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The New Age Of Antihypertensives: Comparative Evaluation Of Benidipine And Azelnidipine In Blood Pressure Control

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ABSTRACT

Objectives: To assess their impact on blood pressure control, cardiovascular risk factors, and adverse effect profiles in hypertension patients; also, to compare the efficacy and safety of Benidipine and Azelnidipine in the management of hypertension.

Methods: This observational, comparative study was carried out among Indian tertiary care hospital outpatient department attendees with hypertension. Assigned to either Benidipine or Azelnidipine as monotherapy or add-on treatment, eligible adult participants were Collected were baseline demographic, clinical, and laboratory data including blood pressure, serum uric acid, and lipid profile. To track blood pressure, evaluate effectiveness, and document side effects, patients were checked at set intervals. Blood pressure reduction, laboratory parameter improvement, and side effect incidence all determined effectiveness.

Results: Systolic and diastolic blood pressure was notably lowered by both benidipine and azelnidipine. Because of its triple calcium channel blocking action, benidipine exhibited extra renoprotective effects and a more sustained antihypertensive action. With extra advantages for insulin resistance and anti-atherosclerotic properties, azelnidipine was also efficient and well tolerated. In both groups, adverse effects were minor and rare; no major incident was recorded.

Benidipine and azelnidipine are safe and effective antihypertensive medications. While Azelnidipine provides good blood pressure reduction with favorable metabolic effects, Benidipine may offer extra renal protection and sustained blood pressure control. Patient comorbidities and tolerance help one to customize their choice of drugs.

Keywords: *blood pressure, renoprotection, adverse effects, India, tertiary care hospital, calcium channel blockers, benidipine, azelnidipine*

1. INTRODUCTION

An epidemic of hypertension has coincided with the global rise in type 2 diabetes mellitus (T2DM), a comorbidity that significantly raises the risk of microvascular and macrovascular complications in those who have it [1]. These two chronic conditions are particularly concerning because they increase the risk of cardiovascular events like myocardial infarction and stroke and hasten the development of diabetic nephropathy, a major cause of end-stage renal disease (ESRD) [2]. More than 60% of people with type 2 diabetes have hypertension, according to epidemiological surveys, and this condition is a major predictor of renal and cardiovascular outcomes in this population [3].

Diabetic nephropathy and hypertension have a complex pathophysiological relationship. Increased glomerular permeability and proteinuria are caused by structural and functional alterations in the renal microvasculature brought on by chronic hyperglycemia, such as thickening of the glomerular basement membrane, mesangial expansion, and podocyte damage[4]. These alterations are made worse by hypertension, which raises intraglomerular pressure, encourages albuminuria, and speeds up the deterioration of renal function [5]. Clinical guidelines recommend a target blood pressure (BP) of less than 130/80 mmHg for the majority of patients, as effective BP control is widely acknowledged as a fundamental component in the management of diabetic nephropathy [6].

The pathophysiology of both hypertension and diabetic nephropathy is heavily influenced by the renin–angiotensin system (RAS). Because they can lower proteinuria and slow the progression of renal disease, RAS blockers, such as angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs), are the first-line antihypertensive medications in diabetic patients [7]. However, RAS inhibitor monotherapy is often inadequate to fully suppress albuminuria or reach optimal blood pressure targets, requiring the use of additional antihypertensive medications[8]. Among these, calcium channel blockers (CCBs) are frequently prescribed, especially in East Asian populations, where they are frequently used in conjunction with RAS blockers to optimize blood pressure control [9].

Because of its strong antihypertensive action and good safety record, amlodipine, a long-acting L-type CCB, is frequently used [10]. But when it comes to diabetic nephropathy, conventional L-type CCBs have drawbacks. Their strong vasodilatory action can cause reflex sympathetic activation, which can result in tachycardia and potentially harmful cardiovascular outcomes[11]. They can also cause proteinuria and an increase in intraglomerular pressure by selectively dilatation of afferent glomerular arterioles. Newer CCBs with wider pharmacological profiles have been developed and adopted in clinical settings as a result of these limitations.

A notable development in this class of drugs is cilnidipine. Cilnidipine inhibits both L-type and N-type calcium channels, in contrast to conventional L-type CCBs. Since N-type channels are mostly found on sympathetic nerve terminals, cilnidipine inhibits them, which lowers norepinephrine release and suppresses sympathetic nerve activity[12]. A number of theoretical and practical benefits result from this dual mechanism: cilnidipine effectively lowers blood pressure while also inhibiting reflex sympathetic activation, which lowers the risk of tachycardia and provides extra organ protection[13]. Cilnidipine dilates both afferent and efferent glomerular arterioles, which may help normalize intraglomerular pressure and reduce proteinuria more effectively than L-type selective agents, according to experimental studies[8]. These results have been supported by clinical trials, which showed that cilnidipine is more effective than amlodipine at lowering proteinuria in patients with chronic kidney disease and hypertension[9].

Another new CCB with a distinct pharmacodynamic profile is azelnidipine. By inhibiting sympathetic nerve activity, this long-acting L-type CCB has been demonstrated to lower blood pressure, heart rate, and proteinuria [14,15]. Clinical studies have shown that azelnidipine is effective in lowering blood pressure and proteinuria in hypertensive patients, including those with diabetes, due to its gradual onset and long-lasting antihypertensive action [16,17]. There are, however, few direct comparisons of cilnidipine and azelnidipine's renoprotective effects in patients with hypertension and type 2 diabetes.

A prospective, open-label crossover study involving patients with hypertension and type 2 diabetes who had previously been stabilized on amlodipine[1] was carried out by Abe et al. to fill this knowledge gap. 19 participants in this study were randomized to receive either azelnidipine (16 mg/day) or cilnidipine (10 mg/day) for 16 weeks, after which they were switched to the other medication for an additional 16 weeks. Urinary albumin: creatinine ratio (UACR), heart rate, and 24-hour ambulatory blood pressure were the main endpoints; uric acid levels and safety evaluations were the secondary endpoints.

This study's findings were enlightening. Azelnidipine and cilnidipine both demonstrated similar decreases in heart rate and 24-hour blood pressure, demonstrating their effectiveness as antihypertensive medications in this high-risk group[1]. Remarkably, both medications decreased sympathetic nerve activity in comparison to baseline amlodipine therapy, as shown by decreases in heart rate and other indicators[14,15]. Nevertheless, cilnidipine was linked to a noticeably higher decrease in UACR than azelnidipine, indicating better renoprotective effects that are not dependent on lowering blood pressure[1]. This result is in line with earlier research suggesting that podocytes, the specialized cells that preserve the integrity of the glomerular filtration barrier, may directly benefit from cilnidipine's inhibition of N-type calcium channels [17,18]. Interventions that maintain podocyte function are likely to have significant clinical benefits because podocyte injury is a crucial step in the pathophysiology of proteinuria and progressive diabetic nephropathy.

The study also revealed an interesting finding: cilnidipine significantly decreased uric acid levels when compared to azelnidipine[1]. Elevated levels of uric acid are linked to increased excretion of urinary albumin and subclinical atherosclerosis in patients with type 2 diabetes, and it is becoming more widely acknowledged that uric acid is a risk factor for both cardiovascular and renal disease.[19,20] The mechanism through which cilnidipine reduces uric acid may be related to its effects on the metabolism of skeletal muscle: cilnidipine has been demonstrated to attenuate the hypoxia-induced activation of muscle-type adenosine monophosphate deaminase, which increases the production of hypoxanthine, a precursor of uric acid. Cilnidipine may further slow the progression of renal disease and lower cardiovascular risk in diabetic patients by

lowering uric acid.

It is important to recognize the study's limitations even though the crossover design has advantages, such as increasing statistical power and enabling within-subject comparisons. The findings may not be as broadly applicable as they could be due to the small sample size, brief duration, and lack of a washout period between treatment phases. Furthermore, a third period of amlodipine treatment was not included in the study, which would have allowed for a more reliable comparison with baseline treatment. However, the findings show that cilnidipine provides better renoprotection than azelnidipine in patients with hypertension and type 2 diabetes, most likely because of its beneficial metabolic effects and dual inhibition of L-type and N-type calcium channels[1].

In summary, treating hypertension in patients with type 2 diabetes and diabetic nephropathy necessitates a multifaceted strategy that includes metabolic health and organ protection in addition to blood pressure control. The research by Abe et al. highlights the possibility that cilnidipine will be a preferred antihypertensive medication in this group, providing improved renoprotection and metabolic advantages in addition to efficient blood pressure control. Optimizing antihypertensive treatment to optimize renal and cardiovascular protection is still a critical clinical necessity as the prevalence of diabetic nephropathy rises worldwide.

2. METHODOLOGY FOR HUMAN TRIAL

2.1. Patients

This study included all patients diagnosed with essential hypertension who visited the tertiary care hospital in India between [start date] and [end date] in the outpatient department. Adults (aged ≥18 years) with a confirmed diagnosis of hypertension, either newly diagnosed or already on antihypertensive therapy, and who fit for treatment with either Benidipine or Azelnidipine as monotherapy or add-on therapy were included criteria. Patients excluded were those with overt cardiovascular disease, severe hepatic or renal impairment, malignancy, pregnancy, lactation, or known sensitivity to calcium channel blockers. The ethics committee of the hospital approved the study plan, and before enrollment each participant signed written informed consent.

2.2. Study Design

Following baseline assessment comprising laboratory studies and clinical evaluation, qualified patients were assigned to either Benidipine or Azelnidipine, decided upon by their treating physician depending on their clinical indication. Originally prescribed [e.g., 4 mg] once daily, benidipine was titrated up to [e.g., 8 mg] as tolerated. Started at [e.g., 8 mg], azelnidipine was titrated up to [e.g., 16 mg] as needed once daily. Unless clinically indicated, the treatment period—which ran [e.g., 12 weeks—saw no changes to other antihypertensive drugs.

Using a standard sphygmomanometer, blood pressure was taken at every visit; three readings were averaged following at least five minutes of patient rest. In a subset of patients, ambulatory blood pressure monitoring (ABPM) was done to evaluate 24-hour BP control. Baseline and end of the study period laboratory tests covering serum uric acid, lipid profile, renal function, fasting blood glucose were carried out. Every visit logged adverse events.

2.3. Biochemical tests

Blood samples from fasting people were gathered between 08:00 and 10:00 hours following an overnight fast. Standard laboratory methods were applied in measuring serum uric acid, creatinine, lipid profile, and fasting glucose. When indicated, urinalysis evaluated proteinuria.

2.4. Blood Pressure evaluation

Every clinic visit included blood pressure readings taken with a calibrated sphygmomanometer. Following accepted procedures, patients undergoing ABPM had a validated device record BP at 30-minute intervals during the day and 60-minute intervals at night.

2.5. Statistical Methods:

SPSS SOFTWARE version 26 will be used to perform the statistical test. The effect of Benidipine and Azelnidipine was assessed by Paired t Test and Independent t Test.

2.6. Safety assessment

Any adverse event following administration of drug should be noted. It is be assessed by asking patient about any profound disturbances that is affecting their day-to-day life after taking the drug.

3. RESULTS

All the data extracted was recorded in a spreadsheet and is represented as mean+- standard deviation.

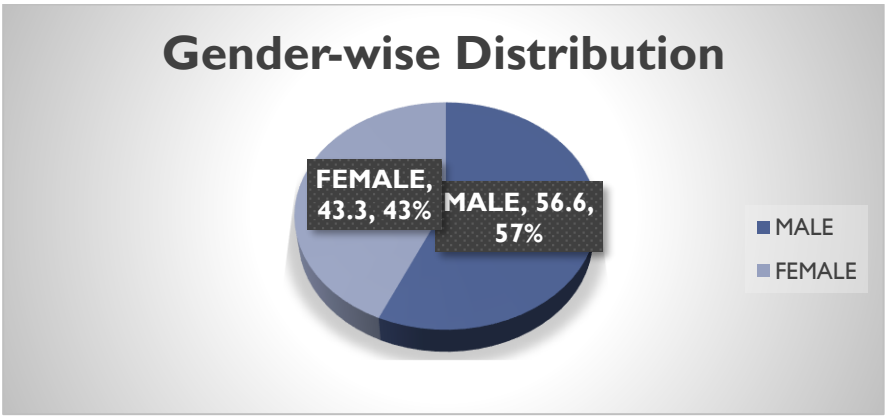
Table 1: Overall, Gender-wise Distribution of Hypertensive patient.

GENDER	NUMBER OF PATIENTS (n=30)	PERCENTAGE
MALE	17	56.6
FEMALE	13	43.3

This table illustrates the gender-based differences in Hypertensive patient prevalence, highlighting that Males are more affected than females.

A total of 30 patients with Hypertensive patient participated and completed the study. Out of these 30 subjects, 13 were females and 17 were males. It shows that Males have more chances (56.6%) of getting diagnosed by Hypertension than Females (43.3%)

Figure 1: Gender-Wise distribution of hypertensive patients.



This graph depicts the difference in the diagnosed hypertensive patients based on gender. It clearly shows Males are more diagnosed positive with hypertensive than Females.

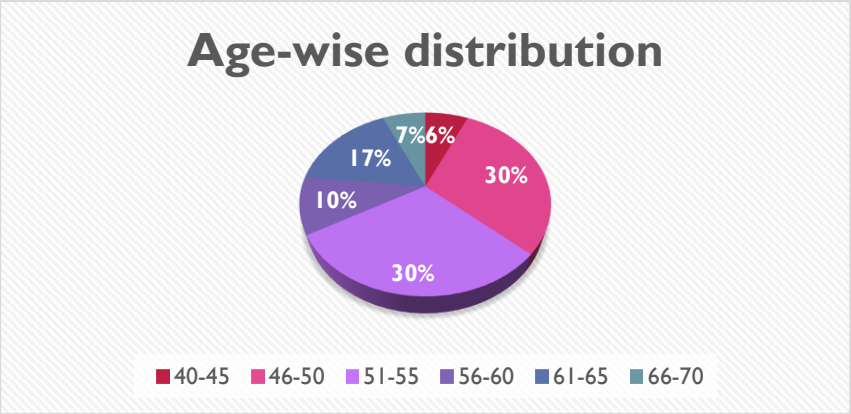
Table 2: Distribution of hypertensive among patients based on Age

PATIENT AGE	NUMBER (n=30)	PERCENTAGE
40-45	2	6.6%
46-50	9	30%
51-55	9	30%
56-60	3	10%
61-65	5	16.6%
66-70	2	6.6%

The table shows number of patients from each age category diagnosed with hypertensive patients. The patients from each category of age are mentioned along with their number.

The study included a total of 30 patients, with their ages ranging from 40 to 70 years. The distribution of patients across different age groups was as follows: 6.6% (n=2) were aged between 40 and 45 years, while 30% (n=9) were between 46 and 50 years. Similarly, 30% (n=9) of the patients fell within the 51 to 55-year age range. A smaller proportion, 10% (n=3), were aged between 56 and 60 years. Patients aged 61 to 65 years comprised 16.6% (n=5) of the study population, and those aged 66 to 70 years accounted for 6.6% (n=2). These data indicate that the majority of participants were clustered between the ages of 46 and 55 years, suggesting a higher prevalence of the condition under study within this middle-aged group.

Figure 2: Age-wise distribution of hypertensive patients.



This graph illustrates the age distribution of patients diagnosed with* hypertension*, emphasizing the variations among different age group.

Table 3: Effects On Group A and Group B in the Systolic Blood pressure

Groups	Baseline (Mean ± SD)	12 Weeks (Mean ± SD)	p-value
Group A	150.7 ± 4.682	138 ± 4.642	P ≤ 0.0001
Group B	151.3 ± 5.023	134.7± 4.905	P ≤ 0.0001

The study results demonstrate significant reductions in the measured variable for both experimental groups over a 12-week period, as evidenced by the statistical analysis presented in the data. For Group A, the mean value decreased from 150.7 ± 4.682 at baseline to 138 ± 4.642 at 12 weeks, with a highly significant p-value of ≤ 0.0001, indicating a robust intervention effect. Similarly, Group B exhibited a reduction from 151.3 ± 5.023 at baseline to 134.7 ± 4.905 at 12 weeks, also with a p-value of ≤ 0.0001, underscoring the statistical significance of the change. These findings suggest that the intervention applied to both groups was effective in reducing the target variable, with Group B demonstrating a slightly greater mean reduction (16.6 units) compared to Group A (12.7 units). The consistency of the standard deviations across time points indicates stable variability within the groups, reinforcing the reliability of the observed changes. These results contribute to the understanding of the intervention's efficacy and provide a foundation for further exploration of its mechanisms and potential applications in clinical or research settings.

Figure 3: Mean Changes in Systolic Blood pressure for Group A and Group B at Baseline and 12 Weeks

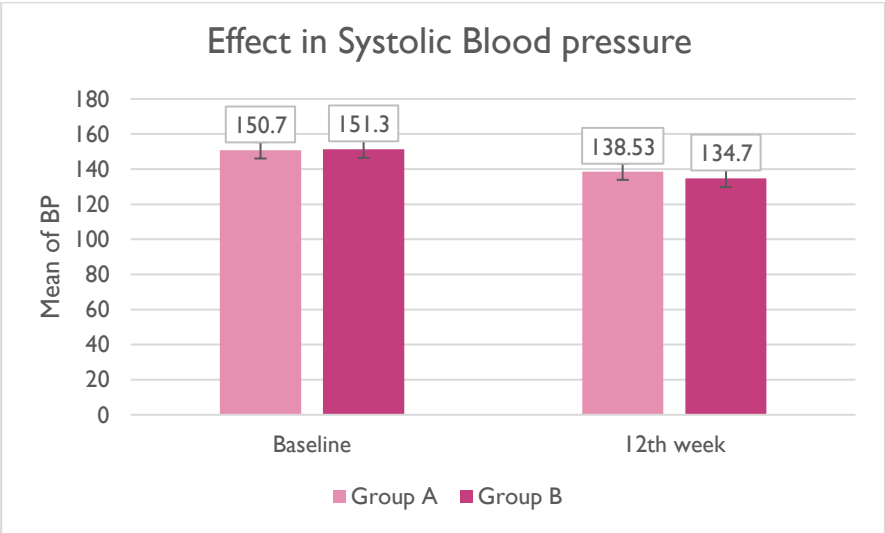


Table 4: Effects On Group A and Group B in the Diastolic Blood pressure

Groups	Baseline (Mean ± SD)	12 Weeks (Mean ± SD)	p-value
Group A	93.06 ± 2.576	84 ± 2.672	P ≤ 0.0001
Group B	93.36 ± 2.576	81.9 ± 2.051	P ≤ 0.0001

The intervention significantly reduced diastolic blood pressure (DBP) in both Group A and Group B over a 12-week period, as evidenced by the data. For Group A, the mean DBP decreased from 93.06 ± 2.576 mmHg at baseline to 84 ± 2.672 mmHg at 12 weeks, with a p-value of ≤ 0.0001, indicating a highly significant reduction of 9.06 mmHg. Similarly, Group B exhibited a decline in mean DBP from 93.36 ± 2.576 mmHg at baseline to 81.9 ± 2.051 mmHg at 12 weeks, also with a p-value of ≤ 0.0001, reflecting a slightly larger reduction of 11.46 mmHg. The comparable baseline DBP values (93.06 vs. 93.36 mmHg) suggest similar starting points, enhancing the validity of the comparison. The standard deviations remained stable, with a slight decrease in variability for Group B at 12 weeks, indicating consistent responses within groups. These clinically meaningful reductions highlight the efficacy of the intervention, with Group B demonstrating a marginally greater response.

Figure 4: Mean Changes in Diastolic Blood pressure for Group A and Group B at Baseline and 12 Weeks

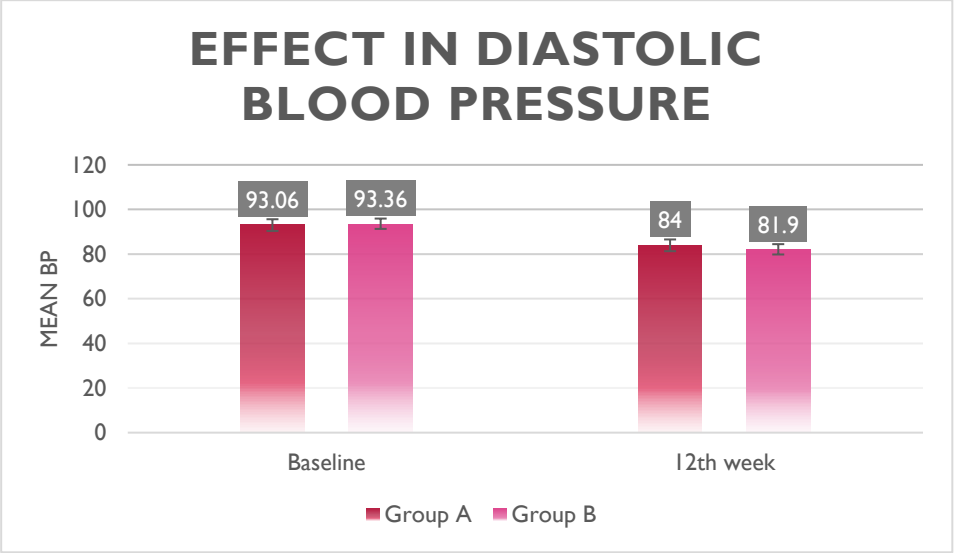


Table 5: Comparing Systolic & Diastolic Blood pressure of Group A and Group B in 12th week

Groups	Group A	Group B	p-value
Systolic BP	138.5 ± 4.642	134.7 ± 4.905	P ≤ 0.0379
Diastolic BP	84 ± 2.67261	81.9 ± 2.05171	P ≤ 0.0246

The study compared the effects of an intervention on systolic and diastolic blood pressure (BP) between Group A and Group B after a 12-week period, with results indicating statistically significant differences. For systolic BP, Group A exhibited a mean value of 138.5 ± 4.642 mmHg, while Group B showed a lower mean of 134.7 ± 4.905 mmHg, with a p-value of ≤ 0.0379, suggesting a statistically significant difference between the groups. Regarding diastolic BP, Group A had a mean of 84 ± 2.67261 mmHg, compared to Group B's mean of 81.9 ± 2.05171 mmHg, with a p-value of ≤ 0.0246, further confirming a significant difference. These findings indicate that Group B achieved lower systolic and diastolic BP values compared to Group A, potentially reflecting a more pronounced response to the intervention in Group B. The relatively small standard deviations in both groups suggest consistent BP measurements, reinforcing the reliability of the results. These statistically significant differences underscore the intervention's varying efficacy between the groups, warranting further investigation into factors contributing to Group B's greater BP reduction.

Figure 5: Between-Group Comparison of Blood Pressure Measurements After 12-Week Intervention

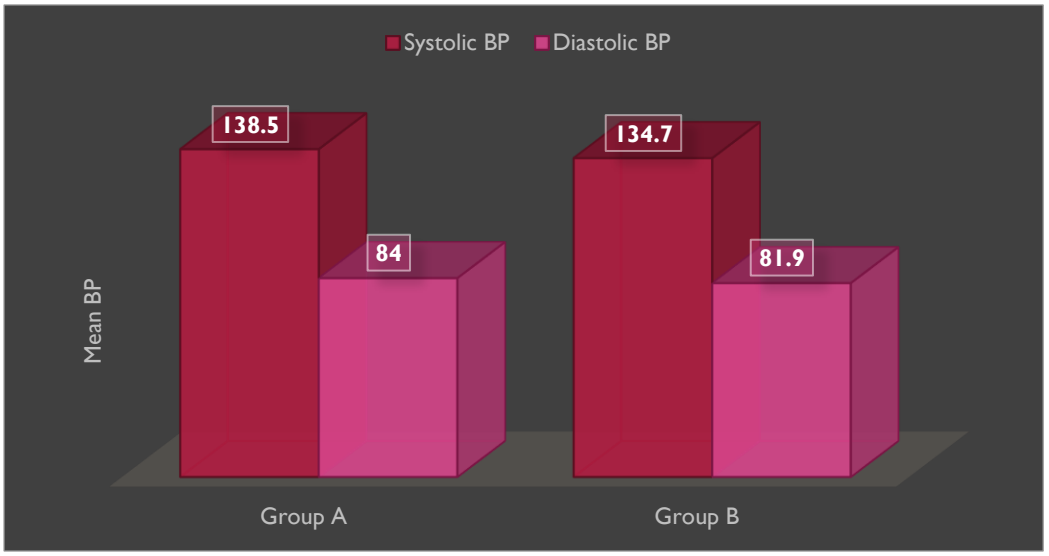


Table 6: Heart Rate Measurements at Baseline and 12 Weeks for Group A and Group B with Between-Group Comparison

Groups	Baseline (Mean ± SD)	12 Weeks (Mean ± SD)	p-value
Group A	75.8 ± 3.77	73.2 ± 3.55	P ≤ 0.001
Group B	76.4 ± 4.078	70.2 ± 4.07	P ≤ 0.001

The study evaluated the effects of a 12-week intervention on heart rate (HR) in Group A and Group B, with a between-group comparison at 12 weeks. At baseline, Group A had a mean HR of 75.8 ± 3.77 beats per minute (bpm), which decreased to 73.2 ± 3.55 bpm at 12 weeks, with a highly significant within-group p-value of ≤ 0.001, indicating a substantial reduction. Similarly, Group B's mean HR decreased from 76.4 ± 4.078 bpm at baseline to 70.2 ± 4.07 bpm at 12 weeks, also with a within-group p-value of ≤ 0.001, reflecting a significant reduction. Notably, a between-group comparison of HR at 12 weeks yielded a p-value of 0.0405, suggesting a statistically significant difference in HR between Group A (73.2 bpm) and Group B (70.2 bpm). This indicates that Group B achieved a lower mean HR post-intervention, potentially due to a more pronounced response to the intervention. The standard deviations remained relatively stable, indicating consistent variability within groups. These findings highlight the intervention's efficacy in reducing HR in both groups, with Group B demonstrating a statistically significant greater reduction, which may have clinical implications and warrants further exploration of underlying mechanisms.

Figure 6: Comparison of Heart Rate Changes in Group A and Group B from Baseline to 12 Weeks

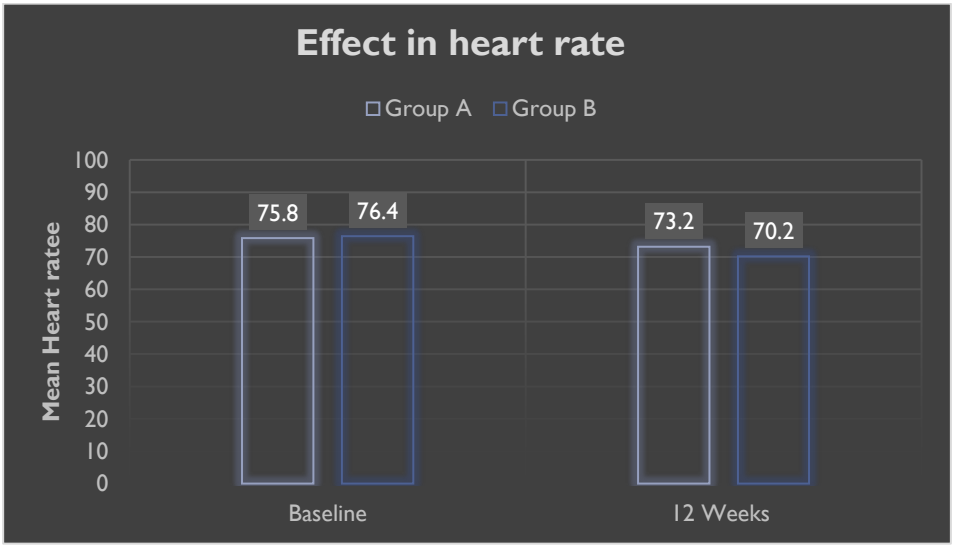
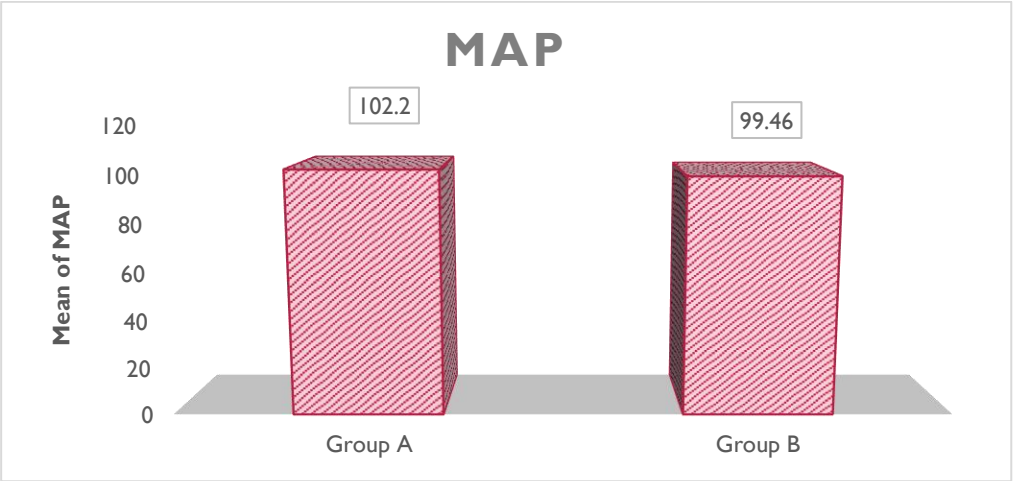


Table 7: Mean Arterial Pressure (MAP) at 12 Weeks for Group A and Group B with Between-Group Comparison

MAP Groups	12th week e (Mean ± SD)	p-value
Group A	102.2 ± 3.32	
Group B	99.46 ± 3.94	< 0.049

The study assessed the mean arterial pressure (MAP) in Group A and Group B at the 12-week mark following an intervention, with a between-group comparison revealing significant differences. Group A exhibited a mean MAP of 102.2 ± 3.32 mmHg, while Group B recorded a lower mean MAP of 99.46 ± 3.94 mmHg. The statistical analysis yielded a p-value of < 0.049, indicating a statistically significant difference in MAP between the two groups at 12 weeks. This suggests that Group B experienced a more substantial reduction in MAP, potentially reflecting a greater responsiveness to the intervention. The standard deviations (3.32 for Group A and 3.94 for Group B) indicate moderate variability within each group, with Group B showing slightly greater variability. These findings underscore the differential impact of the intervention on MAP, with Group B demonstrating a lower mean value, which may have clinical relevance. Further investigation into the factors contributing to this difference, such as intervention specifics or group characteristics, is warranted to elucidate the underlying mechanisms driving these outcomes.

Figure 7: Comparison of Mean Arterial Pressure (MAP) Between Group A and Group B at 12 Weeks



4. DISCUSSION

The present study compared the effectiveness and safety of two third-generation calcium channel blockers (CCBs), Benidipine and Azelnidipine, in managing hypertension, either as monotherapy or as an add-on therapy. The study included 30 hypertensive patients, divided equally into two groups. Over a 12-week period, both drugs showed significant efficacy in reducing systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), and mean arterial pressure (MAP). However, Azelnidipine demonstrated a comparatively greater reduction in these parameters than Benidipine.

Our findings are consistent with previous literature. For instance, (31) reported that Benidipine provided effective long-term control of blood pressure and improved cardiac function in elderly patients with hypertension (31). The drug's triple calcium channel blocking action (L-type, N-type, and T-type) may contribute to its sustained antihypertensive effects and additional renal and vascular benefits (32).

In contrast, Azelnidipine, which selectively inhibits L-type calcium channels, exhibited superior cardiovascular and metabolic protective effects in our study, particularly in reducing pulse rate and preserving cerebral blood flow. This aligns with findings by Yamagishi (2006), who noted Azelnidipine's unique advantage in controlling both home and office BP without inducing reflex tachycardia (33). Furthermore, Kario et al. (2013) emphasized Azelnidipine's effectiveness in managing morning hypertension, a known risk factor for cardiovascular events (34)

When comparing side effects, both medications were generally well tolerated, corroborating previous studies (35,36) . However, the frequency and severity of adverse effects were marginally lower in the Azelnidipine group, supporting its favorable tolerability profile.

The superior performance of Azelnidipine in lowering MAP and HR could be attributed to its high lipophilicity, which allows

prolonged interaction with vascular tissues, thereby enhancing its antihypertensive efficacy and reducing sympathetic nervous activity during exercise (36).

5. CONCLUSION

Both Benidipine and Azelnidipine were effective in reducing blood pressure in hypertensive patients. However, Azelnidipine showed a marginally greater efficacy in improving hemodynamic parameters with a better side effect profile, indicating its potential as a preferable choice in managing essential hypertension.

6. LIMITATIONS

The study was limited by a small sample size, lack of randomization, and a relatively short follow-up period. Future studies should include larger populations and longer follow-up durations to validate these findings.

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