Determining the Optimal Systolic Blood Pressure for Hypertensive Patients: A Network Meta-analysis

Short title: Optimal Systolic Blood Pressure

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BRIEF SUMMARY

The present study provides the evidence base for new guidelines on the treatment of hypertension. A SBP of 120-129 mm Hg is appropriate for most hypertensive patients on treatment. For those who can tolerate the treatment, a SBP below 120 mm Hg lowers the stroke risk further. The SBP should not exceed 150 mm Hg because of the increased risk of myocardial infarction and cardiovascular mortality.

ABSTRACT

Background: There is clinical trial evidence that lowering SBP to <120 mmHg is beneficial, and this has influenced the latest American guideline on hypertension. We therefore used network meta-analysis to study the association between SBP and cardiovascular outcomes.

Methods: We searched for randomized controlled trials targeting different BP levels that reported cardiovascular events. The mean achieved SBP in each trial was classified into five groups (110-119, 120-129, 130-139, 140-149 and 150-159 mmHg). The primary variables of cardiovascular mortality, stroke and myocardial infarction were assessed using frequentist and Bayesian approaches.

Results: Fourteen trials with altogether 44015 patients were included. Stroke and major adverse cardiovascular events were reduced when lowering SBP to 120-129 mmHg compared to 130-139 mmHg (odds ratio 0.83, 95% CI 0.69-0.99 and 0.84, 0.73-0.96), 140-149 mmHg (0.73, 0.55-0.97 and 0.74, 0.60-0.90), and 150-159 mmHg (0.43, 0.26-0.71 and 0.41, 0.30-0.57), respectively. More intensive control to <120 mmHg further reduced stroke (0.58, 0.38-0.87, 0.51, 0.32-0.81, and 0.30, 0.16-0.56). In contrast, SBP $\geqslant$150 mmHg increased myocardial infarction and cardiovascular mortality compared to 120-129 mmHg (1.73, 1.06-2.82 and 2.18, 1.32-3.59), and 130-139 mmHg (1.53, 1.01-2.32 and 1.71, 1.11-2.61). No significant relationship between SBP and all-cause mortality was found.

Conclusions: SBP <130 mmHg is associated with a lower risk of stroke and major adverse cardiovascular events. Further lowering to <120 mmHg can be considered to reduce stroke risk if the therapy is tolerated. Long-term SBP should not exceed 150 mmHg because of increased risk of myocardial infarction and cardiac deaths.

KEYWORDS

Systolic blood pressure; hypertension; cardiovascular outcome; network meta-analysis; intensive BP control.

Elevated blood pressure (BP) is one of the leading causes of cardiovascular morbidity and mortality worldwide.[1, 2] A continuous log-linear association between BP and vascular events is found in epidemiological studies.[3] Cardiovascular risk increases with BP without an apparent threshold, although the gradient becomes appreciable at around 115/75 mmHg. This relationship is consistently seen regardless of sex, age, ethnicity and existing vascular disease.[4] Because of the strong epidemiological evidence, lowering BP is widely believed to reduce the risk of cardiovascular events.

However, the optimal BP for patients with hypertension remains controversial. A J-shape relationship between BP and mortality has been hypothesized.[5] In the *Hypertension Optimal Treatment* (HOT) study, the cardiovascular benefit of a diastolic BP (DBP) target down to 80 mmHg was substantial among patients with diabetes.[6] The *United Kingdom Prospective Diabetes Study* (UKPDS) 38 suggested that macrovascular complications of diabetes might be reduced by tighter BP control.[7] The evidence has led to guidelines recommending more stringent BP control (<130/80 mmHg) in hypertensive diabetic patients for many years.[8, 9] However, this has been put into question by the *Action to Control Cardiovascular Risk in Diabetes* (ACCORD) trial, which did not demonstrate a significant benefit of systolic BP (SBP) target of <120 mmHg over the standard target of <140 mmHg in preventing cardiovascular events.[10] In reconciling the findings of ACCORD with the epidemiological evidence that lower BP is associated with fewer cardiovascular events, the attention shifted to

the harmful effects of aggressive BP lowering with antihypertensive drugs, such as hypotension, syncope, electrolyte abnormalities, and acute kidney injury.[10] The benefits of BP lowering have to be balanced against the risks. Accordingly, the 2013 European Society of Hypertension/European Society of Cardiology (ESH/ESC) guidelines recommended <140/90 mmHg as the target in high-risk hypertensive patients,[11] while an SBP threshold and target of <150 mmHg for patients 60 years or older was proposed by the Eighth Joint National Committee (JNC 8).[12]

The ESH/ESC and JNC8 recommendations were put into question by the *Systolic Blood Pressure Intervention Trial* (SPRINT) trial, which was stopped early because of significant reductions in major cardiovascular events (MACE) and all-cause mortality in high-risk individuals without diabetes randomized to a target SBP of <120 mmHg compared to the conventional target of <140 mmHg.[13] The 2017 American Heart Association/American College of Cardiology (AHA)/ACC) guidelines lowered the threshold of hypertension to 130/80 mmHg, a more aggressive BP treatment goal.[14] In view of the confusion and controversy at present, we performed a network meta-analysis (NMA) of BP-lowering trials to study the relationship between BP levels and cardiovascular outcomes.

METHODS

Search strategy and study selection

The NMA conforms with the reporting standards in the PRISMA statement. We searched MEDLINE, EMBASE, the Cochrane database and ClinicalTrials.gov up to 1 December, 2017 for randomized controlled trials using the terms “antihypertensive agents”, “target blood pressure”, “blood pressure lowering”, “intensive blood pressure control”, and their synonyms and related keywords. The included trials were stratified using the reported mean SBP achieved at the trial-level into five groups: 110-119, 120-129, 130-139, 140-149 and 150-159 mmHg, irrespective of BP difference, medications used or intended BP targets. The influence of DBP on outcome was analyzed for six stratified groups of DBP, which were <65, 65-69, 70-74, 75-79, 80-84 and ≧85 mmHg. Study inclusion criteria for this NMA were: (1) randomized controlled trials; (2) sample size over 100 patients in total; (3) patients over 50 years of age; (4) comparing different BP targets in at least of two treatment arms; (5) mean achieved BP level was reported for each treatment arm; (6) the different arms of the trial should give mean achieved BPs in different BP categories; (7) reporting the number of cardiovascular outcomes of interest. Our NMA was restricted to trials with a treat-to-target design. Those trials not comparing BP targets and those in which achieved BP levels were not able to be stratified were excluded. No trials were excluded because of the presence of baseline comorbidities such as diabetes.

Data extraction

Literature review and inclusion were carried out by two investigators (YF and MFT) independently. Disagreements were resolved by consensus. For eligible studies, information about baseline BP levels, target BP levels, achieved BP levels, BP measurement methods, year of publication, age, gender, sample size, body weight, duration of follow-up, and baseline comorbidities of cardiovascular disease, coronary heart disease, type 2 diabetes, heart failure, and chronic kidney disease were extracted. Risk of bias was assessed using the Cochrane risk of bias assessment tool.

Study Variables

The primary variables were cardiovascular mortality, stroke and myocardial infarction (MI). Secondary variables were all-cause mortality, heart failure (HF) and MACE. We followed the definitions of variables used in each trial.

Statistical analysis

We used both a frequentist approach[15] and a Bayesian framework with non-informative priors[16] to compare the impact of BP reduction on outcomes at the trial level. Odds ratios (ORs), risk ratios (RRs) and 95% confidence intervals (95% CIs) were the summary statistics used. A 95% CI not including 1.00 or a two-tailed p-value less than 0.05 was considered statistically significant. Forest plots using fixed- and random-effects models to compare relative treatment effects were generated with a frequentist

approach using the statistical package 'netmeta' (version 0.9-6, https://cran.r-project.org/web/packages/netmeta/index.html) in R (version 3.3.2).

P-rank scores were generated to determine the probability of the BP levels having the largest effect size for each outcome. Inconsistency in the network was evaluated using loop-specific heterogeneity estimates; τ^2 estimate of 0.04, 0.14, and 0.40 represented as a low, moderate and high degree of heterogeneity, respectively. Heterogeneity in the pairwise meta-analysis was assessed by I^2; I^2 <25%, within 25-50%, and >50% represented mild, moderate, and severe heterogeneity, respectively. Sensitivity analysis was conducted by assessing the effect of removing individual trials. The differences between direct and indirect treatment effect estimates were evaluated using the node-splitting method. We also explored evidence for heterogeneity in estimates of treatment effect attributable to the baseline characteristics by comparing summary results obtained from subgroups of studies grouped by number of patients, cardiovascular event rate, age, diabetes, BP target, and BP level at baseline in the meta-analysis. Small study effects or potential publication bias was assessed using funnel plots, Begg's, Egger's, and trim-and-fill tests for direct comparisons with 3 or more studies in the meta-analysis.

We evaluated the consistency of inferential estimates from hierarchical modelling using Markov chain Monte Carlo simulations with flat priors in order to be similar to the

frequentist estimates, and these were performed with 1000 tuning iterations and 5000 simulation iterations within a Bayesian framework using R statistical package 'gemtc' (version 0.8-2, https://cran.r-project.org/web/packages/gemtc/index.html) and 'rjags' (version 4-6, https://cran.r-project.org/web/packages/rjags/index.html) to minimize Monte Carlo error. The protocol for this NMA was registered with the PROSPERO registry (number CRD42017068000).

RESULTS

A summary of the screening and selection process is described in the PRISMA flowchart (Supplemental Figure S1). Eighteen trials fulfilled the inclusion criteria.[6, 7, 10, 13, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30] However, the mean achieved SBP levels in the two BP-lowering arms in the *Studio Italiano Sugli Effetti CARDIOvascolari del Controllo della Pressione Arteriosa SIStolica* (Cardio-Sis) trial[27] and the *Hypertension Objective Treatment Based on Measurement by Electrical Devices of Blood Pressure* (HOMED-BP) trial[28] were nearly identical, so these trials were not included in the analysis. The mean achieved SBP level of the control group in the *Prevention After Stroke-Blood Pressure* (PAST-BP) trial[29] was not reported, while the sample size in the Schrier *et al*. trial[30] was less than 100 patients, so these trials were also excluded. Fourteen two-armed trials with altogether 44015 patients were eligible for this NMA.[6, 7, 10, 13, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26] The mean follow-up was 3.75 years. Among these trials, the mean SBP achieved in the more intensive BP-lowering group was 110-119 mmHg

in two trials (n = 4863); 120-129 mmHg in six trials (n =15130); 130-139 mmHg in four trials (n = 20747); and 140-149 mmHg (n = 1822), which compared with 150-159 mmHg (n = 1453) in two trials. The five SBP groups resulted in 10 theoretical comparisons for each outcome of interest (Figure 1). The main characteristics of the included trials are shown in Table 1. They all had a low risk of bias assessed using the components recommended by the Cochrane Collaboration (Supplemental Table S1, S2). All the patients were high-risk, with cardiovascular disease, coronary heart disease, renal disease, or diabetes. Ten trials enrolled patients with diabetes but only seven trials (n = 8392) had available data for analysis. Six trials recruited participants with chronic kidney disease (n = 3058) (Supplemental Table S3). Thirteen included trials reported all-cause mortality; twelve trials reported cardiovascular mortality; eleven trials reported the frequency of stroke; nine trials reported the frequency of MI and seven trials reported the frequency of HF. Eleven trials reported MACE, but it should be noted that its definition varied across different trials (Supplemental Table S4). The definition of this composite variable we used was the same as in the original trial. The methods of BP measurement in the trials are summarized in Supplemental Table S5.

NMA of the effect of different SBP levels using a frequentist approach are summarized in Table 2 and Figure 2. Our results showed that stroke, HF, and MACE were significantly reduced when lowering SBP to 120-129 mmHg compared to 130-139 and 140-149 mmHg, respectively. More intensive control to <120 mmHg also reduced

stroke, but had no clear effect on other outcomes when compared with those two BP groups. Compared to SBP ≥150 mmHg, there were fewer strokes, HF and MACE in all the other four BP groups; lower cardiovascular mortality rate when lowering SBP to 120-149 mmHg; and fewer MI when lowering SBP to 110-139 mmHg. No significant relationship between SBP and all-cause mortality was found. Lowering DBP to 65-69 mmHg significantly reduced cardiovascular mortality, all-cause mortality and MACE when compared to 75-79 mmHg, 80-84 mmHg and ⩾85 mmHg, while it also reduced stroke when compared to 80-84 mmHg and ⩾85 mmHg. Lowering DBP to <65 mmHg lowered only the risk of stroke compared to the four DBP groups ⩾70 mmHg (Supplemental Table S6).

P-rank scores derived from Bayesian analysis confirmed the ranking of these BP-lowering strategies. SBP of 120-129 mmHg was ranked the highest in reducing the risk of cardiovascular mortality (55.20% chance of being the best), all-cause mortality (43.20%), HF (44.05%) and MACE (46.90%). More intensive BP lowering to 110-119 mmHg was ranked the highest in reducing the risk of stroke (79.15%) and MI (52.05%), while 120-129 mmHg was ranked the second highest for protecting against these two outcomes. SBP ≥150 mmHg had the highest likelihood to increase the risk of all the outcomes (Supplemental Table S7).

All τ^2 estimates indicated low heterogeneity except for HF (τ^2 = 0.16) (Supplemental Table S8). Significant heterogeneity in the pairwise meta-analysis was found for all-cause mortality (I^2 = 58%, p = 0.04) and MACE (I^2 = 60%, p = 0.06) in the comparison between 120-129 vs. 130-139 mmHg, and was found for cardiovascular mortality (I^2 = 68%, p = 0.03), all-cause mortality (I^2 = 79%, p = 0.002), and stroke (I^2 = 57%, p = 0.07) in the comparison between 130-139 vs. 140-149 mmHg. Sensitivity analysis showed that the heterogeneity for all-cause mortality was due to the *Modification of Diet in Renal Disease* (MDRD) and SPRINT trials while the heterogeneity for MACE was due to the *Ramipril Efficacy In Nephropathy*-2 (REIN-2) and SPRINT trials in the comparison between 120-129 vs. 130-139 mmHg (Supplemental Table S9, S10). The heterogeneity for all the outcomes in the comparison between 130-139 vs. 140-149 mmHg was due to the Wei *et al.* trial (Supplemental Table S11-S13).

When we stratified trials by baseline diabetes, there was a significant difference for stroke (p = 0.01) associated with intensive BP lowering. Patients with prior diabetes (RR 0.60, 95% CI 0.47-0.78) had more stroke risk reduction than those without diabetes (RR 0.84, 95% CI 0.72-0.98) (Supplemental Table S14).

Using random-effects instead of fixed-effects model, or Bayesian instead of frequentist analysis did not materially affect the results (Supplemental Table S15, S16). Inspection of the funnel plots did not reveal any significant publication bias or small study effects

(Supplemental Figure S2-S6 and Supplemental Table S17). There was no significant inconsistency between direct and indirect comparisons in any of the outcomes (Supplemental Table S18- S23).

DISCUSSION

The BP target for patients with hypertension remains controversial. In mild hypertension or in young people with hypertension, it is reasonable to aim to normalize BP using non-pharmacological and pharmacological means; whereas in the vast majority of people with hypertension who are usually middle-aged and elderly, normalization of BP is not always feasible, nor is it desirable because of the adverse effects of antihypertensive medications. There is growing evidence that intensive BP lowering is associated with cardiovascular benefit. However, evidence from clinical trials, especially the ACCORD and SPRINT, has been sending seemingly contradictory messages. It is therefore timely to find common ground reconciling the divergent findings using meta-analysis. Because there have only been a few trials directly comparing different BP targets, NMA becomes valuable as it draws both direct and indirect comparisons. In our NMA, we found that lowering SBP to less than 130 mmHg reduced the likelihood of stroke, HF, and MACE. Reducing SBP to less than 120 mmHg further reduced stroke, but not the other cardiovascular outcomes or mortality. Conversely, not controlling SBP to less than 150 mmHg was associated with a significant increase in cardiovascular mortality, stroke, MI, HF, and MACE.

The SPRINT findings were highly controversial. A much-voiced criticism was that the rigorous BP measurement protocol gave readings that were lower than clinic readings while the mean achieved SBP was actually higher than its target (<120 mmHg) in the intensively-treated arm.[31, 32] Moreover, the exclusion of diabetic patients meant that the SPRINT findings cannot be extrapolated to these patients, who are frequently hypertensive. Our findings partially support the cardiovascular benefits of intensive SBP lowering reported in the SPRINT trial and can be readily translated into clinical practice, in that the SBP should be lower than 130 mmHg, if possible, lower than 120 mmHg, but should not be allowed to exceed 150 mmHg in the long run. This recommendation not only takes into the account the totality of present evidence and the limitation of the SRPINT trial.

Epidemiological studies have shown that the gradient of stroke risk against BP is steep whereas that of coronary events against BP is less steep. For stroke prevention, it appears to be the case that the lower the BP the better.[33, 34, 35] Our NMA demonstrated that lowering SBP to <120 mmHg reduced stroke risk more than <130 mmHg. However, for coronary risk, lowering the BP too much may compromise coronary perfusion, giving rise to the J-curve phenomenon.[34, 35] Very low DBP (<60 mmHg) has been reported to increase the risk of cardiovascular events.[36, 37] Although our results suggest that lowering SBP to <120 mmHg could reduce stroke further, it might result in a low

DBP in some patients. The diastolic J-curve is relevant to stroke risk because of the large BP gradient between large arteries at the base of the brain and small subcortical arterioles over the convexity. Mathematical modelling suggested that when the BP in the brachial artery is 117/75 mmHg, it is 113/73 mmHg in the lenticulostriate artery but only 59/39 mmHg in small branches in the posterior parietal sub-cortex.[38] Thus, patients with wide pulse pressure and hence a low diastolic pressure are at risk of having white matter intensities in the subcortical region.[39] In patients with coronary artery disease and in patients with left ventricular hypertrophy, myocardial ischemia may occur due to the J-curve phenomenon.[40] With these risks in mind, we investigated the influence of different achieved DBP levels on cardiovascular outcomes. Our results showed that lowering DBP to <70 mmHg reduced cardiovascular events when compared to higher DBP levels. Further reduction of DBP to <65 mmHg reduced the risk of stroke. We did not find any evidence of an increase in cardiovascular events with very low achieved DBP, but that could be due to insufficient patient numbers with these low BPs.

Two network meta-analyses published recently showed similar findings to our study.[41, 42] One network meta-analysis[42] included more trials than our study (see Online Reference), and suggested a significant reduction in all-cause mortality when lowering SBP below currently recommended targets. This benefit was not found in another network meta-analysis[41] and our study. Including these studies for analysis showed a similar reduction in all-cause mortality, which might be driven by the high rate of death

in the placebo groups without BP-lowering therapy in most of trials (Supplemental Table S24).

Previous meta-analyses showed a significant benefit of intensive BP lowering in reducing MACE in high-risk patient groups when compared to moderate BP lowering. These beneficial effects were observed across major patient subgroups, baseline SBP levels, and types of antihypertensive drugs.[43, 44, 45, 46, 47] There is, therefore, evidence to support lowering SBP to less than 130 mmHg in patients with a history of cardiovascular disease, coronary heart disease, stroke, heart failure, and chronic kidney disease.[47] However, for diabetic patients with baseline SBP less than 140 mmHg, intensive BP lowering was associated with an increased risk of cardiovascular death, without significant benefits.[45, 46]

There has been much controversy over normalization of BP for patients ≥65 years old and the younger. The 2017 AHA/ACC guidelines recommend an SBP treatment goal of <130 mmHg, lower than previous guidelines for hypertensive patients.[14] Our network meta-analysis provides the evidence to support this intensive SBP target. For older patients at a high risk of comorbidity or mortality, the intensity of BP lowering should be decided after considering the risk and benefit balance. More importantly, the appearance of any adverse effects should be carefully monitored when slowly lowering BP to target. Most trials in hypertension recruited older patients, so whether the more

aggressive BP lowering is beneficial in young patients needs to be explored in clinical trials.

Apart from the HOT trial, there was a lack of trials evaluating different DBP targets. However, SBP alone cannot guide treatment decisions. Chasing a low SBP can result in a very low DBP, which is harmful. Our study assessed also the association between achieved DBP levels and the risk of cardiovascular outcomes, and so provides a firmer basis for the 2017 AHA/ACC guidelines.

It cannot be emphasized more that the treatment of hypertension should be tailored to the individual patient,[48] because each patient has a different benefit-risk ratio. The new American guideline recommends the assessment of 10-year atherosclerotic cardiovascular risk to guide the BP threshold for treatment (http://tools.acc.org/ASCVD-Risk-Estimator-Plus/#!/calculate/estimate).[14] The assessment takes into account risk factors including age, gender, race, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, SBP, use of aspirin or statins, treatment for hypertension, history of diabetes, and current smoking status.

In contrast to intention-to-treat analysis, we used achieved BP as the focus of our NMA. Our results should therefore not be interpreted as the BP set as the goal at the start of treatment but rather, as a desirable BP to achieve in maintenance therapy.

The definition of MACE, as a composite variable, was widely different across the included trials, and was not clearly described in several trials. Not all the trials reported its frequency. Therefore, we did not use MACE as the primary variable to avoid the problem of double counting by simply adding up its individual components.

Although it is customary to use relative risk as the statistic for meta-analysis because it is assumed to be similar in different trials, it is the absolute risk reduction that is a more clinically relevant measure of benefit. However, absolute risks differ across trials and among different patient groups within trials. For the same relative risk reduction, the absolute risk reduction is bigger if the baseline risk is higher. People with higher pre-treatment BP are at higher absolute cardiovascular risk and would benefit more from BP lowering treatment even if the relative risk reduction is not any bigger.

A limitation of this NMA is the lack of patient-level data and the scarcity of head-to-head comparative trials. Patients aged >60 years with vascular disease may have stiff radial arteries, resulting in falsely higher DBP and a falsely lower SBP.[49-51] In one study, half of the patients above age 60 with diastolic cuff pressures >100 mmHg had an intra-

arterial pressure 30 mmHg or more lower than the cuff pressure.[50] Our analysis did not take into account cuff artefact. The mean arterial pressure (DBP plus one third of pulse pressure) may therefore be closer to the intra-arterial mean pressure in these patients. However, without patient-level data, calculation of mean arterial pressure was not possible.

In two comparison groups (110-119 vs. 120-129, and 110-119 vs 130-139 mmHg), there were only single trials. At the same time, large trials such as ACCORD and SPRINT were given a lot of weight. The insufficient data did not allow assessing the risk of kidney disease outcomes, hypotension, or other adverse events concerned with intensive BP lowering. Inevitably, trials included in the NMA varied in patient characteristics, comorbidities, treatment regimens, types of BP measurements, and definitions of outcomes. Outcomes trials tend to recruit patients at high risk of cardiovascular events, and therefore, trial results may be not generalizable to low risk patients and the general population. Therefore, our results should be interpreted with caution. Nevertheless, we used different methods of analysis, such as frequentist and Bayesian analysis, fixed- and random-effects models, sensitivity analysis to support our findings, and obtained consistent results.

In conclusion, our NMA suggested that intensive BP lowering to less than 130 mmHg (120-129 mmHg) reduced the risk of stroke, HF, and MACE. Lowering to less than 120

mmHg would reduce the risk of stroke further if the treatment is tolerated, but other cardiovascular benefits cannot be demonstrated. The long-term SBP should not exceed 150 mmHg as that level of BP is associated with significantly high risks of cardiovascular events and cardiovascular mortality. An SBP target of 120-129 mmHg is appropriate for most high-risk hypertensive patients age 50 and over. Ultimately, the treatment of hypertension should be tailored to the benefit-risk profile of the individual patient, and whether the therapy is tolerated. If a lower SBP is adopted as the target, it is important that patients are more carefully monitored for the adverse effects of therapy.

AUTHORS' CONTRIBUTIONS

YF designed the study, performed statistical analysis, interpreted the data and wrote the first draft. YF, MFT and BMYC contributed to the data interpretation and writing of the final version of the manuscript. All authors have approved the final version of the manuscript and its conclusions. The corresponding author had full access to the data and had final responsibility for the decision to submit for publication.

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DISCLOSURES

None.

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Table 1. Major characteristics of trials included in the network meta-analysis

Studies	Year	Patients (intensive/ control)	Mean baseline BP levels (SBP/DBP) /mmHg	Target BP levels (intensive/ control)/mmHg	Achieved BP levels (intensive/ control)/mmHg	Antihyper -tensive drugs	Primary or reported cardiovascular outcomes
AASK[18]	2010	1094 (540/554)	150.5/95.5	NR/≤92 vs. NR/102-107	128/78 vs. 140/86	ACEI, CCB, β-blocker	MACE defined by the occurrence of CV mortality or first CV hospitalization for MI, stroke, HF, or revascularization procedure
ABCD-N[19]	2001	480 (237/243)	136.4/84	NR/<75 vs. NR/80-89	128/75 vs. 137/81	CCB, ACEI	MI, cerebral vascular accident, congestive HF, CV death
ABCD-2V[17]	2006	129 (66/63)	126/84	NR/<75 vs. NR/<90	118/75 vs. 124/80	ARB	CV vascular disease event

ACCORD[10]	2010	4734 (2363/2371)	139.2/76	<120/NR vs. <140/NR	119.3/64.4 vs. 133.5/70.5	ACEI, CCB, β-blocker, ARB, diuretics, α blocker	MACE defined as the composite of non-fatal MI, non-fatal stroke, or CV death
BBB[26]	1994	2127 (1064/1063)	155/94.5	NR/80 vs. NR/80-100	141/83 vs. 152/91	Unclear	Stroke, MI
HOT[6]	1998	12526 (6262/6264)	169.7/105.4	NR/80 vs. NR/90	139.7/81.1 vs. 143.7/85.2	ACEI, β-blocker, diuretics	MACE defined as fatal/non- fatal MI, fatal/non-fatal stroke, and CV death
JATOS[23]	2008	4418 (2212/2206)	171.6/89.1	<140/NR vs. 140-159/NR	135.9/74.8 vs. 145.6/78.1	CCB	MACE defined as the combined incidence of cerebrovascular disease, cardiac disease (acute MI,

							HF and angina pectoris requiring hospitalization and CV death), vascular disease and renal dysfunction
MDRD[22]	2005	840 (432/408)	130.5/80	NR/<92 vs. NR/<107	126.2/76.9 vs. 133.8/80.7	ACEI, CCB, β-blocker, diuretics	NA
REIN-2[20]	2015	335 (167/168)	130.5/80	<130/80 vs. NR/90	126.2/76.9 vs. 133.8/80.7	CCB	MACE defined as the composite of MI, congestive HF, stroke, ACS, transient ischemic attack
SPRINT[13]	2013	9361 (4678/4683)	139.7/78.1	<120/NR vs. <140/NR	121.4/68.7 vs. 136.2/76.3	ACEI, CCB, ARB, diuretics,	MACE defined as the composite of MI, ACS not resulting in MI,

						α-1 blocker, central α-2 agonists, β-blocker, vasodilator	stroke, acute decompensated HF, or CV death
SPS3[21]	2015	3020 (1501/1519)	143/78.5	<130/NR vs. 130-149/NR	126.7/69.1 vs. 137.4/74.8	ACEI, CCB, β-blocker, ARB, thiazides	Stroke, acute MI
UKPDS 38[7]	1998	1148 (758/390)	160/94	<150/85 vs. <180/105	144/82 vs. 154/87	ACEI, β-blocker	Fatal/nonfatal stroke, fatal/nonfatal MI, HF
VALISH[24]	2010	3079 (1545/1534)	169.5/81.5	<140/NR vs. 140-149/NR	136.6/74.8 vs. 142/76.5	ARB	MACE defined as the composite of CV death, fatal/nonfatal stroke,

							fatal/nonfatal MI, unplanned hospitalization for CV disease, and renal dysfunction
Wei et al.[25]	2013	724 (363/361)	159.5/84.2	<140/90 vs. 150/90	135.7/76.2 vs. 149.7/82.1	ACEI, CCB, β-blocker, diuretics	MACE defined as the composite of fatal/non-fatal stroke, acute MI, and other CV deaths (sudden death and HF death)

Abbreviations in Table 1: ACEI = angiotensin-converting-enzyme inhibitor; ARB = angiotensin receptor blocker; CCB = calcium channel blocker; CV = cardiovascular; DBP = diastolic blood pressure; HF = heart failure; MACE =major adverse cardiovascular events; NA = not applicable; SBP = systolic blood pressure.

Table 2. Effect of different BP-lowering strategies on frequencies of cardiovascular outcomes established by network meta-analysis

	110-119 mmHg	120-129 mmHg	130-139 mmHg	140-149 mmHg	150-159 mmHg
Cardiovascular					
mortality					
110-119 mmHg	1.00	0.75 (0.48-1.17)	0.95 (0.66-1.37)	1.04 (0.68-1.61)	1.63 (0.93-2.85)
120-129 mmHg	1.34 (0.86-2.09)	1.00	1.28 (0.98-1.66)	1.40 (0.98-1.99)	**2.18 (1.32-3.59)**
130-139 mmHg	1.05 (0.73-1.51)	0.78 (0.60-1.02)	1.00	1.09 (0.87-1.38)	**1.71 (1.11-2.61)**
140-149 mmHg	0.96 (0.62-1.48)	0.72 (0.50-1.02)	0.91 (0.72-1.16)	1.00	**1.56 (1.09-2.22)**
150-159 mmHg	0.62 (0.35-1.08)	**0.46 (0.28-0.76)**	**0.59 (0.38-0.90)**	**0.64 (0.45-0.92)**	1.00
Myocardial infarction					
110-119 mmHg	1.00	1.03 (0.72-1.47)	1.16 (0.91-1.49)	1.47 (1.00-2.17)	**1.78 (1.10-2.89)**
120-129 mmHg	0.97 (0.68-1.38)	1.00	1.13 (0.88-1.46)	1.43 (0.97-2.11)	**1.73 (1.06-2.82)**

130-139 mmHg	0.86 (0.67-1.10)	0.89 (0.69-1.14)	1.00	1.27 (0.94-1.70)	**1.53 (1.01-2.32)**
140-149 mmHg	0.68 (0.46-1.00)	0.70 (0.47-1.03)	0.79 (0.59-1.06)	1.00	1.21 (0.90-1.62)
150-159 mmHg	**0.56 (0.35-0.91)**	**0.58 (0.36-0.94)**	**0.65 (0.43-0.99)**	0.83 (0.62-1.11)	1.00
Stroke					
110-119 mmHg	1.00	1.43 (0.91-2.26)	**1.74 (1.15-2.63)**	**2.04 (1.30-3.20)**	**3.67 (1.91-7.08)**
120-129 mmHg	0.70 (0.44-1.10)	1.00	**1.21 (1.01-1.46)**	**1.42 (1.11-1.83)**	**2.56 (1.49-4.41)**
130-139 mmHg	**0.58 (0.38-0.87)**	**0.83 (0.69-0.99)**	1.00	1.13 (0.92-1.40)	**1.93 (1.20-3.10)**
140-149 mmHg	**0.51 (0.32-0.81)**	**0.73 (0.55-0.97)**	0.88 (0.71-1.09)	1.00	**1.70 (1.11-2.60)**
150-159 mmHg	**0.30 (0.16-0.56)**	**0.43 (0.26-0.71)**	**0.52 (0.32-0.83)**	**0.59 (0.38-0.90)**	1.00
Heart Failure					
110-119 mmHg	1.00	0.82 (0.55-1.23)	1.08 (0.80-1.47)	1.75 (0.82-3.74)	**4.03 (1.54-10.59)**
120-129 mmHg	1.22 (0.81-1.82)	1.00	**1.32 (1.01-1.72)**	**2.14 (1.02-4.49)**	**4.92 (1.89-12.76)**

130-139 mmHg	0.92 (0.68-1.25)	**0.76 (0.58-0.99)**	1.00	1.62 (0.81-3.24)	**3.72 (1.49-9.30)**
140-149 mmHg	0.57 (0.27-1.22)	**0.47 (0.22-0.98)**	0.62 (0.31-1.24)	1.00	**2.30 (1.26-4.19)**
150-159 mmHg	**0.25 (0.09-0.65)**	**0.20 (0.08-0.53)**	**0.27 (0.11-0.67)**	**0.43 (0.24-0.79)**	1.00
All-cause mortality					
110-119 mmHg	1.00	0.83 (0.63-1.09)	0.95 (0.75-1.20)	0.98 (0.74-1.30)	0.78 (0.51-1.18)
120-129 mmHg	1.21 (0.92-1.60)	1.00	1.15 (0.99-1.33)	1.19 (0.96-1.47)	0.94 (0.65-1.37)
130-139 mmHg	1.05 (0.83-1.33)	0.87 (0.75-1.01)	1.00	1.03 (0.88-1.21)	0.82 (0.58-1.16)
140-149 mmHg	1.02 (0.77-1.35)	0.84 (0.68-1.04)	0.97 (0.83-1.13)	1.00	0.79 (0.58-1.08)
150-159 mmHg	1.28 (0.85-1.95)	1.06 (0.73-1.54)	1.22 (0.86-1.72)	1.26 (0.93-1.71)	1.00
MACE					
110-119 mmHg	1.00	0.90 (0.74-1.09)	1.07 (0.93-1.22)	1.22 (1.00-1.48)	**2.17 (1.57-2.99)**
120-129 mmHg	1.12 (0.92-1.36)	1.00	**1.19 (1.04-1.37)**	**1.36 (1.11-1.66)**	**2.42 (1.75-3.34)**

130-139 mmHg	0.94 (0.82-1.07)	**0.84 (0.73-0.96)**	1.00	1.14 (0.99-1.31)	**2.03 (1.51-2.71)**
140-149 mmHg	0.82 (0.68-1.00)	**0.74 (0.60-0.90)**	0.88 (0.76-1.01)	1.00	**1.78 (1.38-2.30)**
150-159 mmHg	**0.46 (0.33-0.64)**	**0.41 (0.30-0.57)**	**0.49 (0.37-0.66)**	**0.56 (0.43-0.72)**	1.00

Abbreviations in Table 2: MACE = major adverse cardiovascular events.

Results are the odds ratios (95% confidence interval) in the column-defining therapy compared with the odds ratios in the row-defining therapy.

For efficacy and safety, odds ratio <1 favors the column-defining therapy. Significant results are shown in bold.

CAPTION TO FIGURES

Figure 1. Network profile for the studies comparing different blood pressure levels achieved.

Each node (blue circle) represents an achieved systolic blood pressure group. The size of the nodes corresponds to the number of trials of the groups. Each line represents a pair of direct comparison between different blood pressure levels (mmHg) while each dotted line represents the missing comparison. The thickness of the lines corresponds to the number of trials that assessed the comparison.

Figure 2. Forest plots generated using a frequentist approach to assess the effects of different blood pressure levels on cardiovascular outcomes relative to 130-139 mmHg.

A). Cardiovascular mortality

B). Stroke

C). Myocardial infarction

D). All-cause mortality

E). Heart failure

F). MACE (major adverse cardiovascular events)

Square markers indicate odds ratios for cardiovascular outcomes comparing different mean achieved systolic blood pressure with 130-139 mmHg. The horizontal lines indicate 95% CIs. Targeting blood pressure level to less than 140/90 mmHg is widely recommended in the current hypertensive guidelines for high-risk patients with

cerebrovascular disease, coronary heart disease, renal disease, and diabetes. Therefore, 130-139 mmHg was used as the reference.