Blood pressure targets in patients with coronary artery disease: observations from traditional and Bayesian random effects meta-analysis of randomised trials

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ABSTRACT

Context Most guidelines for treatment of hypertension including the Joint National Committee-7 recommend a blood pressure (BP) goal of <140/90 mm Hg for hypertensive patients and a more aggressive goal of <130/80 mm Hg for patients with coronary artery disease (CAD), based largely on expert consensus.

Objective To evaluate the BP targets in patients with CAD

Data Sources PUBMED, EMBASE and CENTRAL Study Selection: Randomised clinical trials (RCTs) of antihypertensive therapy in patients with CAD, enrolling at least 100 patients, with achieved systolic pressure of <=135 mm Hg in the 'intensive BP' group and <=140 mm Hg in the 'standard BP' group with follow-up for at least 1 year and evaluating cardiovascular outcomes.

Data Extraction The following efficacy outcomes were extracted- all-cause mortality, cardiovascular mortality, myocardial infarction, stroke, angina pectoris, heart failure and revascularisation.

Results We identified 15 RCTs enrolling 66 504 participants with 276 328 patient-years of follow-up. Intensive BP group (≤135 mm Hg) was associated with a 15% decrease in heart failure rate and 10% decrease in stroke rate, driven largely by trials with a more intensive BP group (≤130 mm Hg), with similar outcomes for death and cardiovascular death and was associated with a 105% increase in the risk of hypotension. More intensive BP group (≤130 mm Hg) was also associated with a reduction in myocardial infarction and angina pectoris. The results were similar in a Bayesian random effects model. In addition, lower seemed to be better (based on regression analysis) for the outcomes of myocardial infarction, stroke, heart failure and perhaps angina.

Conclusions The present body of evidence suggests that in patients with CAD, intensive systolic BP control to ≤135 mm Hg and possibly to ≤130 mm Hg is associated with a modest reduction in stroke and heart failure but at the expense of hypotension. Lower was better, although not consistently so for myocardial infarction, stroke, heart failure and perhaps angina. Further trials are needed to prove these findings.

INTRODUCTION

The seventh report of the Joint National Committee on prevention, detection, evaluation and treatment of high blood pressure (BP) recommends a systolic pressure goal of <140 mm Hg in patients with hypertension and a more aggressive goal of <130 mm Hg in patients at high risk.[1] Largely based on expert consensus with scant clinical trial evidence, other major national and international guidelines have echoed this more aggressive BP goal in patients with cardiovascular disease/coronary artery disease (CAD).[2 3]

In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) blood pressure trial (ACCORD BP) at the end of 4.7 years of follow-up, targeting a systolic pressure <120 mm Hg, as compared with <140 mm Hg, did not reduce the rate of fatal and non-fatal major cardiovascular events except stroke.[4] However, in ACCORD only a third of the cohort had cardiovascular disease (including peripheral artery disease, stroke/transient ischaemic attacks, CAD) with an even smaller percentage of patients with known CAD. It is therefore unknown whether or not the results of ACCORD are applicable to patients with CAD, the highest risk subgroup, where aggressive strategies such as lower BP targets should prove to be most beneficial (if any). Data from observational studies and subgroup analyses of randomised trials seem to suggest that lower might not always be better for BP in patients with CAD.[5–7] In a recent analysis, we have shown that in subjects with diabetes mellitus a target systolic BP goal of 130–135 mm Hg is ideal, with target organ heterogeneity below 130 mm Hg such that there is continued benefit for stroke but not for other outcomes and at the expense of increase in adverse events.[8]

Our objective was to evaluate target BP goals for subjects with CAD.

METHODS

Eligibility criteria

We conducted PUBMED, EMBASE and CENTRAL searches using the term 'coronary artery disease' in humans from 1990 until February 2012 using the limits 'randomized controlled trials'. The search criteria were fairly broad to avoid missing studies with a restricted search. We checked the reference lists of review articles, meta-analyses and original studies identified by the electronic searches to find other eligible trials. There was no language restriction for the search. The authors of publications were contacted when results were unclear or when relevant data were not reported.

Eligible trials had to fulfil the following criteria to be included in this analysis: (1) randomised clinical trials (RCTs) of participants with CAD but without heart failure or acute myocardial infarction randomised to antihypertensive agent or placebo; (2) reporting 1 year or longer-term outcomes;

(3) enrolling at least 100 patients (to avoid bias associated with small trials); and (4) achieving systolic pressure at the end of follow-up of ≤140 mm Hg in both arms. Additionally, since the objective was to test outcomes based on two BP targets, the following additional criteria were required: (1) the final achieved systolic pressure in the 'intensive BP' group ≤135 mm Hg; (2) the final achieved systolic pressure in the 'standard BP' group ≤140 mm Hg; and (3) the systolic pressure difference between the intensive and standard BP groups of at least 1 mm Hg. In a sensitivity analysis, we also tested a difference of 3 mm Hg, as was used in our prior analysis.[8] We chose this cut point as a difference less than this is likely clinically not relevant and will not result in differential clinical outcomes based on BP alone. Studies where there was no difference in BP between the groups, defined here as those where final BP was ≤140 mm Hg but where there was no difference in BP between the two groups, were excluded. For example, if a study evaluated two antihypertensive agents, but uptitrated or added medication to ensure no difference in final systolic pressures, they were excluded as such studies are not expected to provide information on BP targets.

Selection and quality assessment

Three authors (SB, SK and AV) independently assessed trial eligibility and trial bias risk and extracted data. Disagreements were resolved by consensus. The bias risk of the trials was assessed using the components recommended by the Cochrane Collaboration:[9] (1) sequence generation of allocation; (2) allocation concealment; (3) blinding of participants, personnel and outcome assessors; (4) incomplete outcome data; (5) selective outcome reporting; and (6) other sources of bias. Of note, the studies did not differ for quality components 4 through 6. Trials with high or unclear risk for bias for any one of the first three components were considered as trials with high-risk of bias. Otherwise, they were considered as low-risk of bias trials.

Data extraction and synthesis

For the purpose of this analysis, the intensive BP group was defined as the group where the final achieved systolic pressure was ≤135 mm Hg and the standard BP group as where the final achieved systolic pressure was ≤140 mm Hg. Of note, these terms are based on the trial mean achieved systolic pressure, are used for descriptive purposes for this manuscript and not necessarily the strategy employed in the trial (ie, no trial tested a BP strategy). The intensive BP group was further divided into a more intensive group with an achieved BP of ≤130 mm Hg and a less intensive group with an achieved BP of >130–≤135 mm Hg (figure 1).

Long-term efficacy and safety outcomes were evaluated. The efficacy outcomes were: all-cause mortality, cardiovascular

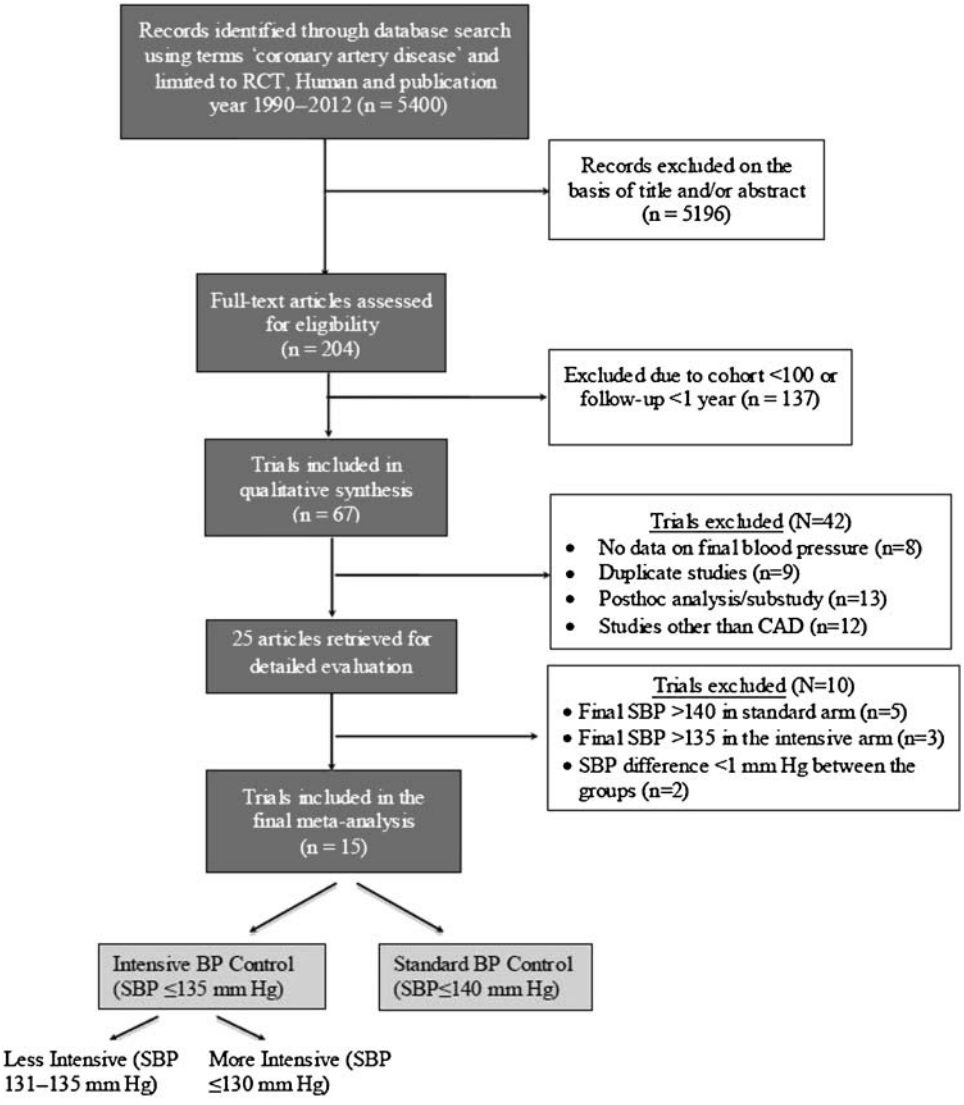


Figure 1 Study selection. BP, blood pressure; CAD, coronary artery disease; RCT, randomised clinical trial; SBP, systolic blood pressure.

Table 1 Baseline characteristics of included trials

Study	Year	Total number (N)	Comparison	Follow-up (months)	Mean age (years)	Men (%)	HTN (%)	DM (%)	Baseline SBP (mm Hg)	Final SBP (mm Hg)
ACTION[22]	2004	7665	Nifedipine GITS versus placebo	59	64	79	52	15	137.3 vs 137.6	130 vs 135
CAMELOT (Amlodipine)[23]	2004	1318	Amlodipine versus placebo	24	57	75	61	19	129.5 vs 128.9	124.7 vs 130
CAMELOT (Enalapril)[23]	2004	1328	Enalapril versus placebo	24	58	73	60	19	128.9 vs 128.9	124 vs 130
COURAGE[24]	2007	2287	Medical therapy versus PCI group	55	62	85	67	34	130 vs 131	122 vs 124
Dorval *et al*[25]	2005	134	Amlodipine/atorvastatin versus atorvastatin/ placebo	12	57	86	NA	9	127 vs 128	118 vs 130
EUROPA[26]	2003	12 218	Perindopril versus placebo	50	60	85	27	12	137 vs 137	128 vs 133
FAMIS[27]	1998	285	Fosinopril versus placebo	24	60	83	37	15	137 vs 136	124 vs 128
HIJ-CREATE[28]	2009	2049	Candesartan based therapy versus non-ARB therapy	75	65	81	100	38	135 vs 135.5	130.7 vs 132
IMAGINE[29]	2008	2553	Quinapril versus placebo	36	61	87	47	9.5	122 vs 121	125 vs 129
Kondo *et al*[30]	2003	406	Candesartan versus placebo	24	65	76	44	25	129 vs 128	127 vs 126
ONTARGET (Telmisartan)[31]	2008	17 118	Telmisartan versus ramipril	56	66	73	69	37	141.7 vs 141.8	134.3 vs 135
ONTARGET (Combination)[31]	2008	17 178	Telmisartan + ramipril versus ramipril	56	66	73	69	38	141.9 vs 141.8	132.1 vs 135
PART-2[32]	2000	617	Ramipril versus placebo	56	61	82	NA	9	133 vs 133	127 vs 132
PEACE[33]	2004	8290	Trandolapril versus placebo	36	64	82	46	17	133 vs 133	128.6 vs 132
PREVENT[34]	2000	825	Amlodipine versus placebo	36	57	80	NA	NA	128.8 vs 130	122 vs 130
ROADMAP[35]	2011	1112	Olmesartan versus placebo	38	58	54	NA	100	137 vs 136	125.7 vs 129
SCAT[36]	2000	460	Enalapril versus placebo	48	61	89	36	11	128 vs 132	122 vs 130

ACTION, A Coronary disease Trial Investigating Outcome with Nifedipine GITS; CAMELOT, Comparison of Amlodipine vs Enalapril to Limit Occurrences of Thrombosis; COURAGE, Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation; EUROPA, EUropean trial on Reduction Of cardiac events with Perindopril in patients with stable coronary Artery disease; FAMIS, Fosinopril in Acute Myocardial Infarction Study; HIJ-CREATE, Heart Institute of Japan Candesartan Randomised Trial for Evaluation in CAD; IMAGINE, Accupril post-bypass Graft via Inhibition of the converting Enzyme; ONTARGET, Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial; PART, Prevention of Atherosclerosis with Ramipril; PEACE, Prevention of Events with Angiotensin Converting Enzyme Inhibition; PREVENT, Prospective Randomized Evaluation of the Vascular Effects of Norvasc Trial; ROADMAP, Randomized Olmesartan and Diabetes Microalbuminuria Prevention; SCAT, Simvastatin/Enalapril Coronary Atherosclerosis Trial.
ARB, angiotensin receptor blocker; DM, diabetes mellitus; GITS, gastrointestinal therapeutic system; HTN, hypertension; PCI, percutaneous coronary intervention; SBP, systolic blood pressure.

mortality, myocardial infarction, stroke, angina pectoris, heart failure and revascularisation. The safety outcome evaluated was hypotension as reported between the two groups.

Statistical analysis

Intention-to-treat meta-analysis was performed in line with recommendations from the Cochrane Collaboration and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement,[10 11] using standard software (Stata V.9.0, Stata corporation).[12] Heterogeneity was assessed using the I^2 statistic.[13] I^2 is the proportion of total variation observed between the trials attributable to differences between trials rather than sampling error (chance) with I^2 <25% considered as low and I^2 >75% as high. The analysis employed rates per 1000 patient-years of follow-up rather than events. This is more appropriate because they incorporate and control for the varying duration of the trials. Patient-years of follow-up were calculated by multiplying the sample size for each trial with the mean follow-up duration. The results are expressed as rate ratios rather than relative risk. If trials were homogeneous ($p>0.05$), a fixed effect model was used to calculate pooled effect sizes. Otherwise, a random effects model of DerSimonian and Laird[14] was applied to calculate overall differences. However, given the clinical heterogeneity between the trials, regardless of statistical heterogeneity, a random effects model was used to make inferences (unless otherwise stated). Publication bias was estimated visually by funnel plots and using the Begg's test and the weighted regression test of Egger *et al*.[15] Analyses were performed after further stratifying the studies based on the final achieved systolic pressure in the intensive group: systolic pressure >130 but ≤135 mm Hg (less intensive group) versus systolic pressure ≤130 mm Hg (more intensive group). We estimated the difference between the estimates of the subgroups according to tests of interaction.[16] A p value <0.05 indicates that the effects of treatment differ between the tested subgroups.

A meta-regression analysis was performed to explore the relationship between systolic pressure (final achieved) and outcomes. For this purpose, the mean achieved systolic pressure was used as a continuous variable. We used residual maximum likelihood to estimate the additive (between-study) component of variance τ^2 for the meta-regression analysis. Bootstrap analyses were performed using a Monte Carlo permutation test for meta-regression using 1000 random permutations.[17]

Table 2 Inclusion criteria and quality of study

Study	Inclusion criteria	Quality of study*	Source of funding
ACTION[22]	Age ≥35 years, stable angina for ≥1 month, and need for oral or transdermal treatment either to treat or prevent anginal attacks and one of three characteristics: (1) history of MI; (2) those with angiographic CAD but no MI; and (3) those with a positive exercise test or perfusion defect who have never had coronary angiography and had no history of MI. LVEF ≥40%.	+++	Non-industry
CAMELOT[23]	Aged 30–79 requiring coronary angiography for chest pain or PCI.	+++	Industry
COURAGE[24]	Stable CAD with a CCS class IV angina and stenosis of ≥70% in ≥ 1 proximal epicardial coronary artery and objective evidence of myocardial ischaemia (EKG or stress test) or 80% coronary stenosis with classic angina.	+++	Non-industry
Dorval *et al*[25]	Aged > 30 with documented CHD by coronary aniography ≥70%, nuclear or stress echo, or by history of MI more than 3 months ago.	+±±	Industry
EUROPA[26]	Aged ≥18 years without clinical evidence of HF and with evidence of CHD, documented previous MI (>3 months before screening), coronary revascularisation (>6 months before screening) or angiographic evidence of ≥70% narrowing of ≥1 major coronary arteries; men with a history of chest pain and a positive EKG, echo or nuclear stress test.	+++	Industry
FAMIS[27]	Aged 18–75 with ICU admission within 9 h of the onset of typical ischaemic chest pain associated with signs of definite anterior wall MI on EKG and who were eligible for thrombolytic treatment.	+++	NA
HIJ-CREATE[28]	Hospitalised patients aged 20–80 years with HTN and CAD diagnosed via coronary angiography (stenotic lesion or a history of spastic angina).	+++	Non-industry
IMAGINE[29]	Hospitalised patients ≥18-years-old 7–10 days after CABG, stable after the surgery and with an LVEF >40% within 6 months prior to surgery.	+++	Industry
Kondo *et al*[30]	Patient with no significant coronary stenosis on 6 month follow-up angiography after coronary intervention.	+±–	Not reported
ONTARGET[31]	Aged ≥55 years with CAD (>2 days post-uncomplicated MI, stable angina or unstable angina >30 days with multi-vessel CAD, multi-vessel PTCA >30 days, multi-vessel CABG >4 years or with recurrent angina following surgery), PAD (previous bypass, angioplasty, amputation or intermittent claudication with ABI ≤0.80 on at least one side, ≥50% stenosis on angiography or non-invasive testing), CVA (stroke or TIA), DM with evidence of end organ damage.	+++	Both industry and non-industry
PART-2[32]	Aged ≤75 years with a hospital diagnosis (within 5 years of enrolment) of any of the following: acute MI, angina with CAD confirmed by angiography or exercise EKG, TIA or intermittent claudication.	+++	Not reported
PEACE[33]	Aged >50 with CAD documented by MI, CABG or PTCA at least 3 months prior or ≥50% obstruction of at least one native vessel and LVEF >40%.	+++	Non-industry
PREVENT[34]	Aged 30–80 years with angiographic evidence of 1 focal coronary lesion ≥30% and ≥1 lesion with 5%–20% stenosis that was not in a vessel with ≥60% stenosis.	+±+	Industry
ROADMAP[35]	Aged 18–75 years with DM2, normoalbuminuria (UACR: ≤35 mg/g for female subjects, ≤25 mg/g for male subjects) and one of the following: total cholesterol >5.2 mmol/l or treatment for hyperlipidaemia, HDL <1.1 mmol/l, TG >1.7 mmol/l, SBP ≥130 and/or DBP ≥80 or HTN medications, BMI ≥28 kg/m^2, high waist circumference (>88 cm for female subjects, >102 cm for male subjects), smoking >5 cigarettes/day.	+++	Industry
SCAT[36]	Age ≥21 years, total serum cholesterol 4.1–6.2 mmol/l, HDL <2.2 mmol/l, TG <4 mmol/l, angiographically detectable coronary atherosclerosis in ≥3 major coronary artery segments, and LVEF ≥35%, no CABG or PTCA within prior 6 months.	+±+	Non-industry

See footnote of table 1 for explanation of trial names.
*Represents risk of bias based on: sequence generation of allocation, allocation concealment and blinding; '+' represents low bias risk, '–' high bias risk and '±' unclear bias risk.
ABI, Ankle Brachial Index; BMI, body mass index; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CCS, Canadian Cardiovascular Society; CHD, coronary heart disease; CVA, cerebrovascular accident; DBP, diastolic blood pressure; DM, diabetes mellitus; DM2, diabetes mellitus type 2; EKG, electrocardiography; HDL, high density lipoprotein; HF, heart failure; HTN, hypertension; LVEF, left ventricular ejection fraction; MI, myocardial Infarction; PAD, peripheral artery disease; PCI; percutaneous coronary intervention; PTCA, percutaneous transluminal coronary angioplasty; SBP, systolic blood pressure; TG, triglyceride; TIA, transient ischaemic attack; UACR, urinary albumin to creatine ratio.

Sensitivity analyses

In a meta-analysis of clinical trials with binary outcomes such as the one described above, a normal approximation for the summary treatment effect measure in each trial may not be appropriate when some of the trials in the meta-analysis are small or the observed risks are close to 0 or 1. In order to avoid this problem, direct use of the binomial distribution within trials can be used as described by Warn *et al*.[18] The advantages of Bayesian methods include a modelling framework which overcomes issues such as the appropriate treatment of small trials, and the ability to consider distributions other than normal for the random effects. In order to confirm the results from the traditional meta-analysis, Bayesian random effects meta-analyses were performed. The BUGS code for implementing the model is as described by Warn *et al*.[18] Minimally informative prior distributions were used, so the findings and interpretation are close to those obtained with frequentist methods. All Bayesian analyses were conducted using WinBUGS 1.4.3 London, United Kingdom.

Further sensitivity analysis was performed by restricting the analysis to low bias risk trials. In addition, further analyses were performed after including trials which narrowly missed the inclusion criteria (where intensive BP group >135 mm Hg), such as the Heart Outcomes Prevention Evaluation (HOPE) trial (achieved systolic BP of 139 and 136 mm Hg),[19] Telmisartan Randomized AssessmeNt Study in aCE iNtolerant subjects with cardiovascular Disease (TRANSCEND) trial (achieved systolic BP of 136.4 and 140.2 mm Hg)[20] and the Japan Multicenter Investigation for Cardiovascular Diseases-B (JMIC-B) randomised trial (CAD subgroup) (achieved systolic BP of 136 and 138 mm Hg).[21] Moreover, further analyses were conducted restricting trials where the BP difference between arms was at least 3 mm Hg, such as that used in our prior analysis.[8]

Role of the funding source

This work was not funded and hence there was no role of any funding source in the conception, data synthesis, analysis, data interpretation or in the drafting of the manuscript.

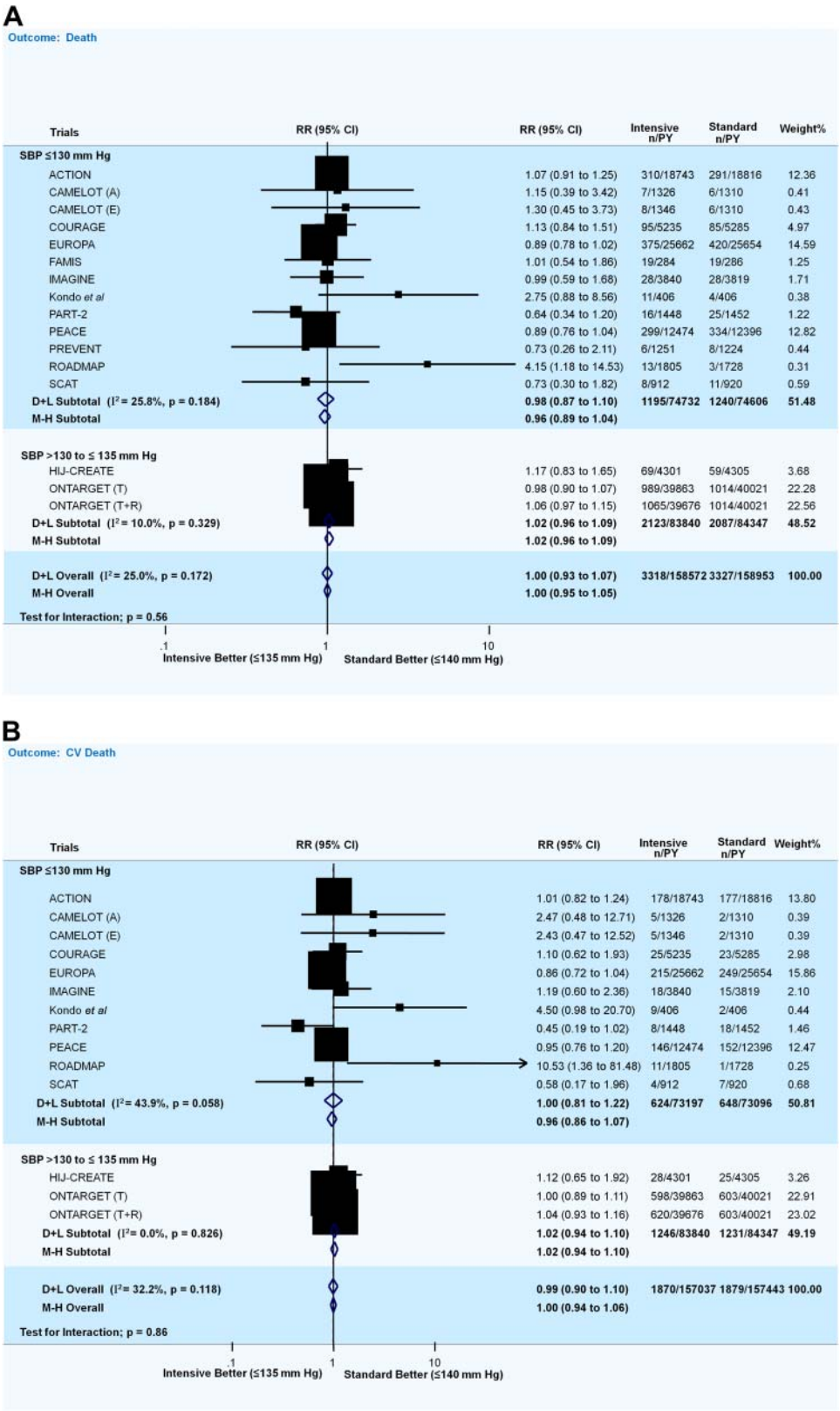


Figure 2 (A) Intensive (≤135 mm Hg) versus standard (≤140 mm Hg) blood pressure control and all-cause mortality. (B). Intensive (≤135 mm Hg) versus standard (≤140 mm Hg) blood pressure control and cardiovascular mortality. (C) Intensive (≤135 mm Hg) versus standard (≤140 mm Hg) blood pressure control and myocardial infarction. (D) Intensive (≤135 mm Hg) versus standard (≤140 mm Hg) blood pressure control and angina pectoris. (E) Intensive (≤135 mm Hg) versus standard (≤140 mm Hg) blood pressure control and revascularisation. Results are further stratified by achieved systolic pressure in the intensive group. The size of the data marker represents the weight of each trial. Expansion of trial names as in table 1. PY, patient-years; RR, rate ratio; SBP, systolic blood pressure. This figure is only reproduced in colour in the online version.

RESULTS

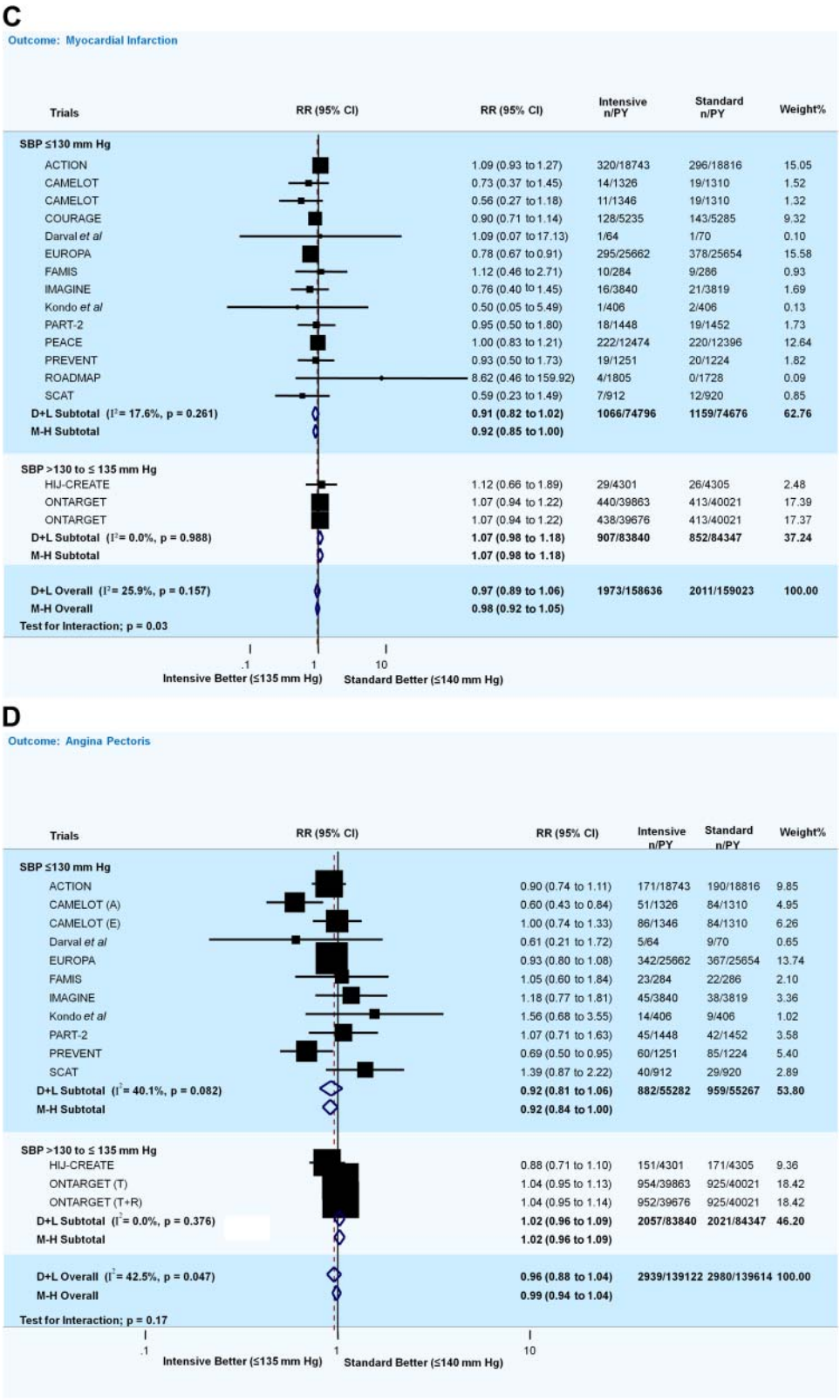
Study selection

We identified 15 RCTs that fulfilled the inclusion criteria and were chosen for this analysis (figure 1). The Randomized Olmesartan and Diabetes Microalbuminuria Prevention (ROADMAP) trial included was the CAD subgroup only. In addition, three other trials (HOPE, TRANSCEND, JMIC-B) that narrowly missed the inclusion criteria were included in a sensitivity analysis as described above.

Characteristics of the trials

The baseline characteristics, inclusion criteria and bias–risk assessment are summarised in tables 1 and 2. The 15 RCTs enrolled 66 504 participants with 276 328 patient-years of follow-up: 37 842

Figure 2 (Continued)

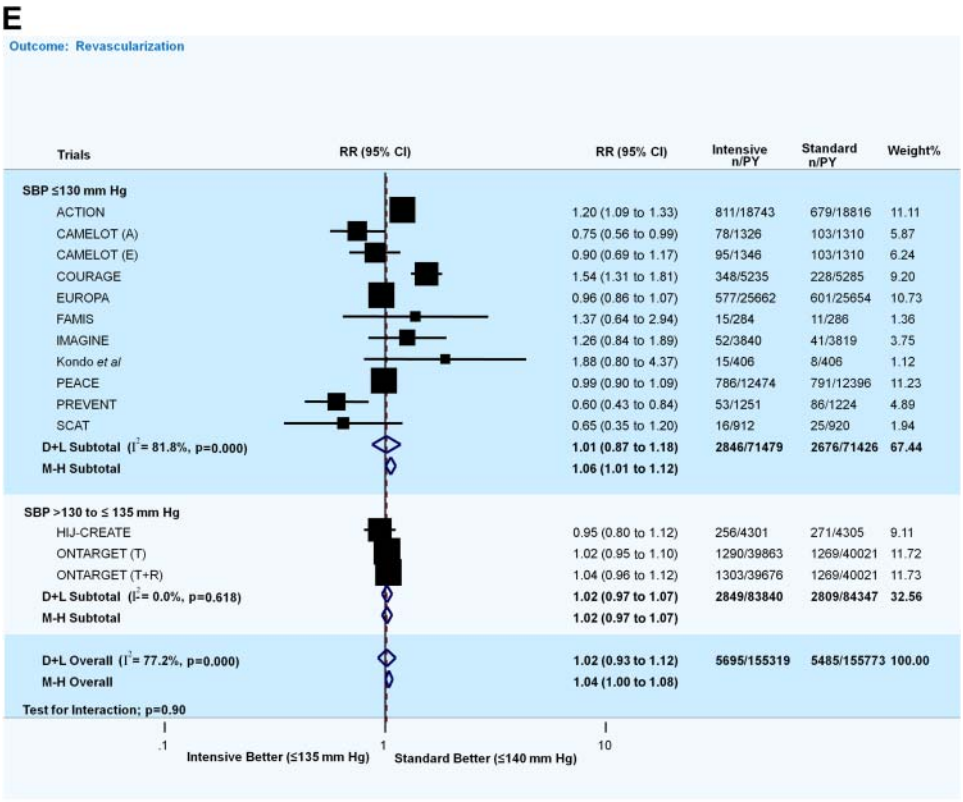


(50.5%) participants to the group with achieved systolic BP ≤135 mm Hg (intensive BP group) and 28 662 (49.5%) participants to the group with achieved systolic BP ≤140 mm Hg (standard BP group) were followed-up for 3.4±1.2 years (weighted mean). Of note, none of the trials were designed to test a BP strategy.

Quality assessments

Among the 15 RCTs considered for this analysis, 11 were considered trials with a low risk of bias as described above and the others were considered trials with unclear or high risk of bias (table 2).

Figure 2 (Continued)



Efficacy outcomes

Intensive BP group (≤135 mm Hg) was not associated with any significant benefit for the outcomes of death (figure 2A), CV death (figure 2B) or revascularisation (figure 2E) when compared with standard BP (≤140 mm Hg). The results were similar for 'more' and 'less' intensive BP subgroups for the above outcomes ($p_{interaction}$ >0.05). For the outcome of myocardial infarction (figure 2C), the test for interaction was significant ($p_{interaction}$=0.03) such that the more intensive BP subgroup was associated with greater reduction in myocardial infarction (figure 2C) compared with the less intensive BP subgroup. In addition, the more intensive BP subgroup was associated with an 8% reduction in myocardial infarction and angina pectoris (figure 2D) when compared with standard BP group in the fixed effect model but not the random effects model (figure 2C,D). There was low heterogeneity for the outcome of death and modest heterogeneity for the outcomes of angina pectoris, CV death and myocardial infarction (figure 2A–D) but high heterogeneity for the outcome of revascularisation (I^2=77.2%).

Intensive BP (≤135 mm Hg) was associated with a 15% decrease in heart failure (figure 3A) and 10% decrease in stroke (figure 3B). More intensive BP control (≤130 mm Hg) was associated with a greater (27% and 17%) reduction in heart failure and stroke when compared with standard BP (figure 3A,B). There was no heterogeneity for the outcome of stroke but modest heterogeneity for the outcome of heart failure (figure 3A,B).

Bias was insignificant for any of the above analyses (online supplementary web appendix figure A1–7). The results were similar when the analysis was restricted to low bias risk trials (data not shown).

Safety outcome

Intensive BP group (≤135 mm Hg) was associated with a 105% increase in hypotension rate (figure 3C) when compared with the standard BP group. The results were similar for more versus less intensive subgroups ($p_{interaction}$=0.97). There was high heterogeneity for this analysis but bias was insignificant (online supplementary web appendix figure A8). Analysis was performed to explore heterogeneity for this outcome. A Galbraith's plot revealed that the ONTARGET trial may be a possible outlier. Excluding this trial reduced the heterogeneity somewhat (I^2=67.7%) but the results were similar with a 103% increase in hypotension rate. No other tested variable reduced the heterogeneity further and the residual heterogeneity could likely be the result of clinical heterogeneity between trials.

Meta-regression analysis

The relationship between final achieved systolic pressure and the risk of efficacy and safety outcomes is shown in figure 4A–F. For the outcomes of death and CV death, lower was not better for systolic BP (figure 4A,B) and was uniformly no different than the standard BP group (log rate ratio ~0). For the outcomes of myocardial infarction, stroke, angina and heart failure, lower systolic BP was associated with a greater rate ratio reduction (figure 4C–F). The relationship between lower systolic BP and heart failure outcomes was significant even after bootstrap analyses performed using a Monte Carlo permutation test for meta-regression with 1000 random permutations (p=0.025), such that for each 10 mm Hg lower systolic pressure, there was a 50% decrease in the log risk ratio for heart failure. Similarly for the outcome of myocardial infarction, there was a trend towards (p=0.049) lower being better with each 10 mm Hg lower systolic pressure associated with a 24% lower log risk ratio. For the safety outcome of hypotension, the rate ratio was uniformly high with intensive BP across systolic pressures (figure 5).

Sensitivity analysis

Sensitivity analysis performed using a Bayesian random effects model showed similar results with an 18% reduction in the rate of heart failure and a 14% reduction in the rate of stroke with

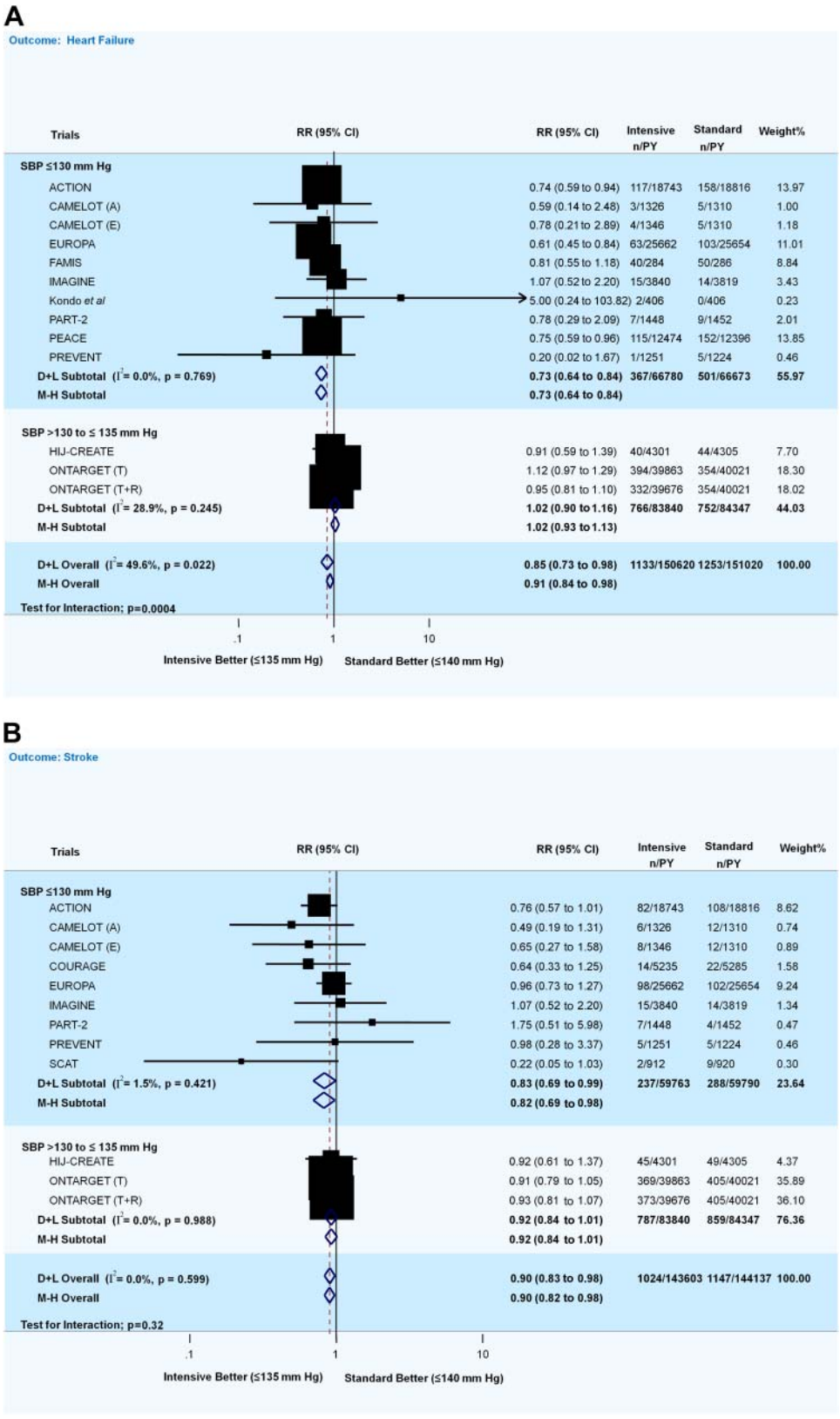
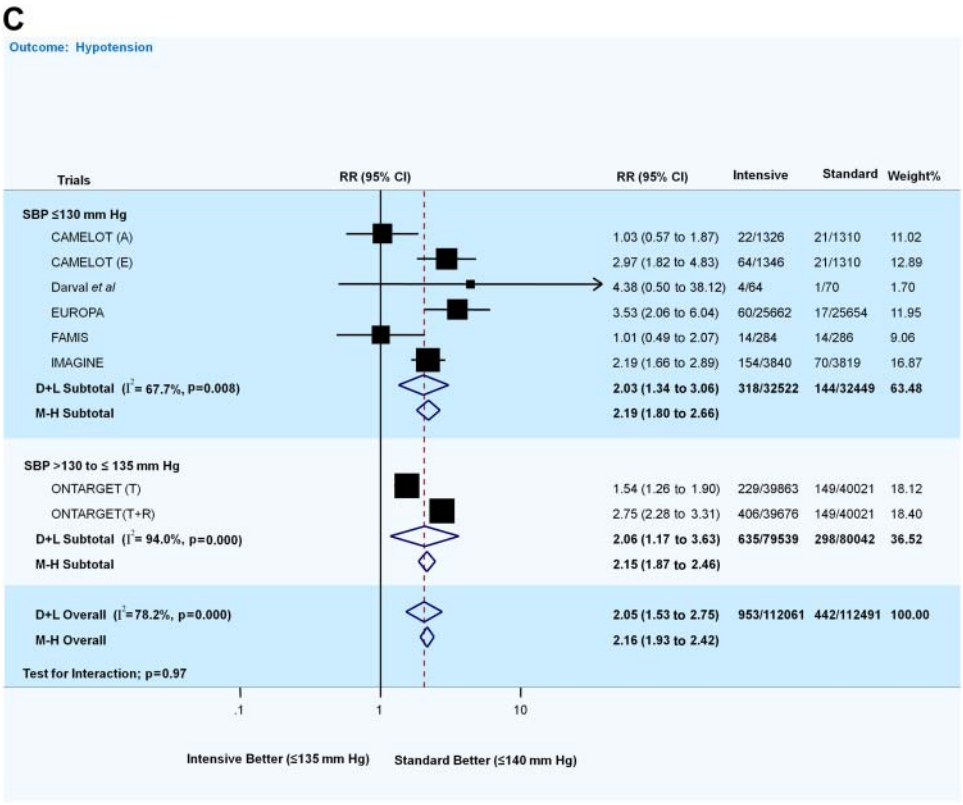


Figure 3 (A) Intensive (≤135 mm Hg) versus standard (≤140 mm Hg) blood pressure control and heart failure. (B) Intensive (≤135 mm Hg) versus standard (≤140 mm Hg) blood pressure control and stroke. (C) Intensive (≤135 mm Hg) versus standard (≤140 mm Hg) blood pressure control and hypotension. Results are further stratified by achieved systolic pressure in the intensive group. The size of the data marker represents the weight of each trial. Expansion of trial names as in table 1. PY, patient-years; RR, rate ratio; SBP, systolic blood pressure. This figure is only reproduced in colour in the online version.

intensive BP control (≤135 mm Hg) when compared with standard BP control but with a 99% increase in the rate of hypotension with intensive BP control (table 3). In addition, a Bayesian random effects model evaluating the relationship between systolic BP and outcomes showed that lower was better for the outcomes of myocardial infarction and stroke (table 3). The results were similar when the analysis was restricted to low bias risk trials or using trials where the systolic pressure difference was at least 3 mm Hg (data not shown).

Further sensitivity analyses performed after inclusion of the HOPE, TRANSCEND and JMIC-B trials showed similar results with a significant benefit of intensive BP control (≤135 mm Hg)

Figure 3 (Continued)



for the outcomes of heart failure and stroke at the expense of an increase in hypotension (table 4).

DISCUSSION

The principal finding of the present study is that compared with a BP target of ≤140 mm Hg, a more intensive BP target of ≤135 mm Hg is associated with significant reduction in stroke and heart failure but at the expense of increased rate of hypotension, consistently seen in both the traditional meta-analysis and using a Bayesian random effects model. In addition, lower seemed to be better (based on regression analysis) for the outcomes of myocardial infarction, stroke, heart failure and perhaps angina.

BP targets in patients without CAD

Data from observational studies involving more than 1 million individuals without pre-existing vascular disease indicate that death from both ischaemic heart disease and stroke increases progressively and *linearly* with BP.[37] Consequently, the notion that 'lower is better' has been popular for management of hypertension. The seventh report of the Joint National Committee on prevention, detection, evaluation and treatment of high BP states 'The relationship between BP and risk of cardiovascular events is *continuous*, consistent, and independent of other risk factors'.[1] As a consequence, a BP of <120/80 mm Hg has been considered as 'optimal' or 'normal'.[1] However, this linear theory has been challenged for nearly 3 decades[5–7 38 39] and the recently published ACCORD BP trial showed no benefit of lowering systolic pressure to <120 mm Hg, except for stroke.[4] In addition, a recently published analysis from our group further confirms the findings from the ACCORD BP trial in subjects with diabetes.[8]

BP targets in patients with CAD

In the American Heart Association scientific statement on 'Treatment of Hypertension in the Prevention and Management of Ischemic Heart Disease,' a target of <130/80 mm Hg has been recommended in patients with CAD and acute coronary syndromes, although it was acknowledged that there were limited data to support this recommendation (*Class IIa, level of evidence B*).[40] Similarly, other national and international guidelines recommend a lower target of ≤130/80 mm Hg in patients with established cardiovascular disease. However, the evidence to support this lower goal is scant.

Antihypertensive therapy for secondary prevention in patients with CAD is distinctly different from primary prevention of CAD (such as tested in ACCORD BP). If aggressive strategies such as intensive BP control were to be efficacious, they can be expected to be so in the highest risk subsets, such as those with known CAD. Increased BP is a significant risk factor for the development of heart failure, stroke and less so for myocardial infarction. On the contrary, lower BP has been shown to often compromise coronary perfusion, leading to increased risk of cardiovascular events.

We have shown in an analysis of 10 001 patients with CAD enrolled in the Treating to New Targets trial that the event rate (a composite of death from coronary disease, non-fatal myocardial infarction, resuscitated cardiac arrest, and fatal or non-fatal stroke) at the end of 4.9 years (median) of follow-up was the lowest at a BP of 146.3/81.4 mm Hg and that a very low BP (<110–120/<60–70 mm Hg) portends an increased risk of events.[5] Similarly, a J-shaped relationship between BP and cardiovascular outcomes has been shown in subgroup analyses from other randomised trials (INVEST,[7] ONTARGET,[41] CAD cohorts of Cruickshank *et al*,[38] Framingham Heart Study[39] and Syst-Eur[42]). In addition, we found similar results in 4162 acute coronary syndrome patients enrolled in the PROVE-IT TIMI 22

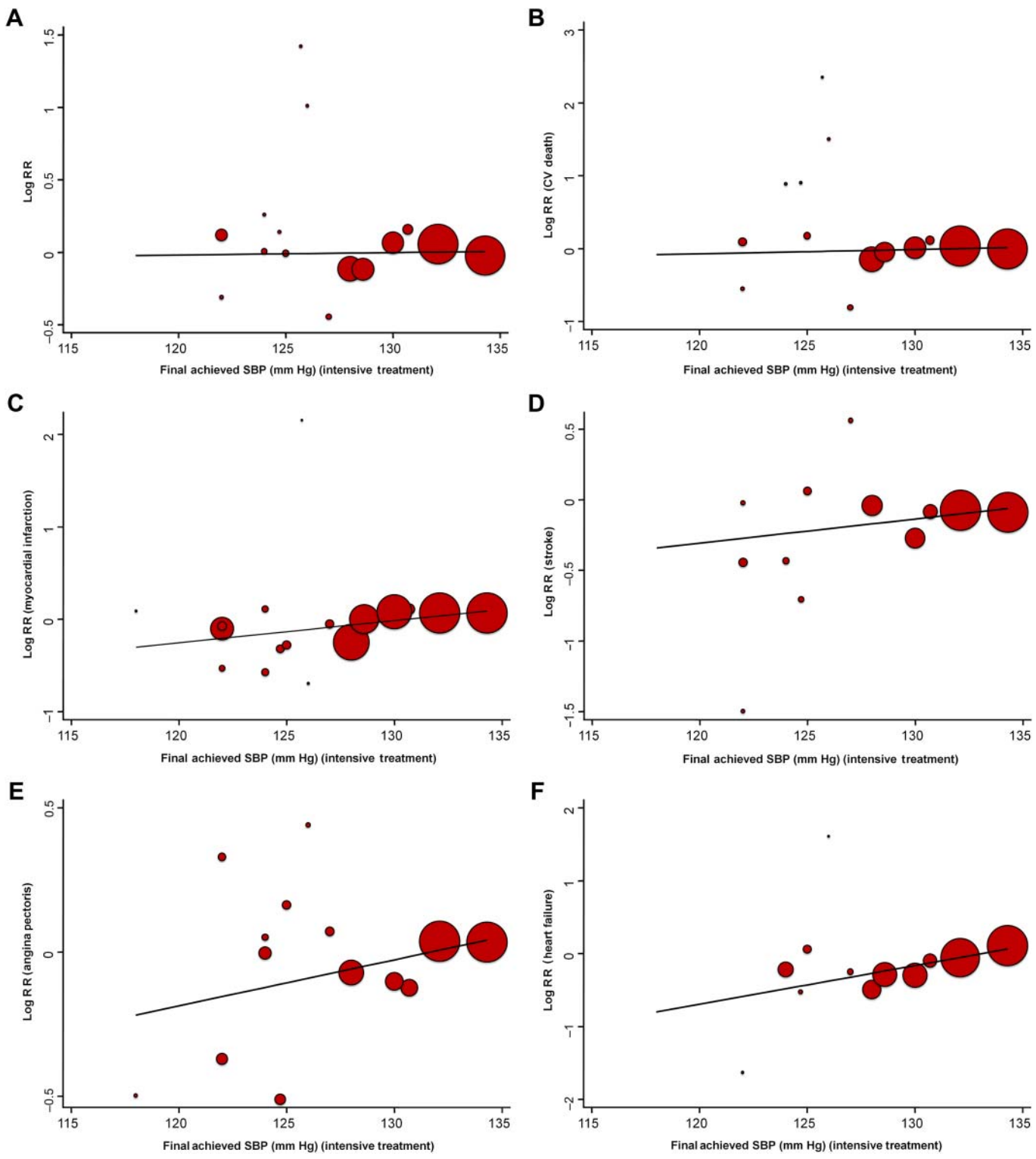


Figure 4 (A) Relationship between all-cause mortality (log relative risk (RR)) and final achieved systolic pressure. (B) Relationship between cardiovascular mortality (log RR) and final achieved systolic pressure. (C) Relationship between myocardial infarction (log RR) and final achieved systolic pressure. (D) Relationship between stroke (log RR) and final achieved systolic pressure. (E) Relationship between angina pectoris (log RR) and final achieved systolic pressure. (F) Relationship between heart failure (log RR) and final achieved systolic pressure. The size of the data marker represents the weight of each trial. The regression fit (solid line) is shown. CV, cardiovascular; SBP, systolic blood pressure. This figure is only reproduced in colour in the online version.

trial (randomised to pravastatin 40 mg vs atorvastatin 80 mg).[6] The nadir BP where the risk of primary outcome (death from any cause, myocardial infarction (MI), unstable angina requiring rehospitalisation, revascularisation after 30 days and stroke) was the lowest for a BP of 136/85 mm Hg, while in INVEST the nadir systolic BP was ~119 mm Hg. In addition, in all of these analyses, the increased risk of cardiovascular outcomes with systolic pressures occurred at very low systolic pressures (<110 mm Hg) with a relatively shallow curve between 110 and 140 mm Hg.

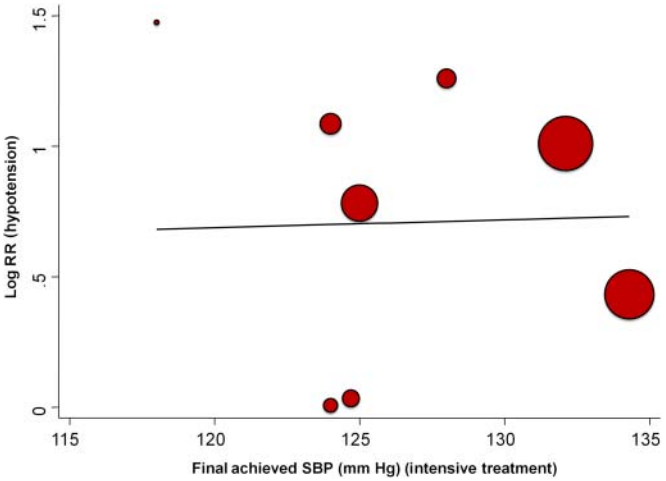


Figure 5 Relationship between hypotension (log relative risk (RR)) and final achieved systolic pressure. The size of the data marker represents the weight of each trial. The regression fit (solid line) is shown. SBP, systolic blood pressure. This figure is only reproduced in colour in the online version.

The result of the present analysis suggests that intensive BP to ≤135 mm Hg was consistently seen to have a *modest effect* at lowering stroke and heart failure, both in the traditional meta-analysis and the Bayesian random effect meta-analysis, but at the expense of hypotension. In addition, BP ≤130 mm Hg was associated with a modest benefit for myocardial infarction and angina when compared with standard BP group. Moreover, meta-regression analysis suggests sustained benefit of aggressive BP control for the outcomes of heart failure and myocardial infarction, with the slope suggesting benefit for outcomes of stroke and angina.

In the INVEST trial analysis described above, the event rate continued to decrease with a nadir systolic pressure of around 120 mm Hg, similar to the finding from this study. Our results are discordant with the main results from the ACCORD BP trial in subjects with diabetes, where lower was better only for the outcome of stroke. In the ACCORD BP trial, in a subgroup analysis in patients with known prior cardiovascular disease, an intensive BP strategy (<120 mm Hg) was associated with a numerically lower primary endpoint rate (2.98%/year) when compared with the standard BP strategy (<140 mm Hg) (3.43%/year), although this was not statistically significant. The analysis was underpowered with only 1593 patients with known cardiovascular disease.

Similarly, our own observation from non-randomised comparisons seems to suggest that lower is better but this only goes so far and systolic BP below 110 mm Hg is not advisable. We however did not see a J-curve association in the present analyses as there was no trial where the systolic BP was very low (below 110 mm Hg). More importantly, none of the trials included were designed to test a BP strategy. Though the findings are hypothesis generating and provide some evidence in the interim, this observation should be further investigated in future clinical trials. Of note, in the ACCORD BP trial only a third of patients had cardiovascular disease (including those with stroke, peripheral arterial disease and not necessarily all CAD) with even lower percentage of patients with CAD and hence the results of ACCORD BP cannot and should not be extrapolated to the CAD cohort.

Randomised controlled trials testing BP strategies (targeting <120 mm Hg vs <140 mm Hg) and powered for hard clinical outcomes (death or myocardial infarction) using therapies that have proven efficacy (ARBs, ACEi, CCB, β blockers and diuretics) are needed to test such an association. The design of such a trial should be an open label design with a treatment escalation strategy to achieve BP goals with a PROBE design with blinded outcome assessors.[43]

Table 3 Sensitivity analysis: random effects Bayesian model

Outcome	RR (95% Cr I)	τ^2	Relationship of SBP to outcomes* Slope†	95% Cr I
Efficacy				
All-cause mortality	1.00 (0.92 to 1.08)	0.008	0.70	−2.59 to 3.65
Cardiovascular mortality	0.99 (0.91 to 1.12)	0.013	1.00	−2.46 to 4.55
Myocardial infarction	0.95 (0.82 to 1.04)	0.021	4.30	1.07 to 10.17
Heart failure	0.82 (0.67 to 0.98)	0.053	3.83	−1.20 to 7.75
Stroke	0.86 (0.70 to 0.97)	0.022	4.14	0.11 to 10.09
Angina pectoris	0.95 (0.84 to 1.05)	0.023	2.31	−0.16 to 2.29
Revascularisation	1.00 (0.86 to 1.16)	0.056	0.69	−3.27 to 4.45
Safety				
Hypotension	1.99 (1.25 to 2.95)	0.296	3.54	−5.53 to 13.59

*Final achieved SBP in the intensive group.
†Negative slope represents an inverse relationship (lower SBP associated with worse outcomes) and positive represents a direct relationship (lower SBP associated with better outcomes).
Cr I, credibility interval; RR, rate ratio; SBP, systolic blood pressure; τ^2 represents the between study variance with higher number representing greater between study variance.

Table 4 Sensitivity analysis (including HOPE, TRANSCEND and JMIC-B trials)

Outcome	RR (95% Cr I)	τ^2	Relationship of SBP to outcomes* RR (95% CI)	p Value
Efficacy				
All-cause mortality	0.98 (0.92 to 1.05)	0.0049	1.00 (0.98 to 1.01)	0.67
Cardiovascular mortality	0.96 (0.87 to 1.07)	0.0146	0.99 (0.96 to 1.02)	0.49
Myocardial infarction	0.93 (0.85 to 1.01)	0.0108	1.00 (0.98 to 1.03)	0.70
Heart failure	0.86 (0.76 to 0.97)	0.0196	1.02 (0.99 to 1.06)	0.13
Stroke	0.86 (0.79 to 0.93)	0.0029	1.00 (0.97 to 1.03)	0.97
Angina pectoris	0.94 (0.88 to 1.02)	0.0083	1.01 (0.97 to 1.02)	0.54
Safety				
Hypotension	1.95 (1.50 to 2.53)	0.1182	0.99 (0.93 to 1.06)	0.76

*Final achieved SBP in the intensive group.
HOPE, Heart Outcomes Prevention Evaluation; JMIC-B, Japan Multicenter Investigation for Cardiovascular Diseases-B; RR, rate ratio; SBP, systolic blood pressure; TRANSCEND, Telmisartan Randomized AssessmeNt Study in aCE iNtolerant subjects with cardiovascular Disease; τ2 represents the between study variance with higher number representing greater between study variance.

Study limitations

As in other meta-analyses, given the lack of data in each trial, we did not adjust our analyses for medications used. Though detailed analyses were undertaken, given the heterogeneity in the study designs and cohort enrolled, clinically relevant differences could have been missed and are best assessed in a meta-analysis of individual patient data. All of the trials did not

report all of the outcomes and none were designed to test a BP strategy. The results are therefore best described as hypothesis generating to be further confirmed in future RCTs. In this analysis, we tested a BP goal of ≤140 mm Hg with that of ≤135 mm Hg and not of a lower goal such as ≤130 mm Hg for several reasons: (1) to ensure that we use data from as many relevant trials as possible as the number of trials if the criteria is tightened to ≤130 mm Hg was very small; (2) test if evidence exists for even a 135 mm Hg goal and finally and more importantly; (3) the cut points are less relevant as in our regression analysis, the mean achieved BP was treated as a continuous variable and our conclusions and recommendations are based on this. Moreover, the intensive group was substratified into a more intensive group (≤130 mm Hg) versus a less intensive group (>130 but ≤135 mm Hg). The relationship tested is for systolic BP targets only (one that is recommended by guidelines and used in clinical practice). Moreover, we did not test for the treatment effect of individual trials as the intention was to test the effect of a given BP target rather than the medication used to achieve such a target.

CONCLUSIONS

The present body of evidence suggests that intensive BP control to ≤135 mm Hg and possibly even to ≤130 mm Hg reduces heart failure and stroke in patients with CAD at the expense of increase in hypotension, with meta-regression analysis suggesting lower the better for myocardial infarction, stroke, heart failure and perhaps angina. Randomised controlled trials testing BP strategies are needed to conclusively prove the efficacy and safety of aggressive BP control in subjects with CAD.

Contributors SB had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: SB and FHM. Acquisition of data: SB, SK and AV. Analysis and interpretation of data: SB and FHM. Drafting of the manuscript: SB, SK, AV and FHM. Critical revision of the manuscript for important intellectual content: SB and FHM. Statistical analysis: SB. Study supervision: SB and FHM. All authors have read and approved the manuscript and the authors' conflicts of interest are listed in the manuscript.

Competing interests Franz H Messerli: Ad hoc consulting: Abbott, Novartis, Pfizer, Bayer, Forest, Takeda, Daiichi. Research/Grants: Novartis, Boehringer.

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Heart

Blood pressure targets in patients with coronary artery disease: observations from traditional and Bayesian random effects meta-analysis of randomised trials

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