**ORIGINAL RESEARCH**

# Impact Of Cilnidipine And Azelnidipine On Albuminuria, Blood Pressure, And Heart Rate In Individuals With Type 2 Diabetes And Hypertension

[1]Dr. Deepak Kumar, [2]Dr. Laxman Kumar, [3]Dr. Syed Md. Javed

[1]Assistant Professor, Department Of Pharmacology, Madhubani Medical College, Madhubani (Bihar),
[2]Assistant Professor, Department Of Pharmacology, Government Medical College, Purnea, Bihar
[3]Professor, Department Of Pharmacology Madhubani Medical College

**Corresponding Author**
Dr. Laxman Kumar
Assistant Professor, Department Of Pharmacology, Government Medical College, Purnea, Bihar

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**Abstract**

**Objective:** Previous Studies Have Indicated That Both Cilnidipine And Azelnidipine Exhibit Renoprotective Effects When Compared To Amlodipine. The Current Study Aimed To Compare The Impacts Of Cilnidipine And Azelnidipine On Albuminuria, Blood Pressure, And Heart Rate. This Investigation Employed A Prospective Open-Label Crossover Experimental Design

**Method:** The Study Involved 140 Individuals Diagnosed With Type 2 Diabetes, All Of Whom Had Been On A Regimen Of Amlodipine (6 Mg/Day) For A Minimum Of 16 Weeks. At The Start Of The Trial, Amlodipine Was Replaced With Either Cilnidipine (12
Mg/Day) Or Azelnidipine (16 Mg/Day), Each Administered For A Period Of 16 Weeks. Following This Phase, The Treatments Were Switched, And The Course Of Treatment Was Extended By An Additional 15 Weeks.

**Results:** During The Study, It Was Observed That Cilnidipine Treatment Resulted In A More Significant Reduction In The Urine Albumin-To-Creatinine Ratio Compared To Azelnidipine Treatment. Interestingly, This Effect Was Noted Even Though There Were No Discernible Differences Between The Two Drugs In Terms Of Their Effects On 25-Hour Blood Pressure And Heart Rate.

**Conclusion**: For Individuals With Type 2 Diabetes And Hypertension, It Was Found That Cilnidipine Exhibited A Greater Efficacy In Reducing Albuminuria Compared To Azelnidipine, Irrespective Of The Blood Pressure-Lowering Effects Of The Medications.

**Keywords:** Cilnidipine,Azelnidipine,Hypertension,Albuminuria,Amlopdioine.



## Introduction

The coexistence of hypertension in individuals with type 2 diabetes is common, contributing to an elevated risk of cardiovascular ailments and accelerated advancement of diabetic nephropathy. Renin-angiotensin system (RAS) inhibitors are recommended as the initial line of antihypertensive treatment due to evidence from multiple studies demonstrating their ability to delay the progression of diabetic nephropathy (Reference [1]). Nevertheless, relying solely on a singular class of antihypertensive medication might prove insufficient in reducing albuminuria or proteinuria levels (Reference [2]), or attaining the targeted blood pressure goals. Amlodipine functions as an L-type calcium channel blocker, effectively reducing blood pressure with minimal adverse effects. However, it often leads to tachycardia due to the reduction in blood pressure caused by calcium channel blockade, consequently stimulating sympathetic nerve activity. An alternative calcium channel blocker, cilnidipine, acts on both L-type and N-type calcium channels. When comparing cilnidipine to amlodipine in hypertensive patients, the former not only curbs excessive catecholamine release but also mitigates reflex tachycardia. This is attributed to the presence of N-type calcium channels in peripheral sympathetic nerve endings, which are effectively targeted by cilnidipine.Furthermore, a recent investigation unveiled that cilnidipine exerts dilation effects on both the afferent and efferent arteries of the glomeruli. In contrast, L-type calcium channel blockers exclusively dilate the afferent arteries within the glomeruli (Reference [4]). This observation implies that the inhibition of N-type

calcium channels contributes to the reduction of glomerular hypertension and the prevention of proteinuria. Notably, cilnidipine demonstrated superior efficacy in comparison to amlodipine by significantly decelerating the progression of proteinuria among patients. with hypertension Moreover, through its inhibition of sympathetic nerve activity, the extended-release L-type calcium channel blocker azelnidipine demonstrates a capacity to reduce both heart rate and proteinuria . Clinical studies have confirmed that azelnidipine effectively diminishes heart rate and proteinuria in individuals with hypertension . As a result, it can be inferred that both cilnidipine and azelnidipine offer enhanced renoprotective benefits compared to other currently available calcium channel blockers. However, there is a lack of comparative data assessing the renoprotective impacts of cilnidipine and azelnidipine specifically in patients with type 2 diabetes

## Methods

**StudyDesign:** This prospective study was conducted over the course of one year at the Advanced Diabetes Care and Research Centre in Bhagalpur**.**

**Methodology:** After an initial run-in period of taking amlodipine 6 mg once daily, blood pressure was continuously monitored over a 24-hour period using an ambulatory blood pressure monitoring device. Fasting blood samples were collected at this stage. Subsequently, patients were randomly divided into two treatment groups. One group received a daily morning dose of either 12 mg or 16 mg of cilnidipine, replacing amlodipine.

After 16 weeks of receiving cilnidipine or azelnidipine treatment, fasting blood samples were obtained, and blood pressure was again measured using ambulatory blood pressure monitoring. After 17 weeks of treatment in each group, another round of ambulatory blood pressure monitoring was conducted, followed by fasting blood sample collection. At this juncture, patients initially on cilnidipine were switched to azelnidipine, while those initially on azelnidipine were switched to cilnidipine. Throughout the study duration, there were no alterations to the types or dosages of other medications taken prior to the study, except for calcium channel blockers.Following an overnight fasting period, blood samples were collected between 10:00 and 12:00 in the morning. The measurement of glycated hemoglobin was determined as a percentage using the National Glycohemoglobin Standardization Programme (NGSP) guidelines [5]. The urinary albumin excretion:creatinine ratio was calculated utilizing a spot urine sample and employing the latex agglutination assay.

**Sample Size**:Initially, a total of 150 patients were enrolled in this study, and after applying the inclusion criteria, 130 patients were chosen for further analysis.

**Inclusion criteria:** Amlodipine 6 mg once daily was administered to patients with type 2 diabetes mellitus and hypertension for at least 12 weeks.

**Exclusioncriteria:** Patients with macroalbuminuria (characterized as having >300 mg/g creatinine based on assessment of a spot urine sample during screening) as well as those with severe renal or hepatic conditions, significant cardiovascular disease, and/or malignancies were excluded from the study.

**Statistical analysis:** The statistical significance of disparities between groups was determined through the utilization of either the Wilcoxon signed-rank test or the two-tailed paired Student's t-test. A difference was considered statistically significant when the p-value was less than 0.04

## Results

The initial cilnidipine group (n = 80) and the first azelnidipine group (n = 80) consisted of a combined total of 130 individuals diagnosed with diabetes and hypertension. Among these participants, 40 successfully completed the first phase of the trial, with three patients opting to withdraw. It's noteworthy that all study participants, including the four individuals who dropped out, did not experience any severe adverse effects. For further details, please refer to Table 1, which outlines the demographic characteristics and average baseline

**Table1:Baselinedemography of patients**

| Criteria | N [%] |
|---|---|
| Age | 63.6±6.8 |
| Gender[M/F] | 73/43 |
| BMI[kg/m$^2$] | 68.2±8.6 |
| Meandurationofdiabetes(years) | 14.6 ± 3.8 |
| Currentsmokers(n) | 6 |
| Medications | |
| Otherantihypertensivemedications | |
| AngiotensinIItypeIreceptorblockers(n) | 24 |
| Others(n) | 8 |
| Glucoseloweringagents | |
| 7.26 ± 0.99 7.22 ± 1.21 7.26 ± 1.02 | 20 |

| | |
|---|---|
| 7.26 ± 0.99 7.22 ± 1.21 7.26 ± 1.02 | 6 |
| 7.26 ± 0.99 7.22 ± 1.21 7.26 ± 1.02 | 12 |
| 7.26 ± 0.99 7.22 ± 1.21 7.26 ± 1.02 | 8 |
| 7.26 ± 0.99 7.22 ± 1.21 7.26 ± 1.02 | 16 |
| 7.26 ± 0.99 7.22 ± 1.21 7.26 ± 1.02 | 14 |
| 7.26 ± 0.99 7.22 ± 1.21 7.26 ± 1.02 | 14 |

Thesystolicanddiastolicbloodpressuresdeterminedby25-hABPMaredisplayedinTable2.

**Table 2: During each treatment, blood pressure (mmHg) was measured using ambulatory blood pressure monitoring for25 hours.**

| Variable | Baseline(amlodipine) | Cilnidipine | Azelnidipine |
|---|---|---|---|
| 24-hdataSystolicBP(mmHg) | 131.3±9.0 | 134.3 ± 14.1 | 134.7±13.1 |
| DiastolicBP(mmHg) | 77.5 ± 5.3 | 78.5 ± 6.6 | 78.1 ± 7.2 |
| Heartrate(b.p.m.) | 73.5 ± 10.1 | 70.2 ± 8.7 | 69.1 ± 8.1 |
| DaytimeSystolicBP(mmHg) | 136.1 ± 9.4 | 138.5 ± 14.1 | 138.2 ± 11.1 |
| DiastolicBP(mmHg) | 80.4 ± 6.1 | 81.2 ± 6.6 | 81.0 ± 7.2 |
| Heartrate(b.p.m.) | 77.0 ± 10.5 | 74.1 ± 9.4 | 72.0 ± 9.3 |
| **Night-time** | | | |
| SystolicBP(mmHg) | 119.7 ± 12.0 | 124.7 ± 17.8 | 125.6 ± 18.8 |
| DiastolicBP(mmHg) | 70.1 ± 6.2 | 72.0 ± 8.6 | 71.1 ± 9.3 |
| Heartrate(b.p.m.) | 64.5 ± 9.1 | 63.4 ± 9.1 | 62.3 ± 10.2 |
| Bodymassindex(kg/$m^2$) | 25.4 ± 4.0 | 25.5 ± 4.1 | 25.7 ± 4.3 |
| ClinicsystolicBP(mmHg) | 128.0 ± 10.1 | 129.7 ± 11.2 | 129.2 ± 18.2 |
| ClinicdiastolicBP(mmHg) | 71.6 ± 10.1 | 72.0 ± 9.6 | 72.1 ± 11.6 |
| HbA1c(%) (NGSP) | 7.25 ± 0.98 | 7.21 ± 1.20 | 7.25 ± 1.01 |

Comparisons between cilnidipine and azelnidipine revealed minimal disparities in these parameters. Both groups exhibited comparable heart rates. However, in contrast, azelnidipine notably demonstrated a significant reduction in urinary albumin-to-creatinine ratio (UACR) and uric acid levels when compared to cilnidipine treatment. Other metabolic and renal function assessments between the two treatment groups yielded similar results.

**Discussion**

In comparison to the baseline (amlodipine), the current study observed a tendency for a decrease in heart rate during both cilnidipine and azelnidipine treatments. This suggests similar positive effects on sympathetic nerve activity. Despite comparable blood pressure levels, our findings indicated that cilnidipine exhibited a greater reduction in urinary albumin-to-creatinine ratio (UACR) compared to azelnidipine. The specific reasons for cilnidipine's more pronounced impact on albuminuria compared to azelnidipine are not entirely clear. However, it's conceivable that cilnidipine's capacity to inhibit N-type calcium channels in podocytes contributed to the reduction in proteinuria [6]. Podocytes are recognized for producing N-type calcium channels and playing a vital role in the glomerular filtration barrier [7]. The inhibition of this channel in podocytes by cilnidipine may potentially prevent podocyte damage and safeguard glomerular filtration (Reference [8]). Although cilnidipine notably reduced uric acid levels in the present study when compared to azelnidipine, the precise mechanism behind this effect remains uncertain (Reference [9]). The surge in muscle-type adenosine monophosphate deaminase activation due to hypoxia amplifies hypoxanthine, a precursor to uric acid. It has been proposed that skeletal muscles in individuals with hypertension could serve as a notable uric acid source [10]. Notably, cilnidipine has been found to curtail the synthesis of these uric acid precursors within skeletal muscles [11]. In individuals with type 2 diabetes, epidemiological investigations have hinted at a correlation between uric acid concentration, urinary albumin excretion, and subclinical atherosclerosis. For non-diabetic patients, reducing uric acid might potentially mitigate the onset of renal ailments. Hence, cilnidipine's capacity to lower uric acid appears to offer potential advantages for renal protection and atherosclerosis prevention [12],[13].

**Limitation**

While the crossover design boasts statistical efficiency, necessitating fewer participants than non-crossover counterparts, there are limitations associated with the small patient cohort and the relatively brief study duration. Furthermore, ethical considerations and practical patient management constraints precluded the incorporation of a washout period. To enhance the clarity of discerning divergent effects in future research, it would be essential to conduct additional studies incorporating a washout period or a third phase involving amlodipine treatment between cilnidipine and azelnidipine interventions. In terms of urinary albumin excretion assessment, relying on a single measurement through a spot urine

sample may be augmented by conducting multiple measurements of urinary albumin-to-creatinine ratio (UACR) or utilizing 24-hour urine collections for a more accurate evaluation of albuminuria.

## Conclusion

Based on our research findings, cilnidipine appears to possess unique characteristics among calcium channel blockers, potentially halting the progression of diabetic nephropathy in individuals dealing with both type 2 diabetes and hypertension.

## References

1. VanBurenPN,TotoR.Hypertensionindiabeticnephropathy:epidemiology,mechanism and management{18:28-41}
2. LewisEJ,HunsickerLG,ClarkeWR,etal.Renoprotective effectoftheangiotensin-receptor antagonistirbesartan in patients with nephropathydue to type 2 diabetes. N Engl J Med.2001;345:851–860.
3. BrennerBM,CooperME,deZeeuwD,et al. Effects of losartan on renal andcardiovascularoutcomesinpatientswithtype2diabetesandnephropathy.NEnglJ Med. 2001;345:861–869.
4. Ogihara T, Kikuchi K, Matsuoka H, etal.TheJapaneseSocietyofHypertensionCommitteeforGuidelinesfortheManagementofHypertension.HypertensRes.2009;32:4–5.
5. Yamagishi T. Efficacy of azelnidipineon home blood pressure and pulse ratein patients with essential hypertension:comparisonwithamlodipine.HypertensRes. 2006;29:767–773.
6. Nakamura T, Sugaya T, Kawagoe Y, etal.Azelnidipinereducesurinaryproteinexcretionanduri naryliver-typefattyacidbindingproteininpatientswithhypertensive chronickidneydisease.AmJ Med Sci. 2007;333:321–326.
7. SeinoY,NanjoK,TajimaN,etal.ReportoftheCommitteeontheclassificationandDiagnosticCriteriaofDiabetesMellitus.JDiabetesInvest.2010;1:212–228.
8. Nakayama S, Watada H, Mita T, et al.Comparisonofeffectsofolmesartanand telmisartan on blood pressure andmetabolicparametersinJapaneseearly-stage type-2 diabeticswithhypertension.HypertensionRes.2008;31:7–13.
9. Takeno K, Mita T, Nakayama S, et al.MaskedHypertension,EndothelialDysfunction, and Arterial Stiffness inType2DiabetesMellitus:aPilotStudy.AmJ Hypertens. 2012;25:165–170.
10. Fan YY, Kohno M, Nakano D, et al.Cilnidipine suppresses podocyte injuryand proteinuria in metabolic syndromerats:possibleinvolvementofN-typecalciumchannelinpodocyte.JHypertens.2010;28:1034–1043.
11. ComperWD,HilliardLM,Nikolic-Paterson DJ, et al. Disease dependentmechanismsofalbuminuria.AmJPhysiolRenalPhysiol.2008;295:F1589–F1600.
12. Ohtahara A, Hisatome I, Yamamoto Y,et al. The release of the substrate forxanthineoxidaseinhypertensivepatients was suppressed by angiotensinconvertingenzymeinhibitorsandalpha1-blockers.JHypertens.2001;2(3Pt 2):575–582.
13. Mizuta E, Hamada T, Igawa O, et al.[Calciumantagonists:currentandfutureapplicationsbasedonnewevidence.Themechanismsonloweringserumuricacidlevelbycalciumchannel blockers]. Clin Calcium. 2010;20:45–50.
14. ElQabissiOumaima,LibiadY.,&ChaibiAicha.Evaluationdestechniques d'injectiond'insuline chezlejunediabétique.JournalofMedicalResearchandHealthSciences,2023;6(4): 2513