Medicine®

SYSTEMATIC REVIEW AND META-ANALYSIS

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Comparative Effectiveness of Blood Pressure-lowering Drugs in Patients who have Already Suffered From Stroke

Traditional and Bayesian Network Meta-analysis of Randomized Trials

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Abstract: Hypertension is the most important risk factor for stroke and stroke recurrence. However, the preferred blood pressure (BP)-lowering drug class for patients who have suffered from a stroke has yet to be determined.

To investigate the relative effects of BP-lowering therapies [angiotensin-converting enzyme inhibitor (ACEI), angiotensin receptor blockers (ARB), β blockers, calcium channel blockers (CCBs), diuretics, and combinations of these drugs] in patients with a prior stroke history, we performed a systematic review and meta-analysis using both traditional frequentist and Bayesian random-effects models and meta-regression of randomized controlled trials (RCTs) on the outcomes of recurrent stroke, coronary heart disease (CHD), and any major adverse cardiac and cerebrovascular events (MACCE). Trials were identified from searches of published hypertension guidelines, electronic databases, and previous systematic reviews.

Fifteen RCTs composed of 39,329 participants with previous stroke were identified. Compared with the placebo, only ACEI along with diuretics significantly reduced recurrent stroke events [odds ratio (OR) = 0.54, 95% credibility interval (95% CI) 0.33–0.90]. On the basis of the distribution of posterior probabilities, the treatment ranking consistently identified ACEI along with diuretics as the preferred BP-lowering strategy for the reduction of recurrent stroke and CHD (31% and 35%, respectively). For preventing MACCE, diuretics appeared to be the preferred agent for stroke survivors (34%). Moreover, the meta-regression analysis failed to demonstrate a statistical significance between BP reduction and all outcomes ($P = 0.1618$ for total stroke, 0.4933 for CHD, and 0.2411 for MACCE).

Evidence from RCTs supports the use of diuretics-based treatment, especially when combined with ACEI, for the secondary prevention of recurrent stroke and any vascular events in patients who have suffered from stroke.

(*Medicine* 95(15):e3302)

Abbreviations: ACEI = angiotensin-converting enzyme inhibitor, ARB = angiotensin receptor blockers, BP = blood pressure, CCB = calcium channel blocker, CHDs = coronary heart disease, CI = credibility interval, HR = hazard ratio, MACCE = major adverse cardiac and cerebrovascular events, MTC = mixed treatment comparisons, NICE = National Institute for Health and Care Excellence, OR = odds ratio, RCTs = randomized controlled trials, RR = relative risk, SUCRA = surface under the cumulative ranking.

INTRODUCTION

Stroke affects 15 million people per year worldwide, and 1 in 6 people will have a stroke in their lifetime.[1] Stroke is the second leading cause of death in people over the age of 60, and it is the fifth leading cause of death in people between the ages of 15 and 59 years.[2] Therefore, stroke prevention is an important public health mission to avoid the long-term neurological deficits and resultant disability burden from acute stroke. Because hypertension is the most important risk factor for stroke[3] and stroke recurrence,[4] several randomized controlled clinical trials (RCTs) have been conducted to investigate the effects of blood pressure (BP)-lowering drugs on the prevention of recurrent vascular events.[4–22]

With broadly similar risk factors, atherothrombotic vascular disease most frequently manifests as stroke and coronary heart disease (CHD).[23] Following the initial stroke events, patients have a higher chance of the occurrence of major adverse cardiac and cerebrovascular events (MACCE), 80% of which were recurrent stroke,[23] highlighting the importance of secondary stroke prevention. However, the optimal BP-lowering agents aimed at the secondary prevention of stroke that have been suggested by the international hypertension guidelines vary substantially. For example, all drug regimens are recommended by the 2013 European Society of Hypertension (ESH)/European Society of Cardiology (ESC) hypertension guidelines for stroke prevention provided that BP is effectively reduced.[24] In contrast, the NICE[25] and the 2015 TSOC/TSH hypertension guidelines suggested that beta-blockers were significantly worse than other drugs at preventing stroke.[26] Diuretics and ACEI are the preferred agents for recurrent stroke prevention in the JNC-7[27] and the 2014 AHA/ASA guidelines for the prevention of recurrent stroke in patients with prior stroke history,[28] but no specific agent was recommended for

Editor: Ovidiu Constantin Baltatu.
Received: January 6, 2016; revised: February 26, 2016; accepted: March 14, 2016.
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The authors report no conflicts of interest.
Supplemental Digital Content is available for this article.

ISSN: 0025-7974
DOI: 10.1097/MD.0000000000003302

preventing stroke recurrence in the 2014 report by the JNC-8 panel.[29] These discrepancies indicate that the preferred agent for the prevention of stroke in patients with prior stroke history has yet to be determined. With the huge socioeconomic burden of stroke, choosing the optimal antihypertensive agent that provides the best protection is imperative. Moreover, it has been suggested that much of the reduction in stroke events is simply related to the magnitude of BP reduction. Therefore, in the present systematic review, which utilized traditional frequentist and Bayesian network meta-analyses and meta-regression analysis, we endeavored to determine the most effective BP-lowering agent and the relationship between BP reduction and adverse outcomes for patients who have suffered from stroke.

METHODS

Study Selection

We searched the reference lists of previous international hypertension guidelines [24–27,29] and meta-analyses[4,20,30,31] and used the search strategies supplemented in the guidelines[29] to identify all possible studies in the MEDLINE, Cochrane Library, and Web of Science databases published through December 2014. The following key words were used in the search queries: BP lowering, BP reduction, stroke, transient ischemic attack, antihypertensive, hypertension, randomized controlled trial, and controlled clinical trial. Inclusion criteria for eligible trials required each of the following: (1) RCTs comparing the effects of any of the 6 most commonly used BP-lowering drug classes [angiotensin-converting enzyme inhibitor (ACEI), angiotensin receptor blocker (ARB), alpha-blocker, beta-blocker, diuretics, and calcium channel blocker (CCB)] versus placebo or comparing one type of antihypertensive agent with another type on patients who have suffered from stroke or transient ischemic attacks; (2) RCTs reporting the outcomes of interest with a follow-up of more than a month. Studies on secondary prevention were eligible if they were RCTs and assessed the effects of antihypertensive agents on subjects with a prior stroke (>14 days after ictus) or transient ischemic attack. The results of subgroup analyses in RCTs were considered eligible if relevant and sufficient information could be provided. To provide guidance on decision making in the care of patients with previous stroke, the present study involved the evidence synthesis of studies already published and no individual patient data were accessed; therefore, ethical approval was not necessary.

Data Extraction

Data were extracted from papers by 2 reviewers (WTW and LKY) independently, and differences in data extraction were resolved through discussions or by discussion with a third investigator (HMC).

Statistical Analysis

Multiple-treatment meta-analysis or network meta-analysis was conducted for mixed treatment comparisons (MTCs) in a Bayesian framework, and the pooled estimates were obtained using the Markov Chains Monte Carlo method. This approach is recommended by the National Institute for Health and Care Excellence (NICE) Decision Support Unit according to the technical support documents on evidence synthesis.[32] We performed a random-effects network meta-analysis in ADDIS Version 1.8 and GeMTC-GUI-0.14.3, which uses Bayesian Markov Chains Monte Carlo methods[33] with 50,000 times random sampling. There were 3 parts in these analyses. First, in the network meta-analysis for the consistency model, we estimated all of the relative effects simultaneously by using the consistency constraint. For example, the parameter dBC was estimated from both direct evidence on BC and indirect evidence on AC and AB. The relative effect results for the consistency model were reported as an odds ratio (OR) with a corresponding 95% credibility interval (95% CI). Then, we estimated the ranking probability for each drug, that is, the most effective drug, the second best, third best, etc. The overall ranks were interpreted using the surface under the cumulative ranking (SUCRA) technique and rank probability sum to one.[34] Rank 1 is considered the preferred agent for the specific outcome. Second, we performed the inconsistency analysis using the inconsistency model and the node-splitting model to check whether the analysis of the trials in the network was indeed consistent. In brief, the inconsistency factors, representing the discrepancy between the direct and indirect evidence, were added to the closed loops of the inconsistency model, that is, $dBC = dAC - dAB + \varphi$ (φ = inconsistency factor). Therefore, the degree of inconsistency, by checking the size of an inconsistency factor within the cycle, was determined for a cycle (e.g., ABC) rather than for individual pairwise comparisons.[34,35] When the 95% CI of the median of the inconsistency factors included zero and if the inconsistency standard deviation was less than or equal to the random effects standard deviation, the inconsistency can be considered as insignificant. MACCE, CHD, and total stroke events were used as the outcome measure for the network meta-analysis.

In addition, traditional pairwise meta-analysis using the random effects model of DerSimonian and Laird was also conducted considering significant heterogeneity was noted across studies. I^2 statistic was quantified to estimate the proportions of inconsistencies across the studies not explained by chance. Cochran's Q test was performed to evaluate the heterogeneity between subgroups. For the trials that tested the combined effects of 2 BP-lowering agents, the analyses were conducted by considering the combination as a specific treatment arm that was then used for the comparisons.[36]

The relationship between event rates and the final achieved BP was also quantified by the linear regression analysis. In addition, we also conducted a meta-regression analysis to test the relationship between BP reduction and the risk of recurrent stroke, CHD, and MACCE. The analyses were performed using R version 3.1.2 and the software package Comprehensive Meta-Analysis version 2 (Biostat, Englewood, NJ).[37] Moreover, the subgroup analysis based on different baseline BP, final achieved BP, time-averaged BP reduction magnitude between treatment and control groups, and study countries was conducted to investigate whether these conditions could modulate the effects of risk reduction.

RESULTS

The literature search identified 1513 articles whose titles and abstracts were reviewed (Figure 1). After an initial screening, the full text of 24 articles was retrieved for detailed assessment. A total of 15 trials (39,329 subjects) for the secondary prevention of stroke in survivors were eligible for the meta-analysis.

Study Characteristics

Table 1 summarizes the characteristics of the studies included in the meta-analysis. Of these patients with previous

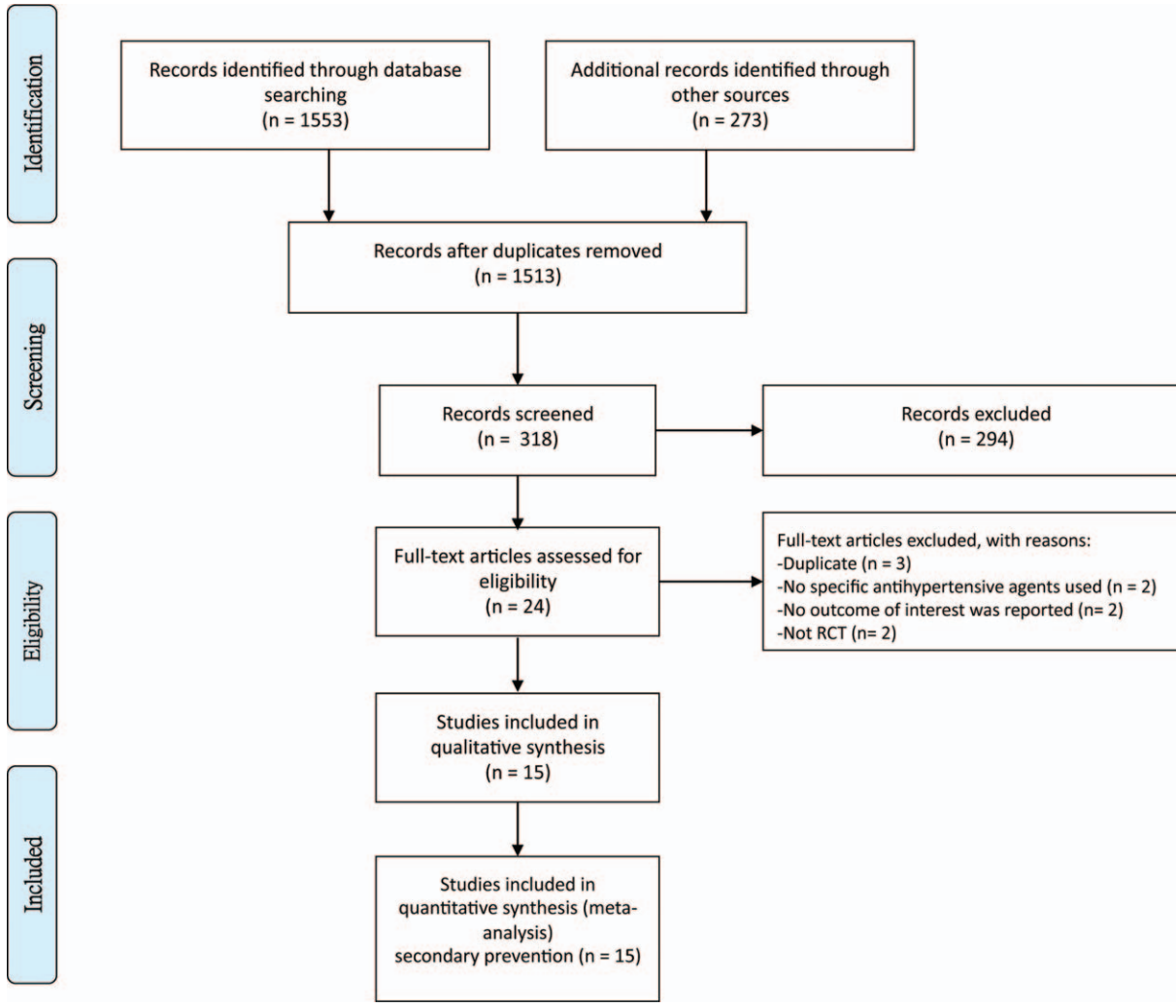

FIGURE 1. Flow chart of the literature search for studies investigating the effects of antihypertensive agents on the secondary prevention of stroke. RCT = randomized controlled trials.

stroke history, 5467 MACCE (event rate 19.1%) were noted with a median follow-up of 2.6 years, and these included 3886 recurrent strokes (event rate 11.7%) and 1233 coronary events (event rate 5.1%). The majority of the MACCE in these patients were recurrent stroke events (71.1%), followed by CHD (22.6%). In these RCTs, 2532 patients (6.44%) were assigned to ACEI along with diuretics [perindopril and indapamide, 2532 (100%)]; 101 (0.26%) to β-blocker and diuretics therapy [atenolol and bendrofluazide, 11 (10.89%); atenolol and chlorthalidone, 59 (58.42%); atenolol/metoprolol/pindolol plus hydrochlorothiazide/amiloride, 31 (30.69%)]; 3109 (7.91%) to diuretics therapy [methyclothiazide, 233 (7.49%); hydrochlorothiazide and triamterene, 35 (1.13%); indapamide, 2841 (91.38%)]; 1781 (4.53%) to ACEI [ramipril, 500 (28.07%); perindopril, 1281 (71.93%)]; 10,827 (27.53%) to ARB [eprosartan, 681 (6.29%); telmisartan, 10,146 (93.71%)], 96 (0.24%) to ARB and diuretics [candesartan and hydrochlorothiazide, 96 (100%)]; 1104 (2.81%) to β blocker [atenolol, 1104 (100%)]; 799 (2.03%) to CCB [nimodipine, 128 (16.02%); nitrendipine, 671 (83.98%)]; and 18,980 patients (48.25%) were randomized to receive placebo.

The construction of the network comparisons between different treatment strategies is shown in Figure 2.

Summarized Results of Network Meta-analysis and Traditional Pairwise Meta-analysis

Effects of BP-lowering Drugs on Recurrent Stroke

Table 2 summarizes the pooled estimates of the above BP-lowering strategies estimated with the pairwise meta-analysis and the network meta-analysis. As shown in the Network meta-analysis results in Table 2, compared with the placebo, ACEI and diuretics significantly reduced recurrent stroke (OR 0.54, 95% CI 0.33–0.90) in stroke survivors. The distribution of probabilities for each treatment being ranked at different positions for the outcome of recurrent stroke is shown in Figure 3. The probability ranking demonstrates that ACEI and diuretics has a higher probability of being at the best ranking positions

TABLE 1. Characteristics of included studies

Trials	Total Patient No.	Patients in Each Group	Follow-up (yrs)	Mean Age, (SD)	BP-lowering Drug	Generic Name	Mean Baseline SBP (SD)	Mean Baseline DBP (SD)	Final SBP (SD)	Final DBP (SD)	*Average BP Reduction of SBP	Average BP Reduction of DBP	No. of MACCE	No. of Total Stroke	No. of CHD
HSCS, 1974, USA[5,13,20]	452	233	2.3	59.0	Diuretics	Methyclothiazide	167	100	140.70 (1.30)	86.70 (0.60)	25	12.3	52	37	7
		219		59.0	Placebo	Placebo	167	100	167.00	100.00			61	42	12
EWPHE, 1985, Europe[6,13,20]	63	35	3.2	72 (8)	Diuretics	Hydrochlorothiazide+ Triamterene	183 (17)	101 (7)	148 (18)	85 (10)	21	8	17	5	4
		28		72 (8)	Placebo	Placebo	182 (16)	101 (7)	167 (22)	90 (9)			25	9	5
HEP, 1986, UK[7,20]	17	11	5.0	64.7 (5.2)	BB/Diuretic	Atenolol+Bendrofluazide	196.7 (16.7)	99.7 (12)	178.7	88.7	18	11	2	2	0
		6		68.8 (5.1)	Placebo	Placebo	196.1 (15.6)	98.0 (11.1)	178.1	87.0			3	1	2
SHEP, 1991, USA[8,13,20]	99	59	4.50	70.2 (6.4)	BB/Diuretics	Atenolol+Chlorthalidone	170.2 (9.2)	76.9 (8.9)			13	4.3	11	8	3
		40		70.5 (6.0)	Placebo	Placebo	170.2 (9.2)	74.8 (10.0)					9	7	2
STOP, 1991, Sweden[9,13,20]	66	31	2.2	75.6 (3.7)	BB/Diuretics	Atenolol, Metoprolol, Pindolol+ Hydrochlorothiazide, Amiloride	195 (14)	102 (7)	167 (21)	87 (9)	19.5	8.1	4	1	3
		35		75.7 (3.7)	Placebo	Placebo	195 (14)	102 (7)	186 (22)	96 (10)			7	4	2
Dutch TIA, 1993, Netherlands[10,20]	1473	732	2.6	66.0	BB	Atenolol	158 (25)	91 (12)	150.00		4	1.7	97	52	45
		741		66.00	Placebo	Placebo	157 (24)	91 (12)	154.80				102	62	40
TEST, 1995, Sweden[20,43]	720	372	2.55	70.7 (9.1)	BB	Atenolol			157.00		4	3	115	81	29
		348		70.1 (10)	Placebo	Placebo			161.00				114	75	36
PATS, 1995, China[12,13,20]	5665	2841	2.0	60 (8)	Diuretics	Indapamide	154 (23)	93 (13)	142.60 (16.90)	85.70 (8.70)	5.8	2.9	252	159	25
		2824		60 (8)	Placebo	Placebo	154 (24)	93 (13)	148.80 (19.10)	88.60 (10.10)			324	217	21
HOPE, 2000, International study[4,44]	1013	500			ACEI	Ramipril	151.0	79.0	141.00		3.1	1.7	101	43	58
		513			Placebo	Placebo	151.0	79.0	151.00				130	51	79
SMIDIT, 2000, Europe[14,20]	259	128	0.54	73.7 (7.1)	CCB	Nimodipine	153.6 (20.6)	83.0 (11.7)	152.50 (20.20)	83.50 (11.30)	6.5	4	7	5	2
		131		74.9 (6.3)	Placebo	Placebo	149.3 (20.6)	82.3 (10.5)	149.80 (18.30)	84.70 (10.70)			18	13	3
PROGRESS, 2001, International study[16,17]	2561	1281	3.90	64 (10)	ACEI	Perindopril	147 (19)	86 (11)	138 (0.3)	82 (0.2)	4.9	2.8	205	157	48
		1280		64 (10)	Placebo	Placebo	147 (19)	86 (11)	147 (19)	86 (11)			217	165	52
	3544	1770	3.90	64 (10)	ACEI/Diuretics	Perindopril + Indapamide	147 (19)	86 (11)	138 (0.3)	82 (0.2)	12.3	5	217	150	67
		1774		64 (10)	Placebo	Placebo	147 (19)	86 (11)	147 (19)	86 (11)			357	255	102

Trials	Total Patient in Each Group No.	Patients Follow-up (yrs)	Mean Age, (SD)	BP-lowering Drug	Generic Name	Mean Baseline SBP (SD)	Mean Baseline DBP (SD)	Final SBP (SD)	Final DBP (SD)	*Average BP Reduction of SBP	Average BP Reduction of DBP	No. of MACCE	No. of Total Stroke	No. of CHD
MOSES, 2005, Germany and Austria[18]	1352	2.5	67.7 (10.4)	ARB	Eprosartan	150.7 (18.5)	87 (10.8)	137.50 (16.70)	80.80 (8.90)	0	0	179	102	77
	671		68.1 (9.5)	CCB	Nitrendipine	152.0 (18.2)	87.2 (9.6)	136.00 (15.60)	80.20 (8.80)			235	134	101
PRoFESS, 2008, International study[19]	20,332	2.5	66.1 (8.6)	ARB	Telmisartan	144.1 (16.4)	83.8 (10.5)	135.80		3.8	2	1103	880	168
	10,186		66.2 (8.6)	Placebo	Placebo	144.1 (16.7)	83.8 (10.6)	141.20				1197	934	169
SCOPE, 2005, Germany[21]	193	96	3.7	70-89	ARB/Diuretics	Candesartan+ Hydrochlorothiazide	160-179	90-99			-0.4	1.5	11	6
		97		70-89	Placebo	Placebo	160-179	90-99					28	15
Liu et al, China[22]	1520	762	4	63.9 (7.5)	ACEI/Diuretics	Perindopril+Indapamide	145.3 (20.2)	86.8 (11.1)	141.3	80.8	14	6		67
		758		63.8 (7.7)	Placebo	Placebo	145.3 (20.2)	87.2 (10.8)						147

ACEI = angiotensin-converting enzyme inhibitor, ARB = angiotensin receptor blockers, BB = β blockers, CCB = calcium channel blockers, CHD = coronary heart disease, DBP = diastolic blood pressure, MACCE = major adverse cardiac and cerebrovascular events, SBP = systolic blood pressure, SD = standard deviation.

*Average BP reduction = blood pressure differences between treatment and control groups averaged from multiple measurements during follow-up.

(31%). β blocker was the treatment with the highest probability (24%) of being in the last ranking position.

Traditional meta-analysis showed that, compared with the control groups, treatment strategies including diuretics had a relative risk (RR) of 0.619 (95% CI 0.515–0.743) for recurrent stroke, which was significantly lower than treatments that did not include diuretics (RR = 0.882, 95% CI 0.800–0.973) with a *P* value for interaction of 0.0008.

Effects of BP-lowering Drugs on CHD

Although most of the treatment regimens exerted protective effects against CHD, none of them significantly outperformed the placebo in the reduction of CHD among the MTCs. However, in the traditional meta-analysis, ACEI and diuretics had an OR of 0.619 (95% CI 0.466–0.811) for the prevention of CHD. As shown in Figure 3, ACEI and diuretics had the highest probability of being ranked as the preferred agent for reducing the risk of CHD (35%).

The traditional pairwise meta-analysis comparing treatment strategies including diuretics to those without diuretics showed comparable RRs [0.707 (95% CI 0.561–0.891) with diuretics vs. 0.842 (95% CI 0.721–0.984) without diuretics; *P* for interaction 0.219].

Effects of BP-lowering Drugs on MACCE

Similarly, all treatment strategies had favorable effects on MACCE as shown in both MTC and the traditional meta-analysis. Diuretics, with the lower point estimates of OR for MACCE, were identified by the probability ranking analysis to be the preferred agent (34%) for preventing MACCE, followed by ACEI and diuretics (18%).

For preventing MACCE, compared with control groups, treatment strategies that included diuretics had a significantly lower RR of 0.633 (95% CI 0.532–0.754) than treatments not including diuretics (RR = 0.837, 95% CI 0.748–0.937) with a *P* for interaction of 0.008.

Comparisons Between Traditional Pairwise and Bayesian Network Meta-analyses

Table 2 also presents the results of traditional pairwise meta-analyses. In general, the confidence intervals from traditional pairwise meta-analyses and the CIs from Bayesian network meta-analyses overlapped. Compared with the results obtained with the Bayesian network meta-analysis, the point estimates of the traditional meta-analysis were largely comparable.

Model Inconsistency

In the network meta-analysis, the disagreement between direct and indirect comparison was concerning and was examined by calculating the inconsistency factors. For all comparisons in the secondary prevention of stroke, the 95% CI of inconsistency factors from all cycles included zero (Table S1, http://links.lww.com/MD/A880), and the node-splitting method showed no significant inconsistency within the networks for any of these outcomes, which suggested that the results in the network were consistent between direct and indirect evidence.

The Relationship Between Outcomes and BP

For patients who suffered from a previous stroke, the associations between the event rates and the final achieved

TABLE 2. Treatment Comparisons Between Different Classes of Blood Pressure Lowering Drugs Made by Bayesian Network Meta-analysis and Traditional Pairwise Meta-analysis for Outcomes of Recurrent Stroke, Coronary Heart Diseases (CHD), and Major Adverse Cardiac and Cerebrovascular Events (MACCE) in Patients With a Prior Stroke

		Pairwise Comparisons			Network Meta-analysis	
Comparison on Recurrent Stroke		**Study No. of Pairwise Comparisons**	**Odds Ratio**	**(95% Confidence Interval)**	**Odds Ratio**	**(95% Credibility Interval)**
Drugs vs. placebo						
ACEI	Placebo	2	0.922	(0.751–1.131)	0.9	(0.48–1.67)
ACEI and and and diuretics	Placebo	2	0.538	(0.391–0.740)	0.54	(0.33–0.90)
ARB	Placebo	2	0.665	(0.269–1.641)	0.69	(0.31–1.11)
BB	Placebo	2	0.928	(0.715–1.204)	0.93	(0.51–1.72)
CCB	Placebo	1	0.369	(0.128–1.067)	0.78	(0.27–1.54)
Diuretics	Placebo	3	0.698	(0.567–0.860)	0.63	(0.28–1.19)
Diuretics and BB	Placebo	3	0.65	(0.257–1.645)	0.61	(0.21–1.72)
Drugs vs. diuretics						
ACEI	Diuretics				1.43	(0.60–3.99)
ACEI and diuretics	Diuretics				0.85	(0.40–2.23)
ARB	Diuretics				1.11	(0.38–2.61)
BB	Diuretics				1.47	(0.61–4.21)
CCB	Diuretics				1.27	(0.35–3.29)
Drugs vs. diuretics and BB						
ACEI	Diuretics+BB				1.49	(0.44–5.10)
ACEI and diuretics	Diuretics+BB				0.89	(0.28–2.89)
ARB	Diuretics+BB				1.11	(0.30–3.57)
BB	Diuretics+BB				1.54	(0.46–5.18)
CCB	Diuretics+BB				1.26	(0.29–4.36)
Diuretics	Diuretics+BB				1.03	(0.27–3.52)
Drugs vs. drugs						
ACEI	ACEI+diuretics				1.66	(0.74–3.64)
ACEI	ARB				1.31	(0.63–3.71)
ACEI	BB				0.97	(0.40–2.35)
ACEI	CCB				1.15	(0.49–4.02)
ACEI+diuretics	ARB				0.78	(0.41–2.08)
ACEI+diuretics	BB				0.58	(0.27–1.30)
ACEI+diuretics	CCB				0.69	(0.31–2.30)
ARB	BB				0.74	(0.26–1.53)
ARB	CCB	1	0.706	(0.532–0.937)	0.87	(0.45–1.93)
BB	CCB				1.18	(0.50–4.18)

Comparison on CHD			**Odds Ratio**	**(95% Confidence Interval)**	**Odds Ratio**	**(95% Credibility Interval)**
Drugs vs. placebo						
ACEI	Placebo	2	0.805	(0.615–1.053)	0.81	(0.40–1.64)
ACEI+diuretics	Placebo	2	0.615	(0.466–0.811)	0.58	(0.29–1.07)
ARB	Placebo	2	0.596	(0.194–1.833)	0.71	(0.30–1.22)
BB	Placebo	2	0.949	(0.680–1.325)	0.94	(0.44–1.93)
CCB	Placebo	1	0.677	(0.111–4.122)	0.95	(0.29–2.24)
Diuretics	Placebo	3	1.073	(0.626–1.839)	1.01	(0.39–2.44)
Diuretics+BB	Placebo	3	0.896	(0.267–3.008)	0.7	(0.19–2.73)
Drugs vs. diuretics						
ACEI	Diuretics				0.79	(0.27–2.64)
ACEI+diuretics	Diuretics				0.57	(0.19–1.80)
ARB	Diuretics				0.69	(0.20–1.97)
BB	Diuretics				0.91	(0.30–3.10)
CCB	Diuretics				0.93	(0.21–3.35)
Drugs vs. diuretics+BB						
ACEI	Diuretics+BB				1.14	(0.25–5.10)
ACEI+diuretics	Diuretics+BB				0.83	(0.18–3.41)

Comparison on CHD			Odds Ratio	(95% Confidence Interval)	Odds Ratio	(95% Credibility Interval)
ARB	Diuretics+BB				0.96	(0.20–3.89)
BB	Diuretics+BB				1.31	(0.28–5.84)
CCB	Diuretics+BB				1.31	(0.23–6.03)
Diuretics	Diuretics+BB				1.44	(0.27–6.83)
Drugs vs. drugs						
ACEI	ACEI+diuretics				1.39	(0.55–3.81)
ACEI	ARB				1.14	(0.49–3.71)
ACEI	BB				0.86	(0.32–2.49)
ACEI	CCB				0.84	(0.29–3.51)
ACEI+diuretics	ARB				0.82	(0.36–2.47)
ACEI+diuretics	BB				0.62	(0.23–1.64)
ACEI+diuretics	CCB				0.61	(0.21–2.39)
ARB	BB				0.75	(0.24–1.79)
ARB	CCB	1	0.719	(0.524–0.989)	0.75	(0.32–1.79)
BB	CCB				0.99	(0.33–4.17)

Comparison on MACCE			Odds Ratio	(95% Confidence Interval)	Odds Ratio	(95% Credibility Interval)
Drugs vs. placebo						
ACEI	Placebo	2	0.866	(0.730–1.027)	0.84	(0.34–2.10)
ACEI+diuretics	Placebo	2	0.534	(0.398–0.716)	0.54	(0.26–1.16)
ARB	Placebo	2	0.517	(0.155–1.726)	0.49	(0.19–1.07)
BB	Placebo	2	0.938	(0.756–1.165)	0.94	(0.37–2.38)
CCB	Placebo	1	0.363	(0.146–0.902)	0.57	(0.17–1.55)
Diuretics	Placebo	3	0.331	(0.053–2.078)	0.44	(0.13–1.09)
Diuretics+BB	Placebo	3	0.624	(0.295–1.320)	0.56	(0.18–1.63)
Drugs vs. diuretics						
ACEI	Diuretics				1.9	(0.55–8.83)
ACEI+diuretics	Diuretics				1.24	(0.40–5.20)
ARB	Diuretics				1.1	(0.32–4.73)
BB	Diuretics				2.12	(0.62–10.37)
CCB	Diuretics				1.3	(0.31–6.25)
Drugs vs. diuretics+BB						
ACEI	Diuretics+BB				1.48	(0.37–6.38)
ACEI+diuretics	Diuretics+BB				0.96	(0.27–3.72)
ARB	Diuretics+BB				0.85	(0.21–3.33)
BB	Diuretics+BB				1.66	(0.41–7.34)
CCB	Diuretics+BB				0.99	(0.21–4.53)
Diuretics	Diuretics+BB				0.76	(0.16–3.22)
Drugs vs. drugs						
ACEI	ACEI+diuretics				1.55	(0.46–4.89)
ACEI	ARB				1.71	(0.52–6.60)
ACEI	BB				0.89	(0.25–3.29)
ACEI	CCB				1.48	(0.38–6.91)
ACEI+diuretics	ARB				1.12	(0.39–3.74)
ACEI+diuretics	BB				0.58	(0.17–1.94)
ACEI+diuretics	CCB				0.96	(0.28–4.00)
ARB	BB				0.52	(0.13–1.76)
ARB	CCB	1	0.662	(0.524–0.835)	0.86	(0.30–2.52)
BB	CCB				1.66	(0.42–7.61)

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blockers, BB = β blockers, CCB = calcium channel blockers.

systolic blodd pressure (SBP) and between BP reductions and the risk reduction of 3 adverse outcomes were analyzed (Figure 4 and Figure S2 to S6, http://links.lww.com/MD/A880). To reduce recurrent stroke, there was a trend suggesting a positive association between event rates and the final achieved SBP from both treatment and control groups combined (Figure 4). However, the regression analysis failed to demonstrate statistical significance using linear and nonlinear (second-order quadratic function) regression with the adjusted model [$R^2 = 0.083$ ($P = 0.067$) and 0.052 ($P = 0.1852$), respectively]. Similarly, the meta-regression analysis revealed a trend toward protection against recurrent stroke through reduced BP (Figure S1, http://links.lww.com/MD/A880) with an adjusted R^2 0.1995 ($P = 0.1618$). The relationships between BP and the

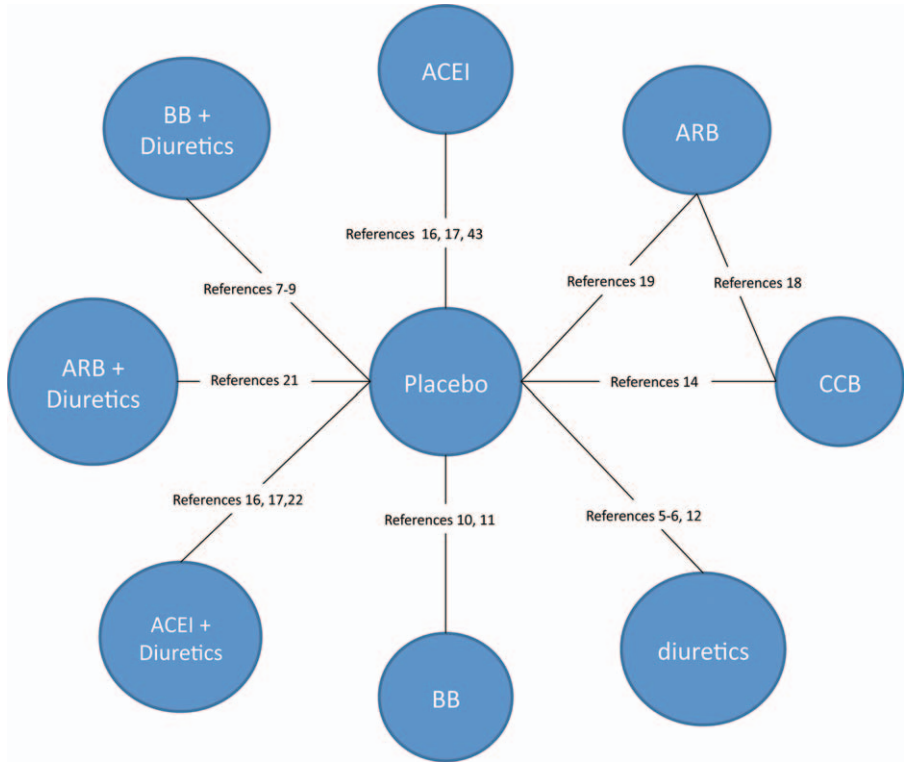

FIGURE 2. Network meta-analysis of antihypertensive agents for the secondary prevention of stroke. ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blockers, BB = β blockers, CCB = calcium channel blocker.

risk of CHD and MACCE are provided in the appendix (Figure S2–S6, http://links.lww.com/MD/A880); all failed to reach statistical significance.

Moreover, we compared the risk ratios between different subgroups and calculated the *P* value for interaction based on the baseline entry BP, final achieved BP, magnitude of BP reduction, and study countries. As shown in Figure 5 and S7, http://links.lww.com/MD/A880, the risk ratios for recurrent stroke and MACCE were comparable across the different subgroups except for the average BP reduction between treatment and control groups with a *P* for interaction of 0.01 for total stroke and 0.012 for MACCE. In contrast, the risk ratios for CHD across all subgroups were similar.

DISCUSSION

In this traditional frequentist meta-analysis and Bayesian network meta-analysis for the secondary prevention of stroke (15 trials, 39,329 patients), the combined direct and indirect evidence suggests that diuretics-based treatment, especially in combination with ACEI, was the most effective treatment for the secondary prevention of stroke. Although none of the between-drug comparisons demonstrated significant differences (Table 2), the probability ranking analysis suggested that the diuretics-based treatment was the preferred agent for the secondary prevention of stroke (Table 2). The information obtained in this meta-analysis will be useful for clinicians and will enable them to select the optimal antihypertensive agents to avoid or reduce the huge health burden resulting from the high rate of MACCE after stroke.

Because patients who have suffered from stroke tend to have recurrent stroke events, medical therapy in these patients should be tailored to include treatments for secondary stroke protection rather than for myocardial protection.[23] The patients included in this review, with a median follow-up of 2.6 years, were characterized by a high event rate (19.1%). The majority of these events were recurrent stroke (71.1%). Therefore, it was important to identify the preferred treatment strategies, based on previous primary studies, to reduce future risk for these patients. Our study represents the most comprehensive meta-analysis that combined direct and indirect comparison through the construction of complex networks (Figure 2) of effects of BP-lowering agents on the secondary prevention of stroke. Using the network meta-analysis of randomized controlled trials, the indirect comparisons between drugs were made possible, and the relative differences between different classes of antihypertensive agents could be determined.

It was frequently argued that much of the reduction in stroke events was simply related to the magnitude of BP reduction. This assertion was supported in part by the PROGRESS trial, in which dual therapy was shown to be superior to monotherapy in lowering both BP and stroke risk.[16,17] This assertion agrees with the concept of primary prevention trials[20] that show a 22% reduction in CHD events and a 41% reduction in stroke associated with a BP reduction of 10 mm Hg SBP. In addition, in our meta-regression analysis, a 10-mm Hg SBP reduction was associated with a 27% reduction in stroke events and a 22% reduction in CHD events. The reduction of stroke risk associated with BP reduction was apparently different from that observed in primary prevention studies. Moreover, in our

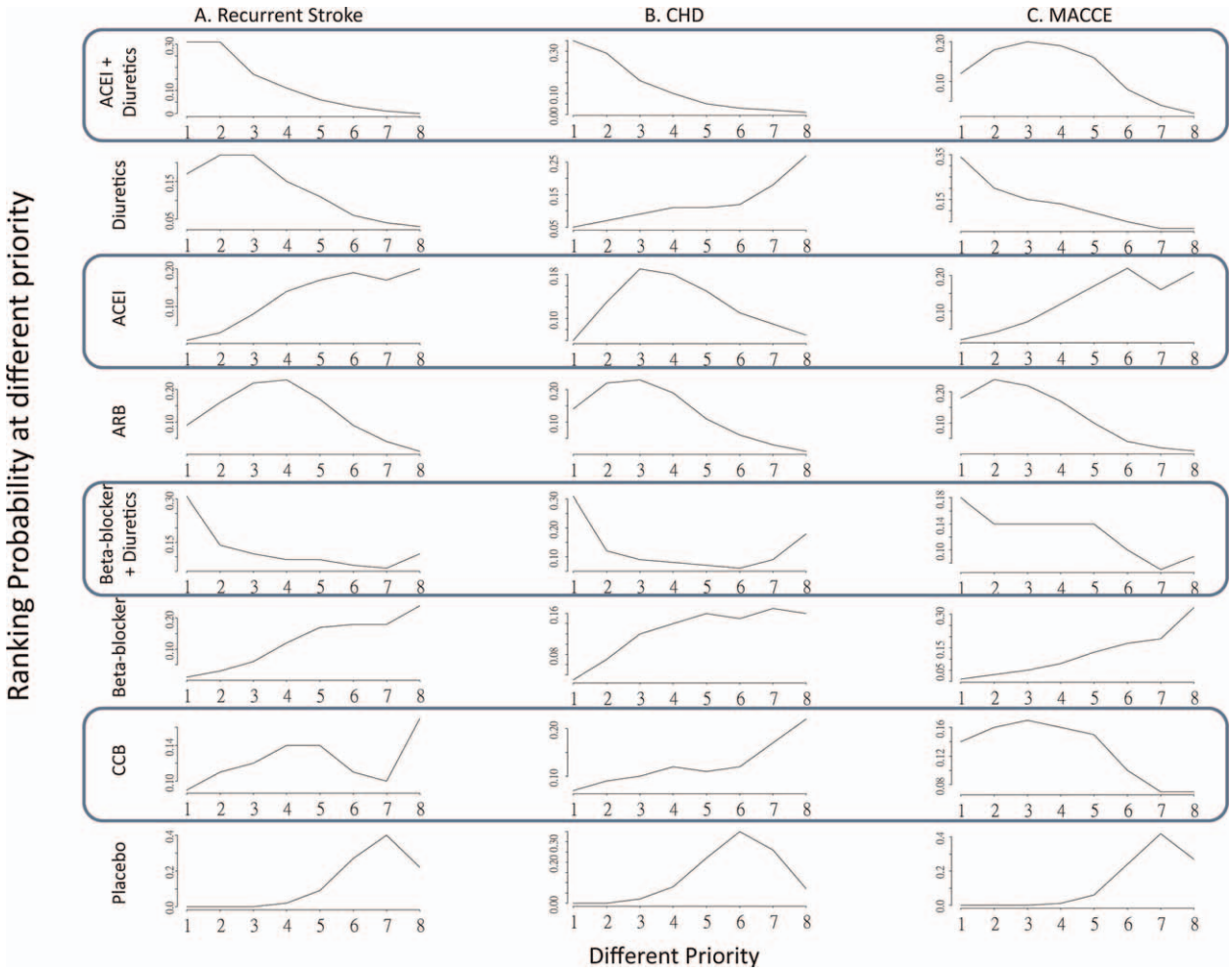

FIGURE 3. Ranking of treatment strategies based on the probability of their protective effects to prevent outcomes of recurrent stroke, cardiovascular events, and major adverse cerebral-vascular events. Rank 1 on the x-axis is considered the preferred agent for the specific outcome, and an increasing number on the x-axis indicates a less preferred ranking.

meta-regression analysis, the relationship between BP decrease and risk reduction was insignificant. The above observations all suggest that the recurrent stroke risk is modulated by a more complex mechanism, compared with the mechanism involved in the primary prevention of stroke, than just BP in patients with previous stroke history; therefore, the choice of the optimal BP-lowering agent is still an important consideration. However, this finding does not disregard the importance of BP reduction for preventing recurrent stroke. Almost all BP-lowering therapies exerted a protective effect that reduced vascular events in these patients. Moreover, in our subgroup analysis, the higher average BP reduction between the treatment and control groups was associated with a larger risk reduction in recurrent stroke events and MACCE.

Our findings are in agreement with the results of a systematic review conducted in 2003,[4] which was conducted earlier than the large PROFESS study (20,032 subjects) published in 2008. This review investigated the effects of BP reduction on recurrent stroke, myocardial infarction, and total vascular events. By using the traditional meta-analysis technique, this review suggested that diuretics and ACEI, especially when combined, reduced vascular events. To reduce total stroke, treatment strategies including diuretics had the lowest OR (0.68, 95% CI 0.50–0.92), followed by ACEI (OR = 0.92, 95% CI 0.75–1.13). For myocardial infarction, ACEI was favored (OR = 0.74, 95% CI 0.56–0.98) over diuretics (OR = 1.06, 95% CI 0.63–1.78). To prevent all vascular events, treatment strategies including diuretics were the preferred method (OR = 0.75, 95% CI 0.63–0.90), and ACEI had a borderline protective effect (OR = 0.83, 95% CI 0.61–1.12).

Subsequent to the 2003 review mentioned above, 2 RCTs investigating the effects of BP-lowering drugs were completed. The MOSES study (2005) investigated comparative effects between ARB and CCBs.[18] With a comparable final achieved BP, ARB had a significantly better protective effect in reducing MACCE than CCBs did. Subsequently, the PROFESS study published in 2008 failed to demonstrate a significant protective effect of ARB versus placebo on the secondary prevention of stroke. Combining the above evidence, ARB and CCBs may

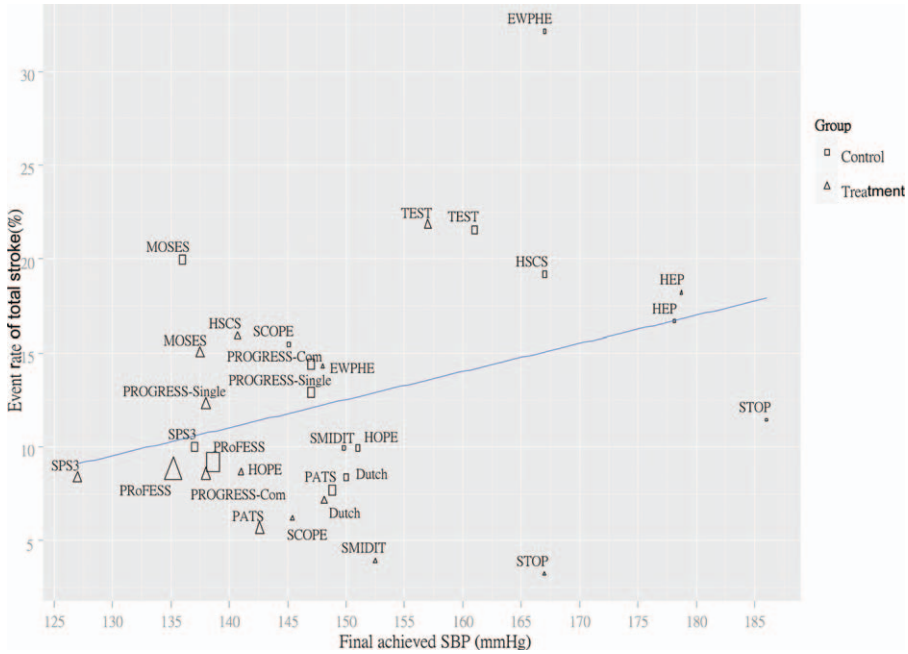

FIGURE 4. Event rate of recurrent stroke plotted against the final achieved SBP from combining the treatment and control groups. The size of the label is proportional to the inverse of the variance. The relationship between event rate and final achieved SBP was expressed as follows: event rate = −9.87817 + 0.14925 x Final achieved SBP with model *P* value: 0.0667, and Adjusted R^2: 0.08345.

have a lower rank than diuretics and ACEI for patients who have already suffered from stroke.

The mechanism underlying the beneficial effects of diuretics remains unknown. It has been suggested that larger BP reduction was observed when the treatment strategies included diuretics.[31] In our study, compared with treatment not including diuretics, the diuretics-based treatment resulted in a significantly larger reduction in BP (12.0 mm Hg, 95% CI 7.0–16.9), which lends support to such a hypothesis. In addition, except for the natriuretic effects, diuretics may also exert vasodilatory effects[38] and decrease the intraneuronal calcium concentration to prevent brain ischemia.[39] A previous study demonstrated that greater salt intake (>10.7 g/day = 4.28 g sodium/day) was associated with higher stroke recurrence rate [hazard ratio (HR) = 2.43 (95% CI 1.04–5.68)].[40] This may also support our finding that diuretic-based treatment strategies could help reduce the risk of recurrent stroke events. More studies should be conducted to elucidate the possible mechanistic relationship between diuretics and stroke prevention.

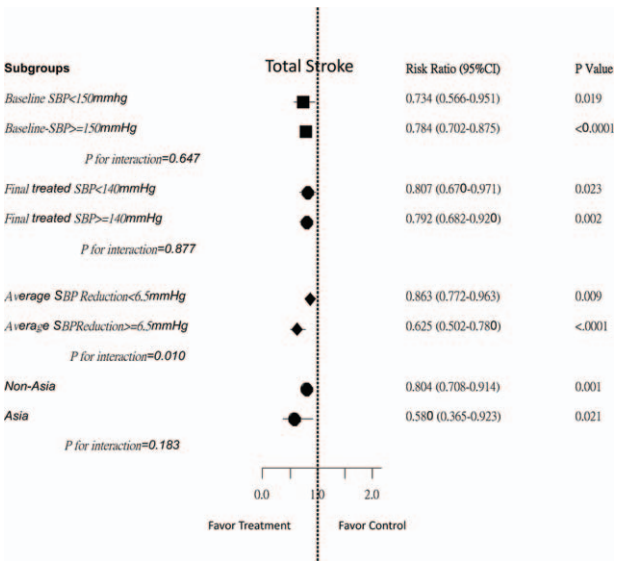

FIGURE 5. Subgroup analysis based on the different baseline BP, final achieved BP, time-averaged BP reduction magnitude, and study countries to compare the risk ratios for recurrent stroke across different subgroups. BP = blood pressure, SBP = systolic blood pressure.

Our results suggest that treatment with diuretics and ACEI for 2.6 years would have resulted in the avoidance of one recurrent stroke and CHD event among every 20 patients (95% CI 13–96) and 53 patients (38–108), respectively. Such a large effect size, obtained from the comprehensive systematic review and evidence synthesis of the substantial body of literature, should not be overlooked by patients and their doctors.

Previous hypertension trials such as ACCOMPLISH[41] and the ASCOT study[42] have identified ACEI and CCB as the best drug combination regimen for preventing major adverse vascular events. However, it is unclear whether this advantage is evident in patients with a previous history of stroke because of the lack of studies investigating the effects of ACEI and CCB on recurrent stroke prevention.

Study Limitations

Our meta-analysis has limitations. First, similar to other meta-analyses, the absence of primary data and the selective reporting of primary studies might confound our study results. Second, despite the comprehensive literature search, we may

have failed to locate some eligible published or unpublished studies. However, similar to trends reported in previous meta-analyses,[4,30,31] the study conclusions would not likely be altered substantially even if there are indeed some un-retrieved studies.

CONCLUSION

Evidence from randomized controlled trials supports the use of diuretics-based treatment for lowering BP in patients with a history of previous stroke. Diuretics, especially when combined with ACEI, are effective for the secondary prevention of stroke, and treatments including diuretics appeared to be the preferred strategies for secondary prevention of stroke. More specifically, the most commonly used diuretics and ACEI in these secondary prevention trials are indapamide and perindopril, respectively. The risk reductions could not simply be explained by the magnitude of BP reductions. With this comprehensive meta-analysis, clinicians and patients can make decisions concerning available treatments for the secondary prevention of stroke based on evidence synthesized from a large body of previous literature.

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