Original Article

Renoprotective Effect and Cost-Effectiveness of Using Benidipine, a Calcium Channel Blocker, to Lower the Dose of Angiotensin Receptor Blocker in Hypertensive Patients with Albuminuria

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In hypertensive patients with chronic renal disease, angiotensin receptor blockers (ARBs) are among the first-line drugs, and calcium channel blockers (CCBs) are recommended as a second line. We examined the effects of two therapeutic strategies using ARBs and benidipine, a CCB, on blood pressure (BP), urinary albumin excretion (UAE), and cost-effectiveness in hypertensive patients with albuminuria. Patients whose BP was 140/90 mmHg or higher despite treatment with low- or medium-dose ARBs were assigned randomly to two groups. In Group A ($n=14$), the ARB dose was maximized and then benidipine was added until BP targets were reached ($<130/85$ mmHg). In Group B ($n=18$), benidipine was administered first and then the ARB dose was increased until BP targets were reached. The BP targets were achieved by ARB alone in 36% of Group A patients and by the addition of benidipine in 83% of Group B patients. Finally, BP decreased in each group, reaching the targets in 93% of Group A patients and 94% of Group B patients after a 4-month therapeutic period. UAE was decreased in both groups after a 4-month therapeutic period compared to the allocation period ($-33\pm6\%$ in Group A, $-31\pm6\%$ in Group B; $p<0.001$, respectively). The monthly drug cost was higher ($11,426\pm880$ vs. $8,955\pm410$ yen, $p=0.012$) and the cost-effectiveness of antihypertensive treatment was lower ($p=0.003$) in Group A than in Group B. We conclude that the addition of benidipine to low- or medium-dose ARB is, in light of the renal protection and the cost-effectiveness of this approach, a useful therapeutic strategy for controlling BP in hypertensive patients with albuminuria. (*Hypertens Res* 2007; 30: 39–47)

Key Words: angiotensin receptor blocker, benidipine, blood pressure, urinary albumin excretion, renal protection

Introduction

For hypertensive patients with chronic renal disease, strict control of blood pressure (BP) is recommended by the results

of several megatrials, including the Modification of Diet in Renal Disease (MDRD) Study (1). The renoprotective effects of angiotensin receptor blockers (ARBs) and angiotensin-converting enzyme inhibitors (ACEIs) have been demonstrated (2–4). As a result, both have been recommended as

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Fig. 1. A 5-month prospective observation, open-label, randomized control study was conducted. Patients whose blood pressures (BPs) were 140/90 mmHg or higher after at least 4 weeks of low- or medium-dose angiotensin receptor blockade (ARB) treatment were assigned at random to either of two additional treatment groups if they also exhibited albuminuria (defined by either urinary protein excretion or a concentration of urinary albumin including 10 mg/g creatinine or greater). In Group A, the ARB dose was increased until either BPs reached their targets (< 130/85 mmHg) or the maximum dose of ARB was reached. If BP targets were not reached by ARB monotherapy, benidipine was added, beginning at 4 mg and increasing incrementally until either BP targets or a dose of 8 mg was reached. In Group B, benidipine (a calcium channel blocker) was added, beginning at 4 mg once daily in the morning. The dose was increased incrementally until either the BP targets or a dose of 8 mg was reached. If BP targets were not reached, ARB was added and increased until optimal BP or the ARB maximum was reached.

Table 1. Definition of Dosage and Drug Price of Each Dose

	Dose		
	Low	Medium	High
ARB			
Losartan	25 mg ¥104.90	50 mg ¥205.80	100 mg ¥411.60
Candesartan	4 mg ¥99.90	8 mg ¥199.80	12 mg ¥299.70
Valsartan	40 mg ¥87.00	80 mg ¥174.00	120–160 mg ¥261.00–348.00
CCB			
Benidipine	4 mg ¥78.30		8 mg ¥156.60

Prices at Jan. 2004. ARB, angiotensin receptor blocker; CCB, calcium channel blocker.

Table 2. Baseline Characteristics of Patients

	A group	B group
n (male/female)	14 (10/4)	18 (16/2)
Age (years)	63.7±11.9	59.9±14.8
Height (cm)	163.2±9.1	166.0±8.4
Body weight (kg)	66.1±14.0	68.5±16.9
Body mass index (kg/m ²)	25.8±4.7	24.6±4.7
Type 2 diabetes	3	4
Hyperlipidemia	10	7
Gout	3	4
Smoker	6	9
Target organ damage (WHO I/II/III)	5/8/1	5/12/1
Serum creatinine (mg/dl)	0.90±0.09	0.97±0.06
Serum β_2 -microglobulin (μ g/l)	2.03±0.26	2.16±0.38

Values are mean±SD. All of the values are not significantly different between the two groups by χ^2 test.

first-line treatments for hypertensive patients with chronic renal disease by international guidelines such as the Japanese Society of Hypertension (JSH 2004) (5), the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) (6), and the European Society of Hypertension (ESH 2003) (7). However, we cannot always control BP by ARBs or ACEIs alone, and international guidelines do not describe therapeutic strategies in detail. Benidipine, a dihydropyridine calcium channel blocker (CCB), may have a renoprotective effect of efferent arteriolar dilatation (8, 9) by the blockade of T- and L-type calcium channels (10, 11), both of which exist at the site of the efferent artery (12).

In this study, we evaluate the effects of two different therapeutic strategies using ARBs and benidipine on BP and urinary albumin excretion (UAE), as well as the cost-effectiveness of each, in hypertensive patients with albuminuria.

Methods

Study Protocol

This 5-month prospective observation study used an open-label, randomized design (Fig. 1). All patients gave prior informed consent to participate, and the protocol was approved by the ethics committee of our institution.

Patients with BPs of 140/90 mmHg or higher despite treatment with low- or medium-dose ARB for 4 weeks or longer and who had albuminuria were assigned at random to either of two treatment groups. Albuminuria was defined as positive urinary protein excretion by qualitative analysis or a urinary albumin concentration higher than 10 mg/g creatinine.

Patients with high serum creatinine levels (>3.0 mg/dl) were excluded. Although none of the patients underwent renal biopsy, urinary protein did not seem to be derived from

Table 3. ARB Doses at Allocation Day and at Final Evaluation Day in Group A and B

ARB dose	At allocation day (visit 2)	At final evaluation day (visit 6)
Group A		
Low	10	0
Medium	4	2
High	0	12
Group B		
Low	9	7
Medium	9	10
High	0	1

χ^2 analysis between A group and B group, n.s. ($p=0.22$) at allocation day, and significantly different at final evaluation day, $p<0.001$.

chronic glomerulonephritis based on clinical data.

On each visit to the outpatient clinic every month (visits 1 to 6), repeated sphygmomanometric BP measurements were performed after the patient had undergone a 5-min rest in the sitting position. All of the patients took antihypertensive drugs once daily in the morning (6–8 AM) throughout the study period and BPs were measured in the outpatient clinic at fixed times after medication. BP levels on the last visit during the low- or medium-dose ARB treatment period were taken as the BP in the observation period of this protocol. ARBs used in this study and the definitions of low, medium and high doses are shown in Table 1.

In Group A, the ARB dose was increased to the maximum until a BP target (less than 130 mmHg in systolic BP and less than 85 mmHg in diastolic BP) was obtained. If BP did not reach the target values by ARB monotherapy, 4 mg benidipine was added and this dose was incrementally increased to 8 mg or until the BP target was reached. In the other group (Group B), benidipine was added at an initial dose of 4 mg once daily in the morning. The dose was incrementally increased up to 8 mg or until the BP target was reached. If the target was not reached after the addition of 8 mg benidipine, the ARB dose was increased until either the BP target or the maximum ARB dose was reached. The final dose for each patient was then maintained for 4–12 weeks (total period after randomization was 4 months).

UAE (μ g/mg creatinine; using the second voided urine in the morning) and BP were measured at the time of group randomization and every month thereafter. The percentages of patients who reached the target BPs were evaluated and compared between the groups. BP and UAE were compared between visits 2 and 6 in each group.

The monthly costs of the final doses of ARB and benidipine in the two groups were calculated from the drug prices in Japan as of January 2004. Mean BPs [(diastolic BP) + {(systolic BP) – (diastolic BP)} / 3] at visit 2 (the allocation day) and visit 6 (the final evaluation day) were calculated, and the

Table 4. Medication Dose at Visits 2 and 6 in Group A and B

ARB	ARB dose (mg/day)		Benidipine dose (mg/day)
	At allocation day (visit 2)	At final evaluation day (visit 6)	At final evaluation day (visit 6)
Group A			
Losartan (<i>n</i> =3)	41.7±8.3	83.3±16.7	
Candesartan (<i>n</i> =4)	5.0±1.0	11.0±1.0	4.3±1.0 (<i>n</i> =14)
Valsartan (<i>n</i> =7)	45.7±5.7	137.1±8.1	
Group B			
Losartan (<i>n</i> =4)	31.3±6.3	31.3±6.3	
Candesartan (<i>n</i> =7)	5.7±0.8	7.4±1.0	6.9±0.4* (<i>n</i> =18)
Valsartan (<i>n</i> =7)	68.6±7.4	68.6±7.4	

**p*=0.03 vs. Group A. ARB, angiotensin receptor blocker.

Fig. 2. Systolic and diastolic BPs were significantly decreased in each group (**p*<0.001, respectively) at visit 6 (final evaluation day) compared to visit 2 (allocation day).

Table 5. Achievement of Optimal Blood Pressure in Group A and B

Group A (<i>n</i> =14)		Group B (<i>n</i> =18)	
Reached by ARB alone	5 (35.7%)	Reached by addition of benidipine	15 (83.3%)
Not reached by ARB alone but reached by addition of benidipine	8 (57.1%)	Not reached by addition of benidipine but reached by addition of ARB	2 (11.1%)
Not reached by ARB alone and also not reached by addition of benidipine	1 (7.2%)	Not reached by addition of benidipine and also not reached by addition of ARB	1 (5.6%)

ARB, angiotensin receptor blocker.

monthly cost of lowering 1 mmHg of mean BP [$\{(\text{monthly cost at visit 6}) - (\text{monthly cost at visit 2})\} / \{(\text{mean BP at visit 6}) - (\text{mean BP at visit 2})\}$] was compared between the two groups.

To determine the effects of benidipine on BP and UAE, a sub-analysis was done as follows. The Group A patients whose BPs were not controlled to the target values by ARB monotherapy were included, as were all of the patients in

Group B. In these Group A patients, data on the day of the maximum ARB dose without benidipine and data at visit 6 (the final evaluation day, the maximum ARB dose with the final dose of benidipine) were compared. In Group B, data at visits 2 and 4 (the final dose of benidipine with the same dose of ARB as at visit 2) were compared.

Statistics

Results are expressed as means $\pm$ SEM. To compare the skewed data of the two groups, nonparametric analysis (Mann-Whitney) was used. Paired data were compared using the Wilcoxon test or the Steel test. A *p*-value of less than 0.05 was considered significant.

Results

Baseline Characteristics

Enrolled in our study were 43 hypertensive patients from 2002 to 2004 at four metropolitan hospitals in Japan. Of these, 4 chose to drop out during the protocol, and 4 others used antihypertensive drugs not allowed by the protocol. Medication non-compliance was observed in 3 patients. Data from the remaining 32 patients (age, 62 $\pm$ 17 years; 14 men), who met all our criteria and completed the protocol, were finally included in the study. Baseline characteristics of the 14 patients in Group A and 18 patients in Group B are shown in Table 2.

ARB and Benidipine Doses in the Two Treatment Strategies

The medication doses of ARBs and benidipine before and after the allocation are shown in Tables 3 and 4. At visit 2, the ARB doses did not differ significantly between the groups, whereas at visit 6 they were significantly higher in Group A than in Group B (Table 3). The actual doses of ARBs and benidipine used in the study are shown in Table 4. Doses of benidipine at visit 6 were lower in Group A than in Group B. Three patients in Group B needed higher doses of candesartan after the addition of the maximum dose of benidipine (Table 4). In 2 of those patients, the target BP was reached after the low candesartan dose (4 mg/day) was increased to a medium dose (8 mg/day). In 94% (17/18) of the Group B patients, the final dose of ARB was low or medium; in other words, the target BP was reached by a low or medium dose of ARB with benidipine.

Effects of Each Treatment Strategy on BP and UAE

In Group A, the BP targets were reached by ARB alone in 35.7% (5/14) of patients. In Group B, the addition of benidipine to low- or medium-dose ARB decreased BP to the target

values in 83% (15/18) of patients. Finally, BP decreased significantly in both groups (Fig. 2) and the BP targets were reached in 93% (13/14) of the Group A patients and in 94% (17/18) of the Group B patients (Table 5).

At visit 2, there was no significant difference in UAE between the groups (*p*=0.178, n.s.). UAE decreased significantly in both groups (*p*<0.001 respectively, Fig. 3) by significant percentages (*p*<0.001 respectively, Fig. 4). In Figs. 3 and 4, the final ARB doses are shown by different colors (blue, green, and red lines: low, medium and high doses, respectively). Most of the patients in Group A received the high dose of ARB. Patients who were finally treated with low-dose ARB tended to have high UAE at visit 2, which was not significantly different from patients who received either of the higher doses.

When all of the data from 32 patients were analyzed, UAE levels at visit 2 were found to correlate significantly with the percentage decreases in UAE at visit 6 (*r*=0.420, *p*=0.018). This correlation was not significant when the data were analyzed in each group.

The relationship between changes in BP and UAE was evaluated in all 32 patients. There was no significant correlation between changes in mean BP and percentage changes in UAE (*r*=0.219, *p*=0.231) or between percentage changes in mean BP and those in UAE (*r*=0.177, *p*=0.334). In the 5 patients in Group A whose target BPs were reached by ARB monotherapy, UAE at visit 2 were 12.7, 17.4, 1,750.0, 1,850.0, and 1,440.0 mg/g creatinine. There was no significant difference in the values of UAE at visit 2 between those 5 patients and the 9 patients in Group A who were given benidipine. The effects of the final doses of ARB on changes in UAE during visits 2 to 6 were also evaluated. There were no significant differences in percentage changes in UAE among the three dose subsets of ARB (low dose [*n*=8]: -39.3 $\pm$ 12.2%, medium dose [*n*=11]: -29.4 $\pm$ 8.1%, high dose [*n*=13]: -28.6 $\pm$ 8.4%, *p*=0.527).

Monthly Cost and Cost-Effectiveness of Each Treatment Strategy

The monthly drug cost was higher in Group A than in Group B (*p*=0.012). The monthly cost of lowering 1 mmHg of mean BP was also higher in Group A than in Group B (*p*=0.003). The cost-effectiveness of lowering BP was higher in Group B. (Fig. 5)

Effects of Benidipine on BP and UAE

Nine patients in Group A whose BPs were not controlled to the target values by ARB monotherapy were included for sub-analysis, as were all 18 patients in Group B. BP and UAE in the 27 patients with benidipine treatment were compared before and after the addition of benidipine.

BP and UAE decreased significantly after the addition of benidipine (systolic BP: 151.1 $\pm$ 2.2 to 127.8 $\pm$ 2.4, diastolic

Fig. 3. Urinary albumin excretion was significantly decreased in both groups (* $p < 0.001$, respectively) at visit 6 (final evaluation day) compared to visit 2 (allocation day). ARB dose category: red, green, and blue lines refer to high, medium, and low doses, respectively. Broken lines refer to patients in whom target BP (130/85 mmHg) was not achieved. Black lines show the average of UAE.

Fig. 4. The percentage decrease in urinary albumin excretion at visit 6 (final evaluation day) compared to visit 2 (allocation day) was also significant in both groups (* $p < 0.001$, respectively). ARB dose category: red, green, and blue lines refer to high, medium, and low doses, respectively. Broken lines refer to the patients in whom target BP (130/85 mmHg) was not achieved. Black lines show average percentage decreases in urinary albumin excretion.

Fig. 5. The monthly drug cost was higher in Group A than in Group B ($p=0.012$). The monthly cost for lowering 1 mmHg of mean BP was also higher in Group A than in Group B ($p=0.003$).

BP: 87.3 ± 1.9 to 74.8 ± 1.8 , UAE 314.2 ± 119.1 to 213.5 ± 90.0 , $p < 0.001$). The percent decrease in UAE was also significant ($-26.8 \pm 6.9\%$, $p < 0.001$). There was no significant correlation between changes in mean BP and percentage changes in UAE ($r=0.045$, $p=0.820$), or between percentage changes in mean BP and percentage changes in UAE ($r=0.159$, $p=0.353$).

The effect of the addition of benidipine on changes in UAE was compared among the three ARB doses. No significant differences were found in the percentage changes in UAE among the three subsets (low-dose ARB [$n=8$]: $-33.0 \pm 11.9\%$, medium-dose ARB [$n=10$]: $-26.2 \pm 8.9\%$, high-dose ARB [$n=9$]: $-21.2 \pm 14.6\%$, n.s.).

We also evaluated changes in UAE from visits 1 to 2 in 11 patients (Group A: 4 patients, Group B: 7 patients) who were not treated with antihypertensive drugs for at least 4 weeks prior to visit 1. Systolic BP decreased significantly but diastolic BP and UAE did not. We compared the data from 7 patients in Group B among visit 1, visit 2, and visits 4–6 (data at visit 4 in 2 patients whose BPs did not reach the optimal values, and data at visit 6 in 5 patients whose BPs did reach the optimal values at visit 4). Significant decreases in systolic and diastolic BP and UAE were observed between visit 2 and visits 4–6, but not between visits 1 and 2 (BP [mmHg]: $162.0 \pm 4.0/101.0 \pm 4.0$ at visit 1, $157.7 \pm 2.1/96.9 \pm 1.4$ at visit 2, $128 \pm 3.5/8.0 \pm 1.5$ at visits 4–6, UAE [$\mu\text{g}/\text{mg creatinine}$]: 283.0 ± 137.8 at visit 1, 374.1 ± 165.1 at visit 2, 174.5 ± 80.2 at visits 4–6, $p < 0.05$ at visits 4–6 vs. visits 1 and 2 in systolic and diastolic BP and UAE). The percent decrease in UAE was also significant between visits 4–6 and visit 2 ($-49.9 \pm 7.0\%$).

Discussion

In this study we have demonstrated that the effects on BP and UAE of adding benidipine to low- or medium-dose ARB prior to increasing the ARB dose are similar to those of another therapeutic strategy, in which the ARB dose is increased first. The addition of benidipine first is the more cost-effectiveness strategy.

Antihypertensive drugs, which inhibit the renin-angiotensin system, are considered the first choice for hypertensive patients with chronic renal disease (5–7), because there is considerable evidence that treatment with ACEIs or ARBs protects against the progression of nephropathy (2–4). Recent papers have shown that proteinuria is a renal risk marker and an important target for the therapy (12, 13). The Irbesartan Diabetic Nephropathy Trial (IDNT) (3) compared the effects of irbesartan, an ARB, and amlodipine, a calcium channel blocker, on renal function. It concluded that irbesartan is effective in protecting against the progression of nephropathy due to type 2 diabetes and that this protection is independent of the reduction in blood pressure. The Microalbuminuria Reduction with Valsartan (MARVAL) (2) study compared the percentage change in the urinary albumin excretion rate (UAER) from baseline to 24 weeks between the valsartan-treated and amlodipine-treated groups. The change in UAER at 24 weeks was -44% in the valsartan group and significantly greater than that in the amlodipine group (-8%). All of the participants in the IDNT and MARVAL studies were apparently diabetic patients, while only 7 of our 32 subjects had diabetes. The degree of renal damage might have been severe in participants of the IDNT study, who had apparent

diabetic nephropathy (mean urinary protein excretion was 4.0 ± 3.5 g/day) and mild in participants of the MARVAL study, all of whom had microalbuminuria. Therefore, we cannot compare our results directly with those of these other studies.

The participants in the African American Study of Kidney Disease and Hypertension (AASK) trial (14) were similar to ours (exclusion criteria: known history of diabetes, urinary protein-to-creatinine ratio >2.5 , BP-related causes of chronic kidney disease, *etc.*). The authors of that study used ramipril (an ACEI instead of ARB to inhibit the renin-angiotensin system), a β -blocker (metoprolol), and a CCB (amlodipine), and followed up their subjects for 4 years. The follow-up BPs were similar among the three groups, but the follow-up proteinuria levels were significantly higher in the amlodipine group than in the other two groups for the 4 years.

The superiority of ACEIs and ARBs over other antihypertensive drugs (2–4) for protecting renal function in hypertensive patients with chronic renal disease might be true. However, a recent meta-analysis study by Casas *et al.* (15) questioned the additional renoprotective actions of ACEIs and ARBs beyond lowering BP. Strict control of BP for hypertensive patients with chronic renal disease is considered the most important factor for renal protection (1), but monotherapy with ARBs or ACEIs cannot always control BP.

In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) (16), only 30% of patients had their BP controlled by monotherapy, whereas almost 30% were receiving three or more medications at year 5. In the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) study of patients with left ventricular hypertrophy, less than 50% of patients had their BP reduced to $<140/90$ mmHg after 5 years of intensive antihypertensive treatment (17). In a study of two university-based cohorts, Garg *et al.* reported that more than 10% of hypertensive patients had resistant hypertension despite the use of three antihypertensive drugs (18). In the present study, it is noteworthy that target BP (less than 130/85 mmHg) was reached in only 35.7% (5/14) of the patients with albuminuria by ARB alone, but in about 94% (30/32) by the combination of ARB and benidipine.

The severity of renal function deterioration and that of background diseases that deteriorate renal function are important factors to consider in interpreting the results. Patients included in this study had albuminuria but not severe deterioration of renal function, as evidenced by high levels of serum creatinine and β_2 -microglobulin. Our study had few apparently diabetic patients and none of the subjects had clinical data suggesting chronic glomerulonephritis. These factors might have affected our results and produced a good response of BP to the combination of ARB and benidipine. However, there was no significant difference in UAE values at visit 2 between the 5 patients whose BPs reached the targets by ARB monotherapy and the 9 patients in Group A whose BPs did not reach the targets at visit 4. Therefore, UAE level may not

be an indicator for hypotensive response to ARB alone.

Although the combination of ARBs and CCBs is a powerful therapeutic strategy, the details of therapeutic strategies using those drugs are not indicated even in international guidelines. Recently, there were some CCBs with not only L-type calcium channel blockade but also additional pleiotropic effects. CCBs, which block T-type or N-type calcium channels, may have a renoprotective effect by dilating the efferent artery and protecting the glomerulus from hyperfiltration injury (9). Benidipine, which blocks T-type and L-type calcium channels (8), decreases the resistance of the efferent and afferent arteries and lowers the glomerular capillary hydraulic pressure in rats (19, 20). Yao *et al.* reported renoprotective effects of benidipine in hypertensive Dahl rats (21, 22). Therefore, benidipine is expected to have a renoprotective effect also in hypertensive patients.

We evaluated the effects of two different therapeutic strategies using ARBs and benidipine on BP, UAE, and cost-effectiveness in hypertensive patients with albuminuria. We formed two different therapeutic groups and compared the results between them. In Group A, the ARB dose was maximized and then benidipine was added. In Group B, benidipine was added to the maximum dose and then the ARB dose was increased. Therefore, in Group A the final ARB dose was larger and the final benidipine dose was smaller than in Group B. In other words, the effect of ARB might be larger in Group A and the effect of benidipine might be larger in Group B. However, similar effects on BP and UAE were observed in the two groups. Furthermore, sub-analysis showed that the addition of benidipine significantly decreased UAE and that the percent decreases in UAE by the addition of benidipine were not different among the three ARB dosage groups (low, medium, and high). These data suggest that benidipine has the peculiar effect of decreasing UAE.

One of the interesting findings of this study is that the cost-effectiveness of adding benidipine to low- or medium-dose ARB prior to increasing the dose of ARB is superior to that of the reverse strategy. ARBs, which are newly developed antihypertensive drugs, are more expensive than CCB.

We conclude that the addition of benidipine to low- or medium-dose ARB is a useful therapeutic strategy for controlling BP, considering the renal protection it provides and its cost-effectiveness in hypertensive patients with albuminuria.

Perspectives

We did not directly compare the effects of ARB and benidipine on BP and UAE in this study. In the present study, most of the patients had been already medicated with antihypertensive drugs before giving prior informed consent to participate. Therefore, we considered that at least low-dose ARB, which the Japanese Society of Hypertension recommends as the first line of drugs in hypertensive patients with chronic renal disease, was necessary as the baseline drug in our study, and our

protocol was approved by the ethics committee of our institution. Our study showed a renoprotective effect of combining benidipine and ARBs in hypertensive patients with albuminuria. Our study showed the renoprotective effect provided by benidipine on top of either the maximum or a lower dose of ARB in hypertensive patients with albuminuria. Moreover, the renoprotective effect of benidipine observed in this study is considered unique compared with other CCBs based on the results of the IDNT, MARVAL, and AASK studies (2, 3, 14), which showed that amlodipine seems to have less renoprotective effect than benidipine. From a clinical perspective, the current findings may change the way we use only ACEIs or ARBs as first-line drugs in hypertensive patients with chronic renal disease, as recommended by the guidelines. CCBs with a T-type channel blockade, such as benidipine, may be potential first-line antihypertensive drugs for patients with chronic renal disease. Further studies comparing renoprotective effects among benidipine, other CCBs, and ARB will be needed.

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