



Effect of antihypertensive treatment at different blood pressure levels in patients with diabetes mellitus: systematic review and meta-analyses

Mattias Brunström, Bo Carlberg

Department of Public Health and Clinical Medicine, Medicine, Umeå University, SE-901 87 Umeå, Sweden

Correspondence to: M Brunström mattias.brunstrom@umu.se

Additional material is published online only. To view please visit the journal online.

Cite this as: *BMJ* 2016;352:i717 <http://dx.doi.org/10.1136/bmj.i717>

Accepted: 12 January 2016

ABSTRACT

OBJECTIVE

To assess the effect of antihypertensive treatment on mortality and cardiovascular morbidity in people with diabetes mellitus, at different blood pressure levels.

DESIGN

Systematic review and meta-analyses of randomised controlled trials.

DATA SOURCES

CENTRAL, Medline, Embase, and BIOSIS were searched using highly sensitive search strategies. When data required according to the protocol were missing but trials were potentially eligible, we contacted researchers, pharmaceutical companies, and authorities.

ELIGIBILITY CRITERIA

Randomised controlled trials including 100 or more people with diabetes mellitus, treated for 12 months or more, comparing any antihypertensive agent against placebo, two agents against one, or different blood pressure targets.

RESULTS

49 trials, including 73 738 participants, were included in the meta-analyses. Most of the participants had type 2 diabetes. If baseline systolic blood pressure was greater than 150 mm Hg, antihypertensive treatment reduced the risk of all cause mortality (relative risk 0.89, 95% confidence interval 0.80 to 0.99), cardiovascular mortality (0.75, 0.57 to 0.99), myocardial infarction (0.74, 0.63 to 0.87), stroke (0.77, 0.65 to 0.91), and end stage renal disease (0.82, 0.71 to 0.94). If baseline systolic blood pressure was

140-150 mm Hg, additional treatment reduced the risk of all cause mortality (0.87, 0.78 to 0.98), myocardial infarction (0.84, 0.76 to 0.93), and heart failure (0.80, 0.66 to 0.97). If baseline systolic blood pressure was less than 140 mm Hg, however, further treatment increased the risk of cardiovascular mortality (1.15, 1.00 to 1.32), with a tendency towards an increased risk of all cause mortality (1.05, 0.95 to 1.16).

Metaregression analyses showed a worse treatment effect with lower baseline systolic blood pressures for cardiovascular mortality (1.15, 1.03 to 1.29 for each 10 mm Hg lower systolic blood pressure) and myocardial infarction (1.12, 1.03 to 1.22 for each 10 mm Hg lower systolic blood pressure). Patterns were similar for attained systolic blood pressure.

CONCLUSIONS

Antihypertensive treatment reduces the risk of mortality and cardiovascular morbidity in people with diabetes mellitus and a systolic blood pressure more than 140 mm Hg. If systolic blood pressure is less than 140 mm Hg, however, further treatment is associated with an increased risk of cardiovascular death, with no observed benefit.

Introduction

Blood pressure goals in people with diabetes mellitus have been extensively debated during the past decade.¹⁻³ For many years, guidelines have recommended treating patients to achieve a blood pressure of less than 130/80 mm Hg.⁴⁻⁶ Systematic reviews have questioned the evidence for these recommendations.^{7,8} During 2013 multiple hypertension guidelines were updated.⁹⁻¹¹ Generally, the treatment goals for people with diabetes were changed to less than 140/90 mm Hg, but some guidelines still opt for lower targets in certain patient groups.^{9,12} Last year, a new systematic review was published,¹³ concluding that treating people with a systolic blood pressure (SBP) already less than 140 mm Hg is associated with a reduced risk of stroke and albuminuria, and therefore challenged the relaxation of guidelines. All previous systematic reviews only analysed previously published data.^{7,8,13}

We assessed the effect of blood pressure lowering treatment in people with diabetes mellitus, including previously unpublished data. Although people with diabetes have been included in many trials of blood pressure lowering treatment, for most of these trials data on people with diabetes have not been published separately. We contacted authors, pharmaceutical companies, and authorities to get access to this data. To assess the effect of treatment at different blood pressure levels, we stratified meta-analyses according to

WHAT IS ALREADY KNOWN ON THIS TOPIC

Hypertension is the most important risk factor for mortality and cardiovascular disease worldwide

People with diabetes mellitus are at increased risk of cardiovascular disease and often have concomitant hypertension

Antihypertensive treatment reduces the risk of cardiovascular disease in people with diabetes mellitus, but the optimal blood pressure level has been debated

WHAT THIS STUDY ADDS

In people with diabetes mellitus and a systolic blood pressure of more than 140 mm Hg, antihypertensive treatment is associated with a reduced risk of mortality and cardiovascular disease

In people with diabetes mellitus and a systolic blood pressure of less than 140 mm Hg, however, antihypertensive treatment is associated with an increased risk of cardiovascular death

The interaction between systolic blood pressure before treatment and the treatment effect is significant

baseline and attained SBP. Baseline SBP is important because it reflects the clinical situation better than attained SBP. Although blood pressure before treatment is known, the attained blood pressure with treatment may vary substantially. Also, attained SBP can be regarded as a product of baseline SBP and SBP lowering. Therefore, trials included in each stratum will be more homogenous for clinical characteristics if stratification is based on baseline values.

Methods

We conducted a systematic review and meta-analyses guided by recommendations of the Cochrane Collaboration.¹⁴ The methods, including search strategy, inclusion criteria, and preliminary analyses were prespecified (see web appendix for protocol). We included randomised controlled trials with a mean follow-up of 12 months or more and including 100 or more participants with diabetes mellitus. Trials had to compare any antihypertensive agent against placebo, any two agents against one, or any blood pressure target against another. We excluded strictly comparative trials, evaluating one agent against another, as well as trials with combined interventions.

During February 2013, we searched CENTRAL, Medline, Embase, and BIOSIS using broad strategies to maximise sensitivity. CENTRAL was searched using the MeSH terms “antihypertensive agent” and “blood pressure”, exploded and combined, without restrictions in publication year or language (see the web appendix for full search strategies in each database). We also browsed reference lists in, and citations of, systematic reviews and guidelines in the discipline, including a more recently updated review.^{7 8 13 15-17} Using EndNote reference software, we combined the search results and removed duplicate records. MB screened titles and abstracts to exclude apparently irrelevant publications. Both authors independently checked the abstracts and full text articles for eligibility and resolved any disagreements by discussion. Data were extracted into specially designed Excel sheets, pretested on 10 included trials and then modified to increase functionality. Risk of bias was assessed at study level using the Cochrane Collaboration’s risk of bias tool.¹⁸ Both authors independently extracted data and assessed risk of bias, with disagreements resolved by a recheck of the original data and discussion.

Prespecified outcomes of interest were all cause mortality, cardiovascular and non-cardiovascular mortality, myocardial infarction, stroke, heart failure, end stage renal disease, amputation, blindness, adverse events, and quality of life. Given the poor reporting of adverse events and quality of life in the original trials, we excluded these outcomes before extraction of any data. We collected data on baseline characteristics at trial level and blood pressure data for the intervention and control groups separately. When any data required according to the protocol were missing, but the trial was potentially eligible, we contacted the authors. If they did not respond to the first email, we reminded them at least once. Where

data were available, we calculated relative risks for each outcome in each trial, and pooled results using random effects meta-analysis. We chose the random effects model over the fixed effects model because the included trials differed to some extent, both clinically and methodologically. The results of random and fixed effects models in analyses with low heterogeneity are the same, and if heterogeneity is present the random effects model is generally more conservative. We performed non-stratified meta-analyses for all outcomes, based on all trials. Prespecified stratified analyses were performed based on mean baseline SBP and diastolic blood pressure (DBP) in all participants, mean in-treatment SBP and DBP for the intervention group, and mean differences in SBP and DBP between groups during follow-up. Cochran Q statistics were used to assess the interaction between blood pressure levels and treatment effect on outcomes, testing the null hypothesis that there is no difference between groups. We carried out prespecified metaregression analyses between each blood pressure variable and the treatment effect on each outcome.

In the stratified analyses, we excluded trials predominantly including patients with heart failure because of the risk of assessing effects independent of blood pressure. Also, we were unable to stratify analyses of amputation and blindness because too few trials reported these outcomes. The blood pressure strata were slightly modified from those given in the protocol. For reasons of power, we excluded the baseline stratum for SBP less than 135 mm Hg and for attained SBP greater than 150 mm Hg. DBP stratification was done to achieve as equal a number of trials in each stratum as possible. Because SBP has the strongest association with cardiovascular disease, explaining more than 95% of events,¹⁹ we report on this in the review. DBP is problematic because it might be confounded by differences in pulse pressure, as seen between included trials. (See web appendix for analyses stratified according to DBP and to differences in SBP and DBP between groups.)

Heterogeneity was assessed by visually inspecting the forest plots, and through I² statistics. When heterogeneity was present, we scrutinised baseline characteristics, blood pressure data, and risk of bias assessments of the included trials for possible explanations. If such explanations were found, we carried out sensitivity analyses if we suspected a potential effect on the main results. Publication bias was assessed using funnel plots for all outcomes separately, and for mortality in the stratified analyses. Analyses were performed using STATA v12.

Patient involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for design or implementation of the study. No patients were asked to advice on interpretation or writing up of results. Since we used only aggregated data from previous trials, we are unable to disseminate the results of the research to study participants directly.

Results

Overall, 49 trials corresponding to 73 738 participants fulfilled the inclusion criteria and provided enough data to be included in at least one meta-analysis (fig 1).²⁰⁻⁷² Twenty five trials (26 625 participants) comprised diabetic subgroups from larger trials, and 24 trials (47 113 participants) were confined to people with diabetes. Unpublished data for 12 studies (8916 participants) were obtained through contact with the authors, pharmaceutical companies, or authorities.^{30 32 36 40 44 50 52 54 63 65 71 72} The mean duration of follow-up was 3.7 years, and most of the participants had type 2 diabetes. Table 1 lists the characteristics of the included studies, including comorbidities.

Figures 2 and 3 present the meta-analyses stratified according to baseline SBP and attained SBP, respectively. The mean difference in SBP between baseline and follow-up in the intervention groups was 10.2 mm Hg. Because of this, the trials included in each baseline SBP strata generally ended up in the strata for 10 mm Hg lower attained SBP. Figure 4 presents the metaregression analyses for baseline SBP.

All cause mortality was reduced if SBP before treatment was more than 140 mm Hg and if SBP with treatment was 130-140 mm Hg. If baseline SBP was less than 140 mm Hg, the point estimate shifted towards an increased risk with treatment, albeit not statistically significant (relative risk 1.05, 95% confidence interval 0.95 to 1.16). The same trend was observed if attained SBP was less than 130 mm Hg. Both baseline and attained SBP significantly interacted with treatment effect on all cause mortality ($P=0.019$ and 0.009 , respectively), indicating that the treatment effect is worse with lower SBP.

Cardiovascular mortality was reduced if baseline SBP was more than 150 mm Hg. If baseline SBP was 140-150 mm Hg, the effect of treatment was not significant, and if baseline SBP was less than 140 mm Hg, treatment increased the risk of cardiovascular death by 15%

(relative risk 1.15, 95% confidence interval 1.00 to 1.32). Results were not significant for the attained SBP analyses but showed similar patterns, towards risk reduction if SBP was more than 130 mm Hg and towards harm if SBP was less than 130 mm Hg. Both baseline and attained SBP significantly interacted with the effect of treatment in the same direction as for all cause mortality ($P=0.002$ and 0.010 , respectively). Metaregression analyses showed 15 percentage points worse treatment effect on cardiovascular mortality for each 10 mm Hg lower baseline SBP ($P=0.015$), crossing the zero line from benefit towards harm at 141 mm Hg.

For myocardial infarction, treatment was beneficial if baseline SBP was more than 140 mm Hg and attained SBP was more than 130 mm Hg. If SBP was less than 140 mm Hg at baseline or less than 130 mm Hg during treatment, however, there was no association between treatment and risk. Interaction was significant between baseline SBP and treatment effect, but not for attained SBP ($P=0.017$ and $P=0.476$, respectively). Metaregression showed 12 percentage points worse treatment effect on myocardial infarction for each 10 mm Hg lower baseline SBP ($P=0.011$), crossing from benefit towards harm at 132 mm Hg.

The risk of stroke was reduced if baseline SBP was more than 140 mm Hg and attained SBP was less than 140 mm Hg. The lowest SBP stratum, for both baseline and attained SBP, had wide confidence intervals, reflecting low numbers of events. Both interaction analyses and metaregression analyses were not significant for both baseline and attained SBP.

The risk of heart failure decreased with treatment if baseline SBP was more than 140 mm Hg and attained SBP was more than 130 mm Hg. For the lowest stratum, however, the effect of treatment was not significant. For end stage renal disease, the only subgroup showing a positive effect of treatment was that with a baseline SBP of more than 150 mm Hg. For both the baseline and attained analyses, the point estimate in the lowest strata was close to 1. Interaction tests and metaregression analyses were negative for heart failure and end stage renal disease.

The web appendix presents non-stratified meta-analyses, meta-analyses stratified according to baseline and in-treatment DBP, and meta-analyses stratified according to differences in SBP and DBP between groups. We observed similar patterns in the DBP analyses as in the SBP analyses. There was a significant interaction between baseline and attained DBP and cardiovascular mortality. Metaregression showed the risk of cardiovascular mortality to increase by 28 percentage points for each 10 mm Hg lower baseline DBP ($P=0.013$), crossing from benefit towards harm at 78 mm Hg. Non-cardiovascular mortality was analysed according to protocol, and was not affected by treatment in any subgroup.

The web appendix presents risk of bias assessment, with explanatory text.

In our overall meta-analyses we judged the risk of bias as low, although it was high for some trials. One trial (DIabetic REtinopathy Candesartan Trials-Protect 2, DIRECT-P2) was judged to have high risk of bias in

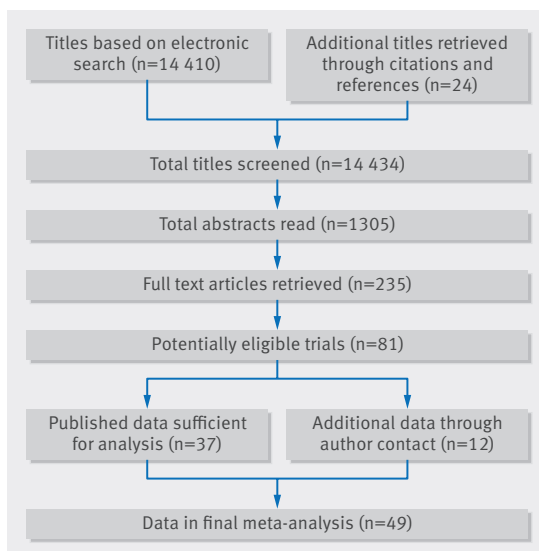


Fig 1 | PRISMA flowchart

Table 1 | Characteristics of included studies

Study ID	No of participants	Comorbidities	Intervention group	Control group	Baseline SBP/DBP (mm Hg)	Mean in-treatment difference SBP/DBP (mm Hg)
ABCD-2 ²⁰	129	6% with previous cardiovascular disease	DBP <75 mm Hg, using valsartan	DBP 80-90 mm Hg using placebo	126/84.7	6/5
ABCD-H ²¹	470	53% with previous cardiovascular disease, 60% with retinopathy	DBP <75 mm Hg	DBP <90 mm Hg	155/98	6/8
ABCD-N ²²	480	29% with previous cardiovascular disease, 50% with retinopathy	10 mmHg DBP reduction	Placebo	136.4/84.4	9/6
ACCORD ²³	4733	34% with previous cardiovascular disease	SBP <120 mm Hg	SBP <140 mm Hg	139.2/75.95	14.2/6.1
ACTION ^{24, 25}	1113	Stable angina in all patients, 51% with myocardial infarction	Nefidipine 60 mg	Placebo	141/80	6/3
ADVANCE ^{26, 27}	11 140	32% with previous cardiovascular disease	Perindopril 4 mg and indapamide 1.25 mg	Placebo	145/81	5.6/2.2
ALTITUDE ²⁸	8561	Chronic kidney disease in all patients, 42% with cardiovascular disease	Aliskiren 300 mg	Placebo	137.3/74.2	1.3/0.6
ATLANTIS ²⁹	140	Microalbuminuria in all patients, no data on cardiovascular disease	Ramipril 1.25 mg or 5.0 mg	Placebo	132.9/76.9	6/3.5
BENEDICT ³⁰	1204	No data on previous cardiovascular disease	Trandolapril 2 mg, verapamil 240 mg, or combination treatment 2/180 mg	Placebo	150.8/87.5	2.3/2
BENEDICT-B ³¹	281	Microalbuminuria in all patients, no data on cardiovascular disease	Verapamil 180 mg and trandolapril 2 mg	Trandolapril 2 mg	150/86.7	0.8/0.7
CAMELOT ³²	364	Coronary artery disease in all patients	Amlodipine 10 mg or enalapril 20 mg	Placebo	133/77.4	4.2/1.8
DEMAND ³³	380	Microalbuminuria in all patients, no data on cardiovascular disease	Manidipine 10 mg+delapril 30 mg or delapril alone	Placebo	147.9/87.3	1.4/1.9
DJABHYCAR ³⁴	4912	Microalbuminuria in all patients, 24% with cardiovascular disease	Ramipril 1.25 mg	Placebo	145.4/82.3	1.3/0.7
DIRECT-P ²³⁵	1905	Retinopathy in all patients, 6% with cardiovascular disease	Candesartan 16 mg	Placebo	132.9/78	3.3/1.3
EWPHE ³⁶	111	64% with previous cardiovascular disease	Hydrochlorothiazide 25 mg and triamterene 50 mg	Placebo	186.8/101.2	16.1/5.3
FEVER ³⁷	1241	42% with previous cardiovascular disease	Felodipine 5 mg	Placebo	155.3/90.2	4.6/1.8
Fogari -02 ³⁸	309	Microalbuminuria in all patients, no cardiovascular disease	Amlodipine 5-10 mg and fosinopril 15-30 mg	Amlodipine 5-15 mg or fosinopril 10-30 mg	160.4/99.3	9.0/4.6
HDFP ³⁹	1079	8% with previous cardiovascular disease	DBP <90 mm Hg or 10 mm Hg DBP reduction by diuretic	Referred care	158.7/101.1	10/6
HOT ⁴⁰	1501	3% with previous cardiovascular disease	DBP <80 mm Hg	DBP <85 or DBP <90 mm Hg	174.1/105.3	3.4/2.9
HSCS ⁴¹	162	Previous stroke/transient ischaemic attack in all patients	Deserpidine 0.5 mg and methyclo-thiazide 5-10 mg	Placebo	167/100	25/12.3
IDNT ⁴²	1715	Diabetic nephropathy in all patients, 29% with cardiovascular disease	Irbesartan 300 mg or amlodipine 10 mg	Placebo	159/87	3.5/3
IRMA 2 ⁴³	590	Microalbuminuria in all patients, 27% with cardiovascular disease	Irbesartan 150 mg or 300 mg	Placebo	153/90.3	2/0
JATOS ⁴⁴	327	7% with previous cardiovascular disease	SBP <140 mm Hg	SBP 140-160 mm Hg	172.3/87.3	5.6/0.9
Lafel -95 ⁴⁵	143	Microalbuminuria in all patients, no cardiovascular disease	Captopril 50 mg	Placebo	120.8/78.5	7/6
Lewis -93 ⁴⁶	409	Diabetic nephropathy in all patients, no cardiovascular disease	Captopril 75 mg	Placebo	138.5/85.5	1.5/2.5
MERIT-HF ⁴⁷	985	Heart failure NYHA II-IV in all patients	Metoprolol CR/XL 200 mg	Placebo	132/78	No data
MICRO-HOPE ⁴⁸	3577	69% with previous cardiovascular disease	Ramipril 10 mg	Placebo	142/79.7	3.8/0.9
ORIENT ⁴⁹	577	Diabetic nephropathy in all patients, 16% with cardiovascular disease	Olmesartan 10-40 mg	Placebo	138.8/76.2	3.8/1.4

PEACE ⁵⁰	1386	Stable coronary artery disease in all patients	Trandolapril 4 mg	Placebo	135.3/76.6	1.5/0.9
PERSUADE ⁵¹	1502	Stable coronary artery disease in all patients	Perindopril 8 mg	Placebo	140.1/81.6	4.6/1.8
PHARAO ⁵²	135	No data on previous cardiovascular disease	Ramipril 5 mg	Placebo	135.5/84.1	1.5/0
PROFESS ⁵³	5743	Previous ischaemic stroke/transient ischaemic attack in all patients	Telmisartan 80 mg	Placebo	144.2/83.8	4/2
PROGRESS ⁵⁴	761	Previous stroke/transient ischaemic attack in all patients	Perindopril 4 mg with or without indapamide	Placebo	149.5/84.5	9.5/4.6
RASS ⁵⁵	285	No previous cardiovascular disease	Losartan 100 mg or enalapril 20 mg	Placebo	120.1/70.6	3/2
RENAAL ^{56, 57}	1513	Diabetic nephropathy in all patients, 20% with cardiovascular disease	Losartan 50-100 mg	Placebo	152.5/82.0	2.3/0.7
ROADMAP ⁵⁸	4447	33% with previous cardiovascular disease	Olmesartan 40 mg	Placebo	136.5/80.5	3.1/1.9
Ravid—98 ⁵⁹	194	No previous cardiovascular disease	Enalapril 10 mg	Placebo	130/80	No data
SAVE ⁶⁰	496	Previous myocardial infarction and ejection fraction <40% in all patients	Captopril 75-150 mg	Placebo	117.8/70.4	No data
SCOPE ⁶¹	597	8% with previous cardiovascular disease	Candesartan 8-16 mg	Placebo	166/90	5.1/1.2
SHEP ⁶²	583	No data on previous cardiovascular disease	SBP <160 mm Hg or ≥20 mm Hg SBP reduction	Placebo	170.2/75.8	10/2
SOLVD ⁶³	1310	Heart failure and ejection fraction <35% in all patients	Enalapril 20 mg	Placebo	124.9/76.8	No data
SPS3 ⁶⁴	1106	Previous lacunar infarction in all patients	SBP <130 mm Hg	SBP 130-149 mm Hg	143/78.5	11/5
STOP ⁶⁵	142	No data on previous cardiovascular disease	Atenolol 50 mg or metoprolol 100 mg or pindolol 5 mg or hydrochlorothiazide 25 mg+amiloride 2.5 mg	Placebo	195.3/100.8	18.2/8.5
Syst-Eur ⁶⁶	492	30% with previous cardiovascular disease	Nitrendipine 10-40 mg with or without enalapril with or without hydrochlorothiazide	Placebo	175.3/84.5	8.6/3.9
TRACE ⁶⁷	237	Previous myocardial infarction and ejection fraction <35% in all patients	Trandolapril 4 mg	Placebo	126/76.5	No data
UKPDS ^{68, 69}	1148	6% with previous cardiovascular disease	Blood pressure <150/85 mm Hg	Blood pressure <180/105 (200/105) mm Hg	159.3/94	10/5
VA-NEPHRON ⁷⁰	1448	Diabetic nephropathy in all patients, 23% with cardiovascular disease	Losartan 100 mg+lisinopril 10-40 mg	Losartan 100 mg	137.0/72.7	1.5/1
VAL-HEFT ⁷¹	1276	Heart failure NYHA II-IV in all patients	Valsartan 320 mg	Placebo	125.6/74.8	No data
VALISH ⁷²	399	No data on previous cardiovascular disease	SBP <140 mm Hg	SBP 140-150 mm Hg	168.0/80.7	3.7/0.9

DBP=diastolic blood pressure; SBP=systolic blood pressure; NYHA=New York Heart Association function class.

three domains. We performed sensitivity analyses excluding this trial from the stratified analyses. This shifted the effect measures of all cause and cardiovascular mortality slightly more towards harm, but did not change the significance level for any outcome.

Discussion

This systematic review and meta-analyses confirms that blood pressure lowering treatment is associated with reduced mortality and cardiovascular morbidity in people with diabetes mellitus, if systolic blood pressure (SBP) before treatment is more than 140 mm Hg. If SBP is less than 140 mm Hg, however, we found no benefit, but potential harm, with an increased risk of cardiovascular death. This fits well with our analyses stratified by attained SBP. Treatment reduced the risk of all cause mortality, myocardial infarction, stroke, and heart failure, if SBP was treated to 130-140 mm Hg, but was associated with a non-significant increase in all cause and cardiovascular mortality if SBP was lowered to less than 130 mm Hg. The results are further supported by metaregression analyses showing that treatment effect on cardiovascular mortality and myocardial infarction is worse for each unit decrease in baseline SBP, and harmful below certain levels.

Strengths and limitations of this review

This review has some limitations that are general to meta-analyses without access to individual patient data, including not being able to account for patient characteristics in a sophisticated way or analyse blood pressure levels within trials. Six other considerations should be borne in mind. Firstly, we identified more potentially eligible trials than could be included in the final analyses. These were trials in which we either knew there were people with diabetes but did not receive data on these participants, or trials in which there were no data on inclusion but participation by people with diabetes could not be excluded. Hence, despite our efforts, additional data exist that are not included in our analyses. Secondly, our analyses are stratified on mean baseline and attained blood pressure within trials. This is an aggregated variable, which opens our results to potential ecological bias. One way to reduce this risk of bias would have been to stratify on eligibility criteria or blood pressure targets instead of on measured values. However, the blood pressure range accepted in each trial is usually wide, with great overlap between trials, making stratification on this variable virtually impossible. Thirdly, we see no increase in the risk of myocardial infarction or stroke, corresponding to the increase in cardiovascular mortality in the lowest SBP strata. This could have two possible explanations. Case fatality might increase with intensive treatment, reflecting lower margins to handle an event with lower blood pressure. It could also reflect stricter definitions for myocardial infarction and stroke in the included trials than those used for cardiovascular mortality. For example, all unexpected deaths, deaths out of hospital, and deaths without known causes, usually qualify as cardiovascular mortality, but not as any

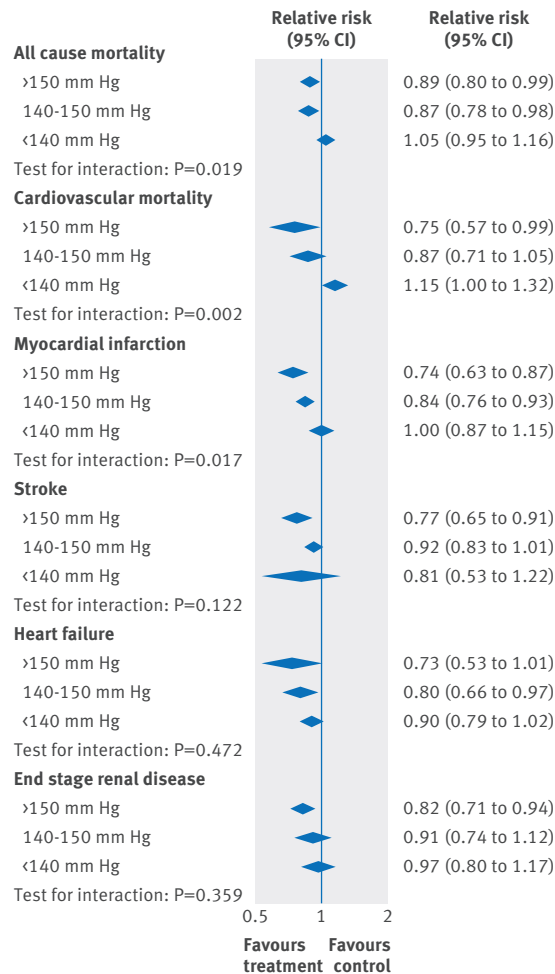


Fig 2 | Results from meta-analyses stratified according to baseline systolic blood pressure (SBP), reported for each outcome separately

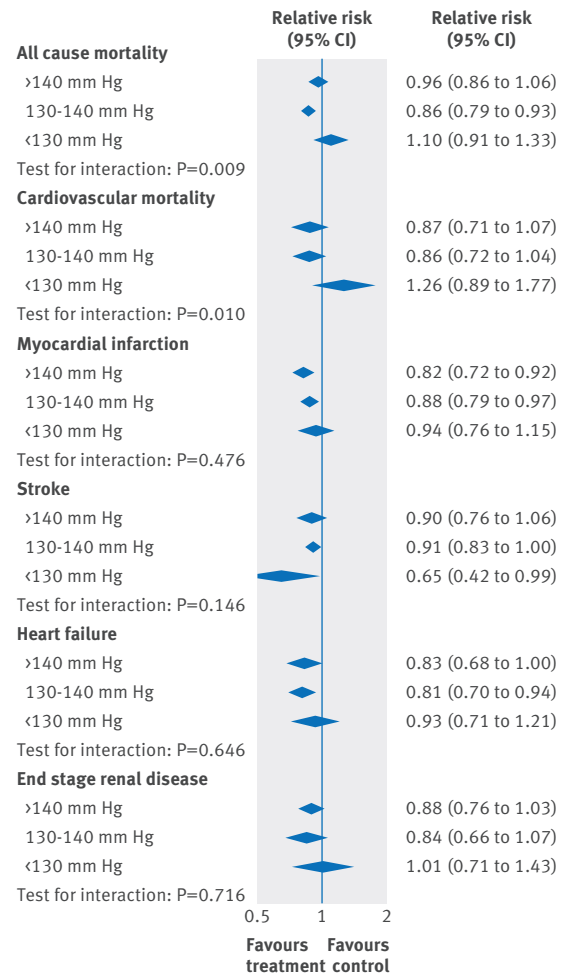


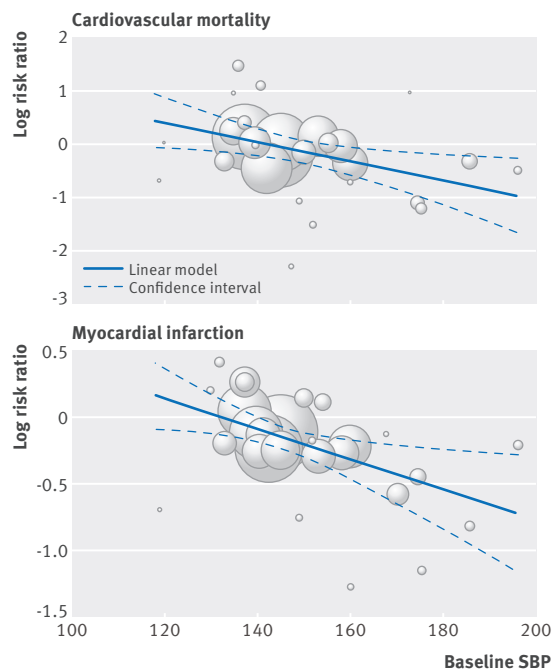
Fig 3 | Results from meta-analyses stratified according to attained systolic blood pressure (SBP), reported for each outcome separately

specific event. Fourthly, most of the included trials were not designed to test different blood pressure targets but rather randomised patients to drug versus placebo. Thus, if blood pressure independent drug effects were present, they could affect our results. A recent systematic review showed no difference in treatment effect between drug classes for all cause and cardiovascular mortality.⁷³ Also, all trials that randomised patients to specific drugs in the lowest blood pressure strata used renin angiotensin system (RAS) blockers. It has been suggested that these agents have a positive effect beyond that of blood pressure lowering,⁴⁸ but still the main results in this stratum were negative. It is thus unlikely that the observed treatment effects in this review are related to drug class. Fifthly, the ALiskiren Trial In Type 2 Diabetes Using Cardio-Renal Endpoints (ALTITUDE) is given large weight in all meta-analyses within the baseline SBP stratum of less than 140 mm Hg. This was a trial of aliskiren, a renin inhibitor, in addition to previous inhibition of RAS.²⁸ Double RAS blocker treatment is no longer recommended as standard treatment in any patient group.⁹⁻¹¹ We therefore performed a sensitivity analysis, excluding ALTITUDE from the cardiovascular mortality analysis, to test its

impact. Importantly, this did not change the point estimate but widened the confidence intervals, indicating that the treatment effect is consistent across trials but that the power to establish such an effect is insufficient without ALTITUDE. In line with this, the shift in significance for cardiovascular mortality and stroke, between the baseline and attained SBP analyses, can also be attributed to ALTITUDE. Although baseline SBP was less than 140 mm Hg, this trial did not lower SBP to below 130 mm Hg. Sixthly, the majority of participants in the included trials in our meta-analyses had type 2 diabetes and were already treated with one or more antihypertensive agents. Therefore, generalisability to people with type 1 diabetes, and people naive to treatment, is probably limited.

Comparison with other studies

Our results are mostly in line with those of a recently published review by Emdin and colleagues.¹³ Both reviews confirm the protective effect of treatment if SBP is more than 140 mm Hg, and that the benefit decreases with decreasing blood pressure. However, the results differ on three important findings. Firstly, we show an increased risk of cardiovascular death, an outcome not



Outcome	Relative risk (95% CI)	P value
Mortality	1.04 (0.98 to 1.10)	0.151
Cardiovascular mortality	1.15 (1.03 to 1.29)	0.015
Myocardial infarction	1.12 (1.03 to 1.22)	0.011
Stroke	1.07 (0.98 to 1.18)	0.137
Heart failure	1.05 (0.93 to 1.20)	0.401
End stage renal disease	1.05 (0.90 to 1.22)	0.496

Fig 4 | Results from metaregression analyses of treatment effect in relation to baseline systolic blood pressure (SBP). Relative risk is expressed as change in treatment effect for each 10 mm Hg lower baseline SBP. See table for results of all outcomes (those with significant results also presented as graphs). Each circle represents one trial and the size of each circle represents the weight given to the trial in metaregression

analysed by Emdin and colleagues. Secondly, Emdin and colleagues showed a decreased risk of stroke, even if baseline SBP was less than 140 mm Hg, which we do not. Thirdly, Emdin and colleagues showed a decreased risk of albuminuria, an outcome we did not analyse. The reviews differ on two methodological points: we include data from 21 additional trials, compared with the stratified analyses in the previous review; and Emdin and colleagues standardised risk ratios and weights according to SBP reduction within trials, whereas we used non-standardised data. In the case of stroke, the difference in results between the two reviews can be explained by the standardisation used by Emdin and colleagues. In their standardised model, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial is given more than 90% weight in the meta-analysis, although it contributed less than 25% of the events in the included trials.²³ On the other hand, ALTITUDE is given only 2% weight in the meta-analysis, although it contributed more than 60% of the events.²⁸ This strongly suggests a study weight bias in the

standardised model. Albuminuria should be regarded as a surrogate for end stage renal disease. In our analyses of trials with baseline SBP less than 140 mm Hg, there was no tendency towards reduction of this outcome (relative risk 0.97, 95% confidence interval 0.80 to 1.17). Even if the best possible scenario, with respect to confidence intervals for end stage renal disease, was true, the absolute number of cardiovascular deaths exceeds that of end stage renal disease, and hence the numbers needed to treat would exceed the numbers needed to harm. The absence of a beneficial effect on stroke if baseline SBP is less than 140 mm Hg also differs compared with another review, including both people with diabetes and people with impaired fasting glucose.⁸ It is reasonable to think that the vessels of people with impaired fasting glucose are less affected than those of people with manifest diabetes, and hence they might be less sensitive to, and perhaps more helped by, additional blood pressure lowering. Recently, the results of the Systolic Blood Pressure Intervention Trial (SPRINT) were published.⁷⁴ This was a randomised controlled trial comparing a systolic blood pressure target of less than 120 mm Hg with one less than 140 mm Hg, in high risk patients with moderately elevated blood pressure. The trial was stopped preterm owing to a highly significant reduction in all cause mortality, suggesting that this population might benefit from very aggressive blood pressure treatment. Importantly, patients with diabetes mellitus were excluded from the trial. Thus our results, combined with those from SPRINT, suggest that blood pressure treatment targets should be less aggressive in people with diabetes than in those without diabetes.

Potential explanation of findings

The concept of a J-shaped, or U-shaped, curve for the relation between blood pressure and cardiovascular disease has been shown previously in observational settings.^{75,76} This has often been dismissed as due to possible confounding.⁷⁷ It is highly unlikely, however, that our results would be due to confounding. This is because we analyse relative risks between groups with the same baseline blood pressure but randomised to different blood pressure levels, thereby preserving the element of randomisation in our meta-analyses.

The most likely biological explanation for our findings is that intensive treatment impairs blood flow to end organs, leading to ischaemia.⁷⁷ In patients with stenosis of the coronary arteries, decreased diastolic blood pressure (DBP) has been shown to lead to lower fractional flow reserve over the stenosed segment, in turn leading to myocardial hypoperfusion.⁷⁸ In arterial stiffening, commonly present in people with diabetes, myocardial perfusion is increasingly dependent on SBP.⁷⁹ This could, at least partly, explain the association between low SBP and worse treatment effect in our analyses. Impaired myocardial perfusion, compared with the superior autoregulation of cerebral blood flow, could also explain the different effects of blood pressure levels on myocardial infarction and stroke. Another potential explanation for our findings is that low blood pressure leads to less

coronary collateral circulation. It has been hypothesised that low blood pressure leads to reduced endothelial stress, the driver of arteriogenesis, and an association between DBP and coronary collaterals has been shown in cross sectional data of patients with coronary occlusion.⁸⁰ This could explain not only an increased number of events with treatment but also a worse prognosis when having an event, as reflected by the possible increase in case fatality suggested by our analyses.

Conclusions and implications

This systematic review and meta-analyses included a large amount of previously unpublished data, thereby increasing precision compared with previous research. Results from the analyses stratified by baseline SBP are largely consistent with those stratified by attained SBP. The interaction between blood pressure and treatment effect is reproducible across exposure variables and outcomes, indicating a robust dose-response relation. Together with a possible biological mechanism, our results suggest that SBP before treatment modifies the effect of treatment in a causal way.

The results are important both conceptually for research on hypertension and for clinicians. Firstly, we show that not only the absolute, but also the relative benefit of blood pressure lowering is attenuated at lower blood pressures. This suggests that the linear relation between blood pressure and cardiovascular disease seen in some observational studies cannot be extrapolated to assumed benefit of treatment. Stretching this further, we show, based on randomised comparisons, that treatment below a certain blood pressure level might be harmful. Secondly, and contrary to what has previously been recommended, our results, combined with those from the SPRINT trial, suggest that blood pressure treatment goals should be less aggressive in people with diabetes than without diabetes. This review strongly supports blood pressure treatment in people with diabetes mellitus if SBP is more than 140 mm Hg. If SBP is already less than 140 mm Hg, however, adding additional agents might be harmful.

We thank the following authors for sharing previously unpublished data, without receiving economic imbursement or any other personal gain: Piero Ruggerenti (BENEDICT), Kathy Wolski (CAMELOT), Lutgarde Thijs (EWPHE and Syst-Eur), Yuhei Kawano (JATOS), Stephan Lüders (PHARAO), Hisatomi Arima (PROGRESS), Lars Hjalmar Lindholm (STOP), Inder Anand (VAL-HEFT), and Hiromi Rakugi (VALISH). We also thank AstraZenica for sharing data from HOT, and the National Heart, Lung, and Blood Institute for sharing data from PEACE, SHEP, and SOLVD.

Contributors: Both authors contributed equally to all aspects of study design and conduct, and the writing of the manuscript. BC is guarantor.

Funding: This study was funded by Västerbotten County Council. The design and conduct of the study, the interpretation of data, and the writing of the manuscript, was done solely by the authors, independent of the funder.

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/doi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: This study was approved by the regional ethical review board at Umeå University.

Data sharing: Results from all meta-analyses are presented in appendix. Additional data, including full forest plots are available on request.

Transparency: The lead author (MB) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 3.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/3.0/>.

- Zanchetti A, Grassi G, Mancia G. When should antihypertensive drug treatment be initiated and to what levels should systolic blood pressure be lowered? A critical reappraisal. *J Hypertens* 2009;27:923-34. doi:10.1097/HJH.0b013e32832aa6b5.
- Mancia G. Effects of intensive blood pressure control in the management of patients with type 2 diabetes mellitus in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. *Circulation* 2010;122:847-9. doi:10.1161/CIRCULATIONAHA.110.960120.
- Deedwania PC. Blood pressure control in diabetes mellitus: is lower always better, and how low should it go? *Circulation* 2011;123:2776-8. doi:10.1161/CIRCULATIONAHA.111.033704.
- Chobanian AV, Bakris GL, Black HR, et al. National Heart, Lung, and Blood Institute Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure National High Blood Pressure Education Program Coordinating Committee. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA* 2003;289:2560-72. doi:10.1001/jama.289.19.2560.
- Mancia G, De Backer G, Dominiczak A, et al. European Society of Hypertension European Society of Cardiology. 2007 Guidelines for the management of arterial hypertension - The task force for the management of arterial hypertension of the European society of hypertension (ESH) and of the European society of cardiology (ESC). *Eur Heart J* 2007;28:1462-536.
- Buse JB, Ginsberg HN, Bakris GL, et al. American Heart Association American Diabetes Association. Primary prevention of cardiovascular diseases in people with diabetes mellitus: a scientific statement from the American Heart Association and the American Diabetes Association. *Circulation* 2007;115:114-26. doi:10.1161/CIRCULATIONAHA.106.179294.
- Reboldi G, Gentile G, Angeli F, Ambrosio G, Mancia G, Verdecchia P. Effects of intensive blood pressure reduction on myocardial infarction and stroke in diabetes: a meta-analysis in 73,913 patients. *J Hypertens* 2011;29:1253-69. doi:10.1097/HJH.0b013e3283469976.
- Bangalore S, Kumar S, Lobach I, Messerli FH. Blood pressure targets in subjects with type 2 diabetes mellitus/impaired fasting glucose: observations from traditional and bayesian random-effects meta-analyses of randomized trials. *Circulation* 2011;123:2799-810. doi:10.1161/CIRCULATIONAHA.110.016337.
- Mancia G, Fagard R, Narkiewicz K, et al. American Heart Association American Diabetes Association. *J Hypertens* 2013;31:1281-357. doi:10.1097/01.hjh.0000431740.32696.cc.
- Weber MA, Schiffrin EL, White WB, et al. Clinical practice guidelines for the management of hypertension in the community a statement by the American Society of Hypertension and the International Society of Hypertension. *J Hypertens* 2014;32:3-15. doi:10.1097/HJH.0000000000000065.
- James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA* 2014;311:507-20. doi:10.1001/jama.2013.284427.
- American Diabetes Association. Standards of medical care in diabetes-2015: summary of revisions. *Diabetes Care* 2015;38:S4doi:10.2337/dc15-S003.
- Emdin CA, Rahimi K, Neal B, Callender T, Perkovic V, Patel A. Blood pressure lowering in type 2 diabetes: a systematic review and meta-analysis. *JAMA* 2015;313:603-15. doi:10.1001/jama.2014.18574.
- Higgins J, Green S. *Cochrane Handbook for Systematic Reviews of Interventions*. John Wiley & Sons Ltd, 2011.
- Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. *BMJ* 2009;338:b1665. doi:10.1136/bmj.b1665.
- Thompson AM, Hu T, Eshelbrenner CL, Reynolds K, He J, Bazzano LA. Antihypertensive treatment and secondary prevention of cardiovascular disease events among persons without hypertension: a meta-analysis. *JAMA* 2011;305:913-22. doi:10.1001/jama.2011.250.

- 17 Sipahi I, Swaminathan A, Natesan V, Debanne SM, Simon DI, Fang JC. Effect of antihypertensive therapy on incident stroke in cohorts with prehypertensive blood pressure levels: a meta-analysis of randomized controlled trials. *Stroke* 2012;43:432-40. doi:10.1161/STROKEAHA.111.636829.
- 18 Higgins JPT, Altman DG, Gøtzsche PC, et al. Cochrane Bias Methods Group Cochrane Statistical Methods Group. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;343:d5928. doi:10.1136/bmj.d5928.
- 19 Rapsomaniki E, Timmis A, George J, et al. Blood pressure and incidence of twelve cardiovascular diseases: lifetime risks, healthy life-years lost, and age-specific associations in 1.25 million people. *Lancet* 2014;383:1899-911. doi:10.1016/S0140-6736(14)60685-1.
- 20 Estacio RO, Coll JR, Tran ZV, Schrier RW. Effect of intensive blood pressure control with valsartan on urinary albumin excretion in normotensive patients with type 2 diabetes. *Am J Hypertens* 2006;19:1241-8. doi:10.1016/j.amjhyper.2006.05.011.
- 21 Estacio RO, Jeffers BW, Gifford N, Schrier RW. Effect of blood pressure control on diabetic microvascular complications in patients with hypertension and type 2 diabetes. *Diabetes Care* 2000;23(Suppl 2):B54-64.
- 22 Schrier RW, Estacio RO, Esler A, Mehler P. Effects of aggressive blood pressure control in normotensive type 2 diabetic patients on albuminuria, retinopathy and strokes. *Kidney Int* 2002;61:1086-97. doi:10.1046/j.1523-1755.2002.00213.x.
- 23 Cushman WC, Evans GW, Byington RP, et al. ACCORD Study Group. Effects of intensive blood-pressure control in type 2 diabetes mellitus. *N Engl J Med* 2010;362:1575-85. doi:10.1056/NEJMoa1001286.
- 24 Poole-Wilson PA, Lubsen J, Kirwan BA, et al. Coronary Disease Trial Investigating Outcome with Nifedipine gastrointestinal therapeutic system investigators. Effect of long-acting nifedipine on mortality and cardiovascular morbidity in patients with stable angina requiring treatment (ACTION trial): randomised controlled trial. *Lancet* 2004;364:849-57. doi:10.1016/S0140-6736(04)16980-8.
- 25 Wagener G. Calcium antagonists and hypertension: role of co-existent coronary disease, impaired renal function and diabetes. Erasmus University Rotterdam; 2007. <http://hdl.handle.net/1765/10627>.
- 26 Patel A, MacMahon S, Chalmers J, et al. ADVANCE Collaborative Group. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. *Lancet* 2007;370:829-40. doi:10.1016/S0140-6736(07)61303-8.
- 27 de Galan BE, Perkovic V, Ninomiya T, et al. ADVANCE Collaborative Group. Lowering blood pressure reduces renal events in type 2 diabetes. *J Am Soc Nephrol* 2009;20:883-92. doi:10.1681/ASN.2008070667.
- 28 Parving HH, Brenner BM, McMurray JJV, et al. ALTITUDE Investigators. Cardiorenal end points in a trial of aliskiren for type 2 diabetes. *N Engl J Med* 2012;367:2204-13. doi:10.1056/NEJMoa1208799.
- 29 O'Hare P, Bilbous R, Mitchell T, O'Callaghan CJ, Viberti GC. ACE-Inhibitor Trial to Lower Albuminuria in Normotensive Insulin-Dependent Subjects Study Group. Low-dose ramipril reduces microalbuminuria in type 1 diabetic patients without hypertension: results of a randomized controlled trial. *Diabetes Care* 2000;23:1823-9. doi:10.2337/diacare.23.12.1823.
- 30 Ruggenenti P, Fassi A, Ilieva AP, et al. Bergamo Nephrologic Diabetes Complications Trial (BENEDICT) Investigators. Preventing microalbuminuria in type 2 diabetes. *N Engl J Med* 2004;351:1941-51. doi:10.1056/NEJMoa042167.
- 31 Ruggenenti P, Fassi A, Ilieva A, et al. BENEDICT-B Study Investigators. Effects of verapamil added-on trandolapril therapy in hypertensive type 2 diabetes patients with microalbuminuria: the BENEDICT-B randomized trial. *J Hypertens* 2011;29:207-16. doi:10.1097/HJH.0b013e32834069bd.
- 32 Nissen SE, Tuzcu EM, Libby P, et al. CAMELOT Investigators. Effect of antihypertensive agents on cardiovascular events in patients with coronary disease and normal blood pressure: the CAMELOT study: a randomized controlled trial. *JAMA* 2004;292:2217-25. doi:10.1001/jama.292.18.2217.
- 33 Ruggenenti P, Lauria G, Iliev IP, et al. DEMAND Study Investigators. Effects of manidipine and delapril in hypertensive patients with type 2 diabetes mellitus: the delapril and manidipine for nephroprotection in diabetes (DEMAND) randomized clinical trial. *Hypertension* 2011;58:776-83. doi:10.1161/HYPERTENSIONAHA.111.174474.
- 34 Marre M, Lievre M, Chatellier G, Mann JF, Passa P, Ménard J. DIABHYCAR Study Investigators. Effects of low dose ramipril on cardiovascular and renal outcomes in patients with type 2 diabetes and raised excretion of urinary albumin: randomised, double blind, placebo controlled trial (the DIABHYCAR study). *BMJ* 2004;328:495-9. doi:10.1136/bmj.37970.629537.0D.
- 35 Tillin T, Orchard T, Malm A, Fuller J, Chaturvedi N. The role of antihypertensive therapy in reducing vascular complications of type 2 diabetes. Findings from the Diabetic RETinopathy Candesartan Trials-Protect 2 study. *J Hypertens* 2011;29:1457-62. doi:10.1097/HJH.0b013e3283480db9.
- 36 Amery A, Birkenhäger W, Brixko P, et al. Mortality and morbidity results from the European Working Party on High blood pressure in the Elderly trial. *Lancet* 1985;1:1349-54. doi:10.1016/S0140-6736(85)91783-0.
- 37 Zhang Y, Zhang X, Liu L, Zanchetti A, Grp FS. FEVER Study Group. Is a systolic blood pressure target <140 mmHg indicated in all hypertensives? Subgroup analyses of findings from the randomized FEVER trial. *Eur Heart J* 2011;32:1500-8. doi:10.1093/eurheartj/ehr039.
- 38 Fogari R, Preti P, Zoppi A, et al. Effects of amlodipine fosinopril combination on microalbuminuria in hypertensive type 2 diabetic patients. *Am J Hypertens* 2002;15:1042-9. doi:10.1016/S0895-7061(02)03017-0.
- 39 Langford HG, Stamler J, Wassertheil-Smolter S, Prineas RJ. All-cause mortality in the Hypertension Detection and Follow-up Program: findings for the whole cohort and for persons with less severe hypertension, with and without other traits related to risk of mortality. *Prog Cardiovasc Dis* 1986;29(Suppl 1):29-54. doi:10.1016/0033-0620(86)90033-2.
- 40 Hansson L, Zanchetti A, Carruthers SG, et al. HOT Study Group. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. *Lancet* 1998;351:1755-62. doi:10.1016/S0140-6736(98)04311-6.
- 41 Hypertension-Stroke Cooperative Study Group. Effect of antihypertensive treatment on stroke recurrence. *JAMA* 1974;229:409-18. doi:10.1001/jama.1974.03230420021019.
- 42 Lewis EJ, Hunsicker LG, Clarke WR, et al. Collaborative Study Group. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med* 2001;345:851-60. doi:10.1056/NEJMoa011303.
- 43 Parving HH, Lehnert H, Bröchner-Mortensen J, Gomis R, Andersen S, Arner P. Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria Study Group. The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. *N Engl J Med* 2001;345:870-8. doi:10.1056/NEJMoa011489.
- 44 JATOS Study Group. Principal results of the Japanese trial to assess optimal systolic blood pressure in elderly hypertensive patients (JATOS). *Hypertens Res* 2008;31:2115-27. doi:10.1291/hyres.31.2115.
- 45 Laffel LMB, McGill JB, Gans DJ. North American Microalbuminuria Study Group. The beneficial effect of angiotensin-converting enzyme inhibition with captopril on diabetic nephropathy in normotensive IDDM patients with microalbuminuria. *Am J Med* 1995;99:497-504. doi:10.1016/S0002-9343(99)80226-5.
- 46 Lewis EJ, Hunsicker LG, Bain RP, Rohde RD. The Collaborative Study Group. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. *N Engl J Med* 1993;329:1456-62. doi:10.1056/NEJM19931113292004.
- 47 Deedwania PC, Giles TD, Klibaner M, et al. MERIT-HF Study Group. Efficacy, safety and tolerability of metoprolol CR/XL in patients with diabetes and chronic heart failure: experiences from MERIT-HF. *Am Heart J* 2005;149:159-67. doi:10.1016/j.ahj.2004.05.056.
- 48 Gerstein HC, Yusuf S, Mann JFE, et al. Heart Outcomes Prevention Evaluation Study Investigators. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. *Lancet* 2000;355:253-9. doi:10.1016/S0140-6736(99)12323-7.
- 49 Imai E, Chan JCN, Ito S, et al. ORIENT study investigators. Effects of olmesartan on renal and cardiovascular outcomes in type 2 diabetes with overt nephropathy: a multicentre, randomised, placebo-controlled study. *Diabetologia* 2011;54:2978-86. doi:10.1007/s00125-011-2325-z.
- 50 Braunwald E, Domanski MJ, Fowler SE, et al. PEACE Trial Investigators. Angiotensin-converting-enzyme inhibition in stable coronary artery disease. *N Engl J Med* 2004;351:2058-68. doi:10.1056/NEJMoa042739.
- 51 Daly CA, Fox KM, Remme WJ, Bertrand ME, Ferrari R, Simoons ML. EUROPA Investigators. The effect of perindopril on cardiovascular morbidity and mortality in patients with diabetes in the EUROPA study: results from the PERSUADE substudy. *Eur Heart J* 2005;26:1369-78. doi:10.1093/eurheartj/ehi225.
- 52 Lüders S, Schrader J, Berger J, et al. PHARAO Study Group. The PHARAO study: prevention of hypertension with the angiotensin-converting enzyme inhibitor ramipril in patients with high-normal blood pressure: a prospective, randomized, controlled prevention trial of the German Hypertension League. *J Hypertens* 2008;26:1487-96. doi:10.1097/HJH.0b013e3283282f8864.
- 53 Yusuf S, Diener HC, Sacco RL, et al. PROGRESS Study Group. Telmisartan to prevent recurrent stroke and cardiovascular events. *N Engl J Med* 2008;359:1225-37. doi:10.1056/NEJMoa0804593.
- 54 Berthet K, Neal BC, Chalmers JP, et al. Perindopril Protection Against Recurrent Stroke Collaborative Group. Reductions in the risks of recurrent stroke in patients with and without diabetes: the PROGRESS Trial. *Blood Press* 2004;13:7-13. doi:10.1080/08037050410029605.

- 55 Mauer M, Zinman B, Gardiner R, et al. Renal and retinal effects of enalapril and losartan in type 1 diabetes. *N Engl J Med* 2009;361:40-51. doi:10.1056/NEJMoa0808400.
- 56 Brenner BM, Cooper ME, de Zeeuw D, et al. RENAAL Study Investigators. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med* 2001;345:861-9. doi:10.1056/NEJMoa011161.
- 57 Kowey PR, Dickson TZ, Zhang Z, Shahinfar S, Brenner BM, Investigators R. RENAAL Investigators. Losartan and end-organ protection--lessons from the RENAAL study. *Clin Cardiol* 2005;28:136-42. doi:10.1002/clc.4960280307.
- 58 Haller H, Ito S, Izzo JL Jr, et al. ROADMAP Trial Investigators. Olmesartan for the delay or prevention of microalbuminuria in type 2 diabetes. *N Engl J Med* 2011;364:907-17. doi:10.1056/NEJMoa1007994.
- 59 Ravid M, Brosh D, Levi Z, Bar-Dayan Y, Ravid D, Rachmani R. Use of enalapril to attenuate decline in renal function in normotensive, normoalbuminuric patients with type 2 diabetes mellitus. A randomized, controlled trial. *Ann Intern Med* 1998;128:982-8. doi:10.7326/0003-4819-128-12_Part_1-199806150-00004.
- 60 Pfeffer MA, Braunwald E, Moyé LA, et al. The SAVE Investigators. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. *N Engl J Med* 1992;327:669-77. doi:10.1056/NEJM199209033271001.
- 61 Trenkwalder P, Elmfeldt D, Hofman A, et al. Study on COgnition and Prognosis in the Elderly (SCOPE). The Study on COgnition and Prognosis in the Elderly (SCOPE) - major CV events and stroke in subgroups of patients. *Blood Press* 2005;14:31-7. doi:10.1080/08037050510008823.
- 62 Curb JD, Pressel SL, Cutler JA, et al. Systolic Hypertension in the Elderly Program Cooperative Research Group. Effect of diuretic-based antihypertensive treatment on cardiovascular disease risk in older diabetic patients with isolated systolic hypertension. *JAMA* 1996;276:1886-92. doi:10.1001/jama.1996.03540230036032.
- 63 Shindler DM, Kostis JB, Yusuf S, et al. Diabetes mellitus, a predictor of morbidity and mortality in the studies of left ventricular dysfunction (SOLVD) trials and registry. *Am J Cardiol* 1996;77:1017-20. doi:10.1016/S0002-9149(97)89163-1.
- 64 Benavente OR, Coffey CS, Conwit R, et al. SPS3 Study Group. Blood-pressure targets in patients with recent lacunar stroke: the SPS3 randomised trial. *Lancet* 2013;382:507-15. doi:10.1016/S0140-6736(13)60852-1.
- 65 Dahlöf B, Lindholm LH, Hansson L, Scherström B, Ekblom T, Wester PO. Morbidity and mortality in the Swedish Trial in Old Patients with Hypertension (STOP-Hypertension). *Lancet* 1991;338:1281-5. doi:10.1016/0140-6736(91)92589-T.
- 66 Staessen JA, Fagard R, Thijs L, et al. The Systolic Hypertension in Europe (Syst-Eur) Trial Investigators. Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. *Lancet* 1997;350:757-64. doi:10.1016/S0140-6736(97)05381-6.
- 67 Køber L, Torp-Pedersen C, Carlsen JE, et al. Trandolapril Cardiac Evaluation (TRACE) Study Group. A clinical trial of the angiotensin-converting-enzyme inhibitor trandolapril in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 1995;333:1670-6. doi:10.1056/NEJM199512213332503.
- 68 UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. *BMJ* 1998;317:703-13. doi:10.1136/bmj.317.7160.703.
- 69 UK Prospective Diabetes Study Group. Efficacy of atenolol and captopril in reducing risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 39. *BMJ* 1998;317:713-20. doi:10.1136/bmj.317.7160.713.
- 70 Fried LF, Emanuele N, Zhang JH, et al. VA NEPHRON-D Investigators. Combined angiotensin inhibition for the treatment of diabetic nephropathy. *N Engl J Med* 2013;369:1892-903. doi:10.1056/NEJMoa1303154.
- 71 Cohn JN, Tognoni G. Valsartan Heart Failure Trial Investigators. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. *N Engl J Med* 2001;345:1667-75. doi:10.1056/NEJMoa010713.
- 72 Ogihara T, Saruta T, Rakugi H, et al. Valsartan in Elderly Isolated Systolic Hypertension Study Group. Target blood pressure for treatment of isolated systolic hypertension in the elderly: valsartan in elderly isolated systolic hypertension study. *Hypertension* 2010;56:196-202. doi:10.1161/HYPERTENSIONAHA.109.146035.
- 73 Thomopoulos C, Parati G, Zanchetti A. Effects of blood pressure-lowering on outcome incidence in hypertension: 5. Head-to-head comparisons of various classes of antihypertensive drugs - overview and meta-analyses. *J Hypertens* 2015;33:1321-41. doi:10.1097/HJH.0000000000000447.
- 74 Wright JT Jr, Williamson JD, Whelton PK, et al. SPRINT Research Group. A randomized trial of intensive versus standard blood pressure control. *N Engl J Med* 2015;373:2103-16. doi:10.1056/NEJMoa1511939.
- 75 Sundström J, Shekhi R, Ostgren CJ, et al. Blood pressure levels and risk of cardiovascular events and mortality in type-2 diabetes: cohort study of 34 009 primary care patients. *J Hypertens* 2013;31:1603-10. doi:10.1097/HJH.0b013e32836123aa.
- 76 Zhao W, Katzmarzyk PT, Horswell R, et al. Aggressive blood pressure control increases coronary heart disease risk among diabetic patients. *Diabetes Care* 2013;36:3287-96. doi:10.2337/dc13-0189.
- 77 Messerli FH, Panjath GS. The J-curve between blood pressure and coronary artery disease or essential hypertension: exactly how essential? *Am Coll Cardiol* 2009;54:1827-34. doi:10.1016/j.jacc.2009.05.073.
- 78 Rabkin SW, Waheed A, Poulter RS, Wood D. Myocardial perfusion pressure in patients with hypertension and coronary artery disease: implications for DBP targets in hypertension management. *J Hypertens* 2013;31:975-82. doi:10.1097/HJH.0b013e32835e831c.
- 79 Ziemann SJ, Melenovsky V, Kass DA. Mechanisms, pathophysiology, and therapy of arterial stiffness. *Arterioscler Thromb Vasc Biol* 2005;25:932-43. doi:10.1161/01.ATV.0000160548.78317.29.
- 80 Shu W, Jing J, Fu LC, et al. The relationship between diastolic pressure and coronary collateral circulation in patients with stable angina pectoris and chronic total occlusion. *Am J Hypertens* 2013;26:630-5. doi:10.1093/ajh/hps096.

Web appendix: supplementary information