Effect of antihypertensive treatment at different blood pressure levels

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Abstract

Background
High blood pressure is associated with an increased risk of cardiovascular disease and premature death. The shape of association between blood pressure and the risk of cardiovascular events is debated. Some researchers suggest that the association is linear or log-linear, whereas others suggest it is J-shaped. Randomized controlled trials of antihypertensive treatment have been successful in hypertension, but ambiguous in the high normal blood pressure range. Previous systematic reviews have not found any interaction between baseline systolic blood pressure and treatment effect, with beneficial effects at systolic blood pressure levels well below what is currently recommended. These reviews, however, use a method to standardize treatment effects and study weights according to within-trial blood pressure differences that may introduce bias.

Methods
We performed two systematic reviews to assess the effect of antihypertensive treatment on cardiovascular disease and mortality at different blood pressure levels. The first review was limited to people with diabetes mellitus. The second review included all patient categories except those with heart failure and acute myocardial infarction. Both reviews were designed with guidance from Cochrane Collaborations Handbook for Systematic Reviews of Interventions, and are reported according to PRISMA guidelines. We included randomized controlled trials assessing any antihypertensive agent against placebo or any blood pressure targets against each other. Results were combined in random-effects meta-analyses, stratified by baseline systolic blood pressure. Non-stratified analyses were performed for coronary heart disease trials and post-stroke trials. Interaction between blood pressure level and treatment effect was assessed with Cochran’s Q in the first review, and multivariable-adjusted metaregression in the second review.

The third paper builds on data from the second paper, and assesses the effect of standardization according to within-trial blood pressure differences on the results of meta-analyses. We performed non-standardized analyses, analyses with standardized treatment effects, and analyses with standardized treatment effects and standard errors. We compared treatment effect measures and heterogeneity across different methods of standardization. We also compared treatment effect estimates between fixed-effects and random-effects meta-analyses within each method of standardization. Lastly, we assessed the association between number of events and study weights, using linear regression.
Results
Forty-nine trials assessed the effect of antihypertensive treatment in people with diabetes mellitus. Treatment effect on cardiovascular mortality and myocardial infarction decreased with lower baseline systolic blood pressure. Treatment reduced the risk of death and cardiovascular disease if baseline systolic blood pressure was 140 mm Hg or higher. If baseline systolic blood pressure was below 140 mm Hg, however, treatment increased the risk of cardiovascular death by 15 % (0-32 %).

Fifty-one trials assessed the effect of antihypertensive treatment in primary prevention. Treatment effect on cardiovascular mortality, major cardiovascular events, and heart failure decreased with lower baseline systolic blood pressure. If baseline systolic blood pressure was 160 mm Hg or higher treatment reduced the risk of major cardiovascular events by 22 % (95 % confidence interval 13-30 %). If systolic blood pressure was 140-159 mm Hg treatment reduced the risk by 12 % (4-20 %), whereas if systolic blood pressure was below 140 mm Hg, treatment effect was neutral (4 % increase to 10 % reduction). All-cause mortality was reduced if systolic blood pressure was 140 mm Hg or higher, with neutral effect at lower levels.

Twelve trials compared antihypertensive treatment against placebo in people with coronary heart disease. Mean baseline systolic blood pressure was 138 mm Hg. Treatment reduced the risk of major cardiovascular events by 10 % (3-16 %), whereas the effect on mortality was neutral (7 % increase to 11 % reduction).

Standardization of treatment effects resulted in more extreme effect estimates for individual trials. This caused increased between-study heterogeneity, and different results with fixed- and random-effects model. Standardization of standard errors shifted weights from trials with many events to trials with large blood pressure differences. This caused biased overall effect estimates. Standardization of standard errors also resulted in wider confidence intervals, masking the previously increased heterogeneity. This reduced the possibility to find different treatment effects at different blood pressure levels.

Conclusion
The effect of antihypertensive treatment depends on blood pressure level before treatment. Treatment reduces the risk of death and cardiovascular disease if baseline systolic blood pressure is 140 mm Hg or higher. Below this level, treatment is potentially harmful in people with diabetes, has neutral effect in primary prevention, but might offer additional protection in people with coronary heart disease. Standardization should generally be avoided in meta-analyses of antihypertensive treatment. Previous meta-analyses using standardized methods should be interpreted with caution.
## Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>ACEi</td>
<td>Angiotensin-converting enzyme inhibitor</td>
</tr>
<tr>
<td>ARB</td>
<td>Angiotensin-receptor blocker</td>
</tr>
<tr>
<td>BB</td>
<td>Beta-blocker</td>
</tr>
<tr>
<td>CCB</td>
<td>Calcium-channel blocker</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>CVD</td>
<td>Cardiovascular disease</td>
</tr>
<tr>
<td>DALY</td>
<td>Disability-adjusted life-years</td>
</tr>
<tr>
<td>DBP</td>
<td>Diastolic blood pressure</td>
</tr>
<tr>
<td>HR</td>
<td>Hazard ratio</td>
</tr>
<tr>
<td>MACE</td>
<td>Major cardiovascular events</td>
</tr>
<tr>
<td>NNT</td>
<td>Numbers needed to treat</td>
</tr>
<tr>
<td>PICO</td>
<td>Patient Intervention Control Outcome</td>
</tr>
<tr>
<td>RAAS</td>
<td>Renin-angiotensin-aldosterone system</td>
</tr>
<tr>
<td>RR</td>
<td>Relative risk</td>
</tr>
<tr>
<td>SBP</td>
<td>Systolic blood pressure</td>
</tr>
<tr>
<td>SE</td>
<td>Standard error</td>
</tr>
<tr>
<td>TD</td>
<td>Thiazide diuretic</td>
</tr>
</tbody>
</table>
Enkel sammanfattning på svenska

Hjärt-kärlsjukdomar leder till fler dödsfall och fler förlorade levnadsår än någon annan sjukdomsgrupp. Den enskilt viktigaste riskfaktorn som bidrar till hjärt-kärlsjukdomar ur ett befolkningsperspektiv är högt blodtryck. Risken att drabbas av hjärt-kärlsjukdomar minskar om man behandlar högt blodtryck men till vilken nivå blodtrycket skall behandlas är kontroversiell.

Denna avhandling innefattar två systematiska översikter och meta-analysers samt ett arbete som jämför olika sätt att hantera skillnader mellan studier i meta-analysers. De systematiska översikterna sammanställer data från randomiserade kontrollerade studier av blodtryckssänkande behandling. Vår övergripande frågeställning var om effekten av behandling påverkas av blodtrycksnivån innan behandling. Mer specifikt studerades hur behandling påverkade risken att dö eller drabbas av hjärt-kärlsjukdom vid olika blodtrycksnivåer.

Det första arbetet fokuserade på personer med diabetes. För dessa fann vi att blodtryckssänkande behandling minskar risken att dö eller drabbas av hjärt-kärlsjukdom vid nivåer ≥ 140 mmHg. Vi fann ingen nytta, men möjlichen en skadlig effekt av behandling, vid lägre blodtrycksnivåer. Det andra arbetet inkluderade studier oberoende av vilka sjukdomar deltagarna hade. Vi fann att den förebyggande effekten av blodtryckssänkande behandling berodde på blodtrycksnivån. Vid blodtryck > 160 mmHg minskade risken att drabas av hjärt-kärlsjukdomar med 22 % hos de som erhöll behandling. Om blodtrycket var 140-160 mmHg minskade risken med 12 %, men om blodtrycket var < 140 mmHg sågs ingen behandlingseffekt. Hos personer med känd kranskärllsjukdom, och ett medelblodtryck på 138 mmHg, fann vi en något minskad risk för hjärt-kärlhändelser med ytterligare behandling. I det tredje arbetet fann vi att skillnader i resultat mellan olika studier inte kan antas bero endast på olika grad av blodtryckssänkning i studierna. När resultaten standardiserades, som om alla studier hade sänkt blodtrycket lika mycket, ökade nämlichen skillnaderna mellan studierna. Detta resulterade i sin tur i snedvridning av resultaten från meta-analys av standardiserade värden.

Sammanfattningsvis minskar blodtryckssänkande behandling risken att dö eller drabbas av hjärt-kärlsjukdomar om blodtrycket är 140 mmHg eller högre. Vid lägre nivåer är nytan med behandling osäker samtidigt som det finns potentiella risker. Standardisering bör inte användas rutinmässigt vid meta-analys av blodtryckssstudier. Tidigare meta-analysers som använt denna metod bör tolkas med försiktighet.
Background

Importance of high blood pressure

Cardiovascular disease (CVD) is the most common cause of death worldwide, ranking second to infectious diseases only in sub-Saharan Africa (1). The most common forms of CVD are ischemic heart disease and stroke, but this group also includes hypertensive heart disease, aortic aneurysms, peripheral vascular disease and atrial fibrillation/flutter, among others (2).

For ischemic heart disease, nine modifiable risk factors (abnormal lipids, diabetes, hypertension, obesity, psychosocial factors, smoking, alcohol, lack of fruit and vegetable intake and lack of physical activity) have been estimated to account for ≥ 90% of incident cases (3). For stroke, the same factors, with the important addition of cardiac causes (such as atrial fibrillation/flutter and prosthetic valves), similarly account for approximately 90%. High blood pressure is more important as a risk factor for stroke, and particularly haemorrhagic stroke, compared to ischemic heart disease. It is estimated that high blood pressure alone accounts for more than half of strokes globally (4). On the other hand, abnormal lipids, diabetes and psychosocial factors appear more important for development of heart disease.

Overall, high blood pressure is considered the most important modifiable risk factor for death, CVD and loss of disability-adjusted life years (DALYs) (5). The World Health Organization (WHO) defines high blood pressure as ≥ 140/90 mm Hg. It is estimated that more than 800 million people worldwide have a systolic blood pressure > 140 mm Hg, causing more than 8 million deaths annually (6). If the cut-off for higher-than-optimal blood pressure is lowered to 115 mm Hg, the corresponding numbers increase to 3.5 billion people and more than 10 million deaths.

Contemporary data from Västerbotten Intervention Project suggest that one third of 50 year-olds in Sweden have hypertension (7). Additionally, 50% of those with high normal blood pressure in their 50s develop hypertension during the following 10-year period. The prevalence of hypertension is higher in rural areas and in people with low educational level, whereas the prevalence is lower in urban areas and in well educated.
The association between blood pressure and CVD risk

The shape of the association between blood pressure and risk of CVD is a long-standing and ongoing debate. Some suggest that blood pressure is associated with CVD risk in a linear or log-linear pattern, basically meaning that lower blood pressure is associated with lower risk. Others suggest a J-shaped or U-shaped association, where both high and low blood pressure is associated with an increased risk of CVD (Figure 1). The aim of this section is to highlight different perspectives.

Figure 1 – Potential associations between blood pressure and risk of cardiovascular disease

![Diagram](image)

Left panel shows a linear association between blood pressure and CVD risk, with increasing risk at increasing blood pressure. Right panel shows a J-shaped curve with increased CVD risk above and below a certain (unspecified) level.

The lower the better

The Framingham Heart Study was of fundamental importance to the notion that high blood pressure is associated with increased risk of CVD.(8) Through several publications during the 60s and 70s, a graded association appeared.(9, 10) Coronary heart disease was two to three times more common in people with systolic blood pressure above 160 mm Hg compared to below 140 mm Hg. This association occurred across sexes and age groups and could be fitted onto a
linear model (8-10). The graded association was confirmed in the Multiple Risk Factor Intervention Trial (MRFIT) screening cohort, with no evidence of a plateau or increased risk at lower diastolic blood pressure levels down to < 70 mm Hg (11, 12). These, and other observational cohort studies were summarized in collaborative meta-analyses during the 1990s (13-15). Such meta-analyses established the log-linear association between diastolic blood pressure and ischemic heart disease, stroke, and mortality.

The most widely cited paper suggesting a log-linear association between blood pressure and death from CVD is a meta-analysis of observational studies from the Prospective Studies Collaboration (PSC), published in 2002. The PSC analysis included data from 61 studies, with almost one million participants, followed for an average of 13 years. Studies were included if they were observational, provided baseline data on blood pressure, total cholesterol and age, as well as follow-up data on cause and age of death. Pre-existing cardiovascular disease was an exclusion criterion. Importantly, this meta-analysis adjusted for regression-dilution in a way that previous meta-analyses had not. This is discussed further in Box 1, because it has substantial impact on the magnitude of the association between blood pressure and CVD. The main finding of the PSC paper was that increased systolic blood pressure was associated with an increased risk of CVD from values ≤ 115 mm Hg and upwards. There was no sign of a plateau or potential harm in the lowest "usual" blood pressure categories, and patterns were similar for ischemic heart disease, stroke and other vascular causes of death. Diastolic blood pressure showed similar associations down to values ≤ 75 mm Hg, regardless of systolic blood pressure. Further, the authors estimated that 20/10 mm Hg lower systolic/diastolic blood pressure was associated with approximately 50 % lower risk of ischemic heart disease, and > 60 % lower risk of stroke in log-linear regression models. The relative risk reduction was larger in younger patients, whereas the absolute risk reduction was larger in elderly patients.

Several subsequent studies have shown similar associations. The Asia Pacific Cohort Studies Collaboration (APCSC) included > 400 000 participants from 37 cohorts. The authors adjusted for regression-dilution, although in a slightly different way compared to the PSC paper (Box 1). The APCSC authors found approximately 40 % lower risk of stroke and 30 % lower risk of ischemic heart disease for each 10 mm Hg lower systolic blood pressure. Similarly as in the PSC paper, the relative risk reduction was larger in younger patients, whereas absolute risk reduction was larger in elderly patients.
Box 1. Adjustment for regression-dilution

Blood pressure is a physiological parameter that varies from heartbeat to heartbeat, minute to minute, and hour to hour. It is subject to diurnal fluctuations, seasonal patterns and long-term patterns along the life-course. Based on this, it is understandable that sequential blood pressure readings within an individual are subject to substantial variability. This variability will inevitably lead to a phenomenon called "regression to the mean". This means that very high values will be followed by lower ones, whereas very low values will be followed by higher ones in series of measurements.

In several of the referred papers that have found a log-linear association between blood pressure and risk of CVD, the authors try to adjust for regression to the mean. The rationale for this is that regression to the mean would result in exposure misclassification because extreme values are not representative for the average blood pressure over time. This would dilute the association between blood pressure and CVD, hence the expression "regression-dilution bias".

Adjustment for regression-dilution can be done in two principle ways, non-parametrically respectively parametrically. The non-parametric method requires two steps. First, participants are divided into categories based on baseline blood pressure values. Second, mean follow-up blood pressure values for each baseline blood pressure category are calculated from subsequent measurements. Follow-up blood pressure values are higher compared to low baseline values, and lower compared to high baseline values, due to regression to the mean. In the PSC paper, the authors build on this further by fitting mean values during follow-up onto a parametric curve.

In the APCSC paper, authors use parametric methods. Here, baseline blood pressure values are plotted against follow-up blood pressure values in linear regression models. The inverse slope of such a model is named "attenuation factor". The attenuation factor is then simply multiplied by the coefficient of the outcome model. For example, if the correlation between baseline and follow-up values is 0.5, the attenuation factor is 2. If, in the same example, the risk of CVD increases by 20 % for each 10 mm Hg higher baseline SBP, the projected increased risk for each 10 mm Hg "usual" SBP would be 44 % ($1.2^2 = 1.44$).

Independent of which method is used, adjustment for regression-dilution will inflate the magnitude of the association between blood pressure and cardiovascular risk compared to observed values.
In the largest cohort study of blood pressure to date, Rapsomaniki et al. used electronic health records linked to several disease registers in the UK to study the association with 12 different cardiovascular disease manifestations. They included 1.25 million participants followed for 5.2 years. The primary analyses were Cox models stratified by age and sex, whereas secondary analyses were adjusted for smoking status, diabetes, total cholesterol, HDL cholesterol, BMI and previous treatment with antihypertensive drugs. Analyses were not adjusted for regression-dilution; instead baseline blood pressure was calculated as an average value for measurements occurring within two years from study entry. The shape of the association differed between outcomes and age groups. For different ischemic heart disease outcomes (myocardial infarction, unstable angina, respectively stable angina) the association was linear across blood pressure levels and age groups. However, the curve for cardiac death had a tendency towards U-shape, especially in elderly patients. Stroke outcomes showed steep associations between blood pressure and disease risk at high blood pressure levels, but plateaued at different levels for different age groups. The risk of abdominal aortic aneurysms had the weakest association with systolic blood pressure, but was strongly associated with diastolic blood pressure.

More recently, an observational analysis from the Swedish National Diabetes Register (NDR) was published. The NDR holds a wide range of clinical variables, allowing for extensive adjustment for potential confounders. The authors restricted their analyses to people with type 2 diabetes, without previous CVD, and created multivariable adjusted Cox models for mortality and CVD outcomes. They found linear associations between systolic blood pressure and composite CVD, ischemic heart disease, and stroke. For heart failure and all-cause mortality, U-shaped associations were observed, with significantly increased risk of events below 120 mm Hg. Of note, the main analyses were adjusted for treatment with antihypertensive agents, as well as interaction terms for antihypertensive agents and blood pressure levels. Several agents and interaction terms were associated with increased risk of composite CVD. This was interpreted by the authors as if treatment with antihypertensive agents is a marker of risk, but might as well be interpreted as an increased risk of events with treatment at low blood pressure levels.
The J-shaped curve

Already during the 1970s, the notion that lower blood pressure was associated with lower risk of CVD was questioned. (24, 25) Anderson reanalyzed the Framingham data and found that, although a linear association was present for systolic blood pressure, the association between diastolic blood pressure and CVD was U-shaped. (26) During the late 80s, the U-shaped curve was confirmed in several larger follow-up studies. (27-29) Similarly to Anderson, Cruickshank et al. found a linear association for systolic blood pressure but an U-shaped association for diastolic blood pressure. Exploratory analyses found that patients with pre-existing ischemic heart disease accounted for the increased risk of CVD events at low diastolic blood pressure levels. (27) Because the coronary arteries are filled during diastole (contrary to other arterial beds), this led to the hypothesis that low diastolic blood pressure causes cardiac ischemia through decreased perfusion pressure in stenosed coronary arteries. (30) In the early 90s, a systematic review of the current literature concluded that there was a consistent J-curve association between diastolic blood pressure and cardiac events in treated hypertensives. (31)

Not only were the linear association between blood pressure and CVD questioned from an empirical point of view. The methods behind the early landmark meta-analyses supporting the linear association were questioned by a group of mathematicians and statisticians. (32) In another re-analysis of the Framingham data, these authors showed that the linear association found in previous analyses was an artefact due to choice of method. Because the raw data of the association between systolic blood pressure and CVD had a J-shape or reversed L-shape, they were better represented by a logistic-spline model, allowing for different slopes at different blood pressure levels. This model found an increased risk of events at systolic blood pressure levels > 140-160 mm Hg for different age categories but no association thereunder. The previously used log-linear model was estimated to exaggerate the risk at the most common blood pressure levels, leading to overtreatment of a large number of people, whereas it underestimated the risk at the extreme ends of the curve.

On the other hand, supporters of the linear association questioned the J-curve, suggesting it was an artefact due to confounding. (33) Because the J-curve was predominantly seen in patients with coronary artery disease or treated hypertension, it was hypothesised that coronary artery stenoses and left ventricular hypertrophy would be the cause of both low blood pressure (through left ventricular dysfunction) and increased risk of clinical events. An individual-patient data meta-analysis from the INDANA (INdividual Data ANalysis of Anti-hypertensive intervention trials) project found a J-shaped association between both systolic and diastolic blood pressure and cardiovascular as well as non-cardiovascular mortality. (34) Because it is pathophysiologically difficult to
explain how low blood pressure could cause non-cardiovascular events, this was taken as a sign that low blood pressure was a marker of bad health in general, and thus the J-curve was dismissed.

In recent years, however, the J-shaped curve has seen a revival.(35) Several post-hoc observational analyses from randomized controlled trials demonstrated a J-shaped association between systolic and/or diastolic blood pressure and several mortality and CVD outcomes. Common to these analyses are that they:

1) Predominantly included patients with previous coronary heart disease
2) Included, and adjusted for, several additional covariates (including heart failure, arrhythmias and renal function), compared to most analyses showing log-linear associations.
3) Excluded patients with short life expectancy due to non-cardiac causes of death, such as cancer or dementia.

First, analyses from International Verapamil-Trandolapril Study (INVEST), found a J-shaped association between diastolic blood pressure and the composite endpoint of all-cause death, myocardial infarction and stroke.(36) The association interacted with coronary revascularization, so that patients receiving revascularization tolerated low diastolic blood pressure better than those who did not. This was taken as support for the hypothesis that low blood pressure might be especially detrimental in people with coronary artery stenoses. Second, analyses from the Systolic Hypertension in Europe (Syst-Eur) trial generally found no J-curve for diastolic blood pressure and cardiovascular mortality, with the notable exception of patients with previous coronary artery disease randomized to treatment.(37) Third, Sleight and colleagues used data from Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET) to assess how the risk of cardiovascular death, myocardial infarction, stroke, heart failure, and a composite of these outcomes, varied depending on how systolic blood pressure changed during follow-up, for different baseline blood pressure levels.(38) Decreased blood pressure during follow-up was associated with decreased risk of the composite outcome if baseline systolic blood pressure was ≥ 143 mm Hg, but increased risk if baseline systolic blood pressure was < 130 mm Hg. Common findings for all analyses described above were that the risk for stroke did not increase at low blood pressure levels, demonstrating target organ heterogeneity compared to coronary heart disease. Importantly, the number of myocardial infarctions and cardiovascular deaths exceeded, by far, the number of strokes at low blood pressure levels.
The findings from ONTARGET were further built on in a recent publication, combining it with data from Telmisartan Randomised Assessment Study in ACE iNtolerant participants with cardiovascular Disease (TRANSCEND). The combined cohorts from ONTARGET and TRANSCEND include > 30,000 patients from 40 different countries followed for 5 years. In this publication, the authors studied baseline blood pressure, mean follow-up blood pressure, and time-updated blood pressure, and their associations with several CVD outcomes. They found that mean follow-up blood pressure was the best predictor of clinical events, showing clear J-shaped associations for combined cardiovascular events, cardiovascular mortality, as well as all-cause mortality. Further, a blood pressure reduction during follow-up was associated with increased risk of combined CVD, cardiovascular mortality, all-cause mortality and heart failure if baseline systolic blood pressure was < 140 mm Hg; and increased risk for myocardial infarction if baseline SBP was < 120 mm Hg.

In 2016, two additional studies added important findings to the J-curve argument. Vidal-Petiot et al. used data from the prospective observational longitudinal registry of patients with stable coronary artery disease (CLARIFY) to study the association between time-updated systolic and diastolic blood pressure and risk of myocardial infarction, stroke, cardiovascular death, and a composite of these outcomes. As previous post-hoc analyses from RCTs, the authors found a J-shaped curve for myocardial infarction, cardiovascular death and the composite cardiovascular outcome, but not for stroke. Importantly, the CLARIFY investigators had access to echocardiographic data for a large proportion of participants. This made it possible to reliably exclude patients with heart failure and adjust for left ventricular ejection fraction. Because one of most frequent arguments against the J-curve has been that left ventricular dysfunction causes low blood pressure and not vice versa (i.e. reverse causality), this was paramount.

Secondly, McEvoy et al., used data from the Atherosclerosis Risk In Communities (ARIC) cohort to assess temporality between low blood pressure, subclinical myocardial injury, and clinical events. Restricting the analyses to participants without previous cardiovascular disease, they found that baseline DBP < 80 mm Hg was progressively associated with increased high-sensitivity troponin T levels (as a marker of subclinical myocardial damage), both cross-sectional at baseline and prospectively during follow-up. This was in turn associated with an increased risk of coronary heart disease and all-cause mortality, but not stroke. The findings from ARIC add another piece in the puzzle, suggesting that low blood pressure precedes myocardial damage, which in turn precedes clinical events.
Summary
Observational analyses of the association between blood pressure and cardiovascular risk have been rather ambiguous. Some argue for a linear or log-linear association, whereas others have found a J-shaped or U-shaped curve. Although the log-linear association has been given most attention during the last 15 years, the scientific basis for this seems questionable.

First of all, the observed log-linear association hinges on choice of statistical model. Linear regression allows only for linear associations. Logistic spline models, used in several of the analyses finding J-shaped associations, allow for different associations, including both linear and U-shaped forms. Secondly, the quality of data is generally better in analyses finding a J-shaped curve compared to those finding a linear curve. In the PSC paper, most of the included participants had only one blood pressure measurement, and analyses were adjusted for very few covariates. In post-hoc analyses from randomized controlled trials, and the analyses from CLARIFY and ARIC, blood pressure is measured several times for a more reliable estimate, and several additional cardiovascular risk factors are included as covariates in the adjusted models.

The debate about the J-shaped curve always comes back to the potential problem with reverse causality. Several recent observational analyses have properties that make reverse causality less likely, however. This includes echocardiographic data to adjust for left ventricular dysfunction, and temporal trends suggesting low blood pressure precedes subclinical and clinical myocardial injury.

The arguments outlined above illustrate the problems with using observational data for causal inference. Reverse causality and confounding always lingers in the dark. Based on the limitations of observational studies, there is general consensus that treatment recommendations should be based on randomized controlled trials. If several similar trials exist, these should be summarized in systematic reviews and meta-analyses. The field of hypertension research is probably one of the most explored fields in medicine with respect to RCTs. Thus, although observational studies were crucial to first establish the link between high blood pressure and cardiovascular disease, they should no longer be the basis for treatment recommendations.
Antihypertensive treatment to prevent CVD

Proof of concept
The first randomized controlled trial to demonstrate that blood pressure lowering treatment reduces the risk of CVD was published in 1967. (45) 143 middle-aged men with baseline DBP 115-129 mm Hg (mean SBP/DBP: 186/121 mm Hg) were randomized to receive combination therapy with three antihypertensive agents or placebo. Blood pressure fell by 43/30 mm Hg in the treatment group, whereas it was unaffected in the placebo group. Results were striking, with 27 clinical events in the placebo group and two events in the treatment group, yielding a remarkable numbers needed to treat (NNT) of 3.

From this point, the issue was no longer if blood pressure lowering treatment was beneficial, but to whom this applied. Several randomized clinical trials found that results were applicable at lower DBP values (46), in cohorts including women (47), and progressively older patients (48, 49). Whereas treatment had previously been based on diastolic blood pressure values, the publication of the Systolic Hypertension in the Elderly Program (SHEP) provided causal evidence to treat isolated systolic hypertension (Table 1). (50)

Table 1 – Major placebo-controlled trials breaking new ground for antihypertensive therapy

<table>
<thead>
<tr>
<th>Study</th>
<th>Pats</th>
<th>Age (years)</th>
<th>Sex (% female)</th>
<th>Intervention</th>
<th>Baseline SBP/DBP mm Hg</th>
<th>Achieved SBP/DBP mm Hg</th>
<th>New ground</th>
</tr>
</thead>
<tbody>
<tr>
<td>VA-1 (1967)</td>
<td>143</td>
<td>51</td>
<td>-</td>
<td>HCTZ + reserpine + hydralazine</td>
<td>186/121</td>
<td>143/91</td>
<td>Effect of tx.</td>
</tr>
<tr>
<td>HDFP (1979)</td>
<td>10,940</td>
<td>51</td>
<td>46</td>
<td>Chlorthalidone +/- reserpine +/- hydralazine</td>
<td>159/101</td>
<td>Not reported</td>
<td>Women</td>
</tr>
<tr>
<td>EWPHE (1985)</td>
<td>840</td>
<td>72</td>
<td>70</td>
<td>HCTZ + triamterene +/- methyldopa</td>
<td>182/101</td>
<td>151/86</td>
<td>Elderly (&gt;60y)</td>
</tr>
<tr>
<td>SHEP (1991)</td>
<td>4,736</td>
<td>72</td>
<td>57</td>
<td>Chlorthalidone +/- atenolol</td>
<td>170/77</td>
<td>143/68</td>
<td>ISH</td>
</tr>
<tr>
<td>STOP (1991)</td>
<td>1,627</td>
<td>76</td>
<td>63</td>
<td>HCTZ + amiloride or 1 of 3 BBs</td>
<td>195/102</td>
<td>167/87</td>
<td>Elderly (&gt;75y)</td>
</tr>
</tbody>
</table>

SBP = systolic blood pressure. DBP = diastolic blood pressure. HCTZ = hydrochlorothiazide. BB = beta-blocker. HT = hypertension. ISH = isolated systolic hypertension.
Blood pressure treatment goals

The first official blood pressure guidelines were published by the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC) in 1977.(51) These recommended initiation of blood pressure lowering treatment if diastolic blood pressure was ≥ 105 mm Hg, based on the Veteran Affairs trials (VA-1 and VA-2, table 1). This threshold was reduced to ≥ 95 mm Hg in 1984, as a reaction to HDFP and the Australian National Blood Pressure Study(52), which both used diastolic blood pressure ≥ 95 mm Hg to include patients.(53) In these guidelines, a systolic blood pressure treatment threshold of 160 mm Hg was also introduced, based on observed systolic blood pressure values in the previous studies. The JNC 5 and the joint International Society of Hypertension/World Health Organization guidelines further lowered treatment thresholds to 140/90 mm Hg in 1993. (54, 55) The rationale for this was mainly benefit from DBP-guided trials and extrapolation of systolic values corresponding to diastolic values for which treatment was beneficial.

The first major clinical trial assessing different blood pressure treatment goals was the Hypertension Optimal Treatment (HOT) study published in 1998.(56) The HOT investigators randomly assigned 18 790 participants with diastolic blood pressure 100-115 mm Hg to treatment targets ≤80, ≤85 or ≤90 mm Hg, using a felodipin-based regimen. This resulted in marked blood pressure reductions in all groups, with small between-group differences. The effects on clinical outcomes were moderate, with only myocardial infarction showing a borderline trend towards benefit. In the subgroup of participants with diabetes mellitus at baseline, however, treatment appeared clearly beneficial with 50 % relative risk reduction for composite major cardiovascular events in the ≤80 mm Hg group compared to the ≤90 mm Hg group. Also, pre-specified observational analyses of event-rate in relation to achieved blood pressure found that the risk of cardiovascular events was lowest if blood pressure was 138.5/82.6 mm Hg. Despite the overall neutral results, HOT was interpreted by the investigators as supporting treatment to levels < 140/85 mm Hg.

During subsequent years several smaller trials comparing different blood pressure targets were published. In people with diabetes mellitus, the Appropriate Blood Pressure Control in Diabetes Trial (ABCD) and the UK Prospective Diabetes Study (UKPDS) found that lower blood pressure targets were associated with less microvascular and macrovascular events. (57-59) In the African American Study on Kidney Disease and Hypertension (AASK), however, a lower blood pressure target was not associated with better renal outcomes in patients with non-diabetic renal disease. (60)

With previously noted exceptions, focus shifted around the millennium, from trials trying to establish blood pressure treatment levels and goals, to trials
trying to widen the indication for blood pressure lowering agents, and trials comparing new agents against older ones. For example, the Heart Outcomes Prevention Evaluation Study (HOPE) randomized 10,000 participants with previous cardiovascular disease or very-high cardiovascular risk to ramipril or placebo. The benefit of ACE-inhibitors was already established for patients with heart failure and hypertension (62, 63), and the investigators hoped to widen this to non-hypertensive non-heart failure high-risk patients in general. Similar large-scale trials were The EUROpean trial On reduction of cardiac events with Perindopril in stable coronary Artery disease (EUROPA) and Prevention of Events with Angiotensin Converting Enzyme Inhibition (PEACE) for coronary artery disease, and the Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) Study for stroke. (64-66) Such trials have previously been called “non-intentional” blood pressure lowering trials. (67) However, subsequent systematic reviews have shown that there are no important blood pressure-independent effects on clinical outcomes for any of the major antihypertensive drug classes. (68, 69) Thus, “non-intentional” blood pressure lowering trials likely contribute with important information regarding the effect of blood pressure lowering.

In 2003, both European and North American guidelines began recommending lower blood pressure goals in high-risk patients and people with diabetes mellitus (70), respectively people with diabetes mellitus and/or chronic kidney disease. (71) Reasons for this recommendation were:

1. The large treatment benefit in the diabetic subgroup of HOT
2. Reduced risk of stroke in the normotensive ABCD trial
3. Beneficial effect in normotensive high-risk patients, such as those included in HOPE
4. No interaction between baseline blood pressure and treatment effect in The perindopril protection against recurrent stroke study (PROGRESS) with very high cardiovascular risk
5. Strong epidemiological evidence for lower cardiovascular risk down to blood pressure levels < 115/75 mm Hg (PSC-02)

Consensus was that, although no trial had compared goals below 140/90 mm Hg against above 140/90 mm Hg, subgroup analyses from randomized controlled trials and recent epidemiological findings coherently suggested that treatment was likely to be beneficial. These recommendations prevailed in the 2007 update of the European guidelines. (72)

In 2009, Zanchetti and colleagues questioned the recommendations to apply lower goals in people with diabetes mellitus. (73) They concluded that most of the randomized clinical trials that had shown benefit in people with diabetes
achieved blood pressures of around 140 mm Hg in the intensive treatment arm; and the only trial achieving a systolic blood pressure < 130 mm Hg (ABCD-N) was only partly positive. Moreover, a plot of achieved blood pressures against cardiovascular risk reductions visualized a marked decrease in effect < 140 mm Hg, and no effect around 130 mm Hg.

**Antihypertensive drug classes**

Early trials of antihypertensive treatment generally assessed thiazide diuretics (TD) against placebo. These were often combined with non-selective adrenergic antagonists, vasodilators or potassium-sparing agents. Beta-blockers (BB) were first assessed as antihypertensive agents in clinical outcome trials in the 1980s, although available as antianginal drugs since the mid 1960s. Following beta-blockers came angiotensin converting enzyme inhibitors (ACEi) and angiotensin-receptor blockers (ARB), targeting the renin-angiotensin-aldosterone system (RAAS); and calcium-channel blockers (CCB) with direct effect on peripheral vasculature.

Ever since beta-blockers were launched as antihypertensive agents, randomized controlled trials have compared different drugs or drug classes against each other. The goal of such trials have often been to compare newer drugs against older ones, to assess potential blood pressure independent effects on clinical outcomes, or improved safety or tolerability. Comparative trials have later been summarized systematic reviews and meta-analyses.

Systematic reviews reveal some differences between drug classes for particular clinical outcomes, although no particular drug class outperform others in general (68, 69). Consistently, beta-blockers perform worse than other agents with respect to stroke, whereas CCBs reduce the risk of stroke compared to other agents (69, 74, 75). No drug class differs significantly compared to the others for prevention of coronary heart disease, including a neutral effect with RAAS inhibitors in patients with established coronary artery disease without heart failure (74, 76, 77). Diuretics are better, and CCBs are worse, for heart failure prevention (69, 74, 78), although some analyses suggest that the inferiority of CCBs are due to biased study design in some trials (79). For composite cardiovascular events and all-cause mortality, some analyses suggest that beta-blockers might be less protective than other agents (74).

The results from randomized controlled trials and systematic reviews have led to the notion that diuretics, ACE-inhibitors, ARBs and CCBs are overall equally effective, and any of these drug classes may be used as first-line therapy (80-82). For this thesis, focusing on treatment effect at different blood pressure levels, we have not made a difference to different antihypertensive agents.
The ACCORD trial
The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial included > 10 000 patients with type 2-diabetes, aiming to assess the effect of intensive glucose lowering, intensive blood pressure lowering, and lowering of triglycerides, on major cardiovascular events.(83) The trial had a 2 x (2+2) design, where the full cohort was randomized to intensive versus standard glucose lowering (84), half the cohort was randomized to intensive versus standard blood pressure lowering (85), and half the cohort was randomised to simvastatin + fenofibrate or simvastatin + placebo.(86)

The blood pressure arm of the trial compared the effect of a systolic blood pressure goal < 120 mm Hg to a systolic blood pressure goal < 140 mm Hg.(85) The investigators included high-risk patients with either previous cardiovascular disease or multiple cardiovascular risk factors. Mean age at baseline was 62 years, mean systolic and diastolic blood pressure was 139/77 mm Hg, median duration of diabetes was 10 years, and mean HbA1c was 8.3 %.

During follow-up, the mean number of antihypertensive medications was 3.4 in the intensive treatment group and 2.1 in the standard treatment group. This resulted in average systolic/diastolic blood pressure values 119/64 respectively 133/71 mm Hg, with a mean difference between groups of 14.2/6.1 mm Hg. The effect on the primary composite outcome of cardiovascular death, myocardial infarction and stroke was neutral (208 versus 237 events, hazard ratio (HR) 0.88, 95 % confidence interval (CI) 0.73-1.06, p=0.20). The same was true for all pre-specified secondary outcomes, including all-cause and cardiovascular mortality, myocardial infarction and heart failure, with the notable exception of stroke (36 versus 62 events, HR 0.59 95 % CI 0.39-0.89). Although nominally significant, the stroke reduction was only 0.2 % per year in absolute terms, yielding NNT = 100 for the overall five-year follow-up.

The results from ACCORD were generally regarded as negative, although some have argued that the trial was underpowered due to lower event-rate than expected.(87) An important result, also weighing against lower goals, was the observation that the number of serious adverse events attributed to treatment increased by more than two-fold in the intensive treatment group compared to the standard treatment group.(85) The absolute risk increase for serious adverse events (2.0 %) was almost twice as large as the total reduction for stroke (1.1 %). In addition, not classified as serious adverse events, the risks of hypokalaemia, hyperkalaemia, and progression to estimated glomerular filtration rate (eGFR) < 30 ml/min/1.73 m² were also doubled.
**Post-ACCORD**

ACCORD provided the best available evidence so far for more versus less aggressive antihypertensive treatment below 140 mm Hg. Due to the overall neutral effect and the increased risk for serious adverse events, guidelines were, for the first time, revised in a more conservative direction. Instead of individualized blood pressure goals depending on comorbidities, focus shifted towards getting all patients < 140/90 mm Hg. (80-82, 88)

Since the publication of ACCORD and the revision of guidelines, three major trials adding important information regarding blood pressure goals have been published.

**SPS3**

First, the Secondary Prevention of Small Subcortical Strokes (SPS3) trial randomized 3020 patients to a systolic blood pressure goal < 130 mm Hg compared to 130-149 mm Hg. (89) Mean age at baseline was 63 years and mean baseline blood pressure was 143/79 mm Hg. The intensive treatment group achieved a systolic blood pressure of 127 mm Hg and the less intensive treatment group achieved a systolic blood pressure of 138 mm Hg. The primary outcome was any recurrent stroke, and secondary outcomes were myocardial infarction, death, and major vascular events. Neither the primary or secondary outcomes were significantly reduced by treatment, although there was a tendency towards benefit for stroke (HR 0.81, 95 % CI 0.64-1.03, p=0.08). The authors interpreted this as if treatment to < 130 mm Hg was likely beneficial in patients with previous lacunar infarction.

**SPRINT**

Second, the Systolic Blood Pressure Intervention Trial (SPRINT) randomized 9361 patients with high cardiovascular risk to a systolic blood pressure < 120 mm Hg compared to < 140 mm Hg. (90) Important exclusion criteria in SPRINT were diabetes mellitus and previous stroke, because these patient categories had already been studied in ACCORD and SPS3. Mean age at baseline was 68 years and mean baseline blood pressure was 139.7/78.1 mm Hg. The intensive treatment group in SPRINT received on average 2.8 medications compared to 1.8 medications in the less intensive treatment group. This resulted in a marked blood pressure reduction in the intensive treatment group, with mean systolic blood pressure 121.5 mm Hg, compared to 134.6 mm Hg in the less intensive group, during follow-up. Contrary to ACCORD and SPS3, SPRINT achieved a significant risk reduction for its primary composite outcome of acute coronary syndrome, heart failure, stroke and cardiovascular death (HR 0.75, 95 % CI 0.64-0.89, p<0.001) as well as for all-cause mortality (HR 0.73, 0.60-0.90, p=0.003). For this reason, SPRINT was stopped preterm after 3.26 years.
Although initially hailed as definitive confirmation of the lower the better hypothesis (91), critical voices soon emerged, questioning the validity of the SPRINT findings. (92) Most notably, SPRINT used a method to measure blood pressure that differed compared to previous randomized controlled trials. In SPRINT, blood pressure was measured using a self-operated automatic measurement device, with no attending personnel. This method results in, on average, 10-20 mm Hg lower blood pressure values compared to attended office measurements. (93-95) Indeed, data from the SPRINT ambulatory blood pressure sub study confirmed that mean ambulatory daytime systolic blood pressures were 126.5 mm Hg respectively 138.8 mm Hg in the intensive and standard treatment groups. (96) These values were 7 respectively 3 mm Hg higher compared to clinic blood pressure values, and correspond to values below versus above the currently recommended ambulatory blood pressure goal. (97, 98) Additional potential problems with SPRINT are listed in Table 2.

Table 2 – Characteristics of SPRINT and associated potential biases

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Potential bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unattended measurement</td>
<td>BP values 10-20 mm Hg lower compared to other trials/clinical practice</td>
</tr>
<tr>
<td>Early termination due to benefit</td>
<td>Overestimation of treatment effect</td>
</tr>
<tr>
<td>More frequent visits in the intensive treatment group</td>
<td>Performance bias</td>
</tr>
<tr>
<td>Cardiovascular and non-cardiovascular deaths contributed equally to all-cause mortality reduction</td>
<td>Treatment not likely to affect non-cardiovascular deaths, large random component?</td>
</tr>
<tr>
<td>Down titration of medications in less intensive treatment group.</td>
<td>Previous evidence suggesting dangers of discontinuing antihypertensive treatment (99)</td>
</tr>
<tr>
<td>Diuretics first-line treatment, compared to less prevalent at baseline</td>
<td>Blood pressure independent effect of diuretics on heart failure? (92)</td>
</tr>
</tbody>
</table>

SPRINT = Systolic Blood Pressure Intervention Trial. BP = blood pressure.
Further fuelling the debate about blood pressure treatment goals, the Heart Outcomes Prevention Evaluation 3 (HOPE-3) study was published in 2016. (100-102) HOPE-3 aimed to evaluate blood pressure lowering treatment and cholesterol lowering treatment in people without previous cardiovascular events and intermediate cardiovascular risk. 12 705 participants were randomized to either candesartan-hydrochlorothiazide 16/12.5 mg fixed combination or placebo, and rosvastatin 10 mg or placebo, in a factorial 2x2 design. Mean age at baseline was 66 years, mean blood pressure was 138/82 mm Hg and mean LDL cholesterol was 3.2 mmol/l. Interestingly, while rosuvastatin reduced the risk of the composite primary outcome cardiovascular death, myocardial infarction and stroke by 25 % (102), the effect of antihypertensive treatment was neutral. (101) In pre-specified subgroup analyses by baseline blood pressure tertiles, candesartan/hydrochlorothiazide reduced the risk of the primary outcome in those with highest baseline systolic blood pressure (>143.5 mm Hg), while there was a non-significant tendency towards harm in those with baseline systolic blood pressure < 131.5 mm Hg (p=0.02 for trend). Such an interaction was not present for cholesterol-lowering treatment in relation to baseline LDL tertiles.

Summary

During the last half-century, hundreds of trials testing the effect of antihypertensive treatment have been published. These have established, with great certainty, that treatment to reduce high blood pressure decreases the risk of death and cardiovascular disease. Several drug classes are available to achieve this. These are safe, effective, and well tolerated. To what level blood pressure should be treated remains elusive, however. Several trials, in different populations, testing different interventions, with different measurement strategies have tried to establish the optimal treatment target. These have come to somewhat conflicting results. In this situation, it is crucial to take into consideration all available evidence, and to weight different trials against each other in a structured way. This is why systematic reviews and meta-analyses are crucial to make informed decisions about antihypertensive treatment.
**Systematic reviews and meta-analyses**

The publication of clinical research has the potential to influence patient care. Historically, however, there has been a huge time lag between findings from clinical trials and change in clinical guidelines. This is best illustrated by the example of thrombolytic therapy for myocardial infarction. The cumulative evidence suggested with high certainty that thrombolytic therapy reduced mortality already in the early 70s. It was not until the early 80s that thrombolytic therapy emerged as recommended treatment in reviews and textbooks, and until the late 80s some reviews still advised against it. It is likely that the introduction of thrombolytic therapy was substantially delayed because the available evidence was not summarized in a structured and quantitative way.

In all branches of science, narrative reviews are used to summarize available evidence. The focus of such reviews, the methods used to search and critically appraise the literature, and the presentation of results and conclusions, differ widely however. The conclusions from narrative reviews depend on who authored it, and reviews addressing the same question often come to different conclusion. In fields with many publications it is often possible to selectively cite references that support ones view, while omitting other, i.e. "cherry picking".

To counteract selective citing, biased assessment of the evidence, and unfounded conclusions, an alternative approach was developed. The systematic review aims to summarize all available evidence concerning a specific clinical question. Through rigorous and transparent methodology, the goal is to minimize bias. Systematic reviews often include quantitative summaries of the results of included studies, called meta-analysis (table 3).

**Table 3 – Comparison of narrative and systematic reviews**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Narrative review</th>
<th>Systematic review</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Question</strong></td>
<td>Usually broad or not specified</td>
<td>Specific and clearly specified</td>
</tr>
<tr>
<td><strong>Literature search</strong></td>
<td>Usually limited or not specified</td>
<td>Comprehensive and clearly specified</td>
</tr>
<tr>
<td><strong>Study selection</strong></td>
<td>Not pre-specified, often based on findings rather than design</td>
<td>Pre-specified criteria, based on study design</td>
</tr>
<tr>
<td><strong>Quality assessment</strong></td>
<td>Usually not addressed or selectively addressed</td>
<td>According to pre-defined criteria, for all included trials</td>
</tr>
<tr>
<td><strong>Synthesis</strong></td>
<td>Qualitative</td>
<td>Quantitative</td>
</tr>
</tbody>
</table>
The systematic review process
The systematic review process is best described in the Cochrane Collaborations Handbook for Systematic Reviews of Interventions. The general structure of the systematic review is outlined here, with specifics for the systematic reviews included in this thesis described in the Methods section.

Research question
The systematic review, just like any other scientific study, starts with a focused research question. For clinical systematic reviews, this should preferably specify patient population, intervention, comparator, and outcomes that will be assessed, often summarized by the acronym Patient Intervention Control Outcome (PICO).

Eligibility criteria
Before commencing the literature review, authors should specify what kind of study design best answers the research question. This will preferably be randomized controlled trials for systematic reviews of interventions, but might be observational studies for reviews of harm, or if randomized controlled trials are not available.

Additional inclusion and exclusion criteria, based on the previously specified PICO, should also be decided. For example, in the case of antihypertensive treatment one needs to specify if only studies comparing different targets should be included, or if studies comparing treatment against placebo also contribute with information about the effect of blood pressure lowering. Another example relating to blood pressure lowering is comorbidities. Many antihypertensive agents are also used to treat heart failure, with blood pressure independent mechanisms of action. Thus inclusion of heart failure trials in meta-analyses of blood pressure lowering will bias their results.

Analytical approach
Preferentially, a statistical analysis plan should be specified to minimize the risk of data dredging. This should include choice of statistical method, any pre-planned subgroup or sensitivity analyses, and how to handle heterogeneity and bias. The statistical analysis plan will also be helpful in deciding which characteristics to extract from the included trials.

Literature search
The literature search in systematic reviews should aim to achieve as high sensitivity as possible, i.e. find all relevant data. This is crucial to maximize the
statistical power and minimize possible bias. Highly sensitive strategies often come at the expense of low specificity. The aim of the literature search should be held in mind both when considering the sources for literature and actual search terms. It is generally not considered adequate to only search PubMed for randomised controlled trials. Additional electronic sources include but is not limited to Cochrane Central Register or Controlled Trials (CENTRAL), and Excerpta Medica database (EMBASE), as well as clinical trial registers such as ClinicalTrials.gov. Additional caveats are not to restrict the literature search to English to reduce the risk for "tower of Babel bias", and not to restrict to study types by filter to avoid bias due to misclassification.

The PICO specified previously might be helpful in formulating search terms. However, many different forms for each term often needs to be included due to inconsistent terminology, and Medical Subject Headings (MeSH) terms could be included to expand the search further down the MeSH tree. It might also be prudent to remove some search terms compared to the PICO, especially if the review concerns certain subpopulations or specific treatment strategies that may be included in trials although not mentioned in the title or abstract.

Study selection
Study selection should be based on pre-specified criteria, and not subjective opinions or study results. Due to the low specificity of comprehensive searches, it is often necessary to screen the search results before going through all records in detail. Usually this is performed in several steps. First, titles are screened to remove apparently irrelevant publications. Second, abstracts are screened for exclusion criteria or trials obviously not fulfilling the inclusion criteria. Third, all records potentially fulfilling the inclusion criteria are retrieved in full text. Importantly, two authors should always conduct the study selection process independently. This is both to reduce the risk of careless mistakes, and because assessments according to eligibility criteria vary substantially between investigators, despite clearly defined criteria. The study selection process is often depicted in a flow chart, showing the number of records discarded at each step, and reasons for exclusion.

Data extraction
When the final decision on inclusion has been made, it is time to extract data from all included trials. This includes data needed to perform analyses, descriptives of the included studies, and information needed to assess the risk of bias. Data extraction should also be done by two authors independently, for similar reasons as stated above.
Risk of bias/quality assessment

One fundamental step in the systematic review process is to critically appraise each study included in the review. Since the dawn of systematic reviews there has been several quality scores and scales to help quantify this assessment. However, the agreement between such scores and scales is poor (108), and none of these are currently recommended in Cochrane Collaborations handbook. Instead, a seven-domain risk of bias assessment tool is recommended.(109) This tool covers aspects of trials that, when failing, have been associated with study outcomes in empirical studies.(110) The risk of bias assessment tool covers:

- Random sequence generation
- Treatment allocation concealment
- Blinding of participants and personnel
- Blinding of outcome assessors
- Incomplete outcome data
- Selective outcome reporting
- Other sources of bias; e.g. early stopping, baseline imbalance or fraud

High risk of bias could be handled in different ways, but should always be considered in the final analysis. Recommended ways to handle trials at high risk of bias include exclusion from all analyses, exclusion in sensitivity analyses or stratification/metaregression exploring associations between risk of bias and effect estimates.

Data analysis

Depending on the review question and the type of studies included in the review, data can be analyzed in different ways. Most commonly, results are summarized in meta-analysis (see below), which is a quantitative method to derive weighted mean results across trials. If data are not presented quantitatively in original studies, or if high risk of bias or large between-study heterogeneity makes meta-analysis unsuitable, data may be presented descriptively with a qualitative analysis.

Publication bias

Many research studies are never published. If this correlates with study results, it will bias overall assessments of the published literature. Studies with negative results tend to be published less frequently (111), in less accessible journals (112), and with a significant time-lag compared to those with positive results (113). This potential problem can be assessed in meta-analyses using funnel plots. Funnel plots assess the correlation between study precision and treatment effect. Large trials with high precision should have treatment effects close to the average treatment effect in the meta-analysis. Smaller trials should by chance differ more from the average effect. If smaller trials systematically deviate from
the average treatment effect (most often towards benefit), this may suggest that negative trials have not been published. If such asymmetry is suspected, it could further be assessed using one of several available statistical tests (114, 115). Of importance, lack of asymmetry does not exclude publication bias. Judgements regarding potential bias should be based on plots, tests and expert knowledge.

**Meta-analysis**
Meta-analysis is the common name of several statistical methods used to summarize effect estimates from individual studies. (116) The basic principle is that study effects are combined in a weighted manner, where each study contributes proportionally to its statistical uncertainty. The input into meta-analyses thus includes one measure of effect and one measure of uncertainty, alternatively raw numbers so that the software calculates these measures itself. This section covers meta-analysis of binary outcomes. Notably, it is also possible to perform meta-analysis of continuous outcomes.

The simplest form of meta-analysis is the fixed-effects inverse-variance method. Here, the weight assigned each trial is proportional to the inverse variance of the logarithm (for purpose of normal distribution) of the relative risk:

\[
\text{Absolute weight} = \frac{1}{\text{variance}} \quad \frac{1}{SE^2}
\]

\[
\text{Relative weight} = \frac{\text{Absolute weight}}{\text{sum of all absolute weights}}
\]

The fixed-effects model assumes that the results from the included studies deviate from a common true effect only by chance. In other words, this method should not be used if the included studies can be expected to differ to some extent, based on clinical or methodological differences. This assumption rarely holds in clinical medicine.

In contrast to the strong assumption underlying the fixed-effects model, random-effects models do not assume the underlying results to be similar in all included studies. (116) This is reasonable in most clinical situations, where study results can be expected to vary for different reasons (aside from chance). Random-effects models assign weights taking both within-study variance and between-study variance into account, thereby creating more balanced weights across trials. This method is generally recommended, but might create what is known as small-study bias if the results from small studies differ systematically from those of larger studies (compare Publication bias, previous page). (107) In this case, smaller trials are given disproportionally large weight, making overall effect estimates non-representative of the underlying data.
Between-study differences in results can be quantified through different heterogeneity measures. Most commonly used is the $I^2$ statistic. This measure quantifies how much of between-study variance that cannot be explained by chance alone. As a rule of thumb, $I^2 < 25\%$ is regarded as low, $25-50\%$ is regarded as moderate, and $> 50\%$ is regarded as high. This comes with several caveats, however. Most importantly, $I^2$ is not sensitive, and might not detect heterogeneity if effect estimates for the included trials are uncertain. It is also important to note that statistical heterogeneity is not the same as clinical heterogeneity. Trials of widely different interventions, or even completely different conditions, may be statistically homogenous but should not be combined in meta-analysis.

Metaregression is a method that combines the weighting feature of (random-effects) meta-analyses with regression modelling. This makes it possible to explore study results in relation to potentially modifying variables. It should be noted that such relationships are observational, even if individual study results are from randomized controlled trials. Metaregression is thus recommended to explore heterogeneity between trials, but should be interpreted carefully with respect to causal inference.
Systematic reviews of antihypertensive treatment

During the 21st century, systematic reviews of antihypertensive treatment trials have become increasingly important. One reason for this is the large number of trials that have accumulated over the years. Different trials have slightly different aims, include different populations, compare different interventions, and come to different conclusions. With this plethora of evidence it is possible to selectively cite studies supporting many different views, making the systematic approach crucial.

One of the most cited systematic reviews during the last decade has been that by Law et al., published in 2009.(76) In this, the authors gathered data from 147 randomized clinical trials, including > 400 000 participants, comparing antihypertensive agents against placebo, agents against each other, or different blood pressure targets. The aim of the review was to answer five different questions:

1. Are beta-blockers superior in patients with coronary heart disease?
2. Does the effect of antihypertensive therapy differ in primary and secondary prevention?
3. Are there any class-specific effects (beyond blood pressure lowering) on clinical outcomes?
4. Should antihypertensive treatment be limited to patients with hypertension?
5. What is the quantitative effect of one or more antihypertensive agents on blood pressure and clinical outcomes at different baseline blood pressure levels and in different age categories?

Of special interest to this thesis are questions 1, 2 and 4. The investigators found that beta-blockers were more protective compared to other antihypertensive agents in the acute phase after myocardial infarction, but not in stable coronary heart disease. Aside from this, the authors found no difference in treatment effect between primary and secondary prevention. Lastly, treatment effect was homogenous across blood pressure strata, with no tendency towards less effect at levels below 140 mm Hg.

There are several important issues with the analyses underlying these conclusions. Especially, the analyses concerning primary versus secondary prevention, and the analyses of treatment effect at different blood pressure levels, require further scrutiny. In the first set of analyses, trials were categorized as without previous vascular disease, with previous coronary heart disease, or with previous stroke. In each category, trials were lumped together
regardless of baseline blood pressure. Homogeneity across meta-analyses was assessed using Chi-square test.

The problem with this approach is that trials in patients without previous vascular disease were early trials with high blood pressure levels, whereas trials with previous coronary heart disease generally had lower blood pressure levels. Also, a notable portion of coronary heart disease trials was in people with heart failure or left ventricular dysfunction in the acute phase post-myocardial infarction (MI).

In the second set of analyses, assessing the effect at different blood pressure levels, the same trials were used as in the previous set of analyses. However, this time they were grouped into 10 mm Hg baseline systolic blood pressure categories. Thus, the same trials that were named coronary heart disease trials in the previous set of analyses, including heart failure trials and trials in the acute phase post-MI, were now classified as 110-119 or 120-129 mm Hg trials. This is correct by definition, but fails to take into account the potential interaction between previous CVD status and treatment effect at different blood pressure levels. Specifically, the inclusion of trials like Survival and Ventricular Enlargement trial (SAVE), Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity (CHARM), and Studies of Left Ventricular Dysfunction (SOLVD) are problematic. These trials do not assess the effect of blood pressure lowering, but rather the effect of treating heart failure, and will thus bias meta-analyses of antihypertensive treatment.

The same problem that has been described above for the meta-analysis by Law et al., applies to the meta-analysis by Thompson et al. aiming to assess the effect of antihypertensive treatment in normotension, and the very recent network meta-analysis by Bundy et al. aiming to assess the effect of treatment to different blood pressure levels. Both these reviews have concluded that antihypertensive treatment is beneficial at blood pressure levels < 140 mm Hg, but in both cases the results are driven by trials specifically aiming to study the effect of treating heart failure or left ventricular dysfunction after myocardial infarction.

Two additional systematic reviews of the effect of intensive blood pressure reduction in the general population were published during 2015. First, Xie et al. aimed to assess the effect of more versus less intensive blood pressure lowering. Nineteen trials, including 45 000 patients, were analyzed. Patient characteristics varied greatly, lumping together trials in children, middle-aged and elderly with varying degrees of hypertension, diabetes, and chronic kidney disease. Mean baseline systolic blood pressure in the included trials ranged from 123 mm Hg to 172 mm Hg, with an overall average of 159 mm Hg.
Mean follow-up blood pressure was 133 mm Hg in the more intensive treatment groups and 140 mm Hg in the less intensive treatment groups, yielding a relative risk reduction of 14 % (95 % CI 4-22 %) for major cardiovascular events, and 22 % (95 % CI 10-32 %) for stroke. Although these findings support the concept that intensive treatment is more beneficial than less intensive treatment, they are not informative about treatment effect at different blood pressure levels, and thus not helpful when formulating blood pressure targets. The applicability of the results has been challenged, due to heterogeneous patient populations and blood pressure levels in the included trials.(123)

Ettehad and colleagues performed a systematic review including 123 randomized clinical trials with > 600 000 participants.(74) The authors had a similar approach as Law et al., aiming to assess the effect of different agents against each other, the effect in primary versus secondary prevention, and the effect at different baseline blood pressure levels. The most notable differences compared to Law et al were the exclusion of heart failure trials and trials in acute myocardial infarction from the primary analyses, and the inclusion of several additional outcomes.

Ettehad et al. found that every 10 mm Hg reduction in systolic blood pressure was associated with 20 % (95 % CI 17-23 %) lower risk of major cardiovascular disease, and 13 % (95 % CI 9-16 %) lower risk for all-cause mortality. They also found significant risk reductions for all separate components of the major cardiovascular disease outcome, including myocardial infarction, stroke and heart failure. Further, the authors stratified analyses by baseline systolic blood pressure, using 10 mm Hg categories from < 130 mm Hg to ≥ 160 mm Hg. Separate meta-analyses were performed for each outcome at each blood pressure level, and heterogeneity across blood pressure levels for each outcome was assessed using Cochran’s Q. The authors found no heterogeneity across blood pressure levels, and therefore concluded that the overall treatment effect estimates were applicable across the whole blood pressure range.

The systematic review by Ettehad and colleagues has some major limitations, however. Firstly, and similarly to the analyses by Law et al., the trials with high blood pressure are more often without previous CVD, whereas trials with lower blood pressure are more often secondary preventive in coronary heart disease patients. Thus, without further stratification, it is impossible to tell from the analyses if these factors interact. Secondly, and perhaps more importantly, the authors standardized relative risks and standard errors according to blood pressure differences within trials in their meta-analyses. The process of standardization is described in detail below, and is the subject of paper 3 in this thesis.
Systematic reviews of antihypertensive treatment in diabetes

Since the publication of ACCORD, several systematic reviews assessing the effect of antihypertensive treatment in patients with diabetes have been published, all with slightly different angle.

Bangalore et al. included trials in people with diabetes mellitus or impaired fasting glucose that had achieved a systolic blood pressure < 135 mm Hg in the intensive treatment arm, compared to < 140 mm Hg in the less intensive arm. (124) Thirteen trials, including 37,000 patients, were analyzed, finding that intensive blood pressure lowering was associated with 10 % (95 % CI 2-17 %) reduction in all-cause mortality and 17 % reduction in stroke, but at the price of 20 % increased risk of serious adverse events. Further lowering < 130 mm Hg reduced the risk of stroke more, but doubled the relative increase in side effects.

Reboldi et al. limited their analysis to trials in patients with diabetes. (125) In addition to trials comparing agents against placebo or different targets, Reboli et al. also included trials comparing different agents against each other. The rationale for this was that such trials would be informative in metaregression analyses investigating the association between blood pressure differences within trials and incidence of stroke and myocardial infarction. The main findings of this review was that 5 mm Hg systolic blood pressure reduction reduced the risk of stroke by 13 % (95 % CI 5-20 %), but not the risk of myocardial infarction.

In 2015, Emdin and colleagues published a systematic review with similar structure as the one by Ettehad et al., described previously. (126) First, the authors assessed the effect of treatment for each 10 mm Hg systolic blood pressure lowering, second they assessed if treatment effect differed depending on baseline blood pressure level. Third, they assessed the effect of different drug classes compared to each other.

Thirty-three trials were included in the analyses of blood pressure lowering and 17 trials compared different agents. The main findings were that 10 mm Hg systolic blood pressure reduction resulted in 13 % (95 % CI 4-22 %) lower risk of all-cause mortality, 11 % (95 % CI 5-17 %) lower risk for composite cardiovascular events, with significant effects also on myocardial infarction, stroke, albuminuria and retinopathy. Importantly, there was an interaction between treatment effect and baseline systolic blood pressure, with less effect in trials < 140 mm Hg for all outcomes except stroke, renal failure and retinopathy. This included a tendency towards increased risk for all-cause mortality and a null effect with high precision for composite cardiovascular events. Of note, this review has the same methodological problems related to standardization as the review by Ettehad et al., described further in the following section.
Standardization

An important issue in meta-analyses of antihypertensive treatment is that included trials will differ with respect to blood pressure differences between treatment groups. This is a potential source for heterogeneity, and it complicates analyses and interpretations of findings. To overcome these problems, there has been a strong will to standardize trial results as if blood pressure was reduced equally much (10 mm Hg) in all studies. This has been done differently in different meta-analyses.

Law et al. calculated the relative risk (RR) in treatment versus control groups for each trial. The RR was then raised to the power of the ratio 10/ΔSBP, where ΔSBP was the systolic blood pressure difference between treatment groups. For example, if the actual relative risk observed in a trial was 0.9, and the systolic blood pressure difference between groups was 5 mm Hg, the standardized RR would be 0.9^(10/5) = 0.9^2 = 0.81. It is important to note that this statistical maneuver builds on the assumptions that

1) Treatment effects on clinical outcomes are linearly associated with the achieved blood pressure reduction
2) This linear association is not modified by any other trial characteristic that varies between trials, such as comorbidities or baseline blood pressure levels.

The reviews by Emdin et al. and Ettehad et al. take this one step further. They standardize relative risks for each trial in the same manner as Law et al. However, they also standardize standard errors (SE) of the included trials. Similarly as for relative risks, they calculate SEs for the logarithm of the RR for each trial, and then raise it to the power of 10/ΔSBP. This means that standard errors will increase for all trials with less than 10 mm Hg systolic blood pressure difference between treatment groups, whereas SEs will decrease for trials achieving very large blood pressure reductions. At first glance this seems reasonable. If the treatment effect is inflated due to standardization, so should uncertainty. This becomes problematic, however, because it assumes that the precision of the relative risk estimate is dependant on ΔSBP. This not only affects confidence intervals, but also weights in meta-analyses, because these are based on the inverse of the SE for log(RR). Thus, trials with ΔSBP < 10 mm Hg are given wider confidence intervals and less weight compared to unstandardized analyses, whereas trials with ΔSBP > 10 mm Hg are given narrower confidence intervals and more weight. Paper 3 in this thesis explores how different forms of standardization affect meta-analyses of antihypertensive treatment. The following example aims to clarify the standardization process, describing each step in a hypothetical scenario with only four trials.
Example of standardization

The following example illustrates how standardization of relative risks and standard errors is done, and how it affects individual study parameters. Imagine four studies. The first one includes 1000 people, the second includes 2000 people, the third includes 3000 people and the fourth one includes 4000 people. Overall death rates are 1% in all studies. In the first study, treatment reduces the risk of all-cause mortality by 50%. In Study 2, 3 and 4, corresponding numbers are 30% reduction, 10% reduction and 10% increased risk with treatment (Table 4 & Figure 2).

Table 4 – Characteristics of imaginary studies.

<table>
<thead>
<tr>
<th>Name</th>
<th>Patients (n)</th>
<th>Deaths (n)</th>
<th>Observed treatment effect (RR)</th>
<th>SBP reduction (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 1</td>
<td>1000</td>
<td>10</td>
<td>0.5</td>
<td>20</td>
</tr>
<tr>
<td>Study 2</td>
<td>2000</td>
<td>20</td>
<td>0.7</td>
<td>6</td>
</tr>
<tr>
<td>Study 3</td>
<td>3000</td>
<td>30</td>
<td>0.9</td>
<td>4</td>
</tr>
<tr>
<td>Study 4</td>
<td>4000</td>
<td>40</td>
<td>1.1</td>
<td>2</td>
</tr>
</tbody>
</table>

The magnitude of blood pressure lowering differs between the hypothetical studies, however. Study 1 achieves an impressive 20 mm Hg difference in systolic blood pressure during follow-up. Study 2 achieves 6 mm Hg, Study 3 achieves 4 mm Hg, and study 4 achieves the least impressive 2 mm Hg (Table 4). An ordinary meta-analysis does not take these numbers into account (Figure 2). This can be handled in different ways. Either, studies are lumped together despite their differences. Whether this is suitable depends on the research question and their clinical characteristics. Other possible approaches include restricting analyses to trials within a certain range of blood pressure difference, or stratifying analyses according to blood pressure differences. These approaches all have limitations. Standardization of relative risks and standard errors according to blood pressure differences within trials aims to overcome this. In theory, standardization would make it possible to analyze trials on equal terms with respect to blood pressure lowering. We will see how this affects individual trial parameters in figure 3 & 4.
Figure 2 – Non-standardized fixed-effects meta-analysis

Non-standardized analysis

<table>
<thead>
<tr>
<th>Study name</th>
<th>Patients (n)</th>
<th>Deaths (n)</th>
<th>ES (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 1</td>
<td>1000</td>
<td>10</td>
<td>0.50 (0.27, 0.93)</td>
<td>10.00</td>
</tr>
<tr>
<td>Study 2</td>
<td>2000</td>
<td>20</td>
<td>0.70 (0.45, 1.08)</td>
<td>20.00</td>
</tr>
<tr>
<td>Study 3</td>
<td>3000</td>
<td>30</td>
<td>0.90 (0.63, 1.28)</td>
<td>30.00</td>
</tr>
<tr>
<td>Study 4</td>
<td>4000</td>
<td>40</td>
<td>1.10 (0.81, 1.50)</td>
<td>40.00</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td>0.87 (0.72, 1.06)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

Overall (I-squared = 52.5%, p = 0.098)

Figure 2 shows that when these studies are analyzed together in a meta-analysis, the overall relative risk of dying with treatment compared to control is 0.87, with a 95% confidence interval of 0.72 to 1.06. This means that treatment might be beneficial, but we cannot be certain based on the available data. Further, we find an $I^2$-value of 52%, indicating moderate to high heterogeneity. A reasonable interpretation of this analysis would be that individual studies vary substantially, and taken together the available studies does not support that treatment is better than no treatment.
Figure 3 – Fixed-effects meta-analysis with standardized relative risks and non-standardized standard errors

In figure 3, the relative risks are standardized according to blood pressure differences within studies. Standardized risks represent the expected risk if blood pressure would have been reduced by 10 mm Hg in all trials. This has different impact on different studies. For study 1, which achieved more than 10 mm Hg blood pressure difference, treatment effect is diminished (RR closer to 1). For all other studies, however, the standardized treatment effect is amplified in comparison with the non-standardized effects because the achieved blood pressure differences were all less than 10 mm Hg. In this example, standardization results in increased heterogeneity, with I² going from 52 % to 86 %. This is mainly due to the effect of standardization on Study 4. Before standardization, Study 4 had a relative risk of 1.1. The achieved blood pressure difference between groups was 2 mm Hg (Table 4). When the relative risk is standardized as if blood pressure was reduced by 10 mm Hg, the relative risk is raised to the power of 10 divided by the blood pressure difference:

\[
\text{Standardized RR} = 1.1^{(10/2)} = 1.1^{5} = 1.61
\]
In figure 4, standard errors have been standardized, in addition to relative risks. Remember that this is done in a similar fashion, raising the standard error to the power of 10 divided by the blood pressure difference. This makes confidence intervals narrower for studies with a blood pressure difference larger than 10 mm Hg (Study 1), but wider for studies with smaller blood pressure differences (Study 2-4). Weights, on the other hand, are proportional to the inverse of the standard error, and therefore increase for Study 1 and decrease for Study 2-4. Note that, in figure 4, relative risks are similar as in figure 3. The only parameters that have changed are weights and confidence intervals. Importantly, this has a profound effect on the overall effect estimate, as well as heterogeneity. What originally was a non-significant result with moderate to high heterogeneity now appears as highly significant and homogeneous.
Rationale for this thesis

In summary, high blood pressure is the most important risk factor for death and cardiovascular disease worldwide. Observational studies have found different shapes of association between blood pressure and risk of CVD, some suggesting lower risk with lower pressure, others suggesting a J-shaped curve. Randomized controlled trials have provided solid evidence that drug treatment to lower blood pressure reduces the risk of death and CVD if blood pressure is high. Treatment effect below 140 mm Hg is controversial, however. Trials assessing treatment effect at this blood pressure level have come to conflicting results. An apparent controversy lies in the results from ACCORD and SPRINT, in which people with, respectively without, diabetes mellitus were randomized to systolic blood pressure goals 120 versus 140 mm Hg. ACCORD found no benefit with treatment on all-cause mortality or composite cardiovascular events, whereas treatment effect in SPRINT was impressive for both outcomes. Several systematic reviews and meta-analyses have tried to synthesize the available trial evidence. These systematic reviews all have limitations, however. Especially, several of the previous meta-analyses have used methods where trial results, and in some cases uncertainty measures, have been standardized according to blood pressure differences within trials. This procedure builds assumptions that do not hold for antihypertensive treatment, and has great impact on the output of meta-analyses. This thesis studies the association between blood pressure level and the effect of antihypertensive treatment in people with and without diabetes, further separating primary preventive and secondary preventive studies. It also explores what happens with meta-analyses of antihypertensive treatment trials when previously used methods of standardization are applied.
Objectives

1. To estimate the effect of antihypertensive treatment on death and cardiovascular disease at different blood pressure levels in people with diabetes mellitus

2. To estimate the effect of antihypertensive treatment on death and cardiovascular disease at different blood pressure levels in primary prevention, and in secondary prevention after coronary heart disease and stroke

3. To assess how standardization of relative risks and standard errors according to blood pressure lowering within trials affects the results of meta-analyses of antihypertensive treatment
Materials and Methods

This thesis includes two systematic reviews and meta-analyses (Paper 1 & 2) and one methodological article concerning standardization in meta-analyses of antihypertensive treatment (Paper 3). The two systematic reviews are described together because of their many similarities, but also to highlight differences. This is followed by the methods specific to the standardization paper, although the data for this paper builds on the second systematic review.

Paper 1 & 2 – Systematic reviews and meta-analyses

The systematic reviews and meta-analyses included in this thesis have been performed with guidance from Cochrane Collaborations Handbook for Systematic Reviews of Interventions (107). The original articles are reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (127). A protocol was written, although not published, for paper 1. No protocol was developed for paper 2.

Research questions and eligibility criteria

The aim of the first paper was to assess the effect of blood pressure lowering in people with diabetes mellitus across blood pressure levels. For this purpose, we included randomized controlled trials including ≥ 100 patients with diabetes mellitus followed for ≥ 12 months. Interventions of interest were any antihypertensive agent compared to placebo, any two agents against one, or any target against another target. Trials comparing different agents against each other and trials with combined interventions were excluded.

The aim of the second paper was to assess the effect of blood pressure lowering at different blood pressure levels in primary prevention, as well as in secondary prevention in patients with coronary heart disease respectively stroke. We included randomized controlled trials with ≥ 1000 patient-years of follow-up comparing any agent against placebo, any two agents against one, or any two blood pressure goals, but excluded comparative trials and trials with combined interventions.

Of note, trials in patients with heart failure and trials in the acute phase after myocardial infarction were excluded from both analyses. This is an important distinction compared to several previous reviews.
Literature search and study selection
For paper 1, we searched PubMed, EMBASE, CENTRAL and BIOSIS in February 2013. We used highly sensitive search strategies for all databases, without restrictions in language or publication year. We manually browsed reference lists of several recently published systematic reviews and major international guidelines. Search results were merged using Endnote X5 reference software, removing duplicate records. I screened titles, whereas abstracts and full text articles were assessed for eligibility by both authors independently. Of note, no trial was discarded if it was not explicitly stated that patients with diabetes were excluded, or that too few patients with diabetes were included to fulfil our inclusion criteria. Any discrepancies in study selection between authors were resolved by discussion.

Due to time constraints, and because our previous comprehensive literature search had not resulted in many new articles compared to existing systematic reviews, we modified our strategy in paper 2. First, we searched PubMed, Cochrane Database of Systematic Reviews (CDSR), and Database of Abstracts of Reviews of Effect (DARE) for systematic reviews addressing our question. These were scrutinized for randomized clinical trials. Second, we searched PubMed and CENTRAL for randomized controlled trials published after the last comprehensive search included in any of the previous reviews (2015). All potentially eligible trials were assessed in full text, and both authors made decision on inclusion together.

Data extraction and Risk of Bias assessment
Data were extracted into specially designed Excel-sheets by both authors separately for both papers. The extracted data were cross read, and when it differed between authors we revisited original publications. Outcomes of interest were all-cause mortality, cardiovascular and non-cardiovascular mortality, myocardial infarction, stroke, heart failure, end stage renal disease, amputation and blindness in paper 1, whereas all-cause mortality, cardiovascular mortality, composite major cardiovascular events, coronary heart disease events, stroke, heart failure and end-stage renal disease were assessed in paper 2. For paper 1, we contacted authors, authorities and pharmaceutical companies when pre-specified data on diabetic patients were missing. No attempt to retrieve missing data was made for paper 2.

Risk of bias was assessed using The Cochrane Collaborations tool for assessing risk of bias.(109) The tool has been described previously (page 21), and includes among other items assessment of “blinding of participants and personnel”. Many antihypertensive trials have used a Prospective Randomized Open-label Blinded Endpoint (PROBE) design.(56) Because the impact of blinding on
objective binary outcomes (such as cardiovascular events) has been questioned, and evidence supporting a placebo effect in hypertension is scarce, we judged the risk of bias in such trials as unclear. (128) For the item "other sources of bias", we systematically sought for early termination, sponsor involvement, changes in protocol, and baseline imbalances. Both authors assessed risk of bias independently, and when judgements differed it was resolved by discussion.

Trials judged to be at high risk of bias were handled differently in the two papers. In paper 1, such trials were retained in the analyses and a qualitative judgement of the overall risk of bias for the results of meta-analyses was made. One trial, judged to be at high risk of bias in three domains, was excluded in sensitivity analyses. In paper 2, all trials with high risk of bias in any of the first four domains (resulting in selection bias, performance bias or detection bias), were excluded from analyses.

**Data synthesis and analysis**

The principles for analysis were similar in paper 1 and 2. Antihypertensive treatment effect across blood pressure levels was assessed in aggregated data meta-analyses stratified by mean baseline systolic blood pressure in the included trials. In the diabetes paper, we categorized trials as < 140 mm Hg, 140-150 mm Hg, or > 150 mm Hg, whereas in paper 2 we used categories < 140 mm Hg, 140-159 mm Hg respectively ≥ 160 mm Hg for primary preventive trials. Coronary heart disease trials, post-stroke trials and mixed CVD trials were not suitable for stratification due to either small blood pressure differences between trials (CHD) or low number of trials (post-stroke and mixed CVD).

We used random-effects model to estimate treatment effect for each blood pressure stratum and comorbidity subgroup, in both papers. In paper 2, we also applied Knapp-Hartung modification to further decrease the risk for type 1-errors.(129) Interaction between blood pressure levels was assessed using Cochran’s Q in paper 1, whereas we used multivariable-adjusted metaregression in paper 2. Metaregression utilize the continuous nature of the explanatory variable (baseline SBP) more efficiently, takes between-study variance into account using random-effects methods, and allows for additional explanatory covariates, compared to Cochran’s Q. We included age, sex, diabetes, and treatment duration as covariates in our primary interaction analysis.

In paper 2, we also performed multiple sensitivity analyses to test the robustness of our results. We excluded trials including heart failure patients, trials with < 5 mm Hg blood pressure difference between treatment groups, trials using automated blood pressure measurement devices, and trials including any level of previous CVD.
Heterogeneity was assessed through inspection of funnel plots, and through $I^2$ statistics in both reviews. The risk of publication bias was assessed through funnel plots for all outcomes. In paper 2, we also tested for funnel plot asymmetry using Eggers and Harboards tests.(114, 115)

**Paper 3 – Standardization in meta-analyses**

The aim of paper 3 was to assess how standardization according to blood pressure differences within trials affects the results of meta-analyses. We used data from paper 2, and hence refer to the previous description for literature search, study selection, data extraction and risk of bias assessment.

Standardization has previously been performed using two different methods (page 28-32). Law et al. standardized relative risks (RR), whereas Emdin et al. and Ettehad et al. also standardized standard errors (SE). We performed three separate sets of meta-analyses, using non-standardized values, standardized RR but non-standardized SE, respectively standardized RR and SE.

We focused our analyses on two outcomes, all-cause mortality and major cardiovascular events. Analyses were stratified according to baseline blood pressure level because we had previously found that it interacts with treatment effect. We used 10 mm Hg blood pressure categories because such categories were applied in both the Law-paper and the Ettehad-paper and we wanted our results to be comparable to those reviews. We used both fixed- and random-effects models because different methods have been used in different reviews, and because we wanted to assess if there was any interaction between choice of method and the effects of standardization.

First, we assessed how standardization affects relative risks and confidence intervals for each trial, for each blood pressure strata, and for overall estimates. We compared the results from the three sets with each other, and the results from fixed- and random-effects model within each set. Second, we assessed heterogeneity, comparing results for each stratum, and overall results, across sets. Heterogeneity quantifies how much trial results differ beyond chance, and we hypothesized that standardization would diminish heterogeneity because blood pressure differences within trials explain some of the between-trial variance. Third, we assessed the effect of standardized SEs on the correlation between number of events and study weights using linear regression. One basic principle of meta-analysis is that each trial should contribute to the overall results proportionally to its statistical uncertainty. Uncertainty, in turn, depends largely on the number of events. We suspected that standardization of SEs would interfere with the correlation between number of events and weight.
Results

Effect of antihypertensive treatment in people with diabetes mellitus (paper 1)

Forty-nine trials, including 73,738 participants, were included in the analyses for diabetes mellitus (table 5). This included previously unpublished data from 12 trials, including 8,916 participants, which were obtained through author contact. Half of the included studies were diabetic subgroups in larger trials, whereas half of the studies were limited to people with diabetes.

For all-cause mortality, cardiovascular mortality and myocardial infarction, we found a significant interaction between baseline blood pressure and treatment effect, using Cochran’s Q (p<0.05). With univariable metaregression, this interaction was confirmed for cardiovascular mortality (p=0.02) and myocardial infarction (p=0.01). If systolic blood pressure was > 150 mm Hg, treatment reduced the risk for all-cause and cardiovascular mortality, myocardial infarction, stroke and end-stage renal disease. If systolic blood pressure was 140-150 mm Hg, treatment reduced the risk of all-cause mortality, myocardial infarction and heart failure. If systolic blood pressure was < 140 mm Hg, treatment had no benefit but increased the risk of cardiovascular death (RR 1.15, 95 % CI 1.00-1.32). Metaregression analyses suggested 15 % worse treatment effect on cardiovascular death for every 10 mm Hg lower baseline systolic blood pressure (95 % CI 3-29 %), causing harm below 141 mm Hg.

In the diabetes paper, we also assessed treatment effect in relation to achieved systolic blood pressure, baseline diastolic blood pressure and achieved diastolic blood pressure. In broad terms, these analyses confirmed the results from the baseline SBP analyses, with the exception that achieving a systolic blood pressure < 130 mm Hg was associated with reduced risk of stroke.

Sensitivity analyses, excluding Diabetic REtinopathy Candesartan Trials-Protect 2 (DIRECT-P2) that was judged to be at high risk of bias, shifted treatment effect more towards harm in the SBP < 140 mm Hg stratum.(130)
### Table 5– Trials including people with diabetes mellitus

<table>
<thead>
<tr>
<th>Trial (ref)</th>
<th>Participants with DM (n)</th>
<th>Baseline SBP/DBP (mm Hg)</th>
<th>Intervention vs. control</th>
<th>Follow-up ΔSBP/ ΔDBP (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABCD-2V (131)</td>
<td>129</td>
<td>126/85</td>
<td>DBP &lt; 75 vs. DBP 80-90</td>
<td>6/5</td>
</tr>
<tr>
<td>ABCD-H (57)</td>
<td>470</td>
<td>155/98</td>
<td>DBP &lt; 75 vs. DBP &lt; 90</td>
<td>6/8</td>
</tr>
<tr>
<td>ABCD-N (58)</td>
<td>480</td>
<td>136/84</td>
<td>ΔDBP &gt; 10 vs. placebo</td>
<td>9/6</td>
</tr>
<tr>
<td>ACCORD (85)</td>
<td>4733</td>
<td>139/76</td>
<td>SBP &lt; 120 vs. SBP &lt; 140</td>
<td>14/6</td>
</tr>
<tr>
<td>ACTION (132)</td>
<td>1113</td>
<td>141/80</td>
<td>CCB vs. placebo</td>
<td>6/3</td>
</tr>
<tr>
<td>ADVANCE (133)</td>
<td>11140</td>
<td>145/81</td>
<td>ACEi + D vs. placebo</td>
<td>6/2</td>
</tr>
<tr>
<td>ALTITUDE (134)</td>
<td>8561</td>
<td>137/74</td>
<td>Renin inhibitor vs. placebo</td>
<td>1/1</td>
</tr>
<tr>
<td>ATLANTIS (135)</td>
<td>140</td>
<td>133/77</td>
<td>ACEi vs. placebo</td>
<td>6/4</td>
</tr>
<tr>
<td>BENEDICT (136)</td>
<td>1204</td>
<td>150/88</td>
<td>ACEi vs. CCB vs. ACEi + CCB vs. placebo</td>
<td>2/2</td>
</tr>
<tr>
<td>BENEDICT-B (137)</td>
<td>281</td>
<td>150/86</td>
<td>ACEi + CCB vs. ACEi</td>
<td>1/1</td>
</tr>
<tr>
<td>CAMELOT (138)</td>
<td>364</td>
<td>133/77</td>
<td>ACEi vs. CCB vs. placebo</td>
<td>4/2</td>
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<tr>
<td>DEMAND (139)</td>
<td>380</td>
<td>148/87</td>
<td>ACEi vs. ACEi + CCB vs. placebo</td>
<td>1/2</td>
</tr>
<tr>
<td>DIABHYCAR (140)</td>
<td>4912</td>
<td>145/82</td>
<td>ACEi vs. placebo</td>
<td>1/1</td>
</tr>
<tr>
<td>DIRECT-P2 (139)</td>
<td>1905</td>
<td>133/78</td>
<td>ARB vs. placebo</td>
<td>3/1</td>
</tr>
<tr>
<td>EWPHE (48)</td>
<td>111</td>
<td>187/101</td>
<td>D vs. placebo</td>
<td>16/5</td>
</tr>
<tr>
<td>FEVER (141)</td>
<td>1241</td>
<td>155/90</td>
<td>CCB vs. placebo</td>
<td>5/2</td>
</tr>
<tr>
<td>Fogari -02 (142)</td>
<td>309</td>
<td>160/99</td>
<td>ACEi + CCB vs. ACEi vs. CCB</td>
<td>9/5</td>
</tr>
<tr>
<td>HDFP (143)</td>
<td>1079</td>
<td>159/101</td>
<td>DBP &lt; 90 / ΔDBP &gt; 10 vs. referred care</td>
<td>10/6</td>
</tr>
<tr>
<td>HOT (56)</td>
<td>1501</td>
<td>174/105</td>
<td>DBP &lt; 80 vs DBP &lt; 85 vs. DBP &lt; 90</td>
<td>3/3</td>
</tr>
<tr>
<td>HSCS (144)</td>
<td>162</td>
<td>167/100</td>
<td>Deserpidine + D</td>
<td>25/12</td>
</tr>
<tr>
<td>Study</td>
<td>Participants</td>
<td>BP Control</td>
<td>Treatment Comparison</td>
<td></td>
</tr>
<tr>
<td>-------</td>
<td>--------------</td>
<td>------------</td>
<td>----------------------</td>
<td></td>
</tr>
<tr>
<td>IDNT (145)</td>
<td>1715</td>
<td>159/87</td>
<td>ARB vs. CCB vs. placebo 4/3</td>
<td></td>
</tr>
<tr>
<td>IRMA-2 (146)</td>
<td>590</td>
<td>153/90</td>
<td>ARB vs placebo 2/0</td>
<td></td>
</tr>
<tr>
<td>JATOS (147)</td>
<td>327</td>
<td>172/87</td>
<td>SBP &lt; 140 vs. SBP 140-160 6/1</td>
<td></td>
</tr>
<tr>
<td>Laffel -95 (148)</td>
<td>143</td>
<td>121/79</td>
<td>ACEi vs. placebo 7/6</td>
<td></td>
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<tr>
<td>Lewis -93 (149)</td>
<td>409</td>
<td>139/86</td>
<td>ACEi vs. placebo 2/3</td>
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<td>MERIT-HF* (150)</td>
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<td>132/78</td>
<td>BB vs. placebo -/-</td>
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<tr>
<td>MICRO-HOPE (151)</td>
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<td>142/80</td>
<td>ACEi vs. placebo 4/1</td>
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<tr>
<td>ORIENT (152)</td>
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<td>139/76</td>
<td>ARB vs. placebo 4/1</td>
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<td>PEACE (65)</td>
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<td>ACEi vs. placebo 1/1</td>
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<tr>
<td>PERSUADE (153)</td>
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<tr>
<td>PHARAO (154)</td>
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<tr>
<td>RASS (156)</td>
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<td>ACEi vs. ARB vs. placebo 3/3</td>
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</tr>
<tr>
<td>RENAAAL (157)</td>
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<td>153/82</td>
<td>ARB vs. placebo 2/1</td>
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</tr>
<tr>
<td>ROADMAP (158)</td>
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<td>137/81</td>
<td>ARB vs. placebo 3/2</td>
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</tr>
<tr>
<td>Ravid -98 (159)</td>
<td>194</td>
<td>130/80**</td>
<td>ACEi vs. placebo -/-</td>
<td></td>
</tr>
<tr>
<td>SAVE* (62)</td>
<td>496</td>
<td>118/70</td>
<td>ACEi vs. placebo -/-</td>
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<tr>
<td>SCOPE (160)</td>
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<td>166/90</td>
<td>ARB vs. placebo 5/1</td>
<td></td>
</tr>
<tr>
<td>SHEP (161)</td>
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<td>170/76</td>
<td>SBP &lt; 160 / ΔSBP &gt; 20 vs. placebo 10/2</td>
<td></td>
</tr>
<tr>
<td>SOLVD* (162)</td>
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<td>125/77</td>
<td>ACEi vs. placebo -/-</td>
<td></td>
</tr>
<tr>
<td>SPS3 (89)</td>
<td>1106</td>
<td>143/79</td>
<td>SBP &lt; 130 vs. SBP 130-149 11/5</td>
<td></td>
</tr>
<tr>
<td>STOP (49)</td>
<td>142</td>
<td>195/101</td>
<td>BB/D vs. placebo 18/9</td>
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</tr>
<tr>
<td>Syst-Eur (163)</td>
<td>492</td>
<td>175/85</td>
<td>CCB +/- ACEi +/- D vs placebo 9/4</td>
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</tr>
<tr>
<td>TRACE*(164)</td>
<td>237</td>
<td>126/75</td>
<td>ACEi vs. placebo -/-</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Participants</td>
<td>Mean BP</td>
<td>Treatment Comparison</td>
<td>Studies</td>
</tr>
<tr>
<td>-----------------</td>
<td>--------------</td>
<td>---------</td>
<td>----------------------</td>
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<tr>
<td>UKPDS (59)</td>
<td>1148</td>
<td>159/94</td>
<td>BP &lt; 150/85 vs. BP &lt; 180/105</td>
<td>10/5</td>
</tr>
<tr>
<td>VA-NEPHRON (165)</td>
<td>1448</td>
<td>137/73</td>
<td>ARB + ACEi vs. ARB</td>
<td>2/1</td>
</tr>
<tr>
<td>Val-HEFT (166)</td>
<td>1276</td>
<td>126/75</td>
<td>ARB vs. placebo</td>
<td>-/-</td>
</tr>
<tr>
<td>VALISH (167)</td>
<td>399</td>
<td>168/81</td>
<td>SBP &lt; 140 vs. SBP 140-149</td>
<td>4/1</td>
</tr>
</tbody>
</table>

* Heart failure trials, not included in stratified analyses. **Estimated SBP/DBP from MAP. DM = diabetes mellitus. SBP = systolic blood pressure. DBP = diastolic blood pressure. ACEi = Angiotensin-converting enzyme inhibitor. ARB = angiotensin receptor blocker. BB = beta-blocker. CCB = calcium-channel blocker. D = diuretic.

**Effect of antihypertensive treatment in primary prevention (paper 2)**

We included 51 trials, corresponding to 192 795 participants in the primary preventive analyses (table 6). Weighted mean age was 63 years, 47% of participants were women, and mean systolic blood pressure at baseline was 153 mm Hg. Treatment reduced systolic blood pressure by 6.6 mm Hg compared to control in all blood pressure strata combined, with slightly larger BP reduction in moderate/severe hypertension (8.6 mm Hg) compared to normotension/high normal blood pressure (5.4 mm Hg).

Treatment effects on clinical outcomes differed significantly across baseline blood pressure levels for cardiovascular mortality (p=0.02), major cardiovascular events (p=0.004) and heart failure (p=0.005), with non-significant trends for other outcomes. Whereas treatment reduced the risk for all outcomes except renal failure if baseline systolic blood pressure was ≥ 160 mm Hg, treatment effect was neutral for mortality outcomes and composite major cardiovascular events (MACE) if baseline systolic blood pressure was < 140 mm Hg. For MACE, treatment was highly beneficial ≥ 160 mm Hg (RR 0.78, 95% CI 0.70-0.87), moderately beneficial at 140-159 mm Hg (RR 0.88, 95% CI 0.80-0.96), and without benefit < 140 mm Hg (RR 0.97, 95% CI 0.90-1.04).

Sensitivity analyses described in the methods section confirmed the beneficial effect of treatment if baseline systolic blood pressure was > 160 mm Hg, and the neutral effect of treatment < 140 mm Hg.
<table>
<thead>
<tr>
<th>Trial (ref)</th>
<th>Participants (n)</th>
<th>Baseline SBP/DBP (mm Hg)</th>
<th>Intervention vs. control</th>
<th>Follow-up ΔSBP/ΔDBP (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABCD-N (58)</td>
<td>480</td>
<td>136/84</td>
<td>ΔDBP &gt; 10 vs. placebo</td>
<td>9/6</td>
</tr>
<tr>
<td>ACCORD (85)</td>
<td>4733</td>
<td>139/76</td>
<td>SBP &lt; 120 vs. SBP &lt; 140</td>
<td>14/6</td>
</tr>
<tr>
<td>ACTIVE I (168)</td>
<td>9016</td>
<td>138/83</td>
<td>ARB vs. placebo</td>
<td>3/2</td>
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<tr>
<td>ADVANCE (133)</td>
<td>11140</td>
<td>145/81</td>
<td>ACEi + D vs. placebo</td>
<td>6/2</td>
</tr>
<tr>
<td>AIPRI (169)</td>
<td>583</td>
<td>143/87</td>
<td>ACEi vs. placebo</td>
<td>8/6</td>
</tr>
<tr>
<td>ALTITUDE(134)</td>
<td>8561</td>
<td>137/74</td>
<td>Renin inhibitor vs. placebo</td>
<td>1/1</td>
</tr>
<tr>
<td>ANBPS (52)</td>
<td>3427</td>
<td>157/101</td>
<td>D vs. placebo</td>
<td>-/6</td>
</tr>
<tr>
<td>BBB (170)</td>
<td>2128</td>
<td>155/95</td>
<td>DBP &lt; 80 vs. DBP 80-100</td>
<td>11/8</td>
</tr>
<tr>
<td>BENEDICT(136)</td>
<td>1204</td>
<td>150/88</td>
<td>ACEi vs. CCB vs. ACEi + CCB vs. placebo</td>
<td>2/2</td>
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<tr>
<td>BENEDICT-B(137)</td>
<td>281</td>
<td>150/86</td>
<td>ACEi + CCB vs. ACEi</td>
<td>1/1</td>
</tr>
<tr>
<td>CARDIO-SIS (171)</td>
<td>1111</td>
<td>163/90</td>
<td>SBP &lt; 130 vs. SBP &lt; 140</td>
<td>4/2</td>
</tr>
<tr>
<td>DEMAND(139)</td>
<td>380</td>
<td>148/87</td>
<td>ACEi vs. ACEi + CCB vs. placebo</td>
<td>1/2</td>
</tr>
<tr>
<td>DIABHYCAR(140)</td>
<td>4912</td>
<td>145/82</td>
<td>ACEi vs. placebo</td>
<td>1/1</td>
</tr>
<tr>
<td>DREAM (172)</td>
<td>5269</td>
<td>136/83</td>
<td>ACEi vs. placebo</td>
<td>4/3</td>
</tr>
<tr>
<td>FEVER (173)</td>
<td>9711</td>
<td>154/91</td>
<td>CCB vs. placebo</td>
<td>4/2</td>
</tr>
<tr>
<td>Fogari -02 (142)</td>
<td>309</td>
<td>160/99</td>
<td>ACEi + CCB vs. ACEi vs. CCB</td>
<td>9/5</td>
</tr>
<tr>
<td>HEP (174)</td>
<td>884</td>
<td>196/99</td>
<td>BB vs. placebo</td>
<td>18/11</td>
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<tr>
<td>HOMED-BP (175)</td>
<td>3518</td>
<td>154/90</td>
<td>BP &lt; 125/80 vs. 125-134/80-84</td>
<td>1/1</td>
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<tr>
<td>HOPE-3 (101)</td>
<td>12705</td>
<td>138/82</td>
<td>ARB + D vs. placebo</td>
<td>6/3</td>
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<tr>
<td>HOT (56)</td>
<td>18790</td>
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<td>DBP &lt; 80 vs DBP &lt; 85 vs. DBP &lt; 90</td>
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<tr>
<td>HYVET (176)</td>
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<td>173/91</td>
<td>D +/- ACEi vs. placebo</td>
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<td>Study</td>
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<td>SBP/DBP</td>
<td>Treatment Comparison</td>
<td>Outcome</td>
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<td>HYVET pilot (177)</td>
<td>1283</td>
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<td>D/ACEi vs. no treatment</td>
<td>23/11</td>
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<tr>
<td>IDNT (145)</td>
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<td>159/87</td>
<td>ARB vs. CCB vs. placebo</td>
<td>4/3</td>
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<td>IPPPSH (178)</td>
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<td>173/108</td>
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<td>IRMA-2 (146)</td>
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<td>153/90</td>
<td>ARB vs placebo</td>
<td>2/0</td>
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<tr>
<td>JATOS (147)</td>
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<td>172/89</td>
<td>SBP &lt; 140 vs. SBP 140-160</td>
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<tr>
<td>Lewis -93 (149)</td>
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<td>ACEi vs. placebo</td>
<td>2/3</td>
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<tr>
<td>MRC-1 (179)</td>
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<td>161/98</td>
<td>D vs. BB vs. placebo</td>
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<tr>
<td>MRC-2 (180)</td>
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<td>NAVIGATOR (181)</td>
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<td>ORIENT (152)</td>
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<tr>
<td>Oslo study (182)</td>
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<td>D +/- methyl-dopa vs. control</td>
<td>17/10</td>
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<td>PHARAO (154)</td>
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<td>134/84</td>
<td>ACEi vs. placebo</td>
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<td>PREVEND IT (183)</td>
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<td>3/3</td>
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<td>D vs. placebo</td>
<td>2/1</td>
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<tr>
<td>RASS (156)</td>
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<td>ACEi vs. ARB vs. placebo</td>
<td>3/3</td>
</tr>
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<td>RENAAL (157)</td>
<td>1513</td>
<td>153/82</td>
<td>ARB vs. placebo</td>
<td>2/1</td>
</tr>
<tr>
<td>ROADMAP (158)</td>
<td>4447</td>
<td>137/81</td>
<td>ARB vs. placebo</td>
<td>3/2</td>
</tr>
<tr>
<td>Ravid -98 (159)</td>
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<td>130/80**</td>
<td>ACEi vs. placebo</td>
<td>-/-</td>
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<td>D vs. placebo</td>
<td>16/5</td>
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<td>195/102</td>
<td>BB/D vs. placebo</td>
<td>20/8</td>
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<td>Syst-Eur (163)</td>
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<td>174/86</td>
<td>CCB +/- ACEi +/- D vs placebo</td>
<td>10/5</td>
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<td>TOMHS (187)</td>
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<td>AB vs. ACEi vs. BB vs. CCB vs. D vs. placebo</td>
<td>7/4</td>
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<tr>
<td>UKPDS (59)</td>
<td>1148</td>
<td>159/94</td>
<td>BP &lt; 150/85 vs.</td>
<td>10/5</td>
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<tr>
<td>Study</td>
<td>SBP</td>
<td>DBP</td>
<td>Treatment</td>
<td>Ratio</td>
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</tr>
<tr>
<td>VA-NEPHRON (165)</td>
<td>1448</td>
<td>137/73</td>
<td>ARB + ACEi vs. ARB</td>
<td>2/1</td>
</tr>
<tr>
<td>VA-2 (46)</td>
<td>380</td>
<td>164/104</td>
<td>Reserpine + D vs. placebo</td>
<td>31/20</td>
</tr>
<tr>
<td>VALISH (167)</td>
<td>3079</td>
<td>170/82</td>
<td>SBP &lt; 140 vs. SBP 140-149</td>
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</tr>
<tr>
<td>Wei -13 (188)</td>
<td>724</td>
<td>160/84</td>
<td>SBP &lt; 140 vs. SBP &lt; 150</td>
<td>14/6</td>
</tr>
</tbody>
</table>

* Mean SBP 139.7 mm Hg, hence rounded to 140 but classified as <140 mm Hg. ** Estimated SBP/DBP from MAP. *** BP measured unattended. SBP = systolic blood pressure. DBP = diastolic blood pressure. AB = alpha-blocker. ACEi = Angiotensin-converting enzyme inhibitor. ARB = angiotensin receptor blocker. BB = beta-blocker. CCB = calcium-channel blocker. D = diuretic.

**Effect of antihypertensive treatment in people with coronary heart disease (paper 2)**

Twelve trials, including 77 562 participants were included in the analyses for secondary prevention in coronary heart disease trials (table 7). Mean age was 64 years, 24 % were women, and mean baseline systolic blood pressure was 138 mm Hg. Treatment reduced mean systolic blood pressure by 3.8 mm Hg compared to control.

Overall meta-analyses suggested that treatment reduce the risk of composite major cardiovascular events (RR 0.90, 95 % CI 0.84-0.97) and its components coronary heart disease, stroke and heart failure. However, the effect on all-cause and cardiovascular mortality was neutral (RR 0.98, 95 % CI 0.89-1.07, respectively RR 0.95, 95 % CI 0.84-1.09).
Table 7 – Coronary Heart Disease trials

<table>
<thead>
<tr>
<th>Trial (ref)</th>
<th>Participants (n)</th>
<th>Baseline SBP/DBP (mm Hg)</th>
<th>Intervention vs. control</th>
<th>Follow-up ΔSBP/ΔDBP (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACTION (189)</td>
<td>7665</td>
<td>138/80</td>
<td>CCB vs. placebo</td>
<td>6/3</td>
</tr>
<tr>
<td>CAMELOT (138)</td>
<td>1991</td>
<td>129/78</td>
<td>ACEi vs. CCB vs. placebo</td>
<td>5/3</td>
</tr>
<tr>
<td>EUROPA (64)</td>
<td>12218</td>
<td>137/82</td>
<td>ACEi vs. placebo</td>
<td>5/2</td>
</tr>
<tr>
<td>HOPE (61)</td>
<td>9297</td>
<td>139/79</td>
<td>ACEi vs. placebo</td>
<td>3/2</td>
</tr>
<tr>
<td>IMAGINE (190)</td>
<td>2553</td>
<td>122/70</td>
<td>ACEi vs. placebo</td>
<td>4/2</td>
</tr>
<tr>
<td>MACB (191)</td>
<td>967</td>
<td>120/70</td>
<td>BB vs. placebo</td>
<td>-/-</td>
</tr>
<tr>
<td>ONTARGET(192)</td>
<td>25620</td>
<td>142/82</td>
<td>ACEi + ARB vs. ACEi vs. ARB</td>
<td>3/2</td>
</tr>
<tr>
<td>PEACE (65)</td>
<td>8290</td>
<td>133/78</td>
<td>ACEi vs. placebo</td>
<td>3/1</td>
</tr>
<tr>
<td>PREVENT (193)</td>
<td>825</td>
<td>129/79</td>
<td>CCB vs. placebo</td>
<td>8/4</td>
</tr>
<tr>
<td>QUIET (194)</td>
<td>1750</td>
<td>123/74</td>
<td>ACEi vs. placebo</td>
<td>-/-</td>
</tr>
<tr>
<td>SCAT (195)</td>
<td>460</td>
<td>130/78</td>
<td>ACEi vs. placebo</td>
<td>5/3</td>
</tr>
<tr>
<td>TRANSCEND (196)</td>
<td>5926</td>
<td>141/82</td>
<td>ARB vs. placebo</td>
<td>4/2</td>
</tr>
</tbody>
</table>

SBP = systolic blood pressure. DBP = diastolic blood pressure. ACEi = Angiotensin-converting enzyme inhibitor. ARB = angiotensin receptor blocker. BB = beta-blocker. CCB = calcium-channel blocker.

Effect of antihypertensive treatment in people with previous stroke (paper 2)

Six trials, including 32 102 participants, were included in our post-stroke analyses (table 8). Mean age was 65 years, 35 % of participants were women, and mean baseline systolic blood pressure was 146 mm Hg. Treatment reduced blood pressure by 5.9 mm Hg compared to control.

Although analyses for post-stroke trials were generally inconclusive due to low power and wide confidence intervals, we found non-significant tendencies towards benefit with treatment for major cardiovascular events (RR 0.88, 95 % CI 0.76-1.01) and stroke (RR 0.86, 95 % CI 0.74-1.01).
### Table 8 – Post-stroke trials

<table>
<thead>
<tr>
<th>Trial (ref)</th>
<th>Participants (n)</th>
<th>Baseline SBP/DBP (mm Hg)</th>
<th>Intervention vs. control</th>
<th>Follow-up ΔSBP/ΔDBP (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dutch TIA (197)</td>
<td>1473</td>
<td>158/91</td>
<td>BB vs. placebo</td>
<td>6/3</td>
</tr>
<tr>
<td>HSCS (144)</td>
<td>452</td>
<td>167/100</td>
<td>Deserpidine + D vs. placebo</td>
<td>25/12</td>
</tr>
<tr>
<td>PROGRESS(198)</td>
<td>6105</td>
<td>147/86</td>
<td>ACEi +/- D vs. placebo</td>
<td>9/4</td>
</tr>
<tr>
<td>PRoFESS (66)</td>
<td>20332</td>
<td>144/84</td>
<td>ARB vs. placebo</td>
<td>4/2</td>
</tr>
<tr>
<td>SPS3 (89)</td>
<td>3020</td>
<td>143/79</td>
<td>SBP &lt; 130 vs. SBP 130-149</td>
<td>11/-</td>
</tr>
<tr>
<td>TEST (199)</td>
<td>720</td>
<td>161/89</td>
<td>BB vs. placebo</td>
<td>4/3</td>
</tr>
</tbody>
</table>

SBP = systolic blood pressure. DBP = diastolic blood pressure. ACEi = Angiotensin-converting enzyme inhibitor. ARB = angiotensin receptor blocker. BB = beta-blocker. D = diuretic.

### Heterogeneity and Reporting bias (paper 1 & 2)

Heterogeneity in the primary prevention analyses and the diabetes mellitus analyses were generally low to moderate ($I^2 < 50\%)$. Subsequent analyses, not included in the published papers, suggest that the present heterogeneity in the lowest blood pressure stratum in the primary prevention analyses were mostly attributable to the results from SPRINT being different from the results of all other studies.

Heterogeneity was higher in coronary heart disease trials, ranging from moderate to high ($I^2 25-75\%)$. This might partly be explained by different treatment effect at different baseline blood pressure values, although the range of blood pressure values within this subgroup was quite small. For stroke trials, heterogeneity was either absent or high (0 % or > 50 %). The apparent absence of heterogeneity for some outcomes should be interpreted with caution due to low number of events, and thus low power of the $I^2$ statistic to detect differences.

We found no evidence of funnel plot asymmetry in the diabetes paper. For primary preventive trials, we found asymmetry for major cardiovascular events and stroke in trials with baseline systolic blood pressure > 160 mm Hg. This may suggest reporting bias for these outcomes, possibly causing overestimation of treatment effect at high blood pressure levels.

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Standardization in meta-analyses (paper 3)

Non-standardized meta-analyses found an overall beneficial effect of antihypertensive treatment for all-cause mortality and major cardiovascular events. Treatment effect was heterogeneous across blood pressure strata (p=0.005 for mortality, p<0.001 for MACE), with less effect at lower levels. Importantly, random-effects model and fixed-effects model did not differ substantially for any strata or outcome.

When RRs were standardized (as in the previous meta-analysis by Law et al.), overall effects with fixed- and random-effects models differed dramatically. Whereas the fixed-effects model suggested close to neutral treatment effect on all-cause mortality (RR 0.97, 95% CI 0.94-0.99), random-effects model suggested an impressive risk reduction (RR 0.79, 95% CI 0.70-0.89). Further, treatment effect within blood pressure strata differed even more. The most extreme example was in the mortality analysis of 140-149 mm Hg, where the fixed-effects model found a significant risk increase with treatment (RR 1.10, 95% CI 1.06-1.15) whereas the random-effects model found a significant risk reduction (RR 0.53, 95% CI 0.37-0.76). Differences between fixed- and random-effects models appear only in presence of statistical heterogeneity. Standardization of RRs resulted in bidirectional extreme values for individual trials, with increased between-study heterogeneity for all strata, reaching extreme values (I² > 90%) in several cases.

When both RRs and SEs were standardized (as in the previous meta-analyses by Ettehad et al. and Emdin et al.), between-study heterogeneity decreased, and fixed- and random-effects models once again showed coherent results. Examination of individual trial results, however, showed that the apparent homogeneity was not due to more balanced relative risks; RRs were identical compared to the previous set of analyses. Instead confidence intervals were widened. Because heterogeneity measured through the I² statistic reflects how much confidence intervals overlap, the underlying heterogeneity caused by standardization of RRs was effectively masked by standardization of SEs.

Standardization of SEs also caused a shift in weight from trials with many participants and events to trials with large blood pressure difference between treatment groups (Because SEs are raised to the power of 1/ΔSBP, and weights are inversely proportional to SEs, high ΔSBP values give large weights). This disrupted the association between number of events and study weights. Whereas number of events predicted 99% of the variance in weights before standardization, corresponding values after standardization were < 10% for both all-cause mortality and MACE.
The shift in weights from trials with many events to trials with large blood pressure differences also caused a secondary shift in weights from trials with low baseline blood pressure to trials with high baseline blood pressure. Because, in non-standardized analyses, there was a highly significant interaction between baseline blood pressure and treatment effect, this in turn made the overall effect estimates more positive. For example, in the non-standardized analysis for all-cause mortality, the 140-149 mm Hg stratum received 35% of overall weight with neutral treatment effect, whereas the ≥ 160 mm Hg stratum received 21% weight with positive treatment effect. When RRs and SEs were standardized, the 140-149 mm Hg stratum received only 14% weight, whereas the ≥ 160 mm Hg stratum received 61% weight.
Discussion

Summary and interpretation of findings

Both systematic reviews included in this thesis find an interaction between baseline systolic blood pressure and the effect of antihypertensive treatment on clinical outcomes. For primary prevention, interaction was significant for cardiovascular mortality, composite major cardiovascular events and heart failure. In diabetes mellitus, this was true for cardiovascular mortality, myocardial infarction, and possibly for all-cause mortality depending on choice of statistical method. Of note, the point estimate for treatment effect was less beneficial with baseline systolic blood pressure < 140 mm Hg compared to the highest blood pressure strata (> 150 mm Hg, respectively > 160 mm Hg) for all outcomes in both analyses. Together, these findings strongly and coherently support the concept of an interaction between blood pressure level and treatment effect.

Stratified analyses found that antihypertensive treatment reduces the risk of all-cause mortality, major cardiovascular events and coronary heart disease in primary preventive trials with baseline systolic blood pressure 140-159 mm Hg. If baseline systolic blood pressure was ≥ 160 mm Hg, treatment effect was highly beneficial for all studied outcomes except end-stage renal disease. In trials of patients with diabetes mellitus, treatment reduced the risk of all-cause mortality, myocardial infarction and heart failure if baseline systolic blood pressure was 140-150 mm Hg. If systolic blood pressure was > 150 mm Hg, treatment was highly beneficial for all outcomes. Taken together, the findings presented here confirm that antihypertensive treatment reduces mortality and cardiovascular morbidity in hypertension, and that treatment is more beneficial at higher blood pressure levels.

At baseline systolic blood pressure levels below 140 mm Hg, results were far less positive. The only statistically significant benefit was for heart failure in primary prevention. This finding should be interpreted carefully in light of no significant treatment effect on heart failure in the 140-159 mm Hg stratum, and highly significant metaregression suggesting less benefit at lower baseline pressures. On the other hand, we found an increased risk of cardiovascular death in the diabetes analysis. This was supported by metaregression analyses in both cohorts, and non-significant point estimates towards harm for all-cause mortality in diabetes and for cardiovascular mortality in primary prevention. These findings together indicate uncertain benefit, and potential harm of antihypertensive treatment in non-hypertensive patients.
The third paper investigated the effect of standardization according to blood pressure differences within trials in meta-analyses of antihypertensive treatment. This paper found that standardization of relative risks (RR) causes bidirectional extreme effect estimates, resulting in very high levels of heterogeneity in several blood pressure strata. This caused inconsistent results with different analytical methods. Additional standardization of standard errors (SE) did not change effect estimates, but caused wider confidence intervals, masking heterogeneity introduced by standardization of RRs. Also, standardization of SEs shifted weights, from trials with many events to trials with large blood pressure reductions, causing exaggerated overall effect estimates. These findings suggest that standardization introduces bias into meta-analyses of antihypertensive treatment, and should thus be avoided.

Limitations

The most important limitation of the meta-analyses included in this thesis is that they are based on study-level data. This confers several potential problems.

Firstly, aggregated data opens the analyses for ecological bias. The effect estimate for each blood pressure stratum, or non-stratified subgroup, builds on comparisons between randomized groups. However, interaction analyses and comparisons between strata are non-randomized. Trials included in one stratum could differ compared to other strata with respect to parameters other than baseline blood pressure level. This includes patient characteristics as well as study design features. If factors that systematically differ between strata also modify treatment effects, the observed interaction in our analyses could be biased. In paper 2, we analyzed primary preventive studies, coronary heart disease studies and post-stroke studies separately to minimize potential bias from previous cardiovascular diseases. Also, we adjusted our metaregression analyses for age, sex, diabetes and treatment duration to reduce the risk of confounding from between-trial differences in these parameters.

Secondly, blood pressure differences between treatment groups differ between trials. It is fair to question if trials with average systolic blood pressure differences < 5 mm Hg should be analyzed together with trials achieving > 10 mm Hg difference. Authors of previous meta-analyses have adjusted for this, using different standardization procedures. In paper 3, we show that such standardization procedures increase heterogeneity and leads to biased results. Thus, our non-standardized results are far from optimal, but represent the best method available. We compared mean blood pressure differences between strata in paper 2, to assess if blood pressure differences within trials could potentially bias comparisons of treatment effect between blood pressure levels. This revealed that blood pressure was actually reduced more in the < 140 mm
Hg stratum compared to the 140-159 mm Hg stratum, and only 3 mm Hg less compared to the >160 mm Hg stratum. These subtle differences in blood pressure lowering can hardly account for the observed differences in treatment effect. In addition, sensitivity analyses excluding trials with < 5 mm Hg blood pressure difference between treatment groups, confirmed the null effect if baseline systolic blood pressure was < 140 mm Hg and the highly beneficial effect if baseline systolic blood pressure was > 160 mm Hg.

Thirdly, reliance on aggregated data made CVD classification in paper 2 very crude. We dichotomized trials as primary or secondary preventive if baseline CVD prevalence was below respectively above 50 %. If trials were categorized as secondary preventive, they were further subcategorized as coronary heart disease, post-stroke or mixed CVD based on which type of cardiovascular disease was most prevalent. Despite this rather crude method, the average weighted prevalence of CVD was 16 % in primary preventive trials, and 92 % in secondary preventive trials, thus making potential bias from previous CVD unlikely. We explored this further in sensitivity analyses, excluding trials with mixed populations, which confirmed our overall findings.

For patients with diabetes mellitus, we found a significant risk increase for cardiovascular death, which was not confirmed in the larger primary preventive material. If this represents a true interaction, or a chance finding in paper 1, is impossible to know. For patients with previous coronary heart disease, we found a potential benefit of additional blood pressure lowering if baseline systolic blood pressure was already < 140 mm Hg, which was not the case in primary prevention. This potential interaction, with greater benefit at lower levels in people with coronary heart disease, goes in the opposite direction compared to the interaction often reported from observational analyses. (27, 36, 37) Whereas the adverse interaction seen in observational studies could be due to reverse causality, the potential beneficial interaction seen in our analyses could occur, for example, if high blood pressure is more important in eliciting cardiovascular events compared to the long-term development of atherosclerosis.

Our meta-analyses are also limited by the characteristics of the included studies. A majority of all trials were fully or partially sponsored by pharmaceutical companies. Meta-epidemiological research has suggested that industry-funded trials have more beneficial findings compared to non-industry funded trials (200). Notably, none of the coronary heart disease trials were fully independent. Thus, we cannot exclude that our results are biased towards the positive, especially in for coronary heart disease secondary prevention. Also, although funnel plots were generally symmetrical, we found significant asymmetry in the highest blood pressure stratum in the primary preventive analyses for major cardiovascular events and stroke. In this stratum, trials are
older and smaller, and therefore potentially more vulnerable to publication bias compared to other strata and subgroups in our analyses. Thus, treatment effects > 160 mm Hg may be exaggerated for these particular outcomes. Lastly, some of our analyses suffered from low power, yielding wide confidence intervals. More specifically, the effects of antihypertensive treatment on end-stage renal disease in primary prevention, on stroke in primary prevention and in diabetes mellitus with systolic blood pressure < 140 mm Hg, and on all outcomes post-stroke, are uncertain.

The patient characteristics in the included studies should be compared to patient characteristics in clinical practise to assess the applicability of our findings. Firstly, mean age in all of our analyses was 60-65 years. This corresponds well to the average age of patients with blood pressure recordings in primary care (201). The prevalence of hypertension increases with age, however; and elderly people are at increased risk of CVD (202). Only two of the included trials have specifically focused on people above 80 years of age (176, 177). The results reported here might therefore not be applicable to a large portion of treated patients. The diabetes analyses build almost exclusively on data from middle-aged or young elderly patients with type 2-diabetes with some duration. Whether results from such analyses should guide treatment for patients with type 1-diabetes, or even newly diagnosed type 2-diabetes, is questionable. Patients with type 1-diabetes are often monitored since childhood, and thus early aggressive treatment would be easy to implement. The evidence supporting such treatment, however, builds on pathophysiological reasoning and data on surrogate markers (203).

Paper 3 is a methodological paper that builds on empirical data. We have included the two most common methods for meta-analyses, and we use the same stratification strategy as previous major systematic reviews in the field. Our findings should be applicable to the field of antihypertensive treatment in general, and the analyses by Law et al., Ettehad et al., and Emdin et al. in particular. However, they may not apply to other conditions. For example, similar methods for standardization have been used in meta-analyses of cholesterol-lowering treatment, and could potentially be used in meta-analyses of trials treating any modifiable risk factor. This needs to be explored further, assessing other risk factors specifically.
Comparison with previous studies

Systematic reviews
Our findings differ compared to most previous systematic reviews and meta-analyses. Neither Law et al. or Ettehad et al. found an interaction between baseline systolic blood pressure and treatment effect. (74, 76) Our results suggest such an interaction is consistent across populations and outcomes, and of clinical importance. Further, previous reviews have found significant benefit with treatment down to levels < 130 mm Hg (74, 76). We find uncertain benefit < 140 mm Hg, with potential harm in patients with diabetes. The differences between our results and others can be explained by differences in methodology.

Firstly, Law et al. and Bundy et al. included heart failure trials and trials in the acute phase after myocardial infarction in their analyses.(76, 121) In patients with acute or chronic heart failure, many antihypertensive agents have blood pressure-independent effects on clinical outcomes.(204) Results from such trials are not applicable to the general hypertensive population, and will therefore bias the results from meta-analyses of antihypertensive treatment.

Secondly, Law, Ettehad and Bundy all included trials regardless of co-morbidities in their stratified analyses.(74, 76, 121) This is problematic, because primary preventive trials and trials in coronary heart disease patients differ widely in their baseline systolic blood pressure (15 mm Hg according to our analyses). Both Law et al. and Ettehad et al. concluded that no interaction exists between baseline systolic blood pressure, or baseline coronary heart disease, and treatment effect. When we separate primary preventive trials from coronary heart disease trials, we find that treatment effect is attenuated with lower baseline blood pressure in primary prevention, and that treatment effect possibly differs between primary prevention and coronary heart disease secondary prevention at low blood pressure levels. This illustrates the problem that arises when clinically heterogeneous trials are combined in meta-analyses, and the importance of exploring interactions between potential effect modifiers.

Thirdly, Law et al. standardized RRs in their analyses. As we show in paper 3, this increases heterogeneity between trials.(76) At very high levels of heterogeneity ($I^2 > 75\%$), meta-analyses are generally discouraged.(116) Law et al. did not present heterogeneity for their stratified analyses, but in our standardized analyses in paper 3, $I^2$ exceeds 90 % for several strata. Also, standardization of relative risks to 10 mm Hg blood pressure lowering exaggerates the effect of treatment compared to relative risks observed in the actual trials, because the average achieved blood pressure reduction is substantially lower.
Ettehad et al. standardized both RRs and SEs in their analyses. (74) This assumes, not only that treatment effect is linearly associated with blood pressure reduction and that this association is not modified by any other factor (e.g. baseline blood pressure), but also that the precision for each trial depends on within-trial blood pressure differences. We show in paper 3 that this causes a major shift in weights, from trials with many events to trials with large blood pressure reductions. An illustrative example of this is that VA-2 (46), with 31 deaths, is given more weight than ONTARGET (192), with 3100 deaths when SEs are standardized.

Aside from biased effect estimates, standardization of SEs also causes wider confidence intervals. Ettehad et al. use Cochran’s Q to assess interaction between treatment effect and baseline blood pressure, a measure that depends on how much confidence intervals overlap. (74) Thus, standardization of SEs impairs the possibility of finding an interaction between blood pressure level and treatment effect. The conclusion that treatment effect does not differ between blood pressure levels thus depends on standardization and not necessarily the underlying data.

In our analyses, we use non-standardized relative risks and standard errors. This builds on fewer assumptions and makes our results more representative of the results from the included trials. The interaction between baseline blood pressure and treatment effect observed in our analyses thus represents different treatment effects at different blood pressure levels. By using multivariable-adjusted meta-regression in paper 2, we have also taken potential confounders such as age, sex, diabetes and treatment duration into account, a method that has not been used in previous meta-analyses.

Finally, Paper 2 in this thesis was based on an updated literature search, with more liberal inclusion criteria regarding size and duration compared to Ettehad et al. This resulted in 19 additional trials compared to Ettehad et al., 35 additional trials compared to Law et al. and 43 additional trials compared to Bundy et al. (74, 76, 121) Close scrutiny of the Bundy-paper revealed that it was missing seven trials that should have been included according to its eligibility criteria, including the large and negative HOPE-3 trial. (101) Of note, HOPE-3 was published 14 months before the Bundy review.

Compared to previous systematic reviews of treatment effect in patients with diabetes, our coverage was more comprehensive. We included 21 additional trials compared to the review by Emdin et al., which was previously most thorough (126). Emdin et al. studied albuminuria and retinopathy, which we did not. They found an overall effect on both outcomes, and significantly lower risk of albuminuria with treatment < 140 mm Hg. This should be compared to the
neutral effect on end-stage renal disease showed in our analyses. Although it is theoretically possible that decreased albuminuria would lead to less renal failure over longer time periods, the predictive value of albuminuria as a surrogate for renal failure in randomized clinical trials is limited. (205) Last but not least, Emdin standardized both RR and SEs in the same manner as Ettehad et al. Thus, their results should be interpreted with great caution.

**SPRINT**

At first glance, our results go against those from SPRINT (90). In SPRINT, a treatment goal < 120 mm Hg was associated with less major cardiovascular events and lower mortality rates compared to a treatment goal < 140 mm Hg. These findings have made many argue for lower blood pressure targets. However, there are several problems with SPRINT that potentially impairs its validity (Table 2, page 16). Especially important for the debate concerning blood pressure goals is the blood pressure measurement method. In SPRINT, blood pressure was measured using self-operated automatic measurement devices, with no attending personnel. This method results in 10–20 mm Hg lower blood pressure values compared to attended measurements (93-95). If blood pressure in SPRINT had been measured in the same way as in all previous trials, it is highly likely that baseline systolic blood pressure would have been in the 140-159 mm Hg range, and attained values below respectively above 140 mm Hg. In this blood pressure range, we find that treatment reduces major cardiovascular events and all-cause mortality, similarly as in SPRINT. Thus, the results from SPRINT are actually very compatible with the results from our meta-analyses, and the recommendations given in current guidelines (80, 81, 88).

When addressing the findings and potential implications of SPRINT, it is also important to consider HOPE-3 (101). In HOPE-3, > 12 000 participants, with mean baseline systolic blood pressure 138 mm Hg, were randomized to combination therapy with candesartan/hydrochlorothiazide or placebo. In other words, HOPE-3 assessed the effect of a potent blood pressure lowering strategy, in a larger cohort with lower baseline blood pressure compared to SPRINT. Importantly, HOPE-3 was overall neutral, with significant interaction between baseline systolic blood pressure and treatment effect, and a tendency towards harm in the lowest blood pressure stratum. Although HOPE-3 aimed to assess treatment effect in a healthier population compared to SPRINT, previous individual-patient data meta-analyses have found no interaction between baseline cardiovascular risk and treatment effect (206). Thus, one likely reason for different results in SPRINT and HOPE-3 is that the actual blood pressure levels in these trials differ more than their published values, and that treatment effect depends on blood pressure level.
Perspectives and future directions

This thesis includes two of the most comprehensive systematic reviews to date concerning the effect of antihypertensive treatment at different blood pressure levels. We include several additional trials, and use more robust methods, compared to previous meta-analyses. Importantly, we also come to different conclusions.

The question if the effect of antihypertensive treatment relates to blood pressure level is one of great importance to clinical practise. If the association between blood pressure and CVD were linear throughout the physiological blood pressure range, the question whether to treat or not would depend solely on absolute risk. We show that not only the absolute, but also the relative benefit of treatment is affected by baseline systolic blood pressure, and that treatment might be harmful below certain levels. Further, treatment effect modification by baseline blood pressure seems to interact with previous cardiovascular disease status. Although this might seem complex at first, our results would be easy to implement in clinical practise. In people without previous cardiovascular disease, treatment should be initiated or intensified if systolic blood pressure is 140 mm Hg or above, whereas (additional) treatment should be withheld if systolic blood pressure is < 140 mm Hg. In people with previous coronary heart disease, treatment seems to be beneficial even if systolic blood pressure is slightly below 140 mm Hg. Thus, a reasonable treatment threshold/target in this population would be 130 or 135 mm Hg.

The importance of blood pressure treatment thresholds/targets cannot be overemphasized. According to the current WHO definition, close to one billion people have hypertension, causing several million excess deaths per year worldwide (6). Given the number of people affected, even small differences in blood pressure on population level will have huge impact on public health and health economy. In this situation, it is crucial that guidelines for treatment of high blood pressure rely on the best available evidence. Systematic reviews and meta-analyses of randomized controlled trials should play a central role in the writing of such guidelines.

Just recently, the American Heart Association and the American College of Cardiology (AHA/ACC) released new hypertension guidelines for the U.S. In the new guidelines, the threshold for hypertension was lowered to 130/80 mm Hg (207). The new definition made more than 30 million Americans hypertensive over night, shifting the prevalence from 32 % to 46 % for the adult population (208). Although it is recommend starting treatment for hypertension with lifestyle modifications for many patients, the new guidelines will inevitably lead to millions of additional patients on antihypertensive medications, and
additional agents for those already receiving treatment. This is questionable based on our findings, because additional treatment below 140 mm Hg appears to be beneficial only in coronary heart disease secondary prevention, with potential harmful effects in people with diabetes. Also, more intensive treatment comes with higher rates of permanent discontinuation of medication and more serious adverse events, including potential life-threatening conditions, like acute kidney injury and severe electrolyte disturbances (209).

Independent analyses suggest that only about one half of people with hypertension are aware of it, and that only about one third of those treated for hypertension achieve appropriate blood pressure control (7, 210). Together with uncertain benefit, potential harm, increased risk of side effects, and incremental costs with more intensive treatment, these data indicate that focus should be on detection, treatment and control of systolic blood pressure ≥ 140 mm Hg instead of lowering targets.

Despite our efforts, the analyses presented here are far from optimal and should be interpreted with some caution. Especially, the aggregated nature of our data makes our analyses susceptible to ecological bias and prevents us from exploring effect modification in a sophisticated way. Individual-patient data meta-analyses could potentially overcome these problems. Assessment of treatment effect in relation to individual-patient baseline blood pressure would increase precision, and adjustment for individual-patient risk factors would mitigate the impact of confounding factors. Previous individual-patient data meta-analyses within the field of hypertension have been performed by the Blood Pressure Lowering Treatment Trialists Collaboration (BPLTTC). An apparent problem with these analyses, however, has been that many trials were not included. Two of the latest publications from BPLTTC have included approximately one third of the trials, representing half the number of participants, compared to paper 2 in this thesis (206, 211). Thus, although individual-patient data meta-analyses might help improve our knowledge further, it is crucial that such meta-analyses are comprehensive, especially including newer trials with low baseline blood pressure levels.

The ambiguous findings from clinical trials and meta-analyses with baseline systolic blood pressure below 140 mm Hg will probably require additional randomized studies to be performed. The Stroke Hypertension Optimal Treatment (SHOT) study will provide additional insights about treatment targets for patients with previous cerebrovascular disease (212). However, the vast majority of people with hypertension have not yet had a cardiovascular event, and thus the aim of treatment is primary prevention. In this setting, the cardiovascular event rate is low, requiring very large cohorts and/or long duration of follow-up to show potential treatment benefit. With a wide arsenal
of efficient and well-tolerated antihypertensive agents with expired patents, it is unlikely that such trials will be performed by the pharmaceutical industry. Hopefully, the emergence of different forms of pragmatic trials could offer cheaper alternatives, feasible through public funding. This includes, but is not limited to, cluster-randomised trials, and register-based trials using electronic health records and health registers for follow-up.

This thesis has focused on treatment effect in relation to systolic blood pressure. We focused on systolic blood pressure because systolic hypertension is more common and contributes more to the global health burden compared to diastolic hypertension (213). Also, in combined systolic-diastolic hypertension, targeting systolic values will cause diastolic control to a very large extent. From an adverse effects point of view, however, diastolic values might still be of interest. Observational studies have consistently found a J-shaped association between diastolic blood pressure and risk of CVD (31). In paper 1, we did examine treatment effect in relation to diastolic blood pressure values, presented in the web appendix. Metaregression was significant for an association between baseline diastolic blood pressure and treatment effect on cardiovascular mortality, indicating potential harm below 78 mm Hg. This is dangerously close the blood pressure goal recommended in the new AHA/ACC guidelines. Thus, if the average blood pressure in the population continues to fall, we might need to revisit diastolic blood pressure once again.
Conclusions and implications

The findings in this thesis have both clinical and research implications. The main conclusions of importance for clinical practice are:

1. The effect of antihypertensive treatment depends on the blood pressure level before treatment.
2. If systolic blood pressure is > 160 mm Hg, treatment is highly beneficial with mortality and marked CVD reductions.
3. If systolic blood pressure is > 140 mm Hg, treatment is beneficial, with mortality and CVD reductions.
4. If systolic blood pressure is < 140 mm Hg, treatment is of uncertain benefit in primary prevention, and could potentially increase the risk of cardiovascular death in people with diabetes.
5. In people with coronary heart disease, antihypertensive treatment likely reduce the risk of non-fatal cardiovascular events if systolic blood pressure is < 140 mm Hg, with unclear lower threshold for benefit.

These conclusions support European treatment recommendations, focusing on a general systolic blood pressure goal < 140 mm Hg (80, 81, 88). Not only the absolute but also the relative risk reduction with treatment is more beneficial at higher blood pressure levels. These findings emphasize the importance of finding and treating people with hypertension, especially those at moderate to severe levels. Our results do not support lower treatment goals, like those in the updated American guidelines (207), especially not in people with diabetes mellitus. Although further blood pressure lowering might reduce the risk of stroke and heart failure, the effect estimates for these outcomes were inconclusive. On the other hand, we found an increased risk of cardiovascular death in people with diabetes. Following the principle not to harm, antihypertensive treatment should not be recommended in people with systolic blood pressure < 140 mm Hg until further evidence from randomized controlled trials have confirmed its safety and efficacy.

Our results do, however, opt for additional treatment in patients with coronary heart disease. At what blood pressure level these patients should be offered treatment remains unclear, but based on our results it seems reasonable to offer treatment if systolic blood pressure is above 130 or 135 mm Hg. Of note, none of the trials included in this subgroup tested different treatment targets, and all were industry-sponsored. An adequately powered independent trial assessing treatment goals, e.g. < 130 versus < 140 mm Hg, would be of great value.
Additional conclusions of methodological interest are:

6. Standardization of RRs according to blood pressure lowering within trials increases heterogeneity, and makes analyses highly sensitive to choice of statistical method.

7. Standardization of SEs according to blood pressure lowering within trials masks the increased heterogeneity induced by standardization of RRs, disrupts the association between number of events and study weights, and introduces bias though systematic shifts in study weights to trials with larger treatment effect.

These conclusions are of great importance to the interpretation of previous systematic reviews of antihypertensive treatment.
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