Drug, Healthcare and Patient Safety

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REVIEW

Long-Term Safety and Effectiveness of Calcium Channel Blockers in Hypertension: A Systematic Review

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Purpose: Calcium channel blockers (CCBs) are widely used as first-line therapy for hypertension, but concerns remain regarding their long-term safety and effectiveness. This review aims to systematically summarize the existing evidence on the long-term safety and effectiveness of CCBs in patients with hypertension.

Methods: A systematic review was conducted using the PubMed database to identify randomized controlled trials (RCTs), cohort studies, and case-control studies assessing the long-term use (≥1 year) of CCBs in adult hypertensive populations. Eligible studies compared CCBs with other antihypertensive agents or placebo and reported outcomes related to systemic safety and effectiveness. The quality of each study was assessed using the Jadad and Newcastle-Ottawa Scales. Evidence was synthesized descriptively and stratified by organ system and clinical outcome.

Results: In total, 29 studies met the inclusion criteria, encompassing both RCTs and observational studies. Long-term CCB use was generally safe, with manageable risks. Renal protective effects were less consistent, while several studies reported a marginal increase in the incidence of new-onset diabetes. Associations with breast cancer remained inconclusive, and the risk of bone fractures appeared modestly reduced. Other systemic effects, including metabolic and reproductive changes, were generally mild. In terms of effectiveness, CCBs consistently reduced stroke incidence, although evidence regarding other cardiovascular outcomes, such as infarction, heart failure, and transient ischemic events, was inconsistent across studies.

Conclusion: Overall, CCBs are safe for long-term use and show sustained effectiveness in stroke and angina, although evidence for heart failure, myocardial infarction, and transient ischemic attack remains inconsistent.

Keywords: calcium channel blockers, hypertensive populations, long-term safety, long-term effectiveness

Introduction

Hypertension is a major contributor to cardiovascular morbidity and mortality worldwide.[1,2] It is defined by systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg, consistent with guidelines from NICE (2019), the Australian guideline (2016), and the ESC/ESH (2018).[3–5] In contrast, the ACC/AHA guidelines (2025) adopt a lower threshold of ≥130/80 mmHg.[6] Despite these differences, hypertension remains highly prevalent and a leading cause of global morbidity and mortality. According to WHO data (2024), in 2020, approximately 1.28 billion adults aged 30 to 79 years experienced hypertension globally, yet only 21% had their blood pressure well controlled.[7] Given the chronic nature of hypertension, which typically requires lifelong pharmacological therapy,[8] long-term outcomes (≥1 year) are particularly important not only to assess the sustainability of blood pressure control but also to capture potential metabolic, renal, oncologic, and skeletal effects that may emerge only after prolonged drug exposure rather than during short-term treatment.[9]

Several pharmacological agents can be used to manage hypertension, including calcium channel blockers (CCBs), angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), beta-blockers, and

https://doi.org/10.2147/DHPS.S576249
Received: 23 October 2025
Accepted: 11 February 2026
Published: 18 March 2026

diuretics.[10,11] CCBs are among the most extensively studied and are frequently recommended as a first-line therapy, both as monotherapy and in combination with other medications.[12]

CCBs act as antihypertensive agents by inhibiting L-type calcium channels located in the vascular and cardiac smooth muscles. This inhibition decreases intracellular calcium levels, leading to relaxation of vascular tone and a subsequent reduction in systemic blood pressure. CCBs are classified into dihydropyridines (DHP), which mainly act on blood vessels (eg, amlodipine, nifedipine, nicardipine), and non-dihydropyridines (non-DHP), which also affect cardiac conduction (eg, verapamil, diltiazem).[11]

Despite being widely prescribed as initial therapy for hypertension, CCBs continue to raise concerns regarding their long-term safety and effectiveness. Several observational studies have reported potential long-term adverse effects associated with CCBs use, including increased risks of new-onset diabetes (NOD),[13] impaired renal safety profiles,[14] and bone fractures.[15] Furthermore, evidence from the CASE-J study and its extended follow-up suggested links between CCB therapy and major cardiovascular outcomes such as stroke, transient ischemic attack (TIA), angina pectoris, and myocardial infarction.[16–18]

Previous systematic reviews and meta-analyses have evaluated the safety and efficacy of CCBs; however, most were limited to specific clinical outcomes. For instance, some focused on the potential association between CCB use and breast cancer,[19] while others examined cognitive or neurological effects such as dementia.[20] To date, a comprehensive synthesis addressing the overall long-term safety profile of CCBs (≥1 year of use) in patients with hypertension has not been established.

Therefore, this systematic review aims to comprehensively synthesize existing evidence from both randomized controlled trials (RCTs) and observational studies regarding the long-term safety (eg, cancer, diabetes, renal impairment) and effectiveness (eg, stroke, myocardial infarction, heart failure) of CCBs in patients with hypertension. This evaluation is critical to guide long-term antihypertensive therapy decisions and inform clinical practice.

Methods

Eligibility Criteria

The eligibility criteria for including studies in this review were developed using the PICO (Population, Intervention, Comparator, Outcomes) framework. A detailed outline of the eligibility criteria is presented in Table 1.

Search Methods

This study adhered to the PRISMA 2020 framework to maintain transparent and structured reporting. Literature retrieval was performed through the PubMed database on May 2, 2025, using a combination of Medical Subject Headings (MeSH) and free text keywords encompassing CCBs, hypertension, long-term use, safety-related outcomes, and study design terms. The complete search string was: ("Calcium Channel Blockers" [MeSH Terms] OR "calcium channel blocker" [tiab] OR "calcium antagonists" [tiab] OR amlodipine [tiab] OR nifedipine [tiab] OR diltiazem [tiab] OR verapamil

Table 1 Study Eligibility Criteria Based on the PICO Framework

Study design	Randomized controlled trials, cohort, and case control studies
Population	Adult patients with hypertension
Intervention	Long-term use (≥1 year) of CCBs, including dihydropyridines (eg, amlodipine, nifedipine, nicardipine) and non-dihydropyridines (eg, verapamil, diltiazem)
Comparator	Other antihypertensive agents (eg, ACEIs, ARBs, beta-blockers), or placebo
Outcome	Long-term adverse effects, such as new-onset diabetes, renal dysfunction, bone mineral density reduction, cancer risk, and other systemic complications; as well as clinical effectiveness outcomes (stroke, myocardial infarction, heart failure, and related cardiovascular events).

Abbreviations: CCBs, Calcium Channel Blockers; ACEIs, Angiotensin Converting Enzyme Inhibitors; ARBs, Angiotensin Receptor Blockers.

[tiab]) AND ("long-term safety" [tiab] OR "long-term use" [tiab] OR "long-term effects" [tiab] OR "adverse event" [tiab] OR "adverse effect" [tiab] OR "adverse drug reaction" [tiab] OR "drug safety" [tiab] OR "drug toxicity" [tiab] OR "systemic complications" [tiab]) AND ("Hypertension" [MeSH Terms] OR hypertension [tiab] OR "high blood pressure" [tiab]) AND ("Randomized Controlled Trial" [pt] OR "Randomized Controlled Trial" [tiab] OR "RCT" [tiab] OR "Cohort Studies" [MeSH Terms] OR cohort [tiab] OR "Case-Control Studies" [MeSH Terms] OR "case control" [tiab] OR "case-control" [tiab]). Only articles published in English were included. No restriction was applied regarding the publication date. Additional studies were identified through hand-searching the reference sections of eligible papers and relevant prior reviews. The finalized PRISMA 2020 checklist is presented as Supplementary Tables 1 and 2.

Selection of Studies

All articles identified through the PubMed search (n = 119) and additional manual reference screening (n = 10) were compiled into Microsoft Excel for organization and screening, yielding a total of 129 records for review. Screening of titles and abstracts was conducted independently by two reviewers (NA and JSA) according to pre-specified eligibility standards. Full texts of studies considered relevant were then obtained and evaluated separately by these investigators. Any differences in judgment were settled through consensus, with input from a third reviewer (WNI) when needed. During full-text assessment, studies were excluded if follow-up duration was less than one year, the population was non-hypertensive, or CCB-specific data were not available; all exclusion reasons were carefully documented.

Data Extraction and Management

Information was collected independently by two investigators (NA and JSA) using a predesigned Microsoft Excel sheet. The extracted dataset covered key study descriptors, such as publication details (first author, publication year, study location, and design type), as well as participant demographics, underlying conditions, treatment and comparator regimens, follow-up periods, and safety endpoints. Any inconsistencies in data capture were reviewed collaboratively, and unresolved differences were adjudicated by a third member of the review team (WNI). The finalized data were summarized in structured tables and used to support the narrative synthesis presented in the results section.

Data Synthesis

Evidence was synthesized narratively and results were organized according to pre-specified outcome categories: renal outcomes (eg, renal dysfunction, dialysis, proteinuria), metabolic outcomes (eg, NOD), bone related parameters (eg, decreased bone mineral density (BMD)), cancer risk, and cardiovascular events (eg, stroke, myocardial infarction, TIA, angina, and heart failure). For each study, data were extracted and reported at the longest available follow-up beyond one year.

Quality Assessment

Two reviewers (NA and JSA) separately appraised the rigor of each eligible study. In the case of randomized trials, quality judgments were based on the Jadad scoring system (0–5 scale), which considers key factors such as randomization process, masking, and participant withdrawals. Trials with scores of 3 or higher were categorized as high quality.[21] For observational studies (case control and cohort), evaluation was conducted using the Newcastle-Ottawa Scale (NOS) tailored to the respective study type. Scores ≥7 indicate strong study quality.[22] Any scoring inconsistencies between reviewers were discussed, and unresolved differences were reviewed by a third author (WNI) to reach consensus.

Results

General Screening

The PubMed search yielded 119 records, with an additional 10 studies identified through manual reference screening, resulting in 129 articles for initial evaluation. After title and abstract screening, 83 articles were excluded as they failed to meet the eligibility requirements. The remaining 46 full-text articles were reviewed in detail, of which 17 were excluded due to the absence of disease-specific outcomes (n = 11), lack of separate results for CCB users (n = 4), publication as

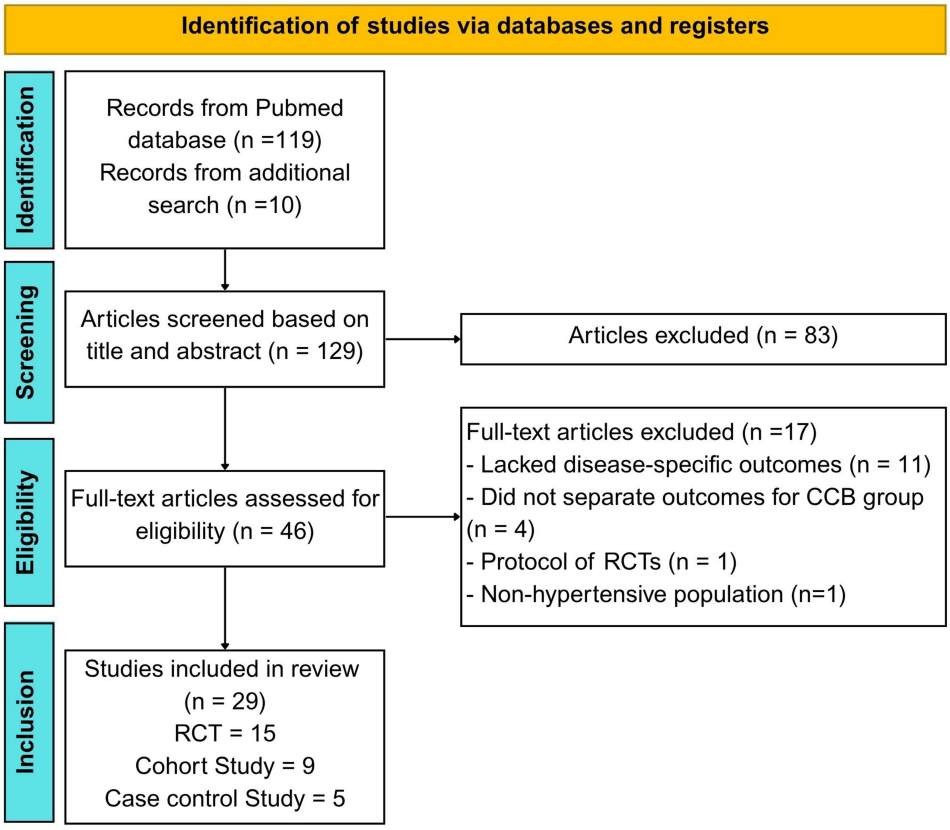

Figure 1 PRISMA Flow diagram of systematic review.
Notes: PRISMA Flow diagram adapted from Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 Statement: an update guideline for reporting systematic reviews. BMJ. 2021;372:n71.[23]

a study protocol (n = 1), or inclusion of non-hypertensive participants (n = 1). Following the screening process, 29 studies met the predefined inclusion standards and were integrated into the final review. The overall procedure for identifying and selecting the studies is depicted in Figure 1, according to the PRISMA framework.[23]

Characteristics of Included Studies

The final selection comprised 29 studies, including 15 randomized controlled trials (RCTs), 9 cohort studies, and 5 case-control studies, published between 1991 and 2022. Most investigations were conducted in Asia, Europe, and North America, enrolling adult hypertensive populations with mean ages spanning from early to older adulthood. The CCB subclasses evaluated encompassed both DHP (eg, amlodipine, nifedipine) and non-DHP (eg, diltiazem, verapamil), with follow-up durations from 1 to 10 years. Comparator treatments most frequently involved ACEIs/ARBs, followed by beta blockers, diuretics, or placebo. Key study characteristics are summarized in Table 2. Detailed findings on long-term safety outcomes are shown in Table 3, while effectiveness outcomes are summarized in Table 4.

Quality Assessment

The methodological quality was generally moderate to high. Among RCTs, Jadad evaluation results ranged from 1 to 5, with most (11 of 15) scoring three or above, indicating adequate randomization and reporting, though older trials often lacked detailed blinding procedures. Cohort studies scored 6–9 on the NOS, with most (7 of 9) achieving ≥7, suggesting good representativeness and outcome assessment, although follow-up completeness was occasionally underreported. Case control studies scored 8–9, with consistently clear case definitions and appropriate control selection, though some failed to report response rates. Overall, the methodological rigor across studies was moderate to high, supporting the

Table 2 Characteristics of Included Studies

No	Author, Publication Year	Setting/Country	Study Design	Number of Participants	Population	Intervention and Comparator	Duration of Study	Outcomes
1.	Ağaçayak, 2014[15]	University of Dicle, Diyarbakır, Turkey	Cohort Study	294	Male > 55 years with hypertension	CCBs versus BB versus control (never used antihypertensive)	5 years	Lower BMD and better effects on bone
2.	Bakris, 1996[24]	The Alton Ochsner Medical Institution, New Orleans, Louisiana	RCT	52	Patients with hypertension aged >45 years, diabetic nephropathy (non–insulin-dependent)	Non-DHP CCBs (verapamil, diltiazem) versus ACEIs (lisinopril), BB (atenolol)	5 years, 3 months	Proteinuria reduction, stable creatinine clearance, and led to faster renal decline
3.	Bianchi, 1991[14]	Spedali Riuniti in Livorno	RCT	16	Patients with hypertension and chronic renal insufficiency	DHP CCBs (nicardipine) versus ACEIs (enalapril)	1 year	Lowered UAE
4.	Bigazzi, 1993[25]	Spedali Riuniti in Livorno	RCT	40	Patients with essential hypertension and microalbuminuria	DHP CCBs (nicardipine SR) versus ACEIs (enalapril)	2 years	Decreased UAE
5.	Brown, 2000[13]	703 centres in eight countries in western Europe and Israel	RCT	6321	Adults (55–80 years) with hypertension	DHP CCBs (nifedipine) versus co-amilozide (hydrochlorothiazide + amiloride)	3 years	Reducing cardiovascular events, but caused more edema, while co-amilozide had higher rates of diabetes and gout
6.	Chan, 2000[26]	Chinese University, Hong Kong.	RCT	102	Patients with hypertension and type 2 diabetes	DHP CCBs (nifedipine) versus ACEIs (enalapril)	5 years	CCBs (nifedipine) were less effective than ACEIs (enalapril) in improving renal outcomes, with fewer patients improving and more worsening
7.	Chang, 2016[27]	Taiwan National Health Insurance	Case Control Study	46.985	Women hypertension aged more than 55	DHP CCBs versus ACEIs, ARBs, BB	6 years	CCBs showed higher risk of breast cancer, but the association was not statistically significant
8.	Chen, 2016[28]	The Taiwan Bureau of National Health Insurance in Central Taiwan, China	Cohort Study	1144	Elderly patients (65–80 years) with hypertension	CCBs versus loop or thiazide diuretics, alpha-blockers, BB, ACEIs, and ARBs	11 years	Patients who took CCBs were at a lower risk of developing NOF than nonusers

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https://doi.org/10.2147/DHPS.S576249

Table 2 (Continued).

No	Author, Publication Year	Setting/Country	Study Design	Number of Participants	Population	Intervention and Comparator	Duration of Study	Outcomes
9.	Fogari, 1999[29]	Italy	RCT	51	Male hypertensive patients with type II diabetes mellitus (non–insulin-dependent) and impaired renal function	DHP CCBs (nitrendipine) versus ACEIs (Ramipril)	2 years	UAE decreased significantly after 1 year but less than with ACEIs (ramipril)
10.	Forette, 2002[30]	Europe	RCT	2902	Patients with hypertension and no dementia > 60 years	DHP CCBs (nitrendipine) + ACEIs (enalapril) or hydrochlorothiazide versus placebo	3.9 years	Reduced the incidence of dementia by 55% compared to placebo. After adjustment, the hazard ratio for dementia with nitrendipine was 0.38
11.	Gómez-Acebo, 2016[31]	10 Spanish provinces (Asturias, Barcelona, Cantabria, Girona, Gipuzkoa, Huelva, León, Madrid, Navarra and Valencia)	Case control Study	3631	Woman aged 20–85 with hypertension and without hypertension	CCBs versus Diuretic, BB, ACEIs, ARBs	5 years	Increased breast cancer risk, CCBs were linked to aggressive tumors: invasive, non-ductal, and ERBB2+. Other antihypertensives showed no risk association
12.	Gress, 2000[32]	Four US regions: Forsyth County, Jackson, the northwest suburbs of Minneapolis, and Washington	Cohort study	3804	Hypertension patients aged 45–64 years non-diabetic	CCBs versus ACEIs, BB, Thiazide diuretic	6 years	Increasing the risk of developing type 2 diabetes mellitus
13.	Grimm, 1996[33]	Four academic clinical research units in the US	RCT	902	Hypertension patients aged 45–69 years	DHP CCBs (amlodipine) versus Placebo, BB (acebutolol), Diuretic (chlorthalidone), α1-antagonist (doxazosin), and ACEIs (enalapril)	4 years	Lowers total cholesterol, triglycerides, LDL, and increases HDL

https://doi.org/10.2147/DHPS.S576249

14.	Grimm, 1997[34]	Four academic clinical research units in the US	RCT	902	Hypertension patients aged 45–69 years	DHP CCBs (amlodipine) versus Placebo, BB (acebutolol), Diuretic (chlorthalidone), α1-antagonist (doxazosin), and ACEIs (enalapril)	2 years	Not associated with changes in sexual function
15.	Kwok, 2016[35]	Six regions of the USA: Birmingham, Minneapolis, the Monongahela Valley near Pittsburgh, Palo Alto, Portland, and San Diego	Cohort Study	2573	Male hypertension patients aged ≥65 years	CCBs versus ACEIs, ARBs	6.8 years	Reduce the risk of non-vertebral fractures
16.	Li, 2013[36]	Three countries of the Seattle-Puget Sound metropolitan area	Case control study	2763	Women aged 55–74 years diagnosed with primary invasive breast cancer with and without hypertension	CCBs versus Diuretic, BB, ACEIs, ARBs	10 years	Increase the risk of breast cancer
17.	Liou, 2008[37]	The National Health Insurance Bureau of Taiwan	Case control study	8638	Taiwanese hypertensive patients aged 65–96 years	CCBs versus ACEIs, ARBs, BB, Diuretic, α-blockers, Vasodilator	6.2 years	Increases the risk of NOD but not significantly
18.	Liu, 2018[38]	Japan	RCT	1313	Patients with hypertension and one or more coexisting cardiovascular risk factors	DHP CCBs (amlodipine) versus ARBs (Candesartan)	10 years	Increases the risk of NOD
19.	Nishida, 2017[39]	Three hospitals in Japan	Cohort Study	114	Hypertension patients aged over 20 year	DHP CCBs (Amlodipine) versus ACEIs (Imidapril)	1 years	No significant changes were detected in renal biomarkers such as creatinine, electrolytes, BUN, or estimated GFR
20.	Ogihara, 2000[16]	Japan	RCT	1748	Hypertension patients aged over 60 years	DHP CCBs (manidipine) versus ACEIs (delapril)	3 years	Reduces the risk of cerebral hemorrhage, TIA, angina pectoris, and heart failure but increases the risk of cerebral infarction and myocardial infarction

(*Continued*)

https://doi.org/10.2147/DHPS.S576249

Table 2 (Continued).

No	Author, Publication Year	Setting/Country	Study Design	Number of Participants	Population	Intervention and Comparator	Duration of Study	Outcomes
21.	Ogihara, 2008[17]	Japan	RCT	4703	Hypertension patients aged 63.9±10.6 years	DHP CCBs (amlodipine) versus ARBs (Candesartan)	4.2 years	Reduces the risk of stroke, heart failure, and peripheral vascular events but increases the risk of TIA, angina pectoris, acute myocardial infarction, creatinine, and new-onset diabetes
22.	Ogihara, 2011[18]	Japan	RCT	4703	Hypertension patients aged 63.9±10.6 years	DHP CCBs (amlodipine) versus ARBs (Candesartan)	6 years	Reduces the risk of stroke, heart failure, and vascular events but increases the risk of TIA, angina pectoris, acute myocardial infarction, creatinine, and new-onset diabetes
23.	Raebel, 2017[40]	3 sites of Kaiser Permanente (KP): Colorado, Northwest, and Southern California, US	Cohort Study	109752	Women Hypertension aged ≥55 years	CCBs versus ACEIs	12 years	Reduces the risk of invasive breast cancer
24.	Rotshild, 2022[41]	Clalit Health Services (CHS) Israel	Case control study	53625	Hypertension female patients aged ≥ 55 years	CCBs versus ACEIs/ARBs, diuretics, BB, α-blockers, α2 agonists, hormonal therapy	16 years	Reduce the risk of breast cancer
25.	Saeed, 2020[42]	Guy's and St Thomas' Hospital, London, United Kingdom	Cohort Study	314	Hypertension patients with moderate or severe aortic stenosis	CCBs versus without CCBs	2 years 8 months	Increase the risk of heart failure
26.	Staessen, 1997[43]	23 countries across western and eastern Europe	RCT	4695	Patient isolated systolic hypertension aged > 60 years	Active [DHP CCBs (nitrendipine) if necessary, combine ACEIs (enalapril) or thiazide] versus Placebo	2 years	Active treatment led to a 42% reduction in total stroke incidence compared to placebo
27.	Weycker, 2007[44]	US health insurance database	Cohort study	28697	Hypertension patients aged ≥ 35 years without diabetes	DHP CCBs (Amlodipine) vs ARBs (Valsartan)	4.2 years	Increases the risk of NOD

28.	Zanchetti, 2006[45]	Milano, Italy	RCT	15245	Adult hypertension patients	DHP CCBs (Amlodipine) versus ARBs (Valsartan)	6 years	CCB use lowered heart failure risk in women but increased it in men. Stroke prevention was evident in patients without prior stroke, yet attenuated in those with previous events
29.	Zhang, 2022[46]	US Nurses' Health Study (NHS) and Health Professionals Follow-up Study (HPFS)	Cohort study	143409	Female (30–55 years), Male (40–75 years), included both hypertensive and non-hypertensive	CCBs versus ACEIs/ARBs, BB, Diuretic	28 years	Not associated with risk of colorectal cancer

Abbreviations: ACEIs, Angiotensin Converting Enzyme Inhibitors; ARBs, Angiotensin Receptor Blockers; BB, Beta Blockers; BMD, Bone Mineral Density; CCBs, Calcium Channel Blockers; DHP, Dihydropyridines; GFR, Glomerular Filtration Rate; HDL, High Density Lipoprotein; LDL, Low Density Lipoprotein; NOD, New-Onset Diabetes Mellitus; NOF, New-Onset Fracture; RCT, Randomized Controlled Trial; SR, Sustained Release; TIA, Transient Ischemic Attack; UAE, Urinary Albumin Excretion; US, United States; USA, United States of America.

https://doi.org/10.2147/DHPS.S576249

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Table 3 Summary of Findings: Long-Term Safety of CCB

Outcomes	Impact	No Participants (Studies)
Renal Safety (8 Studies)		
Follow-up: 1 year	While enalapril significantly reduced albuminuria (641 → 292 mg/24 h, $p < 0.01$), nicardipine did not, showing its limited renal protective effect. Amlodipine preserved renal function over 12 months but did not improve albuminuria or renal parameters, suggesting that while CCBs like amlodipine and nicardipine are renal-safe, ACEIs like enalapril offer superior renal protection through significant reductions in albuminuria.	130 (1 RCT, 1 Cohort Study)[14,39]
Follow-up: 2 years	While CCBs like nicardipine and nitrendipine can lower blood pressure and have some effect on UAE, their renal protective effects are significantly weaker than those of ACEIs. Enalapril and ramipril demonstrated greater reductions in UAE, with enalapril decreasing UAE by over 50% in 1 year (77.1 to 30.4 mg/24 h) and ramipril outperforming nitrendipine. These findings highlight the superior antiproteinuric and renal-protective benefits of ACEIs compared to CCBs in hypertensive patients.	91 (2 RCT)[25,29]
Follow-up: 4.2 years	Creatinine abnormalities were more frequent in the amlodipine group (1.1%) than with candesartan (0.8%), and ESRD also occurred more often (0.4% vs 0.2%). These results suggest that CCBs may carry a slightly higher risk for renal function decline.	4703 (1 RCT)[17]
Follow-up: 5 years	Atenolol, lisinopril, and non-DHP CCBs demonstrated comparable impacts on proteinuria; however, renal function declined more rapidly in patients receiving atenolol. Additionally, enalapril showed superior antiproteinuric efficacy compared to nifedipine (254% vs 111% albuminuria reduction), indicating that ACEIs like enalapril may offer greater renal protection than CCBs in patients with hypertension.	154 (2 RCT)[24,26]
Follow-up: 6 years	The frequency of creatinine abnormalities was marginally greater with amlodipine (1.4%) than with candesartan (1.2%). Similarly, ESRD occurred in 0.6% of the amlodipine group vs 0.3% in candesartan, showing a slightly higher risk with amlodipine.	4703 (1 RCT)[18]
New-Onset Diabetes (NOD) (6 Studies)		
Follow-up: 3 years	Compared with nifedipine users (3.0%), individuals treated with co-amilozide showed an increased occurrence of NOD (4.3%).	6321 (1 RCT)[13]
Follow-up: 4.2 years	Relative to amlodipine (13.3 per 1000 patient-years), candesartan and valsartan were associated with a 29% (HR = 0.71, $p = 0.0495$) and 21% (RR = 0.79; 95% CI: 0.68–0.92) lower incidence of NOD, respectively. These findings suggest a comparatively higher risk of diabetes development among amlodipine users than those receiving ARBs.	33400 (1 RCT, 1 Cohort study)[17,44]
Follow-up: 6 years	Although the overall class effect of CCBs was not statistically associated with NOD (OR = 1.05; 95% CI: 0.96–1.13), amlodipine showed a higher incidence of diabetes compared with candesartan (13.3 vs 9.5 per 1000 patient-years), suggesting a possible increased risk with extended amlodipine exposure.	13341 (1 Case control, 1 RCT)[18,37]
Follow-up: 10 years	Candesartan reduced the risk of NOD by approximately 30% compared with amlodipine (HR = 0.75; 95% CI: 0.57–1.00)	1313 (1 RCT)[38]

Breast Cancer (5 Studies)		
Follow-up: 5 years	CCBs use was associated with an elevated risk of breast cancer (OR = 1.77; 95% CI: 0.99–3.17), particularly among women with BMI ≥25 (OR = 2.54; 95% CI: 1.24–5.22). CCBs were linked to aggressive tumors: invasive (OR = 1.96), non-ductal (OR = 3.97), and ERBB2+ (OR = 2.97).	3631 (1 Case control)[31]
Follow-up: 6 years	DHP CCBs showed a 21% higher likelihood of breast cancer (OR = 1.21; 95% CI: 0.88–1.67), although the association did not reach statistical significance.	46985 (1 Case control)[27]
Follow-up: 10 years	Increased odds of ductal and lobular breast cancers were observed among CCB users, with respective ORs of 2.4 (95% CI: 1.2–4.9; p-trend = 0.036) and 2.6 (95% CI: 1.3–5.3; p = 0.008).	2763 (1 Case control)[36]
Follow-up: 12 years	Prolonged exposure to CCBs, extending up to 12 years, was associated with a modest reduction in the risk of invasive breast cancer among older hypertensive women with a HR of 0.98 (95% CI: 0.31–3.07), but it is not significant.	109752 (1 Cohort Study)[40]
Follow-up: 16 years	Prolonged use of CCBs did not demonstrate an increased risk of breast cancer (OR = 0.91; 95% CI: 0.67–1.21). Overall, the evidence indicates that CCB therapy is not linked to the development of breast malignancy.	53625 (1 Case control)[41]
Bone Fracture (including Osteoporotic Fracture) (3 Studies)		
Follow-up: 5 years	BB users showed superior bone metabolism parameters in maxillary regions (incisor p = 0.034; premolar p = 0.013; mean p = 0.008) compared with CCB users.	294 (1 Cohort)[15]
Follow-up: 6.8 years	Individuals receiving long-term CCB therapy experienced approximately a 34% reduction in the risk of non-vertebral fractures compared with those not using CCBs (HR = 0.66; 95% CI: 0.43–1.02). This potential protective trend appeared less pronounced than the effects observed with ACEIs (HR = 0.62; 95% CI: 0.45–0.85) and was markedly weaker than that associated with ARBs (HR = 0.19; 95% CI: 0.08–0.47).	2573 (1 Cohort)[35]
Follow-up: 11 years	Long-term administration of CCBs appeared to lower the incidence of NOF by about 30% relative to nonusers, as indicated by an HR of 0.70 (95% CI: 0.49–0.99).	1144 (1 Cohort)[28]
Cancer Colorectal (CRC) (1 Study)		
Follow-up: 28 years	CCBs use did not demonstrate a statistically significant relationship with CRC occurrence (HR = 0.92; 95% CI: 0.57–1.46) or mortality related to CRC (HR = 0.49; 95% CI: 0.20–1.19).	143409 (1 Cohort Study)[46]
Dementia (1 Study)		
Follow-up: 3.9 years	Nitrendipine users experienced a 55% reduction in dementia incidence relative to the placebo group (3.3 compared with 7.4 cases per 1000 patient-years). The association persisted after adjustment, showing an HR of 0.38 (95% CI: 0.23–0.64).	2902 (1 RCT)[30]

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https://doi.org/10.2147/DHPS.S576249

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Table 3 (Continued).

Outcomes	Impact	No Participants (Studies)
Dyslipidemia (1 Study)		
Follow-up: 4 years	CCBs (Amlodipine) reduces total cholesterol by 0.17 mmol/L, HDL by 0.05 mmol/L, triglycerides declined by 0.21 mmol/L, and LDL by 0.13 mmol/L. These changes are beneficial but less pronounced compared to those seen with doxazosin or enalapril.	902 (1 RCT)[33]
Gout (1 Study)		
Follow-up: 3 years	Gout occurred in 2.1% of patients receiving co-amilozide compared to 1.3% of those treated with nifedipine	902 (RCT)[13]
Sexual function (1 Study)		
Follow-up: 2 years	Among individuals treated with amlodipine, a reduction in sexual activity was noted in 22.5% of men and 26.4% of women, suggesting a moderate influence on sexual function across both genders.	902 (RCT)[34]
Type 2 Diabetes (1 Study)		
Follow-up: 6 years	CCBs showed a modest 17% elevation in the likelihood of developing type 2 diabetes compared to other antihypertensive agents; however, this increase was not statistically significant (HR = 1.17; 95% CI: 0.85–1.62).	3804 (1 Cohort Study)[32]

Abbreviations: ACEIs, Angiotensin Converting Enzyme Inhibitors; ARBs, Angiotensin Receptor Blockers; BB, Beta Blockers; BMI, Body Mass Index; CCBs, Calcium Channel Blockers; CI, Confident Interval; DHP, Dihydropyridines; ESRD, End Stage Renal Disease; HDL, High Density Lipoprotein; HR, Hazard Ratio; LDL, Low Density Lipoprotein; NOD, New Onset Diabetes Mellitus; NOF, New Onset Fracture; OR, Odds Ratio; RCT, Randomized Controlled Trial; RR, Relative Risk; UAE, Urinary Albumin Excretion.

Table 4 Summary of Findings: Long-Term Effectiveness of CCBs

Outcomes	Impact	No Participants (Studies)
Stroke (including cerebral haemorrhage and infarction) (5 Studies)		
Follow-up: 2 years	The use of DHP CCBs resulted in a 42% decrease in the overall incidence of stroke relative to the placebo group, dropping from 13.7 to 7.9 cases for every 1000 patient-years (p=0.003).	4695 (1 RCT)[43]
Follow-up: 3 years	CCBs (Manidipine) shows a lower incidence of cerebral haemorrhage at 1.6 per 1000 patient-years, while cerebral infarction is higher at 6.3 per 1000 patient-years compared to the ACEIs group.	1748 (1 RCT)[16]
Follow-up: 4.2 years	The incidence of stroke was marginally greater in patients receiving CCBs (Amlodipine) (2.4%) than in those treated with candesartan (2.1%)	4703 (1 RCT)[17]
Follow-up: 6 years	CCBs (Amlodipine) had a slightly lower stroke incidence than candesartan (2.5% vs 3.0%). Compared to valsartan, amlodipine reduced stroke risk in patients without prior stroke (2.6% vs 3.4%), but valsartan was more effective in those with a history of stroke (7.5% vs 8.3%).	19948 (2 RCT)[18,45]
Heart Failure (5 Studies)		
Follow-up: 2 years	Patients receiving CCBs were more frequently diagnosed with heart failure, with a rate of 34% versus 23% in non-CCB users.	314 (1 Cohort study)[42]
Follow-up: 3 years	Heart failure was rare in the CCBs group, with a rate of 0.4 per 1000 patient-years, compared to ACEIs (2.0), implying that manidipine might help decrease heart failure risk among older hypertensive patients.	1748 (1 RCT)[16]
Follow-up: 4.2 years	The rate of heart failure was marginally reduced in patients receiving amlodipine (0.5%) compared to candesartan (0.6%).	4703 (1 RCT)[17]
Follow-up: 6 years	CCBs (Amlodipine) was linked to a marginally lower incidence of heart failure compared to candesartan (0.9% versus 1.1%). However, when compared to valsartan, the outcomes varied by sex: in males, amlodipine showed a higher incidence of heart failure (5.8% versus 4.1%), while in females, it showed a lower incidence (4.6% versus 5.3%).	19948 (2 RCT)[18,45]
Angina Pectoris (3 Studies)		
Follow-up: 3 years	CCBs (Manidipine) showed an incidence of angina pectoris of 6.3 per 1000 patient-years, indicating that this drug has an effect on reducing myocardial ischemic symptoms compared to the ACEIs group which showed a higher incidence (8.0).	1748 (1 RCT)[16]
Follow-up: 4.2 years	Amlodipine users showed a greater frequency of angina pectoris (0.6%) than those on candesartan (0.3%).	4703 (1 RCT)[17]
Follow-up: 6 years	The incidence of angina pectoris was 0.9% in the amlodipine group compared to 0.5% with candesartan.	4703 (1 RCT)[18]
Myocardial Infarction (3 Studies)		
Follow-up: 3 years	The incidence of myocardial infarction in manidipine users was recorded at 2.4 per 1000 patient-years, slightly higher than that of ACEIs (1.6), but this difference is not statistically significant.	1748 (1 RCT)[16]
Follow-up: 4.2 years	CCB (amlodipine) showed a higher risk of AMI 0.8% than candesartan (0.7%).	4703 (1 RCT)[17]

(*Continued*)

https://doi.org/10.2147/DHPS.S576249

Table 4 (Continued).

Outcomes	Impact	No Participants (Studies)
Follow-up: 6 years	AMI occurred in 1.1% of patients treated with amlodipine versus 0.9% in the candesartan group.	4703 (1 RCT)[18]
TIA (3 Studies)		
Follow-up: 3 years	The use of manidipine also shows a low incidence of TIA, namely only 1.2 per 1000 patient-years, indicating a possible protective effect against mild ischemic events.	1748 (1 RCT)[16]
Follow-up: 4.2 years	A marginal increase in TIA incidence was observed among patients on amlodipine (0.6%) relative to those on candesartan (0.4%).	4703 (1 RCT)[17]
Follow-up: 6 years	TIA was numerically more frequent in the amlodipine group (0.2%) versus candesartan (0.1%).	4703 (1 RCT)[18]

Abbreviations: ACEIs, Angiotensin Converting Enzyme Inhibitors; AMI, Acute Myocardial Infarction; ARBs, Angiotensin Receptor Blockers; CCBs, Calcium Channel Blockers; RCT, Randomized Controlled Trial; TIA, Transient Ischemic Attack.

https://doi.org/10.2147/DHPS.S576249

Table 5 Quality Assessment RCTs Using Jadad Scale

No	Author, Publication Year	Randomization Reported	Randomization Adequately Described	Blinding Reported	Blinding Adequately Described	Withdrawals/ Dropouts Reported	Total Score
1.	Bakris, 1996[24]	1	0	0	0	1	2
2.	Bianchi, 1991[14]	1	1	0	0	0	2
3.	Bigazzi, 1993[25]	1	1	0	0	1	3
4.	Brown, 2000[13]	1	1	1	1	1	5
5.	Chan, 2000[26]	1	0	1	1	1	4
6.	Fogari, 1999[29]	1	0	0	0	1	2
7.	Forette, 2002[30]	1	0	1	0	0	2
8.	Grimm, 1996[33]	1	1	1	1	0	4
9.	Grimm, 1997[34]	1	0	1	1	0	3
10.	Liu, 2018[38]	1	1	0	0	1	3
11.	Ogihara, 2000[16]	0	0	0	0	1	1
12.	Ogihara, 2008[17]	1	0	0	0	1	2
13.	Ogihara, 2011[18]	1	0	1	1	1	4
14.	Staessen, 1997[43]	1	1	1	1	1	5
15.	Zanchetti, 2006[45]	1	0	1	1	0	3

credibility of the synthesized findings. A detailed summary of the quality appraisal results is presented in Table 5 for RCTs, Table 6 for cohort studies, and Table 7 for case-control designs.

Long-Term Safety of CCBs

Renal Safety

Studies consistently showed that ACEIs (eg, enalapril, ramipril) provided superior renal protection compared to CCBs (eg, amlodipine, nicardipine).[14,39] Enalapril and ramipril reduced urinary albumin excretion by >50%, while CCBs showed minimal effect on proteinuria.[26,32] In a 4.2-year study, amlodipine was associated with higher creatinine abnormalities (1.1% vs 0.8%) and end-stage renal disease (ESRD) (0.4% vs 0.2%) compared to candesartan.[17]

A 5-year RCT showed that while atenolol, lisinopril, and non-DHP CCBs had comparable effects on proteinuria, atenolol was linked to faster renal function decline. In the same study, enalapril reduced albuminuria by 254%, compared to 111% with nifedipine.[24,26] In a 6-year cohort, creatinine abnormalities were reported in 1.4% of patients receiving amlodipine versus 1.2% in the candesartan group, while ESRD occurred in 0.6% vs 0.3%, respectively.[18]

New-Onset Diabetes (NOD)

Four studies investigated the development of NOD during prolonged exposure to CCBs. In one 3-year RCT, diabetes occurred more frequently in patients treated with co-amilozide (4.3%) than in those receiving nifedipine (3.0%).[13] A combined analysis of a RCTs and cohort study with an average follow-up duration of about 4.2 years, amlodipine use was associated with a higher rate of NOD (13.3 cases per 1000 person-years), whereas treatment with candesartan and

https://doi.org/10.2147/DHPS.S576249

Table 6 Quality Assessment Cohort Study Using Newcastle-Ottawa Scale

No	Author, Publication Year	Selection				Comparability	Outcome			Total Score
		Representativeness	Non-Exposed Group Selection	Ascertainment of Exposure	No Outcome Initially		Outcome Assessment	Follow-Up Adequate	Follow-Up Completeness	
1.	Ağaçayak, 2014[15]	*	*	*	*		*	*		6
2.	Chen, 2016[28]	*	*	*	*	**	*	*	*	9
3.	Gress, 2014[32]	*			*	*	*	*	*	6
4.	Kwok, 2017[35]	*	*			**	*	*	*	7
5.	Nishida, 2017[39]	*	*	*	*	**	*	*	*	9
6.	Raebel, 2017[40]	*	*		*	**	*	*	*	8
7.	Saeed, 2020[42]		*	*	*	**	*	*	*	8
8	Weycker, 2007[44]	*	*	*	*	**	*	*	*	9
9.	Zhang, 2022[46]	*	*	*	*	**	*	*	*	9

Notes: (*) indicates that the criterion was met and awarded one star; (**) indicates that two stars were awarded for the comparability domain.

Table 7 Quality Assessment Case Control Using Newcastle-Ottawa Scale

No	Author, Publication Year	Selection				Comparability	Outcome			Total Score
		Case Definition	Representativeness	Control Selection	Definition of Controls		Assessment of Exposure	Same Method for Cases/ Controls	Non-Response Rate	
1.	Chang, 2016[27]	*	*	*	*	**	*	*	*	9
2.	Gómez-Acebo, 2016[31]	*	*	*	*	**	*	*		8
3.	Li, 2013[36]	*	*	*	*	**	*	*	*	9
4.	Liou, 2008[37]	*	*	*	*	*	*	*	*	8
5.	Rotshild, 2022[41]	*	*	*	*	**	*	*	*	9

Notes: (*) indicates that the criterion was met and awarded one star; (**) indicates that two stars were awarded for the comparability domain.

valsartan was associated with risk reductions of approximately 29% (HR 0.71, p = 0.0495) and 21% (RR = 0.79), respectively.[17,44]

In a 6-year case-control and RCTs analysis, amlodipine again showed higher NOD incidence (13.3 vs 9.5 per 1000 person-years), but the overall CCB group showed no meaningful statistical association (OR = 1.05; 95% CI: 0.96–1.13).[18,37] In a 10-year observational follow-up, candesartan was shown to decrease the risk of NOD by roughly 30% relative to amlodipine (HR = 0.75; 95% CI 0.57–1.00), highlighting differences among antihypertensive drug classes.[38]

Breast Cancer

Several observational studies, including both cohort and case-control designs, have evaluated whether long-term exposure to CCBs contributes to the development of breast cancer. In one investigation with a 5-year observation period, a higher probability of breast cancer was reported among women using CCBs (OR = 1.77; 95% CI: 0.993.17). The risk appeared more pronounced among women with elevated BMI (OR = 2.54) and in those diagnosed with more aggressive histologic subtypes, such as non-ductal (OR = 3.97), invasive (OR = 1.96), and ERBB2-positive cancers (OR = 2.97).[27] Another study reported a 21% increased risk with ≥6 years of DHP CCBs use (OR = 1.21), though not statistically significant (CI: 0.88–1.67).[37] In a 10-year study, current use of CCBs was linked to elevated risks of ductal (OR = 2.4) and lobular breast cancer (OR = 2.6).[33] Conversely, two large studies (12 and 16-year follow-up) found no significant increase in risk (HR = 0.98 and OR 0.91, respectively), suggesting inconsistency in long-term associations.[40,42]

Bone Health

Two cohort studies indicated that prolonged CCB therapy was linked to lower fracture risks. One study found approximately a 34% reduction in non-vertebral fractures, with the effect estimate around 0.66 (CI: 0.43–1.02).[31] Another reported a 30% lower likelihood of femoral neck fractures, with the risk estimate near 0.70 (CI: 0.49–0.99),[28] though these effects were less pronounced than with ACEIs (HR = 0.62) or ARBs (HR = 0.19).[35] Imaging studies also indicated CCBs conferred less benefit to BMD compared to beta-blockers.[15] This suggests CCBs may have a neutral to modestly protective effect, though less consistent than ACEIs/ARBs or beta-blockers.

Other Systemic Effects

A cohort study with a 28-year observation period reported no meaningful correlation between prolonged CCB exposure (≥11 years) and the likelihood of developing colorectal cancer (CRC), with the risk estimate hovering around 0.92 (CI: 9.57–1.46). Likewise, mortality related to CRC showed a comparable pattern, with an estimated value near 0.49 and limits of 0.20 to 1.19.[46] In an RCT conducted over nearly four years, nitrendipine therapy was linked to a 55% reduction in dementia risk compared to placebo. The incidence was 3.3 per 1000 person-years in the treatment group versus 7.4 in the control group (HR = 0.38; 95% CI: 0.23–0.64; p < 0.001).[30] A 4-year trial showed that amlodipine improved lipid profiles modestly, decreasing total cholesterol by 0.17 mmol/L and triglycerides by 0.21 mmol/L, but was less effective than doxazosin or enalapril.[33]

In the INSIGHT trial, gout occurred in 2.1% of patients receiving co-amilozide compared to 1.3% of those treated with nifedipine, indicating a slightly lower gout incidence with long-term CCBs use.[13] Regarding sexual function, 22.5% of men and 26.4% of women reported decreased sexual frequency after 48 months of amlodipine use.[34] The cohort suggested about a 17% rise in diabetes risk among CCB recipients; the estimated HR was close to 1.17, and the CI (0.85–1.62) indicated no statistically meaningful difference.[32]

Long-Term Effectiveness

Multiple studies in hypertensive populations have demonstrated that prolonged CCB therapy correlates with a reduced occurrence of stroke events. Treatment with nitrendipine reduced the total stroke rate by 42% from 13.7 to 7.9 cases per 1000 patient-years.[43] Manidipine showed a lower incidence of cerebral hemorrhage than ACEIs (1.6 vs 6.3 per 1000 patient-years).[16] In the CASE-J trial and its extension study evaluating the same cohort with longer follow-up,

amlodipine showed a slightly lower stroke incidence than candesartan (2.5% vs 3.0%) and demonstrated reduced stroke occurrence particularly, in patients without prior cerebrovascular events.[17,18,45]

For other cardiovascular outcomes, findings varied across studies. Within the CASE-J cohort and its extension, TIA occurred more frequently among amlodipine users than in the candesartan group (eg, 0.6% vs 0.4%).[17,18] Angina pectoris was also more common in CCB users in two studies, with incidence rates of 0.6% and 0.9% versus 0.3% and 0.5% in the candesartan group, respectively.[17,18] However, one study reported a lower angina rate with manidipine compared to ACEIs (6.3 vs 8.0 per 1000 patient-years).[16] Patients in the amlodipine group exhibited a slightly higher rate of acute myocardial infarction (AMI) than those receiving candesartan (1.1% vs 0.9%[18] and 0.8% vs 0.7%[17]). However, other trials did not observe a meaningful difference in AMI rates between treatment groups.[16] Heart failure rates were generally low,[16–18] but appeared marginally increased with CCBs in some studies.[42,45] Overall evidence supports the sustained stroke preventive benefit of CCBs, though their influence on other cardiovascular outcomes, including TIA, angina, heart failure, and myocardial infarction, shows considerable heterogeneity.

Discussion

Overview

Long-term CCB therapy shows acceptable safety and sustained benefit in lowering stroke incidence. Potential safety concerns have been reported in several domains, including renal function,[14,17,18,24–26,29,39] NOD,[17,18,37,38,44] breast cancer risk,[27,31,36,40,41] and bone health.[15,28,35] Cardiovascular outcomes beyond stroke showed mixed results, with some studies reporting benefits in heart failure, while others noted a higher incidence of TIA, angina, and myocardial infarction.[16–18,42,43,45] Additional systemic outcomes, including CRC,[46] dementia,[30] gout,[13] sexual dysfunction,[34] and dyslipidemia,[33] were also reported across the included studies. Importantly, the majority of evidence included in this review is derived from studies evaluating DHP CCBs, particularly amlodipine and nifedipine. In contrast, evidence regarding non-DHP CCBs remains limited. Consequently, the observed safety and effectiveness outcomes primarily reflect the effects of DHP CCBs rather than the entire CCB class. These effects may further vary according to treatment duration and patient characteristics, underscoring the importance of individualized therapy and careful monitoring in long-term clinical use.

Renal Safety

DHP CCBs (eg, amlodipine, nicardipine) are generally safe for kidney function,[14,39] but show limited antiproteinuric effects, with some studies reporting a higher incidence of ESRD over long-term follow-up.[18,24–26,29] In contrast, evidence from one trial suggested that non-DHP CCBs (verapamil, diltiazem) had proteinuria outcomes comparable to lisinopril and atenolol, indicating no clear disadvantage in renal safety.[24] CCBs, particularly DHP, act primarily as vasodilators on afferent arterioles of the glomerulus. This vasodilation increases glomerular capillary pressure, potentially contributing to glomerular hyperfiltration and proteinuria, especially if not balanced by efferent vasodilation.[47]

However, it is important to recognize that not all DHP CCBs exert identical renal hemodynamic effects. While conventional DHP CCBs predominantly dilate the afferent glomerular arteriole, potentially increasing intraglomerular pressure and proteinuria, newer agents such as lercanidipine appear to demonstrate a more balanced renal vascular profile. Owing to its high lipophilicity and sustained interaction with vascular smooth muscle cell membranes, lercanidipine has been reported to induce vasodilation of both afferent and efferent glomerular arterioles. This dual action may contribute to a reduction in intraglomerular pressure and improved control of proteinuria beyond blood pressure lowering alone. Nevertheless, although several randomized and observational studies have evaluated the renal effects of lercanidipine over intermediate follow-up periods, robust long-term randomized trials specifically designed to assess hard renal outcomes are still lacking.[48] Overall, while CCBs are acceptable for long-term use, their renoprotective effects remain limited, warranting close monitoring of renal health in individuals presenting with reduced kidney function or urinary albumin loss.

New-Onset Diabetes (NOD)

Long-term administration of CCBs, particularly amlodipine, has been linked to a modestly elevated risk of NOD.[17,18,37,38,44] Mechanistically, this effect is believed to stem from reduced calcium entry through L-type channels in pancreatic β-cells, leading to impaired insulin release and a decline in glucose tolerance over time.[49] Current evidence mainly involves DHP CCBs, while data for non-DHP CCBs remain limited. Among patients at elevated risk of developing diabetes, including those with impaired glucose tolerance, metabolic syndrome, or a family history of the disease, CCBs should be prescribed with caution and accompanied by regular glucose monitoring.

Breast Cancer

Evidence regarding the association between prolonged CCB exposure and breast cancer risk remains inconsistent and inconclusive. Some studies mention an increased risk,[31] especially with usage of ≥5 years and in aggressive cancer subtypes, whereas others have reported no statistically meaningful difference in incidence.[27] Some hypotheses suggest that CCBs may disrupt cell apoptosis through intracellular calcium regulation, potentially increasing tumor cell proliferation. However, direct biological evidence is still limited.[36,40,41] Given these uncertainties and the observational nature of most studies, the findings should be interpreted with caution. For women at elevated baseline risk, careful monitoring and individualized risk-benefit assessment are warranted when prescribing CCBs.

Bone Health

Several observational studies have reported inconsistent findings regarding the association between CCB use and fracture risk. Two studies reported that CCB users have a lower risk of non-vertebral fractures and femoral neck fractures.[28,35] However, one study showed a negative effect on bone metabolism compared to beta-blockers.[15] CCBs may influence calcium homeostasis in osteoblast and osteoclast cells, which is crucial in bone remodeling. Blocking L-type calcium channels in bones may inhibit osteoblast activity, reducing the formation of new bone.[50] Certain CCBs have been reported to reduce BMD in craniofacial sites such as the maxilla, potentially increasing susceptibility to fractures in older adults.[15]

The protective effect against fractures is seen in studies lasting over 5 years. However, other studies with shorter durations or specific populations (eg, older men) show less consistent results, indicating that the effects may depend on duration and patient characteristics.[15] Given the potential implications for bone health, clinicians are advised to exercise caution when prescribing CCBs to individuals with elevated fracture or osteoporosis risk. Regular monitoring of BMD may be considered in such patients.[51] For elderly patients or postmenopausal women, combining with calcium/vitamin D supplements or lifestyle modifications may be a mitigating step.[52]

Other Systemic Effects

Other systemic effects associated with CCBs use include neurological, metabolic, and reproductive domains. For instance, nitrendipine has been linked to a reduced risk of dementia, possibly because it can penetrate the central nervous system and mitigate neuronal calcium overload, which plays a critical role in neurodegeneration.[30] Amlodipine has also demonstrated minor improvements in lipid parameters, although these effects are not clinically significant compared to lipid-lowering agents.[33] Regarding sexual function, prolonged amlodipine therapy has been associated with a decline in sexual activity among both male and female patients. Although the underlying mechanism has not been fully elucidated, changes in vascular tone and reduced genital blood flow may contribute to this effect.[34]

Moreover, CCBs appear to have a more favorable uric acid profile than diuretics, with a lower incidence gout reported in comparative trials such as INSIGHT.[13] These results suggest that CCBs may be a suitable antihypertensive option for individuals with hyperuricemia or those at risk for gout.[13] In clinical practice, while these adverse effects are generally mild, they warrant consideration in vulnerable populations. When prescribing CCBs, clinicians should weigh these risks, provide appropriate monitoring, and consider patient-specific comorbidities when deciding on long-term antihypertensive therapy.

Long-Term Effectiveness

CCBs have demonstrated sustained effectiveness in preventing stroke among hypertensive individuals, mainly through inhibition of L-type calcium channels that mediate vascular smooth muscle contraction.[16–18,43,45] This mechanism lowers peripheral resistance and improves cerebral perfusion, contributing to reduced stroke risk. In addition, DHP CCBs, such as amlodipine, enhance endothelial nitric oxide activity, improving vascular function beyond blood pressure control.[53]

However, outcomes beyond stroke are more heterogeneous. Some studies have reported increased risks of heart failure, angina, myocardial infarction, and TIA, especially with DHP CCBs,[16–18,42,43,45] potentially related to reflex tachycardia and increased myocardial oxygen demand.[54] By contrast, clinical statements suggest that non-DHP CCBs (verapamil, diltiazem) may confer benefit for ischemic heart disease, owing to their heart rate-lowering and anti-angina properties.[55,56] Taken together, these findings highlight the clinical relevance of subclass differentiation: DHP CCBs appear more favorable for stroke prevention, while non-DHP CCBs show potential value among patients with ischemic heart disease. Overall, while CCBs demonstrate robust effectiveness for stroke prevention, their impact on other cardiovascular outcomes appears variable, underscoring the importance of subclass differentiation, individualized therapy, and careful long-term monitoring.

Strengths and Limitations

This review is among the first to comprehensively evaluate the long-term use of CCBs across multiple organ systems in hypertensive populations. By integrating evidence from both RCTs and observational studies, it provides a broad perspective that captures findings from controlled trial settings as well as real-world practice. A narrative synthesis was chosen given the methodological and clinical heterogeneity across studies, which, while limiting the possibility of direct quantitative comparison, allowed a balanced integration of diverse outcomes and designs.

Nevertheless, several limitations should be acknowledged. The findings may be affected by publication bias and residual confounding inherent to observational studies and should therefore be interpreted with appropriate caution. Importantly, the majority of available evidence pertains to DHP CCBs, whereas data on non-DHP agents remain limited, restricting subclass-specific comparisons and limiting the generalizability of the findings to the entire CCB class. Furthermore, several key trials included in this review were conducted in earlier treatment eras, during which clinical practice patterns, background therapies, and patient risk profiles differed from contemporary hypertension management, potentially limiting the applicability of some findings to current clinical settings.[33]

Suggestions for Further Research

Future studies should employ prospective longitudinal designs to clarify the long-term safety and cardiovascular effectiveness of CCBs, with a focus on outcomes such as renal dysfunction, NOD, bone health, and cancer. Mechanistic investigations are also needed to better explain these associations and to inform more personalized hypertension management.

Conclusion

This systematic review indicates that CCBs remain acceptable for long-term therapy in hypertensive patients, demonstrating an overall reassuring safety profile when appropriately monitored, particularly among high-risk populations. Most supporting evidence is derived from studies of DHP CCBs, whereas evidence for non-DHP CCBs remains limited and warrants cautious interpretation. RCTs support the sustained effectiveness of CCBs in stroke prevention and suggest generally neutral to modest effects on metabolic parameters and selected renal outcomes. In contrast, associations with long-term metabolic, oncologic, and skeletal risks are largely derived from observational studies and remain inconsistent. Evidence regarding heart failure, myocardial infarction, and TIA is heterogeneous across study designs, precluding definitive conclusions. Clinically, these findings support the continued use of CCBs within current hypertension management strategies while emphasizing individualized treatment decisions, appropriate subclass selection, and long-term monitoring. Further high-quality prospective studies are warranted to clarify unresolved safety signals and to inform future clinical guidelines.

Acknowledgments

The authors acknowledge the institutional support provided by Universitas Padjadjaran throughout the conduct of this review.

Disclosure

The authors report no conflicts of interest in this work.

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