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ARTICLE

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Optimal blood pressure targets for patients with hypertension: a systematic review and meta-analysis

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Abstract

Optimal blood pressure (BP) targets for hypertension have been an important clinical issue but have been elusive. The Systolic Blood Pressure Intervention Trial (SPRINT) showed significant benefits of intensive BP-lowering treatment with a target systolic BP level of < 120 mm Hg on major cardiovascular (CV) events and mortality, whereas there was a modest increase in renal events related to BP-lowering treatment. We searched the PubMed, Cochrane CENTRAL, and ICHUSHI databases for randomized trials that assigned participants to intensive versus usual BP-lowering treatment with different BP targets. The outcomes were major CV events, all-cause death, myocardial infarction, stroke, heart failure, renal events, and adverse events. Nineteen trials that enrolled a total of 55,529 participants with a mean follow-up duration ranging from 1.6 to 12.2 years were included in the present analysis. There was a significant reduction in major CV events, myocardial infarction, and stroke and a trend toward a reduction in heart failure associated with intensive BP-lowering treatment, but no differences in the risks of all-cause death, renal events, or adverse events were observed between the randomized groups. Subgroup analyses indicated that intensive BP-lowering treatment with a target of < 130/80 mm Hg and/or achievement of BP < 130/80 mm Hg were associated with a significant reduction in major CV events compared with the usual group. In conclusion, intensive BP-lowering treatment reduces the risk of CV events. A target BP level of < 130/80 mm Hg appears to be optimal for CV protection in patients with hypertension.

Keywords Blood pressure target · Achieved blood pressure · Cardiovascular events · Randomized trial · Systematic review · Meta-analysis

Introduction

Large cohort studies show a positive and continuous relationship between cardiovascular (CV) disease and blood pressure (BP), with hypertension defined as one of the major risk factors for CV events [1–6]. One benefit of BP-lowering treatment has been documented to significantly reduce morbidity and/or mortality in patients with hypertension and in a high-risk population [7–16]. Major guidelines for the management of hypertension recommend a BP target of < 140/90 mm Hg for hypertensive patients [17–19], and a BP goal of < 150/90 mm Hg when treating hypertensive patients ≥ 60 years of age [19]. Recently, the 2017 ACC/AHA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults, as well as the 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure, recommended a BP target of < 130/80 mm Hg for hypertensive patients in general, as well as those with specific comorbidities such as diabetes mellitus (DM),

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chronic kidney disease (CKD), and heart failure [20, 21]. Such guidelines with recommended BP targets have been associated with a shift in the population BP toward lower levels [22]. It is recommended that clinical practice guidelines should be based on accurate systematic reviews and meta-analyses of critical clinical questions for interpretation of the evidence from randomized trials and observational studies and showing the recommendations for the clinical questions [23]. Although several recent meta-analyses showed a benefit of intensive BP-lowering treatment for a reduction in CV events in patients with hypertension and in a high-risk population [7–16], the optimal BP target for antihypertensive therapy has been elusive. The objectives of this study are to clarify the benefits and harms of intensive BP-lowering treatment, as well as the optimal BP targets for patients with hypertension.

Methods

Search strategy

This systematic review and meta-analysis were conducted based on the PRISMA statement for meta-analyses of interventional studies [24]. PubMed, Cochrane CENTRAL, and ICHUSHI (Japanese) were searched from inception to March 2018 using a variation of text words for intensive BP-lowering treatment, such as intensive BP, strict BP, optimal BP, BP target, and BP goal (supplementary Text 1). Reference lists from identified trials and review articles were manually scanned to identify any other relevant studies. Recent meta-analyses from major medical journals [7–16] were also considered for further information regarding studies of interest.

Selection criteria and data extraction

We selected studies that met the following inclusion criteria: (1) randomized controlled trial (RCT) that assigned participants to intensive versus usual BP-lowering treatment with different BP targets; (2) participants aged 18 years and over; (3) published in the English or Japanese language; (4) clear description of baseline characteristics, mean reduction in BP during the trial, outcome events, and inclusion and exclusion criteria; and (5) a follow-up duration of at least 6 months. Data were independently extracted by four reviewers from each study according to the selection criteria and entered onto a structured spreadsheet. We judged the risk of bias and study quality by evaluating trial procedures for randomization, concealment of treatment allocation, completeness of follow-up, and the use of an intention-to-treat analysis [25]. Drs. HS, NN, KY, and AS reviewed all the literature from the citations retrieved by titles or abstracts and subsequently by full text. Data were independently extracted from each study by two authors (HS and AS) and entered into a structured spreadsheet. Disagreements were resolved by consensus or by a third investigator (Dr. HA).

Outcome measures

The primary outcome of interest was major CV events (defined as fatal or non-fatal myocardial infarction, fatal or non-fatal stroke, heart failure, or CV death), and secondary outcomes were all-cause death, myocardial infarction, stroke, renal events including end-stage kidney disease, and adverse events including serious adverse effects.

Statistical analysis

We calculated the risk ratio (RR) and 95% confidence intervals (CIs) for each outcome of each trial before pooling. Pooled analyses were calculated using random-effects models with inverse variance weighting. For BP, we used the mean difference between the groups that received intensive versus usual BP-lowering treatment during the trial. We estimated the percentage of variability across studies attributable to heterogeneity beyond chance using the I^2 statistic [25, 26]. Significant heterogeneity was considered present for an I^2 value of $\geq 50\%$ [26]. The constancy of the results between subgroups defined by target BP category, achieved BP category, sample size, follow-up period, mean baseline age of the participants, mean baseline BP of the trials, or cohorts of patients was tested using chi-squared tests of heterogeneity. Publication bias was assessed using funnel plots. The Cochrane Collaboration meta-analysis software Review Manager 5.3 (available from The Cochrane Collaboration at http://www.cochrane.org) was used for the meta-analysis. A two-tailed P-value of < 0.05 was considered to be statistically significant.

Results

Description of included trials

Overall, 1411 screened citations met the search criteria. After excluding 101 duplicate citations, 1310 citations were screened. Most of these publications were rejected after reading the abstract. The remaining 63 publications were selected for full-text review, and 20 of these publications seemed appropriate for this systematic review (Fig. 1). The detailed analysis of these 20 publications [27–46] revealed 19 RCTs [27–45] from 20 publications that met the inclusion criteria. The Stop Atherosclerosis in Native Diabetic Study (SANDS) was not included in this meta-analysis

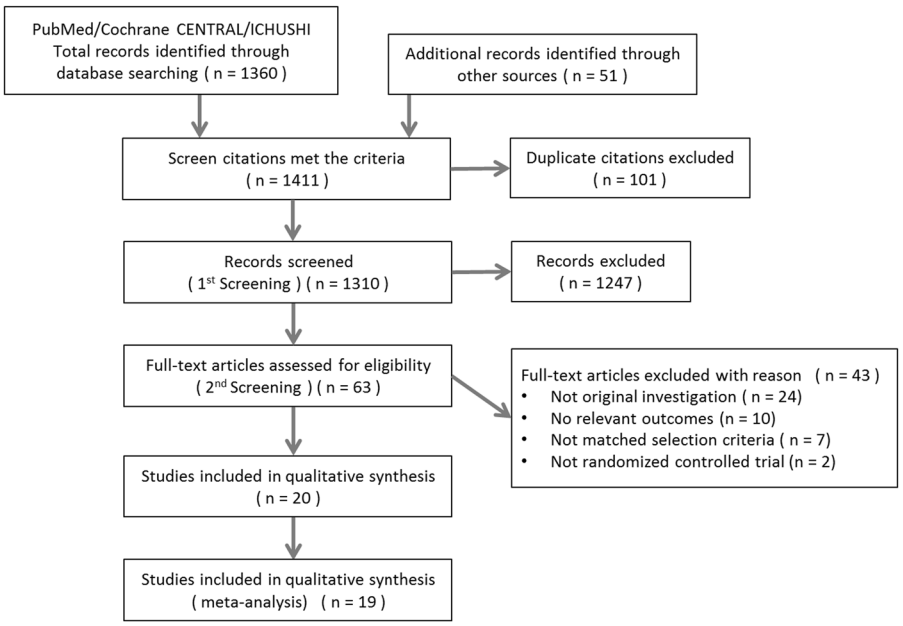

Fig. 1 Study selection. This flow chart summarizes the search results. A total of 332 citations were extracted from PubMed, 997 citations from Cochrane CENTRAL, 31 citations from ICHUSHI (Japanese), and 51 citations from additional records identified through other sources

because the dual intervention of BP-lowering and lipid-lowering treatment would not allow us to address the outcomes associated with a BP target [46]. Table 1 and supplementary Table 1 show the details of the 19 included RCTs. A total of 55,529 participants with 3146 major CV events (14 trials), 2370 all-cause deaths (19 trials), 1096 myocardial infarctions (12 trials), 1243 cases of stroke (13 trials), 539 cases of heart failure (8 trials), 1429 renal events (10 trials), and 9229 adverse events (7 trials) were extracted. Eighteen trials had an open-label design with very few patients lost to follow-up. One trial was a 2×2 factorial, randomized, double-blind placebo-controlled trial [28]. The range of follow-up was 1.6–12.2 years. The risk of bias varied substantially across the studies (supplementary Table 2).

Of the 19 RCTs, five trials enrolled only patients with DM [30–32, 36, 40], and 5 trials enrolled only patients with CKD [28, 33–35, 39]. Two trials recruited patients with DM but without hypertension [32, 36], and one of the CKD trials was conducted in patients with autosomal-dominant polycystic kidney disease [33]. Sixteen of the trials recruited mostly patients with hypertension and CV disease, or other risk factors [27–31, 34, 35, 37–45] (supplementary Table 1). The mean baseline BP levels in the 19 trials were between 123 and 171.6 mm Hg for systolic BP and between 76 and 105.4 mm Hg for diastolic BP. The mean follow-up BP level was 130.5/77.1 mm Hg in the intensive BP-lowering treatment group and 138.8/81.5 mm Hg in the usual group. The BP targets of the intensive BP-lowering treatment group and those of the usual group varied across the trials. Several trials had BP targets of < 140–50 mm Hg for systolic BP and < 85–90 mm Hg for diastolic BP in the intensive BP-lowering treatment group, whereas in other studies, systolic BP targets in the intensive BP-lowering treatment groups were 25–35 mm Hg below these levels. Four trials had a systolic BP target of < 130 mm Hg [35, 38, 42, 43], and seven trials had a diastolic BP target of < 80 mm Hg in the intensive BP-lowering treatment group [27, 31–33, 35, 36, 42]. Two trials had a BP target of < 92 mm Hg for mean arterial pressure, which is lower than the traditional BP target (< 130/80 mm Hg) for patients with CKD [34, 39]. Three trials had a systolic BP target of < 120 mm Hg in the intensive BP-lowering treatment group [33, 40, 45]. The mean follow-up BP was above the BP target in the intensive BP-lowering treatment group for 8 of the 19 trials. Overall, the mean follow-up difference in achieved BP between the intensive versus usual BP-lowering treatment groups was 8.3/4.4 mm Hg (Table 1).

Outcomes

The effects of intensive BP-lowering treatment on major CV events were available from 14 trials, which included a total of 55,529 participants and 3146 CV events. Intensive BP-lowering treatment reduced the risk of major CV events by 14% compared with the usual treatment, without evidence of major heterogeneity among the included studies (Table 2 and Fig. 2a). Myocardial infarction was reported in 12 trials that included a total of 52,509 participants in whom 1096 events were recorded. Intensive BP-lowering treatment reduced the risk of myocardial infarction by 13% compared with the usual treatment (Table 2 and Fig. 2b). Stroke was reported in 13 trials that included a total of 53,603 participants in whom 1243 events were recorded,

Table 1 Baseline characteristics of the patients in the trials included in the meta-analysis

Trials	Year	Follow-up (years)	Sample size (*n*)	Baseline BP (mm Hg)	BP target (mm Hg)		Achieved BP (mm Hg)		BP difference (mm Hg)	
					Intensive Tx	Usual Tx	Intensive Tx	Usual Tx	SBP	DBP
BBB [27]	1994	4.9	2127	155/94.5	DBP < 80	DBP 80–100	141/83	152/91	-11	-8
Toto et al. [28]	1995	3.4	77	123/76	DBP 65–80	DBP 85–95	133/81	138/87	-5	-6
HOT [29]	1998	3.8	18,790	159.3/105.4	DBP ≤ 80	DBP ≤ 85, ≤ 90	139.7/81.1	142.5/84.2	-2.8	-3.1
UKPDS38 [30]	1998	8.4	1148	169.7/94.0	< 150/85	< 180/105	144/82	154/87	-10	-5
ABCD(H) [31]	2000	5	470	155/98	DBP < 75	DBP 80–89	132/78	138/86	-6	-8
ABCD(N) [32]	2002	5.3	480	136.4/84.4	DBP ≤ 70–79	DBP 89–89	128/75	137/81	-9	-6
Schrier et al. [33]	2002	7	75	142.5/95.5	< 120/80	135–140/80–90	119.4/77	130.5/82.1	-11.1	-5.1
MDRD [34]	2005	2.2	840	130.5/80.0	MAP < 92	MAP < 107	126.2/76.9	133.8/80.7	-7.6	-3.8
REIN-2 [35]	2005	1.6	335	136.7/84.1	< 130/80	DBP < 90	129.6/79.5	133.7/82.3	-4.1	-2.8
ABCD(2V) [36]	2006	2	129	126/84	DBP < 75	DBP 80–90	118/75	124/80	-6	-5
JATOS [37]	2008	2	4418	171.6/89.1	SBP < 140	SBP < 160	135.9/74.8	145.6/78.1	-9.7	-3.3
Cardio-Sis [38]	2009	2	1111	163/89.6	SBP < 130	SBP < 140	136/79.2	139.8/80.8	-3.8	-1.5
AASK [39]	2010	8.8–12.2	1094	150.5/95.5	MAP ≤ 92	MAP 102–107	128/78	141/85	-13	-7
ACCORD [40]	2010	4.7	4733	139.2/76.0	SBP < 120	SBP < 140	119.3/64.4	133.5/70.5	-14.2	-6.1
VALISH [41]	2010	2.85	3079	169.6/81.4	SBP < 140	SBP 140- < 150	136.6/74.8	142/76.5	-5.4	-1.7
HOMED-BP [42]	2012	5.31	3518	151.6/89.95	125/80 <	125–134/80–84	128.8/76.1	130.4/76.8	-1.6	-0.8
SPS3 [43]	2013	3.7	3020	143/78.5	SBP < 130	SBP 130–149	SBP 127	SBP 138	-11	N/A
Wei et al. [44]	2013	4	724	159.5/84.2	≤ 140/90	≤ 150/90	135.7/76.2	149.7/82.1	-14	-5.9
SPRINT [45]	2015	3.26	9361	139.7/78.1	SBP < 120	SBP < 140	121.5/75.4	134.6/76.2	-13.1	-0.8

AASK African American Study of Kidney Disease and Hypertension Trial, *ABCD* Appropriate Blood Pressure Control in Diabetes Trial, *ACCORD* Action to Control Cardiovascular Risk in Diabetes Trial, *BP* blood pressure, *BBB* Behandla Blodtryck Bättre study, *Cardio-Sis* Studio Italiano Sugli Effetti CARDIOvascolari del Controllo della Pressione Arteriosa SIStolica, *DBP* diastolic blood pressure, *HOME-BP* Hypertension Objective Treatment Based on Measurement by Electrical Devices of Blood Pressure, (*H*) hypertensive cohort, *HOT* Hypertension Optimal Treatment Study, *JATOS* Japanese Trial to Assess Optimal Systolic Blood Pressure in Elderly Hypertensive Patients, *MAP* mean arterial pressure, *MDRD* Modification of Diet in Renal Disease Trial, (*N*) normotensive cohort, *REIN-2* Rampiril Efficacy in Nephropathy-2, *SBP* systolic blood pressure, *SPS3* Secondary Prevention of Small Subcortical Stroke trial, *SPRINT* Systolic Blood Pressure Intervention Trial, (*2V*) valsartan treatment in normotensive cohort, *UKPDS* United Kingdom Prospective Diabetes Study, *VALISH* Valsartan in Elderly Isolated Systolic Hypertension Study

Table 2 Effects of intensive blood pressure-lowering treatment on the risk of the seven outcomes

Outcomes	Trials (*n*)	BP difference (mm Hg)	Events/patients (*n*)		Risk ratio (95% CI)	Heterogeneity (%)		Test for overall effect	
			Intensive Tx	Usual Tx		I^2	*P*-value	*Z*	*P*-value
Major cardiovascular events	14	-8.9/-4.2	1384/23,905	1762/29,827	0.86 (0.78–0.94)	36	0.09	3.17	0.002
All-cause death	19	-8.3/-4.4	1086/24,824	1284/30,705	0.93 (0.82–1.06)	48	0.01	1.06	0.29
Myocardial infarction	12	-8.8/-3.8	505/23,299	591/29,210	0.87 (0.77–0.98)	0	0.98	2.34	0.02
Stroke	13	-9.1/-4.6	516/23,839	727/29,764	0.78 (0.68–0.90)	28	0.16	3.32	0.0009
Heart failure	8	-10.9/-4.5	244/11,708	295/11,361	0.76 (0.56–1.03)	58	0.02	1.78	0.08
Renal events	10	-9.3/-4.2	761/12,777	668/12,383	1.19 (0.91–1.55)	81	< 0.00001	1.30	0.20
Adverse events	7	-8.8/-2.7	4848/13,023	4381/13,034	1.13 (0.98–1.30)	94	< 0.0001	1.66	0.10

BP blood pressure, *CI* confidence interval, *DBP* diastolic blood pressure, *SBP* systolic blood pressure, *Tx* treatment

and intensive BP-lowering treatment reduced the risk of stroke by 22% compared with the usual treatment (Table 2 and Fig. 2c). A funnel plot analysis showed no obvious evidence of publication bias for the outcomes (Fig. 3). This meta-analysis showed no clear effect of intensive BP-lowering treatment on the risk of all-cause death compared with the usual treatment (Table 2).

Heart failure was reported in eight trials, which included 23,069 participants in whom 539 events were recorded. The trend for the risk reduction of heart failure in the intensive BP-lowering treatment group compared with that in the usual group was not significant, but there was significant heterogeneity among the included studies (Table 2). Renal events were reported in 10 trials that included a total of 25,160 participants, in whom 1429 events were recorded. Compared with the usual treatment, intensive BP-lowering treatment did not significantly affect the renal events, but there was significant heterogeneity among the included studies (Table 2). Adverse events were reported in seven trials that included a total of 26,057 participants, in whom 9229 events were recorded. Although the data of adverse effects were potentially associated with BP-lowering treatment, a trend for the risk of adverse events in the intensive BP-lowering treatment group was not significant, but there was significant heterogeneity among the included studies (Table 2).

In accordance with the baseline characteristics of the trials, we evaluated the observed beneficial effects of intensive BP-lowering treatment on major CV events. Intensive BP-lowering treatment reduced the risk of major CV events by 23% in the subgroup with a mean baseline age of ≥ 65 years, and by 10% in the subgroup with a mean baseline age of < 65 years (Table 3). Intensive BP-lowering treatment reduced the risk of major CV events by 13% in the subgroup with a mean baseline BP of ≥ 140/90 mm Hg, and by 16% in the subgroup with a mean baseline BP of < 140/90 mm Hg (Table 3). Intensive BP-lowering treatment reduced the risk of major CV events by 16% in the cohort of patients with DM, and by 13% in the population of patients with no or concomitant DM (Table 3). Intensive BP-lowering treatment reduced the risk of major CV events by 16% in the subgroup with a follow-up period of < 4 years. The trend for the risk reduction of major CV events in the subgroup with a follow-up period of ≥ 4 years in the intensive BP-lowering treatment group compared with that in the usual group was not significant, but there was significant heterogeneity among the included studies. The median follow-up period of the Systolic Blood Pressure Intervention Trial (SPRINT) was 3.26 years of the planned average of 5 years [45]. This may have affected the results of the subgroup analysis (Table 3). There was no significance in that the beneficial effect of intensive BP-lowering treatment on CV events varied based on the sample size, follow-up period, mean baseline age of the participants, mean baseline BP of the trials, or cohorts of patients with DM (Table 3). As the available trials were limited, we did not evaluate intensive BP-lowering treatment on major CV events in the cohort of patients with CKD.

CV events in relation to lower BP targets

We conducted an exploratory evaluation of the effects of intensive BP-lowering treatment with different BP targets on major CV events (Table 4 and supplementary Figure 1A). There were comparable effects of intensive BP-lowering treatment across different target BP levels of < 140/90 mm Hg, < 130/80 mm Hg, and < 120/– mm Hg. However, there were only two trials available for intensive BP-lowering treatment with a target systolic BP level of < 120 mm Hg [40, 45]. Similar findings were observed for myocardial infarction (Table 5 and supplementary

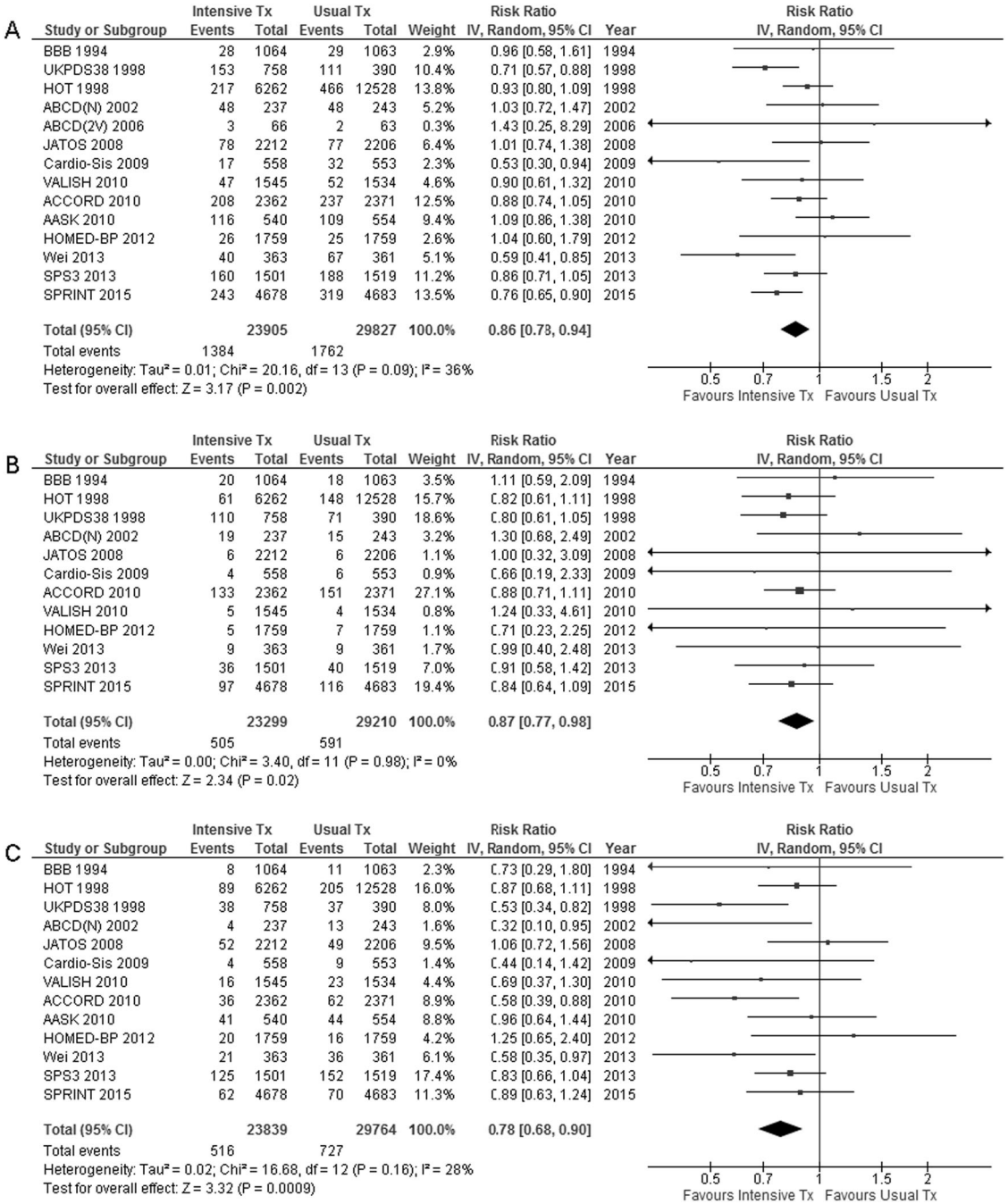

Fig. 2 Effects of intensive blood pressure-lowering treatment on the risk reduction of major CV events, myocardial infarction, and stroke. **a** Major CV event data were available from 14 trials that included a total of 55,529 participants and 3146 CV events. Intensive BP-lowering treatment reduced the risk of major CV events compared with the usual treatment (RR (95% CI) = 0.86 (0.78–0.94)). **b** Myocardial infarction data were available from 12 trials that included a total of 52,509 participants and 1096 events. Intensive BP-lowering treatment reduced the risk of myocardial infarction compared with the usual treatment (RR (95% CI) = 0.87 (0.77–0.98)). **c** Stroke data were available from 13 trials that included a total of 53,603 participants and 1243 events. Intensive BP-lowering treatment reduced the risk of stroke compared with the usual treatment (RR (95% CI) = 0.78 (0.68–0.90)). CI confidence interval, CV cardiovascular, IV inverse variance, RR risk ratio

Figure 2A) and stroke, although separately, significant benefits were not observed for intensive BP-lowering treatment with a target systolic BP level of < 120 mm Hg (Table 6 and supplementary Figure 3A).

CV events in relation to achieved BPs

We also evaluated the effects of intensive BP-lowering treatment with different achieved BPs on major CV events.

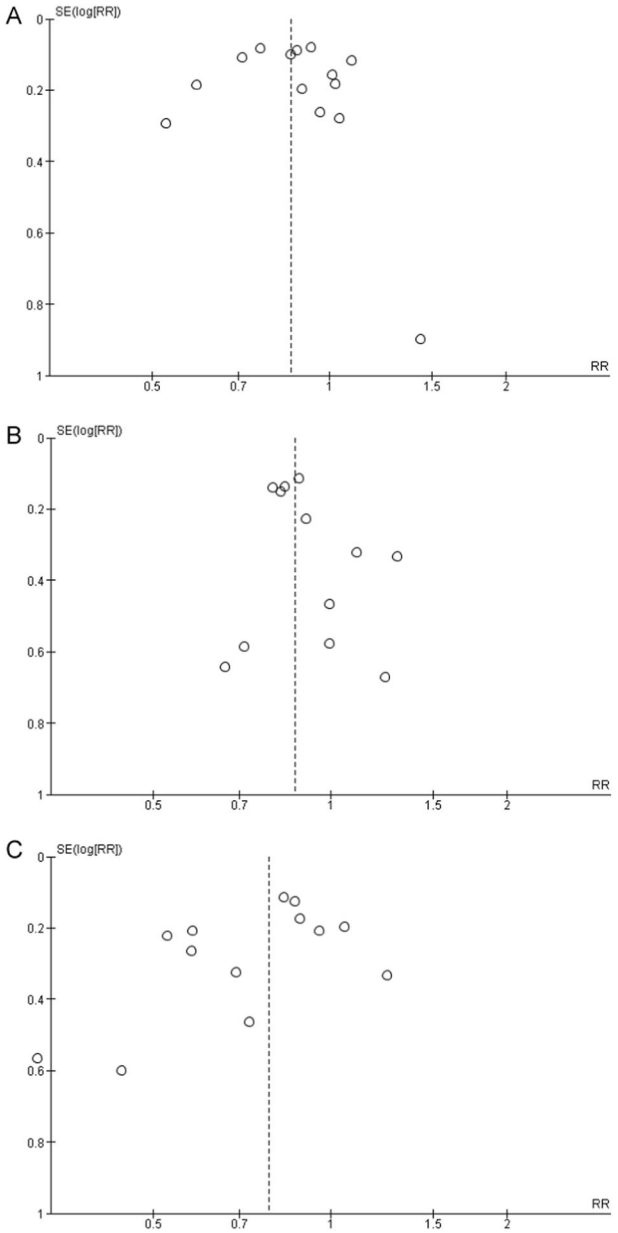

Fig. 3 Funnel plots of the effects of intensive blood pressure-lowering treatment on major CV events, myocardial infarction, and stroke. **a** Major CV events; **b** Myocardial infarction; **c** Stroke. RR risk ratio, SE standard error

There were comparable effects of intensive BP-lowering treatment across different achieved BP levels of < 140/90 mm Hg and < 130/80 mm Hg, although separately, significant benefits were not observed for intensive BP-lowering treatment with an achieved systolic BP level of < 120 mm Hg (Table 4 and supplementary Figure 1B). However, there were only two trials available for intensive BP-lowering treatment with an achieved systolic BP level of < 120 mm Hg [32, 40]. There were comparable effects of intensive BP-lowering treatment across different achieved BPs of < 140/90 mm Hg, < 130/80 mm Hg, and < 120/– mm Hg for myocardial infarction (Table 5 and supplementary Figure 2B) and stroke, and separately, borderline benefits were observed for intensive BP-lowering treatment with an achieved systolic BP level of < 130/80 mm Hg (Table 6 and supplementary Figure 3B). However, there was only one trial available for intensive BP-lowering treatment with an achieved systolic BP of < 120 mm Hg [40].

Discussion

In this meta-analysis of 19 RCTs that assigned participants to intensive versus usual BP-lowering treatment with different BP targets [27–45] and enrolled a total of 55,529 participants with a mean follow-up duration ranging from 1.6 to 12.2 years, we examined the risk of major CV events, all-cause mortality, myocardial infarction, stroke, heart failure, renal events, and adverse events. We showed that intensive BP-lowering treatment significantly reduced the risk of major CV events, myocardial infarction, and stroke, and had a borderline benefit for a reduction of the risk of heart failure. A trend for the increased risk of adverse events in the intensive BP-lowering treatment group was not significant compared with the usual treatment group. Intensive BP-lowering treatment did not have a significant benefit for all-cause mortality or renal events. To clarify whether an optimal BP target for antihypertensive therapy could be recommended, we performed an exploratory evaluation of the effects of intensive BP-lowering treatment with different BP targets on major CV events. There were comparable effects of intensive BP-lowering treatment across different target BP levels of < 140/90 mm Hg, < 130/80 mm Hg, and < 120/– mm Hg. However, the systolic BP target of < 120 mm Hg had a significant increase in the risk of adverse events in patients with DM [40]. We also evaluated the effects of intensive BP-lowering treatment with different achieved BPs on major CV events. There were comparable effects of intensive BP-lowering treatment across different achieved BP levels of < 140/90 mm Hg, < 130/80 mm Hg, and < 120/– mm Hg, although separately, significant benefits were not observed for an achieved systolic BP level of < 120 mm Hg. The results of this meta-analysis indicate that a target BP level of < 130/80 mm Hg appears to be optimal for CV protection in patients with hypertension.

Although the meta-analyses used different methods to examine the threshold at which the benefit of BP-lowering treatment for the prevention of CV events differed by baseline BP levels, target BP levels for antihypertensive therapy, achieved BP levels, age categories (such as elderly), and comorbidities (such as DM), the current meta-analysis is mostly in agreement with the findings of recent meta-analyses [12, 16]. Overall, the meta-analyses showed that the lower BP target compared with any higher BP target

Table 3 Effects of intensive blood pressure-lowering treatment on the risk of major cardiovascular events in subgroups

Baseline characteristics	Trials (*n*)	BP difference (mm Hg)	Events/patients (*n*)		Risk ratio (95% CI)	Heterogeneity (%)		Test for overall effect		*P* heterogeneity
			Intensive Tx	Usual Tx		I^2	*P*-value	*Z*	*P*-value	*P*-value
Sample size										0.769
$n \geq 1000$	11	-8.7/-4.2	1293/23,239	1645/29,160	0.87 (0.79–0.95)	33	0.14	3.01	0.003	
$n < 1000$	3	-9.7/-4.3	91/666	117/667	0.81 (0.51–1.30)	59	0.09	0.86	0.39	
Follow-up period										0.908
≥ 4 years	7	-10.4/-5.5	619/7083	626/6741	0.87 (0.74–1.03)	53	0.05	1.67	0.10	
< 4 years	7	-7.4/-2.6	765/16,822	1136/23,086	0.86 (0.77–0.95)	18	0.30	2.86	0.004	
Mean age at baseline										0.153
≥ 65 years	5	-9.2/-2.1	425/9356	547/9337	0.77 (0.63–0.93)	44	0.13	2.66	0.008	
< 65 years	9	-8.7/-5.4	959/14,549	1215/20,490	0.90 (0.82–0.98)	12	0.34	2.31	0.02	
Mean BP at baseline (mm Hg)										0.796
≥ 140/90	10	-8.2/-4.4	882/16,562	1156/22,467	0.86 (0.76–0.98)	46	0.06	2.31	0.02	
< 140/90	4	-10.6/-3.8	502/7343	606/7360	0.84 (0.74–0.95)	6	0.36	2.88	0.004	
Population										0.743
100% Diabetes mellitus, yes	4	-9.8/-4.9	412/3423	398/3067	0.84 (0.71–1.00)	30	0.23	2.01	0.04	
Diabetes mellitus, no or mixture	10	-8.5/-4.0	972/20,482	1364/26,760	0.87 (0.77–0.98)	42	0.08	2.36	0.02	

BP blood pressure, *CI* confidence interval, *DBP* diastolic blood pressure, *SBP* systolic blood pressure, *Tx* treatment

Table 4 Effects of intensive blood pressure-lowering treatment on the risk of major cardiovascular events in the blood pressure categories

BP categories (mm Hg)	Trials (*n*)	BP difference (mm Hg)	Events/patients (*n*)		Risk ratio (95% CI)	Heterogeneity (%)		Test for overall effect		*P* heterogeneity
			Intensive Tx	Usual Tx		I^2	*P*-value	*Z*	*P*-value	*P*-value
Target BP in intensive group										0.602
SBP < 140 and/or DBP < 90	12	-8.4/-3.9	1191/22,784	1191/22,784	0.89 (0.83–0.97)	8	0.36	2.77	0.006	
SBP < 130 and/or DBP < 80	9	-9.2/-4.4	849/12,765	989/12,808	0.88 (0.79–0.99)	26	0.21	2.19	0.03	
SBP < 120	2	-13.7/-3.5	451/7040	451/7040	0.82 (0.71–0.94)	28	0.24	2.83	0.005	
Achieved BP in intensive group										0.986
SBP < 140 and/or DBP < 90	12	-8.6/-3.7	1203/22,083	1203/22,083	0.88 (0.80–0.97)	33	0.12	2.63	0.009	
SBP < 130 and/or DBP < 80	7	-9.7/-4.3	804/11,143	804/11,143	0.89 (0.80–0.99)	22	0.26	2.08	0.04	
SBP < 120	2	-10.1/-5.6	211/2428	211/2428	0.89 (0.74–1.06)	0	0.59	0.18	0.18	

BP blood pressure, *CI* confidence interval, *DBP* diastolic blood pressure, *SBP* systolic blood pressure, *Tx* treatment

has a benefit for the reduction of the risk of major CV events, myocardial infarction, stroke, and/or heart failure [7–16]. However, no meta-analysis clarified a significant benefit for renal events for the lower BP target compared with any higher BP target.

The optimal BP targets in patients with hypertension have been elusive. A meta-analysis of 61 prospective observational studies in adults with no previous major CV disease showed that the association of BP with the risk for CV events is linear at a BP level of 115/75 mm Hg [1]. Clinical trials suggest that antihypertensive treatment for people ≥ 80 years of age may reduce mortality and CV events [47]; however, nonrandomized epidemiological studies generally associate low BP with higher mortality in elderly people [48–50]. A recent longitudinal analysis of patients' BP records revealed that a terminal decline occurs in systolic BP in the 2 years before death, not accounting for frailty status, sex, or antihypertensive therapy [51]. Delgado et al. retrospectively examined the association between BP trajectory and death in 46,634 participants from the primary care database who were at least 60 years of age at the time of death, and showed that systolic and diastolic BPs decreased for more than a decade before death in patients who died at age 60 or older. These BP decreases were not simply attributable to age, antihypertensive therapy, or better survival without hypertension [52]. These two observations may account for the discrepancy between randomized and nonrandomized studies of BP and mortality in elderly people or illness. Reverse causation may apply if values of lower systolic BP result from the end of life [51, 52]. Therefore, a nonrandomized data-based recommendation of BP targets may not be suitable for antihypertensive therapy.

Several RCTs tried to answer the critical clinical question of whether a systolic BP target of < 120 mm Hg or one of < 130 mm Hg could reduce major CV and renal events more than a standard BP target in patients with hypertension or in a high-risk population [33, 35, 38, 40, 42, 43, 45]. Of these, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial failed to reduce major CV events with the exception of stroke in patients with DM who were assigned an intensive systolic BP target of < 120 mm Hg, compared with patients assigned an intensive systolic BP target of < 140 mm Hg [40]. The SPRINT of patients without DM showed a benefit of a systolic BP target of < 120 mm Hg for the primary composite CV events and all-cause death, compared with the usual systolic BP target of < 140 mm Hg [45]. In the pre-SPRINT era, the benefit of intensive BP targets for antihypertensive therapy was controversial. For example, a meta-analysis of hypertensive patients with type 2 DM or impaired glucose tolerance demonstrated that a systolic

Table 5 Effects of intensive blood pressure-lowering treatment on the risk of myocardial infarction in the blood pressure categories

BP categories (mm Hg)	Trials (*n*)	BP difference (mm Hg)	Events/patients (*n*)		Risk ratio (95% CI)	Heterogeneity (%)		Test for overall effect		*P* heterogeneity
			Intensive Tx	Usual Tx		I^2	*P*-value	*Z*	*P*-value	*P*-value
Target BP in intensive group										0.957
SBP < 140 and/or DBP < 90	10	-8.2/-3.5	386/22,178	511/28,459	0.88 (0.78–1.01)	0	0.97	1.83	0.07	
SBP < 130 and/or DBP < 80	7	-9.1/-3.9	314/12,159	353/12,191	0.89 (0.77–1.04)	0	0.89	1.47	0.14	
SBP < 120	2	-13.7/-3.5	230/7040	267/7054	0.86 (0.73–1.03)	0	0.76	1.66	0.10	
Achieved BP in intensive group										0.993
SBP < 140 and/or DBP < 90	10	-8.5/-3.2	375/21,477	502/27,757	0.88 (0.77–1.00)	0	0.98	1.92	0.05	
SBP < 130 and/or DBP < 80	5	-9.8/-3.4	290/10,537	329/10,575	0.89 (0.76–1.03)	0	0.80	1.52	0.13	
SBP < 120	1	-14.2/6.1	133/2362	151/2371	0.88 (0.71–1.11)	NA	NA	1.07	0.29	

BP blood pressure, *CI* confidence interval, *DBP* diastolic blood pressure, *NA* not applicable, *SBP* systolic blood pressure, *Tx* treatment

Table 6 Effects of intensive blood pressure-lowering treatment on the risk of stroke in the blood pressure categories

BP categories (mm Hg)	Trials (*n*)	BP difference (mm Hg)	Events/patients (*n*)		Risk ratio (95% CI)	Heterogeneity (%)		Test for overall effect		*P* heterogeneity
			Intensive Tx	Usual Tx		I^2	*P*-value	*Z*	*P*-value	*P*-value
Target BP in intensive group										0.781
SBP < 140 and/or DBP < 90	11	-8.6/-3.8	457/22,718	654/29,013	0.84 (0.73–0.95)	10	0.35	2.67	0.008	
SBP < 130 and/or DBP < 80	8	-9.6/-4.3	300/12,699	377/12,745	0.80 (0.66–0.97)	23	0.25	2.32	0.02	
SBP < 120	2	-13.7/-3.5	98/7040	132/7054	0.73 (0.48–1.10)	58	0.12	1.50	0.13	
Achieved BP in intensive group										0.283
SBP < 140 and/or DBP < 90	11	-8.9/-3.6	470/22,017	679/28,311	0.82 (0.71–0.94)	22	0.23	2.78	0.005	
SBP < 130 and/or DBP < 80	6	-10.3/-4.1	288/11,077	357/11,129	0.81 (0.66–1.01)	37	0.16	1.90	0.06	
SBP < 120	1	-14.2/-6.1	36/2362	62/2362	0.58 (0.39–0.88)	NA	NA	2.60	0.009	

BP blood pressure, *CI* confidence interval, *DBP* diastolic blood pressure, *NA* not applicable, *SBP* systolic blood pressure, *Tx* treatment

BP target of < 120 mm Hg was better for stroke, but not for other vascular events, and that a lower BP target increased the risk of serious adverse events [53]. A meta-analysis of antihypertensive therapy in patients with coronary artery disease showed that intensive BP-lowering treatment of ≤ 135 mm Hg reduced the risk of heart failure and stroke, but increased the risk of hypotension and had no benefit for all-cause death or CV death [54]. Therefore, major hypertension guidelines such as the National Institute for Health and Clinical Excellence (NICE) hypertension guideline, the ESH/ESC hypertension guideline, and the Eighth Joint National Committee Hypertension Guideline (JNC8) recommended a BP target of < 140/90 mm Hg [17–19], and JNC8 recommended a BP goal of < 150/90 mm Hg in treating hypertensive patients ≥ 60 years of age [19]. However, in the post-SPRINT era, the results of recent meta-analyses have shown that intensive BP targets compared with standard BP targets significantly reduced the risk of several clinical outcomes, including the risk of major CV events, myocardial infarction, stroke, and/or heart failure [7–16]. Of these, three meta-analyses demonstrated the benefit of a systolic BP target of < 130 mm Hg for a reduction in the risk of CV outcomes [10, 12, 16]. A meta-analysis of intensive versus standard BP targets in patients with hypertension showed that a systolic BP target of < 130 mm Hg reduced the risk of major CV events by 17% and that of stroke by 18% [16]. In a meta-analysis of the effect of antihypertensive treatment on mortality and CV morbidity in patients with DM, Brunström et al. reported that an achieved systolic BP of < 130 mm Hg reduced the risk of stroke by 35% [10]. In a network meta-analysis of RCTs comparing treatments with different BP categories, Bangalore et al. showed that an achieved systolic BP of < 120 mm Hg and that of < 130 mm Hg ranked #1 and #2 as the most efficacious BP levels for CV events, whereas an achieved systolic BP of < 140 mm Hg and that of < 150 mm Hg ranked #1 and #2 as the safest BP levels for serious adverse events, and an achieved systolic BP of < 130 mm Hg had the optimal balance between efficacy and safety [12]. The results of our meta-analysis are mostly in agreement with the findings of these meta-analyses. We have shown a benefit of a BP target of < 130/80 mm Hg for a reduction in the risk of CV events in patients with hypertension. Recently, the 2017 ACC/AHA hypertension guideline recommended a BP target of < 130/80 mm Hg for hypertensive patients [20], and the 2017 ACC/AHA/HFSA guideline for the management of heart failure also recommended a BP target of < 130/80 mm Hg for patients with heart failure [21].

This meta-analysis has several limitations. First, without access to individual patient data, the results of this meta-analysis are limited by unpublished data. Second, there were many differences in sample sizes, baseline BP, follow-up periods during which the studies were conducted, age categories (such as elderly people), comorbidities (such as DM or CKD), and the study designs—including differences in the BP targets for antihypertensive therapy, in the methods for BP measurements such as office BP, home BP, or automated office BP, and in medication use—among each study that may have limited our study in clarifying the benefits of intensive BP-lowering treatment for clinical outcomes. Third, the definition of clinical outcomes also varied by each study. This may lead to a significant heterogeneity of the outcomes from the included studies, such as heart failure, renal events, and adverse events, and under- or overestimate the significance of intensive BP-lowering treatment. Fourth, the individual adverse effects of each intervention were not routinely reported in all of the RCTs. Adverse events were available in only seven RCTs [35, 37, 38, 40, 41, 43, 45]. Although the adverse event data were potentially associated with BP-lowering treatment, there was no suggestion that these adverse effects would exceed the benefits of BP-lowering treatment. We need more evidence regarding the balance between the benefits and harms of BP-lowering treatment for clinical outcomes. Finally, although a BP target of < 130/80 mm Hg for antihypertensive therapy may be optimal in general, we do not have a definite answer as to the optimal BP target for each population, such as patients with DM, CKD, or elderly people ≥ 65 years of age.

In conclusion, this meta-analysis of RCTs that assigned participants to intensive versus usual BP-lowering treatment with different BP targets suggests that intensive BP-lowering treatment reduces the risk of major CV events, myocardial infarction, and stroke in patients with hypertension. We propose that a lower BP target of < 130/80 mm Hg is optimal for CV protection.

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Compliance with ethical standards

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

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