Expert perspectives and practices on the clinical use of cilnidipine + telmisartan in the management of hypertension with comorbid diabetes in Indian settings

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DOI: https://doi.org/10.33545/26649020.2024.v6.i1a.53

Abstract
Objective: To evaluate the clinician’s preferences and practices regarding the use of cilnidipine and telmisartan combination therapy in the management of hypertension and comorbid diabetes in Indian settings.

Methodology: The cross-sectional study consisted of a 24-item, multiple-response questionnaire-based survey, gathering expert opinion on current practices, clinical observations, and experiences related to the use of combination therapy of cilnidipine and telmisartan in routine Indian settings for managing hypertension. The survey respondents were specialists with expertise in managing hypertension. The data were analyzed using descriptive statistics.

Results: The survey involved 533 clinicians of which the majority (63.2%) reported that the cilnidipine + telmisartan combination reduces blood pressure (BP), has a cardioprotective effect, attenuates high blood glucose levels, and offers vasoprotection. Most clinicians (91.2%) indicated that cilnidipine was the most commonly used calcium channel blocker (CCB) for patients with hypertension and diabetes, and 73% reported telmisartan as the preferred combination for diabetic hypertension. Additionally, 91% favored cilnidipine as the preferred CCB with angiotensin receptor blocker (ARB) for managing hypertensive patients with renal comorbidities. About 76% recommended cilnidipine + telmisartan for diabetic hypertensive patients. Reduction in pedal edema was noted as a benefit of this combination by 40% of clinicians. A significant majority (67.2%) of the experts considered the combination excellent for BP management and cardioprotection. As reported by 81% of the respondents, factors improving patient outcomes included smoking cessation, exercise, a healthy salt-restricted diet, and medication compliance.

Conclusion: The survey corroborated the increased preference among clinicians for the combination of cilnidipine and telmisartan in managing hypertension in patients with both diabetes and renal conditions. The survey findings also highlighted its beneficial effects, including effective lowering of blood pressure, regulation of blood glucose levels, and cardioprotective and vasoprotective effects.

Keywords: Hypertension, diabetes, cilnidipine, telmisartan, type 2 diabetes mellitus

Introduction
Hypertension is a significant contributor to the emergence of non-communicable diseases and a leading cause of premature death globally, accounting for 12.8% of all worldwide deaths. It is a major public health issue in India. An estimated 220 million adults in India suffer from hypertension. The government has set a target to reduce the prevalence of hypertension by 25% by 2025. Currently, only about 21% of adults with hypertension have their condition under control.

Hypertension is particularly significant as a comorbidity of diabetes, contributing substantially to death and disability. The prevalence of hypertension among individuals with type 2 diabetes mellitus (T2DM) was particularly higher compared to their age- and sex-matched counterparts without diabetes, with rates ranging from 32% to 82% in India. In India, there has been a tremendous increase in the coexistence of diabetes and hypertension. The occurrence of hypertension was found to be 1.5 to 2 times higher in patients with diabetes compared to those without diabetes. Similarly, nearly one-third of patients with hypertension develop diabetes in later years.
Managing hypertension in diabetes requires a multifaceted approach, combining optimal blood pressure, lipid, and glycemic control. Guidelines recommend several classes of medications, including angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), calcium channel blockers (CCBs), diuretics, and beta-blockers. ACEIs are typically the first-line treatment for diabetic hypertensives, with ARBs serving as alternatives for those intolerant to ACEIs. CCBs, on the other hand, prove effective in elderly patients with large-vessel stiffness, as they dilate blood vessels and reduce peripheral vascular resistance, thereby lowering blood pressure.\textsuperscript{10,11} Combination therapies, which target multiple pathways, are often more effective in controlling BP and improving metabolic outcomes compared to monotherapy.

Cilnidipine, a newer dihydropyridine calcium antagonist, was approved in Japan in 1995 as a primary antihypertensive drug. Its mechanism of action involves blocking calcium channels, particularly those sensitive to L-type and N-type calcium channels, leading to vasodilation and subsequent reduction in blood pressure. Telmisartan, an ARB with high lipophilicity, enhances tissue penetration and bioavailability. It selectively blocks the angiotensin II type 1 (AT1) receptor, thereby inhibiting the vasoconstrictor and aldosterone-secreting effects of angiotensin II. Cilnidipine not only lowers BP but also improves insulin sensitivity. Telmisartan is known for its prolonged action and efficacy in reducing cardiovascular (CV) risk. Combining these two drugs may offer synergistic benefits, improving BP control and metabolic outcomes in patients with comorbid hypertension and diabetes.\textsuperscript{12-14}

The survey aims to evaluate the clinician’s preferences and practices regarding the use of cilnidipine and telmisartan combination therapy in managing hypertension and comorbid diabetes in Indian settings.

**Methodology**

A cross-sectional, multiple-response questionnaire-based survey conducted among physicians specialized in managing hypertension using a combination of cilnidipine + telmisartan in routine settings from June 2023 to December 2023. The study was performed after obtaining approval from Bangalore Ethics, an Independent Ethics Committee which was recognized by the Indian Regulatory Authority, Drug Controller General of India.

An invitation was sent to clinical professionals across India based on their expertise and experience in treating hypertension in the month of March 2023 for participation in this Indian survey. About 533 clinicians from major cities of all Indian states representing the geographical distribution shared their willingness to participate and provide necessary data. Clinicians had the discretion to skip questions they did not wish to answer. Written informed consent was obtained from all participants, who were required to independently complete the questionnaire without consulting peers. Unanswered questions were treated as non-attempts.

The questionnaire booklet titled NT study (Cilnidipine and Telmisartan in Hypertension Management) was sent to the doctors who were interested to participate. The NT study questionnaire comprised 24 questions designed to gather feedback, clinical observations, and experiences from specialists regarding the treatment of hypertension using a combination of cilnidipine + telmisartan in routine settings. It was structured to capture insights into the frequency of use, perceived efficacy, adverse effects, and preferences for specific compositions.

The data were analyzed using descriptive statistics. Categorical variables were presented as percentages to provide a clear insight into their distribution. The frequency of occurrence and the corresponding percentage were used to represent the distribution of each variable. To visualize the distribution of the categorical variables, graphs, and pie charts were created using Microsoft Excel 2013 (version 16.0.13901.20400).

**Results**

Out of the 533 clinicians who participated in the survey, 40\% reported that 21 to 30\% of patients diagnosed with hypertension are diabetic. More than half (55.47\%) of the clinicians stated that diabetes and hypertension are equally common among both genders. According to 62\% of the respondents, 11 to 20\% of the diabetic hypertensive patients also have isolated systolic hypertension. Majority (63.2\%) of the participants reported that combination therapy of cilnidipine + telmisartan reduces BP along with a cardioprotective effect, attenuates high blood glucose levels, and provides vasoprotection (Table 1).

**Table 1**: Distribution of response to the benefits of combination therapy with cilnidipine and telmisartan in hypertensive patients with diabetes

<table>
<thead>
<tr>
<th>Benefits</th>
<th>Response rate (n = 533)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardioprotective effect</td>
<td>24.53%</td>
</tr>
<tr>
<td>Attenuate high blood glucose levels</td>
<td>6.27%</td>
</tr>
<tr>
<td>Vasoprotection</td>
<td>6%</td>
</tr>
<tr>
<td>All of the above</td>
<td>63.2%</td>
</tr>
</tbody>
</table>

A significant proportion of clinicians (91.1\%) responded that cilnidipine is the most commonly used CCB for patients with hypertension and comorbid diabetes (Table 2). As reported by 73\% of the respondents, the most preferred combination with cilnidipine 10 mg for diabetic hypertension is telmisartan (Fig. 1). According to 43\% of the participants, 11 to 20\% of diabetic hypertensive patients also suffer from proteinuria. Almost 49\% of the clinicians reported that 21 to 30\% of diabetic hypertensive patients also suffer from BP variability. Around 42\% of the participants responded that 21 to 30\% of diabetic hypertensive patients are obese.

**Table 2**: Distribution of response to the most commonly used CCB in clinical practice for patients with hypertension and comorbid diabetes

<table>
<thead>
<tr>
<th>CCBs</th>
<th>Response rate (n = 533)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cilnidipine</td>
<td>91.2%</td>
</tr>
<tr>
<td>Amlodipine</td>
<td>7.33%</td>
</tr>
<tr>
<td>Efonidipine</td>
<td>1.2%</td>
</tr>
<tr>
<td>Azelnidipine</td>
<td>0.27%</td>
</tr>
</tbody>
</table>
As reported by 40% of the participants, 11 to 15% of hypertensive patients with comorbid diabetes are at risk of CKD. Majority (91.33%) of the respondents reported that cilnidipine is the preferred CCB combination with ARB for hypertensive patients with renal comorbidity (Table 3). About 76% of the participants indicated that combination of cilnidipine + telmisartan is the recommended drug of choice for diabetic hypertensive patients (Fig. 2). Most of the clinicians (60%) responded that 5 to 10% of cilnidipine + telmisartan patients require a third drug. According to 42% of clinicians, 15 to 25% of patients currently receiving a renin-angiotensin-aldosterone system (RAAS) blocker and a diuretic in routine settings could be transitioned to a combination of cilnidipine and telmisartan.

Table 3: Distribution of response to the preferred CCB in combination with ARB for a hypertensive patient with renal comorbidity

<table>
<thead>
<tr>
<th>Preferred CCB combination with ARB</th>
<th>Response rate (n=533)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amlodipine</td>
<td>7.2%</td>
</tr>
<tr>
<td>Cilnidipine</td>
<td>91.33%</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>0.67%</td>
</tr>
<tr>
<td>Benidipine</td>
<td>0.8%</td>
</tr>
</tbody>
</table>

Majority of clinicians (55.73%) indicated that they prefer prescribing the combination of cilnidipine and telmisartan to 20% to 30% of their newly diagnosed hypertension patients. As reported by 48% of the participants, approximately 11% to 20% of patients can be switched to cilnidipine + telmisartan from other drugs. As responded by 46% of the participants, approximately 21 to 30% of patients with hypertension were controlled with more than two antihypertensive drugs. According to 40% of the clinicians, reduction in pedal edema was the clinical outcome observed with a cilnidipine + telmisartan combination beyond BP control (Fig. 3).
A significant majority of respondents (67.2%) considered the combination of telmisartan and cilnidipine to be excellent for managing BP and providing cardioprotection (Fig. 4). As reported by 61% of the clinicians, CCBs are the drug of choice in hypertensive emergencies. Around 69% of the clinicians stated quality as the most important parameter to be considered while choosing the brand. As stated by 81% of the participants, the factors that will improve the outcome of a patient with hypertension and comorbidities are smoking cessation, exercise, a healthy salt-restricted diet, and compliance with medication (Table 4).

**Table 4:** Distribution of response to the factors that will improve the outcome of a patient with hypertension and comorbidities

<table>
<thead>
<tr>
<th>Factors</th>
<th>Response rate (n = 533)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking cessation</td>
<td>3.07%</td>
</tr>
<tr>
<td>Exercise</td>
<td>11.07%</td>
</tr>
<tr>
<td>Healthy salt-restricted diet</td>
<td>4%</td>
</tr>
<tr>
<td>Compliance to medication</td>
<td>1.33%</td>
</tr>
<tr>
<td>All the above</td>
<td>80.53%</td>
</tr>
</tbody>
</table>

About 71% of the respondents indicated that the most important challenges in treating a patient with uncontrolled hypertension are poor lifestyle management, poor patient compliance, and delay in follow-up visits to a clinic. As indicated by nearly half of the clinicians (49.2%), the most common review interval to be followed in routine clinical practice is monthly.

**Discussion**

The survey findings underscored the preference for the combination of cilnidipine and telmisartan in managing hypertension with diabetes in Indian settings. The study highlighted medication adherence as a critical factor in
achieving successful therapeutic outcomes for hypertensive patients and reported cilnidipine as the preferred CCB to combine with telmisartan. 

Majority of the current survey clinicians noted that the combination therapy of cilnidipine and telmisartan not only reduces BP but also offers cardioprotective effects, attenuates high blood glucose levels, and provides vasoprotective benefits. In line with these findings, Jo et al. concluded that the combination treatment with cilnidipine and telmisartan can be used as an effective strategy for the treatment of hypertension and its related complications. It specifically noted that this combination therapy lowers BP without causing reflex tachycardia, induces cardioprotective effects by increasing the expression of endothelial nitric oxide synthase, and provides vasoprotective benefits by inhibiting DNA synthesis in cuff-induced vascular injury. Additionally, it suggested the potential of this combination to attenuate high blood glucose levels [14]. Sawant et al. demonstrated that telmisartan and cilnidipine combination once daily was effective and well tolerated in the treatment of newly diagnosed stage-I hypertension. Telmisartan provided sustained 24-h BP control and may offer advantages over cilnidipine in terms of BP reductions, particularly over the 18- to 24-h post-dose period or critical early morning hours [15].

A significant proportion of clinicians responded that cilnidipine is the most commonly used CCB for patients with hypertension and comorbid diabetes. Similarly, Masuda et al. showed that cilnidipine has beneficial effects on metabolic parameters in hypertensive patients with diabetes. It indicated a neutral effect on glucose metabolism, which is a significant advantage in these patients [16]. Mahmood and Mohammad concluded that cilnidipine may have a positive impact on insulin sensitivity in individuals with both hypertension and T2DM. This indicates that cilnidipine could be a promising therapeutic option for addressing insulin resistance in these patients [17]. In another large-scale prospective post-marketing surveillance study, post-stroke hypertensive patients treated with cilnidipine demonstrated good BP control [18].

As reported in the current survey, telmisartan is the most preferred combination with cilnidipine 10 mg for diabetic hypertension. Gadge et al. stated that telmisartan is a preferred option for treating high BP in patients with diabetes. It effectively lowers BP and improves metabolic parameters in patients with T2DM, irrespective of the presence of complications [19]. In a prospective, randomized open-label study, cilnidipine 10 mg with telmisartan was found to be effective in the management of hypertension within 24 hours [15].

Majority of the respondents reported that cilnidipine is the preferred CCB combination with ARB for hypertensive patients with renal comorbidity. The Research Society for the Study of Diabetes in India (RSSDI) 2022 guidelines, put forth by Kumar et al., provide a detailed account of the standard, approved, and novel treatment agents to be used in India for controlling hypertension in patients with diabetes mellitus and for managing and reducing the risks of associated complications and organ damage. According to the guidelines, administering CCBs along with ARBs for combination therapy is recommended instead of using beta-blockers or diuretics. Among the CCBs, novel molecules such as cilnidipine are suggested to be used in combination with ARBs for better CV and kidney protection in diabetic hypertensive patients [20]. Dharapur and Patil in their comparative study highlighted that cilnidipine was superior to amlodipine in significantly reducing BP [21]. Chakraborty et al. showed that there was a significant reduction (p<0.05) in BP and pulse rate and was recommended as the first-line CCB for the management of hypertension either as a monotherapy or as a combination therapy [10].

Srivathsan et al. showed that cilnidipine was more effective in reducing proteinuria or preventing its progression and had similar effects on serum creatinine and estimated glomerular filtration rate in hypertensive patients [22]. Mehta et al. stated that cilnidipine is an effective treatment choice for individuals with mild to moderate essential hypertension, whether it is administered alone or in conjunction with other treatment modalities as it has good tolerability and reduces hypertension-related CV and renal diseases [20]. Kumari et al. concluded that cilnidipine is more effective than amlodipine or other CCBs in reducing BP and also shows better renoprotective action by significantly reducing proteinuria [20].

As per the current survey findings, a combination of cilnidipine + telmisartan is the recommended drug of choice in diabetic hypertensive patients presenting to routine settings. Studies have shown that combining telmisartan with CCB-like cilnidipine significantly improved BP control and reduced urinary albumin excretion in hypertensive patients with diabetes. Cilnidipine in combination with telmisartan can improve vascular health and reduce albuminuria in hypertensive patients, further supporting its use in this population [25, 26].

In the landmark trial titled ‘Avoiding Cardiovascular events through COMbination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH)’, Kjeldsen et al. demonstrated that combining a RAAS blocker with a CCB was more effective than combining a RAAS blocker with a diuretic in reducing CV events in patients with hypertension. The study suggested that initiating combination therapy was beneficial in this patient population, offering the greatest advantage by lowering the risk of CV events and potentially being better tolerated [27]. Similarly, the present study proposed that patients currently taking a RAAS blocker and a diuretic in standard practice could switch to a combination of cilnidipine and telmisartan. Studies have shown that cilnidipine is associated with fewer incidences of pedal edema, which is a common complaint among patients. It effectively controls blood pressure with less reflex tachycardia and a decrease in morning surge. Hypertensive patients with concomitant T2DM observed that a combination of cilnidipine and telmisartan not only provided effective BP control but also significantly reduced the incidence of pedal edema compared to other antihypertensive regimens [20, 28, 30]. Similar results were observed in the present survey, showing a reduction in pedal edema with the combination of cilnidipine and telmisartan beyond blood pressure control.

A study comparing the effects of 12-month BP control using cilnidipine and telmisartan on vascular damage in untreated hypertensive patients found that both have unique properties for inhibiting vascular complications [25]. Another study has concluded that combinations such as CCBs and ARBs therapy remain a cornerstone in hypertension management, offering enhanced efficacy, tolerability, and CV protection [31]. This is in line with the current survey findings.
Galluci et al. demonstrated that quitting smoking significantly reduces the risk of CV events and improves overall mortality rates among individuals with hypertension and other comorbidities [32]. Studies have also shown that regular physical activity lowers BP, improves CV health, and enhances insulin sensitivity, benefiting hypertensive patients with diabetes. The dietary approach to stop hypertension (DASH) diet, which emphasizes reduced salt intake and increased consumption of fruits, vegetables, and low-fat dairy products, significantly shows positive outcomes. High adherence to prescribed antihypertensive medications is associated with better BP control and reduced CV events, underscoring the importance of compliance for patients with hypertension and comorbidities [33, 34]. The current survey also highlighted similar benefits. The current survey results can help clinicians enhance treatment strategies and patient care by considering the preferences and prescription practices of combining cilnidipine and telmisartan in the management of hypertension in India. The major strengths of the present survey are the larger sample size and the use of a well-designed and validated questionnaire. However, limitations include potential bias from reliance on expert opinion and the survey's inability to account for emerging evidence or evolving trends in hypertension management. Prospective trials or real-world observational studies are recommended to validate these findings and provide a more comprehensive understanding of optimal treatment approaches.

Conclusion
The survey highlighted that the cilnidipine and telmisartan combination is highly favored by clinicians for managing hypertension in patients with comorbid diabetes and renal conditions. This combination effectively reduces BP, provides cardioprotective and vasoprotective benefits, and helps manage blood glucose levels. The key factors for improving patient outcomes include smoking cessation, regular exercise, a healthy salt-restricted diet, and medication compliance.

Acknowledgement
We would like to thank all the clinicians who were participated in this study.

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