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Examining the therapeutic potential and side effects of calcium channel blockers in mortality and morbidity of patients with stroke: A systematic review of pre-clinical and clinical studies

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ABSTRACT

Background: Blood pressure control is one of the basic steps in preventing stroke and cerebrovascular events. Calcium channel blockers are the first-line drugs in hypertension control. On the other hand, the stroke recovery phase depends on activating calcium channels and N-methyl-D-aspartate (NMDA) receptors. Considering these issues, one of the interdisciplinary challenges of neurology and cardiology is the use of these drugs in hypertensive patients with cerebrovascular accident (CVA) risk and their uses after these events.

Objectives: This study's primary goal is to evaluate the effects of calcium channel blockers on reducing the risk, mortality, morbidity, and long-term outcomes of cerebrovascular events.

Material and Methods: We conducted this systematic literature review by searching PubMed, Scopus, and Google Scholar databases. Our inclusion criteria were randomized clinical trials, cohort studies, case-cross-over studies, case reports, and in-vitro and animal studies in which they evaluated the effects of calcium channel blockers on the CVA risk and mortality, morbidity, and long-term outcomes of stroke. Our exclusion criteria were review studies with no adequate data and non-English articles. Articles that met our criteria were included in the initial search. After the title and abstract screening, 56 human and animal studies were selected to be discussed in this article.

Results: Among 56 selected studies, 33 were human studies, 23 were animal experiments, and one study was carried out both on animals and humans. A total of 1,860,234 patients were enrolled in 24 human studies. A total of 717,131 patients in 22 studies received CCBs. Two studies did not report the number of patients who underwent treatment with CCBs. Among 24 studies, 11 reported favorable outcomes following CCB administration, and two studies reported neuroprotective effects for CCBs without any adverse outcome in stroke patients. Five studies demonstrated that CCBs were associated with adverse outcomes. One study showed favorable and unfavorable outcomes compared to other antihypertensive agents. Stroke was reported in two studies following CCB overdose. Three studies have reported that CCBs had no significant effect on stroke risk, mortality, or long-

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term outcomes. In animal studies, a total of 813 animals were enrolled in 19 studies. Two studies were in vitro using mammalian cells and enzymes, and one study was ex-vivo. Among 24 studies, 18 (75 %) reported beneficial outcomes following treatment with CCBs, three (12.5 %) revealed both favorable and unfavorable results, two (8.3 %) demonstrated adverse outcomes, and one (4.2 %) showed no effect.
Conclusion: Based on the evidence from human and animal studies, authors conclude that CCBs are associated with a lower risk of stroke, lower mortality risk, and improved long-term neurological and other clinical outcomes.

Introduction

The Seventh Joint National Committee on Hypertension's report states that hypertension (HTN) is a significant public health issue, impacting approximately 50 million people in the US and one billion people globally. As the population ages, the prevalence of HT will continue to rise unless effective preventive measures are taken (Wang et al., 2006). HTN, which includes elevated pulse pressure (the difference between systolic blood pressure (SBP) and diastolic blood pressure (DBP)), is a significant contributor to the risk of myocardial infarction (MI), stroke, heart failure, and renal failure. Higher SBP and DBP levels are indicative of long-term risks for chronic heart disease and CVD, leading to a gradual and steady rise in the likelihood of death from heart disease or stroke (Ferini-Strambi et al., 2014). Observational studies have indicated a clear and direct correlation between blood pressure levels and the likelihood of experiencing heart disease or stroke. However, as people age, this connection becomes less pronounced. A recent comprehensive analysis discovered that individuals aged 50–59 who had a 20 mm Hg lower usual systolic blood pressure had a 62 % lower risk of stroke, while those aged 80–89 had a 33 % lower risk (Trialists'Collaboration, 2008).

HTN is a major risk factor for the development of minor vessel diseases of the brain, which are a leading cause of memory loss and are responsible for over 40 % of dementia cases. Clinical studies have shown that high blood pressure in mid-life can lead to cognitive decline later in life. However, the exact cellular mechanisms that connect HTN to memory problems have not been fully determined (Koide et al., 2021). Also, the relationship between HTN and vascular dementia has been established for a long time, and it is becoming increasingly clear that HTN is also a reversible risk factor in the development of Alzheimer's dementia (AD) (Iadecola and Davisson, 2008).

Since HTN is the most influential risk factor for CVD that can be altered, various clinical trials have demonstrated that taking antihypertensive medications such as diuretics, β-blockers, calcium channel blockers (CCBs), angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers can lead to a decrease of 30–40 % in the occurrence of CVD within a short period of time (Kettani et al., 2009). Calcium channel blockers (CCBs) are the primary medications used to manage HTN and can potentially enhance blood flow in the brain and decrease neurodegeneration caused by Aβ. Several clinical studies have investigated the impact of CCBs, particularly nimodipine, which can cross the blood-brain barrier, on dementia. While the results of these trials were not entirely successful, nimodipine demonstrated some effectiveness in treating AD and less so for VaD (Savage et al., 2020; Nimmrich and Eckert, 2013). Besides, it was elucidated that CCBs can have a protective effect against stroke and myocardial infarction (Godfraind, 2017).

So, due to the critical complications of HTN and the crucial role of CCBs in lowering blood pressure, it is important to figure out the beneficial and adverse effects of CCBs regarding cerebrovascular diseases. In this systematic review, we aimed to investigate the impact of CCBs on reducing mortality, morbidity, and long-term outcomes of cerebrovascular events.

Method

Literature inclusion and exclusion criteria

The criteria for inclusion of literature were publicly available original articles, including RCTs, cohort studies, case reports, case crossovers and animal studies in English published until 2023. Research subjects (human/animals) were on CCB administration, and outcomes like stroke, neurological deficit, CVD mortality, and morbidity were assessed. CCBs were initiated after acute cerebrovascular events, and long-term outcomes were intended. Exclusion criteria were narrative and systematic reviews, non-English articles, and articles published before the mentioned date. The ethical approve number for this study of Critical Care Quality Improvement Research Center, Shahid Modarres Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran is IR.SBMU.RETECH.REC.1403.709.

Literature search

All of our searches were done electronically on English-language databases, including PubMed, Scopus, and Google Scholar. Keywords that were used to identify related articles were: Calcium channel blockers, mortality, morbidity, adverse effect, side effect, and stroke. Also, the synonyms, mesh terms, and abbreviations of the mentioned keywords were searched. Two researchers did the literature search.

Literature screening

Two researches were assigned to screen initial search results. By browsing the document title and abstract, clearly unrelated literature was removed. From all 224 results after initial screening, 56 were enrolled in the final evaluation. Researchers conducted full-text screening based on the inclusion and exclusion criteria.

Data extraction

Two researchers first extracted the data independently, and then they cross-checked it. If there were any incompatible data, a third researcher was consulted. The extracted data was recorded in tables and analyzed by researchers. This data included the study title, how it was designed, the country in which it was conducted, follow-up duration, population characteristics and age, treatment, outcomes, underlying comorbidities, limitations and main results.

Quality assessment

In the current study, the SYRCLES checklist was used for quality assessment, which assesses sources of bias, such as selection bias, performance bias, detection bias, attrition bias, and reporting bias.

Results

Study selection

A comprehensive search of PubMed, Scopus, EMBASE, and Web of Science revealed a total of 2146 studies. After removing duplicates, a

total of 1381 papers were left, which underwent title and abstract screening. Following title and abstract screening, 224 studies remained and underwent full-text reading and data extraction. Finally, a total of 56 studies met the inclusion criteria and enrolled in the current study. Details of the study screening process are shown in Fig. 1.

Study characteristics

Finally, a total of 56 studies were enrolled, among which 33 (57.1 %) were human studies, 23 (41.1 %) were animal experiments, and one (1.8 %) study was carried out both on animals and humans. Twenty-one (37.5 %) studies were from the USA, 11 (19.6 %) from Japan, five (8.9 %) from Canada, three (5.4 %) from China, three (5.4 %) from Taiwan, and two (3.6 %) from Sweden. Finland, Sweden, the UK, Greece, Denmark, Belgium, Hungary, South Korea, Germany, Australia, and Israel had one (1.8 %) study each (Table 1).

Human studies

Study characteristics

A total of 33 human studies were included, among which 12 were cohorts, 12 clinical trials, three case reports, two case cross-overs, two communications, one case-control, and one was observational surveillance. Among the studies, 11, three, three, two, two, and two were from the USA, Taiwan, Japan, Canada, Sweden, and China, respectively. Greece, Belgium, Italy, Australia, the UK, Denmark, Hungary, South Korea, Germany, and Israel had one study each. The follow-up duration ranged from 14 days to 6.1 years among 18 studies (Table 1).

Patient characteristics

A total of 1,891,459 patients were enrolled, and the sample size ranged from one to 1,294,548 individuals among 32 studies. A total of 29 studies enrolled 864,552 males and 926,553 females. The mean age of the participants was reported in 18 studies, which ranged from 48.6 to 78.5 years. Two studies reported the median age of the participants to be 60 and 81 years old. The mean age of patients in case report studies (9.1 %) was 30.6 ± 17.7 years, ranging from 6 to 47 years.

The most prevalent comorbidities were HTN, DM, DLP, stroke, and CVD, respectively (Table 1).

Calcium channel blockers

In 31 studies, a total of 737,685 patients received CCBs. Eight studies did not specifically determine the type of administered CCBs. Among the 25 remaining studies, nifedipine, verapamil, amlodipine, felodipine,

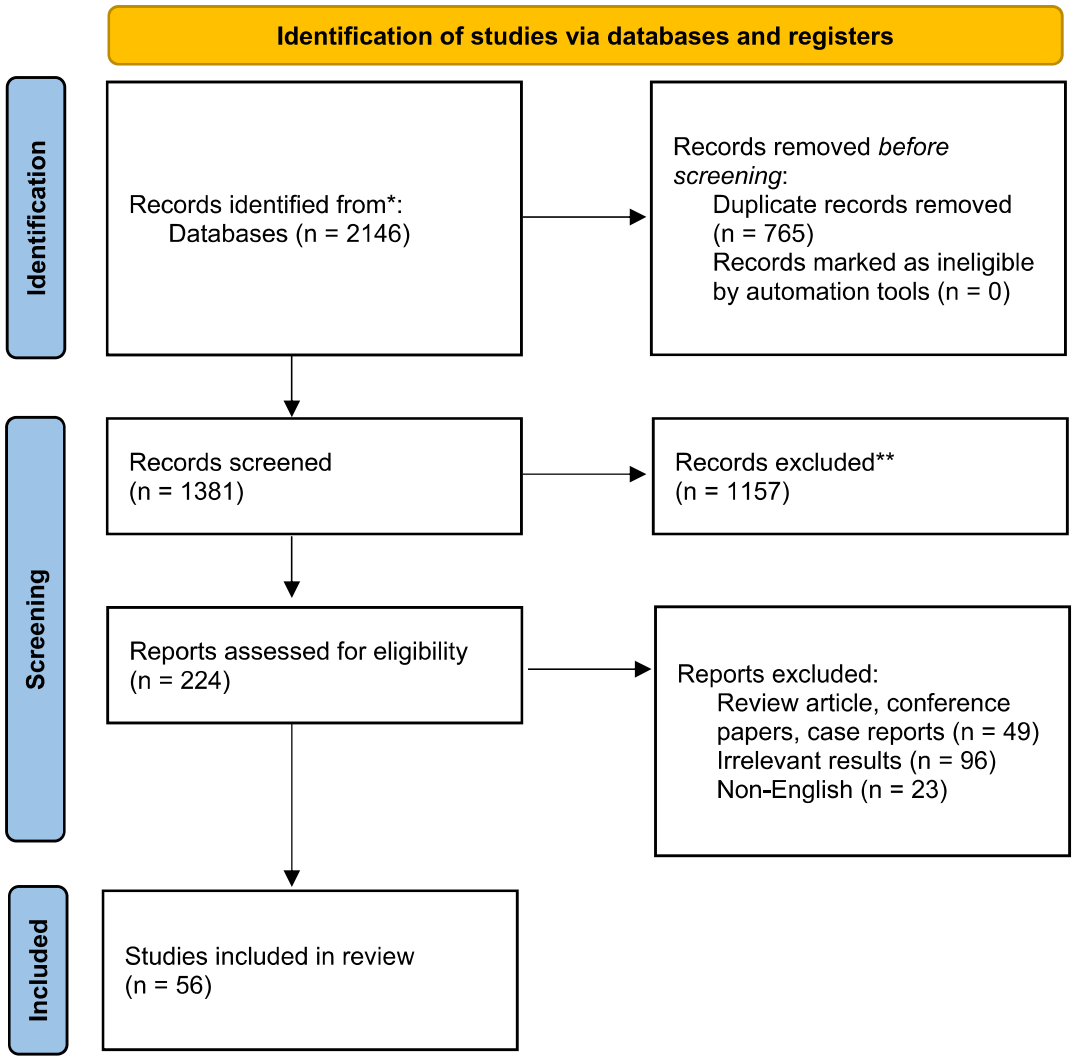

Fig. 1. Screening flow-diagram.

Table 1
Descriptive results of animal studies.

Study	Design	Country	Population		Age (Mean ± SD)		Treatment			Outcomes	Mortality	Limitation	Main results
			Patient group (M/F)	Comparison group (M/F)	Patient group (M/F)	Comparison group (M/F)	Drug	Number	Dose				
Roy et al., 1985 [74]	In vivo	USA	Adult cats with MCA occlusion receiving verapamil or diltiazem (12)	Adult cats with MCA occlusion receiving saline (8)	N/A	N/A	Verapamil Diltiazem	6 6	0.1 μg/kg/min 0.1–1 μg/kg/min	Regional cerebral blood flow Somatosensory evoked potential latency and amplitude Brain edema Non-perfused area of the brain	8	N/A	Verapamil was associated with a deteriorated rCBF in ischemic regions, inappropriate increases in rCBF in non-ischemic areas, lower amplitude and conduction velocity, and a greater non-perfused area and cerebral edema. Diltiazem resulted in a greater rCBF in marginally ischemic regions, better conduction in the ischemic regions, lower cerebral edema, and a considerable increase in the non-perfused area of the brain.
(Sundbøll et al., 2015) In vivo In vitro		USA	Flunarizine -pretreated, ischemic female gerbils (0/8) Verapamil -pretreated, ischemic female gerbils (0/6) Flunarizine -pretreated, sham-operated controls (0/4) Verapamil -pretreated, sham-operated controls (0/4)	Vehicle-pretreated, ischemic female gerbils (0/10) Sham-operated controls (0/16) Untreated controls (0/5)	N/A	N/A	Flunarizine Verapamil	12 10	10 mg/kg 7 mg/kg + 3.5 mg/kg	cAMP basal activity Improvement in neurological symptoms	23	N/A	While pretreatment with flunarizine led to an increased depression in Gpp(NH)p- or Gpp(NH)p plus NE-elicited cAMP, verapamil prevented damage to the enzyme. Both drugs increased basal and decreased forskolin activity of cAMP in vivo. Under in vitro conditions, both drugs had no significant effect on the enzyme preparations.
Phillis et al., 1986 [75]	In vivo	USA	Male Sprague-Dawley rats with anoxia receiving nifedipine or felodipine (20/0)	Male Sprague-Dawley rats with anoxia (N/A)	N/A	N/A	Nifedipine Felodipine	10 10	0.01, 0.05, 0.5, and 1 mg/kg 0.01, 0.05, 0.5, and 1 mg/kg	Cerebral blood flow Time of recovery following anoxia	N/A	N/A	No statistically significant association was found between treatment with felodipine or nifedipine and basal CBF. Both drugs antagonized the anoxia-induced increase in CBF.
Berger et al., 1988 [76]	In vivo	Canada	Male Sprague-Dawley rats with MCA occlusion	Male Sprague-Dawley rats with MCA occlusion	N/A	N/A	Verapamil Nimodipine	5 5	40 μg/kg/min	Local cerebral pH Local cerebral	N/A	N/A	Although verapamil and nimodipine did not significantly change the

(*continued on next page*)

Table 1 (*continued*)

Study	Design	Country	Population		Age (Mean ± SD)		Treatment			Outcomes	Mortality	Limitation	Main results
			Patient group (M/F)	Comparison group (M/F)	Patient group (M/F)	Comparison group (M/F)	Drug	Number	Dose				
			receiving verapamil, nimodipine, or prostacyclin (16/0)	receiving no treatment (6/0)					0.5 μg/kg/min	blood flow Brain infarction area			CBF, the drugs corrected local cerebral pH. Moreover, nimodipine resulted in a decreased cerebral infarct area.
Bevan et al., 1988 [77]	In vivo In vitro	USA	Monkeys with SAH receiving diltiazem (5)	Monkeys with SAH receiving no treatment (N/A)	N/A	N/A	Diltiazem	5	50 mg/kg/day	Passive vessel wall force Wall thickness Vessel circumference MCA lumen diameter Contractility Agonist sensitivity Efferent nerve function Frequency-dependent relaxation Choline Acetyltransferase activity Neuronal Uptake of Tritiated Norepinephrine	N/A	N/A	Diltiazem was found to be protective against damage to vascular smooth muscle and subsequent cerebrovasospasm.
Lin et al., 1990 [78]	In vivo	China	Untreated male Wistar rats with global ischemia receiving vehicle prior to or following ischemic insult and treated male Wistar rats with global ischemia receiving (S)-emopamil prior to or following ischemic insult (50/0)	Non-ischemic male Wistar rats (5/0)	N/A	N/A	(S)-emopamil	25	10 mg/kg	Neuron counts Neuron histological grade	10	N/A	Pretreatment with (S)-emopamil was associated with a protective effect against ischemic injury of hippocampal neurons and an increased histological grade of neocortical neurons. Post-treatment with (S)-emopamil resulted in a higher striatal histological grade.
Hosaka et al., 1991 [79]	In vivo	Canada	Adult male Fischer−344 rats with left MCA occlusion receiving verapamil intravenous route, transvenous perfusion with autologous arterial blood, or transvenous perfusion with saline. (18/0)	Adult male Fischer−344 rats undergoing surgical preparation for MCA occlusion without any treatment (6/0)	N/A	N/A	Verapamil	18	0.1 mg/kg/2 h	Brain infarction size Local CBF	N/A	N/A	Following transverse perfusion with verapamil, a significant reduction in the volume of brain infarct in cortical and subcortical tissue occurred.

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Table 1 (*continued*)

Study	Design	Country	Population		Age (Mean ± SD)		Treatment			Outcomes	Mortality	Limitation	Main results
			Patient group (M/F)	Comparison group (M/F)	Patient group (M/F)	Comparison group (M/F)	Drug	Number	Dose				
Kawamura et al., 1991 [80]	In vivo	Japan	Adult male Sprague-Dawley rats with MCA occlusion receiving nilvadipine (20/0)	Adult male Sprague-Dawley rats with MCA occlusion receiving vehicle (10/0)	N/A	N/A	Nilvadipine	20	1 mg/kg 3.2 mg/kg	Neurologic status Brain infarction volume Left/Right hemispheric volume ratio	N/A	N/A	Following immediate administration of nilvadipine, a significant reduction in cerebral infarct size was found, which was dose-dependent.
Takakura et al., 1991 [81]	Short communication / In vivo	Japan	Hypertensive rats with MCA occlusion receiving nicardipine or nilvadipine (64/0)	Hypertensive rats with MCA occlusion receiving PEG 400 (19/0)	N/A	N/A	Nivaldipine Nicardipine	43 21	0.1, 0.32, 1, 3.2, 10, and 32 mg/kg 3.2, 10, and 32 mg/kg	Brain infarction area	N/A	N/A	Both nilvadipine and nicardipine were associated with a dose-dependent decrease in cerebral infarct area.
Yamamoto et al., 1991 [82]	In vivo	Canada	Adult male Sprague-Dawley rats with MCA occlusion undergoing the bypass of the extracranial femoral artery to the inferior cerebral vein with or without receiving verapamil (12/0)	Adult male Sprague-Dawley rats with MCA occlusion undergoing cannulation of a cerebral vein with no bypass (6/0)	N/A	N/A	Verapamil	12	0.1 mg/kg/mL	Local cerebral blood flow Brain infarction size Brain infarction volume	N/A	The assessed outcomes were short-term.	A significant increase in local CBF and reduction in cerebral infarct volume was found following bypass with retrograde verapamil.
Brooks et al., 1993 [83]	Ex vivo	Finland	Cerebral cortical slices of rat under aglycemic ischemia	-	N/A	-	Nifedipine Diltiazem Verapamil	- - -	25 μM 25 μM 25 μM	Phosphocreatine level Tissue lactate/NAA ratio Tissue glutamate/NAA ratio Phosphocreatine/γ-ATP ratio pH	-	N/A	Post-ischemia treatment with diltiazem resulted in an improvement in metabolic recovery.
Sakaki et al., 1993 [84]	In vivo	Japan	Adult cats of either sex without MCA occlusion receiving TA3090 (26)	Adult cats of either sex with MCA focal cerebral ischemia receiving saline (10)	N/A	N/A	TA3090	26	200 and 400 μg/kg/h	Intracranial pressure Pial arteries diameter Cerebral blood flow Brain edema Brain infarction	N/A	N/A	In normal cerebral areas, TA3090 increases CBF due to the dilation of pial arteries. In ischemic regions, TA3090 antagonizes CBF reduction and pial artery dilation during ischemia and hyperemia during the reperfusion phase. TA3090 results in a reduced brain water content and infarct size.
Li et al., 1994 [85]	In vivo	Japan	Adult Sprague-Dawley rats with MCA received nilvadipine 1–6 h after the onset of	Adult Sprague-Dawley rats with MCA receiving vehicle 1–6 h after the onset of MCA occlusion (35/0)	N/A	N/A	Nilvadipine	65	3.2 mg/kg	Brain infarction volume Brain edema volume	5	N/A	Nilvadipine is associated with a decreased infarct size and cerebral edema when administered

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Table 1 (*continued*)

Study	Design	Country	Population		Age (Mean ± SD)		Treatment			Outcomes	Mortality	Limitation	Main results
			Patient group (M/F)	Comparison group (M/F)	Patient group (M/F)	Comparison group (M/F)	Drug	Number	Dose				
			MCA occlusion. (65/0)										within 3 h and 1 h of stroke, respectively.
Gomi et al., 1995 [86]	In vivo	USA	Adult male cats with occlusion and subsequent reperfusion of MCA undergoing levemopamil infusion (8/0)	Adult male cats with occlusion and subsequent reperfusion of MCA undergoing saline infusion (7/0)	N/A	N/A	Levemopamil	8	4 mg/kg/h + 0.6 mg/kg/h	EEG amplitude ratio Brain infarction area Brain infarction volume Damage severity Severity-weighted infarction volume	N/A	N/A	When administered after stroke, levemopamil has no beneficial effect on ischemia-induced cell damage, recovery improvement, or histological outcomes.
Kawamura et al., 1996 [87]	In vivo	Japan	Male spontaneously hypertensive rats with left MCA occlusion treated with nilvadipine (20/0)	Male spontaneously hypertensive rats with left MCA occlusion treated with vehicle (10/0)	12 weeks	12 weeks	Nilvadipine	20	1 mg/kg/day 3 mg/kg/day	Brain infarction volume	-	N/A	A dose-dependent reduction in cerebral infarct size was found following treatment with nilvadipine.
Kawamura et al., 1998 [88]	In vivo	Japan	Male spontaneously hypertensive rats with left MCA occlusion treated with nilvadipine (23/0)	Male spontaneously hypertensive rats with left MCA occlusion treated with vehicle (22/0)	12 weeks	12 weeks	Nilvadipine	23	3 mg/kg/day	Brain infarction volume Brain edema volume	-	N/A	A time-dependent reduction in cerebral edema and infarct volume was found following nilvadipine administration.
Miyazaki et al., 1999 [89]	In vivo	Japan	Male Sprague-Dawley rats with ischemia receiving CV−159, nicardipine, nifedipine, or W−7 (36/0)	Sham-operated male Sprague-Dawley rats with no ischemia and male Sprague-Dawley rats with ischemia received carboxymethylcellulose (16/0)	N/A	N/A	CV−159 Nicardipine Nifedipine	12 12 6	5 and 10 mg/kg 1 and 10 mg/kg 1 mg/kg	Survived neuron counts Regional cerebral blood flow pre- and post-ischemia Brain infarction size Brain infarction volume Brain edema	N/A	N/A	While neither nifedipine nor nicardipine was associated with significant beneficial effects on outcomes, CV−159 resulted in a decreased hippocampal neuronal death, cerebral edema, and infarct size and volume.
Napoli et al., 1999 [90]	In vivo Ex vivo	USA	Stroke-prone spontaneously hypertensive rats receiving nifedipine, lacidipine, or vitamin E (46/0)	Untreated age-matched male Wistar-Kyoto rats as normotensive controls and stroke-prone spontaneously hypertensive rats without treatment (21/0)	8 weeks	8 weeks	Nifedipine Lacidipine	14 23	80 mg/kg 0.3 and 1 mg/kg	Total plasma lipo peroxide levels Susceptibility to ex vivo peroxidation of LDL Products of lipid oxidation Concentration of peroxidative compounds Oxidation damage of LDL Degree of modification of protein amino group Intimal apolipoprotein B and ox-LDL	11	N/A	Long-term treatment with nifedipine or lacidipine was associated with protective effects against plasma and LDL oxidation and production of oxidation-specific epitopes and significantly reduced mortality.

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Table 1 (*continued*)

Study	Design	Country	Population		Age (Mean ± SD)		Treatment			Outcomes	Mortality	Limitation	Main results
			Patient group (M/F)	Comparison group (M/F)	Patient group (M/F)	Comparison group (M/F)	Drug	Number	Dose				
										epitopes Mortality			
Najarian et al., 2000 [91]	In vitro	USA	Neuronal OMP Decarboxylase and Uridine Kinase enzymes	-	-	-	Nifedipine Nimodipine	- -	N/A N/A	Inhibition of OMP Decarboxylase and Uridine Kinase enzymes	-	N/A	Nifedipine and nimodipine inhibited the activity of OMP Decarboxylase and Uridine Kinase enzymes, which contribute to the repair of neuronal membranes.
Brown et al., 2004 [92]	In vitro	USA	Bovine brain microvessel endothelial cell	-	N/A	-	Nifedipine SKF−96365	- -	100 nM 100 nM	Monolayer permeability Intracellular Ca level Ca influx ROS levels	-	N/A	Although nifedipine of SKF−96365 had no statistically significant effect on ROS levels, they helped in maintaining monolayer permeability in normoxia-normoglycemia and aglycemic conditions.
Yamato et al., 2011 [93]	In vivo	Japan	Male Wistar rats with MCA occlusion receiving or not receiving nifedipine (23/0)	Male Wistar rats with or without MCA occlusion receiving a control diet (16/0)	6 weeks	6 weeks	Nifedipine	11	0.8 mg/kg	Levels of thiobarbituric-reactive substances Levels of mitochondrial glutathione peroxidase Levels of mitochondrial glutathione reductase Levels of mitochondrial superoxide dismutase Levels of cytoplasmic glutathione peroxidase Levels of cytoplasmic glutathione reductase Levels of cytoplasmic superoxide dismutase Levels of mitochondrial complex 1 activity Levels of mitochondrial	N/A	CBF was not assessed. The findings of the study may not be generalizable to other type of CCBs.	Treatment with nifedipine was associated with a significant reduction in lipid peroxidation, cerebral infarct volume, and oxidative stress and an increase in glutathione peroxidase and glutathione reductase.

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Table 1 (*continued*)

Study	Design	Country	Population		Age (Mean ± SD)		Treatment			Outcomes	Mortality	Limitation	Main results
			Patient group (M/F)	Comparison group (M/F)	Patient group (M/F)	Comparison group (M/F)	Drug	Number	Dose				
										complex 2 activity Levels of mitochondrial complex 3 activity Levels of mitochondrial complex 4 activity Brain ischemic volume Brain edema			
Maniskas et al., 2016 [94]	In vivo	USA	Male C57/Bl6 mice with MCA occlusion receiving IA verapamil (35/0)	Naïve male C57/Bl6 mice and male C57/Bl6 mice with MCA occlusion receiving IA saline (35/0)	16 weeks	16 weeks	Verapamil	35	0.15 mg/kg	Cerebral blood flow Brain infarction volume Brain cellular health Astrocytic inflammation/ infiltration Neuronal survival Forced motor movement Behavioral testing Free roam motor movement Open field performance	N/A	A long-term follow-up evaluation was not performed.	Treatment with verapamil was associated with better functional outcomes, reduced cerebral infarct size, lower activation of astrogliosis, and higher survival rate in mature neuronal cells.
(Fraser et al., 2017)	In vivo In vitro Clinical trial	USA	Male C57/Bl6 mice with common carotid and middle cerebral artery occlusion undergoing recanalization (40/0) Primary cortical neuronal cultures from embryonic day−18 C57/Bl6 mice Individuals with a large vessel occlusive stroke candidate for thrombectomy (6/5)	-	16 weeks 18 days	-	Verapamil	51	1–200 mg/kg 250, 300, 500 ng/mL 10 mg	Cell viability Branch length of primary and secondary dendrites Brain infarct volume Brain NeuN preservation Seizure= 1 Self-limited desaturation= 1 ICH= 0	0	The effects of verapamil were assessed only in young male mice without any underlying comorbidities. In the in vitro study, only the direct effects of verapamil on neurons were evaluated.	Intra-arterial injection of verapamil following thrombectomy was safe and associated with neuroprotective effects.
Maniskas et al., 2022 [95]	In vivo	USA	C57Bl/6 J male mice with MCA occlusion receiving IA verapamil/ lubeluzole (7/0)	C57Bl/6 J male mice with MCA occlusion receiving IA saline (7/0)	16 weeks	16 weeks	Verapamil	7	0.15 mg/kg	Rotor rode testing Open field testing Brain infarction volume Astrocytic inflammation/	0	The study sample size was small, and only male animals were enrolled. The dose-	Verapamil, in combination with lubeluzole, was associated with improved functional recovery, reduced

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Table 1 (*continued*)

Study	Design	Country	Population		Age (Mean ± SD)		Treatment			Outcomes	Mortality	Limitation	Main results
			Patient group (M/F)	Comparison group (M/F)	Patient group (M/F)	Comparison group (M/F)	Drug	Number	Dose				
										infiltration Neuronal survival		response effects of the drug were not evaluated.	cerebral infarct volume, improved survival rate of mature neuronal cells, and lower astrogliosis.

Abbreviations: ATP, adenosine triphosphate; Ca, calcium; cAMP, cyclic adenosine monophosphate; CBF, cerebral blood flow; CCB, calcium channel blocker; DHP, dihydrouridine; EEG, electroencephalogram; F, female; Gpp(NH)p, 5′-Guanylyl imidodiphosphate; IA, intra-arterial; ICH, intracerebral hemorrhage; LDL, low density lipoprotein; M, male; MCA, middle cerebral artery; Mn, manganese; N/A, not available; NAA, N-acetyl aspartate; NE, Norepinephrine; NeuN, neuronal nuclear antigen; OMP, uridine-5′-monophosphate; ox-LDL, oxidized low density lipoprotein; PEG, polyethylene glycol; pH, potential of hydrogen; rCBF, Regional cerebral blood flow; ROS, reactive oxygen species; SAH, subarachnoid hemorrhage; SD, standard deviation; USA, United States of America;

diltiazem, nimodipine, and nicardipine were used in ten, nine, five, four, three, three, and two studies, respectively. Among 47,082 patients in 23 studies, 24,064 and 23,018 received dihydropyridine and non-dihydropyridine CCBs, respectively. Verapamil was the most commonly administered CCB, followed by amlodipine, and nifedipine, respectively (Table 1).

Outcomes

Stroke. A total of 387,867 stroke events occurred among 22 studies. Five studies revealed a beneficial effect of CCBs in the prevention of stroke. Kalar et al. showed that in patients suffering from Alzheimer's Dementia, amlodipine was associated with a decreased risk of ischemic stroke (Kalar et al., 2021). In the study carried out by Cheng et al., although no differences in outcomes were found between the lercanidipine group and the group that used other CCBs, in head-to-head comparisons, lercanidipine resulted in a reduced risk of stroke compared to nifedipine in hypertensive patients (Cheng et al., 2017). In a case report, Knierim et al. found that in a patient who suffered from familial hemiplegic migraine type 1, treatment with verapamil prevented new stroke (Knierim et al., 2011). A study conducted by Arioka et al. revealed that in patients with HTN, benidipine decreased the risk of stroke with sequela to a greater extent when compared to nifedipine (Arioka et al., 2008). In the Gong et al. study, nifedipine resulted in a lower risk of stroke in elderly patients who suffered from HTN (Gong et al., 1996).

In eight studies, no statistically significant association was found between treatment with CCBs and risk of stroke development. In the study carried out by Jamerson et al., in comparison to combination therapy with benazepril and hydrochlorothiazide, treatment with the combination of benazepril and amlodipine was not significantly associated with the risk of stroke (Jamerson et al., 2008). Similarly, Nissen et al. revealed that the risk of stroke in normotensive patients was not significantly affected by amlodipine treatment (Nissen et al., 2004). Zanchetti et al. showed that in comparison to atenolol, lacidipine was not significantly associated with the risk of stroke (Zanchetti et al., 2002). In the RCT performed by Dens et al., no association was found between long-acting nisoldipine and stroke risk (Dens et al., 2003). Wassertheil-smoller et al. found no statistically significant association between CCB administration and the risk of stroke in postmenopausal women (Wassertheil-Smoller et al., 2004). Also, Dowlatshahi et al. demonstrated that CCB administration was not significantly associated with the risk of stroke (Dowlatshahi et al., 2006). An RCT study performed by Coca et al. found no statistically significant association between verapamil and the risk of stroke (Coca et al., 2008). Similarly, in another RCT study conducted by Pepine et al., verapamil had no statistically significant effect on the risk of stroke (Pepine et al., 2003). Yui et al. demonstrated that in comparison to ACEI agents, treatment with nifedipine had no significant impact on the risk of stroke in hypertensive patients with concurrent coronary artery disease (Yui et al., 2004).

In seven studies, it was demonstrated that CCBs resulted in an increased risk of stroke in individuals. In two case reports, verapamil overdose following suicide intention led to the development of severe stroke (Shah and Passalacqua, 1992; Samniah and Schlaeffer, 1988). Hsu et al. demonstrated that in patients hospitalized with stroke, either short-term or long-term administration of nifedipine increased the risk of ischemic stroke (Hsu et al., 2019). In another study, Jung et al. also revealed that hypertensive patients for whom treatment with short-acting nifedipine was started within the recent seven days of stroke onset had a higher risk of developing stroke (Jung et al., 2011). A study carried out by Harrison et al. showed that when compared to RAS agents, CCBs were associated with an increased risk of stroke development (Harrison et al., 2021). The study carried out by Wang et al. found that co-prescription of CYP3A4-metabolized statins and those CCBs which inhibit CYP3A4 was associated with a greater risk of ischemic stroke in affected patients (Wang et al., 2016). In the study carried out

by Klungel et al., it was found that CCB monotherapy was associated with a greater risk of ischemic stroke development in hypertensive patients (Klungel et al., 2001).

Regarding treatment with verapamil, although two RCT studies revealed no beneficial effect, their results were affected by some limitations (Coca et al., 2008; Pepine et al., 2003). First, the impact of confounding variables was not fully adjusted. Second, the types of strokes were not differentiated. Moreover, the studies had less than three years of follow-up and administered verapamil in doses up to 240 mg/d. However, it seems that verapamil may exert beneficial effects on stroke prevention in patients suffering from certain diseases, which might pose them with an increased risk of stroke (Knierim et al., 2011). Importantly, although verapamil could be associated with favorable outcomes regarding the reduction of stroke risk, high doses may result in serious adverse outcomes such as irreversible stroke (Shah and Passalacqua, 1992; Samniah and Schlaeffer, 1988). Regarding amlodipine administration, although it may be associated with a reduced risk of stroke development in hypertensive patients who also suffer from dementia (Kalar et al., 2021), it may not have beneficial effects on stroke prevention in normotensive patients (Nissen et al., 2004). Moreover, amlodipine might not be as effective as some other anti-hypertensive agents, such as diuretics, in stroke prevention (Jamerson et al., 2008). Thus, it seems that, although not effective in normotensive patients, amlodipine can reduce the risk of stroke in patients suffering from HTN and can be administered when no other anti-hypertensive drugs with higher efficacy are available. Regarding nifedipine treatment, although it may be associated with beneficial outcomes in stroke prevention in elderly hypertensive patients (Gong et al., 1996), it may not be effective when compared to some other anti-hypertensive agents and when administered in patients with HTN complicated with other CVDs (Yui et al., 2004). Case cross-over studies reported an increased risk of stroke following treatment with nifedipine in hypertensive patients and those hospitalized due to stroke (Hsu et al., 2019; Jung et al., 2011). However, these studies were not without limitations. Altogether, it seems that nifedipine can lower the risk of stroke in hypertensive patients of higher ages who do not suffer from underlying cardiovascular disorders. However, it should not be administered in patients with a prior history of stroke since it might deteriorate clinical outcomes. Moreover, some other types of CCBs, such as lercanidipine and benidipine, may have higher efficacy in reducing the risk of stroke in hypertensive patients than nifedipine and be a more appropriate choice in these affected patients (Cheng et al., 2017; Arioka et al., 2008) (Table 1).

Differences in study design, sample size, inclusion and exclusion criteria, administered CCB, drug dosage and treatment and follow-up duration might be responsible for the differences in study outcomes. Although CCB administration in hypertensive patients may result in a reduction in stroke risk, it may be associated with no or deleterious outcomes in hypertensive patients who suffer from other severe cardiovascular disorders. Furthermore, despite being protective in stroke prevention, CCBs might not be as effective as some other antihypertensive drugs, such as RAS agents. Thus, when it is aimed to reduce the risk of stroke in patients suffering from HTN, it is better to administer other types of anti-hypertensive drugs that have greater efficacy than CCBs, if possible. Moreover, in some hypertensive cases, combination therapy with CCBs and different anti-hypertensive agents may lead to greater efficacy, better management, and improved outcomes compared to CCB monotherapy. One important note in the management of hypertensive patients is to consider drug-drug interactions, which might negatively affect drug efficacy and clinical outcomes. Overall, it seems that CCBs can be helpful in reducing the risk of stroke development. However, drug efficacy may vary according to the type of CCB, either alone or combined treatment and underlying medical conditions.

Other neurological outcomes. In eight studies, CCB administration was associated with an improvement in neurological outcomes. In the study carried out by Heeley et al., early initiation of treatment with CCBs had significant positive effects on 12-month dependency (Heeley et al., 2014). Dowlatshahi et al. demonstrated that patients with non-hemorrhagic stroke who already used CCBs prior to their stroke or were discharged at CCBs after a stroke experienced functional recovery within the first six months (Dowlatshahi et al., 2006). In the study conducted by Low et al., co-administration of CCBs and heparin resulted in the complete elimination of neurological deficits in patients who suffered from embolic stroke (Low et al., 1986). Fraser et al. revealed that injection of intra-arterial verapamil following thrombectomy of patients with thrombotic stroke was associated with neuroprotective effects (Fraser et al., 2017). In the study carried out by Shah et al., administration of intra-arterial nicardipine resulted in neurological improvement in the majority of patients with ischemic stroke (Shah et al., 2007). In the study by Harrison et al., compared to beta-blockers, a reduced risk of developing movement disorders was found following CCB administration (Harrison et al., 2021). Regarding nimodipine administration, Hakim et al. showed that an increase in CBF and improved cerebral oxygen metabolic rate occurred in stroke patients (Hakim et al., 1989). In contrast, Infeld et al. reported that although initiation of treatment with nimodipine within 12 h of stroke was associated with an improvement in cerebral reperfusion, it had no beneficial effect on clinical outcomes (Infeld et al., 1999). One study conducted by Tziomalos et al. showed that treatment with CCBs either alone or in combination with other anti-hypertensive drugs did not significantly affect mRS score (Tziomalos et al., 2017).

In three studies, CCB administration was associated with deleterious effects on neurological outcomes. Fischberg et al. found that rapid blood pressure reduction using antihypertensive agents, including nifedipine and felodipine, resulted in the deterioration of neurological deficits and recommended that BP reduction should be performed slowly and cautiously (Fischberg et al., 2000). In the study performed by Harrison et al., CCBs were associated with a higher risk of dementia when compared to RAS agents (Harrison et al., 2021). A study performed by Ahmed et al. revealed that administration of high-dose nimodipine resulted in diastolic BP reduction, which further tend to neurological and functional status deterioration (Ahmed et al., 2000) (Table 1).

Overall, it seems that CCB administration is safe and tolerable and can exert beneficial effects on individuals' neurological status. However, it is important to note that rapid and prompt BP reduction using CCBs should be avoided to prevent adverse outcomes. It is important to note that the effects of CCBs might vary according to drug dosage and time of treatment initiation. In addition, it is noteworthy that although some CCBs might have positive effects on cerebral perfusion and metabolic parameters, their effect might not necessarily lead to improvement in patient clinical outcomes. Altogether, it seems that CCBs are safe and effective in improving patients' neurological outcomes if administered with caution.

Cardiovascular outcomes. A total of 64,339 cardiovascular adverse events occurred among the studies. In eight studies, CCBs were associated with significant improvement in cardiovascular outcomes. Two studies reported beneficial effects of amlodipine on cardiovascular outcomes. Jamerson et al. showed that combination therapy with amlodipine and benazepril, an ACE inhibitor, led to appropriate BP management and desirable cardiovascular outcomes (Jamerson et al., 2008). In another study by Nissen et al., it was found that treatment with amlodipine resulted in a reduced rate of cardiovascular adverse events (Nissen et al., 2004). Yui et al. showed that nifedipine treatment lowered the incidence of adverse cardiovascular outcomes (Yui et al., 2004). Similarly, Gong et al. showed that nifedipine reduced the risk of cardiovascular outcomes (Gong et al., 1996). In the study conducted by Dens et al., nisoldipine reduced the risk for coronary revascularization procedures (Dens et al., 2003). Pepine et al. demonstrated that anti-hypertensive drug regimens containing verapamil were as effective

Table 2
Descriptive demographics of human studies.

Study	Design	Country	Follow/up duration	Population		Age (Mean ± SD)		Treatment			Outcomes			Underlying comorbidities	Limitation	Main results
				Patient group (M/F)	Comparison group (M/F)	Patient group (M/F)	Comparison group (M/F)	Drug	Number	Dose	Stroke (N)	Mortality (N)	Other outcomes			
(Kalar et al., 2021)	Cohort	Sweden	N/A	Patients with dementia with at least one prescription of CCBs in the last three years before diagnosis of dementia (3737/5266)	Patients with dementia without any prescription of CCBs in the last three years before diagnosis of dementia (4040/5863)	81 (median)	81 (median)	Amlodipine Felodipine Verapamil Diltiazem Nifedipine	3878 3758 217 209 91	N/A	749	8182	N/A	Cardiac arrhythmia= 6130 Angina pectoris= 4474 DM= 4436 Stroke= 4418 CVD= 3463 HF= 3441 Respiratory disease= 2199 HTN= 1115 Renal disease= 1020 Alcohol-related diseases= 648	Results were confounded by indication and prevalent user design.	Patients with Alzheimer's Dementia who used amlodipine had a lower risk of ischemic stroke development compared to those who used other CCBs.
(Harrison et al., 2021)	Cohort	UK	2 years	Patients receiving their first prescription of CCBs, BBs, or RAS agents (586,546/708,002)	-	63.5 ± 11.1 in patients receiving diuretics 64 ± 11.4 in patients receiving RAS 63.1 ± 11.0 in patients receiving BBs 63.3 ± 10.9, 63.9 ± 11.4, and 62.9 ± 10.8 in patients receiving CCBs in diuretic, RAS, and BB cohorts, respectively	-	CCBs (any type)	647,274	N/A	15,367	N/A	Cardiovascular events= 53,797 (including Cerebral hemorrhage=3891) Movement disorders= 24,001 (including Parkinson's disease=4378) Dementia= 14,550 (including Alzheimer's disease=4766 Vascular dementia=1968 Other dementias=10,453 Mild cognitive impairment=5683)	HTN= 1294,548 DM= 183,029	Confounding factors were not fully adjusted. Data regarding concurrent medication use, dosage, and compliance were not gathered.	In comparison to RAS agents, CCBs were associated with a greater risk of dementia and CVD development. In comparison to BBs, CCBs were associated with a lower risk of CVD and movement disorders.
(Hsu et al., 2019)	Case cross-over	Taiwan	N/A	Patients hospitalized with ischemic stroke or ICH (212,044/138,538)	A case was used as its own control in a different time period (212,044/138,538)	N/A	N/A	Nifedipine	N/A	N/A	350582	N/A	N/A	HTN= 183,694 DM= 93,221 DLP= 55,130 CVD= 49,203 HF= 19,021 Liver disease= 17,859 Cancer= 13,280 Renal disease= 13,029 Cardiac arrhythmia= 10,388 Stroke= 440	The assessment of the dose-related effects of the drug and the patient's compliance was not performed.	A greater risk of ischemic stroke was found among patients who used either short-term or long-term nifedipine.
(Nezu et al., 2018)	Observational surveillance	Japan	1 year	Hypertensive patients with a history of stroke with maximum IMT ≥ 1.1 mm (191/110)	Hypertensive patients with a history of stroke with maximum IMT < 1.1 mm (187/115)	70.7 ± 9.2	68 ± 11.4	Cilnidipine	603	10.2 ± 3.1 mg/day	N/A	N/A	Carotid IMT	HTN= 603 Stroke= 475 DLP= 295 DM= 120 CVD= 38	A great number of participants did not have a follow-up carotid ultrasonography. Significant differences in several factors between study groups led to some degree of selection bias.	Cilnidipine resulted in a significant IAD reduction in all post-stroke patients with HTN. Moreover, cilnidipine was associated with the regression of carotid IMT in post-stroke hypertensive patients in the thick-intima group,

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Table 2 (*continued*)

Study	Design	Country	Follow/up duration	Population		Age (Mean ± SD)		Treatment			Outcomes			Underlying comorbidities	Limitation	Main results
				Patient group (M/F)	Comparison group (M/F)	Patient group (M/F)	Comparison group (M/F)	Drug	Number	Dose	Stroke (N)	Mortality (N)	Other outcomes			
																either alone or in combination with ARBs.
(Fraser et al., 2017)	In vivo In vitro Clinical trial	USA	18 days	Individuals with a large vessel occlusive stroke candidate for thrombectomy (6/5)	-	-	-	Verapamil	11	10 mg	N/A	0	Seizure= 1 Self-limited desaturation= 1 ICH= 0	Stroke= 11	The study did not have a control group. The drug efficacy was not evaluated.	Administration of intra-arterial verapamil following thrombectomy is safe and tolerable and can exert neuroprotective effects.
(Cheng et al., 2017)	Cohort	Taiwan	6.11 ± 0.01 years for patient group 5.45 ± 0.02 years for the control group	Hypertensive patients receiving Lercanidipine (802/482)	Hypertensive patients receiving other CCB drugs (nifedipine, amlodipine and felodipine) (3208/1928)	48.61 ± 9.68	48.61 ± 10.10	Lercanidipine Nifedipine/ Amlodipine/ Felodipine	1284 5136	N/A	212	118	DM= 668 PUD= 130 CKD= 117 Peripheral artery disease= 86 CHF= 42 MI= 28	HTN= 6420	Data regarding personal characteristics and BP details were not available. Disease classification could occur due to the implementation of claims data on the ICD codes.	No significant difference in outcomes was found between the study groups. For head-to-head comparisons, lercanidipine showed greater effects in stroke prevention when compared to nifedipine.
(Tziomalos et al., 2017)	Cohort	Greece	N/A	Hospitalized patients with acute ischemic stroke (114/199)	-	78.5 ± 6.3	-	CCBs (any type)	50	N/A	-	77	Adverse outcomes= 180	HTN= 262 Cardiac arrhythmia= 109 Renal disease= 108 DM= 104 CVD= 88 HF= 75	N/A	CCBs did not affect long-term outcomes.
(Wang et al., 2016)	Cohort	Taiwan	90 days	Patients who received CYP3A4-metabolized statins with CCBs that inhibit CYP3A4 (3063/2794)	Patients who received non-CYP3A4-metabolized statins with CCBs that inhibit CYP3A4 (3063/2794)	62.72 ± 12.64	62.72 ± 12.64	Amlodipine Diltiazem Felodipine Nicardipine Nifedipine Verapamil Total	N/A N/A N/A N/A N/A N/A 11714	N/A	339	97	Cardiovascular events = 199 AKI= 85 Hyperkalemia= 33 Acute liver failure= 4	HTN= 11,714 DLP= 11,714 CVD= 7591 DM= 4777 Renal disease= 2301 HF= 1289 Cancer= 839 PVD= 86	Laboratory data, including blood levels of statins and CCBs, were not evaluated.	The co-prescription of CYP3A4-metabolized statins and CCBs inhibiting CYP3A4 resulted in a greater risk of developing acute ischemic stroke.
(Sundbøll et al., 2015)	Cohort	Denmark	N/A	Patients with a first-time stroke who were a CCB or BB non-user, former user, or current user (100,043)	-	N/A	-	CCBs (any type)	18,144	N/A	-	N/A	N/A	Stroke= 100,043	Some degrees of coding errors and disease misclassification have occurred. The effect of residual confounding factors could not be ruled out.	CCB administration before admission did not significantly affect patient mortality.
(Heeley et al., 2014)	Cohort	China	1 year	Patients receiving antihypertensive drugs, including CCBs, ACEI/ARBs, BBs, or diuretics (2007/2339)	-	63.5 ± 11.8 in patients using CCBs, 63.3 ± 11.6 in patients using ACEI/ ARB, 63.4 ± 12.4 in patients using BBs, 64.8 ± 12.8 in patients using diuretics	-	CCBs (any type)	2956	N/A	-	920	Dependency= 1356 Recurrent vascular event= 603	HTN= 5521 DLP= 2592 Stroke= 1788 CVD= 1570 DM= 1440 Cardiac arrhythmia= 563	Data regarding BP and concurrent medication use were not gathered. Enrolling only stroke patients who were hospitalized may affect the generalizability of the results.	In patients for whom treatment with CCBs was initiated early after stroke, an improvement in long-term outcomes was found. CCBs, in combination with ACEI/ARB agents, had a beneficial effect on death and a trend toward

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Table 2 (*continued*)

Study	Design	Country	Follow/up duration	Population		Age (Mean ± SD)		Treatment			Outcomes			Underlying comorbidities	Limitation	Main results
				Patient group (M/F)	Comparison group (M/F)	Patient group (M/F)	Comparison group (M/F)	Drug	Number	Dose	Stroke (N)	Mortality (N)	Other outcomes			
																positive effects on death/dependency. Administration of CCBs that have direct cardiac effects had favorable effects on stroke-related mortality.
(Papp et al., 2012)	Cohort	Hungary	N/A	Death cases related to stroke	-	N/A	-	-	-	-	N/A	N/A	N/A	N/A	N/A	
(Jung et al., 2011)	Case cross-over	South Korea	67 days	Hypertensive patients with at least one prescription of CCBs (7496/8573)	A case was used as its own control in a different time period (7496/8573)	68.3 ± 2.1	68.3 ± 2.1	Nifedipine	4138	N/A	16,069	N/A	N/A	HTN= 16,096 DM= 9794 DLP= 7242 CVD= 6362 Liver disease= 1441 Cancer= 1399 HF= 1164 Cardiac arrhythmia= 887 Renal disease= 513	Disease misclassification, patient adherence to the prescribed drug, and some degrees of protopathic bias have occurred. Results were not adjusted for all of the confounding variables.	An increased risk of stroke was found among patients for whom treatment with short-acting nifedipine was initiated within the most recent seven days.
(Knierim et al., 2011)	Case report	Germany	N/A	A patient with familial hemiplegic migraine type 1 with repeated cerebral infarction (0/1)	-	6	-	Verapamil	1	0.1 and 3 mg/kg	1	0	N/A	Familial hemiplegic migraine type 1 = 1	N/A	In the patient who suffered from familial hemiplegic migraine type 1, treatment with verapamil resulted in the prevention of a new stroke.
(Arioka et al., 2008)	Cohort	Japan	4.4 years	Hypertensive patients treated with CCBs (138/88)	-	N/A	-	Benidipine Nifedipine Diltiazem	155 35 36	7.6 mg/d 40 mg/d 175 mg/d	N/A	N/A	N/A	HTN= 108 Cardiac arrhythmia= 57 DLP= 56 DM= 47 VHD= 43 Stroke= 26 CVD= 19	The study sample was small and homogeneous.	In comparison with nifedipine, benidipine was associated with a greater reduction of stroke with sequela.
(Coca et al., 2008)	RCT	USA	2.7 years	Patients developing stroke during the study (173/204)	Patients without stroke during the study (10,634/11,565)	71.2 ± 10.2	66.0 ± 9.7	Verapamil	11,267	180 mg/d 240 mg/d	377	104	N/A	Angina pectoris= 15,046 CVD= 13,390 DLP= 12,601 DM= 6397 LVH= 4949 PVD= 2709 Unstable angina= 2579 Stroke= 1630 Cardiac arrhythmia= 1602 HF= 1257 Renal disease= 415	Ischemic and intracerebral stroke were not differentiated.	Verapamil did not significantly affect the risk of stroke.
(Jamerson et al., 2008)	RCT	USA	35.7 months	Patients with HTN receiving Benazepril plus Amlodipine (3448//2296)	Patients with HTN receiving Benazepril plus hydrochlorothiazide (3515/2246)	68.4 ± 6.86	68.3 ± 6.86	Amlodipine	5744	7.7 mg	245	Any cause-related death= 498 Death from cardiovascular causes= 241 Composite of death from cardiovascular causes and cardiovascular events= 1231 Composite of	Primary endpoint plus hospitalization for congestive heart failure= 1355 Composite of cardiovascular events= 1086 Coronary revascularization procedure= 720 MI= 284 Hospitalization for congestive heart	HTN= 11,506 DLP= 8540 DM= 6046 IHD= 4117 MI= 2709 LVH= 1521 Stroke= 1498 Angina pectoris= 1324 Arrhythmia= 779 Renal disease= 705	NA	Amlodipine, in combination with benazepril, led to desirable BP control and had a beneficial effect on cardiovascular outcomes.

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Table 2 (*continued*)

Study	Design	Country	Follow/up duration	Population		Age (Mean ± SD)		Treatment			Outcomes			Underlying comorbidities	Limitation	Main results
				Patient group (M/F)	Comparison group (M/F)	Patient group (M/F)	Comparison group (M/F)	Drug	Number	Dose	Stroke (N)	Mortality (N)	Other outcomes			
												death from cardiovascular events, nonfatal myocardial infarction, and nonfatal stroke= 652	failure= 196 Hospitalization for unstable angina= 103 Resuscitation after sudden cardiac arrest= 22			
(Shah et al., 2007)	Cohort	USA	N/A	Patients with acute ischemic stroke receiving intra-arterial Nicardipine (3/7)	-	60 (median)	-	Nicardipine	10	2.85 mg	-	N/A	Neurological improvement= 4 mRS score improvement= 3	N/A	N/A	In patients with acute ischemic stroke, administration of intra-arterial nicardipine in doses up to 5 mg was well tolerated and was not associated with adverse hemodynamic events.
(Dowlatshahi et al., 2006)	Cohort	Canada	6 months	Hypertensive patients under CCB treatment or receiving no CCBs (864/681)	-	69.9	-	CCBs (any type)	420	N/A	370	65	N/A	HTN= 1016 DLP= 552 Transient ischemic attack= 313 CVD= 259 Cardiac arrhythmia= 234 DM= 182 HF= 94 VHD= 55	Since the mortality rate was lower in patients who consented to the registry, the study sample was not representative of a general stroke population. Data regarding drug compliance and BP details in 6 months post-discharge were not gathered. The effect of confounding variables was not fully adjusted.	Improvement in the 6-month mortality rate and functional recovery was found in non-hemorrhagic stroke patients discharged on CCBs and in patients who were already using CCBs prior to their stroke, respectively.
(Nissen et al., 2004)	RCT	USA	N/A	Normotensive patients requiring coronary angiography receiving amlodipine (506/157)	Normotensive patients requiring coronary angiography receiving placebo (478/177) or enalapril (484/189)	57.3 ± 9.7	57.2 ± 9.5 in placebo group and 58.5 ± 9.9 in enalapril group	Amlodipine	663	5–10 mg/d	26	All-cause mortality= 21 Cardiovascular death= 12	Cardiovascular events= 397 Coronary revascularization= 276 Hospitalization for angina= 221 Nonfatal MI= 44 New-onset PVD= 15 Hospitalization for CHF= 12 Resuscitated cardiac arrest= 5	Vessel disease= 1961 HTN= 1204 MI= 766 IHD= 718 DM= 363 Angina pectoris= 175 Stroke= 81	The study had a modest sample size. Confidence intervals were wide. An extended composite endpoint was implemented.	A reduced rate of adverse cardiovascular events was found following treatment with amlodipine.
(Wassertheil-Smoller et al., 2004)	Cohort	USA	5.9 years	Postmenopausal women with hypertension and without a history of CVD receiving antihypertensive drugs (0/15,787)	-	N/A	-	CCBs (any type)	4376	N/A	325	223	Cardiovascular events= 837	HTN= 15,787 DLP= 3180 DM= 1066	Results were confounded by indication. The study was not population-based. Since only post-menopausal women were enrolled, the results could not be generalized to other populations.	In comparison to diuretics alone, CCB alone was associated with higher rates of CVD morbidity and mortality. In comparison to combination therapy of diuretics and beta-blockers, diuretics combined with CCBs were associated with a

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Table 2 (*continued*)

Study	Design	Country	Follow/up duration	Population		Age (Mean ± SD)		Treatment			Outcomes			Underlying comorbidities	Limitation	Main results
				Patient group (M/F)	Comparison group (M/F)	Patient group (M/F)	Comparison group (M/F)	Drug	Number	Dose	Stroke (N)	Mortality (N)	Other outcomes			
																greater risk of CVD mortality.
(Yui et al., 2004)	RCT	Japan	35.7 months	Hypertensive patients with coronary artery disease receiving nifedipine (560/268)	Hypertensive patients with coronary artery disease receiving ACEI (575/247)	65 ± 8	64 ± 9	Nifedipine	828	10–20 mg BD	32	Total mortality= 27 Non-cardiac death= 15 Sudden death/cardiac death= 12	Cardiovascular events= 222 Coronary intervention= 156 Angina pectoris requiring hospitalization= 106 MI= 29 HF requiring hospitalization= 21 Serious arrhythmia= 8 Worsening of renal dysfunction= 8	HTN= 1650 IHD= 1498 Angina pectoris= 1073 MI= 696 DLP= 385 DM= 372 Asymptomatic myocardial ischemia= 199 Others= 314	N/A	Nifedipine resulted in a lower incidence of cardiovascular adverse events and mortality.
(Dens et al., 2003)	RCT	Belgium	N/A	Patients with PTCA receiving nisoldipine (562/130)	Patients with PTCA receiving placebo (564/145)	60.4 ± 8.76 in the intention to treat group and 59.3 ± 8.78 in per protocol group	60.2 ± 8.83 in the intention to treat group and 59.8 ± 8.65 in per protocol group	Nisoldipine	692	N/A	11	26	Total events= 398 PTCA= 131 CABG= 62 Repeat PTCA and PTCA for a lesion that was not dilated at baseline= 61 Repeat PTCA and CABG= 30 MI= 29	DLP= 401 MI= 348 HTN= 332 DM= 85	N/A	Long-acting nisoldipine resulted in a reduced risk of coronary revascularization interventions.
(Pepine et al., 2003)	RCT	USA	2.7 years	CAD patients aged at least 50 with hypertension receiving CCBs (5417/5850)	CAD patients aged at least 50 with hypertension receiving beta-blockers (5389/5920)	66 ± 9.7	66.1 ± 9.8	Verapamil	11,267	240 mg/d	279	1766	Cardiovascular-related hospitalization= 1435 Cardiovascular-related death= 862 CABG/PCI= 555 Angina= 489 Cancer= 378 Nonfatal MI= 304	HTN= 22,756 Angina pectoris= 15,045 IHD= 13,120 DLP= 12,593 MI= 7218 DM= 6400 LVH= 4948 PVD= 2699 Arrhythmia= 1600 HF= 1256 Stroke= 1162 Cancer= 760 Renal disease= 424	Angina frequency was significantly different between the two study groups due to the large study sample size.	The treatment regimen containing verapamil was as effective as the treatment regimen containing atenolol.
(Zanchetti et al., 2002)	RCT	Italy	4 years	Patients with HTN receiving lacidipine (641/516)	Patients with HTN receiving atenolol (1279/1055)	56.1 ± 7.5	55.9 ± 7.5	Lacidipine	1157	4 mg/d	23	N/A	All serious adverse events= 387 MI= 35 IMT change Plaque progression	HTN= 2334	N/A	Compared to atenolol, lacidipine was associated with a greater beneficial effect on IMT progression and plaque numbers.
(Klungel et al., 2001)	Case-control	USA	N/A	Patients receiving antihypertensive drugs who develop ischemic stroke (176/204)	Patients receiving antihypertensive drugs without ischemic stroke (1861/929)	70.3	65.6	CCBs (any type)	533	N/A	2791	N/A	N/A	CVD= 2100 DM= 426 Transient ischemic attack= 229	Some degrees of bias were found due to non-random assignment of drug treatments. Adjustment for all of the confounding factors was not performed.	In those hypertensive patients who did not have CVD, treatment with antihypertensive regimens which did not contain a thiazide resulted in a greater risk of ischemic stroke. This relationship was less pronounced among those patients with CVD.
(Ahmed et al., 2000)	RCT	Sweden	N/A	Patients with recent ischemic	Patients with recent ischemic stroke	N/A	N/A	Nimodipine	173	0.957 mg/h in low-dose group	N/A	50	Death or dependency	Stroke= 265	N/A	Diastolic BP reduction following post-stroke

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Table 2 (*continued*)

Study	Design	Country	Follow/up duration	Population		Age (Mean ± SD)		Treatment			Outcomes			Underlying comorbidities	Limitation	Main results
				Patient group (M/F)	Comparison group (M/F)	Patient group (M/F)	Comparison group (M/F)	Drug	Number	Dose	Stroke (N)	Mortality (N)	Other outcomes			
				stroke receiving nimodipine (173)	receiving placebo (92)					and 1.82 mg/h in high-dose group						administration of high-dose nimodipine deteriorated neurological and functional status in patients with acute stroke.
(Fischberg et al., 2000)	Clinical communication	USA	N/A	Patients who had initiation or worsening of neurologic deficits after moderate BP reduction caused by the administration of antihypertensive medication (3/3)	-	53.5 ± 11.45	-	Nifedipine Felodipine	4 1	20 mg 10 mg 10 mg	5	N/A	Bilateral retinal ischemia= 1	HTN= 5 DM= 3 Stroke= 1 DLP= 1	N/A	Reducing the BP using CCBs should be performed cautiously and gradually to prevent exacerbation of ischemic neurologic deficits.
(Infeld et al., 1999)	RCT	Australia	3 months	Patients with MCA infarction receiving nimodipine (23)	Patients with MCA infarction receiving placebo (23)	69.8 ± 2.5 *	70.7 ± 2.3 *	Nimodipine	23	120 mg/d	N/A	N/A	Cerebral perfusion changes Cerebral tissue damage Barthel Index Canadian Neurological Scale	N/A	N/A	Although improvement in reperfusion was found following nimodipine administration within 12 h of stroke, this effect was counteracted by reperfusion injury.
(Gong et al., 1996)	RCT	China	2.5 years	Hypertensive patients under treatment with nifedipine (409/408)	Hypertensive patients under treatment with a placebo (356/459)	N/A	N/A	Nifedipine	817	10–60 mg BD	52	41	Cardiovascular events = 83 Non-cardiovascular adverse events= 26 Severe arrhythmia= 15 Cancer= 10 HF= 8 Other= 16	HTN= 1632 Abnormal electrocardiogram (including LVH, ST-segment changes, mild arrhythmia)= 460	N/A	Elderly patients with HTN for whom nifedipine was administered experienced a reduction in their serious clinical adverse outcomes.
(Shah and Passalacqua, 1992)	Case report	USA	14 days	A patient with a suicide attempt with verapamil (0/1)	-	47	-	Verapamil	1	7200 mg	1	0	N/A	None	N/A	A stroke with unusual manifestations occurred following a verapamil overdose.
(Hakim et al., 1989)	RCT	Canada	N/A	Patients with stroke receiving nimodipine (3/4)	Patients with stroke receiving carrier (3/4)	65.4 ± 5.8 *	60.7 ± 3.1 *	Nimodipine	7	1 mg/h	N/A	N/A	Cerebral metabolic rate of oxygen Cerebral metabolic rate of glucose CBF Cerebral blood volume Oxygen extraction rate	Stroke= 14 DM= 4 Arrhythmia= 3 Heart disease= 2 HTN= 1	N/A	Compared to the carrier, nimodipine was associated with an increased CBF and the reversion of the decline of the cerebral metabolic rate of oxygen.
(Samniah and Schlaeffer, 1988)	Case report	Israel	N/A	A patient with a suicide attempt with verapamil (0/1)	-	39	-	Verapamil	1	2280 mg	1	0	N/A	None	N/A	A severe, irreversible stroke occurred following a verapamil overdose.
(Low et al., 1986)	Brief communication	USA	N/A	Cardiac patients who suffered acute embolic stroke with significant neurologic deficits (7/3)	-	65.5 ± 8.02	-	Verapamil Nifedipine	8 3	5–10 mg 10–20 mg	10	N/A	N/A	Cardiac arrhythmia= 4 CVD= 3 Mitral valve replacement= 2 Valvular aortic stenosis= 2	N/A	Patients receiving heparin and CCB experienced an improvement or complete elimination of

(*continued on next page*)

Table 2 (*continued*)

Study	Design	Country	Follow/ up duration	Population		Age (Mean ± SD)		Treatment		Outcomes			Underlying comorbidities	Limitation	Main results
				Patient group (M/F)	Comparison group (M/F)	Patient group (M/F)	Comparison group (M/F)	Drug	Number Dose	Stroke (N)	Mortality (N)	Other outcomes			
													HF= 1 Cardiomyopathy= 1 Left ventricular thrombosis= 1 Aortic valve replacement = 1 Mitral stenosis= 1		neurological deficits.

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AKI, acute kidney injury; ARB, angiotensin II receptor blocker; BB, beta-clocker; BD, twice a day; CAD, coronary artery disease; CABG, coronary artery bypass graft surgery; CBF, cerebral blood flow; CCB, calcium channel blocker; CHF, congestive heart failure; CKD, chronic kidney disorder; CVD, cardiovascular disease; DLP, dyslipidemia; DM, diabetes mellitus; F, female; HF, heart failure; HTN, hypertension; IAD, interadventitial diameter; ICH, intracerebral hemorrhage; IHD, ischemic heart disease; IMT, intima-media thickness; LVH, left ventricular hypertrophy; M, male; mg, milligram; mg/d, milligram per day; mg/h, milligram per h; mg/k, milligram per kilogram; MI, myocardial infarction; mRS, Modified Rankin Scale; N, number; N/A, not available; PTCA, percutaneous transluminal coronary angioplasty; PUD, peptic ulcer disease; PVD, peripheral vascular disease; RAS, renin-angiotensin system; RCT, randomized clinical trial; SAH, subarachnoid hemorrhage; SD, standard deviation; UK, United Kingdom; USA, United States of America; VHD, valvular heart disease.
*Standard error is reported.

as those that contained atenolol in improving cardiovascular outcomes (Pepine et al., 2003). Two studies revealed that CCBs were effective in improving carotid artery parameters. Nezu et al. showed that cilnidipine reduced carotid IAD and regressed carotid IMT (Nezu et al., 2018). In addition, a study conducted by Zanchetti et al. found that lacidipine resulted in reversion of IMT progression as well as plaque numbers to a greater extent than atenolol (Zanchetti et al., 2002) (Table 1).

In contrast, Tziomalos et al. found that CCBs had no statistically significant effect on cardiovascular outcomes in patients hospitalized due to ischemic stroke (Tziomalos et al., 2017). Moreover, in one study, CCB monotherapy was associated with a greater rate of cardiovascular morbidity when compared to diuretic monotherapy (Wassertheil-Smoller et al., 2004). However, since this study enrolled only postmenopausal women, the results cannot be generalized to all patients with HTN. Altogether, the majority of included studies reported that CCB treatment resulted in significant improvement in cardiovascular outcomes. However, the efficacy of CCBs in different patient populations in terms of age, sex, or underlying medical conditions needs further evaluation.

Mortality. A total of 12,215 deaths occurred. Five studies reported a beneficial effect of CCB administration on mortality. Yui et al. demonstrated that nifedipine was associated with a significantly lower risk of mortality in hypertensive patients suffering from coronary artery disease (Yui et al., 2004). Heeley et al. showed that CCBs were associated with a lower risk of mortality either when administered in combination with ACEI/ARB drugs or alone early after stroke (Heeley et al., 2014). A cohort study conducted by Papp et al. showed that CCBs with direct cardiac effects reduced mortality rate due to stroke (Papp et al., 2012). Also, Dowlatshahi et al. revealed that CCBs improved the six-month mortality rate in hypertensive patients (Dowlatshahi et al., 2006). Jamerson et al. showed that combination therapy with amlodipine and benazepril significantly reduced the risk of mortality from cardiovascular causes and events (Jamerson et al., 2008).

In seven studies, it was found that CCBs did not significantly affect the risk of mortality. In the study conducted by Tziomalos et al., no significant association was found between CCBs and long-term mortality (Tziomalos et al., 2017). Also, Sundboll et al. reported that administration of CCBs before admission due to stroke did not significantly affect patients' mortality (Sundbøll et al., 2015). In another study conducted by Pepine et al., it was found that compared to atenolol, verapamil had no significant effects on patient mortality (Pepine et al., 2003). Similarly, Nissen et al. reported no statistically significant association between amlodipine and CVD-related or all-cause mortality (Nissen et al., 2004). In addition, in the study conducted by Kalar et al., amlodipine had no significant association with mortality in patients suffering from Alzheimer's Dementia (Kalar et al., 2021). Moreover, Gong et al. found that nifedipine administration had no significant association with mortality (Gong et al., 1996). Dens et al. reported that long-acting nisoldipine did not significantly affect mortality risk (Dens et al., 2003).

In two studies, CCB administration had unfavorable effects on mortality risk. In a study performed by Wassertheil-Smoller et al., CCBs were associated with a greater risk of CVD mortality when compared to diuretics. Moreover, it was found that combination therapy with CCBs and diuretics was associated with an increased risk of CVD mortality than beta-blockers and diuretics (Wassertheil-Smoller et al., 2004). Another study conducted by Ahmed et al. showed that administration of high-dose nimodipine increased the risk of mortality (Ahmed et al., 2000).

Regarding treatment with nifedipine, although it may not be associated with favorable effects on mortality in older patients (Gong et al., 1996), it seems that it can reduce mortality risk in younger patients with HTN who also suffer from cardiovascular diseases (Yui et al., 2004). Although amlodipine, in combination with benazepril, was associated with a reduced risk of CVD-related mortality in hypertensive patients

(Jamerson et al., 2008), it had no beneficial effects either on CVD-related or all-cause mortality in normotensive patients (Nissen et al., 2004). Thus, it seems that amlodipine administration in patients suffering from HTN may lower the risk of CVD-related mortality in the future, especially if combined with appropriate anti-hypertensive agents. However, in patients with normal blood pressure, the decision for treatment initiation with amlodipine should be made by considering its risks and benefits since, although it might be associated with favorable clinical outcomes, its effect on mortality is not guaranteed. Moreover, although it was found that amlodipine was associated with an increased risk of mortality in patients suffering from Alzheimer's Dementia (Kalar et al., 2021), the relationship might be affected by unadjusted confounders and the underlying disease-related factors. It seems that in hypertensive patients who also suffer from underlying cardiovascular or cerebrovascular diseases, treatment with CCBs has no statistically significant effect on the risk of mortality. Although some studies revealed a reduced mortality risk following treatment with CCBs (Dowlatshahi et al., 2006; Heeley et al., 2014; Papp et al., 2012), the findings are not generalizable due to study limitations. Variations in study design and population, sample size, type, dosage, and duration of treatment with CCBs, as well as mortality cause, may be responsible for differences between the findings of the studies. Altogether, although treatment with CCBs can improve neurological and cardiovascular outcomes, these effects do not necessarily affect mortality risk. Especially in hypertensive patients who suffer from concurrent cardiovascular or cerebrovascular diseases, the effects of CCBs on mortality risk may be confounded by related clinical factors (Table 1).

Animal experiments

Study characteristics

A total of 24 animal studies were published. 17 studies were conducted in vivo, two in vitro, two both in vivo and in vitro, one ex vivo, one both in vivo and ex vivo, and one in vivo, ex vivo, and clinical trial. Among 24 studies, 11 were conducted in the USA, eight in Japan, three in Canada, one in China, and one in Finland (Table 2).

Animal characteristics

A total of 813 animals were enrolled, ranging from 15 to 100 animals in 19 studies. Among animals, 724 were males, and 58 were females, and animal sex was not determined in two studies. Rats, cats, and mice were enrolled in 14, three, and three studies, respectively. Gerbils and monkeys were enrolled in one study each. Two in vitro studies used mammalian cells and enzymes. The mean age of animals ranged from 6 to 16 weeks (Table 2).

Calcium channel blockers

Verapamil, nifedipine, nilvadipine, diltiazem, nimodipine, and nicardipine were implemented in nine, seven, five, three, two, and two studies, respectively. Flunarizine, felodipine, (s)-emopamil, levemopamil, lacidipine, clentiazem (TA3090), CA-159, and SKF-96365 were used in one study each. A total of 171, 144, 41, 33, 25, 25, and 23 animals received nilvadipine, verapamil, nifedipine, nicardipine, clentiazem, (s)-emopamil, and lacidipine, respectively. Flunarizine, CV-159, diltiazem, felodipine, levemopamil, and nimodipine were administered in 12, 12, 11, 10, eight, and five animals, respectively (Table 2).

Outcomes

Cerebral infarct size. Among studies, 14 revealed a reduced infarction size following treatment with CCBs. Nilvadipine was found to be associated with a reduced infarct size in five studies (Kawamura et al., 1991; Takakura et al., 1991; Li et al., 1994; Kawamura et al., 1996, 1998). Four studies found that verapamil resulted in a reduction of ischemic size either alone (Hosaka et al., 1991; Yamamoto et al., 1991; Maniskas et al., 2016) or in combination with lubeluzole (Maniskas et al., 2022). Nifedipine, nimodipine, nicardipine, CV-159, and TA3090 were found to be associated with a smaller infarct size in one study each (Takakura et al., 1991; Miyazaki et al., 1999; Sakaki et al., 1993; Berger and Hakim, 1988; Yamato et al., 2011). In contrast, in one study, no statistically significant association was found between treatment with verapamil and brain infarct size (Berger and Hakim, 1988). The authors suggested that short-term treatment and short duration of follow-up might be responsible for these findings (Berger and Hakim, 1988). Miyazaki et al. showed that nicardipine and nifedipine were not significantly associated with brain infarct size reduction (Miyazaki et al., 1999). In a study conducted by Roy et al., verapamil and diltiazem were associated with an increased infarct area, maybe in part due to a reduction of CBF in the ischemic region and transtentorial herniation, respectively (Roy et al., 1985). Hence, it seems that although CCBs can be associated with a decreased infarct area, their effect may be affected by drug type, dosage, and treatment duration. However, it is important to consider drug side effects, which may contribute to an increment in the infarct area and deterioration of clinical outcomes (Table 2).

Cerebral blood flow. Four studies found that CCB administration was associated with an improved CBF. In two studies, verapamil resulted in a higher CBF (Hosaka et al., 1991; Yamamoto et al., 1991). Also, diltiazem (Roy et al., 1985) and TA3090 (Sakaki et al., 1993) were associated with an increased CBF in one study each. In contrast, one study showed that verapamil led to worsened CBF in the ischemic area (Roy et al., 1985). The authors suggested that the increased CBF in non-ischemic areas following treatment with verapamil, which occurred at the expense of decreased CBF in ischemic areas, was responsible for CBF deterioration in infarcted regions (Roy et al., 1985). In the remaining four studies, no statistically significant association was found between treatment with CCBs and CBF. One study showed that nifedipine and felodipine had no beneficial effect on improving CBF (Phillis et al., 1986). The authors proposed that an initial decrease in systemic blood pressure following treatment with nifedipine and felodipine, especially when higher doses of drugs were administered, might counteract CBF improvement (Phillis et al., 1986). Berger et al. demonstrated that neither verapamil nor nimodipine significantly changed CBF within 90 min of stroke (Berger and Hakim, 1988). However, the authors stated that early evaluation of outcomes might be responsible for these results (Berger and Hakim, 1988). Miyazaki et al. revealed that CV-159 did not significantly change CBF (Miyazaki et al., 1999). In the study conducted by Maniskas et al., no statistically significant association was found between verapamil and CBF, however, the authors stated that their results might be affected by short-term follow-up (Maniskas et al., 2016) (Table 2). Altogether, it seems that treatment with CCBs may exert beneficial effects on impaired CBF following stroke, however, it is important to note that these effects are mainly long-term and may not be represented in short-term follow-up. Moreover, rapid dropping of blood pressure due to the implementation of high doses of CCBs may antagonize CBF improvement and should be avoided.

Cerebral edema. Six studies demonstrated that CCB administration resulted in a lower cerebral edema volume. Nilvadipine was associated with reduced brain water content in three studies (Kawamura et al., 1991; Li et al., 1994; Kawamura et al., 1998). Also, diltiazem (Roy et al., 1985), TA3090 (Sakaki et al., 1993), and CV-159 (Miyazaki et al., 1999) were associated with lower cerebral edema in one study each. In the study conducted by Miyazaki et al., no association was found between treatment with either nicardipine or nifedipine and cerebral edema (Miyazaki et al., 1999). Also, Yamato et al. demonstrated that nifedipine administration had no statistically significant effect on cerebral edema (Yamato et al., 2011). It has been suggested that differences in drug half-inhibitory concentrations and the underlying cellular pathways may be responsible for the differences between study outcomes. For

instance, although CV-159, nicardipine, and nifedipine are dihydropyridine CCBs, CV-159 has lower half-inhibitory concentrations than the latter two drugs and is able to inhibit CaM-dependent pathway (Miyazaki et al., 1999), which might be responsible for the differences in effects on cerebral edema between these drugs. One study demonstrated that verapamil resulted in increased cerebral edema (Roy et al., 1985). It has been suggested that verapamil may increase the threshold for edema formation, which may further lead to exacerbation of cerebral swelling, while diltiazem may reduce the threshold (Roy et al., 1985) (Table 2). Altogether, it seems that in animals with recent strokes, CCB administration is safe and may help lower cerebral edema volume. However, among non-dihydropyridine CCBs, verapamil may exert deleterious effects on brain water content and should not be administered following a recent stroke.

Oxidative stress. Napoli et al. found that treatment with lacidipine and nifedipine was associated with protective effects against oxidation (Napoli et al., 1999). Another study conducted by Yamato et al. showed that nifedipine resulted in a reduction in ROS levels (Yamato et al., 2011). However, Brown et al. showed that neither nifedipine nor SKF-96365 had significant effects on ROS levels in endothelial cells of the bovine brain (Brown et al., 2004) (Table 2). The differences in findings of these studies might be due to differences in study design and population since in vivo studies revealed a beneficial effect of CCBs in the prevention of oxidation, while no significant effect was found when the effect of CCBs was evaluated in vitro. Moreover, variations between animal species might be responsible for these differences. Thus, it seems that although CCBs can prevent oxidative stress in rats, their antioxidative effects in other mammalians should be further studied.

Other related outcomes. Several studies reported beneficial effects of CCBs on histological, functional, and survival improvement. Two studies revealed that verapamil improved functional outcomes, reduced astrogliosis, and increased neural cell survival (Maniskas et al., 2016, 2022). Verapamil and nimodipine were found to correct pH in one study (Berger and Hakim, 1988). A study revealed that nifedipine and SKF-96365 were associated with increased intracellular calcium and maintained monolayer permeability in hypoxic conditions (Brown et al., 2004). In one study, nifedipine and lacidipine reduced mortality rates among studied animals (Napoli et al., 1999). A study revealed that diltiazem had protective effects against chronic cerebrovasospasm and vascular smooth muscle damage (Bevan et al., 1988). Moreover, another study showed that diltiazem, but not verapamil or nifedipine, improved cerebral metabolic recovery following stroke (Brooks and Kauppinen, 1993). In one study, (s)-emopamil protected against ischemic injury and improved the histological grade of neural cells (Lin et al., 1990). Moreover, verapamil (Fraser et al., 2017) and CV-159 (Miyazaki et al., 1999) were found to provide neuroprotective effects in one study each.

However, in some studies, non-significant or deleterious effects were observed following treatment with CCBs. One study showed that treatment with levemopamil after stroke was not significantly associated with improvement in histological outcomes (Gomi et al., 1995). However, the authors declared that in addition to the time of treatment initiation and drug dosage, negative effects of reperfusion following ischemia might be responsible for these results (Gomi et al., 1995). A study conducted by Christie-Pope et al. showed that pretreatment with flunarizine and verapamil had inconsistent and opposed effects on the activity of cAMP and adenylate cyclase (Christie-Pope and Palmer, 1986). One in vitro study showed that when administered after acute stroke, nifedipine and nimodipine inhibited the Neuronal OMP Decarboxylase and Uridine Kinase enzymes, which were responsible for nerve cell membrane repair (Najarian et al., 2000). Roy et al. demonstrated that while diltiazem was associated with improved evoked potential latency, verapamil deteriorated evoked potential parameters (Roy et al., 1985). The authors suggested that this difference could be due to differences in CBF following treatment with these drugs since diltiazem increased CBF in ischemic areas and verapamil improved CBF in non-ischemic areas (Roy et al., 1985) (Table 2). Differences in study design, animal species, and experimental techniques may be responsible for different findings between the studies. Moreover, the type of administered drug, CCB dose, time of treatment initiation, and treatment initiation may affect how the drug affects the outcomes. Altogether, in addition to blood pressure management, CCBs can help improve various outcomes when administered either before or after stroke.

Discussion

In this study, we conducted a systematic review to evaluate the effects of CCB on the mortality, morbidity, and outcomes of cerebrovascular diseases. The studies in this review reported data on the cerebrovascular impact of CCBs in humans and animals. Although the results of the included studies were inconsistent,

Our results showed that some studies stated that CCBs can reduce the risk of stroke and stroke-related mortality in patients. Similarly, a meta-analysis of RCTs done by Wang et al (Wang et al., 2022). showed that antihypertensive drugs, especially CCBs, significantly reduced stoke in CVD patients in comparison to placebo. Moreover, another systematic review and meta-analysis by Iyengar et al (Iyengar et al., 2021). revealed that Amlodipine remarkably decreased the risk of stroke and MI in patients with HTN. However, some other studies reported that using CCB is associated with an increased risk of stroke. Hsu et al (Hsu et al., 2019). reported that the short-term and long-term use of short-acting CCBs was associated with a higher risk of stroke. Also, Jung et al (Jung et al., 2011). demonstrated that patients who received short-acting nifedipine in the most recent 7 days had a higher risk of stroke compared to patients who did not receive it.

Besides, the included studies reported the effects of CCBs on neurological outcomes. Although one study reported an increased risk of dementia in patients using CCBs, other studies stated that using CCBs is accompanied by improved neurological outcomes. Also, a review conducted by Nimmrich et al (Nimmrich and Eckert, 2013). reported that there are heterogenous data about the effects of CCBs on dementia, and according to the results of the clinical trials, nimodipine as well as nilvadipine can inhibit cognitive decline since other CCBs cannot. Moreover, Jeong et al. stated in their study that patients with cognitive decline who use CCBs improve their cognition better than patients who do not use CCBs.

Also, in this systematic review, we evaluate the findings of the studies on animals. Ten studies report it assessed the effect of different CCBs on cerebral infarct size that CCBs are associated with lower infarct size. However, one study stated that verapamil and diltiazem can result in increased infarct size. A study done by Kopecky et al (Kopecky et al., 2014). reported the neuroprotective effects of T-type calcium channel blockers. Moreover, in a review, Ovbiagele et al (Ovbiagele et al., 2003). demonstrated that although there are controversies about using CCBs in acute stroke, some animal studies showed that calcium channel inhibitors can significantly decrease the post-ischemic infarct size in rats.

In this systematic review, the CBF and cerebral edema were also evaluated. The findings of this review showed that there were some inconsistencies between the results of the included studies. Two studies reported increased CBF, while one study demonstrated that using verapamil was associated with worsened CBF. Another study reported that there was no significant change in the CBF of patients using CCBs. In a systematic review by Sare et al (Sare et al., 2008). on the CBF, it was shown that three clinical trials did not report a significant change in the CBF after using CCBs. But, when the results of five included studies in the mentioned systematic review were pooled, there was a remarkable reduction in the CBF. The cerebral edema was reported to be reduced after using CCBs in three studies. However, one study indicated that CCBs could lead to increased cerebral edema. In addition, a clinical trial

conducted by Rowland et al (Rowland et al., 2019). suggests that CCBs reduce cytotoxic cerebral edema after acute cerebral hypoxia without a significant increase in CBF.

Besides, the effect of CCBs on oxidative stress was reviewed. According to the reported data by the studies included in our study, CCBs can be used to protect against oxidation and oxidative stress. The same result was reported in a review done by Nishiyama et al (Nishiyama et al., 2010). Also, the antioxidative effects of CCBs are explained in human studies; as Taddei et al (Taddei et al., 2001). reported in their study, Lacidipine, which is a CCB, has the ability to enhance vasodilation that is dependent on the endothelium by restoring the availability of NO. This outcome may be associated with its antioxidant activity.

The results revealed that there is a lot of heterogeneous data about the effects of CCBs on cerebrovascular, cardiovascular, and neurological outcomes. As could be seen in the results, while some research demonstrates significant benefits of CCBs in reducing stroke risk, others show less favorable or even potentially harmful effects. These discrepancies may be attributed to several factors. Differences in study design, such as randomized controlled trials versus observational studies, can lead to varying results. Patient populations also play a crucial role; for example, CCBs showed greater efficacy in reducing stroke risk among elderly patients compared to younger individuals. Also, the effect of CCBs on hypertensive patients differs from normotensive patients. Moreover, the type and dosage of CCBs used in each study can affect the outcomes.

However, some inconsistencies may be solved after considering the data together. In this systematic review, there are some limitations that can be considered for further studies. First, the types of CCBs used in the studies differed, and each CCB's effect may differ from others. So, the data can not be pooled for results. The next limitation was that there was not enough data for each CCB to make a consequence for each topic. Third, the studies did not report data in the same way. The last limitation was that many studies only compared the CCBs with other antihypertensive drugs without a control group. So, we excluded the studies without a control group as we could not evaluate the effect of CCBs separately.

Future research should focus on conducting more head-to-head randomized controlled trials comparing CCBs with other antihypertensive drug classes, particularly in diverse patient populations. It is recommended for further studies to assess different CCBs and compare the effects of each CCB with each other and the control group. Also, they can perform a study which can assess the prognosis and outcome of patients with stroke and other neurological diseases. Additionally, the molecular mechanisms underlying CCBs' potential neuroprotective effects in acute ischemic stroke require further investigation. Studies exploring the optimal timing, dosage, and specific CCB subclasses for stroke prevention and treatment are needed. The mixed results on CCBs' effects on functional recovery and mortality post-stroke also warrant additional research. Long-term studies examining the impact of CCBs on cognitive function and quality of life in stroke survivors could provide valuable insights for clinical decision-making. Furthermore, investigating the relationship between blood pressure variability and stroke outcomes, as well as the differential effects of CCBs on BPV compared to other antihypertensive classes, may offer new perspectives on therapeutic management in the immediate post-stroke period.

Conclusion

In conclusion, it has been demonstrated in this study that CCBs, particularly through the management of HTN, can play a role in reducing the risk of stroke, improving long-term neurological outcomes, and lowering mortality in patients with cerebrovascular diseases. The included articles comprised human and animal studies, revealing that CCBs can reduce cerebral edema, improve cerebral blood flow, and shrink cerebral infarct size. Despite the general evidence supporting their neuroprotective and cardiovascular advantages, notably in lowering oxidative stress, the effectiveness of the CCBs varies based on the drug type, dosage, and patient population. Also, some studies showed that short-acting CCBs have adverse side effects. Therefore, more research is required to elucidate these effects and maximize the use of CCBs in the prevention and treatment of stroke.

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CRediT authorship contribution statement

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Declaration of Competing Interest

The authors declare that they have no competing interests.

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Consent for publication

Not applicable

Data availability

All data analyzed or generated during this study are included in published articles available in Tables 1 and 2.

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