META-ANALYSIS

COMPARATIVE EFFICACY OF ANTIHYPERTENSIVE DRUGS FOR PRIMARY STROKE PREVENTION – A NETWORK META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

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Abstract

Introduction: Hypertension is a major modifiable risk factor for stroke, making antihypertensive therapy essential for primary stroke prevention. However, the comparative efficacy of different antihypertensive drug classes remains uncertain. This study aims to evaluate the comparative efficacy of various antihypertensive drug classes in reducing the risk of stroke in patients with hypertension through a network meta-analysis of randomized controlled trials (RCTs).

Methods: A search was conducted using various online databases, including PubMed, Google Scholar, Scopus, and ScienceDirect, to identify RCTs which were written in English and published before January 2025. A network meta-analysis was performed to compare the effectiveness of different drug classes, including angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), calcium channel blockers (CCBs), beta-blockers, and diuretics in stroke primary prevention. Independently, two reviewers (D.N. and L.D.P.), extracted the data and assess the quality of studies using Cochrane RoB 2.0.

Results: This analysis included 43 RCTs involving 255299 participants with hypertension. Among the evaluated drug classes, non-dihydropyridine CCB demonstrated the highest efficacy in stroke prevention (RR 0.61; 95%CI 0.48 – 0.77), followed by dihydropyridine CCB (RR 0.62; 95%CI 0.54 – 0.72). Most of the studies had decent quality assessment with moderate heterogeneity across them with I^2 = 39%. Egger's test showed nonsignificant results (p= 0.16), suggesting the absence of publication bias in the included trials.

Conclusion: This meta-analysis showed that calcium channel blocker emerges as the most effective option for reducing stroke risk, but considerations of adverse effects and individual patient profiles remain critical in treatment selection.

Keywords: *antihypertensive drugs; stroke; primary prevention*

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Introduction

Epidemiological research conducted over the past several decades has firmly established hypertension as the primary risk factor for stroke, whether ischemic or hemorrhagic stroke. The incidence of this debilitating cerebrovascular event is directly proportional to the degree of elevated blood pressure.[1–3] However, the incidence of stroke could be significantly lowered with effective blood pressure management through antihypertensive medications.[4,5]

Despite the availability of various antihypertensive medications, their comparative efficacy in preventing stroke has yet to be conclusively determined. This uncertainty is particularly evident when considering the distinct pharmacological mechanisms of different antihypertensive drug classes, including angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), calcium channel blockers (CCBs), beta-blockers, and diuretics.[6,7]

Given the importance of optimizing treatment for stroke prevention in hypertensive patients, it is essential to compare the relative effectiveness of these drug classes. A network meta-analysis (NMA) of randomized controlled trials (RCTs) offers a robust method to evaluate and compare multiple treatments simultaneously, providing valuable insights into the best therapeutic options for reducing stroke risk. This study aims to systematically assess the comparative efficacy of various antihypertensive drugs in primary stroke prevention, using a network meta-analysis approach to synthesize data from existing RCTs.

Materials and Methods

The study was conducted in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidance.[8]

Literature search strategy

We conducted a search across several databases, including PubMed, Google Scholar, Scopus, and ScienceDirect, to identify RCTs which were written in English and published before January 2025.

We utilized search terms such as (“stroke” OR “cerebrovascular accident” OR “CVA”) AND (“antihypertensive agents” OR “antihypertensive drugs” OR “blood pressure-lowering” OR “blood-pressure lowering” OR “diuretics” OR “Angiotensin-converting enzyme inhibitors” OR “Angiotensin receptor blocker” OR “Angiotensin receptor antagonists” OR “calcium channel blockers” OR “beta blockers” OR “ACEI” OR “ARB” OR “CCB”). In addition, we performed a manual search of the reference lists of all included studies and relevant reviews to find any other potentially eligible trials.

Study selection criteria

Studies were considered eligible if they met all of the following criteria: 1) they were randomized controlled trials; 2) they compared an antihypertensive agent with another antihypertensive agent, placebo, or control; and 3) they reported outcomes related to stroke both ischemic and hemorrhagic stroke. Trials with a follow-up duration of less than 3 months were excluded. In cases of duplicate trials, the trial with the longest follow-up period was included.

Outcomes assessments

The outcomes we focused on were stroke, both ischemic and hemorrhagic stroke including both fatal and non-fatal events.

Data extraction

Two independent reviewers (D.N. and L.D.P.) assessed the publications and extracted the data. In cases of disagreement, a third investigator (A.A.) would review the data. The following information was extracted: first author, year of publication, sample size, treatment class, duration of interventions, and outcomes of interest.

Study quality assessment

We evaluated the risk of bias in the included randomized trials using the updated version of the Cochrane "Risk of Bias" tool (RoB 2.0). Each trial was classified as having a "low risk of bias," "some concerns," or "high risk of bias".[9]

Statistical analysis

We conducted a frequentist network meta-analysis using R Software Studio version 4.2. We calculated treatment estimates as relative risks (RRs) with their 95% confidence intervals (CIs). We used Eager test and plotted comparison-adjusted funnel plots for each outcome to make visual assessments of possible publication bias.

Results

Search results and study characteristics

A total of 930 entries were identified from the preliminary database search. A total of 873 records were removed for multiple reasons during the title and abstract screening (duplicate and irrelevance to the analysis). The complete texts of the remaining 57 papers were meticulously examined. Subsequently, 14 papers were removed for the following reasons: not full text, not in English, not RCT, and had different outcomes. A total of 43 randomized controlled trials involving 255,299 patients were incorporated into the network meta-analysis.

The selecting process is illustrated in Figure 1. The characteristics of the studies included are presented in Table 1. The quality evaluations of the 43 RCTs are presented in Table 2. The diagram of the network structure is presented in Figure 2. Network structure diagrams are utilized to illustrate the direct relationships among several antihypertensive regimens, with the thickness of the lines indicating the quantity of direct comparisons between two regimens.

Network meta-analysis results

Figure 2 displays the network plot that represents comparisons among the hypertensive patients. This network meta-analysis evaluated the effect of 7 interventions for primary prevention of stroke for the hypertensive patients including angiotensin converting enzyme (ACE) inhibitor, angiotensin receptor blocker (ARB), beta blocker (BB), dihydropyridine calcium channel blocker (DH-CCB), non-dihydropyridine calcium channel blocker (non-DH-CCB), diuretic, and placebo.

Our study included a total of 43 trials involving 255299 participants to analyse stroke incidence in the overall population.

Compared to placebo, all antihypertensive drugs showed efficacy in preventing stroke. In addition, among the evaluated drug classes, non-dihydropyridine CCB demonstrated the highest efficacy in stroke prevention (RR 0.61; 95%CI 0.48 – 0.77), followed by dihydropyridine CCB (RR 0.62; 95%CI 0.54 – 0.72). Furthermore, beta blocker showed the lowest efficacy in stroke prevention (RR 0.75; 95%CI 0.64 – 0.88) (Figure 3).

Publication bias

The comparison-adjusted funnel plots are presented in Figure 4, all of which appear visually symmetrical, indicating the absence of publication bias.

Discussion

This meta-analysis utilized an enhanced categorization of antihypertensive drugs to evaluate the comparative efficacy of all existing treatments in stroke prevention both ischemic and hemorrhagic stroke. Through a comprehensive systematic review and network meta-analysis, the study offers valuable insights to guide the optimal choice of antihypertensive therapy for individuals with hypertension.

The Renin-Angiotensin System (RAS) plays a pivotal role in the pathophysiology of hypertension. Consequently, RAS inhibitor was common therapeutic approach for controlling hypertension.[10] In 2018, Chen et al. carried out a meta-analysis to assess the effectiveness and safety of RAS inhibitors relative to other classes of antihypertensive medications in patients with hypertension. Their findings indicated that first-line use of thiazide diuretics and calcium channel blockers (CCBs) was associated with a reduced incidence of stroke compared to RAS inhibitors. Additionally, RAS inhibitors demonstrated greater efficacy in stroke prevention than beta-blockers (BBs) when used as first-line therapy; however, the analysis did not differentiate between angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs).[54] A separate meta-analysis conducted by Thomopoulos et al. reviewed 50 clinical trials comprising 247,006 individuals, with a hypertension prevalence exceeding 40%. The analysis revealed that RAS inhibitors were more effective than both placebo and beta-blockers in stroke prevention, yet they were outperformed by diuretics and calcium channel blockers (CCBs). Specifically, ACE inhibitors (ACEIs) showed greater efficacy than placebo but were less effective compared to CCBs and other antihypertensive drug classes. In contrast, angiotensin receptor blockers (ARBs) demonstrated superior stroke prevention benefits relative to placebo and beta-blockers.[55] Likewise, our findings demonstrated that both ARBs and ACEIs outperformed placebos but were less effective than diuretics and calcium channel blockers in reducing the incidence of stroke in the general population.

Table 1. Characteristic of Studies

Author	Study	Treatment Class	Treatment Drugs	Duration	Age	N	Stroke	
							n	%
ALLHAT, 2022[11]	ALLHAT	Diuretic DH – CCB ACE Inhibitor	Chlorthalidone Amlodipine Lisinopril	4.9 years	66.9 ± 7.7	15255 9048 9054	675 377 457	4.4 4.2 5.0
Baba, 2001[12]	J-MIND	DH-CCB ACE Inhibitor	Nifedipine Enalapril	2 years	60.2 ± 8.9 59.9 ± 8.6	228 208	2 5	2.2 3.8
Beckett, 2014[13]	HYVET	ACE Inhibitor Placebo	Perindopril Placebo	2.1 years	83.6 ± 3.2 83.5 ± 3.1	1933 1912	51 69	2.6 3.6
Black, 2003[14]	CONVINCE	Non-DH-CCB Conventional Therapy	Verapamil Atenolol or HCT	3 years	65.6 ± 7.4	8179 8297	133 118	1.6 1.4
Borhani, 1996[15]	MIDAS	DH-CCB Diuretic	Isradipine HCT	3 years	58.2 ± 8.3 58.7 ± 8.7	442 441	6 3	1.35 0.68
Brown, 2000[16]	INSIGHT	DH-CCB Diuretic	Nifedipine HCT + amiloride	4 years	65 ± 6.5	3157 3164	67 74	2.1 2.3
Dahlof, 1991[17]	STOP - Hypertension	Conventional Therapy Placebo	Atenolol / HCT / amiloride Placebo	65 months	70 – 84	812 815	29 53	3.6 6.5
Dahlof, 2002[18]	LIFE	ARB Beta Blocker	Losartan Atenolol	4 years	66.9 ± 7.0 66.9 ± 7.0	4605 4588	369 359	8.0 8.0
Dahlof, 2005[19]	ASCOT-BPLA	DH-CCB Beta Blocker	Amlodipine Atenolol	5.5 years	63 ± 8.5 63 ± 8.5	9639 9618	327 422	3.0 4.0
Estacio, 1998[20]	ABCD	DH-CCB ACE Inhibitor	Nisoldipine Enalapril	5 years	57.2 ± 8.2 57.7 ± 8.4	235 235	11 7	4.7 3.0
Hannson, 1993[21]	STOP – Hypertension-2	ACE Inhibitor DH-CCB	Enalapril / Lisinopril Felodipine / Isradipine	4 years	76.1 75.9	2205 2196	50 46	4.5 4.2
Hansson, 1999[22]	CAPPP	ACE Inhibitor Conventional Therapy	Captopril Atenolol / HCT	5.5 years	52.4 ± 8.3 52.7 ± 8.4	5492 5493	193 149	3.5 2.7
Hansson, 2000[23]	NORDIL	Non-DH-CCB Conventional Therapy	Diltiazem Atenolol / HCT	5 years	60.5 ± 6.5 60.3 ± 6.5	5410 5471	159 196	2.9 3.6
Julius, 2004[24]	VALUE	ARB	Valsartan	3.2 years	66.9 ± 8.3	3263	108	3.3

		DH-CCB	Amlodipine		66.8 ± 8.2	3817	127	3.3
Kaplan, 2003[25]	ANBP2	ACE Inhibitor Diuretic	Enalapril HCT	4.1 years	72 71.9	3044 3039	112 107	3.7 3.5
Kasanuki, 2009[26]	HIJ – CREATE	ARB Non-RAASI	Candesartan Non-ARB	4.2 years	64.5 ± 9.4 65 ± 8.9	1024 1025	45 49	4.4 4.8
Kjeldsen, 2008[27]	ACCOMPLISH	DH-CCB Diuretic	Amlodipine HCT	3 years	68.5 ± 6.9 68.2 ± 6.7	5744 5762	112 133	1.9 2.3
Lithell, 2003[28]	SCOPE	ARB Placebo	Candesartan Placebo	3 – 5 years	76.2 ± 4.4 76.5 ± 4.6	1253 845	31 27	2.5 3.2
Liu, 1998[29]	Syst – CHINA	DH-CCB Placebo	Nitrendipine Placebo	2 years	≥ 60	1253 1141	45 59	3.6 5.2
Liu, 2005[30]	FEVER	DH-CCB Placebo	Felodipine Placebo	40 months	61.5 ± 7.1 61.5 ± 7.2	4841 4870	177 251	3.7 5.2
Malacco, 2003[31]	SHELL	Diuretic DH-CCB	Chlorthalidone Lacidipine	32 months	72.4 ± 7.6 72.3 ± 7.5	940 942	38 37	4.0 3.9
Matsuoka, 1995[32]	GLANT	ACE Inhibitor CCB	Delapril CCB	12 months	60 ± 10 60 ± 9	980 956	5 11	0.5 1.2
Matsuzaki, 2011[33]	COPE	ARB Beta Blocker Diuretic	ARB Beta Blocker Thiazide	3.6 years	63 ± 10.6 63.2 ± 10.8 63.1 ± 10.8	1110 1089 1094	17 27 12	1.5 2.5 1.1
MRC, 1992[34]	MRC-2	Beta Blocker Diuretic	Atenolol HCT	5.8 years	70.3 ± 5.6 70.2 ± 5.6	1102 1081	56 45	5.1 4.2
Muramatsu, 2012[35]	NHS	ARB DH-CCB	Valsartan Amlodipine	3.2 years	63 ± 8 63 ± 8	575 575	13 16	2.3 2.8
Narumi, 2016[36]	VART	ARB DH-CCB	Valsartan Amlodipine	3.4 years	60 ± 12 60 ± 11	510 511	10 10	2.0 2.0
NICS-EH, 1999[37]	NICS-EH	DH-CCB Diuretic	Nicardipine Trichlormethiazide	5 years	≥ 60	204 210	1 0	0.5 0.0
Ogawa, 2012[38]	OSCAR	ARB CCB	Olmesartan Amlodipine / Azelnidipine	3 years	73.6 ± 5.3 73.6 ± 5.5	578 586	111 96	19.2 16.4
Ogihara, 2011[39]	PATE-Hypertension	ACE Inhibitor DH-CCB	Delapril Manidipine	3 years	70 ± 7 69 ± 7	699 1049	14 23	2.0 2.2
Ogihara, 2014[40]	COLM	CCB Diuretic	Amlodipine / Azelnidipine HCT / Indapamide	3 years	73.6 ± 5.3 73.6 ± 5.4	2568 2573	63 66	2.5 2.6

Pepine, 2003[41]	INVEST	Non-DH-CCB Beta Blocker	Verapamil Atenolol	2.7 years	66 ± 9.7 66.1 ± 9.8	11267 11309	176 201	1.6 1.8
Rosei, 1997[42]	VHAS	Non-DH-CCB Diuretic	Verapamil Chlorthalidone	2 years	54.5 ± 6.9 53.9 ± 7.0	707 707	3 4	0.4 0.6
Ruggenenti, 2011[43]	BENEDICT-B	Non-DH-CCB ACE Inhibitor	Verapamil Trandolapril	4.5 years	62.3 ± 8.5 62.4 ± 8.2	138 143	1 0	0.7 0.0
Schrader, 2005[44]	MOSES	ARB DH-CCB	Eprosartan Nitrendipine	2.5 years	67.7 ± 10.4 68.1 ± 9.5	681 671	102 134	15.0 20.0
SHEP, 1991[45]	SHEP	Beta Blocker Placebo	Atenolol Placebo	4.5 years	≥ 60	2365 2371	106 163	4.5 6.9
Staessen, 1997[46]	Syst-EUR	Conventional Therapy Placebo	Enalapril / Nitrendipine / HCT Placebo	2 years	70.3 ± 6.7 70.2 ± 6.7	2398 2297	16 21	2.7 3.7
Suzuki, 2005[47]	E-COST	ARB Non-RAASI	Candesartan Non-ARB	3.1 years	35 – 79	1053 995	47 77	4.5 7.7
Tatti, 1998[48]	FACET	ACE Inhibitor DH-CCB	Fosinopril Amlodipine	3.5 years	62.8 ± 0.5 63.3 + 0.4	189 191	4 10	0.7 1.9
UKPDS, 1998[49]	UKPDS 38	Conventional Therapy Placebo	Captopril / Atenolol Placebo	8.4 years	56.4 ± 8.1 56.5 ± 8.1	758 390	38 34	5.0 8.7
UKPDS, 1999[50]	UKPDS 39	ACE Inhibitor Beta Blocker	Captopril Atenolol	9 years	56.3 ± 8.1 56 ± 8.2	400 358	21 17	5.2 4.7
Wikstrand, 1991[51]	MAPHY	Beta Blocker Diuretic	Metoprolol Thiazide	5 years	40 – 64	1609 1625	2 7	0.3 0.9
Yui, 2004[52]	JMIC-B	DH-CCB ACE Inhibitor	Nifedipine Retard Enalapril / Lisinopril / Imidapril	3 years	65 ± 8 64 ± 9	828 822	16 16	1.9 1.9
Zanchetti, 2002[53]	ELSA	Beta Blocker DH-CCB	Atenolol Lacidipine	3.75 years	55.9 ± 7.5 56.1 ± 7.5	1157 1177	14 9	1.2 0.8

Calcium ions are implicated in tissue injury affecting the heart and various organs, contributing to conditions such as stroke and myocardial infarction. Calcium channel blockers (CCBs) are commonly prescribed for managing angina and hypertension. Numerous meta-analyses have examined the influence of CCBs on cardiovascular and cerebrovascular outcomes. In a 2009 meta-analysis, Costanzo et al. assessed the comparative effectiveness of CCBs against other antihypertensive agents. Their findings demonstrated that CCBs were associated with a lower risk of stroke both hemorrhagic and non-hemorrhagic stroke compared to ACE inhibitors, without elevating the risk of cardiovascular mortality, myocardial infarction, or major cardiovascular events.[56] The meta-analysis by Thomopoulos et al., which included 247,006 participants with a hypertension prevalence exceeding 40%, revealed that calcium channel blockers (CCBs) were more effective in stroke prevention than placebos, beta-blockers (BBs), ACE inhibitors (ACEIs), RAS inhibitors, and all other antihypertensive drug classes combined.[55]

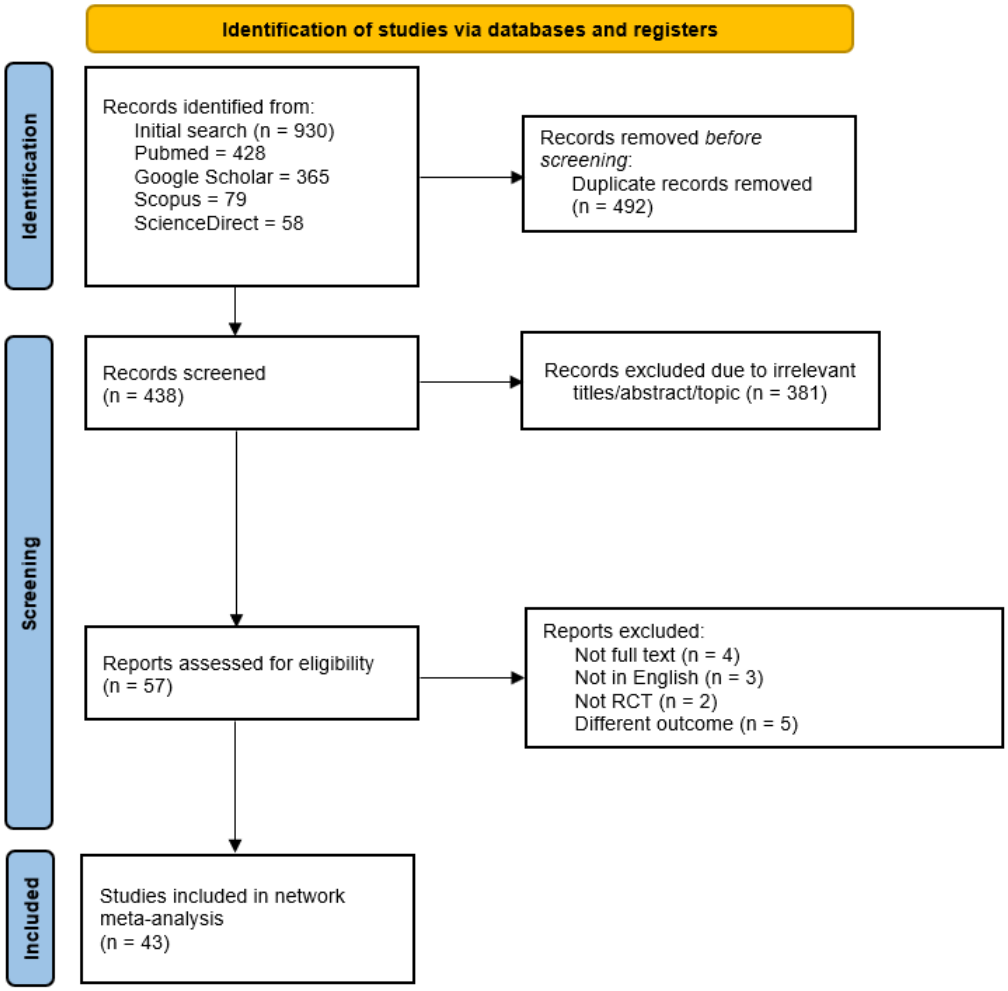

Figure 1. Flowchart of selecting process for this network meta-analysis

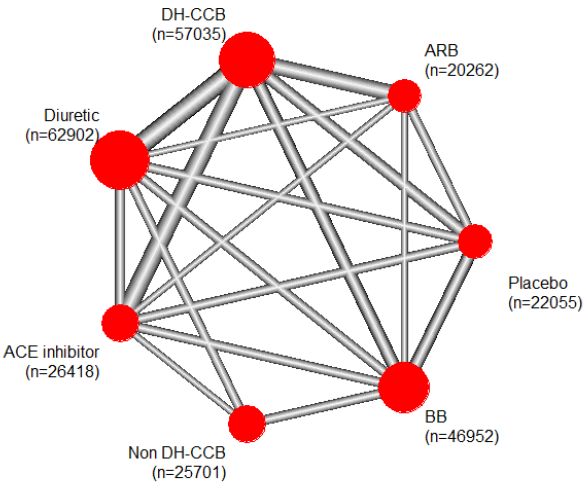

Figure 2. Network structure diagram of this network meta-analysis

Table 2. Quality appraisal of studies included

Study	D1	D2	D3	D4	D5	Overall
Liu, 2005 - FEVER	+	+	+	+	+	+
MRC, 1992	+	+	+	+	-	+
SHEP, 1991	+	+	+	-	+	+
Dahlof, 1991 - STOP	+	+	+	+	+	+
Liu, 1998 - SYST-China	+	+	+	-	-	+
Staessen, 1997 - SYST-Eur	+	+	+	+	-	+
UKPDS, 1998	+	+	+	+	+	+
UKPDS, 1999	+	+	+	+	+	+
Estacio, 1998 - ABCD	+	-	+	+	-	+
Kjeldsen, 2008 - ACCOMPLISH	+	+	-	-	-	-
ALLHAT, 2002	+	+	+	+	+	+
Dahlof, 2005 - ASCOT	+	+	+	+	+	+
Ruggenenti, 2011 - BENEDICT B	+	+	+	+	-	+
Ogihara, 2014 - COLM	+	-	+	+	+	+
Black, 2003 - CONVINCE	+	+	+	+	+	+
Zanchetti, 2002 - ELSA	+	+	+	+	+	+
Tatti, 1998 - FACET	+	+	+	-	+	+
Matsuoka, 1995 - GLANT	+	-	+	-	+	+
Brown, 2000 - INSIGHT	+	-	-	-	-	-
Pepine, 2003 - INVEST	+	+	+	+	+	+
Baba, 2001 - J-MIND	+	+	+	+	-	+
Yui, 2004 - JMIC-B	+	+	+	-	-	+
Dahlof, 2002 - LIFE	+	+	+	+	+	+
Wikstrand 1991 - MAPHY	+	-	-	-	+	-
Borhani, 1996 - MIDAS	+	+	+	-	-	+
Schrader, 2005 - MOSES	+	+	+	+	+	+
Muramatsu, 2012 - NAGOYA HEART	+	+	+	+	+	+
NICS-EH, 1999	+	-	X	-	+	X
Hansson, 2000 - NORDIL	+	-	-	X	-	X
Ogawa, 2012 - OSCAR	+	+	+	+	+	+
Ogihara, 2011 - PATE	+	+	+	+	-	+
Malacco, 2003 - SHELL	+	-	-	+	+	+
Hansson, 1999 - STOP II	+	+	+	-	+	+
Julius, 2004 - VALUE	+	+	+	+	+	+
Narumi, 2016 -VART	+	-	-	-	X	X
Rosei, 1997 - VHAS	+	+	-	+	+	+
Kaplan, 2003 - SANBPS	+	+	+	+	+	+
Matsuzaki, 2011 - CTHPCETG	+	+	+	+	+	+
Suzuki, 2005 - E-COST	+	+	+	-	-	+
Beckett, 2014 - HYVET	+	+	+	+	-	+
Hansson, 1999 - CAPPP	+	+	-	-	-	-
Lithell, 2003 - SCOPE	+	+	+	+	+	+
Kasanuki, 2009 - HIJ-CREATE	+	+	+	+	+	+

Domains:
D1: Bias arising from the randomization process.
D2: Bias due to deviations from intended intervention.
D3: Bias due to missing outcome data.
D4: Bias in measurement of the outcome.
D5: Bias in selection of the reported result.

Judgement
X High
\- Some concerns
\+ Low

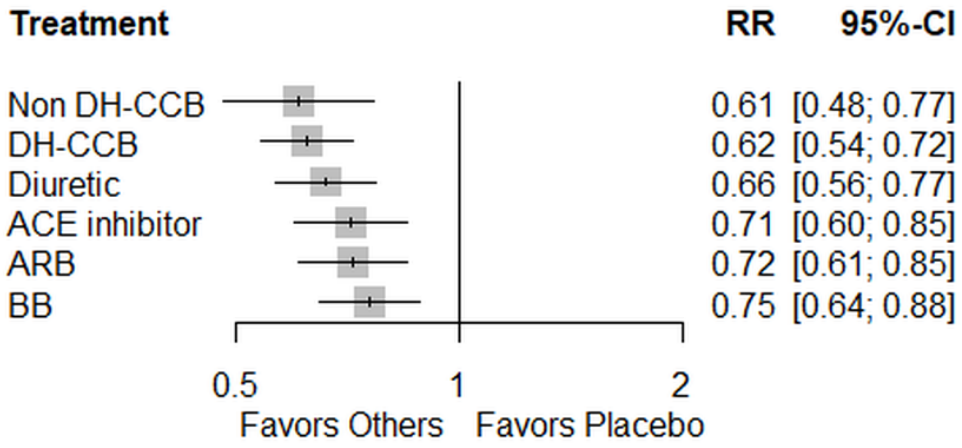

Figure 3. Forest plot of this network meta-analysis

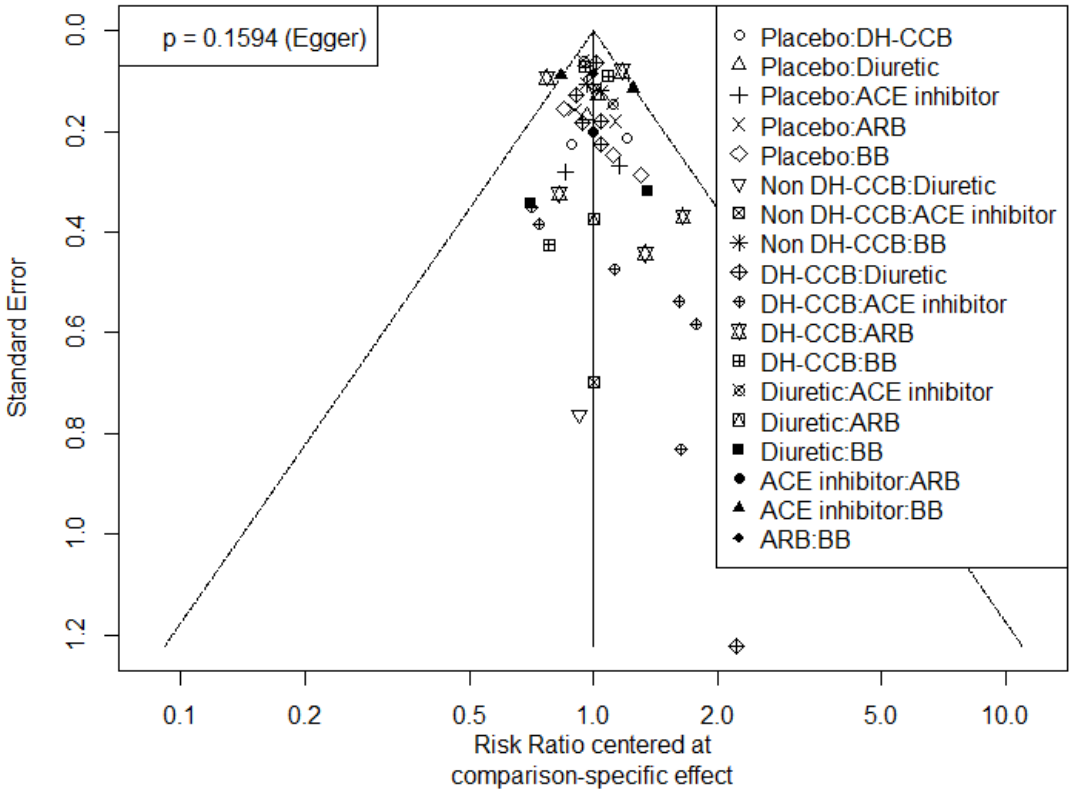

Figure 4. Funnel plot of this network meta-analysis

A meta-analysis encompassing 13 clinical trials with a total of 103,793 participants demonstrated that dihydropyridine calcium channel blockers (CCBs) significantly reduced the risk of stroke compared to non-dihydropyridine CCBs and other antihypertensive agents. Meta-regression analysis further suggested that the stroke risk reduction associated with dihydropyridine CCBs occurs independently of systolic blood pressure lowering. This benefit may partly stem from the neuroprotective properties of CCBs and their ability to slow the progression of carotid atherosclerosis. Moreover, dihydropyridine CCBs—such as benidipine—have been shown to inhibit the generation of reactive oxygen species by polymorphonuclear leukocytes in salt-loaded spontaneously hypertensive rats, likely due to their antioxidant properties and suppression of the Ca^{2+}/protein kinase C/NADPH oxidase signaling pathway.[57] Our findings also confirmed that calcium channel blockers (CCBs) were more effective than placebos, beta-blockers (BBs), ACE inhibitors (ACEIs), and angiotensin receptor blockers (ARBs) in reducing the incidence of stroke in the general population.

Thiazide diuretics, encompassing both thiazide-type agents (such as chlorothiazide, hydrochlorothiazide, bendroflumethiazide, trichlormethiazide, and bendrofluazide) and thiazide-like compounds (such as indapamide and chlorthalidone), have been utilized in hypertension management for over fifty years. In 2015, Chen et al. conducted a meta-analysis to evaluate the cardioprotective benefits of both thiazide-type and thiazide-like diuretics in patients with hypertension. Their analysis indicated that these diuretics were associated with lower risks of cardiovascular disease and heart failure; however, no significant difference was observed in stroke incidence when compared to the control group.[58] Thomopoulos et al.'s meta-analysis demonstrated that diuretic therapy was more effective in reducing the risk of stroke compared to both placebo and renin-angiotensin system (RAS) inhibitors.[55] Our study further validated that diuretics were more effective than placebos, beta-blockers (BBs), ACE inhibitors (ACEIs), and angiotensin receptor blockers (ARBs) in preventing stroke across the general population.

Beta-blockers (BBs) have been a mainstay in hypertension treatment for over forty years. Nonetheless, emerging evidence has questioned their suitability as a first-line option, as randomized placebo-controlled trials have not demonstrated substantial cardiovascular protective benefits. In a 2017 Cochrane systematic review by Wiysonge et al., first-line BB therapy was found to offer only a modest reduction in stroke risk among hypertensive patients, with no significant impact on overall mortality or incidence of coronary heart disease. Moreover, their effectiveness in stroke prevention was inferior compared to calcium channel blockers (CCBs) and renin-angiotensin system (RAS) inhibitors.[59] Additionally, a 2020 meta-analysis by Thomopoulos et al. found that beta-blockers (BBs) were less effective than other classes of antihypertensive agents in reducing the incidence of stroke and all-cause mortality,

both in the overall trial population and in studies focusing solely on individuals with hypertension.[60] Our findings also provide evidence that beta-blockers (BBs) were ineffective in reducing the risk of stroke, all-cause mortality, and cardiovascular mortality in both the general population and individuals with hypertension.

Limitations

This network meta-analysis has several limitations. Firstly, the management of hypertension has evolved considerably over the past three decades, reflecting shifts in clinical perspectives. Variations exist across studies in terms of the classes of antihypertensive agents used, their dosing regimens, and the therapeutic objectives for stroke prevention, particularly when comparing older trials to more recent ones. Second, due to limited available data, we were unable to conduct subgroup analyses to compare the effects of antihypertensive medications based on gender or race. Third, comparisons between patients with and without diabetes or hyperlipidemia across different drug classes could not be performed, as data for these subgroups were insufficient within each drug category. Fourth, there were no primary outcome sub-analysis whether ischemic stroke hemorrhagic stroke due to insufficient clinical outcome data.

Conclusion

In conclusion, the current evidence suggests that calcium channel blockers (CCBs) and diuretics may offer superior protection against stroke in individuals with hypertension.

Conflict of Interest

The authors declared no conflict of interest.

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