THERAPEUTIC SPOTLIGHT

Utility of Azelnidipine, a Unique Calcium Channel Blocker, and Its Combinations in Hypertension Management: A Practice-based Delphi Consensus

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Abstract

Background: Azelnidipine, a third-generation calcium channel blocker, has shown promising antihypertensive efficacy and pleiotropic benefits. This Delphi consensus aimed to establish expert agreement on its role in hypertension management, including monotherapy and combination therapy.

Materials and methods: An expert scientific committee of 20 experts generated 33 evidence-based statements. These were rated by 201 panelists (healthcare professionals) using a 10-point Likert scale (1–10). Statements with a mean score ≥7 were considered accepted. Data analysis was performed using R software.

Results: All 33 statements achieved consensus in the first round, indicating strong agreement. Key themes included sustained blood pressure control with azelnidipine, favorable tolerability, potential renal and metabolic effects, and synergistic benefits when combined with telmisartan or metoprolol.

Conclusion: The consensus supports azelnidipine as a well-tolerated, effective antihypertensive agent with broad applicability across comorbid conditions. It's fixed dose combinations offer enhanced therapeutic value in hypertension management.

Keywords: Calcium channel blocker, Comorbidities, Delphi consensus, Hypertension, Synergistic effect.

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Introduction

Hypertension is typically described as sustained systolic blood pressure (BP) of ≥130 mm Hg and persistent diastolic BP ≥80 mm Hg.[1] Often termed a "silent killer," it typically remains asymptomatic until the development of target-organ damage.[2] It affects approximately 1.28 billion adults aged 30–79 years worldwide, with projections suggesting that this burden may exceed 1.5 billion by 2030.[3] The prevalence of hypertension in India is 22.6%, with men (24.1%) having a higher prevalence than women (21.2%).[4] Poorly controlled hypertension is associated with an increased risk of cardiovascular and renal complications, including coronary artery disease, stroke, chronic kidney disease (CKD), and retinopathy, thereby contributing substantially to morbidity and mortality.[5]

Effective and sustained BP control is essential to reduce the risk of these complications, necessitating the use of well-established and well-tolerated pharmacological therapies. Calcium channel blockers (CCBs) are among the key first-line antihypertensive agents widely used in routine clinical practice due to their proven efficacy across diverse patient populations.[6] However, conventional agents within this class are often associated with tolerability limitations, such as peripheral edema and reflex tachycardia, which may affect treatment adherence and long-term outcomes.[7] Azelnidipine is a newer-generation dihydropyridine CCB. Its clinical use has been associated with effective and stable BP control along with a favorable tolerability profile including a lower incidence of common CCB-related adverse events, particularly peripheral edema and tachycardia.[2,6] When used in

combination with other antihypertensive agents, including angiotensin receptor blockers (ARBs) or beta-blockers (BBs), it has been reported to support improved BP control by targeting complementary mechanisms, improving vascular function, reducing arterial stiffness, providing end-organ protection, and improving tolerability in high-risk hypertensive populations.[8–10] Azelnidipine, beyond its antihypertensive action, has demonstrated some pleiotropic effects such as suppression of sympathetic nerve activity, renoprotective benefits, reduction of proteinuria, and improvement in insulin resistance, making it relevant in patients with coexisting comorbidities such as diabetes or CKD.[2]

This Delphi consensus was conducted to synthesize heterogeneous clinical evidence and real-world experience regarding azelnidipine in hypertension management, where direct extrapolation from available studies remains challenging. The initiative aimed to contextualize published data through structured expert consensus, with a focus on factors influencing CCB selection, the clinical profile of azelnidipine, and its use alone or in combination therapy across diverse patient populations.

Materials and Methods

Study Design

This Delphi consensus study was designed to develop expert recommendations on the clinical use of azelnidipine and its combinations for management of hypertension in routine clinical practice. This Delphi approach was used to synthesize expert opinion on existing evidence and clinical experience, without the intent to replace guideline recommendations.

Literature Review

A comprehensive literature review was conducted in June 2025 to collate existing evidence on the efficacy, safety, and clinical role of azelnidipine in the management of hypertension. The search was performed across PubMed, Embase, Web of Science, the Cochrane Library, and Google Scholar using a combination of Medical Subject Headings (MeSH) and free-text terms including "azelnidipine," "calcium channel blocker," "hypertension," "blood pressure control," "safety," "efficacy," "pleiotropic effects," "renal outcomes," and "patient-reported outcomes." Boolean operators ("AND," "OR") were applied to combine terms appropriately. The review included randomized controlled trials (RCTs), meta-analyses, and observational studies published in English that reported data on azelnidipine or compared it with other CCBs in hypertension. Conference abstracts, editorials, case reports, and nonhuman studies were excluded. Titles and abstracts were independently screened to assess relevance, followed by full-text review for eligible studies. Extracted data included evidence on the efficacy of azelnidipine and other CCBs in blood pressure and heart rate control, safety and tolerability profiles, pleiotropic effects on vascular and metabolic parameters, and patient-reported outcomes such as treatment adherence and quality of life.

Delphi Survey

Healthcare professionals (HCPs) were invited to participate in the survey via email communication and virtual meetings. The generated statements were rolled out as a Delphi survey to a total of 225 panelists (HCPs). All panelists had a minimum of 5 years of clinical experience in hypertension management and demonstrated familiarity with azelnidipine and its fixed-dose combinations. Each panelist was asked to independently rate his/her level of agreement with the proposed clinical statements using a 10-point Likert scale, where 1 indicated "completely disagree," and 10 indicated "completely agree." Responses were collected anonymously to minimize bias and ensure independent judgment. An open-ended comment section was included for each question to capture qualitative insights, contextual justifications, or recommendations for wording refinement. The responses were compiled and analyzed using descriptive statistics.

The Delphi panel comprised clinicians from diverse geographic regions across India, representing both public and private practice settings. Panelists' participation was voluntary, and responses were collected anonymously.

Consensus Criteria

A mean score ≥7 was predefined as the threshold for consensus and acceptance of a statement, whereas a mean score ≤3 indicated rejection.[11] As per the study design, if any statements received mean scores between 4 and 6, further review and refinement by the expert scientific committee were planned, followed by rescoring for consensus development by the same panelists in subsequent Delphi rounds, for up to a maximum of three rounds. Descriptive statistical analyses were performed using R software.

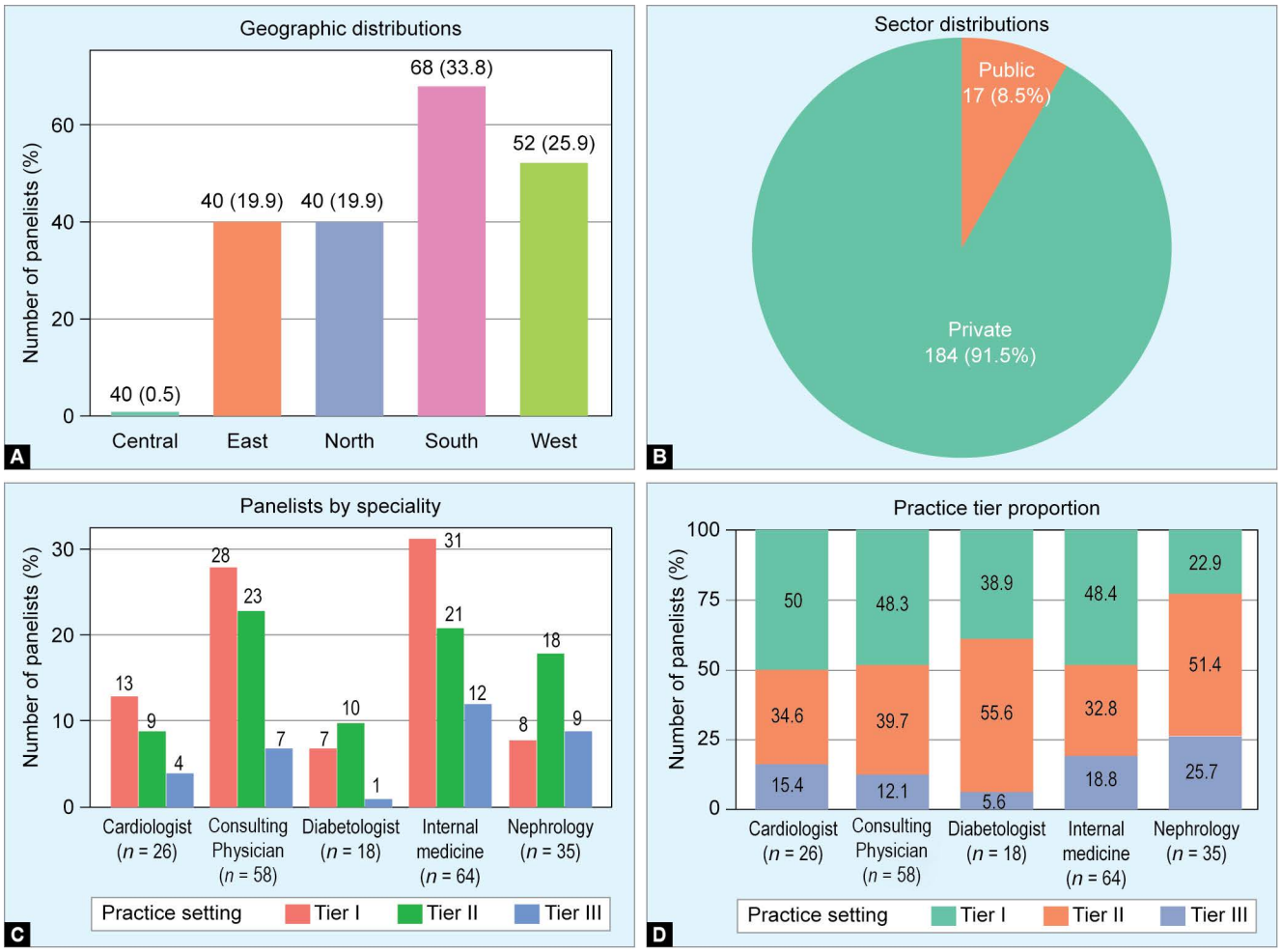
Results

Of the 225 invited panelists, 201 participated and completed the Delphi survey. The panel comprised 26 cardiologists, 58 consultant physicians, 18 diabetologists, 64 internal medicine specialists, and 35 nephrologists. Most panelists were from the private sector (91.5%) and represented all major geographic regions of India. The panelists had a mean clinical experience of approximately 17 years, reflecting substantial professional expertise (Figs 1 and 2). All 33 statements achieved a mean score of ≥7, fulfilling the predefined criteria for consensus and indicating strong agreement among the panelists. As all statements achieved the predefined consensus threshold (mean score ≥7) during the first round, additional rounds were not required. The responses (Table 1) were analyzed to evaluate the clinical perceptions and experiences regarding the role of azelnidipine and its combinations in hypertension management.

Discussion

The management of hypertension has progressively evolved toward structured, evidence-based treatment algorithms emphasizing early and sustained BP control through combination therapy. Contemporary international and Indian hypertension guidelines, including the ESC/ESH and Indian hypertension guidelines-V (IHG-V), recommend initiating therapy with dual antihypertensive combinations in the majority of patients to improve BP target achievement and reduce cardiovascular risk.[3,12] Combination regimens are selected according to age, hemodynamic profile, and associated comorbidities. In elderly patients, where arterial stiffness and salt sensitivity are common, CCBs and thiazide/thiazide-like diuretics are preferred either alone or in combination. In patients with established cardiovascular conditions, including ischemic heart disease, heart failure, or atrial fibrillation, BBs are incorporated into combination regimens due to their role in heart rate control and secondary prevention.[13] Conversely, in younger individuals and in patients with diabetes mellitus, CKD, left ventricular hypertrophy (LVH), or metabolic syndrome, combinations involving renin–angiotensin system (RAS) inhibitors and CCBs are preferred owing to their favorable cardiovascular and renal protective effects (Fig. 3).[14]

Among the available antihypertensives, CCBs remain one of the cornerstones of antihypertensive therapy because of their efficacy, tolerability, and broad applicability across patient populations. Dihydropyridine CCBs are further differentiated according to calcium channel selectivity into L-type, L/T-



Figs 1A to D: Geographic distribution, practice sector, specialty composition, and practice-tier distribution of participating panelists (*N* = 201) in the Delphi consensus study on azelnidipine

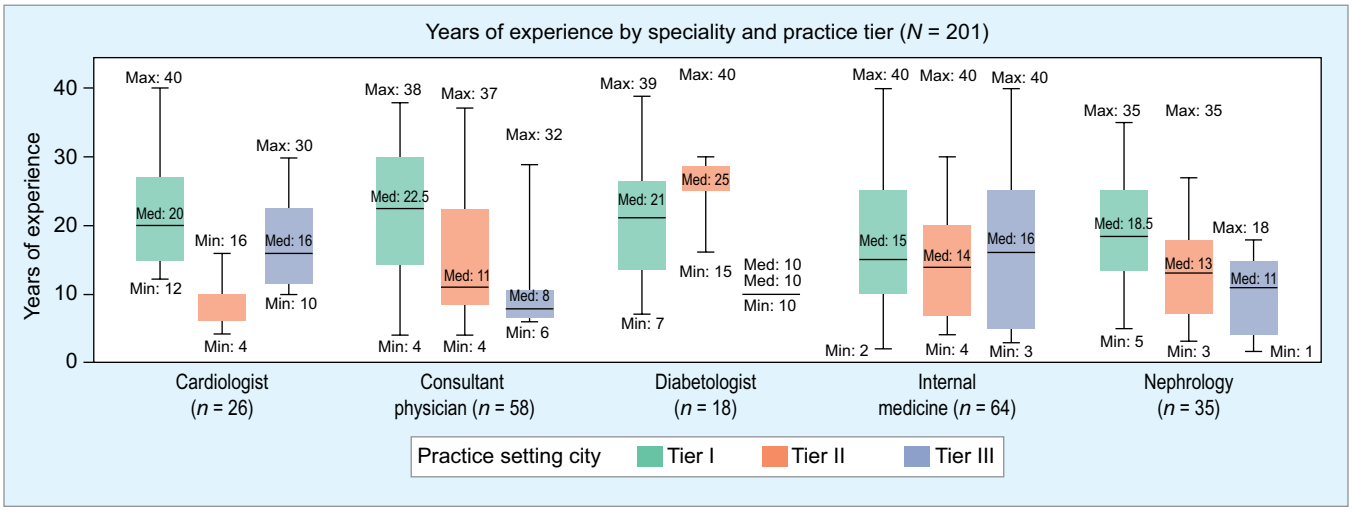


Fig. 2: Distribution of years of clinical experience across medical specialties and practice tiers among participating panelists (*N* = 201)

type, and L/N-type agents.[2] Conventional L-type CCBs, such as amlodipine, produce effective vasodilation but are commonly associated with reflex tachycardia and peripheral edema. L/N-type blockers additionally modulate sympathetic neurotransmission, although this may be associated with metabolic and renal concerns in susceptible patients.[7] Azelnidipine blocks both L- and T-type calcium channels, resulting in sustained vasodilation with minimal reflex sympathetic activation.[15] T-type inhibition is further associated with reduced intraglomerular pressure and modulation of the renin–angiotensin–aldosterone system, supporting reductions in proteinuria and potential renoprotective effects, including in diabetic nephropathy.[16,17]

Table 1: Statement and responses

Sr.No	*Question*	*Median*	*IQR*	*Percent agreement*	*Decision*
1	Calcium channel blockers (CCBs) remain a cornerstone in the pharmacological management of hypertension due to their proven efficacy across diverse populations, including the elderly and patients with isolated systolic hypertension	8	1.25	92.5	Accepted
2	CCBs are preferred for their potent vasodilatory effects and have demonstrated favorable outcomes in long-term cardiovascular morbidity and mortality	8	2.00	88.0	Accepted
3	CCBs can be effectively combined with other antihypertensive classes, such as RAAS inhibitors or BBs or diuretics, to enhance BP control and reduce cardiovascular events	9	2.00	95.0	Accepted
4	Use of CCBs is associated with reduced arterial stiffness and pulse wave velocity contributing to better vascular health, particularly relevant in the elderly and patients with vascular disease	8	3.00	89.0	Accepted
5	Older CCBs, such as amlodipine, may cause reflex tachycardia and peripheral edema, necessitating the use of newer agents like azelnidipine for improved tolerability	8	3.00	84.5	Accepted
6	CCBs are particularly beneficial in patients with salt-sensitive hypertension, including those with chronic kidney disease (CKD), due to their sodium-independent mechanism of action	8	3.00	87.0	Accepted
7	Among CCBs, newer-generation agents with additional pleiotropic effects may provide added clinical benefits beyond conventional BP reduction	9	1.00	90.0	Accepted
8	Azelnidipine is a long-acting dihydropyridine calcium channel blocker that inhibits both L-type and T-type calcium channels	9	2.00	90.5	Accepted
9	Azelnidipine, a third-generation dihydropyridine CCB, offers gradual onset, sustained 24-hour BP reduction, and reduced morning blood pressure surges in hypertensive patients with once-daily dosing	8	2.00	90.0	Accepted
10	In clinical practice, azelnidipine 8 mg is generally considered equivalent to 2.5 mg of amlodipine	8	1.00	88.5	Accepted
11	Unlike older CCBs, azelnidipine is associated with a better reduction in heart rate, making it suitable for patients with high sympathetic activity	8	2.00	87.0	Accepted
12	The heart rate–lowering effect of azelnidipine may offer additional cardiovascular protection in patients with hypertensive heart disease	8	2.00	89.5	Accepted
13	Azelnidipine has demonstrated nephroprotective effects, including reduction in microalbuminuria and stabilization of renal function in hypertensive patients with proteinuria	8	2.00	88.0	Accepted
14	The use of azelnidipine has been associated with a lower incidence of peripheral edema compared to older-generation CCBs like amlodipine	8	3.00	89.0	Accepted
15	Azelnidipine exerts antioxidant effects by reducing oxidative stress markers such as reducing urinary 8-OHdG, contributing to vascular protection and endothelial stabilization	8	2.00	88.0	Accepted
16	Azelnidipine exhibits anti-inflammatory properties by reducing serum levels of hsCRP, MCP-1 and pro-inflammatory cytokines	8	2.00	84.0	Accepted
17	Azelnidipine's pleiotropic effects suggest potential applications in patients with hypertension and early-stage atherosclerotic disease	8	2.00	86.5	Accepted
18	Azelnidipine maintains cerebral blood flow and cerebrovascular reserve in hypertensive patients with ischemic stroke, minimizing the risk of cerebral hypoperfusion	8	2.00	86.0	Accepted
19	Azelnidipine may be a preferred antihypertensive agent in patients with metabolic syndrome due to its favorable effects on insulin resistance	8	2.00	86.5	Accepted
20	The ability of azelnidipine to lower serum uric acid levels presents a clinically relevant advantage of effective blood pressure reduction and potential protective effects against renal dysfunction, cardiovascular events, and metabolic syndrome	8	2.00	83.5	Accepted
21	Azelnidipine may be considered a suitable CCB because of its holistic effects on BP, renal function, cardiovascular health, and metabolic parameters	8	2.00	87.5	Accepted
22	The fixed-dose combination of azelnidipine and telmisartan provides complementary antihypertensive effects by targeting both calcium-mediated vasoconstriction and RAAS activation	9	2.00	93.0	Accepted
23	Azelnidipine and telmisartan demonstrate superior BP control compared to monotherapy with either agent, particularly in patients with stage 2 or above hypertension	9	2.00	92.0	Accepted

Contd…

Contd…

Sr. No	*Question*	*Median*	*IQR*	*Percent agreement*	*Decision*
24	Azelnidipine and telmisartan support faster attainment of BP targets, potentially reducing the time to cardiovascular risk reduction	9	2.00	92.0	Accepted
25	Azelnidipine and telmisartan are associated with better control of morning hypertension and offer smooth 24-hour BP lowering	9	2.00	91.5	Accepted
26	In patients with chronic kidney disease (CKD), the combination of azelnidipine and telmisartan may offer renoprotective benefits by synergistically reducing intraglomerular pressure and proteinuria	8	1.00	89.0	Accepted
27	Azelnidipine and telmisartan are particularly useful in hypertensive patients with metabolic syndrome due to their neutral to positive effects on glucose and lipid metabolism	8	2.00	92.0	Accepted
28	Azelnidipine + telmisartan is ideal for patients with hypertension, CVD, diabetes, and CKD, addressing multiple pathophysiological mechanisms	9	2.00	93.0	Accepted
29	The combination of azelnidipine and metoprolol offers dual control over vascular tone and heart rate, making it effective in patients with high sympathetic tone	8	2.00	90.5	Accepted
30	Azelnidipine + metoprolol is beneficial in patients with hypertension and coexisting IHDs due to its antihypertensive, rate-controlling and vasodilatory effects	8	1.25	90.5	Accepted
31	Azelnidipine + metoprolol provides consistent 24-hour blood pressure control, reducing nocturnal hypertension and morning surges	8	2.00	91.5	Accepted
32	Azelnidipine + metoprolol may be advantageous in younger hypertensive patients with hyperadrenergic symptoms or lifestyle-related BP variability	8	2.00	87.0	Accepted
33	Azelnidipine + metoprolol is effective in reducing left ventricular hypertrophy and may offer additive benefits in myocardial remodeling	8	2.00	88.4	Accepted

8-OHdG, 8-hydroxy-2′-deoxyguanosine; BP, blood pressure; CCB, calcium channel blocker; CKD, chronic kidney disease; CVD, cardiovascular disease; hs-CRP, high-sensitivity C-reactive protein; IHD, ischemic heart disease; IQR, interquartile range; MCP-1, monocyte chemoattractant protein-1; RAAS, renin–angiotensin–aldosterone system

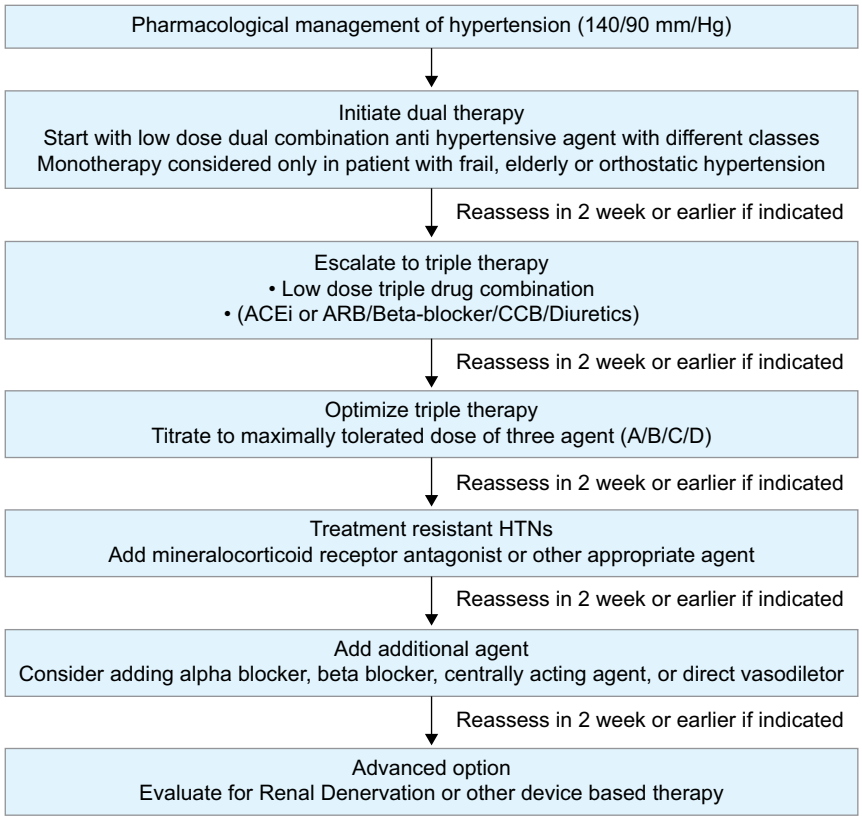


Fig. 3: Stepwise algorithm for hypertension management, illustrating initiation with combination therapy. Treatment progresses from dual to triple therapy, followed by dose optimization and addition of a mineralocorticoid receptor antagonist (MRA) in resistant hypertension. Further escalation includes additional agents or advanced therapies, tailored to patient profile

Additionally, experimental and clinical data indicate reductions in oxidative stress and inflammatory markers such as 8-OHdG, hs-CRP, and MCP-1, although these findings are largely derived from surrogate endpoints.[18–20] A comparative study has also described lower levels of oxidative stress markers, including urinary 8-hydroxy-2′-deoxyguanosine and liver-type fatty acid-binding protein, as well as reduced plasma aldosterone concentrations relative to amlodipine, with these biomarker changes occurring alongside reductions in albuminuria.[19]

Head-to-head comparisons between azelnidipine and amlodipine have shown comparable antihypertensive efficacy. Azelnidipine has shown comparable blood pressure reduction to amlodipine, with a relatively greater reduction in heart rate, likely reflecting lower reflex sympathetic activation.[21] Azelnidipine has been evaluated in patients with comorbid conditions such as chronic kidney disease, diabetes, metabolic syndrome, and cardiovascular disease. A 2025 meta-analysis of six randomized controlled trials involving 731 patients showed a statistically significant reduction in urinary albumin–creatinine ratio (UACR) compared with control therapies (mean difference −47.96; 95% CI −79.56 to −16.37; $p = 0.003$), including in cohorts receiving

background renin–angiotensin–aldosterone system inhibition.[6] However, these findings are primarily based on surrogate markers, with no evidence on definitive renal outcomes. The BOAT2 study similarly reported reductions in albuminuria, carotid intima-media thickness, and circulating inflammatory cytokines without assessment of cardiovascular event rates.[22] In addition, azelnidipine has shown effects on metabolic and neurohumoral parameters. In the AGENT crossover study, azelnidipine was associated with lower post-oral glucose tolerance test and insulin levels compared with amlodipine.[23] Microneurography studies have reported lower muscle sympathetic nerve activity with azelnidipine compared with amlodipine despite similar blood pressure reduction, describing physiological sympatholytic effects without accompanying data on long-term cardiovascular outcomes.[24] A systematic review of preclinical and clinical studies has reported that CCBs were associated with a reduction in stroke risk, primarily through effective blood pressure control.[25] Studies conducted by Watanabe et al. and Kimura et al. reported that azelnidipine effectively lowers blood pressure without compromising cerebral blood flow in post-ischemic stroke patients, indicating a favorable cerebral hemodynamic profile.[16,26]

Recent evidence evaluating azelnidipine includes both neutral and comparative findings across different study designs. In a comparative crossover study involving hypertensive patients with type 2 diabetes, blood pressure control was similar between azelnidipine and cilnidipine, while cilnidipine was associated with greater reductions in albuminuria, suggesting comparatively lesser renal biomarker-based effects with azelnidipine.[27] Additionally, a real-world retrospective cohort analysis comparing olmesartan/azelnidipine with candesartan/amlodipine fixed-dose combinations demonstrated no significant differences in laboratory or renal safety parameters over 1 year of follow-up.[28]

Azelnidipine and telmisartan provide complementary blood pressure-lowering effects through calcium channel inhibition and renin–angiotensin–aldosterone system blockade, respectively. This combination targets both vascular resistance and neurohormonal activation and is therefore suitable for patients with hypertension with coexisting conditions such as chronic kidney disease or metabolic syndrome.[29] In a randomized controlled trial by Bafna, azelnidipine–telmisartan and amlodipine–telmisartan produced comparable reductions in systolic and diastolic BP, while the azelnidipine-based combination was associated with better heart-rate stability and a lower incidence of peripheral edema.[30] In the study by Kojima et al.,[31] azelnidipine combined with olmesartan reduced albuminuria in hypertensive patients with diabetes, with efficacy comparable to thiazide-based regimens.

The combination of azelnidipine with metoprolol succinate, a cardioselective beta-blocker, provides complementary antihypertensive effects by addressing both vascular resistance and heart rate control. This pharmacological profile may be useful in hypertensive patients with increased sympathetic tone, ischemic heart disease, or blood pressure variability related to lifestyle factors. Azelnidipine's gradual onset and sustained vasodilatory action complement the rate-controlling effects of metoprolol, contributing to stable 24-hour blood pressure control and attenuation of nocturnal and early-morning BP fluctuations.[32,33] Echocardiographic studies have reported favorable changes in diastolic functional parameters with azelnidipine-based regimens, including improvements in early diastolic mitral annular velocity (e'), reductions in E/e' ratio, and lower circulating BNP levels. These findings reflect hemodynamic and functional surrogate effects, describing physiological effects associated with therapy rather than demonstrating definitive clinical outcome benefits.[17,34]

Conclusion

This Delphi consensus summarizes expert perspectives on azelnidipine as a CCB with sustained antihypertensive efficacy, favorable tolerability, and additional vascular, renal, and metabolic effects. Its dual L-/T-type calcium channel inhibition is discussed in relation to potential benefits in patients with hypertension and relevant comorbidities. The panel noted its clinical applicability across diverse patient populations, including those with chronic kidney disease, diabetes, and increased sympathetic activity. The use of fixed-dose combinations with telmisartan and metoprolol was considered in the context of complementary mechanisms and blood pressure control. Overall, these findings outline the potential role of azelnidipine within individualized hypertension management approaches.

Limitations and Future Directions

This Delphi consensus is inherently limited by its reliance on expert opinion, which is subject to methodological constraints of the Delphi process, including respondent subjectivity and potential dominance of prevailing clinical perspectives. The findings are based on interpretation of existing literature and clinical experience, in the absence of dedicated prospective, randomized outcome trials evaluating azelnidipine on hard cardiovascular or renal endpoints. In addition, regional prescribing practices and drug availability may have influenced expert viewpoints, thereby limiting generalizability beyond the represented settings. The potential for sponsorship and publication bias cannot be excluded, as these factors were not formally evaluated as part of the Delphi process and may have influenced the evidence base and expert responses informing the consensus statements. Future research should prioritize well-designed, multicenter randomized controlled trials comparing azelnidipine with other calcium channel blockers or contemporary antihypertensive agents. Such studies should include clearly defined populations (e.g., patients with hypertension and chronic kidney disease, diabetes, or high sympathetic activity) and prespecified endpoints such as major adverse cardiovascular events, renal function decline, heart rate effects, and long-term safety. Complementary real-world evidence studies and head-to-head comparative effectiveness analyses may further clarify its role within personalized hypertension management.

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Declarations

Informed Participant Consent for Publication

Steering committee expert panel consent was obtained for publication.

Availability of Data

Data are available with the corresponding author upon reasonable request.

Author Contributions

All authors who fulfilled ICMJE criteria are listed as authors. All authors provided direction and comments on the manuscript, made the final decision about where to publish the manuscript, and approved the final version for submission to the journal.

Conflict of Interest

None.

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None.

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