Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis

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Summary

Background The benefits of blood pressure lowering treatment for prevention of cardiovascular disease are well established. However, the extent to which these effects differ by baseline blood pressure, presence of comorbidities, or drug class is less clear. We therefore performed a systematic review and meta-analysis to clarify these differences.

Method For this systematic review and meta-analysis, we searched MEDLINE for large-scale blood pressure lowering trials, published between Jan 1, 1966, and July 7, 2015, and we searched the medical literature to identify trials up to Nov 9, 2015. All randomised controlled trials of blood pressure lowering treatment were eligible for inclusion if they included a minimum of 1000 patient-years of follow-up in each study arm. No trials were excluded because of presence of baseline comorbidities, and trials of antihypertensive drugs for indications other than hypertension were eligible. We extracted summary-level data about study characteristics and the outcomes of major cardiovascular disease events, coronary heart disease, stroke, heart failure, renal failure, and all-cause mortality. We used inverse variance weighted fixed-effects meta-analyses to pool the estimates.

Results We identified 123 studies with 613 815 participants for the tabular meta-analysis. Meta-regression analyses showed relative risk reductions proportional to the magnitude of the blood pressure reductions achieved. Every 10 mm Hg reduction in systolic blood pressure significantly reduced the risk of major cardiovascular disease events (relative risk [RR] 0·80, 95% CI 0·77–0·83), coronary heart disease (0·83, 0·78–0·88), stroke (0·73, 0·68–0·77), and heart failure (0·72, 0·67–0·78), which, in the populations studied, led to a significant 13% reduction in all-cause mortality (0·87, 0·84–0·91). However, the effect on renal failure was not significant (0·95, 0·84–1·07). Similar proportional risk reductions (per 10 mm Hg lower systolic blood pressure) were noted in trials with higher mean baseline systolic blood pressure and trials with lower mean baseline systolic blood pressure (all $p_{trend}>0·05$). There was no clear evidence that proportional risk reductions in major cardiovascular disease differed by baseline disease history, except for diabetes and chronic kidney disease, for which smaller, but significant, risk reductions were detected. β blockers were inferior to other drugs for the prevention of major cardiovascular disease events, stroke, and renal failure. Calcium channel blockers were superior to other drugs for the prevention of stroke. For the prevention of heart failure, calcium channel blockers were inferior and diuretics were superior to other drug classes. Risk of bias was judged to be low for 113 trials and unclear for 10 trials. Heterogeneity for outcomes was low to moderate; the I^2 statistic for heterogeneity for major cardiovascular disease events was 41%, for coronary heart disease 25%, for stroke 26%, for heart failure 37%, for renal failure 28%, and for all-cause mortality 35%.

Interpretation Blood pressure lowering significantly reduces vascular risk across various baseline blood pressure levels and comorbidities. Our results provide strong support for lowering blood pressure to systolic blood pressures less than 130 mm Hg and providing blood pressure lowering treatment to individuals with a history of cardiovascular disease, coronary heart disease, stroke, diabetes, heart failure, and chronic kidney disease.

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Introduction

Elevated blood pressure is the most important risk factor for death and disability worldwide, affecting more than one billion individuals and causing an estimated 9·4 million deaths every year.[1] Prospective cohort studies have reported a continuous log-linear association between blood pressure and vascular events to a blood pressure of 115/75 mm Hg, with no apparent threshold.[2] This association seems to exist across large and diverse population groups, including men and women, individuals aged 40–89 years, from different ethnicities, with and without established vascular disease.[2–4] Despite this robust observational evidence, whether blood pressure lowering treatment reduces the risk of cardiovascular disease in all patient populations remains unclear.

Although the benefits of blood pressure lowering have long been established in randomised trials of patients with substantially raised blood pressures,[5–8] evidence for the protective effects of pharmacologically-induced blood pressure reduction in individuals with lower blood pressure or with comorbidities, have been less certain.[9–12] Furthermore, the best approach to reduce blood pressure remains subject to controversy.[13–16]

Research in context

Evidence before this study

Although the benefits of blood pressure lowering treatment for prevention of cardiovascular disease are well established, the extent to which these effects differ by baseline blood pressure, presence of comorbidities, or drug class is less clear.

Added value of this study

Our study provides a comprehensive systematic review and meta-analysis of all available large-scale blood pressure lowering randomised trials. Our findings show that pharmacological blood pressure lowering results in similar proportional reductions in risk of cardiovascular disease and death to a mean baseline systolic blood pressure of less than 130 mm Hg. Furthermore, we noted that proportional risk reductions are broadly similar among individuals with or without major cardiovascular comorbidities. Finally, our findings emphasise the fact that, despite the general efficacy of commonly prescribed blood pressure lowering drug classes in preventing cardiovascular disease, there are some significant differences among them in the reduction of risk of specific clinical outcomes. For example, calcium channel blockers seem to be more effective than other classes of drugs for stroke prevention, and diuretics are more effective for prevention of heart failure.

Implications of all the available evidence

Our study has several implications for clinical practice. First, our findings suggest that blood pressure lowering to levels below those recommended in current guidelines (ie, systolic blood pressure of less than 140 mm Hg) will reduce the risk of cardiovascular disease. Second, by showing no evidence for a threshold below which blood pressure lowering ceases to work, the findings call for blood pressure lowering based on an individual's potential net benefit from treatment rather than treatment of the risk factor to a specific target. Third, the broad consistency of the findings across patients with or without prior vascular disease could help to simplify clinical guidelines for use of blood pressure lowering drugs. Fourth, the differences we identified between classes of drugs support more targeted drug use for individuals at high risk of specific outcomes (eg, calcium channel blocker therapy for individuals at high risk of stroke).

Recent major guidelines have reversed a trend toward lower blood pressure thresholds and targets, recommending higher targets and threshold for blood pressure lowering than have previous guidelines.[14,17,18] The SPRINT trial[12] reported the benefits of blood pressure lowering to 120 mm Hg in some high-risk groups of patients. However uncertainty remains as to whether such benefits hold for high-risk individuals excluded from the trial, especially those with diabetes or cerebrovascular disease.[12]

In this systematic review and meta-analysis, we aimed to combine data from all published large-scale blood pressure lowering trials to quantify the effects of blood pressure reduction on cardiovascular outcomes and death across various baseline blood pressure levels, major comorbidities, and different pharmacological interventions.

Methods

Search strategy and selection criteria

The systematic review and tabular meta-analysis adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for meta-analyses of interventional studies.[19] We searched MEDLINE from Jan 1, 1966, to July 7, 2015, using an existing search strategy[16] with the terms "antihypertensive agents" or "hypertension" or "diuretics", "thiazide", or "angiotensin-converting enzyme" or "angiotensin-converting enzyme inhibitors" or "receptors, angiotensin/antagonists & inhibitors" or "tetrazoles" or "calcium channel blockers" or "vasodilator agents" or the names of all blood pressure lowering drugs listed in the British National Formulary as keywords or text words or the MeSH term "blood pressure/drug effects". Search terms used in the MEDLINE search are provided in the appendix (pp 39–41). We restricted our search to clinical trials, controlled clinical trials, randomised controlled trials, or meta-analyses. We applied no language restrictions. Reference lists of eligible studies and related meta-analyses were hand searched to identify further relevant studies.

See Online for appendix

All randomised controlled trials of blood pressure lowering treatment published between Jan 1, 1966, and Nov 9, 2015, were eligible for inclusion. Eligible studies fell into three categories: first, random allocation of participants to a blood pressure lowering drug or placebo; second, random allocation of participants to different blood pressure lowering drugs; and third, random allocation of participants to different blood pressure lowering targets. To minimise the risk of small-study effects,[20] all studies were required to have a minimum of 1000 patient-years of follow-up in each study group, the same criterion applied in the Blood Pressure Lowering Treatment Trialists' Collaboration (BPLTTC).[21] Trials of antihypertensive drugs for indications other than hypertension were eligible. No trials were excluded because of the presence of baseline comorbidities.

Data analysis

Two researchers (DE and CAE) screened all abstracts identified in the initial search and excluded studies in violation of the inclusion criteria. Full-text articles were subsequently reviewed in duplicate and, in cases of disagreement, consensus was achieved through referral

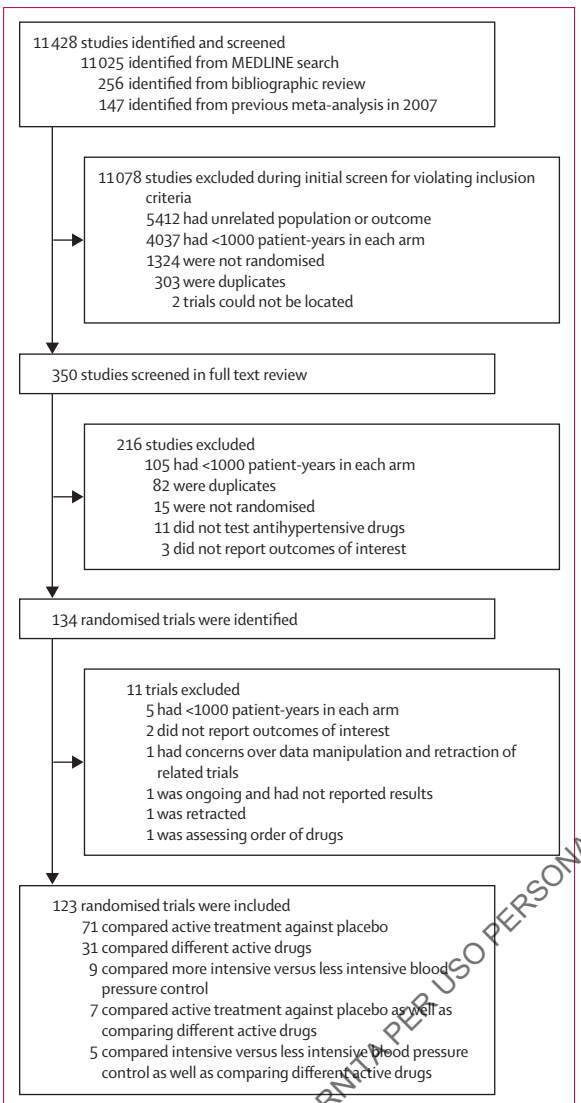

Figure 1: **Study selection**

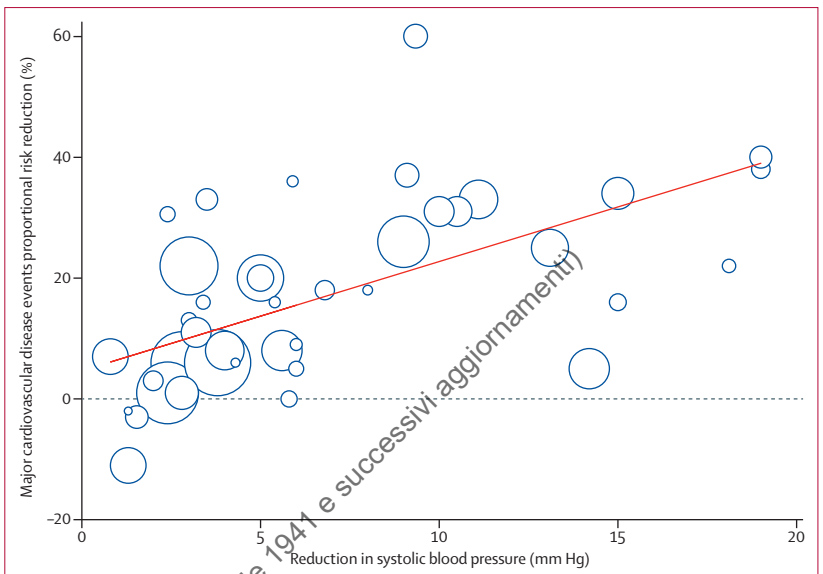

Figure 2: **Meta-regression plot**
Plot shows the percentage risk reduction in major cardiovascular events regressed against the difference in achieved systolic blood pressure between study treatment groups.

to a third reviewer (KR). An electronic data abstraction form was used to record patient and study characteristics, including sample size, treatment comparisons, baseline blood pressure, blood pressure achieved, and mean blood pressure reduction. If not reported, corresponding authors were contacted to obtain data about baseline and achieved blood pressure by use of individually tailored data request forms.

Data were also extracted for major cardiovascular disease events (defined as fatal and non-fatal myocardial infarction, sudden cardiac death, revascularisation, fatal and non-fatal stroke, and fatal and non-fatal heart failure), coronary heart disease (fatal and non-fatal myocardial infarction and sudden cardiac death, excluding silent myocardial infarction), stroke (fatal and non-fatal, excluding transient ischaemic attacks), heart failure (new diagnosis of heart failure, hospital admission, or death), renal failure (end-stage renal disease resulting in dialysis, transplantation, or death), and all-cause mortality. Information was extracted about the number of patients in each group with the baseline comorbidities of cardiovascular disease, coronary heart disease, cerebrovascular accident (history of stroke or transient ischaemic attack), type 2 diabetes, heart failure, and chronic kidney disease (self-reported chronic kidney disease or creatinine clearance <30 mL/min). The SPRINT trial[12] reported renal failure for patients with chronic kidney disease at baseline; this was recorded for the entire trial.

For all outcomes, the number of events in each group and the summary statistic (either relative risk [RR] or hazard ratio [HR] and 95% CIs) were extracted. We used HRs preferentially to RRs because they incorporate time-to-event and allow for censoring.[22] When neither summary statistic was provided, we calculated RRs from the number of events and participants in each treatment group. Conversely, if the total number of events was missing, we estimated it using the summary statistic and its confidence interval.

We used the Cochrane risk of bias tool to assess the methodological quality of the eligible trials.[23] Selection bias (randomisation and allocation concealment), performance bias (blinding of participants and investigators), detection bias (blinding of outcome adjudicators), attrition bias (differential loss to follow-up), and reporting bias (selective outcome reporting) were judged to be of low, unclear, or high risk for each trial. We then judged each trial as a whole to ascertain whether there was low, unclear, or high risk of bias, based on whether the level of bias in each of the defined domains could have led to material biases in the risk estimates.

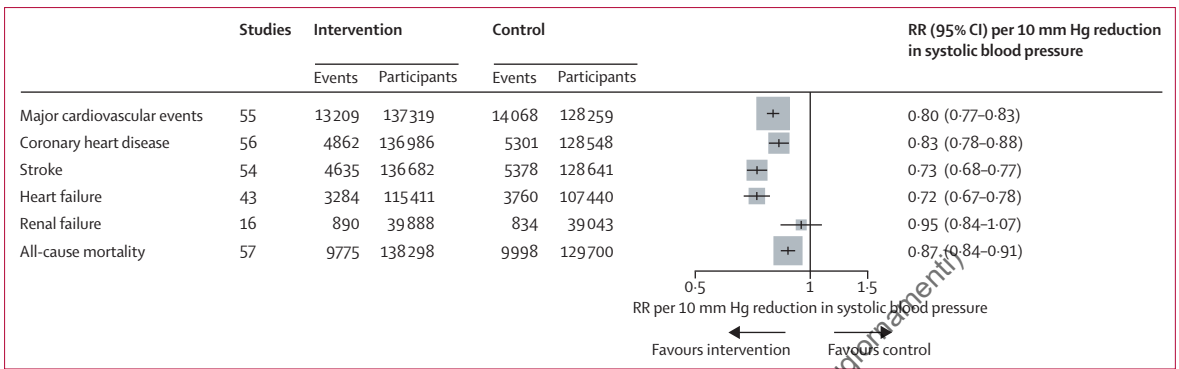

Figure 3: **Standardised effects of a 10 mm Hg reduction in systolic blood pressure**
RR=relative risk.

Statistical analysis

We calculated overall summary estimates and 95% CIs with inverse variance weighted fixed-effects meta-analyses because heterogeneity was low[24] and random-effects meta-analysis might apply inappropriately large weights to smaller studies.[25] We characterised heterogeneity with the I^2 statistic. We used Cochran's Q statistic to test for subgroup interactions and χ^2 tests to test for trend in analyses stratified by baseline systolic blood pressure. All p values were calculated from two-tailed tests of statistical significance with a type I error rate of 5%.

We did analyses to establish, first, the effect of a 10 mm Hg blood pressure reduction on the relative risk of major cardiovascular disease, coronary heart disease, stroke, heart failure, renal failure, and all-cause mortality; second, the effect of a 10 mm Hg blood pressure reduction at different baseline blood pressure levels by stratification of trials into five strata of reported mean baseline systolic blood pressure at the trial level (<130, 130–139, 140–149, 150–159, and ≥160 mm Hg); third, the effects of a 10 mm Hg blood pressure reduction on the relative risk of major cardiovascular disease, coronary heart disease, stroke, heart failure, renal failure, and all-cause mortality in the presence of baseline comorbidities (cardiovascular disease, coronary heart disease, cerebrovascular accident, type 2 diabetes, heart failure, and chronic kidney disease) by investigation of possible interactions in treatment effect by these comorbidities; and fourth, the effects of different classes of blood pressure lowering drugs.

For the first three objectives, we standardised the analyses to a 10 mm Hg reduction in systolic blood pressure because we were interested in the proportional effects of lowering systolic blood pressure by 10 mm Hg and because the trials varied in the relative intensity of blood pressure lowering achieved due to differences in strategies and drugs. We standardised the analyses by multiplying the log of the summary statistic of each trial (and its standard error) by 10/d, where d was the average systolic blood pressure reduction in that trial. For example, if the logHR was −0·2 and the systolic blood pressure reduction was 4 mm Hg, the standardised logHR would be $-0{\cdot}2\times(10/4)=-0{\cdot}5$. We examined non-standardised effects of blood pressure lowering by baseline systolic blood pressure in sensitivity analyses.

We did meta-regression to assess the validity of the assumption that reductions in RR would be proportional to the achieved blood pressure reduction. The percentage reductions in proportional risk of major cardiovascular disease events, coronary heart disease, stroke, heart failure, renal failure, and all-cause mortality were regressed against the difference in mean achieved systolic blood pressure between the intervention and control groups.

Trials of blood pressure lowering drugs versus placebo or higher versus lower blood pressure targets were combined for the purposes of the first three objectives. For the six trials with three arms, including two active groups and a placebo group[10,26–31] and the one trial that had four arms including a placebo group,[32] we combined the active groups for the blood pressure lowering analysis by combining the events and taking a weighted average of baseline blood pressure, achieved blood pressure, and blood pressure reduction.

For the fourth objective, the comparison of drug classes, we did not standardise the analyses in order to account for variations in blood pressure lowering efficacy, tolerability, or non-blood pressure-mediated effects of the different drug classes. In these analyses, we examined possible differences in the effects of blood pressure lowering by drug class by comparing trials that tested a specific class of drug (angiotensin-converting enzyme [ACE] inhibitors, angiotensin receptor blockers [ARB], β blockers, diuretics, and calcium channel blockers [CCB]) against all other classes that it has been compared with. Because the pooled comparators might vary for each class (for example, β blockers might have mostly been tested against CCBs, whereas diuretics might have mostly been tested against ACE inhibitors), we also did an analysis in which we compared each individual drug class to all of the individual classes it has been tested against.

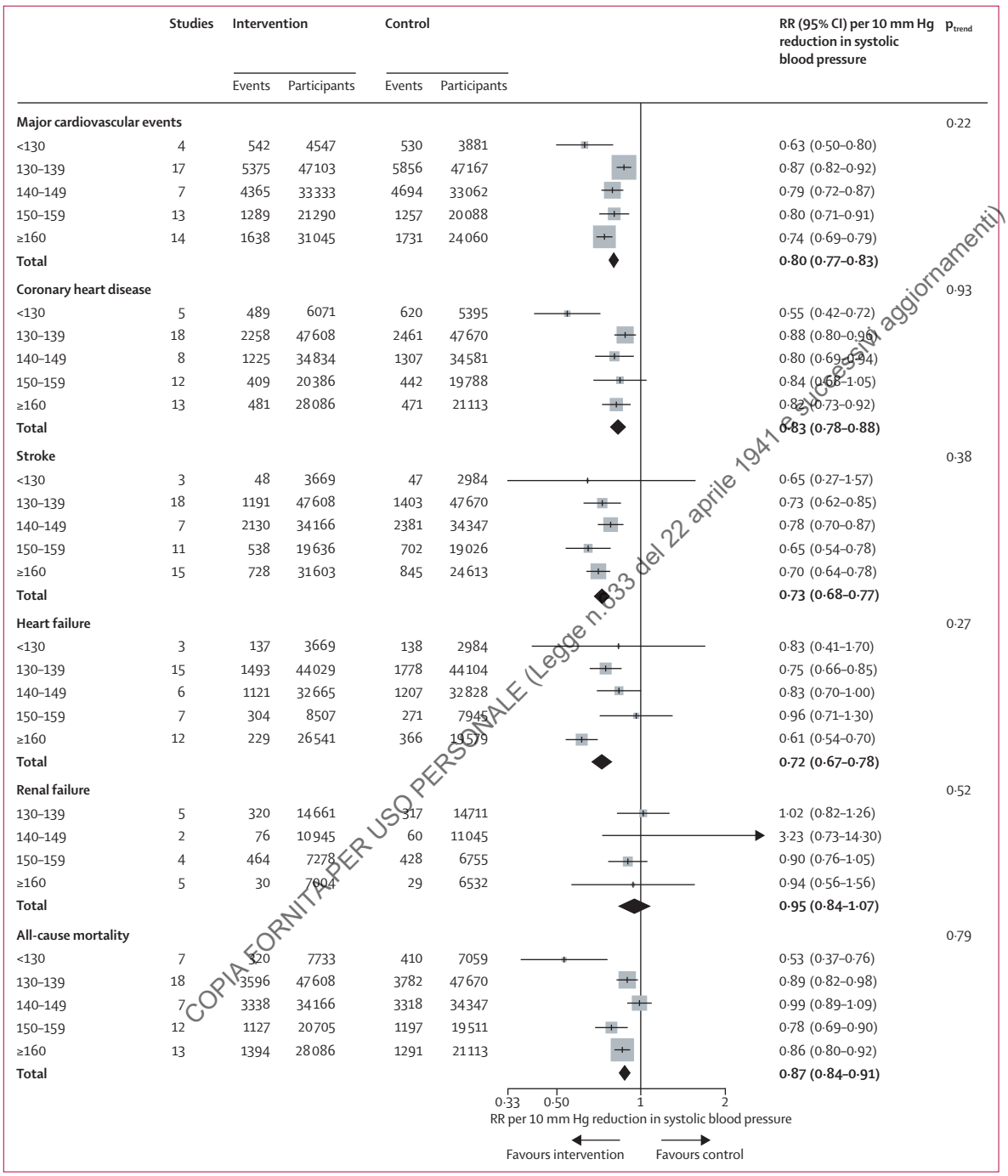

Figure 4: **Standardised effects of a 10 mm Hg reduction in systolic blood pressure stratified by blood pressure**
Blood pressure strata are baseline blood pressure values, not achieved blood pressure after treatment. RR=relative risk.

We excluded trials that were done in populations with heart failure or left ventricular systolic dysfunction from all of the main standardised analyses, because the effects of antihypertensive use on achieved blood pressure in heart failure have been reported to vary substantially with baseline blood pressure within the same trial population (thus rendering mean achieved blood pressure less meaningful).[33–35] Furthermore, only a few heart failure trials have actually reported mean achieved blood pressure by treatment allocation. However, we did complementary sensitivity analyses that included heart failure trials (both standardised and non-standardised) with the available information from published reports.

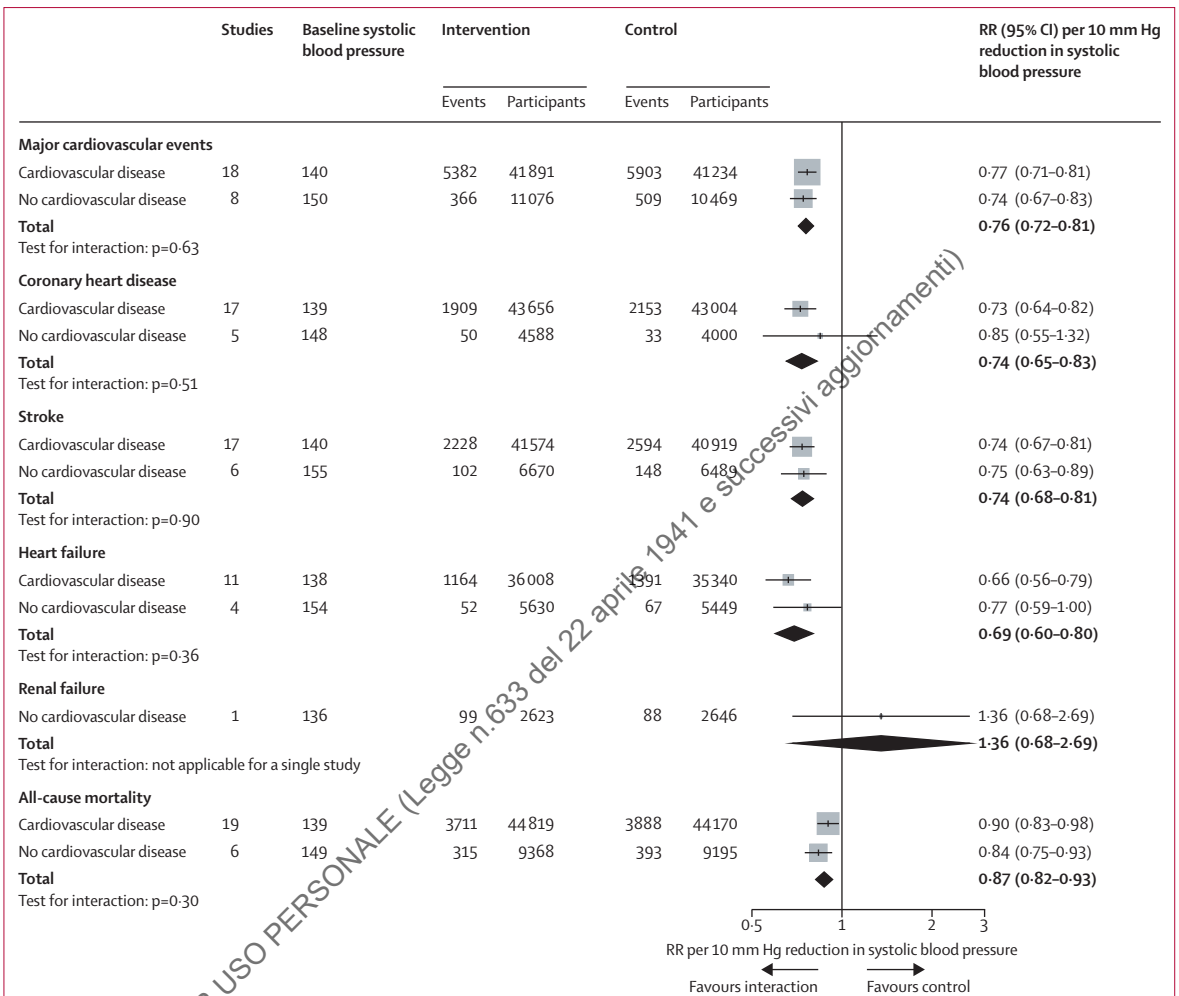

Figure 5: **Standardised effects of a 10 mm Hg reduction in systolic blood pressure stratified by history of cardiovascular disease**
Data are stratified by subgroups in which all (cardiovascular disease) or none (no cardiovascular disease) of the participants had a history of cardiovascular disease at baseline. A cardiovascular disease subgroup is not shown for renal failure because no trial that reported renal failure as an outcome reported an analysis stratified by the presence of cardiovascular disease. RR=relative risk.

We did all analyses with Stata version 13.1 and R version 3.2.0.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. KR and DE had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

In total, we screened 11428 abstracts, of which 350 were eligible for full-text review (figure 1). Of the 134 randomised controlled trials identified, 123 trials with 613815 participants were eligible for inclusion in the meta-analysis. 92 studies were deemed to be trials of blood pressure lowering because they compared either blood pressure lowering drugs to placebo (78 trials) or different blood pressure lowering targets (14 trials; appendix pp 1–6, 10). 43 trials compared different drug classes and were included in the drug comparison analysis (appendix pp 1–10). 12 trials fell into both categories, with five trials assessing different blood pressure lowering targets and drug classes[36–42] and seven trials comparing blood pressure lowering drugs to placebo and different drug classes.[26,28–30,32,43,44] Ten studies were judged to be of unclear risk of bias and 113 were deemed to be at low risk of bias.[45–55] Heterogeneity for outcomes was low to moderate; the I^2 statistic for heterogeneity for major cardiovascular disease events was 41%, for coronary heart disease 25%, for stroke 26%, for heart failure 37%, for renal failure 28%, and for all-cause mortality 35%. The appendix shows details of the methods of blood pressure measurement for the included trials (appendix pp 11–14).

Meta-regression analyses showed relative risk reductions for major cardiovascular disease events

	Studies	Intervention		Control		RR (95% CI)
		Events	Participants	Events	Participants	
Major cardiovascular events						
ACE inhibitor	10	5379	31652	9766	50805	1·03 (1·00–1·06)
ARB	8	3647	27140	3779	29331	0·98 (0·93–1·02)
β blocker	9	2863	25989	2520	27231	1·17 (1·11–1·24)
CCB	21	7857	63693	12808	82904	0·97 (0·94–0·99)
Diuretic	11	5830	38353	6782	42410	0·97 (0·94–1·00)
Coronary heart disease						
ACE inhibitor	13	1718	33054	3355	52157	0·95 (0·90–1·01)
ARB	9	1135	27593	1080	28654	1·06 (0·98–1·15)
β blocker	11	1579	39864	1544	39966	1·03 (0·96–1·10)
CCB	25	2955	76465	4576	95725	0·98 (0·94–1·03)
Diuretic	11	2041	40531	2246	43508	1·02 (0·97–1·09)
Stroke						
ACE inhibitor	14	1502	33355	2297	52460	1·08 (1·01–1·16)
ARB	10	1150	28703	1265	30837	0·92 (0·85–0·99)
β blocker	12	1199	40953	989	42170	1·24 (1·14–1·35)
CCB	26	2245	76768	3470	96026	0·90 (0·85–0·95)
Diuretic	12	1215	41625	1409	45707	0·97 (0·90–1·05)
Heart failure						
ACE inhibitor	13	1494	32304	2706	50277	0·98 (0·92–1·05)
ARB	8	1141	26418	1187	26311	0·96 (0·89–1·04)
β blocker	8	652	33953	634	34185	1·04 (0·93–1·16)
CCB	22	2104	72323	2955	90403	1·17 (1·11–1·24)
Diuretic	8	1108	32580	1570	35435	0·81 (0·75–0·88)
Renal failure						
ACE inhibitor	6	220	19589	503	34992	0·85 (0·72–0·99)
ARB	5	160	19634	185	19589	0·85 (0·69–1·05)
β blocker	3	526	10417	468	10492	1·19 (1·05–1·34)
CCB	12	787	45024	1022	61117	1·02 (0·93–1·12)
Diuretic	3	220	20992	227	23827	0·93 (0·78–1·11)
All-cause mortality						
ACE inhibitor	14	3321	33104	5865	52263	1·01 (0·97–1·05)
ARB	11	2546	29282	2638	31404	0·99 (0·94–1·04)
β blocker	12	2805	40953	2688	42170	1·06 (1·01–1·12)
CCB	26	5602	76672	8428	95932	0·97 (0·94–1·00)
Diuretic	12	3425	41625	3806	45707	1·02 (0·97–1·06)

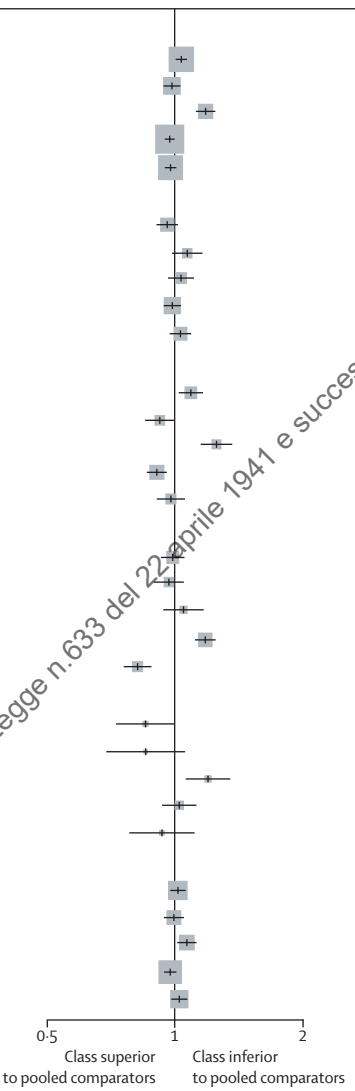

Figure 6: **Non-standardised effects of reductions in systolic blood pressure stratified by class of blood pressure lowering drug**
ACE=angiotensin-converting enzyme. ARB=angiotensin receptor blockers. CCB=calcium channel blockers. RR=relative risk.

(p<0·0001), stroke (p<0·0001), heart failure (p<0·0001), and all-cause mortality (p=0·014) to be proportional to the magnitude of the blood pressure reduction achieved (figure 2, appendix pp 15–16). The meta-regression results were not significant for coronary heart disease (p=0·058) or renal failure (p=0·09; appendix pp 16–17).

Every 10 mm Hg systolic blood pressure reduction significantly reduced the risk of major cardiovascular disease events (RR 0·80, 95% CI 0·77–0·83), coronary heart disease (0·83, 0·78–0·88), stroke (0·73, 0·68–0·77), heart failure (0·72, 0·67–0·78), and all-cause mortality (0·87, 0·84–0·91; figure 3, appendix pp 18–23). The proportional reductions per 10 mm Hg systolic blood pressure reduction were greater for stroke and heart failure than for coronary heart disease. Estimates in non-standardised analyses were consistent with standardised estimates (appendix p 24).

When we stratified trials by mean baseline systolic blood pressure and compared the effects of a 10 mm Hg reduction in systolic blood pressure between strata, we detected no significant trends for any outcomes (p_{trend}>0·05; figure 4). Estimates were similar for non-standardised analysis (appendix p 25).

No evidence of different proportional effects of blood pressure lowering existed when we stratified trials by baseline cardiovascular disease (all $p_{interaction}$>0·05; figure 5) and, in view of the multiplicity of tests done (which increases the likelihood of observing a chance finding when considering all tests), no strong evidence of differences existed when trials were stratified by

baseline coronary heart disease (all $p_{interaction}>0·03$; appendix p 26). Although there was some evidence to suggest that the effect of blood pressure lowering on stroke was modified by presence of baseline coronary heart disease (p=0.03), we cannot rule out that this weak evidence is entirely due to chance given the multiplicity of testing. However, the proportional reduction in stroke risk seemed to be larger in populations without a history of cerebrovascular disease than in populations with such a history ($p_{interaction}=0·0028$; appendix p 27). When we stratified trials by baseline diabetes, we detected a significant interaction (p=0·0006) for major cardiovascular disease events, with significantly larger risk reductions for populations without diabetes (RR 0·75, 95% CI 0·70–0·80) than in populations with diabetes (0·88, 0·82–0·94; appendix p 28). Our subgroup analysis based on the presence of heart failure suggested that a 10 mm Hg blood pressure reduction might increase the risk of renal failure in patients with heart failure (21·67, 3·75–125·21), but this result was based on just 84 renal failure events in two studies (appendix pp 29–30). When we stratified trials by baseline chronic kidney disease, a significant interaction existed for major cardiovascular disease events ($p_{interaction}=0·012$), with larger proportional risk reductions for the populations without chronic kidney disease (0·68, 0·62–0·75) than in the populations with chronic kidney disease (0·84, 0·73–0·96). A significant interaction also existed for heart failure events, with a large and statistically significant risk reduction of 52% (0·48, 0·38–0·62) for every 10 mm Hg systolic blood pressure reduction in the subgroup without chronic kidney disease compared with a non-significant reduction for the subgroup with chronic kidney disease (0·95, 0·70–1·29; $p_{interaction}=0·0008$; appendix p 31).

We examined the five classes of blood pressure lowering drugs in non-standardised analyses. The different drug classes were of largely similar effectiveness for prevention of the various outcomes (figure 6, appendix pp 32–37). However, β blockers were less efficacious than other medications for the prevention of major cardiovascular disease events (RR 1·17, 95% CI 1·11–1·24; figure 6, appendix p 32), stroke (1·24, 1·14–1·35; figure 6, appendix p 33), and renal failure (1·19, 1·05–1·34; figure 6, appendix p 34). Evidence also suggested that β blockers had inferior efficacy in the prevention of all-cause mortality (1·06, 1·01–1·12; figure 6, appendix p 35), although this difference was not significant. CCBs were superior to the other classes for stroke prevention (0·90, 0·85–0·95; figure 6, appendix p 33) but were inferior to the other classes for heart failure prevention (1·17, 1·11–1·24; figure 6, appendix p 37). Diuretics were superior to other classes for heart failure prevention (0·81, 0·75–0·88; figure 6, appendix p 37). Results were similar when heart failure trials were included in the analysis (appendix p 38).

Discussion

In this meta-analysis, blood pressure lowering treatment significantly reduced the risk of cardiovascular disease and death in various populations of patients. Overall, a 10 mm Hg reduction in systolic blood pressure reduced the risk of major cardiovascular disease events by 20%, coronary heart disease by 17%, stroke by 27%, heart failure by 28%, and all-cause mortality by 13%. The size of these proportional reductions was broadly consistent across several major high-risk groups of patients, suggesting that blood pressure lowering provides broadly generalisable benefits. In stratified analyses, we saw no strong evidence that proportional effects were diminished in trials that included people with lower baseline systolic blood pressure (<130 mm Hg), and major cardiovascular events were clearly reduced in high-risk patients with various baseline comorbidities. Both of these major findings—the efficacy of blood pressure lowering below 130 mm Hg and the similar proportional effects in high-risk populations—are consistent with and extend the findings of the SPRINT trial.[12] Collectively, these data suggest that revision is urgently needed to recent blood pressure lowering guidelines that have relaxed the blood pressure lowering thresholds.[14,17,18]

Our finding of a lack of overall benefit of blood pressure lowering for renal failure events is consistent with those of a previous meta-analysis[56] that assessed the effects of intensive versus moderate blood pressure reduction on the risk of end-stage kidney disease. Blood pressure lowering seems to have multiple and sometimes opposing effects on renal outcomes: long-term blood pressure lowering reduces proteinuria and other indicators of structural damage, especially but not exclusively when achieved by renin–angiotensin–aldosterone (RAAS) inhibitors, but increases in acute kidney injury have also been reported.[12,57] These effects might be because of the fact that renal failure is not a single disorder, but a group of diseases with different underlying pathological mechanisms, with both high and low blood pressure contributing to its clinical manifestation.

A key insight from our analysis is that the effects of blood pressure lowering were broadly similar by baseline comorbidity. The proportional reduction in major cardiovascular disease events from blood pressure lowering did not differ substantially with the presence or absence of previous cardiovascular disease events, coronary heart disease, or cerebrovascular disease at the time of trial inclusion. With such consistent relative effects, we expect that the absolute benefits of blood pressure lowering would be greatest among individuals at highest absolute risk of cardiovascular events.[56,58] However, we did note some differences if diabetes or chronic kidney disease were present at baseline. The proportional reduction in major cardiovascular disease events seemed to be larger in trials done in people without diabetes or chronic kidney disease. The cause of these differing proportional reductions is unclear. One possibility is that

the trials done in people with diabetes or chronic kidney disease differed in their methodological characteristics, such as length of follow-up or use of dual renin–angiotensin system inhibition.[59] Another possibility is that the non-significant finding of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, which was weighted heavily in the diabetic subgroup analysis, might have been caused by chance.[57]

Another key finding from our analysis was that, although different drug classes were of largely similar effectiveness for prevention of the vascular outcomes of interest, there was evidence of modest differential effects between drug classes. β blockers seemed to be inferior to other classes of blood pressure lowering drugs for the prevention of major cardiovascular disease events, stroke, renal failure, and all-cause mortality, whereas CCBs seemed to be inferior and diuretics superior for the prevention of heart failure to other classes.[18,60,61] In line with previous research and current recommendations, CCBs seemed to be superior to other drug classes for stroke prevention.[14,16,60] Although we detected small but significant differences between the effectiveness of particular classes for other outcomes, we cannot exclude the possibility that these effects might have arisen from differences in the control regimens, or by chance in view of the multiple comparisons done. Additionally, apparent differences between drug classes might have been modified by the concurrent use of multiple classes of blood pressure lowering drugs in many trials. For example, the ACE inhibitor and CCB combination has been investigated in a large trial[62] and was reported to be more effective for prevention of major cardiovascular disease than was an ACE inhibitor and diuretic combination. Finally, certain drug classes might have particularly strong positive or negative effects in specific patient subgroups (eg, β blockers in the first years after a myocardial infarction[16]); an effect that we did not investigate in this review of the totality of evidence across different populations. Individual patient data meta-analyses of the type done by the BPLTTC might be able to address these questions in the future.

The broad consistency of the proportional effects of blood pressure lowering on cardiovascular outcomes across various baseline blood pressure levels and several disease categories will challenge the current guidelines on blood pressure and will support the case to shift their focus from rigid blood pressure targets to risk-based targets, even when starting systolic blood pressure is lower than 130 mm Hg.[63] Rather than a decision based on an arbitrary threshold for a single risk factor, this approach needs individualised assessment of the balance of absolute risks and benefits when physicians decide on the blood pressure level at which to start blood pressure lowering and the target blood pressure.[64] For this meta-analysis, adverse event data were too disparate and inconsistently reported to allow for formal analysis. However, our analysis did provide evidence against blood pressure lowering causing an increase in major cardiovascular events in patients with previous disease and low baseline blood pressure, which was a concern raised by reports of J-curve associations.

Pooling data from 613 815 patients enrolled in 123 large-scale trials of blood pressure lowering, our study includes substantially more information than any previous meta-analyses that have addressed this question. Unlike in previous studies, we excluded no trials because of baseline comorbidities, thus allowing for greater generalisability of findings and an assessment of treatment effect stratified by the presence of various baseline comorbidities of interest.[65,66]

With ageing populations, chronic kidney disease is becoming an increasingly prevalent and important public health problem, affecting 10–15% of the adult population.[67–70] Our findings show significant relative risk reductions for both patients with and patients without chronic kidney disease. Although proportional risk reductions were smaller in patients with chronic kidney disease than in those without, in view of their higher absolute risks, substantial absolute benefits from blood pressure reduction can be achieved in this population.

A limitation of this meta-analysis is that we had no individual patient data, the use of which would have provided greater detail about the effects of blood pressure lowering at various levels of baseline systolic blood pressure. However, the eligible trials spanned a wide range of baseline blood pressure levels, allowing us to explore the effects of blood pressure lowering across a relatively wide range of blood pressures. A further limitation was that the eligible trials varied in several respects, including differences in trial populations, baseline comorbidities, and treatment regimens, and it is possible that methodological differences might have confounded the differences recorded across subgroups of trials. Although many studies have investigated differences in the clinical efficacy of various drug classes for cause-specific outcomes, relatively few studies have compared different drug combinations. Because most patients need combination therapy, identification of the optimum combinations of therapies might be more clinically relevant than investigating the effectiveness of single therapies. The fact that we had no individual patient data prevented such an analysis.

In conclusion, blood pressure lowering significantly reduces the risk of major cardiovascular disease events, coronary heart disease, stroke, heart failure, and all-cause mortality, with similar proportional reductions across various population subgroups, irrespective of starting blood pressure. Lowering of blood pressure into what has been regarded the normotensive range should therefore be routinely considered for the prevention of cardiovascular disease among those deemed to be of sufficient absolute risk.

Contributors

DE and KR had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. KR, CAE, and DE contributed to the study concept and design.

DE, CAE, SGA, and TC contributed to the acquisition of data. All authors analysed and interpreted the data. DE, CAE, and KR drafted the manuscript with critical revision for important intellectual content from all authors. DE and CAE did the statistical analysis. KR was the study supervisor.

Declaration of interests

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