**Short Communication**

# Hypertension Management Beyond BP Numbers — Exploring the Novel Calcium Channel Blocker Cilnidipine

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**Abstract**

**Background :** Hypertension poses a significant public health challenge in India, contributing substantially to cardiovascular and renal morbidity and mortality. The coexistence of hypertension with Type 2 Diabetes Mellitus (T2DM) and Chronic Kidney Disease (CKD) exacerbates the risk of target organ damage. Cilnidipine, a fourth-generation dihydropyridine calcium channel blocker, uniquely inhibits both L-type and N-type calcium channels.

**Discussion :** This dual action not only facilitates effective blood pressure reduction but also attenuates sympathetic nervous system activity, offering additional cardiovascular and renal protection. Clinical studies have demonstrated cilnidipine's superiority over traditional L-type calcium channel blockers, such as amlodipine, in reducing proteinuria and mitigating sympathetic overactivity. Furthermore, cilnidipine exhibits a favorable safety profile, with a lower incidence of adverse effects like pedal edema and reflex tachycardia, enhancing patient compliance.

**Conclusion :** Given the high prevalence of hypertension, T2DM, and CKD in the Indian population, cilnidipine emerges as a promising antihypertensive agent that addresses both hemodynamic and neurohormonal aspects of hypertension management. Its incorporation into treatment regimens could lead to improved clinical outcomes and reduced progression of hypertension-mediated organ damage.

**Key words :** Hypertension, Organ Damage, Chronic Kidney Disease, Diagnosis, Cilnidipine.

High Blood Pressure (BP) is a major public health concern in South Asia, where it ranked as the third leading risk factor for disease burden in 2010. In India, Hypertension (HTN) significantly impacts cardiovascular health and places a considerable strain on the healthcare system. It is directly responsible for 57% of all stroke-related deaths and 24% of deaths due to Coronary Heart Disease (CHD) in the country. Globally, the World Health Organization (WHO) identifies hypertension as one of the most critical causes of premature mortality. According to the Global and Regional Burden of Disease and Risk Factors Study (2001), hypertension in South Asia is second only to childhood undernutrition (measured as underweight for age) in terms of its contribution to death and disease burden[1].

***Editor's Comment :***

- Hypertension poses a significant public health challenge in India, contributing substantially to cardiovascular and renal morbidity and mortality.
- Diabetes and obesity are the leading co-morbidities seen in Indian Hypertensive patients, which contributes to substantial target organ damage – majorly renal and cardiovascular disease.
- Early and timely evaluation of organ damage is essential for accurate cardiovascular risk stratification and the implementation of effective, targeted treatment strategies. While lifestyle modifications are key in the management of hypertension, pharmacotherapy holds its significance in improving overall hypertension control. Among the Calcium channel blockers, this article focuses on Cilnidipine, a dual L/N-type calcium channel blocker, which has emerged as an ideal antihypertensive agent for Indian patients, offering effective BP control, superior renoprotection, and reduced cardiovascular risk.

## Hypertension Prevalence and Epidemiology – India:

Hypertension (HTN) is a growing epidemic in India, affecting approximately 35% of adults aged 25 years and above, with rural areas reporting a prevalence of 25% and urban areas nearing 40%. India also stands at a staggering 11% reported prevalence of Type 2 Diabetes Mellitus (T2DM), which puts the population at a high risk of organ damage mediated by these 2 lifestyle diseases. The India Microalbuminuria Study quotes a prevalence of 27% of microalbuminuria seen in Indian Hypertensive patients[1,2].

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### Awareness, Treatment and Control of Hypertension in India[2] :

According to the India Hypertension Control Initiative (IHCI), only 12% of individuals with hypertension in India achieve optimal Blood Pressure (BP) control. This poor control places a significant portion of the population at increased risk for cardiovascular events, stroke, and Chronic Kidney Disease (CKD).

A recent study published in the Lancet (2022) quoted that over 75% of individuals with hypertension are uncontrolled in India. Persistent patterns of undiagnosed, untreated and uncontrolled hypertension significantly elevate the risk of Hypertension-mediated Organ Damage (HMOD).

### Hypertension Mediated Organ Damage[3] :

The presence of HMOD is closely linked to increased vascular risk and higher mortality, amplifying the overall burden of hypertension. HMOD commonly affects critical organs such as the heart, kidneys, brain, and eyes. Early and timely evaluation of organ damage is essential for accurate cardiovascular risk stratification and the implementation of effective, targeted treatment strategies.

The Coronary Artery Risk Development in Young Adults (CARDIA) study revealed that individuals who developed hypertension before the age of 35 faced a significantly higher risk of target organ damage in midlife – including Left Ventricular Hypertrophy (LVH), coronary artery calcification, and left ventricular diastolic dysfunction – compared to those who developed hypertension at or after the age of 45. Notably, the study consistently identified the highest burden of organ damage across all evaluated systems in those with early-onset hypertension. The India Microalbuminuria Study also noted that >35% of young Indian hypertensive patients present with microalbuminuria to the physicians' clinic, with an overall 27% of hypertensive Indians suffering from some extent of kidney damage.

*Hypertension Mediated Organ Damage in the Heart*:[3]

Hypertension exerts continuous pressure on the heart, leading to both structural and functional changes that are often asymptomatic in the early stages. However, these changes substantially increase the risk of future cardiovascular events, including heart failure with preserved or reduced ejection fraction (HFpEF/HFrEF), Atrial Fibrillation (AF), Coronary Artery Disease (CAD) and Sudden Cardiac Death (SCD).

The 2023 European Society of Hypertension (ESH) Guidelines for the Management of Arterial Hypertension define cardiovascular Hypertension-mediated Organ Damage (HMOD) as the presence of increased arterial stiffness, non-hemodynamically significant atheromatous plaques detected on imaging, and Left Ventricular Hypertrophy (LVH). The guidelines further characterize preclinical or asymptomatic hypertensive heart disease by the presence of LVH, changes in left ventricular geometry, impaired diastolic and systolic function, left atrial enlargement, and a heightened risk of arrhythmias.

### Hypertension Mediated Organ Damage in the Kidneys[3] :

Hypertension is recognized as the second most common cause of Chronic Kidney Disease (CKD) and can also develop because of primary renal disorders. Kidney function is primarily assessed through estimated Glomerular Filtration Rate (eGFR) and the presence of microalbuminuria – both key indicators of Hypertension-mediated Organ Damage (HMOD) in the kidneys.

Renal HMOD is diagnosed when eGFR falls below 60 mL/min (corresponding to KDIGO stages III-V) or when urinary albumin excretion exceeds 30 mg/g. According to the 2023 European Society of Hypertension (ESH) Guidelines – endorsed by the European Renal Association – renal HMOD is defined as CKD stage G3 (eGFR 30 – 59 mL/min/1.73 $m^2$), or stages G1–G2/A2 (eGFR $\geq$60 mL/min/1.73 $m^2$ with albuminuria between 30 and 300 mg/g). Additional markers of systemic organ damage include an Ankle-brachial Index (ABI) of less than 0.9 and the presence of advanced hypertensive retinopathy. Illustrated in Tab. 01 are some markers to detect early HMOD (Table 1).

### A Step Forward in Hypertension Management: Cilnidipine: A Novel L and N-type Calcium Channel Blocker

Considering the high prevalence of hypertension and associated co-morbidities like diabetes, CKD in India, it is crucial to choose antihypertensive therapies that not only effectively lower BP but also provide cardiovascular and renal protection.

Amongst the multiple classes of anti-hypertensive medications available, Calcium Channel Blockers (CCBs), Renin-Angiotensin-Aldosterone System Inhibitors (RAASi) and Diuretics are recommended as first line therapy according to the recent guidelines

Table 1 — *Tools for assessment of HMOD as per the European Society of Hypertension (ESH) (Adapted from Nath, Dorairaj, Nair 2025)*

**A Step Forward in Hypertension Management: Cilnidipine: A Novel L and N-type Calcium Channel Blocker**

| Tools for assessment of HMOD | Aim |
|---|---|
| **Basic screening test recommendes for HMOD recommendated for all hypertensive patients** | |
| 12 lead ECG | Measure HR and AV conduction, detect cardiac arrhythmias, myocardial ischemia and infarction, screen for LVH |
| Urine albumin creatinine ratio (UACR) | Direct and classify CKD |
| Serum creatinine and eGFR | Detectedand classify CKD |
| **Extended screening for HMOD** | |
| Echocardiography | Evalute the structure and function of the ventricles and left atrium, detect vascular disease. aortic root diameter and ascending aneurysm. |
| cfPWV or baPWV | Evaluate aortic / large artery stiffness |
| Carotid artery ultrasound | Determine carotid intima-media thickness, plaque and stenosis |
| Coronary artery calcium scan | Determine the presence and extent of coronary calcium to predict CAD events |
| Abdominal aorta ultrasound | Screen for aortic aneurysm |
| Kidney ultrasound | Evaluation size and structure of the kidney, detect renovascular disease, determine RRI |
| Spectral Doppler ultrasonography | Diagnosis of renovascular disease and determination of RRI |
| ABI | Screen for LEAD |
| Retina microvasculature | Detect microvascular changes |
| Cognitive function testing (MMSC, MoCA) | Screen for early stages of dementia |
| Brain image (CT, MRI) | Direct structural brain damage |

AV=Atrioventricular; CAD=Coronary Artery Disease; CKD=Chronic Kidney Disease; CT=Computed Tomography; ECG = Electrocardiogram; HMOD=Hypertension-Mediated Organ Damage; LEAD=Lower Extremity Artery Disease; LVH=Left Ventricular Hypertrophy; MMSE=Mini-Mental State Examination; MoCA=Montreal Cognitive Assessment; MRI=Magnetic Resonance Imaging; RRI=Renal Resistive Index.

for elevated BP and hypertension by the European Society of Cardiology (ESC)[4].

CCBs play a pivotal role in hypertension management especially in Indians and the South-east Asian population. Their favourable safety profile and well-understood mechanisms of action support their prominent role in hypertension management[5].

CCBs are broadly categorized into two types: dihydropyridines and non-dihydropyridines. Non-dihydropyridine CCBs primarily target voltage-dependent L-type calcium channels in cardiac and smooth muscle, leading to reduced myocardial contractility and heart rate. In contrast, dihydropyridines exert their effect mainly through vasodilation of the peripheral vasculature, helping to lower blood pressure. Calcium Channel Blockers (CCBs) are among the most extensively studied antihypertensive agents and are widely recommended as first-line therapy, either as monotherapy or in combination with other drug classes[5].

When greater blood pressure control is required, combination therapy that includes a CCB with either an Angiotensin Receptor Blocker (ARB) or an Angiotensin-converting Enzyme (ACE) inhibitor has shown superior efficacy in recent meta-analyses, making it a preferred dual-therapy option. Within CCBs, amlodipine has been a cornerstone for decades. However, the emergence of newer generation DHP-CCBs like Cilnidipine has established the molecule far and wide due to its novel and unique pharmacological properties.

Cilnidipine, a fourth-generation DHP-CCB, exerts its antihypertensive effect by blocking both L-type and N-type calcium channels. The L-type calcium channel blockade reduces peripheral vascular resistance, lowering BP effectively. Simultaneously, the N-type calcium channel blockade suppresses sympathetic nerve activity by inhibiting norepinephrine release, preventing reflex tachycardia and reducing sympathetic overdrive[6].

This dual action makes cilnidipine particularly effective in Indian hypertensive patients, who often present with high sympathetic activity, contributing to increased cardiovascular and renal risk. The major advantage of Cilnidipine over other CCBs is the significant reno-protective benefits it offers due to its N-channel blocking abilities, thereby reducing albuminuria and slowing the progression of CKD.

## Cilnidipine – Evidence

### BP and Proteinuria Reduction :

In multiple trials and observational studies, Cilnidipine has shown to reduce proteinuria notable of which is the CARTER Study published in 2007, which compared Cilnidipine to Amlodipine in Hypertensive-CKD patients, who were already taking ARBs. In this study, the BP reduction in both the groups was similar.

However, the Urinary Protein-to-creatinine Ratio (UPCR) decreased significantly more in the cilnidipine group compared to the amlodipine group, where an increase in the UPCR was observed. Cilnidipine demonstrated a superior antiproteinuric effect, even among patients whose blood pressure had fallen below the target level. These findings suggest that cilnidipine, when used in combination with a Renin-Angiotensin System (RAS) inhibitor, is more effective than amlodipine in preventing the progression of proteinuria in hypertensive patients. Table 2 summarises the key trials with cilnidipine in BP reduction and renoprotection.

## Beneficial Effects on Reducing Sympathetic Overdrive :

Cilnidipine inhibits both L-type and N-type calcium channels. While L-type blockade leads to vasodilation, N-type inhibition suppresses the release of norepinephrine from sympathetic nerve endings, thereby reducing sympathetic nerve activity. Clinical studies have demonstrated that cilnidipine significantly lowers markers of sympathetic activity, such as plasma norepinephrine levels, especially in hypertensive patients with T2DM. Cilnidipine has shown to improve the parasympathetic nerve activity and baroreflex control in patients with hypertension.[13] The ACHIEVE-One trial demonstrated the benefits

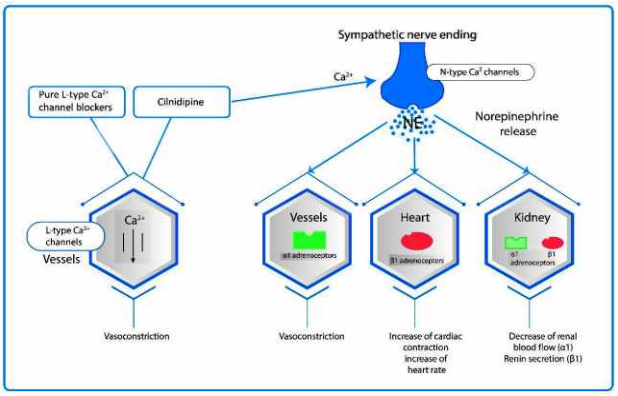


Fig 1 — Cilnidipine Mode of action
[Adapted from Chandra and Ramesh 2013]

of Cilnidipine in reducing morning BP and PR [~9.7 bpm reduction] in patients, especially in those who had higher morning SBP and PR[9] (Fig 1).

## Safety and Tolerability of Cilnidipine :

L-type CCBs (eg Amlodipine) may effectively control BP but are often associated with pedal edema, reflex tachycardia, and sympathetic overactivation – side effects that are poorly tolerated by many Indian patients. Cilnidipine, due to its N-type calcium channel blockade, mitigates these side effects, leading to better compliance and improved patient outcomes. Studies conducted in hypertensive patients have shown that cilnidipine not only maintains BP control

Table 2 — Key Evidences of Cilnidipine in Reno-protection, Cardio-protection and Neuro-protection[7-12]

| Trial Name / Study | Number of Patients | Key Findings | Published in |
|---|---|---|---|
| CARTER Study | 339 | Cilnidipine exerted a greater antiproteinuric effect than amlodipine even in the subgroup whose blood pressure fell below the target level. This study suggests that cilnidipine is superior to amlodipine in preventing the progression of proteinuria in hypertensive patients when coupled with a renin-angiotensin system inhibitor. | Kidney International |
| CLEARED Study | 90 | Cilnidipine has anti-albuminuric effects in diabetic hypertensives; switching from amlodipine to cilnidipine improved albuminuria. | Diabetes Research and Clinical Practice |
| J-CIRCLE Study | 70 | Switching from amlodipine to cilnidipine results in a significant reduction in urinary ACR as well as significant reduction in uric acid production. Thus, cilnidipine is more useful than amlodipine in improving albuminuria and uric acid metabolism in hypertensive patients with chronic kidney disease. | Journal of Clinical Hypertension |
| ACHIEVE-ONE Trial | 2319 | Cilnidipine reduced both morning SBP and PR more markedly in patients with higher baseline morning SBP , and also reduced both morning PR and SBP more markedly in patients with higher baseline morning PR (0.6 beats per minute and -15.6 mm Hg in <70 beats per minute, and -9.7 beats per minute and -20.2 mm Hg in ≥85 beats per minute). Cilnidipine significantly reduced BP and PR in hypertensive patients at the clinic and at home, especially with higher BP and PR in the morning. | Journal of Clinical Hypertension |
| CA-ATTEND Study | 2667 | Cilnidipine was effective in treating uncontrolled blood pressure and was well tolerated in Japanese post-stroke hypertensive patients, over 12 months, in a real-world clinical setting. | Clinical and Experimental Hypertension |
| CA-ATTEND Study [Sub-set] | 603 | Cilnidipine promoted the regression of common carotid IMT in post-stroke hypertensive patients, especially in the thick group. Cilnidipine also reduced the IAD in both normal and thick groups. | Journal of Atherosclerosis and Thrombosis |

Pal J, et al. Hypertension Management Beyond BP Numbers — Exploring the Novel Calcium Channel Blocker Cilnidipine.

comparable to amlodipine but also reduces heart rate by 5-9 bpm (as also described in the ACHIEVE-One study) and significantly lowers the incidence of pedal edema (6% with cilnidipine *versus* 63% with amlodipine)[14].

With its growing evidence base, the molecule finds recommendations through leading Indian Guidelines (RSSDI 2023 and API-ICP 2024) in the management of Hypertension in T2DM, in combination with ARBs[15,16].

## Conclusion :

Cilnidipine, with its dual L/N-type calcium channel blockade, emerges as an ideal antihypertensive agent for Indian patients, offering effective BP control, superior renoprotection, and reduced cardiovascular risk. In comparison to older L-type CCBs (eg Amlodipine), cilnidipine provides better safety, fewer adverse effects, and enhanced tolerability, making it a preferred choice for Indian patients with hypertension, diabetes, and CKD. As India grapples with a rising burden of hypertension and associated organ damage, cilnidipine holds promise in achieving better patient outcomes in the long term.

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**Conflict of Interest :** None

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