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# Comparison effectiveness, side effect and long-term tolerability of amlodipine and cilnidipine

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## Abstract

Hypertensive patients usually benefit from selective antihypertensive medications like Calcium Channel Blockers. Amlodipine and Cilnidipine both comes under Calcium Channel Blockers.Both the drugs use widely to control hypertension. Amlodipine is a third generation CCB comes under dihydropyridine and Cilnidipiene is a (long acting dihydropyridine) fourth generation CCB. Both the drugs has an excellent pharmacokinetic and pharmacodynamic profile. Both the drugs has significant percentage of safety and tolerability but Amlodipine has a typical side effect i.e. B/L Pedal edema. Around 5-10% of the patients are suffering from B/L Pedal edema with Amlodipine therapy which can be recovered after switching to Cilnidipine therapy. CCB related edema is caused by preferential arteriolar or precapillary dilation in the venous or postcapillary circulation. Amlodipine works by demonstrate prolonged efficacy by inhibiting voltage dependent L-type calcium channel. Cilnidipine works by blocking L-type & C-type both the calcium channel. Cilnidipine's dual mechanism of action allows for effective blood pressure reduction through vascular smooth muscle relaxation & arterial dilation, while also suppressing catecholamine release from sympathetic nerves. This unique pharmacological profile may explain cilnidipine's lower incidence of adverse effects, including pedal edema.

**Keywords:** Amlodipine; Cilnidipine; Pedal edema; N & L type Calcium Channel; CCB

## 1. Introduction

Hypertension is one of the most prevalent cardiovascular diseases in the world. It occurs when blood pressure continues to remain higher than what is considered normal, often defined as 140/90 mmHg or higher. Left untreated, it increases the risk of a heart attack, stroke, kidney damage and other complications. A diagnosis may be inferred from high readings of systolic or diastolic pressure, either when a person is already on antihypertensives.(1)

Several factors contribute to hypertension. Age, family history, obesity, physical inactivity, stress, smoking, alcohol consumption, and diets high in salt are some of the most frequent causes. Many individuals do not experience any symptoms, which is why the condition is often called a “silent killer.” However, extremely high readings (around

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180/120 mmHg or more) can produce symptoms such as severe headache, chest discomfort, dizziness, breathing difficulty, nausea, vomiting, blurred vision, confusion, nosebleeds, or irregular heartbeat.

According to the World Health Organisation (WHO), around 1.4 billion adults aged 30–79 years were living with hypertension in 2024—roughly one-third of the global population in that age group. Most of these individuals live in low- and middle-income countries. About 44% of people with hypertension are unaware of their condition, and although many receive treatment, only 23% have their blood pressure adequately controlled. Because hypertension contributes significantly to premature mortality, global health programmes aim to reduce uncontrolled cases by 25% between 2010 and 2025.(1,2)

## 2. Role of calcium channel blockers

Calcium channel blockers (CCBs) are one of the major first-line classes of drug medication used to treat hypertension, along with ACE inhibitors or ARBs and thiazide diuretics. They are widely used because they effectively lower blood pressure. They also work well with different patients of different age groups and generally have good tolerability.(2)

Amlodipine is one of the most commonly prescribed CCBs and has a long-established safety and efficacy record. However, Cilnidipine, which is also a dihydropyridine CCB, has an additional property: it blocks both L-type and N-type calcium channels. This dual action may influence sympathetic activity and produces a different safety profile, particularly regarding edema and kidney effects. Understanding these differences is important in selecting the most suitable agent for patients with conditions such as CKD, diabetes, or a tendency for ankle swelling.(3)

## 3. Mechanism of action

### 3.1. Amlodipine

The mechanism of Amlodipine works mainly by blocking L-type calcium channels in vascular smooth muscle. This causes arterial relaxation and lowers systemic vascular resistance, which reduces blood pressure. The strong arteriolar dilation can raise capillary pressure and may lead to fluid leakage into tissues, which explains the common complaint of ankle or pedal edema. Although amlodipine has a slow onset, mild reflex sympathetic activation may still occur in some patients. (4)

### 3.2. Cilnidipine

Cilnidipine blocks both L-type and N-type calcium channels. The L-type effect produces vasodilation similar to amlodipine, while the N-type effect reduces the release of norepinephrine from sympathetic nerve endings. This additional action can help reduce reflex tachycardia, reduce sympathetic overactivity, and may even reduce vasodilatory edema. Laboratory studies also suggest that N-type channel inhibition may help protect kidney cells (podocytes) and reduce protein loss in urine.(5)

Clinical effects of DHP CCBs, such as the blood pressure-lowering effect, are mainly related to their action on L-type calcium channels. In contrast to arterioles, venules seem not to respond to L-type CCB or agonist. This was proved by many studies which have shown that nifedipine could not dilate venules of striated muscle in spontaneously hypertensive rats, and L-type calcium channel agonists could not constrict venules of frog skin. Despite similar blood pressure reduction, the frequency of pedal edema varies between CCBs. Hence, its occurrence cannot be explained by a difference in their influence on peripheral arteries. Therefore, drugs that specifically inhibit L-type channels, like nifedipine, reduce the blood pressure by dilating resistance arterioles, but not venules, so that the pressure in the afferent capillaries peripheral to the resistance arteries increases above the oncotic pressure and extravasation occurs. In fact, a decrease in the frequency of pedal edema due to L-type calcium blockers is reported when these drugs are combined with ACEI, which have a vasodilatory effect on the venules. N-type calcium channels are distributed in the neurons and have an important role in regulating sympathetic activity. Sympathetic nerves are found in the venules, so drugs that block N-type calcium channels possibly cause vasodilation. Cilnidipine is a 1,4-DHP CCB that suppresses the influx of calcium ions via L-type and N-type calcium channels, thus reducing the blood pressure through vascular smooth muscle relaxation and arterial dilatation. It is used as an antihypertensive agent with a long duration of action that allows once-daily dosing.[25] Cilnidipine is known to suppress the catecholamine release from peripheral sympathetic nerves as it blocks the N-type channels in sympathetic nerve terminals, as well as having a common L-type calcium channel-blocking effect. It has been shown that cilnidipine does not cause coronary sympathetic hypertonia in response to blood pressure reduction, unlike L-type channel blockers. When administered to the patients with essential hypertension, cilnidipine suppressed cardiac sympathetic over activity and an increase of heart rate with blood

pressure reduction.[28] Previous study has also shown that cilnidipine is well-tolerated by hypertensive patients and associated with minor adverse effects such as headache, dizziness, cough, and gastrointestinal symptoms which are comparable to amlodipine. Accordingly, CCBs with an N-type channel blocking effect may dilate the venules through sympathetic nerves distributed to these vessels. Hence have a lesser incidence of pedal edema compared with the other CCBs, which act only on L-type calcium channels. (4)(5)

## 4. Pharmacokinetics

Amlodipine has a long half-life of 30–50 hours, allowing once-daily (OD) dosing and reducing blood pressure control. However, once side effects such as edema develop, they may persist due to the drug's long duration of action. The absolute bioavailability of amlodipine ranges from 64% to 90%. Food does not alter the bioavailability of amlodipine. Peak plasma concentrations are achieved between 6 and 12 hours. Steady-state plasma levels are achieved after 7 to 8 days of daily amlodipine dosing. Patients with hepatic dysfunction have decreased clearance of amlodipine. Accordingly, there is an increase in the area under the curve of approximately 40% to 60% in patients with liver conditions. Amlodipine has high plasma protein binding (93%).

Metabolism: Amlodipine is extensively metabolized by the liver to inactive metabolites. Cytochrome P-450 (CYP) CYP3A4 and CYP3A5 play an important role in the metabolism of amlodipine. Cilnidipine is also taken once daily, but its distribution and absorption is different compared to amlodipine. Its N-type blocking activity reduces the sympathetic responses, which are seen with L-type CCBs. Both drugs are metabolized in the liver, although through different pathways, so co-prescribed medications and liver function should be considered while choosing therapy. (6)

## 5. Comparative efficacy

Across several randomized trials and observational studies, both drugs show similar effectiveness in lowering systolic and diastolic blood pressure. Some studies show minor advantages for cilnidipine in ambulatory blood pressure patterns, but overall, the two drugs perform comparably. Due to this, safety and tolerability often become more influential in deciding which drug to use.(6,7)

## 6. Safety profile differences

### 6.1. Peripheral (Pedal) Edema

Edema is one of the most noticeable differences between the two drugs.

Amlodipine frequently causes dose-dependent peripheral edema because it dilates arterioles without similar venous dilation, thus increasing capillary pressure. (8)

Cilnidipine, however, has consistently shown lower rates of edema in studies involving patients with essential hypertension, diabetes, or CKD. The reduction is estimated to result from its N-type blocking effect, which decreases the sympathetic tone and stabilizes microcirculation. (9,10)

### 6.2. Heart Rate and Sympathetic Activity

As amlodipine acts mainly on L-type channels, some patients may experience mild reflex tachycardia. Cilnidipine, through both of its L-type and N-type inhibition, may reduce this response. Ambulatory monitoring studies often show a smaller increase or even a slight reduction in the heart rate with cilnidipine.(10)

### 6.3. Renal Effects and Proteinuria

Cilnidipine has shown promising kidney-related benefits by:

- Reducing proteinuria in several clinical trials
- Showing better preservation of podocyte structure in experimental models
- Giving synergistic benefits when combined with ACE inhibitors or ARBs

Amlodipine does not generally reduce proteinuria and may even worsen it in some cases of CKD. However, long-term kidney outcome data for cilnidipine are very limited compared with amlodipine's extensive cardiovascular outcome evidence.(11)

### 6.4. Other Adverse Effects

Both drugs can cause headaches, flushing, or dizziness. These effects are usually mild and very dose-dependent. Amlodipine has rare reports of angioedema and liver enzyme elevation due to its widespread global use. Cilnidipine has fewer global data because its use is concentrated mainly in Asian countries, so rare adverse events may not be fully characterized yet.(12,13)

## 7. Evidence summary

- **Randomized trials**: Similar BP-lowering effect; cilnidipine consistently shows lower edema and better proteinuria outcomes.
- **Mechanistic studies**: Support cilnidipine's dual mechanism and potential renal benefits.
- **Regulatory data**: Amlodipine has broader worldwide data; cilnidipine lacks large multinational safety datasets.
- **Meta-analyses**: Generally favour cilnidipine for tolerability, but results may vary due to small sample sizes and regional bias.(14)

## 8. Special populations

### 8.1. Chronic Kidney Disease / Proteinuria

Cilnidipine may be preferred due to its antiproteinuric effects, especially when albuminuria is an important clinical concern.(15)

### 8.2. Elderly Patients

Amlodipine generally has very strong long-term data and is reliable. Cilnidipine may be helpful in elderly individuals who develop edema easily or cannot tolerate swelling.

### 8.3. Diabetes

Both drugs are metabolically neutral. Cilnidipine also offers additional benefits in diabetic patients with proteinuria. (16)

### 8.4. Combination Therapy

Amlodipine-induced edema can often be reduced by adding an ACE inhibitor, ARB, or diuretic. Cilnidipine generally causes less edema, reducing the need for combination therapy purely for tolerability. (16,17)

## 9. Limitations of current evidence

- Much of the cilnidipine research has been conducted in Japan and India, limiting global representation.(17)
- Direct long-term outcome trials comparing the two drugs are lacking.(17,18)
- Sample sizes in many comparative studies are small.(19,20)
- Rare adverse events for cilnidipine are not well documented due to limited worldwide use.(21,22,23)

## 10. Practical takeaways

- Both drugs effectively lower BP. (24)
- Cilnidipine causes less edema and may be better for patients who struggle with swelling.(25)
- Cilnidipine has stronger evidence for reducing proteinuria, making it useful in CKD and diabetic kidney disease. (26)
- Amlodipine has a more extensive global safety record and is a dependable first-line option.(27,28,29)
- Therapy choice should depend on co-morbidities, tolerability, and availability.(30)

## 11. Conclusion

Although amlodipine and cilnidipine provide similar levels of blood pressure control, their safety profiles differ in meaningful ways. Cilnidipine's dual L- and N-type channel blocking action offers potential advantages—particularly less

peripheral edema and improved control of proteinuria. Amlodipine, however, remains a widely trusted and well-studied medication with strong long-term outcome data. Choosing between the two should be based on individual patient needs, side-effect patterns, kidney status, and overall clinical goals. More large-scale trials would help clarify long-term differences in cardiovascular and renal outcomes.

## Compliance with ethical standards

*Disclosure of conflict of interest*

No conflict of interest is there between author's.

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