Ibrahim Card Med J 2024; 14 (1): 19-27

Comparative efficacy and safety of Cilnidipine and Amlodipine in the management of hypertension

Mohammed Akram Hossain,[1] Md. Farid Ahsan,[2] Jadab Kumar Biswas,[3] Sara Farahnaj,[4] Ashraful Alam Khan[5]

ABSTRACT

Background & objective: Hypertensive patients with coronary artery disease and diabetes mellitus usually benefit from selective antihypertensive medications like calcium channel blockers (CCBs). Of the dihydropyridine (DHP) CCBs, amlodipine has an excellent pharmacokinetic and pharmacodynamic profile. The only drawback of amlodipine is that it causes pedal oedema leading to drug discontinuation in many cases. The new generation CCB, cilnidipine has demonstrated equal efficacy in controlling blood pressure, but its adverse effect as is observed in amlodipine has not been widely tested. The present study was, therefore, designed to make a comparative evaluation of cilnidipine and amlodipine in the management of blood pressure in hypertensive individuals.

Patients & Methods: The present non-randomized clinical trial was conducted in the private practices of renowned cardiologists and specialists in internal medicine in Chittagong Metropolitan City over a period of four years, from January 2020 to December 2023. A total of 496 hypertensive patients of both sexes were consecutively enrolled in the study. Among them, 455 patients-246 in the Amlodipine group and 209 in the Clinidipine group completed the two scheduled follow-up visits within six months of the intervention (the study endpoint) and were subsequently included in the final analysis. The study drugs were considered effective if 80% of the subjects in the study experienced control of blood pressure (systolic blood pressure < 140 mmHg and/or diastolic blood pressure < 90 mmHg) after 6 months of intervention with the study drugs. The study drugs were termed safe if they did not cause impairment of renal, neuro, and cardiac functions significantly during the study period. Pedal oedema was assessed by clinical method over the medial malleolus of both legs.

Result: The cilnidipine and amlodipine groups were comparable regarding age and sex. However, obesity and diabetes were more prevalent in the amlodipine group, while smokers were more frequent in the cilnidipine group. Mean systolic and diastolic blood pressures were slightly lower in the cilnidipine group. Fasting blood sugar levels were similar, and dyslipidemia was common in both groups. The comparative evaluation of cilnidipine and amlodipine in the management of systemic hypertension revealed significant differences in heir efficacy and safety profiles. Both medications effectively reduced blood pressure, with a greater mean reduction in systolic blood pressure being observed in the amlodipine group compared to the cilnidipine group (19.9% vs. 15.6%, $p < 0.001$). However, the incidence of adverse effects, particularly pedal edema, was notably higher in the amlodipine group (11% vs. 4.8%, $p = 0.016$), indicating a preference for cilnidipine among hypertensive patients concerned about tolerability. Despite these differences in side effects and blood pressure control, the overall efficacy in achieving target blood pressure levels (SBP < 140 mmHg and DBP < 90 mmHg) was comparable between the two groups, as evidenced by the high control rates of 87% in the amlodipine group and 88.5% in the cilnidipine group ($p = 0.622$).

Conclusion: The study concluded that both cilnidipine and amlodipine are equally effective in reducing blood pressure in hypertensive individuals. However, cilnidipine is less likely to cause pedal oedema than amlodipine. This advantage of cilnidipine makes it a preferred antihypertensive drug over amlodipine.

Keywords: Hypertension, amlodipine, cilnidipine, efficacy, safety, pedal oedema etc.

ORIGINAL ARTICLE

Author's information:

[1] ***Dr. Mohammed Akram Hossain,*** *Senior Consultant, Department of Cardiology, Chattagram General Hospital, Chattagram, Bangladesh.*

[2] ***Dr. Md. Farid Ahsan,*** *Professor, Department of Zoology, University of Chittagong, Chattagram Bangladesh.*

[3] ***Dr. Jadab Kumar Biswas,*** *Associate Professor, Department of Zoology, University of Chittagong, Chattagram Bangladesh.*

[4] ***Dr. Sara Farahnaj,*** *Assistant Professor, Department of Community Medicine, University of Science and Technology, Chittagong*

[5] ***Dr. Ashraful Alam Khan,*** *MD(Chest), MPH, FCCP, Register, ICU, National Institute of Diseases of The Chest and Hospital, Dhaka, Bangladesh*

Correspondence: ***Dr. Mohammed Akram Hossain,*** *Mobile: +880 1716141834 E-mail: drrumong@gmail.com*

INTRODUCTION

Systemic arterial hypertension is a significant global health concern, recognized as the most important modifiable risk factor for all-cause morbidity and mortality. It is closely associated with an increased risk of cardiovascular disease (CVD).[1] Approximately 1 billion individuals worldwide are affected by hypertension,[2] with national reports indicating a rising prevalence in low and middle-income countries since 2000, while rates remain stable or decrease in high-income nations.[3-5] In South Asia, India exhibits the highest prevalence of hypertension, affecting 30% of its population.[6] Meanwhile, in Bangladesh, about 20% of adults and between 40-65% of older individuals are reported to have hypertension.[7] Factors such as metabolic syndrome, obesity, high salt intake, and sedentary lifestyles contribute significantly to the pathophysiology of hypertension.[8] This condition is a potent risk factor for cardiovascular, peripheral vascular, and renal diseases, with even prehypertension increasing the likelihood of developing hypertension and subsequent cardiovascular events.[9]

Despite the effectiveness of pharmacological therapy in lowering blood pressure (BP) and preventing CVD outcomes, awareness and treatment of hypertension remain inadequate. Fewer than half of individuals with hypertension are aware of their condition, and many are either untreated or inadequately treated, despite successful management significantly reducing the global burden of disease and mortality.[1] Various classes of antihypertensive medications are available, including diuretics, sympatholytic drugs, calcium channel blockers (CCBs), angiotensin-converting enzyme inhibitors (ACEIs), and angiotensin receptor blockers (ARBs). These drugs are used for the treatment of hypertension either alone or in combination. The choice of antihypertensive therapy depends on the severity of hypertension, efficacy, safety, and individual patient factors. Cilnidipine, a newer generation CCB, has dual L-type and N-type calcium channel-blocking properties, which may offer advantages over traditional CCBs like amlodipine, particularly concerning side effects such as peripheral edema. Understanding the comparative efficacy and safety of these two CCB agents is particularly relevant as it can inform clinical practice and improve hypertension management, especially in populations where hypertension prevalence is high.

While cilnidipine has shown promise in various studies, including its potential to reduce cardiovascular events and provide renal protection, there is a notable lack of research focusing on its comparative efficacy and safety against amlodipine, particularly in the context of the Bangladeshi population. The specific side effects associated with L-type and N-type CCBs, such as pedal edema, have not been thoroughly investigated, highlighting a critical gap in the literature. This study aims to bridge the gap by evaluating the efficacy and safety of cilnidipine compared to amlodipine in hypertensive individuals. By focusing on the unique properties of cilnidipine, including its dual mechanism of action[10] and potential benefits for patients with obesity and metabolic syndrome,[11] this research could provide valuable insights for clinicians. The findings may enhance the understanding of hypertension management and contribute to developing tailored treatment strategies that consider both efficacy and patient tolerability.

METHODS:

This non-randomized clinical trial was conducted in the private clinics of renowned cardiologists and internal medicine specialists in Chittagong Metropolitan City over a four-year period, from January 2020 to December 2023. A total of 496 hypertensive patients of both sexes were provisionally included in the study. Of these, 41 patients did not complete the required two follow-up visits and were subsequently excluded, leaving 455 patients for final analysis. Among the 455 participants, 246 were assigned to the amlodipine group and 209 to the cilnidipine group. The study included newly diagnosed hypertensive patients (blood pressure ≥ 140/90 mmHg) of either gender, aged 35 to 75 years, attending the private clinics of cardiologists and internal medicine specialists in Chittagong. Patients with preexisting edema, cor

pulmonale, nephrotic syndrome, hypoproteinemia, anemia, pregnancy, or those currently taking medications such as non-steroidal anti-inflammatory drugs and amantadine were excluded. After obtaining ethical clearance from the Ethical Review Committee (ERC) of the 250-bedded Chattogram General Hospital and securing informed verbal consent from the participating patients, data collection commenced.

Patients were evaluated by designated physicians, and blood pressure was measured in the right arm while seated, using the auscultatory method with a standard mercury sphygmomanometer. Two blood pressure recordings were taken at intervals of 15 to 20 minutes by the same physicians, and the average of these recordings was documented on the data sheet. The presence of pedal edema was noted if soft tissue over the medial malleolus of one or both legs demonstrated pitting upon pressure. Following the initial screening, demographic information, past medical history, family history, and clinical examination findings were recorded on the data sheet. The Amlodipine group (n=246) received tablets at a dosage of 5–10 mg/day, while the Cilnidipine group (n=209) received tablets at a dosage of 10–20 mg/day, as prescribed by their consulting physicians based on hypertension severity. Patient compliance was assessed using the pill count method at each visit. All patients were scheduled for follow-up visits with their respective physicians at 3- and 6-month intervals to evaluate blood pressure control and the incidence of pedal edema. Patients were also advised to consult their physicians immediately if any unusual side effects (including pedal edema) occurred prior to the scheduled follow-up. Any protocol violations were documented, and the data were analyzed based on an intent-to-treat principle.

Data were processed and analyzed using SPSS (Statistical Package for Social Sciences), version 17.0. The statistical methods applied included descriptive statistics, Chi-square (χ^2) or Fisher's Exact Probability Test, Unpaired t-Test, and Repeated Measures ANOVA. Categorical data were compared between groups using the Chi-square (χ^2) or Fisher's Exact Probability Test, while continuous data were assessed with the Unpaired t-Test. Changes in blood pressure from baseline to the study endpoint were analyzed using Repeated Measures ANOVA. A significance level of 0.05 was established, with a p-value of less than 0.05 considered statistically significant.

RESULTS:

The age distribution of the study participants revealed no significant differences between the groups regarding age, with patients over 50 years old predominating in both groups (p = 0.675). The mean ages of patients in the Amlodipine and Cilnidipine groups were 55.5 ± 10.5 years and 53.5 ± 10.7 years, respectively. While there was a slightly higher proportion of males in the Cilnidipine group, the male-to-female distribution was similar in the Amlodipine group (p = 0.603) (Table I).

A noteworthy difference was observed in body weight categories, with nearly half (49.4%) of the Amlodipine group classified as overweight or obese, compared to one-third (35.9%) of the Cilnidipine group (p=0.007). Additionally, there was a significantly higher prevalence of diabetes in the Amlodipine group compared to the Cilnidipine group (p=0.016). Conversely, a higher proportion of smokers was noted in the Cilnidipine group (p=0.015). Approximately one-quarter of patients in both groups reported a family history of coronary artery disease, with no significant difference between the groups (p = 0.812). The mean systolic and diastolic blood pressures were slightly lower in the Cilnidipine group compared to the Amlodipine group; however, these differences did not reach statistical significance (p = 0.206 for systolic blood pressure and p = 0.133 for diastolic blood pressure). There was no significant difference in mean pulse rate between the groups (p = 0.488). Baseline laboratory findings were compared between the study groups. Fasting blood glucose levels were comparable between groups (p = 0.203). Low serum HDL cholesterol was similarly prevalent in both groups (p = 0.031). However, the proportion of patients with elevated serum triglycerides was significantly lower in the Amlodipine group compared

to the Cilnidipine group (p < 0.001). Conversely, the Amlodipine group exhibited a significantly higher incidence of elevated serum creatinine levels (> 1 mg/dL) (p = 0.007). Furthermore, mean alanine aminotransferase (ALT) levels were significantly higher in the Cilnidipine group compared to the Amlodipine group (p = 0.026) (Table II).

At baseline, the mean systolic blood pressures (SBP) in the Amlodipine and Cilnidipine groups were 158.6 mmHg and 153.1 mmHg, respectively. After three months of treatment, SBP decreased to 135 mmHg in the Amlodipine group and 134 mmHg in the Cilnidipine group, and by six months, values further reduced to 126 mmHg and 128 mmHg, respectively. The percentage reduction in SBP from baseline to the study endpoint was significantly greater in the Amlodipine group compared to the Cilnidipine group (19.9% vs. 15.6%, p < 0.001) (Fig. 1, Table III). Both groups presented with mean diastolic blood pressures (DBP) exceeding 90 mmHg at baseline, which declined to below 80 mmHg after three months and stabilized around 76 mmHg by the end of the study. No significant difference was observed between groups regarding the percentage reduction in DBP from baseline to endpoint (14.9% vs. 15.5%, p=0.545) (Fig. 2, Table IV). There were no significant differences in pulse rates between the two groups at baseline, nor did either group experience significant changes in pulse rate from baseline to study endpoint. The reduction in heart rate was almost identical in both groups (4% in Amlodipine and 5% in Cilnidipine, p = 0.516) (Fig. 3, Table V).

A majority of patients in both the Amlodipine (87%) and Cilnidipine (88.5%) groups achieved satisfactory blood pressure control (defined as SBP < 140 mmHg and DBP < 90 mmHg), with no significant difference between the groups (p = 0.622) (Table VI). The incidence of pedal edema was significantly higher in the Amlodipine group (11%) compared to the Cilnidipine group (4.8%) (p = 0.016). However, the incidence of stroke did not differ significantly between the two groups (1.6% in Amlodipine vs. 2.9% in Cilnidipine, p = 0.280) (Table VII).

Table I. Comparison of demographic characteristics between groups

Demographic characteristics	Group		p-value
	Amlodipine (n = 246)	Cilnidipine (n = 209)	
Age (yrs)*			
>50	139(56.5)	114(54.5)	
≤ 50	107(43.5)	95(45.5)	0.675
Mean ± SD#	55.5 ± 10.5	53.5 ± 10.7	
Sex*			
Male	127(51.6)	113(54.1)	
Female	119(48.4)	96(45.9)	0.603

Figures in the parentheses indicate the corresponding %; ***Chi-squared (χ^2) Test** was done to analyze the data. #Data were analyzed using an **Unpaired t-Test** and were presented as **mean ± SD.**

Table II. Comparison of baseline characteristics between groups

Baseline characteristics	Group		p-value
	Amlodipine (n = 246)	Cilnidipine (n = 209)	
Presence of risk factors/co-morbidities			
Overweight & obese* (BMI ≥ 25 kg/m2)	119(48.4)	75(35.9)	0.007
Diabetes Mellitus	106(43.1)	67(32.1)	0.016
Smoking habit	54(22.0)	67(32.1)	0.015
Family history of CAD	60(24.4)	53(25.4)	0.812
Baseline haemodynamic variables#			
Systolic blood pressure (mmHg)	156.8 ± 15.5	155.3 ± 14.8	0.206
Diastolic blood pressure (mmHg)	92.4 ± 8.5	91.2 ± 8.7	0.133
Pulse (beats/min)	84 ± 16	83 ± 17	0.488
Laboratory findings at baseline			
Fasting blood sugar# (mmol/L)	7.3 ± 1.7	6.9 ± 1.7	0.203
Raised serum TC* (> 200 mg/dL)	28(11.4)	23(11.0)	0.899
Raised serum LDL* (> 130 mg/dL)	80(32.5)	76(36.4)	0.389
Low serum HDL* (≤ 40 mg/dL)	208(84.6)	160(76.6)	0.031
Elevated serum Tg* (> 150 mg/dL)	146(59.3)	170(81.3)	< 0.001
Raised Serum creatinine (> 1 mg/dL)	124(50.4)	79(37.8)	0.007
ALT# (U/L)	39.5 ± 12.8	42.1 ± 11.9	0.026

Figures in the parentheses indicate the corresponding %; ***Chi-squared (χ^2) Test** was done to analyze the data. #Data were analyzed using an **Unpaired t-Test** and were presented as **mean ± SD.**

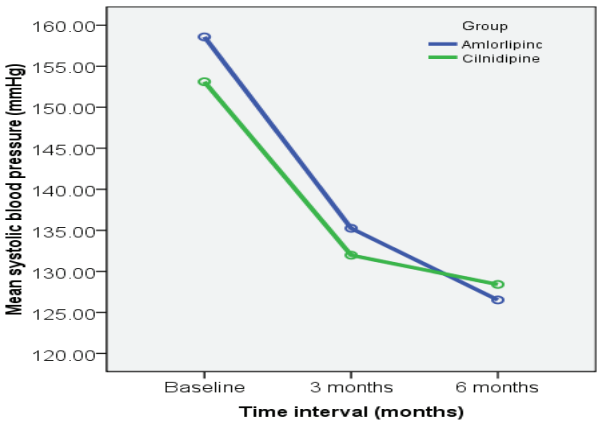

Fig 1. Comparison of changes in systolic blood pressure at different time intervals

Table III. Comparison of changes in systolic blood pressure between group

Systolic BP (mmHg)	Group		p-value
	Amlodipine (n = 246)	Cilnidipine (n = 209)	
Baseline	158.6 ± 13.1	153.1 ± 14.0	< 0.001#
Month 3	135.2 ± 13.5	131.9 ± 13.5	0.010#
Month 6	126.5 ± 15.6	128.4 ± 12.2	0.157#
Percentage of reduction in SBP	19.9 ± 10.5	15.6 ± 9.9	< 0.001*

#Data were analyzed using **Student's t-Test** and were presented as **mean ± SD**; the **p-value** indicates the significance of the difference between groups at different time intervals. *Data were analyzed using **Repeated Measure ANOVA**; the **p-value** indicates the difference in the percentage of reduction of SBP from baseline to the end-point of the study between groups.

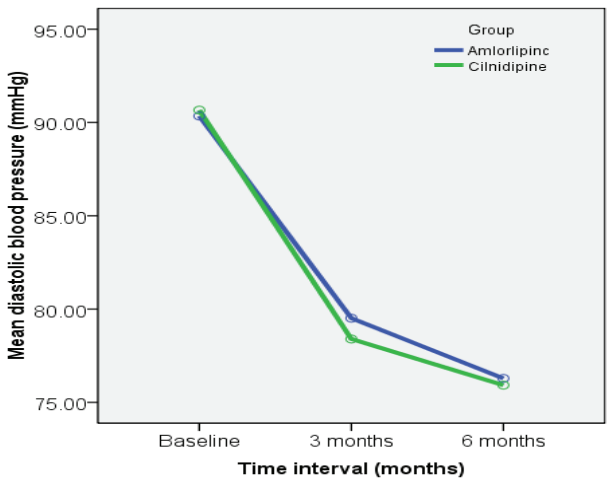

Fig 2. Comparison changes in diastolic blood pressure at different time intervals

Table IV. Comparison of changes in diastolic blood pressure between group

Diastolic BP (mmHg)	Group		p-value
	Amlodipine (n = 246)	Cilnidipine (n = 209)	
Baseline	90.3 ± 8.8	90.7 ± 8.3	0.698#
Month 3	79.5 ± 6.8	78.3 ± 7.6	0.100#
Month 6	76.3 ± 8.4	75.9 ± 7.5	0.632#
Percentage of reduction in DBP	14.9 ± 11.6	15.5 ± 11.3	0.545*

#Data were analyzed using **Student's t-Test** and were presented as **mean ± SD**; the **p-value** indicates the significance of the difference between groups at different time intervals. *Data were analyzed using **Repeated Measure ANOVA**; the **p-value** indicates the difference in the percentage of reduction of SBP from baseline to the end-point of the study between groups.

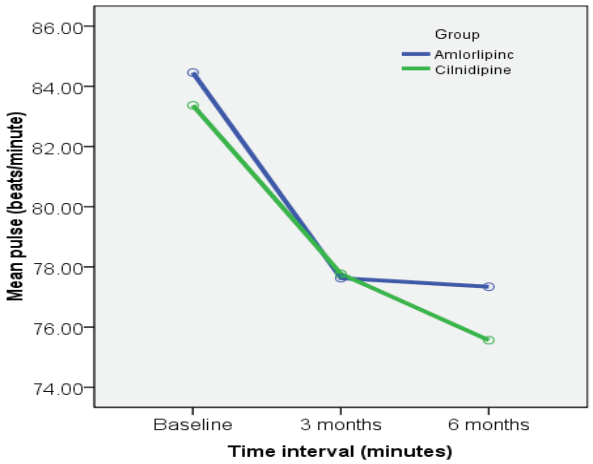

Fig 3. Comparison of changes in pulse rate at different time intervals

Table V. Comparison of changes in pulse between groups

Pulse (beats/minute)	Group		p-value
	Amlodipine (n = 246)	Cilnidipine (n = 209)	
Baseline	84 ± 16	83 ± 17	0.488#
Month 3	78 ± 9	78 ± 9	0.864#
Month 6	77 ± 13	76 ± 9	0.094#
Percentage of change	4 ± 2	5 ± 2	0.516*

#Data were analyzed using **Student's t-Test** and were presented as **mean ± SD**; the **p-value** indicates the significance of the difference between groups at different time intervals. *Data were analyzed using **Repeated Measure ANOVA**; the **p-value** indicates the difference in the percentage of reduction of SBP from baseline to the end-point of the study between groups.

Table VI. Comparison of efficacy of the drugs between groups

Blood pressure*	Group		p-value
	Amlodipine (n = 246)	Cilnidipine (n = 209)	
Controlled	214(87.0)	185(88.5)	0.622
Raised	32(13.0)	24(11.5)	

Figures in the parentheses indicate the corresponding %. ***Fisher's Exact Test** was done to analyze the data.

Table VII. Comparison of complications between groups

Complications*	Group		p-value
	Amlodipine (n = 246)	Cilnidipine (n = 209)	
Pedal oedema*	27(11.0)	10(4.8)	0.016
Jaundice#	0(0.0)	1(0.5)	0.459
Stroke#	4(1.6)	6(2.9)	0.280

*Data were analyzed using **Chi-squared (χ^2) Test**. #**Fisher's Exact Test** was done to analyze the data; figures in the parentheses indicate the corresponding %;

DISCUSSION

This study aimed to compare the efficacy and safety of cilnidipine and amlodipine in managing systemic hypertension. Given the rising global prevalence of hypertension and its associated cardiovascular morbidity, identifying optimal treatment strategies is crucial. The results indicate that while both medications effectively lower blood pressure, their profiles differ significantly in terms of side effects and risk factor management, which has important implications for clinical practice.

In the present study, both cilnidipine and amlodipine groups exhibited comparable biological characteristics in terms of age and sex distribution. However, notable differences were observed in the prevalence of certain comorbidities: obesity and diabetes were more common in the amlodipine group, while a higher proportion of smokers was found in the cilnidipine group. Family history of coronary artery disease (CAD) was similarly distributed between the groups. Additionally, although mean systolic and diastolic blood pressures were slightly lower in the cilnidipine group, these differences did not reach statistical significance. Fasting blood sugar levels were nearly identical across both groups, and dyslipidemia was prevalent in both, displaying characteristics typical of atherogenic dyslipidemia associated with Type 2 diabetes. This dyslipidemia is characterized by elevated plasma triglycerides (TG), reduced high-density lipoprotein cholesterol (HDL-C), and increased low-density lipoprotein cholesterol (LDL-C) concentrations,[12] contributing to a heightened risk of early atherosclerosis independent of other risk factors.[13]

Both treatment groups demonstrated significant reductions in systolic and diastolic blood pressures compared to baseline measurements. A substantial majority of patients achieved blood pressure control by the study's endpoint, with 87% in the amlodipine group and 88.5% in the cilnidipine group, indicating that both medications are effective in managing hypertension. Importantly, there was no significant difference in antihypertensive efficacy between the two groups, suggesting that cilnidipine and amlodipine are similarly effective in reducing blood pressure. However, the incidence of pedal edema was significantly lower in the cilnidipine group (4.8%) compared to the amlodipine group (11%), which supports the preference for cilnidipine as an antihypertensive agent.

Previous studies, such as that by Adake et al.[14] conducted at a tertiary care center in Karnataka, India, corroborate these findings, showing significant reductions in both systolic and diastolic blood pressures for both cilnidipine and amlodipine, without a significant difference in overall efficacy. Notably, Adake et al. reported a markedly lower incidence of pedal edema in the cilnidipine group (6.7%) compared to the amlodipine group (63.3%). The variability in peripheral edema incidence among different calcium channel blockers (CCBs) is well-documented and may be attributed to their dose-dependent effects & individual pharmacological profiles.[15-17] Some dihydropyridine (DHP) CCBs, such as nifedipine and amlodipine, are particularly associated with vasodilatory edema.[18] Amlodipine, while being one of the most widely prescribed CCBs in the United States and included in the World Health Organization's essential medicines list, is often limited by its propensity to cause pedal edema.[19,20]

The underlying mechanisms contributing to pedal edema involve disruptions in normal vasoconstrictor reflexes and complex pharmacological effects that are not yet fully understood.[16] In Dalal's study,[21] the onset of pedal edema was noted within the first three months of treatment for both groups, a finding that aligns with our observations of similar efficacy between the two medications. Although the incidence of pedal edema in the amlodipine group was lower than reported by Adake et al., it still underscores the need for careful monitoring of this side effect.

Several studies have suggested that combination therapy with angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) can effectively reduce the incidence of peripheral edema associated with CCBs, even at reduced doses, particularly in patients with mild

hypertension.[16,22,23] Given that pedal edema is more prevalent with CCB monotherapy, combining these agents with either an ACEI or ARB may not only mitigate edema but also enhance overall blood pressure control.[24,25]

Despite similar reductions in blood pressure, the frequency of pedal edema varies among different CCBs, suggesting that the occurrence cannot solely be attributed to differences in their effects on peripheral arteries.[16] For instance, drugs that selectively inhibit L-type calcium channels, such as nifedipine, primarily lower blood pressure by dilating resistance arterioles, potentially leading to increased capillary pressure & subsequent extravasation.[26] In contrast, CCBs like cilnidipine, which block both L-type & N-type calcium channels, may offer a more favorable profile regarding peripheral edema due to their effects on sympathetic nervous system regulation.[27,28] Cilnidipine's dual mechanism of action allows for effective blood pressure reduction through vascular smooth muscle relaxation & arterial dilation, while also suppressing catecholamine release from sympathetic nerves.[29-31] This unique pharmacological profile may explain cilnidipine's lower incidence of adverse effects, including pedal edema.

While cilnidipine has demonstrated a favorable safety profile, it is important to acknowledge that individual patient responses can vary significantly. The medication is associated with minor adverse effects such as headache, dizziness, cough, and gastrointestinal symptoms, which were not reported in our study. Previous literature has indicated that cilnidipine is generally well-tolerated by hypertensive patients, suggesting that it may be particularly beneficial for those who experience intolerable side effects or inadequate blood pressure control with traditional therapies.[32]

LIMITATIONS:

Despite contributing valuable insights into the comparative safety and efficacy of cilnidipine and amlodipine, this study has several limitations that warrant consideration:

1. Short-term Follow-Up: The study was conducted with a relatively short-term follow-up period, limiting the ability to assess long-term outcomes and the sustained efficacy and safety of both medications in hypertensive patients.

2. Intent-to-Treat Analysis: The analysis was performed on an intent-to-treat basis, which, while appropriate for maintaining randomization benefits, cannot inform treatment outcomes about non-compliant or dropout patients affecting the study groups.

3. Strict Randomization Challenges: As the majority of data were collected from private practice settings, achieving strict randomization was not feasible, potentially introducing biases that could affect the generalizability of the results.

CONCLUSION:

In conclusion, this study underscores the effective use of both cilnidipine and amlodipine in managing systemic hypertension, while also highlighting significant differences in their safety profiles. Cilnidipine's lower incidence of adverse effects, particularly pedal edema, along with comparable efficacy in blood pressure control, suggests it may serve as a preferred treatment option for specific patient populations. Further research is warranted to explore the long-term outcomes associated with these treatments and their impact on quality of life in hypertensive patients.

REFERENCES

1. Oparil S, Acelajado MC, Bakris GL, Berlowitz DR, Cífková R, Dominiczak AF, et al. Hypertension. *Nat Rev Dis Primers*, 2018;4:18014. doi: 10.1038/nrdp.2018.14 PMCID: PMC6477925

2. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL, Jr, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: The JNC 7 report. *JAMA*, 2003;289:2560–72.

3. Danaei G, Finucane MM, Lin JK, Singh GM, Paciorek CJ, Cowan MJ et al. On behalf of the Global Burden of Metabolic Risk Factors of Chronic Diseases Collaborating Group (Blood Pressure) National, regional, and global trends in systolic blood pressure since 1980: systematic analysis of health examination surveys and epidemiological studies with 786 country-years and 5.4 million participants. *Lancet*, 2011:377:568–77.

4. Devi P, Rao M, Sigamani A, Faruqui A, Jose M, Gupta R et al. Prevalence, risk factors and awareness of hypertension in India: a systematic review. *J Hum Hypertens*, 2013;27:281–87.

5. Egan BM, Zhao Y, Axon RN. US trends in prevalence, awareness, treatment, and control of hypertension, 1988-2008. *JAMA*, 2010;303:2043–50.

6. Anchala R, Kannuri NK, Pant H, Khan H, Franco OH, Di Angelantonio E, et al. Hypertension in India: A systematic review and meta-analysis of prevalence, awareness, and control of hypertension. *J Hypertens*, 2014;32:1170–7.

7. Islam AKMM, Majumder AAS. Hypertension in Bangladesh: A review. *Indian Heart J*, 2012;6403: 319-23.

8. World Health Organization 2010. Non-Communicable Disease Risk Factor Survey Bangladesh (cited 2013 July 3). Available from: http://www.ban.searo.who.int/Link Files_NCD_Risk_Factor_Report

9. Vasan RS, Larson MG, Leip EP, Kannel WB, Levy D. Assessment of frequency of progression to hypertension in non-hypertensive participants in the Framingham Heart Study: A cohort study. *Lancet*, 2001;358:1682–6.

10. Fujii S, Kameyama K, Hosono M, Hayashi Y, Kitamura K. Effect of cilnidipine, a novel dihydropyridine Ca++channel antagonist, on N-type Ca++ channel in rat dorsal root ganglion neurons. *Journal of Pharmacology and Experimental Therapeutics*,1997; 280(3):1184-1191.

11. Watanabe M, Tamaoka A, Morishita Y, Noguchi M. Cilnidipine Lowers Plasma Leptin of Patients with Obese Hypertension Associated with Cerebrovascular Disorder. 2012;1:529. doi:10.4172/scientificreports.529

12. Wu L, Parhofer KG. Diabetic dyslipidemia. *Metabolism*, 2014;63:1469-1479.

13. Yanai H, Hirowatari Y, Yoshida H. Diabetic dyslipidemia: evaluation and mechanism. *Glob Health Med*, 2019; 1(1):30–35. doi: 10.35772/ghm.2019.01007

14. Adake, P, Somashekar, HS, Mohammed, Rafeeq, PK, Umar, D, Basheer, B, Baroudi, K. 2015. Comparison of amlodipine with cilnidipine on antihypertensive efficacy and incidence of pedal edema in mild to moderate hypertensive individuals: A prospective study. *J Adv Pharm Technol Res*, 6, pp. 81-5.

15. Messerli FH, Feng Z, Michalewicz L. Vasodilatory edema: synergistic effect of high-dose calcium antagonist/ACE inhibitor combination therapy. *Am J Hypertens*, 1999; 12:121A. doi:10.1016/S0895-7061(99)80424-5.

16. Pedrinelli R, Dell'Omo G, Melillo E, Mariani M. Amlodipine, enalapril, and dependent leg edema in essential hypertension. *Hypertension*, 2000;35:621-625.doi:10.1161/01. HYP.35.2.621

17. Messerli FH. Vasodilatory edema: a common side effect of antihypertensive therapy. *Curr Cardiol Rep*, 2002; 4:479-482. doi:10.1007/s11886-002-0110-9.

18. Cho S, Atwood JE. Peripheral edema. *Am J Med*., 2002;113:580-586. doi:10.1016/S0002-18. 9343(02) 01322-0

19. Elliott WJ, Bistrika EA. Perindopril arginine and amlodipine besylate for hypertension: a safety evaluation. *Expert Opin Drug Saf*, 2018;17:207-216. doi:10.1080/14740338.2018.139 7129

20. Shetty K, Shetty R, Rao P, et al. Comparison of plasma levels of renin, vasopressin and atrial natriuretic peptide in hypertensive amlodipine induced pedal oedema, non-oedema and cilnidipine treated patients. *J Clin Diagn Res*, 2017;11:FC05- FC08. doi:10.7860/ JCDR/2017/25097.9958

21. Dalal J, Sawhney JP, Jayagopal PB, Hazra PK, Khan MY, Gaurav K et al. A Retrospective, Observational, EMR-Based Real-World Evidence Study to Assess the Incidence of Pedal Edema in Essential Hypertensive Patients on Amlodipine or Cilnidipine. Hindawi International *Journal of Hypertension* 2022:2022, Article ID 6868143:9 https://doi.org/10.1155/2022/ 6868143

22. Sangam K, Devireddy P, Konuru V. Calcium channel blockers induced peripheral edema. *Int J Pharm Sci Res*, 2016;7:290- 293.

23. Fogari R, Zoppi A, Derosa G, Mugellini A, Lazzari P, Rinaldi A, et al. Effect of valsartan addition to amlodipine on ankle oedema and subcutaneous tis-sue pressure in hypertensive patients. *J Hum Hypertens*, 2007;21:220-224. doi:10.1038/sj.jhh.1002140

24. Malacco E, Vari N, Capuano V, Spagnuolo V, Borgnino C, Palatini P, Val-Syst study. A randomized, double-blind, active-controlled, parallel-group comparison of valsartan and amlodipine in the treatment of isolated systolic hypertension in elderly patients: the Val-Syst study. *Clin Ther*, 2003;25:2765-2780.doi:10.1016/S0149-29 18(03)80332-6.

25. de la Sierra A. Mitigation of calcium channel blocker-related oedema in hypertension by antagonists of the renin-angiotensin system. *J Hum Hypertens*, 2009;23: 503-511. doi:10.1038/ jhh.2008.157 20.

26. Messing M, Van Essen H, Smith TL, Smits JF, Struyker Boudier HA. Microvascular actions of calcium channel antagonists. *Eur J Pharmacol*, 1991;198:189 95.

27. Mori Y, Nishida M, Shimizu S, Ishii M, Yoshinaga,T, Ino M, et al. Ca (2+) channel alpha (1B) subunit (Ca (V) 2.2) knockout mouse reveals a predominant role of N type channels in the sympathetic regulation of the circulatory system. *Trends Cardiovasc Med*, 2002;12: 270 5.

28. Smyth L, Bobalova J, Ward SM, Keef KD, Mutafova Yambolieva VN. Cotransmission from sympathetic vasoconstrictor neurons: Differences in guinea pig mesenteric artery and vein. *Auton Neurosci*, 2000; 86:18 29.

29. Uneyama H, Uchida H, Konda T, Yoshimoto R. Cilnidipine: Preclinical profile and clinical evaluation. *Cadiovasc Drug Rev*, 1999;17:341 57.

30. Uchida R, Yamazaki J, Kitamura K. Characterization of Ca2+ current inhibition by cilnidipine using a beta subunit antisense oligonucleotide. *Eur J Pharmacol*, 2003;466:53 62.

31. Takahara A. Cilnidipine: A New Generation Ca2+ Channel Blocker with Inhibitory Action on Sympathetic Neurotransmitter Release. *Cardiovasc Ther*, 2009;27: 124–39.

32. Xu GL, Hui X, Wu HD, Ling Q. A meta analysis of the efficacy and safety of cilnidipine in Chinese patients with mild to moderate essential hypertension. *Afr J Pharm Pharmacol*, 2012;6:2393 9.