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REVIEW ARTICLE

Long-Term Anti-Hypertensive Therapy and Stroke Prevention: A Meta-Analysis

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Abstract

Background Stroke causes approximately 6.7 million deaths worldwide per year and is the second leading cause of death. Pharmacotherapy for hypertension, an independent risk factor for stroke, significantly reduces the incidence of stroke. Although prior meta-analyses demonstrate various antihypertensive classes are superior to placebo in reducing stroke risk, which class is most effective is unclear.

Methods We conducted a systematic MEDLINE search including only randomized controlled trials (RCT) of antihypertensive medications published between 1999 and 2014 in adults with stroke as a primary or secondary outcome. Five classes compared against all others were angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), β-adrenoceptor antagonists (β-blockers), calcium channel blockers (CCBs), and thiazide or thiazide-like diuretics (T-TLDs). Among 17 RCTs with 31 comparative arms, risk ratio was used to assess effect size, and a fixed- and random-effect model was used to calculate summary effect size, utilizing comprehensive meta-analysis statistical software version 2.0.

Results The 251,853 subjects (46 ± 11.4 % female; mean age 67.2 ± 6.8 years), were grouped as follows: ACEI 52,887; ARB 7278; ACEI/ARB 60,165; β-blocker 24,099; CCB 98,950; and T-TLD 68,639. The mean follow-up was 42.9 ± 15 months. A random-effect model was used to assess for summary effect size in ACEI, ACEI/ARB, ARB, and T-TLD groups. The summary risk ratio for stroke occurrence in the different antihypertensive drug classes were as follows: ACEIs 1.01 (95 % confidence interval [CI] 0.81–1.27; $p = 0.92$); ACEIs/ARBs 0.94 (95 % CI 0.78–1.13; $p = 0.51$); T-TLDs 0.90 (95 % CI 0.75–1.08; $p = 0.25$); ARBs 0.83 (95 % CI 0.59–1.18; $p = 0.30$); β-blockers 1.42 (95 % CI 1.26–1.61; $p < 0.01$); and CCBs 0.83 (95 % CI 0.79–0.89; $p < 0.01$).

Conclusion Among the antihypertensive classes, CCBs were most effective in reducing the long-term incidence of stroke, whereas β-blockers were associated with significantly increased risk.

Key Points

Stroke is a leading cause of death and disability worldwide and is now second only to ischemic heart disease as a cause of death globally.

Hypertension is directly related to increased stroke risk, and this risk is decreased significantly by appropriate pharmacotherapy.

The differential outcome in stroke between calcium channel blockers (CCBs) versus β-adrenoceptor antagonists (β-blockers) could be explained by the degree of central aortic systolic blood pressure lowering by CCBs.

Which specific class of anti-hypertensive drugs may be more beneficial as compared with others remains unclear.

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1 Introduction

Hypertension is a major risk factor for cardiovascular disease (CVD) and stroke, affecting one in three US adults [1]. Hypertension is an independent risk factor for stroke, heart failure (HF), atherosclerotic CVD, renal failure, and death.

According to data from NHANES (National Health and Nutrition Examination Survey) (2007–2010), an estimated 6.8 million adults aged ≥20 years have experienced a stroke in the USA. The prevalence of stroke in this timeframe is estimated to be 2.8 %. An additional 3.4 million Americans are projected to have had a stroke at age 18 or older by 2030 [2]. Cerebrovascular disease is the second leading cause of death worldwide, with approximately 5 million deaths annually [3].

The BPLTTC (Blood Pressure Lowering Treatment Trialists' Collaboration) was a systematic review that included 29 randomized antihypertensive trials that examined the effects of different blood pressure (BP)-lowering regimens on major cardiovascular events, including stroke. All outcome data collected were from between July 1995 and June 2003 [4, 5]. A statistically significant reduction in risk of stroke was seen with regimens based on angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), and calcium channel blockers (CCBs) when compared with placebo. The BP trials showed no statistically significant difference in stroke risk reduction between the active treatment regimens.

Thus far, it is not clear which antihypertensive regimen is better long term for primary and/or secondary reduction of stroke risk. We performed a systematic review using meta-analytic methods evaluating the efficacy of long-term antihypertensive regimens on primary and/or secondary stroke risk reduction.

2 Methods

2.1 Search Method

We conducted a systematic search using MEDLINE, and included only randomized controlled trials (RCT) in adults that included antihypertensive therapy and stroke outcomes. Medical Subject Heading (MeSH) terms used included stroke, hypertension, randomized controlled trial (publication type), and antihypertensive agents, adrenergic β-antagonists (β-blockers), ARBs, CCBs, thiazide diuretics, and placebo.

2.2 Inclusion/Exclusion Criteria

Studies were included if they were an RCT with published manuscripts between 1999 and 2014 and compared one of five active antihypertensive regimens (thiazide or thiazide-like diuretic [T-TLD], CCB, β-adrenoceptor antagonist [β-blocker], ACEI, ARB) with placebo or with any of the active antihypertensive regimens. Studies were also included if they provided outcome data on stroke. We excluded studies with abstracts only, those with sample sizes <500 subjects, or those with <6 months of median follow-up. Figure 1 is a flow diagram showing the selection of trials included in this review following PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [6].

Approximately 202 manuscripts were reviewed, with 17 meeting criteria for inclusion. Some included studies compared an active antihypertensive regimen with placebo and/or with another active antihypertensive regimen. The active antihypertensive regimens included four studies in the ACEI group, six in the ARB group, ten in the ACEI/ARB group, ten in the CCB group, six in the β-blocker group, and five in the T-TLD comparison group.

2.3 Statistical Analysis

A total of 17 RCTs were selected for this meta-analysis, with 31 derived comparative groups. All extracted data were entered into the Comprehensive Meta-Analysis (CMA) version 2.0 program [7]. The extracted sample size and number of stroke occurrences in each trial were used to calculate an independent risk ratio for stroke with a 95 % confidence interval (CI). Heterogeneity was assessed using the I^2 statistic [8]. The summary effect size was determined using a fixed- or random-effect model based on the presence or absence of heterogeneity. We assumed heterogeneity among the studies when the degree of inconsistency (using I^2 statistics) was >50 % with or without an associated p-value ≤0.05.

We used the DerSimonian and Liard [9] random-effect model and the Mantel–Haenszel [10] fixed-effect model to calculate the summary effect size based on the presence and absence of heterogeneity among studies respectively. Funnel plots were used to visually assess for publication bias, while the Begg and Mazumdar [11] test was used to quantify the amount of publication bias. The Orwin fail-safe N test [12] was used to determine the number of missing studies would be required to make the summary effect trivial.

2.4 Studies Included

The 17 RCTs included in this meta-analysis accounted for 31 comparative arms (Table 1). The ACCOMPLISH (Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension) trial was designed to test the hypothesis that treatment with

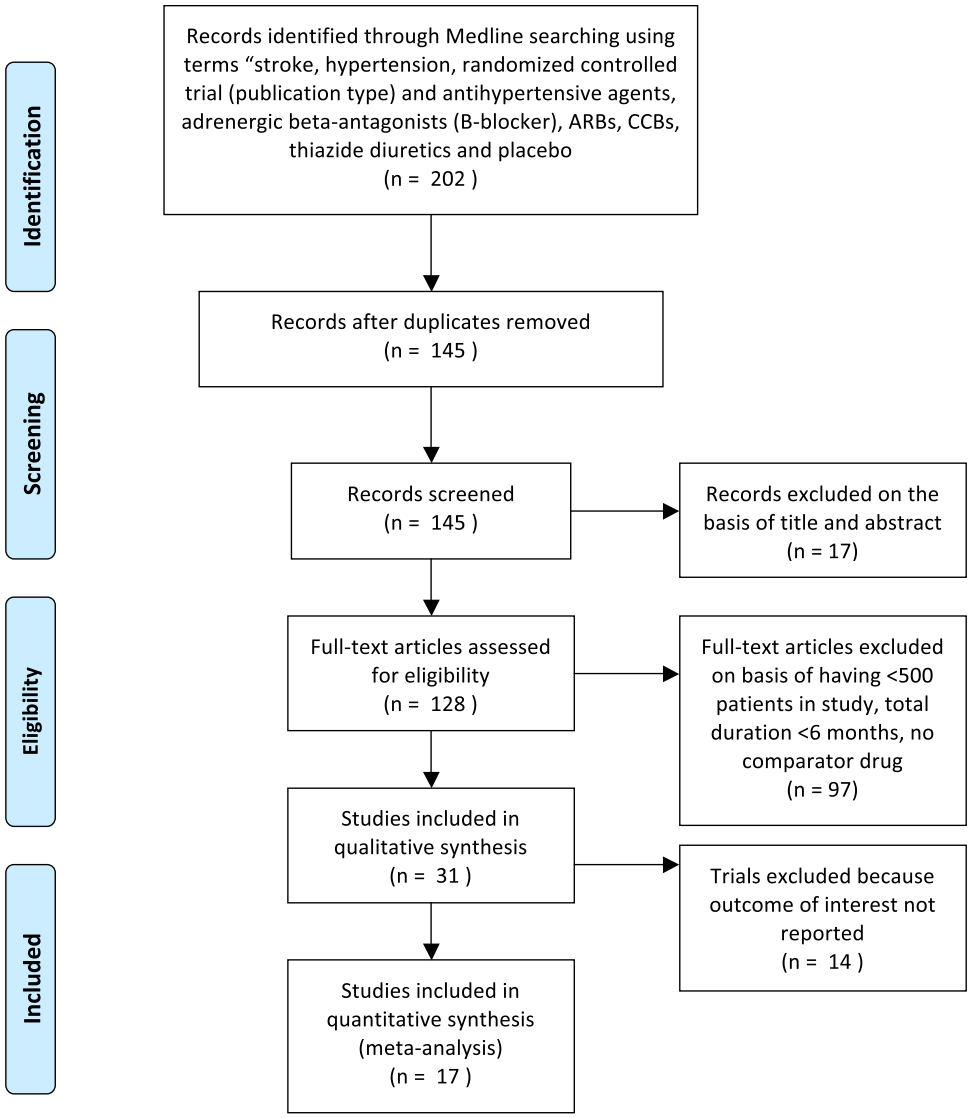

Fig. 1 Flow diagram for the selection of studies examining effects of different antihypertensive therapies on long-term stroke outcome. *ARB* angiotensin receptor blocker, *CCB* calcium channel blocker

an ACEI (benazepril 20–40 mg daily) combined with amlodipine would result in better cardiovascular outcomes than treatment with the same ACEI combined with a thiazide diuretic [13]. In this trial, amlodipine 5–10 mg daily was compared with hydrochlorothiazide 12.5–25 mg daily. The addition of other antihypertensive agents (except CCBs, T-TLDs, ACEIs, or ARBs) was required to achieve a BP target of <140/90 mmHg or <130/80 (diabetic subjects). In ACCOMPLISH, 41 % of subjects had one or more drug added to hydrochlorothiazide, while 42 % of subjects received additional medications in the amlodipine arm.

ALLHAT (Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial) [14] compared three antihypertensive agents (chlorthalidone 12.5–25 mg daily, amlodipine 2.5–10 mg daily, and lisinopril 10–40 mg daily) with a BP goal of <140/90 mmHg. Approximately 80.4 % of subjects were receiving amlodipine or another CCB, while 39.5 % were receiving a step 2 (atenolol, reserpine, or clonidine) or step 3 drug (hydralazine) at 5 years in the amlodipine arm. Likewise, 80.5 % (40.7 % step 2 or 3 drugs) and 72.6 % (43 % step 2 or 3 drugs) of subjects were receiving chlorthalidone and lisinopril, respectively, at 5 years.

The ASCOT-BPLA (Anglo-Scandinavian Cardiac Outcomes Trial Blood Pressure Lowering Arm) [15] was a prospective, randomized, open-label, blinded-endpoint design that compared amlodipine-based regimens with atenolol-based regimens. Perindopril and bendroflumethiazide in the amlodipine-based and atenolol-based regimens, respectively, were added if BP was not at goal. At 5 years, 52 versus 38 % of patients were receiving additional drugs in the atenolol versus amlodipine arm.

The CTHPCE (Combination Therapy of Hypertension to Prevent Cardiovascular Events) trial [16] was a prospective, randomized, open-label, blinded-endpoint trial

Table 1 Baseline characteristics of randomized controlled trials included in this meta-analysis

Study[a]	Comparator drugs (mg)	Mean follow-up (months)	Sample size	Females (%)	Mean age (year)	HO stroke (%)	Baseline BP (mmHg)
ACCOMPLISH-1 2008	Amlodipine 5–10	36	5744	39.5	68.4	13.3	145.3/80.1
	HCTZ 12.5–25		5762			12.8	145.4/80
ACCOMPLISH-2 2008	HCTZ 12.5–25	36	5762	39.5	68.4	12.8	145.4/80
	Amlodipine 5–10		5744			13.3	145.3/80.1
ALLHAT-1 2002	Lisinopril 10–40	58.8	9054	46.2	66.9	NA	146.4/84.1
	Chlorthalidone 12.5–25		15,225	47			146.2/84
ALLHAT-2 2002	Lisinopril 10–40	58.8	9054	46.2	66.9	NA	146.4/84.1
	Amlodipine 2.5–10		9048	47.3			146.2/83.9
ALLHAT-3 2002	Amlodipine 2.5–10	58.8	9048	47.3	66.9	NA	146.2/83.9
	Chlorthalidone 12.5–25		15,225	47			146.2/84
ALLHAT-4 2002	Amlodipine 2.5–10	58.8	9048	47.3	66.9	NA	146.2/83.9
	Lisinopril 10–40		9054	46.2			146.4/84.1
ALLHAT-5 2002	Chlorthalidone 12.5–25	58.8	15,225	47	66.9	NA	146.2/84
	Amlodipine 2.5–10		9048	47.3			146.2/83.9
ALLHAT-6 2002	Chlorthalidone 12.5–25	58.8	15,225	47	66.9	NA	146.2/84
	Lisinopril 10–40		9054	46.2			146.4/84.1
ASCOT-BPLA-1 2010	Amlodipine 5–10	64.8	5824	23.5	63	NA	164.1/94.8
	Atenolol 50–100		5195				163.9/94.5
ASCOT-BPLA-2- 2010	Atenolol 50–100	64.8	5195	23.5	63	NA	163.9/94.5
	Amlodipine 5–10		5824				164.1/94.8
CTHPCE-1 2011	BB	43.3	1166	49.5	63.2	2	153.7/88.7
	Thiazide diuretic		1094	49.5	63.1	2	154.1/88.7
CTHPCE-2 2011	BB	43.3	1166	49.5	63.2	2	153.7/88.7
	ARB		1110	49	63	3	153.9/89
FEVER 2005	Felodipine 5	40	4841	38.3	61.5	14.2	154.2/91.3
	Placebo		4870	39.5		15.5	154.4/91.3
HYVET 2008	Indapamide SR 1.5	21.6	1933	60	83.6	6.7	173/90.8
	Placebo		1912			6.9	173/90.8
INVEST-1 2008	Verapamil SR 240	24	3622	38.9	67.2	9.8	149.8/86.1
	Atenolol 50		3596	37.8	67.2	9.8	150.4/86.5
INVEST-2 2008	Atenolol 50	24	3596	37.8	67.2	9.8	150.4/86.5
	Verapamil SR 240		3622	38.9	67.2	9.8	149.8/86.1
LIFE-ISH-1 2005	Losartan 79	56.4	660	58.8	70.2	10.6	174.2/83
	Atenolol 75		666	61.4	70.4	12.9	174.5/82.3
LIFE-ISH-2 2005	Atenolol 75	56.4	666	61.4	70.4	12.9	174.5/82.3
	Losartan 79		660	58.8	70.2	10.6	174.2/83
NHS-1 2013	Valsartan 80–160	38.4	417	41.2	61.9	NA	147.8/83.7
	Amlodipine 5–10		401				147.5/83.5
NHS-2 2013	Amlodipine 5–10	38.4	401	41.2	61.9	NA	147.5/83.5
	Valsartan 80–160		417				147.8/83.7
NORDIL-1 2000	Diltiazem 180–360	54	5410	51	60	1.4	173.5/105.8
	BB–Diuretic		5471			1.6	173.4/105.7
NORDIL-2 2000	BB–Diuretic	54	5471	51	60	1.6	173.4/105.7
	Diltiazem 180–360		5410			1.4	173.5/105.8
ORIENT 2011	Olmesartan 10–40	38.4	282	29.4	59.1	14.5	141.7/77.8
	Placebo		284	32.4	59.2	14.8	140.8/77.2
PROGRESS 2001	Perindopril 4	49.2	3051	30	64	71	147/86
	Placebo		3054				147/86

Table 1 continued

Study[a]	Comparator drugs (mg)	Mean follow-up (months)	Sample size	Females (%)	Mean age (year)	HO stroke (%)	Baseline BP (mmHg)
SCAST 2011	Candesartan 4–16	6	1017	40	71	85	171.2/90.3
	Placebo		1012	44		86	171.6/90.6
SCOPE 2004	Candesartan 8–16	43.2	754	63.3	77.3	4.2	168.7/82.3
	Placebo		764	65.3	76.9	4.5	169.3/82.5
SHEP 2000	Chlorthalidone 12.5–25	54	2365	56.8	71.6	1.4	170/77
	Placebo		2371				170/77
STOP HTN2 -1 1999	Enalapril/Lisinopril 10–20	60	2205	66	76	3.9	194/98
	Felodipine/Isradipine 2.5–5		2196				194/98
STOP HTN2 -2 1999	Felodipine/Isradipine 2.5–5	60	2196	66	76	3.9	194/98
	Enalapril/Lisinopril 10–20		2205				194/98
VART-1 2011	Valsartan 80–160	40.8	510	43.1	60	NA	158/93
	Amlodipine 5–10		511	42.5			158/94
VART-2 2011	Amlodipine 5–10	40.8	511	42.5	60	NA	158/94
	Valsartan 80–160		510	43.1			158/93

ARB angiotensin receptor blocker, *BB* β-blocker (β-adrenoceptor antagonist), *BP* blood pressure, *HCTZ* hydrochlorothiazide, *HO* history of, *NA* not available, *SR* sustained release

[a] Refer to text for full names of trials

that compared a regimen based on benidipine 4–8 mg daily added to either a β-blocker, ARB, or thiazide diuretic. Additional antihypertensive agents (ARB 21.7 %; β-blocker 26.3 %; and thiazide 29.8 %, respectively) were provided to achieve a BP goal of <140/90 mmHG.

The FEVER (Felodipine Event Reduction) trial [17] was a randomized, prospective double-blind, placebo-controlled trial that compared incidence of stroke in hypertensive patients receiving felodipine 5 mg daily or matched placebo treated to a goal BP of ≤160/95 mmHg. All patients were receiving baseline hydrochlorothiazide 12.5 mg daily. Approximately 33.9 and 42.3 % of patients received add-on therapy (α-blocker, β-blocker, ACEI, ARB, and 12 % CCB) in the felodipine and placebo group, respectively.

HYVET (Hypertension in the Very Elderly) [18] was a randomized, double-blind, placebo-controlled trial to assess the benefit of antihypertensive therapy in the very old population (aged ≥80 years). It compared active treatment with indapamide sustained release (SR) 1.5 with placebo to a target BP of <150/80 mmHg. At 2 years, 25.8, 23.9, and 49.5 % of subjects in the active-treatment group were receiving indapamide alone, indapamide and perindopril (2 mg), and indapamide and perindopril (4 mg), respectively. Meanwhile, in the control arm, 14.2, 13.4, and 71.8 % of subjects, respectively, were receiving the corresponding placebos.

INVEST (INternational VErapamil SR-Trandolapril) [19] was a prospective, randomized, open-label trial. A sub-study of INVEST assessed the effects of a verapamil SR versus an atenolol-based regimen in subjects with prior myocardial infarction (MI). The target BP was <140/90 mm Hg, or <130/85 mm Hg in the presence of diabetes and/or renal impairment. At 2 years, 62.3 and 57.4 % were taking add-on therapy with trandolapril and hydrochlorothiazide, respectively.

LIFE (Losartan Intervention for Endpoint reduction in hypertension) [20] was a prospective, randomized, double-blinded parallel-group study that evaluated the effect of losartan versus atenolol in hypertensive patients with left ventricular hypertrophy (LVH) to a BP goal of <140/90 mmHg. A sub-study of LIFE in patients with isolated systolic hypertension (ISH) was used in this meta-analysis. Approximately 58 % of subjects in both groups received additional therapy with hydrochlorothiazide. At 4.7 years, 83.7 and 74.9 % of subjects continued to take losartan and atenolol, respectively.

In the sub-analysis of the NHS (NAGOYA HEAT Study) [21], the cardiovascular protective effect of valsartan versus amlodipine was assessed in diabetic hypertensive patients without previous documented CVD. The NHS was a prospective, randomized, open-labeled, blinded-endpoint trial. Patients were allocated to either valsartan 80–160 mg or amlodipine 5–10 mg daily to a BP target of ≤130/80 mmHg. At 36 months, 54 % of subjects were receiving the studied drugs in both arms. Add-on drugs included β-blockers (24 vs. 29 %), α-blockers (6 vs. 4 %), aldosterone blockers (3 vs. 2 %), thiazides (17 vs.

8 %), and other diuretics (4 vs. 5 %) for the valsartan versus the amlodipine group, respectively [22].

NORDIL (Nordic Diltiazem) [23] was a prospective, randomized, open-labeled, blinded-endpoint study that compared the effects of a diltiazem-based (180–360 mg) regimen with the effects of regimens based on a thiazide diuretic, β-blocker, or both. The target BP was a diastolic of <90 mmHg. In the diltiazem group, an ACEI followed by a thiazide diuretic or a β-blocker could be added to achieve the target BP. Likewise, in the thiazide diuretic and β-blocker group, both drugs could be combined and then followed by an ACEI or α-blocker to achieve target BP. At the end of the trial, 50 % of patients in the diltiazem versus 45 % in the diuretic and β-blocker group were still taking the assigned randomized monotherapy.

ORIENT (Olmesartan Reducing Incidence of End stage Renal Disease in Diabetic Nephropathy Trial) [24] was a randomized, placebo-controlled study that examined the renoprotective benefit of olmesartan medoxomil. Patients were allocated to receive olmesartan 10–40 mg daily (or placebo) to a target BP <130/85 mmHg. In order to achieve target BP, a diuretic, β-blocker, CCB, or α-blocker could be added. At 144 weeks, 63.4 % of patients were receiving olmesartan 40 mg (or placebo) daily.

PROGRESS (Perindopril pROtection aGainst REcurrent Stroke Study) [3] was a prospective, randomized, placebo-controlled trial designed to determine the risk of recurrent stroke in both hypertensive and non-hypertensive patients with cerebrovascular disease. Patients were assigned either perindopril 4 mg daily or matching placebo, with addition of indapamide 2.0 or 2.5 mg daily at the discretion of the treating physician to achieve target BP. A total of 86 % of patients in the active group continued randomized therapy, while 87 % continued therapy in the placebo group. Indapamide was added in 58 % of patients in both groups.

SCAST (Scandinavian Candesartan Acute Stroke Trial) [25] compared candesartan 4–16 mg with matching placebo in patients with recent stroke and a systolic BP ≥140 mmHg. Approximately 97 % of patients received the allocated study drug in both arms, while 28 and 26 % received an ACEI in the candesartan and placebo groups, respectively.

SCOPE (Study on Cognition and Prognosis in the elderly) [26] was a double-blind randomized candesartan or matching placebo trial. In this sub-analysis, candesartan 8–16 mg daily was compared with matching placebo in a sub-group of elderly patients with ISH. Hydrochlorothiazide was the add-on regimen of choice if systolic BP remained ≥160 mmHg. Only 26 and 18 % of patients received monotherapy with candesartan or matching placebo, respectively. A total of 21 % of subjects in the candesartan group and 15 % in the placebo group received double therapy with hydrochlorothiazide. A total of 53 and 68 % received add-on therapy (diuretic, β-blocker, CCB, ACEI, and ARB) in the candesartan and placebo groups, respectively.

SHEP (Systolic Hypertension in the Elderly Program) [27] was a double-blinded, randomized, chlorthalidone–placebo trial that evaluated the effect of this antihypertensive agent on stroke reduction in an elderly population with ISH to a goal systolic BP of <160 mmHg. The active study drug was chlorthalidone 12.5–25 mg daily or matching placebo; add-on therapy with β-blocker or low-dose reserpine could be added if target BP was not met. At the end of the trial, 46 % of participants were receiving only the active study drug, while 23 % were receiving a combination of active study drug plus add-on drug.

STOP-HTN-2 (Swedish Trial in Old Patients with Hypertension-2) [28] was an RCT designed to investigate the benefit of newer antihypertensive agents (enalapril, lisinopril, felodipine, and isradipine) compared with older agents (atenolol, metoprolol, pindolol, and hydrochlorothiazide plus amiloride) on cardiovascular mortality. In this meta-analysis, we isolated and compared stroke incidence in the ACEI (enalapril 10–20 mg and lisinopril 10–20 mg daily) versus CCB (felodipine 2.5–5 mg and isradipine 2.5–5 mg daily) groups.

VART (Valsartan Amlodipine Randomized Trial) [29] was a prospective open-labeled, blinded-endpoint study that compared the effects of valsartan 80–160 mg daily with those of amlodipine 5–10 mg daily on cardiovascular events in patients with BP ≥140/90 mmHg. Add-on therapy included α-blockers, β-blockers, or diuretics if target BP <140/90 mmHg was not achieved with active treatment. At 36 months, 81.7 versus 69.2 % of patients were receiving monotherapy with amlodipine and valsartan, respectively.

3 Results

This meta-analysis included 17 randomized published clinical trials, accounting for 31 comparative arms (Table 1). The comparative arms included 227,754 patients, of whom 46 ± 11.4 % were female. The ACEI, ARB, ACEI/ARB, β-blocker, CCB, and T-TLD groups included 52,887; 7278; 60,165; 24,099; 98,950; and 68,639 patients, respectively.

The mean follow-up period was 42.9 ± 15 months, with a mean age of 67.2 ± 6.8 years. ALLHAT, ASCOT-BPLA, NHS, and VART did not provide neither provided data on nor included patients with a history of stroke; however, 18 ± 26 % of subjects had a prior history of stroke. PROGRESS and SCAST had more than 50 % of patients with a prior history of stroke at baseline.

The baseline BP in this meta-analysis was 158.8/88.1 mmHg in the ACEI group, 160.2/85 mmHg in the ARB group, 159.5/86.2 mmHg in the ACE/ARB group, 159.2/88.1 mmHg in the β-blocker group, 156.2/83.2 mmHg in the T-TLD group, and 157.9/90.1 mmHg in the CCB group (Table 3). The calculated difference in BP at study end for each group was as follows: ACEI (−)16.3/9.6, ARB (−)21.2/8.5, ACE/ARB (−)19.2/8.9, β-blocker (−)21.8/10.9, T-TLD (−)18.6/8.9, and CCB (−)19.1/11.8 mm Hg (Table 3).

3.1 Risk Ratio of Stroke Occurrence

Incidence of stroke at study end between the comparator drugs and the calculated risk ratios with a 95 % CI are provided in Table 2.

A random-effect model was used to assess for summary effect size in the ACEI, ACEI/ARB, ARB, and T-TLD groups. The summary risk ratio for stroke occurrence in the ACEI group compared with a non-ACEI antihypertensive agent was 1.01 (95 % CI 0.81–1.27; $p = 0.92$ [Table 3 and Fig. 2]) with heterogeneity $I^2 = 93.6$; $Q = 32$; $df = 3$ ($p = 0.92$). While the summary risk ratio for stroke occurrence in the ACEI/ARB group compared with a non-ACEI/ARB antihypertensive agent was 0.94 (95 % CI 0.78–1.13; $p = 0.51$ [Table 3 and Fig. 3]) with heterogeneity $I^2 = 80$; $Q = 45$; $df = 9$ ($p < 0.01$). In addition, the summary risk ratio for stroke occurrence in the T-TLD group compared with the non-T-TLD antihypertensive agents was 0.90 (95 % CI 0.75–1.08; $p = 0.25$ [Table 3 and Fig. 4]) with heterogeneity $I^2 = 79$; $Q = 19$; $df = 4$ ($p < 0.01$). The summary risk ratio for stroke occurrence in the ARB group compared with non-ARB antihypertensive agents was 0.83 (95 % CI 0.59–1.18; $p = 0.30$ [Table 3 and Fig. 5]) with heterogeneity $I^2 = 51.2$; $Q = 10$; $df = 5$ ($p = 0.07$).

A fixed-effect model was used to assess for summary effect size in β-blocker and CCB groups. The summary risk ratio for stroke occurrence in the β-blocker group compared with non-β-blocker antihypertensive agents was 1.42 (95 % CI 1.26–1.61; $p < 0.01$ [Table 3 and Fig. 6]) with heterogeneity $I^2 = 0$; $Q = 3$; $df = 4$ ($p = 0.54$). In addition, the summary risk ratio for stroke occurrence in the CCB group compared with non-CCB antihypertensive agents was 0.83 (95 % CI 0.79–0.89; $p < 0.01$ [Fig. 7]) with heterogeneity $I^2 = 33$; $Q = 13.7$; $df = 9$ ($p = 0.14$). A summary effect size for stroke occurrence in the different antihypertensive drug class is depicted in Fig. 8.

In this meta-analysis, the Orwin's fail-safe N test used 1.0 as a criterion for a trivial risk ratio and 1.0 ± 0.1 for a mean risk ratio in missing studies. Therefore, it would require 7, 36, 97, 100, 177, and 183 studies to bring the risk ratio to 1.0 in the ACEI/ARB, T-TLD, ACEI, ARB, β-blocker, and CCB groups, respectively. Figure 9 depicts a funnel plot to visually assess publication bias on trials comparing CCB with other antihypertensive regimens.

4 Discussion

There is a strong, graded, and continuous relationship between BP and stroke risk, with higher BP associated with greater stroke risk [1, 30]. Primary prevention studies in pre-hypertensive patients have shown a statistically significant stroke risk reduction with active antihypertensive therapy when compared with placebo [31]. In a meta-analysis of 23 trials, any antihypertensive drugs versus no treatment were associated with a statistically significant 32 % relative risk reduction in stroke [32]. Like primary prevention stroke studies, secondary prevention studies have also shown benefit for antihypertensive drugs versus no treatment in stroke risk reductions. In a meta-analysis of 25 trials of antihypertensive drugs versus no treatment in patients with history of stroke but without hypertension, the treatment group was associated with a significant 23 % pooled relative risk reduction of strokes [33].

The SPS3 (Secondary Prevention of Small Subcortical Strokes) trial was a multicenter randomized open-label trial of 3020 participants that investigated the benefit of a BP target 130–149 versus <130 mmHg in patients with recent lacunar stroke [34]. At 1 year, mean systolic BP was 138 mmHg in the higher-target group and 127 mmHg in the lower-target group. The lower-target group had non-significant rates of reduction in the primary endpoint of all stroke (including ischemic strokes and intracranial hemorrhages).

The BPLTTC was a systematic review that included 29 randomized antihypertensive trials that investigated the effects of different BP-lowering regimens on major cardiovascular events, including stroke [4]. This review also showed a stroke risk reduction with intensive BP target (−4/−3 mmHg BP difference).

Similar to the BPLTTC, our meta-analysis showed that ACEIs were the least effective in BP reduction (Table 3). In terms of the different antihypertensive drugs used in the BPLTTC, ACEIs and CCBs reduced stroke risk by 30 and 39 %, respectively, when compared with placebo. However, no significant differences in stroke outcome were observed among the different antihypertensive drug classes. Other studies have suggested that ACEIs and ARBs are more effective in reducing recurrent stroke, but the evidence is sparse. Despite evidence of reduced BP reduction with reduced stroke rates, which antihypertensive medication is most effective for long-term stroke prevention is unclear. In this review, we assessed the effectiveness of individual antihypertensive agents in reducing stroke risk.

Table 2 Change in blood pressure, incidence of stroke, and risk ratio of stroke at the end of each randomized controlled trial

Study[a]	Comparator drugs (mg)	BP change	Incidence of stroke (*n*)	RR (95 % CI)	*p* value
ACCOMPLISH-1 2008	Amlodipine 5–10	(−)13.7/6.8	112	0.84 (0.66–1.08)	0.18
	HCTZ 12.5–25	(−)12.9/5.6	133		
ACCOMPLISH-2 2008	HCTZ 12.5–25	(−)12.9/5.6	133	1.18 (0.92–1.52)	0.18
	Amlodipine 5–10	(−)13.7/6.8	112		
ALLHAT-1 2002	Lisinopril 10–40	(−)10.5/8.7	457	1.14 (1.01–1.28)	0.03
	Chlorthalidone 12.5–25	(−)12.3/8.6	675		
ALLHAT-2 2002	Lisinopril 10–40	(−)10.5/8.7	457	1.21 (1.06–1.38)	<0.01
	Amlodipine 2.5–10	(−)11.5/9.3	377		
ALLHAT-3 2002	Amlodipine 2.5–10	(−)11.5/9.3	377	0.94 (0.83–1.06)	0.32
	Chlorthalidone 12.5–25	(−)12.3/8.6	675		
ALLHAT-4 2002	Amlodipine 2.5–10	(−)11.5/9.3	377	0.83 (0.72–0.94)	<0.01
	Lisinopril 10–40	(−)10.5/8.7	457		
ALLHAT-5 2002	Chlorthalidone 12.5–25	(−)12.3/8.6	675	1.06 (0.94–1.20)	0.32
	Amlodipine 2.5–10	(−)11.5/9.3	377		
ALLHAT-6 2002	Chlorthalidone 12.5–25	(−)12.3/8.6	675	0.88 (0.78–0.99)	0.03
	Lisinopril 10–40	(−)10.5/8.7	457		
ASCOT-BPLA-1 2010	Amlodipine 5–10	(−)25/14.6	279	0.71 (0.61–083)	<0.01
	Atenolol 50–100	(−)22.1/12.4	350		
ASCOT-BPLA-2- 2010	Atenolol 50–100	(−)22.1/12.4	350	1.41 (1.21–1.64)	<0.01
	Amlodipine 5–10	(−)25/14.6	279		
CTHPCE-1 2011	BB	(−)19.8/11.7	27	2.11 (1.07–4.15)	0.03
	Thiazide diuretic	(−20.1)/12.1	12		
CTHPCE-2 2011	BB	(−)19.8/11.7	27	1.51 (0.83–2.76)	0.18
	ARB	(−)19.2/11.8	17		
FEVER 2005	Felodipine 5	(−)16.9/8.5	177	0.71 (0.59–0.86)	<0.01
	Placebo	(−)11.9/6.3	251		
HYVET 2008	Indapamide SR 1.5	(−)29.5/12.9	51	0.73 (0.51–1.04)	0.08
	Placebo	(−)14.5/6.8	69		
INVEST-1 2008	Verapamil SR 240	(−)18.5/9.7	73	0.81 (0.60–1.11)	0.19
	Atenolol 50	(−)19/10	89		
INVEST-2 2008	Atenolol 50	(−)19/10	89	1.23 (0.90–1.67)	0.19
	Verapamil SR 240	(−)18.5/9.7	73		
LIFE-ISH-1 2005	Losartan 79	(−)28.4/8.5	32	0.58 (0.38–0.88)	0.01
	Atenolol 75	(−)28.2/8.8	56		
LIFE-ISH-2 2005	Atenolol 75	(−)28.2/8.8	56	1.73 (1.14–2.64)	0.01
	Losartan 79	(−)28.4/8.5	32		
NHS-1 2013	Valsartan 80–160	(−)15.4/8.6	11	1.51 (0.59–3.86)	0.39
	Amlodipine 5–10	(−)15.9/8.7	7		
NHS-2 2013	Amlodipine 5–10	(−)15.9/8.7	7	0.66 (0.26–1.69)	0.39
	Valsartan 80–160	(−)15.4/8.6	11		
NORDIL-1 2000	Diltiazem 180–360	(−)20.3/18.7	159	0.82 (0.67–1.01)	0.06
	BB–Diuretic	(−)23.3/18.7	196		
NORDIL-2 2000	BB–Diuretic	(−)23.3/18.7	196	0.82 (0.67–1.01)	0.06
	Diltiazem 180–360	(−)20.3/18.7	159		
ORIENT 2011	Olmesartan 10–40	(−)9.9/5.6	8	0.73 (0.3–1.79)	0.50
	Placebo	(−)4.2/3.6	11		
PROGRESS 2001	Perindopril 4	(−)9/4	307	0.73 (0.64–0.84)	<0.01
	Placebo	NC	420		

Table 2 continued

Study[a]	Comparator drugs (mg)	BP change	Incidence of stroke (*n*)	RR (95 % CI)	*p* value
SCAST 2011	Candesartan 4–16	(−)28.2/9.3	68	1.17 (0.83–1.64)	0.37
	Placebo	(−)28.6/9.6	58		
SCOPE 2004	Candesartan 8–16	(−)22/6	20	0.58 (0.34–0.99)	0.05
	Placebo	(−)20/5	35		
SHEP 2000	Chlorthalidone 12.5–25	(−)26/9	103	0.65 (0.51–0.83)	<0.01
	Placebo	(−)15/4	159		
STOP HTN2 -1 1999	Enalapril/lisinopril 10–20	(−)35/17	215	1.03 (0.86–1.24)	0.71
	Felodipine/isradipine 2.5–5	(−)35/18	207		
STOP HTN2 -2 1999	Felodipine/isradipine 2.5–5	(−)35/18	207	0.97 (0.81–1.16)	0.71
	Enalapril/lisinopril 10–20	(−)35/17	215		
VART-1 2011	Valsartan 80–160	(−)23/13	10	1.0 (0.42–2.39)	1.0
	Amlodipine 5–10	(−)23/14	10		
VART-2 2011	Amlodipine 5–10	(−)23/14	10	1.0 (0.42–2.38)	1.0
	Valsartan 80–160	(−)23/13	10		

ARB angiotensin receptor blocker, *BB* β-blocker (β-adrenoceptor antagonist), *BP* blood pressure, *CI* confidence interval, *HCTZ* hydrochlorothiazide, *RR* risk ratio, *SR* sustained release

[a] Refer to text for full names of trials

Table 3 Summary risk ratio for stroke and heterogeneity statistics for individual antihypertensive drug groups

Antihypertensive drug agent	Baseline BP (mmHg)	Change in BP study end	Outcome	Summary RR (95 % CI)	*p* value	Heterogeneity Q	Heterogeneity (*p* value)	I^2
ACEI	158.8/88.1	(−)16.3/9.6	Stroke	1.01 (0.81–1.27)	0.92	32	0.92	93.6
ARB	160.2/85	(−)21.2/8.5	Stroke	0.83 (0.59–1.18)	0.30	10	0.07	51.2
ACEI/ARB	159.5/86.2	(−)19.2/8.9	Stroke	0.94 (0.78–1.13)	0.51	45	<0.01	80
BB	159.2/88.1	(−)21.8/10.9	Stroke	1.42 (1.26–1.61)	<0.01	3	0.54	0
CCB	157.9/90.1	(−)19.1/11.8	Stroke	0.83 (0.79–0.89)	<0.01	13.7	0.14	33
T-TLD	156.2/83.2	(−)18.6/8.9	Stroke	0.90 (0.75–1.08)	0.25	19	<0.01	79

ACEI angiotensin-converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *BB* β-adrenoceptor antagonist (β-blocker), *BP* blood pressure, *CCB* calcium channel blocker, *CI* confidence interval, I^2 I-squared statistics, *RR* risk ratio, *T-TLD* thiazide or thiazide-like diuretic

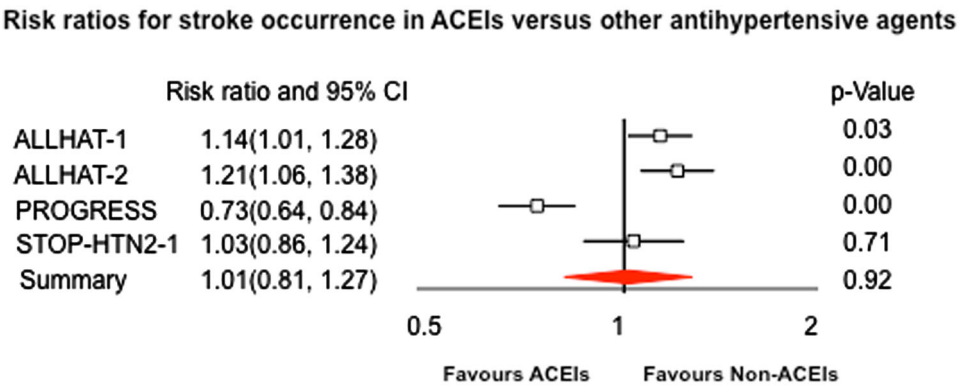

Fig. 2 The risk of stroke with the use of angiotensin-converting enzyme inhibitors when compared with other antihypertensive drugs. $I^2 = 93.6$; $Q = 32$; $df = 3$ ($p = 0.92$). *ACEIs* angiotensin-converting enzyme inhibitors, *CI* confidence interval

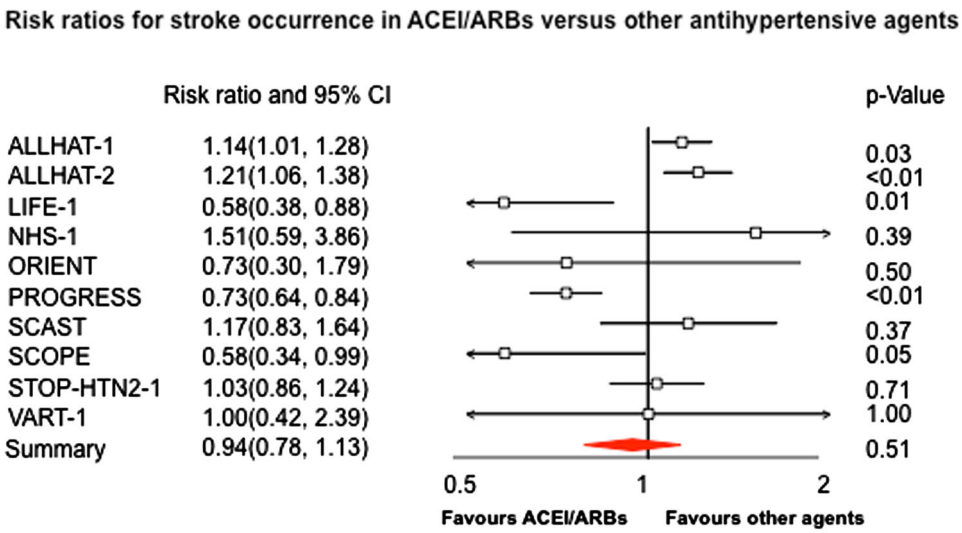

Fig. 3 The risk of stroke with the use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers when compared with other antihypertensive drugs. $I^2 = 80$; $Q = 45$; $df = 9$ ($p < 0.01$). *ACEI* angiotensin-converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *CI* confidence interval

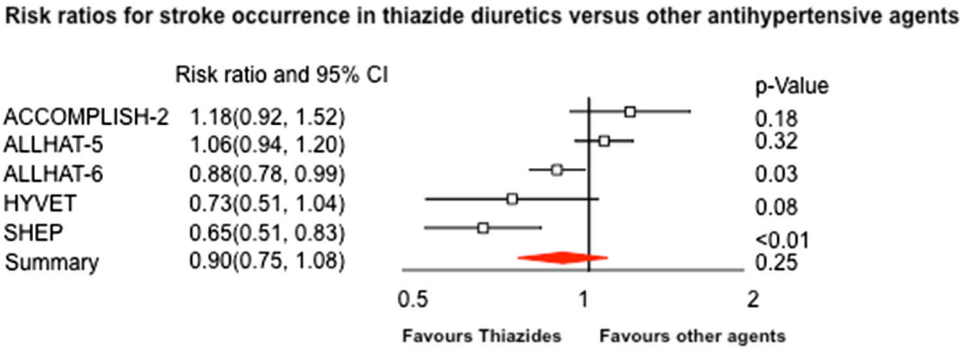

Fig. 4 The risk of stroke with the use of thiazide or thiazide-like diuretics when compared with other antihypertensive drugs. $I^2 = 79$; $Q = 19$; $df = 4$ ($p < 0.01$). *CI* confidence interval

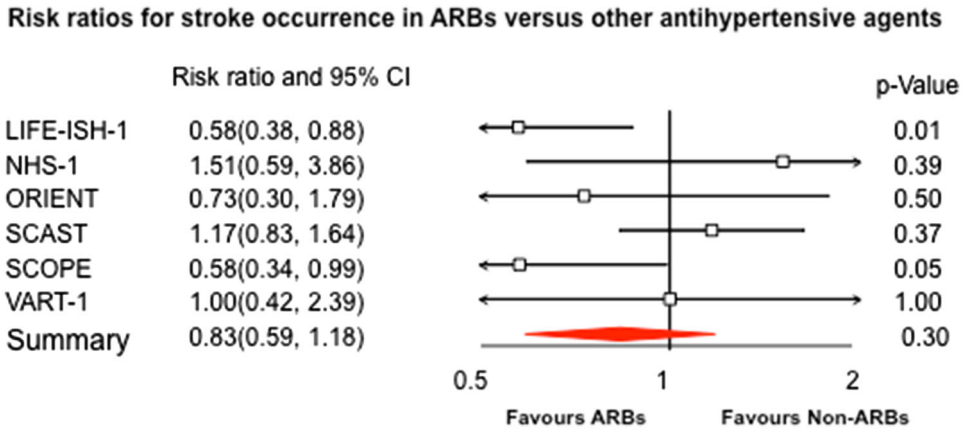

Fig. 5 The risk of stroke with the use of angiotensin receptor blockers when compared with other antihypertensive drugs. $I^2 = 51.2$; $Q = 10$; $df = 5$ ($p = 0.07$). *ARB* angiotensin receptor blocker, *CI* confidence interval

4.1 Angiotensin-Converting Enzyme Inhibitor (ACEI) Versus Non-ACEI Antihypertensive Drugs

The PROGRESS trial was a prospective, randomized, placebo-controlled trial designed to determined the risk of recurrent stroke in both hypertensive and non-hypertensive patients with cerebrovascular disease. Patients were assigned to either perindopril 4 mg daily or matching placebo, with addition of indapamide 2.0 or 2.5 mg daily at the discretion of the treating physician to achieve target BP. BP was lowered by 9/4 mmHg in the perindopril-based group, with a statistically significant 28 % relative risk reduction for total stroke. The PROGRESS trial

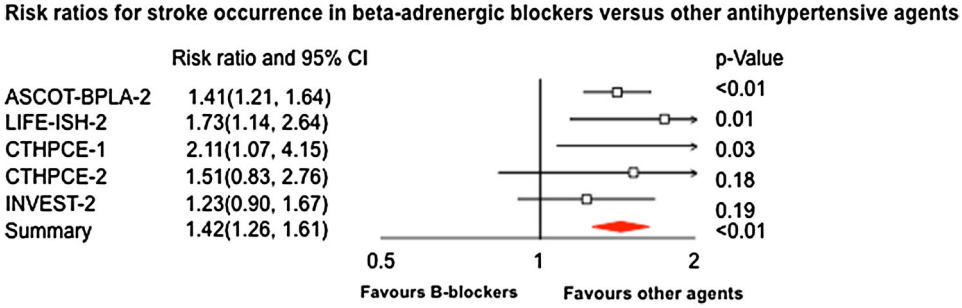

Fig. 6 The risk of stroke with the use of adrenergic beta blockers (B-blockers) when compared with other antihypertensive drugs. $I^2 = 0$; $Q = 3$; $df = 4$ ($p = 0.54$). *CI* confidence interval

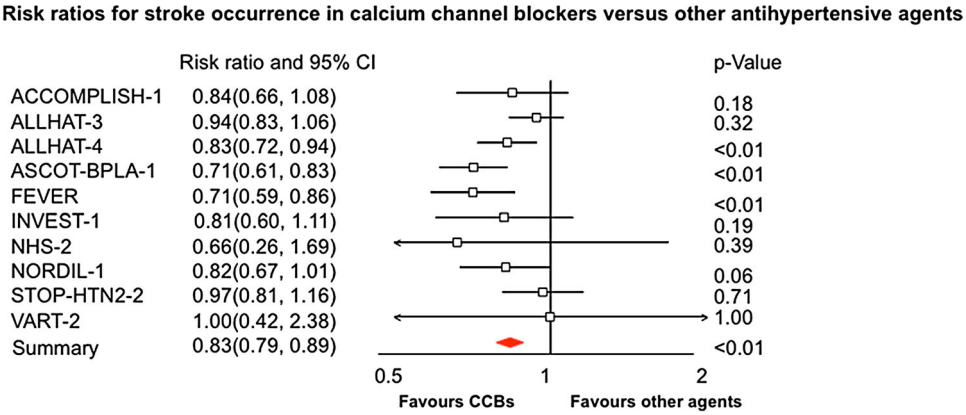

Fig. 7 The risk of stroke with the use of calcium channel blockers when compared with other antihypertensive drugs. $I^2 = 33$; $Q = 13.7$; $df = 9$ ($p = 0.14$). *CCB* calcium channel blocker, *CI* confidence interval

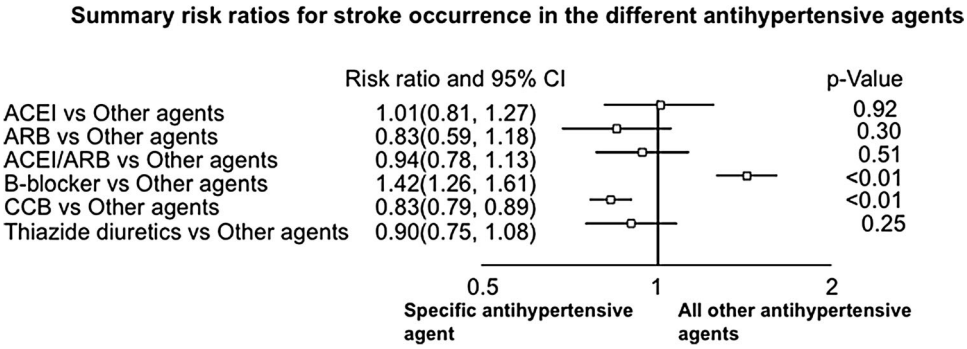

Fig. 8 Summary risk of stroke in the different antihypertensive drug classes *ACEIs* angiotensin-converting enzyme inhibitors, *ARBs* angiotensin receptor blockers, *B-blockers* adrenergic β-blockers, *CCBs* calcium channel blockers, *CI* confidence interval

suggested a linear relationship between BP reduction and stroke. In a meta-analysis of 28 trials in hypertensive or high-risk patients, ACEIs did not show a significant reduction in the prevention of stroke when compared with placebo/diuretics/β-blockers (odds ratio 0.94 [95 % CI 0.83–1.08], $p = 0.41$) [35]. A network meta-analysis of first-line antihypertensive drug treatment showed a significant reduction in stroke of 14 % with low-dose diuretics versus ACEIs [32]. In our systematic review, no statistically significant difference was observed in long-term stroke occurrence with ACEIs when compared with non-ACEI antihypertensive agents. The summary risk ratio for stroke occurrence in the ACEI group compared with non-ACEI antihypertensive agents was 1.01 (95 % CI 0.81–1.27).

4.2 Angiotensin Receptor Blocker (ARB) Versus Non-ARB Antihypertensive Drugs

MOSES (Morbidity and Mortality after Stroke, and Eprosartan compared with Nitrendipine for Secondary Prevention study) enrolled 1405 patients to a target BP <140/90 mmHg. No difference in BP reduction was observed in either group; however, t a statistically significant reduction was seen in fatal and nonfatal cerebrovascular events favoring the eprosartan group. SCOPE showed a similar reduction in stroke (42 % risk reduction) with candesartan compared with placebo in elderly patients with ISH despite little difference in BP reduction [26]. In patients with acute stroke and increased BP, candesartan did not improve cognitive function, quality of life, or

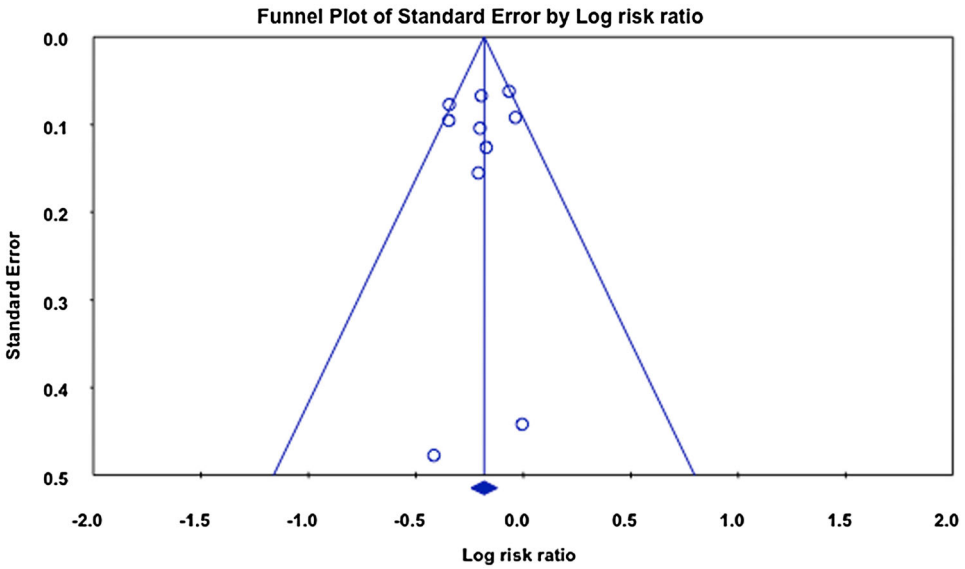

Fig. 9 Funnel plot for visual assessment of publication bias on trials comparing calcium channel blockers and other antihypertensive therapies

vascular endpoints but instead may be harmful in this setting [25, 36]. In a network meta-analysis of first-line antihypertensive drug treatment, a non-statistically significant reduction in stroke of 20 % was observed with ARBs versus low-dose diuretics [32].

Our analysis shows a 15 % non-statistically significant reduction in stroke rate with ARB compared with non-ARB antihypertensive drugs, which suggests that ARBs could be better at reducing stroke rate than ACEIs in hypertensive patients without an otherwise compelling indication to be receiving an ACEI. The reduction in stroke could be explained by the observed difference in BP (−)21.2/8.5 mmHg versus (−)16.3/9.6 mmHg with ARBs versus ACEIs, respectively. Whether an ARB is a better antihypertensive agent than an ACEI remains to be seen.

4.3 β-blocker Versus Non-β-blocker Antihypertensive Drugs

In a recent study by Bangalore et al. [37], β-blocker use in patients with prior MI but no HF was associated with a lower composite cardiovascular outcome. These findings were driven by lower recurrent MI with no difference in mortality. On the other hand, in patients without MI, β-blocker use was not associated with fewer cardiovascular events but instead was associated with increased stroke risk. Evidence is mounting that β-blocker use in patients without MI is not associated with fewer cardiovascular events; however, they are associated with increased stroke risk [38, 39]. In our analysis, β-blocker use was associated with a 42 % statistically significant increase in stroke rate compared with non-β-blocker antihypertensive drugs. The observed changes in BP noted in our study suggest that β-blockers are more effective in reducing BP than other antihypertensive drugs. However, the reduction in BP in the β-blocker groups did not translate to a reduction in stroke occurrence. The increased risk of stroke seen with β-blockers could therefore be explained by its metabolic effects (insulin resistance, lipid disturbance) [40].

4.4 Calcium Channel Blocker (CCB) Versus Non-CCB Antihypertensive Drugs

CCBs have been shown to reduce the incidence of stroke in patients with hypertension. The BPLTTC showed a statistically significant 38 % relative risk reduction in stroke when CCBs were compared with placebo [4, 5]. However, a trend was observed towards an increased risk of HF with CCBs. FEVER [17] also showed a statistically significant reduction in stroke when a CCB-based regimen was compared with placebo. Likewise, in the ALLHAT trial, a CCB (amlodipine) was similar to a TLD (chlorthalidone) in stroke risk reduction despite a trend in favor of the CCB [14]. An increased rate of HF and HF hospitalization was noted in the pre-specified subgroup analysis of the ALLHAT trial. A meta-analysis of 28 trials in hypertensive or high-risk patients showed that CCBs were statistically superior to placebo/diuretics/β-blockers in stroke prevention [35]. This meta-analysis is different from our review study in that it did not include an ACEI or an ARB in the control arm.

In this meta-analysis, CCBs were associated with a statistically significant reduction in stroke rate when compared with all non-CCB antihypertensive drugs. Our findings are in accordance with those of the BPLTTC, which also showed that CCBs were more effective than thiazide diuretics/β-blockers and ACEIs in stroke risk reduction. Our study is different in that it compared CCBs with all four classes of antihypertensive drugs.

4.5 Thiazide Diuretics Versus Other Antihypertensive Drugs

T-TLDs have been maintained as one of the preferred first-line antihypertensive agents for more than a decade [1]. The support for their use comes from the landmark ALLHAT, which showed chlorthalidone (TLD) to be as effective as amlodipine (CCB) in reducing the specified endpoints (non-fatal MI plus coronary heart disease death and all-cause mortality); however, chlorthalidone was superior in the reduction of HF occurrence. Similarly, chlorthalidone was shown to be superior to lisinopril (ACEI) in reducing the occurrence of both stroke and HF events [14].

Our study showed a non-statistically significant reduction in stroke rates with T-TLD compared with other antihypertensive drugs. Despite being an effective antihypertensive drug, T-TLDs have significant metabolic adverse effects, especially at higher doses. In a recently published meta-analysis of ten trials ($\sim$17,000 patients), Mukete and Rosendorff found that even lower doses of T-TLD were significantly associated with a higher odds of elevated plasma glucose and reduced potassium [41]. Despite being recommended as preferred first-line antihypertensive drug because of BP effectiveness and lower cost, caution should be used when prescribing to at-risk populations (those with occlusive coronary artery disease, LVH on electrocardiogram, the elderly with ISH, and those with an increased risk for developing diabetes) [41].

4.6 Differential Outcome in Stroke Seen with CCBs and β-Blockers

The ASCOT-BPLA [42] was a multicenter randomized controlled trial that assessed the antihypertensive effects of a CCB-based (amlodipine) versus a β-blocker-based (atenolol) regimen on the prevention of cardiovascular events. The ASCOT-BPLA BP target was achieved in the two groups. The difference in BP between the two groups was 2.7/1.9 mmHg lower in favor of the CCB-based group. No significant differences were observed in the primary endpoints (non-fatal MI and fatal coronary heart disease) despite a trend in favor of the CCB-based group. Nonetheless, a significant difference in stroke prevention was observed in favor of the CCB-based regimen.

The BPLTTC study suggested that the relative effects on total cardiovascular events was affected by the absolute BP reduction rather than the antihypertensive drug of choice [4]. However, this conclusion was challenged by the life trial [43], in which a losartan-based regimen was better in stroke prevention than the atenolol-based regimen despite only achieving a 1 mmHg difference in systolic BP reduction in favor of the losartan-based regimen.

CAFÉ (Conduit Artery Function Evaluation) [44] was a sub-study of the ASCOT trial that examined the difference in central aortic BP using the radial artery applanation tonometry method between a CCB-based versus a β-blocker-based regimen. In the CAFÉ trial, no significant difference was found in brachial systolic BP between the two groups; however, a substantial reduction was observed in central aortic systolic BP with the CCB-based regimen compared with the β-blocker-based regimen. The difference in central aortic systolic BP was significantly associated with a reduction in total cardiovascular events and procedures.

The differential outcome in stroke could be explained by the degree of central aortic systolic BP lowering with CCBs versus β-blockers. Furthermore, evidence is mounting that suggests an increased incidence of diabetes associated with β-blocker use [45–49]. The increased incidence in diabetes could explain the increased stroke risk with β-blockers when compared with CCBs.

5 Conclusion

This meta-analysis provides us with clarity regarding the most superior antihypertensive drug class for the long-term prevention of stroke in patients with CVD. CCBs appear to be statistically superior in stroke prevention when compared with the other four classes of antihypertensive drugs. Based on our review, CCBs should be first-line agents in patients with hypertension for whom the treatment goal is to reduce stroke occurrence and for whom there are no other compelling indications for an ACEI, ARB, or β-blocker. In patients who cannot tolerate a CCB, an ARB or a T-TLD could be a reasonable alternative. Beta-adrenergic blockers should be avoided in patients without compelling indications for their use (i.e., patients with MI $\leq$3 years, HF, hypertrophic obstructive cardiomyopathy). In our analysis, β-blockers were associated with a statistically significant increased risk of stroke.

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