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ARTICLE

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Target blood pressure level for the treatment of elderly hypertensive patients: a systematic review and meta-analysis of randomized trials

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Abstract

Although recent systematic reviews (SRs) of randomized clinical trials (RCTs) support the benefit of blood pressure (BP) treatment in the elderly, the optimized target BP level remains controversial. We performed a SR to determine the clinical benefit of antihypertensive treatments with a target systolic BP (SBP) of <140 mmHg in the elderly. We searched for RCTs comparing intensive and less intensive treatments or placebo and active treatments reported until May 2017 and identified 11 RCTs in which the target or on-treatment SBP in the intensive or active treatment was less than 140 mmHg. Among the RCTs, 6 RCTs with primary or subanalysis results for patients aged 70 years or older were finally chosen for the meta-analysis. We found that intensive lowering of BP did not reduce the risk ratio (RR) of composite cardiovascular outcomes (95% CI: 0.67–1.05, $p = 0.13$). By contrast, intensive lowering of BP achieved RR reductions of 24% for all-cause death (0.63–0.92) and of 39% for cardiovascular death (0.48–0.77). Intensive lowering of BP did not alter the incidence of stroke (0.63–1.23) and serious adverse events (SAEs) (0.93–1.09). In conclusion, intensive antihypertensive regimens targeting SBP < 140 mmHg did not significantly reduce the risk of cardiovascular diseases compared to that of less intensive treatments, but did reduce the risk of death without increasing adverse events in patients aged 70 years or older. These findings support the benefit of intensive treatment targeting SBP to ≤140 mmHg in the elderly.

Keywords Hypertension · The elderly · Systematic review · Meta-analysis · Randomized clinical trial

Introduction

Hypertension is the most common lifestyle disease in the elderly and affects more than 50% of the population aged 65 years or older in Japan [1]. The recent aging of the population has increased the importance of hypertension management in the elderly, and recent clinical trials have clearly shown the benefit of antihypertensive medications, even in the very elderly [2]. However, the optimized target blood pressure (BP) level that provides superior benefits compared to those of higher target BP levels in the elderly population is a matter of debate [3]. In the current hypertension guideline in Japan (The Japanese Society of Hypertension (JSH) 2014), treatment of patients aged 75 years or older is specially categorized with an initial target BP of 150 mmHg, which is in contrast to the target of 140 mmHg for the younger population [4]. After the JSH2014 launched, the Systolic Blood Pressure Intervention Trial (SPRINT) showed the benefit of intensive treatment of BP targeting a cut-off of less than 120 mmHg, even in patients aged 75 years or older [5]. In this systematic review, we aimed to investigate whether the initial target BP in the JSH2014 needs to be re-adjusted in patients aged 75 years or older. We also investigated whether the optimal initial target BP should be changed in patients with comorbidities, such as diabetes mellitus (DM), stroke history, chronic kidney disease (CKD), or frailty. For this aim, we conducted a meta-analysis to investigate the balance of risks and benefits

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associated with lowering BP to less than 140 mmHg in patients aged 70 years or older, most of whom were 75 years or older (Table 1).

Methods

Data sources and searches

This systematic review (SR) used the recent SR that provided the basis for the recent guideline for treatment of hypertension in adults 60 years old and older released by the American College of Physicians (ACP) and the American Academy of Family Physicians (AAFP) as a reference [6, 7]. The reference SR included 15 randomized trials of adults with a diagnosis of hypertension and a mean age of at least 60 years that directly compared the effects of antihypertensive therapy with either active versus placebo medication or more versus less intensive lowering of BP [2, 5, 8–23]. This SR performed a MEDLINE search in September 2016. We also searched the following data sources to update relevant randomized trials in June 2017: MEDLINE via Ovid, the Cochrane Library database, and the Ichushi for Japanese database. We used relevant text words and medical subject headings according to the reference SR. A total of 1666 articles matched the search, and we added 17 articles cited in the reference SR in the initial screening step (Fig. 1) [2, 5, 8–24].

Study selection

The literature search, data extraction, and quality assessment were conducted independently by two authors using a standardized approach (KY and YT). After the literature search, we selected trials that satisfied the following criteria; target systolic BP of the intensive treatment group <140 mmHg in RCTs comparing intensive and less intensive treatments or achieved systolic BP in the active treatment group <140 mmHg in RCTs comparing placebo and active treatments (the first screening) and a primary analysis or subanalysis targeting patients 70 years or older (or 75 years or older, if available) (the second screening). In this report, we applied the phrase "intensive" therapy to describe a therapy in which the target or on-treatment SBP in an intensive or active treatment regimen was less than 140 or 130 mmHg and a "less intensive" therapy to describe the comparator for each therapy.

The study quality was judged based on the proper conduct of randomization, concealment of treatment allocation, similarity between the treatment groups at baseline, provision of a description of the eligibility criteria, completeness of follow-up, use of an intention-to-treat analysis, selective outcome reporting, early termination of the study, and

Table 1 Characteristics of selected RCTs for second screening in systematic review

Study	Publication year	Mean age (years)	Subjects	Diabetes mellitus (%)	mean Renal function	Follow-up (years)	Patients (*n*)		male (%)	Lower target BP (mmHg)		BP difference (mmHg)		Baseline BP (mmHg)		Achieved BP			
							Intensive	Less intensive		SBP	DBP	SBP	DBP	SBP	DBP	Intensive		Less intensive	
																SBP	DBP	SBP	DBP
ADVANCE subanalysis [15, 16]	2007	77	DM	100	eGFR 66	4.3	483	525	60	Placebo vs. active		−7	−2	151	78	137	72	144	74
JATOS [17]	2008	73.6	SBP ≧ 160	11.8 (Age ≧ 65)	eGRF 56	2	935	934	38.8	<140	–	−9.7	−3.3	172	89.1	136	74.8	146	78.1
VALISH [20]	2010	76.1	SBP ≧ 160 and DBP < 90	13	Cr < 2.0 mg/dL (inclusion crieria)	2.85	925	921	37.6	<140	–	−5.4	−1.7	170	81.4	137	74.8	142	76.5
SPS3 suanalysis [21, 22]	2013	79.9	Lacunar infarction (SBP ≧ 130 or treatment)	26.9	eGFR 66	3.7	248	246	54.3	<130	–	−11	N/A	144	N/A	125	N/A	137	N/A
SPRINT subanalysis [5, 23]	2015	79.9	SBP ≧ 130[a]	0	eGFR 63	3.3	1317	1319	62.1	<120	–	−12	−5	142	71	123	62	135	67
Wei et al. [24]	2013	76.6	SBP ≧ 150 and/or DBP ≧ 90	23.3	Cr 0.98 mg/dL	4	363	361	66	<140	<90	−14	−5.9	160	84.2	136	76.2	150	82.1

[a]Excluding DM, history of stroke, orthostatic hypotension.

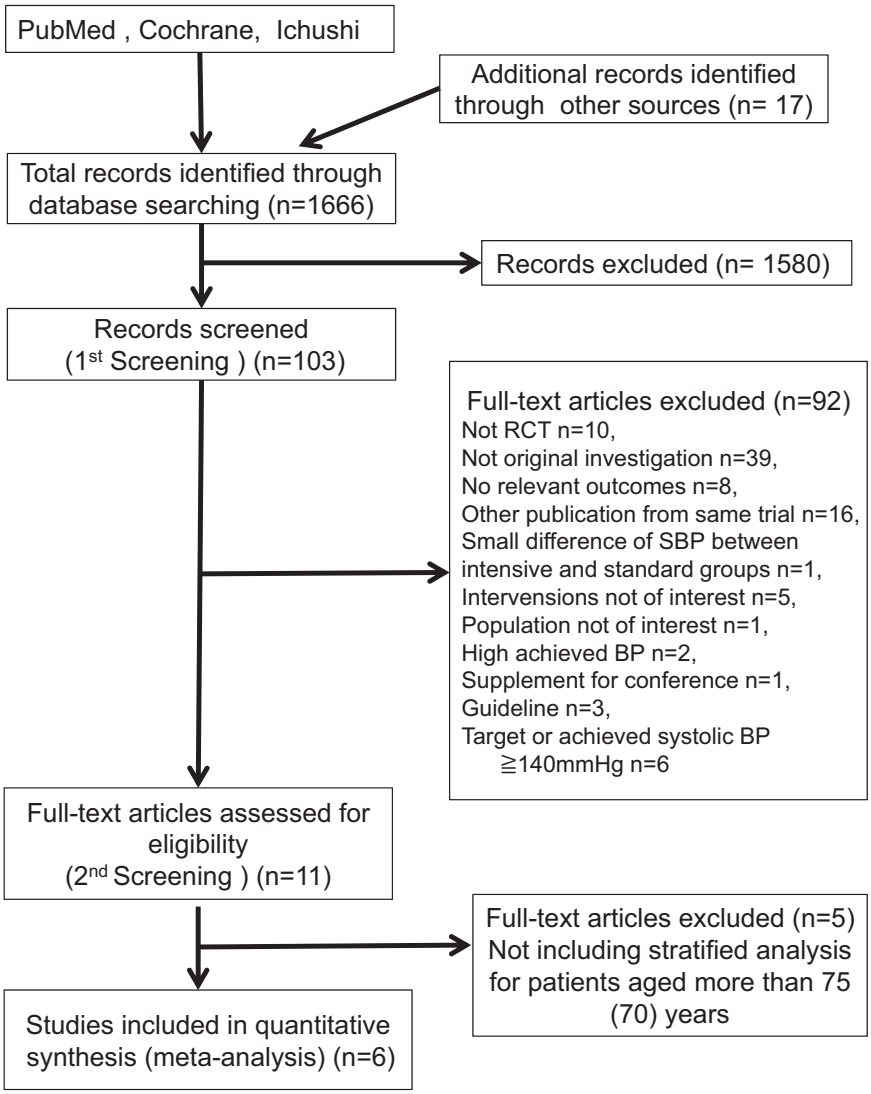


Fig. 1 Identification process of selection of articles in review for treatment of the elderly hypertensive patients

indirectness of the evidence [25]. We further selected articles that showed data for the subgroup of patients with comorbidities.

Outcomes

The outcomes were composite cardiovascular events (i.e., myocardial infarction, stroke, heart failure, and cardiovascular death), all-cause mortality, cardiovascular death, stroke, and severe adverse events.

Data synthesis and analysis

The relative risk (RR) ratio and 95% CIs from the individual studies were calculated for each outcome. Summary estimates of the RR ratios were obtained using an inverse-variance method with random-effects models. The percentage of variability across studies attributable to heterogeneity beyond chance was estimated using the I^2 statistic. A sensitivity analysis was also performed for each meta-analysis by excluding RCTs with a high risk of bias or without an intension to achieve a target BP of less than 140 mmHg. Potential publication bias was represented graphically using Begg's funnel plots of the natural log of the RR versus its standard error. A two-sided p value less than 0.05 was considered statistically significant. The statistical analyses were performed using Review Manager 5.3. (Cochrane Collaboration)

Results

Search results and characteristics of the included studies

The literature search led to the retrieval of 1683 articles, of which 103 were reviewed based on the full text (Fig. 1). A total of 11 RCTs were identified after the first screening that

satisfied the criteria of a target systolic BP of an intensive treatment of less than 140 mmHg [5, 17–24] or a final systolic BP of an active treatment of less than 140 mmHg [11, 12, 14–16]. Among them, 10 RCTs were included in the meta-analysis of the reference SR [5, 11, 12, 14–23], whereas a RCT using Chinese hypertensive patients aged 70 years or older was excluded due to a high risk of bias and a lack of detailed information about the study protocol, including concealment of treatment allocation and use of an intention-to-treat analysis [24]. As shown in the recent SR, we found some significance in including the RCT for Asian elderly [26]. Therefore, we integrated this article into the meta-analysis, followed by a sensitivity analysis with exclusion from the study. We excluded five RCTs with no available results stratified for patients aged 70 years or older in the second screening [11, 12, 14, 18, 19]. We finally selected six RCTs for the meta-analysis for which results of the stratified analysis of patients aged 70 years or older (or 75 years or older, if available) were available in the literature. The quality of the selected RCTs was assessed and shown in Supplemental Table 1.

Effects of intensive BP lowering regimens

Composite cardiovascular events

Data regarding the effects of intensive antihypertensive therapy on composite cardiovascular events were available from 6 RCTs including 8577 participants and 750 cardiovascular events. Intensive BP lowering therapy that achieved a blood pressure of 140/90 or less did not produce a significant risk reduction for composite cardiovascular events compared with that of a less intensive antihypertensive therapy that achieved a higher blood pressure (RR = 0.84, 95% CI: 0.67–1.05, $p = 0.13$). However, moderate heterogeneity was observed in the magnitude of the effect across the included studies ($I^2 = 59\%$, $p = 0.03$) (Fig. 2a).

Fatal events

Five RCTs including 7941 participants recorded 641 all-cause fatal events. Compared to that of the cases with less intensive lowering of BP, the intensive antihypertensive therapy reduced the risk of all-cause mortality by 24% (RR = 0.76, 95% CI: 0.63–0.92, $p = 0.005$) with low-grade heterogeneity ($I^2 = 36\%$, $p = 0.18$) (Fig. 2c). Regarding cause-specific deaths, data on cardiovascular death were only identified in 5 RCTs (7941 participants and 269 events). Compared to that of the cases with less intensive lowering of BP, intensive antihypertensive therapy reduced the risk of cardiovascular death by 39% (RR = 0.61, 95% CI: 0.48–0.77, $p < 0.0001$) with much less heterogeneity ($I^2 = 0\%$, $p = 0.61$) (Fig. 2d).

Stroke

Stroke was reported by 5 trials including 8802 participants, among whom 268 events were observed. No significant effect of intensive lowering of BP was found on the risk of stroke (RR = 0.88, 95% CI: 0.65–1.23, $p = 0.45$) with moderate heterogeneity ($I^2 = 49\%$, $p = 0.10$) (Fig. 2e).

Severe adverse events

Data on severe adverse events were collected from 4 RCTs including 7217 participants, among whom 1470 events occurred. No significant differences in potential harms of treatment were observed between the intensive therapy and the less intensive therapy groups (RR = 1.01, 95% CI: 0.93–1.09, $p = 0.84$) with low heterogeneity ($I^2 = 0\%$, $p = 0.69$) (Fig. 2f).

Effect of intensive therapy on hypertensive patients with comorbidities or frailty

Although we sought to analyze whether comorbidities or frailty of the elderly hypertensive patients affected the intensive therapy outcomes, we could not perform the analysis for elderly patients with a stroke history, CKD or frailty due to a lack of trials relevant to the analysis. Only two RCTs that described composite cardiovascular events of hypertensive patients with diabetes were identified. The analysis showed a tendency for a favorable effect of an intensive therapy on composite cardiovascular events (RR = 0.81, 95% CI: 0.64–1.01, $p = 0.06$) with low heterogeneity ($I^2 = 0\%$, $p = 0.77$) (Fig. 2b).

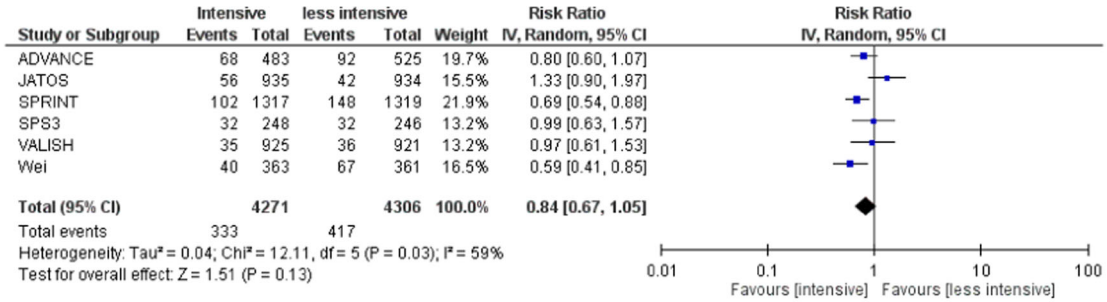
Sensitivity analysis

A sensitivity analysis was performed by excluding the RCT with a high risk of bias by Wei et al. [24] or ADVANCE [15], which was a placebo-controlled study that achieved a systolic blood pressure of 140 mmHg or less unintentionally in the active treatment group. Corresponding results were obtained for primary analyses of composite cardiovascular events, all-cause mortality, cardiovascular death, stroke, and severe adverse events (Supplemental Fig. 1). Notably, the sensitivity analysis excluding Wei's study showed the same tendency as the primary analysis for composite cardiovascular events (RR = 0.90, 95% CI: 0.71–1.14, $p = 0.37$) with moderate heterogeneity ($I^2 = 55\%$, $p = 0.06$).

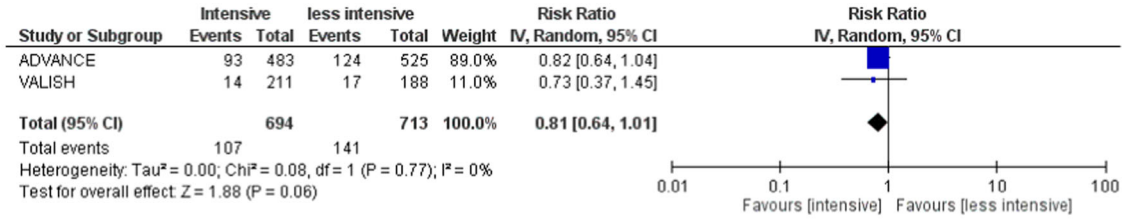
Effects in trial subgroups

The funnel plot analysis showed no obvious evidence of publication bias for the outcomes; however, the power to detect publication bias was limited because only

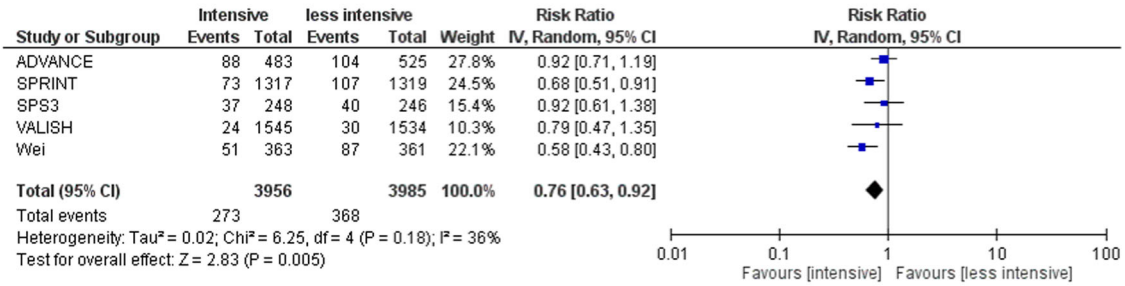
(a) Composite cardiovascular events (all patients)



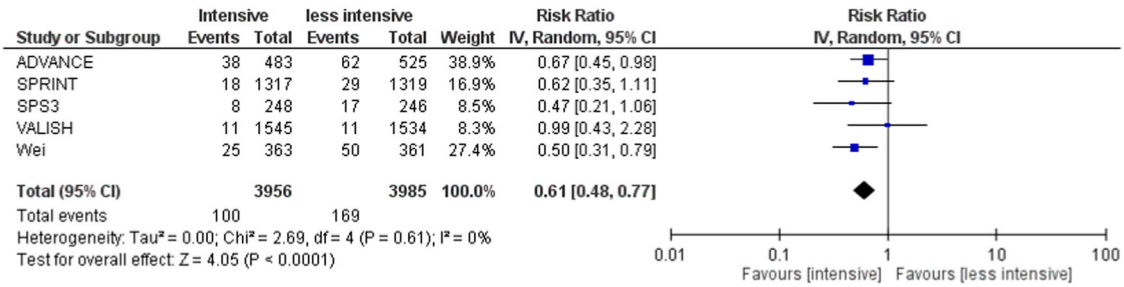
(b) Composite cardiovascular events (patients with DM)



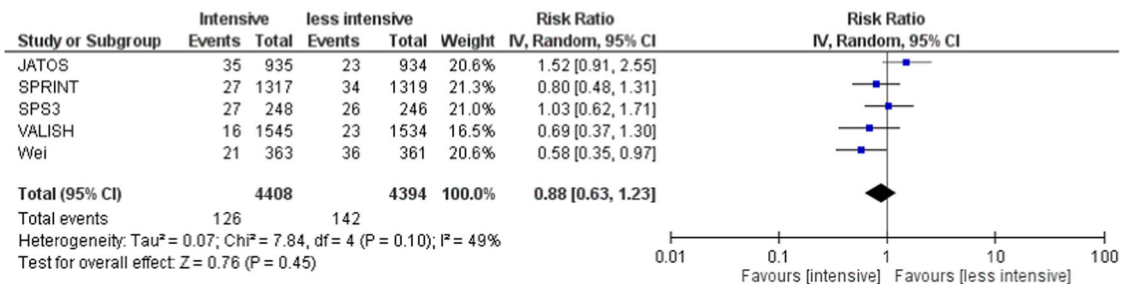
(c) All-cause mortality



(d) Cardiovascular death



(e) Stroke



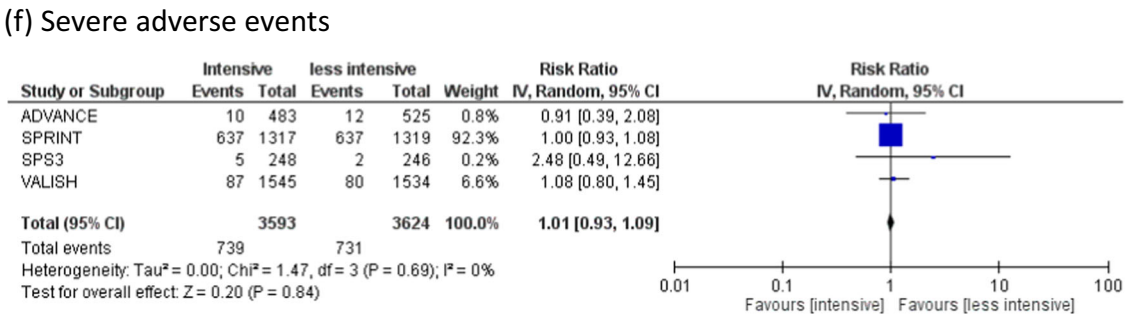


Fig. 2 Effect of intensive BP lowering on risk of composite cardiovascular events (all patients) (**a**), composite cardiovascular events (patients with DM) (**b**), all cause mortality (**c**), cardiovascular death (**d**), stroke (**e**), and severe adverse events. Boxes and horizontal lines represent RR and 95% CI for each trial. Size of boxes is proportional to weight of that trial result. Diamonds represent the 95% CI for pooled estimates of effect and are centered on pooled RR

two to six studies were available for each comparison (Fig. 3).

Effects of intensive therapy resulting in a systolic BP less than 130 mmHg

Only two RCTs were identified for inclusion in a meta-analysis of the effects of lowering the systolic BP to less than 130 mmHg in patients aged 75 years or older [5, 21]. Analysis of these two RCTs showed a trend similar to that obtained for the six final selected RCTs mentioned above (Supplemental Fig. 2). Intensive antihypertensive therapy resulting in a systolic BP less than 130 mmHg showed a tendency for risk reduction of all-cause mortality (RR = 0.76, 95% CI: 0.58–1.01, $p = 0.06$) and significant risk reduction for cardiovascular death (RR = 0.56, 95% CI: 0.35–0.91, $p = 0.02$). We also found that achieving a systolic BP less than 130 mmHg did not demonstrate significant risk reduction for composite cardiovascular events and stroke compared with those of the less intensive therapy. Similarly, more intensive therapy did not increase the risk of severe adverse events.

Discussion

In this SR, we performed a meta-analysis using random-effects models to investigate whether lowering BP to less than 140 mmHg was superior to lowering it to a higher level in terms of improving the clinical outcomes of older hypertensive patients. As a result, we found that antihypertensive treatments with an on-treatment BP of less than 140 mmHg attenuated all-cause and cardiovascular death compared to that of treatments with a higher on-treatment BP in patients aged 70 years or older. Lowering BP to less than 140 mmHg also showed a trend for a reduced incidence of composite cardiovascular events compared to that of lowering BP to a higher level, but the difference was not significant. The analysis of composite cardiovascular events showed high heterogeneity with a high I^2 value for two RCTs with significant reductions in the events in patients whose BP was lowered to less than 140 mmHg, four RCTs with no significant differences between the treatments, and no RCT with worse outcomes in the group with the lower target BP. These trends in favor of lowering BP to less than 140 mmHg were consistent with the sensitivity analysis results obtained by excluding the RCT that did not prespecify the target BP (ADVANCE) [16] or the RCT that was excluded from the reference SR due to a high risk of bias [24]. We did not find any difference in the occurrence of stroke and serious adverse events between treatments with different magnitudes of the on-treatment BP. Given that the higher on-treatment BP in all RCTs analyzed here was less than 150 mmHg and most participants were aged 75 years or older, the present results support the superiority of lowering BP to less than 140 mmHg over lowering it to less than 150 mmHg for improvement of the prognosis of patients aged 75 years or older.

We also attempted to analyze the effect of lowering BP to less than 140 mmHg in patients with specific comorbidities. In patients with diabetes, a nonsignificant trend for a reduction in composite cardiovascular events was observed in favor of lowering BP to less than 140 mmHg, although the statistical power was small due to the limited sample size. We did not perform an analysis for patients with a previous history of stroke, CKD, and frailty due to insufficient data for the meta-analysis. When taken together, we did not find any evidence to recommend a BP target level different from 140 mmHg in older patients with specific comorbidities.

Additionally, we found a similar trend in favor of intensive treatment in the analysis of two RCTs with a lower target systolic BP of less than 130 mmHg (Supplemental Fig. 2). However, this meta-analysis with the SPRINT [5] and SPS3 [21] trials could not provide solid

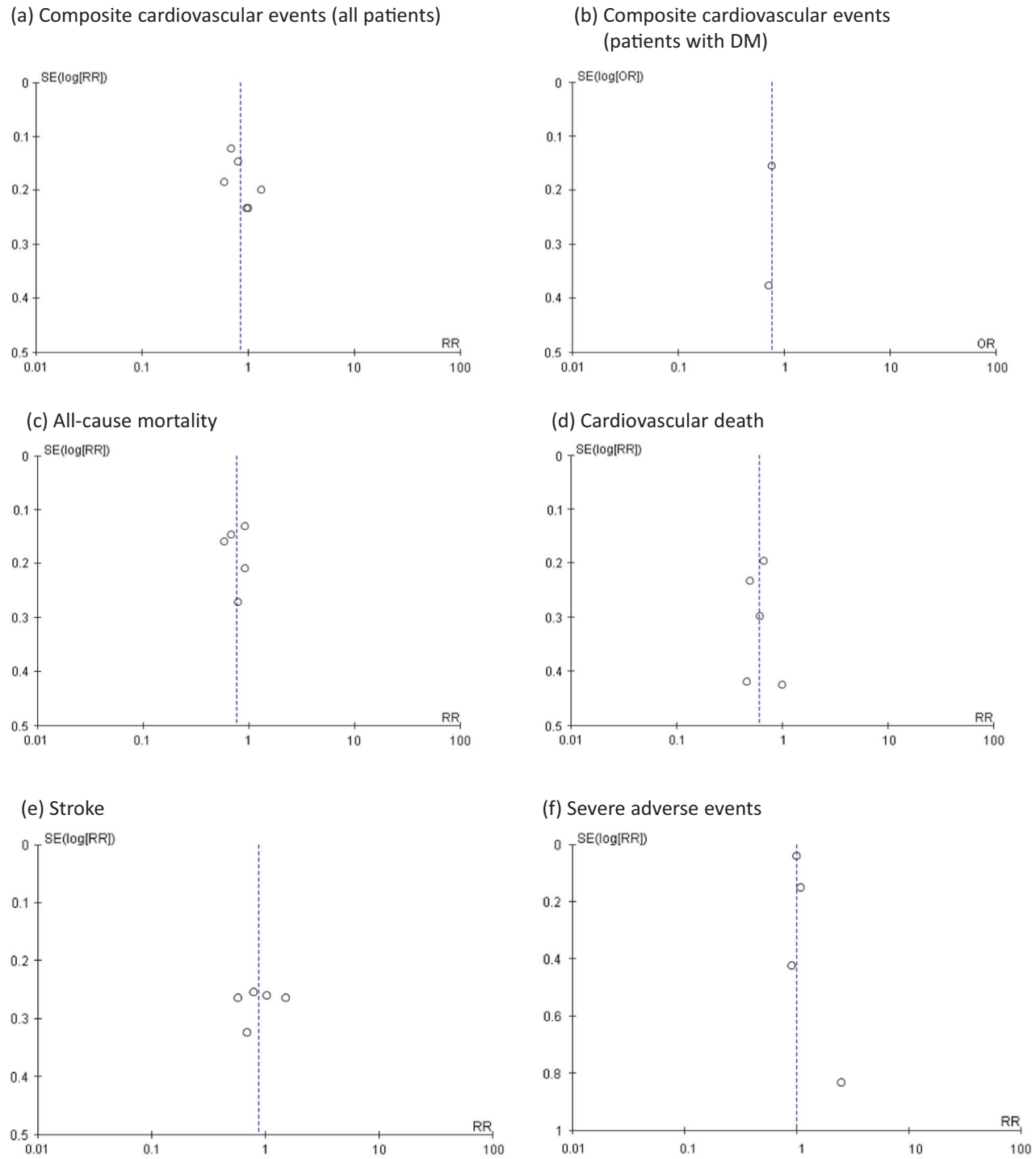


Fig. 3 Funnel plots for each meta-analysis

conclusions concerning whether patients aged 75 years or older whose BP was 130–139 mmHg should be treated further to reduce their BP to less than 130 mmHg due to study limitations. The target BP of the less intensive group was <140 mmHg in SPRINT and 130–149 mmHg in SPS3. BP was evaluated by AOBP (automated office BP) measurement in SPRINT but was converted to a 5–10 mmHg higher BP when evaluated by common office BP measurement [27]. Furthermore, the participants of two RCTs were confined to patients without diabetes and a prior history of stroke (SPRINT [5]) and patients with a recent lacunar stroke (SPS3 [21]). Therefore, further investigation

is required to determine whether the systolic BP should be lowered to less than 130 mmHg in patients aged 75 years or older.

Several study limitation need to be considered when applying the results to clinical practice. First, as mentioned above, individual data extracted from patients with specific comorbidities were limited, leading to insufficient analysis and clarifying the need for individual BP targets for specific comorbidities. Second, we did not extract data from RCTs that satisfied the criteria of our analysis but did not provide age-stratified data for patients aged 70 years or older, including ACCORD, which compared different BP targets in diabetic patients [19]. Third, the baseline comorbidities of the study subjects, including cardiovascular diseases, were variable among the RCTs. Due to the limited data availability, we did not perform an analysis by stratifying patients based on the presence or absence of a history of cardiovascular disease at baseline. Thus, whether the benefit of a lower BP target differs between patients with and without comorbidity burdens remains uncertain.

Fourth, patients who met the exclusion criteria of each RCT were not included in the analysis. In particular, patients with dementia and nursing home residents were excluded from most RCTs. Moreover, the numbers of patients with advanced frailty and extremely old patients were conceivably limited in the RCT participants. Thus, caution should be paid when generalizing the findings to the entire elderly population.

In summary, the present analysis supports the recommendation that lowering BP to at least 140 mmHg provides a positive net-benefit in patients aged 70 years or older. There was no evidence to support the recommendation for different BP targets in patients with comorbidities. Finally, the present results are not applicable to the population not eligible to participate in RCTs, including those with dementia and/or advanced frailty.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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References

1. Miura K, Nagai M, Ohkubo T. Epidemiology of hypertension in Japan: where are we now? Circ J. 2013;77:2226–31.
2. Beckett NS, Peters R, Fletcher AE, Staessen JA, Liu L, Dumitrascu D, et al. Treatment of hypertension in patients 80 years of age or older. N Engl J Med. 2008;358:1887–98.
3. Wilt TJ, Kansagara D, Qaseem A.Clinical Guidelines Committee of the American College of Physician Hypertension Limbo: balancing benefits, harms, and patient preferences before we lower the bar on blood pressure. Ann Intern Med. 2018;168:369–70.
4. Shimamoto K, Ando K, Fujita T, Hasebe N, Higaki J, Horiuchi M. et al.Japanese Society of Hypertension Committee for Guidelines for the Management of Hypertension The Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2014). Hypertens Res. 2014;37:253–390.
5. Williamson JD, Supiano MA, Applegate WB, Berlowitz DR, Campbell RC, Chertow GM, et al. Group SR. Intensive vs standard blood pressure control and cardiovascular disease outcomes in adults aged ≥75 years: A Randomized Clinical Trial. J Am Med Assoc. 2016;315:2673–82.
6. Qaseem A, Wilt TJ, Rich R, Humphrey LL, Frost J, Forciea MA, Clinical Guidelines Committee of the American College of P, the Commission on Health of the P and Science of the American Academy of Family Physician. Pharmacologic treatment of hypertension in adults aged 60 years or older to higher versus lower blood pressure targets: a Clinical Practice Guideline From the American College of Physicians and the American Academy of Family Physicians. Ann Intern Med. 2017;166:430–7.
7. Weiss J, Freeman M, Low A, Fu R, Kerfoot A, Paynter R, et al. Benefits and harms of intensive blood pressure treatment in adults aged 60 years or older: a systematic review and meta-analysis. Ann Intern Med. 2018;166:419–29.
8. Amery A, Birkenhager W, Brixko P, Bulpitt C, Clement D, Deruyttere M, et al. Mortality and morbidity results from the European Working Party on high blood pressure in the elderly trial. Lancet. 1985;1:1349–54.
9. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP). SHEP Cooperative Research Group. J Am Med Assoc. 1991; 265:3255–64.
10. Staessen JA, Fagard R, Thijs L, Celis H, Arabidze GG, Birkenhager WH, et al. Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. The Systolic Hypertension in Europe (Syst-Eur) Trial Investigators. Lancet . 1997;350:757–64.
11. Hansson L, Zanchetti A, Carruthers SG, Dahlof B, Elmfeldt D, Julius S, et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group. Lancet. 1998;351:1755–62.
12. Group PC. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6,105 individuals with previous stroke or transient ischaemic attack. Lancet. 2001; 358:1033–41.
13. Lithell H, Hansson L, Skoog I, Elmfeldt D, Hofman A, Olofsson B, et al. The Study on Cognition and Prognosis in the Elderly (SCOPE): principal results of a randomized double-blind intervention trial. J Hypertens. 2003;21:875–86.
14. Liu L, Zhang Y, Liu G, Li W, Zhang X, Zanchetti A, Group FS. The Felodipine Event Reduction (FEVER) Study: a randomized long-term placebo-controlled trial in Chinese hypertensive patients. J Hypertens. 2005;23:2157–72.
15. Patel A, Group AC, MacMahon S, Chalmers J, Neal B, Woodward M, Billot L, Harrap S, et al. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. Lancet. 2007;370:829–40.
16. Ninomiya T, Zoungas S, Neal B, Woodward M, Patel A, Perkovic V, et al. Efficacy and safety of routine blood pressure lowering in older patients with diabetes: results from the ADVANCE trial. J Hypertens. 2010;28:1141–9. Group AC

17. Group JS. Principal results of the Japanese trial to assess optimal systolic blood pressure in elderly hypertensive patients (JATOS). Hypertens Res. 2008;31:2115–27.
18. Verdecchia P, Staessen JA, Angeli F, de Simone G, Achilli A, Ganau A, et al. Usual versus tight control of systolic blood pressure in non-diabetic patients with hypertension (Cardio-Sis): an open-label randomised trial. Lancet. 2009;374:525–33.
19. Group AS, Cushman WC, Evans GW, Byington RP, Goff DC Jr., Grimm RH Jr., Cutler JA, et al. Effects of intensive blood-pressure control in type 2 diabetes mellitus. N Engl J Med. 2010;362:1575–85.
20. Ogihara T, Saruta T, Rakugi H, Matsuoka H, Shimamoto K, Shimada K, et al. Target blood pressure for treatment of isolated systolic hypertension in the elderly: valsartan in elderly isolated systolic hypertension study. Hypertension. 2010;56:196–202.
21. Group SPSS, Benavente, Coffey OR, Conwit CS, Hart R, McClure RG, Pearce LA, et al. Blood-pressure targets in patients with recent lacunar stroke: the SPS3 randomised trial. Lancet. 2013;382:507–15.
22. White CL, Szychowski JM, Pergola PE, Field TS, Talbert R, Lau H. et al.and Secondary Prevention of Small Subcortical Strokes Study I Can blood pressure be lowered safely in older adults with lacunar stroke? The Secondary Prevention of Small Subcortical Strokes study experience. J Am Geriatr Soc. 2015;63:722–9.
23. Group SR, Wright JT, Jr., Williamson JD, Whelton PK, Snyder JK, Sink KM, Rocco MV, et al. A randomized trial of intensive versus standard blood-pressure control. N Engl J Med. 2015;373:2103–16.
24. Wei Y, Jin Z, Shen G, Zhao X, Yang W, Zhong Y, et al. Effects of intensive antihypertensive treatment on Chinese hypertensive patients older than 70 years. J Clin Hypertens. 2013;15:420–7.
25. Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. Br Med J. 2011;343:d5928.
26. Bavishi C, Bangalore S, Messerli FH. Outcomes of intensive blood pressure lowering in older hypertensive patients. J Am Coll Cardiol. 2017;69:486–93.
27. Hong D, Su H, Li J, Xu J, Peng Q, Yang Q, et al. The effect of physician presence on blood pressure. Blood Press Monit. 2012;17:145–8.