that BP lowering therapy can be used to reduce the risk of AF, that elevated BP may be a risk factor for incident diabetes, and that BP lowering in type 2 diabetes to lower levels than currently recommended in guidelines may further reduce the burden of cardiovascular disease in diabetic populations.

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Dedication

*For my mother. I hope that my future research will, in some way,
repay the sacrifices that you made.*

Publications

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3. **Emdin CA**, Anderson SG, Woodward M, Rahimi K. (2015) Usual blood pressure and risk of new onset diabetes: evidence from 4.1 million adults and a meta-analysis of cohort studies. *JACC*. PMID: 26429079 (F1000 Recommended, JACC Editor's Top Picks of 2015)
4. **Emdin CA**, Anderson SG, Salimi-Khorshidi G, Woodward M, MacMahon S, Dwyer T, Rahimi K. (2016) Usual blood pressure, atrial fibrillation and vascular risk: evidence from 4.3 million adults. *International Journal of Epidemiology*. *In Press*.
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Glossary of Terms

Absolute risk: The overall probability of developing a disease or other outcome over a given period of time. Can be contrasted with proportional risk, which is used to compare the absolute risk of one group to another group.

Cox proportional hazards model: A semi-parametric survival function used to model the proportional risk of an outcome in one group to another group. The baseline hazard function of one group is assumed to be proportional to the other. No assumptions of the shape of this baseline hazard function are required.

Clinical Practice Research Datalink: A large United Kingdom electronic health record database suitable for epidemiological research. The database is composed of the records of United Kingdom general practices that use the Vision GP electronic health record system, representing approximately 5% of the UK population.

Disability adjusted life year: A measure of disease burden defined as years of life lost relative to an expected life expectancy due to death or disability.

Entity code: A code used in the Clinical Practice Research Datalink used to define types of measurements. For example, the entity code “1” is a highly specific code used to define measurements of blood pressure. They can be contrasted to Read codes, which are used by physicians to code a wide variety of observations.

Hazard ratio: A hazard rate refers to the rate of an outcome per unit time in a population. For example, a group of individuals may have a hazard rate of 2 deaths per year. Hazard ratio then refers to the ratio of a hazard rate in one group to another. Hazard ratios are often derived using Cox proportional hazards models.

Log-linear relationship: A linear, additive, increase in one variable is associated with a multiplicative increase in an associated variable. For example, each 10 mm Hg increase in systolic blood pressure may be associated with a doubling in risk of death in a given population.

Measurement error: The difference between the measured value of a quantity and its true value. For example, a true systolic blood pressure of 145 mm Hg may be measured as 140 mm Hg, with a measurement error of 5 mm Hg.

Mendelian randomization: A technique used in epidemiology to determine if a causal relationship exists between a biomarker and an outcome of interest. The technique exploits the fact that genetic variants are randomly assorted in a population. As a result, a genetic variant that affects a biomarker of interest should also affect an outcome of interest.

Proportional risk: The ratio of an absolute risk in one group to another group. Can be contrasted with absolute risk, which refers to the incidence of an outcome of interest in a population of interest without reference to another population.

Read code: In United Kingdom general practices, Read codes are the clinical terminology system used by physicians to code observations including prescription of therapies, measurements and outcomes. These codes are used in CPRD to identify events of interest (for example, diagnoses of coronary heart disease).

Regression dilution bias: When regressing an outcome of interest (e.g. coronary heart disease) on an exposure of interest (e.g. systolic blood pressure), measurement error in the exposure will bias the slope of the line of best fit towards the null. Termed regression dilution bias, this form of bias will attenuate observed associations relative towards their true values.

Reverse causality: When an outcome of interest precedes and causes the exposure of interest. Reverse causality is of greatest concern when it is not observed. For example, undiagnosed coronary heart disease may cause low blood pressure at baseline.

Renin angiotensin system: A hormonal system used to regulate arterial blood pressure. In response to low renal blood flow, juxtaglomerular cells in the kidney release renin, which, through the release and activation of further hormones, causes vasoconstriction and an increase in arterial blood pressure.

Splines: Piecewise functions used to model the relationship between two variables to remove the need for a single function to define the relationship. For example, multiple cubic splines may be used to model the relationship between blood pressure and risk of coronary heart disease to allow for a non-linear relationship.

Threshold effect: In observational epidemiology, an attenuation of the relationship between an exposure of interest and an outcome. When plotted graphically, a threshold effect appears as a plateau before or after a linear or curved relationship.

Usual levels: Refers to the long terms levels of an exposure of interest in an individual or population. Usual levels of an exposure can be contrasted with the measured value at a single point in time. For example, the usual systolic blood pressure of an individual may be 120 mm Hg while the measured value is 125 mm Hg. Usual levels of an exposure can be estimated after adjusting for regression dilution bias.

Chapter 1 Introduction

1.1. A brief history of blood pressure research

Although the global excess of mortality caused by high blood pressure is now well recognised, knowledge of the link between high blood pressure and cardiovascular risk is a relatively recent development. In the early 1900s, high blood pressure was largely considered by physicians to be a natural consequence of aging and not a risk factor to be controlled.¹ In 1910, the United States insurance industry recognized that insurance applicants with high blood pressure were at increased risk of death.² A 1925 report by the Actuarial Society of America provided some of the first quantitative estimates of the association between blood pressure and cardiovascular disease, concluding that the risk of death due to cardiovascular and other causes increases with increasing blood pressure.³

The Framingham Heart Study was one of the first epidemiological studies to both characterize the prevalence of hypertension and to analyze its consequences in a longitudinal prospective cohort.⁴ Of 4469 participants who had their blood pressure measured between 1949 and 1952, 18% had hypertension, then defined as a systolic blood pressure (SBP) ≥ 160 mm Hg. When followed over six years, ischemic heart disease (IHD) events were approximately 3 times more common in hypertensive men than in normotensive men aged 45 to 62 years and 6-fold more common in hypertensive women than normotensive women of the same age group.^{4,5}

Although, by 1960, epidemiological evidence was mounting that high blood pressure was associated with an increased risk of mortality, the majority of physicians continued to view blood pressure lowering as either useless or dangerous. The eminent cardiologist Charles Friedberg noted in the 1966 version of his textbook *Diseases of*

the Heart that the treatment of individuals with a BP <200/100 mm Hg was not indicated.⁶ However, in the late 1960s, the first Veteran Affairs Cooperative Study, comparing a combination of antihypertensives (thiazide diuretic and reserpine) against placebo in hypertensive individuals, was halted due to an excess of morbid and mortal events in the placebo arm. This trial provided the first strong causal evidence that blood pressure lowering reduces the risk of death.⁷

In 1970, the National Heart and Lung Institute convened a task force to recommend ways to treat, prevent and research atherosclerosis. One recommendation provided by the task force was to conduct a large randomized trial to test a complex intervention aimed at dietary change, halting of smoking and treatment of high blood pressure.⁸ In 1972, 350 000 men without prior vascular disease were screened as potential participants for the Multiple Risk Factor Intervention Trial (MRFIT) and had a baseline blood pressure recorded. Although the trial itself did not show a significant benefit of the complex intervention, the MRFIT screening cohort formed one of the largest prospective individual patient cohort studies in blood pressure research. After six years of follow-up, mortality within the MRFIT cohort was found to relate to blood pressure in a graded and continuous manner with no evidence of threshold down to 120 mm Hg systolic (Table 1.1).^{1,9} Similarly, in a 1990 overview of nine prospective observational studies with 420 000 individuals, diastolic blood pressure was continuously associated with risk of coronary heart disease (CHD) and stroke events to a threshold of 70 mm Hg.¹⁰ Overall, a 10 mm Hg lower diastolic blood pressure was associated with 37% lower risk of CHD events and a 56% lower risk of stroke events.

Table 1.1 Large-scale observational analyses of the association of blood pressure with cardiovascular events.

Study	Key Findings
Framingham 1959 ⁴	- Men with hypertension (SBP $\geq$ 160 mm Hg or DBP $\geq$ 95 mm Hg) had a three-fold greater rate of CHD events than men with normotension (then defined as SBP < 140 mm Hg or DBP < 90 mm Hg). - Women with hypertension had a six-fold greater rate of CHD events than normotensive women.
MRFIT 1988 ¹¹	- Mortality within the MRFIT cohort was found to relate to blood pressure in a graded and continuous manner with no evidence of threshold down to 120 mm Hg systolic. - Isolated systolic hypertension is associated with CHD mortality independently of diastolic blood pressure.
MacMahon 1990 ¹⁰	- Diastolic blood pressure was continuously associated with risk of coronary heart disease (CHD) and stroke events to a threshold of 70 mm Hg. - A 10 mm Hg lower diastolic blood pressure was associated with 37% lower risk of CHD events and a 56% lower risk of stroke events.
Prospective Studies Collaboration 2002 ¹²	- After accounting for regression dilution, a 20 mm Hg lower SBP was associated with a hazard ratio (HR) of 0.60 for IHD mortality (95% confidence interval [CI] 0.58, 0.61) and a HR of 0.50 (CI 0.48, 0.52) for stroke mortality in the age group with the largest number of fatal events (70 to 79 years). - Although associations between vascular mortality and blood pressure are half as extreme at age 80-89 as age 40-49, absolute differences in risk are greater.
Rapsomaniki 2014 (CALIBER) ¹³	20 mm Hg lower SBP was associated with HR 0.78 (CI 0.75, 0.80) for myocardial infarction, 0.74 (CI 0.70, 0.78) for ischemic stroke, 0.69 (CI 0.63, 0.76) for intracerebral hemorrhage. - Hypertension ($\geq$ 140/90 mm Hg) was associated with a mean 5 years free of cardiovascular disease lost from age 30. - While stable/unstable angina and myocardial infarction were associated with the greatest number of disease free life years lost at age 30, by age 80, heart failure accounted for most of disease free years lost.

1.2. Blood pressure as a risk factor for cardiovascular disease in general populations

In 2002, the Prospective Studies Collaboration (PSC) reported results from a meta-analysis of prospective observational studies of the association between blood pressure and vascular mortality.¹² Although previous analyses had largely associated measured blood pressure with cardiovascular risk, random measurement error and time-dependent regression to the mean are expected to reduce the calculated association between measured blood pressure and cardiovascular risk (an effect termed regression dilution bias). This large meta-analysis (based on one hundred thousand deaths among one million participants without a history of vascular disease, recruited into 61 prospective cohort studies between 1950 and 1990) controlled for regression dilution bias and therefore provided reliable evidence on the association between “usual” blood pressure (baseline blood pressure unaffected by measurement error and temporal variation) and cardiovascular risk. It found a continuous log-linear relationship between blood pressure and vascular mortality, i.e., for a given absolute difference in blood pressure, the proportional difference in risk of vascular death was similar at all blood pressure levels investigated (Table 1.1).¹² More specifically, irrespective of the baseline blood pressure, a 20 mm Hg lower SBP was associated with a hazard ratio (HR) of 0.60 for IHD mortality (95% confidence interval [CI] 0.58, 0.61) and a HR of 0.50 (CI 0.48, 0.52) for stroke mortality in the age group with the largest number of fatal events (70 to 79 years).

Other vascular causes of mortality that were investigated exhibited similar associations with a 20 mm Hg reduction in SBP. The age-standardised HR for heart failure was 0.53 (CI 0.48, 0.59), while that for aortic aneurysm was 0.55 (CI 0.49, 0.62). Mortality from atherosclerosis and hypertensive heart disease were found to

have HRs of 0.48 (CI 0.42, 0.55) and 0.22 (CI 0.20, 0.25), respectively. This study also found no evidence for an increased risk of non-vascular mortality with lower blood pressure. In fact, each 20 mm Hg lower SBP was associated with a modestly *lower* risk of non-vascular mortality (age-standardised HR 0.88, CI 0.87–0.89), most likely explained by misclassification of vascular diseases rather than a causal relationship between blood pressure and risk of non-vascular mortality.

The large number of events in the PSC meta-analysis provided statistical power for more detailed analyses than had previously been possible. In particular, the collaboration was able to reliably investigate the relationship of blood pressure and vascular mortality by age. When stratified into different age groups, a continuous log-linear relationship was observed at all ages. However, the slope of the association differed significantly between the different age groups. For every 20 mm Hg lower SBP, the HR for death from IHD declined from 0.49 in the age group of 40-49 years to 0.67 in the age group of 80-89 years. For stroke mortality, the HR for a 20 mm Hg lower SBP declined from 0.36 in the 40-49 age group to 0.67 in the 80-89 years age group (Table 1.1).¹² Despite the diminishing strength of the associations between vascular death and blood pressure with increasing age, the absolute annual differences in death rates associated with a given difference in blood pressure were found to be higher in the older age categories. This was because the absolute risks of vascular disease increased steeply with increasing age.¹² This evidence supported the notion that blood pressure control is likely to prevent substantial numbers of vascular events up to old age.

PSC also investigated differences in proportional risks by sex and showed modest differences between men and women. The proportional risk of IHD mortality per 20 mm Hg lower SBP were slightly smaller in men than in women, with HRs of

0.62 (CI 0.60, 0.64) for men and 0.55 (CI 0.53, 0.58) for women in the largest age group. For stroke, HRs for a 20 mm lower SBP were similar, although possibly slightly attenuated in women, with HRs of 0.53 (CI 0.49, 0.56) for women vs. 0.48 (CI 0.46, 0.51) for men in the age group of 70-79 years.

A few studies have also investigated differences in associations by ethnicity or geographical regions. In the Asian Pacific Cohort Studies collaboration (APCSC), risk of ischemic heart disease was similar in Australian and Asian populations and steeper in younger than older people. A slightly stronger relationship between blood pressure and stroke was found in Asian populations (HR 0.59 CI 0.58, 0.60) than in Australian populations (HR 0.70 CI 0.63, 0.78).¹⁴ In the PSC, similar hazard ratios for IHD and stroke mortality were found in different regional populations. For IHD mortality, an age-standardised HR of 0.57 (CI 0.56, 0.58) was observed in Europe, 0.54 (CI 0.51, 0.56) in the United States/Australia and 0.55 (CI 0.48, 0.63) in Asia. For stroke mortality, HRs were 0.49 (CI 0.48, 0.51) in Europe, 0.50 (CI 0.47, 0.53) in the US/Australia and 0.42 in Asia (CI 0.39, 0.46).¹² However, in neither collaboration were reliable data available on stroke sub-types, and there was therefore a possibility that any real difference in the strength of association in Asian and non-Asian populations could reflect differences in the ratio of stroke types.

The PSC and APCSC analyses were based on epidemiological studies that, in large part, preceded the introduction of major public health and medical interventions for blood pressure control. In addition, these collaborations largely focused on fatal stroke and fatal IHD and had little information on non-fatal vascular events. A recent study, however, was able to use data from linked healthcare records for 1.25 million patients in England who were registered with their primary care doctors between 1997 and 2010. In this contemporary cohort studied in the CALIBER project

(CARDiovascular research using LInked Bespoke studies and Electronic health Records), investigators reported the association between measured blood pressure (without formally controlling for regression dilution) and risks of fatal and non-fatal vascular events, including angina, heart failure, peripheral vascular disease and abdominal aortic aneurysm.¹³ A 20 mm Hg lower systolic blood pressure was associated with an HR of 0.71 (CI 0.68, 0.74) for stable angina, 0.80 (CI 0.76, 0.85) for unstable angina, 0.78 (CI 0.75, 0.80) for myocardial infarction, 0.79 (CI 0.76, 0.81) for heart failure, 0.74 (CI 0.70, 0.78) for ischemic stroke, 0.69 (CI 0.63, 0.76) for intracerebral hemorrhage and 0.79 (CI 0.78, 0.80) for total cardiovascular disease. Similar to PSC and APCSC, the strength of the association of systolic blood pressure with cardiovascular disease attenuated significantly in older age groups (Table 1.1). For example, in the age group 30-59, 20 mm Hg higher systolic pressure was associated with a hazard ratio of 0.62 (CI 0.58, 0.66) for stable angina, but was associated with a hazard ratio of 0.78 (0.68, 0.88) in the age group >80 years. Similarly, for ischemic stroke, 20 mm Hg lower systolic blood pressure was associated with an HR of 0.64 (CI 0.56, 0.72) in the age group 30-59 years but an HR of 0.86 (CI 0.77, 0.96) in the age group >80 years.

The proportional reductions per 20 mm Hg lower SBP observed in CALIBER were attenuated relative to those observed in PSC and APCSC. For example, in PSC, the hazard ratio for IHD mortality per 20 mm Hg lower SBP was 0.57 (in European populations) while a hazard ratio of 0.78 was observed for myocardial infarction in CALIBER. There are several potential explanations for these diverging findings. First, while PSC and APCSC adjusted for regression dilution, CALIBER did not, although multiple blood pressure measurements for individuals were averaged when available. Accounting for regression dilution increased the strength of observed associations 1.5

to 2 fold in PSC, when comparing usual blood pressure to measured blood pressure. Second, while PSC contained cohort studies that were conducted before the widespread introduction of antihypertensive therapy, CALIBER contained records from 1997 to 2010, after the widespread introduction of antihypertensive therapy in the UK. Although the CALIBER analysis adjusted for baseline usage of antihypertensive therapy, such interventions are likely to have been introduced for many individuals during the follow-up duration. Consequently, their cardiovascular risk would be reduced relative to what it would be if there baseline blood pressure had remained constant, reducing the association between cardiovascular risk and blood pressure over a range of blood pressures (from normotensive to hypertensive). Finally, the CALIBER cohort, while slightly larger than PSC, was of significantly shorter follow up duration (median of 5.2 years vs. mean of 12 years in PSC), included non-fatal vascular events (which may be less influenced by usual blood pressure and not captured reliably in routine databases) and may have differed in age from PSC.

The observed associations between 20 mm Hg lower systolic pressure and cardiovascular risk in PSC are broadly consistent with randomized evidence of blood pressure lowering. In a meta-analysis of 147 blood pressure lowering trials, a 20 mm Hg reduction in systolic blood pressure was associated with a 39% reduction in CHD events (HR 0.61 CI 0.53, 0.69) and a 65% reduction in stroke events (HR 0.35 CI 0.27, 0.45).¹⁵ In the age group 60-69 (the mean age for the trials included in the meta-analysis), a 20 mm Hg lower systolic blood pressure was associated with a 46% lower rate of CHD events (HR 0.54 CI 0.53, 0.55) and a 57% lower rate of stroke events (HR 0.43 CI 0.41, 0.45). Although IHD estimates and stroke estimates from PSC differ slightly than those from randomized trials, estimates from PSC lie within confidence intervals of estimates from randomized trials.

In summary, large-scale epidemiological studies have provided overwhelming evidence that high blood pressure, in all age groups and in both sexes, is associated with an increased risk of IHD mortality, stroke mortality and vascular mortality without any evidence for a decreased risk of non-vascular mortality and no evidence of material heterogeneity by different ethnicities.

1.3. Diabetes and atrial fibrillation: importance and epidemiological similarities

Although there is reliable evidence on the association between blood pressure and ischemic heart disease and stroke¹², the two leading causes of cardiovascular death worldwide¹⁶, the relationship between blood pressure and risk of other, non-heart disease/stroke events is more poorly characterized. In particular, the relationship between blood pressure and atrial fibrillation (AF) and the relationship between blood pressure and diabetes are less clear. These two chronic diseases have key epidemiologic, clinical and public health similarities.

First, both conditions are associated with increased risk of cardiovascular disease. AF is associated with five times the risk of stroke¹⁷ and two times the risk of death.¹⁸ Recent evidence has also linked to AF to an increased risk of myocardial infarction¹⁹ and sudden cardiac death.²⁰ Diabetes, similarly, is associated with two times the risk of coronary heart disease and cardiovascular death²¹ and is associated with an increased risk of stroke, heart failure and peripheral arterial disease.²² Individuals with type 2 diabetes were at 67.4% lifetime risk of developing cardiovascular disease, versus 44.3% among individuals without diabetes.²² Therefore, there is a strong clinical rationale for prevention of both AF and new onset diabetes, as well as vascular disease in both conditions.

Second, the burden of diabetes and AF worldwide is increasing rapidly.^{23,24} An estimated 285 million people worldwide suffered from diabetes in 2010.²⁵ By 2030, it is estimated that there will be at least 400 million individuals with type 2 diabetes mellitus worldwide, with many of those affected being relatively young and living in low- or middle-income countries.²³ AF affected an estimate 33.5 million individuals worldwide in 2010²⁶, estimated to increase with an increase in AF risk factors worldwide and the aging of the global population.²⁷ In the Global Burden of Disease study, the age and sex standardized disability adjusted life years (DALYs) lost to diabetes increased by 30%, from 523 DALYs per 100 000 people to 680 DALYs per 100 000 people from 1990 to 2010.²⁴ Similarly, the age and sex-standardized DALYs lost to AF increased from 35 DALYs per 100 000 people in 1990 to 52 DALYs per 100 000 people in 2010, a 49% increase. Together, both diseases pose a greater mortality burden than tuberculosis or HIV, highlighting the importance of prevention of both diseases from a public health perspective.²⁴

Finally, examination of each disease, reliably, on a large scale, has been difficult, as both are typically non-fatal, chronic conditions that are difficult to analyze in traditional cohort studies that use fatal endpoints. Indeed, neither the Prospective Studies Collaboration¹² nor the Emerging Risk Factors Collaboration²⁸ have examined the relationship between cardiovascular risk factors (including blood pressure) and incident diabetes and AF. Furthermore, neither collaboration has examined the association between blood pressure and risk of cardiovascular disease in type 2 diabetes. While other cohort studies have provided evidence for associations between blood pressure and incident diabetes and AF^{29,30}, they have been too small to examine interactions by age, BMI or other population subgroups. Thus, the relationship between

blood pressure, diabetes and AF is not entirely clear, is difficult to examine through traditional cohort studies, and is of high clinical and public health importance.

1.4. Blood pressure and risk of atrial fibrillation: prior evidence from observational and randomized studies

Elevated blood pressure is a risk factor for the development of AF. In an analysis of the Framingham cohort, men and women with hypertension (defined as a systolic blood pressure ≥ 160 mm Hg or a diastolic pressure ≥ 95 mm Hg) had 50% and 40% greater risk for the development of AF, respectively.³¹ An analysis of five thousand individuals in the Cardiovascular Health Study indicated that a 10 mm Hg higher baseline systolic pressure was associated with an 11% greater risk of incident AF over a three year follow up.²⁹ Analyses of a Norwegian cohort³² and the ONTARGET and TRANSCEND trials³³ have also demonstrated hypertension to be a significant predictor of incident AF.

In spite of the reliable evidence that elevated blood pressure is a risk factor for development of AF, key uncertainties in the relationship between blood pressure and AF remain. First, unlike ischemic heart disease and stroke, for which the shape of the relationship between blood pressure and each outcome has been adequately described¹², the shape of the relationship between blood pressure and AF is not entirely clear, and it is uncertain if there is a nadir below which lower blood pressure is associated with a higher risk of AF. Elevated blood pressure was associated with higher risk of AF in the Women's Health Study observational cohort, with hypertension (SBP ≥ 140 mm Hg or DBP ≥ 90 mm Hg) associated with a 43% higher risk of AF (HR 1.43 CI 1.36, 1.50).³⁴ However, blood pressure was not considered as either a categorical variable or as a continuous variable using splines – two approaches that could model the shape of the relationship between blood pressure and AF. In a

separate analysis from Women's Health Study randomized trial, risk of AF was observed to increase above a threshold of 130-139 mm Hg. However, number of incident AF events <130 mm Hg was too sparse to allow for reliable determination of the relationship between blood pressure and risk of AF below 130 mm Hg.³⁵ Prior reports from Framingham³¹ and the Cardiovascular Health Study²⁹ cohorts have been underpowered to examine the shape of the association of blood pressure and AF, with 562 and 304 incident AF events, respectively, and have not analysed the shape of the relationship between BP and AF. In contrast, the Prospective Studies Collaboration, which was able to reliably determine the shape of the age specific-relationship between blood pressure and ischemic heart disease from 115 mm Hg to 185 mm Hg SBP, had 34 283 ischemic heart disease events and did not report on AF events.¹² Thus, prior studies have been underpowered to determine the shape of the relationship between blood pressure and risk of AF.

Second, the age-, sex- and subgroup-specific associations of blood pressure and AF are not entirely clear. The Prospective Studies Collaboration has suggested that the association between age and risk of ischemic heart disease and stroke attenuates with age.¹² Similarly, an analysis of CALIBER indicated an attenuation of the association of blood pressure with a range of cardiovascular outcomes (although AF was not considered an outcome) with age.¹³ In contrast, existing studies of the association between blood pressure and risk of AF have not observed any attenuation with age. In an analysis of Women's Health Study randomized trial, 10 mm Hg SBP was associated with a 12% higher risk of AF (HR 1.12 CI 1.05, 1.19). A test for interaction by age was not significant.³⁵ However, with only 644 incident events, this analysis was underpowered to detect any potential interaction between blood pressure and age. Prior landmark analyses from Framingham³¹ and Cardiovascular Health Study²⁹ did not

attempt to detect interactions by sex, age, BMI or other patient characteristics. It is thus uncertain if AF, unlike ischaemic heart disease and stroke, is not modified in its association with blood pressure by age, sex or other characteristics.

Subgroup-specific associations of a risk factor, for example, by age, sex and baseline levels of the risk factor, have a number of important research and clinical implications. First, subgroup-specific associations of blood pressure with risk of AF and other outcomes allows physicians to more accurately communicate risks to different patients. Second, subgroup-specific associations suggest potential stratifications or interactions to include in formal risk prediction modeling. Third, subgroup-specific associations provide estimates for use in the design of randomized trials. Fourth, specifically for modification of risk by baseline levels of the risk factor (for example, differential associations by baseline blood pressure), associations indicate the presence of threshold effects or J-shaped relationships. Thus, determining the subgroup-specific associations of blood pressure with risk of AF has a number of important clinical and research implications.

Finally, even though it is clear that lower blood pressure is associated with a lower risk of AF, it is uncertain if blood pressure lowering reduces the risk of AF. In the Losartan Intervention For Endpoint reduction trial, treatment with an angiotensin receptor blocker significantly reduced the risk of AF over 4.8 years follow up (RR 0.67 CI 0.55, 0.83).³⁶ Similarly, in a meta-analysis of renin angiotensin system (RAS) inhibition trials, RAS inhibition reduced the risk of AF by a third (OR 0.67 CI 0.57, 0.78).³⁷ However, many of the trials included in this meta-analysis were conducted in heart failure populations in which RAS inhibition may have blood pressure independent effects. Indeed, in the six trials included in this meta-analysis conducted in hypertensive populations, RAS inhibition did not reduce the risk of incident AF (OR

0.89 CI 0.75, 1.05). In the Systolic Hypertension in the Elderly Program trial, which tested blood pressure lowering using a diuretic and beta-blocker against a placebo and established a between arm difference of 12 mm Hg, blood pressure lowering did not reduce incident AF (RR 0.78 CI 0.53, 1.16).³⁸ It is thus uncertain if blood pressure lowering reduces the risk of AF, and if it does lower the risk of AF, whether the effects of blood pressure lowering are limited to certain populations or certain classes of medication.

1.5. Blood pressure and risk of diabetes: prior evidence from observational and randomized studies

Diabetes is associated with an elevated risk of cardiovascular disease²¹ and is one of the leading causes of death worldwide.¹⁶ Identification of risk factors for diabetes may allow for the identification of therapies or lifestyle interventions to prevent diabetes. Numerous risk factors for diabetes have been well characterized, including body mass index, weight gain³⁹, smoking⁴⁰ and inflammatory markers such as C-reactive protein and interleukin-6.⁴¹ The relationship between blood pressure and new onset diabetes is less clear. There is an *a priori* rationale to suspect that elevated blood pressure may cause new onset diabetes. In a Mendelian randomization analysis, genetically lower interleukin-6 levels were associated with a non-significantly lower (OR 0.97 CI 0.94–1.00, p=0.06) risk of new onset diabetes.⁴² Chronic inflammation has also been demonstrated to inhibit insulin production in pancreatic beta cells.⁴³ Individuals with elevated blood pressure have elevated interleukin-6 levels⁴⁴ and inflammatory markers have been demonstrated to be reduced by RAS inhibition.⁴⁵ Thus, inflammation may mediate any potential relationship between blood pressure and risk of new onset diabetes. Alternatively, endothelial dysfunction could mediate a potential relationship between blood pressure and diabetes, as elevated markers of

endothelial dysfunction are associated with an increased risk of diabetes⁴⁶ and blood pressure lowering reduces markers of endothelial dysfunction.⁴⁷

However, consistent evidence to support a putative association between blood pressure and new onset diabetes is lacking. In an analysis the Atherosclerosis in Risk Communities cohort, individuals with hypertension were at twice the risk of diabetes relative to non-hypertensive individuals.⁴⁸ However, this analysis was unadjusted for potential confounders such as BMI, which may cause both high blood pressure and incident diabetes in a blood pressure-independent fashion. In a recent analysis of Women's Health Study, elevated blood pressure was associated with an increased risk of new onset diabetes, with hypertensive individuals (SBP >140 mm Hg or treatment with antihypertensive therapy) at two times the risk of diabetes (HR 2.03 CI 1.77–2.32) relative to individuals with a blood pressure <120 mm Hg.⁴⁹ However, several other studies have found no association between elevated blood pressure and risk of diabetes, including a prospective cohort study of 4304 individuals with 262 new onset diabetes events⁵⁰, a prospective study of 14054 individuals with 246 events⁵¹ and a prospective study of 8386 individuals with 361 events.⁵²

Furthermore, the interpretation of any potential association between elevated blood pressure and diabetes is confounded by fact that certain antihypertensive therapies increase the risk of new onset diabetes. In a network meta-analysis of blood pressure lowering drugs, diuretics increased the risk of diabetes by 30% (OR 1.30 CI 1.07, 1.58), while beta-blockers non-significantly increased the risk of diabetes by 17% (OR 1.17 CI 0.98, 1.40, $p=0.08$).⁵³ Both drugs inhibit pancreatic insulin secretion and peripheral insulin sensitivity.⁵⁴ Thus, any observation of an association between blood pressure and new onset diabetes may be due to individuals at high blood pressure being differentially prescribed diabetes promoting antihypertensive therapies, rather than a

causal relationship between blood pressure and new onset diabetes. This could potentially explain different findings of a relationship between blood pressure and diabetes in different studies, if rates of prescription of diabetes-promoting antihypertensive therapies differed between studies. In conclusion, although there is a strong *a priori* rationale to expect an association between blood pressure and diabetes, it is uncertain whether such an association actually exists.

1.6. Blood pressure and risk of cardiovascular disease in type 2 diabetes: prior evidence from observational and randomized studies

As described above, blood pressure has been consistently observed to be continuously associated with risk of ischemic heart disease and stroke, with no evidence of a nadir from 115 mm Hg to 185 mm Hg SBP in general populations.^{12,13} However, prior large observational analyses on the relationship between blood pressure and cardiovascular disease have largely been conducted in non-diabetic populations.^{12,13} Observational analyses of the relationship between blood pressure and cardiovascular disease in diabetic populations have consistently observed that elevated blood pressure is associated with an increased risk of cardiovascular disease.⁵⁵⁻⁵⁷ Similarly, randomized trials of blood pressure lowering in type 2 diabetes have demonstrated that blood pressure lowering in diabetic populations with elevated blood pressure reduces the risk of cardiovascular disease.^{58,59} However, there is considerable uncertainty as to whether a nadir at which blood pressure lowering does not reduce the risk of cardiovascular disease exists in type 2 diabetes, both in observational and randomized analyses.

With regard to observational evidence, in an analysis of the United Kingdom Prospective Study of Diabetes cohort of 4801 individuals, blood pressure was observed to be linearly related to risk of any cardiovascular event, with no evidence of a nadir to a SBP of 120 mm Hg.⁵⁶ However, this analysis did not adjust for regression dilution,

suggesting that the lowest examined blood pressure category of <120 mm Hg (median SBP 114 mm Hg) would likely have a usual blood pressure greater than 120 mm Hg. Furthermore, this analysis included several microvascular components in the primary composite outcome, such as retinal photocoagulation and cataract extraction, which may differ in their relationship with blood pressure relative to macrovascular events such as ischemic heart disease and stroke. In an analysis of the MRFIT cohort, men with a systolic blood pressure <120 mm Hg had the lowest rate of a cardiovascular death.⁶⁰ However, this analysis only adjusted for age, and men with SBP <120 mm Hg may have lower risk of cardiovascular events due to other risk factors. In contrast, in analyses of the diabetic subgroups of the ONTARGET trial⁶¹ and the INVEST trial⁵⁷, a J-shaped association between blood pressure and cardiovascular disease was observed, with increased cardiovascular risk at systolic blood pressures below 130 mm Hg. However, these analyses included individuals with pre-existing cardiovascular disease, and did not exclude early follow up, suggesting that the findings of a J-shaped curve may be due to reverse causality (undiagnosed cardiovascular disease causing lower blood pressure).

Randomized evidence of blood pressure lowering in diabetes has been similarly conflicted. In the 1501 diabetic person subgroup of the HOT trial, intensive blood pressure lowering (to a target DBP less than 80 mm Hg) reduced the risk of major cardiovascular events (RR 0.49 CI 0.29, 0.81) relative to a target DBP less than 90 mm Hg.⁵⁸ Cardiovascular death was also reduced (RR 0.33 CI 0.14, 0.78). In the UKPDS trial, blood pressure lowering to a target of < 150 mm Hg reduced the risk of diabetic complications (both macrovascular and microvascular) by 24% (RR 0.76 CI 0.62, 0.92).⁵⁹ Risk of diabetes-related death and risk of stroke were also reduced by blood pressure lowering (RR 0.68 CI 0.49, 0.94 and RR 0.56 CI 0.35, 0.89, respectively).

However, both trials did not test blood pressure lowering to low (SBP <140 mm Hg) levels; the mean on treatment blood pressure in the intervention group was 140/81 mm Hg in HOT and 144/82 mm Hg in UKPDS.

The Action to Control Cardiovascular Risk in Diabetes trial was designed to test the hypothesis that intensive blood pressure lowering (<120 mm Hg SBP) would further reduce the risk of cardiovascular disease relative to a target of 140 mm Hg.⁶² Surprisingly, intensive blood pressure lowering did not significantly reduce the risk of the primary outcome (a composite of cardiovascular death and myocardial infarction, stroke, HR 0.88 CI 0.73, 1.06). No significant reduction in all-cause mortality, cardiovascular death, myocardial infarction or heart failure was observed. Although stroke (fatal and non-fatal) was reduced by 41% (HR 0.59 CI 0.39, 0.89), the risk of serious adverse events was more than doubled in the intensive arm relative to the control arm (3.3% vs. 1.3%) and the rate of estimated glomerular filtration rate <30 ml per minute per 1.73 m² was elevated.

The failure for ACCORD to demonstrate that intensive blood pressure lowering reduces the risk of a cardiovascular composite may be due to several reasons. First, the event rate in ACCORD was significantly lower than expected and the trial may have been underpowered to detect a clinically meaningful reduction in risk of major cardiovascular events.⁶³ Second, provision of multiple antihypertensive therapies (the mean number of medications in the intervention arm was 3.4) may have had adverse cardiac effects. Third, the low achieved blood pressure (mean of 119.3 mm Hg in the intervention arm) may be located on the increasing portion of a J-shaped curve between systolic blood pressure and risk of cardiovascular disease in diabetes.

In conclusion, although blood pressure is linearly related to risk of cardiovascular disease to 115 mm Hg SBP in general population, the relationship

between blood pressure and cardiovascular disease in type 2 diabetes is less than clear. Although it is apparent from both observational and randomized evidence that blood pressure lowering above 140 mm Hg in diabetes is associated with a lower risk of cardiovascular disease, it is uncertain if blood pressure lowering below 140 mm Hg is associated with a lower risk of risk of all cardiovascular events.

1.7. Aims of thesis

To clarify the existing uncertainty in the relationships between blood pressure, AF and diabetes, this thesis aims to test six main hypotheses:

1. A 20 mm Hg higher systolic blood pressure and a 10 mm Hg higher diastolic blood pressure are associated with higher risks of AF among individuals free of existing cardiovascular disease, and have similar strengths of association by baseline blood pressure, by age, by sex and by body mass index.
2. Atrial fibrillation without antithrombotic therapy is associated with an increased risk of stroke, ischemic heart disease, peripheral arterial disease and cardiovascular disease.
3. Blood pressure lowering therapy reduces the risk of AF in randomized trials, overall and among individuals with and without cardiovascular disease.
4. A 20 mm Hg higher systolic blood pressure and a 10 mm Hg higher diastolic blood pressure are associated with higher risks of new-onset diabetes among individuals free of diabetes, and have similar strengths of association by baseline blood pressure, by age, by sex and by BMI.
5. A 20 mm Hg higher systolic blood pressure and a 10 mm Hg higher diastolic blood pressure are associated with a higher risk of cardiovascular disease among individuals with diabetes, and have similar strengths of association by baseline blood pressure.

6. Blood pressure lowering therapy reduces the risk of cardiovascular disease in randomized trials conducted among individuals with diabetes, as well as among diabetic individuals with both high and low baseline blood pressure and in trials conducted in type 2 diabetes which achieved both high and low blood pressure.

The primary observational dataset used in this thesis is the Clinical Practice Research Datalink, a large and comprehensive, routinely collected, electronic health record database. The primary randomized dataset used in this thesis is summary data from all large (greater than 1000 patient-years in each arm) blood pressure lowering trials, identified using a systematic search strategy. The second chapter of this thesis will explain the general methods used for development of both of these datasets. The observational association of blood pressure with risk of AF and AF with risk of cardiovascular disease will be characterized in the third chapter. Although the primary focus of this thesis is on the relationship between blood pressure and risk of cardiovascular disease and diabetes, I examined the relationship between AF and risk of vascular disease to examine the prognostic implications of development of AF. While historically AF has been associated with an elevated risk of stroke, it is unclear whether AF is associated with the development of stroke in a contemporary population with widespread use of cardiovascular risk reducing therapies such as blood pressure lowering therapy and statin therapy. Furthermore, recent evidence has suggested that AF is associated with an elevated risk of non-stroke vascular outcomes.¹⁹ I consequently examined the association of AF with incident vascular disease to clarify the importance of development of AF and, therefore, the potential importance of blood pressure lowering to prevent AF.

The fourth chapter will then examine randomized evidence of the effect of BP lowering on risk of AF, which will be analyzed in the context of the observational

evidence in the previous chapter. The fifth chapter of this thesis will be used to examine the association of blood pressure and risk of diabetes, and will critically examine the association in light of previously reported randomized evidence. The sixth and seventh chapter of this thesis will examine the association of blood pressure with cardiovascular disease in type 2 diabetes. The observational association in the sixth chapter will be used to inform the interpretation of the randomized evidence presented in the seventh chapter. A discussion of all of the results in this thesis is provided in the eight chapter.

1.8. Rationale for this thesis and the methods used

This thesis examines the relationship between blood pressure and risk of AF, diabetes and cardiovascular disease in type 2 diabetes. These topics were chosen due to the clinical and public health importance of these two diseases (detailed in the previous section) and due to uncertainties in the prevention and management of these diseases through blood pressure lowering. Indeed, there is substantial uncertainty on whether blood pressure lowering can be used to prevent AF or new onset diabetes. Furthermore, it is unclear whether blood pressure lowering to lower levels than recommended in current guidelines (SBP < 130 mm Hg) in type 2 diabetes can further reduce the incidence of cardiovascular disease. Clarification of these uncertainties may allow for the implementation of a novel therapeutic approach (blood pressure lowering) for prevention of AF, prevention of new onset diabetes and prevention of cardiovascular disease in type 2 diabetes.

The two methods used in this thesis (an analysis of an observational cohort in CPRD and a meta-analysis of randomized trials) were selected due to their complementary nature. Analysis of CPRD has significant advantages that are not present in a meta-analysis of randomized trials. First, the practices which contribute to

CPRD are representative of the United Kingdom.⁶⁴ Unlike the population of a randomized trial, which is typically healthier than and unrepresentative of the population under investigation⁶⁵, the CPRD population contains individuals from a wide variety of ethnicities and socioeconomic strata, and individuals with a wide variety of baseline medical conditions conditions.⁶⁴ Second, analysis of CPRD allows for longer follow up of participants than is generally feasible in a randomized trial, providing time for the long term sequelae of a disease or outcome to present. Finally, CPRD has a substantially larger sample size (> 4 million individuals) than any randomized trial and will therefore provide substantially greater power for detection of an effect as well as more precise estimates than a randomized trial.

However, use of CPRD has two significant disadvantages. First, unlike in a traditional cohort study, exposures in CPRD are not measured by trained research staff and endpoints in CPRD have not been adjudicated by a committee. Several approaches, detailed in the next chapter are used to deal with this lack of adjudication. Second, and more importantly, analysis of CPRD is not randomized. Individuals with elevated blood pressure will likely differ from individuals with lower blood pressure in ways that are not observed and, therefore, cannot be adjusted for. Consequently, any results from CPRD are likely to be confounded and the causality of any results is unclear.

Meta-analysis of randomized trials, in contrast, can produce causal estimates of the effects of blood pressure lowering due to the presence of randomization. These causal estimates can be compared to estimates from the observational analysis of CPRD. Consistent estimates using both approaches provides confidence that the results are causal, applicable to a general population and are precisely estimated. In contrast, a lack of consistency suggests that observational estimates are confounded or that the

effect of blood pressure lowering differs in the CPRD population than the randomized trial. By using both approaches, and comparing estimates from both approaches, limitations of both approaches can be more easily identified and greater confidence in estimates obtained.

Chapter 2 Methods

2.1 Data sources of cohort for observational analyses

The Clinical Practice Research Datalink (CPRD) is a large electronic health record database suitable for epidemiological research. The database is composed of the records of United Kingdom general practices that use the Vision GP electronic health record system, representing approximately 5% of the UK population.⁶⁴ As of January 1st, 2014, it contained records of fifteen million individuals. CPRD is available with linkages to secondary care (Hospital Episode Statistics), cause specific mortality (Office of National Statistics) and socioeconomic data. The Clinical Practice Research Datalink has been used extensively for observational research, with more than 850 peer-reviewed studies published.⁶⁴ This includes previous high profile epidemiological analyses into the association between blood pressure and cardiovascular disease¹³, diabetes and cardiovascular disease²² and body-mass index and cancer.⁶⁶

Complete ascertainment of outcomes is necessary to accurately estimate absolute risks in observational studies.⁶⁷ Furthermore, if outcome ascertainment is incomplete and ascertainment is associated with the exposure of interest, measures of relative risk will also be biased.⁶⁸ Consequently, a large body of research has attempted to determine the accuracy of case ascertainment in CPRD.^{69,70} Overall, a systematic review of validation studies of CPRD indicated that 89% of cases of any disease identified using CPRD could be confirmed using a validated diagnosis.⁶⁹ However, this proportion varied significantly by disease category. An analysis of atrial fibrillation diagnoses demonstrated atrial fibrillation diagnoses in CPRD to have similar strengths of associations with defined risk factors compared to analyses of atrial fibrillation diagnoses from traditional cohort studies, such as Framingham.⁷¹ An analysis of diabetes diagnoses within CPRD observed that diabetes diagnoses in primary care have

high (99%) positive predictive value. Acute myocardial infarction diagnoses⁷², cerebrovascular disease diagnoses⁷³ and venous thromboembolism diagnoses⁷⁴ in CPRD have been observed to have 93%, 93% and 88% positive predictive value relative to validated cases. In contrast, analyses of rheumatoid arthritis and acute renal failure suggested both outcomes had relatively poor positive predictive value to validated diagnoses (74.4% and 36.9%, respectively).⁷⁰ Thus, it appears that the sensitivity of diagnoses in CPRD depend on the outcome of consideration. Furthermore, differences in positive predictive values for individual outcomes may reflect genuine clinical uncertainties in the diagnoses of those outcomes rather than differences in ascertainment in electronic health records relative to validated diagnoses (that is, there may be no “gold standard” for some outcomes). Prior validation studies for individual outcomes examined in this thesis are provided in Table 2.1.

Table 2.1 Definition and ICD-10 codes of outcomes used in analysis.

	Definition	ICD-10 Codes	Validation in prior studies
<i>Primary outcomes</i>			
Diabetes	Incident diagnosis of or death due to diabetes or prescription of antidiabetic medication	E11 (fatal and non-fatal)	PPV: 98.6% ⁷⁰
Atrial fibrillation	Incident diagnosis of or death due to atrial fibrillation or atrial flutter, no restrictions on type	I48 (fatal and non-fatal)	Similar association with traditional risk factors as from cohort studies. ⁷¹
<i>Secondary outcomes</i>			
Ischemic heart disease	Incident diagnosis of non-fatal myocardial infarction or death due to ischemic heart disease	I20-I25(fatal), I21-I23(non-fatal)	PPV: 92.6% ⁷⁰
Heart failure	Incident diagnosis of or death due to heart failure	I11.0, I13.0, I13.2, I50 (fatal and non-fatal)	PPV: 81.8% ⁷⁵
Unspecified stroke	Incident diagnosis of or death due to stroke without reference to stroke type	I64 (fatal and non-fatal), I67.2, I67.9 (fatal only)	PPV: 92.7% ⁷⁰
Ischemic stroke	Incident diagnosis of or death due to ischemic stroke	I63 (fatal and non-fatal)	NA
Hemorrhagic stroke	Incident diagnosis of or death due to hemorrhagic stroke	I60-I61 (fatal and non-fatal)	NA
Peripheral arterial disease	Incident diagnosis of or death due to peripheral arterial disease	I73.1, I73.8, I73.9, I74.3, I74.4, I74.5 (fatal and non-fatal)	NA
Aortic aneurysm	Incident diagnosis of or death due to aortic aneurysm	I71 (fatal and non-fatal)	NA
Deep vein thrombosis	Incident diagnosis of or death due to deep vein thrombosis	I80-I82 (fatal and non-fatal)	PPV for VTE (combined DVT and PE): 88.2% ⁷⁰
Pulmonary embolism	Incident diagnosis of or death due to pulmonary embolism	I26 (fatal and non-fatal)	
Chronic kidney disease	Incident diagnosis of or death due to stage 3-5 chronic kidney disease	N18, I12, I13, E08.22, E09.22, E10.22, E11.22, E13.22 (fatal and non-fatal)	Similar prevalence in CPRD to national cross-sectional surveys. ⁷⁶
Vascular dementia	Incident diagnosis of or death due to vascular dementia, including concomitant diagnoses of Alzheimer's disease and vascular dementia (i.e. mixed dementias)	F01 (fatal and non-fatal)	PPV: 75% ⁷⁷

NA: Not available

It is important to note that the validation studies reported in Table 2.1 largely report the positive predictive value of diagnoses, not sensitivity. A recent analysis combined myocardial infarction events from four sources (CPRD, HES, ONS and the Myocardial Infarction National Audit Program, a disease specific registry) to examine

the comprehensiveness of each source for ascertainment of myocardial infarction, and thus the sensitivity of a myocardial infarction diagnosis in any of the databases.⁷⁸ 75% of myocardial infarction events from all sources were captured in CPRD, indicating that CPRD is the most comprehensive of all four databases for myocardial infarction and that it captures a large majority of myocardial infarction events. However, this may not necessarily apply to other outcomes (e.g. diabetes).

Consequently, three approaches are used in this thesis to deal with potentially incomplete case ascertainment. First, when participants are eligible for linkage to HES and ONS, three data sources (CPRD, HES and ONS) are used to more comprehensively capture events. Second, only relative risks are presented, which will not be biased by random incomplete case ascertainment (that is, not detecting all outcomes) or random excess case ascertainment (that is, recording incorrect cases as outcomes).⁷⁹ This can be contrasted to absolute risks, which will be affected by random incomplete or excess case ascertainment. However, relative risks will be biased by incomplete case ascertainment that is associated with the exposure (i.e. non-random case ascertainment). Consequently, a number of sensitivity analyses are undertaken (described in section 2.7 and in Chapters 3-7) to demonstrate the robustness of the results to non-random ascertainment and other potential biases. These include meta-analyses of prior cohort studies (to validate overall estimates), multiple imputation of missing covariates, and analyses with restricted populations and outcomes.

2.2 Identification of eligible participants

I aimed to select a cohort of adults, aged 30-90 years, who had a baseline blood pressure measurement. Only certain general practices that meet quality standards defined by CPRD are eligible for inclusion in the CPRD database; there are termed “research standard” general practices. I therefore included all participants who were

registered at a research-standard general practice for at least one year, had at least one BP measurement between 1990 and 2013 (to restrict the analysis to a contemporary population¹³ and minimize cohort effects⁸⁰) and were between the ages of 30 to 90, inclusive (applied to allow for comparisons to meta-analyses of traditional cohort studies¹²), at baseline. I utilized this first BP measurement at a general practice as the exposure (although, as described in section 2.6, I adjusted for regression dilution using serial BP measurements). As per the recommendation of CPRD, I excluded all individuals who did not have sex recorded. I excluded all individuals with a diagnosis of vascular disease (ischemic heart disease, atrial fibrillation, heart failure, stroke, transient ischemic attack, chronic kidney disease, peripheral arterial disease, aortic aneurysm, deep vein thrombosis, pulmonary embolism or vascular dementia) prior to this baseline blood pressure measurement to minimize the risk of confounding and reverse causality, as has been previously performed.¹² A highly sensitive definition of each diagnosis of vascular disease was used for excluding participants, as I wished to exclude all individuals with possible vascular disease (rather than definite vascular disease) to minimize the risk of reverse causality. Specifically, individuals were excluded if they had any prior diagnosis of heart disease (including stable angina), any diagnosis of cerebrovascular disease, any operation related to heart disease or cerebrovascular disease (e.g. percutaneous coronary intervention), and as well as any diagnosis of any of the cardiovascular outcomes provided in Table 2.1 (heart failure, peripheral arterial disease, atrial fibrillation, chronic kidney disease, aortic aneurysm, vascular dementia and venous thromboembolism).

2.3 Identification and classification of disease outcomes, exposures and covariates

Outcomes were identified through three sources: (1) CPRD (primary care), (2) Hospitalization Episode Statistics (secondary care) and (3) Office of National Statistics (cause-specific mortality). Baseline covariates (Table 2.2) were defined using existing algorithms, described below, provided by the Cardiovascular Disease (CVD) Research using Linked Bespoke Studies and Electronic Health Records cohort (CALIBER).⁸¹ Sex, age and socioeconomic status of participants were provided by CPRD and did not require extraction through phenotyping algorithms. Covariates were either identified by clinical diagnosis (e.g. a healthcare worker recording that a participant was a current smoker using a Read code) or by a recorded measurement (e.g. a healthcare worker recording a blood pressure measurement of 120/80 mm Hg). Clinical diagnoses were identified through Read codes, and measurements were identified through entity types, a code used to distinguish between different types of recorded measurements in CPRD.

Table 2.2 Exposure and baseline covariates

Exposure:

- Blood pressure (systolic over diastolic, mm Hg)
-

Baseline covariates

- Sex
 - Age
 - Socioeconomic status (practice level and individual level)
 - Body mass index (kg/m²)
 - Total cholesterol
 - HDL cholesterol
 - Diabetes
 - Antihypertensive therapy
 - Lipid lowering therapy
-

Baseline covariates were chosen from the Framingham risk score.⁸² Socioeconomic status was additionally included to attempt to adjust for potential socioeconomic differences which have previously been shown to influence cardiovascular risk.⁸³

Blood pressure measurements were identified from the CPRD database as measurements with an entity type of 1 (the entity type corresponding to a blood pressure measurement), as in CALIBER. If an individual did not have both a systolic and diastolic blood pressure recorded, the blood pressure measurement was excluded and a later blood pressure measurement with both a systolic and diastolic blood pressure was used, if available. Body mass index measurements identified from the CPRD database using the identifier as an entity type of 13 or 14 (entity types corresponding to body mass index and weight, respectively). If body mass index was directly recorded (as a measurement of kg/m²), this was used.¹³ If it was not recorded, a height and weight measurement within two years of each other were used to derive a body mass index, on the basis that body mass index has little fluctuation over time.⁸⁴ Smoking status was identified using Read codes, with individuals classified as non-smokers, current smokers and ex-smokers, as in previous analyses of CPRD.¹³ HDL cholesterol was identified as either any measurement of entity type 175 (“High density lipoprotein”) or entity type 288 (“Other laboratory tests”) with an associated HDL read code. Total cholesterol was identified as either any measurement of entity type 163 (“Serum cholesterol”) or entity type 288 (“Other laboratory tests”) with an associated total cholesterol read code. Baseline covariates were defined as the closest measurement within two years of the baseline blood pressure measurement for that covariate. If a measurement was not available within two years of the baseline BP measurement, I classified it as missing.

I classified individuals as having diabetes at baseline, if they had been diagnosed with diabetes (ICD codes provided below) or prescribed an antidiabetic drug prior to their baseline BP measurement. Antidiabetic drugs were defined as any

prescriptions from the British National Formulary chapters 6.1.1 (insulins) and 6.1.2 (antidiabetic drugs including sulphonylureas, biguanides and other antidiabetic drugs).

Use of antihypertensive therapy was defined as a prescription of any drugs from any of the following chapters of the British National Formulary (BNF): 2.2.1 thiazides and related diuretics, 2.2.3 potassium-sparing diuretics and aldosterone antagonists, 2.2.4 potassium sparing diuretics with other diuretics, 2.4 beta-adrenoceptor blocking drugs, 2.5 hypertension and heart failure, and 2.6.2 calcium-channel blockers. Use of lipid lowering therapy was defined as prescription of any drug from BNF chapter 2.12 lipid regulating drugs. Use of baseline antihypertensive or lipid lowering therapies was defined as prescription of any drug in the specified chapters on or in the two years prior to the baseline blood pressure lowering date. Use of antihypertensive or lipid lowering therapies during follow up was defined as prescription of any drugs from the specified chapters after the baseline blood pressure lowering date but before censor date.

Read codes for all exposures, covariates and outcomes are available online (https://www.researchgate.net/profile/Connor_Emdin). These are provided online, rather than being included as a supplementary appendix, due to the substantial size of all of the codes (approaching five hundred pages) and so that other researchers who use CPRD can easily download and manipulate the codes in .csv format.

2.4. Adjustment for regression dilution

Measurement error in an exposure variable will bias any association between an exposure and response variable to the null. Termed “regression dilution”, this form of bias has been shown to reduce prior associations between blood pressure and risk of future vascular disease by one-third, for studies of shorter follow up (six years), to two thirds, for studies of longer follow up (twenty-six years).⁸⁵

In order to adjust for regression dilution bias, I adopted an approach used by the Emerging Risk Factors Collaboration (ERFC)⁸⁶ that has been demonstrated in simulations of cohort studies to generate unbiased estimates of measurement-error free coefficients.⁸⁷ Serial blood pressure measurements, after the baseline blood pressure measurement but within the median follow up time, were regressed on the baseline blood pressure measurement. As the majority of individuals have multiple blood pressure measurements after baseline (e.g. an individual may have a blood pressure measurement at one, two and three years), serial blood pressure measurements are clustered at the participant level. Consequently, any model used must account for different numbers of repeated measurements. ERFC has previously used mixed effects models (i.e. hierarchical models). I instead used generalized estimating equations, which account for repeated blood pressure measurements⁸⁸ but have a significantly decreased computational time relative to mixed effects models. The inverse of the coefficient relating the serial blood pressure measurements to the baseline measurement was used as the regression dilution ratio. The regression dilution ratio for SBP varied between 2.1 and 2.4 and the ratio for DBP varied between 2.5 and 2.6, depending on the particular analysis. These are similar to previously reported regression dilution ratios for blood pressure.^{14,85}

In order to adjust hazard ratios for continuous blood pressure (e.g. hazard ratios per 20 mm Hg higher SBP) for regression dilution, I multiplied the unadjusted log hazard ratios by the regression dilution ratio. To adjust blood pressure as a categorical variable for regression dilution (e.g. for graphing floating absolute risks), the mean of each blood pressure category (e.g. 125-135 mm Hg SBP) was “shrunk” towards the overall mean by the inverse of the regression dilution ratio.⁸⁹ For example, if the mean of the lowest blood pressure category was 120 mm Hg, the regression dilution ratio

was 2, and the mean blood pressure was 130, the usual blood pressure of the lowest category would be 125 mm Hg after adjustment. As a result, the range of the usual blood pressure categories is less than half that of the range of the measured blood pressure categories (since all calculated regression dilution ratios were larger than 2).

2.5. Multiple imputation for missing data

Routinely collected electronic health record data often has substantial missing data. For example, some participants may not have a body mass index measurement at baseline, as it was either not measured or recorded by their general practitioner. In cases where data is missing completely at random (i.e. missingness is random and not dependent on either the covariates or outcomes), complete-case analysis (that is, excluding participants who have missing covariates) will give consistent estimates of parameters.⁹⁰ However, if missingness is dependent on the outcome and covariates, complete-case analysis of missing data will result in biased estimates and standard errors.⁹⁰ In contrast, if missingness is dependent on the outcome and covariates, but is not dependent on unobserved variables (conditional on the observed variables), multiple imputation will result in unbiased estimates.⁹¹ Furthermore, even in cases where data is missing completely at random, and both methods are unbiased, multiple imputation will result in more efficient estimates than complete-case analysis.⁹²

In the cohort analysed in this thesis, smoking, body mass index, HDL cholesterol, total cholesterol and socioeconomic status all had missing values (with baseline HDL and total cholesterol missing in more than 50% of participants). Multiple imputation using chained equations, as implemented by the R module “mice”, was used. Multiple imputation using chained equations has been suggested to generate more accurate estimates of coefficients than joint multivariate imputation, in cases where there are missing categorical variables.⁹³ As my cohort contains categorical

variables (e.g. smoking status), I therefore used multiple imputation with chained equations. As in prior analyses of CPRD, five imputations were generated.^{13,66} In order to examine the validity of the imputation, the distribution of imputed values was compared to non-imputed values.

2.6. Models used for time-to-event analysis

As individuals within CPRD are censored due to death, transfer out of a general practice and the end of follow up, the time participants are able to have an event differs among participants. Consequently, use of traditional linear regression would be inappropriate, as time intervals would not be normally distributed (as they are, a minimum, of zero units of time) and because individuals who left the study prior to the end of follow up would have to be excluded. Consequently, the primary model used in the analysis of the observational cohort was the Cox proportional hazards model. This time-to-event model does not make any assumptions of the baseline survival (hazard) function, only requiring that it be multiplicatively related to any included covariate (the proportional hazards assumption). To verify the proportional hazards assumption, Schoenfeld residuals (the covariate value for each individual who has an event minus the expected value of the covariate) were plotted against log time.⁹⁴ If the proportional hazards assumption is valid, Schoenfeld residuals should be independent of time and thus a plot of Schoenfeld residuals should show a random pattern relative to time.

Data within CPRD is clustered at the practice level, as groups of individuals will attend the same general practice. Use of traditional linear regression models may result in biased estimates and standard errors when applied to clustered data⁹⁵, as covariates of interest may be associated with cluster-level factors. For example, individuals treated at a wealthy general practice may have both lower blood pressure, on average, and a lower risk of cardiovascular disease. In order to account for

clustering at the primary-care practice level, Cox models were stratified by practice⁹⁶, as in prior analyses of CPRD.^{13,22} This means that the baseline hazard function was allowed to vary by practice, accounting for clustering at the general practice level.⁹⁶

Baseline covariates were chosen from the Framingham risk score.⁸² Consequently, the primary analysis was adjusted for age, sex, body mass index, smoking status, diabetes, baseline antihypertensive use and baseline lipid lowering use. Socioeconomic status has additionally been shown to influence cardiovascular risk in UK cohorts.⁸³ Consequently, sensitivity analyses adjusting for socioeconomic status were undertaken. To allow for adjustment for regression dilution (described below), only baseline covariates, rather than time-varying covariates, were used. Blood pressure was considered both as a continuous variable (per 20 mm Hg higher SBP and 10 mm Hg higher DBP), to provide an overall estimate of the association of blood pressure with each outcome, and as a categorical variable, which does not assume any shape of the relationship of blood pressure with each outcome and therefore allows for non-linearity (unlike a continuous variable).

2.7. Common sensitivity analyses used to reduce the risk of confounding

Sensitivity analyses applied in the observational studies included in this thesis are described in the individual Chapters of this thesis (Chapters 3, 5 and 6). However, several common sensitivity analyses were undertaken to deal with potential biases applicable to all observational analyses. First, individuals with undiagnosed cardiovascular disease may have both low blood pressure and a high risk of diagnosis of cardiovascular disease. This form of bias, termed “reverse causality”, may confound the observed association between blood pressure and risk of cardiovascular disease. Therefore, I undertook sensitivity analyses excluding the initial two and four years of follow up, to examine if any J-shaped curve between blood pressure and cardiovascular

disease may be influenced by reverse causality. In this sensitivity analysis, any individuals who had an event (e.g. a diagnosis of atrial fibrillation) or any diagnosis of cardiovascular disease (e.g. coronary heart disease) within the first two and four years of follow up were excluded, to minimize the risk of individuals with any undiagnosed cardiovascular disease (not just the event of interest) being included at baseline. Second, individuals above the age of 70 were excluded, to examine whether any observed association was influenced by elderly populations, among whom reverse causality may play a greater role. Third, models were further adjusted for socioeconomic status, to attempt to capture and control for additional confounders such as nutrition that may be strongly associated with socioeconomic status. Fourth, individuals on antihypertensives at baseline were excluded, as antihypertensive therapy may modify the association between blood pressure and risk of cardiovascular disease. Fifth, a sensitivity analysis restricting the analysis to after 2004, when the Quality and Outcomes Framework was introduced⁹⁷, was undertaken. Introduction of the QOF Framework would be expected to improve data quality, potentially reducing the risk of missing case-ascertainment and outcomes. Sixth, analyses using different Read and ICD-10 codes were undertaken (specified in individual chapters), to examine whether results were modified when using a more specific outcome definition. Additional sensitivity analyses used to reduce the risk of confounding specific to individual analyses are detailed in Chapters 3,4 and 6.

2.8. Systematic identification of large-scale randomized trials of blood pressure lowering

I conducted a systematic review of all large blood pressure lowering trials, using the approach recommended by the PRISMA guidelines for meta-analyses of interventional studies.⁹⁸ A previous systematic review and meta-analysis attempted to

identify all blood pressure lowering trials, using the following search terms “anti-hypertensive agents” OR “hypertension” OR “diuretics, thiazide” OR “angiotensin-converting enzyme” OR “receptors, angiotensin/antagonists & inhibitors” OR “tetrazoles” OR “calcium channel blockers” OR “vasodilator agents” OR the names of all BP lowering drugs listed in the *British National Formulary* as keywords or text words or the MESH term “blood pressure/drug effects”.¹⁵ I used this existing search strategy to identify BP lowering trials published on MEDLINE, from January 1st, 1966 to October 28th 2014, restricted to those published in MEDLINE-defined core clinical journals. Restricting the analysis to only one database is unlikely to miss relevant trials as eligible trials were required to be very large (more than one thousand patient years in each arm). I chose to repeat the search from 1966, rather than the publication date of the prior meta-analysis (2007), because the prior meta-analysis excluded randomized trials conducted in chronic kidney disease populations.

The initial search was conducted by an experienced research librarian and no language restrictions were applied. Studies were restricted to those of type “clinical trial” or “controlled clinical trial” or “randomized controlled trial” or “meta-analysis.” Bibliographies of included studies and bibliographies of identified meta-analyses were searched by hand. I included all trials identified in the previous meta-analysis, in addition to randomized trials identified through the new search.

For inclusion, all trials were required to have greater than 1000 patient years of follow-up in each randomized group to minimize risk of bias associated with small trials.⁹⁹ This inclusion criteria is the same as that applied by the Blood Pressure Lowering Treatment Trialists’ Collaboration.¹⁰⁰ Two researchers screened all abstracts identified in the initial search, excluding studies that violated inclusion criteria. Following the initial abstract screen, full texts of all identified studies were acquired.

Two researchers then screened full text studies in duplicate, with differences resolved by consensus.

2.9. Advantages and limitations of methods used

This thesis used two main approaches, a cohort analysis of routinely collected electronic health records and a meta-analysis of randomized blood pressure lowering trials. As detailed in the previous chapter, these two approaches are complementary and provide greater information than either approach on their own. Each of these two approaches comes with specific benefits and limitations (Table 2.4). The primary advantage of the observational cohort analysis of electronic health records is its convenience and very low cost. Unlike a randomized trial or traditional cohort study, study investigators do not need to recruit participants, measure an exposure of interest or follow up participants for an outcome of interest. Indeed, the fact that the data is already collected means that costs are limited to analysis time and, sometimes, an access fee. As a result, analysis of electronic health records can be conducted in a fraction of the time and cost of a traditional cohort study (or even a case-control study).

However, analysis of routinely collected electronic health records comes with two major limitations. First, as an observational analysis, it is unclear if results are biased by confounding or reverse causality. This limitation is present in all traditional observational studies, including case-control studies and traditional (adjudicated) cohort studies and is of substantial concern. Indeed, there are numerous examples of strong associations in observational epidemiology, consistently observed in multiple studies in different populations, that were later discovered to be due to confounding in randomized trials or Mendelian randomization studies.¹⁰¹ Second, unlike a traditional cohort study, exposures are not measured by trained professionals and endpoints are not adjudicated. This concern is of minor importance relative to the risk of

confounding, in my opinion. First, sensitivity analyses using different definitions of endpoints and measurement of exposures can be used to increase confidence in results of analyses of electronic health records. Second, confounding is almost always present and will affect both cohort analyses of electronic health records and traditional cohort studies.¹⁰¹

The major advantage of meta-analysis of randomized trials is that it removes the substantial risk of bias from confounding present in all observational studies. Because of randomization at baseline in meta-analysed trials, any pooled difference in outcomes between two groups can be attributed to the causal effect of the intervention (e.g. blood pressure lowering, in this thesis). Furthermore, meta-analysis of randomized trials is convenient and of low cost, as it uses existing data. However, meta-analysis comes with the substantial disadvantage that it relies upon existing data and randomized trials that test the intervention of interest may not be available. For example, if one is interested in the effect of blood pressure lowering to a target systolic blood pressure <120 mm Hg, meta-analysis of randomized trials will not be a useful approach if no trials that test such an intervention exist.

There are several other approaches that could have been used in this thesis. First, the most direct and reliable approach to test the hypotheses in this thesis would be to conduct a novel randomized trial. For example, to test the hypothesis that blood pressure lowering to an SBP <120 mm Hg reduces the risk of cardiovascular disease in type 2 diabetes, one could randomize ten thousand diabetic individuals into two groups, reduce systolic blood pressure to below 120 mm Hg in one group and follow up participants for an outcome of interest (e.g. major cardiovascular disease). This would allow for a direct test of the intervention of interest. However, conducting a randomized trial has several substantial disadvantages. First, cardiovascular trials often

require follow up of several years.¹⁰² Second, many cardiovascular trials are extremely expensive, costing in the tens to hundreds of millions dollars.¹⁰³ For these two reasons, such an approach was not feasible for this thesis.

Case-control design and traditional cohort design are two approaches that have, historically, been commonly used in observational epidemiology and could also have been used for this thesis. In the case-control study, participants are selected based on the presence of the outcome of interest (e.g. individuals with cardiovascular disease are selected as cases and individuals without cardiovascular disease are selected as controls). Their exposure status in the past (e.g. presence of hypertension one year prior) is then determined through recall or through examination of medical records. This approach is useful when the outcome of interest is rare and it is not feasible to recruit a large enough sample size for a cohort study of the outcome of interest. However, a case-control design has significant disadvantages relative to the approaches used in this thesis. First, it is more costly than a cohort analysis of electronic health records, as participants have to be recruited for the study and their exposure status ascertained. Second, case-control studies are at greater risk of bias due to reverse causality than cohort studies because outcome status is not ascertained at the time of exposure measurement.¹⁰⁴ Consequently, this approach was not used.

In addition to a case-control study, a traditional cohort study could also have been used. This approach is similar to a cohort analysis of electronic health records, with the exception that the exposure, confounding variables and outcome are, typically, ascertained by trained assessors. This has the advantage, relative to a cohort analysis of electronic health records, that measurement error of the exposure and error in outcome ascertainment are reduced. However, this approach has substantial disadvantages. First, conducting a new cohort study requires a substantial period of follow up (often several

years for cardiovascular disease) and requires financial resources for baseline ascertainment and follow up. Second, even when a cohort study has already been conducted and can be analysed without substantial cost, the sample size is often substantially smaller than that of a cohort of electronic health records. For example, while CPRD allowed for analysis of a cohort of 4 million individuals with more than one hundred thousand new onset diabetes events, no other traditional cohort could be identified with more than one hundred individuals that examined new onset diabetes as an outcome.

A novel genetic epidemiology approach, termed Mendelian randomization, has gained favour in observational epidemiology for determination of causal relationships between exposures and outcomes of interest.¹⁰¹ It relies upon the random assortment of genetic variants in a population. If there is a causal relationship between an exposure and outcome of interest, a genetic variant that increases levels of an exposure of interest should also cause the outcome. For example, if elevated blood pressure causes coronary heart disease, a variant that increases blood pressure should also increase the risk of coronary heart disease. Because genetic variants are randomly assigned at birth within a population, confounding and reverse causality cannot bias estimates, a significant advantage over either a traditional cohort study or a cohort analysis of electronic health records. However, this approach can be biased by pleiotropy, that is, a genetic variant affecting risk of an outcome through a different pathway than the one of interest. For example, if a genetic variant increases both high density lipoprotein cholesterol and coronary heart disease, but increases risk of coronary heart disease through an unobserved inflammatory pathway, high density lipoprotein cholesterol may be incorrectly concluded to cause coronary heart disease. An additional limitation is the much greater sample sizes required for Mendelian randomization studies than

traditional cohort studies, as genetic variants typically only explain a small proportion of variance in the exposure of interest. Despite these limitations, the lack of bias from confounding and reverse causality in Mendelian randomization studies offers an advantage over traditional observational approaches.¹⁰¹ Although I did not use a Mendelian randomization approach, I discuss the changes that I would make to this thesis if I were to repeat this DPhil, including use of Mendelian randomization, in section 8.8 of the discussion.

Table 2.4 Advantages and limitations of methods used.

Method	Description	Advantages	Limitations
<i>Approaches used in this thesis</i>			
Observational cohort study using electronic health records	Routinely collected electronic health records are used to define the exposure of interest (e.g. blood pressure measured by a healthcare provider), an outcome of interest (e.g. diagnosis of myocardial infarction by a primary care physician) and potential confounders (e.g. BMI measured by a health care provider). These records are then analysed as in a traditional cohort study, with the association between the exposure and outcome calculated after adjustment for potential confounders.	• Convenient: Researchers do not need to establish new cohorts themselves and can use existing data. • Very low cost: As data is already collected, researchers often only need to pay an access fee or no fee at all.	• Observational estimates: As an observational analysis, estimates may be biased by confounding and reverse causality. • Lack of adjudication: Unlike in a traditional cohort study, which typically uses standardized measurement and adjudication techniques, exposures and outcomes in an analysis of electronic health records may be more likely to be misclassified.
Meta-analysis of randomized trials	Measures of relative risk for an intervention of interest (e.g. blood pressure lowering in type 2 diabetic populations) are collected from a systematic search for randomized trials in the literature or from individual level data. These measures are then pooled using a statistical model (e.g. inverse variance weighted fixed effects meta-analysis) to derive an overall estimate for the effect of the intervention in a given population.	• Causal estimates: Unlike an observational approach, differences in the outcome can be reliably attributed to the intervention due to randomization present at baseline. • Convenience: Unlike conducting a new randomized trial, meta-analyses of existing randomized trials rely on existing data and are therefore relatively easy to conduct.	• Potential lack of data: Randomized trials of the intervention of interest (e.g. intensive blood pressure lowering to SBP < 120 mm Hg) may not exist or may be underpowered.

<i>Other approaches</i>			
Case-control study	Individuals are selected based on their outcome status (e.g. a cases would have coronary artery disease present, a control would have coronary artery disease absent) and their historical exposure status (e.g. blood pressure) is collected from records or from recall.	• Convenient: More convenient than a randomized trial or traditional cohort study as investigators do not need to randomized participants or follow them up. • Low cost: Lower cost than a cohort study due to the lack of a need for follow up. • Useful for rare outcomes: Can select rare outcomes and compare their exposure status in cases where a cohort study would not be feasible to collect adequate numbers (e.g. an outcome which has a prevalence of one in a million)	• Observational estimates: As an observational analysis, estimates may be biased by confounding and reverse causality. • Reverse causality: Reverse causality is a greater concern in case-control studies than cohort studies, as participants are not ascertained at baseline to ensure they lack the outcome of interest.
Observational cohort study using adjudicated endpoints (traditional cohort study)	Individuals are sampled from a population and their exposure measured at baseline (e.g. blood pressure measured). Individuals are then followed up for the outcome of interest.	• Relative convenience: More convenient that a randomized trial as investigators do not have to randomize the population. • Lower cost: Lower cost than a randomized trial due to a lack of randomization and intervention.	• Observational estimates: As an observational analysis, estimates may be biased by confounding and reverse causality.

Mendelian randomization study	A genetic variant or collection of variants that affect an exposure of interest (e.g. blood pressure) are genotyped in a population of interest. The effect of these variants on the outcome of interest (e.g. coronary heart disease) is then calculated in the same population, in a different population or, more commonly recently, in summary statistics from a meta-analysis of genome wide association studies.	• Causal estimates: Because genetic variants are assigned at birth and are randomly assorted in a population, the effect of the genetic variant on the outcome of interest is causal.	• Pleiotropy: If the variant affects the outcome of interest through a pathway independent of the exposure, this effect can be incorrectly attributed as a causal effect of the exposure on the outcome. For example, if a genetic variant increases cholesterol and increase risk of coronary heart disease through a pro-inflammatory pathway, cholesterol may be interpreted as causing coronary heart disease. • Lack of power: Because current genetic variants often only explain a small proportion of the exposure of interest, sample sizes have to be significantly larger (often more than ten times larger) than a traditional cohort study to observe a significant effect.
Randomized trial	Individuals are randomized into two or more groups and the exposure of interest modified in one or more groups. For example, individuals may be randomized into two groups, and the blood pressure of one group reduced by 10 mm Hg. Individuals are then followed up over a long period for an outcome of interest.	• Causal estimates: Because individuals are randomized, observed and unobserved baseline differences between the two groups are minimized (at sufficiently large sample sizes). Differences in the outcome of interest can then be attributed to the intervention.	• Cost: Randomized trials can be extremely expensive to conduct, due to the cost of randomization, providing the intervention and more detailed follow up due to ethical concerns. • Time: Randomized trials often require several years to conduct, both due to planning and follow up.

Chapter 3 Association of blood pressure with risk of atrial fibrillation: an observational analysis of 4.3 million adults

3.1 Introduction

Atrial fibrillation is the most common cardiac arrhythmia and poses an increasing burden of disease worldwide.^{24,105} Atrial fibrillation was associated with five times the risk of stroke in analyses of the Framingham cohort,^{17,106} and it is also associated with a reduced quality of life.¹⁰⁷ Despite broader usage of anticoagulant therapy for the prevention of stroke¹⁰⁸, the condition remains associated with an increased risk of death.¹⁸

Elevated blood pressure is a risk factor for incident atrial fibrillation. In an analysis of 4731 individuals free of atrial fibrillation, hypertension, defined as provision of antihypertensive medication or a systolic blood pressure of 160 mm Hg or greater, was associated with a 50% higher risk of incident atrial fibrillation in men and a 40% higher risk in women.³¹ In an analysis of 34 221 women and 644 incident atrial fibrillation events in the Women's Health Study randomised trial, 20 mm Hg higher systolic blood pressure was associated with a 35% higher risk of atrial fibrillation (HR 1.35 CI 1.19, 1.51).³⁵ In an analysis of 4731 individuals from the Framingham cohort with 562 atrial fibrillation events, hypertension was associated with an increased risk of incident atrial fibrillation in men and women (OR 1.5 CI 1.2, 2.0 and OR 1.4 CI 1.1, 1.8, respectively).³¹ However, it is unclear if the relationship between blood pressure and atrial fibrillation is consistent among different participant subpopulations. Previous cohort studies (Table 3.1) have not been sufficiently large to permit reliable investigation of the relationship between blood pressure and atrial fibrillation by important patient characteristics, including baseline blood pressure, age, sex and body mass index. Prior landmark analyses from Framingham³¹ and the Cardiovascular

Health Study²⁹ did not attempt to detect interactions by patient characteristics. While no interaction between blood pressure and age was observed in the Women's Health Study randomised trial, this analysis only included 644 incident atrial fibrillation events, making it underpowered to detect any potential interaction.³⁵ It is thus unclear if atrial fibrillation is modified in its association with blood pressure by age, sex, body mass index or other characteristics.

Table 3.1 Previous major studies on the relationship between blood pressure and incident atrial fibrillation and the relationship between atrial fibrillation and vascular risk.

Study	Size	Design	Results	Interpretation
Blood pressure as a risk factor for atrial fibrillation				
Emdin et al. (Current study)	4.3 million individuals/128468 atrial fibrillation events	Cohort study using linked electronic health records	20 mm Hg higher SBP was associated with HR 1.21 (CI 1.19, 1.22) risk of atrial fibrillation, which declined from HR 1.91 (CI 1.75, 2.09) at age 30-40 to HR 1.01 (CI 0.97, 1.04) at age 81-90.	Higher blood pressure associated with higher risk of atrial fibrillation; strength of association declines with age.
Conen et al. ³⁵	34 221 women/644 atrial fibrillation events	Cohort study (Women's Health Study)	10 mm Hg higher SBP associated with HR 1.16 (CI 1.09, 1.23) for atrial fibrillation. Elevated BP in non-hypertensive range associated with increased risk atrial fibrillation.	Higher blood pressure associated with increased risk of atrial fibrillation, even in non-hypertensive range.
Kannel et al. ¹⁰⁹	5191 individuals/98 atrial fibrillation events	Cohort study (Framingham)	Hypertension (SBP $\geq$ 160/95 mm Hg or antihypertensives) associated with non-significant risk ratio of 1.6 in men and 1.8 in women.	Hypertension is not significantly associated with risk of atrial fibrillation.
Krahn et al. ¹¹⁰	3983 individuals/299 atrial fibrillation events	Cohort study (Manitoba Follow-up Study)	Hypertension associated with HR 1.42 (CI 1.10, 1.84) risk of atrial fibrillation after multivariable adjustment.	Hypertension is associated with increased risk of atrial fibrillation.
Nymer et al. ¹¹¹	22 815 individuals/822 atrial fibrillation events	Cohort study (The Tromsø Study) using linked electronic health records	Hypertension was defined as systolic blood pressure (SBP) $\geq$ 140 mmHg <i>or</i> diastolic blood pressure (DBP) $\geq$ 90 mmHg <i>or</i> use of antihypertensive treatment associated with significant risk of 1.98 in women and 1.4 in men	Elevated systolic blood pressure associated with increased risk of atrial fibrillation.
Psaty et al. ²⁹	5201 individuals/304 atrial fibrillation events	Cohort study (Cardiovascular Health Study)	10 mm Hg higher SBP was associated with HR 1.11 (CI 1.05, 1.18) for risk of atrial fibrillation.	Higher SBP associated with higher risk of atrial fibrillation.
Wilhelmsen et al. ¹¹²	7495/754 atrial fibrillation events	Cohort study, hospitalization for atrial fibrillation as primary outcome	Relative to SBP $\leq$ 145 mm Hg, SBP 145-175 and SBP $>$ 175 mm Hg associated with OR 1.30 (CI 1.11, 1.54) and OR 1.37 (CI 1.09, 1.74) respectively.	Elevated systolic blood pressure associated with increased risk of atrial fibrillation.
Atrial fibrillation as a risk factor for vascular events				
Emdin et al. (Current study)	4.3 million individuals/421 084	Cohort study using linked electronic	Baseline atrial fibrillation associated with increased risk of ischemic stroke,	Atrial fibrillation is a risk factor for

study)	vascular events	health records	hemorrhagic stroke, stroke unspecified, ischemic heart disease, heart failure, peripheral arterial disease, chronic kidney disease vascular dementia but not aortic aneurysm. Significantly greater risk of ischemic stroke, stroke unspecified, ischemic heart disease, heart failure, peripheral arterial disease and chronic kidney disease observed among individuals who did not take antithrombotic therapy at baseline.	a range of vascular events.
Bansal et al. 2013 ¹¹³	206 229 individuals/6850 ESRD events	Cohort study using administrative data (Kaiser Permanente)	Among patients with already developed CKD, atrial fibrillation associated with HR 1.67 (CI 1.46, 1.91) for progression of ESRD.	Atrial fibrillation a significant risk factor for progression of CKD to ESRD.
Conen et al. ¹¹⁴	34 772 participants/309 cardiovascular deaths	Cohort study (Women's Health Study)	After exclusion of early deaths, incident atrial fibrillation associated with increased risk of stroke and heart failure, but not myocardial infarction.	Atrial fibrillation is a risk factor for stroke, heart failure, but not myocardial infarction.
Chen et al. ²⁰	15 439 participants/1375 coronary heart disease fatal events	Cohort study (Atherosclerosis Risk in Communities Study and Cardiovascular Health Study)	Incident atrial fibrillation associated with an increased risk of sudden cardiac death and non-sudden cardiac death.	Atrial fibrillation a risk factor for coronary heart disease death.
Soliman et al. ¹⁹	23 928 participants/648 incident myocardial infarction events	Cohort study (Reasons for Geographic and Racial Differences in Stroke)	Baseline atrial fibrillation associated with HR 1.96 (CI 1.52, 2.52) for incident myocardial infarction after socio-demographic adjustment.	Atrial fibrillation is a risk factor for myocardial infarction.
Watanabe et al. 2013 ¹¹⁵	235 818 individuals/7791 CKD events	Cohort study (Niigata Preventive Medicine Study)	Among patients without CKD, atrial fibrillation associated with HR 1.80 (CI 1.54, 2.10) for development of CKD.	Atrial fibrillation a significant risk for incident CKD.
Wolf et al. 1978 ¹¹⁶	5184/345 strokes	Cohort study (Framingham)	Atrial fibrillation associated with 5.6 fold increase in rate of stroke ($p<0.01$).	Atrial fibrillation is a significant risk factor for stroke.
Wolf et al. 1991 ¹⁷	5070 individuals/527 strokes	Cohort study (Framingham)	Atrial fibrillation associated with near five fold excess risk of stroke; relative risk increases from 2.6 ($p<0.001$) at age 60-69 to 4.5 ($p<0.001$) at age 80-89.	Atrial fibrillation is a significant risk factor for stroke, association increases with age.

To clarify these existing uncertainties, I sought to reliably determine the association between blood pressure and atrial fibrillation, by baseline blood pressure, age, sex and body mass index. I further examined whether atrial fibrillation was associated with the risk of nine different vascular events, in a secondary analysis, to examine the prognostic implication of atrial fibrillation in a contemporary population.

3.2 Methods

3.2.1 Participants, exposures and endpoints

I defined participants and baseline covariates as described in the general methods section. I classified individuals as having atrial fibrillation at baseline, if they had been diagnosed with atrial fibrillation (either in primary care or secondary care) prior to the baseline blood pressure measurement. I excluded all individuals with a prior diagnosis of vascular disease to minimize the risk of confounding and reverse causality (that is, I excluded individuals with pre-existing ischemic heart disease, stroke, heart failure, peripheral arterial disease, chronic kidney disease or vascular dementia). From the primary analysis (the determination of the association of blood pressure with incident atrial fibrillation), I excluded all individuals with baseline atrial fibrillation. I included these participants in the secondary analysis, which examined whether baseline atrial fibrillation is associated with vascular events.

In addition to determining whether patients used antihypertensive therapy and lipid lowering therapy at baseline, I also determined whether participants used antithrombotic agents at baseline and during follow up for the secondary analysis. This is because antithrombotic agents may modify the association between baseline atrial fibrillation and risk of vascular events. Participants were defined as using anticoagulant therapy (BNF chapter 2.8) or antiplatelet therapy (BNF chapter 2.9) at baseline if they were prescribed an anticoagulant or antiplatelet agent within three years of the baseline blood pressure measurement.

For the analysis of the association between blood pressure and atrial fibrillation, my primary endpoint was incidence of atrial fibrillation (ICD-10 code I48), either in primary care, secondary care (hospitalization) or through death. Previous research has demonstrated atrial fibrillation diagnoses in CPRD to be highly reliable¹¹⁷

and to have similar associations with risk factors as traditional cohort studies.⁷¹

Previous research has also demonstrated endpoints in CPRD to have high specificity.⁷⁰

Participants were censored at the earliest of an occurrence of a presentation of atrial fibrillation, transfer out of practice, death or last collection date of practice.

For the secondary analysis of the association between atrial fibrillation and vascular event, my primary endpoint was the composite of nine vascular events: ischemic stroke, haemorrhagic stroke, stroke unspecified, ischemic heart disease (a composite of fatal ischemic heart disease and non-fatal myocardial infarction), heart failure, chronic kidney disease, peripheral arterial disease, aortic aneurysm and vascular dementia. I also examined the association of each vascular event individually. I examined both fatal vascular events and combined fatal and non-fatal vascular events. Participants were censored as above.

3.2.2 Statistical analysis

To examine blood pressure as a risk factor for incident atrial fibrillation, I excluded all individuals who were diagnosed with atrial fibrillation before the baseline blood pressure measurement. Cox proportional hazard models, stratified by practice, were used with blood pressure taken both as a continuous variable (per 20/10 mm Hg higher systolic blood pressure/diastolic blood pressure) and as a categorical variable (in 10 mmHg groups for systolic blood pressure, ranging from ≤ 95 mm Hg to > 195 mm Hg). I estimated 95% confidence intervals for categorical blood pressure using floating absolute risks.¹² The primary model was adjusted for age, sex, BMI, smoking status, and diabetes.

To examine whether atrial fibrillation was a risk factor for vascular events I similarly used stratified Cox models. I examined whether there was an interaction between baseline atrial fibrillation and baseline usage of antithrombotic therapy (either

anticoagulant therapy or antiplatelet therapy).^{118,119} The primary model was adjusted for sex, age, BMI, smoking status, diabetes, baseline anticoagulant usage, baseline antiplatelet usage, baseline antihypertensive usage and baseline lipid lowering usage.

In order to correct for regression dilution⁸⁵, serial blood pressure measurements within the median follow up [available for 3248391 (76%) participants], were used to estimate a regression dilution ratio, as described in the general methods section.

Attenuation factors of 2.2 for systolic blood pressure (systolic blood pressure) and 2.6 for diastolic blood pressure (diastolic blood pressure) were calculated.

Multiple imputation using chained equations was used to impute missing covariates, as described in the general methods section. Five imputations were generated.

3.2.3 Sensitivity analyses

In my assessment of the association of usual blood pressure with risk of atrial fibrillation, I conducted six sensitivity analyses. First, I adjusted for total cholesterol and HDL cholesterol. Second, I further adjusted for the period of the baseline blood pressure measurement (1990-1994, 1995-1999, 2000-2004, 2005-2009, 2010-2013), to adjust for potential cohort effects, and socioeconomic status, to adjust for potential confounders associated with socioeconomic status. Third and fourth, I excluded the first two years and four years of follow up (excluding any individual who developed atrial fibrillation, cardiovascular disease or was censored), to examine the possibility that my results were influenced by reverse causality (e.g. undiagnosed atrial fibrillation or other undiagnosed cardiovascular disease causing low blood pressure). Fifth, for the analysis of the association between blood pressure and atrial fibrillation, I excluded individuals prescribed blood pressure lowering drugs at baseline, which may modify the association between baseline blood pressure and incident atrial fibrillation. Sixth, I

restricted the analysis to after 2004, at which the Quality and Outcomes Framework was introduced and coding of events may be expected to improve.⁹⁷ Seventh, for the analysis of the association of baseline AF with incident vascular events, I conducted an analysis stratified by use of antithrombotic therapy at baseline (defined as prescription of antiplatelet therapy or anticoagulant therapy).

3.3 Results

3.3.1 Characteristics of participants

4 301 349 individuals qualified for the primary analysis (blood pressure and incident atrial fibrillation) and the secondary analysis (baseline atrial fibrillation and incident vascular disease, Figure 3.1). 32 155 (0.7%) individuals had a prior diagnosis of atrial fibrillation and were excluded from the primary analysis. The median follow up was 6.9 years (inter-quartile interval IQI 3.0, 11.2); a further 128 468 (3.0%) individuals developed atrial fibrillation during this period. Of the 4 269 194 individuals included in the primary analysis, the median age was 46 (interquartile interval IQI 36, 59), while 55.6% of participants were women. The median body mass index (prior to imputation) was 25.8 (IQI 23.0, 29.3), with increasing body mass index with increasing baseline blood pressure (median BMI of 24.3 among individuals with baseline blood pressure ≤ 120 mm Hg vs. median BMI of 27.4 among individuals with baseline blood pressure >140 mm Hg). 28% of participants were current smokers while 17.8% of participants were previous smokers. 10.1% of participants were prescribed an antihypertensive at baseline, while 1.9% of participants were prescribed a lipid lowering drug at baseline. 3.2% of participants had a prior diagnosis of diabetes at baseline, increasing from 1.8% among individuals with a baseline systolic blood pressure ≤ 120 mm Hg to 4.9% among individuals with a baseline systolic blood pressure >140 mm Hg.

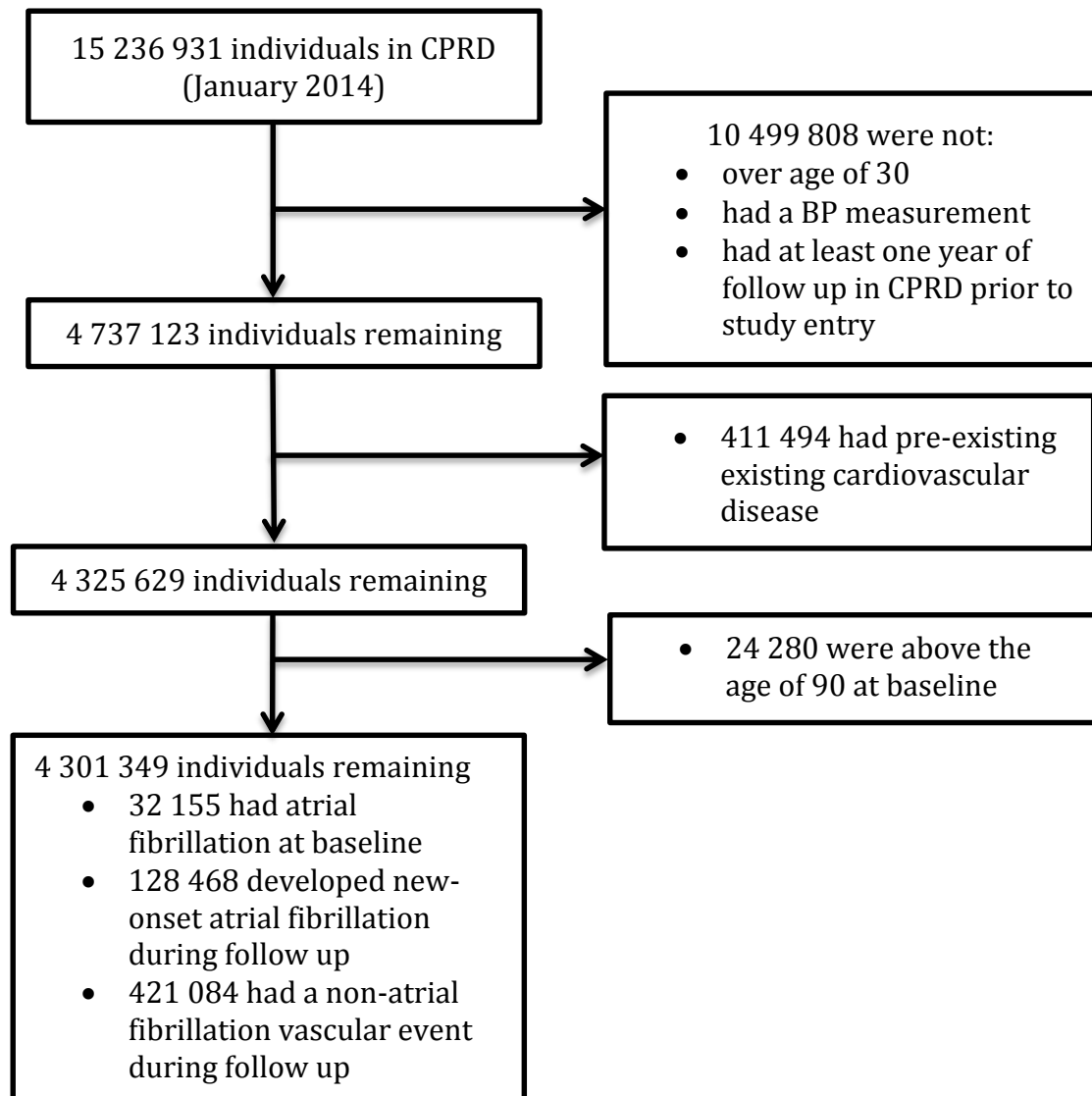


Figure 3.1 Flowchart of cohort identification.

Table 3.2 Characteristics of participants included in the analysis of the association between blood pressure and atrial fibrillation.

	≤120 mm Hg	121-140 mm Hg	>140 mm Hg	Overall
N	1 500 753	1 595 134	1 173 307	4 269 194
Age at Baseline (IQI)	39 (33, 48)	47 (37, 58)	59 (48, 70)	46 (36, 59)
Women	996 546 (66.4%)	794 752 (49.8%)	582 941 (49.7%)	2374239 (55.6%)
BMI (IQI)	24.3 (21.9, 27.4)	26.3 (23.5, 29.7)	27.4 (24.4, 31.1)	25.8 (23.0, 29.3)
Smoking Status				
Current Smoker	375 663 (30.0%)	367 380 (28.2%)	227 331 (24.8%)	970 374 (28.0%)
Never Smoker	683 906 (54.7%)	702 436 (53.9%)	497 242 (54.3%)	1883584 (54.3%)
Ex Smoker	190 863 (15.3%)	234 344 (18.0%)	191 047 (20.9%)	616 254 (17.8%)
Cholesterol				
Total (IQI)	5.2 (4.5, 6.0)	5.4 (4.7, 6.2)	5.6 (4.9, 6.4)	5.5 (4.7, 6.2)
HDL (IQI)	1.4 (1.1, 1.7)	1.3 (1.1, 1.6)	1.4 (1.1, 1.6)	1.4 (1.1, 1.6)
Most deprived quintile	281 413 (18.8%)	297 558 (18.7%)	229 012 (19.5%)	807 983 (18.9%)
Antihypertensive at baseline	57 573 (3.8%)	138 674 (8.7%)	234 798 (20.0%)	431 045 (10.1%)
Antihypertensive during follow up	201 578 (13.4%)	410 998 (25.8%)	623 419 (53.1%)	1235995 (29.0%)
Lipid lowering at baseline	14 034 (0.9%)	34 419 (2.2%)	33578 (2.9%)	82 031 (1.9%)
Lipid lowering during follow up	110 389 (7.4%)	243 492 (15.3%)	311 998 (26.6%)	665 879 (15.6%)
Diabetes at baseline	26 412 (1.8%)	53 484 (3.4%)	57 572 (4.9%)	137 468 (3.2%)

IQI refers to interquartile interval (25th percentile, 75th percentile). Proportion of variables missing: BMI (30.5%), smoking status (18.7%), total cholesterol (73.0%), HDL cholesterol (80.1%).

Absolute rates of incident atrial fibrillation diagnoses per 1000 patient years by age and sex are provided (Table 3.3). Absolute rates increased with increasing age, from 0.6 diagnoses per 1000 patient years among men aged 30-40 to 28.4 per 1000 patient years among men aged 81-90, and from 0.2 per 1000 patient years among women aged 30-40 to 23.8 per 1000 patient years among women aged 81-90. Absolute rates of atrial fibrillation were higher among men than women.

Table 3.3 Incident atrial fibrillation diagnoses (per 1000 patient years) by age and sex.

Age	Male	Female
30-40	0.6	0.2
41-50	1.6	0.8
51-60	4.4	2.5
61-70	10.1	7.2
71-80	19.0	15.1
81-90	28.4	23.8

3.3.2 Association of usual blood pressure with the risk of atrial fibrillation

When analysed as a categorical variable, usual systolic blood pressure was positively related to the risk of atrial fibrillation. There was no evidence of a nadir in the age range 30-60 years, from 110 mm Hg to 170 mm Hg (Figure 3.2). At ages 60 to 90 years, systolic blood pressure was positively related to the risk of atrial fibrillation. However, the association appeared to plateau at approximately 120 mm Hg. When analyzed as a continuous variable, a 20 mm Hg higher systolic blood pressure was associated with a near doubling in risk of atrial fibrillation at age 30-40 years (HR 1.91 CI 1.75, 2.09). However, the strength of the association declined with age such that a 20 mm Hg higher systolic blood pressure was associated with a 42% higher risk of atrial fibrillation at age 51-60 and was not associated with risk of atrial fibrillation at ages 81-90 years (Figure 3.3). However, due to the increasing baseline absolute risk of atrial fibrillation with increasing age, the absolute risk of atrial fibrillation associated with a 20 mm Hg higher systolic blood pressure increased until approximately age 51-60.

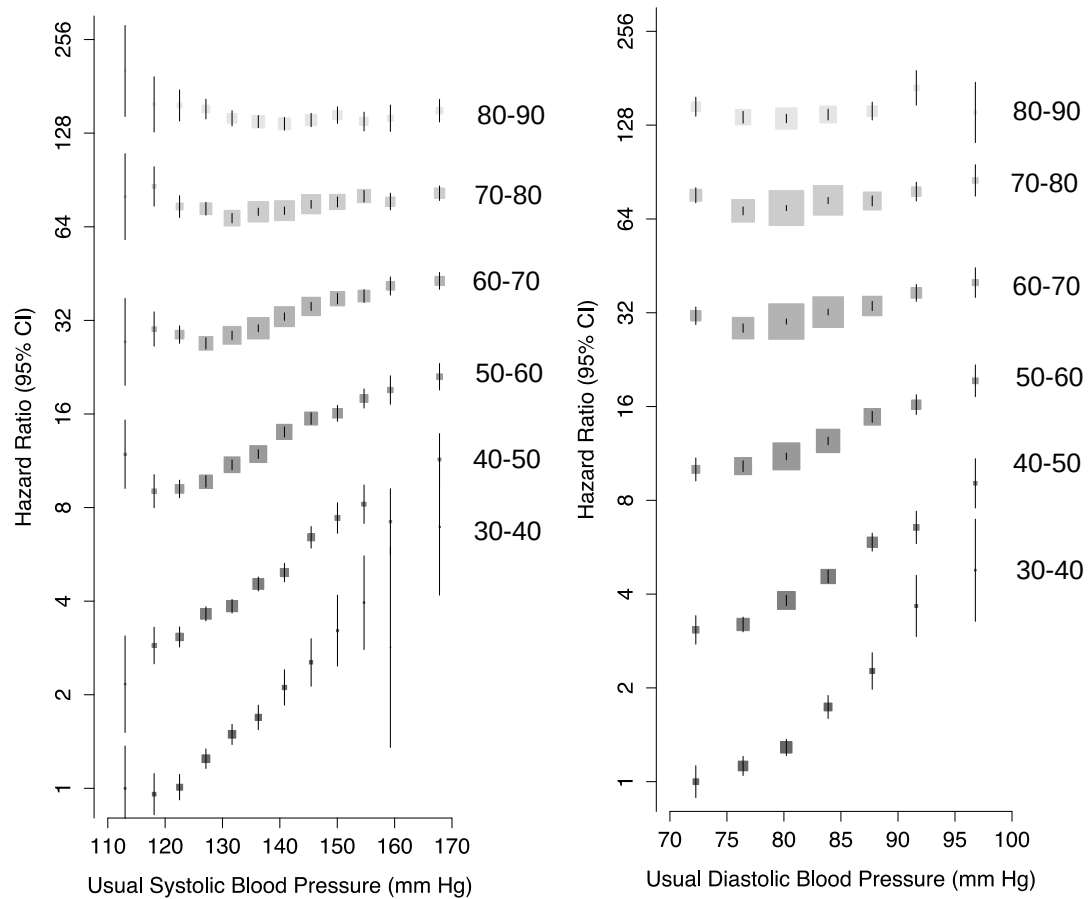


Figure 3.2 Adjusted hazard ratios of systolic blood pressure and diastolic blood pressure for incident atrial fibrillation by age. Adjustments were for BMI, smoking status, sex, baseline diabetes and the interaction between age as a categorical variable and systolic and diastolic blood pressures as categorical variables, respectively (plotted). Confidence intervals are displayed as floating absolute risks with no reference category. Area of each square is proportional to the inverse variance of the estimate.

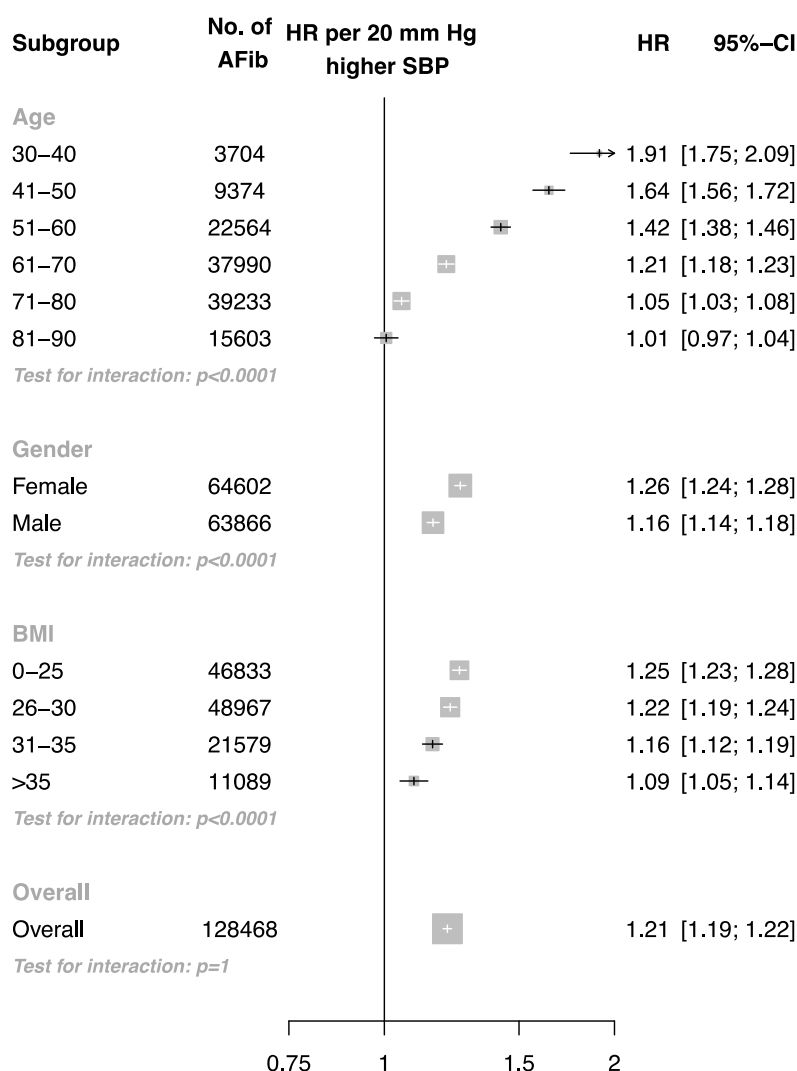


Figure 3.3 Adjusted hazard ratios of a 20 mm Hg higher usual systolic blood pressure for atrial fibrillation by patient subgroup. Adjustments were for age, BMI, smoking status, sex and baseline diabetes. For subgroups of age, adjustment was also for age category and the interaction between systolic blood pressure and age category (plotted). For subgroups of sex, adjustment was also for the interaction between sex and systolic blood pressure (plotted). For subgroups of BMI, adjustments were also for BMI category and the interaction between systolic blood pressure and BMI category (plotted). Area of each square is proportional to the inverse variance of the estimate.

Risk of atrial fibrillation was modestly greater in women than men per 20 mm Hg higher systolic blood pressure (HR 1.26 CI 1.24, 1.28 vs. HR 1.16 CI 1.14, 1.18 per 20 mm Hg higher systolic blood pressure, respectively). There was evidence of decline in the association by body mass index, with 20 mm Hg higher systolic blood pressure associated with a 25% higher risk of atrial fibrillation at a body mass index 0-25 kg/m²

and a 9% higher risk of atrial fibrillation at a body mass index > 35 $0-25 \text{ kg/m}^2$ (p interaction < 0.0001). Overall, per 20 mm Hg higher usual systolic blood pressure, risk of atrial fibrillation increased by 21% (HR 1.21 CI 1.19, 1.22).

When analysed as a categorical variable, usual diastolic blood pressure was similarly associated with risk of atrial fibrillation, with no evidence of a nadir from 70 mm Hg to 100 mm Hg at ages 30-60 and evidence of a plateau at 75 mm Hg at ages 60-90 (Figure 3.2). As a continuous variable, 10 mm Hg higher usual diastolic blood pressure had a similar strength of association with risk of atrial fibrillation as a 20 mm Hg higher usual systolic blood pressure (HR 1.21 CI 1.19, 1.23, Figure 3.4). As with systolic blood pressure, risk of atrial fibrillation per 10 mm Hg higher usual diastolic blood pressure declined with increasing age, from a 91% higher risk at age 30-40 (HR 1.91 CI 1.75, 2.09) to a 21% higher risk at age 61-70 (HR 1.21 CI 1.18, 1.23). However, unlike usual systolic blood pressure, a 10 mm Hg higher usual diastolic blood pressure was still positively associated with the risk of atrial fibrillation at ages 81-90 years (CI 1.06 HR 1.02, 1.11). Risk of atrial fibrillation per 10 mm Hg higher usual diastolic blood pressure was modestly greater in men than in women (HR 1.24 CI 1.21, 1.26 vs. HR 1.19 CI 1.16, 1.21, respectively). An interaction by BMI was also observed, with declining risk of atrial fibrillation with increasing BMI (HR 1.25 CI 1.23, 1.28 at body mass index $< 25 \text{ kg/m}^2$ and HR 1.09 CI 1.50, 1.14 at body mass index $> 35 \text{ kg/m}^2$ per 10 mm Hg higher usual diastolic blood pressure; p interaction < 0.0001).

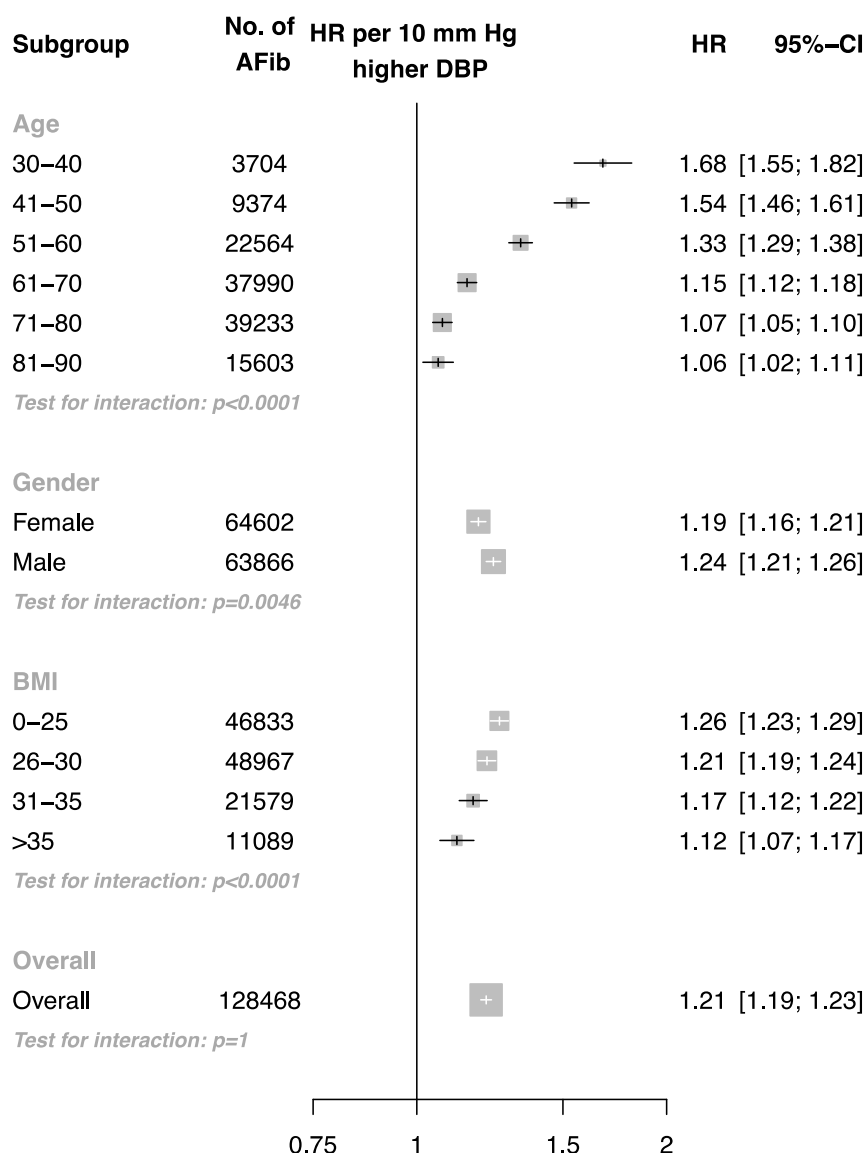


Figure 3.4 Adjusted hazard ratios of a 10 mm Hg higher usual diastolic blood pressure for atrial fibrillation by patient subgroup. Adjustments were for age, BMI, smoking status, sex and baseline diabetes. Further adjustments were for age category and the interaction between systolic blood pressure and age category (plotted, for subgroup Age), the interaction between sex and systolic blood pressure (plotted, for subgroup Sex), and BMI category and the interaction between systolic blood pressure and BMI category (plotted, for subgroup BMI). Area of each square is proportional to the inverse variance of the estimate.

3.3.3 Sensitivity analyses

Estimates were highly consistent with a number of different sensitivity analyses (Figures 3.5-3.10). After adjustment for total and HDL cholesterol, a 20 mm Hg higher usual systolic blood pressure was associated with a 24% higher risk of incident atrial

fibrillation (HR 1.24 CI 1.22, 1.26; Figure 3.5), with interactions by age and BMI. Additional adjustment for period of blood pressure measurement to control for cohort effects and socioeconomic status had little effect on the overall estimate (HR 1.24 CI 1.22, 1.25; Figure 3.6). Exclusion of two and four years of follow up modestly strengthened the observed association (HR 1.25 CI 1.23, 1.26 and HR 1.27 CI 1.25, 1.29, respectively; Figures 3.7 and 3.8). Exclusion of individuals on antihypertensive therapy at baseline and restriction of the analysis to after 2004, when the Quality and Outcomes Framework was introduced, had little effect on the overall estimate (Figures 3.9-3.10).

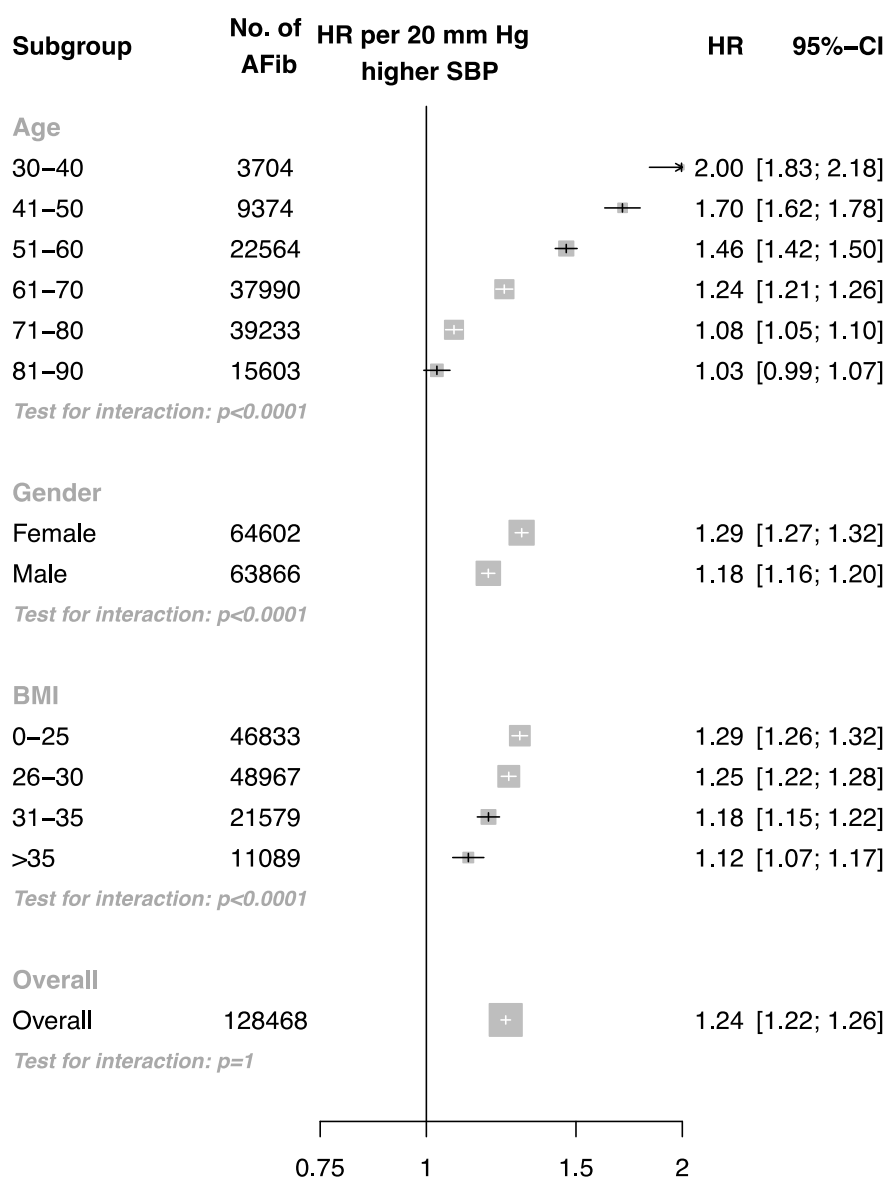


Figure 3.5 Adjusted hazard ratios of a 20 mm Hg higher usual systolic blood pressure for atrial fibrillation by patient subgroup after adjustment for cholesterol. Adjustments were for age, BMI, smoking status, sex, baseline diabetes, total cholesterol and HDL cholesterol. Further adjustments were for age category and the interaction between systolic blood pressure and age category (plotted, for subgroup Age), the interaction between sex and systolic blood pressure (plotted, for subgroup Sex), and BMI category and the interaction between systolic blood pressure and BMI category (plotted, for subgroup BMI). Area of each square is proportional to the inverse variance of the estimate.

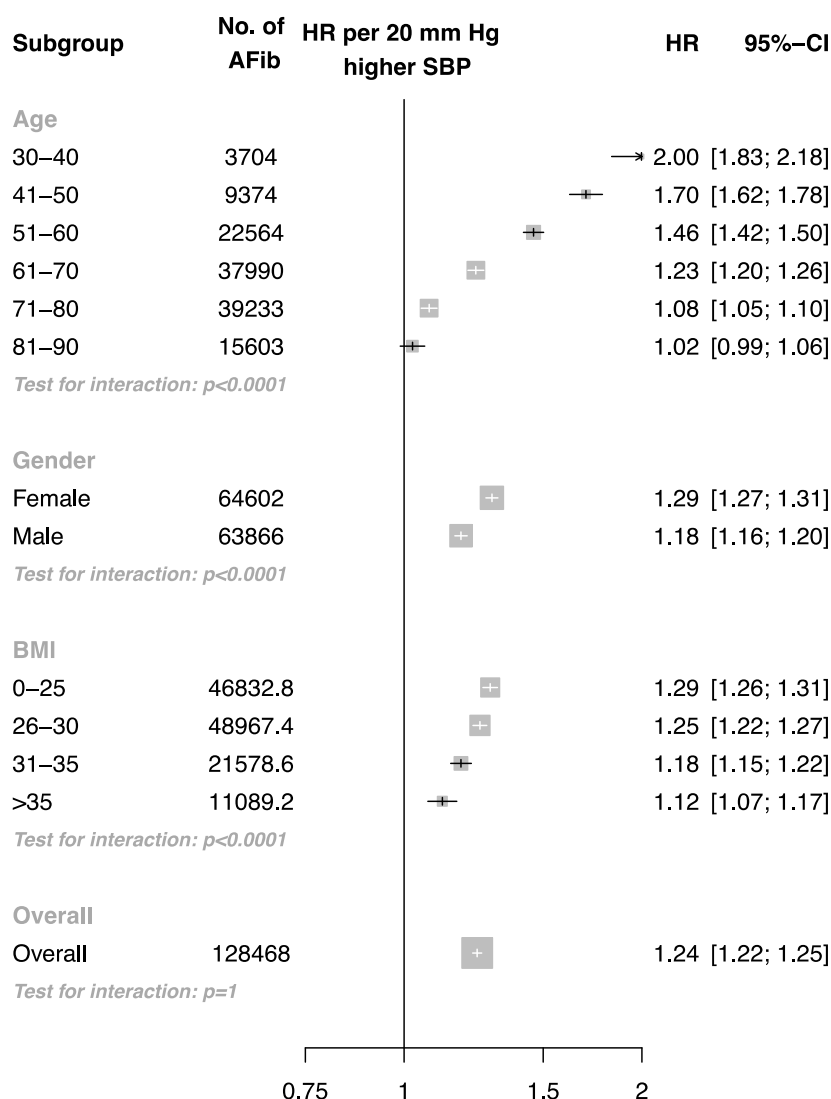


Figure 3.6 Adjusted hazard ratios of a 20 mm Hg higher usual systolic blood pressure for atrial fibrillation by patient subgroup after adjustment for cholesterol, period of BP measurement and socioeconomic status. Adjustments were for age, BMI, smoking status, sex and baseline diabetes, total cholesterol, HDL cholesterol, period of blood pressure measurement and socioeconomic status. Further adjustments were for the interaction between systolic blood pressure and age category (plotted, for subgroup Age), the interaction between sex and systolic blood pressure (plotted, for subgroup Sex), and BMI category and the interaction between systolic blood pressure and BMI category (plotted, for subgroup BMI). Area of each square is proportional to the inverse variance of the estimate.

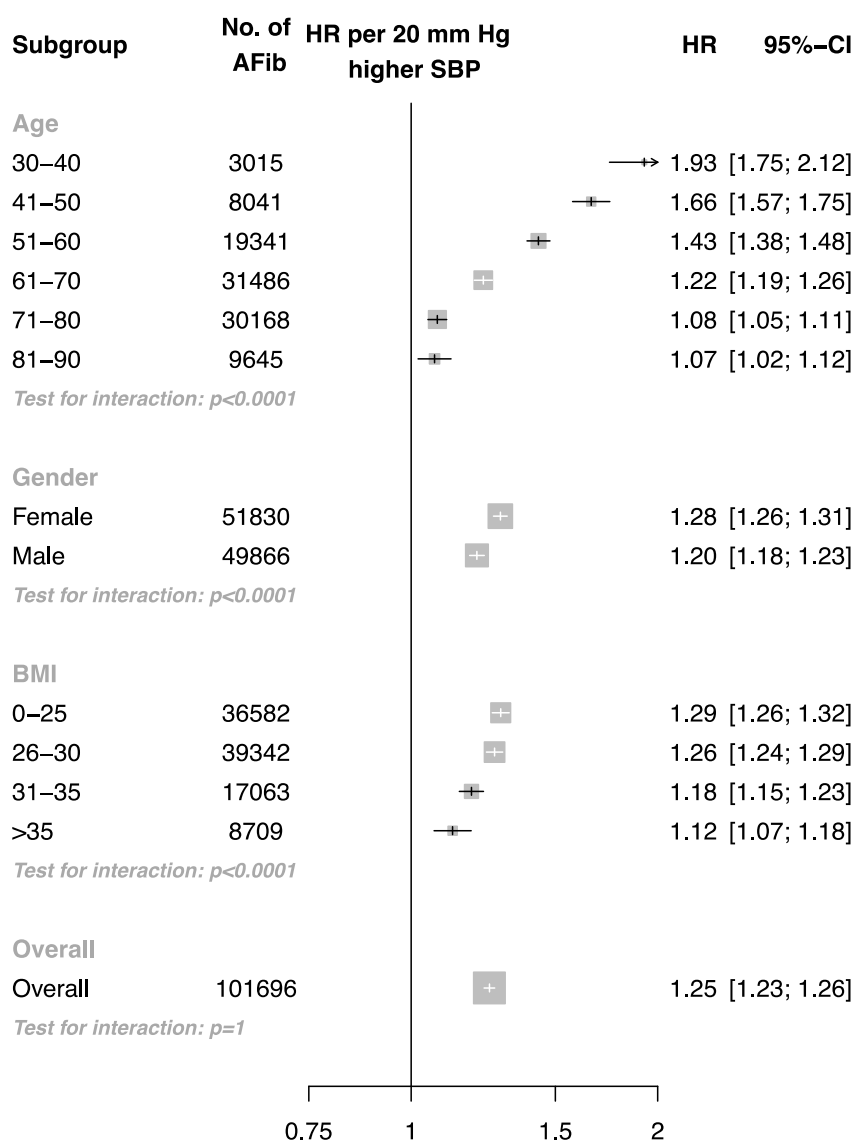


Figure 3.7 Adjusted hazard ratios of a 20 mm Hg higher usual systolic blood pressure for atrial fibrillation by patient subgroup. First two years of follow up are excluded. Adjustments were for age, BMI, smoking status, sex and baseline diabetes. Further adjustments were for age category and the interaction between systolic blood pressure and age category (plotted, for subgroup Age), the interaction between sex and systolic blood pressure (plotted, for subgroup Sex), and BMI category and the interaction between systolic blood pressure and BMI category (plotted, for subgroup BMI). Area of each square is proportional to the inverse variance of the estimate.

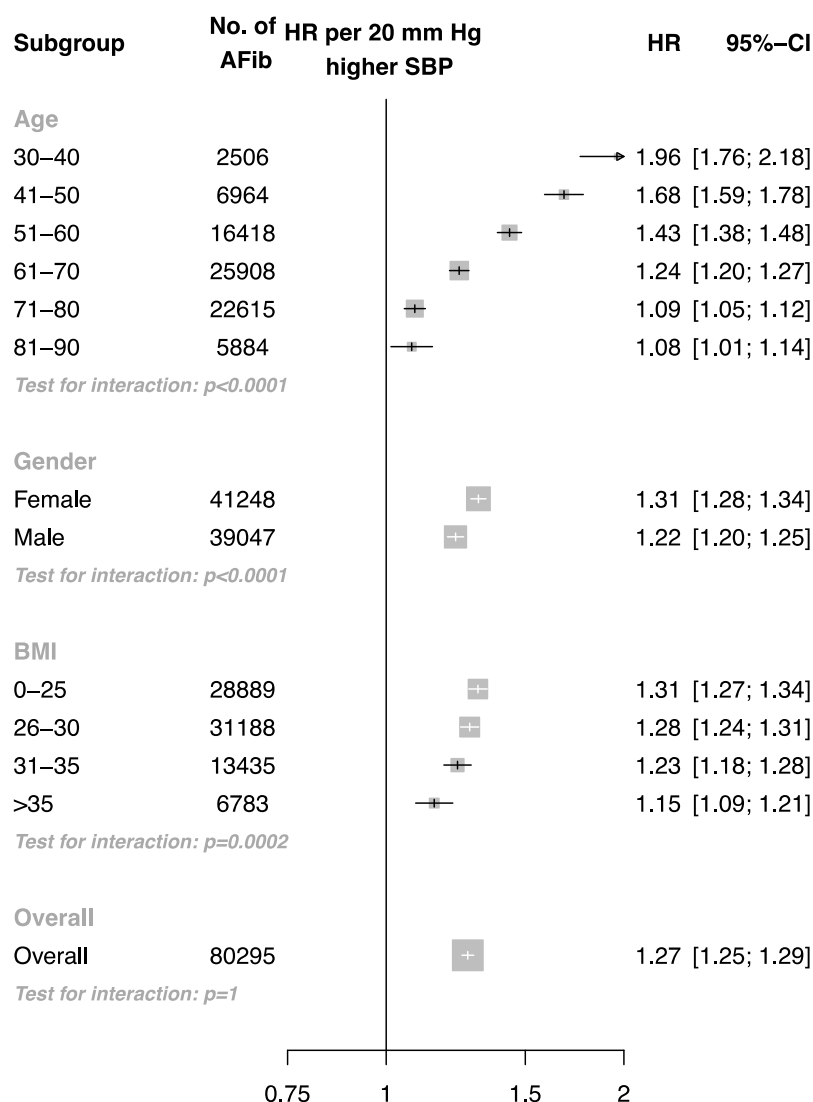


Figure 3.8 Adjusted hazard ratios of a 20 mm Hg higher usual systolic blood pressure for atrial fibrillation by patient subgroup. First four years of follow up are excluded. Adjustments were for age, BMI, smoking status, sex and baseline diabetes. Further adjustments were for age category and the interaction between systolic blood pressure and age category (plotted, for subgroup Age), the interaction between sex and systolic blood pressure (plotted, for subgroup Sex), and BMI category and the interaction between systolic blood pressure and BMI category (plotted, for subgroup BMI). Area of each square is proportional to the inverse variance of the estimate.

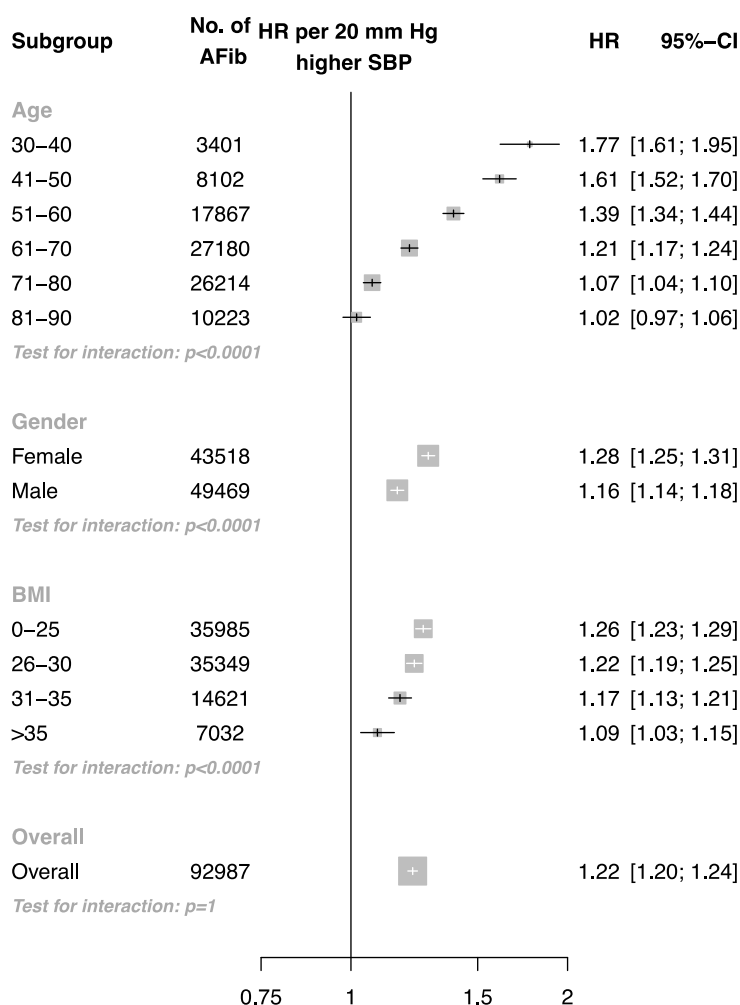


Figure 3.9 Adjusted hazard ratios of a 20 mm Hg higher usual systolic blood pressure for atrial fibrillation by patient subgroup. Individuals prescribed antihypertensive medication at baseline are excluded. Adjustments were for age, BMI, smoking status, sex, baseline diabetes, baseline antihypertensive use, baseline lipid lowering drug (statin) use. Further adjustments were for age category and the interaction between systolic blood pressure and age category (plotted, for subgroup Age), the interaction between sex and systolic blood pressure (plotted, for subgroup Sex), and BMI category and the interaction between systolic blood pressure and BMI category (plotted, for subgroup BMI). Area of each square is proportional to the inverse variance of the estimate.

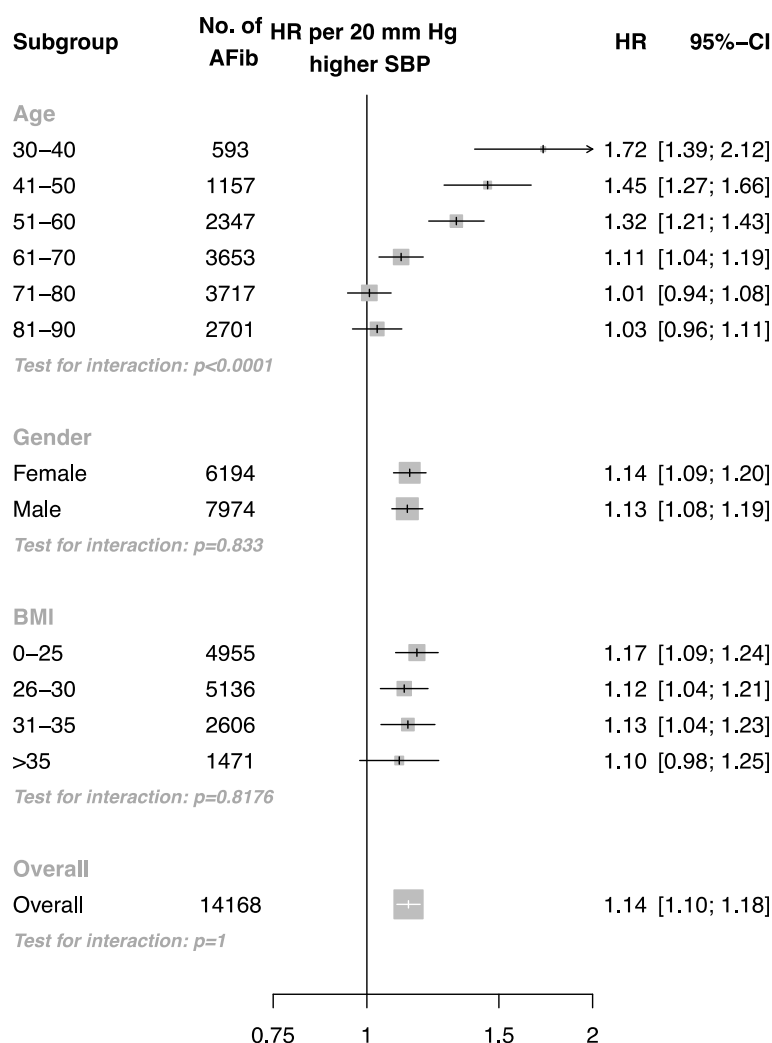


Figure 3.10 Adjusted hazard ratios of a 20 mm Hg higher usual systolic blood pressure for atrial fibrillation by patient subgroup. Follow up was restricted to after 2004, when the Quality and Outcomes Framework was introduced. Adjustments were for age, BMI, smoking status, sex, baseline diabetes, baseline antihypertensive use, baseline lipid lowering drug (statin) use. Further adjustments were for age category and the interaction between systolic blood pressure and age category (plotted, for subgroup Age), the interaction between sex and systolic blood pressure (plotted, for subgroup Sex), and BMI category and the interaction between systolic blood pressure and BMI category (plotted, for subgroup BMI). Area of each square is proportional to the inverse variance of the estimate.

3.3.4 Association of atrial fibrillation with incident vascular disease

Individuals with baseline atrial fibrillation (32 155) were included in a secondary analysis of the association between baseline atrial fibrillation and vascular risk (Table 3.4). Individuals with baseline atrial fibrillation were older than individuals without baseline atrial fibrillation (median age of 72 IQI 61, 80 vs. 46 IQI 36, 59),

were more likely to be prescribed antihypertensive drugs at baseline (39.5% vs. 10.1%) and were more likely to be prescribed lipid lowering drugs at baseline (7.2% vs. 1.9%). These individuals were also more likely to have diabetes at baseline (8.6% vs. 3.2%), were more likely to be prescribed anticoagulant therapies at baseline (40.3% vs. 3.5%) and were more likely to be prescribed antiplatelet therapies at baseline (47.9% vs. 14.3%). During 31.9 million patient years of follow-up, 421 084 vascular events were recorded, including 76 121 ischemic heart disease events, 69 332 stroke events and 66 473 heart failure events.

Table 3.4 Characteristics of participants included in the analysis of the association between baseline atrial fibrillation and vascular risk.

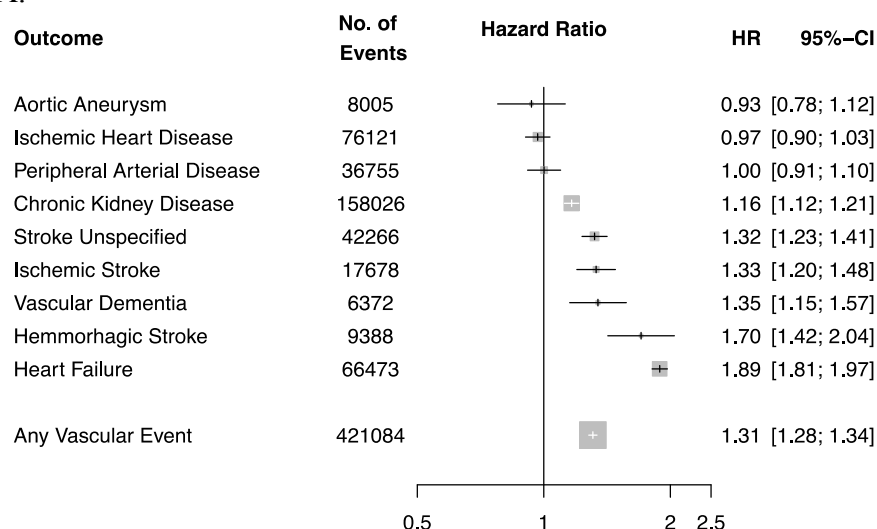
	No atrial fibrillation	Atrial fibrillation	Overall
N	4269194	32 155	4 301 349
Age at Baseline	46 (IQI 36, 59)	72 (IQI 61, 80)	47 (IQI 36, 60)
Women	2 374 239 (55.6%)	14 751(45.9%)	2 388 990 (55.5%)
BMI	25.8 (IQI 23.0, 29.3)	26.1 (IQI 23.1, 29.6)	25.8 (IQI 23.0, 29.3)
Smoking Status			
Current Smoker	970 374 (28.0%)	7006 (28.9%)	973 802 (27.9%)
Never Smoker	616 254 (17.8%)	3428 (14.1%)	623 260 (17.8%)
Ex Smoker	1883584 (54.3%)	13829 (57.0%)	1 897 413 (54.3%)
Cholesterol			
Total	5.5 (IQI 4.7, 6.2)	5.1 (IQI 4.4, 5.9)	5.5 (IQI 4.7, 6.2)
HDL	1.4 (IQI 1.1, 1.6)	1.3 (IQI 1.1, 1.6)	1.4 (IQI 1.1, 1.6)
Most deprived quintile	807 983 (18.9%)	4969 (15.5%)	812 952 (18.9%)
Antihypertensive at baseline	431045 (10.1%)	12 705 (39.5%)	443 750 (10.3%)
Antihypertensive during follow up	1235995 (29.0%)	20450 (63.6%)	1256445 (29.2%)
Lipid lowering at baseline	82031 (1.9%)	2300 (7.2%)	84 331 (2.0%)
Lipid lowering during follow up	665 879 (15.6%)	8731 (27.2%)	674 610 (15.7%)
Anticoagulant at baseline	150 081 (3.5%)	12 972 (40.3%)	163 053 (3.8%)
Antiplatelet at baseline	610 427 (14.3%)	15 398 (47.9%)	625 825 (14.5%)
Diabetes at baseline	137 468 (3.2%)	2758 (8.6%)	140 226 (3.3%)

IQI refers to interquartile interval. Proportion of patients with missing covariates: BMI (30.6%), smoking (18.8%), total cholesterol (72.8%), HDL cholesterol (80.0%)

Overall, baseline atrial fibrillation was associated with a 31% higher risk of any vascular event (HR 1.31 CI 1.28, 1.34) and an 89% higher risk of a fatal vascular event (HR 1.89 CI 1.81, 1.96, Figure 3.11). However, a significant interaction was observed by baseline usage of antithrombotic therapy, defined as prescription of antithrombotic therapy or antiplatelet therapy at baseline (Figure 3.12). While atrial fibrillation with baseline antithrombotic therapy usage was associated with a 15% higher risk of any vascular event (HR 1.15 CI 1.12, 1.18) and a 69% higher risk of a fatal vascular event (HR 1.69 CI 1.61, 1.78), atrial fibrillation without antithrombotic therapy was

associated with two times the risk of any vascular event (HR 2.15 CI 2.05, 2.24, p interaction <0.0001) and two and a half times the risk of a fatal vascular event (HR 2.64 CI 2.43, 2.86). Atrial fibrillation without antithrombotic therapy was associated with a significantly increased risk of ischemic stroke (HR 2.72 CI 2.19, 3.38), stroke unspecified (HR 2.59 CI 2.25, 2.99), ischemic heart disease (HR 2.52 CI 2.23, 2.84), heart failure (HR 3.80 CI 3.50, 4.12), peripheral arterial disease (2.09 CI 1.73, 2.53), chronic kidney disease (HR 1.42 CI 1.31, 1.54) relative to atrial fibrillation with baseline antithrombotic therapy use (all p interaction < 0.001). Risks of hemorrhagic stroke and vascular dementia were associated with atrial fibrillation but did not differ significantly by baseline antithrombotic therapy usage (HR 1.70 CI 1.42, 2.04 and HR 1.35 CI 1.15, 1.57, respectively). Although an increased risk of fatal aortic aneurysm was observed among individuals with atrial fibrillation and antithrombotic usage (but not atrial fibrillation without antithrombotic usage), this may have been due to chance, as no increased risk was observed for fatal and non-fatal aortic aneurysm. Overall, the risk of any stroke (ischemic, hemorrhagic or unspecified) was associated with atrial fibrillation without antithrombotic usage (HR 2.55 CI 2.28, 2.86) and atrial fibrillation with antithrombotic usage (HR 1.24 CI 1.22, 1.27).

A.



B.

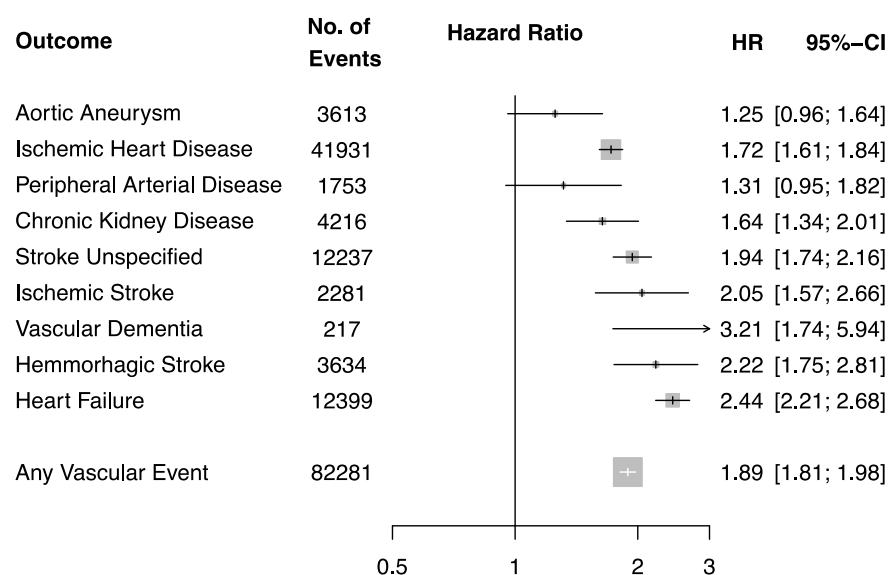


Figure 3.11 Adjusted hazard ratios of baseline atrial fibrillation for nine different vascular events. Adjustments were for age, BMI, smoking status, sex, baseline diabetes, baseline antihypertensive use, baseline lipid lowering drug (statin) use, baseline anticoagulant usage, baseline antiplatelet usage and baseline atrial fibrillation (plotted). Restricted to (A) fatal and non-fatal vascular events and (B) only fatal vascular events. Area of each square is proportional to the inverse variance of the estimate.

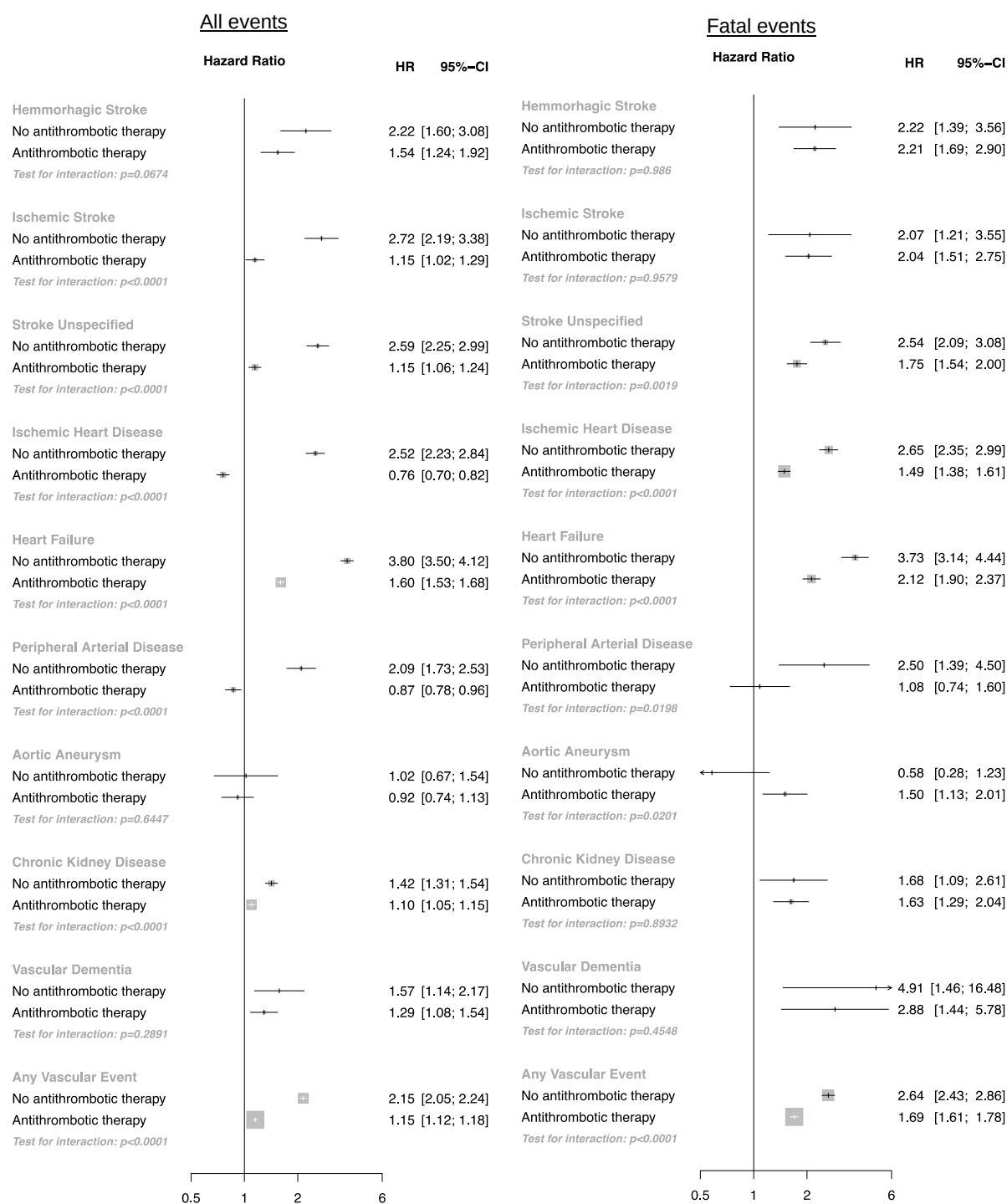


Figure 3.12 Adjusted hazard ratios of baseline atrial fibrillation for nine different vascular events by antithrombotic therapy use. Adjustments were for age, BMI, smoking status, sex, socioeconomic status, baseline diabetes, baseline antihypertensive use, baseline lipid lowering drug (statin) use, baseline anticoagulant usage, baseline antiplatelet usage and the interaction between baseline atrial fibrillation and baseline anticoagulant or antiplatelet use (plotted). Restricted to (A) fatal and non-fatal vascular events and (B) only fatal vascular events. Area of each square is proportional to the inverse variance of the estimate.

3.4 Discussion

In this analysis of 4.3 million individuals and 128 468 incident atrial fibrillation events, systolic blood pressure and diastolic blood pressure were positively related to risk of atrial fibrillation. Overall, a 20 mm Hg higher systolic blood pressure and a 10 mm Hg higher diastolic blood pressure were associated with a 21% higher risk of atrial fibrillation. At age 30-40 years, a 20 mm Hg higher systolic blood pressure and a 10 mm Hg higher diastolic blood pressure were associated with a near doubling in risk of atrial fibrillation. Although proportional associations declined with age, the absolute difference in risk of atrial fibrillation associated with a 20 mm Hg higher systolic blood pressure and 10 mm Hg higher diastolic blood pressure increased until approximately age 51-60 due to the much greater baseline risk of atrial fibrillation in middle and older age. The association of blood pressure with atrial fibrillation was also modified by body mass index, with decreasing strength of association at increasing body mass indices.

Previous analyses of the relationship between blood pressure and atrial fibrillation have generally concluded that elevated blood pressure is a risk factor for atrial fibrillation (Table 3.1). In an analysis of 5201 individuals in the Cardiovascular Health Study, a 20 mm Hg higher systolic blood pressure was associated with a 23% increased risk of atrial fibrillation (HR 1.23 CI 1.10, 1.39), highly similar to the 21% increased risk per 20 mm Hg higher systolic blood pressure observed in this study. In an analysis of the Manitoba Follow-up Study, with 3893 study members and 299 incident atrial fibrillation events, hypertension (blood pressure greater than 160/95 mm Hg or prescription of antihypertensive therapy) was associated with a 42% higher risk of incident atrial fibrillation (HR 1.42 CI 1.10, 1.84).¹¹⁰ In a contemporary cohort study of 22 815 individuals using linked electronic health records, hypertension (blood

pressure $\geq 140/90$ mm Hg or prescription of antihypertensive therapies) was associated with a 98% higher risk of atrial fibrillation in men and a 40% higher risk of atrial fibrillation in women (HR 1.98 CI 1.46, 2.69 and HR 1.40 CI 1.13, 1.74, respectively).¹¹¹

The findings from the present, much larger study, confirm earlier reports that blood pressure is a significant risk factor for atrial fibrillation. In addition, they extend previous findings by demonstrating that the observed association between blood pressure and atrial fibrillation varies significantly by age and body mass index, which previous smaller studies have failed to detect.^{35,120} The present study shows that the relative risk of atrial fibrillation associated with a 20 mm Hg higher systolic blood pressure and 10 mm Hg higher diastolic blood pressure declined with increasing age. However, the absolute risk of atrial fibrillation attributable to high blood pressure is, on average, higher in a middle-aged person than a young person despite stronger relative associations in the younger age group, due to the higher baseline risk of atrial fibrillation in middle age. On the other hand, in elderly people, the very high absolute risk of developing atrial fibrillation is less strongly affected by differences in baseline blood pressure. The understanding of these differential effects of blood pressure on risk of atrial fibrillation will help to inform communication of risks and adaptation of treatment strategies as an important step towards stratified medicine.

There are several possible explanations for the attenuation of the strength of the association of BP with AF with increasing age and increasing BMI. First, these declining associations may be causal and reflect a reduced effect of BP on risk of AF with increasing age and BMI. For example, the heart may be more fibrotic with increasing age and BMI, resulting in an attenuated arrhythmic effect of elevated BP. More likely, however, is that the attenuation of the strength of the association is not

causal. This may be due to greater confounding or reverse causality at older ages and elevated BMI due to a greater prevalence of undiagnosed cardiovascular disease. Another possibility is that the effect of BP on risk of AF is primarily additive, and use of proportional models results in the observation of an attenuated effect due to greater baseline absolute risk of AF with increasing age and BMI.

Importantly, the clinical implications of these interactions differ by their causality. If the declining strength of association of BP with AF is causal, these results would support the targeting of BP lowering therapy to individuals of lower age and lower BMI. However, similar declines in observational associations with increasing age for ischemic heart disease and stroke have not been replicated in meta-analysis of randomized trials.¹²¹ This would suggest that the decline in the strength of association for AF is also not likely to be causal. These results therefore do not provide strong support for the targeting of BP lowering by age or by BMI for prevention of AF.

In my analysis of 421 084 incident vascular events, atrial fibrillation was observed to be a risk factor for cardiovascular disease. However, a significant interaction was observed by baseline usage of antithrombotic therapy (antiplatelet or anticoagulant therapies). Atrial fibrillation without usage of antithrombotic therapy was associated with a two to three times proportional risk of hemorrhagic stroke, ischemic stroke and stroke unspecified, a two and a half times proportional risk of ischemic heart disease, a near four times proportional risk of heart failure, and increased risk of peripheral arterial disease, chronic kidney disease and vascular dementia. However, no association was observed between atrial fibrillation and risk of aortic aneurysm.

Previous analyses of the relationship between AF and vascular risk have largely focused on stroke (Table 3.1). In the Framingham cohort, AF was associated with 2.6

times the risk of stroke at age 60-69, and 4.5 times the risk at age 80-89.¹⁷ However, this analysis largely preceded the widespread use of antithrombotic therapies as well as antihypertensive and lipid lowering therapies. Indeed, in an analysis of a contemporary registry with widespread use of antithrombotic, blood pressure lowering and lipid lowering agents, AF was associated with an unadjusted 1.6 fold risk of non-fatal stroke¹²² In an analysis from the Manitoba Follow-Up Study, AF was associated with a 2 fold risk of stroke (HR 2.07).¹¹⁰ In a recent analysis of Framingham, the risk of stroke associated with AF declined by 74% (CI 50%, 86%) from 1958-1967 to 1998-2007.

My estimate of a 2.5 times risk of stroke associated with AF without baseline antithrombotic usage lies between contemporary estimates and the older Framingham estimates. The lower estimate I observe (relative to the classic Framingham estimate) may reflect the greater usage of anticoagulant, antiplatelet, blood pressure lowering and statin therapies in the contemporary CPRD population compared to Framingham. However, the lowering rates may also be due to the exclusion of individuals with both AF and other prevalent cardiovascular disease (who were excluded to reduce the risk of confounding and reverse causality). They may also be due to greater diagnosis of less severe AF cases in the contemporary CPRD population relative to Framingham, for whom associated stroke rates may be lower.

However, in addition to observing an expected association between AF and risk of stroke, I also observed AF to be associated with an increased risk of a variety of vascular events including ischemic heart disease, chronic kidney disease, peripheral arterial disease and vascular dementia. Previous reports on the relationship between AF and cardiovascular mortality have indicated that AF is associated with an increased risk of cardiovascular death, with stroke deaths composing a minority of excess

deaths.¹⁸ My results substantiate these previous observations and findings from more recent cohort studies indicating that AF is associated with an increased risk of myocardial infarction^{19,123}, and other non-stroke vascular causes (Table 3.1).¹²⁴ These results also confirm a recent analysis of the Reasons for Geographic and Racial Differences in Stroke (REGARDS) cohort in which baseline atrial fibrillation was associated with incident myocardial infarction (HR 1.96 CI 1.52, 2.52).¹⁹ A recent analysis suggested that AF is associated with non-ST-segment elevated myocardial infarction but not ST-segment elevated myocardial infarction¹²⁵, an association that may be mediated by hemostatic factors.¹²⁶ Recent analyses have also suggested that AF is associated with incident chronic kidney disease¹¹³ and end-stage renal disease. These results, therefore, indicate that atrial fibrillation is a risk factor for a variety of different cardiovascular diseases in a contemporary United Kingdom population, highlighting the importance of adequate blood pressure control for prevention of atrial fibrillation.

This analysis has several strengths. It is based on a very large sample, encompassing more than 4 million individuals, one hundred thousand incident atrial fibrillation events and four hundred thousand vascular events, allowing for more detailed analyses than previously possible. It is also contemporary, with many individuals using anticoagulant, antiplatelet, antihypertensive and lipid lowering therapies, unlike in many previous reports.¹¹⁶ A potential limitation is that I utilized routinely collected electronic health records for this analysis and the events used in this analysis were not adjudicated. Although this approach has been previously validated for epidemiological research⁷⁸, and used to examine the associations between (amongst others) blood pressure¹³ and type 2 diabetes²² and vascular risk, the risk of misclassification of events in such an approach is likely to be higher than in a traditional cohort study. However, I undertook a number of sensitivity analyses and

found no changes in the inferences drawn. Indeed, in the large scale Prospective Studies Collaboration¹² and Emerging Risk Factors Collaboration²⁸, ascertainment of fatal events, including stroke subtypes as ischemic, hemorrhagic and unspecified, was based on death certificates, as it was for the linked cause-specific mortality data in this analysis. A further limitation is the potential for confounding due to the observational nature of this analysis. Indeed, the observed increased risk of atrial fibrillation with higher blood pressure may, in part, be due to a greater prevalence of other risk factors for atrial fibrillation with higher blood pressure, that I was unable to adjust for. Similarly, the observed increased risk of a variety of vascular events associated with atrial fibrillation may, in part, be due undiagnosed vascular disease (which I therefore could not exclude) or other undiagnosed comorbidities among patients with atrial fibrillation, while the differences in risk of vascular events by baseline antithrombotic usage may be due, in part, to confounding by indication.

My findings have several possible clinical and research implications. The age-specific associations provided in this analysis between blood pressure and atrial fibrillation may allow clinicians to better personalise management plans. Furthermore, these results highlight the importance of blood pressure control early in life, as blood pressure is strongly associated with risk of atrial fibrillation, even at age 30-40. Among individuals less than 60 years of age, the most recent Joint National Commitment 8 (JNC-8) guidelines recommend treatment of blood pressure to a target of 140/90 mm Hg for prevention of cardiovascular disease.¹²⁷ However, I observe a continuous association of blood pressure with risk of atrial fibrillation among individuals aged 30 to 60. Assuming causality, these results therefore suggest that blood pressure lowering, even in the non-hypertensive range, may prevent atrial fibrillation. However, these results would have to be confirmed in trials or meta-analysis prior to being

implemented in clinical practice. The following chapter examines whether the current body of randomized evidence would support such a recommendation.

3.5 Conclusions

A 20 mm Hg higher systolic blood pressure and a 10 mm Hg higher diastolic blood pressure were associated with a 21% higher risk of atrial fibrillation. However, the association between blood pressure and risk of atrial fibrillation was modified by age and body mass index. Atrial fibrillation was further found to be a risk factor for a range of fatal and non-fatal vascular events in a contemporary population, highlighting the importance of blood pressure control for the prevention of atrial fibrillation.

Chapter 4 Effect on blood pressure lowering therapy on risk of atrial fibrillation: a meta-analysis of 27 large-scale randomized trials

4.1 Introduction

Efforts to reduce the burden of atrial fibrillation through traditional antiarrhythmic drugs have been hampered by the significant safety issues associated with use of such therapies.¹²⁸ On the other hand, some of the safest therapies for cardiovascular risk reduction, such as statins, have not been shown to have any conclusive effect on risk of atrial fibrillation.¹²⁹ Therefore, the identification of other pharmacological therapies to reduce the incidence of atrial fibrillation is of critical importance.

Hypertension has been long recognized as a risk factor for the development of atrial fibrillation.³¹ In an analysis of the Framingham cohort, men and women with hypertension (defined as a systolic blood pressure ≥ 160 mm Hg or a diastolic pressure ≥ 95 mm Hg) had 50% and 40% greater risk for the development of atrial fibrillation, respectively.³¹ As described in the previous chapter, usual systolic blood pressure and usual diastolic blood pressure are continuously related to risk of atrial fibrillation in a contemporary United Kingdom population, with no evidence of a nadir to 110/70 mm Hg blood pressure. Although the association between blood pressure and risk of atrial fibrillation appears to be modified by age and body mass index, overall, a 20 mm Hg lower systolic blood pressure was associated with a 17% lower risk of atrial fibrillation (RR 0.83 CI 0.82, 0.84). Thus, the observational evidence presented in the previous

chapter would predict that antihypertensive therapy would reduce the risk of incident atrial fibrillation by 17% for every 20 mm Hg systolic blood pressure is lowered.

Whether pharmacological blood pressure management reduces the risk of atrial of fibrillation is less certain. A meta-analysis of renin angiotensin inhibitors concluded that such agents reduce the risk of atrial fibrillation by 28% (CI 15%, 40%).¹³⁰ However, this could not be confirmed in a later trial of perindopril and indapamide in patients with diabetes (HR 0.92 CI 0.74, 1.13)¹³¹ and in a second trial of irbesartan in patients with atrial fibrillation (RR 0.97 CI 0.85, 1.10).¹³² On the other hand, a meta-analysis of beta-blockers in heart failure concluded that beta-blockade reduces the risk of atrial fibrillation by 27%.¹³³ However, this analysis did not investigate the effect of other anti-hypertensive agents or the effect of beta-blockade in other patient groups, and prescription of beta-blockers may have blood pressure lowering independent effects in heart failure.¹³⁴ It is, therefore, unclear whether any effect of antihypertensive therapy on risk of atrial fibrillation is specific to beta-blockade, is specific to renin-angiotensin system inhibition, is restricted to patients with heart failure or is mediated through blood pressure lowering.

No meta-analysis, to my knowledge, has attempted to investigate whether antihypertensive therapy in general reduces the risk of atrial fibrillation and whether different classes of antihypertensives have differential effects. I therefore undertook such a meta-analysis and compared the results to those derived in the observational analysis in the previous chapter, in an attempt to reduce existing uncertainties around the effect of antihypertensive therapy and blood pressure lowering on atrial fibrillation.

4.2 Methods

This systematic review was conducted in accordance with the PRISMA guidelines.⁹⁸

4.2.1 Data sources and searches

As described in the general methods section, a systematic search of MEDLINE and relevant references was undertaken, to identify large scale blood pressure lowering trials which reported the effect of antihypertensive therapy on risk of atrial fibrillation. After identification of large scale blood pressure lower randomized trials, two reviewers manually examined whether each trial reported atrial fibrillation events and searched for any reporting of atrial fibrillation in secondary publications.

4.2.2 Study selection

I included all large randomized controlled trials of antihypertensive therapy provided they had reported events of atrial fibrillation as pre-defined study outcome or from adverse event reports. As in the Blood Pressure Lowering Treatment Trialists' Collaboration¹⁰⁰, I defined antihypertensive therapy treatment with diuretics, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB), calcium channel blockers or beta-blockers. For inclusion, all trials were required to have greater than 1000 patient years of follow-up in each randomized group to minimize risk of bias associated with small trials.⁹⁹ I did not place any restriction on the patient populations eligible for inclusion or the primary objective of the trial; trials conducted in patients with heart failure and after myocardial infarction were included. I also did not exclude trials that reported atrial fibrillation as an adverse event or routinely collected event. The use of routine unadjudicated events is unlikely to result in biased estimates (provided sufficient number of events can be gathered) because any under- or over-reporting would affect both arms of the trial equally.^{135,136} Indeed, in prior reports from the ADVANCE trial¹³⁷, the PROGRESS trial¹³⁸ and a meta-analysis of 10 cardiovascular trials with 95 038 participants and more than 9000 events¹³⁶, adjudication had little effect on reported relative risks.

4.2.3 Data extraction and quality assessment

After identification eligible trials, as described in the general methods section, two researchers extracted information independently from each study. Number of individuals in the treatment and control arms, number of atrial fibrillation events in both arms, baseline blood pressure (systolic and diastolic), inclusion criteria and type of event (endpoint/adverse event) were recorded. If a hazard ratio was provided, I used that ratio as a relative risk for the meta-analysis, as hazard ratios avoid censoring associated with use of tabular data and have greater statistical power. However, if a hazard ratio was not provided, a relative risk ratio from the total number of events was used. For one trial, the total number of individuals in each arm without atrial fibrillation at baseline was not available, but the number of atrial fibrillation events in each arm was.¹³⁹ Therefore, to calculate a risk ratio for the trial, equal sized arms were assumed, as randomization would distribute baseline atrial fibrillation approximately equally. Two trials reported summary results for atrial fibrillation/flutter, which were considered as atrial fibrillation for this analysis.¹³⁹⁻¹⁴¹ One trial with three arms compared an ACE inhibitor, to an ARB to a combination of an ACE inhibitor and ARB.¹⁴² To include this trial in the main analysis, one of the ACE inhibitor/ARB arms was randomly selected for comparison to the ACE/ARB combination arm. One study was excluded, as it only provided a single atrial fibrillation event in the treatment arm and no events in the control arm.¹⁴³

Cochrane's risk of bias tool was used to evaluate risk of bias for included trials.¹⁴⁴ Risk of bias was evaluated on five dimensions: selection bias (defined as random sequence generation and allocation concealment), performance bias (blinding of both participants and investigators), detection bias (blinding of evaluators), attrition bias (incomplete outcome data) and reporting bias (selective outcome reporting). Each dimension was judged to be of low, unclear or high risk of bias. The trial, as a whole,

was then judged to be of low, unclear or high risk of bias, depending on whether risk of bias among individual dimensions would have led to bias in the reported atrial fibrillation outcome.

4.2.4 Data synthesis and analysis

For all analyses, overall effect estimates were calculated using inverse variance weighted fixed effects analysis, with 95% confidence intervals. Random effects meta-analysis was performed as a sensitivity analysis. Heterogeneity was quantified using the I^2 statistic and tested between subgroups using Cochran's Q statistic, with a p-value <0.05 considered significant. Analyses were performed to address: (i) whether antihypertensive therapy reduces the risk of atrial fibrillation across all studies identified (ii) whether the proportional effect of antihypertensive therapy differs by prior disease and risk of atrial fibrillation, (iii) whether the proportional effect of antihypertensive therapy, standardized per 20 mm Hg lower systolic blood pressure, differs from what would be predicted by observational evidence and (iv) whether proportional effects vary by class of antihypertensive medication. For the main analysis, to determine whether antihypertensive therapy has an effect on risk of atrial fibrillation, I included all trials that compared either antihypertensive therapy to a placebo, that compared intensive blood pressure lowering to usual care or that compared classes of antihypertensive therapy. As a sensitivity analysis, I excluded trials that recorded atrial fibrillation as an adverse event.

To explore heterogeneity in the effect of antihypertensive therapy on atrial fibrillation, I stratified trials by whether they were conducted in patients without heart disease, with heart disease or with heart failure. I further stratified trials by tertiles of event rate (calculated as the number of atrial fibrillation events per patient-year) to examine whether the effect of antihypertensive therapy differed by event rate.

To compare a pooled estimate from a meta-analysis of randomized trials to an overall estimate from the observational analysis reported in the previous chapter, I restricted the meta-analysis to trials that were conducted in populations free of coronary heart disease, as the prior analysis of the observational cohort excluded individuals with prior coronary heart disease. Furthermore, trials were standardized per 20 mm Hg lower systolic blood pressure, to allow for a direct comparison of a pooled estimate from randomized trials to an observational estimate per 20 mm Hg lower systolic blood pressure. To standardize reported relative risks, the log of the summary statistic of each trial (relative risk or hazard ratio) and the standard error of the log was multiplied by 20 mm Hg/systolic BP reduction. For example, if the log hazard ratio was -0.1, and the BP reduction was 5 mmHg, the standardized log hazard ratio was calculated to be $-0.1 (20 \text{ mm Hg} / 5 \text{ mm Hg}) = -0.4$. Standardized relative risks for trials conducted in non-coronary heart disease populations were then meta-analysed (again using fixed effects) to derive a pooled estimate per 20 mm Hg lower systolic blood pressure.

For analysis by class of medication, I meta-analyzed both the effect of each class of medication against placebo and the effect of each class of medication against all active comparators. For example, for ACE-inhibitors, I meta-analyzed all trials comparing ACE-inhibitors against placebo and all trials comparing ACE-inhibitors against active comparators separately. For one trial, ONTARGET, I excluded the combination arm from comparison by class of medication, as it would have led to active therapy being compared against itself.¹⁴²

All statistical analyses were completed with Stata 12 (Stata Corp, USA).

4.3 Results

4.3.1 Characteristics of studies

10 181 abstracts were identified and screened, of which 9 847 studies were excluded in the initial abstract screen (Figure 4.1). 334 studies were then screened in the full text review, of which 209 studies were excluded. As a result, 125 randomized trials of blood pressure lowering were initially identified, of which 94 were excluded for not fulfilling inclusion criteria (89 for not reporting atrial fibrillation as an adverse event or endpoint). Three trials (CHARM program) reported atrial fibrillation combined for all three trials while two trials (SOLVD program) reported atrial fibrillation combined for both trials. CHARM and SOLVD were then each considered a single trial.

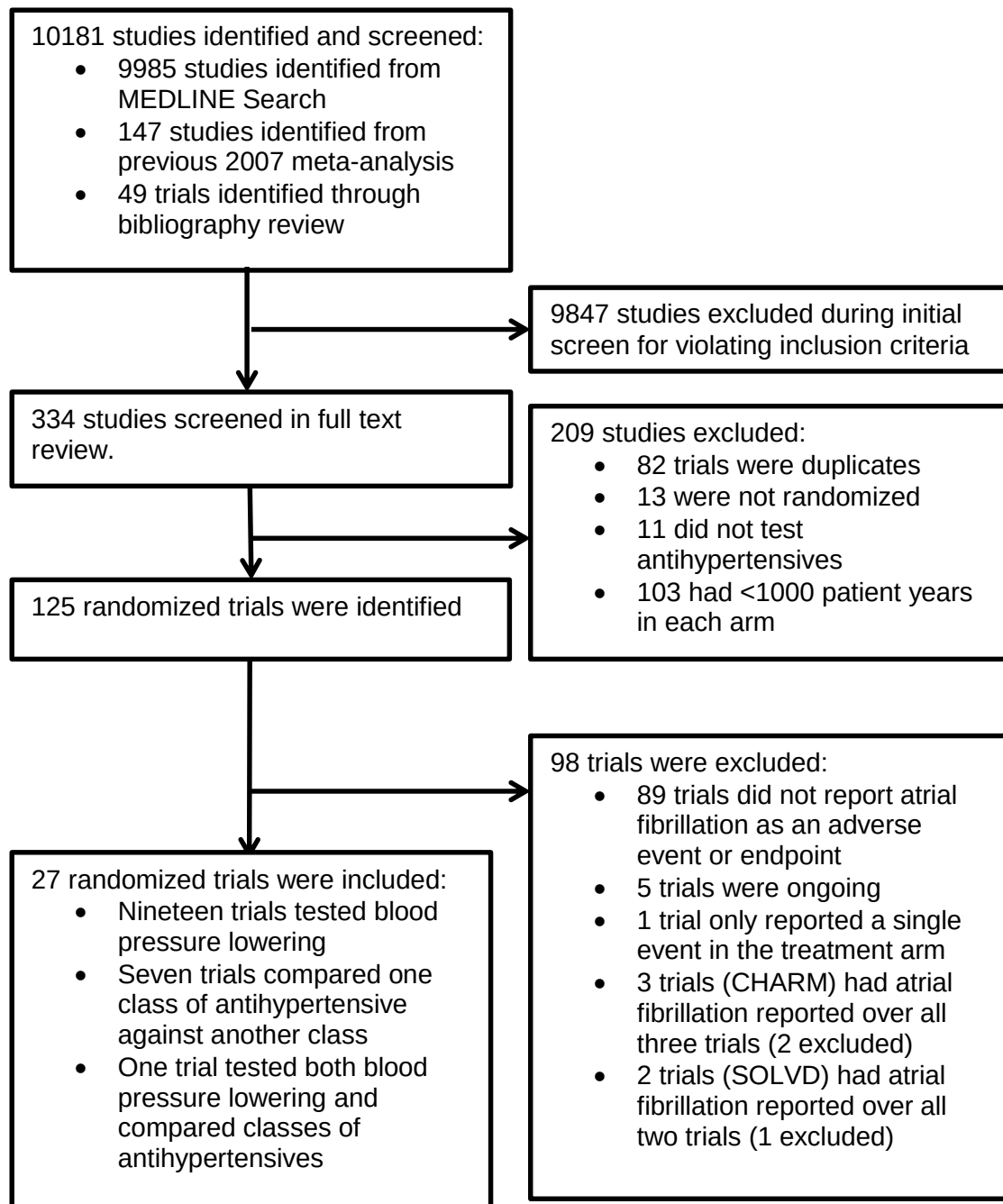


Figure 4.1 Identification of randomized trials reporting atrial fibrillation as an event.

As a result, 27 trials, with 9 929 events in 214 763 patients, were identified (Table 4.1). Twenty trials involved blood pressure lowering (either testing an antihypertensive agent against a placebo or testing intensive lowering against usual care) while eight trials tested an antihypertensive against another antihypertensive agent. Eleven trials reported atrial fibrillation as an adverse event while sixteen trials reported atrial fibrillation as an end point. Of the twenty blood pressure lowering trials,

one trial (ACTIVE I) was conducted in patients with a history of atrial fibrillation, while nineteen trials were conducted in patients who predominantly had no history of atrial fibrillation. Five trials were conducted in patients who predominantly had no history of coronary heart disease, five trials were conducted in patients with a history of coronary heart disease while ten trials were conducted in patients with heart failure or left ventricular systolic dysfunction.

Table 4.1 Summary of characteristics of trials comparing antihypertensive therapy against placebo or against active control.

Name	Inclusion Criteria	Intervention / Control	Total	Mean Age	Male (%)	Duration of Follow Up	BP at Baseline	Type of Prevention	Reported as
ACTIVE I ¹³² (Subgroup)	History of atrial fibrillation (Sinus rhythm at baseline)	Irbesartan / Placebo	1730	70	61	4.1	138/82	Secondary prevention (History of AF)	Endpoint (Committee validated)
ADVANCE ¹³¹	Hypertension (Diabetes mellitus)	Perindopril/Indapamid / Placebo	10293	66	57%	4.3	145/81	Primary (Sinus rhythm on baseline and no history of AF)	Endpoint (Random sample validated)
ALLHAT ¹⁴¹	Hypertension (Cardiovascular risk factor)	Amlodipine / Chlorthalidone	18630	67	53%	4.9	146/84	Unclear (Sinus rhythm on baseline)	Endpoint (Evaluated by external ECG center)
		Lisinopril / Chlorthalidone	18397	67	53%	4.9	146/84		
BEST ¹⁴⁵	Heart Failure (NYHA Class III or IV)	Bucindolol / Placebo	2708	60	78%	2	117/71	Mix of primary and secondary	Adverse event
Cardio-Sis ¹⁴⁶	Hypertension with an additional risk factor	Intense (<130 mm Hg) / Usual (<140 mm Hg)	10985	67	41%	2	163/90	Mix of primary and secondary	Endpoint (Committee validated)
CAPPP ¹⁴⁷	Hypertension	Captopril / Diuretic or Beta blocker	1111	53	54%	6.1	161/99	Primary	Adverse event
Capricorn ¹⁴⁸	Myocardial infarction (LVSD)	Carvedilol / Placebo	1959	63	74%	1.3	122/74	Mix of primary and secondary	Adverse event (Post hoc investigator validated)
CHARM ¹⁴⁹	Heart Failure (Reduced or preserved ejection fraction)	Candesartan / Placebo	6379	65	68%	3.1	131/77	Mix of primary and secondary	Endpoint (investigator reported)
DIABHYCAR ¹⁵⁰	Hypertension (Diabetes mellitus)	Ramipril / Placebo	4912	65	70%	3.9	145/82	Unclear	Adverse event
GISSI-3 ¹⁵¹	Myocardial infarction	Lisinopril / Placebo	17711		78%	0.12	NA	Primary (Sinus rhythm on baseline and no history of AF)	Endpoint (investigator reported)
HOPE ¹⁵²	Hypertension (Cardiovascular disease history with an additional cardiovascular risk factor)	Ramipril / Placebo	8335	66	73%	4.5	138/79	Unclear (Sinus rhythm on baseline)	Endpoint (ECGs analyzed by cardiologists)
LIFE ³⁶	Hypertension (Left ventricular hypertrophy)	Losartan / Atenolol	8851	67	46%	4.8	174/98	Primary (Sinus rhythm on baseline and no history of AF)	Endpoint (evaluated by external ECG center)
MERIT-HF ¹⁵³	Heart Failure	Metoprolol / Placebo	3132	63	76%	1	130/78	Unclear (Sinus rhythm on baseline)	Adverse event
NAVIGATOR ¹⁵⁴	Hypertension (Impaired glucose tolerance)	Valsartan / Placebo	8943	63	49%	6.5	140/82	Primary (Sinus rhythm on baseline and no history of AF)	Adverse event (Post-hoc ECG or investigator reported adverse event)
NORDIL ¹⁵⁵	Hypertension	Diltiazem / Diuretic or Beta blocker	10881	60	49%	4.5	173/106	Mix of primary and secondary	Endpoint

ONTARGET ¹⁴²	Hypertension (Vascular disease or diabetes)	Telmisartan / Ramipril Telmisartan+Ramipril / Ramipril	16555 16514	66 66	73% 73%	4.7 4.7	142/82 142/82	Unclear (Sinus rhythm on baseline)	Endpoint
OPTIMAAL ¹³⁹	Myocardial infarction with signs of heart failure or LVSD	Losartan / Captopril	4822	67	71%	2.7	122/71	Unclear (Sinus rhythm on baseline)	Adverse event
PRAISE - 2 ¹⁵⁶	Heart failure (Non-ischemic cardiomyopathy)	Calcium channel blocker / Placebo	2289	59	66%	2.8	120/81	Mix of primary and secondary	Adverse event
PRoFESS ¹⁵⁷	Hypertension (History of cerebrovascular events)	Telmisartan / Placebo	20332	66	64%	2.5	144/84	Mix of primary and secondary	Adverse event
SENIORS ¹⁵⁸	Heart Failure with reduced or preserved ejection fraction	Nebivolol / Placebo	2128	76	63%	1.8	139/81	Mix of primary and secondary	Adverse event
SHEP ³⁸	Hypertension (Elderly with systolic hypertension)	Active treatment (diuretic or beta-blocker) / Placebo	4736	72	43%	4.5	171/77	Primary (Atrial fibrillation was exclusion criteria)	Endpoint (evaluated by external ECG center)
SOLVD (Montreal site) ¹⁵⁹	Heart failure (Mild to moderate with LVSD)	Enalapril / Placebo	374	57	90%	2.9	128/79	Mix of primary and secondary	Endpoint (ECG interpreted by cardiologist)
STOP-2 ¹⁶⁰	Hypertension (SBP > 180 or DBP > 105)	Enalapril or lisinopril (ACE-I) / Conventional (Diuretics or Beta-blockers)	4418	76	33%	5	194/98	Mix of primary and secondary	Endpoint
		Amloride / Conventional (Diuretics or Beta-blockers)	4409	76	33%	5	194/98		
TRACE ¹⁶¹	Myocardial infarction (LVSD)	Trandolapril / Placebo	1577	67	72%	2.2	NA	Unclear	Endpoint (Post hoc investigator validated)
TRANSCEND ¹⁶²	Hypertension (Cardiovascular diseases or diabetes with end organ damage)	Telmisartan / Placebo	5701	67	57%	4.7	141/82	Primary (described as new onset atrial fibrillation)	Endpoint
Val-HeFT ¹⁶³	Heart failure	Valsartan / Placebo	4395	63	79%	1.9	121/NA	Unclear (Sinus rhythm at baseline)	Adverse event
VALUE ¹⁶⁴	Hypertension (High cardiovascular risk)	Valsartan / Amlodipine	13760	67	58%	4.2	155/88	Unclear	Endpoint (evaluated by external ECG center)

Of the twenty-seven included trials, twenty-four were judged to be of low risk of bias (Table 4.2). One trial was judged to be of unclear risk of bias, while two trials were judged to be of high risk of bias.

Table 4.2 Risk of bias for atrial fibrillation events.

Name	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Overall Risk of Bias
ACTIVE I (Subgroup)	Low	Low	Low	Low	Low	Low
ADVANCE	Low	Low	Unclear	Low	Low	Low
ALLHAT	Low	Low	Low	Low	Low	Low
BEST	Low	Low	Unclear	Low	Low	Low
CAPPP	Low	High	Unclear	Low	Low	High
Cardio-Sis	Low	Low	Low	Low	Low	Low
Capricorn	Low	Low	Unclear	Low	Low	Low
CHARM	Low	Low	Unclear	Low	Low	Low
DIABHYCAR	Low	Low	Unclear	Low	Low	Low
GISSI-3	Low	Low	Unclear	Low	Low	Unclear
HOPE	Low	Low	Low	Low	Low	Low
LIFE	Low	Low	Low	Low	Low	Low
MERIT-HF	Low	Low	Low	Low	Low	Low
NAVIGATOR	Low	Low	Unclear	Low	Low	Low
NORDIL	Low	Low	Unclear	Low	Low	Low
ONTARGET	Low	Low	Low	Low	Low	Low
OPTIMAAL	Low	Low	Low	Low	Low	Low
PRAISE - 2	Low	Low	Unclear	Low	Low	Low
PRoFESS	Low	Low	Unclear	Low	Low	Low
SENIORS	Low	Low	Unclear	Low	Low	Low
SHEP	Low	Low	Low	Low	Low	Low
SOLVD (Montreal site)	Low	Low	Unclear	Low	High	High
STOP-2	Low	Low	Unclear	Low	Low	Low
TRACE	Low	Low	Unclear	Low	Low	Low
TRANSCEND	Low	Low	Low	Low	Low	Low
Val-HeFT	Low	Low	Unclear	Low	Low	Low
VALUE	Low	Low	Low	Low	Low	Low

4.3.2 Effect of antihypertensive therapy on risk of atrial fibrillation

Overall, antihypertensive therapy (regardless of whether it was used for the purpose of blood pressure lowering) reduced the risk of atrial fibrillation by 10% (RR 0.90, CI: 0.86, 0.94, Figure 4.2). In the single trial that focused on prevention of recurrences of atrial fibrillation, there was no clear effect (RR 0.97: CI 0.85, 1.10).

However, there did not appear to be significant heterogeneity between this trial (secondary prevention) and trials for which history of atrial fibrillation was not an inclusion criteria (largely primary prevention, $p=0.229$), although significant heterogeneity was observed among trials overall ($I^2=75.1\%$, $p<0.001$). Exclusion of trials that reported atrial fibrillation as an adverse event had little effect on overall estimates (RR 0.92 CI 0.87, 0.97; Figure 4.3) Estimates did not differ materially when random effects meta-analysis was used (overall RR 0.84 CI 0.75, 0.93; Figure 4.4).

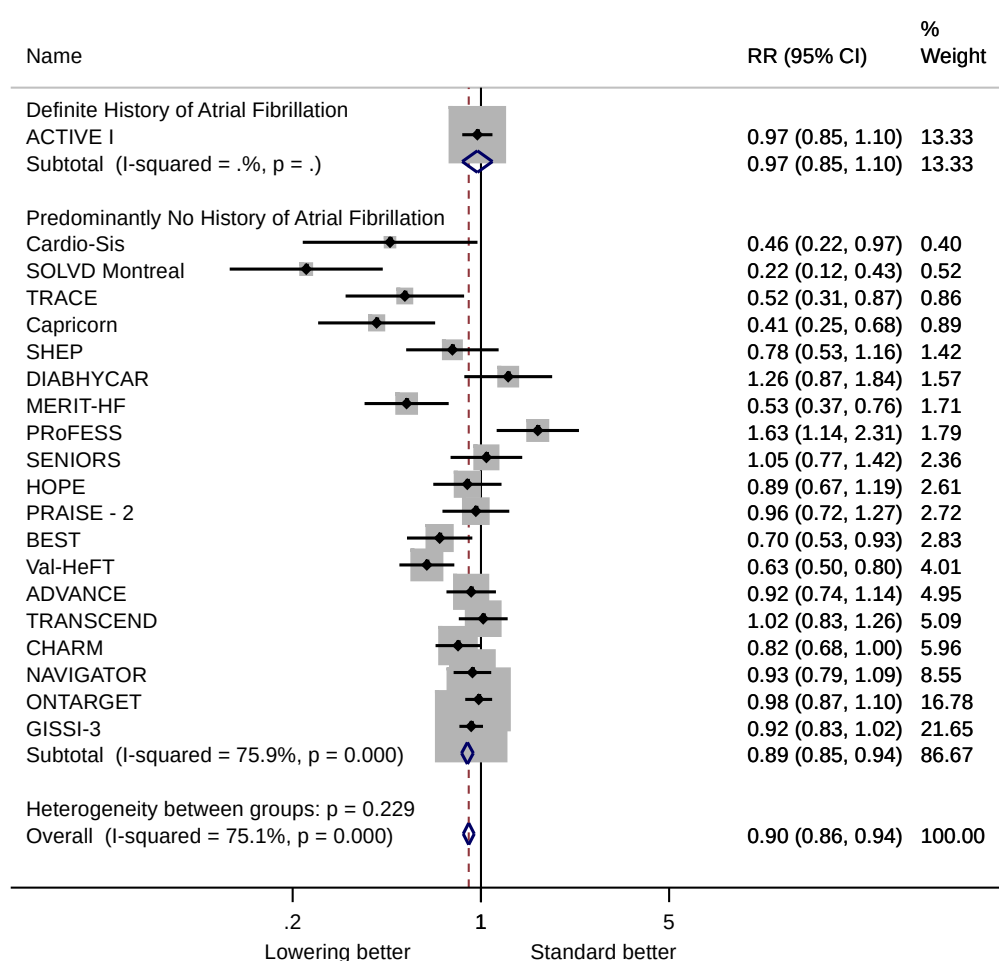


Figure 4.2 Effect of antihypertensive therapy on risk of atrial fibrillation by trial inclusion criterion.

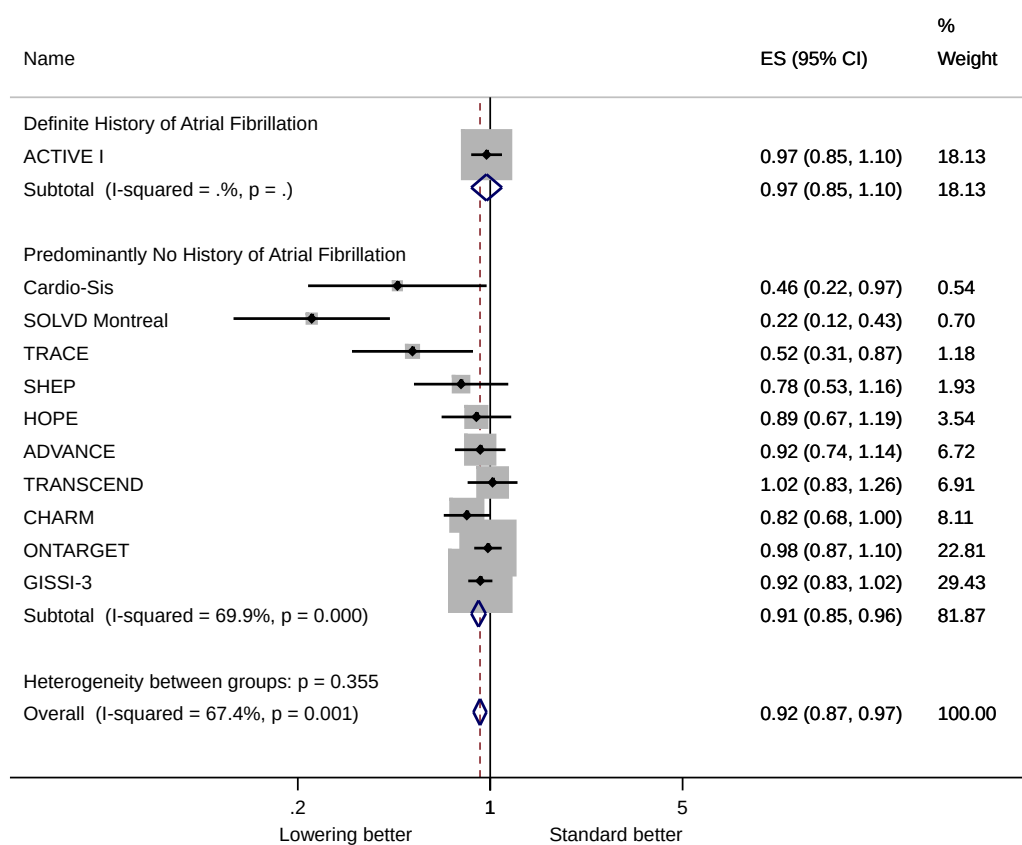


Figure 4.3 Effect of antihypertensive therapy on risk of atrial fibrillation in different patient populations, excluding trials that reported atrial fibrillation as an adverse event.

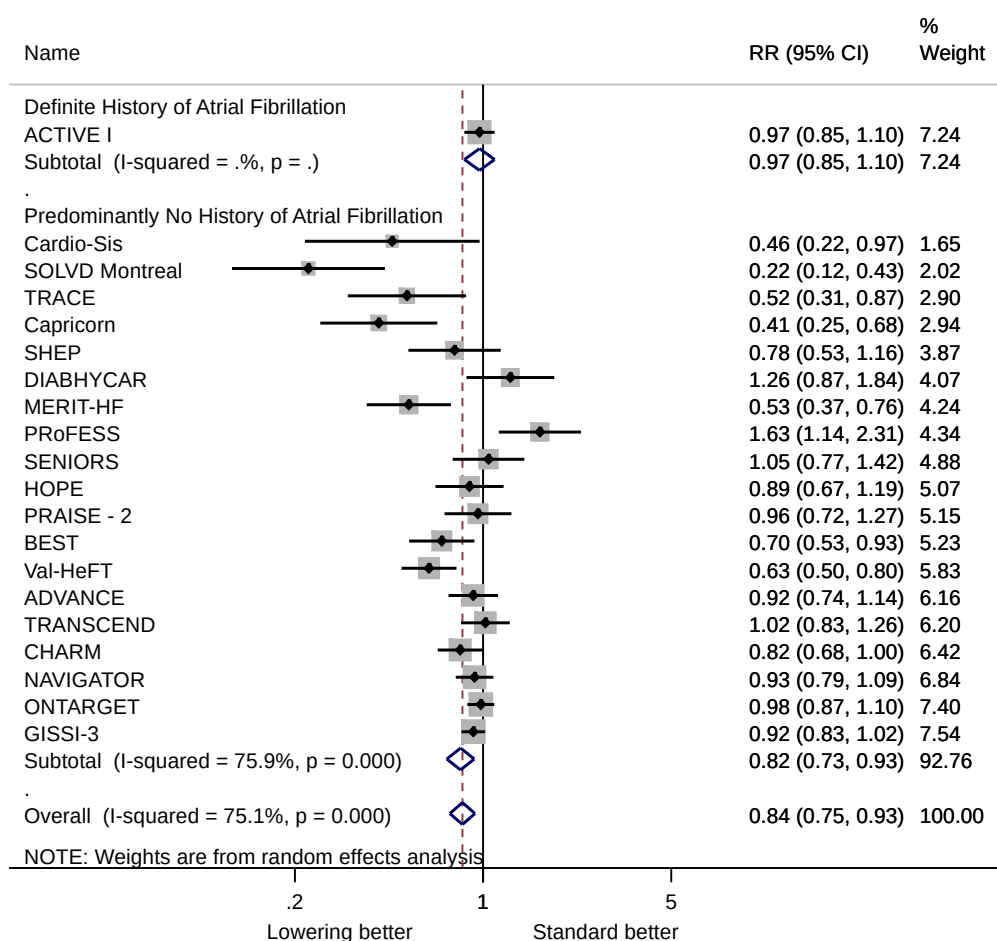


Figure 4.4 Effect of antihypertensive therapy on risk of atrial fibrillation in different patient populations using random effects meta-analysis.

4.3.3 Subgroup analysis

Antihypertensive therapy was significantly more effective in patients with evidence of heart failure (RR 0.81 CI 0.74, 0.87) than in patients with coronary heart disease (RR 0.95 CI 0.89, 1.01) or patients with no previous heart disease (RR 1.02 CI 0.88, 1.18, Figure 4.5, $p_{\text{heterog}} = 0.002$). There was a graded increase in proportional effects with increasing risk of atrial fibrillation across trials (RR 0.86 CI 0.81, 0.93 for highest event rate tertile, RR 0.91 CI 0.48, 0.99 for medium event rate tertile, RR 0.98 CI 0.88, 1.09 for lowest event rate tertile), although a test for heterogeneity by event rate tertile was not significant ($p=0.14$). Proportional effects were slightly greater when random effects meta-analysis was used; in heart failure

trials antihypertensive therapy reduced the risk of atrial fibrillation by 32% (RR 0.68 CI 0.56, 0.84, Figure 4.6) while in the high event rate tertile antihypertensive therapy reduced the risk of atrial fibrillation by 27% (RR 0.73 CI 0.59, 0.90). A test for heterogeneity by event rate tertiles was significant ($p=0.04$, Figure 4.6).

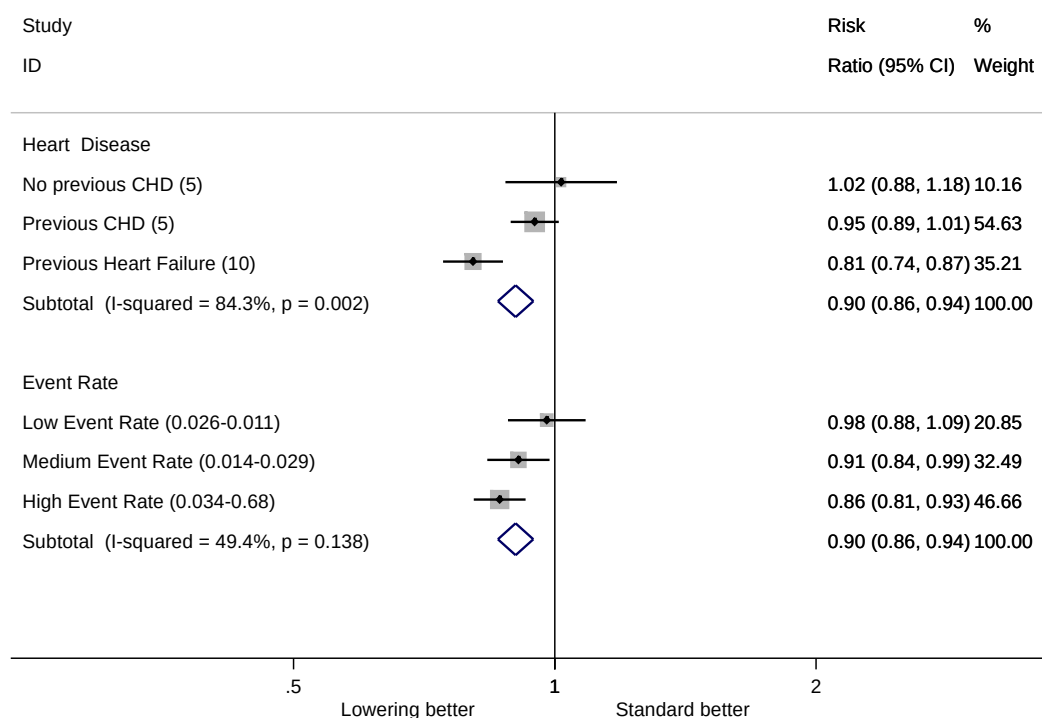


Figure 4.5 Effect of antihypertensive therapy on risk of atrial fibrillation stratified by presence of heart disease and by tertiles of event rate. The ranges of event rate, in units of atrial fibrillation events per patient year is denoted in brackets beside each tertile.

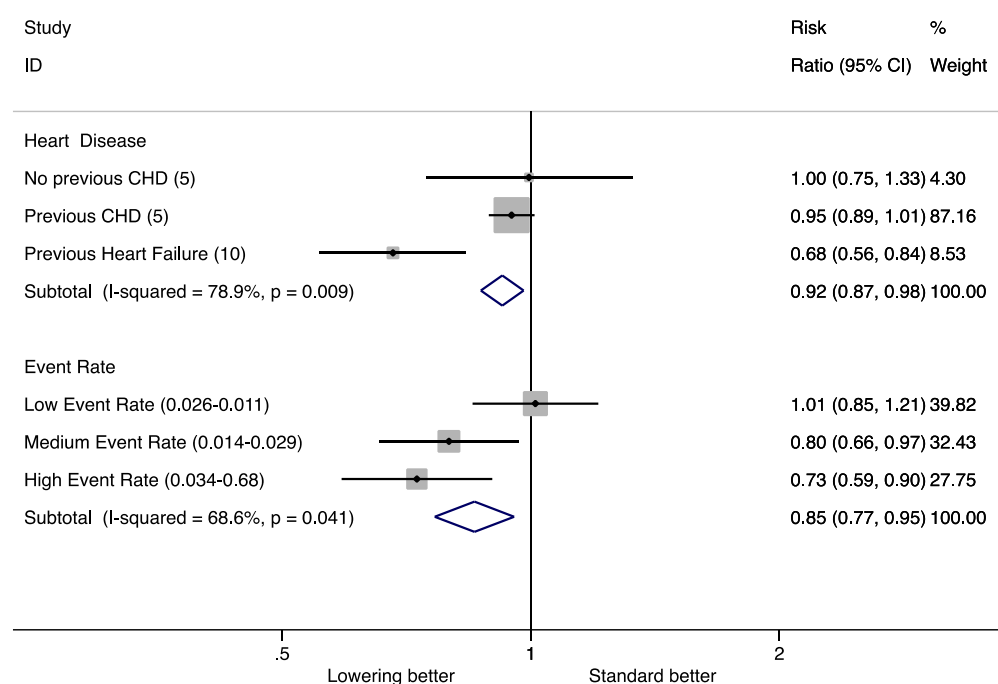


Figure 4.6 Effect of antihypertensive therapy on risk of atrial fibrillation stratified by presence of heart disease and by tertiles of event rate, pooled using random effects meta-analysis. The ranges of event rate, in units of atrial fibrillation events per patient year is denoted in brackets beside each tertile.

4.3.4 Comparison of estimate of meta-analysis with observational association

Overall, antihypertensive therapy had no effect on risk of atrial fibrillation in randomized trials conducted in populations without heart failure or coronary heart disease (RR 1.02 CI 0.88, 1.18, Figure 4.7). When estimates from randomized trials were standardized per 20 mm Hg systolic blood pressure reduction and meta-analysed, to allow for comparison with previously presented observational evidence, no significant effect of blood pressure lowering on risk of atrial fibrillation was observed (RR 0.84 CI 0.53, 1.33 per 20 mm Hg systolic blood pressure reduction, Figure 4.8). However, a test for interaction between the estimate from the meta-analysis and the overall observational estimate in the prior chapter (HR 0.83 CI 0.82, 0.84 per 20 mm Hg lower systolic blood pressure) was not significant (p interaction = 0.9448, Figure 4.8). Indeed, point estimates from observational and randomized

analyses were almost identical (RR 0.83 CI 0.82, 0.84 vs. RR 0.84 CI 0.53, 1.33 for observational vs. randomized, respectively), although confidence interval for the randomized estimate was very large (Figure 4.8).

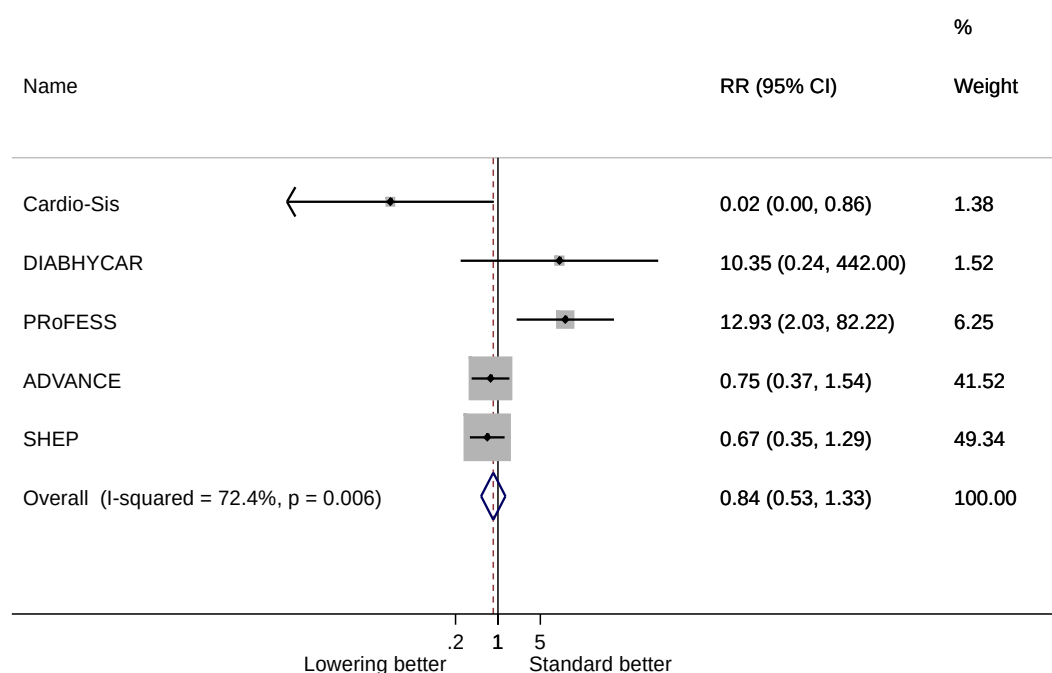


Figure 4.7 Effect of antihypertensive therapy, standardized to 20 mm Hg lower systolic blood pressure, on risk of atrial fibrillation in trials conducted in populations without coronary heart disease.

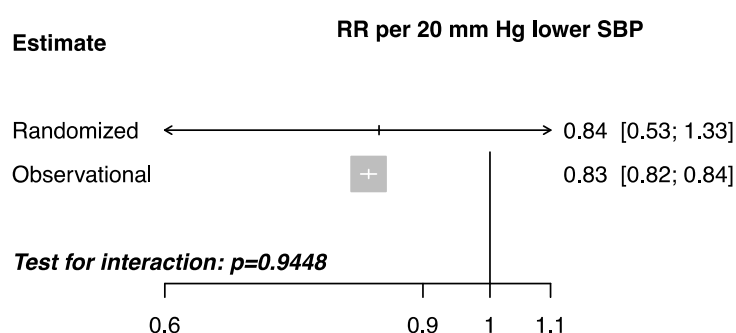


Figure 4.8 Comparison of standardized estimate from meta-analysis to estimate from observational evidence.

4.3.5 Effect of antihypertensive therapy on risk of atrial fibrillation by class of medication

Seventeen trials compared an ACE-inhibitor, angiotensin receptor blocker, calcium channel blocker or beta-blocker against a placebo. When trials were grouped by the class of medication used, significantly greater benefit was observed in trials comparing beta-blockers against placebo (RR = 0.70 CI 0.59, 0.83; Figure 4.9) than other classes of medication against placebo ($p_{\text{heterog}} = 0.002$, Figure 4.9). However, all trials comparing beta-blockers against placebo were conducted in heart failure patients. When excluded, no heterogeneity was observed between the effects of ACE-Is, ARBs and CCBs on incidence of atrial fibrillation ($p=0.972$).

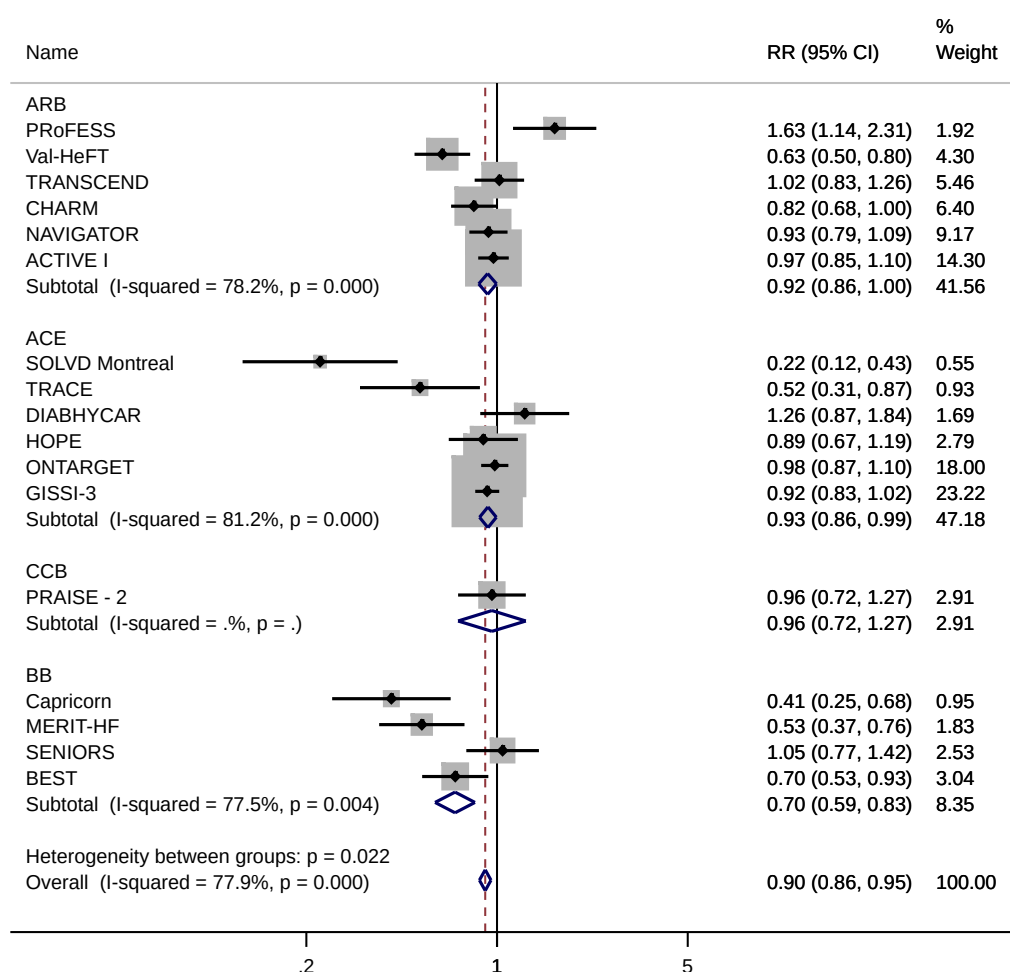


Figure 4.9 Effect of classes of antihypertensive medication against placebo on risk of atrial fibrillation.

As a comparison of placebo-controlled trials may be confounded by differing patient populations between trials, I considered eight trials that compared one class of antihypertensive therapy against another class in a second analysis. When trials were grouped by the class of medication used, beta-blockers were observed to be significantly less effective than other classes of medication (RR 1.49 CI 1.21, 1.83; Figure 4.10). However, this effect was solely due to the LIFE trial (the only trial comparing a beta-blocker against an active comparator). When excluded, no class of medication (ACE-inhibitor, angiotensin receptor blocker, diuretic or calcium channel blocker) was observed to be more effective than any other class of medication for

prevention of atrial fibrillation (Figure 4.11). No significant effects were observed for ARBs vs. any other class (RR 0.95 CI 0.87, 1.03), diuretics vs. any other class (RR 0.97 CI 0.82, 1.15), ACE-inhibitors vs. any other class (RR 1.04 CI 0.96, 1.12) or calcium channel blockers vs. any other class (RR 1.00 CI 0.91, 1.10). Estimates were similar when random effects meta-analysis was used (Figure 4.12), with the exception that even with the LIFE trial included, no significant benefit of ARBs vs. any other class of medication was observed (RR 0.88 CI 0.74, 1.04).

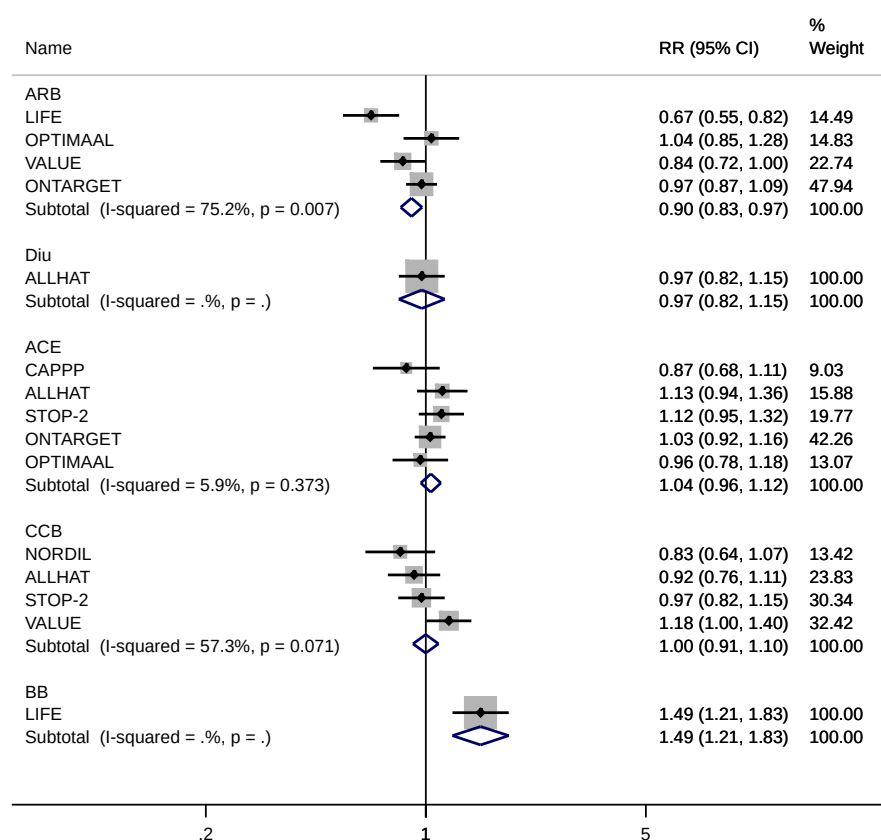


Figure 4.10 Effect of classes of antihypertensive therapies against all active comparators on risk of atrial fibrillation.

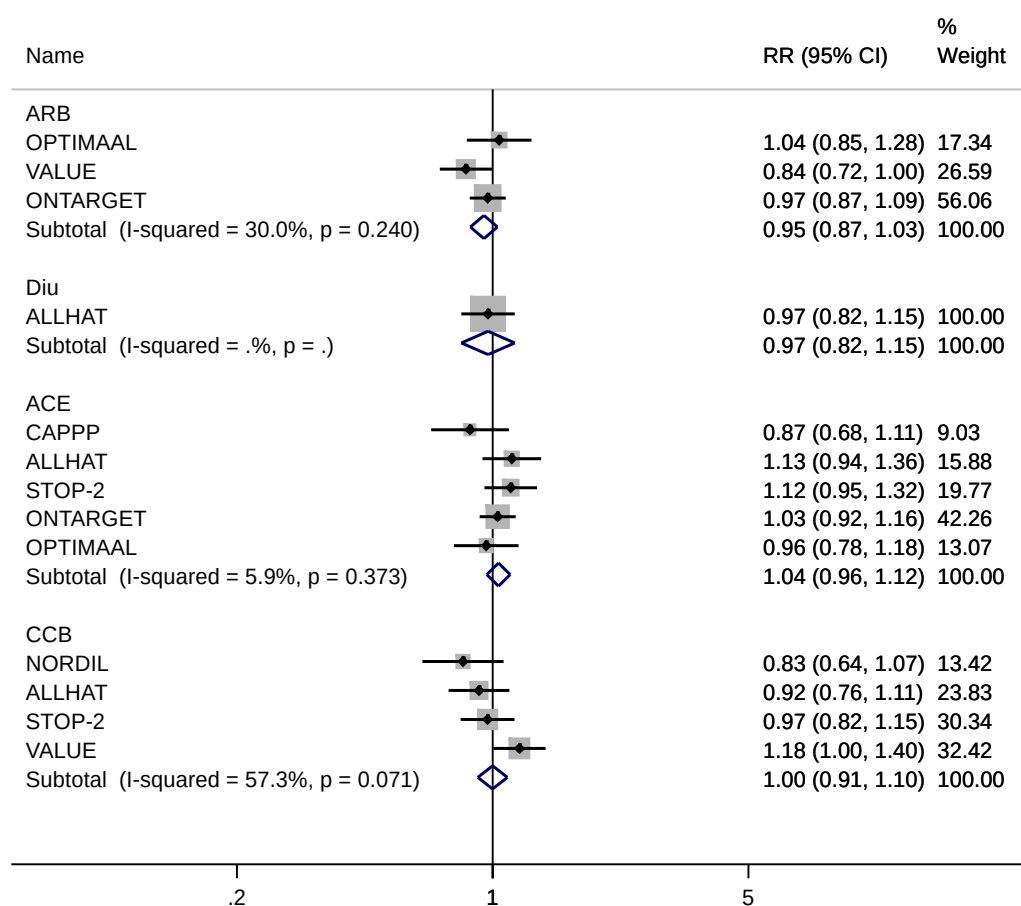


Figure 4.11 Effect of classes of antihypertensive therapies against all active comparators on risk of atrial fibrillation. The LIFE trial was excluded.

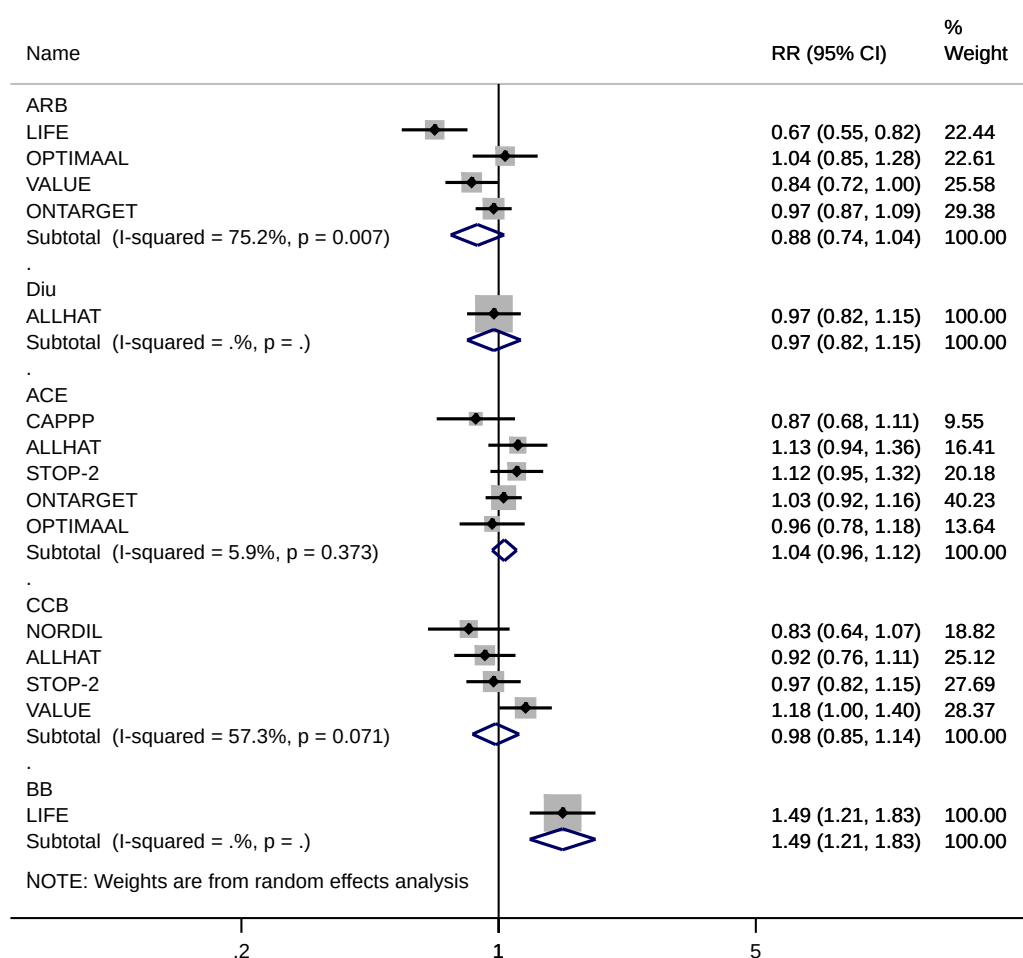


Figure 4.12 Effect of classes of antihypertensive therapies against all active comparators on risk of atrial fibrillation, pooled using random effects meta-analysis.

4.4 Discussion

I identified 27 trials that reported information on 9929 events of atrial fibrillation in 214 763 randomized participants. Although pooled effects across these trials suggests that antihypertensive therapy reduces the risk of atrial fibrillation by 10% overall, proportional effects appear to be significantly greater in trials conducted in heart failure patients, where the risk of atrial fibrillation was reduced by about a quarter. Conversely, no significant effects were observed in trials conducted in patients without heart failure. When classes of medication were compared against each other, no significant differences in effects on atrial fibrillation were observed,

although a single trial suggested that beta blockers may be less effective than angiotensin receptor blockers in individuals without heart failure.

The comprehensive approach of identifying all large blood pressure lowering trials enabled the investigation of the effect of antihypertensive therapy (regardless of whether it was used for blood pressure lowering) on atrial fibrillation by subgroups of patients and risk. The significant heterogeneity in proportional effects by disease status, with no benefit observed in patients without prior heart disease to significant benefit observed in those with known heart failure, is likely to be of clinical relevance. In response to the increasing burden of atrial fibrillation, there is growing interest in the use of antihypertensive therapy for primary prevention of atrial fibrillation.¹⁶⁵ These results suggest that such therapy may have greater proportional benefits in patients with heart failure than those without clinical heart disease.

The greater relative effect observed in patients with heart failure could be either due to a heart failure-specific physiological feature or to a higher baseline risk for development of atrial fibrillation in this patient population. In support of the latter hypothesis, greater proportional effects were observed in the highest event rate tertile relative to the lowest event rate tertile. However, six of the seven trials in the highest event rate tertile were conducted in patients with a history of heart failure. It is therefore difficult to determine which hypothesis is valid or if both hypotheses are valid. Evidence against the hypothesis that higher baseline risk is associated with higher proportional risk reductions comes from two previous trials that specifically investigated the effect of ARBs in people with previous history of atrial fibrillation.^{132,166} Although such patients are at very high risk of recurrent atrial fibrillation, these trials did not detect any significant effects.

In spite of the greater proportional effects observed in heart failure populations, it is unlikely that blood pressure lowering has no effect on risk of atrial fibrillation in populations without heart disease. When trials conducted in non-heart disease populations were standardized per 20 mm Hg reduction in systolic blood pressure, the overall estimate was non-significant (RR 0.84 CI 0.53, 1.33). However, the non-significant 16% reduction is highly similar to the predicted 17% reduction per 20 mm Hg lower systolic blood pressure from the observational analysis proposed in the prior chapter and a test for interaction between the randomized and observational estimates was not significant. It is likely that the meta-analysis of the five trials conducted in non-coronary heart disease populations was not powered to detect the modest association of blood pressure with atrial fibrillation observed in the prior chapter. The mean follow up of the meta-analysed trials was 3.44 years while the mean systolic reduction was 5.5 mm Hg. To detect a 5% reduction in incident atrial fibrillation (the reduction associated with a 5.5 mm Hg lower systolic blood pressure that would be predicted from the observational analysis) with 80% power, the meta-analysed trials would need to have 11 933 events when pooled. In contrast, the meta-analysed trials had only 740 events in total. If a randomized trial or meta-analysis of randomized trials is to demonstrate that blood pressure lowering reduces the risk of atrial fibrillation in non-heart failure populations, they would need to have significantly greater reductions in systolic blood pressure (approaching 20 mm Hg) and number of events than the five trials pooled in this analysis.

Although it cannot be concluded that pharmacological blood pressure lowering reduces the risk of atrial fibrillation outside of heart failure populations, the robust associations between blood pressure and risk of atrial fibrillation observed in the previous chapter and the lack of interaction between the observational and

randomized estimates are consistent with a causal relationship between blood pressure and new onset atrial fibrillation. At minimum, these results suggest that blood pressure lowering (particularly during middle age) may prevent atrial fibrillation.

The reported associations in both the observational and randomized analyses are significantly lower than the associations between blood pressure and risk of stroke and ischemic heart disease. In a meta-analysis of 147 blood pressure lowering trials, a 20 mm Hg reduction in systolic blood pressure was associated with a 39% reduction in CHD events (HR 0.61 CI 0.53, 0.69) and a 65% reduction in stroke events (HR 0.35 CI 0.27, 0.45)¹⁵, consistent with observational associations reported from Prospective Studies Collaboration.¹² Assuming causality, these results therefore suggest that individual-level efforts to reduce blood pressure will have a much greater effect on prevention of cardiovascular disease through prevention of ischemic heart disease and stroke, rather than prevention of atrial fibrillation. However, among individuals at high absolute risk of atrial fibrillation, such as those with a family history of the disease¹⁶⁷, blood pressure lowering may still result in a substantial reduction in risk of atrial fibrillation. Furthermore, at a population level, even small reductions in blood pressure, particularly at middle age, may result in societally important reductions in atrial fibrillation.

In addition to allowing for investigation of population-specific effects of antihypertensive therapy, inclusion of all large antihypertensive trials also allowed for the examination of evidence for antihypertensive class-specific effects on atrial fibrillation. When compared against all active comparators, ACE-inhibitors, ARBs, calcium channel blockers and diuretics were not observed to be more effective than other classes of medication. There was the suggestion that beta-blockers may be less effective than angiotensin receptor blockers in patients with hypertension, although

this estimate was derived from a single trial.³⁶ However, this analysis largely rules out the existence of significant class-specific effects on risk of atrial fibrillation, particularly renin-angiotensin specific effects above and beyond those provided by diuretics or calcium channel blockers.

The absence of a clear class-specific effect contrasts markedly with previous observational analyses and meta-analyses of randomized trials. A propensity score matched analysis of the Danish population from 1995 to 2010 concluded that the use of ACE-inhibitors and ARBs was associated with an approximate 90% risk reduction for the onset of atrial fibrillation compared to beta-blocker therapy and a 50% risk reduction for the onset of atrial fibrillation compared to diuretics.¹⁶⁸ These results were interpreted as evidence that renin-angiotensin inhibition significantly reduces the risk of atrial fibrillation, above and beyond the effect of blood pressure lowering. Similarly, an analysis of CPRD concluded that use of ACE-inhibitors, ARBs and beta-blockers are associated with 25% (OR 0.75 CI 0.65, 0.87), 29% (OR 0.71 CI 0.57, 0.89) and 22% (OR 0.78 CI 0.67, 0.92) lower risk of atrial fibrillation relative to CCBs, respectively.¹⁶⁹ A case-control study of 810 AF cases and 1512 controls concluded that use of ACE-inhibitors/ARBs was associated with a 37% lower risk of prevalent atrial fibrillation than diuretic use (OR 0.63 CI 0.44–0.91).¹⁷⁰ The current analysis of randomized trials indicates that the reported effects from such non-randomized comparisons are likely due to uncontrolled confounding.

With regard to randomized evidence, a meta-analysis of trials of beta-blockers in heart failure demonstrated a 27% reduction in onset of atrial fibrillation through beta-blocker therapy. The authors speculated that this observed effect may be due to beta-blockers' ability to prevent ventricular remodeling or their ability to shorten the action potential through beta adrenergic stimulation.¹³³ Similarly, in a meta-analysis

concluding that renin-angiotensin inhibitors reduce the risk of atrial fibrillation by 33%, authors suggested that this effect was greater than that predicted by blood pressure lowering alone.³⁷ This analysis demonstrates that these proposed class-specific effects are due to meta-analyses examining only a portion of the evidence, and not undertaking a comprehensive examination of all trials investigating antihypertensive therapy.

This analysis has several strengths. To my knowledge, this is the largest meta-analysis of the effects of antihypertensive therapy on risk of atrial fibrillation. The unique search strategy used (attempting to identify all large blood pressure lowering trials and individually searching for reporting of atrial fibrillation events) allowed me to identify trials that would have been missed if key words for atrial fibrillation were used in the search strategy. Additionally, the comprehensive approach of attempting to identify all trials using antihypertensive therapies applied in this meta-analysis allows valid conclusions to be drawn on the existence of class-specific effects and analysis of effects by subgroups of patients. However, this analysis also has several limitations. First, eleven trials reported atrial fibrillation as an investigator reported adverse event, and the majority of the trials included in this analysis reported atrial fibrillation in a post-hoc manner (rather than a primary or secondary adjudicated endpoint). However, removal of trials reporting atrial fibrillation as an adverse event in a sensitivity analysis had no effect on the results and prior analyses on the impact of adjudication have suggested that adjudication has little effect on reported relative risks.^{136,138} Second, propensity for post-hoc analyses on atrial fibrillation to be published if significant may be a source of bias. Although this would be expected to bias the results towards the extreme, I did not observe an effect for antihypertensive therapy to prevent atrial fibrillation in many of the included trials. Third, the relatively

short follow up of included trials (the majority with a median follow up less than five years) may have precluded a longer term effect of blood pressure lowering on risk of atrial fibrillation from being observed. A fourth limitation of this analysis is that I did not have access to individual patient data, which would have allowed detailed time-to-event analyses. In meta-analyses of longer term studies when information about timing of the events is not available, shorter term treatment effects may be missed if a large proportion of people has experienced an event by the end of the study. A large individual patient data meta-analysis, such as the Blood Pressure Lowering Treatment Trialists' Collaboration, is better suited to investigate this possibility comprehensively.¹⁰⁰ Alternatively, the relatively short follow up of trials included in this meta-analysis (mean follow up of 3.44 years in the five non-heart disease trials) may have prevented a long term effect of antihypertensive therapy on risk of atrial fibrillation from being observed.

4.5 Conclusions

While antihypertensive therapy is associated with a significant 10% relative reduction in the risk of atrial fibrillation, proportional effects were greater in patients with heart failure. Although no significant effect of antihypertensive therapy on risk of atrial fibrillation was observed in populations without heart disease, the magnitude of the estimate from randomized evidence was consistent with that observed in the observational analysis of the prior chapter, suggesting that the lack of a significant effect of BP lowering on atrial fibrillation observed in randomized trials is due to a lack of power. In contrast with previous analyses, I found little evidence to support class specific effects of antihypertensive therapies on risk of atrial fibrillation.

Chapter 5 Association of blood pressure with risk of new onset diabetes: an observational analysis of 4.1 million adults

5.1 Introduction

In 2011, type 2 diabetes affected 366 million people worldwide and this prevalence is estimated to increase to 552 million by 2030.¹⁷¹ As with atrial fibrillation, type 2 diabetes is associated with an increased risk of major cardiovascular events, including ischemic heart disease, stroke and heart failure.¹⁷² In a contemporary analysis of a United Kingdom primary care population, type 2 diabetes was associated with twice the risk of all-cause mortality and three times the risk of cardiovascular mortality relative to age and sex-matched controls.¹⁷³ Consequently, prevention of diabetes is of critical importance for reducing the burden of cardiovascular disease.

While high blood pressure has long been recognized as an independent risk factor for fatal and non-fatal vascular events¹², the reports of the relationship between blood pressure and risk of new onset diabetes has been less consistent. Elevated blood pressure is associated with chronic inflammation⁴⁴ and endothelial dysfunction⁴⁷, both of which have been suggested to be mediators of new onset diabetes.^{42,46} There is, therefore, a biological rationale to suspect that elevated blood pressure may cause new onset diabetes. Indeed, in an analysis of the Women's Health Study with 38172 women and 1672 cases of new onset diabetes, women with hypertension (>140/90 mm Hg or prescription of antihypertensives) were at two times the risk of diabetes as women with a systolic blood pressure between 120-129 mm Hg (HR 2.03 CI 1.77, 2.32). However, among 30 cohort studies that have reported the association of blood pressure with new onset diabetes, 12 have concluded that no such association is apparent, while the others reported a considerably variable strength of association

(Table 5.1). In a South Korean cohort of 14 045 individuals with 246 new onset diabetes events, no association between blood pressure and risk of diabetes was observed.⁵¹ Moreover, even the largest previous cohorts have had limited power to investigate whether any observed positive association between blood pressure and new onset diabetes varied significantly by important patient features.⁴⁹

Table 5.1 Previous analyses of the relationship between blood pressure and risk of new onset diabetes.

Study (Author, Year)	Name of Cohort(s)	Location	Baseline Year	Population	Participants	Incident Diabetes	Adjustments	Median Follow Up (Years)	Was a significant association between BP and diabetes observed?
<i>Previous cohort studies</i>									
Ohlson, 1988 ¹⁷⁴	Gothenburg 1913 Cohort	Gothenburg, Sweden	1967	General population, men born in 1913	766	47	Adjusted for body mass index, family history of diabetes, other clinical/demographic variables	13.5	Yes
Stolk, 1993 ¹⁷⁵	Zoetermeer	Zoetermeer, Netherlands	1975-1978	Men from general population	3809	65	Stratified by sex, adjustment for age, body mass index	11.5	Yes for men, no for women
Li, 1994 ¹⁷⁶	Daqing (Li)	Daqing, China	1986	General population	465	125	Age, body mass index, sex, fasting glucose	6	Yes
Mykkanen, 1994 ¹⁷⁷	Kuopio	Kuopio, Finland	1986-1988	Elderly subjects aged 65-74	805	60	Age, sex, body mass index, 2-h insulin and other clinical/demographic variables	3.5	No
Burchfiel, 1995 ¹⁷⁸	Honolulu Heart Program 45-54	Hawaii, United States	1965-1968	Men from general population	5863	334	Age, body mass index, exercise, other clinical/demographic characteristics (restricted to men)	6	Yes
Perry, 1995 ¹⁷⁹	British Regional Heart Study	United Kingdom	1978-1980	Men from general population	7097	194	Age, body mass index, exercise, other clinical/demographic characteristics	12.8	No
Njolstad, 1998 ¹⁸⁰	Finnmark	Finnmark, Norway	1977-1978	General population	11654	162	Age, body mass index, cholesterol, other clinical/demographic characteristics	12	No
Hayashi, 1999 ¹⁸¹	Osaka Health Survey	Osaka, Japan	1981-1991	Male employees of a gas company	7594	600	Age, body mass index, alcohol consumption, smoking habit, other clinical/demographic variables	9.6	Yes
Chihaooui, 2000 ¹⁸²	Tunis	Tunis, Tunisia	1985	General population	701	77	Stratification by age, adjustment for body mass index, age, family history of diabetes, other clinical/demographic variables	10	No
Bjornholt, 2001 ¹⁸³	Oslo	Oslo, Norway	1972	Healthy men	1947	143	Age, body mass index, family history of diabetes, other clinical/demographic variables	22.5	No
Golden, 2003 ¹⁸⁴	Johns Hopkins Precursor Study	Baltimore, United States	1948-1964	Male former medical students	1152	77	body mass index, family history of diabetes, smoking, physical activity	38	Yes
Kumari, 2004 ⁵²	Whitehall II	London, United Kingdom	1985-1988	Men from general population	8386	361	Stratified by sex, adjusted for age, body mass index, other demographic/clinical characteristics	10.5	No
Conen, 2007 ⁴⁹	Women's Health Study	United States	1993	Female health professionals	15982	599	Age, body mass index, ethnicity, alcohol consumption, family history of diabetes, other clinical and demographic characteristics	10.2	Yes

Norberg, 2007 ¹⁸⁵	Vasterbotten Health Study	Vasterblott en, Sweden	1989-2000	General population	513	177	Stratification by sex, adjustment for age, body mass index, glucose and other clinical/demographic variables	8.8	No
Meisinger, 2008 ¹⁸⁶	MONICA Augsburg	Augsburg, Germany	1984-1985/1989-1990/1994-1995	General population	6166	213	Stratified by sex, adjusted for age, survey and body mass index	7.6	Yes
Mullican, 2009 ¹⁸⁷	San Antonio Heart Study	San Antonio, United States	1979-1988	Mexican Americans and non-Hispanic Whites in General Population	2767	213	Age, sex, body mass index, ethnicity, family history of diabetes, other clinical/demographic characteristics	7.8	No
Weycker, 2009 ¹⁸⁸	Kaiser	United States	1998	General population	104368	7706	Age, sex, body mass index	5	Yes
Hatami, 2010 ¹⁸⁹	Tehran Lipid and Glucose	Tehran, Iran	1999-2001	Women from general population	3028	220	Stratification by family history of diabetes, adjustment for age, body mass index, other demographic/clinical variables	6.4	Yes with no family history of diabetes, no with family history of diabetes
Kramer, 2010 ¹⁹⁰	Rancho Bernardo	California, United States	1984-1987	Middle-class Caucasian adults	1125	85	Age, sex, body mass index, family history of diabetes, physical activity	8.3	Yes
Lee, 2010 ⁵¹	Seoul	Seoul, Korea	2003-2008	General population	14054	246	Age, sex, body mass index and fasting glucose	5	No
Nagaya, 2010 ¹⁹¹	Nagoya	Nagoya, Japan	1988-1991	General population without disease	25196	1093	Matched for age, adjusted for body mass index, cholesterol and other clinical/demographic variables	8.2	Yes
Sawada, 2010 ¹⁹²	Tokyo Gas Company	Tokyo, Japan	1985	Men from gas company	4187	274	Age, body mass index, alcohol, smoking, other clinical/demographic variables	14	Yes
Fukui, 2011 ⁵⁰	Kyoto	Kyoto, Japan	1998-2003	General population	4304	262	Age, sex, body mass index, cholesterol, other clinical/demographic variables	5	No
Wei, 2011 ¹⁹³	ARIC/CARDIA/Framingham	United States	1987-1989/1985-1986/1971-1975	General population	10593	1029	Age, sex, body mass index, cholesterol, other clinical/demographic variables	8.9	Yes
Stahl, 2012 ¹⁹⁴	Gothenburg Primary Prevention Study	Gothenburg, Sweden	1970-1973	Men from general population	7333	509	Age, body mass index, antihypertensive treatment, cholesterol, other demographic/clinical variables	28	Yes
Previous observational analyses of randomized trials									
Niklason, 2004 ¹⁹⁵	CAPPP	Sweden and Finland	1990-1994	Untreated hypertensive individuals	5033	NA	Age, body mass index, other clinical characteristics (sex not independently associated)	6.1	No
Barzilay, 2006 ¹⁹⁶	ALLHAT	United States/Canada	1994-1998	Hypertension, coronary heart disease risk factor	6486	534	Age, sex, ethnicity, body mass index, randomized treatment, other clinical/demographic variables	2	Yes

Gupta, 2008 ¹⁹⁷	ASCOT	UK/Ireland /Nordic countries	1998-2000	Hypertensive individuals with cardiovascular risk factors	14120	1366	Age, sex, body mass index, randomized treatment, other clinical/demographic characteristics	5.5	Yes
Yasuno, 2010 ¹⁹⁸	CASE-J	Japan	2001-2002	High cardiovascular risk hypertensive patients	2685	97	Age, sex, body mass index, anihypertensive use, other demographic/clinical variables	3.3	No
Okin, 2013 ¹⁹⁹	LIFE	United States, Europe	1995-1997	Hypertension and left ventricular hypertrophy	7485	520	Age, sex, body mass index, anihypertensive use, other demographic/clinical variables	4.7	Yes
<i>Current study</i>									
Emdin, 2015	CPRD	United Kingdom	1990-2012	General population, free of vascular disease	4132138	186698	Age, body mass index, smoking status, other clinical/demographic characteristics	6.8	Yes

A detailed understanding of blood pressure as a potential risk factor for diabetes will help to better understand and communicate risks with patients and can lead to more targeted approach to prevention and management. I therefore undertook an analysis of 4.1 million individuals free from diabetes and cardiovascular disease, in a contemporary United Kingdom primary care population, and a meta-analysis of existing prospective studies, to reliably determine the association between blood pressure and new onset diabetes.

5.2 Methods

5.2.1 Participants, exposures and endpoints

As described in the general methods section, I utilized prospectively collected records from the UK Clinical Practice Datalink (CPRD) to assemble a cohort of 4.1 million patients free from vascular disease and diabetes. All patients with pre-existing vascular disease (ischemic heart disease, cerebrovascular disease, heart failure, peripheral vascular disease and renal disease) and diabetes (either type 1 or type 2) were excluded. Baseline covariates were defined as specified in the general methods section.

The primary outcome was a diagnosis of type 2 diabetes, defined as either clinical diagnosis of type II diabetes or diabetes unspecified (as 90% of diabetes cases are type II²⁰⁰) or prescription of insulin/antidiabetic drugs, as defined in the British National Formulary (BNF) chapters 6.1.1 and 6.1.2. Participants were censored at the earliest of an occurrence of the primary outcome, transfer out of practice, death or last collection date of practice.

5.2.2 Statistical analysis

Cox models, stratified by practice to account for clustering at the practice level, were used to determine hazard ratios for blood pressure categories for each outcome. The primary analysis was adjusted for age, gender, body mass index, smoking status, baseline

antihypertensive use and baseline lipid lowering agent use, although further adjustment was undertaken in sensitivity analyses (listed below). Multiple imputation using chained equations was used to impute missing covariates; five imputations were generated. In order to correct for regression dilution bias, regression dilution ratios were calculated by regressing serial measurements on baseline values using generalized estimating equations. Regression dilution ratios of 2.1 for systolic blood pressure and 2.5 for diastolic blood pressure were estimated.

5.2.3 Sensitivity analyses

Eight sensitivity analyses were conducted. First, models were further adjusted for total cholesterol and HDL cholesterol. Second, models were further adjusted for year of the initial BP measurement, as a categorical variable (1990-1994, 1995-1999, 2000-2004, 2005-2009, 2010-2013) and socioeconomic status. Third and fourth, to minimize the risk of reverse causality, individuals with either a diagnosis of diabetes or a cardiovascular event in the first two years of follow up and in the fourth year of follow up were excluded. Fifth, individuals prescribed antihypertensive medication or lipid lowering drugs at baseline or during follow up were excluded, as statins and classes of antihypertensives have been associated with an increased risk of new onset diabetes.^{53,201} Sixth, diagnosis of diabetes was defined as explicit diagnosis of type II diabetes (that is, excluding individuals who were only diagnosed with unspecified diabetes or prescribed antidiabetic medicine without a concomitant diagnosis of type II diabetes). Seventh, analysis was restricted to after 2006, after which the World Health Organization and UK guidelines revised their criteria for diagnosis of diabetes. Eighth, only death due to diabetes was examined, to mitigate the risk that individuals with elevated blood pressure are more likely to be diagnosed with diabetes.

5.2.4 Meta-analysis

A systematic search strategy was designed and conducted by an experienced research librarian to identify previous studies of the association between blood pressure and risk of new onset diabetes. The strategy included MeSH terms and synonyms for the terms blood pressure, incident and diabetes. MEDLINE was searched from 1966 to January 2015, with no language restrictions applied. Prospective observational studies, including observational analyses of randomized trials, were eligible for inclusion if they: (1) had at least one year of follow up, (2) reported a risk per unit of systolic blood pressure that could be standardized to 20 mm Hg higher systolic blood pressure and (3) adjusted for, at minimum, sex, age and body mass index. Body mass index was required for adjustment as it is a strong risk factor for new onset diabetes¹⁷⁹ and is associated with elevated blood pressure.⁸⁴ Therefore, any study that did not adjust for body mass index would likely be confounded, as elevated body mass index would cause both new onset diabetes and elevated blood pressure. Studies conducted in populations immediately after renal transplantation and studies that examined gestational diabetes were excluded. Measures of relative risks (e.g. hazard ratios, odds ratios), difference in blood pressure, study population, number of incident diabetes events and degree of adjustment were extracted in duplicate. As no study adjusted for regression dilution bias, I pooled relative risks standardized to 20 mm Hg higher usual systolic blood pressure by multiplying the reported relative risks per 20 mm Hg higher measured systolic blood pressure by the calculated regression dilution coefficient. Random effects meta-analysis was used due to the presence of high heterogeneity ($I^2 > 50\%$). Test for interaction between subgroups was performed using Cochran's Q test.

One study reported a relative risk of new onset diabetes per 10 mm Hg higher diastolic blood pressure; this was assumed to correspond to a relative risk per 20 mm Hg higher systolic blood pressure. Five studies reported relative risks of new onset diabetes

comparing one fifth of blood pressure relative to another fifth but did not explicitly reported a difference in systolic blood pressure between fifths.^{49,178,179,182,192} A normal approximation was therefore assumed to determine the approximate difference in blood pressure between fifths to allow for standardization per 20 mm Hg higher systolic blood pressure. These five studies were excluded in a sensitivity analysis.

Analyses were performed using R version 3.0.

5.3 Results

5.3.1 Characteristics of participants

4 694 120 individuals in the CPRD cohort had at least one blood pressure measurement with at least one year of follow-up and were between the ages of 30 and 90 years, inclusive. After excluding 195 623 patients with existing diabetes and an additional 366 359 patients who had pre-existing cardiovascular disease, I identified a cohort of 4 132 138 individuals (Figure 5.1).

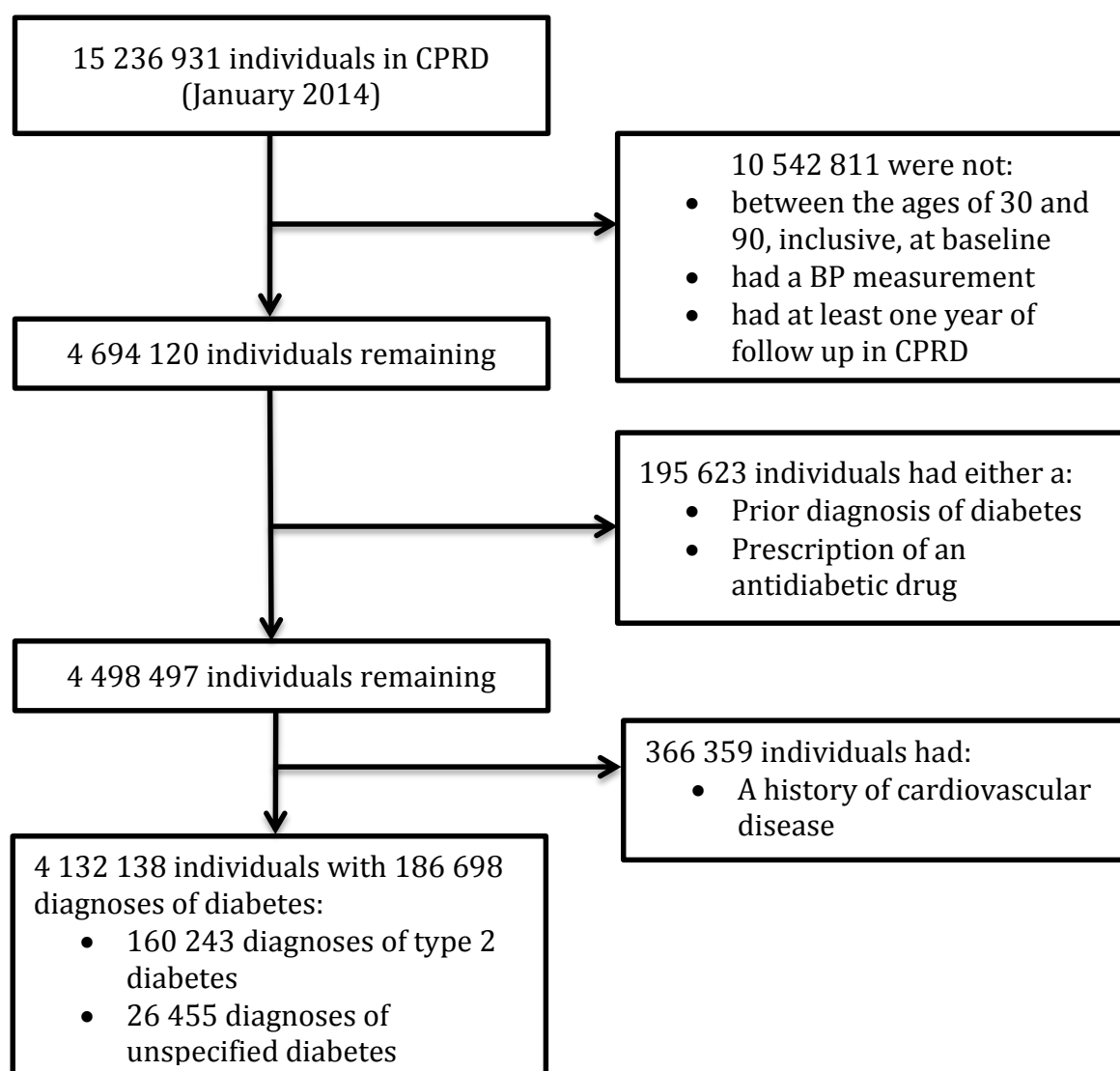


Figure 5.1 Flowchart of cohort identification.

Baseline characteristics for participants are provided in Table 5.2. 2 310 268 (55.9%) participants were women. 28.2% of participants were smokers; the proportion of smokers decreased with increasing blood pressure, from 30.1% of smokers at usual systolic blood pressure <127 mm Hg to 25.2% of smokers at usual systolic blood pressure > 136 mm Hg. Total cholesterol also increased with increasing blood pressure, from 5.2 mmol/L at usual systolic blood pressure <127 mm Hg to 5.7 mmol/L at >136 mm Hg. The median age was 46 years (IQI 36, 59) while the median body mass index, prior to imputation, was 25.7 kg/m² (IQI 23.0, 29.2). Prescription of antihypertensive medications at baseline and during follow up increased with increasing blood pressure; 3.6% and 13.0% of individuals

with a usual systolic blood pressure <127 mm Hg were prescribed antihypertensives at baseline and during follow up, respectively, while 19.1% and 52.2% of individuals with a usual systolic blood pressure >136 mm Hg were prescribed antihypertensives at baseline and during follow up, respectively. The proportion of women decreased with increasing usual blood pressure; 66.7% of individuals with a usual systolic blood pressure <127 mm Hg were women while 49.8% of individuals with a usual systolic blood pressure >136 mm Hg were women. Over a median follow up of 6.8 years, 186 698 cases of new onset diabetes were observed.

Table 5.2 Baseline characteristics of participants stratified by baseline usual blood pressure.

	<u>Baseline Usual BP¹</u>			
	<127 mm Hg	127-136 mm Hg	>136 mm Hg	Overall
N	1 474 462	1 541 802	1 115 874	4 132 138
Years of Follow-up (IQI)	6.4 (2.7, 11.1)	6.7 (3.0, 11.0)	7.3 (3.4, 11.2)	6.8 (3.0, 11.1)
Age at Baseline (years, IQI)	39 (33, 48)	46 (37, 57)	59 (48, 70)	46 (36, 59)
Women	983 263 (66.7%)	771 273 (50.0%)	555 732 (49.8%)	2 310 268 (55.9%)
Body mass index (kg/m ² , IQI)	24.3 (21.9, 27.3)	26.2 (23.5, 29.6)	27.3 (24.4, 30.9)	25.7 (23.0, 29.2)
<i>Smoking Status</i>				
Current Smoker	369263 (30.1%)	356553 (28.4%)	218099 (25.2%)	943915 (28.2%)
Never Smoker	671681 (54.7%)	677155 (53.9%)	469610 (54.2%)	1818446 (54.3%)
Ex Smoker	186428 (15.2%)	223496 (17.8%)	179436 (20.7%)	589360 (17.6%)
<i>Cholesterol (mmol/L)</i>				
Total (IQI)	5.2 (4.6, 6.0)	5.5 (4.8, 6.2)	5.7 (5.0, 6.4)	5.5 (4.8, 6.3)
HDL (IQI)	1.4 (1.1, 1.7)	1.4 (1.2, 1.7)	1.3 (1.1, 1.6)	1.4 (1.1, 1.7)
Most deprived fifth	275 902 (18.7%)	286 718 (18.6%)	217 095 (19.5%)	779 715 (18.9%)
<i>Medication Usage</i>				
Antihypertensive at baseline	53248 (3.6%)	124596 (8.1%)	212781 (19.1%)	390 625 (9.5%)
Antihypertensive during follow up	191575 (13.0%)	381426 (24.7%)	581966 (52.2%)	1154967 (28.0%)
Lipid lowering at baseline	10037 (0.7%)	24215 (1.6%)	24604 (2.2%)	58 856 (1.4%)
Lipid lowering during follow up	98305 (6.7%)	214055 (13.9%)	280189 (25.1%)	592549 (14.3%)

IQI refers to interquartile interval (25th percentile, 75th percentile). Proportion of variables missing: body mass index (31.2%), smoking status (18.9%), total cholesterol (74.6%), HDL cholesterol (81.3%). No other variables contained missing values.

¹Note that baseline usual blood pressure categories of < 127 mm Hg, 127-136 mm Hg and >136 mm Hg correspond to baseline measured blood pressure categories of <121 mm Hg, 121-140 mm Hg and >140 mm Hg.

5.3.2 Associations of usual blood pressure with new onset diabetes

Usual systolic blood pressure was continuously related to risk of new onset diabetes (Figure 5.2). Although there was no evidence of a nadir down to a usual systolic blood

pressure level of 110 mm Hg, a flattening of the curve was observed below approximately 120 mm Hg. The association was strongest among individuals with a normal to mildly elevated BP, with an additional flattening of the curve above 150 mm Hg. Usual diastolic blood pressure was also continuously related to risk of new onset diabetes, with no evidence of a nadir or plateau in the range 70 mm Hg to 100 mm Hg (Figure 5.2). Overall, a 20 mm Hg higher systolic blood pressure and a 10 mm Hg higher diastolic blood pressure were associated with a 58% increase (HR 1.58 CI 1.56, 1.59) and 52% increase (HR 1.52 CI 1.51, 1.54) in risk, respectively, of newly diagnosed diabetes.

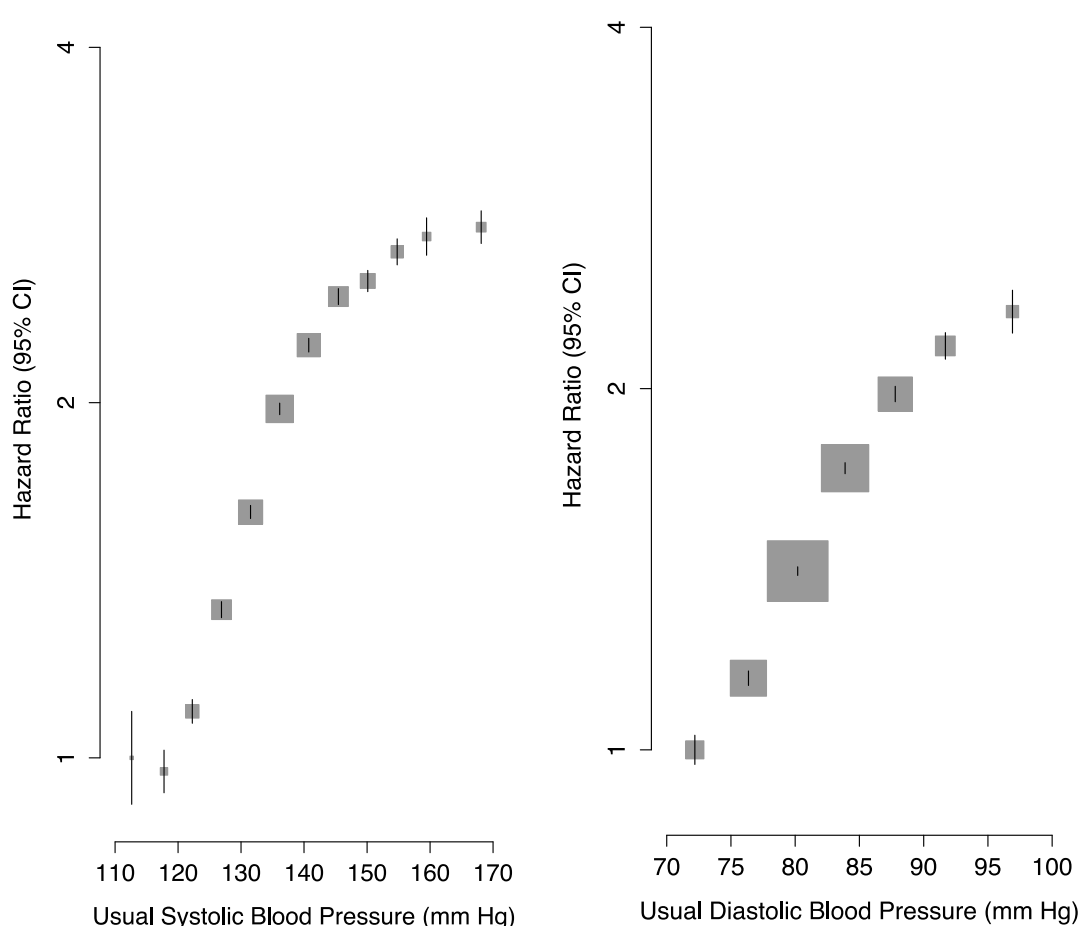


Figure 5.2 Adjusted hazard ratio of systolic blood pressure categories and diastolic blood pressure categories for incident diabetes. Adjustments were for age, body mass index, smoking status, gender and blood pressure category (plotted). Confidence intervals are displayed as floating absolute risks. Area of each square is proportional to the inverse variance of the estimate.

The association between systolic blood pressure and newly diagnosed diabetes was modified by baseline body mass index and age (Figures 5.2 and 5.3). A 20 mm Hg higher systolic blood pressure was associated with a greater proportional increase in the risk of diabetes among individuals with a body mass index ≤ 25 kg/m² (HR 1.89 CI 1.84, 1.94) than among individuals with a body mass index >35 kg/m² (HR 1.19 CI 1.16, 1.22; p interaction <0.0001). However, the higher baseline absolute risk at body mass index >35 kg/m² resulted in larger absolute risk increases in new onset diabetes per 20 mm Hg higher systolic blood pressure in this high body mass index range (Figure 5.3). As with the overall curve, there appeared to be a plateau at a usual systolic blood pressure of 120 mm Hg for each of the body mass index strata.

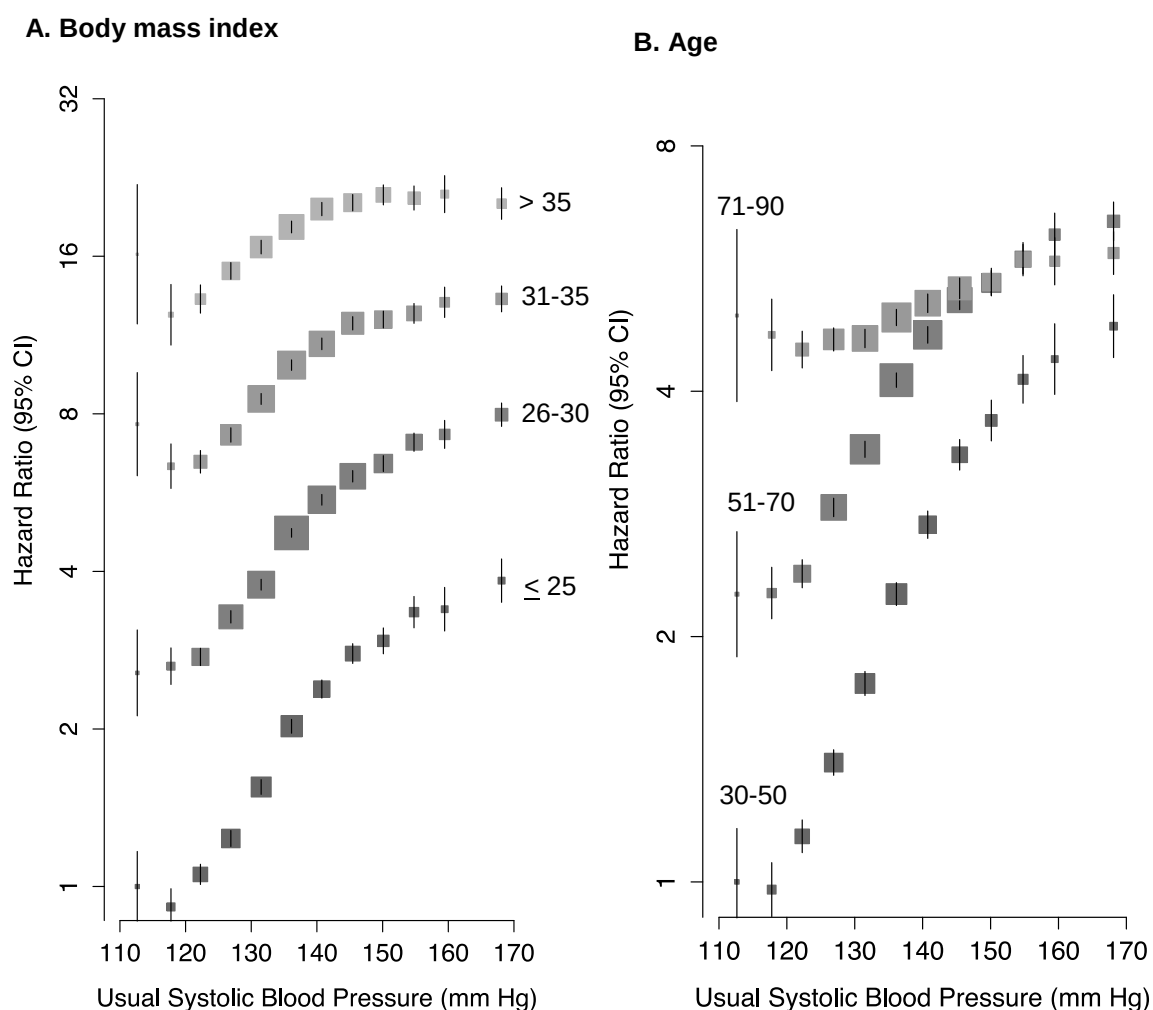


Figure 5.3 Adjusted hazard ratio for diabetes of (A) systolic blood pressure and body mass index categories (<25, 25-30, 31-35, >35), and (B) systolic blood pressure and age categories (30-50, 51-70, 71-90). Models are adjusted for smoking status and gender, in addition to age for (A) and body mass index for (B). Adjusted hazard ratios of systolic blood pressure for incident atrial fibrillation by (A) body mass index and (B) age. Adjustments were for smoking status, sex and the interaction between systolic blood pressure as a categorical variable and (A) body mass index category (plotted) and (B) age category (plotted). Confidence intervals are displayed as floating absolute risks. Area of each square is proportional to the inverse variance of the estimate. Note the differing scales.

A 10 mm Hg higher usual diastolic blood pressure was associated with a 73% higher risk of diabetes among individuals with a body mass index < 20 kg/m² (HR 1.73 CI 1.68, 1.78), while it was associated with a 19% higher risk among individuals with a body mass index >35 kg/m² (HR 1.19 CI 1.16, 1.22; *p* interaction <0.0001).

The relative risk of new onset diabetes per 20 mm Hg higher usual systolic blood pressure declined with increasing age, from an HR of 2.00 (CI 1.96, 2.04) at age 30 to 50

years to an HR of 1.14 (CI 1.11, 1.17) at age 71 to 90 years (Figures 5.3 and 5.4). However, because of the increasing absolute risk of diabetes with older age, the absolute risk differences per 20 mm Hg usual systolic blood pressure were similar across the different age groups despite the declining relative risks. Risk of diabetes per 10 mm Hg higher diastolic blood pressure similarly declined with increasing age, from an HR of 1.89 (CI 1.86, 1.92) to an HR 1.01 (CI 0.98, 1.04) (Figure 5.4).

The association of new onset diabetes with blood pressure appeared modestly stronger in men than in women. A 20 mm Hg higher systolic blood pressure was associated with a 61% higher risk of new onset diabetes in men but a 54% higher risk of new onset diabetes in women (HR 1.61 CI 1.59, 1.64 vs. HR 1.54 CI 1.52, 1.56, respectively; p interaction < 0.0001). A 10 mm Hg higher diastolic blood pressure was associated with a 57% higher risk of new onset diabetes in men while a 47% higher risk of new onset diabetes in women (Figure 5.4).

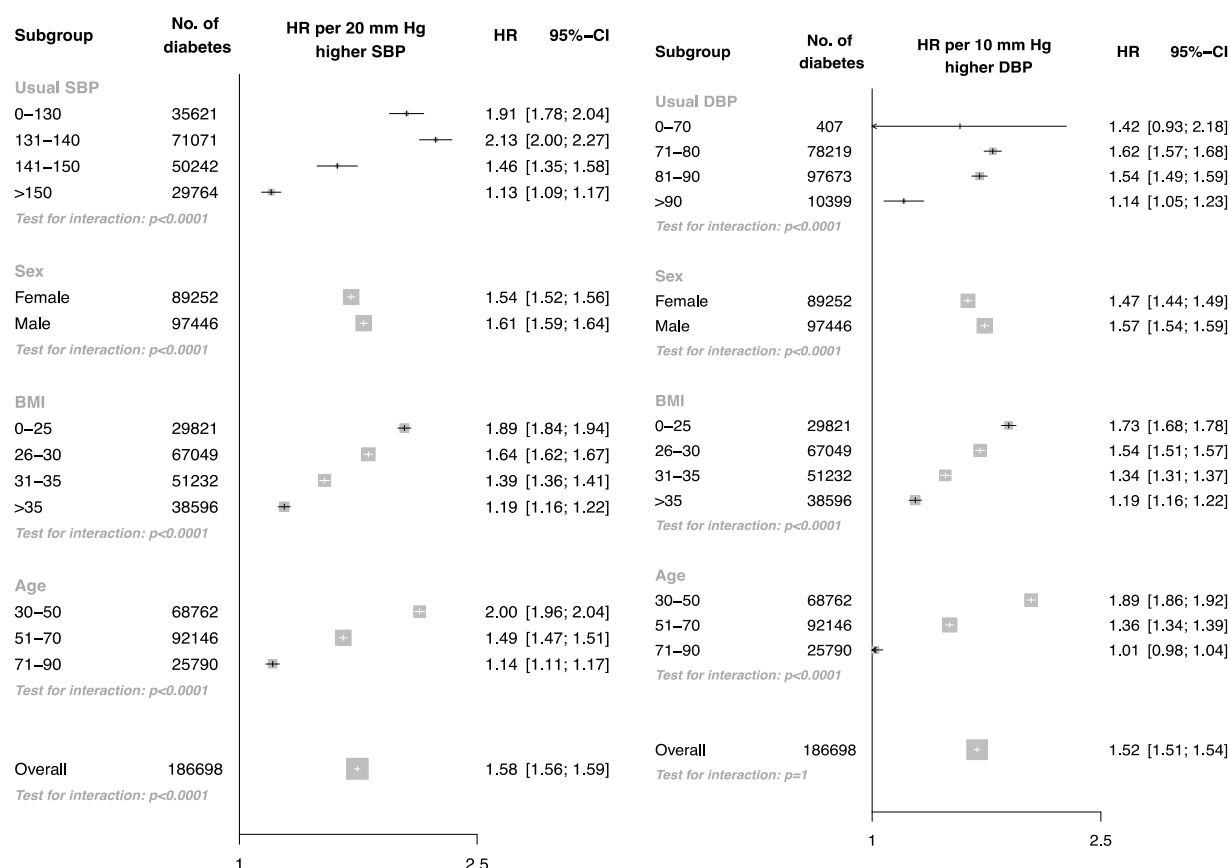


Figure 5.4 Adjusted hazard ratios of a 20 mm Hg higher systolic blood pressure for incident diabetes by blood pressure, sex, body mass index and age. Adjustments were for age, sex, body mass index, baseline antihypertensive use and baseline lipid use. For subgroups of age, adjustment was also for age category and the interaction between systolic BP and age category (plotted). For subgroups of sex, adjustment was also for the interaction between sex and systolic BP (plotted). For subgroups of body mass index, adjustments were also for body mass index category and the interaction between systolic BP and body mass index category (plotted). Area of each square is proportional to the inverse variance of the estimate.

5.3.3 Sensitivity analyses

When all individuals prescribed blood pressure lowering drugs or statins at baseline or during follow-up were excluded in a sensitivity analysis, estimates were similar; 20 mm Hg higher systolic blood pressure was associated with a 52% higher risk of new onset diabetes (HR 1.52 CI 1.49, 1.56; Figure 5.5). However, the interactions by body mass index and age appeared modestly attenuated, with similar strengths of associations among individuals with a body mass index of 0-25 kg/m² and 26-30 kg/m², and among individuals of age 30 to 50 and 51 to 70. Further adjustment for total cholesterol, HDL cholesterol,

socioeconomic status and period of initial BP measurement also had little effect on estimated associations between systolic blood pressure and risk of new onset diabetes (Figures 5.6 and 5.7). After adjustment for cholesterol, 20 mm Hg higher systolic blood pressure was associated with a 59% higher risk of new onset diabetes (HR 1.59 CI 1.57, 1.61), and after further adjustment for socioeconomic status and period of blood pressure measurement, 20 mm Hg higher systolic blood pressure was associated with a 59% higher risk of new onset diabetes (HR 1.59 CI 1.58, 1.61).

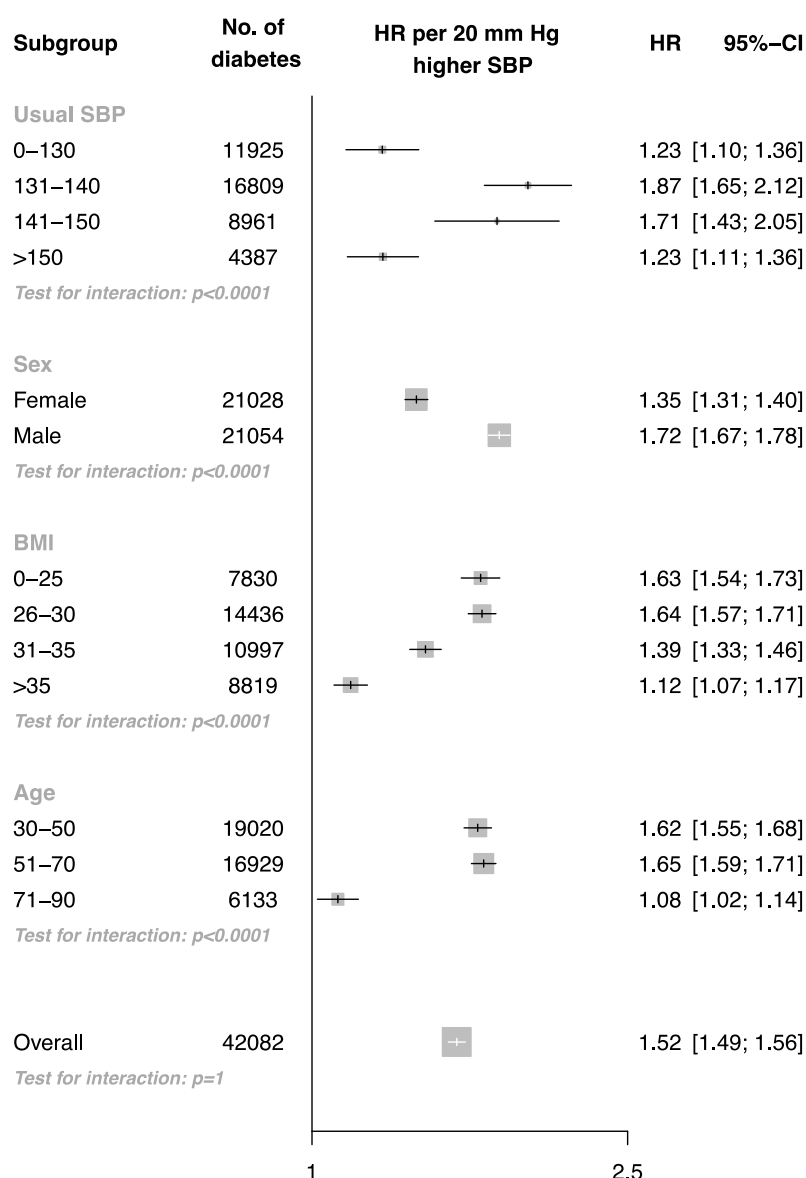


Figure 5.5 Adjusted hazard ratios of a 20 mm Hg higher systolic blood pressure for incident diabetes by blood pressure, sex, body mass index and age. All individuals prescribed lipid lowering drugs or antihypertensives at baseline or at any time during follow up are excluded. Adjustments were for age, sex, body mass index, baseline antihypertensive use and baseline lipid use. For subgroups of age, adjustment was also for age category and the interaction between systolic BP and age category (plotted). For subgroups of sex, adjustment was also for the interaction between sex and systolic BP (plotted). For subgroups of body mass index, adjustments were also for body mass index category and the interaction between systolic BP and body mass index category (plotted). Area of each square is proportional to the inverse variance of the estimate.

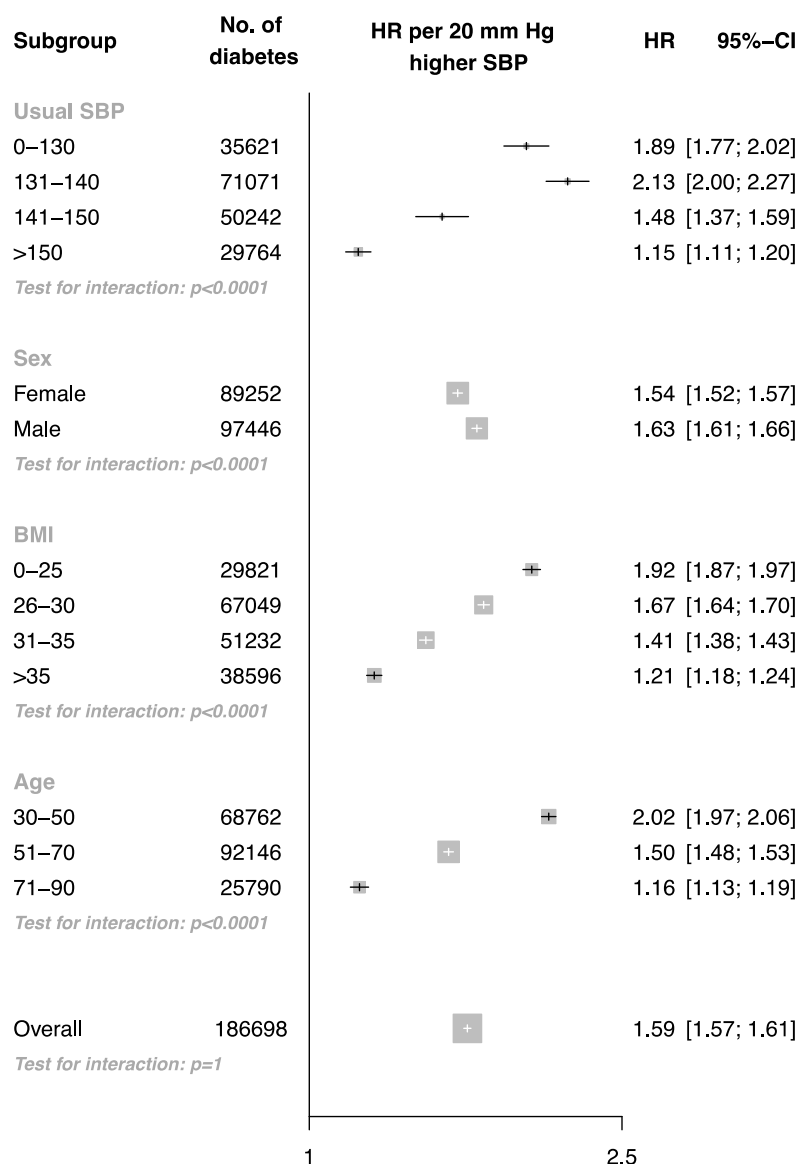


Figure 5.6 Adjusted hazard ratios of a 20 mm Hg higher systolic blood pressure for incident diabetes by blood pressure, sex, body mass index and age after adjustment for cholesterol. Adjustments were for age, sex, body mass index, baseline antihypertensive use, baseline lipid use, total cholesterol and HDL cholesterol. For subgroups of age, adjustment was also for age category and the interaction between systolic BP and age category (plotted). For subgroups of sex, adjustment was also for the interaction between sex and systolic BP (plotted). For subgroups of body mass index, adjustments were also for body mass index category and the interaction between systolic BP and body mass index category (plotted). Area of each square is proportional to the inverse variance of the estimate.

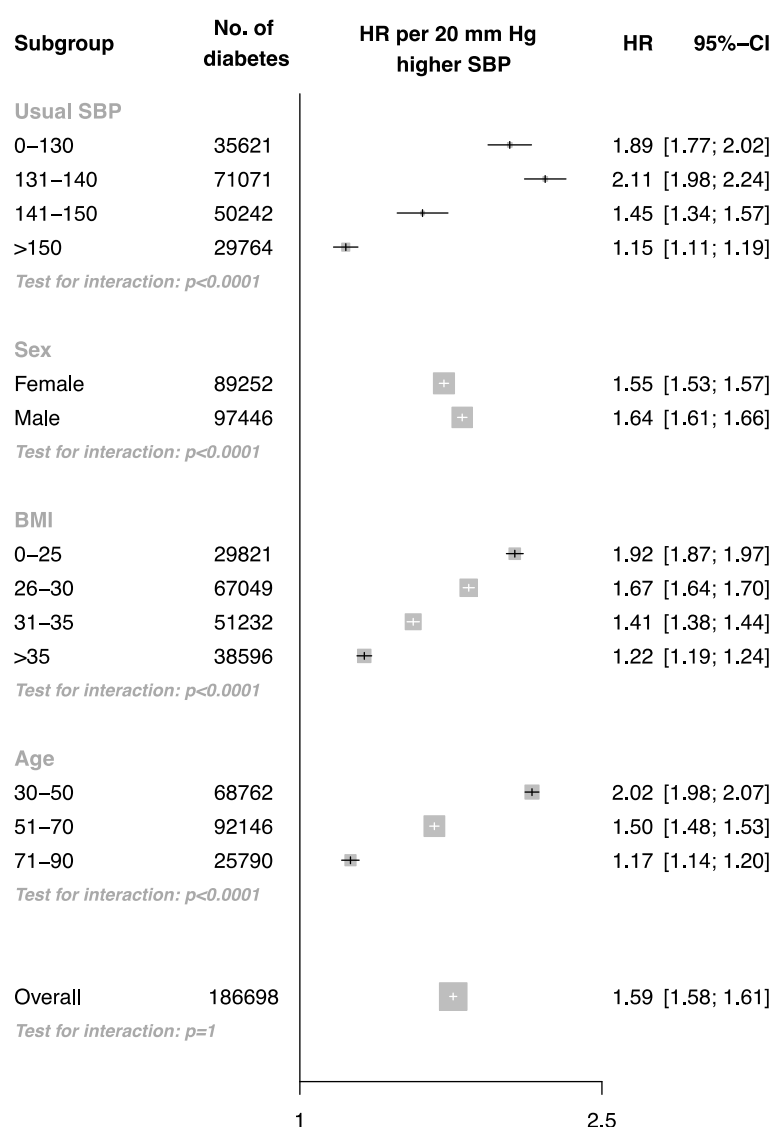


Figure 5.7 Adjusted hazard ratios of a 20 mm Hg higher systolic blood pressure for incident diabetes by blood pressure, sex, body mass index and age after adjustment for cholesterol, period of BP measurement and socioeconomic status. Adjustments were for age, sex, body mass index, baseline antihypertensive use, baseline lipid use, total cholesterol, HDL cholesterol, period of blood pressure measurement (1990-1994, 1995-1999, 2000-2004, 2005-2009, 2010-2013) and socioeconomic status. For subgroups of age, adjustment was also for age category and the interaction between systolic BP and age category (plotted). For subgroups of sex, adjustment was also for the interaction between sex and systolic BP (plotted). For subgroups of body mass index, adjustments were also for body mass index category and the interaction between systolic BP and body mass index category (plotted). Area of each square is proportional to the inverse variance of the estimate.

Exclusion of individuals diagnosed with new onset diabetes or cardiovascular disease within the first two years and within the first four years of follow up also had little effect on associations; 20 mm Hg higher systolic blood pressure was associated with a 54% higher risk of new onset diabetes after exclusion of two and four years of follow up (HR

1.54 CI 1.52, 1.56 and HR 1.55 CI 1.53, 1.58, respectively; Figures 5.8 and 5.9). Estimates also did not change materially when diabetes was restricted to explicit diagnosis of type 2 diabetes; 20 mm Hg higher systolic blood pressure was associated with a 62% higher risk of new onset diabetes (HR 1.62 CI 1.60, 1.64; Figure 5.10), when follow up was restricted to after 2006 (Figure 5.11) or when only death due to diabetes was considered (Figure 5.12).

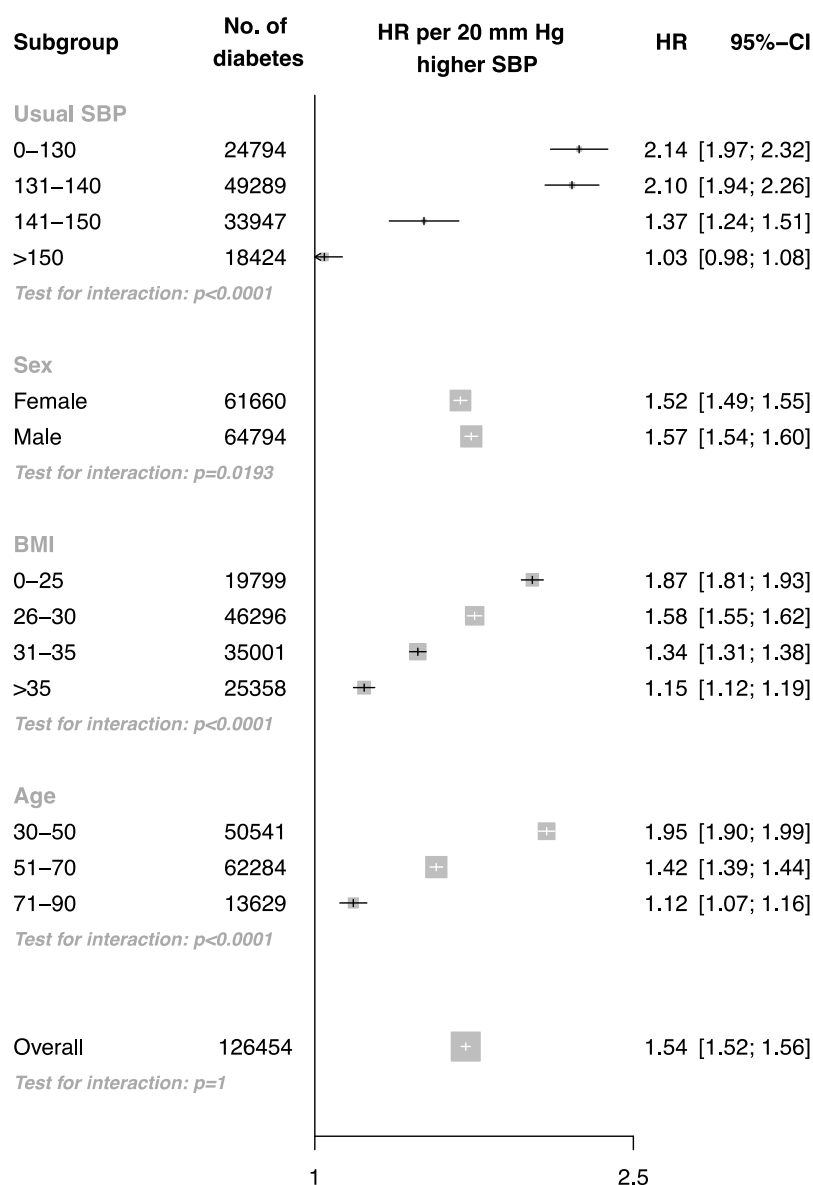


Figure 5.8 Adjusted hazard ratios of a 20 mm Hg higher systolic blood pressure for incident diabetes by blood pressure, sex, body mass index and age. First two years of follow up are excluded. Adjustments were for age, sex, body mass index, baseline antihypertensive use and baseline lipid use. For subgroups of age, adjustment was also for age category and the interaction between systolic BP and age category (plotted). For subgroups of sex, adjustment was also for the interaction between sex and systolic BP (plotted). For subgroups of body mass index, adjustments were also for body mass index category and the interaction between systolic BP and body mass index category (plotted). Area of each square is proportional to the inverse variance of the estimate.

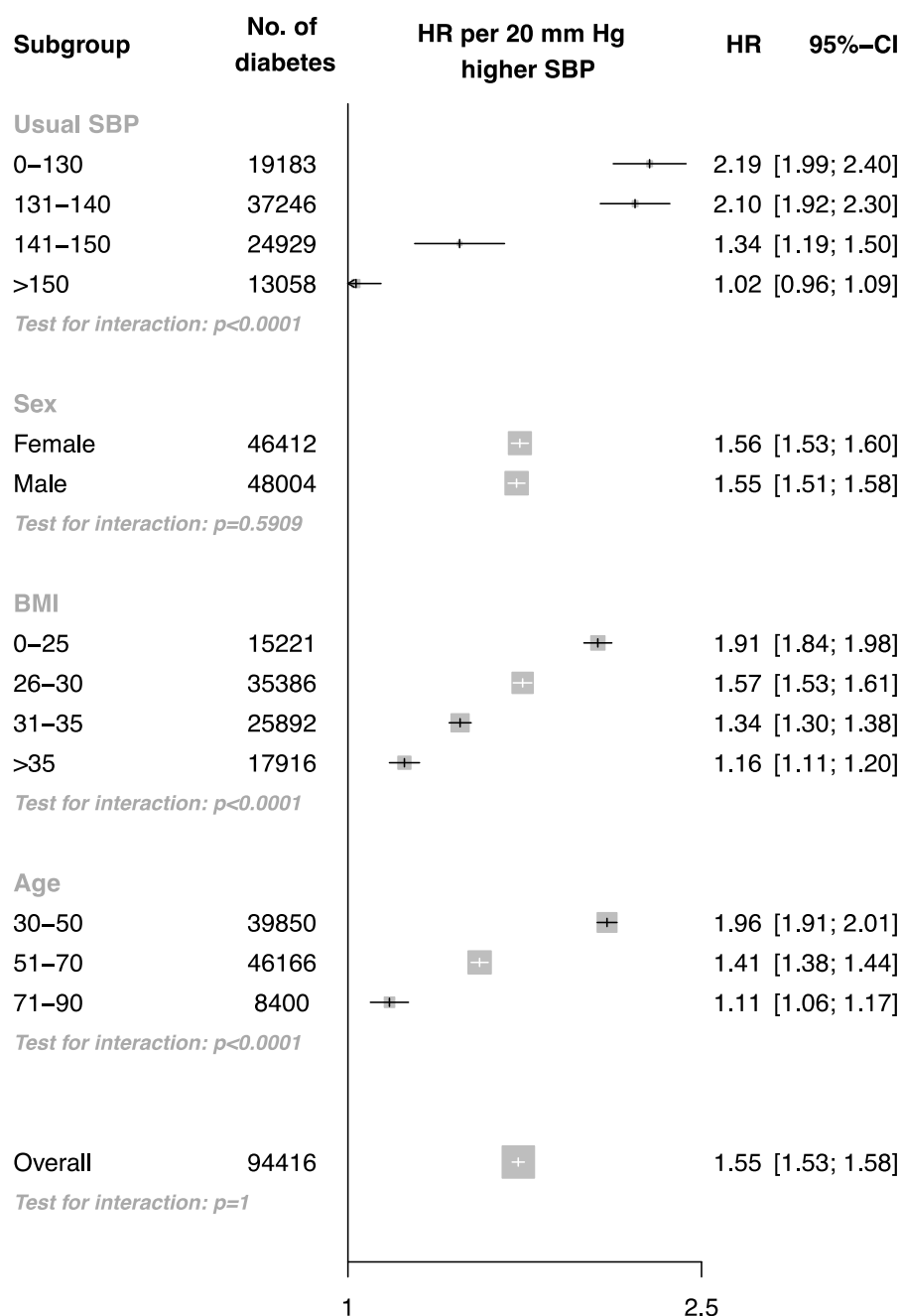


Figure 5.9 Adjusted hazard ratios of a 20 mm Hg higher systolic blood pressure for incident diabetes by blood pressure, sex, body mass index and age. First four years of follow up are excluded. Adjustments were for age, sex, body mass index, baseline antihypertensive use and baseline lipid use. For subgroups of age, adjustment was also for age category and the interaction between systolic BP and age category (plotted). For subgroups of sex, adjustment was also for the interaction between sex and systolic BP (plotted). For subgroups of body mass index, adjustments were also for body mass index category and the interaction between systolic BP and body mass index category (plotted). Area of each square is proportional to the inverse variance of the estimate.

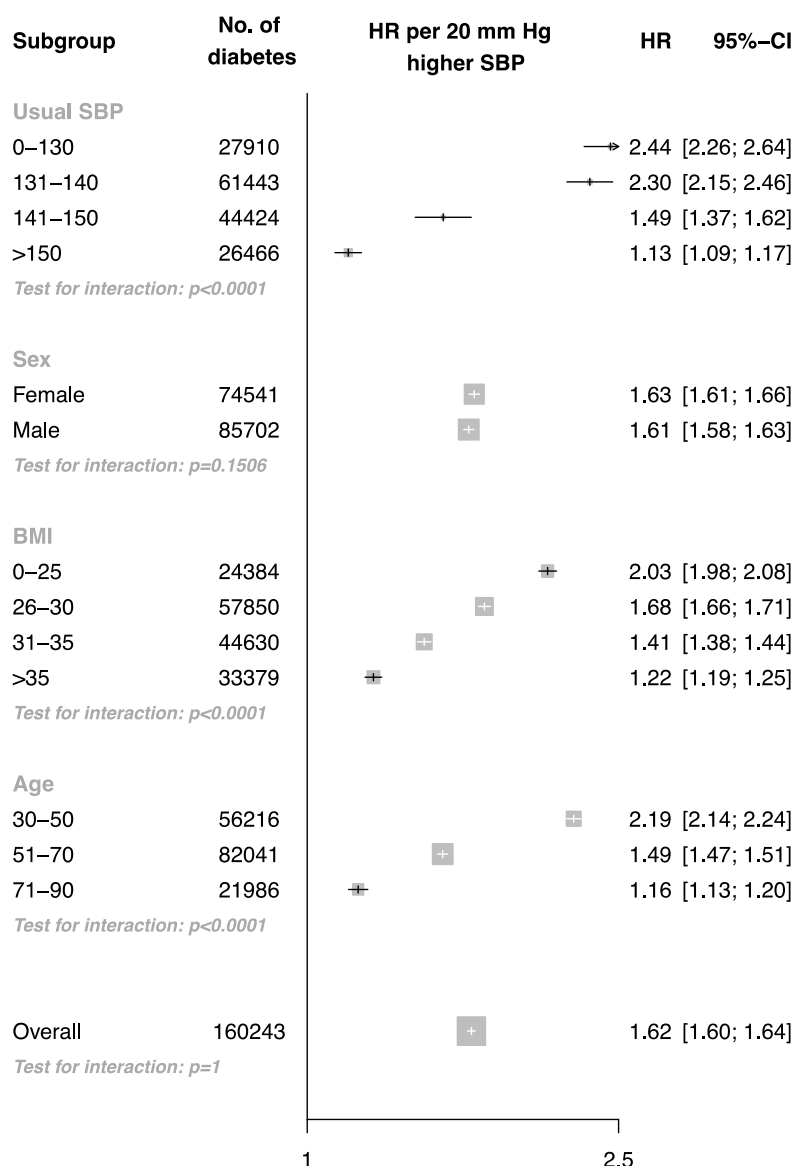


Figure 5.10 Adjusted hazard ratios of a 20 mm Hg higher systolic blood pressure for incident diabetes by blood pressure, sex, body mass index and age. Diabetes diagnoses are restricted to explicit diagnoses of type 2 diabetes, with prescription of antidiabetic drugs and diagnoses of unspecified diabetes excluded. Adjustments were for age, sex, body mass index, baseline antihypertensive use and baseline lipid use. For subgroups of age, adjustment was also for age category and the interaction between systolic BP and age category (plotted). For subgroups of sex, adjustment was also for the interaction between sex and systolic BP (plotted). For subgroups of body mass index, adjustments were also for body mass index category and the interaction between systolic BP and body mass index category (plotted). Area of each square is proportional to the inverse variance of the estimate.

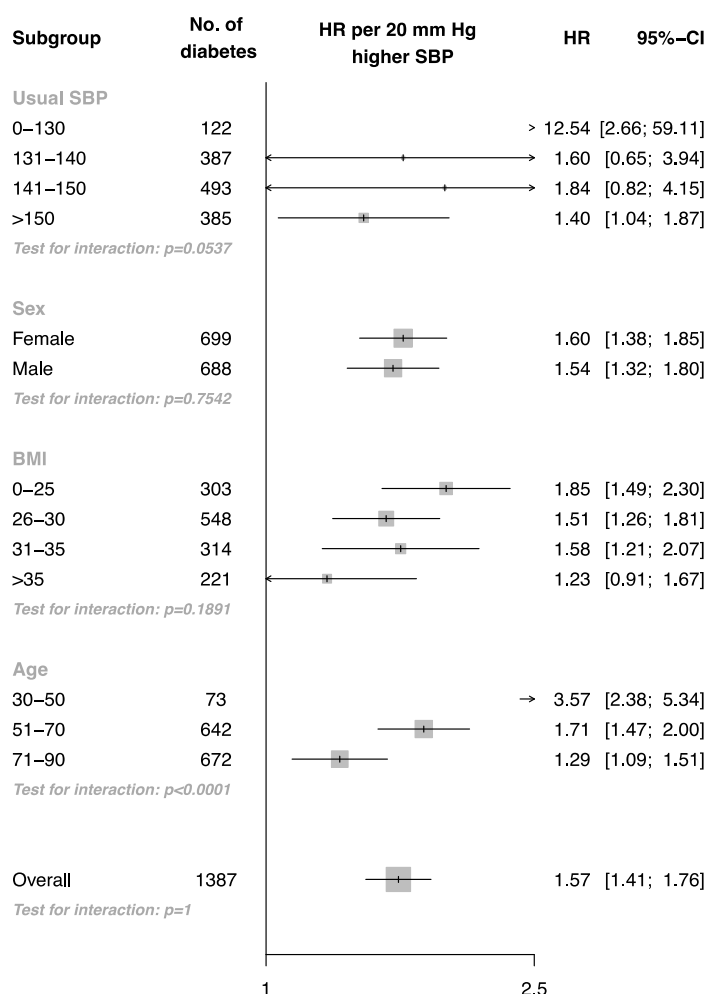


Figure 5.12 Adjusted hazard ratios per 20 mm Hg higher systolic blood pressure by blood pressure, sex, body mass index and age. Only death due to diabetes was analysed. Adjustments were for age, sex, body mass index, baseline antihypertensive use and baseline lipid use. For subgroups of age, adjustment was also for age category and the interaction between systolic BP and age category (plotted). For subgroups of sex, adjustment was also for the interaction between sex and systolic BP (plotted). For subgroups of body mass index, adjustments were also for body mass index category and the interaction between systolic BP and body mass index category (plotted). Area of each square is proportional to the inverse variance of the estimate.

5.3.4 Meta-analysis of prior observational studies

A flowchart of study identification is provided (Figure 5.13). After screening 4512 abstracts from MEDLINE and 4 abstract from a bibliography review, 4343 studies were excluded. 173 were then screened in full text, with 143 excluded, the majority for not reporting an association of blood pressure with new onset diabetes.

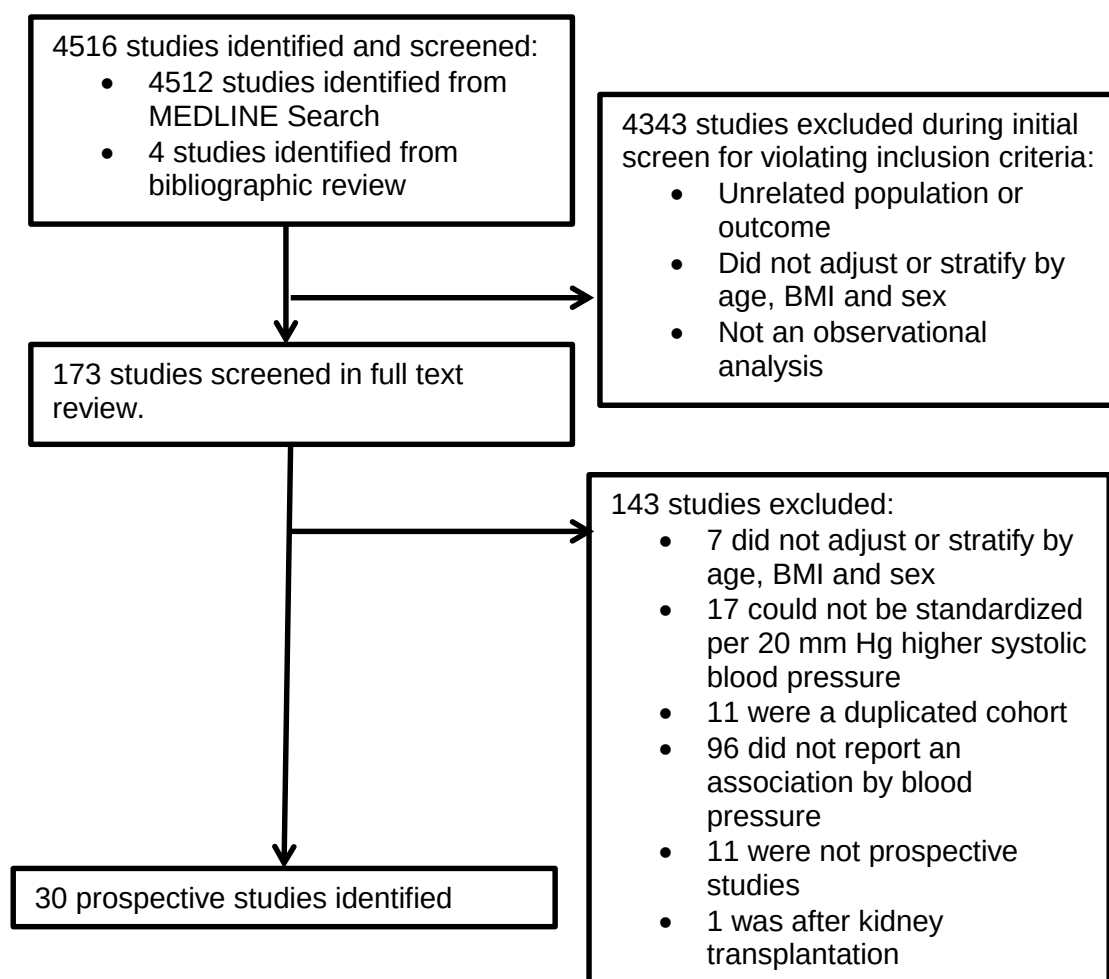


Figure 5.13 Flowchart of study identification.

As a result, 30 prospective observational studies were identified, with 285 664 participants and 17 388 incident diabetes events. Five of these studies were observational analyses of randomized trials, while twenty five were non-randomized cohorts. Twelve studies were conducted in Europe, nine studies were conducted in Asia (including the Middle East), eight studies were conducted in North America and one study was conducted both in Europe and North America. The median follow up ranged from 2 to 38 years (mean 9.9 years). All studies adjusted for or stratified by, at minimum, age, sex and body mass index.

Pooled random effects meta-analysis of the identified 30 studies showed that each 20 mm Hg higher usual systolic blood pressure from prior cohort studies was associated with a 77% higher risk of new onset diabetes (RR 1.77 CI 1.53, 2.06, Figure 5.14). A test

for interaction with the estimate of a 58% higher risk of diabetes per 20 mm Hg usual systolic blood pressure from CPRD was not significant ($p=0.13$). The overall pooled estimate, including my and previous cohort studies, was 76% per 20 mm Hg higher usual systolic blood pressure (RR 1.76 CI 1.56, 1.98). Estimates were similar when five studies that used a normal approximation to determine the blood pressure difference associated with the provided relative risk were excluded; a test for interaction between my estimate and the pooled estimate (RR 1.75 CI 1.49, 2.06) was not significant (Figure 5.15).

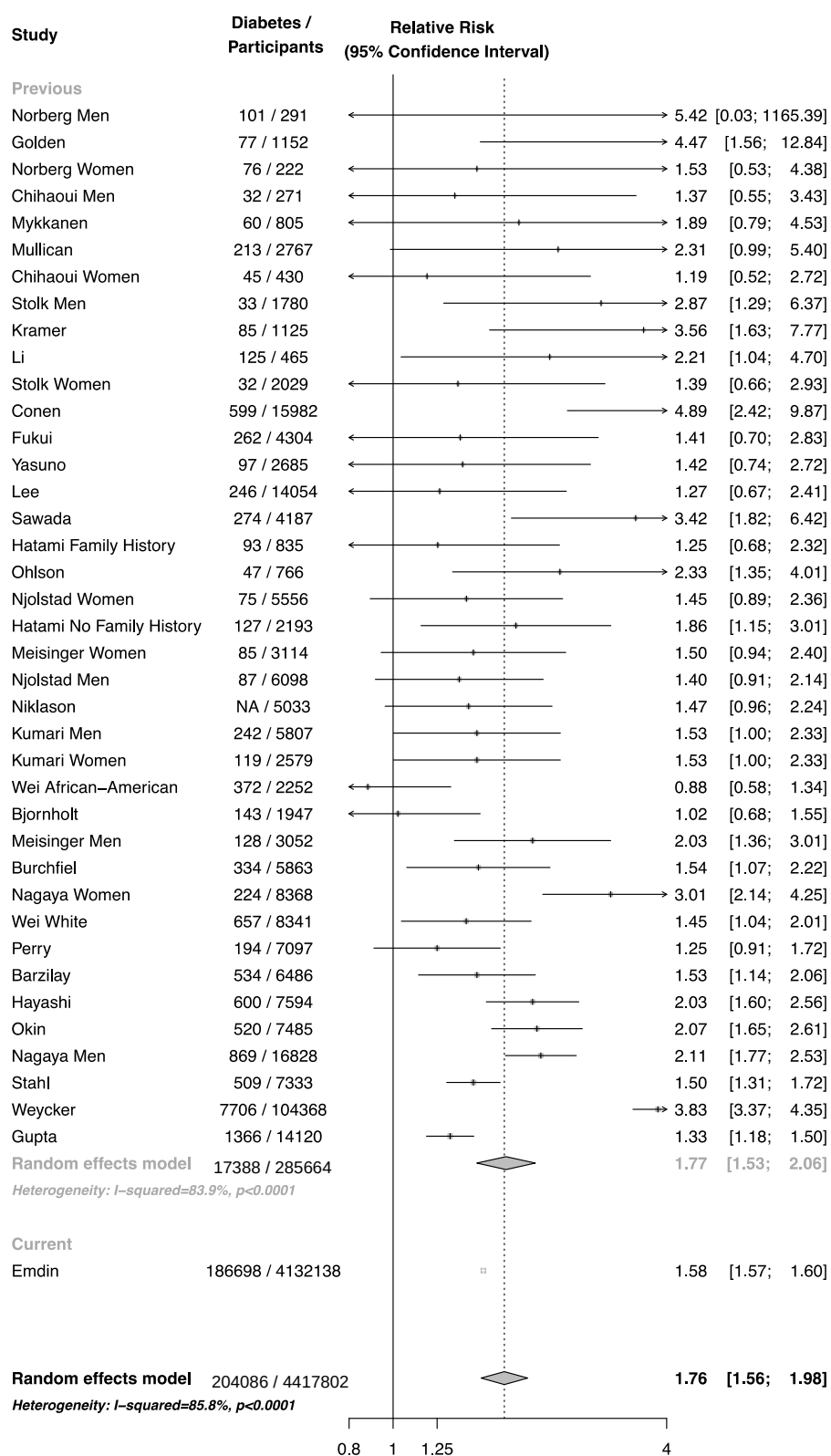


Figure 5.14 Meta-analysis of the association of a 20 mm Hg higher usual systolic blood pressure and risk of diabetes. Study refers to first author of study (characteristics provided in Supp. Table 1).

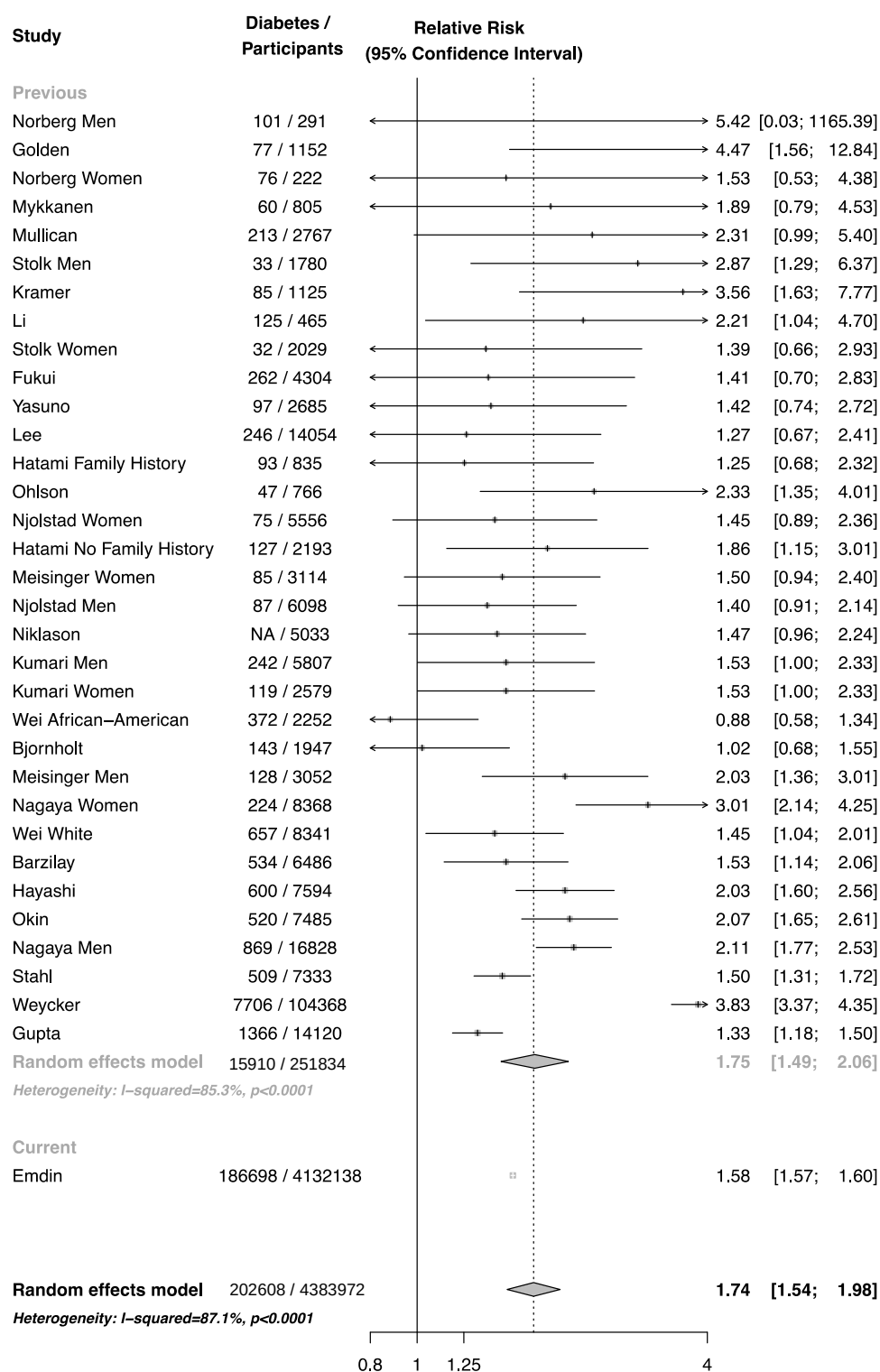


Figure 5.15 Meta-analysis of the association of a 20 mm Hg higher usual systolic blood pressure and risk of diabetes. Five trials for which a normal approximation was used to standardize reported relative risks to a difference in blood pressure were excluded. Study refers to first author of study (characteristics provided in Supp. Table 1).

5.4 Discussion

In a cohort of people without known prior vascular disease and with more than 180000 presentations of newly diagnosed diabetes, systolic and diastolic blood pressure were found to continuously relate to risk of new onset diabetes, with no evidence of a nadir down to 110/70 mm Hg. The associations varied substantially between different subpopulations. In particular, relative risks per 20 mm Hg higher systolic blood pressure declined with increasing age and with increasing body mass index. Nevertheless, because of higher absolute risk of diabetes at older age and with higher body mass index, a 20 mm Hg difference in systolic blood pressure was still associated with substantial absolute risk differences in old age and overweight. It is important to note, however, that it is unclear if these associations are causal and it is highly plausible that they are not causal and due to confounding and/or reverse causality.

Previous observational analyses have been conflicted on the relationship between elevated blood pressure and risk of diabetes (Table 5.1). For example, in an observational analysis of the Losartan Intervention for Endpoint study, 20 mm Hg higher systolic blood pressure was associated with a 39% higher risk of new onset diabetes (HR 1.39 CI 1.25, 1.56).²⁰² In an analysis of the Women's Health Study, hypertensive individuals were at two times the risk of developing new onset diabetes relative to those with systolic blood pressure between 120-129 mm Hg (HR 2.03 CI 1.77, 2.32).⁴⁹ In an analysis of the INternational VERapamil SR-Trandolapril Study (INVEST), higher on treatment systolic blood pressure was associated with a higher risk of new onset diabetes.²⁰³ However, in a prospective cohort study of risk factors for new onset diabetes in 7097 men, no association between baseline blood pressure and risk of diabetes after adjustment for clinical and demographic covariates was observed.¹⁷⁹ These qualitatively and quantitatively discrepant findings are most likely due to limited power of individual studies to reliably measure

modest risk associations, as supported by the meta-analysis, which shows that the pooled estimate across these studies support a modest association between elevated systolic blood pressure and risk of diabetes (Figure 5.14).

These results support the hypothesis that elevated blood pressure is associated with increased risk of new onset diabetes. Indeed, my estimate of a 58% increase in risk of new onset diabetes per 20 mm Hg higher usual systolic blood pressure did not differ significantly from a pooled estimate. In addition to confirming the overall effects from previous reports, the large sample size in this analysis extends previous reports by investigating the differences in associations by key population characteristics such as age, sex and body mass index. The importance of these more detailed subpopulation analyses is highlighted by the large differences in the relative risks by patient characteristics in this cohort. For example, by contrast with a previous report, which did not observe an interaction by body mass index (based on 1672 events), I found that a 20 mm Hg higher systolic blood pressure was associated with an 89% higher risk among individuals with a body mass index ≤ 25 kg/m², but a 19% higher risk among people with a body mass index > 35 kg/m². Similarly, I observed that a 20 mm Hg higher systolic blood pressure was associated with a 100% higher risk of new onset diabetes among individuals aged 30-50 but a 14% higher risk among individuals aged 71 to 90.

As certain classes of antihypertensive therapies, including diuretics and beta-blockers, can increase the risk of type 2 diabetes⁵³, it was unclear if previous reported associations between BP and type 2 diabetes were due to hypertensive individuals being prescribed pro-diabetic antihypertensive therapies. However, in this analysis, a similar association between BP and new onset diabetes was observed when individuals prescribed antihypertensive therapy at baseline or during follow up were excluded. These results

therefore provide strong evidence that the association between elevated BP and incident diabetes is not due to prescription of pro-diabetic therapies to hypertensive individuals.

Despite this evidence, it is unclear whether the observed association between blood pressure and new onset diabetes is causal. Supporting a causal relationship is the NAVIGATOR trial, which randomized 9306 patients to valsartan or placebo and established a 2.8 mm Hg systolic blood pressure difference between arms. The incidence of diabetes in the valsartan arm was significantly reduced (HR 0.86 CI 0.80, 0.92).²⁰⁴ However, a network meta-analysis of randomized trials of antihypertensive medication observed that only ACE-inhibitors and angiotensin receptor blockers reduced the risk of new onset diabetes.⁵³ This would suggest that it is renin angiotensin system (RAS) activation that is causally related to risk of new onset diabetes, and not blood pressure per se. However, the lack of a reduction in new onset diabetes observed for diuretics, beta-blockers and calcium channel blockers may be due to off target effects for these therapies rather than a lack of a relationship between blood pressure and new onset diabetes.²⁰⁵ Previous analyses have suggested that a causal relationship between mediators of chronic inflammation, specifically interleukin-6, and incident diabetes may exist.^{41,42} Chronic inflammation characterizes both obesity²⁰⁶ and elevated blood pressure⁴⁴, risk factors for new onset diabetes, and is reduced by RAS inhibition.⁴⁵ Thus, chronic inflammation may mediate, in part, the relationship between both risk factors (obesity and hypertension) and incident diabetes. Alternatively, endothelial dysfunction may link elevated blood pressure and diabetes, with elevated blood pressure causing endothelial dysfunction, which further causes new onset diabetes.^{46,47} An individual patient data meta-analysis, such as the Blood Pressure Lowering Treatment Trialists' Collaboration, would be ideally suited to examine whether blood pressure lowering, independent of renin angiotensin system inhibition, reduces the risk of new onset diabetes.

Like the significant interactions observed for AF, the significant interactions by age and BMI for new onset diabetes may be due to a number of causes. First, elevated BP may actually have a reduced causal effect on new onset diabetes at higher age and BMI. More likely, however, is that the lower associations are not causal and are due to a greater presence of reverse causality and confounding at older ages and elevated BMI. For example, there may be a greater prevalence of undiagnosed diabetes at older age and elevated BMI whose presentation after baseline may be less influenced by baseline BP. Alternatively, the effect of BP on diabetes may be primarily additive than proportional (for example, BP may increase the risk of diabetes by an absolute increase of 3% per year rather than by a proportional 30% increase), resulting in attenuated proportional increases at higher ages and BMI using a proportional hazards model.

Assuming causality, this analysis suggests that individual and population based efforts to lower blood pressure may, as well, reduce the incidence of diabetes. As renin-angiotensin inhibition has been demonstrated to reduce the incidence of new onset diabetes in randomized trials, prescription of ACE-inhibitors and ARBs has the most reliable evidence base for reducing the incidence of diabetes at an individual level. Although I observed a declining proportional association between blood pressure and risk of diabetes with increasing body mass index, the greater absolute risk of diabetes at higher body mass index would support the targeting of individuals with high body mass index for blood pressure lowering to prevent diabetes. Population based efforts to lower blood pressure, for example, by reducing alcohol consumption through policy implementation or by promoting exercise, may also lead to reductions in the incidence of diabetes. However, further research is needed to examine the causality of the described associations and determine whether blood pressure lowering without renin-angiotensin inhibition would reduce risk of new onset diabetes.

This analysis has several strengths, including its large size, encompassing more than 4.1 million individuals and 180 000 incident diabetes events, and contemporary nature. A potential limitation is that I utilized routinely collected electronic health records for this analysis. Although this approach has recently been used to examine the relationship between type 2 diabetes and cardiovascular risk, it is possible that some of the type 2 diabetes events may have been misclassified (e.g. metabolic syndrome but not type 2 diabetes). However, a previous study suggested that physician-diagnosed type 2 diabetes events in CPRD are highly reliable.⁷³ Furthermore, I supplemented my analysis with a meta-analysis of prospective observational studies which included 285 664 individuals and 17 388 incident diabetes events. This complementary approach increased the reliability of this study, allowing me to first validate my estimate against previous studies and then to examine the relationship between blood pressure and risk of diabetes in various subpopulations. The estimate of a 58% increase per 20 mm Hg higher usual systolic blood pressure in CPRD was consistent with a meta-analysis of previous observational studies that largely used adjudicated diabetes events and was consistent in eight sensitivity analyses, including an analysis of explicit diagnoses of type 2 diabetes (rather than unspecified diabetes). A final limitation of this analysis is its observational nature. It is possible that the reported association between blood pressure and new onset diabetes is, in part, caused by a confounding variable. Individuals with elevated blood pressure may be at high risk for new onset diabetes due to the presence of other pro-diabetic risk factors that I was unable to adjust for.

5.5 Conclusions

In conclusion, a 20 mm Hg higher systolic blood pressure is associated with a 58% higher risk of new onset diabetes, while a 10 mm Hg higher diastolic blood pressure is associated with a 52% higher risk of new onset diabetes. The strength of the association

declined with increasing body mass index and age. Further investigation is needed to determine whether this association is causal.

Chapter 6 Association of blood pressure with risk of cardiovascular disease in type 2 diabetes: evidence from 73 658 individuals with type 2 diabetes

6.1 Introduction

In the previous chapter, blood pressure was observed to be strongly associated with risk of new onset diabetes. In addition to being a likely risk factor for new onset diabetes, elevated blood pressure among individuals with diabetes is a causal risk factor for cardiovascular disease, and blood pressure lowering reduces the risk of cardiovascular disease among individuals with and without type 2 diabetes.^{207,208} However, the optimal blood pressure among individuals with diabetes is unclear.

In the Prospective Studies Collaboration (PSC) analysis of largely non-diabetic participants with no prior vascular disease, a log-linear association between blood pressure and risk of stroke and ischemic heart disease was observed, with no evidence of a nadir down to 115 mm Hg systolic blood pressure.¹² A log-linear relation between blood pressure and cardiovascular risk has also been observed in analyses of MRFIT and other prospective cohort studies conducted in the general population.^{11,209} However, the association between blood pressure and cardiovascular disease in people with diabetes is less clear. Observational analyses among trial participants with type 2 diabetes have been conflicting, with some reporting a J-shaped association between systolic blood pressure and cardiovascular disease^{57,61} and others supporting a more continuous association without evidence of a nadir.⁵⁶

However, prior observational analyses in type 2 diabetes have largely: (1) not controlled for regression dilution bias (which would bias any observed association between blood pressure and cardiovascular disease to the null)^{56,210}, (2) not excluded individuals with pre-existing cardiovascular disease (which may confound any observed association by causing low blood pressure while increasing cardiovascular risk)²¹⁰⁻²¹² and (3) not excluded

early follow up.^{61,210,213,214} These limitations suggest that reports of a J-shaped association between blood pressure and cardiovascular disease in diabetes may be due to reverse causality and confounding.

To clarify this uncertainty, I aimed to reliably determine the association between blood pressure and risk of cardiovascular disease in type 2 diabetes. I also aimed to characterize the association between blood pressure and cardiovascular disease in type 2 diabetes for a range of different cardiovascular events.

6.2 Methods

6.2.1 Participants, exposures and endpoints

I used the United Kingdom Clinical Practice Research Datalink to identify a cohort of 73658 individuals with prior diagnosis of diabetes (either type 2 or unspecified, with type 1 excluded). This was defined as either a physician-recorded diagnosis of diabetes or prescription of antidiabetic drugs. CPRD is a system of linked, prospectively collected, primary care electronic health records that have been validated for epidemiological research.⁷⁰ Participants were additionally linked to Hospital Episode Statistics (a secondary care database containing cause-specific hospital admissions) and to cause-specific mortality data.

The primary exposure was the first blood pressure measurement at a general practice between 1990 to 2013. Individuals who were between the ages of 30 and 90, inclusive, and had a prior diagnosis of diabetes (either unspecified or type 2) were included. Previous research has demonstrated diagnoses of diabetes in CPRD to be highly reliable (specificity of 99%).⁷⁰ Individuals with a prior or incident diagnosis of type 1 diabetes were excluded. Baseline covariates (BMI, smoking status, total cholesterol and HDL cholesterol) were defined as the closest measurement to the baseline blood pressure measurement, within two years. I defined baseline use of antihypertensive therapy (BNF chapters 2.2.1,

2.2.3-5 and 2.6.2) or lipid lowering therapy (BNF chapter 2.12) as prescription of a therapy in the two years prior to the baseline blood pressure measurement.

The primary outcome was the time to first major cardiovascular event, defined as a fatal cardiovascular event or non-fatal ischemic heart disease, stroke or heart failure. Individuals were censored at the first of each of these outcomes, transfer out of practice, death or end of follow up. To minimize the risk of reverse causality, I excluded the three years of follow up (excluding individuals who were censored within three years of follow up or who had a cardiovascular event within three years of follow up).

6.2.2 Statistical analysis

Cox models, stratified by practice to account for clustering at the general practice level, were used to examine time from the baseline blood pressure measurement to any cardiovascular event. The primary model was adjusted for age, gender, smoking status, baseline antihypertensive use, baseline lipid lowering use, total cholesterol and HDL cholesterol. Blood pressure was analysed both as a continuous variable and as a categorical variable. A test for linear trend was performed by including blood pressure as a continuous variable. Test for nonlinearity was then performed by using a likelihood ratio test to compare a nested model with the addition of blood pressure as a categorical variable to a model with blood pressure as a continuous variable. Penalized splines were additionally used to model the relationship between blood pressure and risk of a cardiovascular event in a nonlinear manner.²¹⁵

To determine the strength of the association of blood pressure with each cardiovascular event, I modeled blood pressure as a continuous variable (per 20 mm Hg higher SBP and 10 mm Hg higher DBP). I restricted this analysis to individuals with a usual blood pressure greater than 130 mm Hg (as I did not observe a lower risk of cardiovascular events below this threshold).

In order to account for regression dilution bias⁸⁵, serial blood pressure measurements within the median follow up were regressed against the baseline blood pressure measurement using generalized estimating equations. Attenuation factors of 2.4 and 2.7 were calculated for systolic and diastolic blood pressure, respectively. Calculated hazard ratios were multiplied by these factors to determine the associations of usual blood pressure with vascular risk.

Multiple imputation using chained equations was used to impute missing covariates for smoking status, BMI, total cholesterol, HDL cholesterol and socioeconomic status.

6.2.3 Sensitivity analyses

Six sensitivity analyses were conducted. First, the initial four years of follow up were excluded, to examine if any J-shaped curve between blood pressure and cardiovascular disease may be influenced by residual reverse causality. Second, individuals above the age of 70 were excluded, to examine whether any association was influenced by elderly populations, among whom reverse causality may play a greater role. Third, models were further adjusted for socioeconomic status. Fourth, individuals on antihypertensives at baseline were excluded. Fifth, individuals who were not explicitly diagnosed with type 2 diabetes (that is, only diagnosed with unspecified diabetes) were excluded. Sixth, the analysis was restricted to after 2004, when the Quality and Outcomes Framework was introduced⁹⁷, after which data quality would be expected to be improved. In addition to these six sensitivity analyses, no years of follow up were excluded, to examine if a J-shaped curve between blood pressure and cardiovascular disease would be observed (as has been observed in prior studies that did not exclude initial follow up).

To validate a subset of my results, I compared my estimates for ischemic heart disease, hemorrhagic stroke and ischemic stroke in diabetes to estimates for the Australasian subpopulation of the Asia Pacific Cohort Studies Collaboration (APCSC).⁵⁵

This subpopulation was chosen both because it is most similar to the UK population and because APCSC has found significantly stronger associations between systolic blood pressure and both ischemic heart disease and stroke in its Asian subpopulation, compared to Australasians.^{14,216} APCSC also used the same methodology to determine relationships with usual SBP as used in this chapter. Additionally, I examined the association between usual systolic blood pressure and risk of any cardiovascular event and major cardiovascular event in non-diabetic adults with usual SBP between 115 mm Hg and 180 mm Hg. I aimed to confirm prior reports by the PSC that blood pressure is continuously associated with vascular risk in this population, with no evidence of a nadir.¹² As in the analysis in the diabetic population, the first three years of follow up were excluded.

Analyses were performed using R version 3.0.

6.3 Results

I identified 73 658 participants who had a prior diagnosis of type 2 or unspecified diabetes (Figure 6.1, Table 6.1). 33 118 participants were women (45.0%). The median age was 59 (interquartile interval IQI 48, 68), while the median BMI was 28.7 (IQI 25.4, 32.8). Over a median follow up of 7.4 years, 22 239 initial cardiovascular events were observed (30.2% of participants). 10 447 major cardiovascular events, 4499 ischemic heart disease events, 4543 heart failure events and 3367 stroke events were observed.

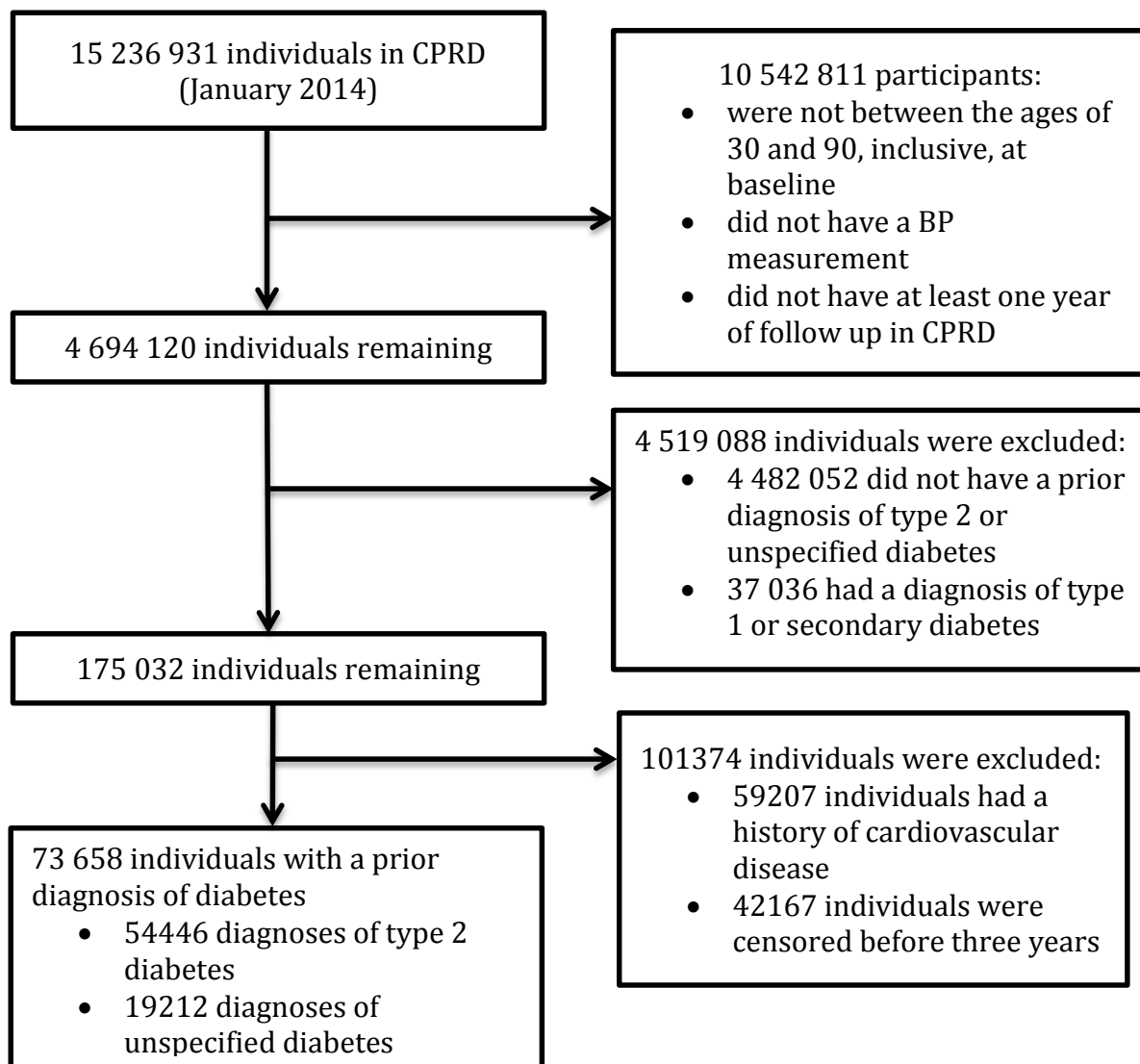


Figure 6.1 Identification of cohort.

Table 6.1 Characteristics of included participants

	Usual SBP (mm Hg)						
	0-130	131-140	141-150	151-160	161-170	>170	Overall
N	4641	25103	32871	8749	2034	260	73658
Age at Baseline (years, IQI)	46 (36, 57)	53 (43, 64)	61 (51, 69)	65 (56, 72)	68 (60, 74)	68 (59, 75)	59 (48, 68)
Women	2285 (49.2%)	10571 (42.1%)	14535 (44.2%)	4385 (50.1%)	1178 (57.9%)	164 (63.1%)	33118
BMI (kg/m ² , IQI)	26.0 (23.1, 29.9)	28.3 (25.1, 32.4)	29.2 (25.9, 33.3)	29.3 (26.0, 33.4)	29.0 (25.6, 33.3)	29.3 (25.7, 33.1)	28.7 (25.4, 32.8)
<i>Smoking Status</i>							
Current Smoker	1222 (29.9%)	5371 (24.3%)	5486 (19.5%)	1254 (17.4%)	250 (15.6%)	36 (17.3%)	13619
Ex Smoker	662 (16.2%)	4792 (21.7%)	6636 (23.6%)	1733 (24.1%)	353 (22.0%)	44 (21.2%)	14220
Never Smoker	2201 (53.9%)	11964 (54.1%)	16025 (56.9%)	4210 (58.5%)	1003 (62.5%)	128 (61.5%)	35531
<i>Cholesterol (mmol/L)</i>							
Total (IQI)	4.9 (4.2, 5.7)	5.0 (4.3, 5.7)	5.1 (4.4, 5.9)	5.3 (4.6, 6.1)	5.5 (4.7, 6.4)	5.6 (4.9, 6.6)	5.1 (4.4, 5.9)
HDL (IQI)	1.2 (1.0, 1.5)	1.2 (1.0, 1.5)	1.2 (1.0, 1.5)	1.2 (1.0, 1.5)	1.3 (1.1, 1.5)	1.2 (1.0, 1.5)	1.2 (1.0, 1.5)
Most deprived fifth (socioeconomic status) ¹	564 (20.4%)	2807 (19.2%)	3403 (17.7%)	865 (16.9%)	214 (17.5%)	32 (20.6%)	7885 (18.3%)
<i>Medication Usage</i>							
Antihypertensive at baseline	554 (11.9%)	5323 (21.2%)	10224 (31.1%)	3622 (41.4%)	929 (45.7%)	135 (51.9%)	20787 (28.2%)
Antihypertensive during follow up	1855 (40.0%)	13987 (55.7%)	23400 (71.2%)	6946 (79.4%)	1685 (82.8%)	227 (87.3%)	48100 (65.3%)
Lipid lowering at baseline	563 (12.1%)	4373 (17.4%)	4919 (15.0%)	1073 (12.3%)	154 (7.6%)	19 (7.3%)	11101 (15.1%)
Lipid lowering during follow up	2538 (54.7%)	15823 (63.0%)	20723 (63.0%)	5250 (60.1%)	1117 (54.9%)	142 (54.6%)	45593 (61.9%)

IQI refers to interquartile interval (25th percentile, 75th percentile). Proportion of variables missing: BMI (8.0%), smoking status (14.0%), total cholesterol (20.5%), HDL cholesterol (47.2%), socioeconomic status (41.4%).

¹Whether local region of residence was in the most socioeconomically deprived fifth of regions, nationally.

6.3.1 Relationship of blood pressure with cardiovascular disease

When blood pressure was analysed as a continuous variable, using penalized splines, a linear relationship between systolic blood pressure and a major cardiovascular was observed above 130 mm Hg. However, a threshold was observed at approximately 130 mm Hg, although confidence intervals were wide (Figure 6.2). A similar relationship was observed between blood pressure and risk of a major cardiovascular event (fatal cardiovascular event, ischemic heart disease, heart failure or stroke).

When blood pressure was modeled as a categorical variable, a usual SBP 131-140 mm Hg was not associated with a higher or lower risk of a major cardiovascular event (HR 0.97 CI 0.86, 1.1, Table 6.2) relative to an SBP $\leq$ 130 mm Hg. A SBP of 131-140 mm Hg was also not associated with a higher or lower risk of ischemic heart disease (HR 1.02 CI 0.85, 1.23) and heart failure (HR 0.94 CI 0.76, 1.15) relative to an SBP of $<$ 130 mm Hg. Associations between systolic blood pressure and risk of a major cardiovascular event and heart failure were nonlinear ($p < 0.05$ for nonlinearity), while tests for non-linearity for any cardiovascular event and ischemic heart disease were nonsignificant. Linear associations were observed for unspecified stroke, ischemic stroke, chronic kidney disease, and peripheral arterial disease ($p > 0.05$ for nonlinearity, $p < 0.001$ for linear trend, Table 6.2).

A linear association was observed for DBP and risk of any cardiovascular event and major cardiovascular events above 75 mm Hg was observed when modeled using penalized splines (Figure 6.2). Although a possible threshold was observed at 75 mm Hg DBP, confidence intervals were very wide and did not exclude either a modest increase or decrease in proportional risk of any cardiovascular event (Table 6.3).

Table 6.2 Hazard ratios for fourteen cardiovascular events by usual systolic blood pressure. Confidence intervals provided in parentheses.

	Events	0-130 (reference)	<i>Usual Systolic Blood Pressure (mm Hg)</i>					Test for Non- linearity	Test for linear trend
			131-140	141-150	151-160	161-170	>170		
Major cardiovascular event	10447	1	0.97 (0.86, 1.1)	1.09 (0.96, 1.23)	1.26 (1.1, 1.44)	1.61 (1.38, 1.88)	1.45 (1.08, 1.94)	0.007	<0.001
Ischemic heart disease	4499	1	1.02 (0.85, 1.23)	1.17 (0.98, 1.4)	1.33 (1.09, 1.62)	1.89 (1.5, 2.37)	1.55 (1.01, 2.39)	0.103	<0.001
Heart failure	4543	1	0.94 (0.76, 1.15)	1.05 (0.86, 1.29)	1.24 (1.01, 1.53)	1.67 (1.32, 2.12)	1.36 (0.89, 2.09)	0.043	<0.001
Atrial Fibrillation	4056	1	1.04 (0.82, 1.31)	1.13 (0.9, 1.41)	1.25 (0.99, 1.59)	1.46 (1.11, 1.91)	1.17 (0.69, 1.98)	0.772	<0.001
Unspecified Stroke	2468	1	0.92 (0.71, 1.2)	1.11 (0.86, 1.43)	1.29 (0.99, 1.69)	1.61 (1.18, 2.2)	1.27 (0.69, 2.33)	0.409	<0.001
Ischemic Stroke	1297	1	1.11 (0.77, 1.6)	1.32 (0.92, 1.89)	1.44 (0.98, 2.12)	1.9 (1.22, 2.95)	1.35 (0.52, 3.54)	0.743	<0.001
Hemorrhagic Stroke	325	1	1.23 (0.6, 2.5)	1.26 (0.62, 2.52)	1.41 (0.67, 2.99)	2.44 (1.05, 5.67)	1.97 (0.41, 9.56)	0.776	0.025
Chronic Kidney Disease	12441	1	1.1 (0.97, 1.24)	1.31 (1.16, 1.48)	1.53 (1.35, 1.74)	1.62 (1.39, 1.88)	1.82 (1.37, 2.41)	0.125	<0.001
Aortic Aneurysm	213	1	0.87 (0.36, 2.09)	0.83 (0.35, 1.96)	0.68 (0.27, 1.74)	1.46 (0.51, 4.2)	-	0.504	0.811
Peripheral arterial disease	3028	1	1.06 (0.86, 1.32)	1.29 (1.04, 1.6)	1.52 (1.21, 1.92)	1.95 (1.47, 2.59)	1.83 (1.04, 3.21)	0.754	<0.001
Deep vein thrombosis	1141	1	1.1 (0.77, 1.56)	1.04 (0.73, 1.47)	0.97 (0.66, 1.42)	1.06 (0.65, 1.73)	1.55 (0.67, 3.56)	0.638	0.949
Pulmonary embolism	613	1	1.57 (0.84, 2.93)	1.44 (0.78, 2.67)	1.68 (0.88, 3.2)	1.01 (0.45, 2.28)	0.6 (0.08, 4.75)	0.189	0.544
Vascular Dementia	692	1	1.28 (0.73, 2.27)	1.06 (0.61, 1.85)	1 (0.55, 1.8)	1.25 (0.64, 2.43)	0.32 (0.04, 2.5)	0.393	0.156

Model adjusted for blood pressure, age, gender, body mass index, smoking status, baseline antihypertensive use, baseline lipid lowering use, total cholesterol and high density lipoprotein cholesterol.

Table 6.3 Hazard ratios for fourteen cardiovascular events by usual diastolic blood pressure. Confidence intervals provided in parentheses.

Usual Diastolic Blood Pressure (mm Hg)									
	Events	0-75 (reference)	76-80	81-85	86-90	91-95	>95	Non- linearity (p-value)	Linear trend (p-value)
Major cardiovascular events	10447	1	0.98 (CI 0.86, 1.12)	1.03 (CI 0.9, 1.17)	1.12 (CI 0.97, 1.29)	1.31 (CI 1.09, 1.56)	1.68 (CI 1, 2.81)	0.360	0.000
Ischemic heart disease	4499	1	1.01 (CI 0.83, 1.25)	1.09 (CI 0.89, 1.33)	1.17 (CI 0.94, 1.45)	1.28 (CI 0.97, 1.69)	1.04 (CI 0.38, 2.87)	0.474	0.027
Heart failure	4543	1	0.96 (CI 0.78, 1.18)	0.98 (CI 0.81, 1.2)	1.06 (CI 0.86, 1.31)	1.32 (CI 1.01, 1.73)	0.65 (CI 0.2, 2.08)	0.250	0.004
Atrial Fibrillation	4056	1	0.93 (CI 0.75, 1.15)	0.93 (CI 0.76, 1.14)	1.03 (CI 0.82, 1.29)	0.91 (CI 0.67, 1.24)	0.77 (CI 0.24, 2.47)	0.147	0.093
Unspecified Stroke	2468	1	1.13 (CI 0.85, 1.49)	1.13 (CI 0.86, 1.48)	1.4 (CI 1.04, 1.87)	1.55 (CI 1.07, 2.23)	2.99 (CI 1.17, 7.62)	0.318	0.000
Ischemic Stroke	1297	1	1.26 (CI 0.84, 1.91)	1.34 (CI 0.9, 2)	1.68 (CI 1.1, 2.57)	2.72 (CI 1.65, 4.5)	2.47 (CI 0.57, 10.72)	0.230	0.000
Hemorrhagic Stroke	325	1	0.75 (CI 0.39, 1.45)	0.76 (CI 0.4, 1.43)	0.96 (CI 0.48, 1.92)	1.18 (CI 0.47, 2.96)	5.83 (CI 1.15, 29.57)	0.196	0.165
Chronic Kidney Disease	12441	1	0.94 (CI 0.84, 1.06)	0.98 (CI 0.87, 1.1)	1.04 (CI 0.92, 1.18)	1.26 (CI 1.07, 1.49)	1.29 (CI 0.75, 2.23)	0.081	0.000
Aortic Aneurysm	213	1	1.82 (CI 0.55, 5.97)	2.12 (CI 0.66, 6.82)	1.97 (CI 0.57, 6.78)	5.09 (CI 1.29, 20.13)	-	0.520	0.097
Peripheral arterial disease	3028	1	1.02 (CI 0.8, 1.29)	0.98 (CI 0.78, 1.23)	1.02 (CI 0.8, 1.31)	1.16 (CI 0.83, 1.61)	1.21 (CI 0.38, 3.89)	0.566	0.292
Deep vein thrombosis	1141	1	1.66 (CI 0.99, 2.78)	1.61 (CI 0.97, 2.66)	1.52 (CI 0.89, 2.58)	2.14 (CI 1.15, 3.98)	2.78 (CI 0.62, 12.5)	0.253	0.434
Pulmonary embolism	613	1	0.96 (CI 0.54, 1.69)	1.02 (CI 0.59, 1.76)	0.99 (CI 0.55, 1.78)	0.98 (CI 0.44, 2.17)	-	0.999	0.991
Vascular Dementia	692	1	0.64 (CI 0.43, 0.96)	0.59 (CI 0.4, 0.87)	0.49 (CI 0.31, 0.77)	0.63 (CI 0.3, 1.31)	-	0.220	0.060

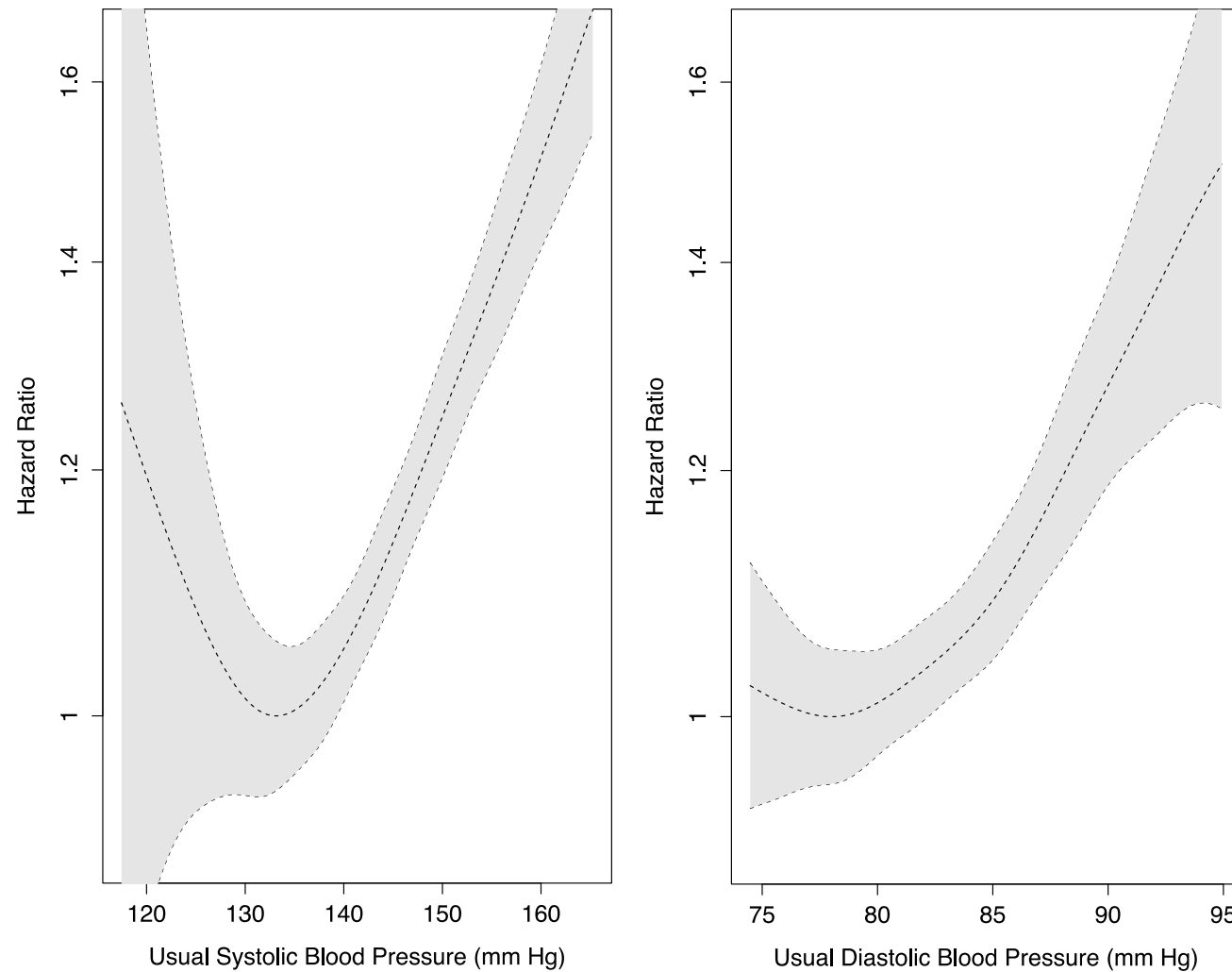


Figure 6.2 Risk of a major cardiovascular event by usual systolic and diastolic blood pressure. Hazard ratio predicted by penalized splines. Model adjusted for age, gender, body mass index, smoking status, baseline antihypertensive use, baseline lipid lowering use, total cholesterol and high density lipoprotein cholesterol.

6.3.2 Strength of the association of blood pressure with cardiovascular disease

When restricted to individuals with a usual SBP >130 mm Hg, the association between systolic and diastolic blood pressure and risk of cardiovascular disease differed significantly by cardiovascular disease. Overall, systolic blood pressure was more strongly associated with cardiovascular risk than diastolic blood pressure. A 20 mm Hg higher SBP was associated with a 40% higher risk of a major cardiovascular event, while a 10 mm Hg higher DBP was associated with a 12% higher risk of any cardiovascular event and a 17% higher risk of a major event. However, the strength of the association between BP and risk of cardiovascular disease differed substantially by disease (Figure 6.3). While SBP was not associated with risk of aortic aneurysm (HR 0.99 CI 0.65, 1.51 per 20 mm Hg higher SBP), 10 mm Hg higher DBP was associated with a 63% higher risk of aortic aneurysm (HR 1.63 CI 1.04, 2.57). Conversely, while 20 mm Hg higher SBP was associated with a 38% higher risk of chronic kidney disease and a 53% higher risk of peripheral arterial disease, 10 mm Hg higher DBP was not associated with risk of either outcome. Neither systolic nor diastolic blood pressure were significantly associated with risk of pulmonary embolism, deep vein thrombosis or vascular dementia. However, there were very few events (<1000) for these outcomes.

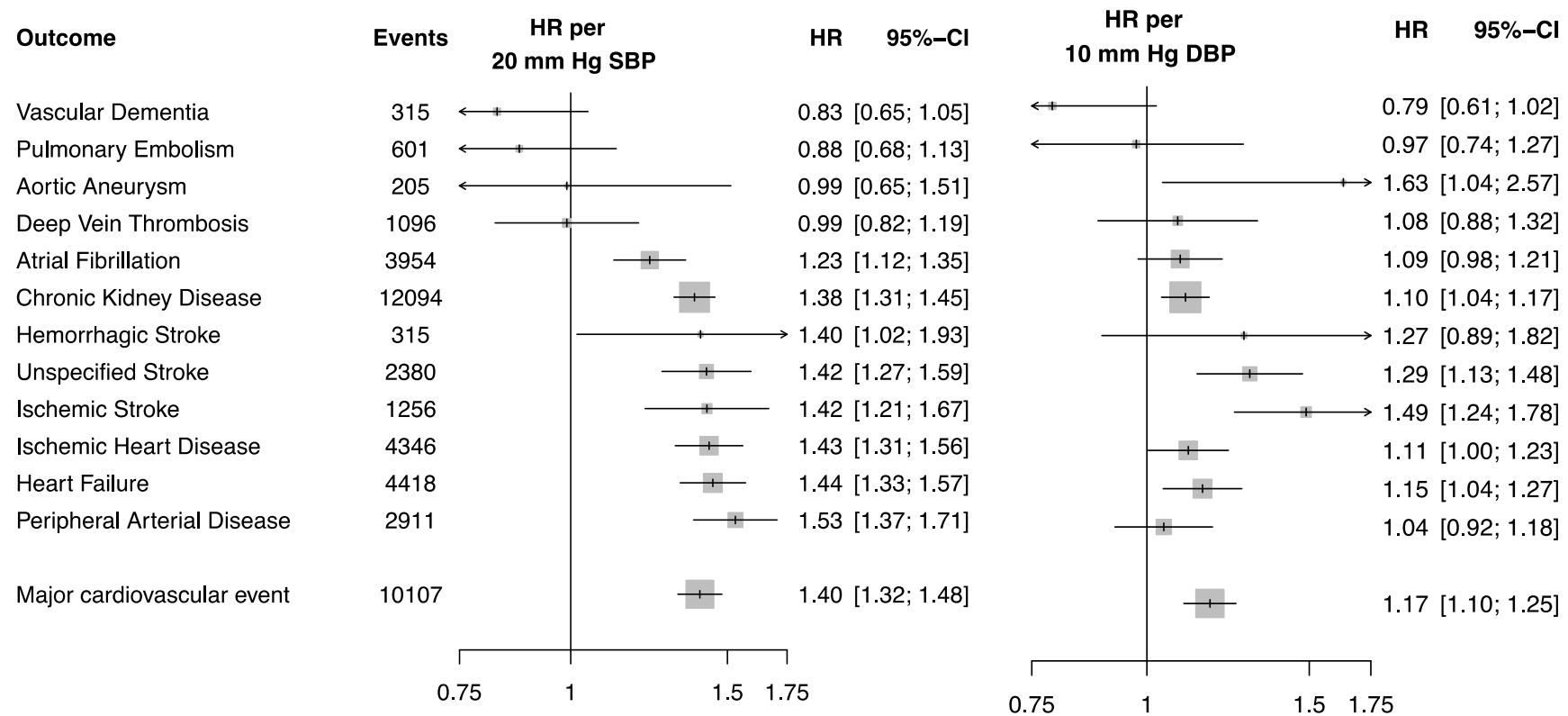


Figure 6.3 Associations of blood pressure with risk of fourteen cardiovascular events in the range >130 mm Hg usual systolic blood pressure. Model adjusted for age, gender, body mass index, smoking status, baseline antihypertensive use, baseline lipid lowering use, total cholesterol and high density lipoprotein cholesterol.

6.3.3 Sensitivity analyses

Estimates of the association of blood pressure and risk of a cardiovascular event were broadly consistent (Tables 6.4-6.16). However, when no years of follow up were excluded (unlike the primary analysis, in which three years were excluded), a strong J-shaped curve was observed, with increasing risk of a major cardiovascular event below 130 mm Hg SBP (Figure 6.4, Table 6.17). Estimates for ischemic heart disease and stroke subtypes were also similar to estimates in the Australasian subpopulation of the APCSC (Figure 6.5); tests for interaction between estimates from CPRD and APCSC estimates of the association of ischemic heart disease, unspecified stroke and ischemic stroke per 20 mm Hg higher SBP were insignificant.

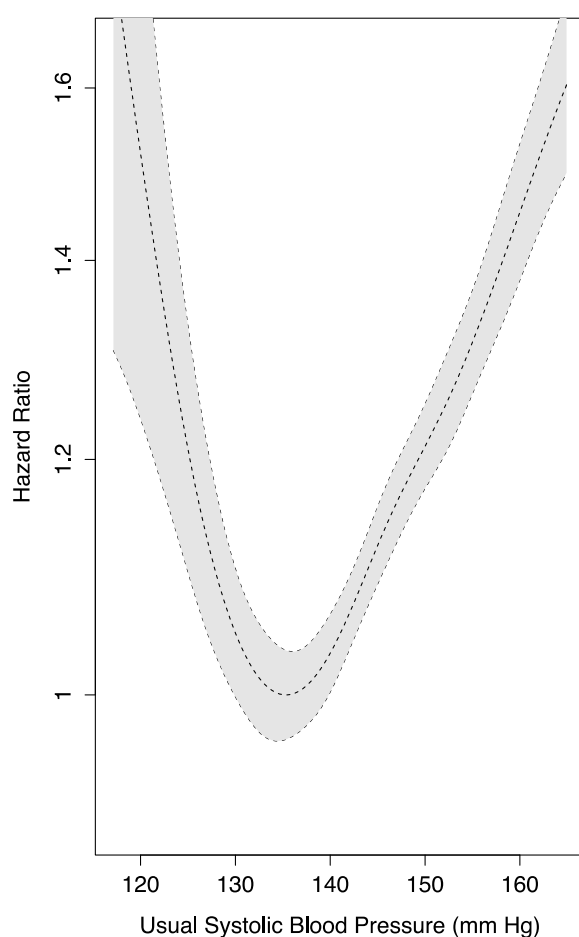


Figure 6.4 Association of systolic blood pressure with risk of any cardiovascular event and major cardiovascular event. No years of follow up were excluded.

Table 6.4 Hazard ratios for a major cardiovascular event by usual systolic blood pressure in seven sensitivity analyses. Confidence intervals provided in parentheses.

	Events	<i>Usual Systolic Blood Pressure (mm Hg)</i>						Non-linearity (p-value)	Linear trend (p-value)
		0-130 (reference)	131-140	141-150	151-160	161-170	>170		
Primary analysis	10447	1	0.97 (0.86, 1.1)	1.09 (0.96, 1.23)	1.26 (1.1, 1.44)	1.61 (1.38, 1.88)	1.45 (1.08, 1.94)	0.007	<0.001
1. Ex. 4 years	9004	1	1.02 (0.89, 1.17)	1.14 (1, 1.31)	1.33 (1.15, 1.54)	1.7 (1.44, 2.02)	1.57 (1.14, 2.17)	0.141	<0.001
2. ≤ 70 years	6685	1	1.02 (0.88, 1.18)	1.19 (1.03, 1.37)	1.47 (1.26, 1.72)	1.96 (1.62, 2.36)	1.5 (1, 2.24)	0.030	<0.001
3. Adjust. socioeconomic status	10447	1	0.97 (0.86, 1.11)	1.09 (0.96, 1.23)	1.26 (1.1, 1.44)	1.62 (1.39, 1.89)	1.44 (1.07, 1.93)	0.006	<0.001
4. Ex. antihypertensives	6611	1	1.03 (0.89, 1.18)	1.14 (0.99, 1.31)	1.44 (1.24, 1.68)	1.67 (1.38, 2.03)	1.58 (1.05, 2.38)	0.149	<0.001
5. Restriction to type 2 diabetes	7513	1	0.98 (0.84, 1.15)	1.1 (0.94, 1.28)	1.28 (1.09, 1.5)	1.62 (1.34, 1.95)	1.4 (0.98, 2)	0.098	<0.001
6. 2004 or later	808	1	1.07 (0.74, 1.56)	1.18 (0.81, 1.71)	1.29 (0.84, 1.97)	2.11 (1.21, 3.67)	2.52 (0.73, 8.69)	0.414	<0.001

Table 6.5 Hazard ratios for ischemic heart disease by usual systolic blood pressure in seven sensitivity analyses. Confidence intervals provided in parentheses.

	Events	<i>Usual Systolic Blood Pressure (mm Hg)</i>						Non-linearity (p-value)	Linear trend (p-value)
		0-130 (ref.)	131-140	141-150	151-160	161-170	>170		
Primary analysis	4499	1	1.02 (0.85, 1.23)	1.17 (0.98, 1.4)	1.33 (1.09, 1.62)	1.89 (1.5, 2.37)	1.55 (1.01, 2.39)	0.103	0.000
1. Ex. 4 years	3977	1	1.12 (0.91, 1.37)	1.23 (1, 1.51)	1.38 (1.1, 1.72)	2.11 (1.64, 2.72)	1.78 (1.13, 2.8)	0.044	0.000
2. ≤ 70 years	3111	1	1.08 (0.88, 1.33)	1.25 (1.02, 1.54)	1.45 (1.16, 1.81)	2.17 (1.66, 2.85)	1.94 (1.15, 3.27)	0.282	0.000
3. Adjust. socioeconomic status	4499	1	1.03 (0.85, 1.24)	1.17 (0.98, 1.41)	1.33 (1.09, 1.62)	1.9 (1.51, 2.39)	1.54 (1, 2.37)	0.088	0.000
4. Ex. antihypertensives	2948	1	1.04 (0.85, 1.28)	1.16 (0.95, 1.42)	1.53 (1.22, 1.91)	1.94 (1.46, 2.56)	1.44 (0.78, 2.66)	0.170	0.000
5. Restriction to type 2 diabetes	3099	1	0.96 (0.76, 1.22)	1.12 (0.89, 1.4)	1.24 (0.98, 1.59)	1.85 (1.39, 2.44)	1.34 (0.78, 2.3)	0.065	0.000
6. 2004 or later	284	1	1.18 (0.63, 2.19)	1.56 (0.84, 2.89)	1.75 (0.86, 3.55)	3.94 (1.61, 9.66)	2.35 (0.28, 19.45)	0.805	0.000

Table 6.6 Hazard ratios for heart failure by usual systolic blood pressure in seven sensitivity analyses. Confidence intervals provided in parentheses.

	Events	0-130 (reference)	<i>Usual Systolic Blood Pressure (mm Hg)</i>					Non-linearity (p-value)	Linear trend (p-value)
			131-140	141-150	151-160	161-170	>170		
Primary analysis	4543	1	0.94 (0.76, 1.15)	1.05 (0.86, 1.29)	1.24 (1.01, 1.53)	1.67 (1.32, 2.12)	1.36 (0.89, 2.09)	0.043	<0.001
1. Ex. 4 years	4011	1	0.96 (0.76, 1.2)	1.09 (0.87, 1.36)	1.31 (1.03, 1.65)	1.75 (1.34, 2.27)	1.53 (0.96, 2.42)	0.179	<0.001
2. ≤ 70 years	2838	1	0.88 (0.7, 1.11)	1.01 (0.81, 1.27)	1.27 (0.99, 1.61)	1.83 (1.38, 2.43)	1.44 (0.82, 2.53)	0.022	<0.001
3. Adjust. socioeconomic status	4543	1	0.94 (0.77, 1.15)	1.06 (0.87, 1.29)	1.25 (1.01, 1.54)	1.68 (1.33, 2.13)	1.35 (0.88, 2.08)	0.038	<0.001
4. Ex. antihypertensives	2753	1	1.01 (0.8, 1.28)	1.13 (0.9, 1.42)	1.47 (1.15, 1.89)	1.93 (1.44, 2.59)	1.24 (0.65, 2.38)	0.090	<0.001
5. Restriction to type 2 diabetes	3321	1	0.99 (0.77, 1.27)	1.13 (0.88, 1.44)	1.37 (1.06, 1.78)	1.8 (1.35, 2.41)	1.25 (0.73, 2.14)	0.137	<0.001
6. 2004 or later	282	1	1.09 (0.55, 2.16)	1.16 (0.59, 2.29)	1.28 (0.61, 2.71)	1.91 (0.73, 4.99)	2.96 (0.36, 24.7)	0.960	0.063

Table 6.7 Hazard ratios for atrial fibrillation by usual systolic blood pressure in seven sensitivity analyses. Confidence intervals provided in parentheses.

	Events	0-130 (reference)	<i>Usual Systolic Blood Pressure (mm Hg)</i>					Non-linearity (p-value)	Linear trend (p-value)
			131-140	141-150	151-160	161-170	>170		
Primary analysis	4056	1	1.04 (0.82, 1.31)	1.13 (0.9, 1.41)	1.25 (0.99, 1.59)	1.46 (1.11, 1.91)	1.17 (0.69, 1.98)	0.772	<0.001
1. Ex. 4 years	3603	1	1.09 (0.84, 1.4)	1.19 (0.93, 1.54)	1.37 (1.05, 1.79)	1.64 (1.22, 2.21)	1.44 (0.83, 2.49)	0.661	<0.001
2. ≤ 70 years	2512	1	0.98 (0.75, 1.28)	1.13 (0.87, 1.47)	1.39 (1.05, 1.83)	1.63 (1.17, 2.28)	0.95 (0.44, 2.04)	0.304	<0.001
3. Adjust. socioeconomic status	4056	1	1.04 (0.82, 1.31)	1.13 (0.9, 1.41)	1.25 (0.99, 1.59)	1.46 (1.11, 1.91)	1.17 (0.69, 1.97)	0.761	<0.001
4. Ex. antihypertensives	2405	1	1.1 (0.85, 1.44)	1.16 (0.89, 1.5)	1.49 (1.13, 1.97)	1.61 (1.15, 2.25)	1.87 (0.95, 3.68)	0.397	<0.001
5. Restriction to type 2 diabetes	3200	1	1.1 (0.83, 1.45)	1.21 (0.93, 1.59)	1.3 (0.98, 1.72)	1.68 (1.22, 2.3)	1.47 (0.83, 2.61)	0.257	<0.001
6. 2004 or later	410	1	0.78 (0.45, 1.38)	0.83 (0.48, 1.46)	1.08 (0.59, 1.98)	0.97 (0.4, 2.31)	1.25 (0.15, 10.13)	0.773	0.150

Table 6.8 Hazard ratios for unspecified stroke by usual systolic blood pressure in seven sensitivity analyses. Confidence intervals provided in parentheses.

	Events	0-130 (reference)	<i>Usual Systolic Blood Pressure (mm Hg)</i>					Non-linearity (p-value)	Linear trend (p-value)
			131-140	141-150	151-160	161-170	>170		
Primary analysis	2468	1	0.92 (0.71, 1.2)	1.11 (0.86, 1.43)	1.29 (0.99, 1.69)	1.61 (1.18, 2.2)	1.27 (0.69, 2.33)	0.409	<0.001
1. Ex. 4 years	2103	1	1.01 (0.75, 1.36)	1.23 (0.92, 1.65)	1.43 (1.05, 1.95)	1.62 (1.13, 2.31)	1.32 (0.66, 2.66)	0.730	<0.001
2. ≤ 70 years	1480	1	1.03 (0.75, 1.42)	1.35 (0.99, 1.84)	1.79 (1.28, 2.5)	2.15 (1.44, 3.22)	1.66 (0.69, 3.98)	0.547	<0.001
3. Adjust. socioeconomic status	2468	1	0.93 (0.71, 1.2)	1.12 (0.86, 1.44)	1.3 (0.99, 1.7)	1.63 (1.19, 2.22)	1.26 (0.68, 2.31)	0.394	<0.001
4. Ex. antihypertensives	1562	1	0.96 (0.71, 1.29)	1.15 (0.86, 1.54)	1.39 (1.02, 1.91)	1.72 (1.17, 2.52)	1.53 (0.68, 3.47)	0.802	<0.001
5. Restriction to type 2 diabetes	1779	1	0.86 (0.63, 1.18)	1.06 (0.78, 1.44)	1.17 (0.84, 1.61)	1.53 (1.05, 2.21)	1.25 (0.6, 2.61)	0.345	<0.001
6. 2004 or later	168	1	0.73 (0.35, 1.54)	0.85 (0.41, 1.79)	1.16 (0.5, 2.7)	2.36 (0.76, 7.35)	5.5 (0.62, 49)	0.425	0.004

Table 6.9 Hazard ratios for ischemic stroke by usual systolic blood pressure in seven sensitivity analyses. Confidence intervals provided in parentheses.

	Events	0-130 (reference)	<i>Usual Systolic Blood Pressure (mm Hg)</i>					Non- linearity (p-value)	Linear trend (p-value)
			131-140	141-150	151-160	161-170	>170		
Primary analysis	1297	1	1.11 (0.77, 1.6)	1.32 (0.92, 1.89)	1.44 (0.98, 2.12)	1.9 (1.22, 2.95)	1.35 (0.52, 3.54)	0.743	<0.001
1. Ex. 4 years	1172	1	1.21 (0.8, 1.82)	1.42 (0.95, 2.14)	1.67 (1.09, 2.57)	1.87 (1.14, 3.09)	1.77 (0.66, 4.73)	0.978	<0.001
2. ≤ 70 years	844	1	1.15 (0.75, 1.76)	1.56 (1.03, 2.38)	2 (1.27, 3.14)	2.41 (1.39, 4.2)	1.45 (0.33, 6.32)	0.793	<0.001
3. Adjust. socioeconomic status	1297	1	1.11 (0.77, 1.6)	1.32 (0.92, 1.9)	1.45 (0.98, 2.13)	1.9 (1.22, 2.96)	1.35 (0.52, 3.53)	0.734	<0.001
4. Ex. antihypertensives	835	1	1.23 (0.8, 1.88)	1.44 (0.95, 2.19)	1.71 (1.09, 2.69)	2.2 (1.28, 3.77)	2.03 (0.59, 7.01)	0.985	<0.001
5. Restriction to type 2 diabetes	1015	1	1.47 (0.9, 2.39)	1.72 (1.07, 2.79)	1.97 (1.19, 3.25)	2.6 (1.48, 4.56)	0.91 (0.21, 4.03)	0.458	<0.001
6. 2004 or later	123	1	3.2 (0.76, 13.44)	3.78 (0.89, 15.99)	3.53 (0.75, 16.58)	11.34 (2.1, 61.09)	0 (0, Inf)	0.477	0.014

Table 6.10 Hazard ratios for hemorrhagic stroke by usual systolic blood pressure in seven sensitivity analyses. Confidence intervals provided in parentheses.

	Events	<i>Usual Systolic Blood Pressure (mm Hg)</i>						Non-linearity (p-value)	Linear trend (p-value)
		0-130 (reference)	131-140	141-150	151-160	161-170	>170		
Primary analysis	325	1	1.23 (0.6, 2.5)	1.26 (0.62, 2.52)	1.41 (0.67, 2.99)	2.44 (1.05, 5.67)	1.97 (0.41, 9.56)	0.776	0.025
1. Ex. 4 years	287	1	1.17 (0.55, 2.5)	1.25 (0.59, 2.62)	1.35 (0.6, 3.02)	2.26 (0.9, 5.66)	1.11 (0.13, 9.31)	0.816	0.134
2. ≤ 70 years	218	1	1.63 (0.69, 3.87)	1.75 (0.74, 4.13)	2.11 (0.83, 5.33)	4.3 (1.52, 12.16)	3.93 (0.44, 34.79)	0.751	0.002
3. Adjust. socioeconomic status	325	1	1.23 (0.6, 2.5)	1.26 (0.62, 2.53)	1.41 (0.67, 2.99)	2.44 (1.05, 5.66)	1.96 (0.4, 9.54)	0.778	0.025
4. Ex. antihypertensives	216	1	1.56 (0.66, 3.7)	1.72 (0.73, 4.04)	2.11 (0.84, 5.29)	3.44 (1.18, 10.06)	3.03 (0.34, 27.26)	0.945	0.015
5. Restriction to type 2 diabetes	236	1	1.26 (0.53, 3.02)	1.33 (0.57, 3.13)	1.53 (0.62, 3.78)	2.39 (0.85, 6.66)	1.4 (0.16, 12.28)	0.684	0.190
6. 2004 or later	37	1	0.82 (0.2, 3.3)	0.9 (0.22, 3.64)	1.22 (0.22, 6.67)	7.14 (0.98, 51.83)	0 (0, Inf)	0.544	0.086

Table 6.11 Hazard ratios of chronic kidney disease by usual systolic blood pressure in seven sensitivity analyses. Confidence intervals provided in parentheses.

	Events	<i>Usual Systolic Blood Pressure (mm Hg)</i>						Non- linearity (p-value)	Linear trend (p-value)
		0-130 (reference)	131-140	141-150	151-160	161-170	>170		
Primary analysis	12441	1	1.1 (0.97, 1.24)	1.31 (1.16, 1.48)	1.53 (1.35, 1.74)	1.62 (1.39, 1.88)	1.82 (1.37, 2.41)	0.125	<0.001
1. Ex. 4 years	11185	1	1.14 (1, 1.3)	1.39 (1.22, 1.58)	1.61 (1.4, 1.85)	1.73 (1.46, 2.04)	1.92 (1.41, 2.6)	0.102	<0.001
2. ≤ 70 years	8648	1	1.09 (0.95, 1.25)	1.31 (1.14, 1.5)	1.54 (1.33, 1.78)	1.8 (1.5, 2.16)	2.1 (1.48, 2.99)	0.821	<0.001
3. Adjust. socioeconomic status	12441	1	1.1 (0.97, 1.24)	1.31 (1.16, 1.48)	1.54 (1.35, 1.74)	1.62 (1.39, 1.89)	1.81 (1.36, 2.4)	0.124	<0.001
4. Ex. antihypertensives	7723	1	1.1 (0.96, 1.27)	1.32 (1.15, 1.52)	1.58 (1.36, 1.83)	1.87 (1.54, 2.25)	1.92 (1.27, 2.92)	0.840	<0.001
5. Restriction to type 2 diabetes	10007	1	1.06 (0.92, 1.22)	1.27 (1.11, 1.46)	1.46 (1.26, 1.7)	1.53 (1.29, 1.83)	1.8 (1.31, 2.47)	0.208	<0.001
6. 2004 or later	1198	1	1.11 (0.79, 1.56)	1.32 (0.95, 1.85)	1.87 (1.3, 2.68)	2.09 (1.28, 3.42)	1.67 (0.61, 4.57)	0.255	<0.001

Table 6.12 Hazard ratios for aortic aneurysm by usual systolic blood pressure in seven sensitivity analyses. Confidence intervals provided in parentheses.

	Events	0-130 (reference)	<i>Usual Systolic Blood Pressure (mm Hg)</i>					Non-linearity (p-value)	Linear trend (p-value)
			131-140	141-150	151-160	161-170	>170		
Primary analysis	213	1	0.87 (0.36, 2.09)	0.83 (0.35, 1.96)	0.68 (0.27, 1.74)	1.46 (0.51, 4.2)	0 (0, Inf)	0.539	0.852
1. Ex. 4 years	182	1	0.76 (0.31, 1.85)	0.68 (0.29, 1.64)	0.41 (0.15, 1.1)	0.74 (0.22, 2.47)	0 (0, Inf)	0.369	0.922
2. ≤ 70 years	121	1	0.93 (0.31, 2.75)	0.75 (0.26, 2.19)	0.63 (0.19, 2.11)	1.43 (0.37, 5.56)	0 (0, Inf)	0.116	0.811
3. Adjust. socioeconomic status	213	1	0.87 (0.36, 2.08)	0.83 (0.35, 1.96)	0.68 (0.27, 1.73)	1.44 (0.5, 4.14)	0 (0, Inf)	0.538	0.847
4. Ex. antihypertensives	136	1	0.97 (0.33, 2.86)	0.97 (0.34, 2.78)	0.97 (0.3, 3.09)	2.29 (0.62, 8.4)	0 (0, Inf)	0.644	0.700
5. Restriction to type 2 diabetes	169	1	2.03 (0.48, 8.62)	2.23 (0.53, 9.34)	2.21 (0.5, 9.7)	3.88 (0.8, 18.93)	0 (0, Inf)	0.376	0.436
6. 2004 or later	17	-	-	-	-	-	-	-	-

Table 6.13 Hazard ratios of peripheral arterial disease by usual systolic blood pressure in seven sensitivity analyses. Confidence intervals provided in parentheses.

	Events	0-130 (reference)	<i>Usual Systolic Blood Pressure (mm Hg)</i>					Non-linearity (p-value)	Linear trend (p-value)
			131-140	141-150	151-160	161-170	>170		
Primary analysis	3028	1	1.06 (0.86, 1.32)	1.29 (1.04, 1.6)	1.52 (1.21, 1.92)	1.95 (1.47, 2.59)	1.83 (1.04, 3.21)	0.754	<0.001
1. Ex. 4 years	2635	1	1.14 (0.89, 1.44)	1.32 (1.04, 1.67)	1.58 (1.23, 2.05)	2.06 (1.51, 2.81)	1.82 (0.97, 3.41)	0.854	<0.001
2. ≤ 70 years	2332	1	1.04 (0.83, 1.31)	1.27 (1.01, 1.59)	1.49 (1.16, 1.91)	1.86 (1.34, 2.57)	1.64 (0.81, 3.35)	0.826	<0.001
3. Adjust. socioeconomic status	3028	1	1.07 (0.86, 1.33)	1.3 (1.05, 1.6)	1.53 (1.21, 1.93)	1.96 (1.48, 2.6)	1.83 (1.04, 3.22)	0.752	<0.001
4. Ex. antihypertensives	2050	1	1.18 (0.93, 1.51)	1.43 (1.12, 1.82)	1.76 (1.34, 2.3)	2.36 (1.66, 3.34)	1.31 (0.52, 3.3)	0.611	<0.001
5. Restriction to type 2 diabetes	2159	1	1.08 (0.82, 1.43)	1.31 (1, 1.71)	1.5 (1.13, 2)	1.85 (1.31, 2.62)	1.76 (0.87, 3.55)	0.945	<0.001
6. 2004 or later	200	1	0.9 (0.47, 1.73)	1.03 (0.53, 1.99)	1.23 (0.57, 2.65)	0.97 (0.25, 3.72)	9.77 (1.05, 91.24)	0.645	0.148

Table 6.14 Hazard ratios for deep vein thrombosis by usual systolic blood pressure in seven sensitivity analyses. Confidence intervals provided in parentheses.

	Events	0-130 (reference)	<i>Usual Systolic Blood Pressure (mm Hg)</i>					Non-linearity (p-value)	Linear trend (p-value)
			131-140	141-150	151-160	161-170	>170		
Primary analysis	1141	1	1.1 (0.77, 1.56)	1.04 (0.73, 1.47)	0.97 (0.66, 1.42)	1.06 (0.65, 1.73)	1.55 (0.67, 3.56)	0.638	0.949
1. Ex. 4 years	1011	1	1.04 (0.71, 1.51)	1.03 (0.71, 1.49)	0.96 (0.64, 1.46)	1.04 (0.61, 1.77)	1.59 (0.65, 3.93)	0.826	0.741
2. ≤ 70 years	845	1	0.96 (0.67, 1.38)	0.95 (0.66, 1.36)	0.88 (0.58, 1.34)	1.12 (0.64, 1.97)	1.13 (0.34, 3.78)	0.941	0.966
3. Adjust. socioeconomic status	1141	1	1.1 (0.77, 1.56)	1.04 (0.73, 1.47)	0.97 (0.66, 1.42)	1.06 (0.65, 1.73)	1.55 (0.67, 3.57)	0.636	0.953
4. Ex. antihypertensives	758	1	1.1 (0.75, 1.62)	1.04 (0.71, 1.54)	0.97 (0.62, 1.52)	1.18 (0.64, 2.16)	2.16 (0.7, 6.7)	0.733	0.964
5. Restriction to type 2 diabetes	868	1	1.15 (0.76, 1.76)	1.04 (0.68, 1.58)	0.94 (0.59, 1.48)	0.92 (0.5, 1.67)	1.41 (0.52, 3.82)	0.617	0.416
6. 2004 or later	111	1	1.07 (0.4, 2.81)	1.23 (0.47, 3.27)	1 (0.32, 3.13)	1.82 (0.37, 8.95)	4.15 (0.23, 73.35)	0.822	0.671

Table 6.15 Hazard ratios for pulmonary embolism by usual systolic blood pressure in seven sensitivity analyses. Confidence intervals provided in parentheses.

	Events	0-130 (reference)	<i>Usual Systolic Blood Pressure (mm Hg)</i>					Non-linearity (p-value)	Linear trend (p-value)
			131-140	141-150	151-160	161-170	>170		
Primary analysis	613	1	1.57 (0.84, 2.93)	1.44 (0.78, 2.67)	1.68 (0.88, 3.2)	1.01 (0.45, 2.28)	0.6 (0.08, 4.75)	0.189	0.544
1. Ex. 4 years	560	1	1.45 (0.75, 2.79)	1.41 (0.74, 2.71)	1.56 (0.79, 3.09)	1.17 (0.51, 2.7)	0.74 (0.09, 5.93)	0.666	0.926
2. ≤ 70 years	445	1	1.33 (0.69, 2.58)	1.3 (0.68, 2.5)	1.41 (0.7, 2.83)	0.81 (0.31, 2.1)	1 (0.12, 8.14)	0.538	0.520
3. Adjust. socioeconomic status	613	1	1.57 (0.84, 2.92)	1.44 (0.78, 2.67)	1.68 (0.88, 3.19)	1.01 (0.45, 2.27)	0.6 (0.08, 4.75)	0.190	0.537
4. Ex. antihypertensives	392	1	1.33 (0.71, 2.52)	0.96 (0.51, 1.81)	1.29 (0.65, 2.56)	0.54 (0.18, 1.6)	0 (0, Inf)	0.091	0.084
5. Restriction to type 2 diabetes	450	1	2.44 (0.99, 6.04)	2.09 (0.85, 5.15)	2.28 (0.9, 5.75)	1.7 (0.59, 4.93)	1.39 (0.16, 12.21)	0.311	0.505
6. 2004 or later	68	1	2.51 (0.33, 19.15)	2.26 (0.29, 17.55)	2.19 (0.25, 19.45)	1.85 (0.11, 31.67)	0 (0, Inf)	0.970	0.834

Table 6.16 Hazard ratios for vascular dementia by usual systolic blood pressure in seven sensitivity analyses. Confidence intervals provided in parentheses.

	Events	<i>Usual Systolic Blood Pressure (mm Hg)</i>						Non-linearity (p-value)	Linear trend (p-value)
		0-130 (reference)	131-140	141-150	151-160	161-170	>170		
Primary analysis	692	1	1.28 (0.73, 2.27)	1.06 (0.61, 1.85)	1 (0.55, 1.8)	1.25 (0.64, 2.43)	0.32 (0.04, 2.5)	0.393	0.156
1. Ex. 4 years	648	1	1.24 (0.67, 2.3)	1.13 (0.61, 2.06)	1.12 (0.59, 2.1)	1.29 (0.63, 2.66)	0.38 (0.05, 2.99)	0.721	0.504
2. ≤ 70 years	326	1	1.76 (0.69, 4.47)	1.71 (0.68, 4.3)	1.86 (0.71, 4.87)	2.2 (0.75, 6.46)	1.55 (0.17, 14.29)	0.898	0.384
3. Adjust. socioeconomic status	692	1	1.28 (0.73, 2.27)	1.06 (0.61, 1.85)	1 (0.55, 1.8)	1.25 (0.64, 2.43)	0.32 (0.04, 2.5)	0.394	0.156
4. Ex. antihypertensives	424	1	0.99 (0.53, 1.83)	0.84 (0.46, 1.53)	0.8 (0.41, 1.56)	1.65 (0.76, 3.58)	0 (0, Inf)	0.140	0.704
5. Restriction to type 2 diabetes	557	1	2.11 (0.96, 4.63)	1.77 (0.82, 3.86)	1.68 (0.75, 3.75)	2.06 (0.86, 4.96)	0.62 (0.07, 5.27)	0.267	0.527
6. 2004 or later	61	1	2.44 (0.3, 20.01)	1.22 (0.15, 10.18)	0.13 (0.01, 2.58)	0 (0, Inf)	0 (0, Inf)	0.115	0.005

Table 6.17 Hazard ratios for fourteen cardiovascular events by usual systolic blood pressure. No years of follow up were excluded. Confidence intervals provided in parentheses.

	Events	0-130 (reference)	<i>Usual Systolic Blood Pressure (mm Hg)</i>					Test for Non- linearity	Test for linear trend
			131-140	141-150	151-160	161-170	>170		
Any cardiovascular event	35607	1	0.95 (0.89, 1.01)	1.04 (0.98, 1.1)	1.17 (1.1, 1.25)	1.36 (1.25, 1.47)	1.64 (1.4, 1.91)	<0.001	<0.001
Major cardiovascular event	18385	1	0.94 (0.86, 1.03)	1.03 (0.94, 1.12)	1.18 (1.08, 1.3)	1.48 (1.33, 1.66)	1.57 (1.28, 1.93)	<0.001	<0.001
Ischemic heart disease	7943	1	0.99 (0.86, 1.13)	1.14 (1, 1.3)	1.28 (1.11, 1.47)	1.71 (1.45, 2.01)	1.61 (1.18, 2.21)	0.060	<0.001
Heart failure	8206	1	0.81 (0.7, 0.92)	0.92 (0.81, 1.05)	1.05 (0.92, 1.21)	1.29 (1.1, 1.52)	1.47 (1.1, 1.97)	<0.001	<0.001
Atrial Fibrillation	6601	1	0.86 (0.74, 1.01)	0.94 (0.81, 1.09)	1.02 (0.87, 1.19)	1.19 (0.98, 1.44)	1.5 (1.05, 2.13)	0.063	<0.001
Unspecified Stroke	4494	1	0.92 (0.77, 1.11)	1.07 (0.89, 1.28)	1.25 (1.03, 1.52)	1.55 (1.24, 1.93)	1.91 (1.32, 2.77)	0.285	<0.001
Ischemic Stroke	2161	1	1.3 (0.98, 1.72)	1.42 (1.08, 1.88)	1.57 (1.17, 2.11)	2.05 (1.46, 2.87)	2.48 (1.36, 4.52)	0.690	<0.001
Hemorrhagic Stroke	589	1	1.08 (0.66, 1.77)	1.28 (0.79, 2.07)	1.24 (0.73, 2.1)	2.18 (1.2, 3.97)	2.36 (0.78, 7.14)	0.565	0.003
Chronic Kidney Disease	17928	1	0.98 (0.89, 1.07)	1.08 (0.99, 1.18)	1.23 (1.12, 1.35)	1.33 (1.18, 1.49)	1.73 (1.39, 2.16)	0.058	<0.001
Aortic Aneurysm	365	1	1.04 (0.55, 1.98)	1.01 (0.53, 1.89)	1 (0.51, 1.99)	1.19 (0.52, 2.71)	-	0.986	0.750
Peripheral arterial disease	5431	1	1.13 (0.96, 1.32)	1.31 (1.12, 1.53)	1.6 (1.35, 1.89)	1.95 (1.59, 2.39)	2.59 (1.82, 3.7)	0.956	<0.001
Deep vein thrombosis	2002	1	0.93 (0.73, 1.18)	0.88 (0.7, 1.11)	0.85 (0.65, 1.11)	0.92 (0.65, 1.31)	0.97 (0.48, 1.96)	0.774	0.533
Pulmonary embolism	1030	1	1.18 (0.8, 1.73)	1.04 (0.71, 1.52)	1.08 (0.71, 1.62)	0.86 (0.5, 1.46)	0.71 (0.21, 2.37)	0.646	0.085
Vascular Dementia	1128	1	0.99 (0.7, 1.39)	0.76 (0.55, 1.07)	0.72 (0.5, 1.05)	0.78 (0.5, 1.22)	0.37 (0.09, 1.54)	0.275	<0.001

Model adjusted for blood pressure, age, gender, body mass index, smoking status, baseline antihypertensive use, baseline lipid lowering use, total cholesterol and high density lipoprotein cholesterol.

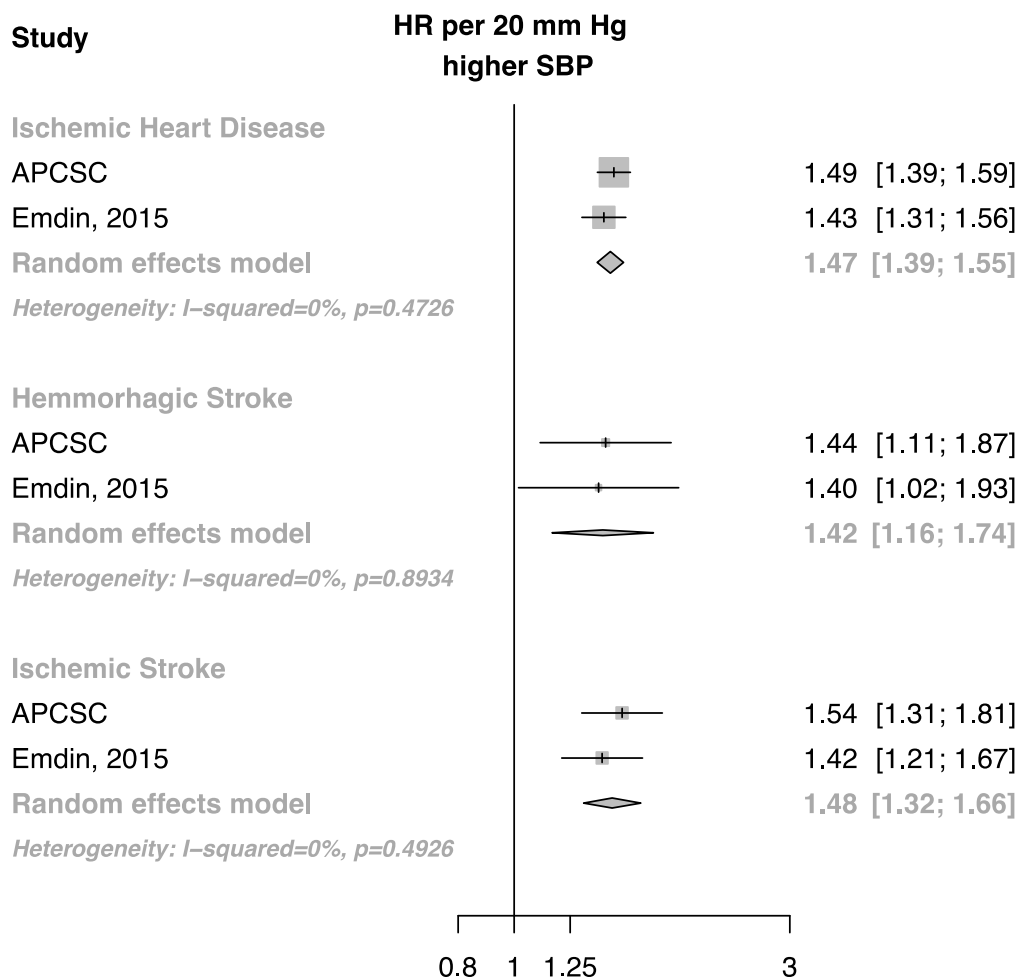


Figure 6.5 Comparison of hazard ratios for risk of ischemic heart disease and stroke subtypes in the Australia and New Zealand subpopulation of the Asia Pacific Cohort Studies Collaboration and this analysis.

I identified 2 977 972 adults without diabetes with a usual systolic blood pressure of 115 mm Hg to 180 mm Hg. In this population, SBP was continuously associated with risk of any cardiovascular event and major cardiovascular event, with the lowest risk at 115 mm Hg and no evidence of a threshold (Figure 6.6).

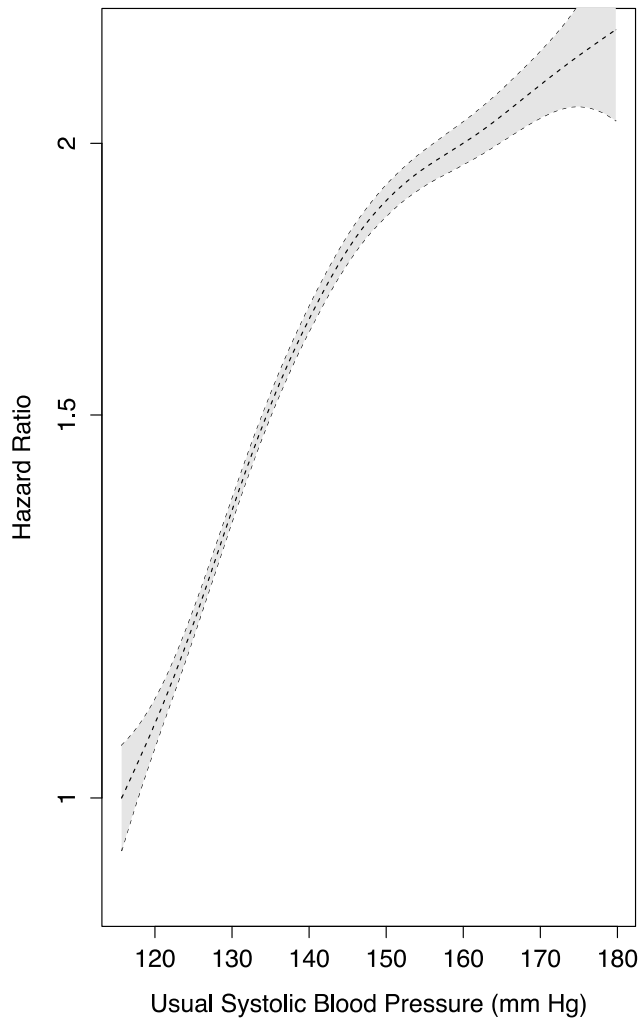


Figure 6.6 Association of systolic blood pressure with risk of a major cardiovascular event in non-diabetic adults with usual systolic blood pressure of 115 mm Hg to 180 mm Hg.

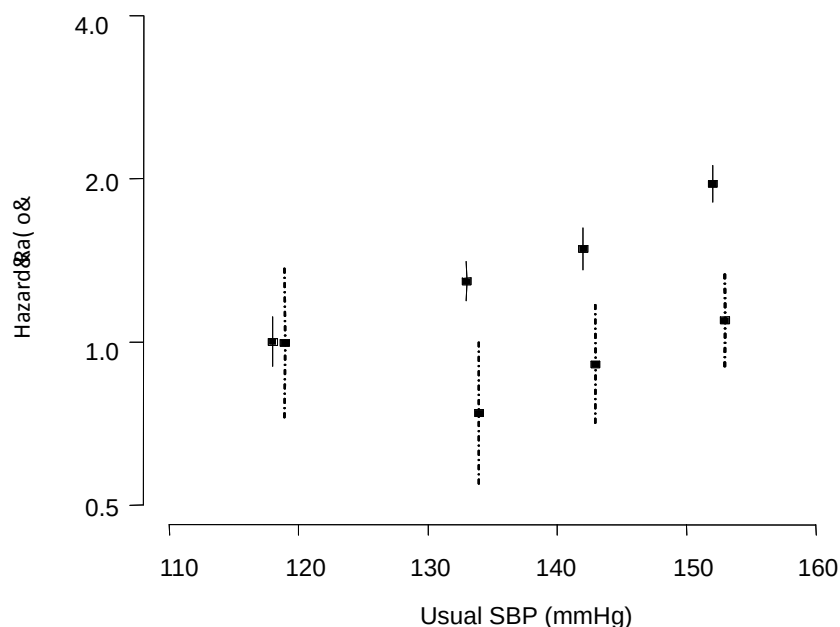
6.4 Discussion

In this analysis of data from 73 658 individuals with diabetes, a linear association between blood pressure and risk of a major cardiovascular event was observed above a blood pressure of 130/75 mm Hg. While there was the suggestion of a threshold at 130/75 mm Hg when BP was modeled continuously, confidence intervals did not exclude either a modest increase or decrease in the proportional risk of cardiovascular disease below 130/75 mm Hg. SBP and DBP were observed to have significantly differing strengths of associations with different cardiovascular diseases. 20 mm Hg higher SBP was associated

with a 53% higher risk of peripheral arterial disease, 44% higher risk of heart failure and 43% higher risk of ischemic heart disease, but was not associated with risk of deep vein thrombosis, pulmonary embolism or vascular dementia.

Prior reports on the association between blood pressure and risk of cardiovascular disease in type 2 diabetes have been conflicting. In an analysis of the UKPDS cohort, a linear relationship between blood pressure and risk of cardiovascular disease was observed, with no evidence of a nadir to 115 mm Hg.⁵⁶ However, this analysis included a number of microvascular outcomes in the composite endpoint, including retinal photocoagulation and cataract extraction. An analysis of the Multiple Risk Factor Intervention Trial cohort suggested the lowest risk of cardiovascular death among men with a systolic blood pressure <120 mm Hg.⁶⁰ However, this analysis did not adjust for other risk factors and did not adjust for regression dilution. In an analysis of the APCSC, there appeared to be a threshold below 130 mm Hg at which lower systolic blood pressure was not associated with a lower risk of coronary heart disease (Figure 6.7), consistent with my results.⁵⁵ In contrast, analyses of two other trial cohorts have suggested an increase in risk of major cardiovascular events (cardiovascular death, ischemic heart disease and stroke) at on-treatment blood pressures below 130 mm Hg.^{57,61} As I also observed the presence of a J-shaped curve when no period of follow up was excluded from the analysis, these results suggest that these J-shaped curves may be due to reverse causality, that is, diagnosed and undiagnosed cardiovascular disease causing low blood pressure among individuals at high cardiovascular risk.

A.



B.

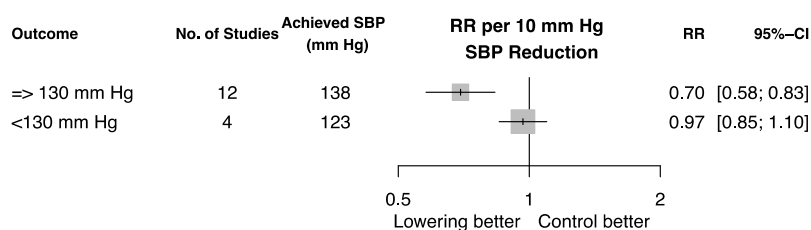


Figure 6.7 Association of blood pressure with coronary heart disease in APCSC and meta-analysis of randomized trials. A. Hazard ratios (with 95% confidence intervals) for CHD for Australasia (Australia and New Zealand) from the Asia Pacific Cohort Studies Collaboration. The dashed line represents subjects with diabetes and the solid line represents those without diabetes.⁵⁵ B. Meta-analysis of randomized trials testing blood pressure lowering (standardized per 10 mm Hg lower SBP) in type 2 diabetes on CHD.²⁰⁷

Consistent with the PSC¹² and prior analyses of CPRD¹³, I observed a continuous relationship between SBP and cardiovascular risk in non-diabetic adults in the range 115 mm Hg to 180 mm Hg usual SBP, with no evidence of a nadir. However, this analysis suggests that there may be a threshold at 130 mm Hg below which lower SBP is not associated with a lower risk of cardiovascular disease, although confidence intervals were wide. These findings are consistent with randomised evidence from the ACCORD trial, which did not observe a reduction in risk of a cardiovascular composite at a target SBP of 120 mm Hg vs. 140 mm Hg among diabetics.⁶² These findings therefore suggest that the

presence of diabetes may modify the relationship between blood pressure and risk of cardiovascular disease. If the observed relationship is, in fact, causal, the biological reasons for the potentially different associations in people with and without diabetes may be due to different haemodynamic consequences of lower blood pressure in people with diabetes. However, it is important to note that these results may be due to reverse causality, with diabetics having a greater prevalence of undiagnosed cardiovascular disease, resulting in both low blood pressure at baseline and a higher risk of diagnosis of cardiovascular disease during follow up. Under this interpretation, the threshold observed in these results is due to confounding by undiagnosed cardiovascular disease rather than a true causal attenuation of the effect of blood pressure on risk of cardiovascular disease less than 130 mm Hg.

This analysis has a number of strengths. It is very large, comprising 73 658 individuals with 22 239 events, and the analysed population is contemporary, with broad use of antihypertensives and lipid lowering medications. I took a number of steps to mitigate the risk of reverse causality and confounding, excluding individuals with pre-existing cardiovascular disease, excluding the first three and four years of follow up and undertaking a number of sensitivity analyses to test the robustness of my results. One limitation of this analysis is that I utilized linked electronic health records. Although CPRD has been validated for epidemiological research into diabetes²², and previously used to examine the associations between diabetes and cardiovascular disease²², the risk of misclassification of events may be higher with routinely collected data. However, previous analyses have suggested classification of cardiovascular events in CPRD to have high specificity.⁷⁰ Furthermore, estimates for ischemic heart disease and stroke were broadly consistent with a collaborative meta-analysis of traditional cohort studies in Australasia. A

second limitation is the observational nature of this design. Although I took a number of steps to minimize the risk of reverse causality and confounding, it is possible that the threshold observed in this study is due to undiagnosed macrovascular disease or microvascular disease causing lowering blood pressure among individuals with type 2 diabetes. Another possibility is that observed or unobserved risk factors modified the association between blood pressure and risk of cardiovascular disease, resulting in a nonlinear curve.²¹⁷

These results have implications both for future research and for clinical practice. Although intensive blood pressure lowering did not reduce a composite cardiovascular outcome in ACCORD⁶², the primary outcome used in this trial was similar to the major cardiovascular event definition used in this analysis (cardiovascular death, non-fatal stroke, myocardial infarction and heart failure). These results suggest that future trials testing intensive blood pressure lowering (<130 mm Hg SBP) should consider including chronic kidney disease and peripheral arterial disease in any primary outcome, both which appeared to be log-linearly related to blood pressure. These results also highlight the need for greater evidence on the effects of blood pressure lowering on cardiovascular disease at systolic blood pressure levels below 130 mm Hg in diabetes and the importance of blood pressure control for prevention of major cardiovascular disease in the range > 130 mm Hg SBP.

6.5 Conclusions

Above an SBP of 130 mm Hg, a 20 mm Hg higher SBP was associated with a 40% higher risk of a major cardiovascular event (HR 1.40 CI 1.32, 1.48). While a threshold was observed at 130 mm Hg, confidence intervals did not exclude either a modest increase or modest decrease in the risk of a major cardiovascular event < 130 mm Hg SBP.

Chapter 7 Effect of blood pressure lowering therapies on cardiovascular disease in type 2 diabetes: a meta-analysis of 45 large-scale randomized trials

7.1 Introduction

Type 2 diabetes is associated with a substantially increased risk of macrovascular events such as myocardial infarction and stroke.²¹⁸ It is also now the leading cause of blindness in developed countries and is a leading cause of end stage kidney disease through its effects on the microvasculature.^{219,220} As shown in the previous chapter and in prior studies^{221,222}, elevated blood pressure is a risk factor for cardiovascular disease, including ischemic heart disease, stroke, heart failure and microvascular disease, among people with diabetes.

In general adult populations, the association of blood pressure with cardiovascular disease is continuous, with increasing risks of cardiovascular events with rising blood pressure levels from as low as 115 mm Hg systolic and 75 mm Hg diastolic.^{12,13} Similar associations have been reported for blood pressure and the risks of macrovascular⁵⁵ and microvascular⁵⁶ disease in prior analyses of patients with type 2 diabetes. However, in the analysis presented in the previous chapter, a non-linear relationship was observed between blood pressure and cardiovascular disease in type 2 diabetes, with a possible threshold at 130 mm Hg. Whether this association reflects a causal relationship between blood pressure and risk of cardiovascular disease or is due to confounding is unclear and can only be resolved by an analysis of randomized evidence.

To address this question, I conducted a comprehensive meta-analysis of the effects of blood pressure lowering treatment in people with diabetes. I aimed to determine the extent to which blood pressure lowering treatment reduces risk of macrovascular outcomes

and microvascular outcomes, with a specific focus on heterogeneity by baseline and by achieved blood pressure.

7.2 Methods

7.2.1 Systematic search strategy

As described in the general methods section, a systematic search of MEDLINE and relevant references was undertaken, to identify large scale blood pressure lowering trials which reported the effect of antihypertensive therapy on risk of atrial fibrillation. After identification of large scale blood pressure lower randomized trials, two reviewers manually examined whether each trial was conducted in patients with diabetes or, if the trial was not conducted in patients with diabetes, whether a diabetic subgroup was reported in a secondary publication.

7.2.2 Eligibility

I included all randomized controlled trials of blood pressure lowering treatment where the entire trial population comprised diabetics, or where the results of a diabetic subgroup were able to be obtained. No trial was excluded due to the presence of comorbidities at baseline; trials conducted in type 2 diabetic patients with heart failure and after myocardial infarction were included. However, trials that were conducted in patients predominantly with type 1 diabetes were excluded. Studies that did not make a specific reference to diabetes type were included, assuming that the great majority of patients in these studies were of type 2 diabetes. For inclusion, all trials were required to have greater than 1000 patient years of follow-up in each randomized group to minimize risk of bias associated with small trials.⁹⁹

7.2.3 Search and extraction

Two researchers screened all abstracts identified in the initial search, excluding studies that violated inclusion criteria. Following the initial abstract screen, full texts of all identified studies were acquired. Two researchers then screened full text studies in duplicate, with differences resolved by consensus. Once all eligible trials were identified, macrovascular and microvascular outcomes for diabetic subgroups were extracted independently by two researchers. Data on the patient population, drug/intervention in the treatment group, drug/intervention in the control group, sample size, duration, baseline blood pressure, achieved blood pressure in the treatment group and mean reduction in blood pressure were extracted. If the baseline blood pressure, each treatment group blood pressure or difference in blood pressure between groups was unavailable for the diabetic subgroup, the value for the entire trial was recorded.

In addition to all-cause mortality, data on four macrovascular outcomes were extracted: cardiovascular events (defined as myocardial infarction, sudden cardiac death, revascularization, fatal and non-fatal stroke and fatal and non-fatal heart failure), major coronary heart disease events (defined as fatal and non-fatal myocardial infarction (MI) and sudden cardiac death, with silent MI excluded¹⁵); stroke (fatal and non-fatal); and heart failure (both new diagnosis of heart failure for those without heart failure at baseline and hospitalization for individuals with heart failure at baseline). For microvascular outcomes, retinopathy (defined as progress of three or more steps on the Early Treatment of Diabetic Retinopathy Scale²²³), renal failure (defined as end stage renal disease requiring dialysis or transplantation, or death due to renal disease), and albuminuria (development of microalbuminuria, as well as the composite of new or worsening albuminuria) were

extracted. For one trial, retinopathy was identified as participants requiring laser therapy for treatment of retinopathy rather than progression on the Early Treatment of Diabetic Retinopathy Scale scale; this was included in the meta-analysis.²²⁴ For six trials, peripheral arterial disease was included in the reported cardiovascular composite; these were included in the meta-analysis.²²⁵⁻²³⁰

For each outcome, both the total number of events and the summary statistic (either risk ratio or hazard ratio with confidence intervals) were extracted, if available. If a hazard ratio was provided, I utilized that ratio as a relative risk for the meta-analysis, as hazard ratios avoid censoring associated with use of tabular data and have greater statistical power. However, if a hazard ratio was not provided, a relative risk ratio from the total number of events was calculated and used.

7.2.4 Assessment of methodological quality

I used Cochrane's risk of bias tool to evaluate this risk within included trials.¹⁴⁴ Selection bias (random sequence generation and allocation concealment), performance bias (blinding of both participants and investigators), detection bias (blinding of evaluators), attrition bias (incomplete outcome data) and reporting bias (selective outcome reporting) were judged to be of either low, unclear or high risk. The trial, as a whole, was then judged to be of low, unclear or high risk of bias, based on whether the level of bias in domains may have led to material bias in the outcomes of interest.

7.2.5 Statistical analysis

For all analyses, overall estimates of association were calculated using inverse variance weighted fixed effects analysis, with 95% confidence intervals. Fixed effects was used as heterogeneity was low to moderate²³¹ and random effects, in certain circumstances,

can give inappropriate weight to smaller studies.²³² Heterogeneity was characterized using the I^2 statistic. Tests of interaction between subgroups were performed using Cochran's Q statistic. For the primary analysis, I restricted the meta-analysis to trials judged to be of low risk of bias (forty in total).

Analyses were performed to determine: (i) whether blood pressure lowering treatment reduces the risk of all-cause mortality, macrovascular outcomes and microvascular outcomes, and the magnitude of any such reductions; (ii) the proportional effect of blood pressure lowering treatment on these outcomes stratified by initial blood pressure level; (iii) the proportional effect of blood pressure lowering treatment on these outcomes stratified by achieved blood pressure level and (iv) the proportional effect of blood pressure lowering treatment on these outcomes based on different classes of blood pressure lowering medication used.

For the first objective, I included all trials that assigned individuals to a blood pressure lowering medication against placebo or assigned individuals to higher or lower blood pressure targets. For two trials that had three groups including a placebo, and for one trial that had four groups including a placebo, the active groups were combined for analysis by adding together all events and taking a weighted average of baseline blood pressure, achieved blood pressure and blood pressure reduction.^{58,233,234}

To determine the standardized effects of blood pressure lowering treatment for every 10 mm Hg reduction in systolic blood pressure, the log of the summary statistic of each trial (relative risk or hazard ratio) and the standard error of the log was multiplied by 10 mm Hg/systolic blood pressure reduction. For example, if the log hazard ratio was -0.1, and the blood pressure reduction was 5 mmHg, the standardized log hazard ratio was

calculated to be -0.1 ($10 \text{ mm Hg} / 5 \text{ mm Hg}$) = -0.2 . If a standardized effect was significant, I additionally calculated the absolute risk reduction for each significant outcome in events per 1000 patient years of follow up. I derived the absolute risk reduction for each outcome using the formula $ARR = (1 - RR)(ACR)$ where ARR is the absolute risk reduction, RR is the relative risk per 10 mm Hg lower systolic blood pressure and ACR is the assumed control risk (ACR).¹⁴⁴ I used the pooled event rate (in events per patient years) in the control groups of meta-analysed trials for each outcome as the assumed control risk (ACR). The number needed to treat over ten years (NNT) was derived from the inverse of the absolute risk reduction (per ten patient years) and its confidence interval. For trials that did not report the number of events (and only reported a relative risk), I derived the number of events from the reported relative risk to allow for calculation of absolute risk reduction.

As many trials conducted in patients with diabetes and heart failure did not report the magnitude of blood pressure reduction, and therefore could not be standardized, I examined whether there was heterogeneity between heart failure trials and non-heart failure trials in non-standardized analyses.

To determine if the associations between blood pressure lowering treatment and outcomes varied by *initial* systolic blood pressure, I stratified trials into categories of ≥ 140 mmHg and < 140 mmHg according to the mean baseline blood pressure of participants. Similarly, to determine if the associations between blood pressure lowering treatment and outcomes varied by *achieved* blood pressure, I stratified trials into categories of ≥ 130 mmHg and < 130 mmHg according to the mean systolic blood pressure achieved in the intervention group. As a sensitivity analysis, I: (1) excluded trials (twelve in total) from relevant analyses where it was necessary to impute blood pressure data (either baseline,

follow up or difference between groups) for the diabetic subgroup from the entire population, (2) examined non-standardized associations by baseline and achieved blood pressure and (3) included five trials which were judged to be of unclear or high risk of bias.

Possible variation in the associations between blood pressure lowering treatment and outcomes by class of medication was examined by comparing all trials that tested a given class of medication (ACE inhibitor [ACE-I], angiotensin receptor blocker [ARB], beta-blocker [BB], diuretic, calcium channel blocker [CCB]) against another class. One trial comparing classes of medication had three groups, but only provided summary statistics (relative risk reductions) for macrovascular outcomes.²³⁰ As inclusion of both comparisons would have led to duplicate counting of participants, I randomly selected a group for inclusion in the analysis. I did not include microvascular outcomes in the analysis by class of medication as there were not enough trials to allow for meta-analysis.

7.2.6 Comparison of observational estimates to randomized estimates

I compared estimates from the prior chapter for major cardiovascular event, coronary heart disease, stroke, heart failure and chronic kidney disease to those in the meta-analysis. As estimates in the prior chapter were restricted to individuals with a blood pressure greater than 130 mm Hg systolic blood pressure, I compared those estimates to the meta-analysis of trials with a baseline blood pressure >140 mm Hg. Chronic kidney disease from the observational analysis was considered to correspond to renal failure from the meta-analysis. Analyses were performed using STATA version 12 and R version 3.0.

7.3 Results

7.3.1 Characteristics of studies

In total, 10 386 abstracts were screened and 10 043 excluded (Figure 7.1). 343 studies were reviewed in full and an additional 213 then excluded, the majority for either having less than 1000 patient years in each arm or being a duplicate report of a randomized trials. Of the 134 randomized trials identified, 89 trials were excluded, the majority because they did not provide separate results for patients with diabetes.

Thirty-three were considered trials that tested blood pressure lowering, by either comparing a blood pressure lowering drug against a placebo (26 trials) or comparing blood pressure lowering to different target levels (7 trials; Table 7.1). Seventeen trials compared different classes of drugs against each other. All 45 trials reported on at least all-cause mortality or one pre-specified macrovascular outcome, and 16 trials reported on at least one of the three pre-specified microvascular outcomes. Twelve blood pressure lowering trials only reported a baseline blood pressure or achieved blood pressure for the entire study population, but not separately for the diabetic subgroup.

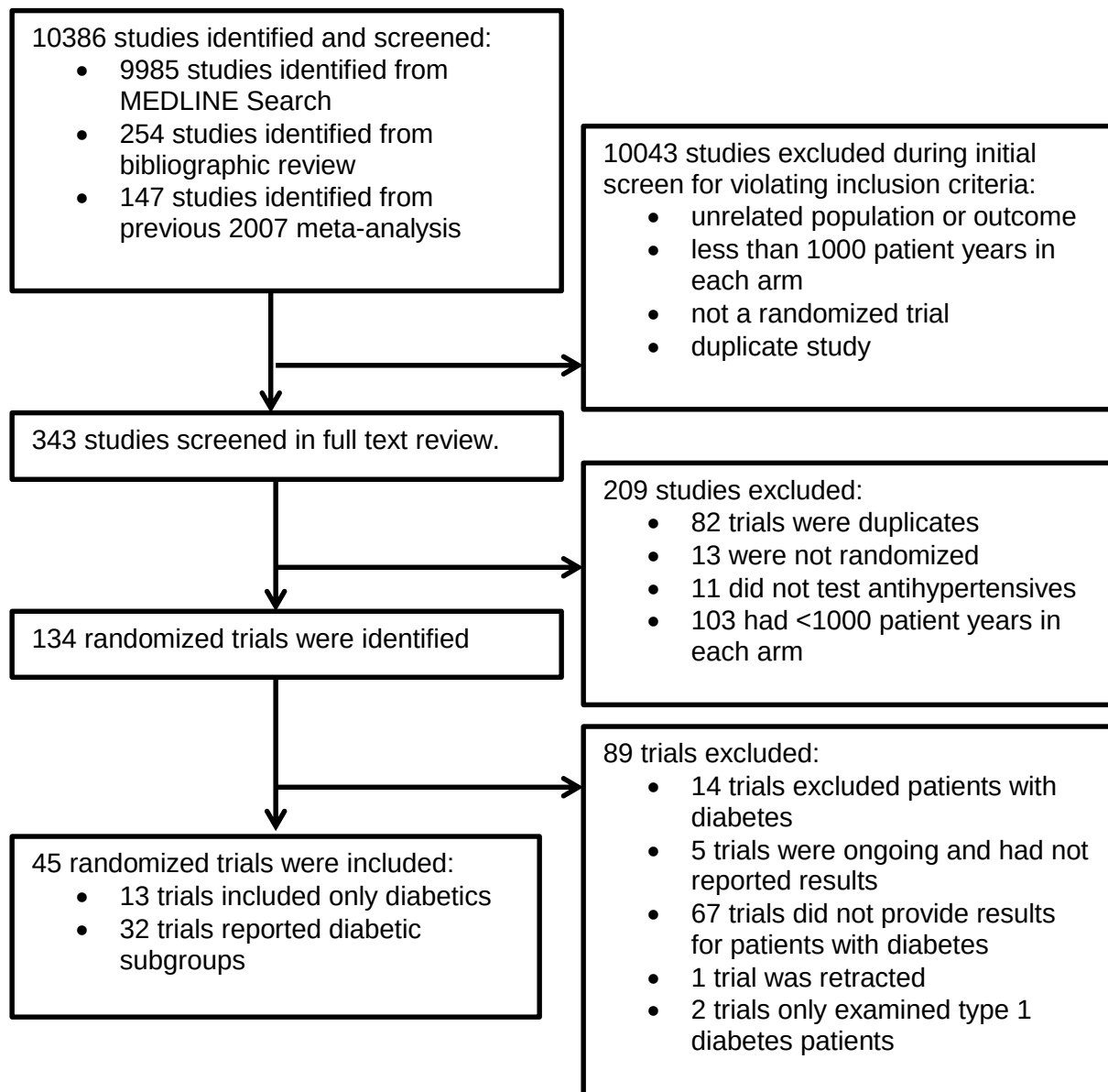


Figure 7.1 Flow chart of trial identification.

One trial was judged to be of high risk of bias, due to evidence of poor allocation concealment, while 4 trials were judged to be of unclear risk of bias and 40 trials of low risk of bias (Table 7.2). Therefore, 40 trials involving 100 354 participants formed the primary analysis, with an additional 5 trials (at unclear or high risk of bias) involving 4232 participants included in secondary analyses.

Table 7.1 Summary of baseline characteristics of included trials.

Name	Main Inclusion Criteria	Intervention	Control	No. Participants With Diabetes	Mean Age (yrs)	Men, No. (%)	Mean Duration of Follow Up (Yrs)	Mean BP at Baseline (Sys/Dia mm Hg)	Mean BP in Treatment Group (Sys/Dia mm Hg) over Follow Up
Blood pressure lowering drug vs. placebo									
ADVANCE ^{235,236} 2007	Diabetes mellitus	ACE+Diu (Perindopril + Indapamide)	Placebo	11140	66	6405 (57%)	4.3	145 / 81	136 / 73
ALTITUDE ²³⁷ 2012	Diabetes mellitus with either albuminuria (Micro or Macro) or cardiovascular disease	Aliskiren	Placebo	8561	65	5826 (68%)	2.7	137 / 74	139 / 75
BENEDICT ²³⁴ 2004	Diabetes mellitus without microalbuminuria	ACE (Trandolapril) +CCB (Verapamil)	Placebo	600	63	314 (52%)	3.6	151 / 88	139 / 80
		ACE (Trandolapril)	CCB (Verapamil)	604	63	321 (53%)	3.6	151 / 88	139 / 81
BEST ²³⁸ 2003	Heart Failure	BB (Bucindolol)	Placebo	964	61	750 (78%)	2	120 / 72	NA
CIBIS-2 ²³⁹ 2001	Heart Failure	BB (Bisoprolol)	Placebo	312	NA	250 (80%) ²	NA	130 / 80	NA
CONSENSUS II ²⁴⁰ 1992	ST elevated acute myocardial infarction	ACE (Enalapril)	Placebo	685	66	500 (73%) ²	0.5	134 / 80	NA
DIABHYCAR ¹⁵⁰ 2004	Diabetes mellitus with high urinary albuminum secretion	ACE (Rampiril)	Placebo	4912	65	3432 (70%)	3.9	145 / 82	142 / 80
DIRECT-Protect-2 ²⁴¹⁻²⁴³ 2008	Diabetes mellitus	ARB (Candesartan)	Placebo	1905	57	948 (50%)	4.7	133 / 77	NA
EUROPA (PERSUADE) ²⁴⁴ 2005	Coronary artery disease	ACE (Perindopril)	Placebo	1502	62	1231 (82%)	4.3	140 / 82	135 / 80
FEVER ²²⁷ 2011	Hypertension + cardiovascular risk factor	CCB (Felodipine)	Placebo	1241	62	757 (61%) ²	3.3	154 / 91	139 / 82
HOPE (MICRO-HOPE) ²²⁴ 2000	Cardiovascular disease history with an additional cardiovascular risk factor	ACE (Rampiril)	Placebo	3577	65	2255 (63%)	4.5	142 / 80	140 / 77
IDNT ^{245,246} 2001	Diabetes mellitus	ARB (Irbesartan)	Placebo	1148	59	781 (68%)	2.6	159 / 87	140 / 77

		CCB (Amlodipine)	Placebo	1136	59	762 (67%)	2.6	159 / 87	141 / 77
MERIT-HF 134,247 2005	Heart failure (NYHA II-IV)	BB (Metoprolol)	Placebo	985	65	714 (78%)	1	132 / 78	NA
Norwegian-1 248 1983	Acute myocardial infarction	BB (Timolol)	Placebo	99	NA	60 (61%)	1.4	NA	NA
PRoFESS 157 2008	History of cerebrovascular events	ARB (Telmisartan)	Placebo	5743	66	3676 (64%) ²	2.5	144 / 88	135 / 79
PROGRESS 249,250 2001	History of cerebrovascular events	ACE (Perindopril)	Placebo	761	64	548 (72%)	3.9	149 / 84	NA
RENAAL 226 2001	Diabetes mellitus	ARB (Losartan)	Placebo	1513	60	956 (63%)	3.4	153 / 82	140 / 74
ROADMAP 225 2011	Diabetes mellitus	ARB (Olmesartan)	Placebo	4447	58	2052 (46%)	3.2	136 / 81	126 / 74
SAVE 251,252 1992	Myocardial infarction with left ventricular dysfunction	ACE (Captopril)	Placebo	492	59	408 (83%) ²	3.5	113 / 70	NA
SCOPE 253 2005	Elderly with hypertension	ARB (Candesartan)	Placebo	599	76	216 (36%) ²	3.7	166 / 90	145 / 80
SHEP 254 1996	Elderly with systolic hypertension	Diuretic (Chlorothalidone) with addition of BB (Atenolol)	Placebo	583	70	289 (50%)	4.5	170 / 76	143 / 68
SOLVD Treatment 255,256 1991	Signs of heart failure and ventricular dysfunction after myocardial infarction	ACE (Enalapril)	Placebo	663	61	506 (76%)	3.4	125 / 77	NA
SOLVD Prevention 255,257 1992	Ventricular dysfunction after myocardial infarction without signs of heart failure	ACE (Enalapril)	Placebo	647	59	552 (85%)	3.1	125 / 78	NA
Syst-Eur 258 259 1997	Elderly patients with isolated systolic hypertension	CCB (Nitrendipine) ± ACE (Enalapril) ± Diu (Hydrochlorothiazide)	Placebo	492	70	162 (33%) ²	2	175 / 85	153 / 78
TRACE 260 1999	Left ventricular systolic dysfunction after myocardial infarction	ACE (Trandolapril)	Placebo	237	70	142 (60%)	2.2	126 / 77	NA
VA NEPHRON-	Diabetes mellitus	ACE (Lisinopril) + ARB (Losartan)	ARB (Losartan)	1448	65	1436 (99%)	2.2	137 / 73	132 / NA ¹

More intensive lowering vs. less intensive lowering									
ACCORD ^{62,26}									
² 2010	Diabetes mellitus	Intense	Usual	4733	62	2475 (52%)	4.7	139 / 76	119 / 64
HDFP ^{263,264}									
1979	Hypertension	Stepped care	Referred care	772	51	NA	NA	159 / 101	NA
HOT ⁵⁸ 1998	Hypertension		Usual (<90 mm Hg)			531			
		Intense (<85 mm Hg)	Hg)	1002	62	(53%) ²	3.8	170 / 105	141 / 83
		Intense (<80 mm Hg)	Hg)	1000	62	(53%) ²	3.8	170 / 105	140 / 81
SPS3 ²⁶⁵ 2013	History of cerebrovascular events	Intense	Usual	1106	63	697 (63%) ²	3.7	143 / 79	127 / NA ¹
UKPDS ^{59,266} 1998	Diabetes mellitus with hypertension	Intense	Usual	1148	56	637 (55%)	8.4	160 / 94	144 / 82
		ACE (Captopril)	Beta-blocker (Atenolol)	758	56	410 (54%)	8.4	159 / 94	144 / 83
Blood pressure lowering drug vs. another drug									
ACCOMPLISH ²⁶⁷ 2010	Hypertension	CCB (Amlodipine + Benazepril)	Diu (Hydrochlorothiazide + Benazepril)	6946	68	3954 (57%)	2.5	145 / 79	132 / 73
		CCB (Amlodipine)	Diu (Chlorothalidone)	8851	67	4691 (53%) ²	4.9	146 / 84	135 / 75
ALLHAT ²³⁰ 2002	Hypertension + cardiovascular risk factor	ACE (Lisinopril)	Diu (Chlorothalidone)	8740	67	4632 (53%) ²	4.9	146 / 84	136 / 75
ASCOT ²²⁹ 2008	Hypertension + three cardiovascular risk factors	CCB (Amlodipine)	BB (Atenolol)	5137	63	3723 (73%)	5.5	165 / 93	136 / 75
CAPP ^{147,268} 1999	Hypertension	ACE (Captopril)	Conventional treatment (Diuretics or Beta-blockers)	572	55	354 (62%)	6.2	164 / 97	156 / 89
CASE-J ²²⁸ 2010	Hypertension + cardiovascular risk factor	ARB (Candesartan)	CCB (Amlodipine)	2018	64	1126 (56%)	3.3	160 / 88	136 / 77
INSIGHT ²⁶⁹ 2003	Hypertension + cardiovascular risk factor	CCB (Nifedipine)	Diu (Co-amilozone)	1302	66	624 (48%)	4	176 / 98	144 / 82
INVEST ²¹² 2004	Coronary artery disease with hypertension	CCB (Verapamil)	BB (Atenolol)	6400	66	2947 (46%)	2.7	151 / 85	NA

JMIC-B ²⁷⁰ 2004	Coronary artery disease with hypertension	CCB (Nifedipine)	ACE-inhibitor	372	64	257 (69%)	3	147 / 82	138 / 76
LIFE ²⁷¹ 2002	Hypertension + left ventricular hypertrophy	ARB (Losartan)	BB (Atenolol)	1195	67	561 (47%)	4.7	177 / 96	146 / 79
MOSES ^{272,273} 2005	History of cerebrovascular events	ARB (Eprosartan)	CCB (Nitrendipine)	498	70	279 (56%)	2.5	152 / 86	140 / 82
NORDIL ¹⁵⁵ 2000	Hypertension	CCB (Diltiazem)	Diuretic/Beta blocker	727	60	353 (49%) ²	4.5	173 / 106	155 / 89
STOP-2 ²⁷⁴ 2000	Elderly patients with systolic hypertension	ACE (Enalapril or Lisinopril)	Diuretics/Beta-blockers	488	76	201 (41%)	4	195 / 96	161 / 80
		CCB (Felodipine or Isradipine)	Diuretics/Beta-blockers	484	76	194 (40%)	4	195 / 96	162 / 79
Factorial design						317			
		Intense	Usual	470	57	(67%)	5	155 / 98	133 / 78
ABCD (H) ²⁷⁵⁻²⁷⁸ 1998	Diabetic mellitus + hypertension (DBP >90)	CCB (Nisoldipine)	ACE (Enalapril)	470	57	317 (67%)	5	155 / 98	NA
		Intense	Usual	480	59	262 (55%)	5.3	136 / 84	128 / 75
ABCD (N) ^{278,279} 2002	Diabetic mellitus + normotension (80 - 89 mm Hg DBP)	CCB (Nisoldipine)	ACE (Enalapril)	480	59	262 (55%)	5.3	136 / 84	132 / 78

NA: Not available

¹Systolic blood pressure available, diastolic blood pressure unavailable

²For these trials, the number of men or proportion of men in the diabetic subgroup was not available. The number of men was imputed by multiplying the proportion of men for the overall trial by the number of participants in the diabetic subgroup.

Table 7.2 Risk of bias of included trials.

Name	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Overall Risk of Bias
Blood pressure lowering drug vs. placebo						
ADVANCE ^{235,236} 2007	Low	Low	Low	Low	Low	Low
ALTITUDE ²³⁷ 2012	Low	Low	Low	Low	Low	Low
BENEDICT ²³⁴ 2004	Low	Low	Low	Low	Low	Low
BEST ²³⁸ 2003	Low	Low	Low	Low	Unclear	Low
CIBIS-2 ²³⁹ 2001	Low	Low	Low	Low	Low	Low
CONSENSUS II ²⁴⁰ 1992	Low	Low	Low	Low	Low	Low
DIABHYCAR ¹⁵⁰ 2004	Low	Low	Low	Low	Low	Low
DIRECT-Protect-2 ²⁴¹⁻²⁴³ 2008	Low	Low	Low	Low	Low	Low
EUROPA (PERSUADE) ²⁴⁴ 2005	Low	Low	Low	Low	Low	Low
FEVER ²²⁷ 2011	Low	Low	Low	Low	Low	Low
HOPE ²²⁴ (MICRO-HOPE) 2000	Low	Low	Low	Low	Low	Low
IDNT ^{245,246} 2001	Low	Unclear	Low	Low	Low	Low
MERIT-HF ^{134,247} 2005	Low	Low	Low	Low	Unclear	Low
Norwegian-1 ²⁴⁸ 1983	Low	Low	Low	Low	Unclear	Low
PRoFESS ¹⁵⁷ 2008	Low	Low	Low	Low	Low	Low
PROGRESS ^{249,250} 2001	Low	Low	Low	Low	Low	Low
RENAAL ²²⁶ 2001	Low	Low	Low	Low	Low	Low
ROADMAP ²²⁵ 2011	Low	Low	Low	Low	Low	Low
SAVE ^{251,252} 1992	Low	Low	Low	Low	Unclear	Low
SCOPE ²⁵³ 2005	Low	Low	Low	Low	Low	Low
SHEP ²⁵⁴ 1996	Low	Low	Low	Low	Low	Low
SOLVD Treatment ^{255,256} 1991	Low	Low	Low	Low	Unclear	Low
SOLVD Prevention ^{255,257} 1992	Low	Low	Low	Low	Unclear	Low
Syst-Eur ^{258,259} 1997	Low	Low	Low	Low	Low	Low

TRACE ²⁶⁰ 1999	Low	Low	Low	Low	Unclear	Low
VA NEPHRON-D ²⁶¹ 2013	Low	Low	Low	Low	Low	Low
More intensive lowering vs. less intensive lowering						
ACCORD ^{62,262} 2010	Low	Unclear	Low	Low	Low	Low
HDFP ^{263,264} 1979	Low	Unclear	Low	Low	Unclear	Unclear
HOT ⁵⁸ 1998	Low	Unclear	Low	Low	Low	Low
SPS3 ²⁶⁵ 2013	Low	Unclear	Low	Low	Low	Low
UKPDS ^{59,266} 1998	Low	Unclear	Low	Low	Low	Low
Blood pressure lowering drug vs. another drug						
ACCOMPLISH ²⁶⁷ 2010	Low	Low	Low	Low	Low	Low
ALLHAT ²³⁰ 2002	Low	Low	Low	Low	Low	Low
ASCOT ²²⁹ 2008	Low	Unclear	Low	Low	Low	Low
CAPPP ^{147,268} 1999	High	Unclear	Low	Low	Low	High
CASE-J ²²⁸ 2010	Low	Unclear	Low	Low	Unclear	Unclear
INSIGHT ²⁶⁹ 2003	Low	Low	Low	Low	Low	Low
INVEST ²¹² 2004	Low	Unclear	Low	Low	Low	Low
JMIC-B ²⁷⁰ 2004	Low	Unclear	Low	Low	Unclear	Unclear
LIFE ²⁷¹ 2002	Low	Low	Low	Low	Low	Low
MOSES ^{272,273} 2005	Low	Unclear	Low	Low	Unclear	Unclear
NORDIL ¹⁵⁵ 2000	Low	Unclear	Low	Low	Low	Low
STOP-2 ²⁷⁴ 2000	Low	Unclear	Low	Low	Low	Low
Factorial design						
ABCD (H) ²⁷⁵⁻²⁷⁸ 1998	Low	Low	Low	Low	Low	Low
ABCD (N) ^{278,279} 2002	Low	Low	Low	Low	Low	Low

7.3.2 Effect of blood pressure lowering therapy on cardiovascular disease

A 10 mm Hg reduction in systolic blood pressure reduced the risk of all-cause mortality (RR 0.87, 95% confidence interval 0.78, 0.96), cardiovascular disease events (RR 0.89, CI 0.83, 0.95), coronary heart disease events (RR 0.88, CI 0.80, 0.98) and stroke events (RR 0.73, CI 0.64, 0.83; Figures 7.2-7.10).

The proportional reductions for heart failure events (RR 0.86, CI 0.74, 1.00) and renal failure (RR 0.91, CI 0.74, 1.12) were not significant (Figure 7.2, Figures 7.7, 7.8). For microvascular outcomes, a 10 mm Hg reduction in systolic blood pressure reduced the risk of risk of retinopathy (RR 0.87, CI 0.76, 0.99) and albuminuria (RR 0.83, CI 0.79, 0.87) (Figure 7.2, Figures 7.9-7.10). The corresponding absolute risk reductions, in events per 1000 patient years of follow up, were 3.16 (CI 0.90, 5.22) for all-cause mortality (NNT over 10 years = 32 [CI 19, 111]), 3.90 (CI 1.57, 6.06) for cardiovascular events (NNT = 26 [CI 17, 64]), 1.81 (CI 0.35, 3.11), for CHD events (NNT 55 [CI 32, 284]), 4.06 (CI 2.53, 5.40) for stroke events (NNT 25 CI [19, 40]), 2.23 (CI 0.15, 4.04) for retinopathy events (NNT [45 CI 25, 654]) and 9.33 (CI 7.13, 11.37) for albuminuria (NNT 11 [CI 9, 14]).

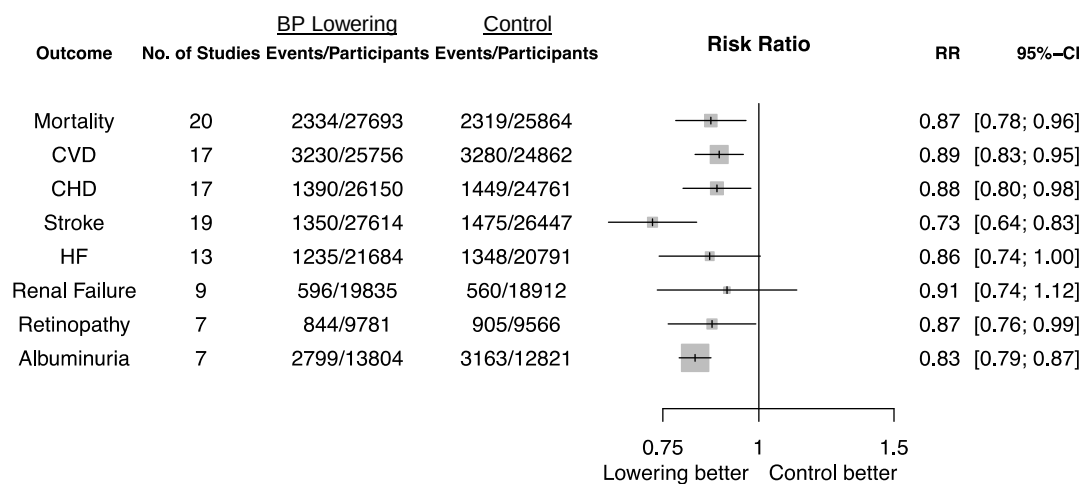


Figure 7.2 Standardized effect of a 10 mm Hg systolic blood pressure reduction on all-cause mortality and vascular outcomes in diabetic patients. The area of each square is proportional to the inverse variance of the estimate. Horizontal lines represent the 95% confidence interval of the estimate.

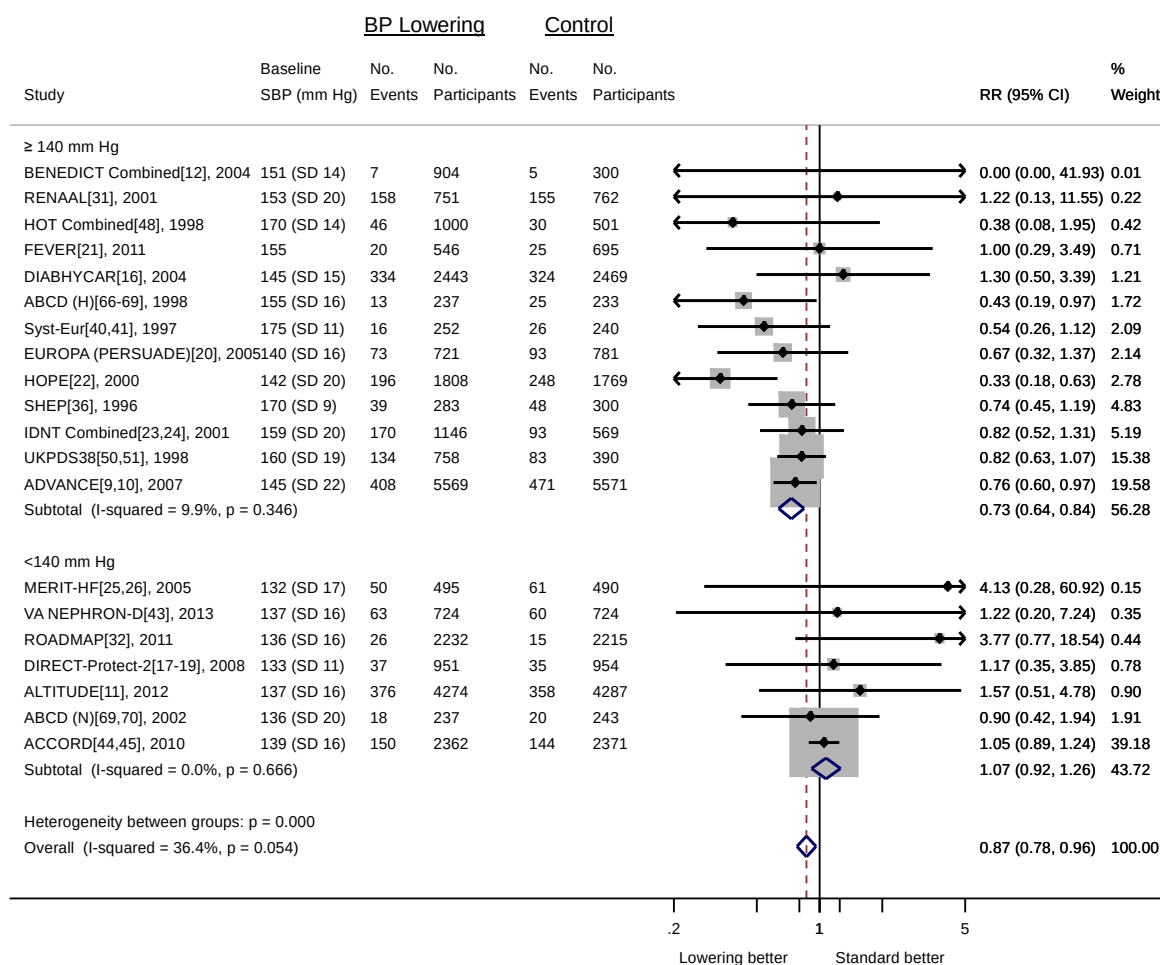


Figure 7.3 Standardized effect of a 10 mm Hg systolic blood pressure reduction on all-cause mortality stratified by baseline blood pressure. For each trial, non-standardized estimates in Figure 7.11 were standardized per 10 mm Hg blood pressure reduction by multiplying the log hazard ratio and standard error by 10 mm Hg divided by the between arm systolic difference. These standardized estimates were then meta-analyzed. Trials that did not report level of blood pressure reduction for either the diabetic subgroup or main group were excluded. Baseline systolic blood pressure refers to the mean baseline systolic blood pressure, with the standard deviation in systolic blood pressure in the study population provided in parentheses. The area of each square is proportional to the inverse variance of the estimate. Horizontal lines represent the 95% confidence interval of the estimate.

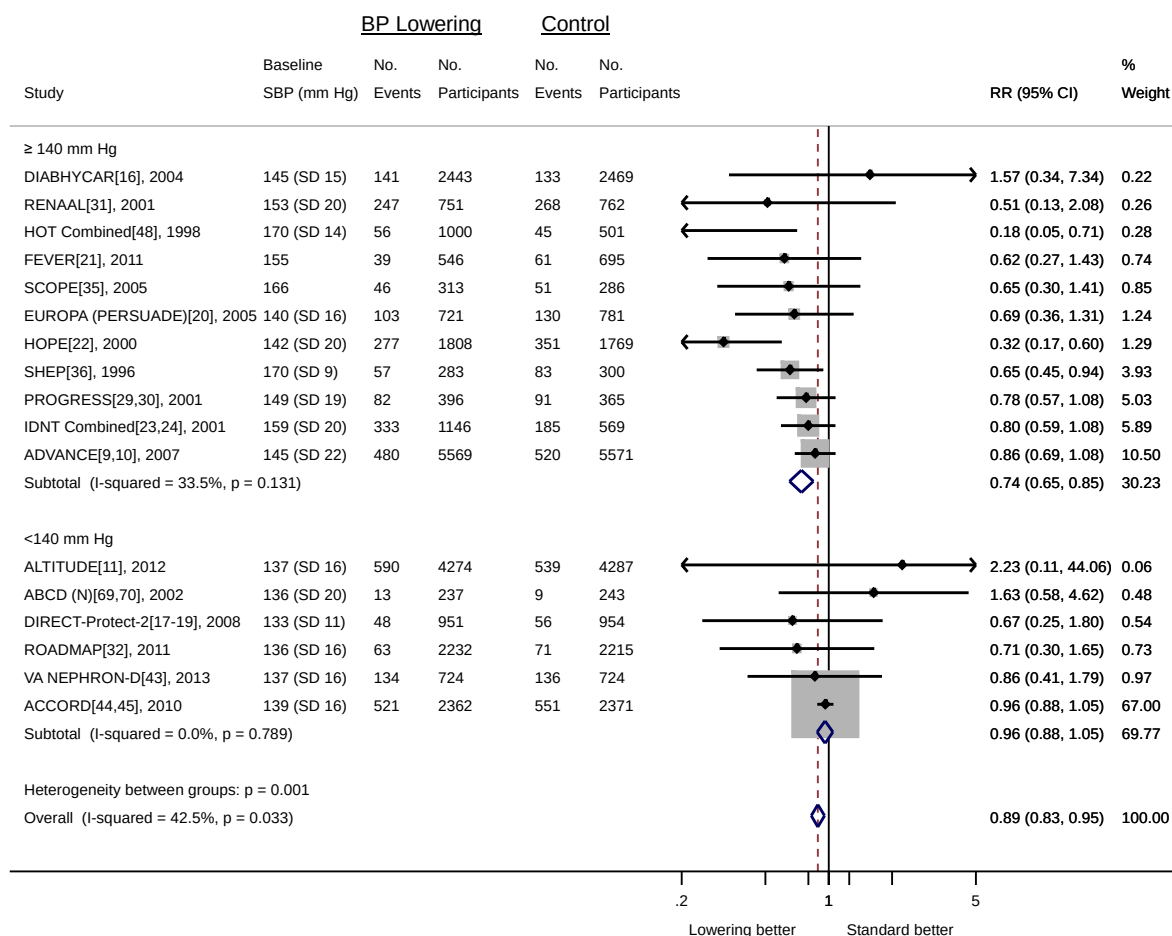


Figure 7.4 Standardized effect of a 10 mm Hg systolic blood pressure reduction on cardiovascular events stratified by baseline blood pressure. For each trial, non-standardized estimates in Figure 7.12 were standardized per 10 mm Hg blood pressure reduction by multiplying the log hazard ratio and standard error by 10 mm Hg divided by the between arm systolic difference. These standardized estimates were then meta-analyzed. Trials that did not report level of blood pressure reduction for either the diabetic subgroup or main group were excluded. Baseline SBP refers to the mean baseline systolic blood pressure, with the standard deviation in systolic blood pressure in the study population provided in parentheses. The area of each square is proportional to the inverse variance of the estimate. Horizontal lines represent the 95% confidence interval of the estimate.

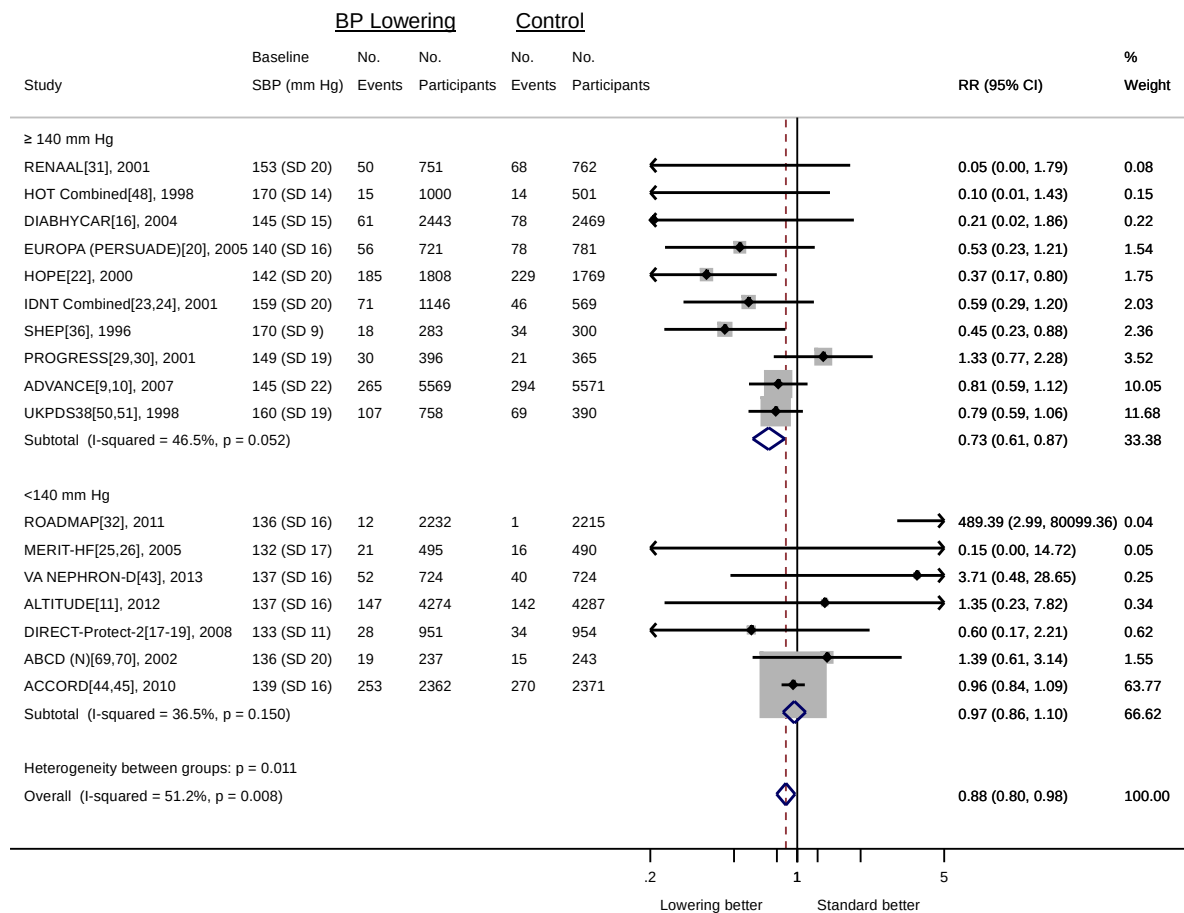


Figure 7.5 Standardized effect of a 10 mm Hg systolic blood pressure reduction on coronary heart disease stratified by baseline blood pressure. For each trial, non-standardized estimates in Figure 7.13 were standardized per 10 mm Hg blood pressure reduction by multiplying the log hazard ratio and standard error by 10 mm Hg divided by the between arm systolic difference. These standardized estimates were then meta-analyzed. Trials that did not report level of blood pressure reduction for either the diabetic subgroup or main group were excluded. Baseline systolic blood pressure refers to the mean baseline systolic blood pressure, with the standard deviation in systolic blood pressure in the study population provided in parentheses. The area of each square is proportional to the inverse variance of the estimate. Horizontal lines represent the 95% confidence interval of the estimate.

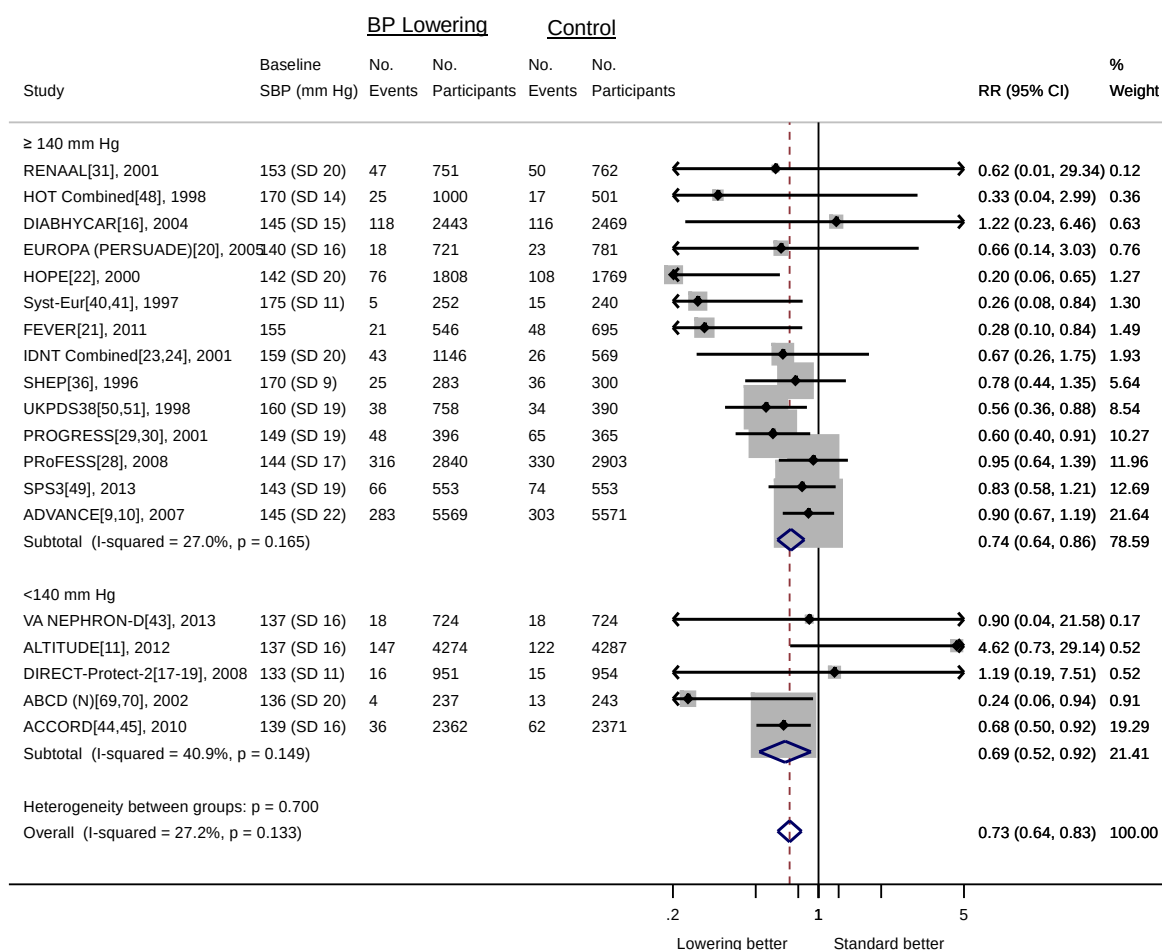


Figure 7.6 Standardized effect of a 10 mm Hg systolic blood pressure reduction on stroke stratified by baseline blood pressure. For each trial, non-standardized estimates in Figure 7.14 were standardized per 10 mm Hg blood pressure reduction by multiplying the log hazard ratio and standard error by 10 mm Hg divided by the between arm systolic difference. These standardized estimates were then meta-analyzed. Trials that did not report level of blood pressure reduction for either the diabetic subgroup or main group were excluded. Baseline systolic blood pressure refers to the mean baseline systolic blood pressure, with the standard deviation in systolic blood pressure in the study population provided in parentheses. The area of each square is proportional to the inverse variance of the estimate. Horizontal lines represent the 95% confidence interval of the estimate.

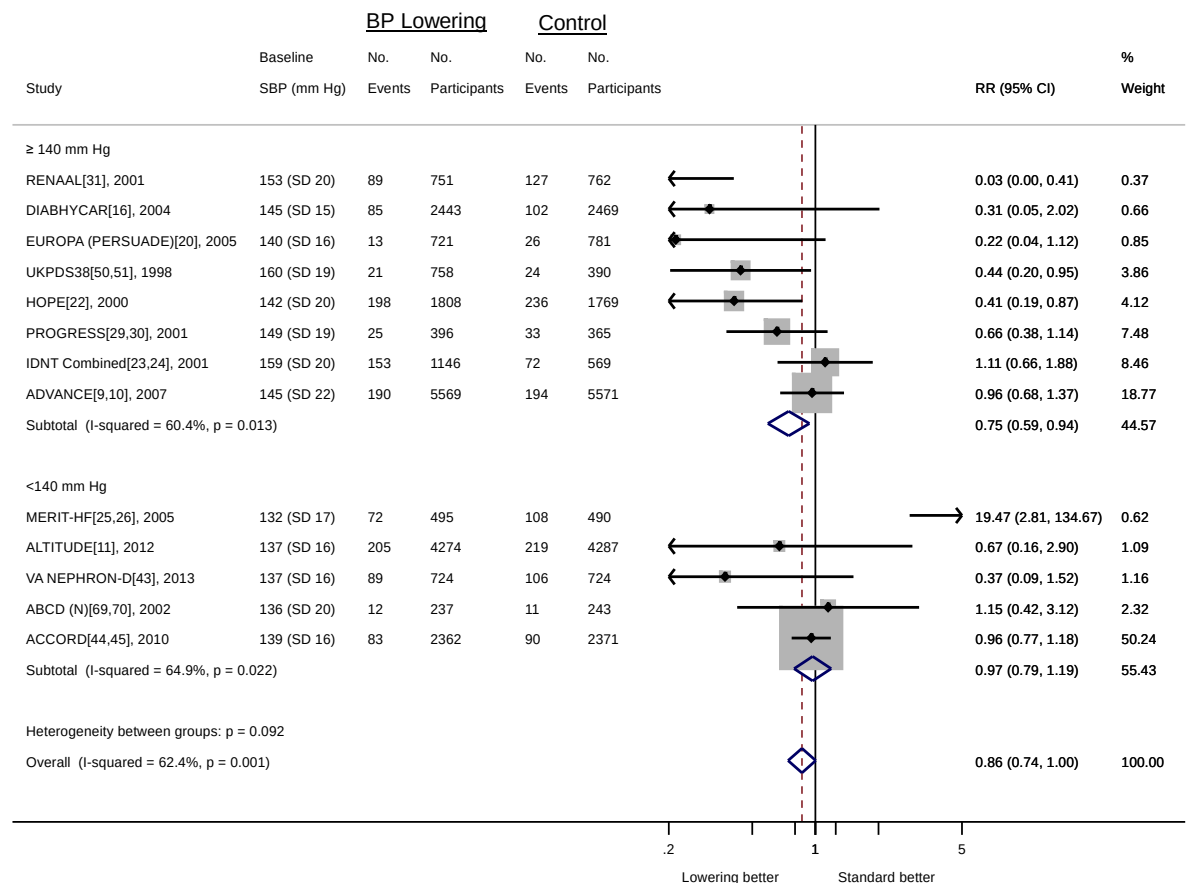


Figure 7.7 Standardized effect of a 10 mm Hg systolic blood pressure reduction on heart failure stratified by baseline blood pressure. For each trial, non-standardized estimates in Figure 7.15 were standardized per 10 mm Hg blood pressure reduction by multiplying the log hazard ratio and standard error by 10 mm Hg divided by the between arm systolic difference. These standardized estimates were then meta-analyzed. Trials that did not report level of blood pressure reduction for either the diabetic subgroup or main group were excluded. Baseline systolic blood pressure refers to the mean baseline systolic blood pressure, with the standard deviation in systolic blood pressure in the study population provided in parentheses. Note that the significant increase in HF per 10 mm Hg observed in the MERIT-HF trial is due to the blood pressure elevation observed in that trial. The area of each square is proportional to the inverse variance of the estimate. Horizontal lines represent the 95% confidence interval of the estimate.

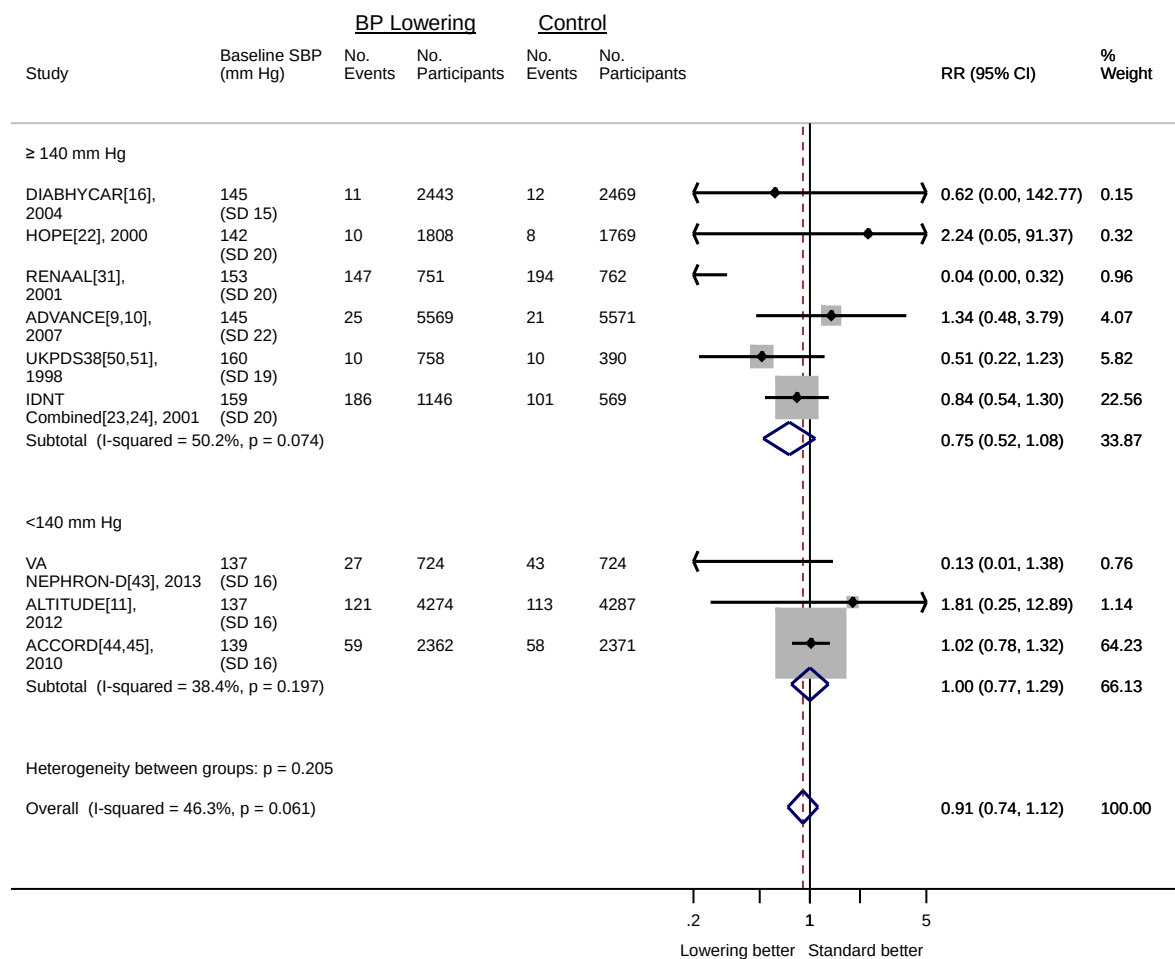


Figure 7.8 Standardized effect of a 10 mm Hg systolic blood pressure reduction on renal failure stratified by baseline blood pressure. For each trial, non-standardized estimates in Figure 7.16 were standardized per 10 mm Hg blood pressure reduction by multiplying the log hazard ratio and standard error by 10 mm Hg divided by the between arm systolic difference. These standardized estimates were then meta-analyzed. Trials that did not report level of blood pressure reduction for either the diabetic subgroup or main group were excluded. Baseline systolic blood pressure refers to the mean baseline systolic blood pressure, with the standard deviation in systolic blood pressure in the study population provided in parentheses. The area of each square is proportional to the inverse variance of the estimate. Horizontal lines represent the 95% confidence interval of the estimate.

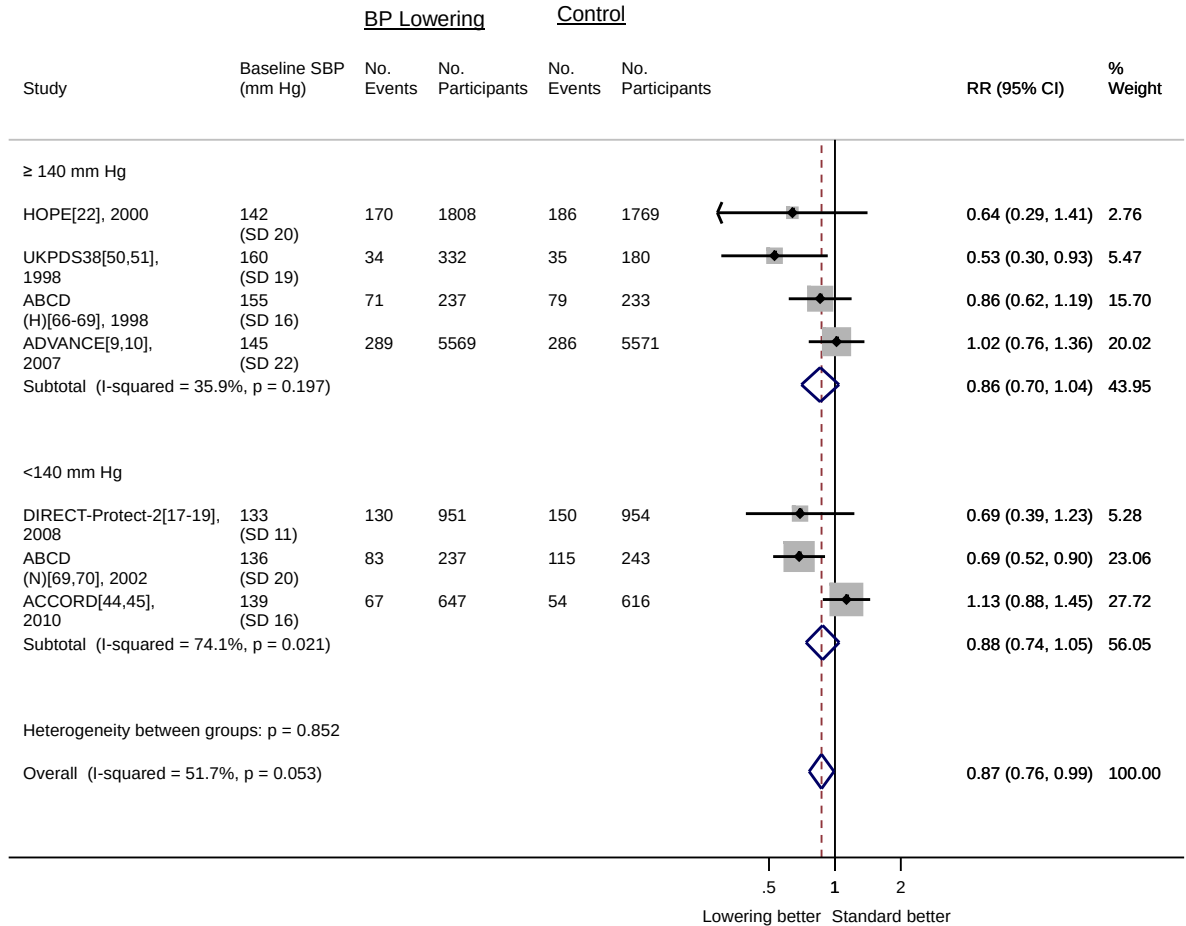


Figure 7.9 Standardized effect of a 10 mm Hg systolic blood pressure reduction on retinopathy stratified by baseline blood pressure. For each trial, non-standardized estimates in Figure 7.17 were standardized per 10 mm Hg blood pressure reduction by multiplying the log hazard ratio and standard error by 10 mm Hg divided by the between arm systolic difference. These standardized estimates were then meta-analyzed. Trials that did not report level of blood pressure reduction for either the diabetic subgroup or main group were excluded. Baseline systolic blood pressure refers to the mean baseline systolic blood pressure, with the standard deviation in systolic blood pressure in the study population provided in parentheses. The area of each square is proportional to the inverse variance of the estimate. Horizontal lines represent the 95% confidence interval of the estimate.

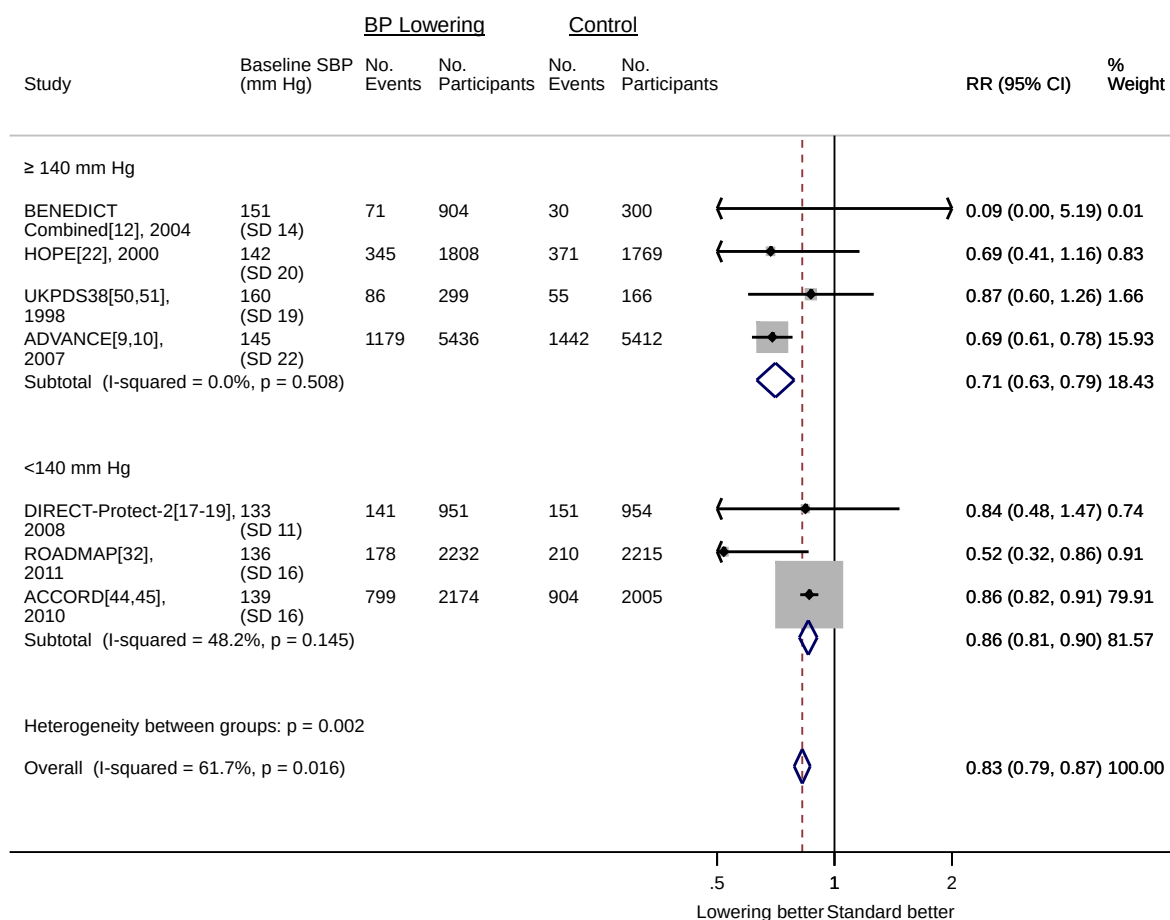


Figure 7.10 Standardized effect of a 10 mm Hg systolic blood pressure reduction on albuminuria stratified by baseline blood pressure. For each trial, non-standardized estimates in Figure 7.18 were standardized per 10 mm Hg blood pressure reduction by multiplying the log hazard ratio and standard error by 10 mm Hg divided by the between arm systolic difference. These standardized estimates were then meta-analyzed. Trials that did not report level of blood pressure reduction for either the diabetic subgroup or main group were excluded. Baseline systolic blood pressure refers to the mean baseline systolic blood pressure, with the standard deviation in systolic blood pressure in the study population provided in parentheses. The area of each square is proportional to the inverse variance of the estimate. Horizontal lines represent the 95% confidence interval of the estimate.

Analyses not standardized to a 10 mm Hg blood pressure reduction showed broadly similar results to standardised analyses; blood pressure lowering treatment reduced the risk of all-cause mortality (RR 0.92 CI 0.87, 0.96), cardiovascular events (RR 0.89 CI 0.85, 0.93), coronary heart disease events (RR 0.88 CI 0.81, 0.94), stroke events (RR 0.89 CI 0.83, 0.96), retinopathy (RR 0.90 CI 0.82, 0.98) and albuminuria (RR 0.83 CI 0.79, 0.86; Figures 7.11-7.18). In contrast to standardized analyses, in

non-standardised analyses, blood pressure lowering treatment significantly reduced the risk of heart failure (RR 0.81, CI 0.76, 0.86) and renal failure (RR 0.88, CI 0.79, 0.99; Figures 7.15-7.16).

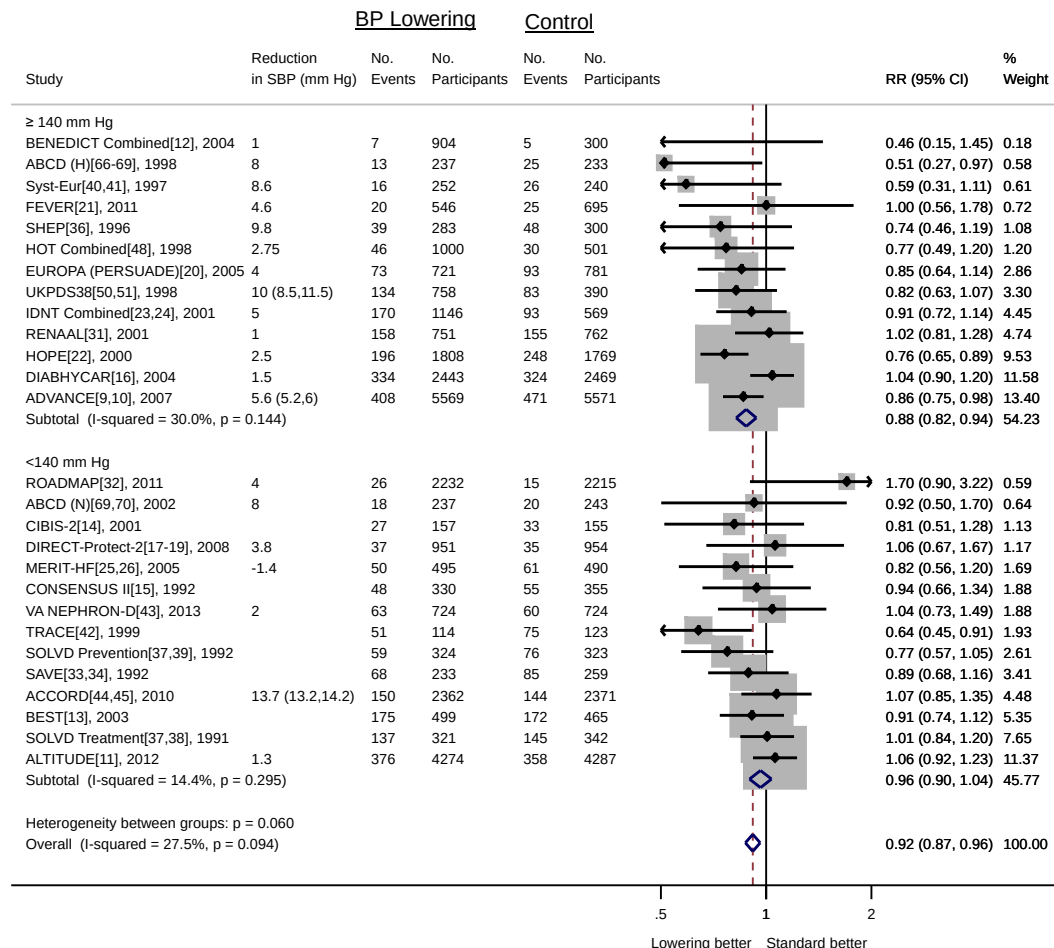


Figure 7.11 Non-standardized effect of blood pressure lowering on all-cause mortality stratified by baseline blood pressure. Reduction in systolic blood pressure refers to the mean reduction in systolic blood pressure between arms. A 95% confidence interval is provided for three trials which reported a standard error for the reduction in systolic blood pressure. The trial Norwegian-1 was excluded as it did not provide a baseline blood pressure. The area of each square is proportional to the inverse variance of the estimate. Horizontal lines represent the 95% confidence interval of the estimate.

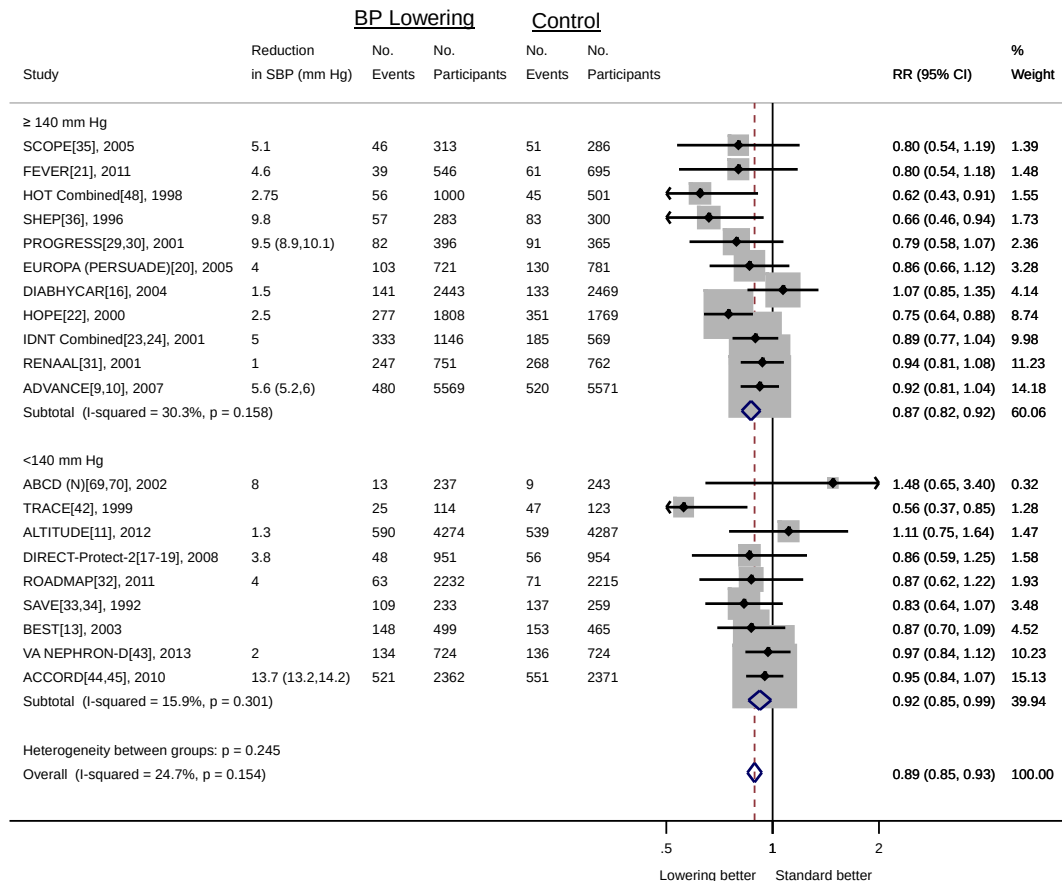


Figure 7.12 Non-standardized effect of blood pressure lowering on cardiovascular events stratified by baseline blood pressure. Reduction in systolic blood pressure refers to the mean reduction in systolic blood pressure between arms. A 95% confidence interval is provided for three trials which reported a standard error for the reduction in systolic blood pressure. The area of each square is proportional to the inverse variance of the estimate. Horizontal lines represent the 95% confidence interval of the estimate.

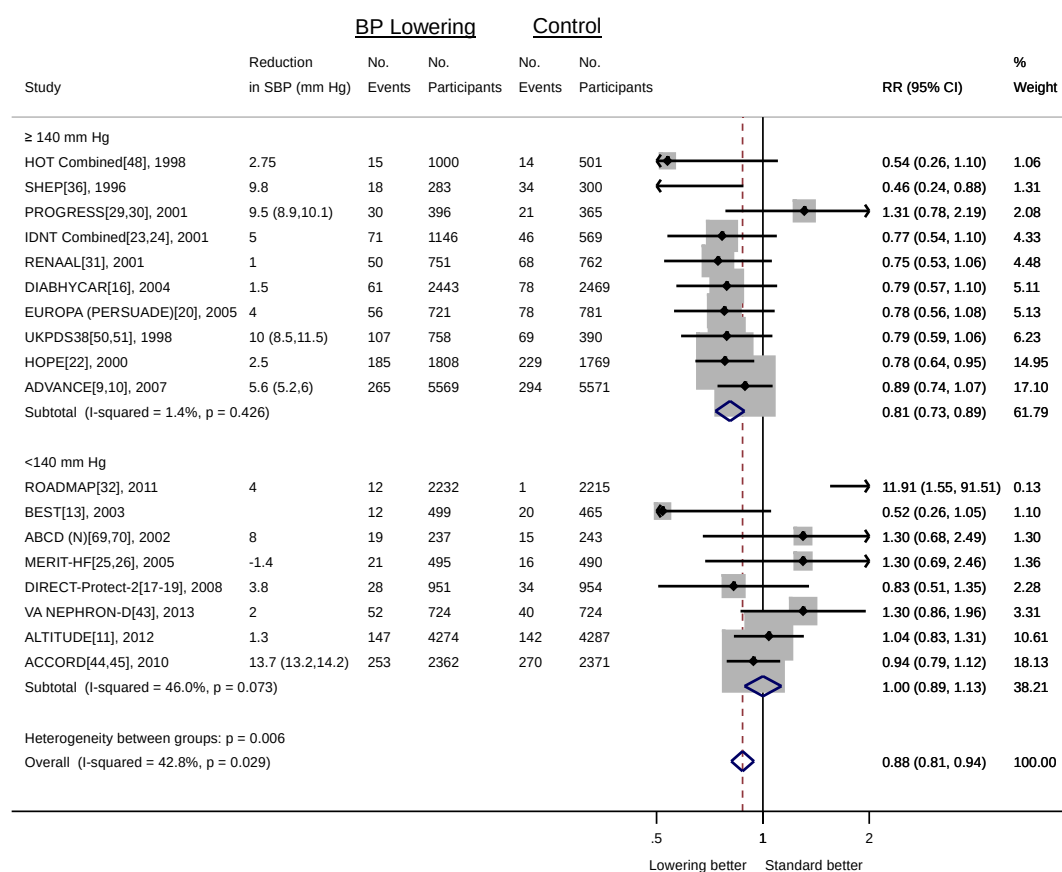


Figure 7.13 Non-standardized effect of blood pressure lowering on coronary heart disease stratified by baseline blood pressure. Reduction in systolic blood pressure refers to the mean reduction in systolic blood pressure between arms. A 95% confidence interval is provided for four trials which reported a standard error for the reduction in systolic blood pressure. The area of each square is proportional to the inverse variance of the estimate. Horizontal lines represent the 95% confidence interval of the estimate.

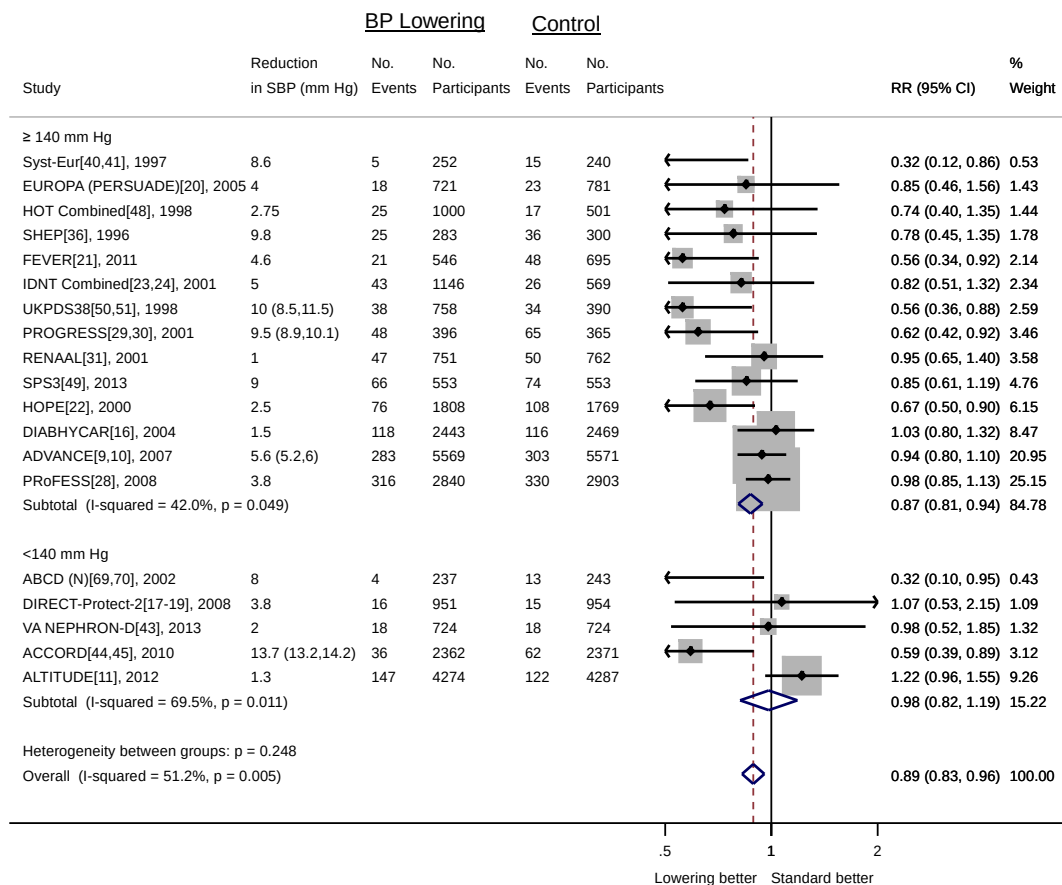


Figure 7.14 Non-standardized effect of blood pressure lowering on stroke stratified by baseline blood pressure. The trial Norwegian-1 was excluded as it did not provide a baseline blood pressure. Reduction in systolic blood pressure refers to the mean reduction in systolic blood pressure between arms. A 95% confidence interval is provided for four trials which reported a standard error for the reduction in systolic blood pressure. The area of each square is proportional to the inverse variance of the estimate. Horizontal lines represent the 95% confidence interval of the estimate.

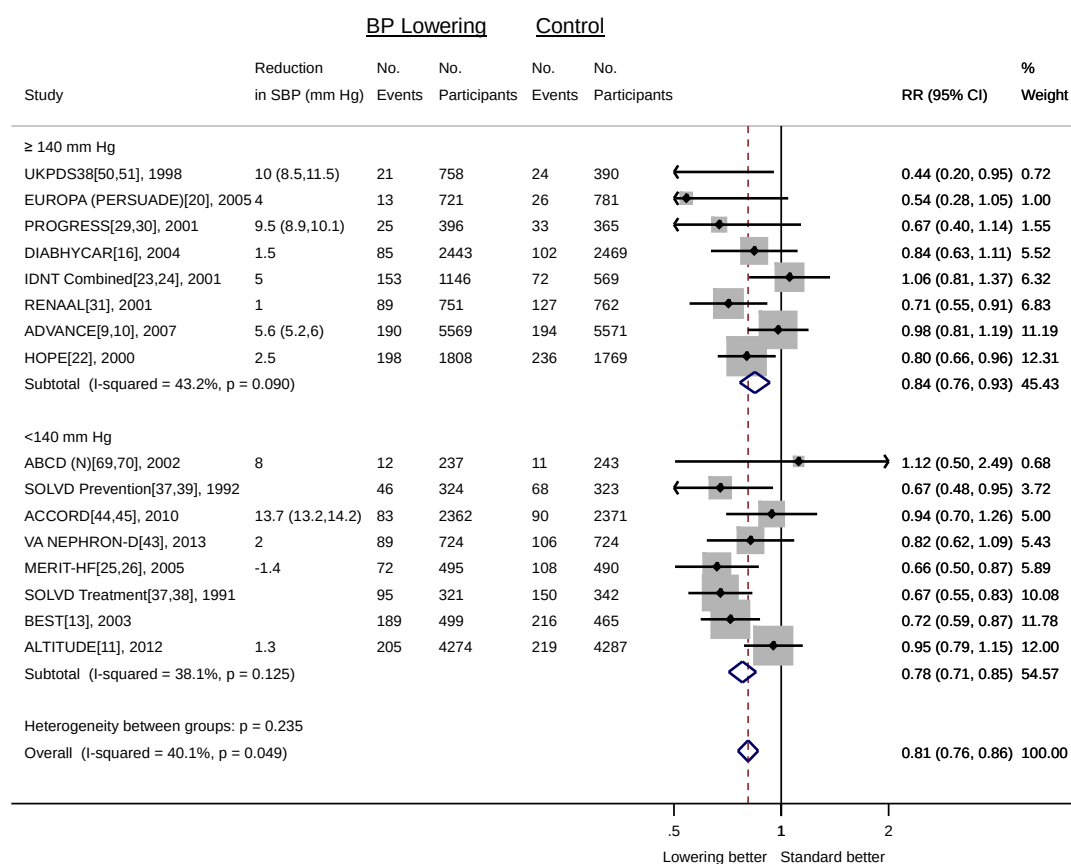


Figure 7.15 Non-standardized effect of blood pressure lowering on heart failure stratified by baseline blood pressure. The trial Norwegian-1 was excluded as it did not provide a baseline blood pressure. Reduction in systolic blood pressure refers to the mean reduction in systolic blood pressure between arms. A 95% confidence interval is provided for four trials which reported a standard error for the reduction in systolic blood pressure. The area of each square is proportional to the inverse variance of the estimate. Horizontal lines represent the 95% confidence interval of the estimate.

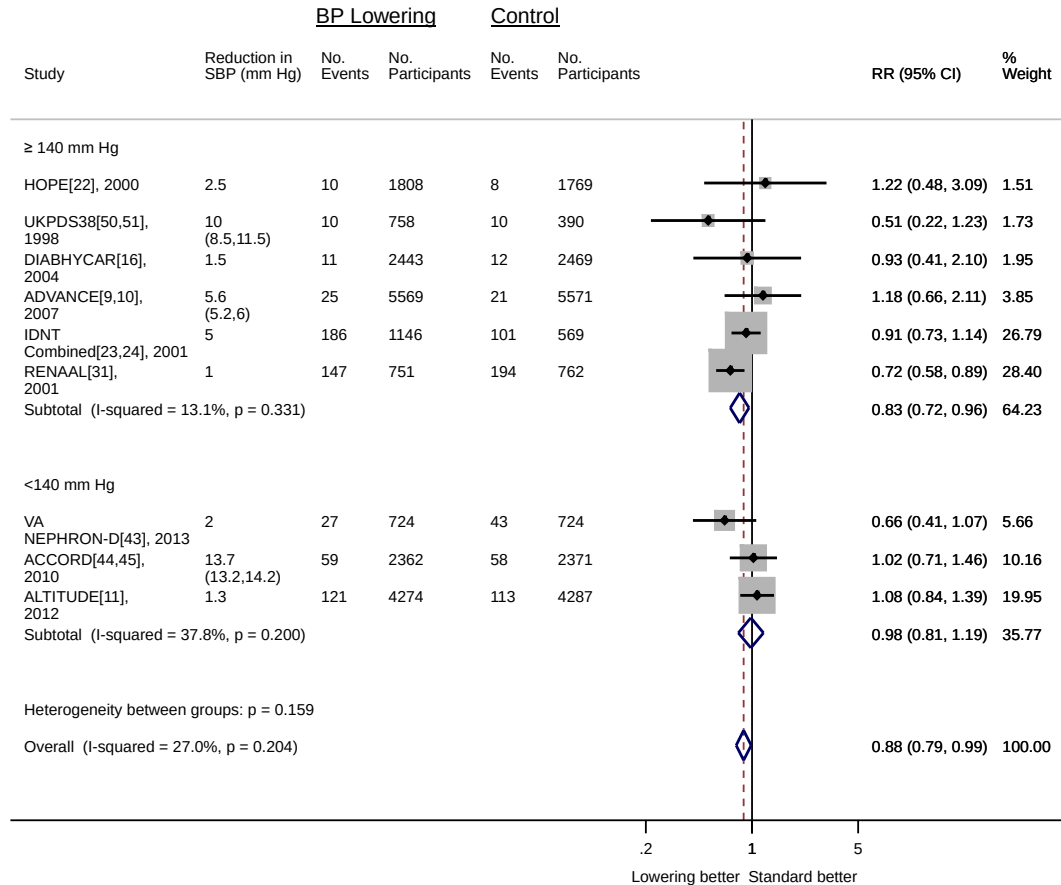


Figure 7.16 Non-standardized effect of blood pressure lowering on renal failure stratified by baseline blood pressure. Reduction in systolic blood pressure refers to the mean reduction in systolic blood pressure between arms. A 95% confidence interval is provided for three trials which reported a standard error for the reduction in systolic blood pressure. Note that both VA Nephron-D and ALTITUDE were dual renin angiotensin blockade trials. The area of each square is proportional to the inverse variance of the estimate. Horizontal lines represent the 95% confidence interval of the estimate.

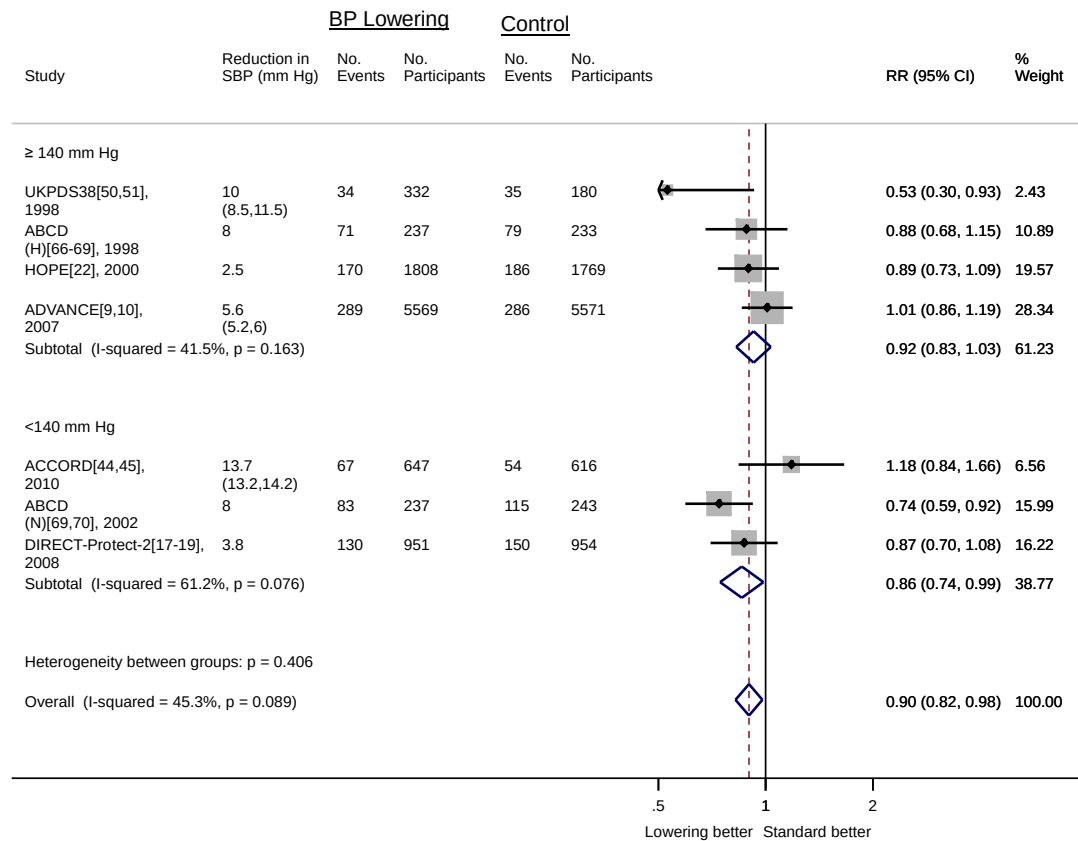


Figure 7.17 Non-standardized effect of blood pressure lowering on retinopathy stratified by baseline blood pressure. Reduction in systolic blood pressure refers to the mean reduction in systolic blood pressure between arms. A 95% confidence interval is provided for three trials which reported a standard error for the reduction in systolic blood pressure. The area of each square is proportional to the inverse variance of the estimate. Horizontal lines represent the 95% confidence interval of the estimate.

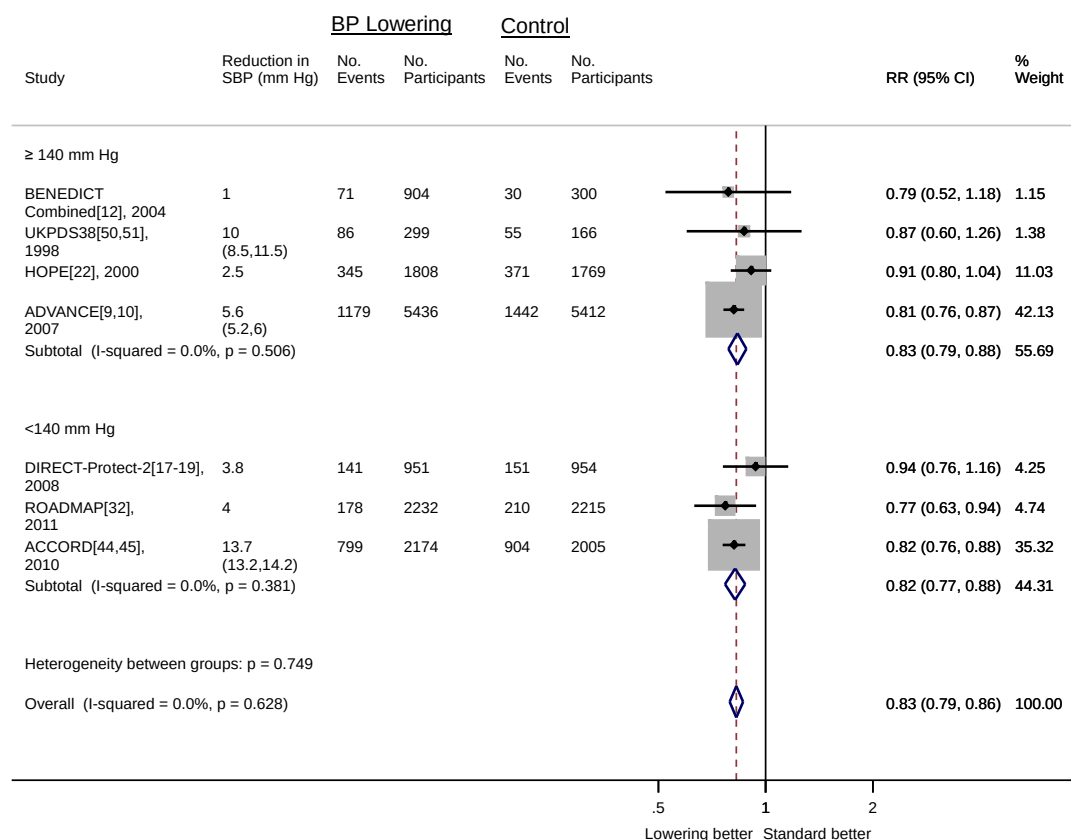


Figure 7.18 Non-standardized effect of blood pressure lowering on albuminuria stratified by baseline blood pressure. Reduction in systolic blood pressure refers to the mean reduction in systolic blood pressure between arms. A 95% confidence interval is provided for three trials which reported a standard error for the reduction in systolic blood pressure. The area of each square is proportional to the inverse variance of the estimate. Horizontal lines represent the 95% confidence interval of the estimate.

Estimates were also similar in trials that were conducted in heart failure/left ventricular systolic dysfunction (HF/LVSD) patients and non-HF/LVSD patients (Figure 7.19). No significant interaction was observed for all-cause mortality, cardiovascular disease events or coronary heart disease events. A significant interaction was observed for heart failure, where the relative risk was significantly lower in HF/LVSD patients (RR 0.69 CI 0.61, 0.77 in HF/LVSD vs. RR 0.87 CI 0.80, 0.94 in non-HF/LVSD, p interaction =0.0012).

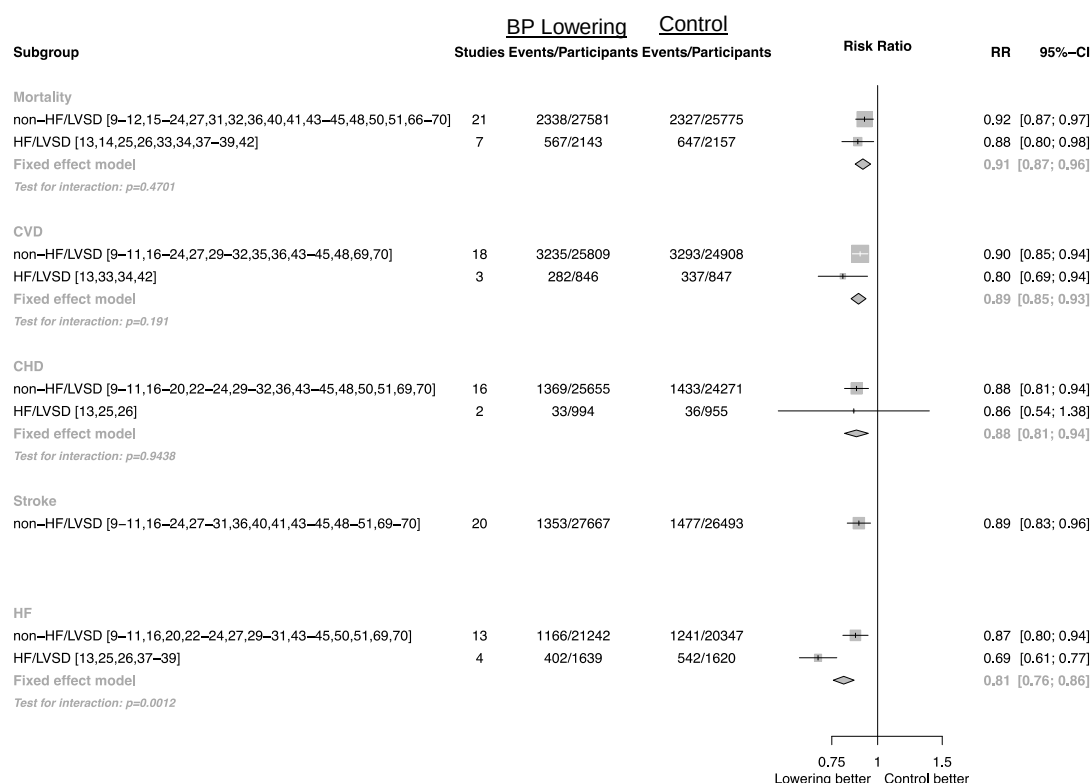


Figure 7.19 Non-standardized effect of blood pressure lowering on mortality and vascular outcomes stratified by whether the trial was or was not conducted in heart failure/left ventricular systolic dysfunction patients. No heart failure/left ventricular systolic dysfunction trial reported microvascular outcomes. The area of each square is proportional to the inverse variance of the estimate. References are listed beside each subgroup in brackets. The area of each square is proportional to the inverse variance of the estimate. Horizontal lines represent the 95% confidence interval of the estimate.

7.3.3 Effect of blood pressure lowering therapy on cardiovascular disease by initial systolic blood pressure

Trials were stratified by mean initial systolic blood pressure level (range ≥ 140 to <140 mmHg) and the effect of a 10 mmHg systolic blood pressure reduction on macrovascular and microvascular outcomes compared between strata (Figure 7.20). Significant interactions were observed for mortality, CHD, CVD and heart failure (all $p<0.1$), with lower relative risks observed amongst those trials with mean baseline systolic blood pressure ≥ 140 mmHg and no significant effects amongst the group with baseline systolic blood pressure <140 mmHg. In the ≥ 140 mm Hg strata, a 10 mm Hg

systolic blood pressure reduction reduced the risk of all-cause mortality (RR 0.73 CI 0.64, 0.84), cardiovascular events (RR 0.74 CI 0.65, 0.85), coronary heart disease events (RR 0.73 CI 0.61, 0.87) and heart failure events (RR 0.74 CI 0.59, 0.94). Additionally, a 10 mm Hg systolic blood pressure reduction reduced the risk of stroke and albuminuria regardless of initial systolic blood pressure. Excluding trials with imputed blood pressure values did not alter the main findings; significant interactions by baseline systolic blood pressure continued to be observed for all-cause mortality, cardiovascular events and coronary heart disease events (Figure 7.21). Conclusions were broadly similar for the non-standardized analyses (Figure 7.22) although tests for interactions for cardiovascular events was non-significant. Non-standardized estimates were similar when one trial at unclear risk of bias was included (Figure 7.23).

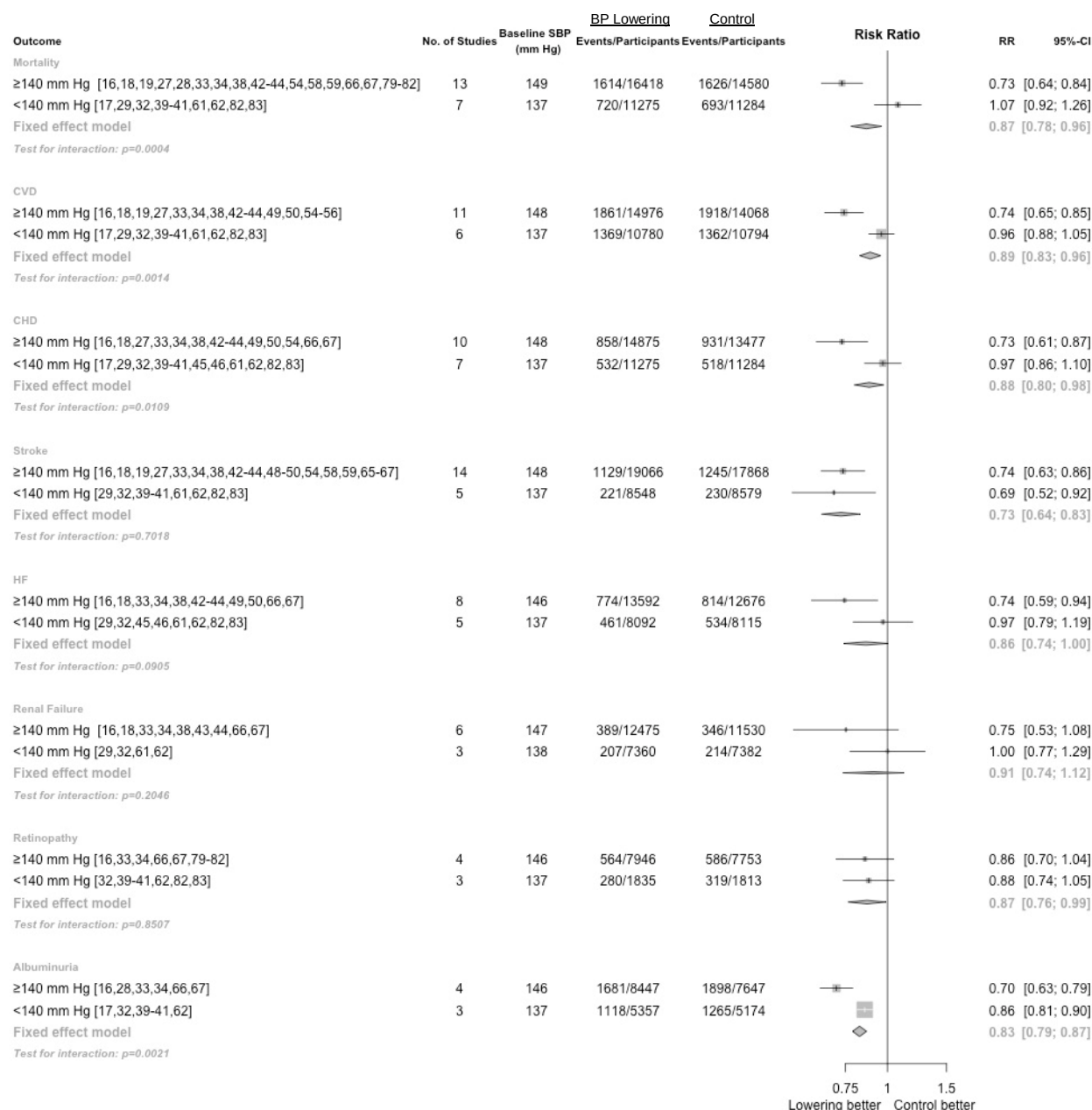


Figure 7.20 Standardized effect of a 10 mm Hg systolic blood pressure reduction on mortality and vascular outcomes by baseline blood pressure. Number of trials for each category are listed in brackets, while the mean baseline BP (weighted by number of participants) is listed in an adjacent column. The area of each square is proportional to the inverse variance of the estimate. Horizontal lines represent the 95% confidence interval of the estimate.

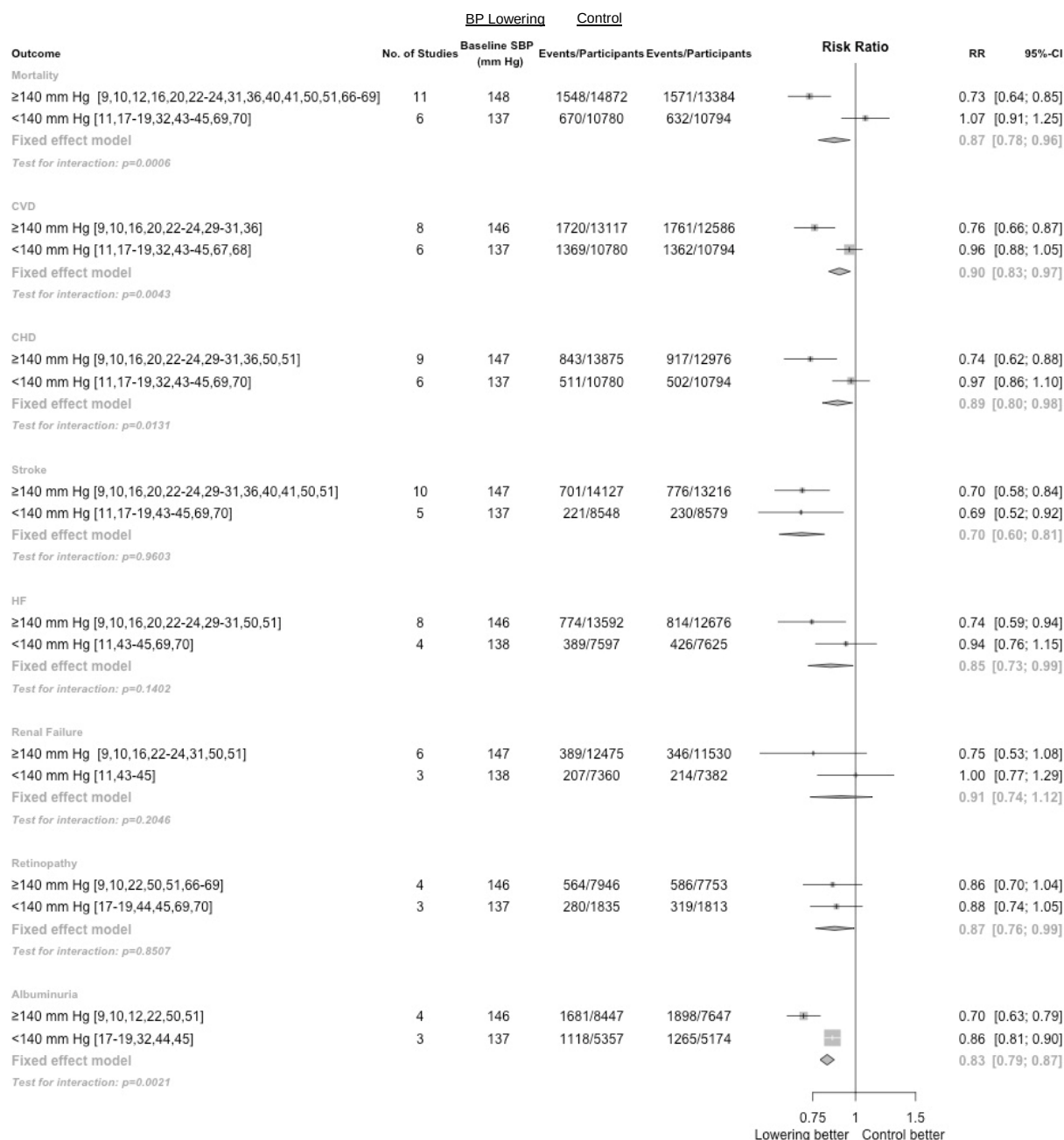


Figure 7.21 Standardized effect of a 10 mm Hg systolic blood pressure reduction on mortality and vascular outcomes stratified by baseline blood pressure. Trials for which baseline blood pressures or reductions in blood pressure were imputed were excluded. Number of trials is listed in brackets, while the mean baseline blood pressure is listed in an adjacent column. The area of each square is proportional to the inverse variance of the estimate. Horizontal lines represent the 95% confidence interval of the estimate.

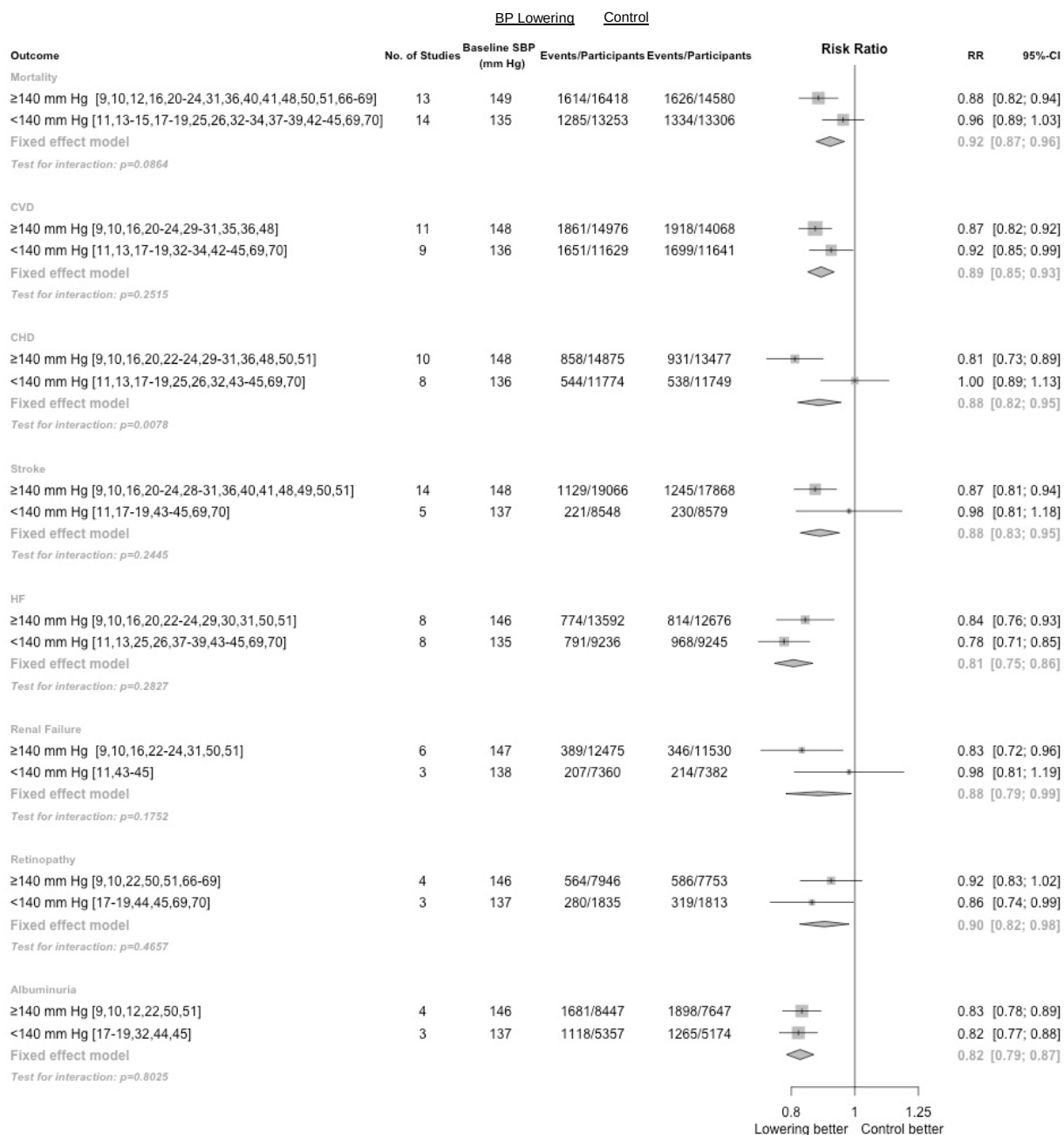


Figure 7.22 Non-standardized effect of blood pressure lowering on mortality and vascular outcomes stratified by baseline blood pressure. Baseline systolic blood pressure refers the weighted mean of the baseline systolic blood pressure of included trials. The area of each square is proportional to the inverse variance of the estimate. Horizontal lines represent the 95% confidence interval of the estimate.

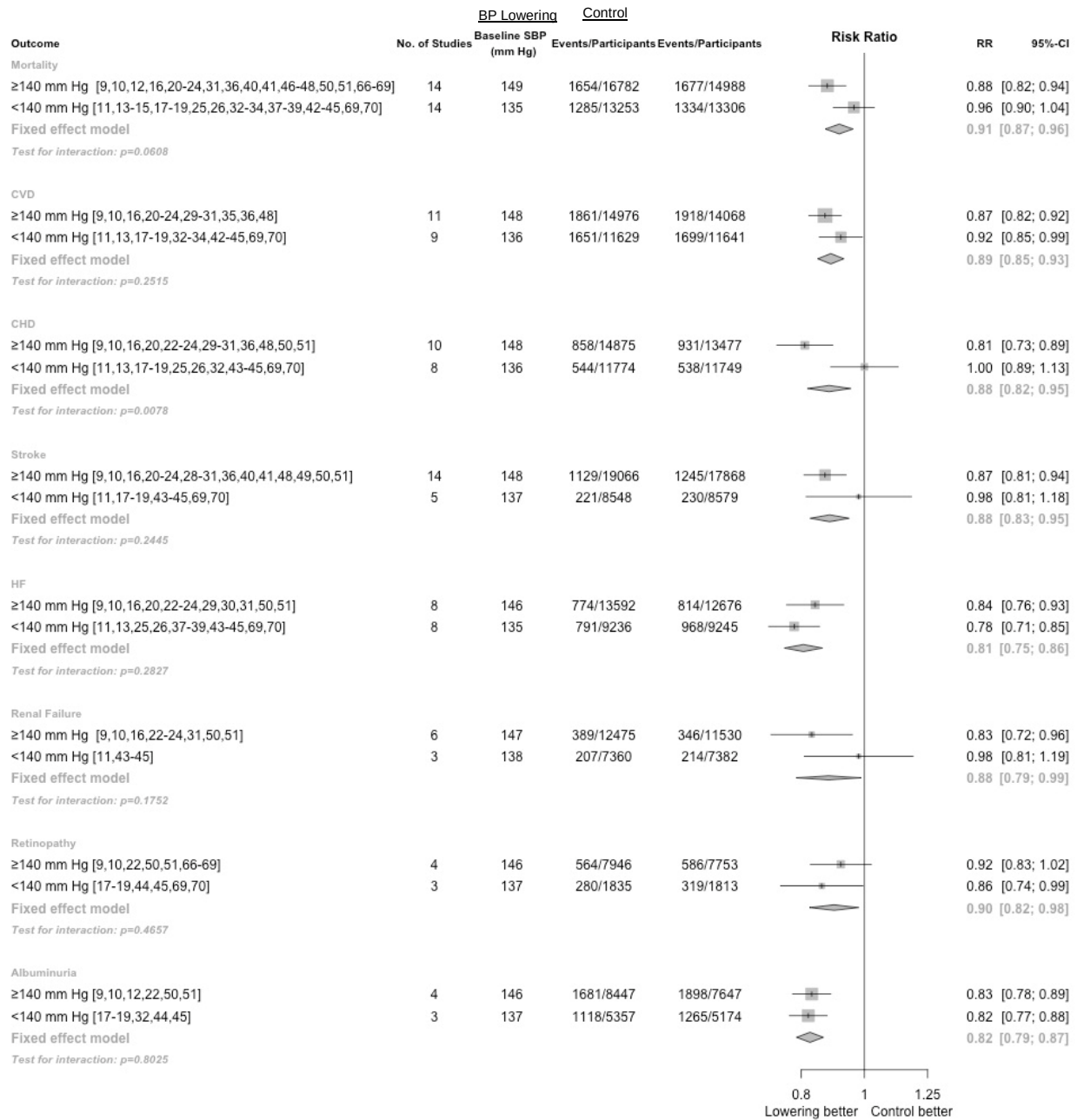


Figure 7.23 Non-standardized effect of blood pressure lowering on mortality and vascular outcomes stratified by baseline blood pressure. One trial which was judged to be of unclear risk of bias (HDFP^{263,264}, 1979) was included. Number of trials is listed in brackets, while the mean baseline blood pressure is listed in an adjacent column. The area of each square is proportional to the inverse variance of the estimate. Horizontal lines represent the 95% confidence interval of the estimate.

7.3.4 Effect of blood pressure lowering treatment on cardiovascular disease by achieved systolic blood pressure

Trials were stratified by the systolic blood pressure achieved in the treatment group (≥ 130 or < 130 mmHg) and the effect of a 10 mmHg systolic blood pressure lowering on risk of outcomes compared between strata (Figure 7.24). Significant interactions were observed for mortality, CHD, CVD, heart failure and albuminuria (all $p < 0.1$), with lower relative risks in the ≥ 130 mm Hg stratum than the < 130 mm Hg stratum. In the ≥ 130 mm Hg stratum, a 10 mm Hg systolic blood pressure reduction reduced the risk of all cause mortality by 25% (RR 0.75 CI 0.65, 0.86), cardiovascular events by 25% (RR 0.75 CI 0.65, 0.87) and coronary heart disease events by 30% (RR 0.70 CI 0.58, 0.84), with no significant effects of blood pressure lowering treatment observed in the < 130 mm Hg stratum. No significant interaction was observed for stroke or retinopathy. The effect of blood pressure lowering treatment on risks of stroke and albuminuria were significant for both strata. Standardized estimates made excluding trials with imputed blood pressure values were not substantively different; significant interactions between strata continued to be observed for all-cause mortality, cardiovascular events and coronary heart disease events (Figure 7.25).

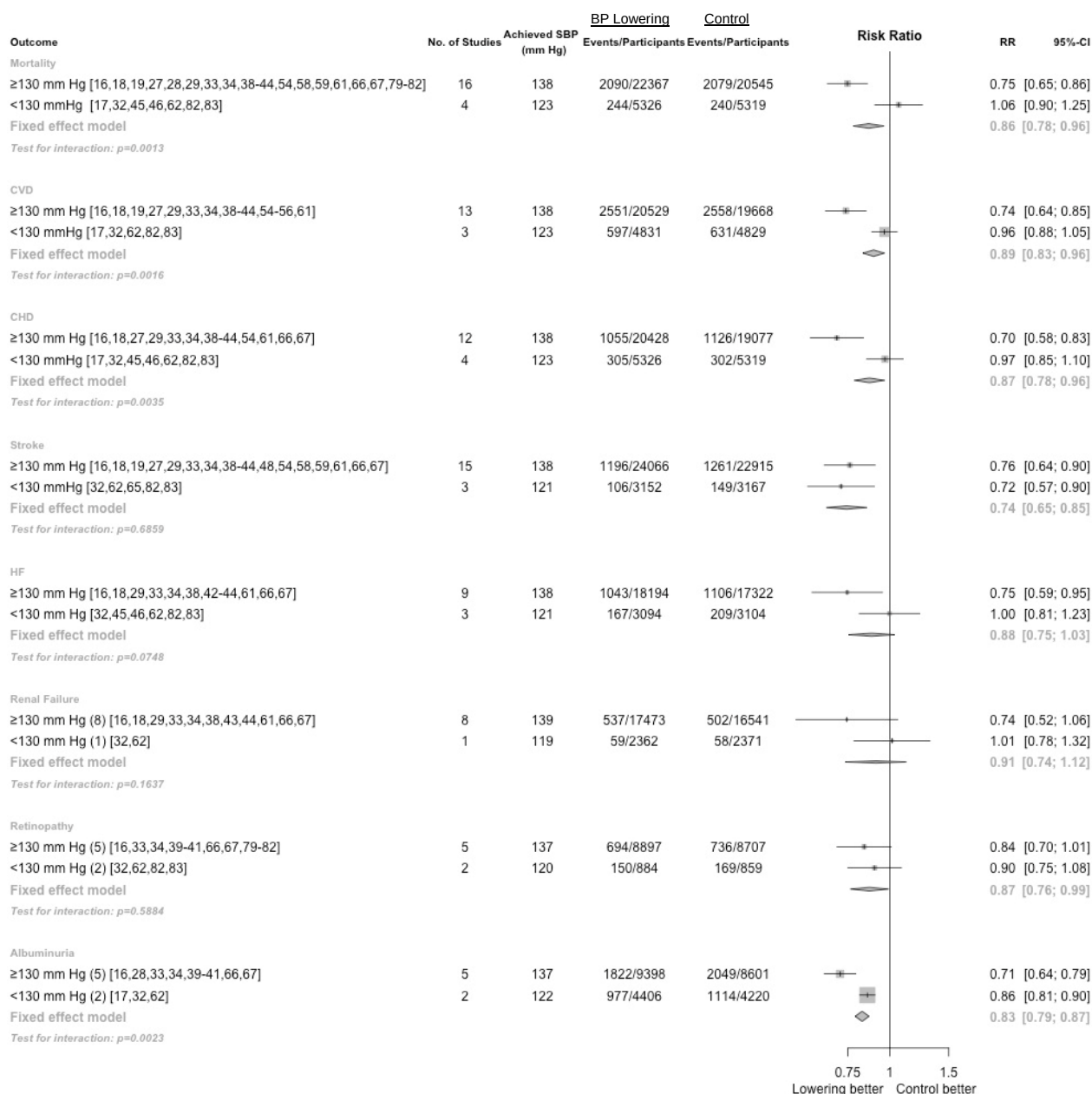


Figure 7.24 Standardized effect of a 10 mm Hg systolic blood pressure reduction on mortality and vascular outcomes stratified by achieved blood pressure. Number of trials for each category are listed in brackets, while the mean achieved blood pressure (weighted by number of participants) is listed in an adjacent column. The area of each square is proportional to the inverse variance of the estimate. Horizontal lines represent the 95% confidence interval of the estimate.

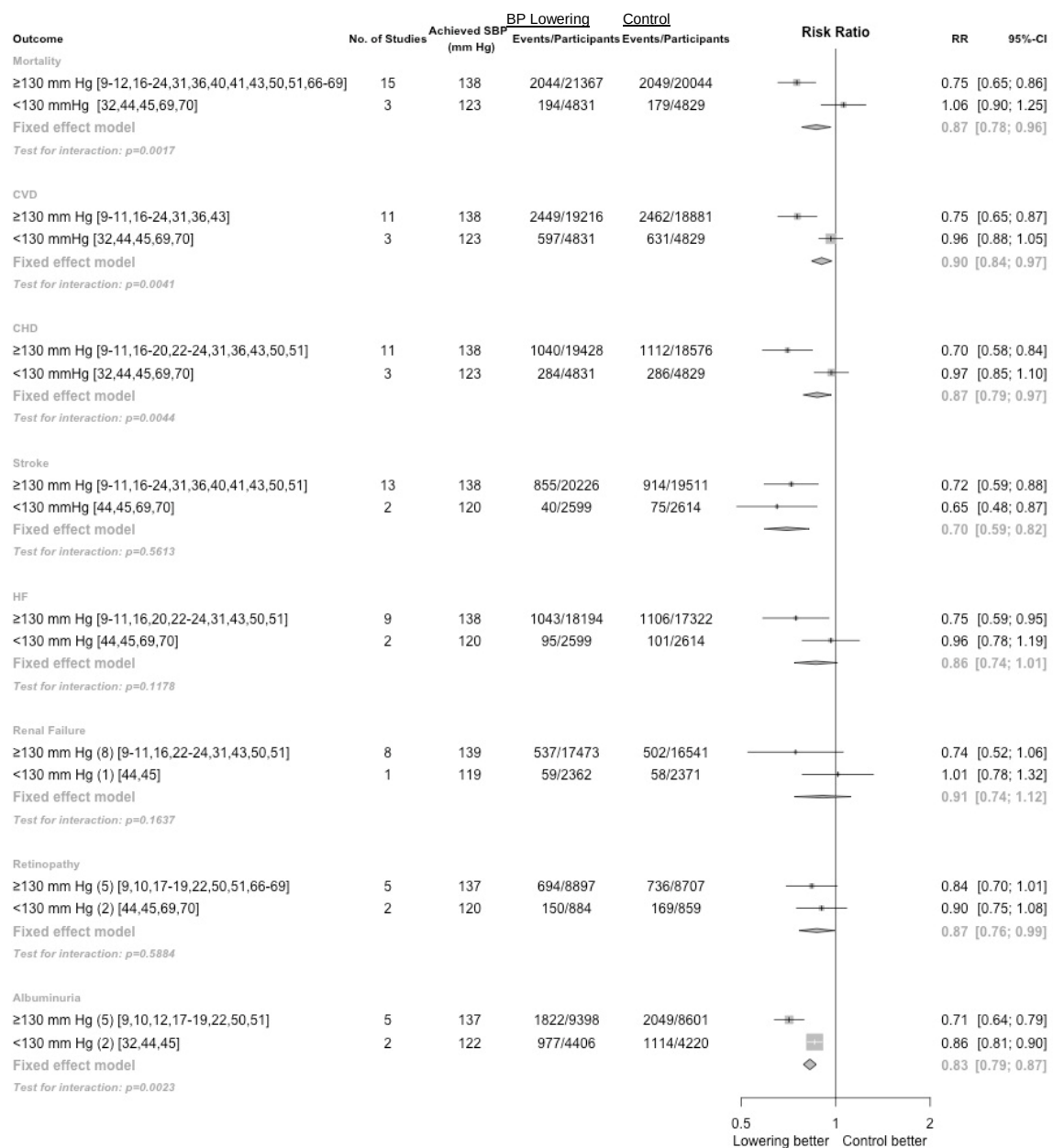


Figure 7.25 Standardized effect of a 10 mm Hg systolic blood pressure reduction on mortality and vascular outcomes stratified by achieved blood pressure. Trials for which achieved blood pressures or reductions in blood pressure were imputed were excluded. Achieved systolic blood pressure refers to the mean achieved systolic blood pressure, weighted by number of participants. The area of each square is proportional to the inverse variance of the estimate. Horizontal lines represent the 95% confidence interval of the estimate.

For non-standardized estimates, a significant interaction between strata continued to be observed CHD and stroke (Figure 7.26). Although tests for interaction between strata for all-cause mortality and cardiovascular events were no longer significant, the mean blood pressure reduction in the lower strata (<130 mm Hg) was more than two times as great as the upper strata (≥ 130 mm Hg, Figure 7.26)

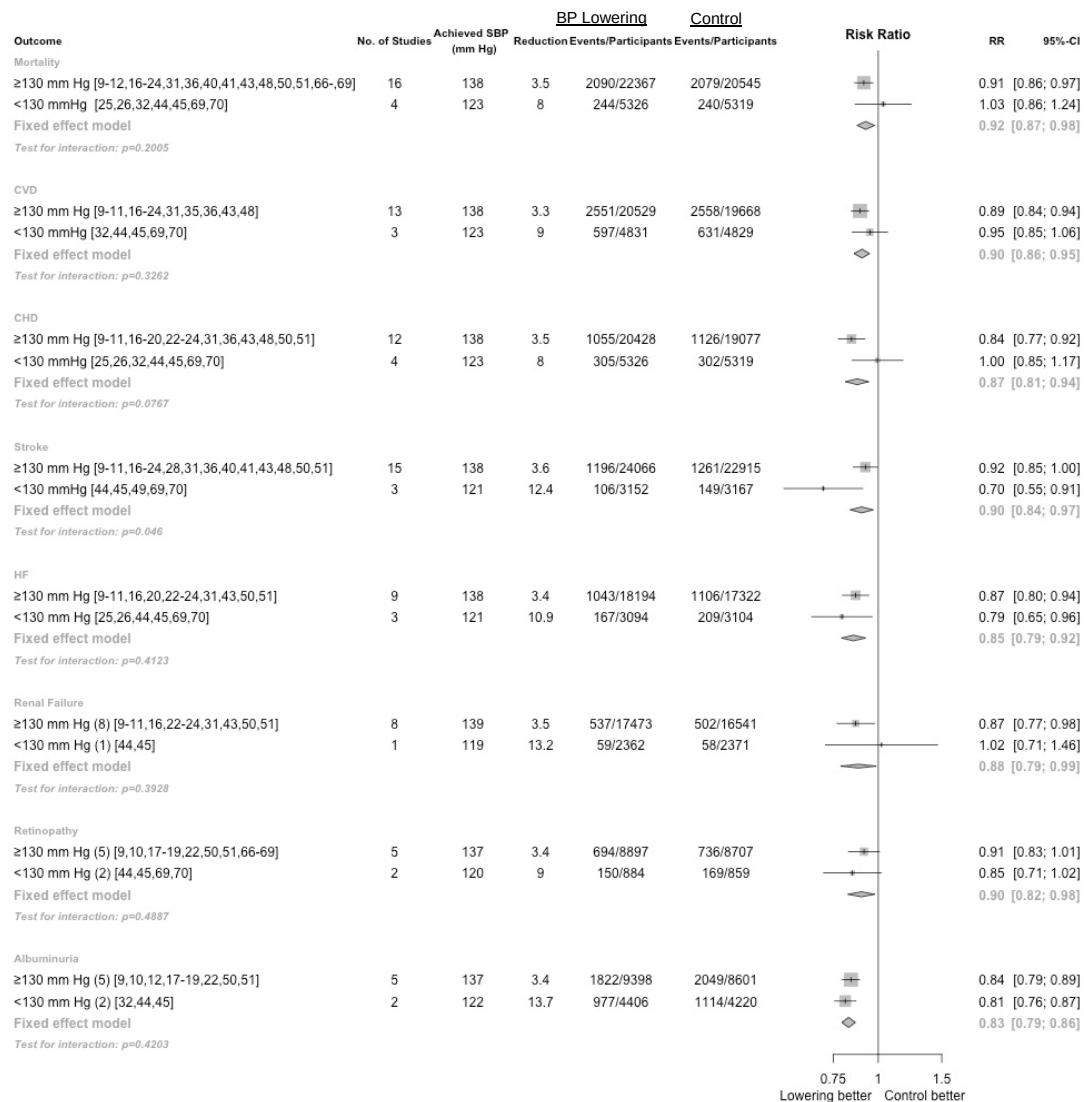


Figure 7.26 Non-standardized effect of blood pressure lowering on mortality and vascular outcomes stratified by achieved blood pressure. Achieved systolic blood pressure refers to the mean systolic blood pressure in the treatment arm of included studies. The area of each square is proportional to the inverse variance of the estimate. Horizontal lines represent the 95% confidence interval of the estimate.

7.3.5 Effect of blood pressure lowering therapy on cardiovascular disease by class of medication

Few differences were observed in the effects of blood pressure lowering treatment and outcomes for regimens based on different classes of medication used (Figure 7.27). No class of medication was more effective at reducing the risk of mortality relative to other classes, with the exception of ARBs. However, this result was largely due to the LIFE study, which compared an ARB against a beta-blocker. No class of medication was observed to be more effective at reducing the risk of cardiovascular events or coronary heart disease events. Calcium channel blockers were more effective at reducing the risk of stroke than other classes of medication (RR 0.86, CI 0.77, 0.97) while beta-blockers were less effective than other classes of medication (RR 1.25 CI 1.05, 1.50 Figure 7.27). Diuretics were more effective at reducing the risk of heart failure than all other forms of medication, driven largely by the results of ALLHAT (RR 0.83, CI 0.72, 0.95). ARBs also appeared to be more effective at reducing the risk of heart failure (RR 0.61 CI 0.48, 0.78), although data were only available from two trials and the confidence intervals were wide. By contrast, CCBs were less effective at reducing the risk of heart failure compared to all other classes of medications (RR 1.32 CI 1.18, 1.47).

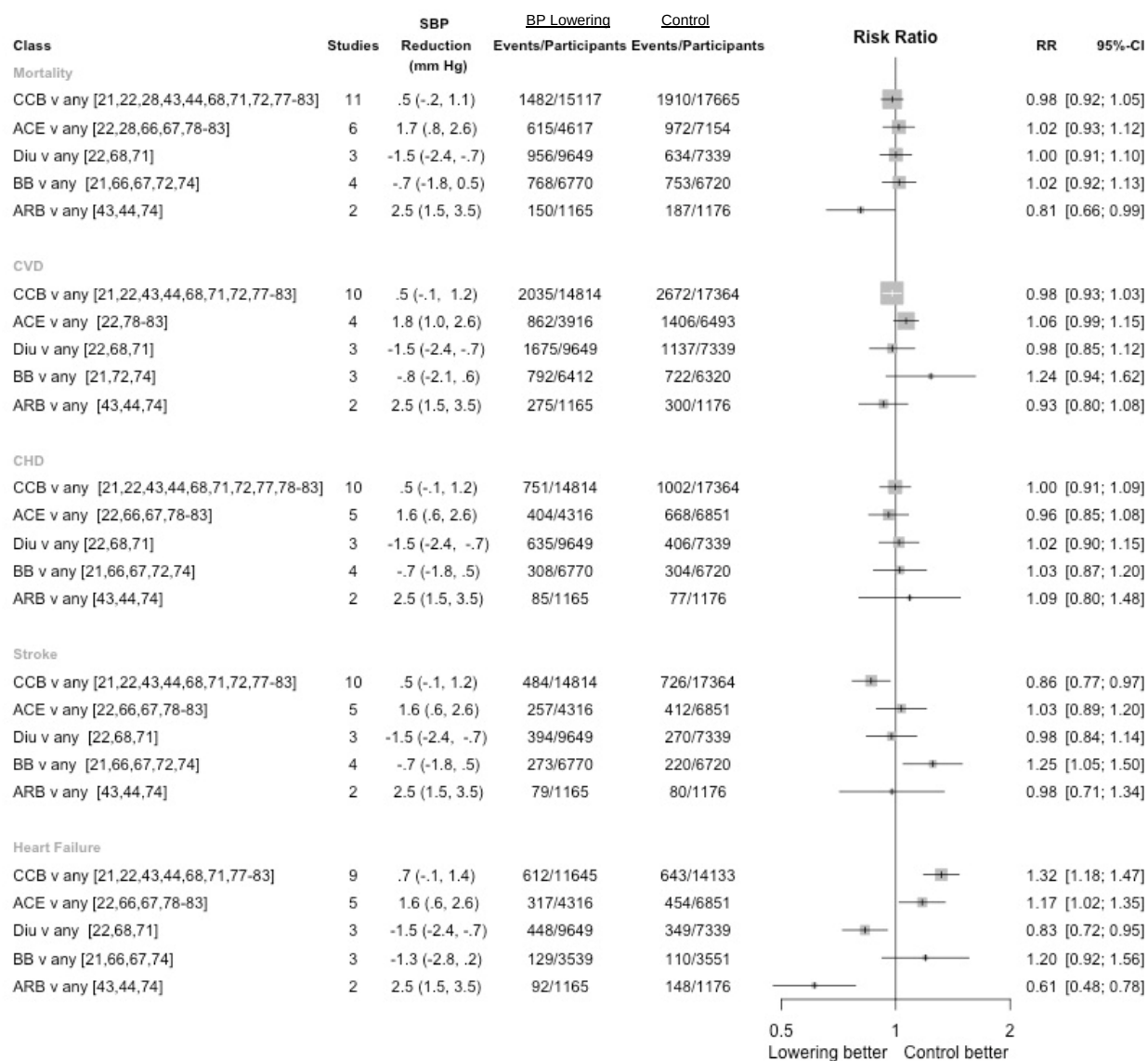


Figure 7.27 Effect of each class of antihypertensives on mortality and vascular outcomes compared to all other classes of antihypertensives. The area of each square is proportional to the inverse variance of the estimate. Horizontal lines represent the 95% confidence interval of the estimate.

Estimates were similar when one trial judged to be of high risk of bias and three trials judged to be of unclear risk of bias were included (Figure 7.28). Calcium channel blockers continued to be more effective at reducing the risk of stroke and less effective at reducing the risk of heart failure than any other class of medication. Diuretics and angiotensin receptor blockers continued to be more effective at reducing the risk of heart failure than any other class of medication.

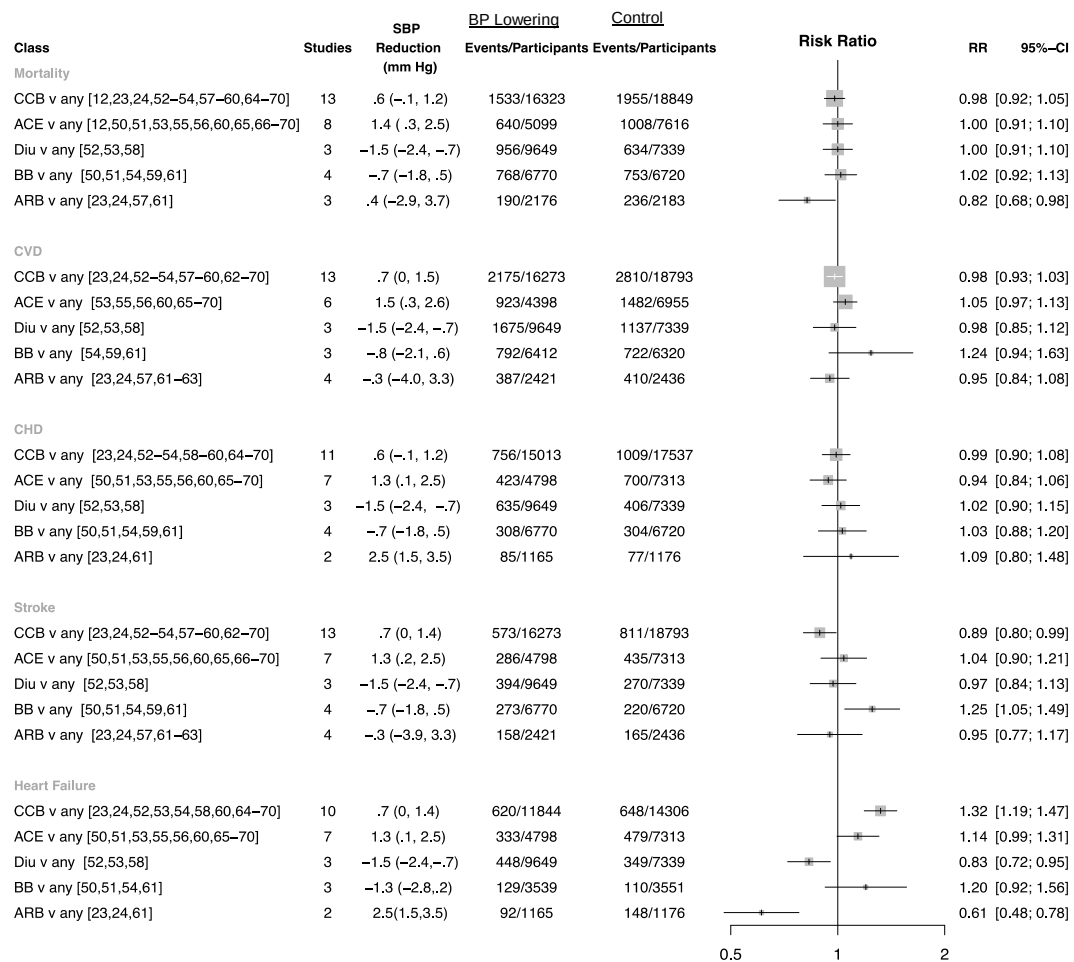


Figure 7.28 Effect of each class of antihypertensives on mortality and vascular outcomes compared to all other classes of antihypertensives. One trial (CAPPP^{147,268}) at high risk of bias and three trials (CASE-J²²⁸, JMIC-B²⁷⁰, and MOSES^{272,273}) at unclear risk of bias were included. The area of each square is proportional to the inverse variance of the estimate. Horizontal lines represent the 95% confidence interval of the estimate.

7.3.6 Comparison of estimates of meta-analysis with observational associations from prior chapter

Overall, estimates from the observational analysis were attenuated relative to estimates from the meta-analysis of randomized trials (Figure 7.29). A test for interaction for cardiovascular events was significant, with 10 mm Hg lower systolic blood pressure associated with a 15% lower risk of a cardiovascular event in the observational analysis (RR 0.85 CI 0.84, 0.87) but a 26% lower risk in the meta-analysis of trials (RR 0.74 CI 0.65, 0.85). Although tests for interaction for coronary heart disease, heart failure and chronic kidney disease were not significant, this is likely due to wide confidence intervals in the randomized estimates; differences between the randomized and observational estimates were similar to the cardiovascular event.

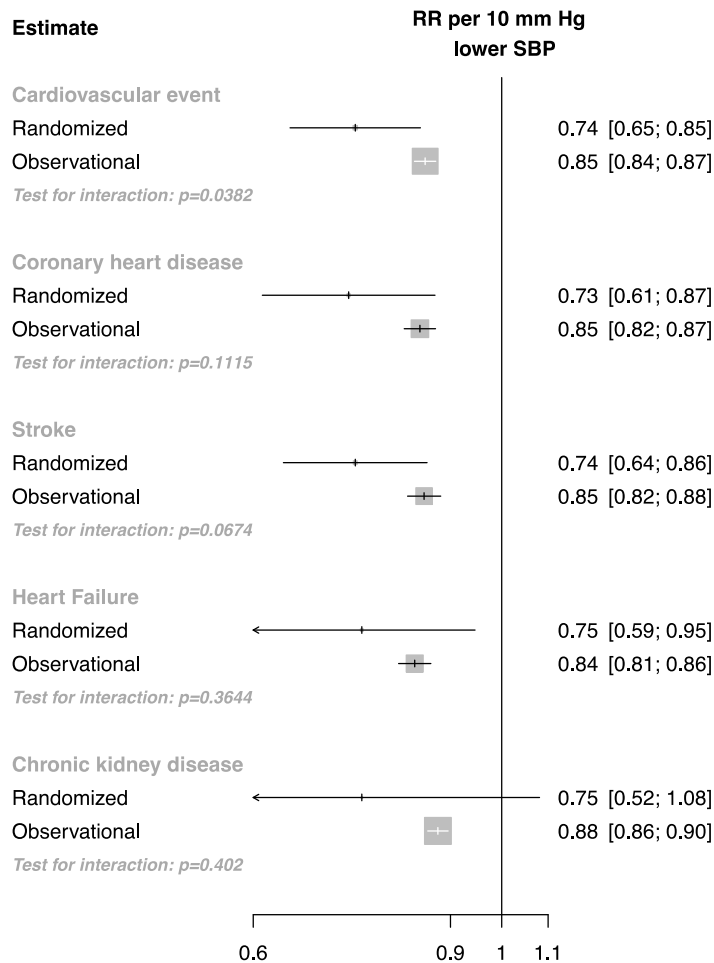


Figure 7.29 Comparison of estimates from observation analysis presented in the prior chapter to estimate from meta-analysis of randomized trials with baseline blood pressure ≥ 140 mm Hg. Chronic kidney disease refers to renal failure in meta-analysis of randomized trials.

7.4 Discussion

This overview indicates that blood pressure lowering treatment reduces the risk of all-cause mortality, cardiovascular events, coronary heart disease events, and stroke events in diabetics. Additionally, I find evidence that blood pressure lowering treatment reduces the risk of retinopathy and albuminuria. While the proportional effects of blood pressure lowering treatment on risk of vascular outcomes were largely not significantly different across classes of medication, my results provide evidence of differential effects between

classes for heart failure and stroke, as has been previously observed in the general population.¹⁵

Although I performed both standardized and non-standardized analyses of the data, I elected to primarily focus on the standardized analyses, which are less impacted by any effects that may not be mediated through blood pressure lowering. However, while there are some differences, the conclusions are broadly similar with and without standardization. These analyses suggest that blood pressure lowering treatment has greater proportional effects on risk of outcomes in trials that included patients with initial mean blood pressure level ≥ 140 mmHg compared to those with initial mean blood pressure level < 140 mmHg, with the exception of stroke, albuminuria and retinopathy. Similarly, when trials were stratified by achieved systolic blood pressure, blood pressure lowering treatment only reduced the risk of stroke and albuminuria in the < 130 mmHg stratum in standardized analyses.

The failure to identify an effect of blood pressure lowering treatment on risk of the cardiovascular composite with lower achieved blood pressure levels is contrary to the findings of a large prior meta-analysis of 147 randomized trials done in a broader population which found clear evidence of a lower risk of CHD and stroke events at much lower achieved blood pressure levels.¹⁵ A key difference between the prior overview and the current study is the inclusion of large numbers of patients with heart failure or recent myocardial infarction in the prior overview, amongst whom mechanisms of action independent of blood pressure lowering have been hypothesized. These results also contrast with the recently published Systolic Blood Pressure Intervention Trial (SPRINT), which observed a reduction in a cardiovascular composite outcome with BP lowering from 140

mm Hg to 121 mm Hg among non-diabetics¹⁰², and a meta-analysis of 123 randomized trials, primarily conducted among non-diabetics, that observed consistent proportional risk reductions with BP lowering regardless of baseline BP.²⁸⁰ Although the contrasting results of this meta-analysis with SPRINT and the larger meta-analysis in non-diabetics would suggest that BP lowering may have differential effects in non-diabetics and diabetics, it is also likely that the inclusion of a number of recent trials of dual renin angiotensin system blockade (particularly the ALTITUDE study²³⁷) has attenuated the anticipated benefits of achieving lower blood pressure levels. Additionally, the null results of the ACCORD trial, which received substantial weight in this meta-analysis, may be due to chance. These results also contrast with a previous meta-analysis, which did not observe an association between blood pressure lowering to a target of ≤ 130 mm Hg and risk of retinopathy or an association between blood pressure lowering to any target (≤ 135 or ≤ 130 mm Hg) and risk of myocardial infarction.²⁸¹ Our differing results are likely due to the greater power of this meta-analysis (45 trials, 104 586 participants), relative to the previous review, which examined 13 trials enrolling 37 736 participants.

The shape of the association of randomized evidence was broadly comparable to that of observational evidence presented in the prior chapter. For trials with a baseline blood pressure below 140 mm Hg and those with an achieved blood pressure less than 130 mm Hg, no significant effect of blood pressure lowering on risk of any cardiovascular event or coronary heart disease was observed. This is consistent with the J-shaped curve presented in the prior chapter for a major cardiovascular event, coronary heart disease and heart failure, with a nadir at approximately 130 mm Hg. In contrast, no interaction was observed for stroke by baseline blood pressure or achieved blood pressure in the meta-

analysis while a test for nonlinearity in the prior chapter was not significant for stroke subtypes.

While the shape of the association was broadly comparable between randomized and observational analyses, the strength of the association was attenuated in the observational analysis compared to the randomized analysis. It is unclear what could explain this discrepancy. One possibility is that the observational analysis is confounded by reverse causality, with a portion of individuals at high cardiovascular risk having both undiagnosed cardiovascular disease that causes low baseline blood pressure. Another is that diabetic individuals with higher blood pressures are more aggressively treated during follow up of the observational analysis, attenuating the association that would be observed without cardiovascular risk reducing therapies.

Lowering blood pressure in individuals with diabetes is an area of current controversy with particular debate surrounding who should be offered therapy, and the blood pressure targets to be achieved. A number of recent guidelines (Table 7.3) have focused entirely on individuals with diabetes who have been diagnosed with hypertension and have established target levels for blood pressure lowering that are less aggressive than previous recommendations. It is unclear whether the new guidelines have utilized the entire evidence base with respect to recommendations for blood pressure lowering in people with type 2 diabetes. For example, the recent JNC-8 guidelines relaxed the threshold for initiation of blood pressure lowering treatment from 130 mm Hg to 140 mm Hg in individuals with diabetes.¹²⁷ The ACCORD trial, which compared a target of <120 mm Hg to <140 mm Hg, was cited in support of this decision, as no significant reduction in the composite outcome of cardiovascular death, non-fatal MI and non-fatal stroke was

observed.⁶² While I also observed that blood pressure lowering was not associated with a lower risk of CVD or CHD events at baseline systolic blood pressure <140 mm Hg, I did observe lower risks of stroke, retinopathy and progression of albuminuria, in both the observational and randomized analyses. Thus, in contrast with the recommendations of the JNC 8 guidelines, for individuals at high risk of these outcomes (e.g. individual with a history of cerebrovascular disease or individuals with mild non-proliferative diabetic retinopathy), the commencement of blood pressure lowering therapy below an initial systolic blood pressure level of 140 mmHg and treatment to a systolic blood pressure level below 130 mmHg should be considered.

Table 7.3 Current major hypertension treatment guidelines.

Guideline	Recommendations on thresholds and targets for patients with diabetes	Recommendations on class of drugs to use in patients with diabetes
American Society of Hypertension / International Society of Hypertension Clinical Practice Guidelines for the Management of Hypertension in the Community, 2014 ²⁸²	- Hypertension has the same definition in diabetics and non-diabetics (systolic BP ≥ 140 mmHg or diastolic BP ≥ 90 mmHg). - Evidence to support a lower target in diabetics is lacking, so the goal of less than 140/90 mmHg should be used, although some experts still recommend less than 130/80 mmHg if albuminuria is present in patients with chronic kidney disease.	- ARB or ACE-I should be used initially (except in black patients where initial use of CCB or thiazide is acceptable). - Thiazides and CCB are acceptable second and third line drugs.
Evidence-Based Guideline for the Management of High Blood Pressure in Adults written by panel members appointed to the Eight Joint National Committee (JNC-8), 2014 ¹²⁷	- No definitions for hypertension provided but threshold for treatment in diabetics is 140 mmHg (systolic) and 90 mmHg (diastolic). - Treat to a goal of less than 140/90 mmHg.	- In the general nonblack population, including those with diabetes, initial antihypertensive treatment should include a thiazide-type diuretic, CCB, ACE-I, or ARB. - In the general black population, including those with diabetes, initial antihypertensive treatment should include a thiazide-type diuretic or CCB.
An effective approach to high blood pressure control. A science advisory from the American Heart Association, the American College of Cardiology and the Centers for Disease Control and Prevention, 2013 ²⁸³	- Defines Stage 1 hypertension (systolic 140-159 mmHg) or Stage 2 hypertension (systolic >160 mmHg or diastolic >100 mmHg) as the premise for consideration of blood pressure lowering. - For most people, the goal is <140 mmHg and <90 mmHg; however, lower targets may be appropriate for some populations such as African-Americans, the elderly, or patients with LV hypertrophy, systolic or diastolic LV dysfunction, diabetes mellitus or chronic kidney disease.	- No specific recommendations made for individuals with diabetes. - Thiazides preferred as first-line therapy in Stage 1 hypertension. - Initial combination therapy preferred in Stage 2 hypertension.
European Society of Cardiology Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the European Association for the Study of Diabetes, 2013 ²⁸⁴	- No definitions for hypertension provided. - Reasonable to reduce BP to less than 140/85 mmHg in diabetics, recognizing that further reduction may be associated with increased serious adverse events.	All available BP lowering drugs can be used in patients with diabetes, but available evidence strongly supports use of ACE-I or ARB in the presence of proteinuria.
European Society of Hypertension / European Society of Cardiology Guidelines for the management of arterial hypertension, 2013 ²⁸⁵	- While initiation of antihypertensive drug treatment in diabetic patients whose systolic BP is ≥ 160 mmHg is mandatory, it is strongly recommended to start drug treatment also when systolic BP is ≥ 140 mmHg. - A systolic BP goal <140 mmHg is recommended	- All classes of antihypertensive agents are recommended and can be used in patients with diabetes. - RAS blockers may be preferred, especially in the presence of proteinuria or microalbuminuria. - It is recommended that individual drug choice takes comorbidities into account.

	- in patients with diabetes. - The diastolic BP target in patients with diabetes is recommended to be <85 mmHg.	Simultaneous administration of two blockers of the RAS is not recommended and should be avoided in patients with diabetes.
American Diabetes Association Clinical Practice Recommendations, 2013 ²⁸⁶	- People with diabetes and hypertension should be treated to a systolic BP goal of <140 mmHg. - Lower systolic BP targets, such as <130 mmHg, may be appropriate for certain individuals, such as younger patients. - Patients with diabetes should be treated to a diastolic BP <80 mmHg.	- Commence with a regimen that includes either an ACE inhibitor or ARB; if one class is not tolerated, substitute the other. - Multiple drug therapy (two or more agents at maximal doses) generally required to achieve BP targets.
International Diabetes Federation Global Guideline for Type 2 Diabetes, 2012 ²⁸⁷ http://www.idf.org/sites/default/files/IDF-Guideline-for-Type-2-Diabetes.pdf	- Consider BP lowering treatment if BP is consistently above 130/80 mmHg. - All people with known cardiovascular disease should receive BP lowering therapy unless contraindicated or not tolerated. - Aim to maintain BP $\leq$ 130/80 mmHg, if therapy is well tolerated. - Revise individual targets upwards if there is significant risk of postural hypotension and falls. - Higher targets should be used in the elderly	- In the absence of a raised albumin excretion rate any agent can be used as first line therapy except for α-adrenergic blockers. - ACE inhibitors and ARBs may offer some advantages over other agents in some situations, but do not use the two together. - CCBs should be avoided in heart failure. - Use β-adrenergic blockers in people with angina; β-adrenergic blockers and ACE inhibitors in people with coronary artery disease; ACE-inhibitors or diuretics in those with heart failure; ACE inhibitor plus low dose thiazide or thiazide-like diuretic, or ACE-inhibitor plus CCB in people with cerebrovascular disease. - Care should be taken with combined thiazide and β-adrenergic blockers because of risk of deterioration in metabolic control. - Add further medications from a different class if targets are not reached on maximal doses of current medications.
Seventh Report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7), 2003 ²⁸⁸	- Patients not at goal blood pressure (<130/80 mmHg) following attempts at lifestyle modification should be commenced on drug treatment - BP in diabetics should be controlled to levels of 130/80 mmHg or lower.	- Regarding the selection of medications, clinical trials with diuretics, ACE-I, beta blockers, ARB, and CCB have a demonstrated benefit in the treatment of hypertension in type 2 diabetics. - The question of which class of agent is superior for lowering BP is somewhat moot because the majority of diabetic patients will require two or more drugs to achieve BP control.

Abbreviations: BP – blood pressure; ACE-I – angiotensin converting enzyme inhibitor; ARB – angiotensin receptor blocker; CCB – calcium channel blocker

When deciding whether to commence blood pressure lowering treatment in individuals with systolic blood pressure below 140 mm Hg or whether to aim for systolic blood pressure levels below 130 mmHg, the risk of adverse events associated with blood pressure lowering treatments will need to be considered. This will require individualized assessment of the likely absolute benefits and risks with shared decision making between patients and clinicians. While many trials reported select adverse events, these data was too disparate to allow formal meta-analysis. In ACCORD, the rate of serious adverse events attributed to blood pressure lowering in the intensive treatment group (which reached an achieved blood pressure of 119 mm Hg) was 2.5 times that of the control group (an achieved blood pressure of 133 mm Hg), however, the absolute rate of these adverse events in the intensive group was low, and was substantially lower than that of the primary outcome (0.70% per year vs. 1.87% per year).⁶² It is possible that there is a higher risk of some important adverse events with large reductions at lower blood pressure levels. Additionally, as many trial participants will have been treated with multiple classes of blood pressure lowering medications, differences between classes with regard to efficacy and adverse events may have been obscured. An individual patient data meta-analysis of efficacy and adverse events, stratified by patient characteristics, baseline blood pressure and class of medication, is necessary to provide the reliable evidence required to fully evaluate the overall balance of risks and benefits.

With data from 104 586 patients enrolled in 45 large trials, these analyses included substantially more information than previous published meta-analyses addressing this question (Table 7.4). This was, in large part, due to my efforts to identify all relevant data,

by including not just trials done in patients with diabetes, but also the results reported for the diabetic subgroups in large trials done in mixed populations. For the effects of treatment based on initial blood pressure level and target blood pressure levels, I base my interpretation of the data primarily on the presence or absence of statistical heterogeneity across subgroups rather than the significance of the results in each individual subgroup. This approach minimizes the impact of the wide confidence intervals obtained for each individual subgroup consequent upon the division of the data, and provides for a more robust interpretation. The uncertainty that ensues from the subgroup analyses does serve to emphasize the need for more clinical trial data, particularly in relation to systolic blood pressure targets below 130 mm Hg. Further trials that evaluate blood pressure lowering treatment into the 120-130 mm Hg range among hypertensive and non-hypertensive diabetic individuals would clarify whether lowering systolic blood pressure to a target of <130/80 mm Hg would further reduce vascular risk relative to a target of <140/ 90 mm Hg, as the reliability of this meta-analysis is limited by the scarcity of large trials with achieved blood pressure in the 120-130 mm Hg range. Additionally, the relatively short follow up of included trials may also have prevented associations of blood pressure lowering treatment with vascular outcomes from being observed, particularly for outcomes such as heart failure and renal failure, which are often a consequence of myocardial infarction and albuminuria, respectively.

Table 7.4 Previously conducted systematic reviews.

Systematic Review	Inclusion criteria	Number of trials	Number of patients	Major outcomes	Conclusions
Emdin et al. (current)	Trials of any BP lowering in patients, representing either the whole trial population or a subgroup reported separately.	45	104 586	All-cause mortality; CVD events; major CHD events; stroke; heart failure; retinopathy; renal failure; development of albuminuria.	Each 10 mm Hg lower systolic blood pressure was associated with a significantly lower risk of all-cause mortality (RR 0.87, 95% confidence interval 0.78, 0.96; absolute risk of 8.4% vs. 9.0%), cardiovascular events (RR 0.89, CI 0.83, 0.95; 12.5% vs. 13.2%), coronary heart disease events (RR 0.88, CI 0.80, 0.98; 5.3% vs. 5.9%), stroke events (RR 0.73, CI 0.64, 0.83; 4.9% vs. 5.6%), new or worsening albuminuria (RR 0.83, CI 0.79, 0.87; 20.3% vs. 24.7%) and retinopathy (RR 0.87, CI 0.76, 0.99; 8.6% vs. 9.7%). When trials were stratified by mean initial systolic BP above or below 140 mm Hg, the relative risks of mortality, cardiovascular disease, coronary heart disease, heart failure and albuminuria were smaller in studies with higher baseline SBP (all p interaction<0.1), while these associations did not differ significantly for stroke, retinopathy and renal failure. Few class differences were observed.
Evidence-Based Guideline for the Management of High Blood Pressure in Adults written by panel members appointed to the Eight Joint National Committee (JNC-8), 2014 ¹²⁷	Trials with a prespecified subgroup of diabetes.	4	6956	Overall mortality, cardiovascular mortality, myocardial infarction, stroke, heart failure, end stage renal disease	Treatment to an SBP <150 mm Hg improves cardiovascular and cerebrovascular health outcomes in diabetics. Based on expert opinion, treatment in diabetics should be to SBP < 140 mm Hg and DBP < 90 mm Hg.
Reboldi G et al, J Hypertens 2011 ²⁸⁹	Trials comparing various BP-lowering agents vs. placebo or another active treatment; inclusion of patients with diabetes mellitus at baseline (representing either the whole trial population or a subgroup reported separately).	31	73,913	MI; Stroke	More BP lowering is associated with reduced risk of stroke (RR 0.87 CI 0.80, 0.95 per 5 mm Hg lower SBP). Trend for reduction in MI per 5 mm Hg lower SBP but not statistically significant (RR 0.98 CI 0.86, 1.13). No “J-curve” phenomenon suggesting harm on meta-regression.

Lv J et al, PLoS Med 2012 ²⁹⁰	Trials that randomly assigned individuals to different target BP levels, with or without diabetes.	15	37,348	Major CV events as a composite of MI infarction, stroke, heart failure, and CV death; individuals components of this; mortality; ESKD; progression of albuminuria; retinopathy	Lower BP targets were associated with significant reductions in major cardiovascular events (RR 0.89 CI 0.79, 0.99), myocardial infarction (RR 0.87 CI 0.75, 1.00), stroke (RR 0.76 CI 0.63, 0.92), ESKD (RR 0.89 CI 0.82, 0.97) and progression of albuminuria (RR 0.90 CI 0.84, 0.96) that were proportional to the achieved difference in systolic BP.
Bangalore S et al, Circulation 2011 ²⁸¹	Trials of participants with type 2 diabetes mellitus/IFG/IGT that achieved systolic BP <140 mm Hg in standard control arm and < 135 mm Hg in the intensive control arm, with systolic BP difference between the intensive and standard BP group of at least 3 mm Hg.	13	37 736	All-cause mortality; CV mortality; MI; stroke; heart failure; angina pectoris; revascularization; development of microalbuminuria; overt nephropathy; ESKD; doubling of serum creatinine; neuropathy; retinopathy; SAEs.	More intensive BP lowering resulted in significantly reduced risks of death (OR 0.90 CI 0.83, 0.98), stroke (OR 0.83 CI 0.73, 0.95), nephropathy (OR 0.73 CI 0.64, 0.84), microalbuminuria (OR 0.83, CI 0.77, 0.89), but no significant effects on cardiovascular mortality (OR 0.93 CI 0.82, 1.06), MI (OR 0.92 CI 0.80, 1.06), heart failure (OR 0.90 CI 0.75, 1.06), angina pectoris (OR 1.07 CI 0.92, 1.24), revascularization (OR 0.97 CI 0.85, 1.12) and retinopathy (OR 0.93 CI 0.83, 1.05). BP lowering to <130 mmHg associated with lower stroke (OR 0.53 CI 0.38, 0.75) and nephropathy (OR 0.64 CI 0.53, 0.78) risks but more SAEs (OR 1.40 CI 1.19, 1.64).
Arguedas JA et al, Cochrane 2013 ²⁹¹	Trials comparing people with diabetes randomized to <130/85 mmHg or to <140-160/90-100 mmHg target BP.	5	7314	Total mortality; Total serious adverse events; MI; Stroke; Congestive heart failure and ESKD.	Blood pressure lowering to lower diastolic targets is associated with a reduced risk of total mortality (RR 0.64, CI 0.45, 0.92). A trend towards a reduced risk of non-vascular mortality (RR 0.62 CI 0.35, 1.08) and vascular mortality (RR 0.64 CI 0.39, 1.03) was observed. No significant association was observed for MI (RR 0.98 CI 0.65, 1.48), stroke (RR 0.64 CI 0.39, 1.06) or heart failure (RR 1.06 CI 0.58, 1.92). Only one trial compared a lower systolic blood pressure target and was not meta-analysed. SAEs were not meta-analysed. There is insufficient evidence to support BP targets of <130/80 mmHg.

7.5 Conclusions

Blood pressure lowering treatment reduces the risk of death, macrovascular and microvascular outcomes in patients with diabetes. Proportional effects of blood pressure lowering treatment on all-cause mortality, cardiovascular events and coronary heart disease were attenuated and non-significant below an achieved systolic blood pressure of 130 mm Hg, consistent with the observational analysis presented in the prior chapter. However, data indicated that further reduction below 130 mm Hg will reduce the risk of stroke, retinopathy and albuminuria, potentially leading to net benefit for individuals with type 2 diabetes at high risk of these outcomes.

Chapter 8 Discussion

8.1. Results in the context of prior hypotheses

This thesis aimed to test five hypotheses (Table 8.1):

1. A 20 mm Hg higher systolic blood pressure and a 10 mm Hg higher diastolic blood pressure are associated with higher risks of AF among individuals free of existing cardiovascular disease, and have similar strengths of association by baseline blood pressure, by age, by sex and by body mass index.
2. Atrial fibrillation without antithrombotic therapy is associated with an increased risk of stroke, ischemic heart disease, peripheral arterial disease and cardiovascular disease.
3. Blood pressure lowering therapy reduces the risk of AF in randomized trials, overall and among individuals with and without cardiovascular disease.
4. A 20 mm Hg higher systolic blood pressure and a 10 mm Hg higher diastolic blood pressure are associated with higher risks of new-onset diabetes among individuals free of diabetes, and have similar strengths of association by baseline blood pressure, by age, by sex and by BMI.
5. A 20 mm Hg higher systolic blood pressure and a 10 mm Hg higher diastolic blood pressure are associated with a higher risk of cardiovascular disease among individuals with diabetes, and have similar strengths of association by baseline blood pressure.
6. Blood pressure lowering therapy reduces the risk of cardiovascular disease in randomized trials conducted among individuals with diabetes, as well as among diabetic individuals with both high and low baseline blood pressure and in trials conducted in type 2 diabetes which achieved both high and low blood pressure.

With regard to the relationship between blood pressure and AF, risk of AF increased by 21% per 20/10 mm Hg higher blood pressure (HR 1.21 CI 1.19, 1.22), and did not appear to differ by baseline blood pressure. No evidence of a nadir was observed when blood pressure was examined as a categorical variable (Figure 3.2). However, risk of AF differed significantly with increasing age, declining from a 100% higher risk per 20 mm Hg higher systolic blood pressure at age 30-40 (HR 2.00 CI 1.83, 2.18) to no significant association at age 81-90 (HR 1.03 CI 0.99, 1.07). Furthermore, risk of AF per 20/10 mm Hg higher BP was also modified significantly by BMI.

For the second hypothesis, AF without antithrombotic therapy was associated with a 172% higher risk of ischemic stroke, a 109% higher risk of peripheral arterial disease, a 152% higher risk of ischemic heart disease and a 115% higher risk of a cardiovascular event. Consistent with this hypothesis, AF was associated with a wide range of cardiovascular events, in addition to the expected association with ischemic stroke. However, the strength of association with stroke was attenuated relative to the classic Framingham estimate of a five-fold risk of stroke with AF.

In spite of the significant observational association of blood pressure with risk of AF, blood pressure lowering did not significantly reduce the risk of AF in trials conducted in populations without cardiovascular disease (RR 0.84 CI 0.53, 1.33 per 20 mm Hg lower SBP). However, this relative risk was highly similar to the hazard ratio observed in observational evidence (HR 0.83 CI 0.82, 0.84, p interaction = 0.94). Consequently, I would not interpret the second hypotheses as being refuted by the meta-analysis presented in Chapter 4. Rather, it appears that existing trials of blood pressure lowering in non-cardiovascular disease populations were underpowered to detect a modest proportional reduction in risk of AF. More evidence is needed before it

can be determined whether blood pressure lowering does or does not reduce the risk of AF in primary prevention populations. However, it can be concluded that the proportional effects of antihypertensive therapy in heart failure populations are significantly greater than those in non-heart failure populations, as I observed an independently significant proportional reduction in risk of AF in trials conducted in HF populations (RR 0.81 CI 0.74, 0.87), which was significantly greater than the proportional reduction in trials without CHD (RR 1.02 CI 0.88, 0.98; p interaction = 0.002),

With regard to the relationship between blood pressure and new onset diabetes, risk of diabetes increased with higher blood pressure; a 20 mm Hg higher systolic blood pressure was associated with a 58% higher risk of diabetes while a 10 mm Hg higher diastolic blood pressure was associated with a 52% higher risk of diabetes. However, proportional risk of diabetes per 20/10 mm Hg blood pressure decreased with increasing usual blood pressure, body mass index and age. Thus, while part of the third hypothesis was supported (proportional risk of diabetes increases with higher blood pressure), part of the third hypothesis was refuted (proportional risk of diabetes is not modified by patient characteristics). Assuming that there is a causal effect of blood pressure on diabetes, this modification by patient characteristics may be due to a true modification of the causal effect of BP on diabetes (e.g. elevated BP has a greater proportional effect on diabetes at younger ages) or may be due to confounding (e.g. younger individuals with high blood pressure may have a greater number of pro-diabetic confounders than older individuals with high blood pressure).

With regard to the relationship between blood pressure and cardiovascular disease in type 2 diabetes, proportional risk of cardiovascular disease appeared to be positively and continuously related to blood pressure above 130/75 mm Hg. When

modeled continuously, there appeared to be a threshold at 130/75 mm Hg, below which risk of any cardiovascular event was not associated with higher blood pressure.

However, confidence intervals were wide and did not preclude either an increase or decrease in proportional risk of cardiovascular disease below 130/75 mm Hg. When randomized trial evidence was examined in a meta-analysis, blood pressure lowering reduced the risk of death and cardiovascular disease in type 2 diabetes. However, consistent with the observational evidence, the proportional effect of blood pressure lowering therapy was modified by the baseline and achieved blood pressure at the trial level. Among trials with a mean baseline systolic blood pressure ≥ 140 mm Hg, blood pressure lowering reduced the risk of all cause mortality (RR 0.73 CI 0.64, 0.84) and cardiovascular events (RR 0.74 CI 0.65, 0.85) per 10 mm Hg reduction in systolic blood pressure. However, among trials with a baseline systolic blood pressure < 140 mm Hg, blood pressure lowering did not significantly reduce the risk of either all-cause mortality or cardiovascular events (p interaction < 0.001). Among trials with an achieved blood pressure ≥ 130 mm Hg, blood pressure lowering reduced the risk of all cause mortality (RR 0.75 CI 0.65, 0.86) and cardiovascular events (RR 0.74 CI 0.64, 0.85). However, among trials with an achieved systolic blood pressure < 130 mm Hg, blood pressure lowering did not significantly reduce the risk of either all cause mortality or cardiovascular events (p interaction < 0.001).

These results are consistent with the observational analysis presented in Chapter 6 and would suggest that the proportional effects of BP lowering on risk of all-cause mortality and cardiovascular events differs by baseline and achieved BP in type 2 diabetes, with attenuated proportional benefits at achieved SBP < 130 mm Hg. Two meta-analyses of randomized trials in largely non-diabetic populations have observed consistent proportional effects regardless of baseline BP. Furthermore, the recently

published SPRINT trial (conducted among individuals without diabetes), used a similar protocol to the ACCORD trial (conducted among individuals with diabetes) but observed a significant reduction in risk of major cardiovascular events (RR 0.75 CI 0.64, 0.89), in contrast to the non-significant findings of the ACCORD trial. In totality, these results suggest that the proportional effect of BP lowering on risk of major cardiovascular events may be modified by baseline BP among individuals with type 2 diabetes but not among individuals with diabetes.

However, there are several other possible explanations for why modification by baseline BP was observed in type 2 diabetes. The inclusion of a number of recent trials of dual renin angiotensin system blockade (particularly the ALTITUDE study²³⁷) may have attenuated the anticipated benefits of achieving lower blood pressure levels. Additionally, the null results of the ACCORD trial, which received substantial weight in this meta-analysis, may be due to chance. A large randomized trial, conducted among individuals with type 2 diabetes and using an identical protocol to SPRINT, is needed to determine whether BP lowering to very low levels can reduce the risk of cardiovascular disease among individuals with diabetes.

Table 8.1 Summary of analyses undertaken in thesis.

Hypothesis	Design	Sample Size	Conclusions
1. BP is associated with risk of AF	Observational analysis of cohort study	4269194 participants (individual-level data)	BP is modestly associated with risk of AF (HR 1.21 CI 1.19, 1.22 per 20 mm Hg higher SBP)
2. AF without antithrombotic therapy is associated with risk of cardiovascular disease	Observational analysis of cohort study	4301349 participants (individual-level data)	AF without antithrombotic therapy is associated with a higher risk of ischemic stroke (HR 2.72 CI 2.19, 3.38), ischemic heart disease (HR 2.52 CI 2.23, 2.84), peripheral arterial disease (HR 2.09 CI 1.73, 2.53) and a cardiovascular event (HR 2.15 CI 2.05, 2.24).
3. BP lowering reduces the risk of AF	Meta-analysis of randomized trials	27 trials, 214763 individuals (summary-level data)	BP lowering did not significantly reduce risk of AF (RR 0.84 CI 0.53, 1.33 per 20 mm Hg lower SBP) although randomized estimate was similar to observational estimate
4. BP is associated with risk of new onset diabetes	Observational analysis of cohort study / meta-analysis of cohort studies	4132138 participants (individual-level data); 30 cohort studies, 285 664 individuals (summary-level data)	20 mm Hg higher SBP is associated with a 74% higher risk of new onset diabetes (HR 1.74 CI 1.54, 1.94)
5. BP is associated with cardiovascular disease in diabetes	Observational analysis of cohort study	73658 participants with type 2 diabetes (individual level data)	BP is associated with risk of cardiovascular disease in diabetes (HR 1.4 CI 1.32, 1.48); strength of association declines at SBP < 130 mm Hg.
6. BP lowering reduces the risk of cardiovascular disease in diabetes	Meta-analysis of randomized trials	45 trials, 104 586 individuals (summary-level data)	BP lowering reduced the risk of major cardiovascular events (RR 0.89 CI 0.83, 0.95 per 10 mm Hg SBP lowering); proportional reductions were attenuated among trials with an achieved SBP < 130 mm Hg

8.2. Contributions of this thesis to an understanding of the relationship between blood pressure and risk of atrial fibrillation in the context of prior evidence

It may be expected from previous epidemiological studies that blood pressure lowering prevents AF. Blood pressure is a causative risk factor for coronary heart disease and heart failure^{12,15}, themselves risk factors for AF.³¹ It is plausible that the increase in risk of coronary heart disease and heart failure caused by elevated blood pressure would lead to an increase in incident AF. Indeed, observational analyses have supported such an association between elevated blood pressure and incident AF. Prior reports of Framingham³¹, Women's Health Study³⁵ and Atherosclerosis Risk in Communities²⁹² studies have all observed that elevated blood pressure is associated with a higher risk of AF.

This thesis confirms these prior reports and, to my knowledge, reliably quantifies the association of blood pressure with risk of atrial fibrillation for the first time. I observe that a 20 mm Hg higher systolic blood pressure is associated with a 21% higher risk of AF. Furthermore, the analysis presented here extends past results by characterizing the shape of the relationship between blood pressure and risk of atrial fibrillation, demonstrating there to be no nadir to at least 115/70 mm Hg. This analysis also demonstrates an interaction by age and BMI, similar to what has been reported for stroke and ischemic heart disease.¹²

However, unlike stroke and coronary heart disease, for which a 20 mm Hg higher systolic blood pressure is associated with an approximate doubling in risk¹², blood pressure is much more modestly associated with AF. Given this, it is plausible that any observed association between blood pressure and AF is due to confounding,

with healthier individuals having independently lower blood pressure and lower risk of AF.

Because of the limitations of observational studies, examination of randomized trial evidence is necessary. Two landmark meta-analyses have concluded that renin-angiotensin system inhibitors prevent atrial fibrillation.^{37,130} In contrast, a recent secondary prevention trial of atrial fibrillation in a predominantly non-heart failure population did not observe benefit for an angiotensin receptor blocker for prevention of recurrence of atrial fibrillation.¹³² By pooling together all available trials of antihypertensive therapies (rather than arbitrarily restricting the analysis to renin-angiotensin system inhibitors), the analysis presented in this thesis helps explain these discordant findings by demonstrating significant heterogeneity in the effect of antihypertensive therapy on risk of atrial fibrillation by the presence of heart failure but not by class of antihypertensive therapy. Observational studies have suggested that renin-angiotensin inhibitors may be more effective for prevention of AF than other antihypertensive therapies.^{168,169} This thesis suggests that these prior results are due to confounding and that different classes of antihypertensive therapy have similar effects on risk of AF.

Although I also observed heterogeneity in the effects of antihypertensive therapy by baseline absolute risk, with greater proportional effects in trials conducted in populations at high risk of AF, there was substantial overlap between trials conducted in high risk populations and heart failure populations. In ACTIVE I, a secondary prevention trial conducted among individuals without heart failure but with a history of atrial fibrillation who were currently in sinus rhythm, no significant effect of antihypertensive therapy on risk of incident atrial fibrillation was observed despite participants being at high absolute risk for AF.¹³² These results therefore suggest that

the proportional effects of antihypertensive therapy is modified by heart failure, rather than absolute risk of AF. As atrial fibrillation is a marker for the progression of heart failure²⁹³, these results suggest that the greater proportional effects of antihypertensive therapy in heart failure populations for the prevention of AF may be due to antihypertensive therapy preventing the progression of heart failure, rather than antihypertensive therapy directly preventing atrial fibrillation. Indeed the non-significant reduction in risk of AF observed in non-heart failure populations in this meta-analysis is consistent with the modest association observed in the observational analysis presented in Chapter 3.

In conclusion, this thesis delineates between the effects of blood pressure lowering therapy on risk of atrial fibrillation in heart failure and non-heart failure populations for the first time and demonstrates, through both observational and randomized analyses, that any proportional effect of blood pressure therapy on risk of atrial fibrillation in non-heart failure populations is likely to be modest.

8.3. Contributions of this thesis to understanding of blood pressure and risk of diabetes in the context of prior evidence

Unlike atrial fibrillation, for which elevated blood pressure is a known risk factor, it was unclear prior to this thesis whether elevated blood pressure was a risk factor for diabetes. Although a recent analysis from Women's Health Study had suggested that elevated blood pressure is associated with an increased risk of type 2 diabetes after adjustment for traditional diabetes risk factors⁴⁹, several prior observational studies had concluded that there was no such association.^{50,195,198} Further complicating the interpretation of these discordant findings, different classes of blood pressure lowering medications have differential effects on risk of diabetes.⁵³ While renin-angiotensin system inhibitors have been suggested to reduce the risk of diabetes,

diuretic and beta-blockers have been suggested to increase the risk of diabetes.^{53,205} It was therefore unclear whether blood pressure is associated with risk of diabetes, or whether randomized evidence and meta-analyses of randomized trials demonstrating that renin-angiotensin system inhibitors prevent diabetes is due to a blood pressure independent mechanism.

By conducting the largest observational analysis, to date, and a meta-analysis of prior prospective studies, this thesis demonstrates that blood pressure is a risk factor for diabetes. Furthermore, this thesis characterizes the shape of the relationship of diabetes with blood pressure, demonstrating no evidence of a nadir to at least 115 mm Hg systolic blood pressure. This finding has the important clinical implication that, if there is a causal effect of BP on type 2 diabetes, BP lowering may reduce the risk of diabetes even among individuals with low to normal BP levels.

8.4. Contributions of this thesis to understanding of blood pressure and risk of cardiovascular disease in type 2 diabetes in the context of prior evidence

Prior observational studies on the association of cardiovascular disease with blood pressure in diabetes have been conflicting. Analyses of the MRFIT⁶⁰ and UKPDS⁵⁶ cohorts have suggested no nadir between blood pressure and cardiovascular risk among individuals with diabetes, down to a systolic blood pressure of 120 mm Hg. In contrast, an analysis of the Australian and New Zealand populations of the Asia Pacific Cohort Studies Collaboration suggested the existence of a threshold at 130 mm Hg.⁵⁵ Two prior observational studies of the relationship of on-treatment blood pressure with risk of cardiovascular events have concluded that cardiovascular risk increases at systolic blood pressure <135 mm Hg.^{57,61} However, these prior observational studies are highly likely to be confounded, as undiagnosed heart failure and ischemic heart disease may cause lower blood pressure in trial participants prior to

diagnosis. No prior studies have attempted to exclude an initial period of follow up to reduce the risk of this reverse causality.

To improve upon prior analyses, I examined the association of blood pressure with cardiovascular disease after excluding the first three years of follow up. Although I observed a threshold at 130 mm Hg, I did not observe the strong J-shaped curves present in prior analyses, suggesting that these prior results have been due to reverse causality. Furthermore, I observed significantly different strengths of association of blood pressure with twelve different vascular outcomes, extending recent work demonstrating heterogeneous associations of blood pressure with different cardiovascular events in a general population.¹³

However, as an observational analysis, the results presented in Chapter 6 are likely to be confounded. Examination of all available randomized evidence is necessary to reliably determine the effects of blood pressure lowering in diabetes. Prior meta-analyses of blood pressure lowering in diabetes have produced inconsistent results, likely due to their failure to consider all available evidence. In a meta-analysis of blood pressure lowering therapy in diabetes and impaired fasting glucose populations, no benefit of blood pressure lowering on risk of myocardial infarction was observed, inconsistent with evidence from general populations¹⁵ and observational evidence from diabetes.⁵⁶ This null finding was likely due to the study only identifying 13 randomized trials with 37 736 participants.²⁸¹ In another meta-analysis of 31 trials with 73 913 participants, more intensive BP lowering was associated with a reduced risk of stroke, but not myocardial infarction.²⁸⁹

The meta-analysis presented in this thesis provides the most comprehensive overview of the effects of blood pressure lowering in type 2 diabetes. This thesis demonstrates that blood pressure lowering reduces the risk of a range of outcomes,

including all-cause mortality, cardiovascular events, coronary heart disease, stroke and microvascular outcomes. However, significant heterogeneity for some but not all outcomes was observed by baseline and achieved blood pressure. Although no significant proportional effects of BP lowering therapy on risk of all-cause mortality, cardiovascular events and coronary heart disease below a baseline blood pressure of 140 mm Hg was observed in this meta-analysis, significant benefit continued to be observed for stroke, retinopathy and microalbuminuria. Furthermore, this thesis demonstrates the existence of class effects in diabetes, with calcium channel blockers more effective and beta-blockers less effective for prevention of stroke, and diuretics more effective for prevention of heart failure. The implications of these results are described below.

8.5 Importance of this thesis for clinical care

The importance of this analysis can be broadly divided into its relevance to clinical care, public health and future research. With regard to clinical care, this thesis demonstrates that provision of antihypertensive therapy can prevent AF in patients with heart failure. It also suggests that the beneficial effect of AF in non-heart failure populations is likely to be modest, at best. As prior landmark meta-analyses of renin-angiotensin system inhibition for prevention of AF had broadly failed to distinguish between trials conducted in heart failure populations and those not conducted in heart failure populations, the existing literature suggested that renin-angiotensin system inhibition provided large benefits for prevention of AF regardless of population. The analysis presented in this thesis clarifies that these large proportional reductions are likely to be confined to heart failure, and provides information so that patients who may be at risk of AF but without heart failure can make informed choices about whether to begin antihypertensive therapy.

Second, for prevention of diabetes, this analysis demonstrates that even at elevated age (>75 years), high BMI (>35 kg/m²) and low blood pressure (<130 mm Hg systolic), risk of new onset diabetes continues to be associated with blood pressure. Prior large randomized trials have demonstrated that renin-angiotensin system inhibition prevents diabetes.^{204,294} These results therefore provide evidence that prescription of blood pressure lowering therapies, particularly renin-angiotensin system inhibitors, may reduce the risk of diabetes even among individuals with low blood pressure. However, individual patient data meta-analysis of randomized trials, such as the Blood Pressure Lowering Treatment Trialists' Collaboration should confirm this finding.

Third, for prevention of cardiovascular disease in type 2 diabetes, these results demonstrate that blood pressure lowering in type 2 diabetes has heterogeneous effects on cardiovascular outcomes by baseline blood pressure. In the most recent JNC-8 guidelines, a threshold for intervention at 140 mm Hg systolic blood pressure was proposed in type 2 diabetes.¹²⁷ Although my results are concordant with this threshold for all-cause mortality, cardiovascular events and coronary heart disease, for stroke, retinopathy and albuminuria, my results indicate that blood pressure lowering below 140 mm Hg will reduce risk. This thesis therefore suggests that guidelines for blood pressure lowering in diabetes should consider individuals' absolute risk of different cardiovascular outcomes. For individuals at high absolute risk of stroke (e.g. individuals with a history of cerebrovascular disease), retinopathy, or kidney disease, blood pressure lowering below 140 mm Hg may result in further benefits.

8.6 Importance of this thesis for public health

These results have a number of implications for public health. First, for prevention of AF, these results indicate that efforts to prevent AF through blood

pressure lowering may reduce population-level incidence of AF if directed at heart failure populations. Previous research has demonstrated substantial gaps in the proportion of heart failure patients who receive guideline recommended therapies such as beta-blockers and ACE-inhibitors.²⁹⁵ The meta-analysis presented in this thesis provides an additional motivation for policy makers and physicians to increase the provision of beta-blockers and ACE-inhibitors in heart failure patients, as AF is associated with an elevated risk of death²⁹⁶ and with reduced quality of life.¹⁰⁷

Second, for prevention of diabetes, these results indicate that population-level efforts to lower blood pressure (e.g. reduction in alcohol intake through taxation or reduction in salt intake through voluntary withdrawal of salt by food manufacturers) may well reduce the incidence of diabetes, if the observed association between elevated BP and diabetes is causal. When considering the substantial disability and economic cost that diabetes poses in both developing and developed countries^{24,297,298}, inclusion of the benefit of diabetes prevention in formal cost effectiveness modeling of blood pressure lowering interventions will lead to different measures of the cost effectiveness of potential population level interventions for blood pressure lowering and, consequently, different priority setting. Furthermore, in the Global Burden of Disease study, blood pressure is the leading risk factor for death and disability worldwide.²⁹⁹ However, diabetes is not included as a potential consequence of elevated blood pressure in Global Burden modeling. Inclusion of blood pressure as a causative risk factor for diabetes in the Global Burden of Disease study would lead to an increase in the estimated burden of hypertension and may thus lead to changes in global and regional priority setting. However, any inclusion of diabetes as a sequela of hypertension in formal modelling will require further evidence (e.g. through meta-analysis of randomized trials or Mendelian randomization analysis) that blood pressure

is a causal risk factor for diabetes. Therefore current policy and guidance around BP lowering for prevention of diabetes should not be changed until further evidence is available.

Third, for prevention of cardiovascular disease in diabetes, these results suggest that changes to blood pressure lowering guidelines in type 2 diabetes may lead to reductions in the sequelae of diabetes. Although all-cause mortality was not reduced, blood pressure lowering to a target systolic blood pressure <130 mm Hg reduced the risk of stroke, albuminuria and retinopathy, outcomes that are important to many patients. These results therefore suggest that BP lowering guidelines should target <130/85 mm Hg in type 2 diabetes, rather than the 140/90 mm Hg target recommended in the current JNC-8 guidelines.

Furthermore, when considering that stroke is the leading cause of death in East Asia and Southeast Asia¹⁶, and that a 20 mm Hg lower systolic blood pressure is associated with a 70% lower risk of stroke¹², widespread blood pressure lowering to low levels (<120 mm Hg systolic blood pressure) in patients with diabetes in high stroke and diabetic burden countries (such as China²⁴) may lead to large population-level reductions in stroke mortality. As calcium channel blockers were more effective for prevention of stroke than other classes of medication, preferential use of calcium channel blocker based therapies may also lead to population level reductions in stroke mortality. These results therefore suggest that BP lowering guidelines in countries where stroke is the leading cause of death, including China, should use a BP lowering target of <120/80 mm Hg with calcium channel blockers as the recommended therapy. Furthermore, these results suggest that guidelines worldwide, including in the United States and United Kingdom, should include a BP target of <120/80 mm Hg for diabetic

individuals with existing cerebrovascular disease, with calcium channel blockers as the recommended therapy.

The significant interactions observed between BP and proportional risk of AF, and BP and proportional risk of new onset diabetes, may have public health implications if interpreted causally. Although the proportional risk of new onset diabetes per 20 mm Hg higher SBP declined with both increasing age and increasing BMI, the absolute increase in risk of diabetes per 20 mm Hg higher SBP increased with higher age and BMI due to the much higher baseline absolute risk of diabetes at higher age and BMI (Figure 5.3). As treatment decisions should be based on absolute, rather than relative benefit, these results support the targeting of individuals at older age and elevated BMI for BP lowering for prevention of diabetes.³⁰⁰ However, for AF, even absolute incidences per 20 mm higher SBP declined in the highest age and BMI subgroups (with no association between SBP and AF at all at age 81-90). If causal, this would suggest that BP lowering should be targeted towards individuals at lower age and lower BMI. However, similar declines in observational associations with increasing age for ischemic heart disease and stroke have not been observed in meta-analysis of randomized trials.¹²¹ This would suggest that the declines in association for AF and new onset diabetes observed in this thesis are also not likely to be causal. If this is the case, these results would not support the targeting of BP lowering by age or by BMI (except how they influenced baseline absolute risk of AF and new onset diabetes).

8.7 Importance of this thesis for future research

The results presented in this thesis both inform the design of future research and suggest questions for further exploration. The observational and randomized analyses of the relationship between blood pressure and incident AF presented in

Chapter 3 and 4 of this thesis demonstrate that existing randomized trials have been underpowered to detect an effect of blood pressure lowering on AF in populations without overt cardiovascular disease. These results suggest that if a trial or meta-analysis is to conclusively demonstrate that blood pressure lowering reduces the risk of AF by that predicted from the observational analysis presented here (an increase of 21% per 20 mm Hg higher systolic blood pressure), it must accumulate 3457 events (assuming fixed effects weighting) if a 10 mm Hg between arm difference is established, and must accumulate even more events if a lower between arm blood pressure difference is established. Given that such a trial may be prohibitively expensive, a less-costly approach would be to conduct a Mendelian randomization study. The International Consortium for Blood Pressure Genome-Wide Association Studies has previously demonstrated that a genetic risk score associated with elevated blood pressure is also associated with risk of myocardial infarction and risk of stroke³⁰¹, suggesting that such an approach would be feasible. Another possibility would be to conduct an individual patient data meta-analysis using routinely collected adverse event data. Such an approach could be relatively easily conducted by the Blood Pressure Lowering Treatment Trialists' Collaboration, which has collected data from more than twenty blood pressure lowering trials.¹⁰⁰

With regard to blood pressure and risk of new onset diabetes, the analysis presented in Chapter 5 suggests that blood pressure lowering may reduce the risk of diabetes, even among elderly individuals, individuals with high BMI and individuals at low blood pressure levels. Although existing trials, including DREAM²⁹⁴ and NAVIGATOR²⁰⁴, have demonstrated that renin-angiotensin inhibition prevents diabetes, the mean blood pressure prior to treatment in these trials was relatively high (136 mm Hg and 140 mm Hg systolic blood pressure, respectively). As I did not

observe a nadir to at least 115 mm Hg, these results suggest that future trials could test RAS inhibition for prevention of diabetes in the “normotensive” range (115 mm Hg to 130 mm Hg) among individuals at high risk of diabetes (e.g. individuals with metabolic syndrome or pre-diabetes).

The results also suggest future areas of exploration for basic science and translational research. A recent paper demonstrated that inflammatory cytokines are elevated in diabetic pancreatic beta cells, causing oxidation and endoplasmic reticulum stress and leading to impaired insulin synthesis and secretion.⁴³ As elevated blood pressure is associated with an increase in cytokines and other inflammatory markers^{41,42}, these results suggest that inflammation may, in part, mediate the relationship between elevated blood pressure and risk of new onset diabetes. If this hypothesis is suggested to be correct in further animal or genetic studies, trials using anti-inflammatory agents in hypertensive individuals for prevention of diabetes may be warranted.

With regard to the meta-analyses presented on blood pressure lowering in diabetes, these results suggest that future blood pressure lowering trials in diabetes should consider using select populations and endpoints. In this meta-analysis, significant heterogeneity was observed with regard to coronary heart disease and heart failure by baseline and achieved blood pressure, but not stroke. Therefore, future trials should consider testing blood pressure lowering to low levels (<120 mm Hg SBP) among individuals at high risk of stroke and should consider using a primary endpoint of fatal and non-fatal stroke.

8.8 Conclusions

This thesis has, in my opinion, made several important contributions to the existing knowledge of the epidemiology of blood pressure. With regard to the

relationship between blood pressure and atrial fibrillation, this work has demonstrated that blood pressure lowering has greater proportional effects in heart failure populations than populations without prevalent coronary heart disease and that the proportional effects of blood pressure lowering on atrial fibrillation in populations without coronary heart disease is likely to be modest. With regard to the relationship between blood pressure and new onset diabetes, this thesis reliably demonstrates that elevated blood pressure is associated with a higher risk of new onset diabetes. With regard to the relationship between blood pressure and cardiovascular disease in type 2 diabetes, this thesis demonstrates that blood pressure lowering to lower levels than currently recommended in guidelines (SBP <130 mm Hg) will reduce the risk of stroke, renal failure and albuminuria. However, proportional reductions in risk of all-cause mortality and cardiovascular disease are attenuated and non-significant at target SBP < 130 mm Hg in type 2 diabetes. These observations on the relationships between blood pressure, atrial fibrillation, new onset diabetes and cardiovascular disease in type 2 diabetes have not been previously shown, to my knowledge.

Although I view these contributions as important, I would make several changes to the methods if I were to repeat this thesis. Most importantly, I would use Mendelian randomization to estimate the causal effect of blood pressure on new onset diabetes, on atrial fibrillation and on cardiovascular disease in type 2 diabetes, rather than conduct an observational analysis of CPRD. Mendelian randomization exploits the natural random assortment of genetic variants in a population.¹⁰¹ If there is a causal relationship between a biomarker and outcome of interest, a genetic variant that affects levels of the biomarker should also influence risk of the outcome. For example, if elevated systolic blood pressure causes coronary heart disease, a genetic variant that increases systolic blood pressure should also increase the risk of coronary heart

disease. The major advantage to a Mendelian randomization study is that, because genetic variants are randomly assigned at birth within a population, they cannot be influenced by either confounding or reverse causality, unlike a traditional cohort study.¹⁰¹ In a previous study of thirty-two thousand individuals, a 32 single nucleotide polymorphism blood pressure genetic risk score (a collection of genetic variants that influence blood pressure) was significantly associated with incident coronary heart disease and stroke, validating such an approach.³⁰² The causal effect of blood pressure on atrial fibrillation, type 2 diabetes and cardiovascular disease in type 2 diabetes could be estimated using a blood pressure genetic risk score.

The major disadvantage with a Mendelian randomization approach is that any effect of a genetic variant or genetic risk score on an outcome of interest may be due to pleiotropy, that is, a variant causing the outcome outside of the proposed pathway.¹⁰¹ For example, a genetic variant that increases blood pressure may also increase the risk of coronary heart disease through a blood pressure independent mechanism (e.g. inflammation). This off-pathway effect will then be incorrectly interpreted as a causal effect of BP on risk of coronary heart disease. Although the risk of bias due to pleiotropy should not be minimized, several recent methodological developments including MR-Egger regression and median regression allow for the estimation of valid causal estimates in the presence of pleiotropy.³⁰³ Use of Mendelian randomization would thus represent a methodological advancement over the observational methods used in this thesis and in traditional observational epidemiology. Furthermore, UK Biobank has released the genetic data of one hundred and fifty thousand individuals, and will release the genetic data for another three hundred and fifty thousand individuals in the coming months.³⁰⁴ This would allow a Mendelian randomization analysis to be conducted without the need for a proprietary data source.

Despite the methodological limitation of analyses included in this thesis, the results presented here provide important implications for future work. First, this thesis demonstrates the uncertainty around whether blood pressure lowering prevents atrial fibrillation in populations without existing cardiovascular disease. Many individuals, whether due to a family history of atrial fibrillation ¹⁶⁷ or due to the presence of risk factors for atrial fibrillation, may be at high risk of developing atrial fibrillation and wish to prevent it. This thesis demonstrates that further evidence is needed before blood pressure lowering can be recommended as a therapeutic option for AF prevention outside of heart failure. These results suggest that a Mendelian randomization approach using UK Biobank may allow for a demonstration that genetic blood pressure lowering prevents atrial fibrillation. Alternatively, a meta-analysis of routinely collected atrial fibrillation adverse events in the Blood Pressure Lowering Treatment Trialists' Collaboration may provide the requisite power to demonstrate an effect of BP lowering on risk of AF.

Second, and more importantly, this thesis demonstrates the need for another large randomized trial in type 2 diabetes, testing the effect of blood pressure lowering to lower levels than currently recommended in guidelines. Although the primary endpoint of ACCORD was non-significant ⁶², and can be contrasted to the significant finding of SPRINT in non-diabetic populations ¹⁰², this null result may have been due to chance. Replication of ACCORD in a similar sized population to SPRINT (e.g. 9361 individuals) would provide a strong test of whether BP lowering to low levels (SBP <120 mm Hg) reduces the risk of cardiovascular disease in type 2 diabetes.

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