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REVIEW

# Optimal Blood Pressure Control Target for Older Patients with Hypertension: A Systematic Review and Meta-Analysis

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## Abstract

**Objective:** This study evaluated the optimal systolic blood pressure (SBP) target for older patients with hypertension.
**Method:** A Bayesian network meta-analysis was conducted. The risk of bias of the included studies was assessed by using a modified version of the Cochrane risk of bias. The trial outcomes comprised the following clinical events: major adverse cardiovascular events (MACE), cardiovascular mortality, all-cause mortality, myocardial infarction, heart failure and stroke.
**Results:** A total of six trials were included. We reclassified all treatment therapies into three conditions according to the final achieved SBP after intervention (<130 mmHg, 130–139 mmHg and ≥140 mmHg). Our results demonstrated that anti-hypertensive treatment with an SBP target <130 mmHg, compared with treatment with an SBP target ≥140 mmHg, significantly decreased the incidence of MACE (OR 0.43, 95%CI 0.19–0.76), but no statistical difference was found in other comparisons. Although the results showed a trend toward more intensive anti-hypertension therapy having better effects on preventing cardiovascular mortality, all-cause mortality, myocardial infarction, heart failure, and stroke, no significant differences were found among groups.
**Conclusions:** Our meta-analysis suggested that SBP <130 mmHg might be the optimal BP control target for patients ≥60 years of age; however, further evidence is required to support our findings.

**Keywords:** blood pressure control target; hypertension; older patients; meta-analysis

**Systematic review registration:** PROSPERO CRD42022320387

## Introduction

Hypertension is an independent risk factor for cardiovascular disease and it is closely associated with conditions such as hemorrhagic stroke, heart failure, renal insufficiency and aortic dissection [1–3]. Hypertension is also an age-related disease with a prevalence that increases with aging [4]. Observational data from the Framingham Study have indicated that the risk of developing hypertension exceeds 90% for adults 55–65 years of age [5]. Data from the National Health and Nutrition Examination Survey suggest that nearly 70% of

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older patients have hypertension, whereas only 32% of adults 40–59 years of age have hypertension [6]. Although patients may benefit from lower BP treatment, older patients with hypertension tend to have more isolated systolic hypertension, elevated pulse pressure, blood pressure (BP) fluctuation, numerous and serious complications, and higher mortality rates than younger patients [7, 8]. The treatment of hypertension in older people is challenged by the very high functional heterogeneity in this population [9]. Therefore, the BP target and intensity of anti-hypertensive treatment recommended for young patients may be improper for older people. The debate regarding the optimal BP target for antihypertensive treatment in older patients with hypertension remains ongoing.

Several previous guidelines have listed the BP targets for older patients separately, but the recommended BP targets substantially vary among these guidelines. The BP target recommended in the 2017 Guidelines for the prevention and treatment of hypertension in adults in the United States is less than 130/80 mmHg [10]. A BP target of 130–139/70–79 mmHg for patients ≥65 years of age (including ≥80 years) is recommended in the 2018 ESC/ESH Guidelines for the management of arterial hypertension [11]. Canada's 2020 Guidelines suggest that high-risk patients 50 years or older with systolic blood pressure (SBP) ≥130 mmHg should consider intensive management to an SBP target <120 mmHg [12]. These different recommendations for BP control targets in older patients make clinical decision-making difficult and confusing. Therefore, the optimal SBP target for older patients with hypertension must be determined. This Bayesian network meta-analysis was designed to explore this issue by considering all existing evidence.

## Methods

### Search Strategy and Selection Criteria

The electronic databases PubMed, Embase and Cochrane Central Registry of Controlled Trials (CENTRAL) were searched for randomized controlled trials (RCTs) investigating the effects of different blood pressure control strategies in older patients, published until January 2022. The inclusion criteria were as follows: 1) clinical RCTs; 2) all eligible patients ≥60 years of age; 3) patients diagnosed with hypertension; 4) trials designed to compare the effects of different treatments within commensurately different SBP targets; 5) trial outcomes including the following clinical events: major adverse cardiovascular events (MACE), cardiovascular mortality, all-cause mortality, myocardial infarction, heart failure and stroke. We excluded data from patients younger than 60 years and trials in which the follow-up was less than 3 months.

The search terms included the following: hypertension, hypertensive patients, high blood pressure, optimal blood pressure control, intensive blood pressure control, intensive antihypertension therapy, blood pressure targets, target blood pressure, elderly, old patients, older patients, gerontal patients and senile patients. A highly sensitive search strategy for RCTs was also applied. Two investigators independently searched the electronic databases and retrieved all eligible trials by viewing the title and abstract, then the full text. Disagreements were resolved by discussion and seeking advice from a third party.

### Data Extraction and Quality Assessment

Two investigators independently extracted detailed basic characteristics of all included trials, including study type, patient population characteristics, baseline blood pressure, antihypertension strategies in the intervention and control groups, blood pressure levels after treatment, and clinical outcomes. The extracted data were compared, and differences in opinion were resolved by discussion or involvement of a third party to achieve consensus, as needed. Bias risk evaluation tools from the Cochrane Collaboration for assessment of risk of bias in RCTs were used, which contained the following items: random sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting and other bias.

### Data Analysis

Dichotomous data were calculated with odds ratios (ORs) and 95% confidence intervals (CIs). Because the antihypertensive therapies varied in intensity among the included trials, all treatment therapies

were reclassified according to the final achieved SBP level, and the effects of these antihypertensive strategies were compared with a mixed comparison method that allowed us to consider all trials simultaneously and integrate direct evidence from head-to-head trials with indirect evidence. We used Bayesian hierarchical random-effects models for mixed treatment comparison, using four chains, and running 50,000 iterations with 20,000 tuning iterations. Analyses were performed with Markov Chain Monte Carlo simulation implemented with the gemtc package in R4.2.0 software. Node-splitting method was used to evaluate the presence of inconsistency.

## Result

The trial selection flow chart is displayed in Figure 1. A total of 575 potential primary trials were obtained from electronic databases through manual searching. After careful screening and evaluation, six trials (including a total of 19,567 patients) met our eligibility criteria and were included in the analysis. The detailed information on these included trials is presented in Table 1. The JATOS [13] trial included patients ≥65 years of age; VALISH [14] and Wei et al. [15] included patients ≥70 years of age; SPRINT-SENIOR [16] and INFINITY [17] included patients ≥75 years of age; and the STEP [18] trial included patients ≥60 years of age. The median follow-up periods ranged from 2 to 4 years.

Among these six trials, the SBP was decreased to 139.3 mmHg on average in the intensive treatment group and 146.5 mmHg in the control group in the JATOS trial. In the SPRINT-SENIOR trial, the mean SBP after intensive treatment was 123.4 mmHg and 134.8 mmHg after standard treatment. In the VALISH trial, the SBP reached 136.6 mmHg in the intensive group and 142.0 mmHg in the standard group. In Wei et al., the mean achieved SBP was 135.7 mmHg and 149.7 mmHg for the intensive and control groups, respectively. In the INFINITY trial, the mean SBP was 127.7 mmHg in the intensive-treatment group after a median treatment period of 3 years and 144 mmHg in the standard-treatment group. In the STEP trial, the mean SBP reached 126.7 mmHg in the intensive-treatment group and 135.9 mmHg in the standard-treatment group

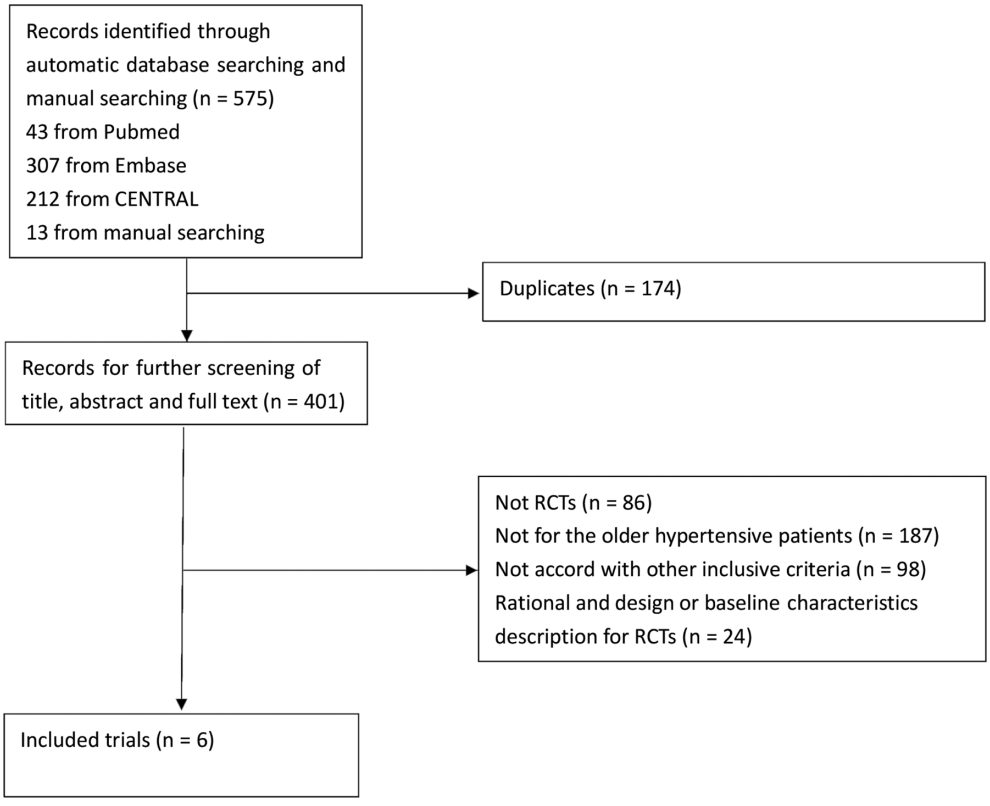


**Figure 1** Flow Diagram of Included Trials.

**Table 1** Baseline Characteristics of the Included Trials.[a]

| Study | JATOS | VALISH | Wei et al. | SPRINT-SENIOR | INFINITY | STEP |
|---|---|---|---|---|---|---|
| Year | 2008 | 2010 | 2013 | 2016 | 2019 | 2021 |
| Age range | 65 to 85 years | 70 to 84 years | older than 70 years | 75 years or older | 75 years or older | 60 to 80 years |
| Comparison | <140 mmHg vs. 140–159 mmHg | <140 mmHg vs. 140–149 mmHg | ≤140 mmHg vs. ≤150 mmHg | <120 mmHg vs. <140 mmHg | ≤130 mmHg vs. ≤145 mmHg | 110–130 mmHg vs. 130–150 mmHg |
| Mean final SBP | 135.9 mmHg vs. 145.6 mmHg | 136.6 mmHg vs. 142.0 mmHg | 135.7 mmHg vs. 149.7 mmHg | 123.4 mmHg vs. 134.8 mmHg | 127.7 mmHg vs. 144.0 mmHg | 126.7 mmHg vs. 135.9 mmHg |
| Mean baseline SBP | 171.6 mmHg | 169.6 mmHg | 159.6 mmHg | 141.6 mmHg | 149 mmHg | 146.1 mmHg |
| Mean in-treatment difference | 9.7 mmHg | 5.4 mmHg | 14 mmHg | 11.4 mmHg | 16.3 mmHg | 9.2 mmHg |
| Number of participants | 4,418 | 3,079 | 724 | 2,636 | 199 | 8,511 |
| Mean age(y) | 73.6 | 76.1 | 76.6 | 79.9 | 80.5 | 66.2 |
| Median follow-up period (y) | 2 | 3.07 | 4 | 3.14 | 3 | 3.34 |
| Primary endpoints | Combined incidence of cerebrovascular disease, cardiac and vascular disease, and renal failure | A composite of cardiovascular events: sudden death, fatal or nonfatal stroke, fatal or nonfatal myocardial infarction, death because of heart failure, other cardiovascular death, unplanned hospitalization for cardiovascular disease, and renal dysfunction | combined incidence of fatal/ nonfatal stroke, acute myocardial infarction, and other cardiovascular deaths | A composite of nonfatal myocardial infarction, acute coronary syndrome not resulting in a myocardial infarction, nonfatal stroke, nonfatal acute decompensated heart failure, and death from cardiovascular causes | Changes in mobility (gait speed) and accrual of WMH volume following 3 years | A composite of stroke, acute coronary syndrome, acute decompensated heart failure, coronary revascularization, atrial fibrillation, or death from cardiovascular causes |
| Secondary endpoints | deaths from any causes and any safety problems | each component of the primary end point, total mortality, and new onset or exacerbation of angina pectoris | deaths from any causes | all-cause mortality, decline in kidney function or development of end-stage renal disease, incident dementia, decline in cognitive function, and small-vessel cerebral ischemic disease | Changes in cognitive function (executive processing) and adverse events | the individual components of the primary outcome, death from any cause, major adverse cardiac events, and renal outcomes |

**Table 1** (continued)

| Study | JATOS | VALISH | Wei et al. | SPRINT-SENIOR | INFINITY | STEP |
|---|---|---|---|---|---|---|
| MACE definition | Angina pectoris, MI, congestive heart failure, obstructive arterial disease, abdominal aortic rupture, aortic aneurysm enlargement, sudden death | cardiovascular death, nonfatal stroke (exclude transient ischemic attack), and nonfatal myocardial infarction | Acute MI, heart failure death, cardiovascular death | nonfatal myocardial infarction, acute coronary syndrome not resulting in a myocardial infarction, nonfatal stroke, nonfatal acute decompensated heart failure, and death from cardiovascular causes | Arrhythmia, heart failure, stroke, MI, unstable angina with revascularization, severe aortic stenosis, transient ischemic attack, pulmonary embolism | acute coronary syndrome, acute decompensated heart failure, coronary revascularization, atrial fibrillation |

[a]Abbreviations: MI, Myocardial infarction; SBP, systolic blood pressure; WMH, White matter hyperintensity.

throughout follow-up. We reclassified all treatment therapies into three groups according to the final achieved SBP after intervention (<130 mmHg, 130–139 mmHg and ≥140 mmHg). JATOS, VALISH and Wei et al. compared the effects of achieving SBP 130–139 mmHg versus ≥140 mmHg. SPRINT-SENIOR and STEP compared the results of treatment targeting SBP <130 mmHg and 130–139 mmHg. The INFINITY trial compared the difference between the intensive intervention group, with an achieved SBP <130 mmHg, and the control group, with an achieved SBP ≥140 mmHg. Subsequently, we compared the effects of the three antihypertensive strategies with a mixed comparison method. The network of eligible comparisons for our mixed comparison meta-analysis is shown in Figure 2.

As shown in Figure 3, antihypertensive treatment with an SBP goal <130 mmHg, compared with treatment with an SBP goal ≥140 mmHg, significantly decreased the incidence of MACE in older patients with hypertension (OR 0.43, 95% CI 0.19–0.76), but no statistical difference was found in the other comparisons. Although the results showed a trend in which more intensive antihypertension therapy had better effects on preventing cardiovascular mortality, no significant differences were found among groups. Similar results were also obtained in evaluation of the risk of all-cause mortality, myocardial infarction, heart failure and stroke (Figure 3). We also analyzed the rank probability of each antihypertension strategy, and found that SBP <130 mmHg correlated with the lowest probability of the occurrence of all included clinical outcomes (Figure 4).

For inconsistency evaluation, analyses for MACE, all-cause mortality, myocardial infarction, heart failure and stroke were successfully performed through the node-splitting method, except for cardiovascular mortality with open loop of eligible comparison. Lacking direct comparison between the treatment with target SBP <130 mmHg and SBP ≥140 mmHg, made the inconsistency assessment not applicable. As shown in Figure 5, no significant inconsistency between direct and indirect evidence was found for MACE, all-cause mortality, heart failure and stroke with $P<0.05$. However, a significant inconsistency was detected in the mixed comparison of myocardial infarction;

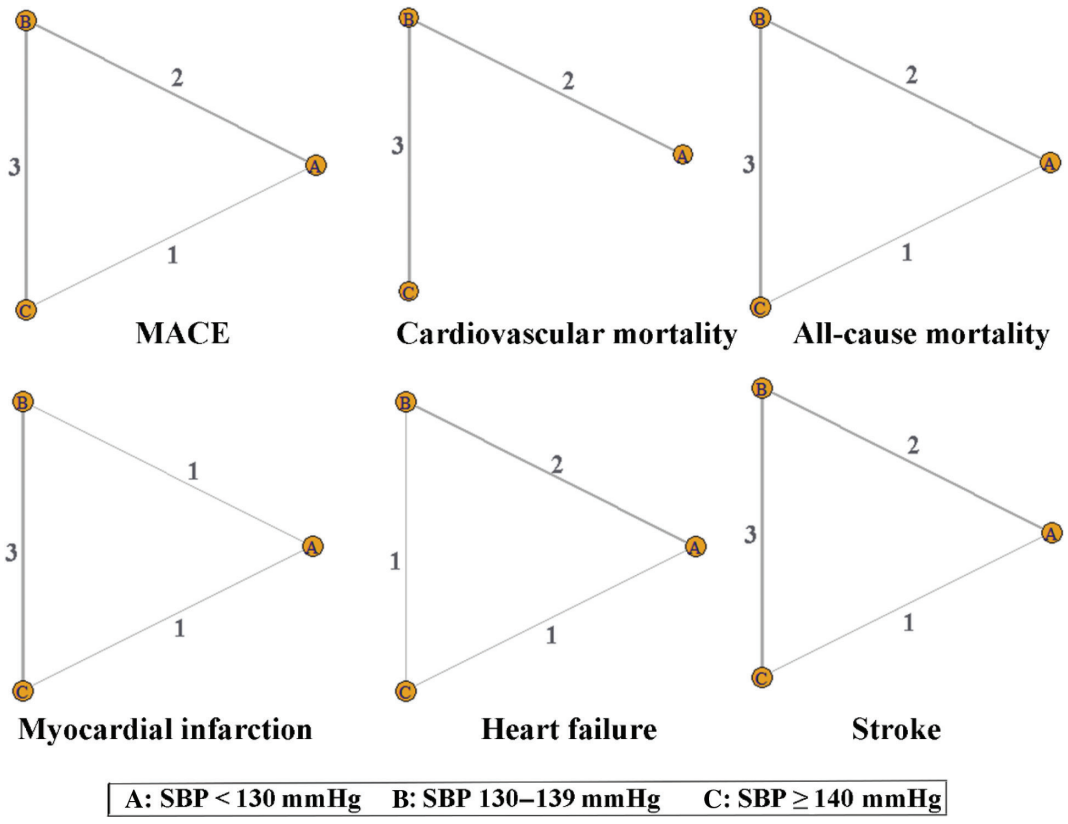


**Figure 2** Evidence Network of Eligible Comparison for the Mixed Comparison Meta-Analysis.
The cumulative number of enrolled studies for each direct comparison was indicated by the numbers by the lines.

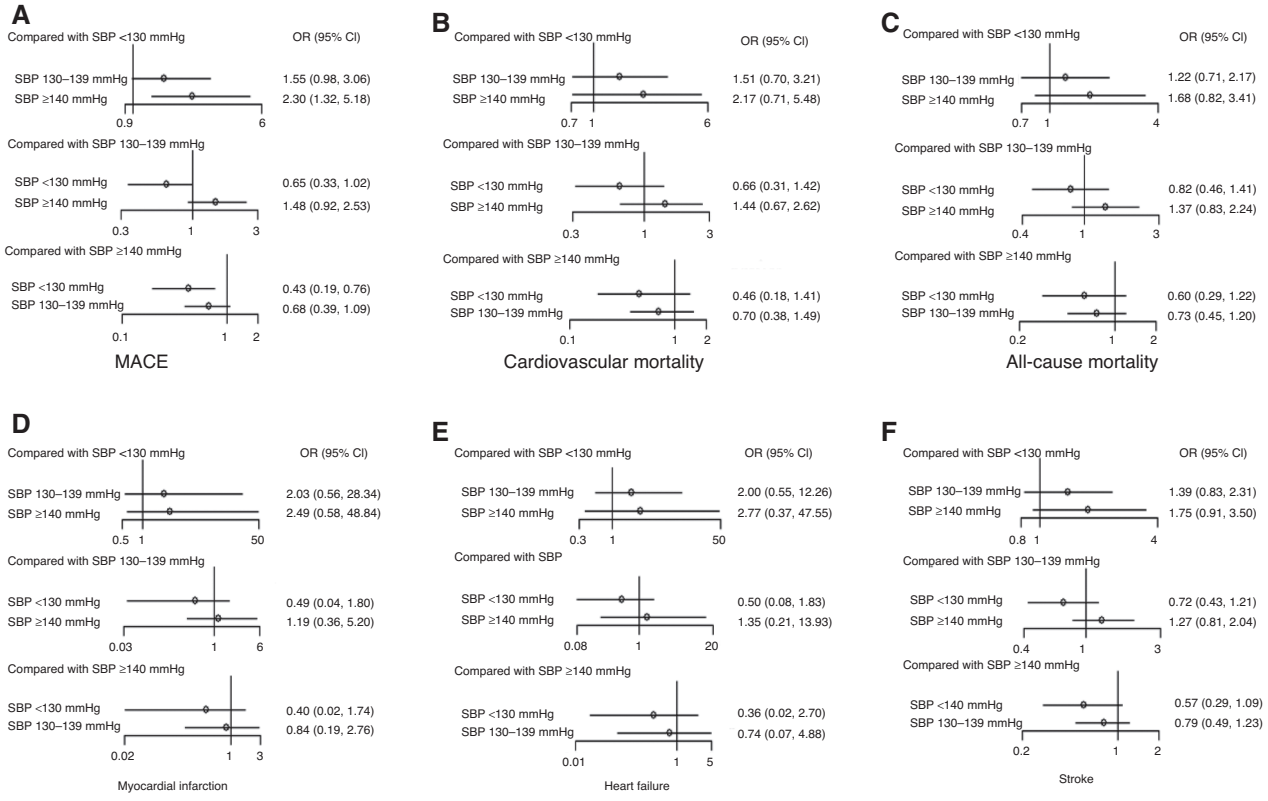


**Figure 3** Comparison Results of (A) MACE, (B) Cardiovascular Mortality, (C) All-Cause Mortality, (D) Myocardial Infarction, (E) Heart Failure and (F) Stroke.

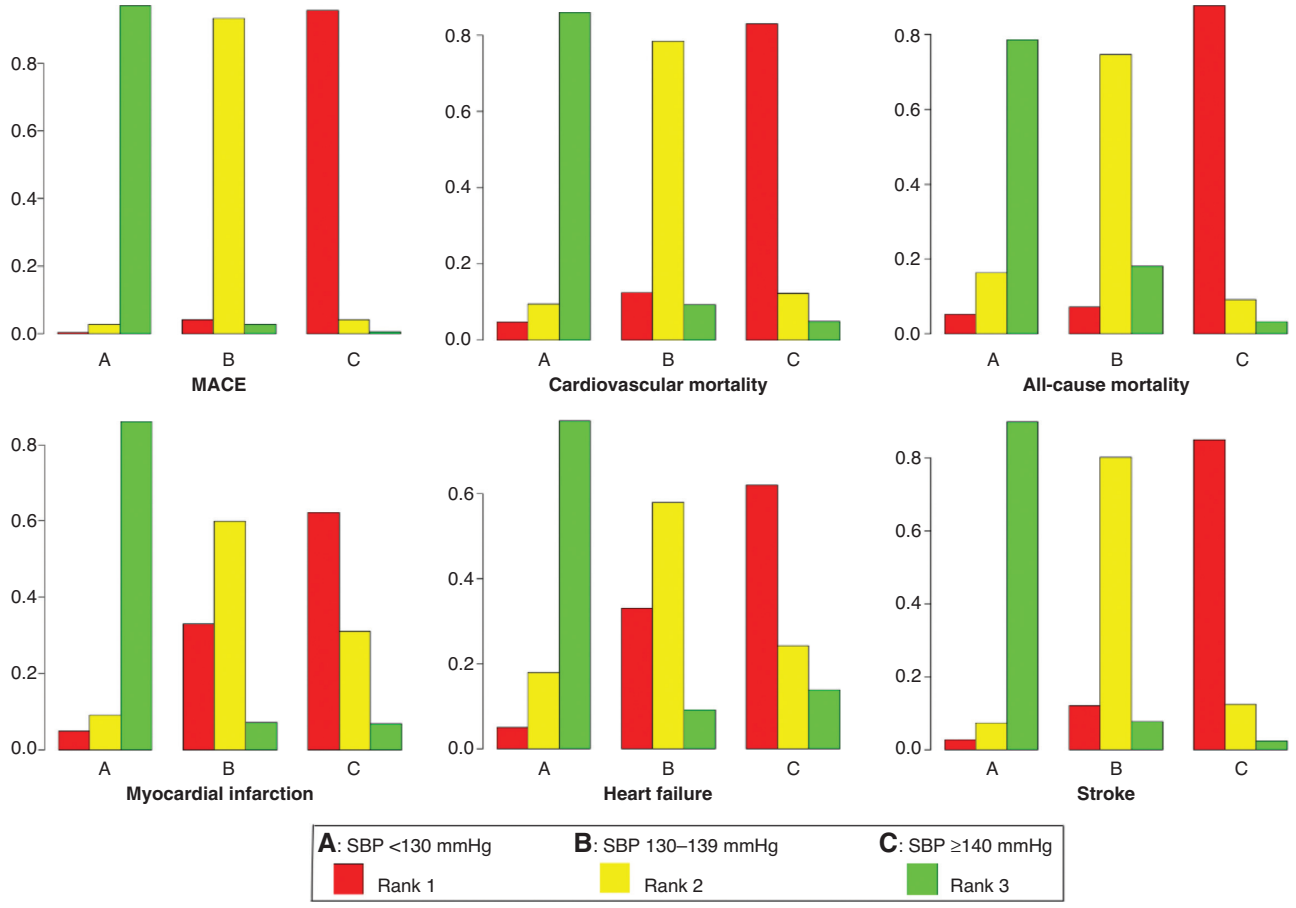


**Figure 4** Rank Probability of Different SBP Goals.
The vertical axis is values representing the probability of different ranks in the different groups with different SBP goals. Red represents Rank 1 which means the highest probability of event occurrence; yellow represents Rank 2 which means low probability of event occurrence and green represents Rank 3 which means the lowest probability of event occurrence.

therefore, the pooled results should be interpreted with caution. When we performed pair-wise comparison, the results also indicated a trend toward significance, suggesting that treatment with target SBP <130 mmHg might benefit older patients (SBP <130 mmHg vs. SBP ≥140 mmHg: OR 0.12, 95% CI 0.01–2.33; SBP <130 mmHg vs. SBP 130–139 mmHg: OR 0.45, 95% CI 0.45–1.06).

## Discussion

Our meta-analysis is the first trial designed to determine the optimal SBP target for older patients with hypertension by using a mixed treatment comparison method. The results indicated that antihypertensive treatment with an SBP target <130 mmHg tended to provide greater benefit than other antihypertensive treatments with different SBP targets in preventing clinical events; however, the comparison results did not show statistical significance. Further clinical evidence is still required to address this issue.

Whether strict BP control may benefit older patients more than younger patients, and what the optimal BP target might be have long been a matter of intense debate. The JATOS study was designed to compare the effects of strict antihypertensive treatment to maintain an SBP <140 mmHg with treatment to maintain an SBP 140–159 mmHg in older patients (65–85 years old) with essential hypertension; the incidence of the primary endpoint and total deaths were found to be similar between groups. The same result has also been observed in the VALISH study, which aimed to determine whether intensive BP control (<140 mmHg) is superior to moderate BP control (≥140 mmHg to <150 mmHg) in decreasing cardiovascular mortality and morbidity in patients 70–84 years of age with isolated systolic hypertension. No significant difference in the rate of the primary composite endpoint between groups was found. Most earlier published antihypertension

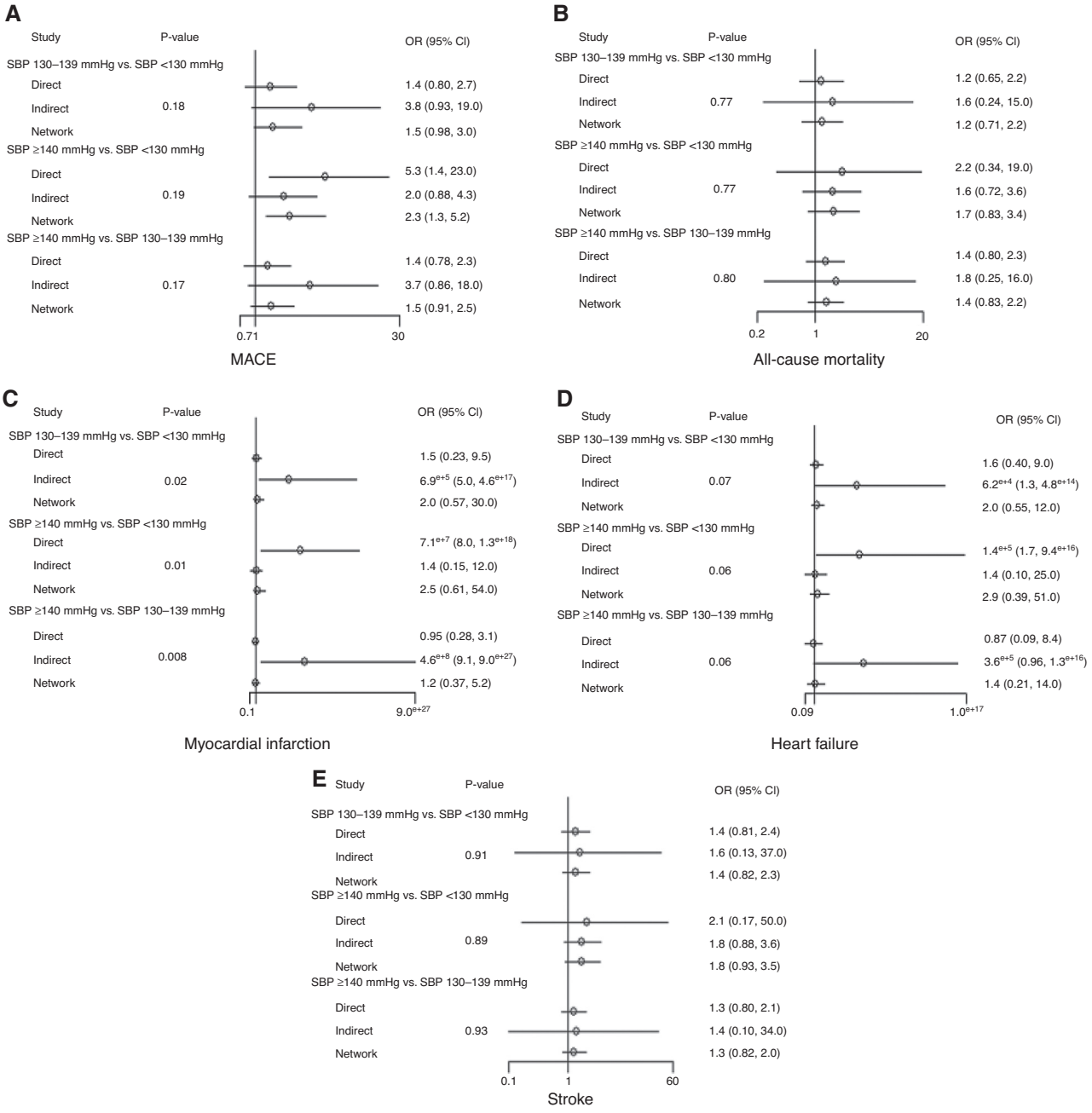


**Figure 5** Inconsistency Evaluation between Direct and Indirect Evidence through Node-Splitting Method. (A) MACE, (B) all-cause mortality, (C) myocardial infarction, (D) heart failure, and (E) stroke.

guidelines recommend a loose BP control strategy (BP <150/90 mmHg) for older patients with hypertension, although the age range substantially varies among guidelines. For example, NICE 2011 [19], ISH 2014 [20] and CHEP 2013 [21] provide recommendations for patients ≥80 years of age, whereas JSH 2014 [22] provides recommendations for patients ≥75 years of age, and JNC8 [23] provides recommendations for patients ≥60 years of age.

However, this variation is gradually changing with the emergence of new clinical evidence. Wei et al. have discovered that Chinese patients >70 years with hypertension benefit from intensive antihypertensive treatment with a BP target ≤140/90 mmHg, which is associated with decreased incidence of major cardiovascular events. The SPRINT-SENIOR trial has also reported that among ambulatory people 75 years of age or older, treating to achieve an SBP target <120 mmHg (although the final achieved SBP was 123 mmHg) was superior to an SBP target <140 mmHg in decreasing the incidence of the primary composite outcome by 34%

and all-cause mortality by 33%. Our head-to-head meta-analysis assessed the efficacy and safety of intensive BP-lowering strategies in 10,857 patients with ≥65 years of age with hypertension in JATOS, VALISH, SPRINT-SENIOR and Wei et al. [24]. The pooled analysis demonstrated that older patients may benefit more from lower blood pressure level, which decreased the risks of MACE by 29%, of cardiovascular mortality by 33% and of heart failure by 37%. However, although all trials mentioned above suggest that older patients with hypertension may benefit more from intensive blood control, the optimal BP target for these patients remains unclear, because clinical trials have suggested different recommendations. The ACC/AHA 2017 guidelines recommend intensive anti-hypertensive treatment, with SBP <130 mmHg as a target goal for hypertensive patients ≥65 years of age [10], whereas the ESH/ESC 2018 and JSH 2019 guidelines suggest an SBP <140 mmHg for older patients (including very old patients), and the ESH/ESC 2018 guidelines recommend an SBP target less than 130 mmHg, if tolerated, for older patients [11, 25]. However, most of these recommendations have come from expert opinions and experience. The extent to which the BP goal or target should be achieved, and the optimal BP target for older patients remain unclear, and further exploration is required. Our meta-analysis was designed to address this issue. The results showed a trend in which older patients may benefit more from intensive anti-hypertensive therapy with an SBP target <130 mmHg, thus indicating that this SBP target might be optimal for older patients with hypertension.

Although our trial demonstrated that anti-hypertensive treatment with an SBP goal <130 mmHg, as compared with an SBP goal ≥140 mmHg, significantly decreased the incidence of MACE; no statistical difference was found in the other comparisons. Several factors are speculated to have influenced the mixed results after detailed analysis. A slight difference in age range was found among the included trials: 65–85 years of age in JATOS; 70–84 years of age in VALISH; ≥70 years of age in Wei et al.; ≥75 years in SPRINT-SENIOR and INFINITY; and 60–80 years of age in STEP. Small age discrepancies could not be ruled out as a factor potentially affecting our conclusions. Moreover, the mean baseline SBP level varied considerably, from 171.0 mmHg to 141.6 mmHg, among the six included trials, thus potentially making the magnitude of SBP reduction vary greatly across trials and influencing our analysis. Additional factors among our included trials probably affected our mixed comparison results; for example, SPRINT-SENIOR excluded patients with diabetes, and INFINITY required patients to have a diagnosis of systolic hypertension and visible white matter hyperintense lesions on magnetic brain imaging screening. Therefore, more clinical evidence is needed to support our findings and to support further exploration of the optimal BP target for older patients.

During intensive antihypertensive therapy, the potential for increased side effects associated with lower target BP levels must be carefully considered in older patients. A systematic review has concluded that lower BP targets are closely associated with hypotension, syncope, and greater medication burden [26]. Unfortunately, our meta-analysis did not investigate adverse effects within the disparate data from all included trials. Whether controlling SBP to <130 mmHg in older patients is safe requires further exploration. The SPRINT-SENIOR trial showed no statistical differences in the absolute rate of side effects related to blood pressure control between the intensive treatment group (SBP <120 mmHg) and the control group (SBP <140 mmHg). The safety evaluation and renal outcomes from STEP also did not differ significantly between intervention groups (target SBP 110–130 mmHg versus 130–150 mmHg), except for the risk of hypotension, which was higher in the intensive group. Beyond the differences in the included populations and interventions, additional differences existed in the safety evaluation results between trials. Thus, more clinical evidence exploring this issue in depth is required, and more attention should be paid to older patients at high risk taking intensive antihypertensive therapy.

With increasing age, patients ≥80 years of age with hypertension tend to have arteriosclerosis aggravation, decreased vascular elasticity and renal function, and endocrine impairment; therefore, the pathophysiological state of these patients differs from that in younger patients [27]. Moreover, most of these older patients have many concomitant diseases and take a combination of drugs; these additional aspects must be considered during blood

pressure control. Patients ≥80 years of age have been shown to benefit from antihypertensive therapy, on the basis of decreased cardiovascular events. The results of the HYVET study have demonstrated that anti-hypertensive treatment achieving a BP of 143.5/77.9 mmHg benefits patients older than 80 years, on the basis of 30% lower incidence of stroke, 39% lower stroke mortality, 23% lower all-cause death and 64% lower heart failure than that observed in the placebo group, with an achieved average BP of 158.4/84 mmHg [28]. Although some guidelines for hypertensive management recommend an SBP target <150 mmHg for very old people, no specific recommendations for antihypertensive goals have been made for very old patients in other guidelines. However, only three trials included in our study included patients ≥80 years of age; thus it is difficult to make sure that whether the optimal SBP we discussed in the trial is also suitable for very old patients. Thus, research investigating the optimal BP goal for patients ≥80 years of age is much needed.

## Limitation

This study has several limitations. Aggregated study-level data other than individual participant data were used in our trial, thus leading to discrepancies between the results and real-world situations. Moreover, variability existed in the characteristics of the included populations, in baseline BP, choice of different anti-hypertensive drugs, and definition of outcomes. Finally, the trials included a small number of patients with cerebrovascular and cardiovascular disease, thus making our findings potentially not applicable to high-risk patients.

## Conclusion

Our results demonstrated that antihypertensive treatment with a target SBP <130 mmHg, compared with a target of ≥140 mmHg, provides a significant advantage in decreasing the risk of MACE. The observed trend suggesting that antihypertensive treatment with an SBP target <130 mmHg provides greater benefits to patients ≥60 years requires further clinical exploration to provide confirmation and verification.

## Contributions

YLY, YH, SBD, JLD and QS were responsible for the conception and design of the study. YLY, YH, and JD together conducted database searching for the initial trial collection. YLY and JW conducted trial screening and were responsible for the acquisition of data with the help of QS. YLY and BL analyzed the data and interpreted the analysis results in collaboration with XDJ, JLD, YJL, YRL and SQ. YLY contributed to the first draft of the article. All authors critically revised the article and approved the final version.

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## Conflicts of Interest

All authors completed the ICMJE uniform disclosure form at http://www.icmje.org/coi_disclosure.pdf and declare no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years, and no other relationships or activities that could appear to have influenced the submitted work.

## Transparency

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

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