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Review Article

SYSTEMATIC REVIEW OF ANGIOTENSIN CONVERTING ENZYME INHIBITORS AND CALCIUM CHANNEL BLOCKERS IN STROKE ISCHEMIC PREVENTION

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ABSTRACT

Introduction : Ischemic stroke is a leading cause of disability and death worldwide, with hypertension being one of the most significant modifiable risk factors. Among antihypertensive agents, ACE Inhibitors (ACEIs) and Calcium Channel Blockers (CCBs) are commonly used. However, their relative efficacy in preventing ischemic stroke remains a subject of clinical interest.

Material and methods : A systematic search was conducted using PubMed, Cochrane Library, and ScienceDirect for articles published between 2010 and 2025. Eligible studies included research article that evaluated the effect of ACE inhibitors or Calcium Channel Blockers on the prevention of ischemic stroke in adults with hypertension. Reviewers independently screened titles, abstracts, and full texts, and extracted data. Study quality was assessed using the Cochrane Risk of Bias tool.

Discussion : From 8,991 screened articles, 17 studies met the inclusion criteria. Both ACE inhibitors and Calcium Channel Blockers showed effectiveness in reducing ischemic stroke risk. Some studies showed a slightly better effect with Calcium Channel Blockers like amlodipine, while others reported similar results between ACE inhibitors and Calcium Channel Blockers. Differences in study designs and patient groups made direct comparison difficult.

Conclusion : Both ACE Inhibitors and Calcium Channel Blockers are effective in reducing the risk of ischemic stroke in hypertensive patients, although the relative benefit between the two remains complex. Calcium Channel Blockers may offer a slight advantage in certain populations, but ACE Inhibitors continue to be a cornerstone of stroke prevention strategies, particularly in patients with additional cardiovascular risk factors.

Keywords: ACEi, CCBs, stroke, systematic review

INTRODUCTION

Stroke is one of the leading causes of death and disability worldwide. Each year, approximately 15 million people suffer a stroke globally, and one-third of them die. Among survivors, about one-third experience permanent disability, which significantly affects their quality of life and imposes a substantial burden on families, communities, and society at large. The incidence of stroke is projected to increase markedly over the next two decades.[1]

Risk factors for stroke can be categorized into two groups: non-modifiable and

modifiable factors. Non-modifiable factors include advanced age, male sex, Asian or Black ethnicity, and a family history of stroke. In contrast, modifiable risk factors include hypertension, smoking, diabetes, dyslipidemia, obesity, atrial fibrillation (AF), carotid artery stenosis, a history of prior stroke, transient ischemic attack (TIA), or myocardial infarction.[2]

Hypertension is the most important modifiable risk factor for stroke.[3] The majority of stroke cases occur in patients with uncontrolled blood pressure. There is a strong correlation between elevated blood pressure and stroke risk. Meta-analyses have shown that effective blood pressure reduction can lower the risk of stroke by up to 40%.[4] Several clinical trials have also confirmed that greater reductions in blood pressure lead to better stroke prevention outcomes.[5]

Blood pressure reduction has been proven effective for both primary and secondary prevention of stroke, regardless of age, sex, or ethnicity. Even a small decrease of 1–3 mmHg in systolic blood pressure can reduce stroke risk by up to 30%. Among individuals aged 60–69 years, a 10 mmHg reduction in systolic pressure lowers the risk of stroke by approximately 35%. In patients with a history of stroke or transient ischemic attack (TIA), antihypertensive therapy can reduce the recurrence of stroke by 28%, whereas discontinuation of therapy increases the risk.[1]

Selecting the appropriate antihypertensive agent enhances therapeutic effectiveness. The five major classes recommended as first-line therapy include angiotensin-converting enzyme inhibitors (ACEIs), calcium channel blockers (CCBs), angiotensin receptor blockers (ARBs), diuretics, and beta-blockers (BBs). ACEIs reduce blood pressure by inhibiting the formation of angiotensin II, while CCBs relax vascular smooth muscles, leading to vasodilation.[6]

Systematic reviews and meta-analyses have compared the effects of various antihypertensive agents according to patient characteristics.[7] However, because each drug class includes multiple agents, their relative efficacy remains uncertain. Among these, ACEIs and CCBs are two major classes recommended as first-line antihypertensive agents in most clinical guidelines. Nevertheless, few studies have directly compared the efficacy and safety of individual drugs within these two classes.[6]

Therefore, this study aims to conduct a systematic review of the existing literature evaluating the effects of ACEis and CCBs in preventing ischemic stroke among patients with hypertension and to provide a comprehensive overview of their effectiveness as preventive strategies.

MATERIAL AND METHODS

Eligible studies were identified through searches in the PubMed, Cochrane Library, and ScienceDirect databases. The search covered studies published between 2010 and 2025. The search strategy was developed based on the Cochrane Handbook for Systematic Reviews of Interventions. The search terms included: “ACE inhibitors,” “AngiotensinConverting Enzyme Inhibitors,” “Calcium Channel Blockers,” “CCB,” “Stroke,” “Ischemic Stroke,” “Stroke Prevention,” and “Hypertension.” Screening was performed independently by two researchers through a cross-checking process, starting with title and abstract screening, followed by the exclusion of irrelevant articles, and then a full-text assessment. In cases of disagreement, the final decision was reached through discussion and consensus between the two reviewers.

Inclusion Criteria

1. Patients aged ≥ 18 years.
2. Clinically diagnosed with essential hypertension with or without complications. The diagnostic criteria for hypertension were defined as systolic blood pressure (SBP) ≥ 140 mmHg and/or diastolic blood pressure (DBP) ≥ 90 mmHg.
3. Studies included were original research articles published in Eng;ish, with a minimum treatment duration of two weeks.

Exclusion Criteria

1. Studies with unavailable or incomplete data
2. Inappropriate study design
3. Participants with SBP ≥ 180 mmHg or DBP ≥ 110 mmHg

Data Extraction

Two reviewers independently screened the titles and abstracts, excluding studies that did not meet the inclusion and exclusion criteria. Full texts of potentially relevant articles were then reviewed to determine final eligibility.

Microsoft Excel was used to manage the data and extract the required information. Extracted data included study characteristics (author name, study design, title, sample size, investigated drugs, follow-up duration, and outcomes) as well as the reported effectiveness of ACEIs and CCBs in preventing ischemic stroke.

Compliance with Ethical Guidelines

This article is based on previously published studies and does not include any new research involving human participants or animals conducted by any of the authors.

Study Quality and Risk of Bias Assessment

To ensure the quality of the analyzed studies, all eligible articles were independently reviewed by two researchers to assess the risk of bias. The RoB 2 tool was used for randomized controlled trials (RCTs), the AMSTAR 2 checklist for systematic reviews and meta-analyses, and the Newcastle–Ottawa Scale (NOS) for observational studies.

RESULT

The literature search across multiple databases identified a total of 8,991 articles. After removing 104 duplicates, 8,887 articles were screened based on their titles and abstracts, and 141 articles were selected for full-text review. Following further assessment, 124 articles were excluded, leaving 17 studies that met the eligibility criteria and were included in this review. The study selection process is illustrated in the PRISMA flow diagram (**Figure 1**).

The included studies demonstrated diverse characteristics, comprising seven observational studies, five randomized controlled trials (RCTs), and five systematic reviews and metaanalyses. In total, approximately 2,929,788 patients were analyzed, with sample sizes ranging from 14 to 1,891,459 participants per study. The duration of follow-up varied from a minimum of 14 days to a maximum of 23 years.

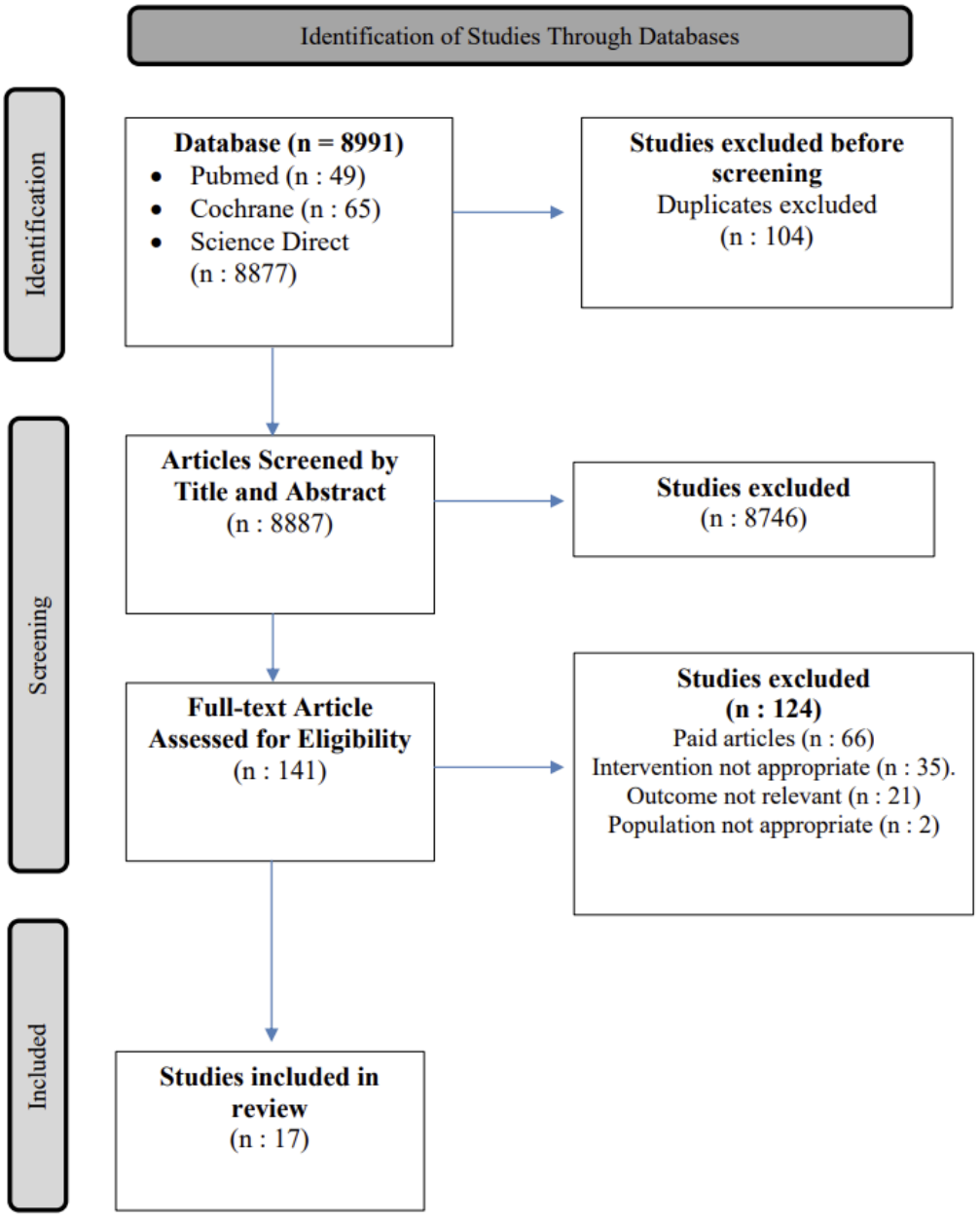

Figure 1. PRISMA Flow Diagram Depicting Literature Search and Study Selection

Table 1. Characteristics of Studies Assessing the Effectiveness of ACE Inhibitors and Calcium Channel Blockers in Stroke Prevention

Author	Study Design	Title	Sample Size	Comparator Drugs	Follow up	Primary Outcome
Davison et al.[8]	Feasibility RCT (Randomised, Open-Label Trial)	A Calcium Channel Or Angiotensin Converting Enzyme Inhibitor/Angiotensin Receptor Blocker Regime To Reduced Blood Pressure Variability In Acute Ischaemic Stroke (CAARBS): A Feasibility Trial	14 patients	CCB vs ACEI/ARB	3 months	Blood pressure variability and feasibility of recruiting acute ischemic stroke patients
Yamal et al.[9]	Secondary analysis dari RCT (ALLHAT Trial)	Mortality And Morbidity Among Individuals With Hypertension Receiving A Diuretic, ACE Inhibitor, Or CCB	32.084 patients	Diuretic (chlorthalidone), ACEI (lisinopril), CCB (amlodipine)	Up to 23 years	Cardiovascular mortality, stroke, and all-cause mortality
Zhong et al.[10]	Systematic review & network metaanalysis	Role of Blood Pressure Management in Stroke Prevention: A Systematic Review and Network Meta-Analysis of 93 RCTs	504.613 patients	ACEI, ARB, CCB, diuretic, beta-blocker, renin inhibitor (monotherapy & combination)	Mean 3,3 years	Stroke prevention and drug tolerability

Author	Study Design	Title	Sample Size	Comparator Drugs	Follow up	Primary Outcome
Yu et al.[11]	Network MetaAnalysis of RCTs	Comparative Efficacy Of Different Antihypertensive Drug Classes For Stroke Prevention	487.076 patients	ACEI, ARB, CCB, DI, BB, RI, and combination (ACEI+CCB, ACEI+BB, ARB+CCB, etc)	≥6 months (rata-rata >3 tahun)	Stroke, cardiovascular mortality, and all-cause mortality
Karagiannaki et al.[12]	Prospective Cohort Observasional	Association Between Antihypertensive Treatment, Blood Pressure Variability, And Stroke Severity And Outcomes In Acute Ischemic Stroke	228 patients	ACEI, ARB, CCB, beta blocker, diuretic, vasodilator, aldosterone antagonist, alpha blocker	3 months	Three-month mortality after acute ischemic stroke
Neves et al.[13]	Cross-sectional	Antihypertensive Use For Stroke In United States Emergency Departments	1.208 patients	Beta blocker, CCB, ACEI, diuretic, vasodilator	Not reported	Frequency and patterns of antihypertensive use in the emergency department for stroke patients

Author	Study Design	Title	Sample Size	Comparator Drugs	Follow up	Primary Outcome
Yao et al.[14]	Network MetaAnalysis (RCT)	A Network Meta-Analysis Comparative The Efficacy Of Angiotensin-Converting Enzyme Inhibitors And Calcium Channel Blockers In Hypertension	9.176 patients	ACEI (lisinopril, enalapril, etc), CCB (amlodipine, felodipine, nitrendipine, etc)	8–156 weeks	Reduction of systolic/diastolic blood pressure, adverse events, and effectiveness ranking based on SUCRA
Maïer et al.[15]	Post-hoc analysis from RCT	Effect Of Baseline Antihypertensive Treatments On Stroke Severity And Outcomes In The BP TARGET Trial	203 patients	ACEI, ARB, beta blocker (RAS inhibitor); CCB, diuretic (non-RAS inhibitor)	3 months	Baseline NIHSS, 24-hour intracranial hemorrhage, and neurological improvement
Hatamian et al.[16]	Systematic review (pre-clinic & clinic)	Examining The Therapeutic Potential And Side Effects Of Calcium Channel Blockers In Mortality And Morbidity Of Patients With Stroke	1.891.459 patients	CCBs (nifedipine, verapamil, amlodipine, felodipine, diltiazem, etc.); compared with ACEI, ARB, BB, and diuretic	14 days – 6,1 years	Stroke risk, mortality, morbidity, and long-term neurological and cardiovascular outcomes

Author	Study Design	Title	Sample Size	Comparator Drugs	Follow up	Primary Outcome
A. Coca et al.[17]	Article Review	Single-Pill Combination For Treatment Of Hypertension: Just A Matter Of Practicality Or Is There A Real Clinical Benefit?	RCT and observational	Combination ACEI/ARB + CCB, Diuretic, Beta-blocker (SPC vs monotherapy)	6 – 12 months and >1 year	Single-pill combinations (SPCs) lower blood pressure more effectively, achieve faster BP control, and reduce adverse effects
Fakadu et al.[18]	Prospective Observational	Management Protocols And Encountered Complications Among Stroke Patients At Jimma University	116 patients	ACEI (enalapril, captopril), CCB (amlodipine, nifedipine), diuretic, etc.	During hospitalization	Persistence of secondary prevention therapy after stroke, particularly antihypertensive and cardiovascular medications
Sarfo et al.[19]	Retrospective Observational	Baseline Prescription And One-Year Persistence Of Secondary Prevention Drugs After Stroke	418 patients	ACEI, ARB, CCB, beta-blocker, diuretic, statin, antiplatelet	1 year	Persistence of secondary prevention therapy after stroke, particularly antihypertensive and cardiovascular medications
Safro et al.[20]	Case Control Study	Stroke Occurrence By Hypertension Treatment Status In Ghana And Nigeria	3684 patients	Antihypertensive (not specified by class; included; ACEI, CCB)	Not specified	The impact of hypertension treatment status stroke occurrence

Author	Study Design	Title	Sample Size	Comparator Drugs	Follow up	Primary Outcome
Tuttolomondo et al.[21]	Retrospective Observational	Effects Of Clinical And Laboratory Variables And Of Pretreatment With Cardiovascular Drugs In Acute Ischaemic Stroke	1096 patients	ACEI, CCB, ARB, Antyplatelet, Heparin, VKA	During hospitalization	In-hospital mortality, HAMT cognitive score, and functional ADL status at discharge
Mukete et al.[22]	Cohort Retrospective	Long-Term Anti-Hypertensive Therapy Is Associated With Decreased Stroke Risk	2.212 patients	ACEI, ARB, CCB, Diuretic	10 years	Incidence of ischemic stroke
Iyengar et al.[23]	Systematic Meta-Analysis	Effect Of Amlodipine In Stroke And Myocardial Infarction: A Systematic Review And Meta-Analysis	13 studies (12 RCT and 1 cohort)	Amlodipine (CCB)	3 years	Incidence of stroke and myocardial infarction in hypertensive patients
Ferreira Jr. et al.[24]	Systematic Review	Adherence To Antihypertensive Therapy And Its Determinants: A Systematic Review	45 studies	Various antihypertensive agents	Not specified	Factors influencing adherence to antihypertensive therapy

Study Quality and Risk of Bias Assessment

Among the 17 studies reviewed, most demonstrated good methodological quality. Five RCTs were assessed using the *RoB 2* tool—two studies had a low risk of bias, while three showed a moderate risk due to missing data. Seven observational studies were evaluated using the *Newcastle–Ottawa Scale (NOS)*, all of which were of good quality with scores ranging from 7 to 8. Five meta-analyses or systematic reviews were assessed using *AMSTAR 2*; three were rated as high quality and two as moderate. Overall, the majority of the studies exhibited strong methodological rigor.

Hypertension is a major modifiable risk factor in the prevention of ischemic stroke. Therefore, selecting the optimal antihypertensive agent plays a crucial role in reducing stroke-related morbidity and mortality. The two most commonly used drug classes in clinical practice are ACE inhibitors (ACEIs) and calcium channel blockers (CCBs). However, the evidence regarding their comparative effectiveness varies depending on study design, population characteristics, and outcome parameters.

Based on the 17 systematically reviewed studies, both ACEIs and CCBs were effective in lowering blood pressure and reducing the risk of ischemic stroke. Several key findings emerged from this review:

1. Effectiveness in Lowering Blood Pressure and Stroke Prevention

Several studies demonstrated that CCBs—particularly the dihydropyridine subclasses such as amlodipine and felodipine—were more effective than ACEIs in reducing systolic blood pressure. One study reported that felodipine and nitrendipine ranked highest in blood pressure–lowering efficacy based on SUCRA analysis.[14] Another study found that CCBs were significantly superior to ACEIs and beta-blockers in reducing stroke incidence, both as monotherapy and in combination therapy.[11] Moreover, a combination of CCBs with thiazide diuretics (THZ) showed the highest effectiveness for stroke prevention.[10] Overall, CCBs appeared to be more effective for stroke prevention in patients with essential hypertension.

2. Safety and Tolerability

CCBs demonstrated a better tolerability profile and higher adherence rates compared to ACEIs. A 2017 study reported that persistence with CCB therapy reached 94.2% after 12 months, compared with 85.4% for ACEIs.[19] On the other hand, some evidence supports the role of ACEIs in reducing stroke severity and improving functional outcomes. One study found that patients receiving ACEIs had lower initial NIHSS scores and experienced fewer intracranial hemorrhages than those on CCBs.[15] Additionally, ACEIs were associated with significant reductions in mortality and functional impairment during hospitalization.[21] These findings suggest that ACEIs may provide additional protective benefits through modulation of the renin–angiotensin system (RAS).

3. Effectiveness of Combination Therapy

Several studies supported the effectiveness of combining ACEIs and CCBs compared with monotherapy. One study reported that a single-pill combination (SPC) of ACEI and CCB provided greater benefits in lowering blood pressure, reducing side effects, and improving patient adherence.[17] Another study concluded that the combination of ACEIs and CCBs offered stronger preventive effects against stroke and cardiovascular mortality compared with monotherapy.[11]

4. Study Heterogeneity and Challenges in Cross-Study Comparison

There were notable differences in study design, population characteristics, and outcome definitions, which made direct comparison between ACEIs and CCBs challenging. Some small-scale studies focused on blood pressure variability and recruitment feasibility,[8] while others evaluated long-term outcomes extending over two decades.[9] Observational studies described patterns of antihypertensive use in healthcare settings but did not always include standardized clinical data.[18-19] Additionally, other studies indicated that the effectiveness of CCBs depends greatly on the specific drug

type, dosage, and patient condition.[16]

DISCUSSION

The aim of this study was to conduct a systematic review of research evaluating the effects of ACE inhibitors (ACEIs) and calcium channel blockers (CCBs) in the prevention of ischemic stroke, based on studies published within the past ten years. The effectiveness of these drugs and the influencing factors are summarized in Table 2.

The findings of this systematic review indicate that both angiotensin-converting enzyme inhibitors (ACEIs) and calcium channel blockers (CCBs) are effective in preventing ischemic stroke among hypertensive patients. However, the majority of studies suggest that CCBs—particularly the dihydropyridine subclasses such as amlodipine, felodipine, and nitrendipine—tend to show superior efficacy.

Of the 17 studies analyzed, seven explicitly reported the superiority of CCBs over ACEIs. For instance, the ALLHAT trial demonstrated that lisinopril (an ACEI) increased the risk of stroke by 19% compared to amlodipine (HR: 1.19; 95% CI: 1.01–1.40).[9] Another study reported that the combination of CCBs with thiazide diuretics was the most effective therapy (OR: 0.89; 95% CI: 0.80–0.99), whereas ACEIs were associated with a higher risk of adverse effects.[11] Two additional studies supported these findings, showing that CCBs were superior to ACEIs and beta-blockers, and that the combination of ACEI and CCB provided greater stroke protection compared with monotherapy.[11,14] A meta-analysis further confirmed that amlodipine significantly reduced stroke risk (OR: 0.87; 95% CI: 0.79–0.96).[23] Moreover, one study found that CCBs achieved a greater systolic blood pressure reduction (-35 mmHg) than ACEIs (-22 mmHg), although the functional outcomes of both drugs were comparable (8). In terms of adherence, persistence with CCBs at 12 months was higher (94.2%) than with ACEIs (85.4%).[19]

Table 1. Results of the Comparative Effectiveness of ACE Inhibitor vs Calcium Channel Blocker in Preventing Ischemic Stroke.

Effectiveness Category	Author	Year	Clinical & Statistical Effects	Influencing Factor
CCB more effective (7 studies)	Yama et al. [9]	2021	HR for stroke (ACEI vs CCB): 1.19 (95% CI: 1.01– 1.40); lisinopril associated with increased stroke risk	ALLHAT population, diuretic comparator
	Zhong et al.[10]	2023	OR ACEI vs CCB: 1.12; CCB+thiazide most effective (OR vs placebo: 0.89)	Drug combinations, tolerability, SUCRA ranking
	Yu et al.[11]	2025	RR CCB vs BB: 0.81; ACEI+CCB combination superior to monotherapy	SPC combinations, CCB subclasses
	Yao et al.[14]	2024	Felodipine & nitrendipine ranked highest (SUCRA); ACEI superior only for DBP reduction	CCB subclasses, essential hypertension types
	Iyengar et al.[23]	2021	OR stroke: 0.87 (95% CI: 0.79–0.96); OR MI: 0.88	Asian population, primary hypertension
	Safro et al.[19]	2017	Persistence at 12 months: CCB 94.2% vs ACEI 85.4%	Medication adherence, long-term post-stroke management
	Davison et al.[8]	2020	ΔSBP: CCB -35 mmHg vs ACEI -22 mmHg; similar functional outcomes	Small sample, BP variability effects
ACEi more effective (4 studies)	Maïer et al.[15]	2022	ICH incidence lower with ACEI (6.2% vs 12.1% with CCB); lower NIHSS with ACEI	RAS pathway protection, vascular inflammation
	Mukete et al.[22]	2020	ACEI/ARB significantly reduced long-term stroke risk ($p < 0.05$)	Long-term therapy, Chinese population
	Tuttolomondo et al.[21]	2011	ACEI reduced mortality and functional impairment (OR: 3.42–5.55)	Pre-stroke use, functional outcomes

Effectiveness Category	Author	Year	Clinical & Statistical Effects	Influencing Factor
	Safro et al.[20]	2024	Adequate ACEI therapy associated with lower stroke risk	Adequate hypertension control
Combination/ both effective (4 studies)	Coca et al.[17]	2024	SPC ACEI+CCB superior to monotherapy	Synergistic effect, BP control, tolerability
	Tuttolomondo et al.[21]	2011	CCB also reduced mortality and improved recovery (OR: 5.12)	retreatment ACEI/CCB, neurovascular protection
	Fekadu et al.[18]	2019	ACEI more common in ischemic stroke; CCB in hemorrhagic stroke	Stroke type, ER practice, absence of national protocol
	Yu et al.[11]	2025	Amlodipine ↓SBP by -34 mmHg; captopril ↓DBP by -20 mmHg	Onset of action, ER treatment response
Variable/inconsistent (2 studies)	Hatamian et al.[16]	2025	Effectiveness varied by CCB subtype; some outperform ACEI; results not always significant	CCB type/dose (benidipine, lercanidipine), study design, patient population
	Neves et al.[13]	2020	CCB more frequently used for hemorrhagic stroke; ACEI for ischemic stroke	ER practice, drug availability, stroke subtype

Conversely, three studies supported the effectiveness of ACEIs, particularly in secondary prevention or in patients with high cardiovascular risk. One study reported that patients receiving ACEIs experienced milder strokes and a lower incidence of intracranial hemorrhage (ICH: 6.2% with ACEIs vs. 12.1% with CCBs).[15] Another study found that long-term ACEI/ARB therapy significantly reduced the risk of ischemic stroke ($p < 0.05$).[22] Additionally, ACEIs were associated with significant reductions in mortality and functional impairment (OR: 3.42–5.55), although CCBs demonstrated similar benefits (OR: 5.12).[21]

Four studies concluded that ACEIs and CCBs were equally effective, especially when used in combination. One study emphasized that a single-pill combination (SPC) of ACEI and CCB was more effective than monotherapy.[17] Another reported that amlodipine more rapidly reduced systolic blood pressure, while captopril was more effective in lowering diastolic pressure.[11] One study highlighted the importance of tailoring therapy according to stroke subtype—ACEIs being more beneficial for hemorrhagic stroke, and CCBs for ischemic stroke.[18]

The therapeutic effectiveness of CCBs also varied depending on the specific drug and dosage. Certain agents, such as benidipine and lercanidipine, were more effective than nifedipine, indicating that the efficacy of CCBs cannot be generalized across all subclasses.[16]

In conclusion, CCBs appear to be more effective for the prevention of ischemic stroke in patients with essential hypertension. However, ACEIs remain important, particularly for patients with a history of cardiovascular disease or prior stroke. Combination therapy with ACEIs and CCBs—including single-pill combinations—provides optimal benefits in terms of efficacy, tolerability, and adherence. The relative effectiveness of these two drug classes is also influenced by the specific subclass, dosage, duration of therapy, target blood pressure, and other non-clinical factors.

ETHICAL CONSIDERATIONS

This study is a systematic review that utilized only secondary data from previously published articles. No direct interaction with human or animal subjects was involved; therefore, ethical approval was not required.

AUTHOR DECLARATION

The author declares that this manuscript is an original work and has not been submitted for publication elsewhere. All writing and analysis were conducted independently, based on a comprehensive review of relevant scientific literature. The author takes full responsibility for the content and authenticity of this manuscript.

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