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Review

Role of Blood Pressure Management in Stroke Prevention: A Systematic Review and Network Meta-Analysis of 93 Randomized Controlled Trials

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Background and Purpose The present study aimed to compare the efficacy and tolerability of different blood pressure (BP)-lowering strategies.

Methods Randomized controlled trials that compared various antihypertensive treatments and stroke outcomes were included. Eligible trials were categorized into three scenarios: single or combination antihypertensive agents against placebos; single or combination agents against other agents; and different BP-lowering targets. The primary efficacy outcome was the risk reduction pertaining to strokes. The tolerability outcome was the withdrawal of drugs, owing to drug-related side effects (PROSPERO registration number CRD42018118454 [20/12/2018]).

Results The present study included 93 trials (average follow-up duration, 3.3 years). In the pairwise analysis, angiotensin-converting enzyme inhibitors (ACEis) and beta-blockers (BBs) were inferior to calcium channel blockers (CCBs) (odds ratio [OR], 1.123; 95% confidence interval [CI], 1.008 to 1.252) (OR, 1.261; 95% CI, 1.116 to 1.425) for stroke prevention, BB was inferior to angiotensin II receptor blockers (ARB) (OR, 1.361; 95% CI, 1.142 to 1.622), and diuretics were superior to ACEi (OR, 0.871; 95% CI, 0.771 to 0.984). The combination of ACEi+CCB was superior to ACEi+diuretic (OR, 0.892; 95% CI, 0.823 to 0.966). The network meta-analysis confirmed that diuretics were superior to BB (OR, 1.34; 95% CI, 1.11 to 1.58), ACEi+diuretic (OR, 1.47; 95% CI, 1.02 to 2.08), BB+CCB (OR, 2.05; 95% CI, 1.05 to 3.79), and renin inhibitors (OR, 1.87; 95% CI, 1.25 to 2.75) for stroke prevention. Regarding the tolerability profile, the pairwise analysis revealed that ACEi was inferior to CCB and less tolerable, compared to the other treatments.

Conclusions Monotherapy using diuretics, CCB, or ARB, and their combinations could be employed as first-line treatments for stroke prevention in terms of efficacy and tolerability.

Keywords Antihypertensive agents; Stroke; Meta-analysis

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Introduction

Stroke is a leading cause of morbidity and mortality across the globe. In 2017, stroke was the second most frequent cause of death, after ischemic heart disease, and caused 6.2 million deaths worldwide.[1] Moreover, hypertension is a leading cause of stroke and the significance of blood pressure (BP) lowering in stroke prevention is already established in literature.[2] Considering the high prevalence of stroke, achievement of the most appropriate or ideal BP could have a significant impact on public health.

A recent meta-analysis reported that the reduction in systolic blood pressure (SBP) by 10 mm Hg was associated with a 27% reduction in the risk associated with stroke.[3] Moreover, the magnitude of reduction in BP was linearly associated with the extent of risk reduction pertaining to recurrent strokes.[4] A systematic review of the 2017 American College of Cardiology (ACC)/American Heart Association (AHA)/American Academy of Physician Assistants (AAPA)/Association of Black Cardiologists (ABC)/American College of Preventive Medicine (ACPM)/American Geriatrics Society (AGS)/American Pharmacists Association (APhA)/American Society of Hematology (ASH)/American Society for Preventive Cardiology (ASPC)/National Medical Association (NMA)/Preventive Cardiovascular Nurses Association (PCNA) guidelines for the prevention, detection, evaluation, and management of high BP in adults (the 2017 high BP guidelines) has recommended intensive BP-lowering treatments (to a target of below 130 mm Hg) other than the standard antihypertensive therapies.[5] However, despite the well-established and widespread use of BP-lowering agents for the prevention of stroke, the most appropriate treatments pertaining to various populations are still under debate. A meta-analysis published in 2016 demonstrated that calcium channel blockers (CCBs) were superior to other drugs for the prevention of stroke in the general population.[3] A systematic review of the 2017 high BP guidelines employed network meta-analysis and reported that thiazides and thiazide-like diuretics (THZs) were associated with a significantly lower risk of stroke in patients with hypertension.[5] Another meta-analysis reported that CCBs were at least as effective as the other first-line antihypertensive agents in the management of hypertensive patients with a previous history of stroke.[6] Nevertheless, previous meta-analyses have rarely involved the comprehensive analysis of the most appropriate antihypertensive agents for different target populations. Moreover, previous meta-analyses did not consider the tolerability and safety profiles pertaining to the antihypertensive strategies. Furthermore, combined antihypertensive strategies were recommended by several guidelines, in order to achieve better BP control and to slow the progression of hypertension. However, previous studies provided limited evidence on the efficacy of combined antihypertensive therapies in stroke prevention.

Traditional meta-analysis could only compare the treatments assessed in the same study, whereas network meta-analysis could compare multiple treatments from different studies through common comparators. Consequently, several treatments could be ranked.[7,8] Hence, the present study performed a network meta-analysis to compare the efficacy and tolerability profiles of both single and combined antihypertensive strategies for stroke prevention in different populations.

Methods

Search strategy and selection criteria

The present meta-analysis adhered to the preferred reporting items for systematic reviews and meta-analysis PRISMA) statement[9] and the PRISMA network meta-analysis extension statement.[10] The current study used an existing strategy[11] with additional items, such as cerebrovascular disorders, stroke, brain infarction, cerebral infarction, brain ischemia, cerebral hemorrhage, or intracranial hemorrhage, in order to identify the relevant trials from the Pubmed database, published during the time period from January 1, 1966 to December 1, 2018. The detailed search terms are provided in Appendix 1. The present study restricted the search to randomized controlled trials (RCTs) alone without any language restrictions. The Cochrane Collaboration database was also searched. Furthermore, in order to identify eligible studies, the present study performed a manual inspection of the reference list pertaining to the studies included in the review. Subsequently, a manual examination was performed to ascertain whether each trial reported stroke as a primary or secondary outcome. Studies that fulfilled the following criteria were included in the current meta-analysis: (1) RCTs; (2) greater than 1,000 patient-years of follow-up in each study group; (3) trials that reported stroke as the primary or secondary outcome; and (4) trials that used antihypertensive drugs for indications other than the management of hypertension such as proteinuria. Eligible trials were extracted and categorized into three scenarios: single, or a combination antihypertensive agents against placebos, single, or combination agents against others, and different BP-lowering targets. Trials that documented the presence of baseline comorbidities were not excluded.

Data extraction and quality assessment

The literature search, data extraction, and quality assessment were performed independently by two researchers (X.L.Z. and Y.D.). In case of disagreements, consensus was achieved through

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the referral to a third reviewer (J.T.Y.). Data were extracted into specially designed Excel sheets that listed the baseline characteristics pertaining to each group, which is provided in Supplementary Table 1.

The primary efficacy outcome was measured by the incidence of stroke. Outcomes of interest were all-cause mortality, cardiovascular-related deaths, all strokes (fatal or nonfatal), fatal or disabling stroke, ischemic stroke, and hemorrhagic stroke by groups. The tolerability outcome was measured by the withdrawal, owing to drug-related side effects.

The quality of each study was critically appraised by the two researchers who performed the literature review, on the basis of a 7-point tool, in order to assess the risk of bias using the Cochrane Collaboration tool.[12]

Statistical analysis

The present study performed the meta-analysis in two steps. First, a traditional meta-analysis was performed to clarify the effects of antihypertensive agents on the odds ratio (OR) of various outcomes. Second, a pairwise and network analysis was performed to compare the efficacy and tolerability of all antihypertensive agents in stroke prevention.

Effects of BP-lowering for various outcomes

In this step, the present study combined the trials involving antihypertensive agents versus placebos and higher versus lower BP-lowering targets, and performed a traditional meta-analysis. The OR was estimated from the number of events and participants pertaining to each outcome in each trial and pooled results with the Mantel-Haenszel and Hartung-Knapp adjustment for random effects models. The magnitude of the statistical heterogeneity among the studies was assessed using the standard Cochrane chi-square test. Subgroup analyses were stratified by age, history of stroke, cardiovascular disease, diabetes mellitus, baseline SBP levels, and achieved SBP level. Publication bias was evaluated both graphically using a funnel plot and using the Egger statistical test for funnel plot asymmetry,[13] if a minimum of 10 studies were available for each outcome. A leave-one-out sensitivity analysis was performed to determine whether any one study had a disproportionately large impact on the pooled OR.

Pairwise and network analysis of BP-lowering agents for stroke prevention

In this step, the current study included all the eligible trials and performed the pairwise and network meta-analysis. The primary outcome was measured as all types of stroke reduction and the tolerability outcome was assessed by the incidence of drug withdrawal, owing to drug-related side effects. First, a pairwise meta-analysis was performed with a random effects model to analyze direct treatment comparisons. Heterogeneity was assessed using the I^2 metric. Second, the present study analyzed the pooled data pertaining to all BP-lowering treatments with random effects models within a Bayesian framework in OpenBUGS (http://openbugs.net).[14] The details pertaining to the OpenBUGS codes that were used in the study are shown in Appendix 2. A valid network meta-analysis will satisfy the assumption of transitivity. Differences between the direct and indirect comparisons could suggest that the transitivity assumption might not hold. The present study assessed the evidence consistency in the networks in two ways. One was the node-split approach to contrast direct evidence with indirect evidence from the entire network on each node.[15-17] The other was the design-by-treatment interaction model that provided a single inference, using the chi-square test, regarding the plausibility of assuming consistency throughout the entire network.[18] The surface under the cumulative ranking curve (SUCRA) and rankograms were used to provide a hierarchy of the regimens.[19] The two-dimensional plots and clustering methods were conducted to obtain meaningful groups of the treatments.[20] In addition, the current study assessed the small study effects using comparison adjusted funnel plot symmetry.[20]

Sensitivity analyses

In order to examine the generalizability of the findings, the present study assessed for the effects of different trials and participant characteristics on the outcomes of sensitivity analyses by restricting the analyses to studies with the following design characteristics: hypertensive participants, no heart failure, published in or after 2000, and duration of follow-up of more than 3 years. The present study performed the subgroup analyses, in accordance with the age, history of stroke, history of diabetes, and baseline SBP. More details about the statistical analysis are shown in Supplementary methods.

Traditional meta-analyses were performed using R version 3.4.1 (R Foundation for Statistical Computing, Vienna, Austria) and network meta-analyses were performed using OpenBUGS 3.2.3 and STATA 14.0 (StataCorp., College Station, TX, USA).

Results

In the present study, a total of 93 RCTs met the inclusion criteria, which enrolled 504,613 participants with an average follow-up period of 3.3 years and provided sufficient data to be included in the traditional or network meta-analysis (Figure 1). Among the aforementioned studies, 66 were deemed to be tri-

als pertaining to the lowering of BP (52 compared a single BP-lowering agent against a placebo; 14 compared different BP-lowering targets) and they were included in the analysis to explore the association between the BP-lowering treatments and various outcomes. Among the 64 studies, 44 focused on patients above the age of 60 years. Four studies involved participants without any prior history of stroke and five studies included participants with a previous history of stroke. A total of 82 trials with 14 different BP-lowering strategies were included to compare the efficacy of the treatments. Six drug classes, alone or in combination, were compared with each other or the placebos. Among the 82 studies, five studies focused on participants without any prior history of stroke, whereas seven studies included patients with a previous history of stroke. Among the studies, 60 trials were published after 2000 and 42 studies focused on participants with hypertension. The present study included 22 trials that reported the events pertaining to drug-related side effects and withdrawal, in order to compare the tolerability of the treatments. In the current study, 36 trials compared different BP-lowering agents against each other and nine of them were included in both the analyses. Among them, five trials compared the BP-lowering agents to placebos and four trials compared the different BP-lowering targets with different antihypertensive agents.

Regarding the quality of the studies, 88 trials were judged to be at a low risk of bias; the risk of bias was unclear in three trials and two trials were deemed to be at a high risk of bias. The baseline characteristics and summary of risk bias assessment of the trials are shown in Supplementary Table 1 and Supplementary Figure 1.

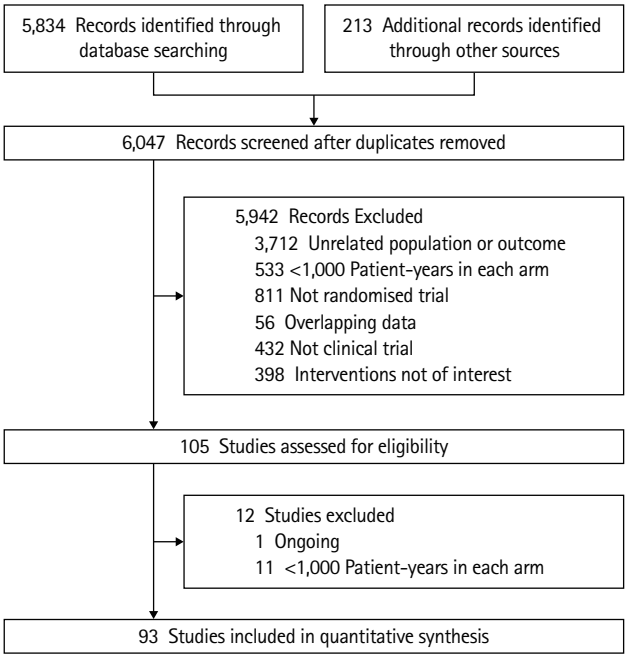

Figure 1. Flow diagram depicting the study selection.

Meta-analysis of the association between BP-lowering treatment and various outcomes

The significance of SBP reduction pertaining to various outcomes is shown in Figure 2. BP-lowering treatment was associated with a significant risk reduction in all strokes (OR, 0.79; 95% confidence interval [CI], 0.74 to 0.85). Consistently, the reduction in BP was associated with a reduction in all-cause mortality, cardiovascular-related death, fatal or disabling stroke, ischemic stroke, and hemorrhagic stroke. The Q statistics and I^2 metrics indicated that the heterogeneity pertaining to all the concerned outcomes was moderate (Supplementary Figures 2-7).

	No. of studies	Intervention		Control		OR (95% CI)
		Events	Participants	Events	Participants	
Stroke	66	5,264	166,416	6,173	158,396	0.79 (0.74–0.85)
Ischemic stroke	6	1,606	24,268	1,805	24,288	0.86 (0.73–1.02)
Hemorrhagic stroke	6	177	24,268	247	24,288	0.72 (0.54–0.96)
Fatal or disabling stroke	18	448	43,087	637	42,928	0.72 (0.61–0.81)
MI	55	4,138	135,816	4,383	127,822	0.90 (0.85–0.95)
Cardiovascular death	52	6,384	152,222	6,939	144,674	0.88 (0.83–0.94)
All cause death	56	11,326	155,586	11,779	148,155	0.91 (0.87–0.95)

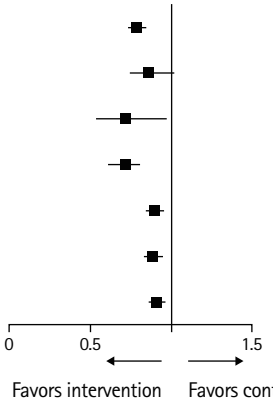

Figure 2. Significance of systolic blood pressure reduction pertaining to multiple outcomes. OR, odds ratio; CI, confidence interval; MI, myocardial infarction.

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The association between BP reduction and stroke prevention, categorized according to the different study characteristics, is shown in Figure 3. The results of the subgroup analyses were generally concurrent with the main analyses, which showed a significant association between the stroke incidence and BP-lowering treatments. However, among the patients with

Subgroup	No. of studies	Intervention		Control		OR (95% CI)
Age (yr)		Events	Participants	Events	Participants	
≤60	20	438	35,110	600	33,394	0.67 (0.56–0.80)
>60	44	4,751	130,155	5,467	123,845	0.80 (0.74–0.85)
History of stroke						
All	5	1,523	18,270	1,787	18,325	0.80 (0.67–0.95)
Mixed	33	2,883	95,604	3,233	88,591	0.84 (0.77–0.92)
No	4	141	14,063	177	14,057	0.80 (0.53–1.21)
History of CVD						
All	14	796	29,241	889	28,525	0.84 (0.76–0.94)
Mixed	14	1,259	33,768	1,477	33,049	0.81 (0.66–0.99)
No	3	79	9,385	107	9,374	0.64 (0.14–2.95)
History of DM						
All	11	735	20,933	719	20,026	0.89 (0.72–1.11)
Mixed	36	3,806	108,634	4,375	101,626	0.83 (0.77–0.89)
No	9	385	24,738	540	24,773	0.70 (0.57–0.87)
Baseling SBP (mm Hg)						
<130	9	329	11,470	316	11,488	1.07 (0.84–1.36)
130–139	20	1,356	57,114	1,596	57,156	0.83 (0.75–0.93)
140–149	7	2,026	33,059	2,277	32,533	0.86 (0.76–0.98)
150–159	12	616	20,969	834	20,553	0.71 (0.63–0.79)
≥160	17	912	42,800	1,133	35,684	0.67 (0.58–0.77)
Achieved SBP (mm Hg)						
<120	1	36	2,362	62	2,371	0.58 (0.38–0.87)
120–129	10	250	14,303	305	13,665	0.79 (0.61–1.03)
130–139	14	2,179	45,114	2,528	45,210	0.84 (0.75–0.95)
140–149	9	575	22,524	589	15,322	0.72 (0.58–0.88)
≥150	1	29	812	53	815	0.53 (0.33–0.85)

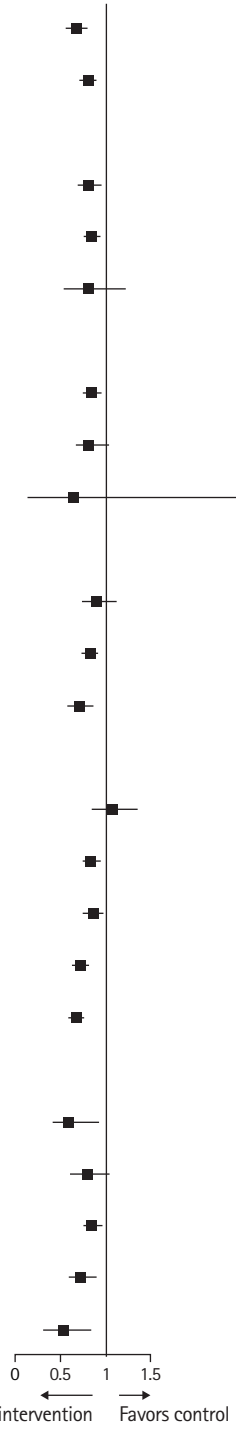

Figure 3. Association of blood pressure lowering and stroke prevention, categorized in accordance with the multiple study characteristics. OR, odds ratio; CI, confidence interval; CVD, cardiovascular disease; DM, diabetes mellitus; SBP, systolic blood pressure.

baseline SBP below 130 mm Hg, there was no significant association between the stroke incidence and BP-lowering treatments (OR, 1.07; 95% CI, 0.84 to 1.36). The present study observed a trend of increased benefits that could be gained with the increase in baseline SBP. Moreover, BP-lowering treatments were associated with a low risk of stroke at all target levels of SBP, except for the levels of 120 to 129 mm Hg. The present analyses showed a potential benefit pertaining to the association between BP reduction and stroke prevention in patients without a previous history of stroke. However, the results were not statistically significant (OR, 0.80; 95% CI, 0.53 to 1.21). Heterogeneity pertaining to the subgroups, measured using I^2, is demonstrated in the subgroup plots in Supplementary Figures 8-13.

The possibility of publication bias was analyzed using Funnel-plot-based methods, which showed statistical significance pertaining to the outcomes of stroke and all-cause mortality (Egger's test, *P*=0.03 and *P*=0.02, respectively). The Duval and Tweedie trim and fill procedure suggested little changes in the OR and 95% CI after the adjustment (OR, 0.82; 95% CI, 0.80 to 0.88) for stroke and (OR, 0.94; 95% CI, 0.90 to 0.97) all-cause mortality (Supplementary Figures 14-21).

A leave-one-out sensitivity analysis was performed and the pooled OR slightly varied from the original analysis (ranging from 0.91 to 0.92 for all-cause mortality; 0.88 to 0.89 for cardiovascular-related death; 0.79 to 0.80 for all stroke subtypes; 0.69 to 0.72 for fatal or disabling stroke; 0.83 to 0.89 for ischemic stroke; and 0.67 to 0.81 for hemorrhagic stroke) (Supplementary Figures 22-27). Hence, the effect of any one study on the overall summary estimates remained low.

Comparison of different BP-lowering treatments using pairwise and network meta-analysis

A total of 82 studies were included in the BP-lowering treatment comparison. Pairwise and network meta-analyses were performed to analyze the efficacy and tolerability as outcomes. Networks of eligible comparisons for efficacy and tolerability are presented in Figure 4, showing predominantly pairwise comparisons of agents with CCB, angiotensin II receptor blocker (ARB), angiotensin-converting enzyme inhibitor (ACEi), or placebo. Thirty pairwise treatment comparisons had direct evidence pertaining to efficacy and 11 pairwise treatment comparisons had direct evidence pertaining to tolerability.

Pairwise meta-analysis

The results of the pairwise meta-analysis for efficacy and tolerability profiles were summarized in Supplementary Table 2. Among the monotherapies, CCB and diuretics were associated

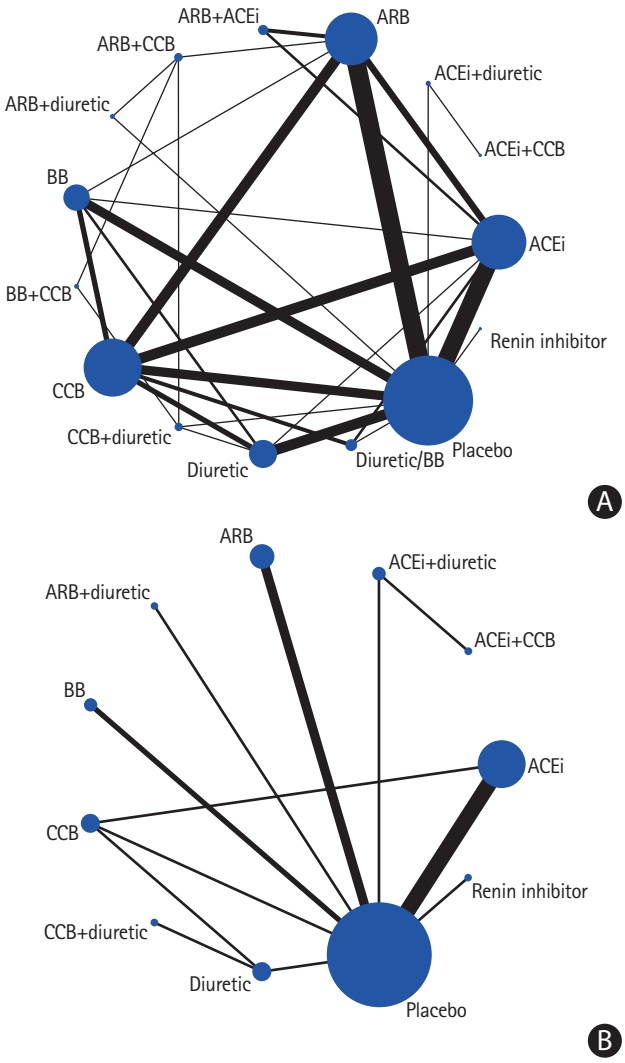

Figure 4. (A) Network of the studies included in the review with the available direct comparisons regarding efficacy. (B) Network of the studies included in the review with the available direct comparisons regarding tolerability. The width of the lines and the size of the nodes are proportional to the number of studies compared in each pair of treatments and the total sample size pertaining to each treatment, respectively. ARB, angiotensin II receptor blocker; ACEi, angiotensin-converting enzyme inhibitor; CCB, calcium channel blocker; BB, beta-blocker.

with a reduced incidence of about one-third of strokes, while beta-blockers (BBs) and ACEis were associated with a risk reduction of 19% and 8%, respectively. Among the combination treatments, the combination of CCB+THZ was associated with a 30% reduction in stroke risk, compared to the placebo. An assessment of the comparative efficacy of different strategies revealed that ACEi and BB were inferior to CCB (ACEi vs. CCB [OR, 1.123; 95% CI, 1.008 to 1.252], BB vs. CCB [OR, 1.261; 95% CI, 1.116 to 1.425]), BB was inferior to ARB (OR, 1.361; 95% CI, 1.142 to 1.622), and diuretics were superior to ACEi (OR, 0.871; 95% CI, 0.771 to 0.984). Regarding the tolerability profile of

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Efficacy in stroke prevention

Tolerability														
Placebo	**0.74 (0.67–0.82)**	**0.81 (0.73–0.89)**	**0.81 (0.73–0.90)**	**0.68 (0.59–0.77)**	0.90 (0.78–1.03)	0.99 (0.71–1.37)	**0.71 (0.53–0.94)**	0.78 (0.54–1.07)	**0.79 (0.65–0.94)**	**0.78 (0.63–0.96)**	0.72 (0.47–1.05)	0.84 (0.50–1.34)	1.38 (0.72–2.53)	1.26 (0.85–1.79)
1.43 (0.53–3.09)	CCB	1.09 (0.97–1.22)	1.09 (0.97–1.23)	0.91 (0.78–1.05)	**1.21 (1.05–1.39)**	1.34 (0.91–1.88)	0.96 (0.70–1.30)	1.05 (0.72–1.46)	1.06 (0.88–1.25)	1.05 (0.84–1.31)	0.97 (0.62–1.42)	1.14 (0.67–1.84)	1.86 (0.96–3.47)	**1.70 (1.14–2.45)**
1.10 (0.54–2.01)	0.94 (0.27–2.43)	ARB	1.00 (0.89–1.12)	0.84 (0.71–0.97)	1.12 (0.95–1.29)	1.23 (0.86–1.71)	0.89 (0.64–1.19)	0.96 (0.66–1.34)	0.98 (0.80–1.18)	0.97 (0.79–1.18)	0.89 (0.58–1.30)	1.05 (0.61–1.68)	1.72 (0.88–3.15)	**1.56 (1.04–2.25)**
2.15 (1.30–3.52)	1.80 (0.66–4.19)	2.18 (0.90–4.65)	ACEi	0.84 (0.71–0.97)	1.11 (0.95–1.30)	1.23 (0.86–1.72)	0.88 (0.64–1.19)	0.96 (0.66–1.35)	0.98 (0.80–1.17)	0.97 (0.78–1.19)	0.87 (0.58–1.31)	1.05 (0.61–1.69)	1.71 (0.88–3.16)	**1.56 (1.04–2.26)**
1.86 (0.56–4.59)	1.45 (0.42–3.71)	1.89 (0.44–5.28)	0.91 (0.24–2.33)	Diuretic	**1.34 (1.11–1.58)**	**1.47 (1.02–2.08)**	1.06 (0.76–1.44)	1.16 (0.79–1.63)	1.17 (0.94–1.45)	1.16 (0.91–1.48)	1.07 (0.68–1.58)	1.25 (0.73–2.03)	**2.05 (1.05–3.79)**	**1.87 (1.25–2.75)**
1.26 (0.44–2.89)	1.08 (0.24–3.21)	1.28 (0.35–3.38)	0.62 (0.18–1.52)	0.91 (0.17–2.92)	BB	1.11 (0.77–1.57)	0.80 (0.57–1.09)	0.87 (0.59–1.23)	0.88 (0.70–1.09)	0.87 (0.69–1.11)	0.80 (0.52–1.20)	0.94 (0.55–1.53)	1.55 (0.80–2.89)	1.41 (0.94–2.05)
3.10 (0.64–9.27)	2.68 (0.39–9.42)	3.15 (0.54–10.52)	1.53 (0.28–4.78)	2.28 (0.29–8.45)	3.13 (0.43–11.23)	ACEi+ diuretic	0.74 (0.47–1.11)	0.81 (0.49–1.25)	0.82 (0.55–1.17)	0.81 (0.54–1.18)	0.75 (0.43–1.20)	0.85 (0.58–1.21)	1.43 (0.68–2.78)	1.31 (0.76–2.11)
1.82 (0.14–7.68)	1.41 (0.11–6.01)	1.88 (0.12–8.23)	0.89 (0.64–3.76)	0.95 (0.12–3.46)	1.87 (0.10–8.63)	0.99 (0.04–4.58)	CCB+ diuretic	1.11 (0.70–1.67)	1.13 (0.79–1.56)	1.12 (0.77–1.59)	1.02 (0.64–1.56)	1.21 (0.65–2.04)	**2.00 (1.03–3.61)**	**1.80 (1.09–2.80)**
1.20 (0.26–3.51)	1.06 (0.16–3.63)	1.23 (0.21–3.93)	0.60 (0.11–1.81)	0.88 (0.11–3.15)	1.23 (0.18–4.24)	0.63 (0.06–2.53)	2.03 (0.86–9.90)	ARB+ diuretic	1.05 (0.70–1.51)	1.04 (0.69–1.52)	0.93 (0.64–1.34)	1.12 (0.58–1.95)	1.82 (0.89–3.42)	1.67 (0.98–2.66)
–	–	–	–	–	–	–	–	–	Diuretic /BB	1.00 (0.76–1.31)	0.92 (0.58–1.39)	1.08 (0.61–1.79)	1.77 (0.88–3.34)	**1.61 (1.05–2.39)**
–	–	–	–	–	–	–	–	–	–	ARB+ ACEi	0.93 (0.58–1.40)	1.09 (0.61–1.80)	1.79 (0.89–3.35)	**1.63 (1.04–2.45)**
–	–	–	–	–	–	–	–	–	–	–	ARB+ CCB	1.23 (0.62–2.21)	**1.96 (1.04–3.58)**	**1.83 (1.03–3.01)**
3.62 (0.35–14.55)	3.20 (0.22–13.90)	3.72 (0.30–15.73)	1.79 (0.15–7.27)	2.87 (0.16–11.98)	3.87 (0.25–16.20)	1.14 (0.24–3.38)	9.05 (0.14–31.86)	5.35 (0.24–22.43)	–	–	–	ACEi+ CCB	1.75 (0.74–3.65)	**1.59 (1.81–2.83)**
–	–	–	–	–	–	–	–	–	–	–	–	–	BB+ CCB	1.01 (0.45–1.91)
1.89 (0.40–5.58)	1.64 (0.24–5.68)	1.94 (0.33–6.30)	0.93 (0.17–2.92)	1.38 (0.17–5.06)	1.96 (0.26–6.74)	0.98 (0.09–3.98)	3.18 (0.18–15.67)	2.49 (0.25–9.90)	–	–	–	1.52 (0.07–6.62)	–	Renin inhibitor

Figure 5. Comparative efficacy and tolerability of all blood pressure lowering treatments in stroke prevention, as per the network meta-analyses. Effect sizes represent summary odds ratios and 95% credible intervals. In the upper triangle (efficacy in stroke prevention), values greater than 1 favor the treatment in the corresponding row, whereas values less than 1 favor the treatment in the corresponding column. In the lower triangle (tolerability), values greater than 1 favor the treatment in the corresponding column, whereas values less than 1 favor the treatment in the corresponding row. Significant results are in bold and underlined. CCB, calcium channel blocker; ARB, angiotensin II receptor blocker; ACEi, angiotensin-converting enzyme inhibitor; BB, beta-blocker.

monotherapies, ACEi was inferior to CCB (OR, 4.201; 95% CI, 2.206 to 7.998) and the combination of ACEi+CCB was superior to the combination of ACEi+THZs (OR, 0.892; 95% CI, 0.823 to 0.966).

Network meta-analysis-efficacy

The results of the network meta-analysis are shown in Figure 5. Compared to the placebos, all BP-lowering treatments, including CCB (OR, 0.74; 95% CI, 0.67 to 0.82), ARB (OR, 0.81; 95% CI, 0.73 to 0.89), ACEi (OR, 0.81; 95% CI, 0.73 to 0.90), diuretic (OR, 0.68; 95% CI, 0.59 to 0.77), CCB+THZ (OR, 0.71; 95% CI, 0.53 to 0.94), diuretic/BB (OR, 0.79; 95% CI, 0.65 to 0.94), and ARB+ACEi (OR, 0.78; 95% CI, 0.63 to 0.96), showed a benefit in stroke prevention. However, there was no correlation between the CCB+BB (OR, 1.38; 95% CI, 0.72 to 2.53) or the renin inhibitor (OR, 1.26; 95% CI, 0.85 to 1.79) strategy and stroke prevention. Diuretic use was superior to BB (OR, 1.34; 95% CI, 1.11 to 1.58), ACEi+THZ (OR, 1.47; 95% CI, 1.02 to 2.08), BB+CCB (OR, 2.05; 95% CI, 1.05 to 3.79), and renin inhibitor strategy (OR, 1.87; 95% CI, 1.25 to 2.75) in stroke prevention. The renin inhibitor was probably inferior to all the other treatments. Results from the pairwise meta-analysis and network meta-analysis for stroke prevention are summarized in Supplementary Table 3.

The SUCRA values pertaining to the 15 different antihypertensive strategies were 88.4, 76.7, 74.8, 72.9, 62.5, 61.4, 59.2, 53.6, 53.1, 52.3, 32.9, 25.7, 17.9, 10.6, and 8.0 for diuretic, CCB+THZ, ARB+CCB, CCB, ARB+THZ, ARB+ACEi, diuretic/BB, ACEi+CCB, ARB, ACEi, BB, ACEi+THZ, placebo, BB+CCB, and renin inhibitor, respectively (Supplementary Figure 28). The mean

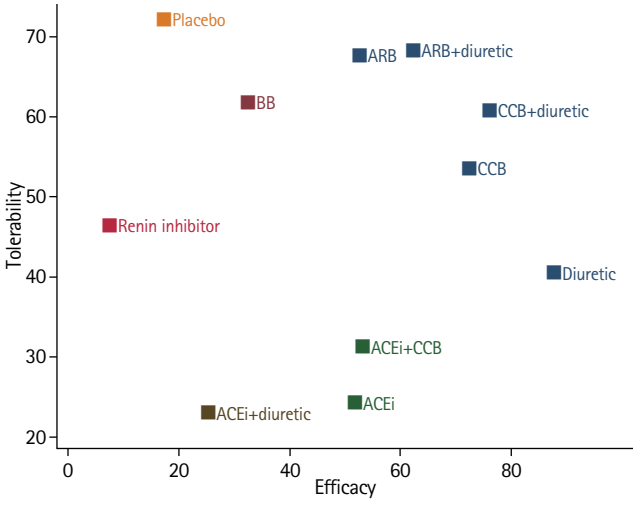

Figure 6. Cluster ranking for efficacy and tolerability of blood pressure lowering treatments in network meta-analyses. Each color represents a group of treatments that belong to the same cluster. Treatments located on the upper right corner are more effective and acceptable, compared to the other treatments. ARB, angiotensin II receptor blocker; BB, beta-blocker; CCB, calcium channel blocker; ACEi, angiotensin-converting enzyme inhibitor.

rank associated with all the treatments is shown in Supplementary Figure 29. The cluster rank plot indicated that diuretics, CCB+THZ, CCB, ARB+THZ, and ARB were associated not only with a reduction in stroke risk, but also a lower rate of withdrawal, owing to drug-related side effects (Figure 6). Sensitivity analyses stratified by age (age ≤60 or >60 years), comorbidities (history of hypertension, stroke, diabetes, or heart failure), and baseline SBP (baseline SBP ≤150 or >150 mm Hg) showed robust results pertaining to the efficacy (Supplementary Table 4). Diuretics ranked first in most of the analyses. It is worth mentioning that the combination of ARB+CCB ranked first in the participants with baseline SBP above 150 mm Hg.

Network meta-analysis-tolerability

Network meta-analysis also confirmed that ACEi (OR, 2.15; 95% CI, 1.30 to 3.52) was likely to be associated with a significantly higher risk of withdrawal, owing to drug-related side effects compared to placebo. The comparative tolerability of different strategies is shown in Figure 5.

The SUCRA values for the 11 antihypertensive agents were 23.0, 24.3, 31.3, 40.4, 46.3, 53.6, 60.6, 61.9, 67.8, 68.4, and 72.5, for ACEi+THZ, ACEi, ACEi+CCB, diuretic, renin inhibitor, CCB, CCB+THZ, BB, ARB, ARB+THZ, and placebo, respectively (Supplementary Figure 30). The mean ranks pertaining to all the treatments is shown in Supplementary Figure 31. Visual inspection of funnel plots for efficacy did not show any distinct asymmetry (Supplementary Figure 32). However, several trials fell outside the significance boundaries in the tolerability analysis (Supplementary Figure 33), which could be attributed to the limited number of trials.

The assessment of transitivity is shown in Supplementary Figure 34. No inconsistency between direct and indirect estimates in node splitting was apparent, except for the two comparisons (placebo-ARB, CCB-ARB) on efficacy (Supplementary Table 5) and two nodes (placebo-ACEi, CCB-ACEi) on tolerability (Supplementary Table 6). Finally, the design-by-treatment inconsistency model was applied, and inconsistency for efficacy or tolerability was not detected in the current analyses (Supplementary Table 7).

Discussion

Using the data pertaining to 504,613 participants in 93 large RCTs, the current study has supplemented the information regarding the selection of the most appropriate antihypertensive agents for different populations with regard to the efficacy and tolerability, and confirmed that the reduction in BP was significantly associated with lower mortality rates and stroke incidence. The therapeutic benefits existed regardless of the stratification by comorbidities, age, and baseline SBP. All the achieved SBP levels were associated with a 15% to 45% stroke risk reduction. An interesting, but unexpected finding in the current study was that diuretics were more effective in stroke prevention, compared to the other BP-lowering treatments. CCB+THZs, CCB, ARB+THZs, and ARB were also appropriate options in terms of efficacy and tolerability.

The observations in the present study are concurrent with the previously published meta-analyses with reference to the target SBP.[3,21] Moreover, the present study supplemented the information that BP-lowering was significantly associated with the reduced stroke incidence in all subtypes including ischemic, hemorrhagic, and fatal or disabling stroke. The current study showed that lowering BP to a target of below 130 mm Hg could reduce the risk associated with stroke. However, this should be interpreted with caution. Among the ischemic stroke patients without intracranial artery stenosis (lacunar infarction), intensive lowering of BP to a target of below 130 mm Hg is more beneficial in the reduction of intracerebral hemorrhage, rather than risk of ischemic stroke.[22] Moreover, intensive BP-lowering in patients with intracranial atherosclerotic stenosis may increase the ischemic lesion volume in the subacute stage.[23] Hence, intensive BP control to a target of below 130 mm Hg should mainly be recommended for the primary prevention of both ischemic and hemorrhagic strokes. The results of the present study, confirmed that a changed in target SBP from 140 to 130 mm Hg was necessary.[2,3] The target SBP for antihypertensive treatment is controversial, especially for the populations in different age groups. The guidelines of the Eighth Joint National Committee (JNC8) (2014) recommend a goal of BP below 140/90 mm Hg in patients younger than 60 years and a more relaxed goal of below 150/90 mm Hg in those older than 60 years.[24] Another meta-analysis explored the benefits and harms of intensive BP management in adults aged 60 years or above and found that the treatment with a target BP below 150 mm Hg improves the health outcomes including stroke in older adults and lower targets (≤140/85 mm Hg) are associated with a marginally significant decrease in stroke incidence.[25]

In the present study, the network meta-analysis suggested that diuretics, CCB, ARB, ACEi, and all diuretic-based combination therapies were effective in stroke prevention. This was consistent with the 2017 high BP guideline, which observed that no class of antihypertensive medications were better than THZs in reducing the risk of stroke and various cardiovascular outcomes.[5] However, the present study differs from the 2017 high BP guideline in some aspects. For instance, the 2017 high BP guideline excluded placebo-controlled trials, whereas the

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current study included the trials that compared BP-lowering agents to placebo controls. Moreover, the 2017 high BP guideline examined only the first-line antihypertensive medications including diuretics, ACEis, ARBs, CCBs, and BBs, whereas the current study examined all the available antihypertensive medications.

Diuretics have been preferred as the first-line antihypertensive agents since the release of the results of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), which suggested that diuretics were as effective as CCBs in reducing specified endpoints.[26] However, a previous meta-analysis explored the efficacy of CCBs and other antihypertensive agents and reported that there was no significant difference between CCBs and other comparators with regard to the efficacy.[6] the present analysis included the trials published in or after 2000 and suggested that CCB+THZs is the most effective therapy for the reduction of stroke incidence, followed by ARB+CCB, diuretics, and ARB+diuretics. In view of these findings, CCB, ARB, and diuretics could be employed as the first-line drugs for stroke prevention. However, in view of the adverse effects of diuretics, especially at high dosages, caution should be exercised when prescribing to populations with an increased risk of developing diabetes and gout. In the aforementioned patients, monotherapy using CCBs and ARBs or combinations with diuretic therapies might be appropriate alternatives.

Thus far, no network meta-analysis has been performed to examine the efficacy and tolerability of various antihypertensive agents for stroke prevention in the entire population. A previous network meta-analysis studied the various antihypertensive agents for stroke prevention in patients with type 2 diabetes and concluded that none of the antihypertensive agents were superior to one another, including the placebos.[27] The current study demonstrated that ACEi-based single or combination therapies were most likely to be associated with the withdrawal, owing to drug-related side effects, whereas ARB-based single or combination therapies were well tolerated. This advantage might be helpful in the decision-making process when balancing the efficacy and feasibility.

The current study has certain limitations. First, a relatively small number of trials exploring the effects of antihypertensive agents for secondary stroke prevention were included, which precluded the execution of a formal network meta-analysis to determine the relative efficacy of different antihypertensive therapies for secondary stroke prevention. Second, the transitivity assumption during the network analysis was unavoidable. Many RCTs included in the present analysis involved combination therapies and the inclusion of combination therapies in network meta-analysis of first-line treatments would introduce intransitivity.[28] Third, the concurrent discretionary use of statins, dual anti-platelets therapy, stringent glycemic control by new diabetes drugs, lifestyle coaching, and the 'add-on' antihypertensive drugs allowed in the recent/newer trials might diminish the marginal benefit of the new classes of antihypertensive drugs. Fourth, the present study failed to acquire the relevant data from studies involving diabetic subgroups, stroke subtypes, reason for withdrawal, the elapsed time between initiation of antihypertensive agents and the index stroke, as most of these studies were not included. Fifth, as the present review includes the studies that were published over a long period of time (1966–2018), the definition of stroke and the incorporation of the advances in neuroimaging can be considered to be different among the trials. Sixth, considering the ageing population, an average duration of follow-up of 3.3 years remains limited and trials with longer follow-up periods are warranted. Lastly, the trials included in the current study varied in several aspects, including the study population, race, baseline characteristics, study methodology, and concurrent use of multiple classes of antihypertensive drug. Consequently, the possibility that the differences between treatment strategies attributed to the aforementioned biases could not be excluded. The present study attempted to minimize the heterogeneity by performing sensitivity and subgroup analyses, in order to provide more robust conclusions.

In conclusion, the BP-lowering strategy is significantly associated with the risk reduction of all-cause mortality, cardiovascular-related death, all stroke types (fatal or nonfatal), disabling stroke, ischemic stroke, and hemorrhagic stroke. Monotherapy with diuretics, CCB or ARB, and their combinations could be employed as the first-line treatments for stroke prevention in terms of the efficacy and tolerability. Relatively, ACEi has a higher risk of side effect-related withdrawal.

Supplementary materials

Supplementary materials related to this article can be found online at https://doi.org/10.5853/jos.2020.02698.

Disclosure

The authors have no financial conflicts of interest.

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Appendix 1. Electronic search strategies

HYPERTENSION/dt [dt=Drug Therapy]
BLOOD PRESSURE/de [de=Drug Effects]
ANTIHYPERTENSIVE AGENTS/tu [tu=Therapeutic Use]
VASODILATOR AGENTS/(vasodilator AND agent*).ti
ambrisentan.ti
bosentan.ti
*DIAZOXIDE/diazoxide.ti
*HYDRALAZINE/hydralazine.ti
*ILOPROST/iloprost.ti
*MINOXIDIL/minoxidil.ti
sildenafil.ti
*NITROPRUSSIDE/nitroprusside.ti
tadalafil.ti
*METHYLDOPA/methyldopa.ti
*CLONIDINE/clonidine.ti
moxonidine.ti
*GUANETHIDINE/guanethidine.ti
*ADRENERGIC ALPHA–ANTAGONISTS/*DOXAZOSIN/doxazosin.ti
*INDORAMIN/indoramin.ti
*PRAZOSIN/prazosin.ti
terazosin.ti
*PHENOXYBENZAMINE/phenoxybenzamine.ti
*PHENTOLAMINE/phentolamine.ti
*ADRENERGIC BETA–ANTAGONISTS/*ATENOLOL/atenolol.ti
*METOPROLOL/metoprolol.ti
*PINDOLOL/pindolol.ti
*TIMOLOL/timolol.ti
*OXPRENOLOL/oxprenolol.ti
nebivolol.ti
*NADOLOL/nadolol.ti
*LABETALOL/labetalol.ti
*CELIPROLOL/celiprolol.ti
carvedilol.ti
*BISOPROLOL/bisoprolol.ti
*ACEBUTOLOL/acebutolol.ti
*PROPRANOLOL/propranolol.ti
SODIUM CHLORIDE SYMPORTERINHIBITORS/(diuretic ANDthiazide*).ti
*HYDROCHLOROTHIAZIDE/hydrochlorothiazide.ti
*TRICHLORMETHIAZIDE/trichlormethiazide.ti
*SPIRONOLACTONE/spironolactone.ti
*CHLORTHALIDONE/chlorthalidone.ti
*INDAPAMIDE/indapamide.ti
ANGIOTENSIN–CONVERTING ENZYMEINHIBITORS/(ace AND inhibitor).ti
*CAPTOPRIL/captopril.ti
*CILAZAPRIL/cilazapril.ti
*ENALAPRIL/enalapril.ti
*FOSINOPRIL/fosinopril.ti
imidapril.ti
*LISINOPRIL/lisinopril.ti
moexipril.ti
*PERINDOPRIL/perindopril.ti
quinapril.ti
*RAMIPRIL/ramipril.ti
trandolapril.ti
*ANGIOTENSIN II TYPE 1 RECEPTOR BLOCKERS/azilsartan.ti
candesartan.ti
eprosartan.ti
irbesartan.ti
*LOSARTAN/losartan.ti
olmesartan.ti
telmisartan.ti
valsartan.ti
(renin AND inhibitor*).ti
aliskiren.ti
*CALCIUM CHANNEL BLOCKERS/*AMLODIPINE/amlodipine.ti
*DILTIAZEM/diltiazem.ti
*FELODIPINE/felodipine.ti
*ISRADIPINE/isradipine.ti
lacidipine.ti
lercanidipine.ti
*NICARDIPINE/nicardipine.ti
*NIFEDIPINE/nifedipine.ti
*NISOLDIPINE/nisoldipine.ti
*VERAPAMIL/verapamil.ti
*NITRENDIPINE/nitrendipine.ti
Or/1–75
Cerebrovascular Disorders[all fields]
stroke[all fields]
Brain infarction[all fields]
Cerebral infarction[all fields]
Brain ischemia[all fields]
Cerebral hemorrhage[all fields]
Intracranial Hemorrhages[all fields]
Or/77–83
76 and 84

Appendix 2. The OpenBUGS code for random effects model

```
# Binomial likelihood, cloglog link
# Random effects model for multi-arm trials
model{                          # *** PROGRAM STARTS
for(i in 1:ns){                 # LOOP THROUGH STUDIES
   w[i,1] <- 0    # adjustment for multi-arm trials is zero for control arm
   delta[i,1] <- 0           # treatment effect is zero for control arm
   mu[i] ~ dnorm(0,.0001)          # vague priors for all trial baselines
   for (k in 1:na[i]) {            # LOOP THROUGH ARMS
      r[i,k] ~ dbin(p[i,k],n[i,k]) # Binomial likelihood
# model for linear predictor
      cloglog(p[i,k]) <- log(time[i]) + mu[i] + delta[i,k]
      rhat[i,k] <- p[i,k] * n[i,k] # expected value of the numerators
#Deviance contribution
      dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))
         +  (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))        }
#  summed residual deviance contribution for this trial
   resdev[i] <- sum(dev[i,1:na[i]])
   for (k in 2:na[i]) {            # LOOP THROUGH ARMS
# trial-specific LOR distributions
      delta[i,k] ~ dnorm(md[i,k],taud[i,k])
# mean of LOR distributions, with multi-arm trial correction
      md[i,k] <-  d[t[i,k]] - d[t[i,1]] + sw[i,k]
# precision of LOR distributions (with multi-arm trial correction)
      taud[i,k] <- tau *2*(k-1)/k
# adjustment, multi-arm RCTs
      w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]])
# cumulative adjustment for multi-arm trials
      sw[i,k] <- sum(w[i,1:k-1])/(k-1)
    }
  }
totresdev <- sum(resdev[])          #Total Residual Deviance
d[1]<-0      # treatment effect is zero for reference treatment
# vague priors for treatment effects
for (k in 2:nt){  d[k] ~ dnorm(0,.0001) }
sd ~ dunif(0,5)     # vague prior for between-trial SD
tau <- pow(sd,-2)   # between-trial precision = (1/between-trial variance)
 for (c in 1:(nt-1)) {
for (k in (c+1):nt) {
or[c,k] <- exp(d[k] - d[c])
lor[c,k] <- (d[k]-d[c])
}
}
 for(k in 1:nt) {
      order[k]<- rank(d[],k)
 # this is when the outcome is positive - omit 'nt+1-' when the outcome is
negative
           most.effective[k]<-equals(order[k],1)

           for(j in 1:nt) {
               effectiveness[k,j]<- equals(order[k],j)
           }
      }
   for(k in 1:nt) {
             for(j in 1:nt) {
          cumeffectiveness[k,j]<- sum(effectiveness[k,1:j])
             }
       }
 #SUCRAS#

      for(k in 1:nt) {
           SUCRA[k]<- sum(cumeffectiveness[k,1:(nt-1)])/(nt-1)
   }
}                       # *** PROGRAM ENDS
```


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Supplementary methods. Details about statistical analysis

To clarify the effects of blood pressure lowering agents on the relative risk of stroke, ischemic stroke, hemorrhagic stroke, fatal or disabling stroke, cardiovascular death, and all cause death, we combined trials of blood pressure lowering agents versus placebo and higher versus lower blood pressure lowering targets and performed traditional meta–analysis. Two trials which compared angiotensin II receptor blocker (ARB)+angiotensin-converting enzyme inhibitor (ACEi) with ACEi were also included for the first objective.[1,2] For another two trials with two active groups and a placebo group,[3,4] we combined the events of the active groups for blood pressure lowering analysis. For one trial with three different blood pressure lowering targets,[5] we combined the two lower targets for analysis. We calculated relative risks from the number of events and participants for each outcome in each trial and pooled results with Mantel-Haenszel and Hartung-Knapp adjustment for random effects models. Random model other than fixed model was chosen because the included trials differed to some extent, both clinically and methodologically, and random model is generally more conservative compared with fixed effects model if heterogeneity is present. We assessed the magnitude of statistical heterogeneity among studies using standard cochrane chi-square test, the I^2 statistic (I^2values of at least 50% were considered to represent substantial heterogeneity, while values of at least 75% indicated considerable heterogeneity).[6] We explored evidence for heterogeneity in estimates of treatment effect attributable to the baseline characteristics of trials by comparing summary results obtained from subsets of studies grouped by age, history of cardiovascular disease, history of stroke, history of diabetes, baseline, and achieved blood pressure level. Publication bias was evaluated both graphically using a funnel plot and with the Egger statistical test for funnel plot asymmetry,[7] if at least 10 studies were available for each outcome. A leave-one-out sensitivity analysis was performed by repeating the meta-analysis, each time with one of the included studies omitted, to see whether any one study had disproportionately large impact on the pooled relative risk. Data used in this meta-analysis were intention to treat because most of the included trials did not report as treated results.

To clarify the efficacy and tolerability of different blood pressure lowering drugs for prevention of stroke, we combined the three groups of trials and did pair-wise and network meta-analysis. Ten trials of different blood pressure lowering targets which undefined any specific drugs were excluded from analysis. The outcome measure for efficacy and tolerability are stroke and drug-related side effects withdraw, respectively. First, we did pair-wise meta-analysis with a random effects model to analyze direct treatment comparisons. We calculated the summary effect sizes as odds ratios, with 95% confidence intervals. We assessed heterogeneity among studies with the I^2 statistic. We did not do funnel plots to test publication bias because most of the comparisons had less than 10 trials. Second, we analyzed pooled data for all blood pressure lowering treatments with random effects models, within a Bayesian framework in OpenBUGS.[8] See Appendix 2 for details about the OpenBUGS codes used. Models were computed with Markov chain Monte Carlo simulations, using three chains with over-dispersed initial values, with Gibbs sampling based on 100,000 iterations after a burn-in phase of 50,000 iterations. Non-informative or vague priors for the overall mean effect (θ to N (0, 1002)) and the between-study standard deviation (τ to uniform (0, 2)) were given.[9-11] The mean of the posterior distribution was reported as the point estimate odds ratio, and the corresponding 95% credible intervals were obtained with the 2.5th and 97.5th percentiles of the posterior distribution, after adjustment for multiple arm trials. We tested the adequacy of burn-in and convergence (reaching a stable equilibrium distribution) using visual inspection of parameter fluctuation depicted in trace plots and estimating the values of the Brooks-Gelman-Rubin statistic.[12] Model fit was evaluated with the total residual deviance, which indicated good fit, if it approximated the number of data points.

Inconsistency between direct and indirect evidence can suggest that the transitivity assumption might not hold. We assessed evidence for consistency in the networks in two ways. First, we used node-split approach to contrast direct evidence with indirect evidence from the entire network on each node.[11,13,14] A Bayesian *P*-value was calculated to estimate difference between direct and indirect evidence by counting the proportion of times the direct treatment effect exceeded the indirect treatment effect.[14] Second, we used the design-by-treatment interaction model that provides a single inference, using the chi-square test, about the plausibility of assuming consistency throughout the entire network.[15]

The surface under the cumulative ranking curve (SUCRA) and rankograms was used to provide a hierarchy of the regimens.[16] We also used two-dimensional plots and clustering methods to obtain meaningful groups of the treatments.[17] We assessed small study effects with comparison adjusted funnel plot symmetry.[17]

To investigate the generalisability of the findings, we assessed the effects of differing trial and participant characteristics on the outcomes in sensitivity analyses by restricting analyses to

studies with the following design characteristics: hypertensive participants; excluding heart failure participants; published in 2000 or later; duration of follow-up longer than 3 years. We did subgroup analyses according to age (age ≤60 and >60 years), history of stroke (no defines as participants with a history of stroke account for less than 5% of overall participants in a trial, yes defines as all of the participants has a history of stroke in a trial), history of diabetes mellitus (DM; no defines as participants with a history of DM account for less than 5% of overall participants in a trial, yes defines as all of the participants has a history of DM in a trial), and baseline systolic blood pressure (≤150 or >150 mm Hg).

For traditional meta-analyses we used R version 3.4.1 (R Foundation for Statistical Computing, Vienna, Austria). For network meta-analyses we used OpenBUGS 3.2.3 and STATA 14.0 (StataCorp., College Station, TX, USA).

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Supplementary Table 1. Baseline characteristics of included studies

Study	Intervention: Inclusion criteria	Intervention: Type of drug	Intervention: Type of drug	Mean age (yr): Intervention	Mean age (yr): Control	No. of female (%): Intervention	No. of female (%): Control	No. of participants: Intervention	No. of participants: Control	No. of participants with these conditions at baseline (%): CVD	CHD	Stroke	Hypertension	No. of participants with these conditions at baseline (%): PAD	DM	HF	AF	CKD	Follow-up duration (yr)	Mean SBP/DBP intervention group (mm Hg): Baseline	Achieved BP	Mean SBP/DBP control group (mm Hg): Baseline	Achieved BP	Drug-related side effect withdraw: Intervention	Control	Outcomes (intervention/control): All stroke	Death from all causes	Cardiovascular death
Action[18]	Stable ngina+ history of MI/CAD	CCB (nifedipine GITS)	Placebo	63.5±9.3	63.4±9.3	744 (19.5)	797 (20.8)	3,825	3,840	7,665 (100)	7,665 (100)	NA	3,977 (51.9)	985 (12.9)	1,110 (14.5)	0	NA	NA	4.9	137.3±18.8/ 79.9±9.4	130.3/75.8	137.6±18.6/ 79.8±9.5	NA	389	172	82/108	310/291	178/177
Active I[19]	AF+risk factors for stroke	ARB (irbesartan)	Placebo	69.5±9.7	69.6±9.7	1,773 (39.2)	1,768 (39.3)	4,518	4,498	9,016 (100)	NA	1,212 (13.4)	7,929 (87.9)	236 (2.6)	1,787 (19.8)	2,881 (32)	9,016 (100)	NA	4.1	138.3±17.6/ 82.6±11.5		138.2±17.2/ 82.2±11.1		NA	NA	379/411	949/929	NA
ADVANCE[20]	DM2+at least 1 risk factor for CVD	ACEi (perindopril) & diuretic (indapamide)	Placebo	66±6	66±7	2,366 (42.5)	2,369 (42.5)	5,569	5,571	NA	1,334 (12.0)	1,022 (9)	NA	NA	11,140 (100)	NA	NA	401 (4)	4.3	145±22/ 81±11	136/73	145±21/ 81±11	NA	300	125	215/218	408/471	211/257
Altitude[21]	DM2+microal buminuria/macroalbuminuria/CVD	Renin inhibitor (aliskiren)	Placebo	64.6±9.6	64.4±9.9	1,393 (32.6)	1,342 (31.3)	4,274	4,287	3,619 (42.3)	NA	847 (9.9)	8,086 (94.5)	NA	8,561 (100)	872 (10.2)	731 (8.5)	8,390 (98)	2.7	137.3±16.2/ 74.1±9.8	139/75	137.3±16.7/ 74.3±9.9	NA	325	221	147/122	376/358	246/215
AIRE[22]	AMI+HF/LVD	ACEi (ramipril)	Placebo	64.9±10.8	65.1±10.8	270 (27)	255 (26)	1,004	982	1,986 (100)	1,986 (100)	NA	554 (28)	NA	240 (12)	1,986 (100)	NA	0	1.3	NA	NA	NA	NA	NA	NA	25/17	170/222	NA
Australian trial[23]	Mild HTN without risk for CVD	Diuretic (chlorothiazide)	Placebo	50.4±9.0	50.5±8.9	636 (37.0)	621 (36.4)	1,721	1,706	NA	NA	NA	3,427 (100)	NA	NA	NA	NA	NA	4	157.7±15.0/ 100.5±4.0	NA/88.3	157.1±14.4/ 100.4±3.8	NA/93.9	NA	NA	10/16	25/35	8/18
BCAPS[24]	Plaque in the right carotid artery+no symptoms of CAD	BB (metoprolol CR/XL)	Placebo	61.6±5.4	61.9±5.3	221 (55.8)	211 (53.1)	396	397	34 (4.3)	NA	NA	96 (12.1)	NA	25 (3.2)	NA	NA	NA	3	138.5/ 84.7	NA	139.4/ 84.8	NA	79	87	1/7	4/7	NA
BHAT[25]	Hospitalised for AMI	Propranolol	Placebo	54.7	54.9	310 (16.2)	286 (14.9)	1,916	1,921	3,837 (100)	3,837 (100)	NA	1,564 (40.8)	NA	441 (11.5)	353 (9.2)	NA	NA	2.1	112.3/72.5	127/80	111.7/ 72.3	130/81	243	179	29/30	138/188	127/171
CAMELOT[4]	CAD (>20% stenosis by coronary angiography)+DBP <100 mm Hg	CCB (amlodipine)	Placebo	57.3±9.7	57.2±9.5	157 (23.7)	177 (27)	663	655	1,318 (100)	1,318 (100)	51 (3.9)	802 (60.8)	NA	245 (18.6)	0	NA	NA	2	129.5±15.5/ 77.7±9.1	124.7/75.2	128.9±15.8/ 77.6±8.9		NA	NA	6/12	7/6	5/2
		ACEi (enalapril)	Placebo	58.5±9.9	57.2±9.5	189 (28.1)	177 (27)	673	655	1,328 (100)	1,328 (100)	57 (4.3)	797 (60.0)	NA	248 (18.7)	0	NA	NA	2	128.9±16.3/ 77.2±9.4	124/74.8	128.9±15.8/ 77.6±8.9		NA	NA	8/12	8/6	5/2
		CCB (amlodipine)	ACEi (enalapril)	57.3±9.7	58.5±9.9	157 (23.7)	189 (28.1)	663	673	1,336 (100)	1,336 (100)	54 (4.0)	809 (60.6)	NA	233 (17.4)	0	NA	NA	2	129.5±15.5/ 77.7±9.1	124.7/75.2	128.9±16.3/ 77.2±9.4		NA	NA	6/8	7/8	5/5
CHARM-Preserved[26]	CHF+LVEF >40%	ARB (candesartan)	Placebo	67.2±11.1	67.1±11.1	594 (39.2)	618 (41.0)	1,514	1,509	NA	1,340 (44)	268 (9)	1,943 (64.3)	NA	857 (28)	3,023 (100)	881 (29.1)	NA	3.1	136.0±18.6/ 77.8±10.9	NA	136.3±18.3/ 77.8±10.5	NA	NA	NA	23/30	NA	170/170
CHARM-Added[27]	CHF+LVEF ≤40%	ARB (candesartan)	Placebo	64.0±10.7	64.1±11.3	270 (21.2)	272 (21.4)	1,276	1,272	NA	1,417 (56)	220 (9)	1,228 (48.2)	NA	758 (30)	2,548 (100)	687 (27.0)	NA	3.4	124.7±18.6/ 75.0±10.8	NA	125.6±18.6/ 75.2±10.7	NA	NA	NA	17/9	NA	302/347
CHARM-Alternative[28]	Symptomatic CHF+LVEF ≤40%+Intolerance to ACEi	ARB (candesartan)	Placebo	66.3±11.0	66.8±10.5	322 (31.8)	324 (31.9)	1,013	1,015	NA	1,247 (62)	175 (9)	1,015 (50.0)	NA	518 (27)	2,028 (100)	515 (25.4)	NA	2.8	129.9±19.0/ 76.6±10.9	NA	130.3±18.5/ 76.9±10.5	NA	NA	NA	16/12	NA	219/252
DIABHYCAR[29]	DM2+ microalbuminuria or proteinuria+serum creatinine ≤150 mol/L	ACEi (ramipril)	Placebo	65.2±8.4	65.0±8.3	742 (30.4)	738 (29.9)	2,443	2,469	1,201 (24.5)	295 (6.0)	207 (4.2)	2,735 (55.7)	503 (10.2)	4,912 (100)	NA	NA	4,912 (100)	3.9	145.8± 15.0/ 82.4 ±8.7		145.1±15.2/ 82.2±8.5		609	554	207/200	NA	320/308
DIRECT-Protect 2[30]	DM2+normoalbuminuric, normotensive, or treated hypertensive+mild to moderately severe retinopathy	ARB (candesartan)	Placebo	56.9±7.6	56.8±7.9	485 (51.0)	472 (49)	951	954	125 (6.6)	99 (5.2)	26 (1.4)	1,180 (62.0)	NA	1,905 (100)	NA	NA	0	4.7	123±9/ 75±6 (normotensive)	128/74	123±9/76±6	132/76	NA	NA	6/3	NA	6/4
																				139±13/ 79±7 (hypertensive)	136/77	139±12/ 80±7	139/78	NA	NA	10/12	NA	12/21
Dream[31]	Non-diabetic+impaired fasting glucose levels or impaired glucose tolerance+no CVD	ACEi (ramipril)	Placebo	54.7±10.9	54.7±10.9	1,567 (59.7)	1,553 (58.7)	2,623	2,646	0	0	0	2,291 (43.5)	0	0	0	0	NA	3	136.1±18.6/ 83.4±10.8	127.8/78	136.0±18.1/ 83.4±10.8	132.1/ 80.4	798	615	4/8	31/32	12/10
Dutch TIA[32]	TIA/nondisabling ischemic stroke less than 3 months before	BB (atenolol)	Placebo	NA	NA	249 (34.0)	282 (38.1)	732	741	NA	81 (5.5)	1,473 (100)	420 (28.5)	37 (2.5)	74 (5.0)	NA	NA	NA	2.6	158±25/ 91±12	149.5/NA	157±24/ 91±12		NA	NA	52/62	64/58	41/33
EUROPA[33]	Stable CAD without HF	ACEi (perindopril)	Placebo	60±9	60±9	884 (14.5)	895 (14.7)	6,110	6,108	12,218 (100)	12,218 (100)	409 (3.3)	3,312 (27.1)	883 (7.2)	799 (6.5)	0	NA	0	4.2	137 (16)/ 82 (8)	NA	137 (15)/ 82 (8)	NA	1,391	1,266	98/102	375/420	215/249
EWPHE[34]	HTN DBP: 90-119 mm Hg and SBP: 160-239 mm Hg	Diuretic (hydrochlorothiazide+triamterene)	Placebo	72±8	72±8	287 (69)	299 (70.5)	416	424	NA	NA	840 (100)	840 (100)	NA	NA	0	NA	NA	4.7	183±17/ 101±7	148+18/ 85±10	182±16/ 101±7	167±22/ 90±9	NA	NA	12/19	73/89	42/61
FEVER[35]	Untreated HTN: DBP ≤115 mm Hg and SBP ≤210 mm Hg Treated HTN: SBP 160–210 mm Hg or DBP 95–115 mm Hg	CCB (felodipine)+diuretic (hydrochlorothiazide)	Placebo	61.5 ±7.1	61.5 ± 7.2	1,858 (38.2)	1,933 (39.5)	4,841	4,870	NA	1,318 (13.6)	1,438 (14.8)	9,711 (100)	48 (0.5)	1,241 (12.8)	614 (6.3)	NA	NA	3.3	158.7±17.6/ 92.4 ± 9.6	138.1±11.6/ 82.3± 7.3	158.9±17.3/ 92.7±9.6	141.6±12.2/ 82.3±7.7	NA	NA	177/251	112/151	73/101
HEP[36]	Aged 60–79 years old HTN	BB (atenolol)±diuretic (bendrofluazide)	Placebo	NA	NA	NA	NA	419	416	NA	NA	NA	884 (100)	NA	0	0	0	NA	4.4	196/99	NA	NA	NA	NA	NA	23/44	60/69	NA
Hope[37]	CVD/DM2+CVD risk factor without low ejection fraction or HF	ACEi (ramipril)	Placebo	66±7	66±7	1,279 (27.5)	1,201 (25.8)	4,645	4,652	NA	7,477 (80)	1,013 (11)	4,355 (46.8)	4,051 (43.6)	3,577 (38.5)	0	NA	0	5	139±20/ 79±11	136/76	139±20/ 79±11	139/77	NA	NA	156/226	482/569	282/377
Hope-3[38]	HTN at intermediate risk without CVD	ARB/diuretic (candesartan/ hydrochlorothiazide) (HCTZ)	Placebo	65.7±6.4	65.8±6.4	2,910 (45.8)	2,964 (46.7)	6,356	6,349	0	0	0	4,814 (37.9)	0	731 (5.8)	0	NA	350 (2.8)	5.5	138.2±14.7/ 82.0±9.4		137.9±14.8/ 81.8±9.3		1,552	1,598	75/94	342/349	155/170
Hunan province[39]	HTN	CCB (nitrendipine)	No placebo	51.8±0.11		NA	NA	1,040	1,040	NA	NA	NA	2,080 (100)	NA	NA	NA	NA	NA	4.72	160.8±0.82/ 98.6±0.52	140.7±0.72/ 85.2±0.46	160.2±0.80/ 98.42±0.52	148.9±0.16/ 90.6±0.46	NA	NA	37/79	48/62	NA
HYVET[40]	HTN aged ≥80 years+SBP ≥160 mm Hg	Diuretic (indapamide)	Placebo	83.6±3.2	83.5±3.1	1,174 (60.7)	1,152 (60.3)	1,933	1,912	452 (11.8)	NA	261 (6.8)	3,455 (89.9)	NA	263 (6.8)	111 (2.9)	NA	NA	1.8	173.0±8.4/ 90.8±8.5		173.0±8.6/ 90.8±8.5		NA	NA	51/69	196/235	99/121
IDNT[3]	Nephropathy due to DM2+HTN+proteinuria	ARB (irbesartan)	CCB (amlodipine)	59.3±7.1	59.1±7.9	201 (34.7)	208 (36.7)	579	567	329 (28.7)	NA	NA	NA	NA	1,146 (100)	NA	NA	1,146 (100)	2.6	160±20/ 87±11	140/77	159±19/ 87±11	141/77	NA	NA	28/15	NA	52/37
		ARB (irbesartan)	Placebo	59.3±7.1	58.3±8.2	201 (34.7)	166 (29.2)	579	569	322 (28.0)	NA	NA	NA	NA	1,148 (100)	NA	NA	1,148 (100)	2.6	160±20/ 87±11	140/77	158±20/ 87±11	144/80	NA	NA	28/26	NA	52/46
		CCB (amlodipine)	Placebo	59.1±7.9	58.3±8.2	208 (36.7)	166 (29.2)	567	569	335 (29.5)	NA	NA	NA	NA	1,136 (100)	NA	NA	1,136 (100)	2.6	159±19/ 87±11	141/77	158±20/ 87±11	144/80	NA	NA	15/26	NA	37/46
I-Preserve[41]	HF (NYHA II-IV)+LVEF ≥45%+≥60 years	ARB (irbesartan)	Placebo	72±7	72±7	1,227 (59)	1,264 (61)	2,067	2,061	4,128 (100)	969 (23)	399 (10)	3,650 (88.4)	NA	1,134 (27)	4,128 (100)	1,209 (29.3)	NA	4.1	137±15/ 79±9	NA	136±15/ 79±9	NA	NA	NA	68/79	221/226	NA
ONTARGET[2]	Vascular disease/ DM+high risk	ARB (telmisartan)+ ACEi (ramipril)	ACEi (ramipril)	66.5±7.3	66.4±7.2	2250 (26.5)	2,331 (27.2)	8,502	8,576	NA	12,735 (74.6)	3,584 (21.0)	11,745 (68.8)	2,307 (13.5)	6,366 (37)	0	NA	1,858 (11)	4.7	141.9±17.6/ 82.1±10.4	NA	141.8±17.4/ 82.1±10.4	NA	NA	NA	373/405	1,065/ 1,014	620/603
		ARB (telmisartan)	ACEi (ramipril)	66.4±7.2	66.4±7.2	2,250 (26.3)	2,331 (27.2)	8,542	8,576	NA	12,749 (74.5)	3,563 (20.8)	11,780 (68.8)	2,297 (13.4)	6,392 (37)	0	NA	1,852 (11)	4.7	141.7±17.2/ 82.1±10.4	NA	141.8±17.4/ 82.1±10.4	NA	NA	NA	369/405	989/1,014	598/603
OSCAR[42]	HTN aged 65-84 years+DM2/CVD	ARB (olmesartan)+CCB (amlodipine or azelnidipine)	ARB (olmesartan)	73.6±5.5	73.6±5.3	325 (55.5)	324 (56.1)	586	578	812 (69.8)	NA	207 (17.8)	1,164 (100)	25 (2.1)	NA	89 (7.6)	NA	127 (10.9)	3	157.2±11.3/ 84.6±9.8	132.6/72.6	158.2±12.6/ 85.2±10.1	135.0/74.3	NA	NA	15/24	NA	NA
Oslo Study[43]	HTN aged 20–49 years (SBP 150–179 mm Hg, DBP <110 mm Hg)	Diuretic (hydrochlorothiazide)±Alphaadrenergic agonist (alphamethyldopa)/BB (propranolol)	Placebo	45.3±2.9	45.2±2.8	0	0	406	379	0	0	0	785 (100)	0	0	0	0	0	5.5	156.2±7.1/ 97.4±6.9	NA	155.3±7.6/ 96.2±7.2	NA	NA	NA	0/5	NA	NA
PART-2[44]	CHD/CVD without HF	ACEi (ramipril)	Placebo	60±8	61±8	55 (17.9)	56 (18.1)	308	309	617 (100)	259 (42.0)	20 (3.2)	617 (100)	40 (6.5)	38 (6.2)	0	NA	NA	4.7	133±17/ 79±9	127/74	133±16/ 79±10	132/78	31	3	7/4	16/25	8/18
PATS[45]	History of TIA/ non-disablling stroke	Diuretic (indapamide)	Placebo	60.1±8.3	60.4±8.5	803 (28.3)	785 (27.8)	2,840	2,825	NA	NA	5,665 (100)	4,752 (83.9)	NA	NA	0	0	0	2	153.6±23.8/ 92.6±13.3		154.0±23.3/ 93.0±12.7		NA	NA	159/219	145/161	86/102
PEACE[46]	CAD	ACEi (trandolapril)	Placebo	64±8	64±8	790 (19)	702 (17.0)	4,158	4,132	8,290 (100)	8,290 (100)	539 (7.0)	3,772 (45.5)	NA	1,410 (17)	0	NA	NA	4.8	134±17/ 78±10		133±17/ 78±10		599	269	71/92	299/334	146/152
PHARAO[47]	Aged 50-85 years with high-normal office BP	ACEi (ramipril)	Placebo	62.2±8.2	62.3±7.9	254 (50.3)	266 (52.9)	505	503	NA	65 (6)	NA	1,008 (100)	15 (1.5)	135 (13)	0	NA	0	3	134.4±3.7/ 83.6±4.2	130.2/79.0	134.4±3.4/ 83.6±4.7	133.0/79.9	NA	NA	2/1	5/2	0/0
PREVEND IT[48]	Microalbuminuria	ACEi (fosinopril)	Placebo	51.1±12.2	51.5±11.4	146 (33.9)	157 (36.3)	431	433	29 (3)	NA	7 (1.0)	NA	5 (0.6)	22 (3)	0	NA	864 (100)	3.8	129±17/ 76±10	129±18	131±18/ 76±10	132±18	58	18	1/10	NA	5/3
PREVENT[49]	CAD	CCB (amlodipine)	Placebo	56.8	57	84 (20.1)	80 (19.6)	417	408	NA	825 (100)	25 (3.0)	NA	NA	NA	NA	NA	NA	3	128.8/ 78.8	122/75	130.0/ 78.9	NA	NA	NA	5/5	6/8	NA
PRoFESS[50]	Ischaemic stroke	ARB (telmisartan)	Placebo	66.1±8.6	66.2±8.6	3,619 (35.7)	3,691 (36.2)	10,146	10,186	NA	NA	20,332 (100)	15,048 (74.0)	NA	5,743 (28)	NA	540 (2.7)	NA	2.5	144.1±16.4/ 83.8±10.5	135/79	144.2±16.7/ 83.8±10.6	NA	1,450	1,127	880/934	755/740	223/263
PROGRESS[51]	Stroke/TIA±HTN	ACEi (perindopril)± diuretic (indapamide)	Placebo	64±10	64±10	923 (30)	929 (30)	3,051	3,054	6,105 (100)	983 (16.1)	6,105 (100)	2,916 (47.8)	244 (4.0)	762 (12)	0	488 (8.0)	NA	3.9	147±19/ 86±11	134/79	147±19/ 86±11	NA	111	98	307/420	306/319	181/198
ROADMAP[52]	DM2+ normoalbuminuria+≥1 CVD risk factor	ARB (olmesartan)	Placebo	57.7±8.8	57.8±8.6	1,182 (53.0)	1,212 (54.7)	2,232	2,215	NA	1,104 (24.8)	104 (2.3)	NA	25	4,447 (100)	NA	NA	0	3.2	137±16/ 81±10	125.7/74.3	136±15/ 80±9	128.7/76.2	85	89	NA	26/15	15/3
SCOPE[53]	Elderly HTN (mild-moderate)	ARB (candesartan)	Placebo	76.4	76.4	1,605 (64.8)	1,579 (64.2)	2,477	2,460	NA	NA	193 (4.0)	4,937 (100)	NA	607 (12.3)	NA	NA	NA	3.7	166.0/ 90.3	145.2/79.9	166.5/90.4	148.5/81.6	372	418	89/115	259/266	145/152
SHEP[54]	Elderly ISH (SBP 160-219 mm Hg, DBP <90 mm Hg)	Diuretic (chlorthalidone)± BB (atenolol)	Placebo	71.6±6.7	71.5±6.7	1,339 (56.6)	1,361 (57.4)	2,365	2,371	NA	NA	66 (1.4)	4,736 (100)	NA	478 (10.1)	NA	NA	NA	4.5	170.5±9.5/ 76.7±9.6	144.0±19.3/ 67.7±10.2	170.1±9.2/ 76.4±9.8	155.1±20.9/ 71.1±12.8	307	166	96/149	213/242	90/112
SOLVD-Treatment[55]	CHF+EF ≤35%	ACEi (enalapril)	Placebo	60.7	61.0	245 (19.1)	259 (20.2)	1,285	1,284	2,569 (100)	1,687 (66)	NA	1,083 (42.2)	NA	663 (26)	2,569 (100)	249 (9.7)	NA	3.5	125.3/ 77.3	NA	124.5/76.4	NA	NA	NA	10/11	452/510	399/461
SOLVD-Prevention[56]	EF ≤35%+LVD	ACEi (enalapril)	Placebo	59.1	59.1	243 (11.5)	241 (11.4)	2,111	2,117	4,228 (100)	3,380 (80)	NA	1,566 (37.0)	NA	645 (15)	4,228 (100)	167 (4.0)	NA	3.1	125.3/ 77.9	NA	125.6/78.0	NA	NA	NA	10/13	313/334	265/298
SUPPORT[57]	CHF+HTN	ARB (olmesartan)	Placebo	65.8±10.4	65.5±10.1	149 (25.8)	142 (24.8)	578	569	1,147 (100)	545 (48)	NA	NA	NA	575 (50)	1,147 (100)	NA	0	4.4	128.7±18.2/ 74.8±12.2	NA	127.1±18.0/ 73.9±11.7	NA	NA	NA	34/26	98/85	48/38
STONE[58]	Elderly HTN (60-79 years, SBP≥ 160 mm Hg, DBP ≥96 mm Hg)	CCB (nifedipine)	Placebo	66.1	66.7	408 (49.9)	459 (56.3)	817	815	NA	NA	NA	1,632 (100)	NA	NA	NA	NA	NA	2.5	168.5±13/ 98.5±7		168.5±15/ 97±7		NA	NA	16/36	15/26	11/14
STOP-Hypertension[59]	Elderly HTN (70-84 years), SBP: 180-230 mm Hg, DBP ≥90 mm Hg (or DBP 105-120 irrespective of SBP)	3BB+1 diureteic (atenolol, hydrochlorothiazide, amiloride, metoprolol, or pindolol)	Placebo	75.6±3.7	75.7±3.7	510 (63)	509 (63)	812	815	NA	NA	NA	1,627 (100)	NA	NA	NA	NA	NA	2.1	195±14/ 102±7	166±21/ 85±10	195±14/ 102±7	193±20/ 95±11	NA	NA	29/53	36/63	17/41
Syst-China[60]	ISH elderly (≥60 years, SBP 160-219 mm Hg, DBP <95 mm Hg)	CCB (nitrendipine)±ACEi (captopril) and/or diuretic (hydrochlorothiazide)	Placebo	66.4±5.4	66.7±5.7	438 (35.0)	415 (36.4)	1,253	1,141	269 (11)	224	34 (1.4)	2,394 (100)	NA	98 (4.1)	NA	NA	NA	3	170.7±10.9/ 86.1±6.7		170.2±11.4/ 85.9±7.0		NA	NA	45/59	61/82	33/44
Syst-Eur[61]	ISH elderly (≥60 years, SBP 160-219 mm Hg, DBP <95 mm Hg)	CCB (nitrendipine)±ACEi (enalapril) and/or diuretic (hydrochlorothiazide)	Placebo	70.3±6.7	70.2±6.7	1,520 (63.4)	1,618 (70.4)	2,398	2,297	1,402 (30)	NA	NA	4,695 (100)	NA	NA	NA	NA	NA	2	173.8±9.9/ 85.5±5.8		173.9±10.1/ 85.5±5.9		NA	NA	47/77	123/137	59/77
TRANSCEND[62]	ACEi intolerance+CVD/ DM	ARB (telmisartan)	Placebo	66.9±7.3	66.9±7.4	1,280 (43.3)	1,267 (42.6)	2,954	2,972	NA	4,418 (74.6)	1,302 (22.0)	4,528 (76.4)	672 (11.3)	2,118 (35.7)	0	NA	NA	4.7	140.7±16.8/ 81.8±10.1	134.2/NA	141.3±16.4/ 82.0±10.2	NA	NA	NA	112/136	364/349	227/223
VA-NEPHRON[63]	DM2+nephropathy	ACEi (lisinopril)+ARB (losartan)	Placebo+ARB (losartan)	64.5±7.9	64.7±7.7	9 (1.2)	3 (0.4)	724	724	NA	NA	NA	NA	NA	1,448 (100)	NA	NA	1,448 (100)	2.2	136.9±16.5/ 72.5±10.6	132/NA	137.0±16.0/ 72.8±9.9	NA	NA	NA	18/18	63/60	NA
AASK[64]	African American hypertensive CKD (DBP ≥95 mm Hg), without DM/HF	Intensive (SBP/DBP ≤130/80 mm Hg)	Moderate (SBP/DBP ≤140/90 mm Hg)	54.5±10.9	54.7±10.4	206 (38.1)	219 (39.5)	540	554	NA	564 (52)	NA	1,094 (100)	NA	0	0	NA	1,094 (100)	4.1	152±25/ 96±15	128±21/ 78±14	149±23/ 95±14	140±18/ 86±11	NA	NA	26/29	38/47	16/15
		ACEi (ramipril)	BB (metoprolol)	54.4±10.9	54.9±10.4	168 (38.5)	170 (38.6)	436	441	NA	NA	NA	877 (100)	NA	0	0	NA	877 (100)	4.1	151±23/ 96±15	135±14/ 82±9	150±24/ 95±14	135±13/ 81±9	NA	NA	23/23	NA	12/12
		CCB (amlodipine)	BB (metoprolol)	54.5±10.7	54.9±10.4	86 (39.6)	170 (38.6)	217	441	NA	NA	NA	658 (100)	NA	0	0	NA	658 (100)	4.1	150±25/ 96±14	133±12/ 81±8	150±24/ 95±14	135±13/ 81±9	NA	NA	9/23	NA	7/12
		ACEi (ramipril)	CCB (amlodipine)	54.4±10.9	54.5±10.7	168 (38.5)	86 (39.6)	436	217	NA	NA	NA	653 (100)	NA	0	0	NA	653 (100)	4.1	151±23/ 96±15	135±14/ 82±9	150±25/ 96±14	133±12/ 81±8	NA	NA	23/9	NA	12/7
ABCD-H[65]	DM2+HTN (DBP ≥90 mm Hg)	Intensive (DBP <75 mm Hg)	Moderate (DBP 80-90 mm Hg)	57.5±0.5	57.2±0.5	78 (32.9)	75 (32.2)	237	233	NA	115 (24.5)	5 (1.1)	470 (100)	NA	470 (100)	3 (0.6)	NA	37 (7.9)	5	156.1±1.1/ 98.0±0.4	133/78	154.9±1.2/ 97.8±0.4	NA	NA	NA	9/9	13/25	NA
		Nisoldipine	Enalapril	57.2±8.2	57.7±8.4	75 (31.9)	78 (33.2)	235	235	NA	115 (24.5)	5 (1.1)	470 (100)	NA	470 (100)	3 (0.6)	NA	37 (7.9)	5	155±19/ 98±7	NA	156±17/ 98±7	NA	NA	NA	11/7	17/13	10/5
ABCD-N[66]	DM2+normotensive (<140/90 mm Hg)	Intensive (DBP 10 mm Hg below the baseline DBP)	Moderate (DBP 80-89 mm Hg)	58.5±0.6	59.6±0.5	111 (46.8)	107 (44.0)	237	243	NA	115 (24.0)	17 (3.5)	0	NA	480 (100)	10 (2.1)	NA	NA	5.3	135.6±0.8/ 84.4±0.2	128±0.8/ 75±0.3	137.2±0.9/ 84.4±0.2	137±0.7/ 81±0.3	NA	NA	4/13	18/20	13/9
		CCB (nisoldipine)	ACEi (enalapril)	59.1±0.5	59.4±0.5	115 (46.7)	103 (44)	234	246	NA	115 (24.0)	17 (3.5)	0	NA	480 (100)	10 (2.1)	NA	NA	5.3	135.4±0.8/ 84.3±0.2	132.1±0.7/ 78.0±0.4	137.4±0.9/ 84.5±0.2	132.4±0.9/ 78.0±0.4	NA	NA	11/6	19/19	8/14
ACCORD[67]	DM2+high risk	Intensive (SBP <120 mm Hg)	Standard (SBP <140 mm Hg)	62.2±6.9	62.2±6.9	1,128 (47.8)	1,130 (47.7)	2,362	2,371	1,593 (34)	NA	NA	NA	NA	4,733 (100)	203 (4.3)	NA	NA	4.7	139.0±16.1/ 75.9±10.6	119.3/64.4	139.4±15.5/ 76.0±10.2	133.5/ 70.5	NA	NA	36/62	150/144	60/58
BBB[68]	Treated HTN (DBP 90-100 mm Hg) without CHD	Intensive (DBP ≤80 mm Hg)	Usual (DBP 80-100 mm Hg)	59.6	60.1	NA	NA	1,064	1,063	NA	0	NA	2,127 (100)	NA	NA	NA	NA	NA	4.9	155±15/ 95±4	141/83	155±15/ 94±4	152/91	NA	NA	8/11	NA	NA
Cardio-sis[69]	HTN SBP ≥ 150 mm Hg+≥1 risk factor	Intensive (SBP <130 mm Hg)	Usual (SBP <140 mm Hg)	67±7	67±7	329 (59)	324 (59)	558	553	NA	128 (11.5)	91 (8.2)	1,111 (100)	NA	0	0	0	0	2	163.3±11.3/ 89.6±8.8		163.3±11.1/ 89.7±8.8		NA	NA	4/9	4/5	NA
HDFP[70]	HTN	Intensive (stepped care)	Usual (referred care)	50.8	50.8	2,529 (46.1)	2,509 (46.0)	5,485	5,455	NA	564 (5.2)	273 (2.5)	10,940 (100)	NA	771 (7)	NA	NA	NA	5	159.0/101.1	NA/84.1	158.5/101.1	NA/89.1	NA	NA	102/158	349/419	195/240
HOMED-BP[71]	HTN+>40 years	Tight (125/80 mm Hg)	Usual (SBP 125–134 mm Hg, DBP 80–84 mm Hg)	59.6±10.2	59.6±9.9	883 (50)	880 (50)	1,759	1,759	106 (3)	NA	NA	3,518 (100)	NA	538 (15)	NA	NA	NA	5.3	151.5±12.3/ 90.0±9.8		151.7±12.6/ 89.9±10.3		NA	NA	20/16	27/31	3/5
		ACEi	ARB	59.8±10.0	59.5±10.1	589 (50)	588 (50)	1,172	1,175	75 (3)	NA	NA	2,347 (100)	NA	372 (16)	NA	NA	NA	5.3	151.6±12.5/ 89.8±10.0	129.3±13.3/ 76.1±9.4	151.6±12.4/ 89.8±10.1	129.8±13.0/ 76.5±9.6	NA	NA	11/9	17/16	2/2
		CCB	ACEi	59.5±10.1	59.8±10.0	586 (50)	589 (50)	1,171	1,172	65 (3)	NA	NA	2,343 (100)	NA	347 (15)	NA	NA	NA	5.3	151.6±12.6/ 90.1±9.9	130.1±13.3/ 76.8±9.7	151.6±12.5/ 89.8±10.0	129.3±13.3/ 76.1±9.4	NA	NA	16/11	25/17	4/2
		CCB	ARB	59.5±10.1	59.5±10.1	586 (50)	588 (50)	1,171	1,175	72 (3)	NA	NA	2,346 (100)	NA	357 (15)	NA	NA	NA	5.3	151.6±12.6/ 90.1±9.9	130.1±13.3/ 76.8±9.7	151.6±12.4/ 89.8±10.1	129.8±13.0/ 76.5±9.6	NA	NA	16/9	25/16	4/2
HOT[5]	HTN (DBP 100-115 mm Hg)	DBP 85 mm Hg	DBP 90 mm Hg	61.5±7.5	61.5±7.5	2,944 (47.0)	2,944 (47.0)	6,264	6,264	NA	745 (5.9)	150 (1.2)	12,528 (100)	NA	1,002 (8)	NA	NA	NA	3.8	170±14.0/ 89±23	141.4±11.7/ 83.2±4.8	170±14.4/ 89±26	143.7±11.3/ 85.2±5.1	NA	NA	111/94	194/188	90/87
		DBP 80 mm Hg	DBP 90 mm Hg	61.5±7.5	61.5±7.5	2,944 (47.0)	2,943 (47.0)	6,262	6,264	NA	739 (5.9)	150 (1.2)	12,526 (100)	NA	1,000 (8)	NA	NA	NA	3.8	170±14.1/ 89±23	139.7±11.7/ 81.1±5.3	170±14.4/ 89±26	143.7±11.3/ 85.2±5.1	NA	NA	89/94	207/188	96/87
		DBP 80 mm Hg	DBP 85 mm Hg	61.5±7.5	61.5±7.5	2,944 (47.0)	2,943 (47.0)	6,262	6,264	NA	745 (5.9)	150 (1.2)	12,526 (100)	NA	1,000 (8)	NA	NA	NA	3.8	170±14.1/ 89±23	139.7±11.7/ 81.1±5.3	170±14.0/ 89±23	141.4±11.7/ 83.2±4.8	NA	NA	89/111	207/194	96/90
JATOS[72]	Elderly+HTN	Strict (SBP <140 mm Hg)	Mild (SBP 140-159 mm Hg)	73.6±5.3	73.6±5.2	1,338 (60.5)	1,363 (61.8)	2,212	2206	NA	134 (3.0)	192 (4.3)	4,418 (100)	NA	521 (11.8)	0	NA	439 (9.9)	2	171.6±9.7/ 89.1±9.5	135.9±11.7/ 74.8±9.1	171.5±9.8/ 89.1±9.5	145.6±11.1/ 78.1±8.9	NA	NA	43/38	44/42	9/8
SPRINT[73]	High risk of CVD, >50 years, SBP 130-180 mm Hg, without DM2	Intensive (SBP <120 mm Hg)	Standard (SBP <140 mm Hg)	67.9±9.4	67.9±9.5	1,684 (36.0)	1,648 (35.2)	4,678	4,683	1,877 (20.1)	NA	NA	9,361 (100)	NA	0	0	NA	2,646 (28.3)	3.3	139.7±15.8/ 78.2±11.9	121.5/NA	139.7±15.4/ 78.0±12.0	134.6/NA	NA	NA	62/70	155/210	37/65
SPS3[74]	Previous strok	SBP <130 mm Hg	SBP 130-149 mm Hg	63±10.7	63±10.8	589 (39)	529 (35)	1,501	1,519	3,020 (100)	317 (10.5)	3,020 (100)	2,264 (75.0)	NA	1,106 (37)	NA	NA	NA	3.7	142.4±18.5/ 77.6±10.4	126.7±16.5/ 69.1±10.4	143.6±19.1/ 79.0±10.8	137.4±16.2/ 74.8±10.9	NA	NA	125/152	106/101	36/41
UKPDS 38[75]	HTN+DM2	Strict BP control (<150/85 mm Hg)	Less strict BP control (<180/105 mm Hg)	56.4±8.1	56.5±8.1	348 (46)	163 (42)	758	390	NA	NA	NA	1,148 (100)	NA	1,148 (100)	0	NA	NA	8.4	159±20/ 94±10	144±14/ 82±7	160±18/ 94±9	154±16/ 87±7	NA	NA	38/34	134/83	NA
VALISH[76]	Aged ≥70 and <85 years with ISH (SBP >160 mm Hg and DBP <90 mm Hg)	Strict (SBP <140 mm Hg)	Moderate (SBP 140-149 mm Hg)	76.1±4.1	76.1±4.1	963 (62.3)	961 (62.5)	1,545	1,534	NA	153	202 (6.6)	3,079 (100)	NA	399 (13)	53 (1.7)	NA	43 (1.4)	2.9	169.5±7.9/ 81.7±6.6	136.6±13.3/ 74.8±8.8	169.6±7.9/ 81.2±6.8	142±12.5/ 76.5±8.9	NA	NA	16/23	24/30	11/11
CAPPP[77]	DBP ≥100 mm Hg	Diuretic/BB	ACEi (captopril)	55.7±7.4	55.0±7.6	105 (39.9)	113 (36.6)	263	309	52 (9.1)	NA	10 (1.7)	572 (100)	NA	572 (5)	9 (1.6)	NA	57 (10.0)	6.1	163.3±20.6/ 97.3±10.1	153.5/88.0	163.6±18.8/ 97.1±9.6	155.5/ 89.0	NA	NA	19/23	NA	NA
IPPPSH[78]	HTN (DBP 100-125 mm Hg)	BB (oxprenolol)	Non-BB	52.3±6.5	52.2±6.5	1,580 (49.6)	1,583 (49.9)	3,185	3,172	0	0	0	6,357 (100)	0	NA	0	NA	0	4	173/107.9	143.6/88.9	173/ 107.6	147.4/ 90.1	NA	NA	45/46	108/114	NA
NORDIL[79]	HTN (DBP ≥100 mm Hg)	Diuretic/BB	CCB (diltiazem)	60.3±6.5	60.5±6.5	2,805 (51.3)	2,786 (51.5)	5,471	5,410	NA	NA	162 (1.5)	10,881 (100)	NA	727 (7)	NA	101 (0.9)	NA	4.5	173.4±17.5/ 105.7±5.3	151.7/88.7	173.5±17.7/ 105.8±5.3	154.9/ 88.6	NA	NA	196/159	228/231	115/131
ACCOMPLISH[80]	HTN+high risk	CCB+ACEI (benazepril–amlodipine)	Diuretic+ ACEI (benazepril–hydrochlorothiazide)	68.4±6.86	68.3±6.86	2,296 (40)	2,246 (39)	5,744	5,762	NA	2,709 (24)	1,498 (13.0)	11,506 (100)	NA	6,946 (60)	0	769 (6.7)	705 (6.1)	3	145.3±18.4/ 80.1±10.8	131.6/73.3	145.4±18.1/ 80.0±10.7	132.5/ 74.4	1,654	1,798	112/133	236/262	107/134
ALLHAT[81]	HTN+CVD/risk factors for CVD	CCB (amiodipine)	Diuretic (chlorthalidone)	66.9±7.7	66.9±7.7	4,280 (47.3)	7,171 (47.0)	9,048	15,255	18,263 (75.1)	6,145 (25.3)	NA	24,303 (100)	NA	8,851 (36)	NA	NA	NA	4.9	146±16/ 84±10	134.7± 14.9/ 74.6± 9.9	146±16/ 84±10	133.9±15.2/ 75.4±9.8	NA	NA	377/675	1,256/ 2,203	592/992
		ACEIi (lisinopril)	Diuretic (chlorthalidone)	66.9 ± 7.7	66.9 ± 7.7	4187 (46.2)	7171 (47.0)	9054	15255	18340 (75.4)	6213 (25.6)	NA	24309 (100)	NA	8740 (36)	NA	NA	NA	4.9	146±16/ 84±10	135.9±17.9/ 75.4±10.7	146±16/ 84±10	133.9±15.2/ 75.4±9.8	NA	NA	457/675	1,314/ 2,203	609/992
ASCOT[82]	HTN aged 40–79 years+≥3 risk factors for CVD, no CHD	CCB (amiodipine)	BB (atenolol)	63.0±8.5	63.0±8.5	2,258 (23)	2,257 (23)	9,639	9,618	NA	NA	2,113 (11.0)	19,257 (100)	1,199 (6.2)	5,145 (27)	NA	230 (1.2)	NA	5.5	164.1±18.1/ 94.8±10.4	136.1±15.4/ 77.4±9.5	163.9±18.0/ 94.5±10.4	137.7±17.9/ 79.2±10.0	NA	NA	327/422	738/820	263/342
CASE-J[83]	HTN+≥1 risk factor	ARB (candesartan)	CCB (amiodipine)	63.8±10.5	63.9±10.6	1,092 (46.4)	1,014 (43.2)	2,354	2,349	NA	2,030 (43.2)	473 (10.1)	4,703 (100)	NA	2,018 (43)	NA	NA	1,115 (23.7)	3.2	162.5±14.2/ 91.6±11.0	136.1±12.9/ 77.3±9.6	163.2±14.2/ 91.8±11.4	134.4±12.1/ 76.7±9.3	NA	NA	60/47	73/86	NA
COLM[84]	Elderly HTN +history CVD/risk factor(s)	ARB (olmesartan)+CCB (amlodipine, azelnidipine)	ARB (olmesartan)+diuretic	73.6±5.3	73.6±5.4	1,245 (48.5)	1,243 (48.3)	2,568	2,573	1,225 (23.8)	563 (11.0)	751 (14.6)	5,141 (100)	NA	1,362 (26)	NA	NA	NA	3.3	158.0±12.7/ 87.1±10.8	132.9±12.6/ 73.2±9.8	158.0±12.5/ 86.9±10.8	132.9±13.6/ 73.5±9.8	NA	NA	63/66	64/76	13/18
CONVINCE[85]	HTN+≥1 risk factor	CCB (COER verapamil)	BB (atenolol) or diuretic (hydrochlorothiazide)	65.6±7.4	65.6±7.4	4,596 (56.2)	4,528 (55.8)	8,179	8,297	NA	1,259 (7.6)	763 (4.6)	16,602 (100)	NA	3,239 (20)	0	NA	0	3	150.1±15.8/ 86.8±9.8		150.1±16.0/ 86.8±9.8		NA	NA	133/118	337/319	152/143
COPE[86]	HTN (SBP ≥140 mm Hg or DBP ≥90 mm Hg)	BB+CCB (benidipine)	ARB+CCB (benidipine)	63.2±10.8	63.0±10.6	539 (49.5)	544 (49.0)	1,089	1,110	268 (12)	16 (0.7)	60 (2.7)	2,199 (100)	NA	309 (14)	0	NA	570 (25.9)	3.6	153.7±10.9/ 88.7±9.6	133.9±15.3/ 77.0±10.6	153.9±11.8/8 9.9±9.8	134.7±15.2/ 77.2±10.6	NA	NA	27/17	23/25	NA
		ARB+CCB (bbenidipine)	TD+CCB (benidipine)	63.0±10.6	63.1±10.8	544 (49.0)	541 (49.5)	1,110	1,094	281 (13)	16 (0.7)	61 (2.8)	2,204 (100)	NA	311 (14)	0	NA	551 (25.0)	3.6	153.9±11.8/ 89.9±9.8	134.7±15.2/ 77.2±10.6	154.1±12.0/ 88.7±9.8	134.0±14.4/ 76.6±10.6	NA	NA	17/12	25/23	NA
		BB+CCB (benidipine)	TD+CCB (benidipine)	63.2±10.8	63.1±10.8	539 (49.5)	541 (49.5)	1,089	1,094	261 (12)	12 (0.5)	51 (2.3)	2,183 (100)	NA	312 (14)	0	NA	547 (25.1)	3.6	153.7±10.9/ 88.7±9.6	133.9±15.3/ 77.0±10.6	154.1±12.0/ 88.7±9.8	134.0±14.4/ 76.6±10.6	NA	NA	27/12	23/23	NA
E-COST[87]	HTN	ARB (candesartan)	Conventional (other than ACEi or ARB)	NA	NA	585 (55.6)	480 (48.2)	1,053	995	341 (17)	NA	NA	2,048 (100)	NA	0	0	NA	NA	3.1	162.1±9.2/ 91.1±6.1	140.1±7.6/ 78.9±5.4	165.9±5.8/ 95.9±5.6	138.4±7.9/ 81.1±7.5	NA	NA	47/77	NA	NA
ELSA[88]	SBP (150-210 mm Hg) and DBP (95-115 mm Hg)	BB (antenolol)	CCB (lacidipine)	55.9±7.5	56.1±7.5	516 (45.6)	539 (45.8)	1,157	1,177	NA	NA	NA	2,334 (100)	NA	NA	NA	NA	NA	3.75	163.1±12.5/ 101.3±4.9		163.9±12.2/ 101.4±5.3		NA	NA	14/9	17/13	8/4
INSIGHT[89]	HTN (BP ≥150/95 mm Hg or ≥160 mm Hg)+≥1 CVD risk factor	CCB (nifedipine)	Diuretic (co-amilozide: hydrochlorothiazide-amiloride)	65±6.5		1,701 (53.9)	1,691 (53.4)	3,157	3,164	NA	405 (6.4)	NA	6,321 (100)	353 (5.6)	1,302 (21)	NA	NA	NA	4	173±14/ 99±8	138±12/ 82±7	173±14/ 99±8	138/82	NA	NA	67/74	153/152	60/52
INVEST[90]	HTN+CAD	CCB (verapamil)	BB (atenolol)	66.0±9.7	66.1±9.8	5,850 (51.9)	5,920 (52.3)	11,267	11,309	22,576 (100)	22,576 (100)	1,162 (100)	22,576 (100)	2,699 (12.0)	6,400 (28)	1,256	NA	424 (1.9)	2.7	149.5±19.7/ 86.3±12.0		149.5±19.7/ 86.3±11.9		NA	NA	131/148	873/893	431/431
LIFE[91]	LVH+HTN (160-200/95-115 mm Hg)	ARB (losartan)	BB (atenolol)	66.9±7.0	66.9±7.0	2,487 (54)	2,476 (54)	4,605	4,588	NA	1,469 (16.0)	728 (8)	9,193 (100)	520 (5.7)	1,195 (13)	0	324 (3.5)	NA	4.8	174.3±14.2/ 97.9±8.8		174.5±14.4/ 97.7±9.0		NA	NA	232/309	383/431	204/234
MOSES[92]	HTN+history of a cerebrovascular events	ARB (eprosartan)	CCB (nitrendipine)	67.7±10.4	68.1±9.5	316 (46.4)	303 (45.2)	681	671	1,352 (100)	110 (8.1)	1,352 (100)	1,352 (100)	NA	498 (37)	NA	0	72 (5.3)	2.5	150.7±18.5/ 87.0±10.8	NA	152.0±18.2/ 87.2±9.6	NA	NA	NA	102/134	57/52	NA
MRC-1[93]	HTN 90-109 mm Hg	Diuretic (bendrofluazide)	Placebo	NA	NA	2,059 (47.9)	4,129 (47.7)	4,297	8,654	NA	NA	NA	12,951 (100)	NA	0	0	NA	NA	5.5	161.5/98.5	NA	161.5/ 98.5	NA	NA	NA	18/109	128/253	69/192
		BB (propranolol)	Placebo	NA	NA	2,118 (48.1)	4,129 (47.7)	4,403	8,654	NA	NA	NA	13,057 (100)	NA	0	0	NA	NA	5.5	161.5/98.5	NA	161.5/ 98.5	NA	NA	NA	42/109	120/253	65/192
		Diuretic (bendrofluazide)	BB (propranolol)	NA	NA	2,059 (47.9)	2,118 (48.1)	4,297	4,403	NA	NA	NA	8,700 (100)	NA	0	0	NA	NA	5.5	161.5/98.5	NA	161.5/ 98.5	NA	NA	NA	18/42	128/120	69/65
MRC-2[94]	HTN elderly (SBP 160-209 mm Hg, DBP <115 mm Hg)	Diuretic (amiloride, hydrochlorothiazide)	BB (atenolol)	NA	NA	627 (58.0)	646 (58.6)	1,081	1,102	NA	NA	NA	2,183 (100)	NA	0	0		0	5.8	184.5/91	NA	184.5/ 91	NA	NA	NA	45/56	134/167	66/95
		Diuretic (amiloride, hydrochlorothiazide)	Placebo	NA	NA	627 (58.0)	1,287 (58.2)	1,081	2,213	NA	NA	NA	3,294 (100)	NA	0	0		0	5.8	184.5/91	NA	184.5/ 90.5	NA	NA	NA	45/134	134/315	66/180
		BB (atenolol)	Placebo	NA	NA	646 (58.6)	1,287 (58.2)	1,102	2,213	NA	NA	NA	3,315 (100)	NA	0	0		0	5.8	184.5/91	NA	184.5/ 90.5	NA	NA	NA	56/134	167/315	95/180
NHS[95]	HTN+DM2/ IGT	ARB (valsartan)	CCB (amlodipine)	63±8	63±8	197 (34)	199 (34)	575	575	306 (26.6)	NA	54 (4.7)	1,150 (100)	NA	942 (81.9)	NA	NA	NA	3.2	145±18/ 82±13	131/73	144±19/ 81±13	132/74	NA	NA	13/16	22/16	4/4
NICS-EH[96]	HTN ≥60 years with SBP 160-220 mm Hg and DBP <115 mm Hg	CCB (nicardipine) +diuretic (hydrochloride)	Diuretic (trichlormethiazide)	69.7±6.5	69.9±6.4	122 (59.8)	155 (73.8)	204	210	0	0	0	414 (100)	0	0	0	0	0	5	171.9±12.9/ 94.2±10.2	147±15/ 81±8	172.6±11.0/ 93.4±10.2	147±16/ 79±9	6	9	12/8	NA	NA
PATE[97]	HTN+>60 years	ACEi (delapril)	CCB (manidipine)	70±7	69±7	431 (61.7)	595 (56.7)	699	1,049	NA	17 (1)	85 (5)	1,748 (100)	NA	228 (13)	NA	NA	42 (2)	2.4	151±17/ 84±10	142±12/ 80±8	148±18/ 82±10	141±12/ 78±9	35	13	12/20	11/18	7/10
SHELL[98]	Elderly ISH (≥60 years, SBP ≥160 mm Hg, DBP ≤95 mm Hg)	CCB (lacidipine)	Diuretic (chlorthalidone)	72.3±7.5	72.4±7.6	569 (60.4)	585 (62.2)	942	940	576 (31)	NA	NA	1,882 (100)	NA	249 (13)	NA	NA	0	2.7	178.1±10.2/ 86.9±5.7	142/79.2	178.2±10.3/ 86.8±5.8	NA	NA	NA	37/38	145/122	NA
STOP-2[99]	Elderly HTN (70-84 years)	ACEi (enalapril or lisinopril)	Conventional BB/diuretic (atenolol, metoprolol, pindolol, or hydrochlorothiazide plus amiloride)	76.1	76	1,462 (66.3)	1,505 (68.0)	2,205	2,213	NA	NA	172 (3.9)	4,418 (100)	NA	488 (11.0)	84 (1.9)	221 (5.0)	NA	4	194/98	159/81	194/98	158/81	NA	NA	215/237	380/369	226/221
		CCB (felodipine or isradipine)	Conventional BB/diuretic (atenolol, metoprolol, pindolol, or hydrochlorothiazide plus amiloride)	75.9	76	1,449 (66.0)	1,505 (68.0)	2,196	2,213	NA	NA	169 (3.8)	4,409 (100)	NA	483 (11.0)	77 (1.7)	194	NA	4	194/98	159/80	194/98	158/81	NA	NA	207/237	362/369	212/221
		ACEi (enalapril or lisinopril)	CCB (felodipine or isradipine)	76.1	75.9	1,462 (66.3)	1,449 (66.0)	2,205	2,196	NA	NA	169 (3.8)	4,401 (100)	NA	467 (10.6)	95 (2.2)	207 (4.7)	NA	4	194/98	159/81	194/98	159/80	NA	NA	215/207	380/362	226/212
VALUE[100]	HTN+risk factor (SBP 160-210 mm Hg, DBP <115 mm Hg)	ARB (valsartan)	CCB (amlodipine)	67.2±8.21	67.3±8.1	3,420 (42.4)	3,228 (42.5)	7,649	7,596	NA	6,981 (46)	3,014 (20)	15,245 (100)	2,114 (13.9)	NA	0	NA	NA	4.2	154.5±19.0/ 87.4±10.9	139.3±17.6/ 79.2±9.8	154.8±19.0/ 87.6±10.7	137.5±15.0/ 77.7±9.0	NA	NA	322/281	841/818	304/304
VART[101]	HTN (SBP ≥140 mm Hg, DBP ≥90 mm Hg)	ARB (valsartan)	CCB (amlodipine)	60±12	60±11	220 (43.1)	217 (42.5)	510	511	NA	35 (3.4)	NA	NA	NA	83 (8)	8 (0.8)	NA	NA	3.4	158±19/ 93±13	135±13/ 80±10	158±18/ 94±13	135±14/ 80±10	NA	NA	10/10	2/3	NA
VHAS[102]	HTN (SBP ≥160 mm Hg, DBP ≥95 mm Hg)	CCB (verapamil)	Diuretic (chlorthalidone)	54.5±6.9	53.9±7.0	369 (52.2)	353 (49.9)	707	707	NA	NA	NA	1,414 (100)	NA	NA	0	NA	0	2	169.1±10.4/ 102.2±5.1		168.8±10.5/ 102.3±5.0		18	18	2/0	5/4	5/4
OPTIMAAL[103]	AMI+HF/LVD	ARB (losartan)	ACEi (captopril)	67.6±9.9	67.2±9.8	775 (28.2)	800 (29.3)	2,744	2,733	5,477 (100)	5,477 (100)	185 (3)	1,970 (36.0)	140 (2.6)	940 (17)	5,477 (100)	562 (10.3)	NA	2.7	123.0±17.0/ 71.5±10.9	NA	122.5±16.9/ 71.4±11.1	NA	NA	NA	140/132	499/447	420/363
ELITE II[104]	HF (NYHA II IV)+EF ≤40%+≥60 years	ARB (losartan)	ACEi (captopril)	71.4±6.7	71.5±6.9	475 (30)	491 (31)	1,578	1,574	3,152 (100)	1,841 (58)	NA	1,540 (48.9)	NA	749 (24)	3,152 (100)	951 (30.2)	NA	1.5	134±19.0/ 78±9.5	NA	134.4±18.6/ 78±9.9	NA	NA	NA	18/11	280/250	NA
VALIANT[1]	AMI+HF/LVD	ARB (valsartan)+ ACEi (captopril)	ACEi (captopril)	64.6±11.9	64.9±11.8	1,490 (30.5)	1,536 (31.3)	4,885	4,909	9,794 (100)	9,794 (100)	603 (6)	5,422 (55.4)	NA	2,266 (23)	9,794 (100)	NA	0	2.1	122.5±17.1/ 72.3±11.4	125/75	122.8±17.0/ 72.4±11.2	127/76	NA	NA	183/211	941/958	827/830
		ARB (valsartan)	ACEi (captopril)	65.0±11.8	64.9±11.8	1,544 (31.5)	1,536 (31.3)	4,909	4,909	9,818 (100)	9,818 (100)	590 (6)	5,390 (54.9)	NA	2,254 (23)	9,818 (100)	NA	0	2.1	122.7±16.8/ 72.3±11.3	127/75	122.8±17.0/ 72.4±11.2	127/76	NA	NA	180/211	979/958	827/827
NAVIGATOR[105]	Impaired glucose tolerance+CVD	ARB (valsartan)	Placebo	63.7±6.8	63.8±6.8	2,314 (50.0)	2,397 (51.3)	4,631	4,675	2,266 (24.3)	816 (8.8)	275 (3.0)	7216 (77.5)	54 (0.6)	0	NA	NA	NA	6.5	139.4±17.8/ 82.5±10.4		139.9±17.1/ 82.6±10.1		556	531	105/132	295/327	128/116

Values are presented as mean±standard deviation or number (%).

SBP, systolic blood pressure; DBP, diastolic blood pressure; CVD, cardiovascular disease; CHD, coronary heart disease; PAD, peripheral artery disease; DM, diabetes mellitus; HF, heart failure; AF, atrial fibrillation; CKD, chronic kidney disease; BP, blood pressure; MI, myocardial infarction; CAD, coronary artery disease; CCB, calcium channel blocker; GITS, gastrointestinal therapeutic system; NA, not available; ARB, angiotensin II receptor blocker; ADVANCE, action in diabetes and vascular disease: preterax and diamicron-MR controlled evaluation; ACEi, angiotensin-converting enzyme inhibitor; AIRE, acute infarction ramipril efficacy; AMI, acute myocardial infarction; LVD, left-ventricular dysfunction; HTN, hypertension; BCAPS, β-blocker cholesterol-lowering asymptomatic plaque study; BB, beta-blocker; CR, controlled release; XL, extended release; BHAT, β-blocker heart attack trial; CAMELOT, comparison of amlodipine vs enalapril to limit occurrences of thrombosis; CHARM, candesartan in heart failure: assessment of reduction in mortality and morbidity; CHF, chronic heart failure; LVEF, left-ventricular ejection fraction; DIABHYCAR, noninsulin-dependent diabetes, hypertension, microalbuminuria or proteinuria, cardiovascular events, and ramipril; DIRECT, diabetic retinopathy candesartan trials; TIA, transient ischemic attack; EUROPA, European trial on reduction of cardiac events with perindopril in patients with stable coronary artery disease; EWPHE, European working party on high blood pressure in the elderly; FEVER, felodipine event reduction; HEP, hypertension in elderly patients; HYVET, hypertension in the very elderly trial; IDNT, irbesartan diabetic nephropathy trial; NYHA, New York heart association; ONTARGET, ongoing telmisartan alone and in combination with ramipril global endpoint trial; OSCAR, olmesartan and calcium antagonists randomized study; PART-2, randomized, placebo-controlled trial of the angiotensin-converting enzyme inhibitor, ramipril, in patients with coronary or other occlusive arterial disease; PATS, post-stroke antihypertensive treatment study; PEACE, prevention of events with angiotensin converting enzyme inhibition trial; PHARAO, prevention of hypertension with the angiotensin-converting enzyme inhibitor ramipril in patients with high-normal blood pressure; PREVEND IT, prevention of renal and vascular endstage disease intervention trial; PRoFESS, prevention regimen for effectively avoiding second strokes; PROGRESS, perindopril protection against recurrent stroke study; ROADMAP, randomized olmesartan and diabetes microalbuminuria prevention; SCOPE, study on cognition and prognosis in the elderly; SHEP, systolic hypertension in the elderly program; ISH, isolated systolic hypertension; SOLVD, studies of left ventricular dysfunction; EF, ejection fraction; SUPPORT, supplemental benefit of ARB in hypertensive patients with stable heart failure using olmesartan; STONE, Shanghai trial of nifedipine in the elderly; STOP, Swedish trial in old patients with hypertension; TRANSCEND, telmisartan randomized assessment study in ACEi intolerant subjects with cardiovascular disease; VA-NEPHRON, veterans affairs nephropathy in diabetes; AASK, African-American study of kidney disease and hypertension; ABCD, appropriate blood pressure control in diabetes; ACCORD, action to control cardiovascular risk in diabetes; BBB, treat blood Pressure Better; HDFP, hypertension detection and follow-up program; HOMED-BP, hypertension objective treatment based on measurement by electrical devices of blood pressure; HOT, hypertension optimal treatment; JATOS, Japanese trial to assess optimal systolic blood pressure in elderly hypertensive patients; SPRINT, systolic blood pressure intervention trial; SPS3, secondary prevention of small subcortical strokes; UKPDS 38, secondary prevention of small subcortical strokes 38; VALISH, valsartan in elderly isolated systolic hypertension; CAPPP, captopril prevention project; IPPPSH, international prospective primary prevention study in hypertension; NORDIL, nordic diltiazem study; ACCOMPLISH, avoiding cardiovascular events through combination therapy in patients living with systolic hypertension; ALLHAT, antihypertensive and lipid-lowering treatment to prevent heart attack trial; ASCOT, Anglo-Scandinavian cardiac outcomes trial; CASE-J, candesartan antihypertensive survival evaluation in Japan trial; COLM, combinations of olmesartan study; CONVINCE, controlled onset verapamil investigation of cardiovascular end points trial; COER, controlled-onset extended-release; COPE, combination therapy of hypertension to prevent cardiovascular events; TD, thiazide diuretic; E-COST, efficacy of candesartan on outcome in saitama trial; ELSA, European lacidipine study on atherosclerosis; INSIGHT, intervention as a goal in hypertension treatment; INVEST, intervention as a goal in hypertension treatment; LIFE, losartan intervention for endpoint reduction in hypertension study; LVH, left ventricular hypertrophy; MOSES, morbidity and mortality after stroke, eprosartan compared with nitrendipine for secondary prevention; MRC, medical research council trial of treatment of hypertension in older adults; NHS, NAGOYA heart study; NICS-EH, national intervention cooperative study in elderly hypertensives; PATE, practitioner's trial on the efficacy of antihypertensive treatment in the elderly hypertension; SHELL, systolic hypertension in the elderly: lacidipine long-term study; VALUE, valsartan antihypertensive long-term use evaluation; VART, valsartan amlodipine randomized trial; VHAS, verapamil in hypertension and atherosclerosis study; OPTIMAAL, optimal trial in myocardial infarction with the angiotensin II antagonist losartan; ELITE II, evaluation of losartan in the elderly study II; VALIANT, valsartan in acute myocardial infarction trial; NAVIGATOR, nateglinide and valsartan in impaired glucose tolerance outcomes research.

Supplementary Table 2. Pairwise meta-analysis results of efficacy and tolerability for direct comparisons of interventions

Comparisons		Pairwise meta-analysis odds ratio (95% CI)	*P*	No. of trials	No. of participants	Heterogeneity I^2
Efficacy						
CCB	vs. Placebo	0.642 (0.539–0.765)	<0.001	7	19,665	0
ARB		0.919 (0.864–0.978)	0.008	13	69,891	0
ACEi		0.813 (0.747–0.885)	<0.001	13	58,691	49.4
Diuretic		0.632 (0.556–0.718)	<0.001	8	35,543	30.6
BB		0.791 (0.673–0.929)	0.004	7	29,667	20.8
ACEi+Diuretic		0.986 (0.814–1.195)	0.886	1	11,140	NA
CCB+Diuretic		0.698 (0.574–0.850)	<0.001	1	9,711	NA
ARB+Diuretic		0.795 (0.585–1.078)	0.140	1	12,705	NA
Diuretic/BB		0.532 (0.335–0.847)	0.008	1	1,627	NA
Renin inhibitor		1.209 (0.954–1.531)	0.116	1	8,561	NA
ARB	vs. CCB	0.977 (0.869–1.099)	0.698	8	29,011	72.3
ACEi		1.123 (1.008–1.252)	0.036	8	29,533	12
Diuretic		1.063 (0.947–1.194)	0.300	4	33,920	0
BB		1.261 (1.116–1.425)	<0.001	4	4,825	0
Diuretic/BB		0.922 (0.762–1.114)	0.399	3	31,766	55.8
ACEi	vs. ARB	1.074 (0.972–1.186)	0.159	5	37,912	5.5
BB		1.361 (1.142–1.622)	0.001	1	9,193	NA
ARB+ACEi		1.017 (0.908–1.139)	0.771	3	28,320	0
ARB+CCB		0.606 (0.315–1.168)	0.135	1	1,164	NA
Diuretic	vs. ACEi	0.871 (0.771–0.984)	0.026	1	24,309	NA
BB		0.988 (0.546–1.789)	0.968	1	877	NA
Diuretic/BB		1.097 (0.911–1.321)	0.329	2	4,990	0
ARB+ACEi		0.909 (0.813–1.017)	0.097	2	26,872	0
BB	vs. Diuretic	1.629 (0.890–2.982)	0.113	2	10,883	68.3
CCB+Diuretic		1.578 (0.631–3.945)	0.329	1	414	NA
ACEi+CCB	vs. ACEi+Diuretic	0.842 (0.653–1.085)	0.184	1	11,506	NA
ARB+CCB	vs. CCB+Diuretic	1.402 (0.667–2.950)	0.373	1	2,204	NA
BB+CCB		2.292 (1.155–4.549)	0.018	1	2,183	NA
ARB+CCB	vs. ARB+Diuretic	0.955 (0.673–1.355)	0.798	1	5,141	NA
BB+CCB	vs. ARB+CCB	1.635 (0.886–3.016)	0.116	1	2,199	NA
Safety						
CCB	vs. Placebo	2.414 (2.006–2.906)	<0.001	1	7,665	NA
ARB		1.141 (1.081–1.204)	<0.001	4	39,022	89.9
ACEi		1.682 (1.271–2.226)	<0.001	7	31,306	94.4
Diuretic		1.981 (1.625–2.416)	<0.001	1	4,736	NA
ACEi+Diuretic		2.481 (2.007–3.067)	<0.001	1	11,140	NA
ARB+Diuretic		0.960 (0.886–1.041)	0.327	1	12,705	NA
Renin inhibitor		1.475 (1.250–1.741)	<0.001	1	8,561	NA
ACEi	vs. CCB	4.201 (2.206–7.998)	<0.001	1	1,748	NA
Diuretic		1.000 (0.516–1.938)	1.000	1	1,414	NA
CCB+Diuretic	vs. Diuretic	0.677 (0.236–1.937)	0.467	1	414	NA
ACEi+CCB	vs. ACEi+Diuretic	0.892 (0.823–0.966)	0.005	1	11,506	NA

An odds ratios <1 favor the former intervention and an odds ratios >1 favor the latter intervention.
CI, confidence interval; CCB, calcium channel blocker; ARB, angiotensin II receptor blocker; ACEi, angiotensin-converting enzyme inhibitor; BB, beta-blocker; NA, not applicable.

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Supplementary Table 3. Summary of results from pairwise meta-analysis and network meta-analysis for stroke prevention from randomized controlled trials

Comparison		No. of trials	OR (95% CI)	
			Pairwise meta-analysis	Network meta-analysis
Efficacy				
CCB	vs. Placebo	7	0.642 (0.539–0.765)	0.74 (0.67–0.82)
ARB		13	0.919 (0.864–0.978)	0.81 (0.73–0.89)
ACEi		13	0.813 (0.747–0.885)	0.81 (0.73–0.90)
Diuretic		8	0.632 (0.556–0.718)	0.68 (0.59–0.77)
BB		7	0.791 (0.673–0.929)	0.90 (0.78–1.03)
ACEi+THZ		1	0.986 (0.814–1.195)	0.99 (0.71–1.37)
CCB+THZ		1	0.698 (0.574–0.850)	0.71 (0.53–0.94)
ARB+THZ		1	0.795 (0.585–1.078)	0.78 (0.54–1.07)
Diuretic/BB		1	0.532 (0.335–0.847)	0.79 (0.65–0.94)
Renin inhibitor		1	1.209 (0.954–1.531)	1.26 (0.85–1.79)
ARB	vs. CCB	8	0.977 (0.869–1.099)	1.09 (0.97–1.22)
ACEi		8	1.123 (1.008–1.252)	1.09 (0.97–1.23)
Diuretic		4	1.063 (0.947–1.194)	0.91 (0.78–1.05)
BB		4	1.261 (1.116–1.425)	1.21 (1.05–1.39)
Diuretic/BB		3	0.922 (0.762–1.114)	1.06 (0.88–1.25)
ACEi	vs. ARB	5	1.074 (0.972–1.186)	1.00 (0.89–1.12)
BB		1	1.361 (1.142–1.622)	1.12 (0.95–1.29)
ARB+ACEi		3	1.017 (0.908–1.139)	0.97 (0.79–1.18)
ARB+CCB		1	0.606 (0.315–1.168)	0.89 (0.58–1.30)
Diuretic	vs. ACEi	1	0.871 (0.771–0.984)	0.84 (0.71–0.97)
BB		1	0.988 (0.546–1.789)	1.11 (0.95–1.30)
Diuretic/BB		2	1.097 (0.911–1.321)	0.98 (0.80–1.17)
ARB+ACEi		2	0.909 (0.813–1.017)	0.97 (0.78–1.19)
BB	vs. diuretic	2	1.629 (0.890–2.982)	1.34 (1.11–1.58)
CCB+THZ		1	1.578 (0.631–3.945)	1.06 (0.76–1.44)
ACEi+CCB	vs. ACEi+THZ	1	0.842 (0.653–1.085)	0.85 (0.58–1.21)
ARB+CCB	vs. CCB+THZ	1	1.402 (0.667–2.950)	1.02 (0.64–1.56)
BB+CCB		1	2.292 (1.155–4.549)	2.00 (1.03–3.61)
ARB+CCB	vs. ARB+THZ	1	0.955 (0.673–1.355)	0.93 (0.64–1.34)
BB+CCB	vs. ARB+CCB	1	1.635 (0.886–3.016)	1.96 (1.04–3.58)
Tolerability				
CCB	vs. Placebo	1	2.414 (2.006–2.906)	1.43 (0.53–3.09)
ARB		4	1.141 (1.081–1.204)	1.10 (0.54–2.01)
ACEi		7	1.682 (1.271–2.226)	2.15 (1.30–3.52)
Diuretic		1	1.981 (1.625–2.416)	1.86 (0.56–4.59)
ACEi+THZ		1	2.481 (2.007–3.067)	3.10 (0.64–9.27)
ARB+THZ		1	0.960 (0.886–1.041)	1.20 (0.26–3.51)
Renin inhibitor		1	1.475 (1.250–1.741)	1.89 (0.40–5.58)
ACEi	vs. CCB	1	4.201 (2.206–7.998)	1.45 (0.42–3.71)
Diuretic		1	1.000 (0.516–1.938)	1.45 (0.42–3.71)
CCB+THZ	vs. diuretic	1	0.677 (0.236–1.937)	0.95 (0.12–3.46)
ACEi+CCB	vs. ACEi+THZ	1	0.892 (0.823–0.966)	1.14 (0.24–3.38)

OR, odds ratio; CI, confidence interval; CCB, calcium channel blocker; ARB, angiotensin II receptor blocker; ACEi, angiotensin-converting enzyme inhibitor; BB, beta-blocker; THZ, thiazide-like diuretic.

Supplementary Table 4. Results of sensitivity analyses for efficacy

Drug name	Standard analysis		Published in 2000 or later only		Duration of follow-up longer than 3 years		Trials including hypertensive participants only		Trials excluding hearts failure participants		Age ≤60 years		Age >60 years		Participants without history of stroke		Participants with history of stroke		Participants without history of DM		Participants with history of DM		Participants with baseline SBP ≤150 mm Hg		Participants with baseline SBP >150 mm Hg	
	OR (95% CI)	SUCRA rank	OR (95% CI)	SUCRA rank	OR (95% CI)	SUCRA rank	OR (95% CI)	SUCRA rank	OR (95% CI)	SUCRA rank	OR (95% CI)	SUCRA rank	OR (95% CI)	SUCRA rank	OR (95% CI)	SUCRA rank	OR (95% CI)	SUCRA rank	OR (95% CI)	SUCRA rank	OR (95% CI)	SUCRA rank	OR (95% CI)	SUCRA rank	OR (95% CI)	SUCRA rank
CCB	0.74 (0.67–0.82)	4	0.83 (0.72–0.94)	6	0.75 (0.66–0.86)	4	0.64 (0.54–0.74)	5	0.73 (0.65–0.82)	4	0.80 (0.56–1.11)	4	0.74 (0.66–0.82)	3	0.86 (0.66–1.09)	5	-	-	0.74 (0.30–1.35)	7	-	-	0.76 (0.63–0.92)	1	0.64 (0.54–0.75)	5
ARB	0.81 (0.73–0.89)	9	0.84 (0.76–0.9)	8	0.80 (0.71–0.90)	8	0.61 (0.49–0.73)	3	0.80 (0.71–0.89)	9	0.94 (0.60–1.39)	6	0.83 (0.75–0.91)	9	0.84 (0.66–1.02)	3	-	-	0.62 (0.23–1.28)	4	-	-	0.88 (0.79–0.98)	8	0.65 (0.53–0.78)	6
ACEi	0.81 (0.73–0.90)	10	0.85 (0.76–0.94)	9	0.80 (0.70–0.90)	7	0.69 (0.55–0.85)	8	0.78 (0.69–0.89)	8	0.75 (0.52–0.99)	2	0.83 (0.75–0.92)	10	0.86 (0.68–1.02)	4	-	-	0.54 (0.20–1.05)	2	-	-	0.86 (0.76–0.95)	7	0.64 (0.48–0.84)	3
Diuretic	0.68 (0.59–0.77)	1	0.79 (0.66–0.94)	3	0.65 (0.55–0.77)	1	0.60 (0.49–0.72)	1	0.66 (0.56–0.76)	1	0.39 (0.22–0.60)	1	0.72 (0.63–0.82)	1	0.62 (0.40–0.86)	1	-	-	0.41 (0.17–0.72)	1	-	-	0.78 (0.60–0.99)	2	0.63 (0.53–0.74)	2
BB	0.90 (0.78–1.03)	11	1.03 (0.83–1.24)	12	0.90 (0.76–1.06)	11	0.79 (0.66–0.93)	9	0.88 (0.75–1.02)	11	0.90 (0.67–1.21)	5	0.94 (0.78–1.11)	12	1.01 (0.59–1.62)	8	-	-	0.66 (0.36–0.98)	6	-	-	0.84 (0.61–1.12)	6	0.83 (0.69–0.98)	9
ACEi+ diuretic	0.99 (0.71–1.37)	12	1.00 (0.71–1.36)	11	1.00 (0.70–1.40)	12	1.08 (0.79–1.41)	13	1.01 (0.68–1.43)	12	-	-	1.01 (0.74–1.33)	13	-	-	-	-	-	-	-	-	0.99 (0.73–1.32)	9	-	-
CCB+ diuretic	0.71 (0.53–0.94)	2	0.69 (0.50–0.91)	1	0.70 (0.51–0.95)	2	0.68 (0.47–0.91)	6	0.70 (0.50–0.96)	2	-	-	0.71 (0.54–0.92)	2	1.15 (0.35–2.60)	7	-	-	0.87 (0.12–2.79)	5	-	-	-	-	0.68 (0.48–0.92)	7
ARB+ diuretic	0.78 (0.54–1.07)	5	0.78 (0.55–1.08)	4	0.77 (0.53–1.10)	5	0.559 (0.27–1.15)	4	0.78 (0.53–1.12)	7	-	-	0.78 (0.54–1.07)	5	0.83 (0.53–1.20)	2	-	-	-	-	-	-	0.80 (0.54–1.15)	3	0.65 (0.30–1.22)	4
Diuretic /BB	0.79 (0.65–0.94)	7	0.87 (0.65–1.13)	10	0.82 (0.65–1.02)	10	0.68 (0.53–0.85)	7	0.77 (0.62–0.94)	5	0.77 (0.30–1.60)	3	0.79 (0.65–0.94)	6	0.93 (0.68–1.19)	6	-	-	0.64 (0.10–1.88)	3	-	-	-	-	0.67 (0.52–0.84)	8
ARB+ ACEi	0.78 (0.63–0.96)	6	0.81 (0.65–0.98)	5	0.78 (0.57–1.04)	6	-	-	0.77 (0.57–1.02)	6	-	-	0.80 (0.66–0.96)	7	-	-	-	-	-	-	-	-	0.83 (0.68–1.00)	4	-	-
ARB+ CCB	0.72 (0.47–1.05)	3	0.72 (0.48–1.05)	2	0.71 (0.47–1.03)	3	0.56 (0.31–0.94)	2	0.71 (0.46–1.06)	3	-	-	0.72 (0.49–1.05)	4	1.81 (0.36–4.88)	10	-	-	-	-	-	-	-	-	0.60 (0.33–0.99)	1
ACEi+ CCB	0.84 (0.50–1.34)	8	0.86 (0.51–1.36)	7	0.86 (0.50–1.39)	9	1.16 (0.68–1.34)	12	0.86 (0.47–1.44)	10	-	-	0.86 (0.54–1.30)	8	-	-	-	-	-	-	-	-	0.85 (0.52–1.29)	5		-
BB+ CCB	1.38 (0.72–2.53)	14	1.40 (0.71–2.49)	14	1.42 (0.68–2.61)	14	0.21 (0.58–2.25)	10	1.40 (0.68–2.58)	14	-	-	1.42 (0.76–2.44)	15	2.76 (0.63–7.84)	11	-	-	-	-	-	-	-	-	1.27 (0.61–2.32)	11
Renin inhibitor	1.26 (0.85–1.79)	15	1.23 (0.85–1.73)	15	-	-	-	-	-	-	-	-	0.82 (0.35–1.64)	11	-	-	-	-	-	-	-	-	1.23 (0.88–1.68)	11		-

The table shows the effect sizes (ORs) and the rank order (SUCRA ranks) compared to placebo before (standard analysis) and after sensitivity analyses. In subgroup of participants without history of stroke, most of the results were stable except for ARB+CCB. Sensitivity analyses were not feasible for two subgroups (participants with history of stroke and participants with history of DM) due to limited number of trials. Sensitivity and subgroup analyses on tolerability were not feasible due to the low event rate and few trials reported such endpoint.

DM, diabetes mellitus; SBP, systolic blood pressure; OR, odds ratio; CI, confidence interval; SUCRA, surface under the cumulative ranking curve; CCB, calcium channel blocker; ARB, angiotensin II receptor blocker; ACEi, angiotensin-converting enzyme inhibitor; BB, beta-blocker.

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Supplementary Table 5. Inconsistency test by node-splitting for efficacy

Side	Direct		Indirect		Difference		*P*>|*z*|	tau
	Coefficient	SE	Coefficient	SE	Coefficient	SE		
A B	−0.451284	0.1068399	−0.2510002	0.0631098	−0.2002838	0.1243141	0.107	0.1242378
A C	−0.0993669	0.0520806	−0.3976046	0.0644907	0.2982377	0.0829809	0.000	0.0888897
A D	−0.1920362	0.0714549	−0.232732	0.076429	0.0406958	0.1053677	0.699	0.1283594
A E	−0.4643451	0.0847979	−0.2713766	0.1006676	−0.1929685	0.1293544	0.136	0.1182247
A F	−0.2418242	0.0961056	0.0165464	0.0910915	−0.2583706	0.1313758	0.050	0.1158177
A G*	−0.0140438	0.1571743	0.0781284	217.4085	−0.0921723	217.4086	1.000	0.1228489
A H	−0.3589984	0.1597569	−0.3847499	0.334987	0.0257515	0.3711314	0.945	0.1243285
A I	−0.2299547	0.1994513	−0.3698523	0.3509167	0.1398976	0.4036376	0.729	0.1244593
A J	−0.6301822	0.2651127	−0.1922366	0.0978299	−0.4379456	0.2825871	0.121	0.119769
A O	-	-	-	-	-	-	-	-
B C	−0.0701689	0.0855201	0.1973536	0.0743317	−0.2675225	0.1141232	0.019	0.120526
B D	0.0495561	0.0963298	0.1198465	0.0790357	−0.0702904	0.1255804	0.576	0.1287696
B E	0.0605161	0.1030118	−0.2094289	0.0979282	0.269945	0.1424187	0.058	0.1165115
B F	0.2197186	0.105716	0.1710801	0.0985393	0.0486385	0.1449476	0.737	0.127049
B J	0.0822924	0.0974244	−0.0422592	0.1880368	0.1245516	0.2117605	0.556	0.1264311
C D	0.0514294	0.0883482	−0.0205073	0.0719231	0.0719367	0.1138033	0.527	0.124331
C F	0.3083339	0.1486445	0.0536351	0.0817897	0.2546988	0.1696607	0.133	0.1186854
C K*	0.0172791	0.1024207	−0.3017673	0.2237688	0.3190464	0.246183	0.195	0.1211038
C L	−0.5002282	0.3563764	0.0453293	0.2466586	−0.5455575	0.4334104	0.208	0.1229408
D E	−0.1350791	0.1418873	−0.1944038	0.0911882	0.0593247	0.1688091	0.725	0.1276075
D F	−0.012024	0.3272441	0.1095738	0.0798881	−0.1215978	0.3368545	0.718	0.1237679
D J	0.081128	0.1434105	−0.1187521	0.1217839	0.1998801	0.1881917	0.288	0.1223478
D K	−0.1067001	0.105547	0.1686203	0.1995086	−0.2753204	0.2250074	0.221	0.1207032
E F	0.3827491	0.1882641	0.2493307	0.1005048	0.1334183	0.2139697	0.533	0.1259243
E H	0.4562378	0.483335	−0.0271547	0.1642594	0.4833925	0.510484	0.344	0.1229657
G M*	−0.1723831	0.1785902	0.0668541	438.5716	−0.2392372	438.5717	1.000	0.122849
H L*	0.3381917	0.399266	−0.139543	0.2746922	0.4777347	0.484633	0.324	0.1241665
H N*	0.8295874	0.3710168	−0.125879	0.8421779	0.9554665	0.9692651	0.324	0.1241662
I L	−0.0457219	0.2175149	−0.1856204	0.3400159	0.1398984	0.4036379	0.729	0.1244593
L N*	0.4913958	0.3363546	1.446865	0.8847719	−0.9554689	0.9692654	0.324	0.1241666

SE, standard error; A, placebo; B, calcium channel blocker (CCB); C, angiotensin II receptor blocker (ARB); D, angiotensin-converting enzyme inhibitor (ACEi); E, diuretic; F, beta-blocker (BB); G, ACEi+diuretic; H, CCB+diuretic; I, ARB+diuretic; J, BB/diuretic; K, ARB+ACEi; L, ARB+CCB; M, ACEi+CCB; N, BB+CCB.
*Warning: all the evidence about these contrasts comes from the trials which directly compare them.

Supplementary Table 6. Inconsistency test by node-splitting for tolerability

Side	Direct		Indirect		Difference		*P*>|z|	tau
	Coefficient	SE	Coefficient	SE	Coefficient	SE		
A B	0.8814234	0.4786115	−0.2520848	0.47102	1.133508	0.6715123	0.091	0.4691702
A C	-	-	-	-	-	-	-	-
A D	0.5349264	0.1638938	2.2638	0.5903911	−1.728874	0.613268	0.005	0.3675151
A E	0.6838528	0. 5614273	0.190057	0.7790083	0.4937958	0.9602367	0.607	0.5522498
A F	-	-	-	-	-	-	-	-
A G*	0.9085095	0. 5370918	0.0566346	69.0073	0.8518749	69.00939	0.990	0.5260806
A I	-	-	-	-	-	-	-	-
A K	-	-	-	-	-	-	-	-
B D	1.435238	0.4929838	−0.2936447	0.3647816	1.728883	0.6132688	0.005	0.367515
B E	7.31E-10	0.6472978	0.4937874	0.7092778	−0.4937874	0.9602445	0.607	0.5522505
E H*	−0.3904272	0.7513723	−1.078526	338.4009	0.6880987	338.4016	0.998	0.5260769
G J*	−0.1147697	0.5276537	−1.818516	138.0747	1.703746	138.0757	0.990	0.5260807

SE, standard error; A, placebo; B, calcium channel blocker (CCB); C, angiotensin II receptor blocker (ARB); D, angiotensin-converting enzyme inhibitor (ACEi); E, diuretic; F, beta-blocker (BB); G, ACEi+diuretic; H, CCB+diuretic; I, ARB+diuretic; J, BB/diuretic; K, ARB+ACEi.
*Warning: all the evidence about these contrasts comes from the trials which directly compare them.

Supplementary Table 7. Inconsistency test by design-by-treatment for efficacy and tolerability

Network outcome	Chi-square	*P* for test of global inconsistency
Efficacy	31.35	0.26
Safety	7.14	0.03

Assessment of global inconsistency in networks for efficacy and tolerability in preventing stroke using the 'design-by-treatment' interaction model.

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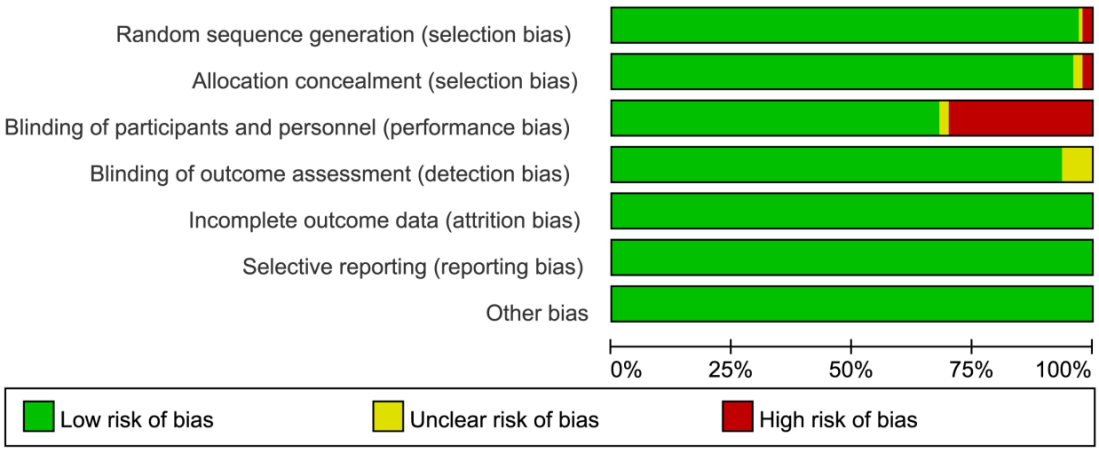

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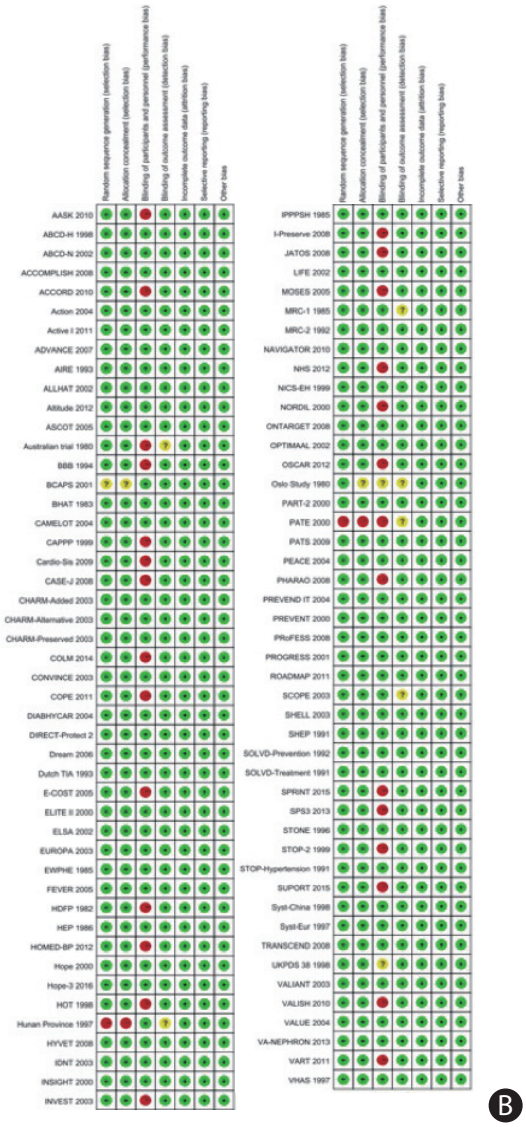
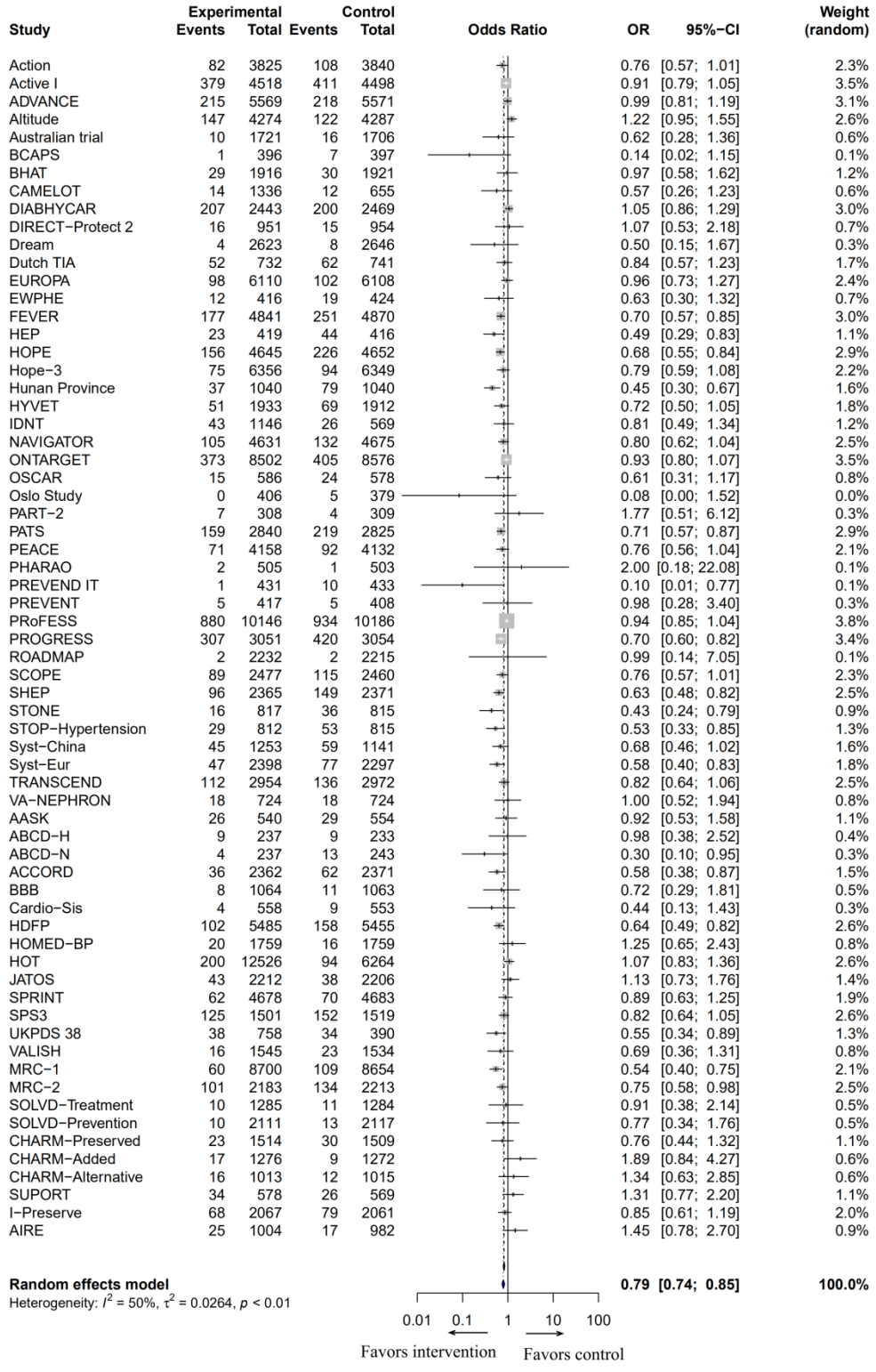


B

Supplementary Figure 1. Risk of bias of the included studies. (A) Risk of bias graph. (B) Risk of bias summary. "+" indicates low risk of bias; "?" indicates unclear risk of bias; "–" indicates high risk of bias.



Supplementary Figure 2. Reduction in systolic blood pressure on the odds ratio (OR) of stroke. CI, confidence interval.

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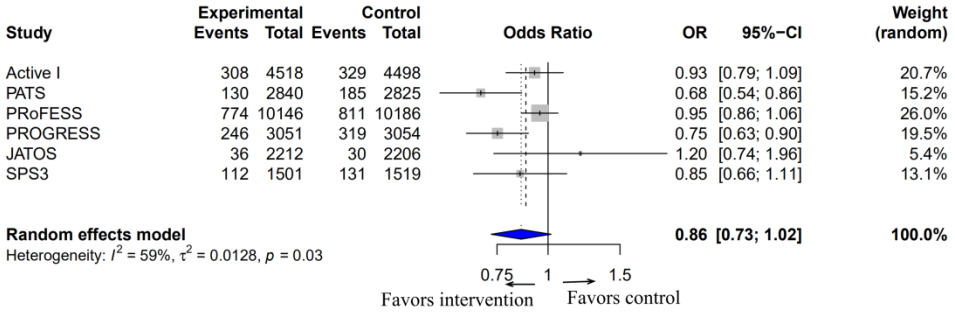
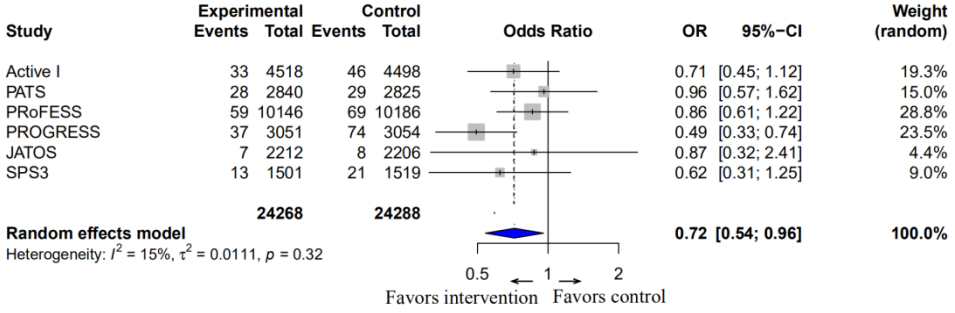
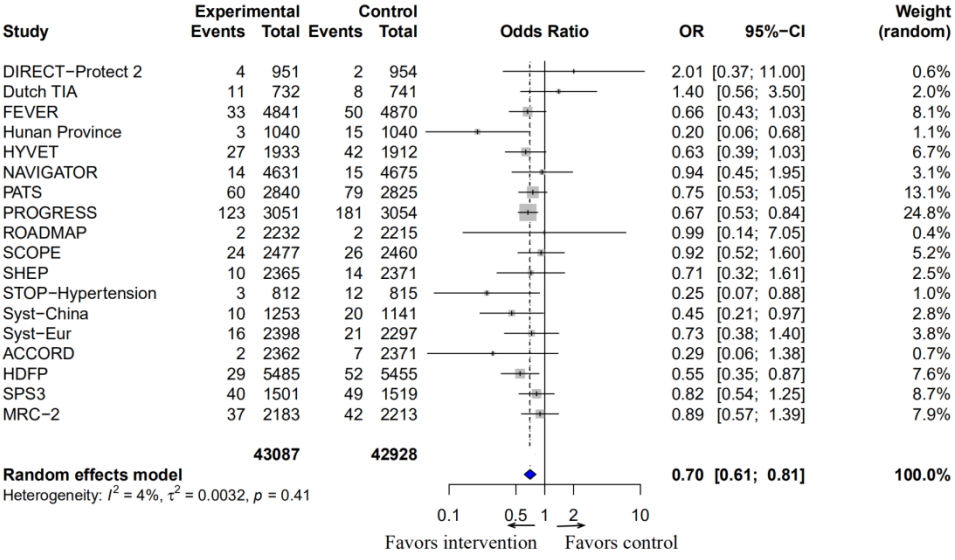


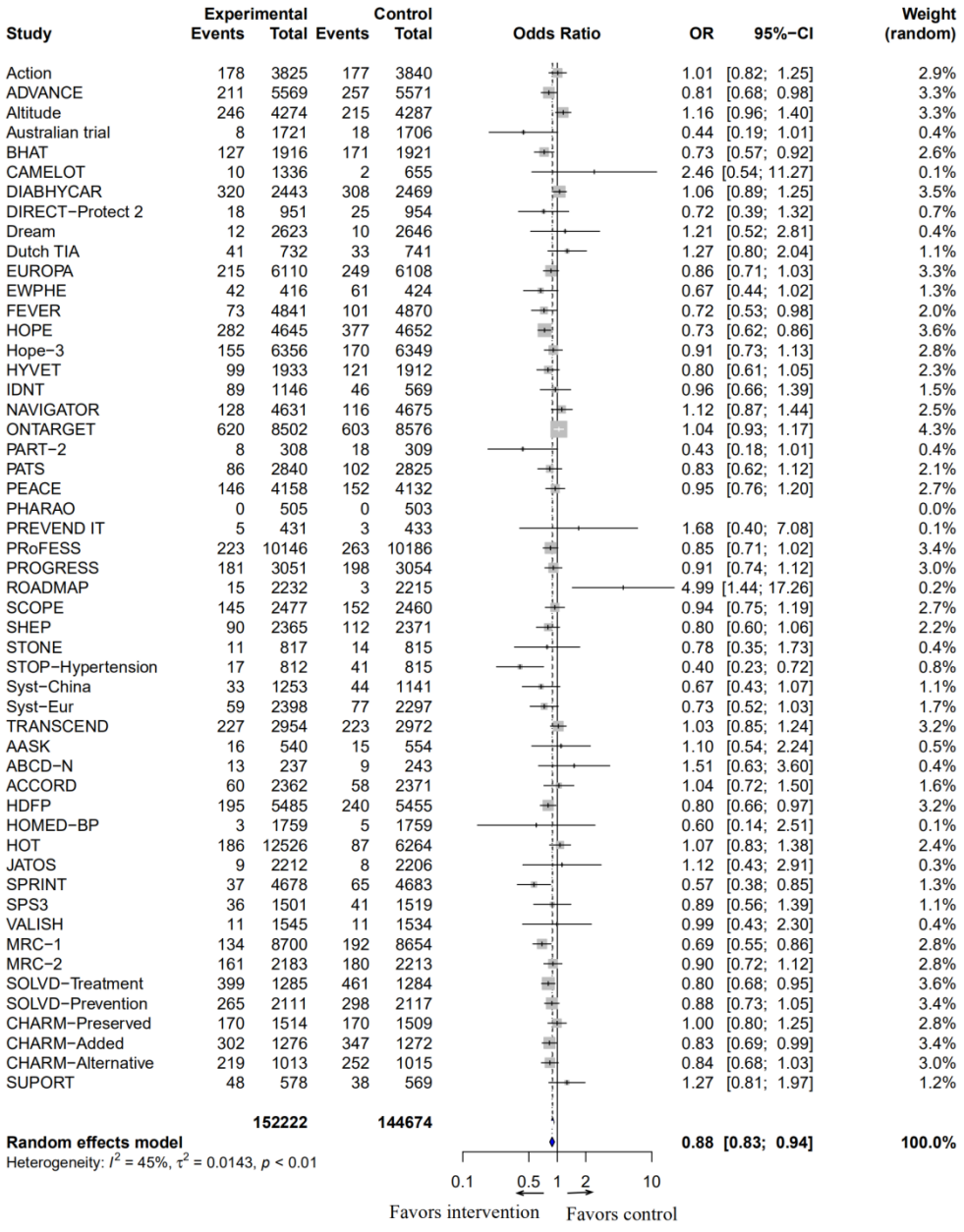
Supplementary Figure 3. Reduction in systolic blood pressure on the odds ratio (OR) of ischemic stroke. CI, confidence interval.



Supplementary Figure 4. Reduction in systolic blood pressure on the odds ratio (OR) of hemorrhagic stroke. CI, confidence interval.

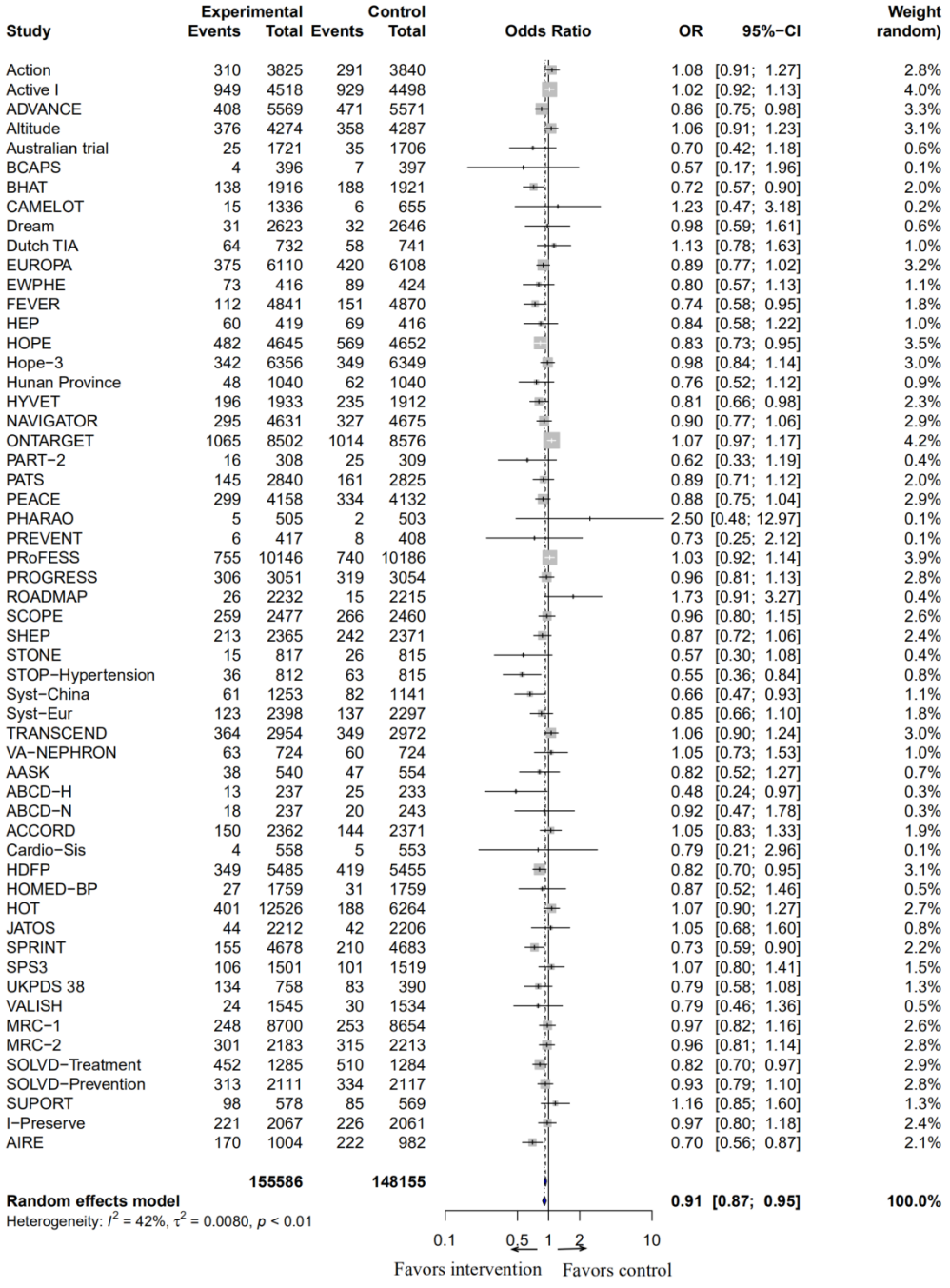


Supplementary Figure 5. Reduction in systolic blood pressure on the odds ratio (OR) of fatal or disabling stroke. CI, confidence interval.

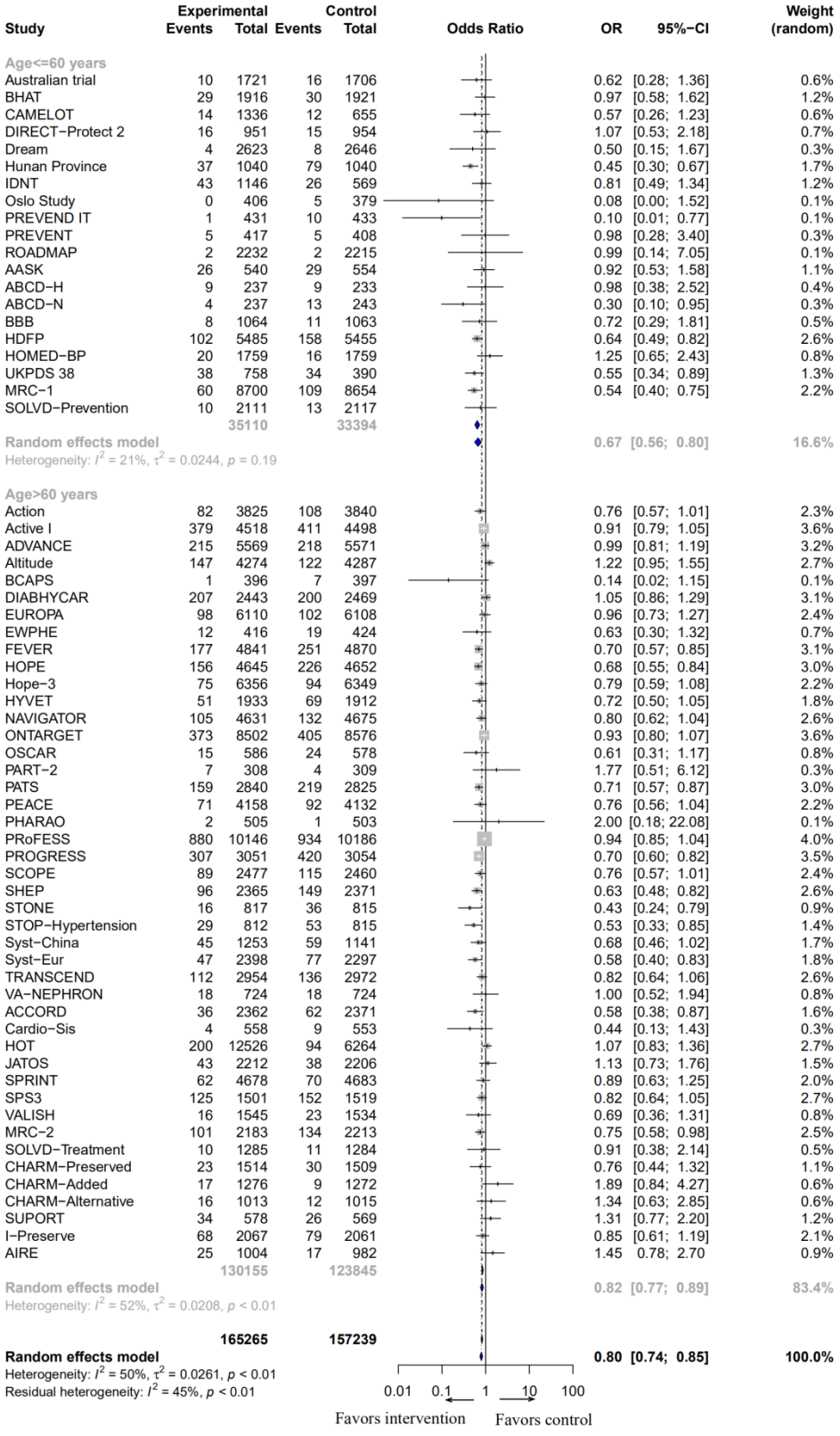


Supplementary Figure 6. Reduction in systolic blood pressure on the odds ratio (OR) of cardiovascular death. CI, confidence interval.

https://doi.org/10.5853/jos.2020.02698

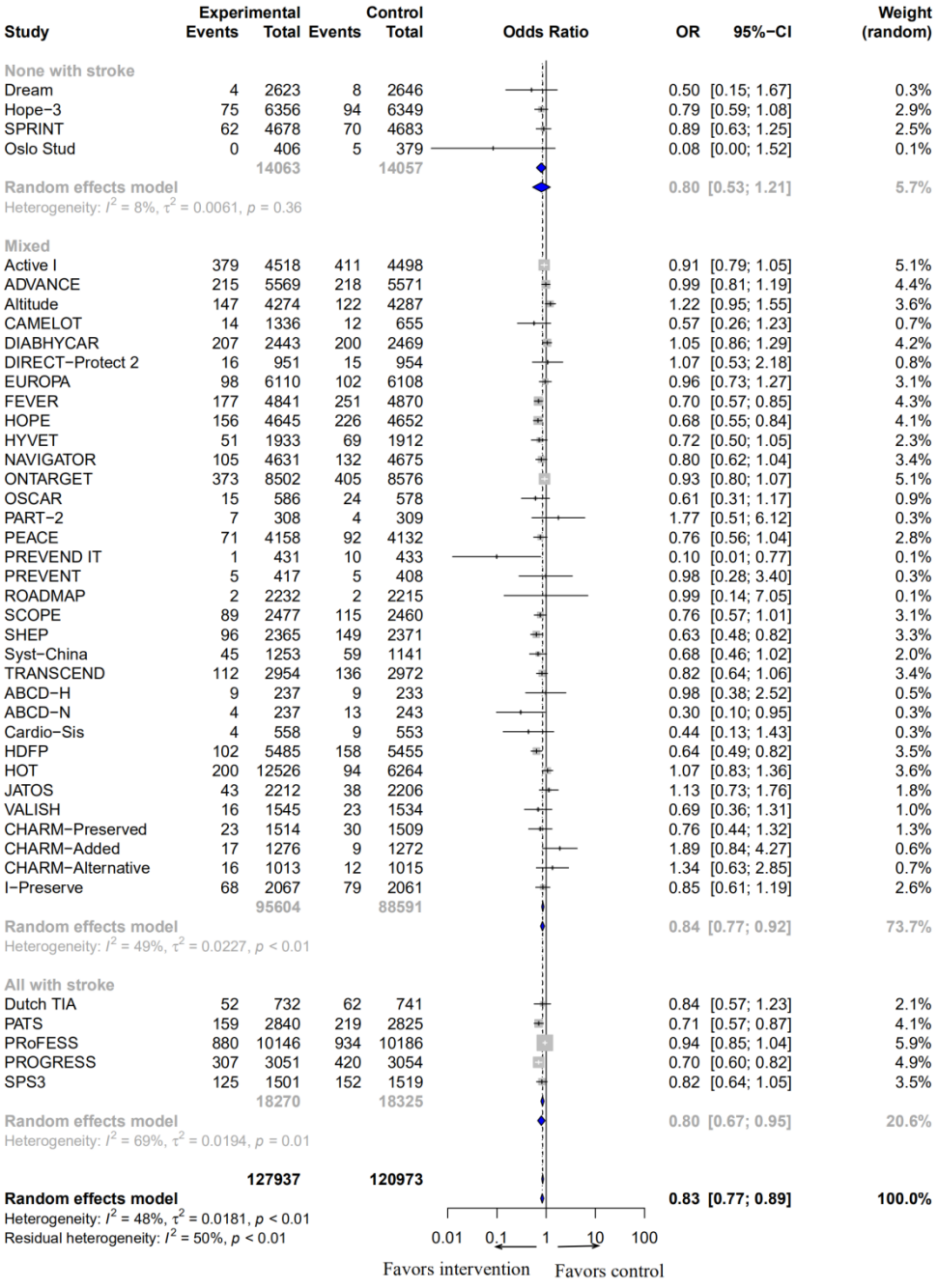


Supplementary Figure 7. Reduction in systolic blood pressure on the odds ratio (OR) of all cause death. CI, confidence interval.

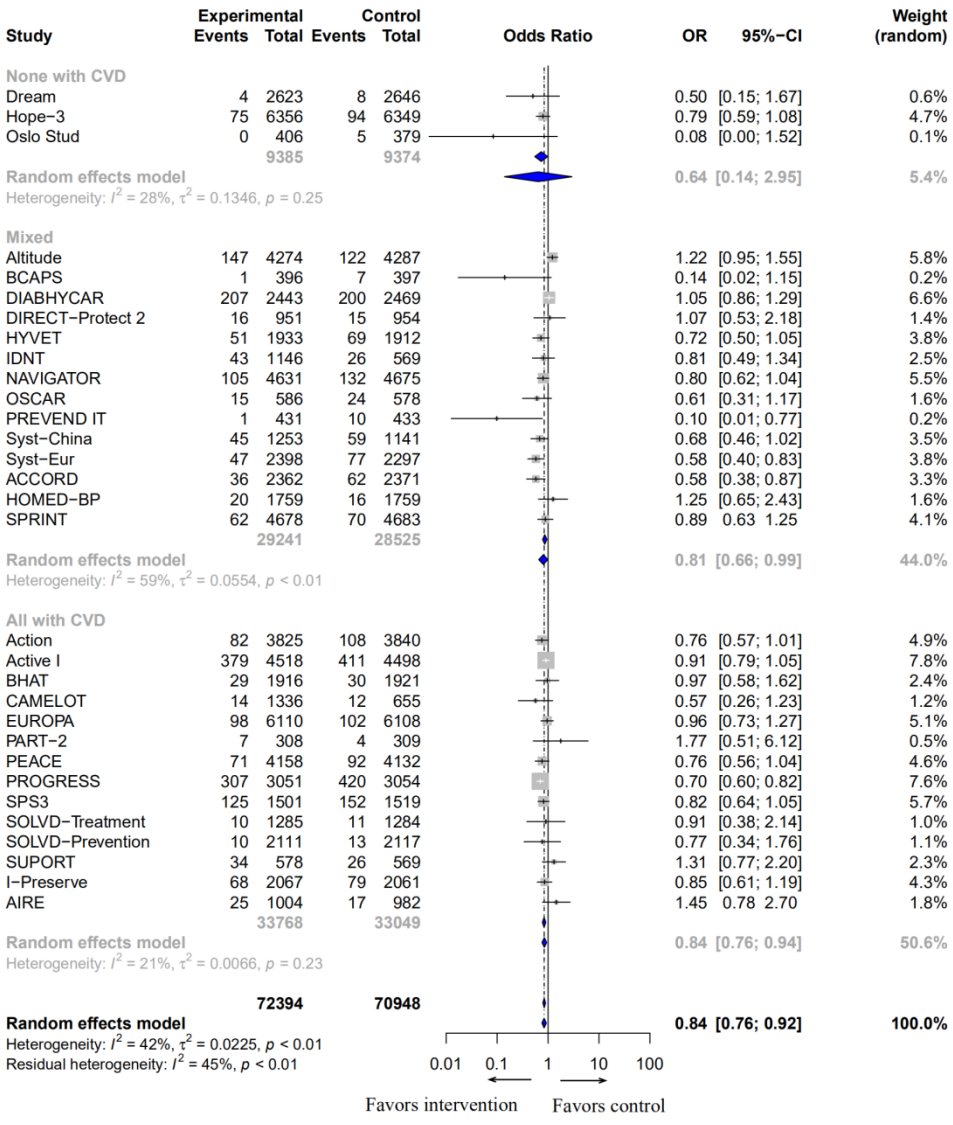


Supplementary Figure 8. Reduction in systolic blood pressure on the odds ratio (OR) of stroke stratified by age. CI, confidence interval.

https://doi.org/10.5853/jos.2020.02698

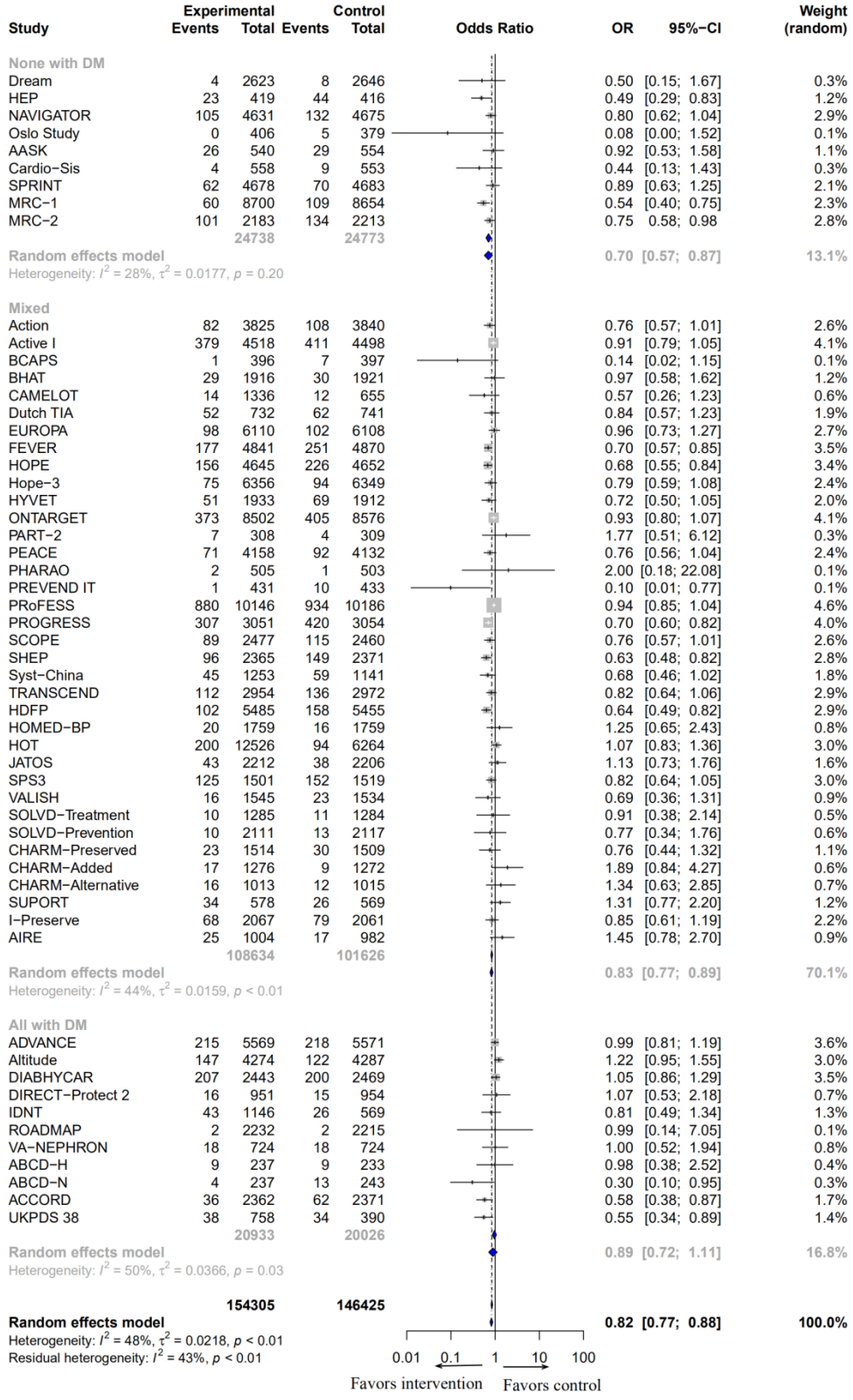


Supplementary Figure 9. Reduction in systolic blood pressure on the odds ratio (OR) of stroke stratified by history of stroke. CI, confidence interval.

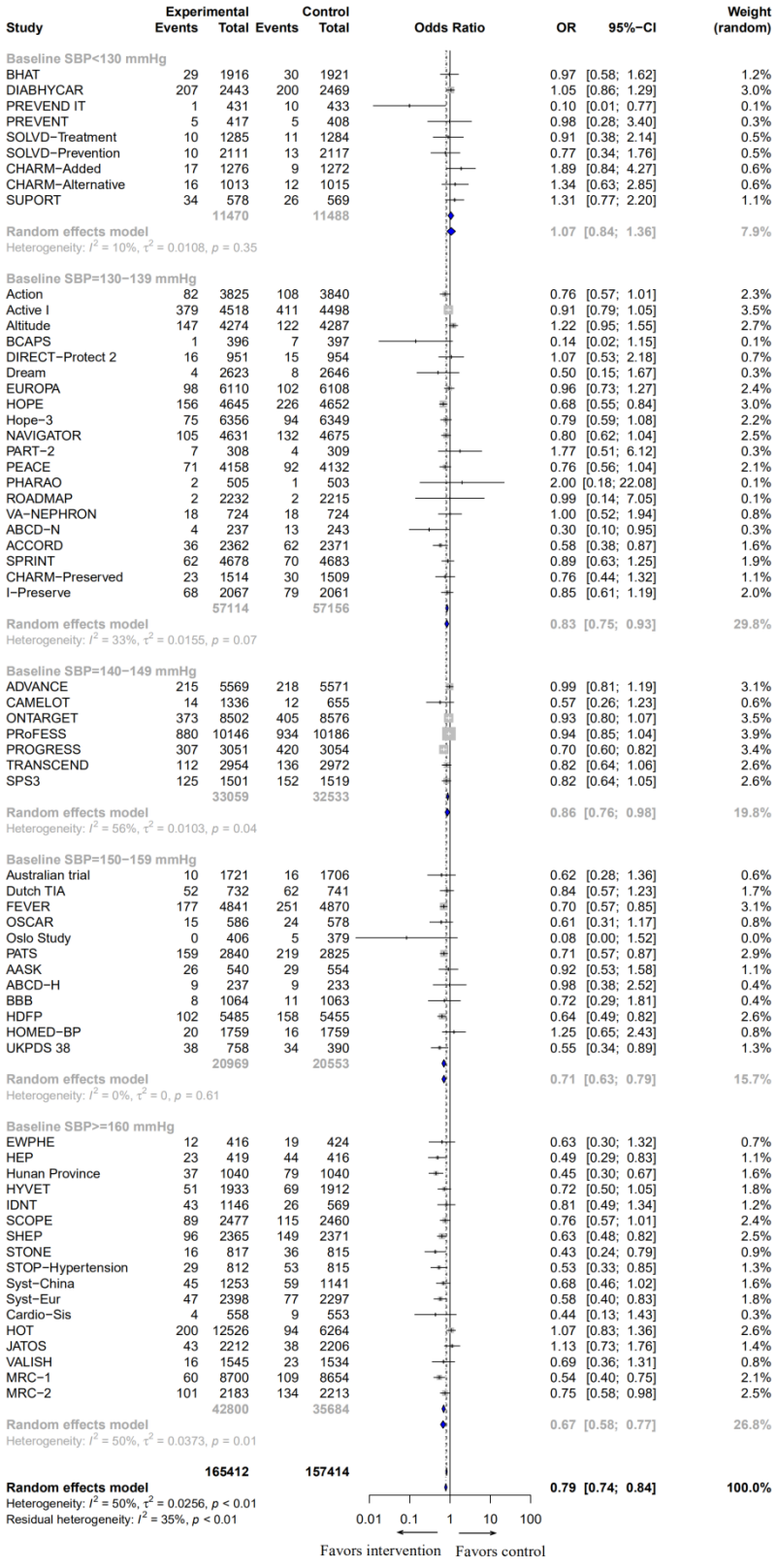


Supplementary Figure 10. Reduction in systolic blood pressure on the odds ratio (OR) of stroke stratified by history of cardiovascular disease (CVD). CI, confidence interval.

https://doi.org/10.5853/jos.2020.02698

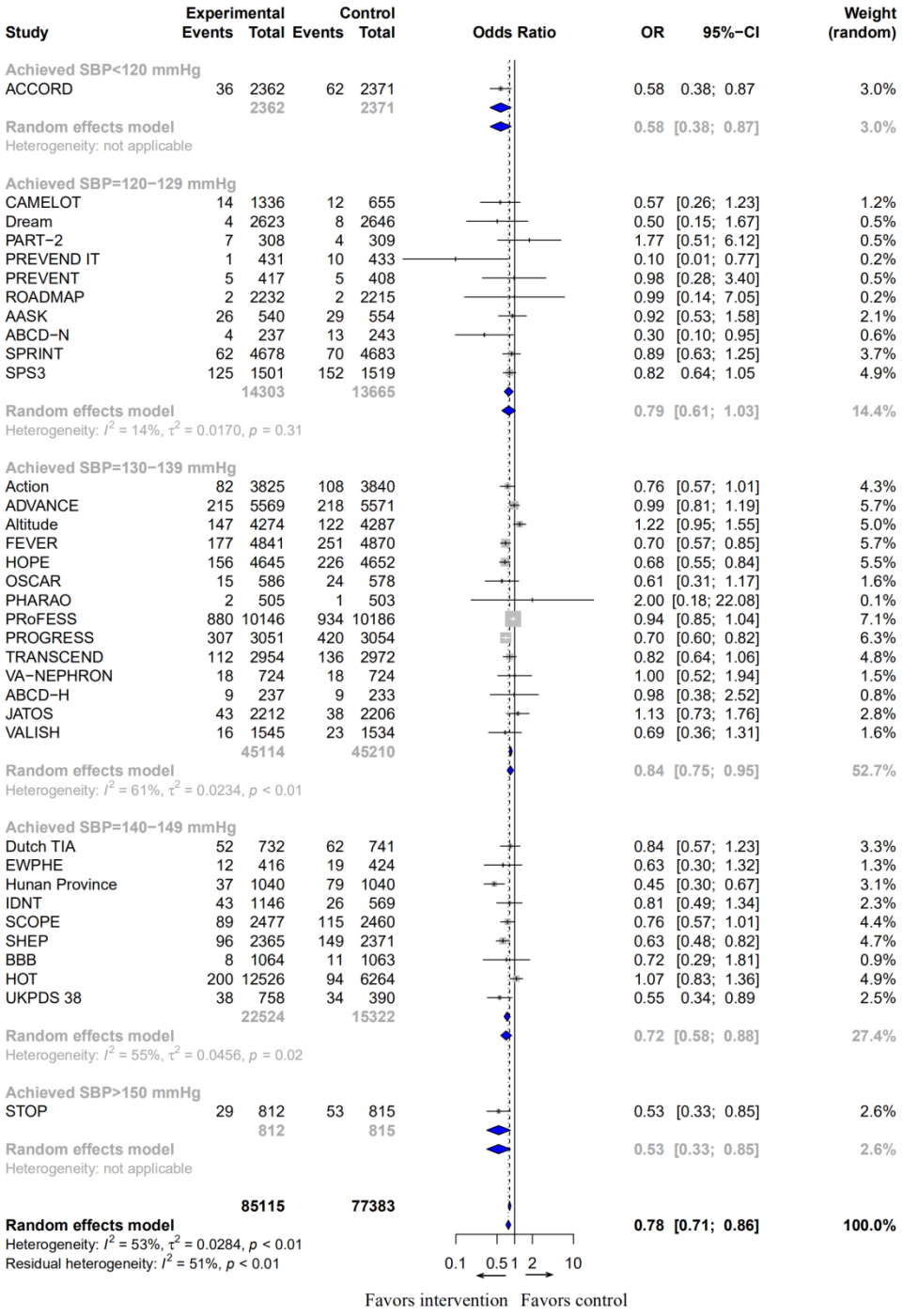


Supplementary Figure 11. Reduction in systolic blood pressure on the odds ratio (OR) of stroke stratified by history of diabetes mellitus (DM). CI, confidence interval.

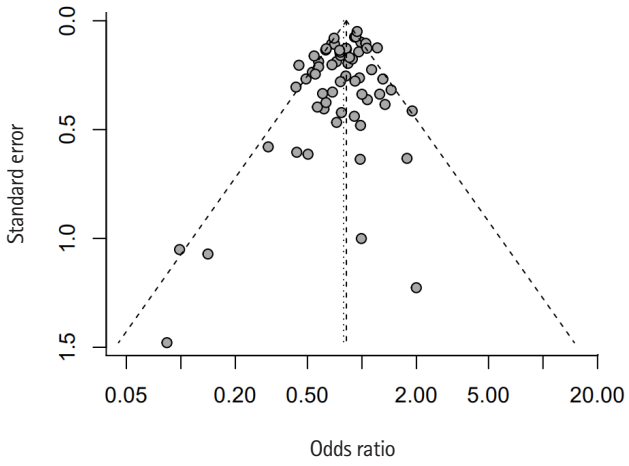


Supplementary Figure 12. Reduction in systolic blood pressure (SBP) on the odds ratio (OR) of stroke stratified by baseline SBP levels. CI, confidence interval.

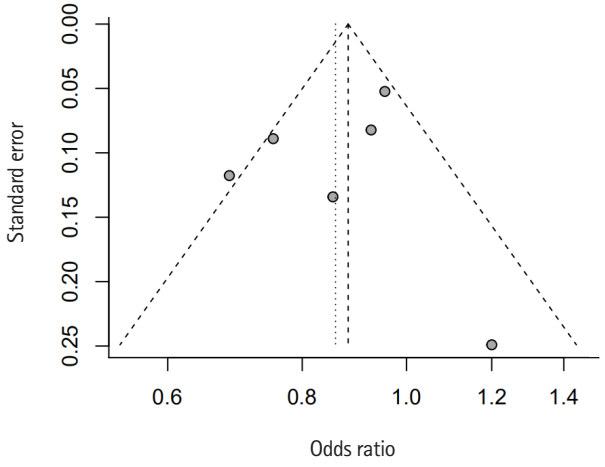
https://doi.org/10.5853/jos.2020.02698



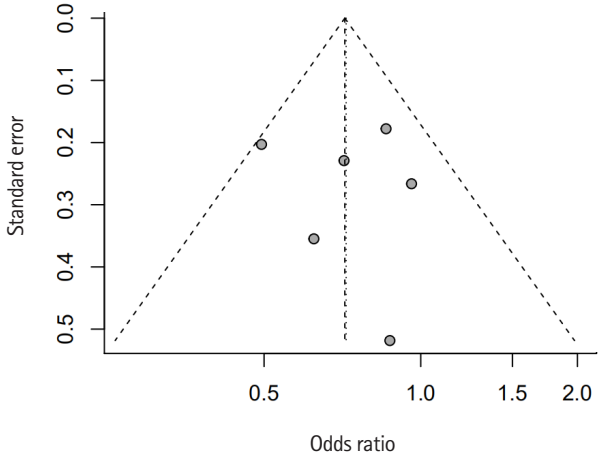
Supplementary Figure 13. Reduction in systolic blood pressure (SBP) on the odds ratio (OR) of stroke stratified by achieved SBP levels. CI, confidence interval.



Supplementary Figure 14. Funnel plot for stroke.

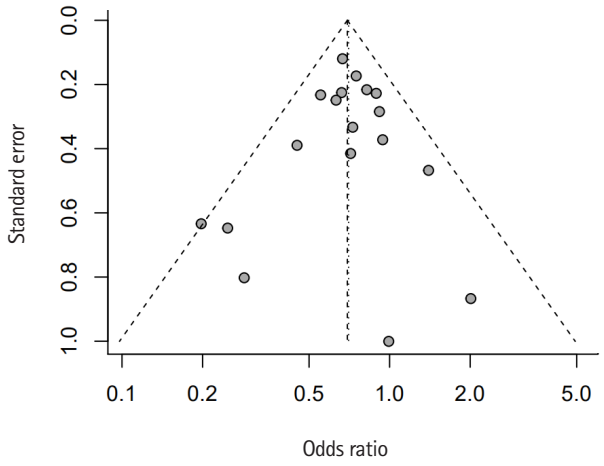


Supplementary Figure 15. Funnel plot for ischemic stroke.

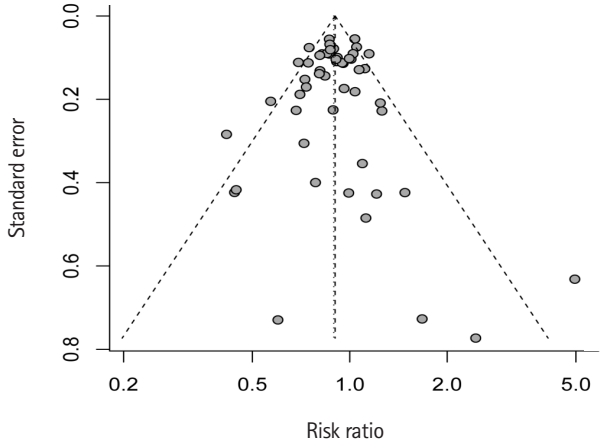


Supplementary Figure 16. Funnel plot for hemorrhagic stroke.

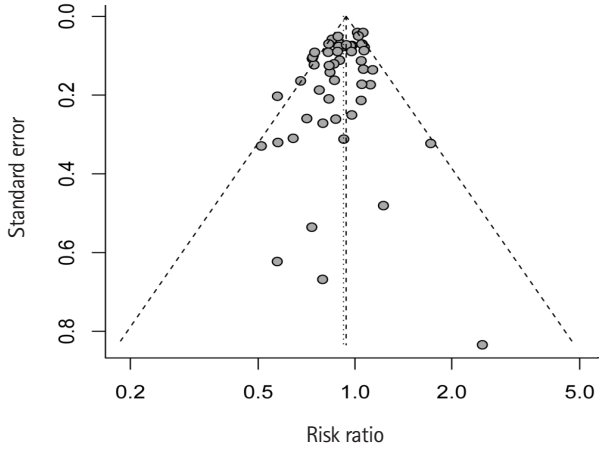
https://doi.org/10.5853/jos.2020.02698



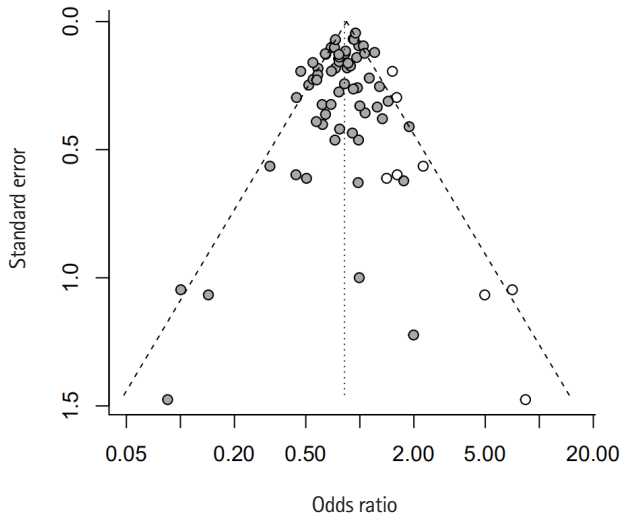
Supplementary Figure 17. Funnel plot for fatal or disabling stroke.



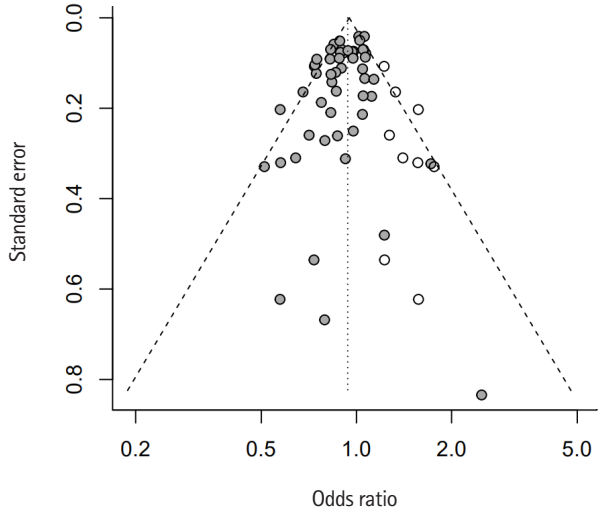
Supplementary Figure 18. Funnel plot for cardiovascular death.



Supplementary Figure 19. Funnel plot for all cause death.

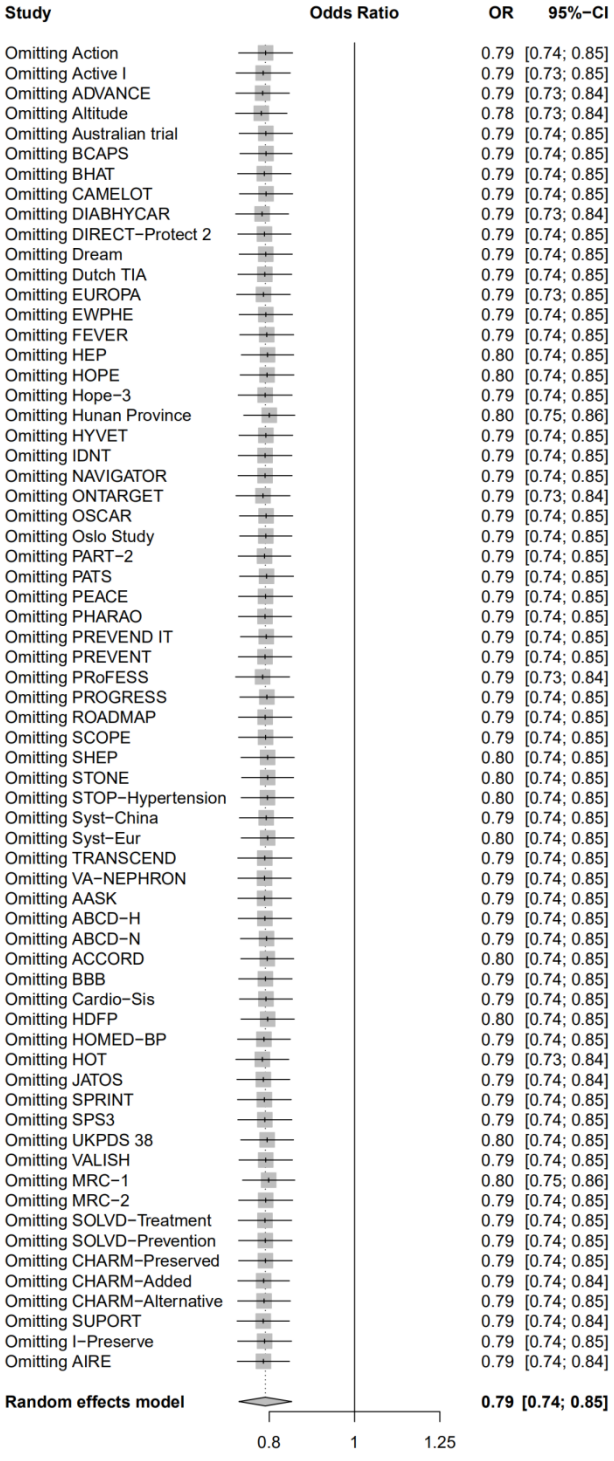


Supplementary Figure 20. Trimmed funnel plot for stroke.

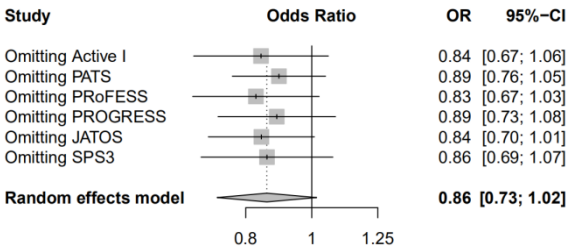


Supplementary Figure 21. Trimmed funnel plot for all cause death.

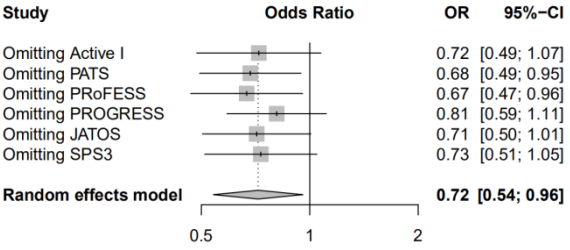
https://doi.org/10.5853/jos.2020.02698



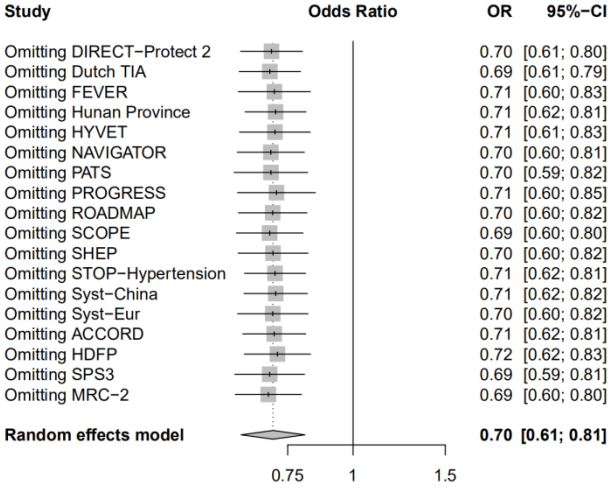
Supplementary Figure 22. Sensitivity analysis for stroke. OR, odds ratio; CI, confidence interval.



Supplementary Figure 23. Sensitivity analysis for ischemic stroke. OR, odds ratio; CI, confidence interval.

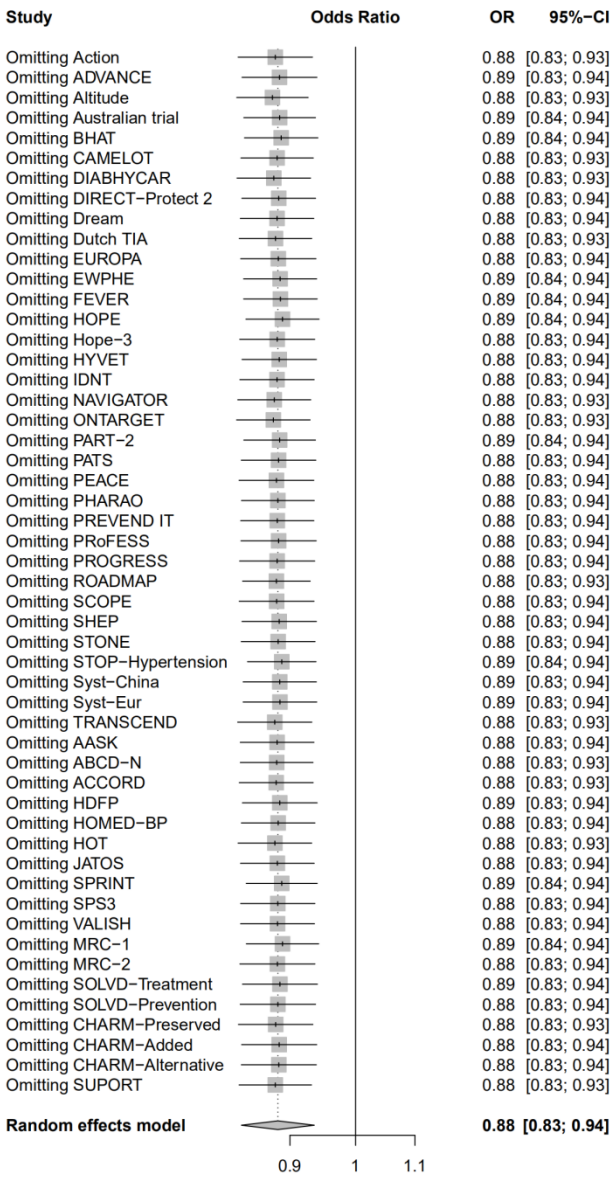


Supplementary Figure 24. Sensitivity analysis for hemorrhagic stroke. OR, odds ratio; CI, confidence interval.

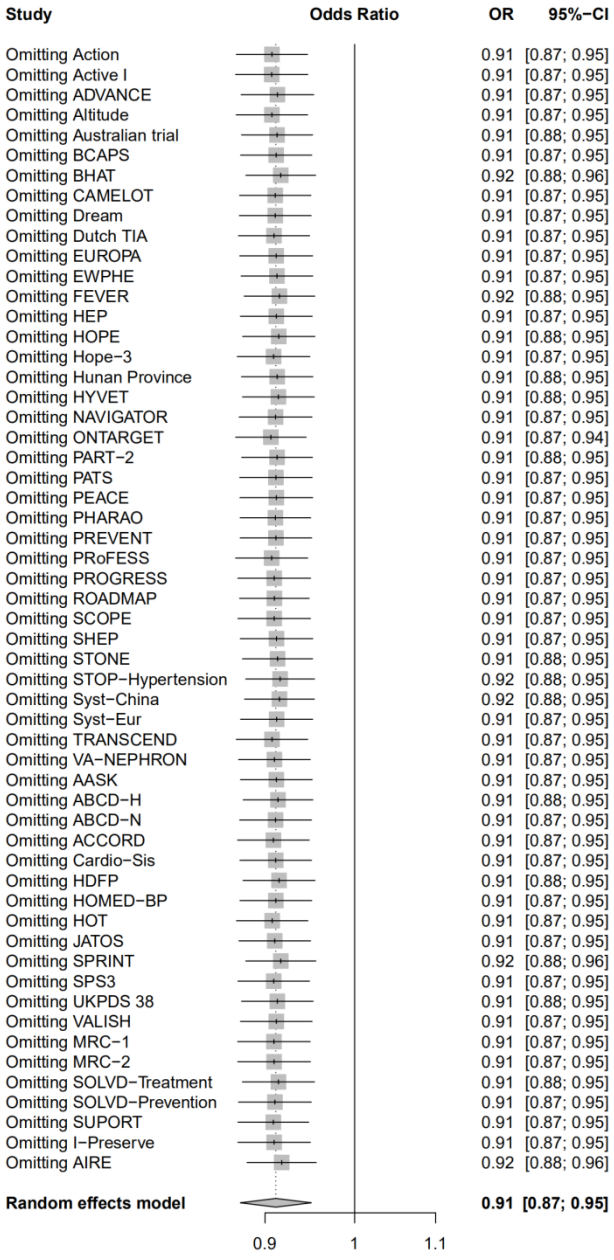


Supplementary Figure 25. Sensitivity analysis for fatal or disabling stroke. OR, odds ratio; CI, confidence interval.

https://doi.org/10.5853/jos.2020.02698

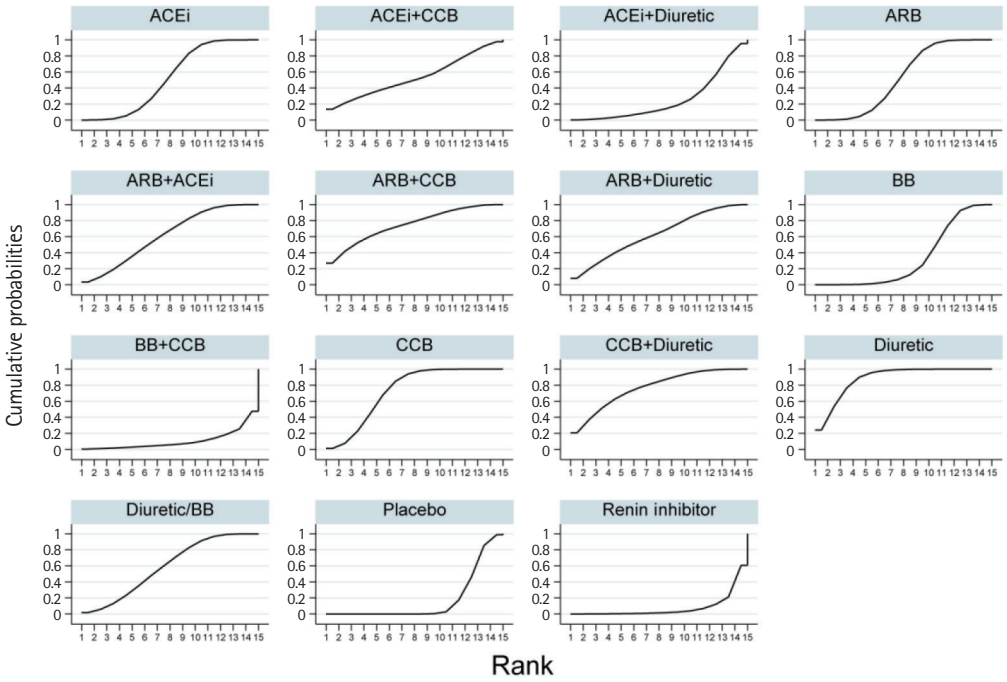


Supplementary Figure 26. Sensitivity analysis for cardiovascular death. OR, odds ratio; CI, confidence interval.

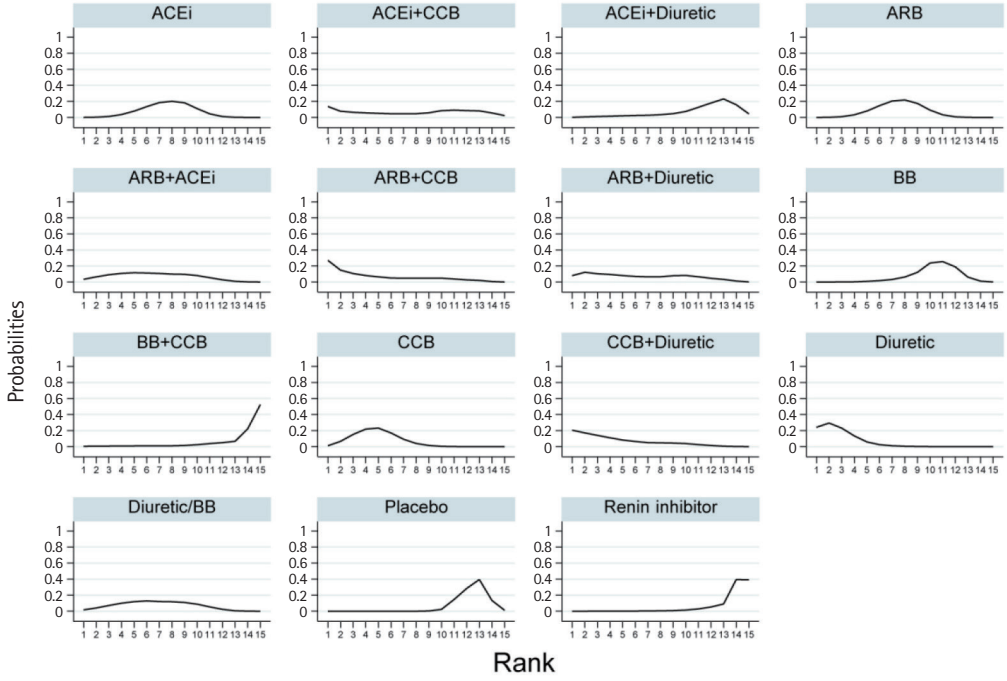


Supplementary Figure 27. Sensitivity analysis for all cause death. OR, odds ratio; CI, confidence interval.

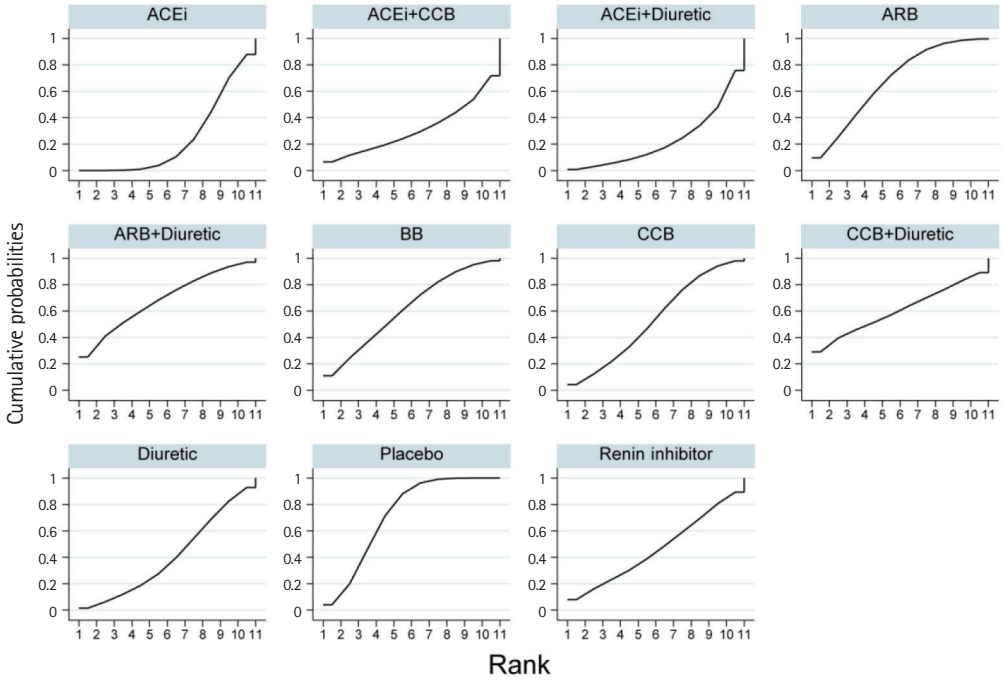
https://doi.org/10.5853/jos.2020.02698



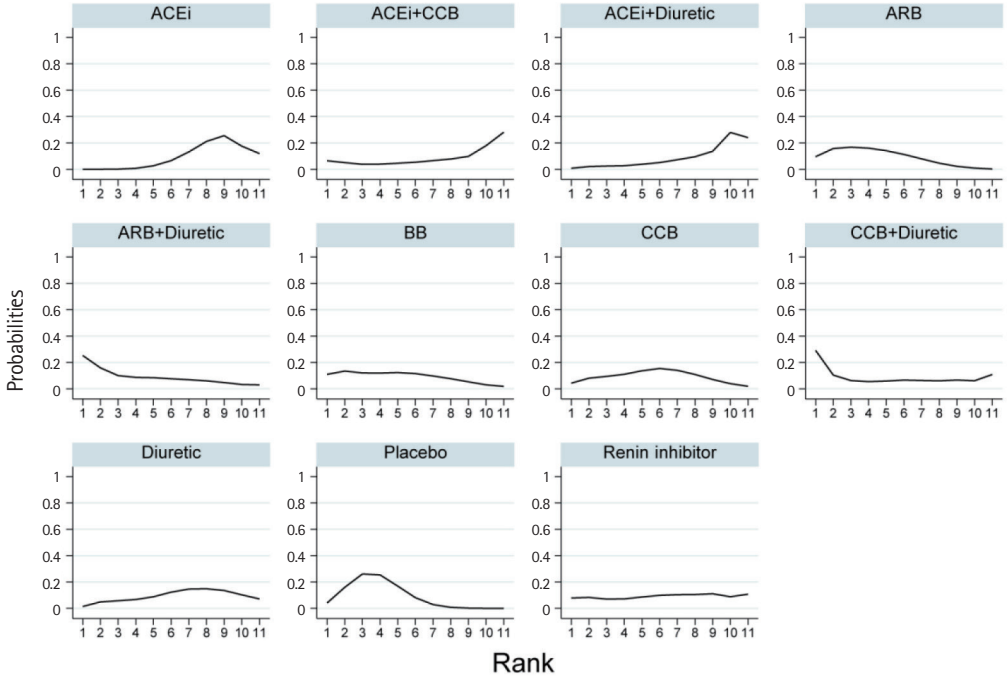
Supplementary Figure 28. The surface under the cumulative ranking curve (SUCRA) values of multiple treatments for efficacy. SUCRA, ranging from 1 to 0, indicating that the treatment has a high likelihood of being best and has a high likelihood of being worst, respectively. ACEi, angiotensin-converting enzyme inhibitor; CCB, calcium channel blocker; ARB, angiotensin II receptor blocker; BB, beta-blocker.



Supplementary Figure 29. Ranking of multiple treatments for efficacy. Ranking positions for all interventions (1 [best] to 15 [worst]). ACEi, angiotensin-converting enzyme inhibitor; CCB, calcium channel blocker; ARB, angiotensin II receptor blocker; BB, beta-blocker.



Supplementary Figure 30. The surface under the cumulative ranking curve (SUCRA) values of multiple treatments for tolerability. SUCRA, ranging from 1 to 0, indicating that the treatment has a high likelihood of being best and has a high likelihood of being worst, respectively. ACEi, angiotensin-converting enzyme inhibitor; CCB, calcium channel blocker; ARB, angiotensin II receptor blocker; BB, beta-blocker.



Supplementary Figure 31. Ranking of multiple treatments for tolerability. Ranking positions for all interventions (1 [best] to 15 [worst]). ACEi, angiotensin-converting enzyme inhibitor; CCB, calcium channel blocker; ARB, angiotensin II receptor blocker; BB, beta-blocker.

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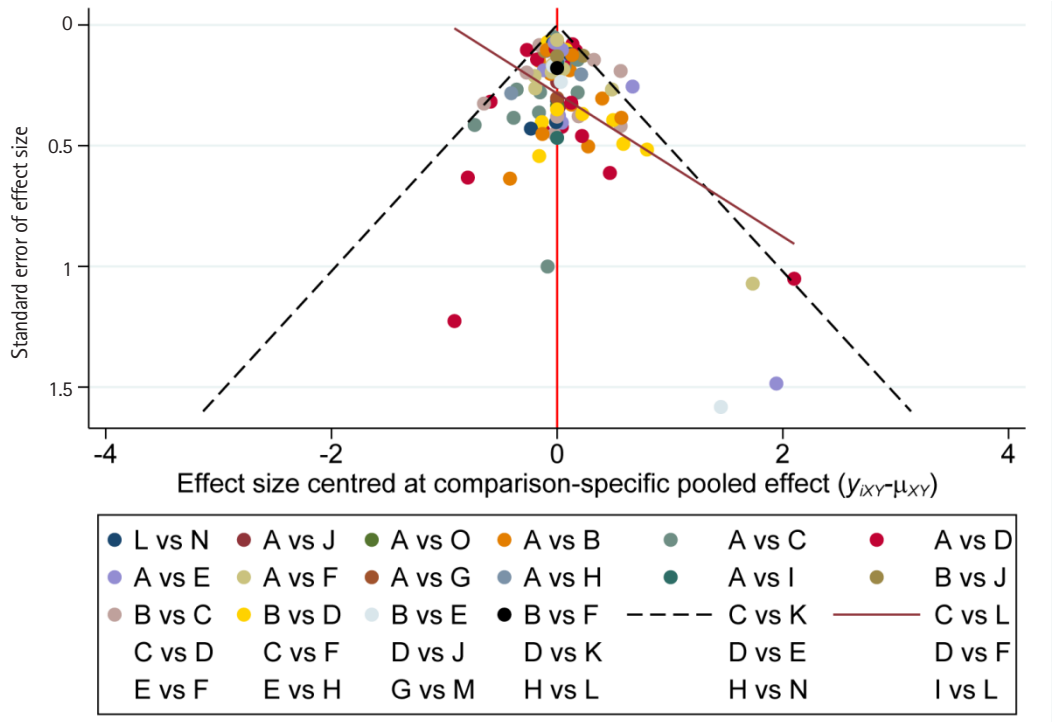
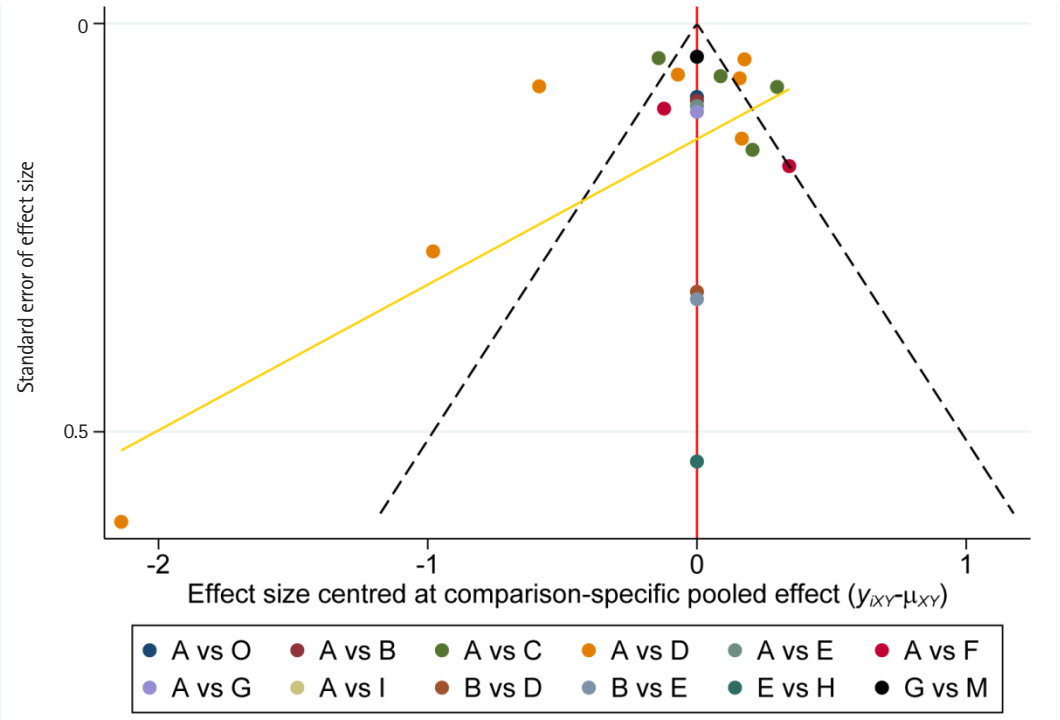
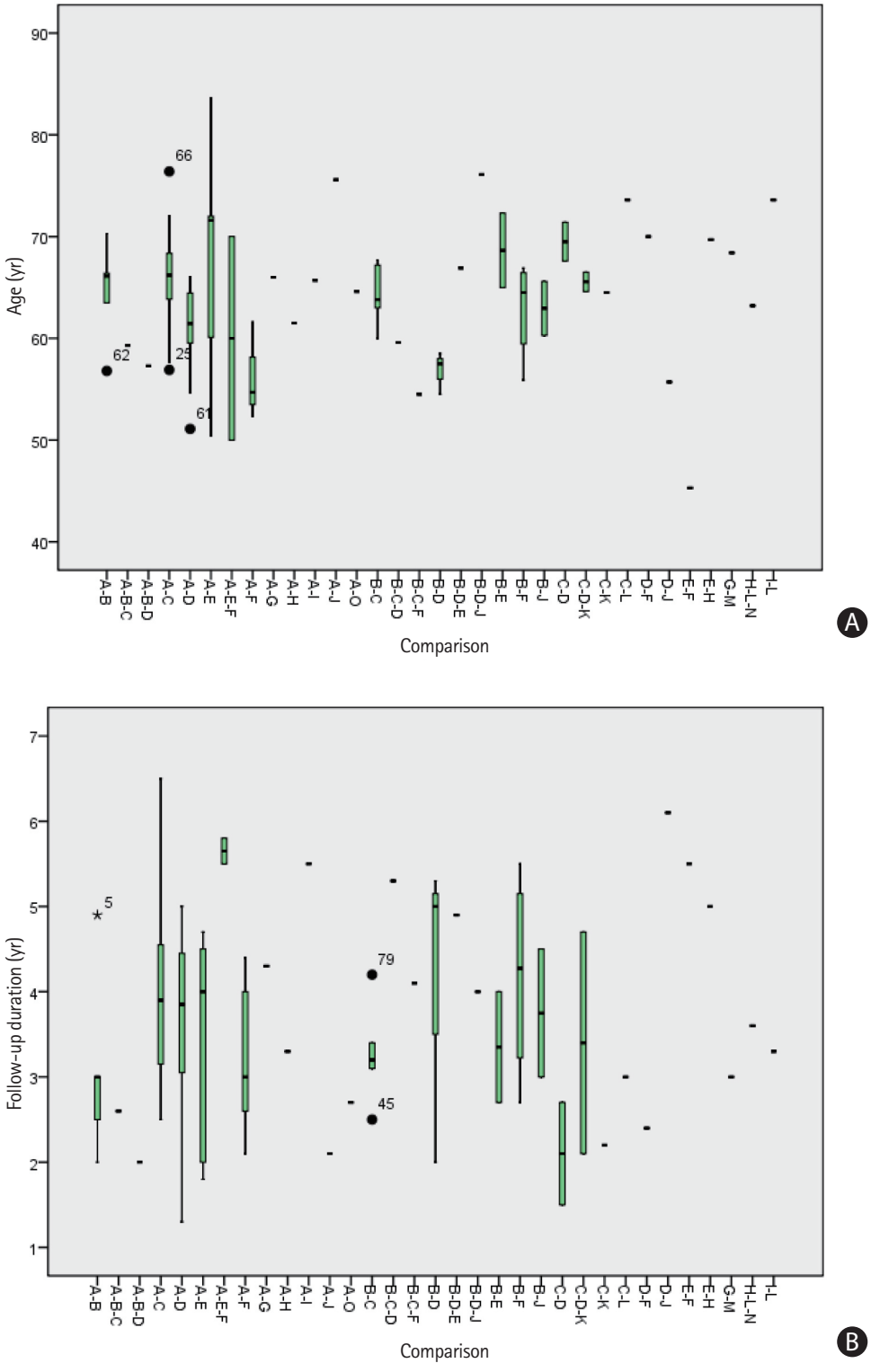


Supplementary Figure 32. Comparison-adjusted funnel plot for efficacy. A, placebo; B, calcium channel blocker (CCB); C, angiotensin II receptor blocker (ARB); D, angiotensin-converting enzyme inhibitor (ACEi); E, diuretic; F, beta-blocker (BB); G, ACEi+diuretic; H, CCB+diuretic; I, ARB+diuretic; J, BB/diuretic; K, ARB+ACEi; L, ARB+CCB; M, ACEi+CCB; N, BB+CCB; O, renin inhibitor. This is drawn only for comparisons with two or more studies.



Supplementary Figure 33. Comparison-adjusted funnel plot for tolerability. A, placebo; B, calcium channel blocker (CCB); C, angiotensin II receptor blocker (ARB); D, angiotensin-converting enzyme inhibitor (ACEi); E, diuretic; F, beta-blocker (BB); G, ACEi+diuretic; H, CCB+diuretic; I, ARB+diuretic; M, ACEi+CCB; O, renin inhibitor. This is drawn only for comparisons with two or more studies.



Supplementary Figure 34. Assessment of transitivity. (A) Age. (B) Follow-up duration. A, placebo; B, calcium channel blocker (CCB); C, angiotensin II receptor blocker (ARB); D, angiotensin-converting enzyme inhibitor (ACEi); E, diuretic; F, beta-blocker (BB); G, ACEi+diuretic; H, CCB+diuretic; I, ARB+diuretic; J, diuretic/BB; K, ARB+ACEi; L, ARB+CCB; M, ACEi+CCB; N, BB+CCB; O, renin inhibitor.

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