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Original Research Article

Comparative Efficacy of Cilnidipine Combined with Angiotensin Receptor Blocker Versus Angiotensin Receptor Blocker Monotherapy in Reducing Proteinuria in Hypertensive Patients with Chronic Kidney Disease

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Abstract

Background: Proteinuria represents a critical marker of renal dysfunction and cardiovascular risk in patients with chronic kidney disease (CKD) and hypertension. While angiotensin receptor blockers (ARBs) are established as first-line agents for proteinuria reduction, the addition of cilnidipine, an L/N-type calcium channel blocker, may provide superior renoprotective benefits through complementary mechanisms of action.

Methods: This prospective randomized controlled study enrolled 126 hypertensive patients with CKD and significant proteinuria. Participants were randomly allocated to receive either combination therapy with cilnidipine plus ARB (n=63) or ARB monotherapy (n=63). The primary endpoint was reduction in urinary protein-to-creatinine ratio (UPCR) at 12 months. Secondary endpoints included blood pressure control, estimated glomerular filtration rate (eGFR) changes, and adverse effects. Statistical analysis employed paired and unpaired t-tests with significance set at $p<0.05$.

Results: At 12 months, the combination therapy group demonstrated significantly greater reduction in UPCR compared to ARB monotherapy (mean reduction 0.89±0.34 g/g vs 0.42±0.28 g/g, $p<0.001$). Both groups achieved comparable blood pressure control (134.2±8.4/82.3±5.6 mmHg vs 135.8±9.1/83.7±6.2 mmHg, $p>0.05$). The combination group showed superior preservation of eGFR (mean change -2.3±4.1 mL/min/1.73m² vs -5.8±4.9 mL/min/1.73m², $p=0.002$). Heart rate reduction was significantly greater in the combination group ($p<0.001$). Adverse events were comparable between groups.

Conclusion: Combination therapy with cilnidipine plus ARB demonstrated superior antiproteinuric efficacy compared to ARB monotherapy in hypertensive patients with CKD, independent of blood pressure reduction. This strategy represents a promising approach for enhanced renoprotection in this high-risk population.

Keywords: Cilnidipine, Angiotensin Receptor Blocker, Proteinuria, Chronic Kidney Disease, Hypertension, Renoprotection.

Introduction

Chronic kidney disease (CKD) represents a major global health challenge, affecting approximately 10-15% of the adult population worldwide and contributing significantly to cardiovascular morbidity and mortality.[1] The bidirectional relationship between hypertension and CKD is well-established, with hypertension serving both as a leading cause and a consequence of progressive renal dysfunction. Proteinuria, defined as urinary protein excretion exceeding 300 mg per 24 hours, constitutes not only a hallmark of glomerular injury but also an independent predictor of accelerated decline in renal function and increased cardiovascular risk.[2,3] The magnitude of proteinuria exhibits a graded association with the risk of progression to end-stage renal disease and cardiovascular events, making proteinuria reduction a critical therapeutic target in the management of CKD. The renin-angiotensin-aldosterone system (RAAS) plays a central role in the pathophysiology of hypertensive nephropathy and progressive renal damage. Angiotensin II, through activation of type 1 (AT1) receptors, induces glomerular hypertension, promotes inflammatory pathways, and stimulates fibrogenic cascades within the kidney.[4] Angiotensin receptor blockers (ARBs) have emerged as cornerstone agents in the management of proteinuric kidney disease, demonstrating efficacy in reducing proteinuria and delaying progression of renal dysfunction in both diabetic and non-diabetic CKD. Multiple landmark trials have established

that ARB therapy significantly reduces proteinuria through preferential dilation of efferent arterioles, thereby decreasing intraglomerular pressure and protecting glomerular endothelium.[5,6] Meta-analytic evidence confirms that ARB treatment in patients with hypertension and CKD significantly lowers proteinuria with mean reductions ranging from 0.60 to 0.90 g/L depending on treatment duration.[7]

Despite the proven benefits of RAAS blockade, a substantial proportion of patients continue to demonstrate residual proteinuria and progressive renal function decline despite optimal ARB therapy, highlighting the need for adjunctive therapeutic strategies. Calcium channel blockers (CCBs) are frequently combined with RAAS inhibitors for blood pressure control; however, traditional dihydropyridine CCBs that selectively block L-type calcium channels have shown variable effects on proteinuria, with some studies suggesting potential for proteinuria increase despite effective blood pressure reduction. This paradoxical effect has been attributed to preferential dilation of afferent arterioles with resultant increase in intraglomerular pressure.

Cilnidipine represents a unique fourth-generation calcium channel blocker distinguished by its dual inhibitory action on both L-type and N-type calcium channels. Unlike conventional L-type selective CCBs, cilnidipine blocks N-type calcium channels located on sympathetic nerve terminals, thereby attenuating norepinephrine release and reducing sympathetic hyperactivity.[8] This distinctive pharmacological profile translates into several potential advantages including reduced reflex tachycardia, balanced vasodilation of both afferent and efferent arterioles, and preservation of renal autoregulation. Multiple experimental and clinical studies have demonstrated that cilnidipine exerts superior antiproteinuric effects compared to conventional L-type CCBs such as amlodipine, even when blood pressure reduction is comparable between agents.[9,10] The renoprotective mechanisms of cilnidipine extend beyond hemodynamic effects and include suppression of sympathetic nerve activity, reduction in oxidative stress, inhibition of the intrarenal RAAS, and preservation of podocyte integrity. In the landmark CARTER (Cilnidipine versus Amlodipine Randomised Trial for Evaluation in Renal Disease) study, cilnidipine demonstrated superior efficacy in preventing proteinuria progression compared to amlodipine when added to renin-angiotensin system inhibitor therapy in hypertensive patients with chronic renal disease.[9] The superior antiproteinuric effect of cilnidipine persisted even in subgroups achieving target blood pressure, suggesting blood pressure-independent renoprotective mechanisms.

Given the complementary mechanisms of action between ARBs and cilnidipine in modulating glomerular hemodynamics and the documented superiority of cilnidipine over conventional CCBs in reducing proteinuria, we hypothesized that combination therapy with cilnidipine plus ARB would provide enhanced renoprotection compared to ARB monotherapy. This study aimed to compare the efficacy of cilnidipine combined with ARB versus ARB alone in reducing proteinuria in hypertensive patients with CKD, while simultaneously evaluating effects on blood pressure control, renal function preservation, and safety parameters.

Aims and Objectives: The primary objective of this study was to evaluate and compare the antiproteinuric efficacy of combination therapy with cilnidipine plus angiotensin receptor blocker versus angiotensin receptor blocker monotherapy in hypertensive patients with chronic kidney disease over a 12-month follow-up period.

The secondary objectives included assessment of blood pressure control achieved by both treatment regimens, evaluation of changes in estimated glomerular filtration rate as a marker of renal function preservation, comparison of heart rate changes between the two groups as an indicator of sympathetic nerve activity modulation, and comprehensive documentation of adverse effects and safety parameters in both treatment arms. Additionally, the study aimed to determine whether the antiproteinuric benefits of combination therapy were independent of blood pressure reduction and to identify potential predictors of therapeutic response in this patient population.

Materials and Methods

Study Design and Setting: This prospective, randomized, open-label, parallel-group study was conducted at the Department of Nephrology between January 2022 and December 2023. The study protocol received approval from the Institutional Ethics Committee, and all participants provided written informed consent prior to enrollment. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

Sample Size Calculation: Sample size calculation was based on previous studies demonstrating mean proteinuria reduction differences between combination therapy and monotherapy. Assuming a mean difference of 0.45 g/g in urinary protein-to-creatinine ratio reduction with a standard deviation of 0.85, power of 80%, alpha error of 0.05, and accounting for 10% dropout rate, a total sample size of 126 participants (63 per group) was determined to be adequate for detecting clinically significant differences.

Inclusion Criteria: Patients were eligible for inclusion if they met the following criteria: age between 30 and 70 years, documented diagnosis of essential hypertension with blood pressure between 140-180/90-110 mmHg on current antihypertensive therapy or requiring initiation of treatment, presence of chronic kidney disease stages 2-3 defined as estimated glomerular filtration rate between 30-89 mL/min/1.73m², persistent proteinuria with urinary protein-to-creatinine ratio exceeding 0.5 g/g on two consecutive measurements at least one week apart, stable renal function with less than 20% variation in serum creatinine over the preceding three months, and willingness to comply with study protocol and attend regular follow-up visits.

Exclusion Criteria: Patients were excluded from the study if they had known hypersensitivity or contraindications to cilnidipine or angiotensin receptor blockers, secondary causes of hypertension including renovascular disease or primary aldosteronism, advanced chronic kidney disease with estimated glomerular filtration rate below 30 mL/min/1.73m² or stage 5 disease requiring renal replacement therapy, diabetes mellitus with poor glycemic control defined as glycated hemoglobin exceeding 9%, acute kidney injury within the preceding three months, active urinary tract infection or glomerulonephritis requiring immunosuppressive therapy, pregnancy or lactation in female participants, severe cardiovascular disease including recent myocardial infarction within six months or unstable angina, heart failure with reduced ejection fraction below 40%, severe hepatic impairment with transaminases exceeding three times upper limit of normal, hyperkalemia with serum potassium exceeding 5.5 mEq/L, or any condition that in the investigator's judgment would preclude safe participation in the study.

Randomization and Treatment Allocation: Following baseline evaluation and confirmation of eligibility, participants were randomized in a 1:1 ratio to either the combination therapy group or the ARB monotherapy group using computer-generated random numbers with sealed envelope technique. The combination therapy group received cilnidipine 10 mg once daily plus telmisartan 40 mg once daily, while the ARB monotherapy group received telmisartan 40 mg once daily. Dosage adjustments were permitted based on blood pressure response and tolerability. Cilnidipine could be titrated to 20 mg once daily and telmisartan to 80 mg once daily if target blood pressure was not achieved after four weeks. Additional antihypertensive medications excluding other calcium channel blockers or renin-angiotensin system inhibitors were permitted if blood pressure remained uncontrolled despite maximum study drug doses.

Follow-up Protocol: Participants were evaluated at baseline, and subsequently at 1, 3, 6, 9, and 12 months. At each visit, clinical assessment included measurement of blood pressure using standardized mercury sphygmomanometer after five minutes of rest in sitting position with average of three readings recorded, heart rate assessment, body weight and height measurements for body mass index calculation, and inquiry regarding adverse events and medication compliance. Laboratory investigations performed at baseline and at 3, 6, 9, and 12 months included spot urine protein-to-creatinine ratio as the primary outcome measure, serum creatinine with estimation of glomerular filtration rate using the Chronic Kidney Disease Epidemiology Collaboration equation, complete blood count, serum electrolytes including sodium and potassium, liver function tests, fasting blood glucose, and lipid profile. Additional investigations including renal ultrasonography were performed at baseline for characterization of renal disease.

Outcome Measures: The primary outcome measure was the change in urinary protein-to-creatinine ratio from baseline to 12 months, expressed as grams of protein per gram of creatinine. Secondary outcome measures included the proportion of patients achieving proteinuria reduction exceeding 30% from baseline, changes in estimated glomerular filtration rate from baseline, changes in systolic and diastolic blood pressure, achievement of target blood pressure defined as less than 140/90 mmHg, changes in heart rate from baseline, and incidence of adverse events including hyperkalemia, acute kidney injury, hypotension, peripheral edema, and other drug-related adverse effects.

Statistical Analysis: Statistical analysis was performed using SPSS version 25.0 software. Continuous variables were expressed as mean ± standard deviation and categorical variables as frequencies and percentages. Normality of distribution was assessed using Kolmogorov-Smirnov test.

Baseline characteristics between groups were compared using independent t-test for continuous variables and chi-square test for categorical variables. Within-group changes from baseline were analyzed using paired t-test, while between-group comparisons were performed using independent t-test. Analysis of covariance was employed to adjust for baseline differences where applicable. Time-course changes were analyzed using repeated measures analysis of variance. Correlation analysis was performed using Pearson correlation coefficient. A two-tailed p-value less than 0.05 was considered statistically significant.

Intention-to-treat analysis was performed for all randomized participants, with last observation carried forward method for handling missing data.

Results

A total of 126 patients were randomized into the study, with 63 patients allocated to each treatment group. The combination therapy group and ARB monotherapy group demonstrated comparable baseline characteristics with no statistically significant differences in age, gender distribution, body mass index, duration of hypertension, or renal function parameters. The mean age was 54.3±9.2 years in the combination group versus 55.1±8.8 years in the monotherapy group (p=0.612). Male patients constituted 60.3% and 57.1% of the combination and monotherapy groups respectively (p=0.714). Baseline systolic blood pressure was 158.6±12.4 mmHg in the combination group compared to 156.9±13.1 mmHg in the monotherapy group (p=0.461), while diastolic blood pressure measured 96.4±8.7 mmHg versus 95.8±9.2 mmHg (p=0.715). Baseline urinary protein-to-creatinine ratio was comparable between groups at 1.84±0.62 g/g in the combination group and 1.79±0.58 g/g in the monotherapy group (p=0.652). Estimated glomerular filtration rate at baseline was 52.3±14.6 mL/min/1.73m² in the combination group and 53.7±15.2 mL/min/1.73m² in the monotherapy group (p=0.608). At 12 months follow-up, both treatment groups demonstrated significant reduction in urinary protein-to-creatinine ratio from baseline values. The combination therapy group showed a mean reduction of 0.89±0.34 g/g (reduction of 48.4% from baseline, p<0.001), while the ARB monotherapy group demonstrated a mean reduction of 0.42±0.28 g/g (reduction of 23.5% from baseline, p<0.001). The between-group difference in proteinuria reduction was highly significant, with the combination therapy group achieving significantly greater reduction compared to monotherapy (mean difference 0.47±0.31 g/g, p<0.001). At 12 months, the proportion of patients achieving more than 30% reduction in proteinuria was significantly higher in the combination group compared to the monotherapy group (79.4% versus 52.4%, chi-square=9.82, p=0.002). Blood pressure control was achieved in both treatment groups with no significant between-group differences. At 12 months, mean systolic blood pressure was 134.2±8.4 mmHg in the combination group versus 135.8±9.1 mmHg in the monotherapy group (p=0.316), representing mean reductions of 24.4±10.2 mmHg and 21.1±11.4 mmHg from baseline respectively. Mean diastolic blood pressure at 12 months was 82.3±5.6 mmHg in the combination group compared to 83.7±6.2 mmHg in the monotherapy group (p=0.197), with mean reductions of 14.1±7.3 mmHg and 12.1±8.1 mmHg from baseline. The proportion of patients achieving target blood pressure less than 140/90 mmHg was 74.6% in the combination group and 69.8% in the monotherapy group (p=0.549), indicating comparable antihypertensive efficacy.

Estimated glomerular filtration rate changes demonstrated superior renal function preservation in the combination therapy group. At 12 months, the mean change in estimated glomerular filtration rate was -2.3±4.1 mL/min/1.73m² in the combination group compared to -5.8±4.9 mL/min/1.73m² in the monotherapy group (p=0.002). The rate of estimated glomerular filtration rate decline was significantly slower in patients receiving combination therapy, suggesting enhanced renoprotective effects independent of blood pressure reduction. Subgroup analysis of patients achieving target blood pressure in both groups confirmed that the superior antiproteinuric effect of combination therapy persisted even with comparable blood pressure control (p<0.01). Heart rate assessment revealed significant differences between treatment groups. Baseline heart rate was comparable between groups at 78.4±9.6 beats per minute in the combination group and 79.2±8.8 beats per minute in the monotherapy group (p=0.632). At 12 months, the combination therapy group demonstrated significantly greater heart rate reduction with mean heart rate of 68.7±7.4 beats per minute compared to 76.8±8.2 beats per minute in the monotherapy group (p<0.001). The mean reduction in heart rate was 9.7±6.3 beats per minute in the combination group versus 2.4±5.1 beats per minute in the monotherapy group (p<0.001), reflecting the sympatholytic effects of cilnidipine through N-type calcium channel blockade.

Adverse events were comparable between treatment groups with no significant differences in overall incidence. Hyperkalemia defined as serum potassium exceeding 5.5 mEq/L occurred in 7.9% of the combination group and 6.3% of the monotherapy group (p=0.729). Episodes of symptomatic hypotension were reported in 4.8% of combination therapy patients and 3.2% of monotherapy patients (p=0.653). Peripheral edema occurred in 12.7% of the combination group compared to 4.8% of the monotherapy group (p=0.117), though most cases were mild and did not require treatment discontinuation. No cases of acute kidney injury requiring hospitalization or dialysis were observed in either group. Treatment discontinuation due to adverse events occurred in 3 patients (4.8%) in the combination group and 2 patients (3.2%) in the monotherapy group (p=0.648).

Table 1: Baseline Characteristics of Study Population

Parameter	Combination Therapy (n=63)	ARB Monotherapy (n=63)	p-value
Age (years)	54.3 ± 9.2	55.1 ± 8.8	0.612
Male gender, n (%)	38 (60.3%)	36 (57.1%)	0.714
Body Mass Index (kg/m²)	26.8 ± 3.4	27.2 ± 3.7	0.534
Duration of hypertension (years)	6.8 ± 3.2	7.1 ± 3.5	0.628
Systolic BP (mmHg)	158.6 ± 12.4	156.9 ± 13.1	0.461
Diastolic BP (mmHg)	96.4 ± 8.7	95.8 ± 9.2	0.715
Heart rate (bpm)	78.4 ± 9.6	79.2 ± 8.8	0.632
Serum creatinine (mg/dL)	1.68 ± 0.42	1.64 ± 0.45	0.603
eGFR (mL/min/1.73m²)	52.3 ± 14.6	53.7 ± 15.2	0.608
UPCR (g/g)	1.84 ± 0.62	1.79 ± 0.58	0.652
Serum potassium (mEq/L)	4.3 ± 0.4	4.2 ± 0.5	0.701
Hemoglobin (g/dL)	12.4 ± 1.6	12.6 ± 1.5	0.489

Data presented as mean ± SD or n (%). BP, blood pressure; bpm, beats per minute; eGFR, estimated glomerular filtration rate; UPCR, urinary protein-to-creatinine ratio.

Table 2: Changes in Urinary Protein-to-Creatinine Ratio at Different Time Points

Time Point	Combination Therapy (n=63)	ARB Monotherapy (n=63)	Between-Group Difference	p-value
Baseline	1.84 ± 0.62	1.79 ± 0.58	0.05 ± 0.60	0.652
3 months	1.42 ± 0.51*	1.61 ± 0.53*	-0.19 ± 0.52	0.043
6 months	1.18 ± 0.46*	1.52 ± 0.49*	-0.34 ± 0.48	<0.001
9 months	1.02 ± 0.41*	1.44 ± 0.47*	-0.42 ± 0.44	<0.001
12 months	0.95 ± 0.38*	1.37 ± 0.45*	-0.42 ± 0.42	<0.001
Reduction from baseline	0.89 ± 0.34	0.42 ± 0.28	0.47 ± 0.31	<0.001
% Reduction	48.4 ± 15.2%	23.5 ± 12.8%	24.9 ± 14.3%	<0.001

Data presented as mean ± SD in g/g. *p<0.001 compared to baseline within group (paired t-test).

Table 3: Blood Pressure and Heart Rate Changes at 12 Months

Parameter	Combination Therapy (n=63)	ARB Monotherapy (n=63)	p-value
Systolic BP (mmHg)			
Baseline	158.6 ± 12.4	156.9 ± 13.1	0.461
12 months	134.2 ± 8.4*	135.8 ± 9.1*	0.316
Change	-24.4 ± 10.2	-21.1 ± 11.4	0.097
Diastolic BP (mmHg)			
Baseline	96.4 ± 8.7	95.8 ± 9.2	0.715
12 months	82.3 ± 5.6*	83.7 ± 6.2*	0.197
Change	-14.1 ± 7.3	-12.1 ± 8.1	0.164
Heart Rate (bpm)			
Baseline	78.4 ± 9.6	79.2 ± 8.8	0.632
12 months	68.7 ± 7.4*	76.8 ± 8.2*	<0.001
Change	-9.7 ± 6.3	-2.4 ± 5.1	<0.001
BP Control <140/90 mmHg, n (%)	47 (74.6%)	44 (69.8%)	0.549

Data presented as mean ± SD. *p<0.001 compared to baseline (paired t-test). BP, blood pressure; bpm, beats per minute.

Table 4: Renal Function Parameters and eGFR Changes

Parameter	Combination Therapy (n=63)	ARB Monotherapy (n=63)	p-value
Serum Creatinine (mg/dL)			
Baseline	1.68 ± 0.42	1.64 ± 0.45	0.603
3 months	1.72 ± 0.44	1.69 ± 0.48	0.711
6 months	1.74 ± 0.46	1.76 ± 0.51	0.824
12 months	1.77 ± 0.48*	1.86 ± 0.54*	0.334
eGFR (mL/min/1.73m²)			
Baseline	52.3 ± 14.6	53.7 ± 15.2	0.608
3 months	51.2 ± 14.2	52.4 ± 14.8	0.654
6 months	50.6 ± 13.9	50.8 ± 14.6	0.937
12 months	50.0 ± 14.1*	47.9 ± 14.5*	0.432
Change at 12 months	-2.3 ± 4.1	-5.8 ± 4.9	0.002
Annual eGFR decline rate (mL/min/1.73m²/year)	2.3 ± 4.1	5.8 ± 4.9	0.002

Data presented as mean ± SD. *p<0.05 compared to baseline (paired t-test). eGFR, estimated glomerular filtration rate.

Table 5: Laboratory Parameters at Baseline and 12 Months

Parameter	Combination Therapy (n=63)	ARB Monotherapy (n=63)	p-value
Serum Potassium (mEq/L)			
Baseline	4.3 ± 0.4	4.2 ± 0.5	0.701
12 months	4.6 ± 0.5*	4.5 ± 0.6*	0.589
Serum Sodium (mEq/L)			
Baseline	139.6 ± 3.2	140.1 ± 3.4	0.408
12 months	139.2 ± 3.1	139.8 ± 3.3	0.310
Hemoglobin (g/dL)			
Baseline	12.4 ± 1.6	12.6 ± 1.5	0.489
12 months	12.2 ± 1.5	12.3 ± 1.6	0.732
Fasting Glucose (mg/dL)			
Baseline	98.6 ± 12.4	96.8 ± 13.2	0.437
12 months	97.2 ± 11.8	95.6 ± 12.6	0.482
Total Cholesterol (mg/dL)			
Baseline	186.4 ± 34.6	189.2 ± 36.8	0.667
12 months	182.6 ± 32.4	185.4 ± 35.2	0.654

Data presented as mean ± SD. *p<0.05 compared to baseline (paired t-test).

Table 6: Adverse Events and Safety Parameters

Adverse Event	Combination Therapy (n=63)	ARB Monotherapy (n=63)	p-value
Hyperkalemia (K^+>5.5 mEq/L)	5 (7.9%)	4 (6.3%)	0.729
Symptomatic Hypotension	3 (4.8%)	2 (3.2%)	0.653
Peripheral Edema	8 (12.7%)	3 (4.8%)	0.117
Headache	4 (6.3%)	3 (4.8%)	0.698
Dizziness	5 (7.9%)	4 (6.3%)	0.729
Cough	2 (3.2%)	1 (1.6%)	0.559
Fatigue	3 (4.8%)	2 (3.2%)	0.653
Acute Kidney Injury	0 (0%)	0 (0%)	-
Treatment Discontinuation	3 (4.8%)	2 (3.2%)	0.648
Total Adverse Events	33 (52.4%)	22 (34.9%)	0.054
Serious Adverse Events	0 (0%)	0 (0%)	-

Data presented as n (%).

Discussion

The present study demonstrated that combination therapy with cilnidipine plus angiotensin receptor blocker resulted in significantly greater reduction in proteinuria compared to ARB monotherapy in hypertensive patients with chronic kidney disease

over 12 months of follow-up. The superior antiproteinuric efficacy of combination therapy was independent of blood pressure reduction, as both treatment groups achieved comparable blood pressure control.

These findings support the hypothesis that cilnidipine exerts renoprotective effects through mechanisms beyond blood pressure reduction, including modulation of sympathetic nerve activity, preservation of glomerular hemodynamics, and direct anti-inflammatory and antioxidant properties. The magnitude of proteinuria reduction observed in this study is clinically significant and consistent with previous research demonstrating superior antiproteinuric effects of cilnidipine compared to conventional calcium channel blockers when combined with renin-angiotensin system inhibition. Our results align closely with the findings of Fujita and colleagues in the CARTER study, where cilnidipine demonstrated greater antiproteinuric effect than amlodipine when added to renin-angiotensin system inhibitor treatment in hypertensive patients with chronic renal disease.[11] Similarly, Kojima and colleagues reported that cilnidipine resulted in greater suppression of proteinuria increase compared to amlodipine in proteinuric hypertensive patients with renal diseases, with effects similar to renin-angiotensin inhibitors.[12] The consistency of these findings across multiple studies strengthens the evidence for preferential use of cilnidipine over conventional L-type calcium channel blockers in patients with proteinuric kidney disease.

The superior renoprotective effects of cilnidipine can be attributed to its unique dual L/N-type calcium channel blocking properties. Unlike conventional dihydropyridine calcium channel blockers that selectively dilate afferent arterioles leading to increased intraglomerular pressure and potentially increased proteinuria, cilnidipine achieves balanced vasodilation of both afferent and efferent arterioles through N-type calcium channel blockade on sympathetic nerve terminals.[13] This balanced vasodilation maintains favorable glomerular hemodynamics while reducing systemic blood pressure, thereby preventing the proteinuria-enhancing effects observed with some conventional calcium channel blockers. The N-type calcium channel blocking activity of cilnidipine also suppresses sympathetic hyperactivity, which plays a crucial role in progression of chronic kidney disease through activation of the renin-angiotensin-aldosterone system and promotion of renal fibrosis.[14]

In our study, the significantly greater reduction in heart rate observed in the combination therapy group compared to ARB monotherapy provides indirect evidence of sympathetic nerve suppression by cilnidipine. This heart rate reduction occurred without compromising blood pressure control and was not associated with symptomatic bradycardia requiring treatment discontinuation. Previous studies have demonstrated that elevated heart rate is independently associated with progression of chronic kidney disease and increased cardiovascular risk, suggesting that the sympatholytic effects of cilnidipine may contribute to both renoprotection and cardioprotection.[15] The absence of reflex tachycardia with cilnidipine, in contrast to conventional calcium channel blockers, represents an additional advantage particularly in hypertensive patients with chronic kidney disease who frequently have elevated sympathetic activity.

The superior preservation of estimated glomerular filtration rate in the combination therapy group represents another important finding of this study. While both groups demonstrated some decline in estimated glomerular filtration rate over 12 months, consistent with the natural history of chronic kidney disease, the rate of decline was significantly slower in patients receiving combination therapy. The annual estimated glomerular filtration rate decline rate of 2.3 mL/min/1.73m² in the combination group compared to 5.8 mL/min/1.73m² in the monotherapy group suggests enhanced renoprotection with combination therapy. This finding is particularly relevant given that reduction in proteinuria has been established as a surrogate marker for slowing chronic kidney disease progression, with greater proteinuria reduction associated with more pronounced preservation of renal function.[16] Our results corroborate the findings of Soeki and colleagues who demonstrated that cilnidipine, but not amlodipine, ameliorated urinary albumin excretion and decreased markers of oxidative stress in hypertensive patients receiving renin-angiotensin system inhibitor therapy.[17]

The blood pressure-independent renoprotective effects of cilnidipine observed in our study are consistent with experimental evidence demonstrating multiple mechanisms beyond hemodynamic effects. Toba and colleagues demonstrated in animal models that cilnidipine ameliorated proteinuria and inhibited the renal renin-angiotensin-aldosterone system in salt-sensitive hypertensive rats without affecting blood pressure, suggesting direct effects on intrarenal pathophysiological mechanisms.[18] The ability of cilnidipine to suppress oxidative stress, reduce inflammatory cytokines, and preserve podocyte integrity has been documented in multiple experimental studies and may contribute to the superior antiproteinuric effects observed clinically.[19] The complementary mechanisms of action between ARBs, which primarily target the renin-angiotensin system, and cilnidipine, which

modulates sympathetic activity and provides direct cellular protection, provide a strong rationale for combination therapy in proteinuric chronic kidney disease. Comparison with studies evaluating dual renin-angiotensin system blockade provides interesting insights. While combination therapy with angiotensin-converting enzyme inhibitors and angiotensin receptor blockers demonstrated greater proteinuria reduction than monotherapy in some studies, this approach has raised safety concerns particularly regarding hyperkalemia and acute kidney injury, with recent large trials showing no cardiovascular benefit and potential harm.[20] In contrast, our study demonstrated that combination of cilnidipine with ARB achieved substantial proteinuria reduction without increased risk of hyperkalemia or acute kidney injury. The incidence of hyperkalemia was comparable between groups and remained within acceptable limits, suggesting that this combination therapy represents a safer alternative to dual renin-angiotensin system blockade for enhanced proteinuria reduction.

The safety profile of combination therapy in our study was generally favorable with comparable overall adverse event rates between groups. The slightly higher incidence of peripheral edema in the combination therapy group, although not statistically significant, is consistent with the known side effect profile of calcium channel blockers. However, most cases of peripheral edema were mild and did not require treatment discontinuation. The absence of serious adverse events in both groups and the low treatment discontinuation rates support the safety and tolerability of combination therapy. These findings align with previous safety data on cilnidipine demonstrating improved tolerability compared to conventional calcium channel blockers, particularly with respect to pedal edema. Several limitations of this study warrant consideration. The open-label design without blinding represents a potential source of bias, although the use of objective laboratory endpoints for proteinuria and renal function measurements minimizes this concern. The relatively short follow-up duration of 12 months, while adequate for evaluating antiproteinuric effects, may be insufficient for assessing hard renal outcomes such as progression to end-stage renal disease or requirement for dialysis. Longer-term studies are needed to determine whether the superior antiproteinuric effects and slower estimated glomerular filtration rate decline observed with combination therapy translate into reduced incidence of end-stage renal disease and improved patient survival. The study population consisted primarily of patients with chronic kidney disease stages 2-3, and extrapolation of results to patients with more advanced chronic kidney disease or those with specific etiologies such as diabetic nephropathy requires caution. Additionally, the study did not include detailed assessment of albuminuria subtypes or urinary biomarkers of renal injury, which might have provided mechanistic insights into the differential effects of the two treatment regimens.

Future research directions should include long-term randomized controlled trials powered to detect differences in hard renal outcomes, investigation of cilnidipine-ARB combination therapy in specific chronic kidney disease populations such as diabetic nephropathy or glomerulonephritis, evaluation of optimal dosing strategies and treatment algorithms, assessment of cost-effectiveness compared to alternative treatment strategies, and mechanistic studies examining the molecular and cellular pathways through which cilnidipine exerts renoprotective effects when combined with renin-angiotensin system blockade. Additionally, comparative studies evaluating cilnidipine combination therapy against other emerging antiproteinuric agents would be valuable for informing treatment guidelines.

Conclusion

Combination therapy with cilnidipine plus angiotensin receptor blocker demonstrated superior antiproteinuric efficacy compared to angiotensin receptor blocker monotherapy in hypertensive patients with chronic kidney disease, independent of blood pressure reduction. The combination therapy also resulted in superior preservation of estimated glomerular filtration rate and significant heart rate reduction, suggesting enhanced renoprotection through complementary mechanisms including sympathetic nerve suppression, balanced glomerular hemodynamics, and direct cellular protective effects. The safety profile of combination therapy was favorable with adverse event rates comparable to monotherapy. These findings support the use of cilnidipine in combination with angiotensin receptor blockers as an effective therapeutic strategy for patients with hypertensive chronic kidney disease and proteinuria. Given the established association between proteinuria reduction and improved renal outcomes, this combination therapy represents a promising approach for delaying progression of chronic kidney disease and reducing cardiovascular risk in this high-risk population. Further long-term studies are warranted to confirm whether the superior antiproteinuric effects translate into reduced incidence of end-stage renal disease and improved patient survival.

References

1. Agrawal V, Marinescu V, Agarwal M, McCullough PA. Cardiovascular implications of proteinuria: an indicator of chronic kidney disease. Nat Rev Cardiol. 2009;6(4):301-311.

2. Methven S, MacGregor MS, Traynor JP, O'Reilly DS, Deighan CJ. Assessing proteinuria in chronic kidney disease: protein-creatinine ratio versus albumin-creatinine ratio. Nephrol Dial Transplant. 2010;25(9):2991-2996.
3. Deckert T, Feldt-Rasmussen B, Borch-Johnsen K, Jensen T, Kofoed-Enevoldsen A. Albuminuria reflects widespread vascular damage: the Steno hypothesis. Diabetologia. 2013;56(12):2523-2533.
4. Kobori H, Nangaku M, Navar LG, Nishiyama A. The intrarenal renin-angiotensin system: from physiology to the pathobiology of hypertension and kidney disease. Pharmacol Rev. 2007;59(3):251-287.
5. Barnett AH. Preventing renal complications in diabetic patients: the Diabetics Exposed to Telmisartan and Enalapril (DETAIL) study. Acta Diabetol. 2005;42(Suppl 1):S42-S49.
6. Brenner BM, Cooper ME, de Zeeuw D, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med. 2001;345(12):861-869.
7. Haller H, Ito S, Izzo JL Jr, et al. Effect of angiotensin receptor blockers on blood pressure and renal function in patients with concomitant hypertension and chronic kidney disease: a systematic review and meta-analysis. Blood Press. 2019;28(6):358-374.
8. Chandra KS, Ramesh G. The fourth-generation calcium channel blocker: cilnidipine. Indian Heart J. 2013;65(6):691-695.
9. Fujita T, Ando K, Nishimura H, et al. Antiproteinuric effect of the calcium channel blocker cilnidipine added to renin-angiotensin inhibition in hypertensive patients with chronic renal disease. Kidney Int. 2007;72(12):1543-1549.
10. Kojima S, Shida M, Yokoyama H. Comparison between cilnidipine and amlodipine besilate with respect to proteinuria in hypertensive patients with renal diseases. Hypertens Res. 2004;27(6):379-385.
11. Fujita T, Ando K, Nishimura H, Ideura T, Yasuda G, Isshiki M, Takahashi K; CARTER Study Investigators. Antiproteinuric effect of the calcium channel blocker cilnidipine added to renin-angiotensin inhibition in hypertensive patients with chronic renal disease. Kidney Int. 2007;72(12):1543-1549.
12. Kojima S, Shida M, Yokoyama H. Comparison between cilnidipine and amlodipine besilate with respect to proteinuria in hypertensive patients with renal diseases. Hypertens Res. 2004;27(6):379-385.
13. Ando K, Konder A, Enomoto A, Matsushita J, Takahara A, Moriyama T. The N- and L-type calcium channel blocker cilnidipine suppresses renal injury in Dahl rats fed a high-sucrose diet, an experimental model of metabolic syndrome. Nephron Physiol. 2005;101(1):p1-13.
14. Konoshita T, Kato N, Fuchs S, et al. Genetic variant of the renin-angiotensin system and diabetes influences blood pressure response to angiotensin receptor blockers. Diabetes Care. 2009;32(8):1485-1490.
15. Hoshide S, Kario K, Tomitani N, et al. Different patterns of home blood pressure and pulse rate variability between diabetic and non-diabetic hypertensive patients. J Clin Hypertens (Greenwich). 2013;15(8):544-552.
16. Lea J, Greene T, Hebert L, et al. The relationship between magnitude of proteinuria reduction and risk of end-stage renal disease: results of the African American study of kidney disease and hypertension. Arch Intern Med. 2005;165(8):947-953.
17. Soeki T, Kitani M, Kusunose K, et al. Renoprotective and antioxidant effects of cilnidipine in hypertensive patients. Hypertens Res. 2012;35(11):1058-1062.
18. Toba H, Yoshida M, Tojo C, et al. L/N-type calcium channel blocker cilnidipine ameliorates proteinuria and inhibits the renal renin-angiotensin-aldosterone system in deoxycorticosterone acetate-salt hypertensive rats. Hypertens Res. 2011;34(4):521-529.
19. Fan YY, Kohno M, Nakano D, et al. Cilnidipine suppresses podocyte injury and proteinuria in metabolic syndrome rats: possible involvement of N-type calcium channel in podocyte. J Hypertens. 2010;28(5):1034-1043.
20. Fried LF, Emanuele N, Zhang JH, et al. Combined angiotensin inhibition for the treatment of diabetic nephropathy. N Engl J Med. 2013;369(20):1892-1903.