Expert perspectives on the clinical use of olmesartan + calcium channel blockers + diuretics combination therapy in the management of hypertension in Indian settings

ABSTRACT

Background: Although there are several studies available regarding the safety and effectiveness of olmesartan + calcium channel blockers (CCBs) + diuretics, there were dearth of studies among experts regarding the clinical use and prescription practices of olmesartan + calcium channel blockers (CCBs) + diuretics in Indian settings.
Methods: This cross-sectional study utilized a 23-item, multiple-response questionnaire to gather expert opinions from specialists with expertise in BP and hypertension-related management. The survey comprised questions regarding guideline compliance, prevailing prescription practices, and experiences associated with the use of mono, dual, and triple combination treatments for managing uncontrolled BP and hypertension-related comorbidities.
Results: Out of the 566 surveyed clinicians, around 50% adhered to the American College of Cardiology/American Heart Association (ACC/AHA) guidelines. Almost 43% of the clinicians reported that 10-20% of patients require triple-drug antihypertensive combination therapy. Around 34% of the experts indicated that 21-30% of patients achieve a BP below 130/80 mm Hg with triple antihypertensive combination therapy. Nearly 46% reported that 21-30% of their patients exhibit comorbid dyslipidemia. Approximately 53% of the clinicians noted increased prevalence of proteinuria in patients aged 46-60 years, and about 76% stated that angiotensin receptor blockers (ARBs) are most frequently used as first-line antihypertensive drugs. Nearly 90% of the respondents suggested that olmesartan monotherapy provided superior BP reduction. Around 58% of the experts reported that in individuals with co-morbid diabetes, the most commonly prescribed combination was olmesartan + CCB.
Conclusion: The survey highlighted clinician's preference for the triple-drug combination therapy of olmesartan, CCBs, and diuretics, emphasizing its benefits in improving BP regulation and reducing hypertension-related complications. It also underscored the superior effectiveness of this combination over alternatives, noting advantages such as vasodilation and reductions in glucose and lipid levels.

Keywords: Hypertension, dyslipidemia, proteinuria, olmesartan, calcium channel blockers, diuretics

1. INTRODUCTION

Hypertension is a significant contributor to premature death on global scale, affecting approximately 1 in 4 men and 1 in 5 women [1]. It often co-exists with other risk factors for cardiovascular disease (CVD), such as metabolic syndrome, characterized by a combination of closely linked risk variables. Notably, the presence of additional risk factors, particularly diabetes, significantly amplifies the risk of CVD. Diabetes not only increases the prevalence of hypertension but also contributes to 35-75% of CVD and renal complications in individuals

with diabetes [2]. Dyslipidemia, closely linked with the pathophysiology of CVD, serves as a significant independent modifiable risk factor for CVD [3]. Proteinuria is also recognized as a risk factor for CVD and mortality [4].

Globally, approximately 1.3 billion individuals suffer from hypertension, with nearly 82% of them residing in low- and middle-income countries. Remarkably, over the past two decades, the highest prevalence of hypertension has shifted from high-income to middle-income countries, largely due to lifestyle changes and other contributing factors [5]. In India, an estimated 220 million adults are affected by hypertension, highlighting its critical significance in the nation's healthcare landscape. Approximately 207 million individuals in India, comprising 112 million men and 95 million women, are estimated to be affected by hypertension [6,26,27,28,29]. Despite some progress in hypertension awareness over the last 25 years, India lags behind countries such as the USA, UK, Australia, and Canada [5].

Two highly regarded clinical practice guidelines on hypertension are ACC/AHA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults and the recently released 2023 European Society of Hypertension (ESH) Guidelines for the Management of Arterial Hypertension [7]. Studies have shown that a combination therapy involving angiotensin receptor blockers (ARBs), calcium channel blockers (CCBs), and diuretics was highly effective and well-tolerated for patients with mild-to-severe hypertension. ARBs selectively inhibit angiotensin II by competitively antagonizing its receptors, thereby reducing blood pressure (BP) [8]. Olmesartan, an ARB, binds to both angiotensin type I and type II receptors, counteracting the effects mediated by these receptors, resulting in vasodilation and decreased arteriolar resistance [9]. CCBs act by blocking the inward flow of calcium through L-type voltage-gated calcium channels in the heart, vascular smooth muscle, and pancreas. This inhibition reduces Ca2+ entry into excitable cells, acting as a dilator of smooth muscle and exerting a negative inotropic effect on myocardial cells in the atria and ventricles [10]. Diuretics increase urine flow and facilitate sodium and water elimination by acting on the nephron, aiding in the management of hypertension [11].

Although there are several studies available regarding the safety and effectiveness of olmesartan + calcium channel blockers (CCBs) + diuretics, this cross-sectional survey aimed to gather expert opinion on the clinical use and prescription practices of antihypertensive medications, with a particular focus on the combination therapy of olmesartan, CCBs, and diuretics for managing hypertension and hypertension-related comorbidities in Indian settings.

2. MATERIALS AND METHODS

A cross sectional, multiple-response questionnaire based survey conducted among physicians specialized in managing hypertension and hypertension-related comorbidities in Indian settings from June 2023 to December 2023.

An invitation was sent to clinical professionals across India based on their expertise and experience in treating hypertension and hypertension-related comorbidities in the month of March 2023 for participation in this Indian survey. About 566 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 HOPS-2 study (Hypertension and Olmesartan: Perspectives by Specialists-2) was sent to the doctors who were interested to participate. The HOPS-2 study questionnaire comprised 23-questions focused on gathering expert opinion regarding guideline compliance, prevailing prescription practices, and experiences associated with the use of mono, dual, and triple combination treatments for managing uncontrolled BP and hypertension-related comorbidities, specifically, the dual combination of ARBs + diuretics and the triple combination of ARBs + CCBs + diuretics.

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).

3. RESULTS

Out of the 566 clinicians surveyed, nearly half (49.56%) of them reported complying with the ACC/AHA guidelines for managing hypertension in routine practice (Fig. 1). Approximately 53% of the experts cited irregular follow-up visits as a significant drawback to meeting BP targets.

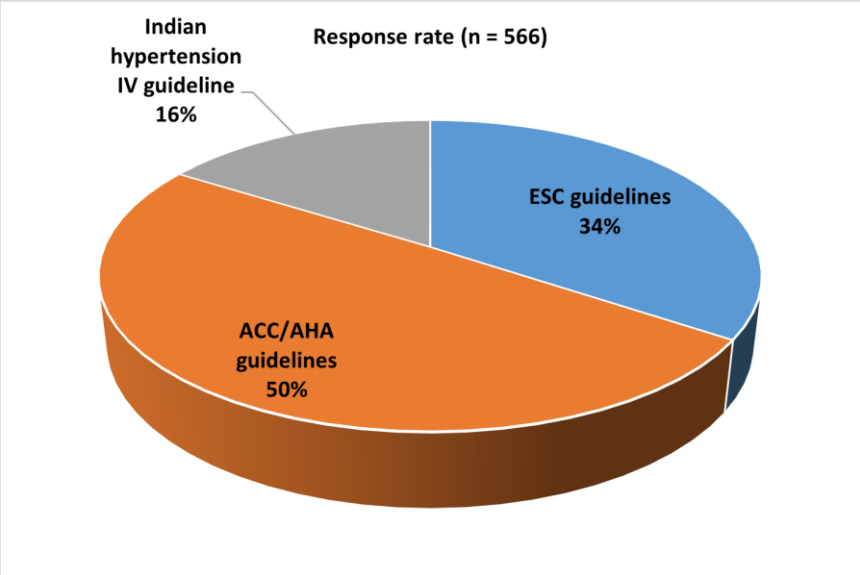

Fig. 1: Distribution of response to guidelines followed by clinicians for managing hypertension in routine practice

About 40% of the clinicians stated that 21-40% of patients attend follow-up appointments in routine settings. Nearly half (46%) of the respondents reported that 20-40% of patients receive dual-drug antihypertensive combination therapy, and a similar proportion (42%) of clinicians indicated that 20-40% of patients met their BP targets with dual-drug antihypertensive therapy. Furthermore, almost 43% reported that 10-20% of patients require triple-drug antihypertensive combination therapy. Approximately 34% of the respondents stated that 21-30% of patients achieved a BP target of <130/80 mm Hg with triple-drug antihypertensive combination therapy (Fig. 2).

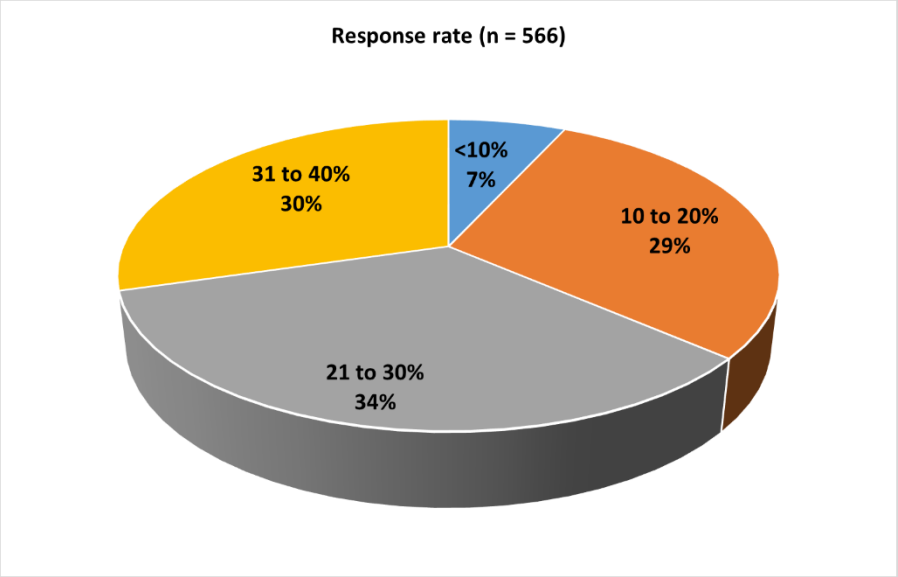

Fig. 2: Distribution of response to the proportion of patients who achieved BP <130/80 mm Hg following triple antihypertensive medication

More than half (51.56%) of the clinicians reported that 21-30% of hypertension patients also have diabetes. Nearly 46% of the experts stated that 21-30% of their patients have comorbid dyslipidemia (Table 1). According to 53% of the respondents, proteinuria is prevalent in patients aged 46-60 years (Table 2).

Table 1: Distribution of response to proportion of hypertensive patients with comorbid dyslipidemia

Percentage (%)	Response rate (n = 566)
<10	7.97%
10 to 20	32.88%
21 to 30	45.58%
31 to 40	13.57%

Table 2: Distribution of response to age group of patients regularly reported with proteinuria

Age (years)	Response rate (n = 566)
20-30	2.99%
31-45	20.05%
46-60	53.18%

60-75	22.04%
>75	1.74%

According to 58% of the respondents, proteinuria and hypertension are equally prevalent in both men and women, and 67% reported that 11-25% of patients are below 45 years of age. About 41% of the clinicians reported that 21-30% of adolescent hypertension patients are obese. Around 76% of the experts noted that ARBs are the most commonly used first-line antihypertensive drugs (Fig. 3) and approximately 90% suggested that olmesartan monotherapy provides greater BP reduction (Fig. 4).

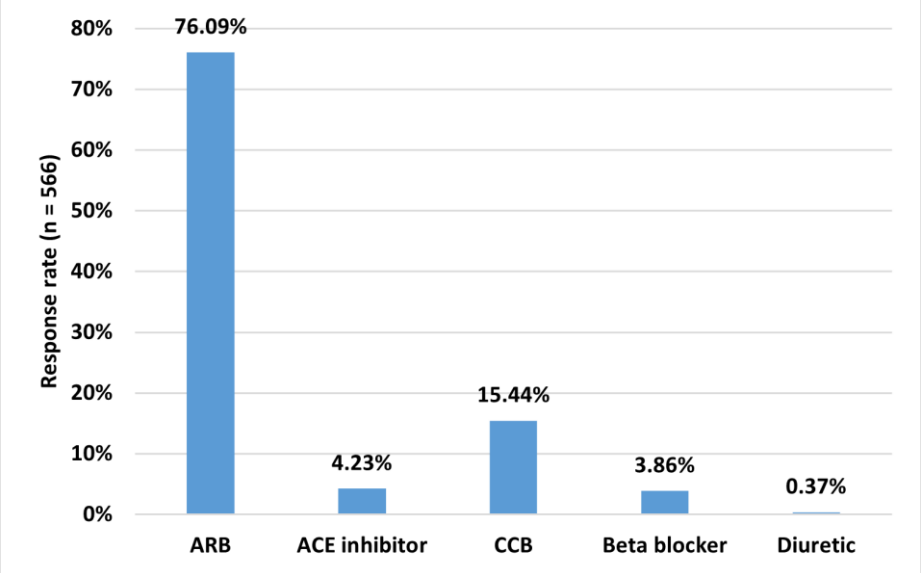

Fig. 3: Distribution of response to frequently favored first-line antihypertensive medication

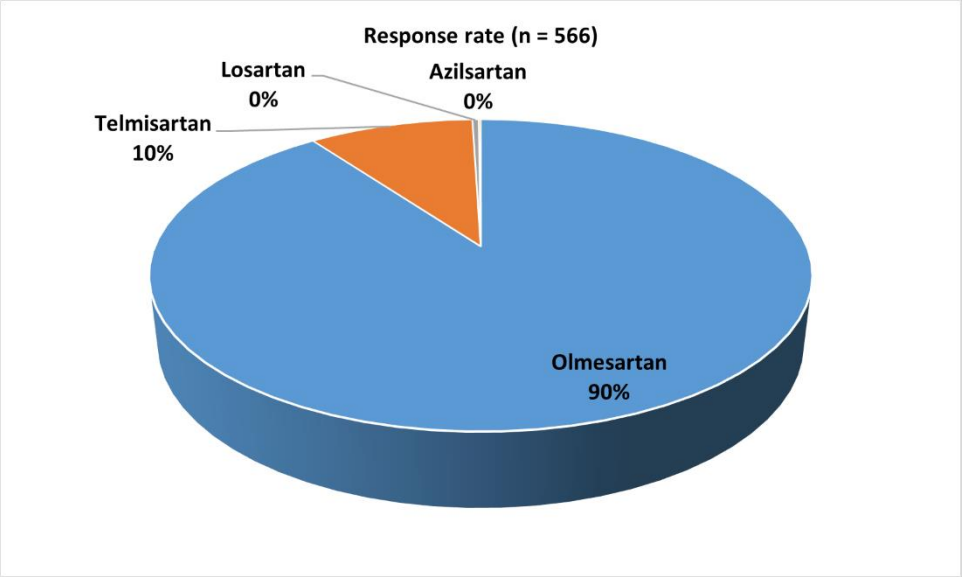

Fig. 4: Distribution of response to monotherapy of ARBs that produces improved BP reduction

Around 58% of the clinicians reported that the most commonly prescribed combination in individuals with comorbid diabetes is olmesartan + CCBs (Table 3). Nearly half of the survey participants (46.7%) recommended olmesartan + diuretic as the most commonly administered medication in patients over 60 years of age (Table 4). According to 75% of respondents, the most commonly preferred triple medication combination in hypertensive patients was olmesartan + CCB + diuretics. Around 51% indicated that chlorthalidone along with olmesartan was the most widely used diuretic in routine practice.

Approximately 61% of the clinicians indicated that 11-20% of patients are aware of their BP and associated complications. Nearly 62% of the respondents believed that raising awareness and training family members/caregivers would be a better strategy to enhance patient adherence to treatment and diet to achieve the BP goal. About 63% stated that 11-20% of their patients consistently monitor their BP at home. Approximately 54% advised ECG and ECHO evaluations every three months for high-risk hypertension patients.

Table 3: Distribution of response to the commonly recommended combination therapy with olmesartan in hypertensive patients with comorbid diabetes

Combination therapy	Response rate (n = 566)
Olmesartan + CCB	57.91%
Olmesartan + Diuretic	31.13%
Olmesartan + Beta blocker	10.83%
All combination	0.12%

Table 4: Distribution of response to commonly recommended combination therapies along with olmesartan in elderly patients (>60 years)

Combination therapy	Response rate (n = 566)
Olmesartan + CCB	37.98%
Olmesartan + Diuretic	46.7%
Olmesartan + Beta blocker	15.32%

4. DISCUSSION

This survey-based study provides valuable insights into the prescription practice and clinical implications of using ARBs, CCBs, and diuretics. These findings can aid clinicians in decision-making in routine practice and enhance treatment outcomes. Nearly half of the survey participants adhered to the ACC/AHA guidelines. The 2017 ACC/AHA and 2018 ESH guidelines, established by Whelton et al., are globally recognized as key clinical practice guidelines for hypertension. Both sets of guidelines advocate initial therapy involving angiotensin converting enzyme inhibitors (ACEIs), ARBs, thiazide or thiazide-like diuretics, and CCBs [7].

The current survey findings underscore the significance of triple combination therapy in reducing BP below 130/80 mm Hg. According to Zaman et al., triple combination therapy has emerged as a successful strategy in managing hypertension, particularly for individuals who fail to achieve adequate BP control with monotherapy alone. The primary benefit of triple combination therapy is its superior efficacy compared to standard monotherapy. By combining drugs with diverse mechanisms of action, this approach effectively targets different pathways involved in BP regulation, leading to improved control [12]. Similarly, Volpe et al. found that triple combination therapy surpasses dual combination therapy in several aspects, including the percentage of well-controlled subjects, reductions in office and 24-hour BP, and the time required to achieve BP goals. Importantly, these benefits are achieved without a notable increase in adverse events. The enhanced efficacy and safety profile of triple combination therapy makes it a valuable option for optimizing hypertension management and improving patient outcomes [13].

The survey highlights the common association of comorbid dyslipidemia among patients with hypertension, significantly elevating the risk of CVD. To reduce the risk of CVD, stroke, and other related conditions, regular monitoring of both BP and lipid profile is recommended, aligning with global hypertension management guidelines [14]. This association between hypertension and dyslipidemia is frequently observed in clinical practice, as noted by Otsuka et al., and is consistent with the baseline characteristics of participants in various clinical studies. Dyslipidemia not only contributes to increased atherosclerosis but also adversely affects the structural and functional properties of arteries. These alterations may complicate BP regulation, thereby increasing the risk of hypertension among individuals with dyslipidemia [15]. Additionally, majority of the current survey respondents indicated an increased prevalence of proteinuria among individuals aged between 40 and 60 years.

According to most experts, the most commonly prescribed first-line antihypertensive medication is ARB. Chen et al. suggested that both ACEIs and ARBs are equally recommended as first-line treatments for hypertension due to their effective reduction of BP by inhibiting the renin-angiotensin system [16]. Poulter observed that ACEI and CCBs show gradual improvements in patient compliance, while ARBs exhibit the highest compliance rates with antihypertensive therapy [17]. The findings of a head-to-head analysis, published in the journal *Hypertension*, indicated that ARBs and ACEIs are equally effective as first-line

therapy for hypertension, with safety being an advantage for ARBs. The study findings favored prescribing ARBs over ACEIs for patients initiating high BP medication [18].

The majority of the current survey respondents corroborated the potential of olmesartan monotherapy in providing superior BP reduction. Nakayama et al. reported that among the various ARBs available, olmesartan was believed to have a significantly stronger BP-lowering effect compared to losartan or valsartan at their respective starting doses [19]. Bell et al. highlighted the lack of hepatic metabolism as one of the key advantages of olmesartan over other ARBs [20]. Redon et al. suggested that, based on BP-lowering efficacy, goal achievement, and safety, olmesartan should be strongly considered as an initial treatment choice for hypertension management in elderly patients, including those with mild renal impairment or diabetes [21]. Hyeon et al. suggested that, in comparison to other ARBs, olmesartan exhibits a more potent -lowering effect and a prolonged half-life [22].

More than half of the survey respondents reported olmesartan combined with CCBs as the most commonly prescribed combination in patients with comorbid diabetes. Daikuhara et al. reported clinically relevant differences between two combinations of an ARB and a CCB in diabetic hypertensive patients. Specifically, the combination of olmesartan and a CCB exhibited a more enduring early morning antihypertensive effect and induced greater reductions in heart rate and fasting blood glucose levels [23]. Kalra et al. reported that combined therapy with an ARB and a CCB has a potentially useful antiproteinuric effect in patients with type 2 diabetic nephropathy, even in patients with compromised renal function [24].

According to the survey, almost half of the participants reported that the most frequently prescribed medication for patients over 60 years old was a combination of olmesartan and diuretics. Mark Greathouse noted that this combination reduces systolic and diastolic BP more effectively than either component alone. The olmesartan and hydrochlorothiazide combination was proven to be an effective and well-tolerated therapy for hypertension, leading to substantial reductions in BP and improved control in numerous patients [25].

ARBs offer several therapeutic advantages and can be effectively combined as antihypertensive drugs for managing hypertension. The current study holds significant relevance in comprehending prescription patterns, especially considering the limited literature available on the triple combination of ARBs, CCBs, and diuretics. The major strengths of the survey are larger sample size and the use of a well-designed and validated questionnaire for data collection from clinicians. However, it is crucial to acknowledge certain limitations inherent in the survey methodology.

Relying solely on expert opinion introduces the potential for bias, given the diverse perspectives and preferences among clinicians, which may have influenced the reported results. Therefore, it is essential to consider these limitations when interpreting the findings. Furthermore, the survey may not have captured emerging trends or new evidence in hypertension management. Thus, prospective trials or real-world observational studies are necessary to validate the survey results and provide a more comprehensive understanding of optimal treatment approaches.

4. CONCLUSION

This study underscored the clinician’s preference for the triple-drug fixed combination therapy of olmesartan + CCBs + diuretics, highlighting significant advantages such as enhanced BP control, reduced risk of hypertension-related complications. Additionally, the study highlighted the superior efficacy of olmesartan + CCBs + diuretics compared to other

combinations, demonstrating benefits such as vasodilation and notable reductions in glucose levels, lipid levels, and the incidence of cardiovascular disease.

Consent

As per international standards or university standards, Participants' written consent has been collected and preserved by the author(s).

Ethical Approval:

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.

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.

Disclaimer (Artificial intelligence)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of manuscripts.

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