Expert Opinion on Investigational Drugs

ISSN: 1354-3784 (Print) 1744-7658 (Online) Journal homepage: https://www.tandfonline.com/loi/ieid20

Comparison between the antiproteinuric effects of the calcium channel blockers benidipine and cilnidipine in combination with angiotensin receptor blockers in hypertensive patients with chronic kidney disease

Masanori Abe, Kazuyoshi Okada, Noriaki Maruyama, Shiro Matsumoto, Takashi Maruyama, Takayuki Fujita, Koichi Matsumoto & Masayoshi Soma

To cite this article: Masanori Abe, Kazuyoshi Okada, Noriaki Maruyama, Shiro Matsumoto, Takashi Maruyama, Takayuki Fujita, Koichi Matsumoto & Masayoshi Soma (2010) Comparison between the antiproteinuric effects of the calcium channel blockers benidipine and cilnidipine in combination with angiotensin receptor blockers in hypertensive patients with chronic kidney disease, Expert Opinion on Investigational Drugs, 19:9, 1027-1037, DOI: 10.1517/13543784.2010.505918

To link to this article: https://doi.org/10.1517/13543784.2010.505918

Published online: 22 Jul 2010.

Expert Opinion

Comparison between the antiproteinuric effects of the calcium channel blockers benidipine and cilnidipine in combination with angiotensin receptor blockers in hypertensive patients with chronic kidney disease

Masanori Abe†, Kazuyoshi Okada, Noriaki Maruyama, Shiro Matsumoto, Takashi Maruyama, Takayuki Fujita, Koichi Matsumoto & Masayoshi Soma
†*Division of Nephrology, Hypertension and Endocrinology, Department of Internal Medicine, Nihon University School of Medicine, 30-1, Oyaguchi Kami-chou, Itabashi-ku, Tokyo, Japan*

Aims: Benidipine, an L-/T-type calcium channel blocker, dilates renal efferent and afferent arterioles and reduces glomerular pressure; therefore, it may exert renoprotective effects. We conducted an open-labeled randomized trial to compare the effects of benidipine with cilnidipine in hypertensive patients with chronic kidney disease (CKD).

Methods: The patients who were already being treated with angiotensin receptor blockers (ARBs) received one of the following treatment regimens: benidipine at a dose of 2 mg/day that was increased up to a dose of 8 mg/day (benidipine group; n = 118) or cilnidipine at a dose of 5 mg/day that was increased up to a dose of 20 mg/day (cilnidipine group; n = 115).

Results: After 12 months of treatment, we observed a significant and comparable reduction in the systolic and diastolic blood pressure in both groups. The urinary protein:creatinine ratio was significantly decreased in both groups after 3 months of treatment and thereafter; however, the difference between both groups was not significant after 12 months of treatment. Benidipine exerted an antiproteinuric effect to a greater extent than cilnidipine in patients with diabetes.

Conclusion: The addition of benidipine as well as cilnidipine reduces urinary protein excretion in hypertensive patients with CKD who are already being administered ARBs.

Keywords: angiotensin receptor blocker, benidipine, calcium channel blocker, chronic kidney disease, cilnidipine, hypertension, proteinuria

Expert Opin. Investig. Drugs (2010) ***19****(9):1027-1037*

1. Introduction

Proteinuria is one of the clinical parameters for diagnosing renal damage, particularly in glomerular hypertension, and it has been reported to be a risk factor and predictor of cardiovascular events [1,2]; therefore, the suppression of proteinuria is a major goal in the treatment of hypertensive patients with chronic kidney disease (CKD). The renoprotective effects of angiotensin receptor blockers (ARBs) and

informa
healthcare

10.1517/13543784.2010.505918 © 2010 Informa UK, Ltd. ISSN 1354-3784

ACE inhibitors (ACEIs) have been previously indicated [3-5]. Blockade of the renin-angiotensin system (RAS) with ACEIs or ARBs is currently the most effective pharmacological strategy for renoprotection. These agents reduce proteinuria more effectively than other antihypertensive agents [6,7]. On the basis of these results, ARBs and ACEIs are recommended as the first-choice drugs for the treatment of hypertensive patients with CKD according to the guidelines of the Japanese Society of Hypertension for the Management of Hypertension (JSH 2009), the 7th Joint National Committee Report and the European Society of Hypertension/European Society of Cardiology [8-10]. However, monotherapy is not sufficient to control blood pressure (BP), particularly in patients with CKD, highlighting the need for combination drug therapy [11,12].

Calcium channel blockers (CCBs) reduce BP and are useful antihypertensive drugs. There are several variants of calcium channels, such as L, N, T, P/Q and R [13,14]. L-type calcium channels are widely distributed in the smooth muscle cells of peripheral resistance arteries, N-type channels are located in brain cells, and T-type channels are found in the sinus node and the brain. In renal tissues, L-type calcium channels are present only in the afferent arterioles, while the N-type and T-type calcium channels are located in the efferent and afferent arterioles [15,16].

Cilnidipine, an L-/N-type dihydropyridine CCB, suppresses renal injury in hypertensive animals and humans [17-20]; however, this effect was not observed with the L-type CCBs amlodipine [4,21] and felodipine [22]. Cilnidipine exerts a greater renoprotective effect than amlodipine in rat and clinical studies [18,20,22,23]. Benidipine, a dual L-/T-type CCB, dilates efferent and afferent arterioles and reduces glomerular pressure [24]; therefore, it may also exert renoprotective effects [25]. Although the L-/N-type CCB cilnidipine demonstrated antiproteinuric effects in patients with CKD when compared to the L-type CCB amlodipine, no significant difference was observed in diabetic subjects. Conversely, although the L-/T-type CCB benidipine demonstrated an antiproteinuric effect in diabetic patients, even in those with CKD, compared to amlodipine, the number of patients studied was small [25]. These two CCBs have similar intrarenal hemodynamic effects, causing the dilation of afferent and efferent arterioles, although no prospective studies have compared their action in CKD patients with or without diabetes; therefore, we evaluated the efficacy of benidipine and cilnidipine for the prevention of renal events in hypertensive patients with CKD who were already being treated with the maximal recommended dose of ARBs.

2. Patients and methods

This study was a 12-month-long, single-center, prospective, randomized, open-labeled clinical trial. We designed this study to compare the BP-lowering and antiproteinuric effects of benidipine and cilnidipine in hypertensive patients with stage 3 – 5 CKD. These subjects were already being administered the maximal recommended dose of ARBs. We obtained written informed consent for participation in the trial from all patients, and the protocol of the trial was approved by the ethics committee of our institution. The study was conducted in accordance with the Declaration of Helsinki between June 2008 and January 2010, and the subjects were followed up for 12 months.

The enrollment criteria for the subjects were as follows: i) hypertension, that is, systolic and diastolic BP $\geq$ 130/80 mmHg, as measured in the sitting position on at least two separate visits to the clinics; ii) stage 3 – 5 CKD, as indicated by an estimated glomerular filtration rate (eGFR) of < 60 ml/min/1.73 m^2; iii) proteinuria, that is, urinary protein:creatinine (Cr) ratio $\geq$ 300 mg/g (average of two consecutive measurements taken during a 4-week period before treatment) and iv) treatment with the maximal recommended dose of an ARB (40 mg/day of olmesartan or 80 mg/day of telmisartan) for at least 8 weeks before the study.

The exclusion criteria were as follows: i) age < 20 years or older than 80 years; ii) hypertensive emergency; iii) history of severe heart failure, angina, myocardial infarction or stroke within 6 months before the start of the trial; iv) previous treatment with steroids or immunosuppressants; v) renovascular hypertension or endocrine hypertension and vi) severe diabetes mellitus that led to hospitalization because of extremely high plasma glucose or associated with complications such as diabetic ketoacidosis.

The subjects were randomly assigned to two groups before the commencement of the experiment. An independent investigator, who did not treat or know the profiles of the subjects before the commencement of trial, monitored randomization in the order of the entry of the subjects; then, the particulars of the assignments were immediately delivered to the individual investigators. Dynamic balancing randomization was carried out on the basis of the levels of serum Cr (sCr), urinary protein:Cr ratio measured at the time of registration and the presence or absence of diabetic nephropathy. Thus, we ensured that there were no significant differences between the baseline characteristics of the two groups. The patients received one of the following treatment regimens: benidipine, 2 mg/day, which was increased to a daily dose of 8 mg (benidipine group), and cilnidipine, 5 mg/day, which was increased to a daily dose of 20 mg (cilnidipine group). In addition, seven subjects from our previous study were included in the benidipine group of this study [25].

BP was measured at the out-patient clinic at fixed times after the medications were administered. BP measurement was carried out according to the JSH 2009 guidelines [8]. BP was measured at the out-patient clinic each month using a sphygmomanometer (Nippon Colin Co. Ltd, Tokyo, Japan); the measurements were performed twice with the patient in the sitting position after a 5 min rest. The patients, particularly those with dietary restrictions, were provided guidance on how to maintain their diet.

The doses of the ARBs and ACEIs were not altered during the study period. The target BP level was < 130/80 mmHg. During the first 6 months of the study, the patients were administered combination drug therapy with other conventional antihypertensive agents at baseline. However, if the combination of benidipine or cilnidipine with an RAS inhibitor failed to reduce the BP to the target level within 6 months, additional antihypertensive medications (other than RAS inhibitors or CCBs) were administered to achieve the target BP. Withdrawal of drug treatment was considered in patients who developed an allergy/intolerance to benidipine or cilnidipine during the study period, developed a hypertensive emergency, or showed any other condition or received another therapy that, in the opinion of the investigators, may have posed a risk for the patient or confounded the results of the study.

The changes in the urinary protein:Cr ratio were measured from the pretreatment period to 1, 3, 6 and 12 months of treatment. The primary end point was assessed in all subjects and subjects with diabetes. The key secondary outcomes were the initiation of renal replacement therapy (RRT), cardiovascular events and death. The parameters that were used for monitoring the effects of the drugs were evaluated once every month during the 12-month period of treatment. Laboratory values such as sCr and potassium were measured with commercially available kits using routinely used clinical chemistry procedures. To assess urinary protein excretion, we measured the urinary concentrations of protein and Cr (protein:Cr ratio). Urinary protein was measured by the pyrogallol red method. The treatment compliance and safety variables were assessed at each hospital visit.

The eGFR was calculated using the recommended modified equation for Japanese patients by the Japanese Society of Nephrology-Chronic Kidney Disease Initiatives because the eGFR obtained by this method is more accurate in Japanese CKD patients [26]. The eGFR was calculated using the following formula: eGFR (ml/min/1.73 m^2) = 194 $\times$ $sCr^{-1.094}$ $\times$ $Age^{-0.287}$ ($\times$ 0.739 in the case of women).

2.1 Statistical analysis

Data were analyzed according to the randomly assigned groups of the participants, regardless of their subsequent medication status (intention-to-treat analysis) and expressed as mean ± s.e.m. Assuming that there would be a relative intergroup difference of 15% in the change of the urinary protein:Cr ratio from baseline between groups with an s.d. of 40%, the required number of participants to have 80% power with $\alpha = 0.05$ (two-sided) would be 113/group [23,25]. Taking dropouts into consideration, the required number of participants per group was estimated to be 120. The baseline characteristics of the enrolled patients were determined to compare between the benidipine and cilnidipine groups using the unpaired *t*-test or Fisher's exact test. The mean values of the two groups were compared by performing the unpaired *t*-test. Analysis of variance with repeated measurements and subsequent multiple comparison tests were applied to determine the effect of treatment on BP, heart rate and urinary protein:Cr ratio. Statistical significance was set at $p < 0.05$.

3. Results

3.1 Study population and baseline characteristics

We enrolled 233 subjects for this study and randomly allocated them to the benidipine (n = 118) or cilnidipine (n = 115) group. The baseline characteristics and medications administered to the subjects in the two groups are shown in **Table 1**. No significant differences were observed between the two groups with regard to the baseline characteristics or the number of patients with diabetic nephropathy. Although the subjects were not obese (mean body mass index of all subjects, 23.8 ± 0.15 kg/m^2) and their baseline blood glucose and lipid levels were normal, adequate BP control had not been achieved in any of the enrolled patients. During treatment, 9 subjects from the benidipine group (adverse reaction, n = 2; initiation of RRT, n = 5; cardiovascular events, n = 1 and death, n = 1) and 9 subjects from the cilnidipine group (adverse reaction, n = 2; initiation of RRT, n = 5; cardiovascular events, n = 1 and death, n = 1) withdrew from the study. Therefore, 215 subjects completed the trial (**Figure 1**).

3.2 BP-lowering effect

Other antihypertensive agents listed in **Table 1**, such as ACEIs and α-blockers, were administered throughout the trial period. In addition, antihypertensive drugs other than ARBs and CCBs were administered to 23 patients from the benidipine group and 24 patients from the cilnidipine group during the study period (benidipine group: diuretics, n = 9; α–blocker, n = 6; β-blocker, n = 6 and central sympatholytic agent, n = 2; cilnidipine group: diuretics, n = 10; α-blocker, n = 7; β-blocker, n = 5 and central sympatholytic agent n = 2).

The final doses of benidipine and cilnidipine were 7.9 ± 0.1 and 18.5 ± 0.4 mg/day, respectively, in the two groups. **Figure 2** shows the changes in the systolic and diastolic BP. In both groups, the systolic and diastolic BP values were significantly lower than the baseline values 1 month after the initiation of the CCB therapy. The values of systolic and diastolic BP were not significantly different between the two groups during the course of the treatment. In the last month of treatment, no significant differences were observed between systolic BP (benidipine group: 130.6 ± 1.3 mmHg and cilnidipine group: 132.9 ± 1.3 mmHg, NS) and diastolic BP (benidipine group: 74.7 ± 0.9 mmHg and cilnidipine group: 74.7 ± 0.9 mmHg, NS) in the two groups. In the benidipine and cilnidipine groups, we observed 75 and 71% of patients with BP < 140/90 mmHg (NS), respectively. The BP target value (130/80 mmHg) was achieved in 55 and 58% of all subjects in the benidipine and cilnidipine groups (NS), respectively. The heart rate of the participants at the end of the study was significantly reduced in both groups compared to the baseline (benidipine group: from 73.5 ± 1.1 to 71.4 ± 1 beats/min,

Table 1. Baseline characteristics and medication.

	Benidipine group	Cilnidipine group	p Value
Number of patients (male/female)	118 (76/42)	115 (77/38)	NS
Age (years)	67.5 ± 1.1	67.3 ± 1.2	NS
Body mass index (kg/m^2)	24.4 ± 0.2	24.1 ± 0.2	NS
Diabetes (%)	52.5	51.3	NS
Hyperlipidemia (%)	29.6	28.7	NS
Smoker (%)	16.7	15.7	NS
Systolic blood pressure (mmHg)	151.9 ± 1.4	151.6 ± 1.5	NS
Diastolic blood pressure (mmHg)	86.8 ± 0.9	85.7 ± 1	NS
Pulse rate (/min)	73.2 ± 1.2	73.5 ± 1.2	NS
Serum creatinine (mg/dl)	2.48 ± 0.14	2.49 ± 0.13	NS
eGFR (ml/min/1.73 m^2)	27.9 ± 1.6	26.8 ± 1.5	NS
Urinary protein:creatinine ratio (mg/g)	3082 ± 291	3028 ± 320	NS
Sodium (mEq/l)	139.5 ± 0.26	139.2 ± 0.23	NS
Potassium (mEq/l)	4.4 ± 0.2	4.4 ± 0.1	NS
Plasma glucose (mg/dl)	119 ± 3.7	116 ± 4.4	NS
Hemoglobin A1c (%) (for diabetes)	6.33 ± 0.08 (n = 62)	6.43 ± 0.08 (n = 59)	NS
Diagnosis of CKD (%)			
Diabetic nephropathy	52.5	51.3	NS
Chronic glomerulonephritis	26.3	26.1	NS
Hypertensive nephrosclerosis	16.1	17.4	NS
Tubulointerstitial nephritis	1.7	1.7	NS
ADPKD	3.4	3.5	NS
CKD stage (%)			
Stage 3	31.5	32.4	NS
Stage 4	42.6	40.7	NS
Stage 5	25.9	26.9	NS
Antihypertensive agents (%)			
Details of ARB			
Olmesartan (40 mg/day)	42.6	44.4	NS
Telmisartan (80 mg/day)	57.4	55.6	NS
ACE inhibitor	19.4	18.9	NS
α-Blocker	17.6	16.7	NS
β-Blocker	18.5	19.4	NS
Diuretics	21.5	22.4	NS
Central sympatholytic agent	4.6	3.7	NS

ADPKD: Autosomal dominant polycystic kidney disease; ARB: Angiotensin receptor blocker; CKD: Chronic kidney disease; eGFR: Estimated glomerular filtration rate.

$p < 0.0001$ and cilnidipine group: from 73.2 ± 1.2 to 71.6 ± 1 beats/min, $p < 0.0001$), but there was no significant difference between the two groups at the end of the trial (benidipine group: 71.4 ± 1 beats/min and cilnidipine group: 71.6 ± 1 beats/min, NS).

3.3 Renoprotective effects

The sCr levels were significantly increased in both groups after 12 months of treatment (**Figure 3**); however, the difference in the increase observed between the two groups was not significant (benidipine group: 2.82 ± 0.19 mg/dl and cilnidipine group: 2.94 ± 0.17 mg/dl, NS). Furthermore, the eGFR levels were significantly reduced in both groups at the end of the study period; however, the difference in the decrease observed between both groups was not significant (benidipine group: 26.3 ± 1.7 ml/min/1.73 m^2 and cilnidipine group: 24.8 ± 1.5 ml/min/1.73 m^2, NS).

The urinary protein:Cr ratio was significantly decreased in both groups after 3 months of treatment and thereafter; however, the difference between the decrease in both groups was not significant after 12 months of treatment (benidipine group: 1744 ± 209 mg/g Cr and cilnidipine group: 2092 ± 328 mg/g Cr, NS). When the percent change from baseline was calculated, there was no significant change between the two groups (-35.2 ± 1.8% vs -30.6 ± 3.2%, NS) (**Figure 4**). However, in the patients with diabetic nephropathy, although no significant difference was observed in the urinary protein:Cr ratio, we observed a significant difference in the percent reduction in urinary protein excretion from baseline values between the two treatment groups from 6 months of treatment (**Figure 5**).

However, in those subgroups with different baselines, specifically in terms of urinary protein:Cr ratio, age, sex or BP after the 12 months of treatment, there was no significant change

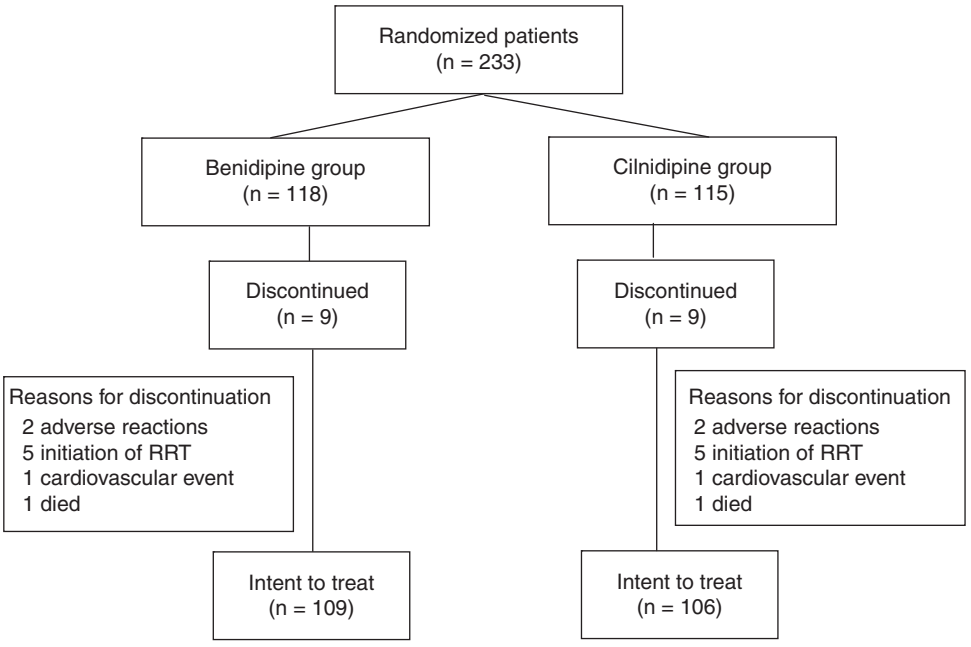

Figure 1. Patient disposition.

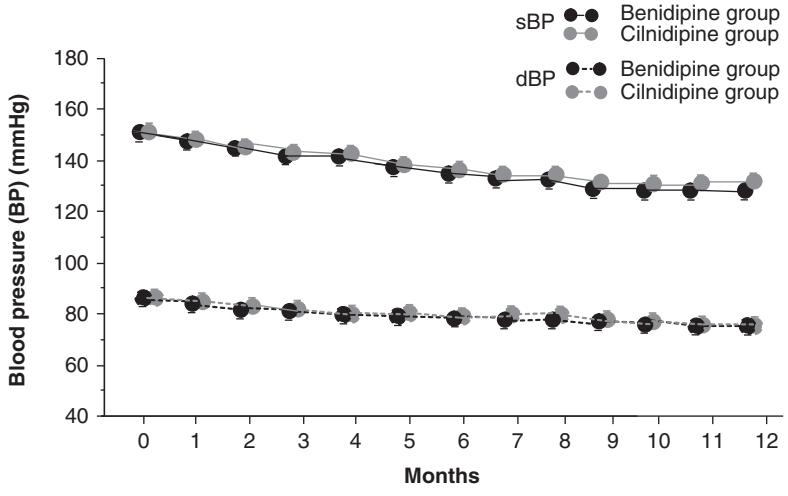

Figure 2. Changes in sBP and dBP during the study period. BP was almost the same in the benidipine (closed circles) and cilnidipine (grey circles) groups. sBP and dBP values were significantly reduced to a greater extent from 1 month and thereafter than the baseline values in the two groups.
BP: Blood pressure; dBP: Diastolic blood pressure; sBP: Systolic blood pressure.

in the percent reduction rate in urinary protein excretion from baseline values. Furthermore, in the non-diabetic subjects, there was no significant difference between the two groups. However, in the subgroup with stage 3 CKD at the baseline, benidipine caused a significant reduction in the percent change of urinary protein:Cr ratio compared to cilnidipine (**Figure 6**). Although systolic and diastolic BPs were significantly reduced by both treatments, there was no significant correlation between the degree of BP reduction and the percent change of proteinuria (data not shown).

As shown in **Table 2**, the patients with nephrotic syndrome were comparable between the two groups at baseline. Serum albumin levels were significantly increased at the end of the study compared to baseline in both groups. Furthermore, the number of patients with nephrotic syndrome was significantly decreased at the end of the study.

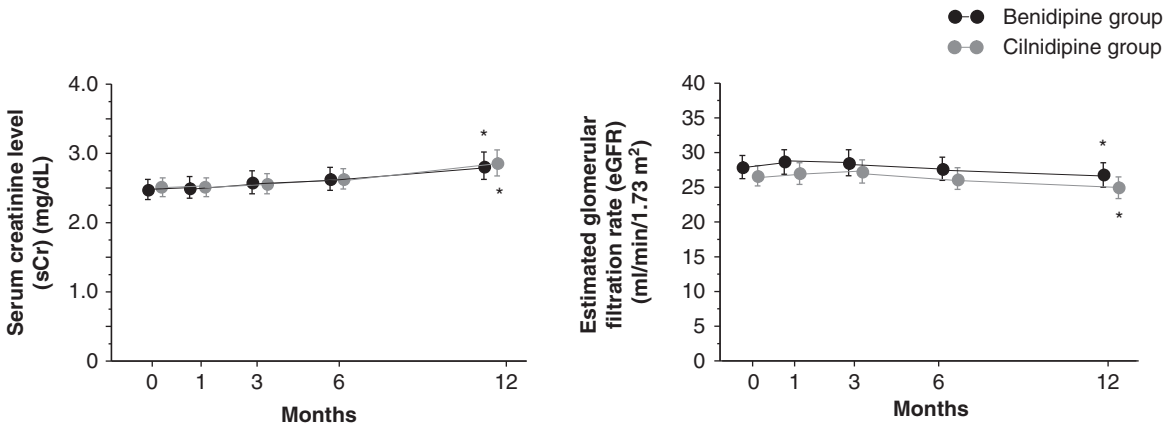

Figure 3. Changes in sCr and estimated glomerular filtration rate during the study period. The sCr level was significantly increased 12 months after treatment, and the eGFR decreased significantly 12 months after treatment in both groups compared to the baseline values.

*p < 0.05 vs baseline.

eGFR: Estimated glomerular filtration rate; sCr: Serum creatinine.

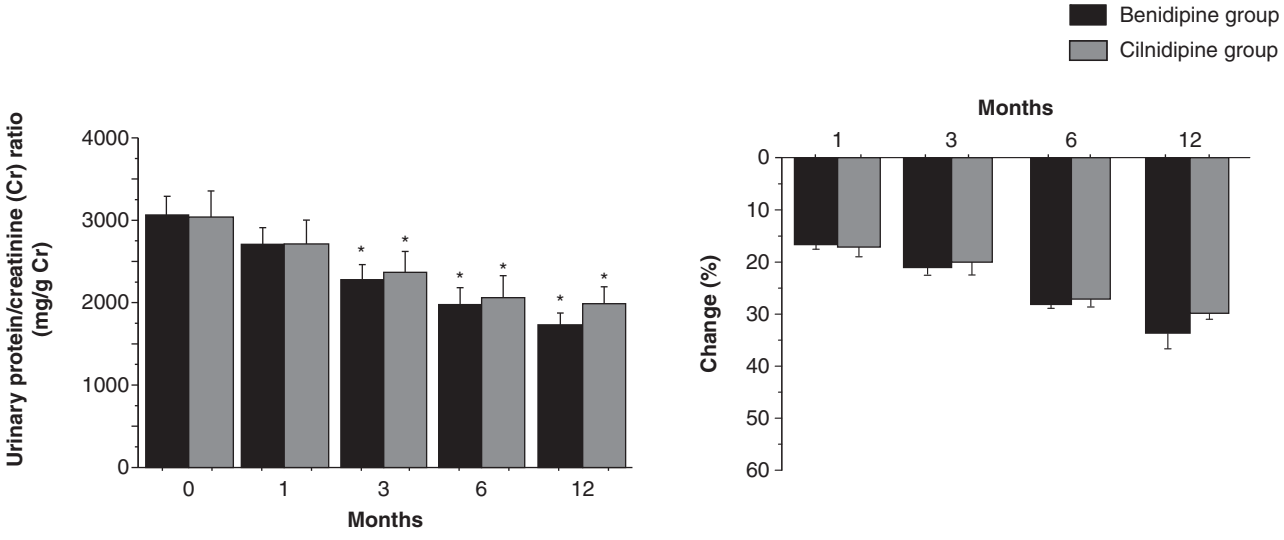

Figure 4. Changes in the urinary protein:Cr ratio and the respective percent changes from baseline. Results are expressed as the mean ± s.e.m. The urinary protein:Cr ratio was suppressed to a greater extent in both groups from 3 months than the baseline values.

*p < 0.05 vs baseline.

Cr: Creatinine.

3.4 Cardiovascular events, death and initiation of renal replacement therapy

The occurrence of cardiovascular disease was observed in one subject from each group. No cases of cardiovascular death were reported in the two groups; however, one subject died in each group (due to pneumonia in the benidipine group and lung cancer in the cilnidipine group). RRT was required in five subjects in each group for the progressive loss of renal function during the observation period. These subjects were all diagnosed as stage 5 CKD at baseline.

3.5 Adverse events

Adverse reactions were observed in two subjects from each group. These effects were considered to be associated with the study drugs. One subject reported skin reaction and another reported general fatigue in the benidipine group;

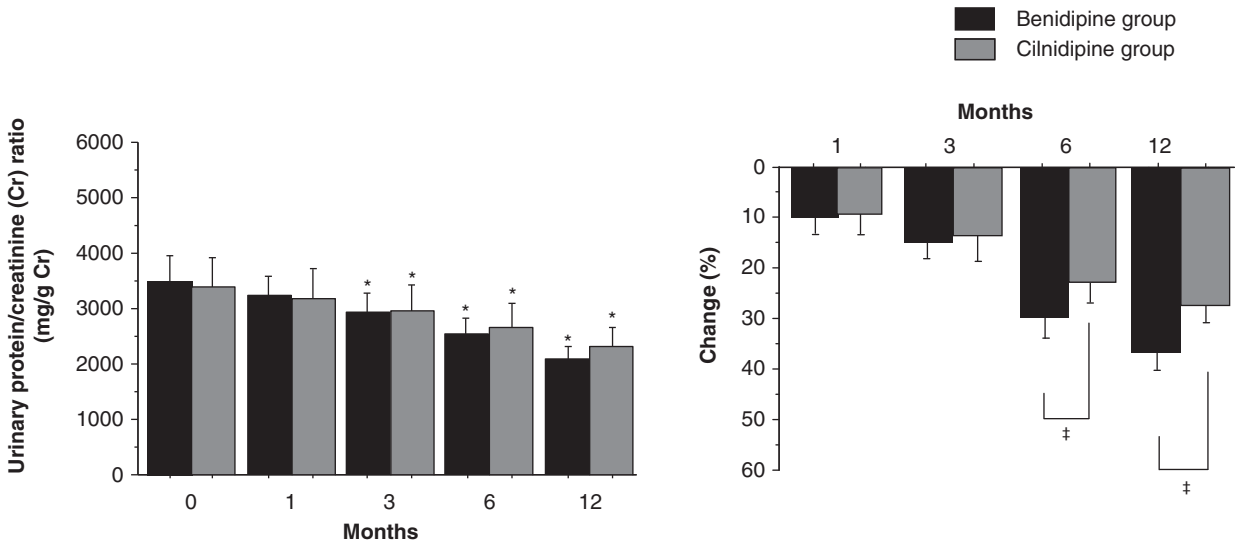

Figure 5. Changes in the urinary protein:Cr ratio and the respective percent changes from baseline in patients with diabetic nephropathy. Results are expressed as the mean ± s.e.m. The urinary protein:Cr ratio was suppressed in both groups from 3 months compared to the baseline values. There was a significant reduction in the benidipine group in the respective percent changes from baseline compared to the cilnidipine group 6 and 12 months after treatment.

*$p < 0.05$ vs baseline.

‡$p < 0.05$ vs cilnidipine group.

Cr: Creatinine.

one subject had headache and another reported general fatigue in the cilnidipine group. These adverse reactions were improved by the interruption of benidipine or cilnidipine administration. None of the subjects in either group required emergency RRT due to hyperkalemia and exhibited no severe adverse reactions.

4. Discussion

Recent large clinical trials demonstrated that the combination of RAS inhibitors and the CCB amlodipine is more effective than using diuretics to reduce cardiovascular and renal events in high risk patients. The Gauging Albuminuria Reduction with ACE inhibitor and CCB in Diabetic Patients with Hypertension (GUARD) study showed that although treatment with the ACEI benazepril and a diuretic resulted in a greater reduction in albuminuria compared to the benazepril and CCB amlodipine group, the decline in the glomerular filtration rate was slower in the benazepril plus amlodipine groups than in the benazepril plus hydrochlorothiazide groups in hypertensive type 2 diabetic patients with albuminuria [27]. Furthermore, the Avoiding Cardiovascular Events Through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial demonstrated that the combination of the ACEI benazepril and the CCB amlodipine was superior to the combination of benazepril and hydrochlorothiazide in reducing cardiovascular events in patients with hypertension who were at a high risk for such events [28]. Therefore, treatment with CCBs may be more beneficial than diuretics as an additional option to RAS inhibitors in high-risk populations, including diabetic patients with CKD.

Some CCBs not only block L-type calcium channels but also exert additional pleiotropic effects. CCBs that block either T-type or N-type calcium channels may exert renoprotective effects by dilating the efferent artery and protecting the glomerulus from hyperfiltration injury [29,30]. Benidipine, which blocks L- and T-type calcium channels, decreases the resistance of the efferent and afferent arteries and lowers the hydrostatic pressure in the glomerular capillary in rats [31]. Therefore, benidipine and cilnidipine may exert renoprotective effects in hypertensive patients with CKD.

In addition to L-type and T-type CCBs, several CCBs have been developed with L- and N-type calcium channel-blocking activity [32,33], such as cilnidipine. This class of CCBs is unique because of its pharmacological characteristics, that is, its inhibitory action on norepinephrine secretion [34] and neurally stimulated renal vasoconstriction [35]. Cilnidipine predominantly acts on the afferent arteriole in the *in vitro* isolated perfused hydronephrotic kidney [36]. In contrast, Hayashi *et al.* found that cilnidipine caused substantial vasodilation of efferent and afferent arterioles in the canine kidney *in vivo* [35]. As the sympathetic nerve is distributed along afferent and efferent arterioles, the inhibition of N-type calcium channels would dilate both arterioles. The apparent discrepancy in the *in vivo* and *in vitro* experimental results for cilnidipine suggests that the integrity of sympathetic nerves is required for the full action of N-type CCBs [35]. Our results demonstrated that benidipine

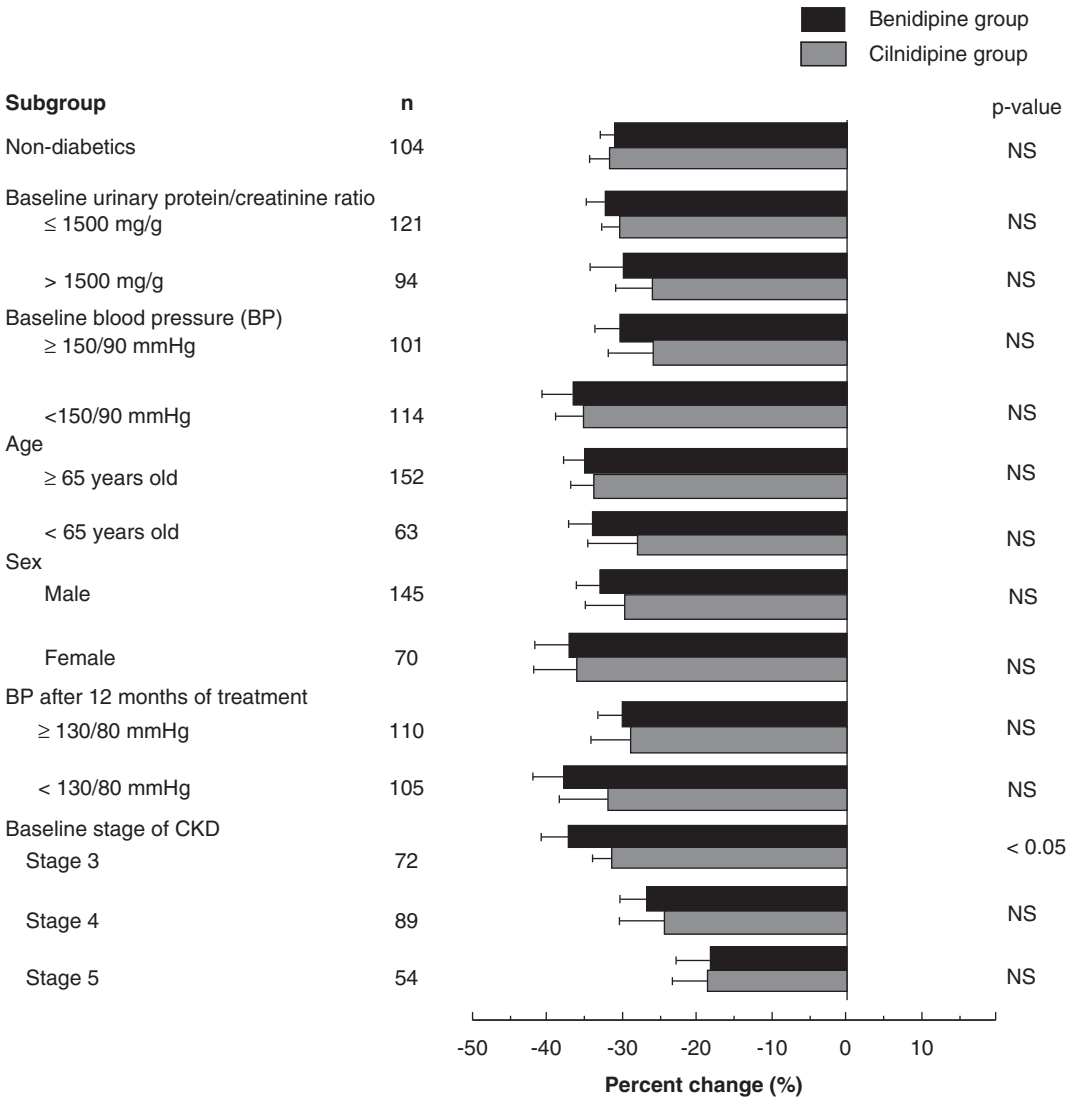

Figure 6. Changes in urinary protein:Cr ratio in subgroups according to: different baseline etiology of kidney disease, urinary protein:Cr ratio, age, sex and BP after 12 months of treatment, and stage of kidney disease. Results are expressed as the mean ± s.e.m. The antiproteinuric effect was superior in the benidipine group compared to the cilnidipine group in patients with stage 3 CKD.

BP: Blood pressure; CKD: Chronic kidney disease; Cr: Creatinine.

Table 2. Changes in serum albumin levels and the number of nephrotic syndrome cases at baseline and at the end of the study.

	Benidipine group		Cilnidipine group		p Value between the two groups
	At baseline	At end	At baseline	At end	
Serum albumin (g/dl)	3.91 ± 0.03	3.94 ± 0.02*	3.85 ± 0.04	3.89 ± 0.03*	NS
Nephrotic syndrome (n (%))	24 (20.3)	11 (12)*	25 (21.7)	12 (11.3)*	NS
Causes of nephrotic syndrome (n (%))					
Diabetic nephropathy	16 (67)	11 (85)*	17 (68)	11 (92)*	NS
Chronic glomerulonephritis	8 (33)	2 (15)*	8 (32)	1 (8)*	NS

*$p < 0.05$ vs baseline.

significantly reduced urinary protein excretion in diabetic nephropathy. It is well known that neuropathy and retinopathy are anticipated in addition to the nephropathy observed in diabetes mellitus subjects. Therefore, in those subjects with moderate to advanced diabetic nephropathy who lack sympathetic nerve integrity, it was considered that T-type CCBs, which are not dependent on sympathetic nerves, may exert their effects. The intraglomerular pressure is higher in patients with diabetic nephropathy than in patients with chronic glomerulonephritis or hypertensive nephrosclerosis, and the number of patients with diabetic nephropathy in this present study was high; hence, it was considered that benidipine might be more effective than cilnidipine in these patients. However, further studies would be needed to evaluate whether the coexistence of diabetic neuropathy reduced the effects of the N-type CCB, as the present study could not confirm this.

Our study is limited by its relatively small sample size and short period of treatment. Although the prospective, randomized, open-label, parallel-group comparison design was used in this study, additional longitudinal, double-blind, comparative multi-center clinical trials should be conducted in a larger number of patients in order to further clarify the therapeutic differences between the two agents; in addition to the BP profile, the percentage of RRT-requiring patients and other renal or cardiovascular events should also be considered as end points. Furthermore, benidipine and cilnidipine were developed in Japan and are not marketed in the US. Therefore, to evaluate their renoprotective effect, further studies would be needed in other countries. In our study, we noted that benidipine and cilnidipine significantly reduced BP and the severity of proteinuria even when administered for a short duration. However, there was no correlation between the reduction of BP and proteinuria, suggesting that T-type and N-type CCBs have potential effects beyond their BP lowering effect. Therefore, we believe that these agents may be beneficial for hypertensive patients with stage 3 – 5 CKD. In the present study, both CCBs were well tolerated and only mild adverse events were observed. In addition to the inhibition of the RAS through the maximal recommended dose of ARBs, it was considered that calcium channel blockage using T-type and N-type CCBs may protect against renal injury via mechanisms other than L-type channel blockage.

5. Conclusions

We conclude that the addition of benidipine as well as cilnidipine reduces BP and urinary protein excretion in hypertensive patients with moderate- to advanced-stage CKD who are already being administered ARBs. It was suggested that benidipine has the potential to be more effective at reducing proteinuria in the case of diabetic patients. However, further studies are needed to evaluate whether there was a difference in renal protection between the different calcium channel subtypes in diabetic nephropathy.

Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

Bibliography

1. Hcmmclgarn BR, Manns BJ, Lloyd A, et al. Relation between kidney function, proteinuria, and adverse outcomes. JAMA 2010;303:423-9
2. Marin R, Gorostidi M, Fernandez-Vega F, Alvarez-Navascues R. Systemic and glomerular hypertension and progression of chronic renal disease: the dilemma of nephrosclerosis. Kidney Int 2005;99:S52-6
3. Viberti G, Wheeldon MN.; for the MicroAlbuminuria Reduction with VALsartan (MARVAL) Study Investigators. Microalbuminuria reduction with valsartan in patients with type 2 diabetes mellitus: a blood pressure-independent effect. Circulation 2002;106:672-8
4. Lewis JE, Hunsicker GL, Clarke RW, et al. Renoprotective effect of angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. N Engl J Med 2001;345:851-60
5. Jafar TH, Stark PC, Schmid CH, et al. Progression of chronic kidney disease: the role of blood pressure control, proteinuria, and angiotensin-converting enzyme inhibition, a patient-level meta-analysis. Ann Intern Med 2003;139:244-52
6. Weidmann P, Boehlen LM, Courten M. Effects of different antihypertensive drugs on human proteinuria. Nephrol Dial Transplant 1993;8:582-4
7. Lavermann GD, Henning RH, De Jong PE, et al. Optimal antiproteinuric dose of losartan in nondiabetic patients with nephrotic range proteinuria. Am J Kidney Dis 2001;38:1381-4
8. Japanese Society of Hypertension. Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2009). Hypertension Res 2009;32:4-107
9. Chobanian AV, Bakris GL, Black HR, et al. Seventh Report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure. The JNC Report. JAMA 2003;289:2560-72
10. Mancia G, Backer GD, Dominiczak A, et al. 2007 Guidelines for the management of arterial hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). J Hypertens 2007;25:1105-87
11. Sheinfield GR, Bakris GL. Benefits of combination angiotensin-converting enzyme inhibitor and calcium antagonist therapy for diabetic patients. Am J Hypertens 1999;12:80-5
12. Waeber B. Managing hypertension in high-risk patients: lessons and promises from the STRATHE and ADVANCE trials. J Hypertens 2006;24:19-27
13. Ertel EA, Campbell KP, Harpold MM, et al. Nomenclature of voltage-gated calcium channels. Neuron 2000;25:533-5
14. Catterall WA. Structure and regulation of voltage-gated Ca2+ channels. Annu Rev Cell Dev Biol 2000;16:521-55
15. Hayashi K, Wakino S, Homma K, et al. Pathophysiological significance of T-type Ca2+ channels: role of T-type Ca2+ channels in renal microcirculation. J Pharmacol Sci 2005;99:221-7
16. Ohishi M, Takagi T, Ito N, et al. Renal-protective effect of T- and L-type calcium channel blockers in hypertensive patients: an amlodipine-to-benidipine changeover (ABC) study. Hypertens Res 2007;30:797-806
17. Zhou X, Ono H, Ono Y, et al. N- and L-type calcium channel antagonist improves glomerular dynamics, reverses severe nephrosclerosis, and inhibits apotosis and proliferation in an I-NAME/SHR model. J Hypertens 2002;20:993-1000
18. Konda T, Enomoto A, Matsushita J, et al. The N- and L-type calcium channel blocker cilnidipine suppresses renal injury in Dahl rats fed a highsucrose diet, an experimental model of metabolic syndrome. Nephron Physiol 2005;101:1-13
19. Rose GW, Kanno Y, Ikebukuro H, et al. Cilnidipine is as effective as benazepril for control of blood pressure and proteinuria in hypertensive patients with benign nephrosclerosis. Hypertens Res 2001;24:377-83
20. Kojima S, Shida M, Yokoyama H. Comparison between cilnidipine and amlodipine besilate with respect to proteinuria in hypertensive patients with renal disease. Hypertens Res 2004;27:379-85
21. Wright JT Jr, Bakris G, Greene T, et al. African American study of kidney disease and hypertension study group: effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease: results from the AASK trial. JAMA 2002;288:2421-31
22. Roggenenti P, Perna A, Loriga G, et al. REIN-2 study group: blood-pressure control for renoprotection in patients with non-diabetic chronic renal disease (REIN-2): multicentre, randomized controlled trial. Lancet 2005;365:939-46
23. 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;72:1543-9
24. Morikawa T, Okumura M, Konishi Y, et al. Effects of benidipine on glomerular hemodyanamics and proteinuria in patients with nondiabetic nephropathy. Hypertens Res 2002;25:571-6
25. Abe M, Okada K, Maruyama T, et al. Comparison of the antiproteinuric effects of the calcium channel blockers benidipine and amlodipine administered in combination with angiotensin receptor blockers to hypertensive patients with stage 3-5 chronic kidney disease. Hypertens Res 2009;32:270-5
26. Matsuo S, Imai E, Horio M, et al. Revised equations for estimated GFR from serum creatinine in Japan. Am J Kidney Dis 2009;53:982-92
27. Bakris GL, Toto RD, McCullough PA, et al. Effects of different ACE inhibitor combinations on albuminuria: results of the GUARD study. Kidney Int 2008;73:1303-9
28. Bakris GL, Sarafidis PA, Weir MR, et al. Renal outcomes with different fixed-dose combination therapies in patients with hypertension at high risk for cardiovascular events (ACCOMPLISH): a prespecified secondary analysis of a randomized controlled trial. Lancet 2010;375:1173-81

29. Ishimitsu T, Kameda T, Akashiba A, et al. Efonidipine reduces proteinuria and plasma aldosterone in patients with chronic glomerulonephritis. Hypertens Res 2007;30:621-6

30. Yue W, Kimura S, Fujisawa Y, et al. Benidipine dilates both pre- and post-glomerular arteriole in the canine kidney. Hypertens Res 2001;24:429-36

31. Kawata T, Hashimoto S, Koike T. Diversity in the renal hemodynamic effects of dihydropyridine calcium blockers in spontaneously hypertensive rats. J Cardiovasc Pharmacol 1997;30:431-6

32. Uneyama H, Uchida H, Konda T, et al. Selectivity of dihydropyridines for cardiac L-type and sympathetic N-type Ca2+ channels. Eur J Pharmacol 1999;373:93-100

33. Murakami M, Mori T, Nakagawasai O, et al. Inhibitory effect of pranidipine on N-type voltage-dependent Ca channels in mice. Neurosci Lett 2004;367:118-22

34. Nap A, Mathy MJ, Balt JC, et al. The evaluation of the N-type channel blocking properties of cilnidipine and other voltage-dependent calcium antagonists. Fund Clin Pharmacol 2004;18:309-19

35. Hayashi K, Wakino S, Sugano N, et al. Ca2+ channel subtypes and pharmacology in the kidney. Circ Res 2007;100:342-53

36. Nagahama T, Hayashi K, Fujiwara K, et al. Characterization of the renal action of pranidipine in the rat. Arzneimittel Forschung 2000;50:248-53

Affiliation

Masanori Abe[†1] MD, Kazuyoshi Okada[1], Noriaki Maruyama[1,2], Shiro Matsumoto[1], Takashi Maruyama[1], Takayuki Fujita[1], Koichi Matsumoto[1] & Masayoshi Soma[1,3]
[†]Author for correspondence
[1]Division of Nephrology, Hypertension and Endocrinology, Department of Internal Medicine, Nihon University School of Medicine, 30-1, Oyaguchi Kami-chou, Itabashi-ku, Tokyo, 173-8610, Japan
Tel: +81 3 3972 8111; Fax: +81 3 3972 1098; E-mail: mabe@med.nihon-u.ac.jp
[2]Department of Internal Medicine, Nihon University Nerima Hikarigaoka Hospital, Tokyo, Japan
[3]Division of General Medicine, Department of Internal Medicine, Nihon University School of Medicine, Tokyo, Japan