

BMJ Open Benefits and harms of lower blood pressure treatment targets: systematic review and meta-analysis of randomised placebo-controlled trials

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ABSTRACT

Objectives To assess the effect of antihypertensive treatment in the 130–140 mm Hg systolic blood pressure range.

Design Systematic review and meta-analysis.

Information sources PubMed, CDSR and DARE were searched for the systematic reviews, which were manually browsed for clinical trials. PubMed and Cochrane Central Register of Controlled Trials were searched for trials directly in February 2018.

Eligibility criteria Randomised double-blind trials with ≥ 1000 patient-years of follow-up, comparing any antihypertensive agent against placebo.

Data extraction and risk of bias Two reviewers extracted study-level data, and assessed risk of bias using Cochrane Collaborations risk of bias assessment tool, independently.

Main outcomes and measures Primary outcomes were all-cause mortality, major cardiovascular events and discontinuation due to adverse events. Secondary outcomes were cardiovascular mortality, myocardial infarction, stroke, heart failure, hypotension-related adverse events and renal impairment.

Results Eighteen trials, including 92 567 participants (34% women, mean age 63 years), fulfilled the inclusion criteria. Primary preventive antihypertensive treatment was associated with a neutral effect on all-cause mortality (relative risk 1.00, 95% CI 0.95 to 1.06) and major cardiovascular events (1.01, 0.96 to 1.06), but an increased risk of discontinuation due to adverse events (1.23, 1.03 to 1.47). None of the secondary efficacy outcomes were significantly reduced, but the risk of hypotension-related adverse events increased with treatment (1.71, 1.32 to 2.22). In coronary artery disease secondary prevention, antihypertensive treatment was associated with reduced risk of all-cause mortality (0.91, 0.83 to 0.99) and major cardiovascular events (0.85, 0.77 to 0.94), but doubled the risk of adverse events leading to discontinuation (2.05, 1.62 to 2.61).

Conclusion Primary preventive blood pressure lowering in the 130–140 mm Hg systolic blood pressure range adds no cardiovascular benefit, but increases the risk of adverse events. In the secondary prevention, benefits should be weighed against harms.

PROSPERO registration number CRD42018088642.

Strengths and limitations of this study

- Meta-analysis restricted to randomised double-blind placebo-controlled trials, thereby minimising the risk of performance bias.
- Adverse events included as coprimary outcome, putting emphasis on both benefits and harms.
- Separate analyses for primary and secondary preventive trials, reducing the risk of confounding from coronary artery disease and increasing the usefulness of the results in different clinical contexts.
- Main limitation is the use of study-level data, with the potential for ecological bias.

INTRODUCTION

For decades, hypertension has been defined as a blood pressure (BP) $\geq 140/90$ mm Hg.¹ The definition has been uniform across the world, and for most patients, the recommended treatment goal has been $<140/90$ mm Hg.^{2–4} In 2017, the American College of Cardiology (ACC) and the American Heart Association (AHA) updated the US guidelines, changing the definition of hypertension to $\geq 130/80$ mm Hg.⁵ For secondary preventive patients, and for primary preventive patients with a 10-year cardiovascular risk $\geq 10\%$, the treatment goal is now $<130/80$ mm Hg. Recently, the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC) followed, retaining the old definition of hypertension, but lowering the treatment goal to $120–130/70–80$ mm Hg for most patients.⁶

The revisions of both sets of guidelines were heavily influenced by the Systolic Blood Pressure Intervention Trial (SPRINT).⁷ SPRINT randomised >9000 high-risk patients (without previous stroke or diabetes) to a systolic BP (SBP) target <120 mm Hg compared with <140 mm Hg, and was stopped preterm due to lower risk of death and cardiovascular disease in the intensive treatment group.⁷ In

addition to SPRINT, the ACC/AHA performed a systematic review and meta-analysis including only non-blinded randomised trials comparing different treatment goals, finding a reduced risk of major cardiovascular events and stroke in trials comparing a target ≤ 130 mm Hg to any higher target.⁸

Blinding of participants and study personnel is desirable to minimise the risk of performance bias.⁹ In non-blinded studies, such as SPRINT and those included in the ACC/AHA systematic review, participants may be handled differently depending on the treatment group, thereby confounding the assessment of the intervention. Meta-epidemiological studies have found that trials with unclear or incomplete blinding produce more favourable results compared with trials that are double blind.¹⁰ Additionally, in the clinic, we know the patients' BP, but not what BP he or she will have after adding an additional drug. Placebo-controlled trials mimic the clinical situation where the question is—should we add another drug or not?

This systematic review and meta-analysis aims to evaluate the benefits and harms associated with anti-hypertensive treatment in randomised double-blind placebo-controlled trials with mean SBP 130–140 mm Hg at randomisation. Such an approach eliminates the risk of performance bias, yet produces treatment effect estimates reasonably specific for the SBP interval for which the new recommendations differ from the previous ones. Because the ACC/AHA systematic review was restricted to non-blinded target trials and this review is restricted to placebo-controlled trials of different agents, our analyses serves as validation of the ACC/AHA systematic review findings in a different population with theoretically more robust methods.

METHODS

We performed a systematic review and meta-analysis guided by the recommendations from the Cochrane Collaboration.⁹ Reporting follows the Preferred Reporting for Systematic Reviews and Meta-Analyses guidelines.¹¹

Studies were eligible if they were randomised double-blind placebo-controlled trials with ≥ 1000 patient-years of follow-up; assessing the effect of any antihypertensive agent against placebo, with mean baseline SBP ≥ 130 and < 140 mm Hg. The 1000 patient-year cut-off was chosen to reduce the risk of small-study bias. Target-driven trials were excluded due to reasons described above, and trials comparing different antihypertensive agents against each other were excluded because they risk assessing BP-independent effects of agents.^{9 10} We also excluded trials in patients with acute myocardial infarction or heart failure/left ventricular dysfunction because several antihypertensive agents are thought to affect on clinical outcomes through BP-independent mechanisms, like reduced preload, reduced afterload and sympathetic inhibition, in these settings.^{12 13}

We used one of our recent, more comprehensive systematic reviews, assessing treatment effect of antihypertensive

treatment across BP levels in a wide range of patient categories, for study selection.¹⁴ Search strategies for the previous review are presented in the online supplementary eMethods. In addition, we searched PubMed and Cochrane Central Register of Controlled Trials from the date of the previous search to February 2018, using search terms (“blood pressure lowering” OR “blood-pressure lowering” OR “blood pressure-lowering” OR antihypertensive) AND (mortality OR myocardial OR stroke). Titles were screened by MB and apparently irrelevant publications were removed. Two authors judged abstracts separately, after which final decision on eligibility was reached through discussion (online supplementary eFigure 1).

Data were extracted from the included studies into specially designed Excel sheets by two authors separately. When extracted data differed between authors, we revisited original publications. Descriptive data were collected on study level, whereas BP data and outcome data were collected for each treatment group individually. All trials were judged for risk of bias by two authors separately, using Cochrane Collaboration's Risk of Bias assessment tool.¹⁵ The risk of bias tool covers six specific domains related to randomisation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, attrition and outcome reporting. Also, we assessed sponsor involvement, protocol changes and premature study discontinuation as other potential sources of bias. Trials judged to be at high risk of selection bias, performance bias, detection bias or attrition bias (first five domains) were excluded from all analyses (online supplementary eTable 1). Risk of bias for selective reporting should be considered interpreting the overall analyses for each outcome rather than individual trials, because lack of data, rather than biased data, may produce biased overall results.^{9 15}

Primary outcomes were all-cause mortality, MACE (defined as cardiovascular death, myocardial infarction and stroke if not specified otherwise) and discontinuation due to adverse events (AEs). Secondary outcomes were cardiovascular mortality, myocardial infarction, stroke, heart failure, hypotension-related AEs and discontinuation due to renal impairment/acute kidney injury.

Results were analysed according to the intention-to-treat principle, in the sense that participants were analysed in their assigned treatment group. When study participants were lost to follow-up, relative risks (RRs) were calculated using complete cases in the denominator, according to the recommendations from the Cochrane Collaboration.⁹ In two sets of sensitivity analyses, we calculated RRs using the observed number of events in the numerator and the total number of randomised participants in the denominator (assuming that all participants lost to follow-up were event free), and the observed number of events plus number of participants lost to follow-up in the numerator and the total number of randomised participants in the denominator (assuming that all participants lost to follow-up had experienced an event). RRs were not standardised for BP differences in trials, because

such standardisation is associated with increased heterogeneity, unbalanced study weights and biased overall results.¹⁶

RRs from individual trials were pooled using DerSimonian-Laird random-effects meta-analyses. We separated primary preventive studies from studies in people with established coronary artery disease (CAD), because these represent clinically different populations, and because we have previously observed potentially different treatment effects in these groups.¹⁴ Trials with mixed populations were classified as CAD trials if $\geq 50\%$ of participants had previous CAD. Treatment effect interaction between primary preventive studies and CAD studies was assessed using random-effects meta-regression. Prespecified sensitivity analyses, excluding trials in people with diabetes, trials of dual renin-angiotensin-aldosterone system (RAAS) inhibition, trials not reaching <130 mm Hg in the intervention group, trials of previously treated/hypertensive patients and trials of treatment naïve patients, were performed to test the impact of different patient/trial characteristics on overall results for primary outcomes. We explored the potential effect modification by diabetes and absolute cardiovascular risk as continuous explanatory variables using random-effects meta-regression. Lastly, we performed ad hoc subgroup analyses, stratifying primary preventive trials by a 10-year MACE event rate above versus below 10%, to approximate the cut-off used in the 2017 ACC/AHA guidelines.⁵

Between-study heterogeneity in meta-analyses was assessed calculating I squared, which represents the percentage of variance between studies that cannot be explained by chance alone. When statistical heterogeneity was present, we sought for corresponding clinical heterogeneity. If statistically deviating studies differed with respect to clinical characteristics, they were excluded in sensitivity analyses. Small-study effects were assessed through funnel plots for all primary and secondary outcomes, using Harbord's test for asymmetry.¹⁷ All analyses were performed using STATA V.12.

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 advise 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

Eighteen trials,^{18–35} including 92 567 participants (34% women; mean age 63 years), fulfilled the inclusion criteria (table 1). During an average of 4.5 years under randomised double-blind treatment, 2042 participants were lost to follow-up (2.2 %), resulting in 90 525 complete cases and 407 000 patient-years of follow-up. Twelve trials,^{19–22 25–27 30–33 35} including 54 020 participants,

were classified as primary preventive. Mean baseline SBP in primary preventive trials was 138 mm Hg, mean follow-up SBP was 132 mm Hg respectively 135 mm Hg with active treatment versus placebo, with a weighted mean difference between groups of 3.4 mm Hg. Six trials,^{18 23 24 28 29 34} including 38 547 participants, were classified as CAD trials; mean baseline SBP was 137 mm Hg, mean follow-up SBP was 130 mm Hg in the active treatment group, 134 mm Hg in the placebo group, with 4.2 mm Hg difference between groups.

In primary prevention (figure 1), treatment was not associated with any effect on all-cause mortality (RR 1.00, 95% CI 0.95 to 1.06) or MACE (1.01, 0.96 to 1.06), but an increased risk of AEs leading to discontinuation (1.23, 1.03 to 1.47). In CAD trials (figure 2), treatment reduced the risk of all-cause mortality by 9% (0.91, 0.83 to 0.99), and the risk of MACE by 15% (0.85, 0.77 to 0.94), but doubled the risk of AEs leading to discontinuation (2.05, 1.62 to 2.61). Heterogeneity was low in mortality and MACE analyses for primary prevention, moderate to high in CAD trials, and very high for AEs in both cohorts. The difference between primary preventive trials and CAD trials was significant for MACE ($p=0.019$) and borderline for all-cause mortality and AEs ($p=0.051$, respectively 0.070).

None of the secondary efficacy outcomes were affected by primary preventive treatment (table 2; online supplementary eFigures 2–7). Hypotension-related AEs increased by 71% (1.71, 1.32 to 2.22) whereas discontinuation due to renal impairment showed a non-significant tendency towards harm (1.20, 0.93 to 1.55). Of note, heterogeneity was high in the renal impairment analysis, mostly due to one study in patients with type 1 diabetes and macroalbuminuria.²⁶ When this study was removed in a sensitivity analysis, heterogeneity decreased and the observed risk increase became nominally significant (1.30, 1.06 to 1.58).

In CAD trials (table 2; online supplementary eFigures 2–7), treatment reduced the risk of myocardial infarction (0.83, 0.72 to 0.97), stroke (0.79, 0.66 to 0.94), heart failure (0.76, 0.67 to 0.86) and cardiovascular death (0.86, 0.74 to 1.00, $p=0.047$). Differences between primary prevention and CAD trials were significant or borderline significant for all efficacy outcomes except stroke (online supplementary eFigures 2–7). The RR of AEs was similar as in primary preventive studies, although estimates were less precise and reporting was poor (only one trial reported renal impairment).

Sensitivity analyses, testing the impact of different trial characteristics, shifted effect estimates slightly (online supplementary eFigures 8–12), but not enough to affect the interpretation of our main findings. Meta-regression analyses, exploring potential effect modification by observed cardiovascular risk and diabetes mellitus, were non-significant. Both sensitivity analyses and meta-regression analyses should be interpreted carefully due to small number of trials. Of note, the absolute 10-year risk of MACE was well above the 10% threshold for

Table 1 Study characteristics

Acronym (year)	Participants (n, age, sex)	Comorbidity	Intervention/control	Baseline SBP/DBP (mm Hg)	SBP/DBP difference (mm Hg)
ACTION (2004)	7665 63 years 21% female	100% CAD 14% DM	Nifedipine 60 mg versus placebo	137.5/79.8	5.7/3.0
ACTIVE I (2011)	9016 70 years 29% female	36% CAD 20% DM 100% AF	Irbesartan 300 mg versus placebo	138.3/82.4	2.9/1.9
ALTITUDE (2012)	8561 64 years 32% female	26% CAD 100% DM 98% CKD	Aliskiren 300 mg versus placebo	137.3/74.2	1.3/0.6
BCAPS (2001)	793 62 years 55% female	4% CAD 3% DM All had carotid plaques	Metoprolol CR/XL 25 mg versus placebo	138.9/84.7	1.3/ -
DREAM (2006)	5269 55 years 59% female	0% CAD 0% DM All had IGT/IFG	Ramipril 15 mg versus placebo	136/83.4	4.3/2.7
EUROPA (2003)	12 218 60 years 15% female	100% CAD 12% DM	Perindopril 8 mg versus placebo	137/82	5/2
HOPE (2000)	9297 66 years 27% female	81% CAD 38% DM	Ramipril 10 mg versus placebo	139/79	3/2*
HOPE-3 (2016)	12 705 66 years 46% female	0% CAD 6% DM	Candesartan/HCTZ 16/12.5 mg versus placebo	138.1/81.9	6/3
Lewis (1993)	409 35 years 47% female	100% DM (type 1) All with nephropathy	Captopril 75 mg versus placebo	138.5/85.5	1.5/2.5
NAVIGATOR (2010)	9306 64 years 51% female	24% CAD 0% DM 100% IGT	Valsartan 160 mg versus placebo	139.7/82.6	2.8/1.4
PART-2 (2000)	617 61 years 18% female	68% CAD (100% CVD) 9% DM	Ramipril 5–10 mg versus placebo	133/79	5.5/4
PEACE (2004)	8290 64 years 18% female	100% CAD 17% DM	Trandolapril 4 mg versus placebo	133/78	3.0/1.2
PHARAO (2008)	1008 62 years 52% female	6% CAD 13% DM	Ramipril 5 mg versus placebo	134.4/83.6	2.8/0.9
PREVEND-IT (2004)	864 51 years 35% female	3% CAD 3% DM	Fosinopril 20 mg versus placebo	130/76	3/3
Ravid (1998)	194 55 years 51% female	0% CAD 100% DM	Enalapril 10 mg versus placebo	MAP 97	-/ -
ROADMAP (2011)	4447 58 years 54% female	25% CAD 100% DM	Olmesartan 40 mg versus placebo	136.5/80.5	3.1/1.9
SCAT (2000)	460 61 years 11% female	100% CAD 11% DM	Enalapril 10 mg versus placebo	130/77.5	5.2/3.3
VA-NEPHRON (2013)	1448 65 years 0.3% female	23% CAD 100% DM with nephropathy	Losartan/lisinopril 100/10–40 mg versus losartan 100 mg	137.0/72.7	1.5/1.0

*A substudy assessing ABPM found larger BP differences between groups during follow-up, indicating potentially underestimated BP differences in the main publication. ABPM, ambulatory blood pressure measurement; AF, atrial fibrillation; BP, blood pressure; CAD, coronary artery disease; CKD, chronic kidney disease; DBP, diastolic blood pressure; DM, diabetes mellitus; HCTZ, hydrochlorothiazide; HOPE3, third Heart Outcomes Prevention Evaluation; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; MAP, mean arterial pressure; SBP, systolic blood pressure.

recommending treatment in the ACC/AHA guidelines, with an average risk across studies of 26% (online supplementary eTable 2); subgroup analyses of primary preventive trials stratified by a 10-year cardiovascular event rate

found no interaction between risk of MACE and treatment effect (online supplementary eFigure 13).

Risk of bias was generally judged as low for individual trials (online supplementary eTable 3 and eResults). We

Primary prevention

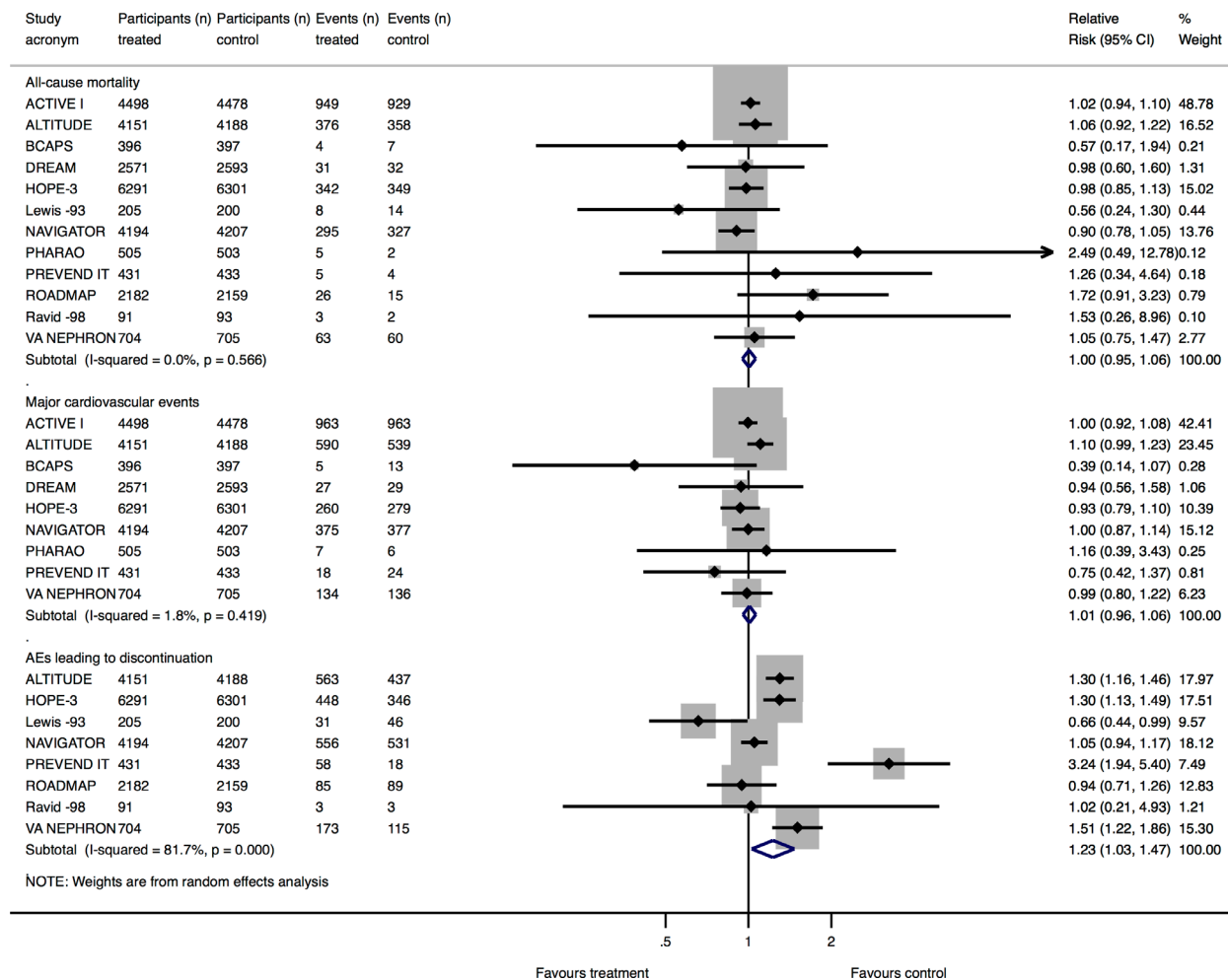


Figure 1 Treatment effect on primary outcomes in primary prevention. AE, adverse event; HOPE-3, third Heart Outcomes Prevention Evaluation.

required studies to be described as randomised double-blind placebo-controlled trials to be eligible. Lost to follow-up was limited, and sensitivity analyses imputing all participants lost to follow-up as either having an event or being event-free did not alter effect estimates (online supplementary eFigures 14 and 15). Three trials were judged to be at high risk of bias for individual domains.^{20 24 26} We performed sensitivity analyses, testing the impact of these trials on our primary outcomes (online supplementary eFigure 16). This had marginal effects on RRs and confidence intervals, but no effect on nominal significance for any analysis.

Funnel plots showed no signs of asymmetry (online supplementary eFigures 17–25), although such analyses should be interpreted carefully due to the small number of trials. The possible exception was hypotension-related AEs where interaction was borderline significant despite low statistical power ($p=0.06$). When we explored this further, we found that treatment effect correlated with a number of events but not study size (online supplementary eTable 4). The frequency of hypotension-related

AEs varied by a factor of 50 between trials, presumably representing different thresholds for reporting. Thus, the observed association between number of AEs and the RR of AEs might represent a stronger association between treatment and severe events compared with less severe events.

DISCUSSION

This systematic review and meta-analysis evaluates if antihypertensive treatment in the 130–140 mm Hg SBP interval is supported by findings from randomised double-blind placebo-controlled trials. This does not seem to be the case in primary prevention, with no treatment effect on all-cause mortality or MACE, but an increased risk of AEs leading to discontinuation. In people with previous CAD, treatment might be beneficial, though these findings should be interpreted more cautiously due to statistical heterogeneity and wider CIs. While the type of trials included here do not assess SBP targets by design, they correspond to the clinical situation of adding an extra



Figure 2 Coronary artery disease

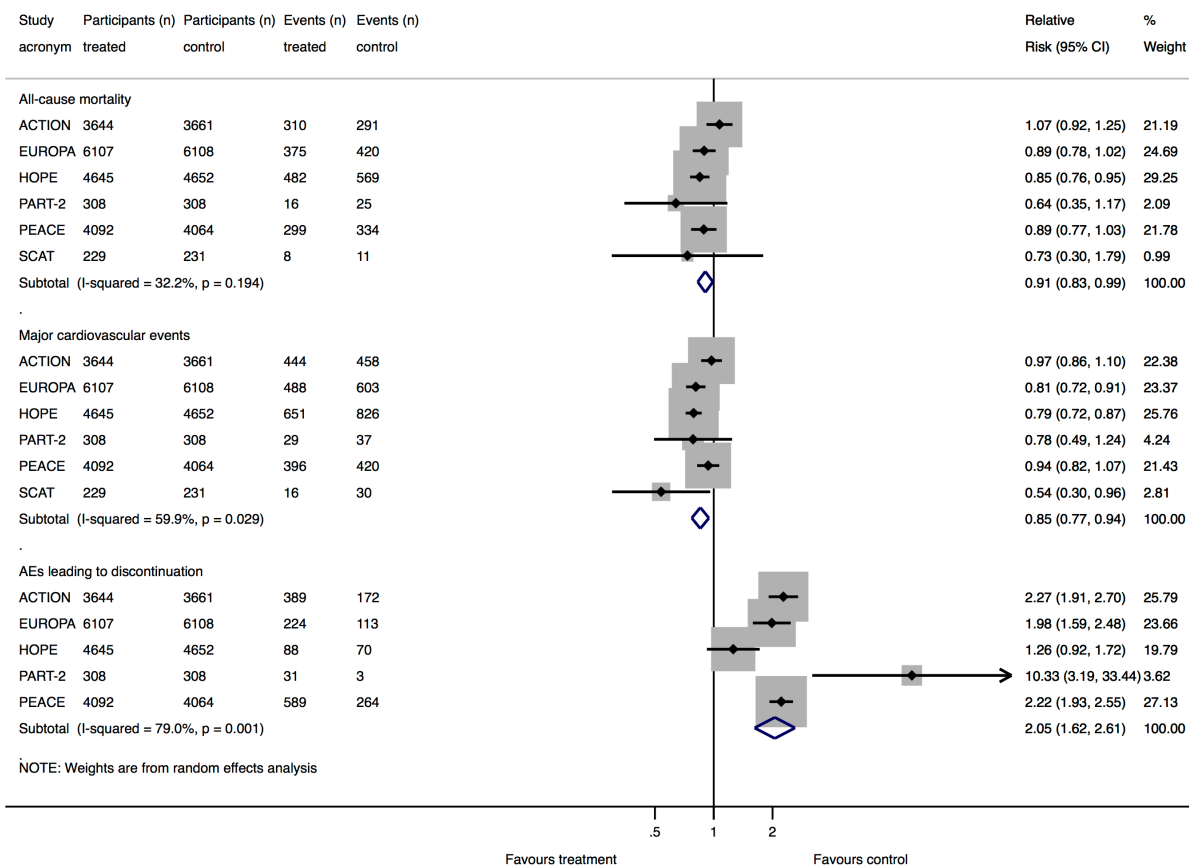


Figure 2 Treatment effect on primary outcomes in coronary artery disease trials. AE, adverse event; HOPE, Heart Outcomes Prevention Evaluation.

pill to patients with an SBP between 130 and 140 mm Hg. Overall, the results presented here do not support such treatment, except for in patients with established CAD.

This paper has several important limitations that need to be addressed. First, we only had access to aggregated data, making analyses susceptible to ecological bias. Studies were included based on average SBP levels, meaning that individual participants with an SBP

>140 mm Hg or <130 mm Hg were included in the analyses because the average SBPs in their trials were within the accepted range. Similarly, individual participants with an SBP within our accepted range were missed because they were included in trials with an average SBP outside our accepted range. Notably, this problem is not unique to this review, but applies to most meta-analyses in the field, including those comparing different BP targets cited by

Table 2 Secondary outcomes

		Primary prevention trials			Coronary artery disease trials		
		Trials/ participants/ events (n)	RR (95% CI)	I ² (%)	Trials/ participants/ events (n)	RR (95% CI)	I ² (%)
Efficacy outcomes	Cardiovascular mortality	8/49 685/2390	1.07 (0.95 to 1.21)	27.3	5/37 589/1802	0.86 (0.74 to 1.00)	55.7
	Myocardial infarction	8/46 682/1092	1.03 (0.91 to 1.15)	0.0	5/29 893/2367	0.83 (0.72 to 0.97)	60.0
	Stroke	9/47 546/1536	0.89 (0.73 to 1.09)	52.9	6/38 049/943	0.79 (0.66 to 0.94)	36.6
	Heart failure	6/44 881/1903	0.90 (0.81 to 1.00)	17.7	5/37 589/957	0.76 (0.67 to 0.86)	0.0
Safety outcomes	Hypotension-related AEs	6/44 058/5141	1.71 (1.32 to 2.22)	90.3	3/28 817/793	1.63 (1.01 to 2.63)	85.9
	Renal impairment	8/49 627/992	1.20 (0.93 to 1.55)	71.6	1/12 215/36	1.25 (0.65 to 2.41)	–

AEs, adverse events; RR, relative risk.

the guidelines.^{8 36 37} Overcoming this would require individual-patient data, unfortunately not available to date. Second, the aggregated nature of our data also affects categorisation of trials as primary or secondary preventive. In trials categorised as primary preventive, 17% of participants had CAD, whereas in secondary preventive trials the corresponding number was 95%. This represents reasonable separation between groups, although this aspect could also be explored further in individual-patient data meta-analyses. Third, additional possible effect modifiers like age, sex and other comorbidities would also require individual-patient data and were, therefore, not assessed. Fourth, SBP was only moderately reduced in the trials included in our analyses; less so compared with previous meta-analyses including target-driven trials. Although a less pronounced effect on clinical outcomes would be expected, the observed SBP difference of 3.4 mm Hg during >200 000 person-years of follow-up should have resulted in at least a tendency towards primary preventive benefit if such were present. Instead CIs were fairly narrow around the null effect. We cannot exclude that larger SBP reductions with more ambitious treatment would have resulted in clinical benefit, such as in the SPRINT trial, although based on our findings it seems unlikely. Fifth, all but two of the included trials assessed the effect of RAAS inhibitors. Whereas the generalisability of our findings to other drugs, therefore, could be questioned, previous meta-analyses have found no clinically meaningful difference between RAAS inhibitors and other first-line agents for hypertension control.

The arguments for lowering SBP treatment goals differ slightly between the ACC/AHA guidelines compared with the ESH/ESC guidelines.^{5 6} Common to both sets of guidelines is that they put emphasis on the results of systematic reviews and meta-analysis. Whereas the ACC/AHA performed their own systematic review of trials comparing different targets,⁸ the ESH/ESC refers mainly to two previously published papers combining results from target trials and placebo-controlled trials.^{36 37}

The main strength of this review, compared with the systematic reviews underlying the ACC/AHA and the ESH/ESC guidelines, is that it is limited to randomised double-blind placebo-controlled trials, protecting it against performance bias. Although the magnitude of this potential problem is unknown, target-driven trials may be susceptible to performance bias due to their non-blinded nature.⁹ Possible indicators of such bias might be 20%–30% more unscheduled visits in the intensive treatment group, and a large non-cardiovascular component of the all-cause mortality reduction, seen in SPRINT.⁷ Meta-analyses restricted to target trials, such as the one by the ACC/AHA,⁸ may be especially susceptible to these kinds of biases, whereas the risk is probably lower in meta-analyses combining target trials and placebo-controlled trials, such as those underlying the ESH/ESC recommendations.^{36 37} Notwithstanding, the different findings in our analysis compared with the ACC/AHA analysis should raise the question if performance bias

does play a role in target trials of antihypertensive treatment, exaggerating treatment effect estimates.

Another important difference between this analysis and the ones underlying the ACC/AHA and ESH/ESC guidelines is that we analyse primary preventive studies and secondary preventive studies separately. This is important because the evidence for BP lowering in the 130–140 mm Hg interval comes to a large extent from trials in people with established CAD. Before primary and secondary preventive trials are combined one has to ask if it is reasonable to extrapolate findings from patients with CAD to healthy individuals. To answer this, it is important to consider possible mechanistic differences in these populations. In primary prevention, development of atherosclerosis is a sine qua non for succeeding cardiovascular events, and hence the effect of BP lowering treatment on the early stages of atherosclerosis becomes most important. In people with established CAD, on the other hand, angina and heart failure symptoms are closely related to myocardial oxygen balance, depending to a large extent on cardiac afterload which is proportional to SBP.³⁸ Also, SBP has been associated with changes in atheroma size, indicating that higher BP may increase the risk of plaque rupture.³⁹ Therefore, it is not beyond reasonable doubt that BP lowering might work through different mechanisms depending on CAD status; in this situation, lumping trials with and without CAD patients should be avoided. The analyses presented here provide statistical support to the pathophysiologically based decision to separate patient categories. Indeed, it shows that the observed benefit in previous analyses depends on inclusion of secondary preventive studies.

Lastly, the systematic reviews referred to as supportive of lower treatment targets in the ESH/ESC guidelines used meta-analyses standardised to SBP reductions of 10 mm Hg.^{36 37} This might seem reasonable at first, but affects the results in ways that might not be clear to most readers.¹⁶ First, standardisation amplifies treatment effects by about 50%, because SBP reduction in the included trials was on average 6–8 mm Hg whereas results are standardised to 10 mm Hg. Second, standardisation assumes that there is a linear association between BP reduction and cardiovascular outcomes, which may not be the case in this BP interval and may also be different for different outcomes. If indeed the associations between BP reduction and cardiovascular event reduction were linear, one would expect decreased heterogeneity with standardisation. Our previous results indicate that standardisation increases heterogeneity and makes analyses highly sensitive to choice of statistical methods.¹⁶ This is probably due to amplification of differences not related to BP lowering, paradoxically making standardised results less BP dependent. Third, standardisation of SEs, which was applied in one of the referred meta-analyses, disrupts the association between number of events within trials and weight given to trials in meta-analyses.^{16 36} For example, the European Working Party on High Blood Pressure in the Elderly trial were given 7.3% weight the all-cause mortality analysis,



despite contributing with less than 0.3% of participants.³⁶ Simply put, standardisation makes results less representative of the underlying data.

Although arguments can be made for including target trials, lumping different populations, and using standardisation, all these approaches build on assumptions that the current analysis does not make. If the treatment benefit hinges on these assumptions, results are simply not robust enough to change guidelines for hundreds of millions of people worldwide. Meta-analyses using non-standardised methods have consistently found that the effects of antihypertensive treatment are attenuated at lower BP levels.^{14 40–42} In a recent paper, we found that 22% reduced risk of MACE if baseline SBP was >160 mm Hg, 12% reduced risk in the 140–159 mm Hg SBP range, whereas in trials with baseline SBP below 140 mm Hg treatment effect was neutral for all efficacy outcomes. These results are well in line with the third Heart Outcomes Prevention Evaluation (HOPE-3) study, where 12 705 participants with average baseline BP 138/82 mm Hg were randomised to candesartan/hydrochlorothiazide combination therapy or matching placebo.²⁵ In fact, HOPE-3 is the only mega-trial aiming to assess the effect of antihypertensive treatment against double-blind placebo in the mostly treatment naïve normotensive primary preventive patients. Neither the primary combined endpoints nor individual cardiovascular outcomes were reduced by the treatment. However, there was a significant interaction between baseline SBP and treatment effect on MACE, with treatment benefit in the highest SBP tertile but a tendency towards harm in the lowest SBP tertile.

Treatment decisions should always be based on consideration of both benefit and harm. In situations where interventions are unlikely to be harmful, one may consider treatment despite weak or conflicting evidence. Unfortunately, randomised clinical trials and systematic reviews of such trials show incriminating signs of harm for antihypertensive treatment at BP levels now recommended in the guidelines. In people with diabetes mellitus, we have previously shown that BP-lowering treatment at SBP levels <140 mm Hg is associated with 15% increased risk of cardiovascular death.⁴⁰ Further down the ladder of seriousness and irreversibility comes an increased risk of chronic kidney disease,⁴³ acute kidney injury,⁴⁴ as well as hypotension-related AEs and AEs leading to treatment discontinuation presented here.

In summary, randomised double-blind placebo-controlled trials do not support primary preventive BP lowering in the 130–140 mm Hg SBP range. Such treatment does not affect all-cause mortality or incident cardiovascular disease, but increases the risk of AEs. In people with previous CAD, treatment may reduce the risk of all-cause mortality and MACE, at the cost of more pronounced risk increase for AEs. In patients with CAD, therefore, benefits should be balanced against potential harms for individual patients.

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Patient consent for publication Not required.

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Data availability statement All data relevant to the study are included in the article or uploaded as online supplementary information.

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