Expert opinion on the treatment options and comorbidities of Indian hypertensive patients

ABSTRACT

Objective: To investigate expert opinions regarding the preferred therapy options for hypertensive patients in an Indian clinical setting, with a specific focus on the prescription practice of cilnidipine.

Methodology: The cross-sectional study was conducted using a 25-question survey to gather insights from specialists regarding their perspectives on prescribing cilnidipine for hypertensive patients. The survey questions focused on the experts' choice of prescribing an antihypertensive medication for hypertensive patients with comorbid conditions.

Results: The survey collected data from 612 respondents. Nearly half of the respondents (43.79% and 42.97%) reported that individuals with systolic blood pressure (SBP) ranging from 140-159 mm Hg and diastolic blood pressure (DBP) ranging from 90-99 mm Hg, as well as those with SBP ranging from 160-179 mm Hg and DBP ranging from 100-109 mm Hg, are newly diagnosed with hypertension. According to the experts, the most common comorbidities among hypertensive patients were chronic kidney disease, diabetes, and obesity. Calcium-channel blockers (CCBs) were recommended as the preferred antihypertensive drug. Among CCBs, cilnidipine was favoured by a majority of the respondents for patients with renal problems, as it not only provided continuous BP control but also demonstrated benefits in reducing cardiovascular risk, pedal edema, and ensuring renal safety. Telmisartan, chlorthalidone, olmesartan, and other drug combinations were frequently mentioned as preferred adjuncts to cilnidipine at a dosage of 10 mg.

Conclusion: The surveyed experts recommend CCBs as the preferred antihypertensive drugs. Cilnidipine, among the CCBs, is the preferred choice for patients with renal problems due to its ability to provide continuous BP control and its additional benefits in reducing cardiovascular risk, managing pedal edema, and ensuring renal safety.

Keywords: Hypertension, Calcium-channel blockers, Antihypertensive medication, Cilnidipine, Cardiovascular death

1. INTRODUCTION

Two-thirds of the 1.28 billion global population with hypertension reside in low- and middle-income nations. This increased prevalence can be attributed to growing urbanization, poor lifestyle choices, restricted access to healthcare facilities, and a lack of awareness of the condition. One of the global targets for non-communicable diseases is to reduce the hypertension prevalence by 33% between 2010 and 2030 [1]. Non-communicable diseases account for 63% of deaths in India with cardiovascular disease (CVD) affecting 45% of

adults between the ages of 40 and 69 years and responsible for 27% of mortality [2]. European and US guidelines emphasize the need for comprehensive pharmacologic treatment for the effective management of hypertension and to reduce the risk of CV events [3].

Currently, beta-blockers, angiotensin II receptor blockers (ARBs), angiotensin-converting enzyme (ACE) inhibitors, calcium-channel blockers (CCBs), and diuretics are the five drug classes used to treat hypertensive patients presenting with post myocardial infarction, angina, or heart failure, according to guidelines of the European Society of Hypertension and the European Society of Cardiology [4]. A fourth-generation antihypertensive drug, cilnidipine (a CCB), differs from other L-type CCBs or even and other antihypertensives due to its pleiotropic effects, and both L- and N-type calcium channels blocking activity. It may serve as a promising therapeutic option while selecting an antihypertensive medication based on the specific pathophysiological condition of an individual [5]. CCBs, known as calcium antagonists, act by dilating blood vessels to reduce peripheral vascular resistance, lowering blood pressure (BP). CCBs reduce peripheral vascular resistance and promote vasodilation by blocking calcium influx into vascular smooth muscle cells [6].

Cilnidipine has been found to be effective in reducing sympathetic nerve over activity in hypertensive patients with morning hypertension. The drug has also been found to be effective in reducing BP significantly in hypertensive patients with abnormal nocturnal BP, especially when sympathetic nerve activation is exaggerated during sleep [7]. Both amlodipine, an older CCB, and cilnidipine, a newer CCB, have comparable efficacy in reducing high BP. Compared to amlodipine, which blocks only the L-type calcium channel, cilnidipine is associated with a lower incidence of pedal edema [8]. Cilnidipine has only been the subject of one meta-analysis among several published studies on the role of CCBs in CVDs [9]. To comprehensively assess the effectiveness of cilnidipine in hypertensive patients, it is crucial to consider expert opinions on its prescription practices. Expert opinions offer valuable insights into the utilization of cilnidipine, including its efficacy, safety profile, and suitability for specific patient populations. In order to bridge the knowledge gap, the current study examined the expert opinions on the preferred therapy options for hypertensive patients in an Indian clinical setting with a special focus on the prescription practice of cilnidipine.

2. MATERIALS AND METHODS

We carried out a cross sectional, multiple-response questionnaire-based study involved experts in the management of hypertensionin the major Indian cities from June 2022 to December 2022.

2.1 Questionnaire

The questionnaire booklet titled CILREN (CILnidipine in the management of hypeRtENsion) study was sent to the physicians who were interested to participate. The CILRENstudy questionnaire comprised of25 questions, seeking expert opinions on the prescription pattern of cilnidipine. Though, this was a non-interventional, clinician's perspective study, we had received the ethics committee approval from Bangalore Ethics, an Independent Ethics Committee which was recognized by the Indian Regulatory Authority, Drug Controller General of India dated 12 May 2022 [Ethics committee, registration bearing no. ECR/918/Inst/KA/2017/RR-20].

2.2 Participants

An invitation was sent to leading physicians in treatinghypertensionin the month of March 2022 for participation in this Indian survey. About 612 clinicians from major cities of all Indian states representing the geographical distribution shared their willingness to participate and provide necessary data. Clinical Practitionerswere asked to complete the questionnaire without discussing with their peers.

2.3 Statistical Methods

The data were analyzed by using descriptive statistics. Percentages were used to represent categorical variables. Frequency and percentage distribution were used to represent the distribution of each variable. Pie and bar charts were made using Excel 2013 (16.0.13901.20400).

3. RESULTS

Based on the data provided by 612 participants in this survey, nearly half of the respondents (43.79% and 42.97%) reported that individuals with systolic BP (SBP) ranging from 140-159 mm Hg and diastolic BP (DBP) ranging from 90-99 mm Hg, as well as those with SBP ranging from 160-179 mm Hg and DBP ranging from 100-109 mm Hg, are newly diagnosed with hypertension. On average, approximately 44% and 42% of respondents stated that hypertensive patients adhere to diet guidelines, while 49% reported adherence to physical activity on the same scale. In contrast, about 56% of the participants expressed a positive view regarding patients' adherence to antihypertensive medication.

Of 612 participants, 59% of the respondents reported diabetes mellitus as the prevalent comorbid condition noted in hypertensive patients, while 31% reported it as chronic kidney disease (CKD). Furthermore, 56% of responders indicated renal conditions as one of the comorbidities in approximately 11-20% of hypertensive patients, while 47% of them mentioned diabetes within the same patient range. Additionally, 47% of the participants indicated obesity as a comorbid condition in 11-20% of hypertensive patients. As a result, it was reported that 11-20% of patients with hypertension suffer from comorbidities such as renal conditions, diabetes, and obesity.

Majority of the experts (64.70%) reported CCB as the primary antihypertensive medication used for managing hypertension. This was followed by 30% of respondents who indicated ARBs as the medication of choice for treating hypertension (Fig. 1). Furthermore, 55% of the respondents suggested that 21 to 40% of hypertensive patients would require more than two antihypertensive drugs for treatment, while 48% and 45% of the experts recommended monotherapy for 21 to 40% and more than 20% of hypertensive patients, respectively (Table 1).

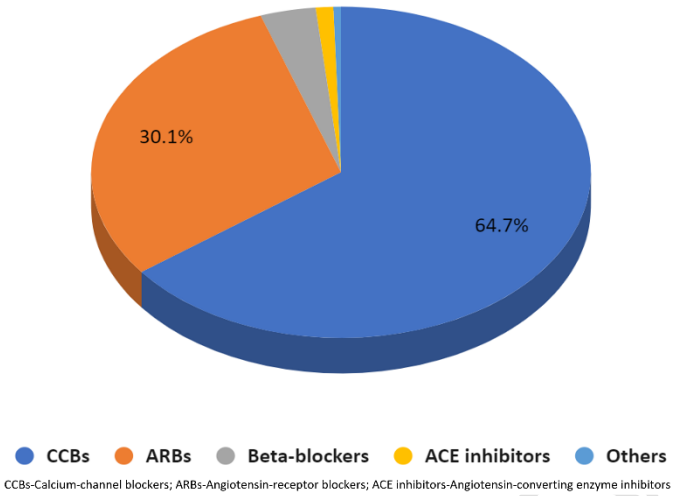

Fig. 1. Experts' choice of anti-hypertensive medication for the management of hypertension

Table 1: Response to distribution of hypertensive patients controlled with monotherapy and more than two antihypertensive drugs

Percentage of patients with hypertension	Response rate (n=612)	
	Monotherapy	More than two antihypertensive drugs
>20 %	274 (44.77%)	92 (15.03%)
21 to 40%	292 (47.71%)	338 (55.22%)
41 to 60%	42 (6.86%)	178 (29.08%)
>10%	1 (0.16%)	0
Others	3 (0.49%)	4 (0.65%)

Majority of the respondents (78.43%) reported using CCBs as the preferred treatment for individuals with hypertension and renal problems (Fig 2a). Furthermore, 93% of the experts suggested cilnidipine, a medication from the CCBs class, for the treatment of hypertension (Fig 2b). Additionally, approximately 79% of the respondents indicated that cilnidipine provides 24-hour blood pressure control (Fig 2c).

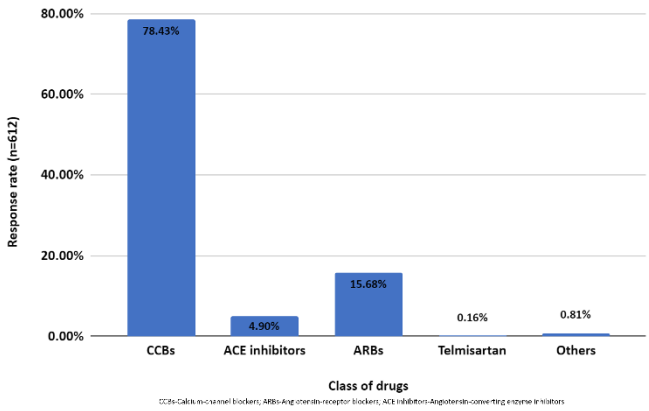

Fig. 2a. Drugs preferred in hypertensive patients with comorbid renal conditions

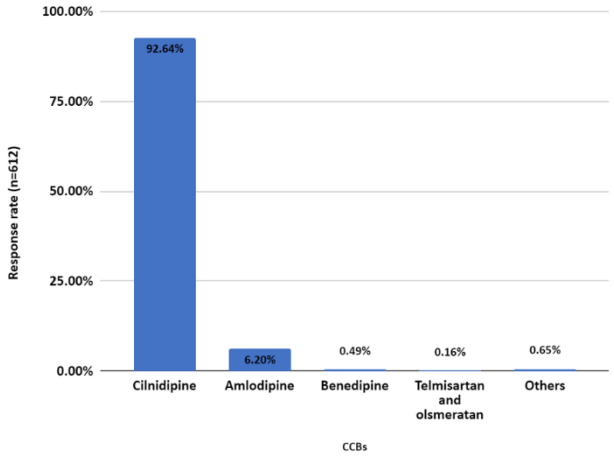

Fig. 2b. Preference of CCBs in patients with comorbid renal conditions

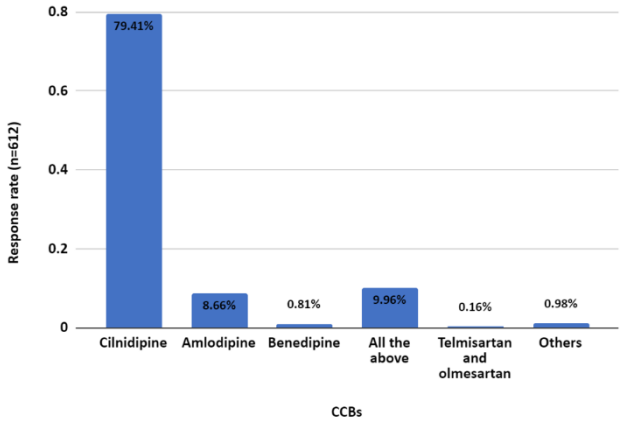

Fig. 2c. Response to distribution of CCBs that offers 24-hour BP control

The survey also assessed the clinical outcomes of cilnidipine, in addition to blood pressure control (Table 2). The results revealed that 39% of the respondents reported a reduction in pedal edema, while 37% and 22% indicated a decrease in cardiovascular risk and renal

safety outcomes, respectively. Regarding drug combinations, 53% of the respondents preferred telmisartan, while 32% mentioned chlorthalidone and olmesartan as adjuncts to 10 mg cilnidipine (Fig 3).

Table 2: Clinical outcomes of cilnidipine apart from BP control

Clinical outcomes of cilnidipine	Response rate (n=612)
Reduction in CV risk	227 (37.09%)
Reduction in pedal edema	240 (39.21%)
Renal safety	134 (21.89%)
All the above	5 (0.81%)
Others	6 (0.97%)

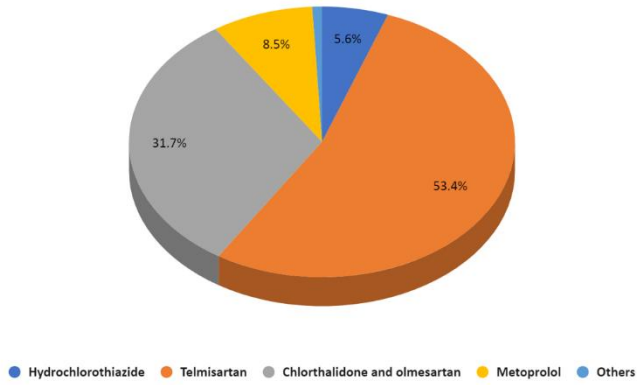

Fig. 3. Experts' preference on antihypertensive drug combinations with cilnidipine 10 mg

4. DISCUSSION

The current study, involving 612 participants, demonstrated that hypertensive patients who adhere to antihypertensive medication had better clinical outcomes compared to untreated patients. The choice of antihypertensive medication depends on the specific pathophysiological condition of the patient. Among the antihypertensive medications used in therapeutic settings, cilnidipine stands out due to its pleiotropic effects and unique mechanism of action, which differentiate it from existing L-type CCBs and other antihypertensives [5].

The present study revealed that a considerable proportion of participants with hypertension also had comorbid conditions such as diabetes mellitus, CKD, and obesity. These findings are consistent with previous literature findings indicating that CKD is the commonly found comorbid condition with hypertension, diabetes, and CVD [10]. A hospital-based study conducted in Ethiopia reported the prevalence of CKD to be 26% in hypertensive and diabetes mellitus patients. The researchers identified uncontrolled BP, fasting blood sugar >150 mg/dl, and long-duration hypertension as predictors of CKD [11]. The findings of the

non-communicable disease risk factor STEPS survey indicated a high burden of comorbid diabetes and hypertension among the elderly, with a prevalence rate of 4.5% in the general adult population [12]. The presence of these comorbidities further complicates managing hypertension and comprehensive approaches are necessary to address all these aspects of these interconnected conditions to optimize patient care and outcomes.

CCBs are commonly prescribed antihypertensive drugs and are found to be effective in managing hypertension in the elderly with increased large-vessel stiffness [13]. The current study has corroborated the pleiotropic effects of cilnidipine beyond its BP regulatory effects. These additional benefits include a reduction in pedal edema, decreased CV risk, and positive renal safety outcomes. The current also emphasizes the role of cilnidipine as a monotherapy option for managing various comorbidities commonly associated with hypertension, such as renal disease, diabetes, and obesity.

In the ACHIEVE-ONE study, experts reported that cilnidipine effectively reduces BP and pulse rate in hypertensive patients, both in clinical settings and at home. Cilnidipine directly reduces the release of sympathetic neurotransmitters through the blocking of N-type Ca^{2+} channels. This makes cilnidipine a successful treatment option for CVD [7]. This fourth-generation CCB stands out for its ability to simultaneously target multiple causes of hypertension while lowering BP, making it highly recommended for hypertension treatment. Additionally, a study conducted by Tatsumi Moriya et al. demonstrated the positive benefits of L- and N-type CCBs on glucose and lipid metabolism, as well as renal function, in patients with hypertension and type II diabetes mellitus [14].

Rose and Ikebukuro demonstrated that cilnidipine, similar to the ACE inhibitor benazepril, effectively reduced urine albumin excretion in hypertensive individuals without affecting blood creatinine concentration [15]. Further investigations by Kojima et al. and Tsuchihashi et al. revealed that cilnidipine had superior kidney protective effects compared to pure L-type CCBs [16,17]. Hence. this study evaluates the role of cilnidipine in managing hypertension, considering its potential benefits.

In hypertensive patients, cilnidipine exhibited greater reductions in urine albumin excretion, 8-hydroxy-20-deoxyguanine, and liver-type fatty acid-binding protein compared to amlodipine, indicating its renoprotective properties. Additionally, cilnidipine improved glucose tolerance and insulin sensitivity without affecting body weight or adiposity in hypertensive patients. These favorable effects of cilnidipine suggest its potential to address comorbid conditions alongside hypertension treatment [18].

Renin-angiotensin system inhibitors, including ACE inhibitors and ARBs, are commonly prescribed in combination with calcium antagonists for hypertension patients with renal issues [19]. In a Japanese observational study involving 2920 hypertensive patients, treatment with cilnidipine and ARBs demonstrated a significant reduction in heart rate, particularly in individuals with higher baseline heart rates (75 beats per minute). Importantly, the study found minimal adverse effects associated with central nervous system functions [20].

A notable number of responders indicated that hypertensive patients might require more than two antihypertensive drugs. There were few participants who suggested monotherapy treatment for hypertensive patients. A significant number of respondents reported telmisartan, chlorthalidone, and olmesartan as preferable drug combinations when used as adjuncts to 10 mg cilnidipine. Jo et al. concluded that the combination therapy involving a fixed dose of cilnidipine and telmisartan effectively reduces BP without causing reflex tachycardia. The researchers noted that the combination treatment has the potential to

induce cardioprotective effects by promoting the expression of endothelial nitric oxide synthase and vasoprotective effects by inhibiting DNA synthesis in cuff-induced vascular injury [21]. A study conducted by Surech et al. in Indian hypertensive patients concluded that for hypertensive patient's refractory to amlodipine and hydrochlorothiazide, switching to the combination of cilnidipine and chlorthalidone can be a viable option. The researchers noted significant reductions in SBP and DBP at 4 weeks compared to baseline in patients who did not achieve their BP targets with amlodipine and hydrochlorothiazide [22]. There are very limited studies exploring the combined use of cilnidipine with telmisartan, chlorthalidone, and olmesartan as adjuncts.

The current expert opinions highlight cilnidipine's significant role in managing hypertension and associated conditions. The study contributes to a comprehensive understanding of the drug's potential benefits, highlighting its versatility and potential synergistic effects. The inclusion of expert recommendations enhances the credibility and relevance of the drug's clinical use in routine hypertension management. A smaller sample size is one of the major limitations of the current study, which may restrict the generalizability of the results to a larger hypertensive population. Studies conducted using a more extensive and representative sample would provide a more precise and comprehensive understanding of the subject. Additionally, relying on expert judgment in the study introduces the possibility of bias, as different viewpoints and preferences might have influenced the reported results. Therefore, it is crucial to consider these limitations when evaluating the findings and to conduct further research to support and expand upon the results.

4. CONCLUSION

Experts strongly recommend cilnidipine as an ideal CCB drug for treating hypertension, which lowers BP and the risk of renal edema and CV events. The use of cilnidipine as a monotherapy for managing numerous comorbidities such as renal disease, diabetes, and obesity in hypertension patients is advised by medical professionals. They also recommended the use of cilnidipine in conjunction with telmisartan medication to treat hypertension. The use of cilnidipine as an adjunct to telmisartan, chlorthalidone, or olmesartan is a favorable approach for the management of hypertension.

Ethical Approval: ethics committee approval from Bangalore Ethics, an Independent Ethics Committee which was recognized by the Indian Regulatory Authority, Drug Controller General of India dated 12 May 2022 [Ethics committee, registration bearing no. ECR/918/Inst/KA/2017/RR-20].

Consent:A written informed consent was obtained from each doctors before initiation of the study.

COMPETING INTERESTS

Authors have declared that they have no known competing financial interests OR non-financial interests OR personal relationships that could have appeared to influence the work reported in this paper.

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