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A Prospective Efonidipine Efficacy Evaluation in Cardiovascular and Renal Outcomes in Hypertensive Patients: The PERFECT Trial

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ABSTRACT

Background*: Efonidipine, an L and T-type calcium channel blocker (CCB), is known for effectively lowering blood pressure and targeting proteinuria by balancing glomerular capillary pressure. There remains a gap in understanding how its clinical benefits and safety profile compare to other CCBs, particularly those targeting L and N-type channels. The present trial evaluated the effect of Efonidipine and Cilnidipine on cardiovascular and renal outcomes in hypertensive patients. Methods*: A randomized, comparative trial was conducted from May 2019 to August 2023 in adults with hypertension (≥140/90 mmHg). The patients (n=1035) received one of the drugs daily for 90 days. The primary endpoint was the change in blood pressure with secondary endpoints including improvement in proteinuria, and safety assessment. Results*: Both Efonidipine and Cilnidipine reduced blood pressure to a similar extent (Efonidipine, from 155.17 ± 10.38 to 132.92 ± 9.60 mmHg, p<0.001; Cilnidipine, from 154.75 ± 10.05 to 132.90 ± 9.47 mmHg, p<0.001) and maintained heart rate significantly lower from baseline (Efonidipine, from 83.5 ± 7.2 to 80.1 ± 6.3 beats/ min, p<0.001; Cilnidipine, from 83.3 ± 6.9 to 80.0 ± 6.8 beats/min; p<0.001). Efonidipine demonstrated a more pronounced reduction (from 151.45 ± 4.4 to 123.52 ± 3.9 mg/g Cr, p<0.001) in

proteinuria compared to Cilnidipine (from 161.64 ± 8.9 to 152.10 ± 3.9 7.8 mg/g Cr, p=4240). An independent decrease in proteinuria relative to blood pressure reduction was observed with Efonidipine. Adverse events were similar between groups, with no incidences of peripheral edema. Conclusion*:* Efonidipine and Cilnidipine effectively controlled blood pressure and reduced proteinuria. The antiproteinuric effect was more apparent with Efonidipine. Efonidipine improves cardiovascular and renal outcomes and may be considered an initial treatment option in hypertensive patients.

Keywords: Efonidipine, Hypertension, Cardioprotection, Renoprotection, Calcium Channel Blocker

INTRODUCTION

The prevalence of hypertension has doubled in the last decade, posing a considerable threat to millions of people globally [1] and exacerbating chronic kidney disease (CKD) [2]. Proteinuria, a marker of kidney dysfunction, is also a recognized risk factor for cardiovascular disease (CVD) in hypertensive individuals [3]. Hypertension and proteinuria elevate the risk of kidney damage, especially when both coexist [4]. Therefore, precisely managing these factors is essential to reduce the CVD risk and CKD progression.

Effective blood pressure control can improve the prognosis of CKD. Calcium channel blockers (CCBs) have emerged as the preferred initial therapy for hypertension [5, 6]. A consistent blood pressure-lowering effect and minimal side effects are observed for CCBs [7] primarily with dihydropyridines (DHPs), a type of CCB [8]. However, selecting a DHP subtype based on its properties presents significant challenges. Typical DHPs mainly block L-type calcium channels, leading to reflex tachycardia [9]. Newer agents, with slow-onset and long-acting properties, target L- and T/N-type calcium channels, providing renal-protective effects by reducing glomerular hypertension [10, 11].

Efonidipine, a long-acting dual L- and T-type DHP-CCB, induces vasodilation by selectively inhibiting L-type calcium channels in vascular smooth muscle cells and regulates heart rate by inhibiting T-type calcium channels in the sinoatrial node (SA) [12]. Efonidipine is recognized for its negative chronotropic effect [13]. Efonidipine demonstrates a potent dilation of afferent and efferent arterioles to an equal extent in *in-vitro* [14] and *in-vivo* [15] studies. Furthermore, its beneficial effects in reducing proteinuria, as observed in clinical studies [16, 17], support its renoprotective action. Efonidipine is more effective in managing mild-to-moderate hypertension and renal functions compared to Amlodipine [18-20], Nifedipine [21] and ACE inhibitors [22]. Therefore, Efonidipine can favourably reduce CVD risk and CKD progression. Similarly, the antihypertensive literature reports the use of Cilnidipine (L- and N-Type CCB) in hypertensive patients and renal impairment compared with other first-line antihypertensive drugs commonly used in practice [22, 23].

Dual-acting DHP-CCBs have the potential to provide more benefits compared to those only targeting L-type channels. However, there is a limited direct comparative analysis of dual-acting DHP-CCBs. The objective of this study is to evaluate the cardiovascular and renoprotective effects of dual-acting Efonidipine and Cilnidipine in hypertensive patients.

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MATERIALS AND METHODS

Patients

Adults aged 18 years or older were enrolled in the study. The criteria for diagnosing hypertension with a blood pressure of ≥140/90 mmHg was as per the 7th Joint National Committee (JNC) hypertension guideline [24]. Naïve patients or patients who were not responding to their current blood pressure medication, necessitating a switch to alternative treatment were enrolled. Patients with cerebrovascular disease, congestive heart failure, sick sinus syndrome, cardiac rhythm abnormalities like sinus bradycardia or second- or third-degree atrioventricular block, hypersensitivity, or contraindication to the study medications were excluded from the study. Pregnant or lactating women and those with childbearing potential who were not using adequate birth control were excluded from the study.

Study Design

This was a randomized, double-blind, multicentre, parallel-group, comparative trial conducted from May 2019 to August 2023 in 15 hospitals in 7 cities across India. The study followed the ethical standards outlined in the Declaration of Helsinki, the Good Clinical Practice guidelines laid down by the International Council for Harmonization, and the New Drugs Clinical Trial Rules, 2019, India. Approval for the study protocol was obtained from the ethics committees at each study centre. The written informed consent was obtained from the patients. The trial was prospectively registered with the 'Clinical Trials Registry – India' under registration number CTRI/2019/03/018167. The patients underwent eligibility assessment, informed consent, clinical and physical examinations for their eligibility in the study. Following the screening, eligible patients were randomly assigned to the Efonidipine group (Efonidipine 40 mg tablets) and the Cilnidipine group (Cilnidipine 10 mg tablets) in a 3:1 ratio. Centralized block randomization-maintained study blinding for both patients and investigators. The patients adhered to their assigned treatments for a duration of 90 days, and dosing compliance was monitored through the assessment of diary cards.

Patients were followed up on the Day 30, 60, and 90 post-randomizations for blood pressure measurements and laboratory tests. Seated blood pressure was measured using a standard manual cuff sphygmomanometer at screening, baseline (before randomization), and each follow-up day. Blood pressure readings were averaged from three consecutive measurements of the dominant arm, with the first reading taken after 15 minutes of rest and the subsequent two readings recorded at 2-minute intervals. Heart rate was measured concurrently with blood pressure. Laboratory measurements mainly focused on renal function tests and analysis of urine samples.

Assessment

The primary endpoint was to assess the efficacy of Efonidipine compared to Cilnidipine in reducing mean sitting blood pressure among hypertensive patients. Secondary endpoints included the change in urine albumin/creatinine ratio (UACR) after 90 days of treatment, change in mean sitting blood pressure after 30 and 60 days of treatment, and the number of patients who achieved the target goal blood pressure after 90 days of treatment as per JNC 8 guideline. Safety was evaluated by monitoring adverse events (AEs) throughout the study and assessed as per the World Health Organization-Uppsala Monitoring Centre Causality Categories.

Statistical Methods

The efficacy analysis primarily included patients who completed the trial as defined in the per-protocol population. The safety was evaluated in patients who received at least one dose of study treatment. Descriptive data for continuous variables were presented as mean ± SD, while categorical variables were in number and percentage. The baseline characteristics of the patients were compared using an unpaired t-test and Pearson-chi^2 test. A two-sample t-test was used to compare the change in blood pressure, heart rate, serum creatinine, UACR, and estimated glomerular filtration rate (eGFR) from baseline and between groups. Spearman Rank Correlation was used to correlate the two parameters. The categorical data were assessed using the Fisher exact or Pearson-chi^2 test. The results from the trial were presented as comparative statistics with 95% confidence intervals (CI). The statistical significance was set at $p<0.05$. The analysis was performed with STATA statistical analysis software, version 15.0 (StataCorp LLC, USA).

The sample size calculation was carried out to achieve 80% statistical power, assuming a mean reduction in blood pressure of 6.5 mmHg between the groups with a standard deviation of 12.4 mmHg. The non-inferiority of Efonidipine compared to Cilnidipine was assessed using a margin of 10 mmHg for the mean difference in blood pressure at a one-sided significance level of 2.5%. Based on the sample size calculation, 238 patients were to be recruited in each arm. A 3:1 randomization ratio was used to maximize the exposure of Efonidipine and enhance the precision within the Efonidipine group. The study required a sample size of at least 954 patients to fulfil the criteria for demonstrating non-inferiority. A 10% dropout rate was estimated and accordingly the planned sample size for this clinical trial was calculated to be 1,048 patients.

RESULTS

Patient Allocation and Baseline Characteristics

A total of 1048 patients who met the eligibility criteria were randomized to either of the treatment groups. Among these, 1035 were treated with the Efonidipine (n=780) and the Cilnidipine (n=255) as per the randomization schedule. The 90-day treatment period was completed by 984 patients and considered for the efficacy analysis (Figure 1). The safety analysis included patients who had received at least one dose of the assigned treatment.

The mean (SD) age of the patients was 46.47 (11.57) years; 61% of the patients were men (59.38%, Efonidipine group; 65.02%, Cilnidipine group). The mean (SD) body mass index was 25.03 (3.2) kg/m^2 with only 6% of patients above 30 kg/m^2. The patients with diabetes and CKD were 190 (19.31%) and 71 (7.22%), respectively in the study. On average, the patients had a history of hypertension for 3.1 years. Baseline blood pressure and heart rate were similar in both treatment groups. Demographic and clinical characteristics were well distributed between the groups, and no significant differences between-group were observed (Table 1).

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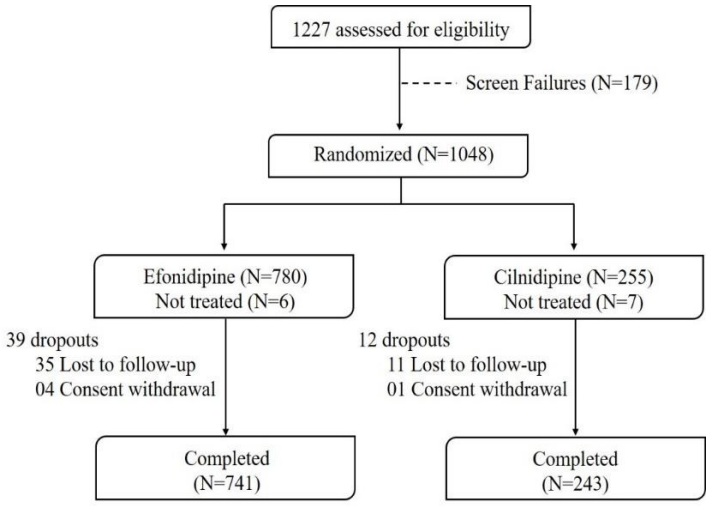

Figure 1: Disposition of patients in the study

Table 1: Demographics and clinical characteristics of the patients at baseline

Baseline characteristic	Efonidipine group (n=741)	Cilnidipine group (n=243)	p-value [a]
Age, years	46.40 ± 11.58	46.69 ± 11.55	0.7306
< 60 years	653 (88.12)	213 (87.65)	0.8450
≥ 60 years	88 (11.88)	30 (12.35)	
Gender, n(%)			
Male	440 (59.38)	158 (65.02)	0.1180
Female	301 (40.62)	85 (34.98)	
BMI (Kg/m^2)	25.00 ± 3.29	25.12 ± 2.83	0.6058
Hypertension			
SBP (mmHg)	155.17 ± 10.38	154.75 ± 10.05	0.5877
DBP (mmHg)	96.17 ± 5.69	96.00 ± 5.94	0.6848
Heart rate (beats/min)	83.53 ± 7.20	83.33 ± 6.93	0.7145
Grade of hypertension, n(%)			
Stage I hypertension	498 (67.21)	160 (65.84)	0.695
Stage II hypertension	243 (32.79)	83 (34.16)	
Comorbidities, n(%)			
Diabetes	141 (19.03)	49 (20.16)	0.6968
CKD	54 (7.29)	17 (7.00)	0.8788
Serum creatinine (mg/dL)	1.03 ± 0.36	0.99 ± 0.21	0.1940
eGFR (mL/min/1.73 m^2)	75.41 ± 22.47	77.58 ± 21.35	0.1862
BUN (mg/dL)	18.31 ± 6.45	17.58 ± 5.26	0.1110
UACR (mg/g of creatinine)	151.45 ± 118.12	161.64 ± 138.53	0.2676
Baseline medications, n (%)			
ACE inhibitors	64 (8.64)	18 (7.41)	-
ARBs	215 (29.01)	77 (31.69)	-
α-blockers	4 (0.54)	0	-
β-blockers	46 (6.21)	16 (6.58)	-
CCBs	174 (23.48)	53 (21.81)	-
Diuretics	57 (7.69)	22 (9.05)	-
Statins	1 (0.13)	0	-

Multiple agents	99 (13.36)	31 (12.76)	-

Data are represented in Mean ± SD or Number (%). ACE: Angiotensin-converting enzyme; ARBs: angiotensin II receptor blockers; BMI: Body mass index; BUN: Blood urea nitrogen; CCB: Calcium channel blockers; CKD: Chronic Kidney Disease; DBP: Diastolic blood pressure; FDCs: Fixed-dose combinations; SBP: Systolic blood pressure; UACR: Urinary albumin/creatinine ratio. [a] T-test for continuous variables and Pearson chi^2 test for categorical variables were used to calculate the p values

Effect on Blood Pressure

The systolic and diastolic blood pressure after 90 days of treatment were significantly reduced from baseline in both groups (Efonidipine group, △ 22.25/11.70, p<0.001; Cilnidipine group, △ 21.85/11.15, p<0.001). The reduction in blood pressure across the two groups was not statistically different. The treatment difference in systolic blood pressure was -0.45 mmHg (95%CI: -2.01 to 1.11; p = 0.5744), and that in diastolic blood pressure was -0.47 mmHg (95%CI: -1.34 to 0.40; p = 0.2895) (Table 2).

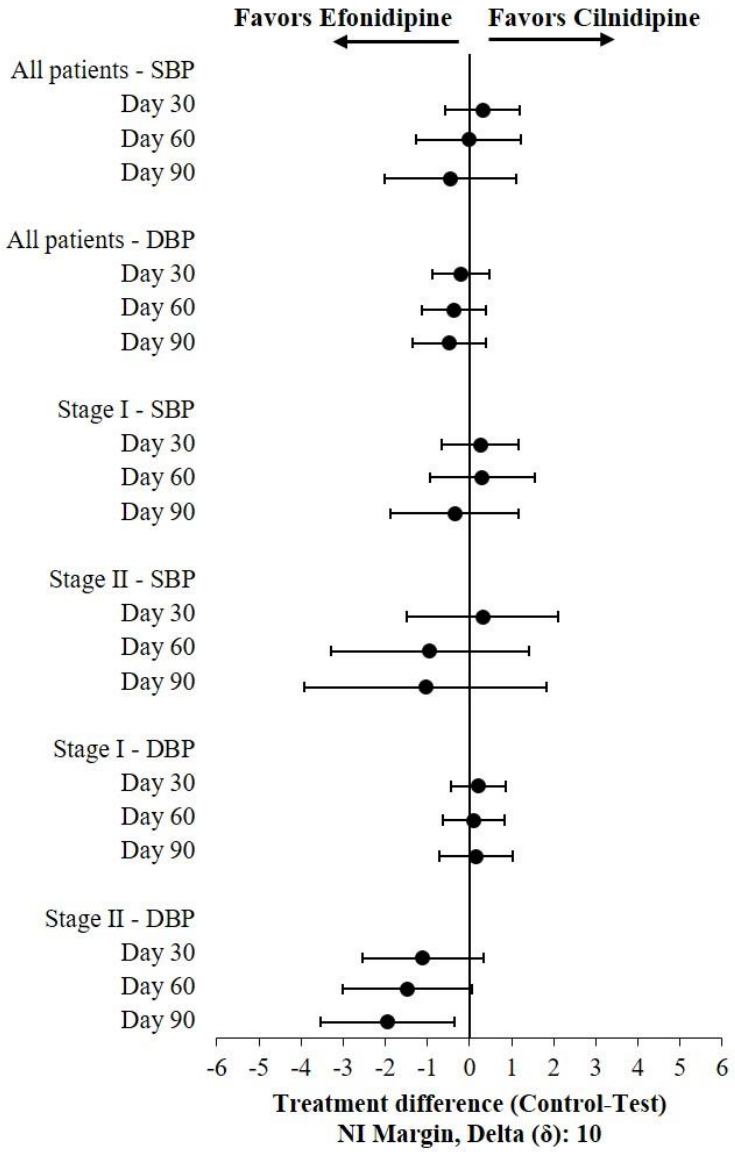

Figure 2: Non-inferiority between Efonidipine and Cilnidipine

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The upper limit of the 95%CI was below the margin of 10 mmHg, confirming the non-inferiority of the Efonidipine with the Cilnidipine treatment. It was observed that the Efonidipine was superior to the Cilnidipine in reducing diastolic blood pressure in patients with Stage II hypertension (Figure 2).

The blood pressure target (140/80 mmHg) was achieved in 78% and 76% of the patients in the Efonidipine and Cilnidipine groups, respectively. Figure 3 presents the number of patients who achieved their target blood pressure in subgroups.

Effect on Heart Rate

Heart rate was significantly reduced at the end of the study in both groups compared with baseline (Efonidipine group, from 83.53 ± 7.20 to 80.13 ± 6.35 beats/ min; △ 3.39; 95%CI: 2.70 to 4.09; p<0.001); Cilnidipine group, from 83.33 ± 6.93 to 80.01 ± 6.19 beats/min; △ 3.32; 95%CI: 2.15 to 4.49; p<0.001), however, there was no significant difference (△ 0.07; 95%CI: -1.04 to 0.88; p=0.8747) between the groups (Table 3).

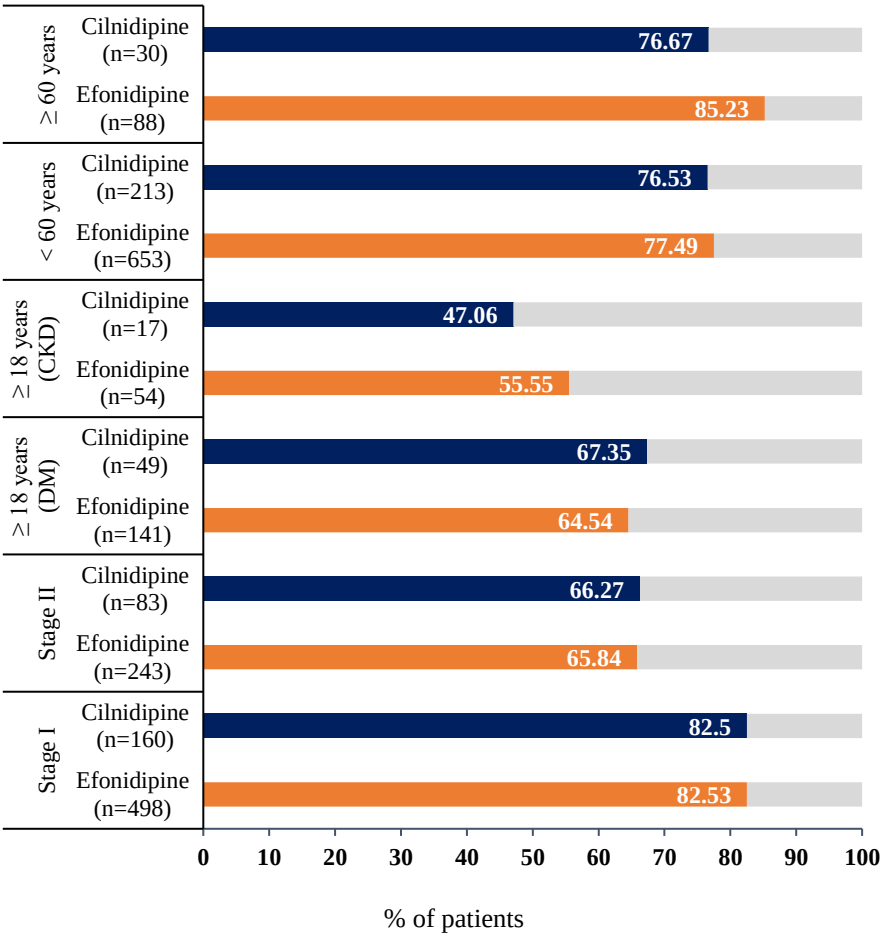

Figure 3: Number of patients who achieved target blood pressure at the end of the study. The target of blood pressure in patients ≥ 60 years was 150/90 mmHg whereas 140/90 mmHg in the rest of the subgroups as per JNC8 guideline. DM: Diabetes Mellitus; CKD: Chronic Kidney Disease. The Efonidipine and Cilnidipine groups had similar rates of patients achieving target blood pressure, with no significant difference (p>0.05) in subgroups.

Table 2: Change in blood pressure

	SBP (mmHg)					DBP (mmHg)			
	Efonidipine group	Cilnidipine group	Between-group difference			Efonidipine group	Cilnidipine group	Between-group difference	
			Mean difference (95%CI) [a]	p-value				Mean difference (95%CI) [a]	p-value
All patients									
Day 0	155.17 ± 10.38	154.75 ± 10.05	-	-		96.17 ± 5.69	96.00 ± 5.94	-	-
Day 30	146.44 ± 9.99 [b]	145.65 ± 9.70 [b]	0.32 (-0.57 to 1.20)	0.4819		90.85 ± 5.46 [b]	90.88 ± 5.65 [b]	-0.20 (-0.87 to 0.46)	0.5462
Day 60	138.89 ± 9.48 [b]	138.52 ± 9.67 [b]	-0.02 (-1.26 to 1.22)	0.9765		87.26 ± 4.83 [b]	87.51 ± 5.19 [b]	-0.38 (-1.14 to 0.38)	0.3265
Day 90	132.92 ± 9.60 [b]	132.90 ± 9.47 [b]	-0.45 (-2.01 to 1.11)	0.5744		84.47 ± 4.39 [b]	84.84 ± 4.75 [b]	-0.47 (-1.34 to 0.40)	0.2895
Stage I hypertension									
Day 0	149.61 ± 5.87	148.97 ± 5.65	-	-		93.79 ± 3.45	93.56 ± 3.96	-	-
Day 30	141.98 ± 6.79 [b]	141.06 ± 6.73 [b]	0.25 (-0.67 to 1.18)	0.5899		89.33 ± 4.20 [b]	88.88 ± 4.39 [b]	0.21 (-0.44 to 0.86)	0.5241
Day 60	135.82 ± 7.23 [b]	134.91 7.42 [b]	0.31 (-0.93 to 1.55)	0.6273		86.34 ± 3.76 [b]	86.04 ± 3.81 [b]	0.09 (-0.64 to 0.83)	0.8016
Day 90	130.77 ± 7.76 [b]	130.48 ± 7.63 [b]	-0.35 (-1.88 to 1.17)	0.6493		84.07 ± 4.01 [b]	83.76 ± 3.90 [b]	0.17 -0.70 to 1.04	0.7054
Stage II hypertension									
Day 0	166.56 ± 8.04	165.90 ± 6.72	-	-		101.05 ± 6.26	100.69 ± 6.33	-	-
Day 30	155.59 ± 9.25 [b]	154.51 ± 8.32 [b]	0.31 (-1.49 to 2.11)	0.7354		93.96 ± 6.36 [b]	94.76 ± 5.81 [b]	-1.11 (-2.54 to 0.32)	0.1284
Day 60	45.16 ± 10.40 [b]	145.48 ± 9.75 [b]	-0.95 (-3.30 to 1.40)	0.4276		89.16 ± 6.08 [b]	90.33 ± 6.26 [b]	-1.47 -3.01 to 0.07)	0.0612
Day 90	37.32 ± 11.38 [b]	37.57 ± 10.88 [b]	-1.04 (-3.91 to 1.83)	0.4754		85.29 ± 4.99 [b]	86.94 ± 5.51 [b]	-1.94 (-3.53 to -0.36)	0.0166

Data is expressed as mean ± SD; DBP: Diastolic blood pressure; SBP: Systolic blood pressure
[a] Day 0 versus Day 30, 60, and 90 in both groups; [b] p<0.001 compared to Day 0

Table 3: Change in heart rate

	Heart rate (beats per min)			
	Efonidipine group	Cilnidipine group	Between-group difference	
			Mean difference (95%CI) [a]	p-value
Day 0	83.53 ± 7.20	83.33 ± 6.93	-	-
Day 30	81.87 ± 6.36 [b]	82.06 ± 5.99 [c]	-0.38 (-1.00 to 0.24)	0.2242
Day 60	81.12 ± 5.90 [b]	80.84 ± 5.97 [b]	-0.08 (-0.73 to 0.90)	0.8385
Day 90	80.13 ± 6.35 [b]	80.01 ± 6.19 [b]	-0.08 (-1.04 to 0.88)	0.8747

Data is expressed as mean ± SD
[a] Day 0 versus Day 30, 60, and 90 in both groups; [b] p<0.001 and [c] p=0.0304 as compared to Day 0

Renoprotective Effect

Serum creatinine levels were significantly reduced in both groups after 90 days of treatment (Efonidipine group: 1.03±0.01 to 0.94±0.007 mg/dL, p<0.001; Cilnidipine group: 1.0±0.2 to 0.95±0.01 mg/dL, p= 0.0058). The difference between the two groups was non-significant (△ 0.09±0.3 vs. 0.05±0.2; p=0.0707). The eGFR was significantly improved in the Efonidipine (△ 6.93; 95%CI: 4.46 to 9.41; p<0.001) and Cilnidipine (△ 4.11; 95%CI: 0.29 to 7.93; p=0.0353) groups. Furthermore, the increased levels of eGFR were strongly (Spearman's r for Efonidipine: -0.9688 and Cilnidipine: -0.9657) and significantly (p<0.001) correlated with the decrease in serum creatinine in both groups.

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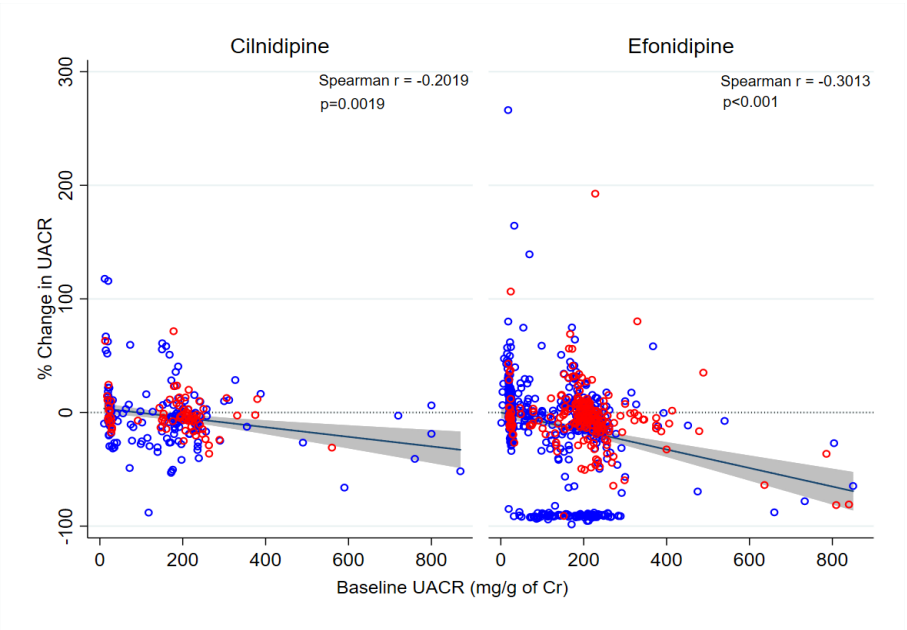

Figure 4: Correlation between baseline UACR and % change in UACR. Efonidipine effectively reduced Urinary albumin/creatinine ratio (UACR) compared to Cilnidipine, demonstrating proactive management of proteinuria in both stage 1 (blue circles) and stage 2 (red circles) hypertension.

The UACR decreased from its baseline values in both the Efonidipine (Spearman r = -0.3013, p<0.001) and the Cilnidipine (Spearman r = -0.2019, p=0.0019) group (Figure 4). However, the UACR significantly reduced in the Efonidipine group (151.45 to 123.52 mg/g of Cr, p<0.001) compared to the Cilnidipine group (161.64 to 152.10 mg/g of Cr, p=0.4240) (Figure 5). A significant correlation was observed between the reduction of UACR and the reduction of blood pressure in the Cilnidipine group (for systolic blood pressure: Spearman r = 0.2130, p=0.0010; and for diastolic blood pressure: Spearman r = 0.1328, p= 0.0425). Whereas, in the Efonidipine group, no correlation was observed (for systolic blood pressure: Spearman r = 0.0176, p=0.6387; and for diastolic blood pressure: Spearman r = 0.0472, p= 0.2073) (Supplementary Material). These findings indicate that Efonidipine reduces proteinuria independently of its blood pressure-lowering effects, whereas Cilnidipine does not.

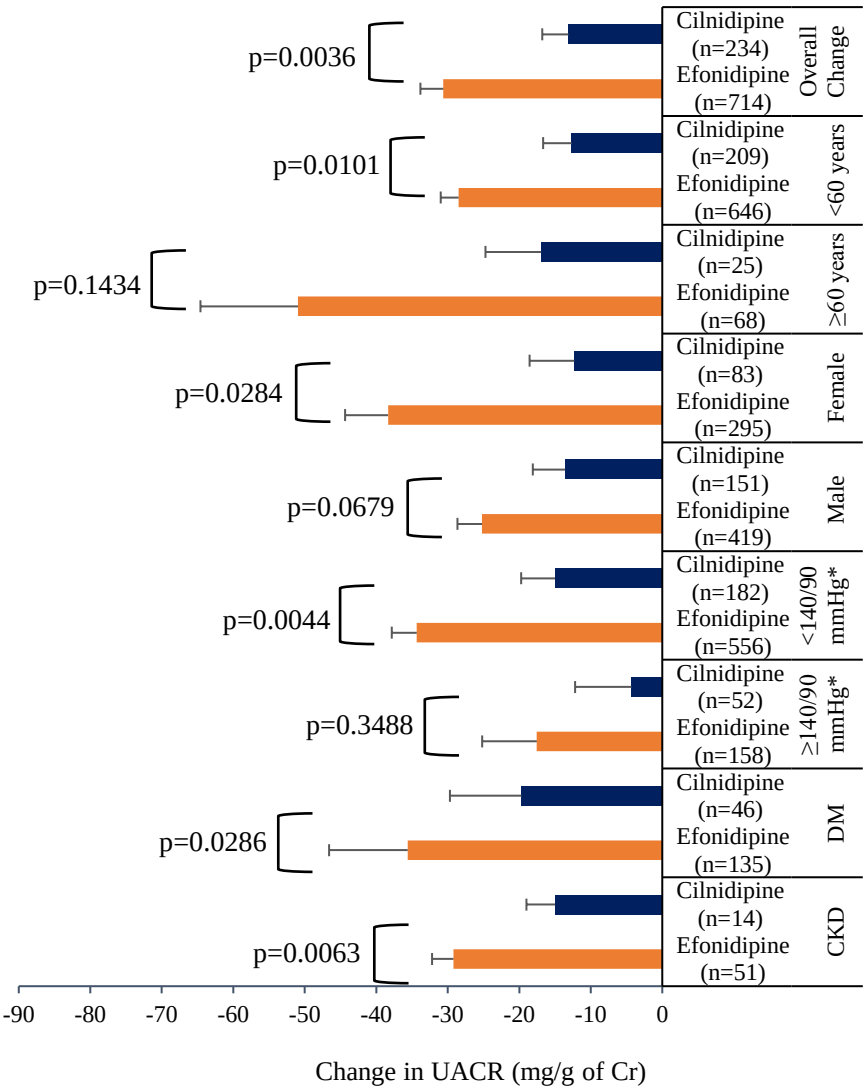

Figure 5: Change in UACR. UACR: Urinary albumin/creatinine ratio; DM: Diabetes Mellitus; CKD: Chronic Kidney Disease. *Blood pressure after Day 90.

Adverse Effects and Tolerability

The incidences of adverse events were low and similar in the Efonidipine group (2.18%) and Cilnidipine (1.96%) groups (p=0.8290). The reported adverse events were mild in severity and resolved without sequel (Table 4). No peripheral edema was seen in either of groups. There was no severe adverse event reported. The study treatments were well-tolerated. The investigators reported drug tolerability in 93.8% of Efonidipine-treated patients and 91.4% of Cilnidipine-treated patients.

Table 4: Adverse events

	Efonidipine n(%)	Cilnidipine n(%)
Headache	7 (0.90)	2 (0.78)
Nausea	5 (0.64)	1 (0.39)
Abdominal pain	2 (0.26)	0

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Dizziness	2 (0.26)	0
Vomiting	1 (0.13)	1 (0.39)
Giddiness	0	1 (0.39)
Total adverse events	17 (2.18)	5 (1.96)

DISCUSSION

High blood pressure is a key controllable factor in reducing the risk of CVD, renal failure, and mortality. Studies have demonstrated that BP-lowering interventions should be initiated when BP exceeds thresholds to reduce the risk of CVD and CKD [25, 26]. DHP-CCBs serve as an effective agent that reduces BP with minor adverse effects and are recommended as monotherapy or in combination for the treatment of hypertension. In this trial, Efonidipine and Cilnidipine have reduced blood pressure to a similar extent as reported in earlier studies [20, 23, 27, 28]. Despite the effective blood pressure-lowering abilities of L-type CCBs, their utilization can be limited in patients with angina because of their potential to increase heart rate. Both the studied drugs decreased the heart rate significantly. These findings indicate that Efonidipine and Cilnidipine modulate heart rate by acting not only on L-type calcium channels but also on T and N-type calcium channels respectively. Efonidipine has been reported to have stronger negative chronotropic effects than Cilnidipine due to its specific inhibition of T-type calcium channels [29, 30]. Whereas, Cilnidipine regulates the heart rate by attenuating cardiac sympathetic nerve activity [31]. The collective evidence indicates that Efonidipine has a dual impact on regulating blood pressure and heart rate contributing to its cardiovascular benefits.
Calcium channel blockers are effective treatments for proteinuria, following renin-angiotensin-aldosterone system (RAAS) blockers. The studies indicated that Efonidipine and Cilnidipine have a favourable impact on proteinuria and eGFR [32, 33]. A meta-analysis showed that net change in proteinuria favours L/T over L/N-type CCBs [34]. Moreover, blocking N- and T-type calcium channels has varying effects on renal microcirculation. Our study results suggest that Efonidipine reduced proteinuria to a greater extent than Cilnidipine even in patients with diabetes and CKD. Efonidipine may offer superior organ protection as compared to Cilnidipine due to its balanced dilation of the efferent and afferent glomerular arterioles, whereas Cilnidipine predominantly dilates afferent arterioles [35]. Thus, Efonidipine controls glomerular hypertension more efficiently than Cilnidipine. The study emphasizes the proactive approach of Efonidipine to managing proteinuria across both stages of hypertension, as shown in Figure 4, reaffirming the importance of addressing hypertension in its early stage as a risk factor for proteinuria development [36].

The study findings suggest that Efonidipine has a renal-specific protective effect, which was independent of its impact on blood pressure [16, 37]. This effect was not observed for Cilnidipine. Imagawa et al. [38], and Okayama et al. [39], reported that Efonidipine significantly reduces aldosterone synthesis and secretion. Furthermore, an experimental study found that Efonidipine substantially reduced proteinuria to the same extent as Enalapril [40]. These findings indicate that the ability of Efonidipine to block T-type calcium channels is responsible for its renal-specific effect and it achieves renoprotection through balanced renal arteriolar dilatation, suppression of aldosterone synthesis, and inhibition of rho-kinase activity [11, 41].
Efonidipine prolongs phase 4 depolarization at the SA node, counteracting reflex tachycardia [42]. On the other hand, Cilnidipine reduces noradrenaline release, inhibiting reflex tachycardia [22]. Efonidipine lowers blood pressure without affecting cardiac contractility, unlike other calcium antagonists [12]. There were no incidences of symptomatic hypotension associated

with the use of Efonidipine in the present study. Jariwala et al, corroborate the findings [43]. Peripheral edema is a common adverse effect associated with CCB that frequently results in discontinuation of treatment. However, in this study, neither drug group experienced peripheral edema, indicating a favourable safety profile and allowing continued therapy. In the diabetic patients of the present study, the antiproteinuric effect of Cilnidipine was not significant as observed in the CARTER study [28], possibly due to compromised integrity of sympathetic nerve terminals in diabetes. This implies that Cilnidipine's action targeting N-type calcium channels may not completely address proteinuria in diabetic patients, and Efonidipine may be an alternative treatment approach.

CONCLUSIONS

In summary, our findings indicate that both Efonidipine and Cilnidipine effectively control blood pressure however, Efonidipine shows superior results in lowering diastolic blood pressure compared to Cilnidipine. Additionally, Efonidipine shows better efficacy in reducing proteinuria compared to Cilnidipine among hypertensive patients. Efonidipine could be a valuable alternative to Cilnidipine in managing hypertension with renal complications. Nonetheless, additional research is warranted to assess the long-term efficacy and safety of Efonidipine. Considering its potential benefits, Efonidipine may be considered as an initial treatment option for hypertensive patients.

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Declarations

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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Consent and Ethical Approval

Informed consent was obtained from all patients enrolled in the study. All procedures performed in studies involving human participants were as per the ethical standards of the institutional ethics committee, the Indian Council of Medical Research (ICMR), the New Drugs Clinical Trial Rules 2019 and the Declaration of Helsinki. Approval was obtained from the Institutional Ethics Committee of each study center.

References

[1] NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in hypertension prevalence and progress in treatment and control from 1990 to 2019: a pooled analysis of 1201 population-representative studies with 104 million participants. Lancet. 2021;398(10304):957-980. doi:10.1016/S0140-6736(21)01330-1

[2] Kovesdy CP. Epidemiology of chronic kidney disease: an update 2022. Kidney Int Suppl (2011). 2022;12(1):7-11. doi: 10.1016/j.kisu.2021.11.003

[3] Currie G, Delles C. Prosteinuria and its relation to cardiovascular disease. Int J Nephrol Renovasc Dis. 2014; 7:13-24 doi:10.2147/IJNRD.S40522

[4] Lee H, Park MS, Kang MK, Song TJ. Association between Proteinuria Status and Risk of Hypertension: A Nationwide Population-Based Cohort Study. J Pers Med. 2023;13(9):1414. doi: 10.3390/jpm13091414

[5] Mancia G, Kreutz R, Brunström M, et al. 2023 ESH Guidelines for the management of arterial hypertension The Task Force for the management of arterial hypertension of the European Society of Hypertension: Endorsed by the International Society of Hypertension (ISH) and the European Renal Association (ERA). J Hypertens. 2023;41(12):1874-2071. doi:10.1097/HJH.0000000000003480

[6] Whelton PK, Carey RM, Aronow WS, et al. ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertension. 2018;71(6):1269-1324. doi:10.1161/HYP.0000000000000066

[7] Shetty S, Malik AH, Feringa H, El Accaoui R, Girotra S. Meta-Analysis Evaluating Calcium Channel Blockers and the Risk of Peripheral Arterial Disease in Patients with Hypertension. Am J Cardiol. 2020;125(6):907-915. doi: 10.1016/j.amjcard.2019.12.026

[8] Ghamami N, Chiang SH, Dormuth C, Wright JM. Time course for blood pressure lowering of dihydropyridine calcium channel blockers. Cochrane Database Syst Rev. 2014;(8):CD010052.

[9] Lee EM. Calcium channel blockers for hypertension: old, but still useful. Cardiovasc Prev Pharmacother. 2023;5(4):113-125. doi:10.36011/cpp.2023.5. e16

[10] Wang AL, Iadecola C, Wang G. New generations of dihydropyridines for treatment of hypertension. J Geriatr Cardiol. 2017;14(1):67-72. doi: 10.11909/j.issn.1671-5411.2017.01.006

[11] Abe M, Soma M. Multifunctional L/N- and L/T-type calcium channel blockers for kidney protection. Hypertens Res. 2015;38(12):804-806. doi:10.1038/hr.2015.106

[12] Tanaka H, Shigenobu K. Efonidipine hydrochloride: a dual blocker of L- and T-type Ca2+ channels. Cardiovasc Drug Rev. 2002;20(1):81-92

[13] Masuda Y, Miyajima M, Shudo C, Tanaka S, Shigenobu K, Kasuya Y. Cardiovascular selectivity of 1,4-dihydropyridine derivatives, efonidipine (NZ-105), nicardipine and structure related compounds in isolated guinea-pig tissues. Gen Pharmacol. 1995;26(2):339-345. doi:10.1016/0306-3623(94)00187-r

[14] Hayashi K, Nagahama T, Oka K, Epstein M, Saruta T. Disparate effects of calcium antagonists on renal microcirculation. Hypertens Res. 1996;19(1):31-36. doi:10.1291/hypres.19.31

[15] Honda M, Hayashi K, Matsuda H, et al. Divergent renal vasodilator action of L- and T-type calcium antagonists in vivo. J Hypertens. 2001;19(11):2031-2037. doi:10.1097/00004872-200111000-00014

[16] Hayashi K, Kumagai H, Saruta T. Effect of efonidipine and ACE inhibitors on proteinuria in human hypertension with renal impairment. Am J Hypertens. 2003;16(2):116-122. doi:10.1016/s0895-7061(02)03147-3

[17] Ishimitsu T, Kameda T, Akashiba A, et al. Efonidipine reduces proteinuria and plasma aldosterone in patients with chronic glomerulonephritis. Hypertens Res. 2007;30(7):621-626. doi:10.1291/hypres.30.621

[18] Tanaka T, Tsutamoto T, Sakai H, Fujii M, Yamamoto T, Horie M. Comparison of the effects of efonidipine and amlodipine on aldosterone in patients with hypertension. Hypertens Res. 2007;30(8):691-697. doi:10.1291/hypres.30.691

[19] Nakano N, Ishimitsu T, Takahashi T, et al. Effects of efonidipine, an L- and T-type calcium channel blocker, on the renin-angiotensin-aldosterone system in chronic hemodialysis patients. Int Heart J. 2010;51(3):188-192. doi:10.1536/ihj.51.188

[20] Sasaki H, Saiki A, Endo K, et al. Protective effects of efonidipine, a T- and L-type calcium channel blocker, on renal function and arterial stiffness in type 2 diabetic patients with hypertension and nephropathy. J Atheroscler Thromb. 2009; 16(5): 568-75

[21] Oshima, T., Ozono, R., Yano, Y. et al. Beneficial Effect of T-Type Calcium Channel Blockers on Endothelial Function in Patients with Essential Hypertension. Hypertens Res. 2005;28(11): 889–894. doi:10.1291/hypres.28.889

[22] Chandra KS, Ramesh G. The fourth-generation Calcium channel blocker: cilnidipine. Indian Heart J. 2013;65(6):691-695. doi: 10.1016/j.ihj.2013.11.001

[23] Chakraborty RN, Langade D, More S, Revandkar V, Birla A. Efficacy of Cilnidipine (L/N-type Calcium Channel Blocker) in Treatment of Hypertension: A Meta-Analysis of Randomized and Non-randomized Controlled Trials. Cureus. 2021;13(11): e19822. doi:10.7759/cureus.19822

[24] National High Blood Pressure Education Program. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Bethesda (MD): National Heart, Lung, and Blood Institute (US); 2004. Available from: https://www.ncbi.nlm.nih.gov/books/NBK9630/

[25] Lee H, Kwon SH, Jeon JS, Noh H, Han DC, Kim H. Association between blood pressure and the risk of chronic kidney disease in treatment-naïve hypertensive patients. Kidney Res Clin Pract. 2022;41(1):31-42. doi: 10.23876/j.krcp.21.099

[26] Wu S, Li M, Lu J, et al. Blood Pressure Levels, Cardiovascular Events, and Renal Outcomes in Chronic Kidney Disease Without Antihypertensive Therapy: A Nationwide Population-Based Cohort Study. Hypertension. 2023;80(3):640-649. doi:10.1161/HYPERTENSIONAHA.122.19902

[27] Dewan B, Wani V. A Comparative Clinical Trial of Efonidipine and Amlodipine in Management of Stage-I Hypertension: A Randomized, Double-Blind Study in Indian Population. JAMMR. 2018;25(1):1-12. doi: 10.9734/JAMMR/2018/38509

[28] Fujita T, Ando K, Nishimura H, Ideura T, Yasuda G, Isshiki M, Takahashi K. Antiproteinuric effect of the calcium channel blocker cilnidipine added to renin-angiotensin inhibition in hypertensive patients with chronic renal disease. Kidney international. 2007;72(12):1543-9

[29] Tanaka H, Masumiya H, Sekine T, et al. Myocardial and vascular effects of efonidipine in vitro as compared with nifedipine, verapamil and diltiazem. Gen Pharmacol. 1996;27(3):451-4. doi: 10.1016/0306-3623(95)02065-9

[30] Takeda K, Yamagishi R, Masumiya H, Tanaka H, Shigenobu K. Effect of cilnidipine on L- and T-type calcium currents in guinea pig ventricle and action potential in rabbit sinoatrial node. J Pharmacol Sci. 2004;95(3):398-401. doi: 10.1254/jphs. scj04001x

[31] Shete MM. Cilnidipine: Next Generation Calcium Channel Blocker. J Assoc Physicians India. 2016 Apr;64(4):95-99. PMID: 27734656.

[32] Li X, Yang MS. Effects of T-type calcium channel blockers on renal function and aldosterone in patients with hypertension: a systematic review and meta-analysis. PLoS One. 2014;9(10): e109834. doi: 10.1371/journal.pone.0109834

[33] Srivathsan M, Vardhan V, Naseem A, Patil S, Rai V, Langade DG. Renal Function in Hypertensive Patients Receiving Cilnidipine and L-Type Calcium Channel Blockers: A Meta-Analysis of Randomized Controlled and Retrospective Studies. Cureus. 2022;14(8): e27847. doi: 10.7759/cureus.27847

[34] Thamcharoen N, Susantitaphong P, Wongrakpanich S, et al. Effect of N- and T-type calcium channel blocker on proteinuria, blood pressure and kidney function in hypertensive patients: a meta-analysis. Hypertens Res. 2015 Dec;38(12):847-55. doi: 10.1038/hr.2015.69

[35] Hayashi K, Homma K, Wakino S, et al. T-type Ca channel blockade as a determinant of kidney protection. Keio J Med. 2010;59(3):84-95. doi:10.2302/kjm.59.84

[36] Suzuki Y, Kaneko H, Okada A, et al. Risk for Proteinuria in Newly Defined Hypertensive People Based on the 2017 American College of Cardiology/American Heart Association Blood Pressure Guideline. Am J Cardiol. 2022 Apr 1; 168:83-89. doi: 10.1016/j.amjcard.2021.12.023.

[37] Hayashi K, Saruta T, Goto Y, Ishii M; JATOS Study Group. Impact of renal function on cardiovascular events in elderly hypertensive patients treated with efonidipine. Hypertens Res. 2010;33(11):1211-20. doi: 10.1038/hr.2010.162

[38] Imagawa K, Okayama S, Takaoka M, et al. Inhibitory effect of efonidipine on aldosterone synthesis and secretion in human adrenocarcinoma (H295R) cells. J Cardiovasc Pharmacol. 2006;47(1):133-8. doi: 10.1097/01.fjc.0000197539. 12685.f5

[39] Okayama S, Imagawa K, Naya N, et al. Blocking T-type Ca2+ channels with efonidipine decreased plasma aldosterone concentration in healthy volunteers. Hypertens Res. 2006;29(7):493-7. doi: 10.1291/hypres.29.493

[40] Fujiwara K, Kanno Y, Hayashi K, Takenaka T, Saruta T. Renal protective effects of efonidipine in partially nephrectomized spontaneously hypertensive rats. Clin Exp Hypertens. 1998;20(3):295-312. doi:10.3109/10641969809052123

[41] Sugano N, Wakino S, Kanda T, et al. T-type calcium channel blockade as a therapeutic strategy against renal injury in rats with subtotal nephrectomy. Kidney Int. 2008;73(7):826-34. doi: 10.1038/sj.ki.5002793.

[42] Masumiya H, Shijuku T, Tanaka H, Shigenobu K. Inhibition of myocardial L- and T-type Ca2+ currents by efonidipine: possible mechanism for its chronotropic effect. Eur J Pharmacol. 1998;349(2-3):351-357. doi:10.1016/s0014-2999(98)00204-0

[43] Jariwala P, Jadhav K, The safety and efficacy of efonidipine, an L- and T-Type dual calcium channel blocker, on heart rate and blood pressure in Indian patients with mild-to-moderate essential hypertension, European Heart Journal, 2022;43: Supplement_1: ehab849.143. doi: 10.1093/eurheartj/ehab849.143