

# An Open Label Prospective Study on Evaluation of Safety and Efficacy of Cilnidipine Over Amlodipine in Stage 1 Hypertensive Patients

Harlalka S, Roy UK, Majumdar G, Das K, Mandal P

Department of Pharmacology  
Burdwan Medical College and Hospital,  
India.

## Corresponding Author

Uttam Kumar Roy  
Department of Pharmacology  
Burdwan Medical College and Hospital,  
India.  
E-mail: uroy951@gmail.com

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## ABSTRACT

### Background

Calcium channel blockers are considered the first line drug over renin-angiotensin-aldosterone system inhibitor in black population and with renin-angiotensin-aldosterone system inhibitor in non-black population with Hypertension. Amlodipine has longer biological half life and lower potential to stimulate SNS. But, is associated with reflex tachycardia and pedal oedema. Cilnidipine has potent inhibitory both on voltage gated L-type and N-type calcium channels with better anti-proteinuric effect and good tolerability. Hence, our study compared the efficacy, safety and compliance of cilnidipine over amlodipine in Stage 1 hypertensive subjects.

### Objective

To find out antihypertensive and renoprotective effect of cilnidipine.

### Method

The study was open-label, single centre, prospective, parallel design, randomized controlled was done in Outdoor Patient Department (OPD) of Medicine and Department of Pharmacology in Burdwan Medical College and Hospital (BMCH). Patients with stage 1 HTN received cilnidipine while the other group received amlodipine. There were 4 follow-up visits for each participant consisting of baseline, 1 week, 6 weeks and after 12 weeks. Clinical parameters including pulse rate, blood pressure and ankle oedema noted also laboratory investigations were done. Safety parameters with adverse events and compliance by traditional pill count method.

### Result

Blood pressure was effectively decreased by both amlodipine and cilnidipine. Cilnidipine significantly decreased Pulse Rate while amlodipine increased it and the difference in Pulse Rate comparing both the groups was statistically significant. None of the ADRs were statistically significant except pedal oedema. Pedal oedema was noted only in amlodipine arm and was statistically significant. Compliance to both the drugs was excellent. Total cost of therapy was higher with cilnidipine.

### Conclusion

Though amlodipine is preferred drug, cilnidipine should be a better alternative when we consider subjects with sympathetic over activity, proteinuria or pedal oedema.

## KEY WORDS

*Amlodipine, Cilnidipine, Efficacy, Hypertension*

## INTRODUCTION

Hypertension remains one of the most important preventable contributors to disease and death.<sup>1</sup> It doubles the risk of cardiovascular diseases and is reported to be the fourth contributor to premature death in developed countries and the seventh in developing countries.

The renin-angiotensin-aldosterone system contributes to the regulation of arterial pressure primarily via the vasoconstrictor properties of angiotensin II and the sodium-retaining properties of aldosterone. However, there is increasing evidence to suggest that sympathetic nervous activity in both central and peripheral nervous systems may play a major role in the regulation of blood pressure. Cilnidipine is a novel fourth generation dihydropyridine calcium antagonist with potent inhibitory action not only on voltage gated L-type calcium channels but also on N-type calcium channels. By blocking N-type calcium channels, it reduces sympathetic over activity, which account not only for its antihypertensive efficacy but also for its absence of reflex tachycardia. In addition, it has been shown to possess better anti-proteinuric effect and good tolerability than any other calcium channel blockers. However, the drug has been backed by few studies, mostly based on pre-clinical trials.<sup>3</sup>

Hence, this study was planned to compare the efficacy, safety and compliance of cilnidipine over a time tested calcium channel blocker amlodipine in Stage 1 hypertensive subjects.

## METHODS

It was an open-label, single centre, prospective, parallel design, randomized controlled study carried out in the Medicine OPD and Department of Pharmacology of Burdwan Medical College and Hospital from November 2012 to October 2014. A sample size of 52 was calculated to detect a difference of 10 mm of Hg of systolic blood pressure (SBP) between two groups. (80% power and 5% probability of Type 1 error assuming a standard deviation of 14 and considering analysis of covariance (ANCOVA) as a statistical test to detect the difference) It was decided to include 30 participants in each group (sample size of 60). Assuming 30% drop-out rate, it came out to be sample size of 78 participants. After getting approval from Institutional Ethics Committee and taking written informed consent from each of the participants, stage 1 hypertensive subjects of either sex aged  $\geq 18$  years were screened. Exclusion criteria were patients having uncontrolled diabetes mellitus, hepatic (Bilirubin  $> 3$  mg%) or renal impairment (Creatinine  $> 1.5$  mg%), ischaemic heart disease or congestive heart failure, pregnant or lactating mother and those having hypersensitivity to dihydropyridine calcium channel blockers. Eligible participants were randomized to one of the two study arms using a computer generated random

number table. One group received cilnidipine 10 mg/day maximum up titrated to 20 mg/day while the other group received amlodipine 5 mg/day maximum up titrated to 10 mg/day. There were 4 follow-up visits for each participant consisting of baseline visit when the study medication was started, 1<sup>st</sup> follow up visit after 1 week of baseline visit, 2<sup>nd</sup> follow up visit after 6 weeks of baseline visit and end follow-up visit after 12 weeks of baseline visit when the study medication was stopped. Clinical parameters including pulse rate, blood pressure and ankle oedema were noted in each of the visit. Laboratory investigations were done before the baseline visit and at the end follow up visit.

The efficacy parameters considered were systolic blood pressure (SBP), diastolic blood pressure (DBP), mean blood pressure (MBP), pulse pressure (PP) and urinary albumin-creatinine ratio (UACR). Safety parameters considered were adverse events those spontaneously reported by the participant himself, those elicited as clinical signs by the investigators during the scheduled visits and adverse laboratory test results. Causality analysis of adverse events was done using World Health Organization-Uppsala Monitoring Centre (WHO-UMC) standardized case causality assessment criteria. Investigation done included blood for haemoglobin, total count, fasting blood sugar, urea, creatinine, total bilirubin, total cholesterol and triglycerides; electrocardiogram to look for QTc interval was also considered. Compliance was assessed by the traditional pill count method. It was deemed to be excellent if not more than 10% of schedule doses were missed, good if not more than 20% were missed, fair if not more than 30% were missed, and poor for any situation worse than fair. Data were entered in Microsoft Excel 2007 and analysis was done with the help of SPSS version 17. P value  $< 0.05$  was considered to be significant. Appropriate statistical analysis was done to compare different variables between the two study arms.

## RESULTS

A total of 110 stage 1 hypertensive subjects were screened. Among them 78 participants were recruited- 39 in each group. Final analysis was done only for 63 participants- 32 in cilnidipine arm and 31 in amlodipine arm. Figure 1 show the participant flow.

As seen from table 1, study subjects were comparable at baseline with respect to their age, sex, religion, residence and occupation. Table 2 summarizes the medical history of study subjects, i.e., history of diabetes mellitus, proteinuria, dyslipidaemia and smoking. It shows that the study subjects were comparable at these parameters also.

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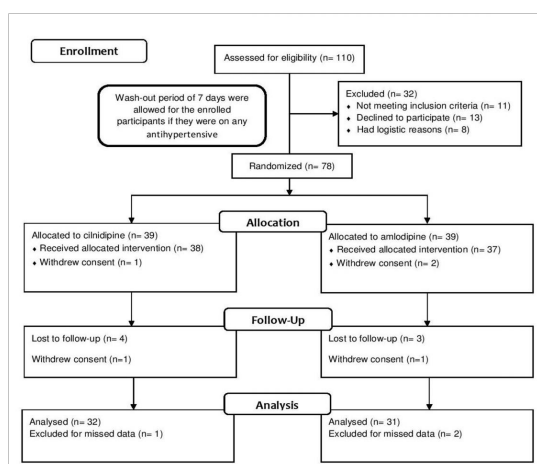


Figure 1. Figure denoting participant flow

Table 1. Demographic profile of study population

Categories		Cilnidipine group (n=32)	Amlodipine group (n=31)	p-value (between groups)
Age (years)	Range	28 - 64	26 - 65	0.488
	Mean ± SD	42.22 ± 10.4	44.16 ± 11.68	
Sex	Male	14	11	0.503
	Female	18	20	
Residence	Rural	17	20	0.359
	Urban	15	11	

Table 2. Medical history of the study subjects

Categories		Cilnidipine group (n=32)	Amlodipine group (n=31)	p-value (between groups)
H/O diabetes mellitus		14	12	0.685
H/O proteinuria		11	10	0.859
H/O dyslipidaemia		15	14	0.891
H/O smoking		9	7	0.613

p-value is calculated by chi-squared test of association in all the categories

The changes in SBP and DBP over the 12 weeks treatment period are depicted in table 3 and table 4 respectively. It is evident that both SBP and DBP decreased in both the treatment arms over the period specified and was statistically significant ( $p < 0.001$ ). Pairwise comparison with bonferroni correction revealed that there was significant reduction in SBP and DBP between any two visits of each of the two treatment arms. However, between groups comparisons did not show any significant difference in reduction of SBP and DBP in both the treatment arms.

P value within groups are calculated by repeated measures ANOVA with greenhouse-geissure correction in cilnidipine arm and by repeated measures ANOVA with sphericity assumed in amlodipine arm. p-value between groups are calculated by analysis of co-variance (ANCOVA) considering baseline visit and end follow-up. Effect size calculated here is partial eta squared.

Table 3. Changes in SBP over 12 weeks treatment period

SBP (mm Hg)	Cilnidipine group (n = 32)	Amlodipine group (n = 31)	p-value (between groups)
Baseline Mean ± SD	142.75 ± 9.17	144.71 ± 10.89	
1 <sup>st</sup> follow-up Mean ± SD	139.13 ± 8.54	140.90 ± 10.1	
2 <sup>nd</sup> follow-up Mean ± SD	132.31 ± 7.81	133.16 ± 9.41	F(1,60) = 3.686
End follow-up Mean ± SD	131.5 ± 7.92	132.39 ± 8.88	p = 0.06
p-value (within groups)	F(1.986, 61.581) = 585.47, p < 0.001, effect size = 0.950	F(1.606, 48.187) = 510.76, p < 0.001, effect size = 0.945	effect size = 0.058

Table 4. Changes in DBP over 12 weeks treatment period

DBP (mm Hg)	Cilnidipine group (n = 32)	Amlodipine group (n = 31)	p-value (between groups)
Baseline Mean ± SD	87.88 ± 8.97	88.13 ± 8.25	
1 <sup>st</sup> follow-up Mean ± SD	86 ± 8.45	86.65 ± 7.7	
2 <sup>nd</sup> follow-up Mean ± SD	81.06 ± 7.75	80.39 ± 7.58	F(1,60) = 3.686
End follow-up Mean ± SD	79.63 ± 7.33	79.23 ± 7.44	p = 0.06
p-value (within groups)	F(2.131,66.052) = 336.483, p < 0.001, effect size = 0.916	F(3,90) = 498.52, p < 0.001, effect size = 0.943	effect size = 0.058

The changes in MBP over the 12 weeks treatment period are depicted in Table 5. It is evident that MBP decreased in both the treatment arms over the period specified and was statistically significant ( $p < 0.001$ ). Pairwise comparison with bonferroni correction revealed that there was significant reduction in MBP between any two visits of each of the two treatment arms. Between groups comparisons showed that the decline of MBP was more with amlodipine than cilnidipine.

The changes in PP over the 12 weeks treatment period are depicted in Table 6. Within group comparison showed that PP decreased in both the treatment arms over the period specified and was statistically significant ( $p < 0.001$ ). Pairwise comparison with bonferroni correction revealed that PP significantly decreased from baseline visit to 1<sup>st</sup> follow-up, from baseline visit to 2<sup>nd</sup> follow-up and from baseline visit to end follow-up in each of the arm. PP did not change significantly from 1<sup>st</sup> follow-up to 2<sup>nd</sup> follow-up, from 1<sup>st</sup> follow-up to end follow-up and from 2<sup>nd</sup> follow-up to end follow-up in amlodipine group. But, in cilnidipine group, PP significantly decreased from 1<sup>st</sup> follow-up to 2<sup>nd</sup> follow-up while there was no significant change between

**Table 5. Changes in MBP over 12 weeks treatment period**

MBP (mm Hg)	Cilnidipine group (n = 32)	Amlodipine group (n = 31)	p-value (between groups)
Baseline Mean ± SD	106.16 ± 3.89	106.99 ± 3.77	
1 <sup>st</sup> follow-up Mean ± SD	103.71 ± 3.56	104.73 ± 3.41	
2 <sup>nd</sup> follow-up Mean ± SD	98.15 ± 3.43	98.06 ± 3.55	F(1,60) = 3.081
End follow-up Mean ± SD	96.92 ± 3.32	96.95 ± 3.62	<b>p = 0.084</b>
p-value (within groups)	F(3,93) = 1133.843, <b>p &lt; 0.001</b> , effect size = 0.973	F(3,90) = 1024.654, <b>p &lt; 0.001</b> , effect size = 0.972	effect size = 0.049

SD = Standard Deviation

**Table 6. Changes in PP over 12 weeks treatment period**

PP (mm Hg)	Cilnidipine group (n = 32)	Amlodipine group (n = 31)	p-value (between groups)
Baseline Mean ± SD	54.88 ± 17.31	56.58 ± 17.83	
1 <sup>st</sup> follow-up Mean ± SD	53.13 ± 16.33	54.26 ± 16.69	
2 <sup>nd</sup> follow-up Mean ± SD	51.25 ± 14.79	53.03 ± 15.84	F(1,60) = 0.065
End follow-up Mean ± SD	51.88 ± 14.35	53.16 ± 15.01	<b>p = 0.799</b>
p-value (within groups)	F(1.819,56.384) = 17.914, <b>p &lt; 0.001</b> , effect size = 0.366	F(1.935,58.039) = 21.467, <b>p &lt; 0.001</b> , effect size = 0.417	effect size = 0.001

1<sup>st</sup> follow-up to end follow-up and from 2<sup>nd</sup> follow-up to end follow-up. Between groups comparisons showed that the decrease of PP in both the group was similar and not statistically significant.

The changes in UACR(Urinary Albumine to Creatinine Ratio) in participants having microalbuminuria have been shown in table 7. Within group comparison showed that there was significant decrease in UACR in cilnidipine arm but not in that of amlodipine arm. Between group comparison points out that there was no difference in UACR in both the treatment arms in baseline visit, but there was a significant difference in UACR in both groups in end follow-up visit.

**Table 7. Changes in UACR over 12 weeks treatment period**

UACR	Cilnidipine group (n = 32)	Amlodipine group (n = 31)	p-value (between groups)
Baseline Mean ± SD	152.82 ± 82.39	149.2 ± 75.69	t(19) = 0.104, p = 0.918
End follow-up Mean ± SD	39.55 ± 17.28	138.1 ± 64.84	t(10.161) = -4.659, <b>p = 0.001</b>
p-value (within groups)	t(10) = 5.731, <b>p &lt; 0.001</b>	t(9) = 2.094, p = 0.066	

The changes in pulse rate in the two treatment arms have been shown in Table 8. Within group comparison show a significant decrease in pulse rate in cilnidipine group while a significant rise in heart rate in amlodipine group. Between groups comparison do not show any significant difference in pulse rate of two arms during baseline visit. But it shows a significant difference in pulse rate in two groups during end follow-up.

**Table 8. Changes in pulse rate over 12 weeks treatment period**

Pulse rate	Cilnidipine group (n = 32)	Amlodipine group (n = 31)	p-value (between groups)
Baseline Mean ± SD	72.94 ± 9.87	75.8 ± 10.85	t(61) = -1.098, p = 0.276
End follow-up Mean ± SD	71.31 ± 9.4	77 ± 9.68	t(61) = -2.365, <b>p = 0.021</b>
p-value (within groups)	t(31) = 9.119, <b>p &lt; 0.001</b>	t(30) = -4.325, <b>p &lt; 0.001</b>	

P-value within groups are calculated by paired t-test, p-value between groups are calculated by independent samples t-test with equal variances assumed.

There was statistically no significant difference in laboratory parameters (Haemoglobin, TLC, Urea, Creatinine, Sodium, Potassium, Total bilirubin, QTc interval, Fasting blood sugar, Total cholesterol, Triglycerides.) when within group and between group comparisons was made.

**Table 9. Adverse drug reactions in the two treatment arms**

ADRs	Cilnidipine group (n=38)	Amlodipine group (n=37)	p-value (between group)
Nausea / Vomiting	3	2	0.513
Heart burn	1	1	0.747
Decreased appetite	1	1	0.747
Abdominal pain	0	1	0.493
Constipation	1	3	0.297
Headache	1	2	0.490
Insomnia	1	1	0.747
Postural hypotension	1	3	0.297
Pedal oedema	0	6	0.012
Palpitation	1	2	0.490
Raised triglycerides	3	3	0.650

The numbers represent count in individual groups p-value is calculated from Fischer's exact test

All the patients who received at least one dose of the treatment medication were analyzed. This included 38 participants in cilnidipine arm and 37 participants in amlodipine arm. During the 12 weeks study period, 46 subjects suffered from adverse events out of 75 participants. No serious adverse event was encountered during the study period. There was no withdrawal on account of adverse

events and the preparations were well accepted by the study subjects. Differences in the distribution of ADRs in the two treatment groups were not statistically significant except in case of pedal oedema as shown in table 9. Pedal oedema was noticed only in the amlodipine arm and was statistically significant.

Compliance assessment covered only those subjects who completed the study as per protocol. Compliance assessment is depicted in table 10. The end-of-study compliance assessment indicates adherence to treatment was excellent for all patients in both treatment groups.

**Table 10. Overall compliance of the patients towards study medication**

Grade of compliance	Cilnidipine group (n = 32)	Amlodipine group (n = 31)	p-value (between groups)
Excellent ≤ 10% missed doses	30	28	0.803
Good > 10-20% missed doses	2	2	
Fair > 20-30% missed doses	0	1	
Poor > 30% missed doses	0	0	

The numbers represent count in individual groups  
p-value is calculated from Fisher-Freeman-Halton Exact test

The price of 10 tablets each of amlodipine 5 mg and cilnidipine 10 mg of all the brands available in India, as seen from <http://www.mims.com/india> on 24<sup>th</sup> August 2014, were compared. The cost of therapy was found to be higher in cilnidipine group than in amlodipine group as seen in table 11.

**Table 11. Comparing cost of therapy in two treatment arms**

Price of 10 tablets of cilnidipine 10 mg (Rs.)	Price of 10 tablets of amlodipine 5 mg (Rs.)	p-value (between groups)
59 (14)	20.49 (13)	< 0.001

Value is expressed as Median (Interquartile range)  
p-value is calculated by Mann-Whitney U test.

## DISCUSSION

Our study was designed as open label, parallel design randomized controlled study comparing amlodipine and cilnidipine in stage 1 hypertensive subjects. The study population in both the groups were comparable in their baseline characteristics including age, sex, religion, residence, literacy and occupation. Most of the study subjects were in their forties and females outnumbered males. Study subjects were more from the rural area than from urban settings. Both worldwide and national data, however, show that prevalence of HTN increases with age and is greater in age > 75 years.<sup>4-7</sup> World statistics suggest that prevalence of HTN were more in male gender compared to females, although controlled HTN were noted more in females.<sup>4-6</sup>

National statistics, however, show that HTN prevalence is more among female population.<sup>7</sup>

Urban population had higher HTN prevalence as per national statistics, although there was a rising trend more in the rural settings.<sup>7</sup>

Our study subjects were also comparable in accordance to their medical history, which included history of diabetes mellitus, proteinuria, dyslipidaemia and smoking. Previous study shows the prevalence of diabetes mellitus in hypertensive subjects to be around 37.5% which is comparable to our study.<sup>8</sup> Another study done in china shows the prevalence to be around 24.3% which was lower compared to our study.<sup>9</sup> Prevalence of dyslipidaemia in hypertensive subjects was 49% in SAKURA trial which was similar to what we obtained in our study.<sup>9</sup> Prevalence of proteinuria among hypertensive subjects was a bit higher in our study compared to that obtained in a previous study.<sup>8</sup>

Efficacy variables in our study were SBP, DBP, MBP, PP and UACR. Most of the studies have incorporated SBP and DBP as efficacy parameter, but possibly none have considered MBP and PP. But, MBP and PP are considered as independent predictor of cardiovascular mortality.<sup>11,12</sup>

In fact, PP is a better predictor of survival compared to other BP parameters.<sup>13</sup> Cilnidipine have clearly shown to decrease proteinuria in both preclinical and clinical studies.<sup>14,15</sup> Hence, it was also included as efficacy variable.

SBP, DBP and MBP were effectively decreased by each of both amlodipine and cilnidipine over a 12 week period. Decline in both SBP and DBP were similar in both the arm. Decline in MBP was more in amlodipine group. PP declined in both the arm initially over 6 week period and then stabilised. Decline was, however, significant over first 1 week period only in amlodipine arm. There was no difference obtained in the decline of PP in both the arm over 12 week period.

Studies of the past have clearly shown that both the drug effectively decreases SBP and DBP and is not statistically significant when compared among them.<sup>8,10</sup> Greater decline of MBP suggest amlodipine may possess greater cardiovascular safety. Initial decline of PP by both of them suggest decreased cardiovascular mortality. Later, stabilisation is also probably beneficial as it show that the body has quickly adapted to the decreased PP. This may point to the better cardiovascular safety profile of both the drug. Previous studies have shown PP to be a better predictor of survival than SBP, DBP and MBP.<sup>13</sup> As we did not obtain any significant difference in decline of PP between the two drugs, both drug must possess similar cardiovascular safety profile. Between and within group comparison suggest that UACR significantly decline in cilnidipine group over 12 week period but not in the amlodipine group. Over a 12 week period, cilnidipine reduced the mean UACR from 152.82 to 39.55 mg/g. This shows renoprotective effect of cilnidipine. The result is in accordance with the previous preclinical



and clinical studies on cilnidipine.<sup>14-16</sup> Konoshita et al. have shown in a cross-over study that anti-albuminuric effect of cilnidipine was greater than that of amlodipine in a relatively large number of hypertensive subjects (n = 110).<sup>17</sup> Similarly, Kyoto cilnidipine study have shown the renoprotective effect of cilnidipine.<sup>15</sup>

The anti-albuminuric and renoprotective effect of cilnidipine can be at least partially explained by the amelioration of the glomerular HTN through efferent arteriolar vasodilatation, which the drug achieves by its sympatholytic action.<sup>10</sup> Cilnidipine significantly decreased PRT in our study while amlodipine increased it and the difference in PRT comparing both the groups was statistically significant. ACHIEVE-ONE trial support that cilnidipine produces bradycardia. It has also been supported by other trials too.<sup>18-20</sup> Again, SAKURA trial does not support this where PRT was unaffected by both amlodipine and cilnidipine.<sup>9</sup> Bradycardia due to cilnidipine can be attributed to sympatholytic action. Elevated PRT is a risk factor for cardiovascular events.<sup>21,22</sup> Hence, the drug may be a more useful addition to our antihypertensive armoury, more in hypertensive subjects with tachycardia.

Laboratory parameters were unaffected by either of the drugs. Change in QTc interval by both the drugs was also insignificant statistically. Gastrointestinal side effects, which included, nausea/vomiting, heart burn, decreased appetite, abdominal pain and constipation were the common side effects in both the arm. None of the ADRs were statistically significant except pedal oedema.

Pedal oedema was noted only in amlodipine arm but not in the cilnidipine arm and was statistically significant. In fact, cilnidipine have been claimed to reduce pedal oedema in amlodipine treated subjects.<sup>20</sup> Cilnidipine, hence, may be considered as an alternative agent to amlodipine or other L-type calcium channel blockers in hypertensive subjects with pedal oedema. However, there are rare reports of cilnidipine induced pedal oedema.<sup>23,24</sup>

Compliance to both the drugs was excellent in > 90% of the cases. However, the total cost of therapy was higher in the

cilnidipine arm than that in amlodipine arm. This is quite obvious as cilnidipine is relatively a newer drug.

Overall, amlodipine being a time tested cost effective drug, it should be definitely preferred over cilnidipine to treat hypertensive subjects requiring calcium channel blockers. Systolic, diastolic and pulse pressure were equally reduced by both the drugs and amlodipine had an upper hand when mean blood pressure was considered. But, cilnidipine should be a better alternative to other calcium channel blockers when we consider hypertensive subjects with sympathetic over activity or proteinuria or pedal oedema.

Our study was conducted with an aim to substantiate the clinical data available on cilnidipine. But, the study was not devoid of any limitation. It was an open label study recruiting only limited number of subjects. Each patient was followed-up for duration of 12 weeks. Longer follow-up may be needed to look for persistence of antihypertensive and anti proteinuric effect and any late onset ADR. Due to logistic reasons, electronic instrument for recording blood pressure was not considered. We did not recruit subjects with macroalbuminuria. Effects of both the drugs were not compared separately on diabetic and non-diabetic subjects. Finally, we did not consider echocardiography due to infeasibility, although there are reports that cilnidipine reduces left ventricular mass index.<sup>25</sup>

Till date, ACEIs or ARBs are considered a gold standard therapy for hypertensive subjects with proteinuria. But, cilnidipine is also blossoming as an anti-proteinuric agent. There is no head to head trial between cilnidipine and ACEIs / ARBs in hypertensive subjects with proteinuria. So, future research should encompass this domain too.

## CONCLUSION

Though amlodipine is preferred drug, cilnidipine should be a better alternative when we consider subjects with sympathetic over activity, proteinuria or pedal oedema.

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