

## DRUG CORNER

# Cilnidipine: Next Generation Calcium Channel Blocker

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## Abstract

Hypertension is one of the most common conditions seen in primary care and a major public health problem in India. It can lead to various complications if not detected early and treated appropriately. As per the latest Eighth Joint National Committee (JNC 8) the goal BP in most hypertensive patients age <60 years should be <140/90 mmHg and treatment can be started by selecting drugs from among 4 specific medication classes i.e. angiotensin converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB), calcium channel blocker (CCB) or diuretics. CCB is one of the first line drugs in the management of hypertension. Among CCB, Cilnidipine is a unique Ca<sup>2+</sup> channel blocker as it has inhibitory action on the sympathetic N-type Ca<sup>2+</sup> channels along with its effect on L-type Ca<sup>2+</sup> channels. This article focuses on the current status of cilnidipine in the management of hypertension and co-morbidities. Cilnidipine by attenuating norepinephrine release from sympathetic nerve endings leads to vasodilatation, decreases heart rate and increases renal blood flow. Cilnidipine has an advantage of causing less reflex tachycardia, less pedal edema and better control of proteinuria in comparison to L-type CCB. By causing dilatation of efferent arteriole, it causes less damage to glomeruli and suppresses podocyte injury. Cilnidipine also increases insulin sensitivity. Therefore, cilnidipine as CCB can be a good choice in hypertensive patients with diabetes, chronic kidney disease and in patients developing pedal edema with other CCB.

## Introduction

Hypertension can lead to Myocardial infarction, stroke, renal failure, and death if not detected and treated appropriately.<sup>1</sup> It is the most common condition seen in primary care.<sup>1</sup> Also, its prevalence is rapidly increasing in India among both urban (5% to between 20-40%) and rural (12-17%) populations.<sup>2,3</sup> The number of hypertensive individuals is expected to be nearly 213 million by the year 2025.<sup>3</sup> Hypertension is directly responsible for 57% of all stroke deaths and 24% of all coronary heart disease deaths in

India.<sup>4</sup> In more than 90- 95% of cases of hypertension the cause is unknown.<sup>5,6</sup> It is also called "silent killer", since symptoms can go undetected until damage to the organs has occurred. Because of this, it is one of the most significantly under-diagnosed and under-treated medical conditions all over the world.<sup>7</sup>

## Patho-physiology of Hypertension

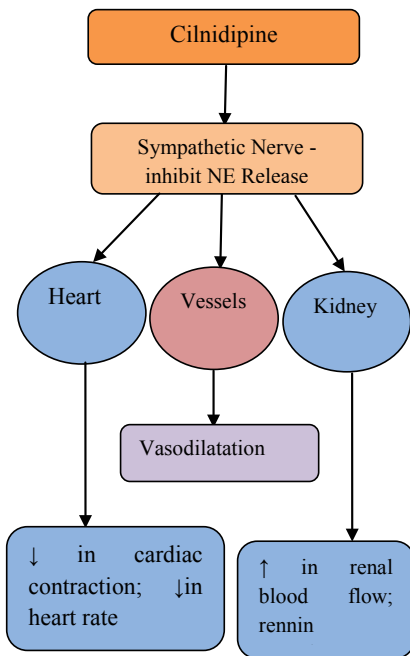
Although it has frequently been indicated that the causes of essential hypertension are not known, a number of pathophysiologic factors have been implicated in the origin of essential hypertension. Among several factors which clearly contribute to the pathogenesis and maintenance of blood pressure elevation, renal mechanisms probably play a primary role. Other mechanisms intensify the effect for e.g. sympathetic nervous system activity and vascular remodeling, the pressor effects of renal salt and water retention.

Understanding these complex mechanisms of hypertension helps in selecting antihypertensive therapy to achieve benefits beyond lowering blood pressure.<sup>5</sup>

## Management of Hypertension and Co-morbid Conditions

Hypertension is one of the most important preventable contributors to disease and death. There are many treatment guidelines for hypertension; however as per the latest Eighth Joint National Committee (JNC 8):

- Goal SBP <140 and DBP <90 mm of Hg is recommended for
  - Hypertension with no diabetes or chronic kidney



**Fig. 1: Cilnidipine by attenuating norepinephrine release from sympathetic nerve endings leads to vasodilatation in vessels, decrease in heart rate and increase in renal blood flow<sup>7</sup>**

disease (CKD) and age <60 years

- Hypertension with diabetes and no CKD
- Hypertension with CKD with or without diabetes.
- Goal SBP <150 and DBP <90 mm of Hg is recommended for:
  - Hypertensive patient with no diabetes or CKD and age ≥60 years

The latest guideline (JNC 8) recommends selection among 4 specific medication classes (ACEI or ARB, CCB or diuretics).<sup>1</sup>

Therefore, Calcium channel blocker is one of the first line drugs in the management of hypertension.<sup>7</sup>

## Role of Cilnidipine in Management of Hypertension and Co-morbid Conditions

Cilnidipine a unique Ca<sup>2+</sup> channel blocker because of its inhibitory

action on the sympathetic N-type Ca<sup>2+</sup> channels along with L-type Ca<sup>2+</sup> channels.<sup>7</sup>

Cilnidipine has been classified as a fourth-generation CCB based on its actions on sympathetic neurotransmitter release (Figure 1).<sup>7</sup>

Cardioprotective, renoprotective and neuroprotective effects of cilnidipine have been reported in clinical or animal studies.<sup>7</sup>

### Cardio-protective Action

N-type calcium channels regulate sympathetic nerve activity, and aberrant sympathetic nerve stimulation is a major cause of hypertension.<sup>8,9</sup>

#### Antihypertensive Effects

The antihypertensive effect of cilnidipine has been demonstrated in various studies conducted in hypertensive patients and also in patients with severe hypertension.<sup>7</sup>

Once-daily administration of cilnidipine (5-20 mg) for 1-3 weeks decreased the 24-hour average BP significantly from 149±4/88±2 mmHg to 141±3/82±2 mmHg without any change in the pulse rate. Cilnidipine is thus a useful antihypertensive drug that may not cause an excessive decrease in BP or a reflex tachycardia.<sup>10</sup>

In another study conducted by Minami J et al in patients with mild to moderate essential hypertension, Cilnidipine significantly decreased the 24 h blood pressure by 6.5 ± 1.7 mm Hg systolic (P<0.01) and 5.0±1.1 mmHg diastolic (P < 0.01), also cilnidipine did not change heart rate. It was concluded that Cilnidipine is effective as a once-daily antihypertensive agent and causes little influence on heart rate.<sup>11</sup>

Kai T et al conducted a study to examine the effects of cilnidipine, on blood pressure, pulse rate, and autonomic functions in patients with mild-to-moderate hypertension. The systolic or diastolic blood pressure decreased

significantly from 151±15 mmHg to 129±14 mmHg or 84±11 mmHg to 71±9 mmHg, respectively. No significant changes in pulse rate reported.<sup>12</sup>

#### Effect on Morning Hypertension

An elevated morning BP has been associated with target organ damage. Treatment with cilnidipine significantly decreased morning hypertension.<sup>13,14</sup>

In ACHIEVE-ONE trial, the effects of cilnidipine on morning hypertension were examined in 2319 patients treated with cilnidipine for 12 weeks. Cilnidipine reduced both morning SBP and PR more markedly in patients with higher baseline morning SBP and PR.<sup>15</sup> Also a 12-week treatment with cilnidipine significantly, restored abnormal nocturnal dipping in hypertensive patients.<sup>16</sup>

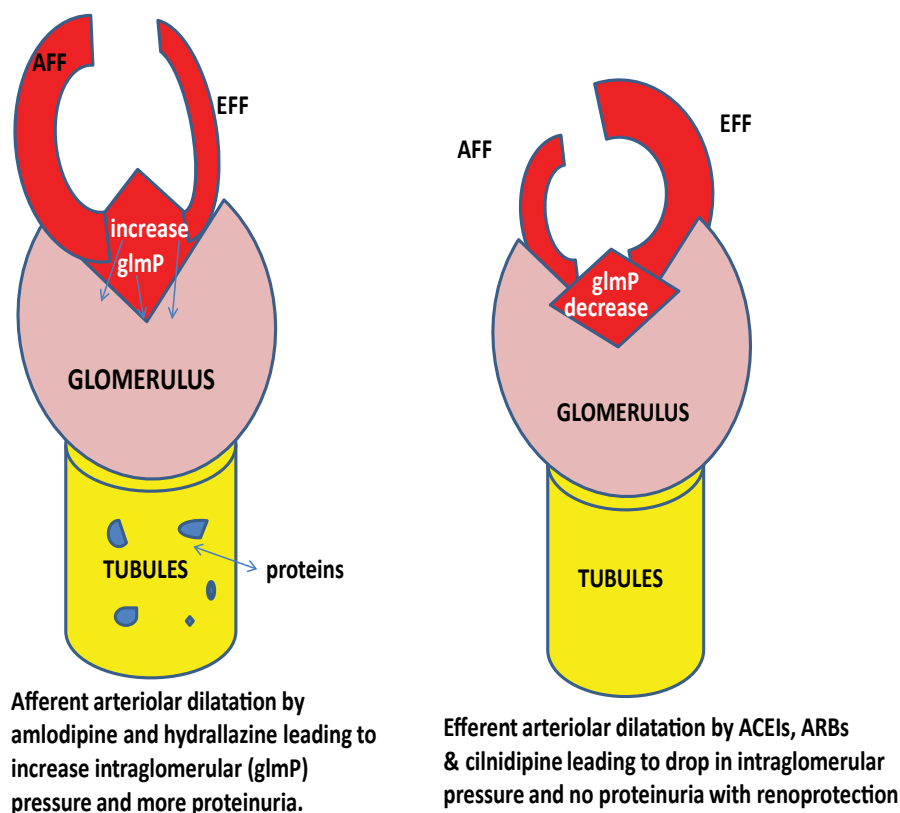
Also clinical trials comparing the effect of Cilnidipine with Amlodipine reported significant reduction in BP, whereas reductions in pulse rate were significantly greater in the cilnidipine than with amlodipine.<sup>17</sup>

Cilnidipine has also emerged as a good candidate for combination therapy. Treatment with cilnidipine and ARB showed a significant reduction in SBP (p<0.0001) and DBP (p<0.0001).<sup>18</sup>

#### Effect on Left Ventricular (LV) Diastolic Dysfunction/Left Ventricular Hypertrophy (LVH)

Left ventricular (LV) diastolic dysfunction is related to increased cardiac sympathetic activity. The effects of cilnidipine, on LV were evaluated in various studies.<sup>19</sup>

Six months treatment with cilnidipine improved LV diastolic function in patients with hypertensive heart disease by suppressing cardiac sympathetic over activity.<sup>19</sup> Also, 8 weeks treatment with cilnidipine 5-10 mg/day can improve left-ventricular systolic function independently of blood pressure changes.<sup>20</sup> Cilnidipine produced a greater decrease in Left Ventricular Mass



**Fig. 2: Cilnidipine and glomerular protection**

(LVM) in essential hypertension than quinapril.<sup>21,22</sup>

## Renoprotective/ Antialbuminuric Effects

Several clinical studies<sup>23-25</sup> have indicated that cilnidipine, displays better renal protection compared with other antihypertensive drugs, including diuretics and the other dihydropyridine CCBs.<sup>25,26</sup>

The precise mechanisms by which cilnidipine elicits its strong anti-proteinuric effect remain unclear; however, effective podocyte protection may play an important role.

### Role of Podocytes in Renal Function

Podocytes act as a permeability barrier restricting the passage of large molecules like albumin. Increased amount of albumin in the urine is the primary indication of a defective glomerular filtration barrier, a condition commonly known as “proteinuria” or “albuminuria”. Various glomerular diseases that induce proteinuria

also demonstrate significant structural damage to podocytes. Structural damage to podocytes has become the hallmark of proteinuria and serves as the diagnostic marker for various glomerular diseases.<sup>27</sup> Also, a decrease in the number and/or density of podocytes has been reported in diabetic nephropathy.<sup>28</sup>

Therefore, podocyte injury is considered as an important therapeutic target in hypertensive renal disease.<sup>28,29</sup> Furthermore, experimental studies have advocated that N-type calcium channels are present in podocytes).<sup>30</sup>

### Cilnidipine Activity and Podocyte Protection

Cilnidipine provides protection of glomeruli by efferent arteriolar vasodilation via attenuation of glomerular hypertension (Figure 2). This is known to significantly reduce glomerular pressure offering effective podocyte protection, which further results in significant anti-proteinuric effect.<sup>27</sup> The inhibiting effects of cilnidipine on renal RAS and oxidative stress may

also be involved in its beneficial effect in metabolic syndrome patients.<sup>30</sup>

Many trials compared antiproteinuric effect of cilnidipine with amlodipine.

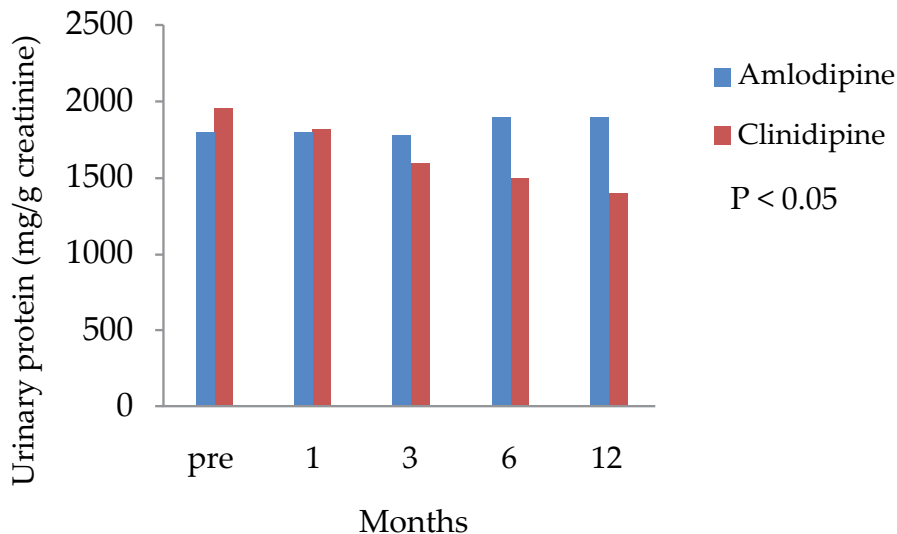
Kojima S et al compared cilnidipine and amlodipine with respect to their effects on renal function and proteinuria. Amlodipine showed a significant increase in proteinuria, whereas it was suppressed by cilnidipine at 12 months of treatment.<sup>24</sup> In an open-label, randomized controlled trial the effects of cilnidipine in 60 patients with CKD were investigated. After 12 months, proteinuria and heart rate were significantly decreased in the cilnidipine treated patients, but proteinuria increased and heart rate remained unchanged in patients treated with CCB acting on L-type channel (L-CCB).<sup>31</sup>

J-Circle study: CCBs in general have no influence on uric acid metabolism. However, the J-CIRCLE study by Uchida S et al conducted to compare the effects of cilnidipine versus amlodipine on albuminuria and uric-acid metabolism, suggest that cilnidipine significantly suppresses uric acid production associated with myogenic hyperuricemia through its dual-blocking actions on L and N types of calcium channels.<sup>32</sup>

*CLEARED study* demonstrated significant antialbuminuric effect of cilnidipine as compared to other L-type CCBs in type-2 diabetic patients presenting with normoalbuminuria and microalbuminuria.

Clinically, antialbuminuric effect of cilnidipine was reported to be continued after treatment period for at least 6 months.<sup>33</sup>

*TACTICAL trial* evaluated antioxidative and antiproteinuric effects of cilnidipine as compared to amlodipine. This study reported significant decrease in the urinary albumin/creatinine ratio after 6



**Fig. 3: Changes in urinary protein/Cr ratio during the treatment period. Urinary protein/Cr ratio was suppressed in the cilnidipine group but not in the amlodipine group. \*P<0.05<sup>25</sup>**

month treatment with cilnidipine as compared to amlodipine treatment ( $p < 0.005$ ).<sup>34</sup>

CARTER study which is a multi-center, open-labeled, and randomized trial compared the antiproteinuric effect of cilnidipine with that of amlodipine in 339 hypertensive patients with kidney disease. This study suggests that cilnidipine is superior to amlodipine (Figure 3) in preventing the progression of proteinuria in hypertensive patients when coupled with a renin-angiotensin system inhibitor.<sup>25</sup>

A recently published article showed greater reduction in microalbuminuria in patient treated with enalapril with cilnidipine in comparison with enalapril alone ( $P < 0.001$ ).<sup>35</sup>

### Neuro-protective Effects

In animal studies, cilnidipine has been reported to reduce neuronal damage.<sup>36</sup> The cerebral blood flow was maintained regardless of whether blood pressure was decreased by cilnidipine or not. Thus, the drug may be suitable for hypertensive patients with a risk of brain attack.<sup>36,37</sup> Also, a clinical study of cold pressor test has shown that cilnidipine decreased

plasma level of  $\beta$ -thromboglobulin, a marker of platelet activation,<sup>38</sup> which may prevent arterial thrombosis formation associated with increased sympathetic tone.

### Effect on Insulin Sensitivity

Twelve weeks administration of cilnidipine at 5 to 10 mg/day in patients with hypertension, significantly increased glucose infusion rate by 20.8%. cilnidipine improves insulin sensitivity, possibly due to its exerting a vasodilatory action without stimulating sympathetic nervous activity. The favorable effects of cilnidipine on glucose metabolism are of clinical importance for the treatment of hypertensive patients with insulin resistance and/or diabetes mellitus.<sup>39</sup> Hypertensive obese patients treated with 10 mg of cilnidipine showed improved insulin resistance.<sup>40</sup>

### Conclusion

Hypertension is one of the most common conditions seen in primary care and if not treated appropriately can lead to various co-morbidities. CCB is one of the first line drugs in the management of hypertension. Among CCB, Cilnidipine by its unique action on

sympathetic N-type  $Ca^{2+}$  channels attenuates norepinephrine release and leads to vasodilatation, decrease in heart rate and increase in renal blood flow. Cilnidipine by causing less reflex tachycardia, less pedal edema, better control of proteinuria, suppressing podocyte damage, increasing insulin sensitivity has become a CCB of choice in hypertensive patients with diabetes, chronic kidney disease and in patients developing pedal edema with other CCB.

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