Improvements in Augmentation Index and Urinary Albumin Excretion With Benidipine in Hypertensive Patients With Chronic Kidney Disease

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SUMMARY

Although calcium channel blockers (CCB) are expected to improve the augmentation index (AI) in CKD patients, the potential effect of benidipine on AI has been poorly studied.

The present study aimed to compare the effect of benidipine and amlodipine in the treatment of CKD patients as measured through AI and urinary albumin excretion (UAE). Eligible patients with CKD were randomized to either the benidipine group or amlodipine group. Changes in UAE and AI were compared with target blood pressure level set at < 130/80 mmHg. A total of 108 patients were enrolled; 88 patients who were followed up were included in the analysis. Although no significant change in renal function was noted in either group, there was a significant improvement in AI only in the benidipine group ($85.7 \pm 13.3\%$ to $81.4 \pm 15.2\%$; $P = 0.021$). A subgroup analysis of 64 patients who achieved SBP < 140 mmHg at the end of follow-up (31 on amlodipine and 33 on benidipine) was carried out. Significant improvement in AI was noted only in the benidipine group ($84.5 \pm 13.6\%$ to $79.5 \pm 15.2\%$; $P = 0.0138$). In another subgroup of patients with UAE ≥ 300 mg/g Cr, a significant improvement in UAE in the benidipine group was found compared with the amlodipine group (-25 ± 46 , $51 \pm 60\%$, $P = 0.031$, respectively).

These results suggest that benidipine might reduce significantly AI and might have potentially greater improvements in UAE than amlodipine in advanced CKD patients receiving RAS inhibitors. (Int Heart J 2016; 57: 53-60)

Key words: Calcium channel blocker, CKD, AI, Endothelial function

Chronic kidney disease (CKD) is associated with significant cardiovascular disease.¹⁾ It is important to consider organ protective effects in the treatment of hypertensive CKD patients. Assessment of vascular function or urinary albumin plays an important role as in the assessment of organ damage. Urinary albumin has been reported as an independent determinant of cardiovascular events, as well as blood pressure.²⁾ In addition, the evaluation of vascular endothelial function and arterial stiffness is useful as an index of the progress of the arteriosclerotic change.³⁾

The augmentation index (AI) is the proportion of reflected pressure waves in the pulse pressure waves in systole. The height and timing of reflected pressure waves are dependent on vascular stiffness. As the AI is believed to reflect the structure and function of blood vessels based on measurements of arterial stiffness, it is expected to be a useful tool in predicting cardiovascular outcomes.⁴⁾

Inhibitors of the renin-angiotensin system (RAS) (angiotensin-converting enzyme [ACE] inhibitors or angiotensin receptor blockers [ARBs]) are recommended as first-line agents in hypertensive CKD patients.⁵⁾ However, in most cases, it is difficult to achieve a strict target blood pressure of < 130/80

mmHg, as recommended in the guidelines for the management of hypertension^{4,6)} with RAS inhibitors alone, and antihypertensive combination therapy is therefore necessary.

Dihydropyridine (DHP) calcium channel blockers (CCBs) are recommended as second-line agents in hypertensive CKD patients on RAS inhibitors.^{4,6)} Among the CCBs, L-type Ca channels (L-type CCBs) dilate only afferent arterioles to increase intraglomerular pressure, which might not result in reduced urinary albumin excretion (UAE) through blood pressure lowering.⁷⁾ In contrast, T-type and L-type calcium channel blockers (T/L-type CCBs) may have renal protective effects by lowering intraglomerular pressure.⁸⁾

Benidipine is a T/L-type CCB and is reported to result in a potentially greater reduction in urinary protein or albumin than amlodipine, although only in small-scale clinical studies.^{6,9)} In addition, because benidipine improves the prognosis of coronary spastic angina, which is highly prevalent in Japanese people, benidipine may have a stronger vascular endothelial protective effect than other types of CCB.^{10,11)} The present study aimed to compare the effects of T/L-type CCB benidipine and L-type CCB amlodipine in the treatment of hypertensive CKD patients as measured through the AI and UAE.

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METHODS

Study design and patient selection: This study was a prospective, open-label, randomized, parallel-comparison study.

Hypertensive patients who satisfied the following criteria were enrolled: 1) male or female patients aged ≥ 20 years; 2) patients receiving RAS inhibitors for at least 3 months before enrolment; 3) patients who had received DHP CCB for ≥ 4 weeks before enrolment; 4) patients with a UAE ≥ 30 mg/g Cr; 5) patients with an estimated glomerular filtration rate (eGFR) < 60 mL/minute/1.73 m²; 6) patients who gave informed consent for participation in this study. The exclusion criteria were as follows: 1) patients who had received DHP CCB for the treatment of coronary spasms; 2) patients who underwent coronary angiography within the last 6 months; 3) patients who planned to undergo coronary angiography within the next 1 year; 4) patients with a history of serious adverse drug reactions to CCBs, ARBs, or ACE inhibitors; 5) patients with type 1 or type 2 diabetes who required inpatient treatment for a hemoglobin A1c level $\geq 9.0\%$, marked hyperglycemia (≥ 300 mg/dL), or diabetic ketoacidosis; 6) patients with concurrent cerebrovascular events that occurred < 6 months before the start of study treatment; 7) patients who had concurrent severe heart failure (New York Heart Association functional class III or higher) or serious arrhythmia (frequent ventricular or atrial extrasystole, persistent ventricular tachycardia, atrial tachycardia with extreme tachycardia, atrial fibrillation/flutter with extreme tachycardia, sick sinus syndrome with extreme bradycardia, or atrioventricular block with extreme bradycardia); 8) patients who had liver dysfunction with aspartate aminotransferase (AST) and alanine aminotransferase (ALT) > 5 times the institutional upper limit of normal; 9) patients who were pregnant, of childbearing age, or intending to become pregnant; and 10) patients who were not considered appropriate for other reasons in the opinion of the investigator.

Treatments: Eligible patients were randomized to the amlodipine or benidipine group by using a dynamic allocation procedure based on the minimization method according to assignment factors of blood pressure and renal function. Eligible patients stopped the CCB that had been administered before study enrolment and started receiving their newly assigned study drug. Treatment was either amlodipine 2.5–10 mg/day or benidipine 4–16 mg/day (in patients without concurrent angina pectoris, benidipine 4–8 mg/day) and was administered for 12 months. Use of concomitant CCB except for study drugs was not permitted. During the course of the study, modification of the dosage regimen of RAS inhibitors was not permitted. Concomitant use of diuretics, α -blockers, β -blockers, and so on, was allowed.

Outcomes measures: Investigations included blood pressure, pulse rate (PR), UAE, eGFR, and AI. Measurement of AI was performed using an HEM-9000AI (OMRON, Kyoto, Japan). Blood pressure and PR were measured after resting while seated for ≥ 5 minutes. Blood pressure measurements were taken twice and the mean value was calculated. PR was counted for 15 seconds and multiplied by 4 to obtain the PR/min. The eGFR was calculated using the formula for estimating GFR in the Japanese population developed by the Japanese Society of Nephrology.¹²⁾ UAE (in random urine samples) was determined at baseline (mean of 2 determinations during the screening period) and at 12 months.

The primary endpoints were comparing changes in hemodynamics (blood pressure and PR), AI, and UAE in the benidipine group to those in the amlodipine group between baseline and follow-up in patients with CKD.

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and the protocol was approved by the Institutional Review Board of Nihon University Itabashi Hospital. Patients were given a full explanation of the protocol and provided written voluntary informed consent.

Statistical analysis: Data are expressed as the mean $\pm$ standard deviation (SD). Baseline characteristics at study enrolment were compared between the groups using unpaired *t*-test or chi-squared test. The paired *t*-test was used to compare the mean values before and after treatment in each group. Means and percent changes were compared between the groups using unpaired *t*-test. The correlation between AI and PR and its *P* value were calculated using least-squares method. A *P* value < 0.05 was considered statistically significant.

RESULTS

Study population and baseline characteristics: A total of 108 patients who provided written informed consent between January 1, 2010, and March 31, 2013 were enrolled and randomly assigned to the benidipine group ($n = 53$) or amlodipine ($n = 55$) group. These two groups of patients were followed up and compared. There were 20 dropouts or withdrawals from the study, and ultimately 41 patients in the benidipine group and 47 patients in the amlodipine group were included in the analysis. The baseline characteristics of the patients included in the analysis are shown in Table I. Patients in the amlodipine group were significantly older than those in the benidipine group, but there were no significant differences in any of the other characteristics between the groups. The mean dose was 6.3 ± 2.4 mg/day (4 mg: $n = 15$, 8 mg: $n = 34$, 12 mg: $n = 1$, 16 mg: $n = 3$) in the amlodipine group and 7.4 ± 2.8 mg/day (2.5 mg: $n = 3$, 5 mg: $n = 36$, 7.5 mg: $n = 1$, 10 mg: $n = 15$) in the benidipine group. The mean duration of follow-up was 330 ± 62 days in the amlodipine group and 339 ± 49 days in the benidipine group.

Antihypertensive effects and AI values (Table II): SBP changed from 136.8 ± 15.1 mmHg at baseline to 133.6 ± 16.1 mmHg at follow-up ($P = 0.178$) in the amlodipine group and from 134.7 ± 16.6 mmHg at the start of the study to 127.5 ± 16.2 mmHg at the end of study ($P = 0.002$) in the benidipine group, with no significant reduction in blood pressure observed in the amlodipine group. Diastolic blood pressure (DBP) changed from 69.8 ± 9.7 mmHg to 62.4 ± 12.4 mmHg ($P < 0.001$) in the amlodipine group and from 71.6 ± 9.0 mmHg to 64.3 ± 10.4 mmHg ($P < 0.001$) in the benidipine group. No significant differences were found between the groups.

There was no significant difference in the change in PR before and after study treatment between the amlodipine ($68.8 \pm 11.3 \rightarrow 72.5 \pm 13.2$, $P = 0.006$) and benidipine ($70.4 \pm 9.0 \rightarrow 73.9 \pm 11.7$, $P = 0.011$) groups. In the amlodipine group, AI values showed a decreasing trend from $87.0 \pm 15.9\%$ before treatment to $84.3 \pm 17.4\%$ after treatment, although the difference was not significant. In contrast, AI values in the benidipine group showed a significant decrease from $85.7 \pm 13.3\%$ to $81.4 \pm 15.2\%$ ($P = 0.021$). No significant differences

Table I. Baseline Characteristics of Patients Included in the Analysis

	Amlodipine (<i>n</i> = 47)	Benidipine (<i>n</i> = 41)	<i>P</i>
Age (years)	72.9 ± 10.2	68.3 ± 9.8	0.026
Male, <i>n</i> (%)	31 (66.0)	30 (73.2)	0.464
Body mass index (kg/m ²)	25.3 ± 3.7	25.4 ± 3.6	0.984
AI	85.1 ± 13.8	84.5 ± 13.6	0.868
eGFR (mL/minute)	56.0 ± 19.9	52.5 ± 16.2	0.473
UAE (mg/gCr)	262 ± 477.7	238 ± 358	0.819
Concurrent conditions, <i>n</i> (%)			
Myocardial infarct	15 (31.9)	17 (41.5)	0.353
Angina pectoris	13 (28.3)	17 (41.5)	0.464
Cerebrovascular disease	8 (17.0)	2 (4.9)	0.073
Dyslipidemia	33 (70.2)	28 (68.3)	0.846
Type 2 diabetes	21 (44.7)	19 (46.3)	0.876
Heart failure	3 (6.4)	4 (9.8)	0.560
Arteriosclerosis obliterans	0 (0.0)	2 (4.9)	0.126
Hyperuricemia	5 (10.6)	5 (12.2)	0.818
Concomitant drugs			
ARB	42 (89.4)	38 (92.7)	0.589
ACE inhibitors	6 (12.8)	4 (9.8)	0.657
Diuretics	17 (36.2)	9 (22.0)	0.145
α -Blockers	3 (6.4)	0 (0.0)	0.100
β -Blockers	21 (44.7)	17 (41.5)	0.761
$\alpha 1\beta$ -Blockers	1 (2.1)	0 (0.0)	0.348
Rasilez	0 (0.0)	1 (2.4)	0.282
Statins	19 (40.4)	22 (53.7)	0.214

Table II. Primary Endpoint

		Amlodipine	Benidipine	<i>P</i> (amlodipine versus benidipine)
SBP (mmHg)	Baseline	136.8 ± 15.1	134.7 ± 16.6	0.535
	After treatment	133.6 ± 16.1	127.5 ± 16.2	0.081
	<i>P</i> (versus pre)	0.178	0.002	
DBP (mmHg)	Baseline	69.8 ± 9.7	71.6 ± 9.0	0.379
	After treatment	62.4 ± 12.4	64.3 ± 10.4	0.466
	<i>P</i> (versus pre)	< 0.001	< 0.001	
PR (bpm)	Baseline	68.8 ± 11.3	70.4 ± 9.0	0.477
	After treatment	72.5 ± 13.2	73.9 ± 11.7	0.602
	<i>P</i> (versus pre)	0.006	0.011	

SBP indicates systolic blood pressure; DBP, diastolic blood pressure; and PR, pulse rate.

were found between the groups (Figure 1).

UAE changed from 458 ± 1097 mg/g Cr to 667 ± 1616 mg/g Cr in the amlodipine group and from 281 ± 394 mg/g Cr to 314 ± 492 mg/g Cr in the benidipine group, with no significant changes observed in either group (Figure 1). The eGFR changed from 55.5 ± 18.5 mL/minute/1.73 m² to 54.1 ± 19.0 mL/minute/1.73 m² in the amlodipine group and from 54.6 ± 16.6 mL/minute/1.73 m² to 52.5 ± 17.6 mL/minute/1.73 m² in the benidipine group, with no significant changes observed in either group.

Subgroup analysis of patients achieving SBP < 140 mmHg: A subgroup analysis was performed in 64 patients achieving SBP < 140 mmHg (31 patients on amlodipine [66.0%] and 33 patients on benidipine [80.5%]) as no significant reduction in SBP was found in the amlodipine group. The baseline characteristics of these patients are shown in Table III. As in the overall population, the amlodipine group was significantly older than the benidipine group, but there were no significant differ-

ences in any of the other characteristics between the groups. The mean dose was 6.4 ± 2.4 mg/day in the amlodipine group and 7.3 ± 2.5 mg/day in the benidipine group. The mean duration of follow-up was 331 ± 63 days in the amlodipine group and 342 ± 47 days in the benidipine group.

SBP changed from 133.8 ± 16.7 mmHg at the start of study treatment to 124.3 ± 10.4 mmHg at the end of study treatment (*P* < 0.001) in the amlodipine group and from 130.8 ± 15.2 mmHg at the start of study treatment to 121.7 ± 12.0 mmHg at the end of study treatment (*P* < 0.001) in the benidipine group. There was no significant difference between the groups. DBP changed from 67.6 ± 8.5 mmHg to 58.0 ± 10.2 mmHg in the amlodipine group (*P* < 0.001) and from 71.3 ± 9.3 mmHg to 63.2 ± 10.6 mmHg in the benidipine group (*P* < 0.001). There was no significant difference between the groups.

There was no significant difference in the change in PR before and after study treatment in the amlodipine (from 67.4

Figure 1. Changes in AI and UAE in patients included in the analysis. AI values in the benidipine group showed a significant decrease from $85.7 \pm 13.3\%$ to $81.4 \pm 15.2\%$ ($P = 0.021$). In AI and UAE, no significant differences were found between the groups.

Table III. Baseline Characteristics of the Subgroup of Patients Achieving SBP < 140 mmHg

	Amlodipine (n = 31)	Benidipine (n = 33)	P
Age (years)	73.5 ± 10.5	67.9 ± 10.4	0.039
Male, n (%)	21 (67.7)	24 (72.7)	0.663
Body mass index (kg/m ²)	25.0 ± 3.5	25.7 ± 3.9	0.442
Concurrent conditions, n (%)			
Myocardial infarct	12 (38.7)	14 (42.4)	0.762
Angina pectoris	8 (26.7)	15 (45.5)	0.102
Cerebrovascular disease	5 (16.1)	2 (6.1)	0.197
Dyslipidemia	22 (71.0)	23 (69.7)	0.911
Type 2 diabetes	10 (32.3)	15 (45.5)	0.280
Heart failure	2 (6.5)	3 (9.1)	0.694
Arteriosclerosis obliterans	0 (0.0)	2 (6.1)	0.164
Hyperuricemia	3 (9.7)	4 (12.1)	0.754
Concomitant drugs			
ARB	27 (87.1)	30 (90.9)	0.625
ACE inhibitors	5 (16.1)	4 (12.1)	0.645
Diuretics	11 (35.5)	8 (24.2)	0.325
α-Blockers	2 (6.5)	0 (0.0)	0.138
β-Blockers	14 (45.2)	13 (39.4)	0.641
α1β-Blockers	1 (3.2)	0 (0.0)	0.298
Direct renin inhibitor	0 (0.0)	1 (3.0)	0.329
Statins	14 (45.2)	18 (54.5)	0.453

± 11.2 to 69.8 ± 10.8 , $P = 0.115$) and benidipine (from 69.6 ± 9.5 to 73.6 ± 12.7 , $P = 0.016$) groups.

In the amlodipine group, there was a slight decrease in AI values from $85.1 \pm 13.8\%$ before study treatment to $82.5 \pm 14.9\%$ after study treatment, although the difference was not significant. In contrast, there was a significant decrease in AI values in the benidipine group from $84.5 \pm 13.6\%$ to $79.5 \pm 15.2\%$ ($P = 0.0138$). No significant differences were found between the groups (Figure 2).

UAE changed from 262 ± 478 mg/g Cr to 344 ± 751 mg/g Cr in the amlodipine group and from 238 ± 358 mg/g Cr to 216 ± 319 mg/g Cr in the benidipine group, with no significant changes observed in either group. Although a slight increase was noted in the amlodipine group, no significant difference was also found compared with the benidipine group (Figure 2).

The eGFR changed from 55.9 ± 19.9 mL/minute/1.73 m² to 54.3 ± 20.0 mL/min/1.73 m² in the amlodipine group and from 52.5 ± 16.2 mL/minute/1.73 m² to 50.8 ± 16.8 mL/minute/1.73 m² in the benidipine group, with no significant changes observed in either group.

A stratified analysis of UAE showed that there was no statistical difference in the percent change in UAE among patients with UAE of < 300 mg/g Cr between the groups. The percent change in UAE among patients with a high UAE of ≥ 300 mg/g Cr and advanced renal impairment was $51 \pm 60\%$ in the amlodipine group and $-25 \pm 46\%$ in the benidipine group. There was no significant change in either group between baseline and follow-up; however, there was significant change between the groups ($P = 0.031$).

Characterization of an improvement in AI with benidipine: In

Figure 2. Changes in AI and UAE in the subgroup of patients achieving SBP < 140 mmHg. There was a significant decrease in AI values in the benidipine group from $84.5 \pm 13.6\%$ to $79.5 \pm 15.2\%$ ($P = 0.0138$). However, no significant differences were found between the groups in AI and UAE.

Figure 3. Changes in AI in the groups with decreased and increased PR in the subgroup of patients achieving SBP < 140 mmHg. Δ pulse rate is defined as following the equation of Δ pulse rate (Δ PR) = PR (follow-up) - PR (baseline). AI values decreased from $87.7 \pm 11.6\%$ to $82.4 \pm 15.8\%$ in the amlodipine group and from $83.2 \pm 13.2\%$ to $77.6 \pm 15.0\%$ in the benidipine group, although only the change in the benidipine group was significant ($P = 0.012$).

a subgroup of patients with a decrease in PR (Δ PR < 0), AI increased from $80.3 \pm 16.0\%$ to $82.6 \pm 13.1\%$ in the amlodipine group and showed a slight decrease (from $87.4 \pm 14.0\%$ to $84.0 \pm 14.7\%$) in the benidipine group, although the changes were not significant (Figure 3). There were no significant differences between the groups. In contrast, in a subgroup of patients with an increase in PR (Δ PR ≥ 0), AI values decreased from $87.7 \pm 11.6\%$ to $82.4 \pm 15.8\%$ in the amlodipine group and from $83.2 \pm 13.2\%$ to $77.6 \pm 15.0\%$ in the benidipine group, although only the change in the benidipine group was significant ($P = 0.012$). However, no significant difference was found between the groups. An analysis of the correlation between the percent changes in AI and PR (Figure 4) showed a significant negative correlation in the amlodipine group, while

there was no correlation in the benidipine group.

DISCUSSION

The present study aimed to compare the effects of benidipine and amlodipine in the treatment of hypertensive CKD patients as measured through the AI and UAE. This study is, to the best of our knowledge, the first report to compare benidipine and amlodipine in terms of AI and UAE. A significant decrease in AI was only found in the benidipine group ($85.7 \pm 13.3\% \rightarrow 81.4 \pm 15.2\%$; $P = 0.021$), however, there was no significant difference in BP as a primary endpoint at follow-up between the groups. Therefore, we performed a subgroup

Figure 4. Correlation of changes in AI and PR in the subgroup of patients achieving SBP < 140 mmHg. An analysis of the correlation between the percent changes in AI and PR showed a significant negative correlation in the amlodipine group (left), while there was no correlation in the benidipine group (right).

analysis of 64 patients who achieved SBP < 140 mmHg at the end of follow-up (31 on amlodipine and 33 on benidipine). Significant improvement in AI was noted only in the benidipine group (from $84.5 \pm 13.6\%$ to $79.5 \pm 15.2\%$; $P = 0.0138$). In another subgroup of patients with UAE ≥ 300 mg/g Cr, a significant improvement in UAE in the benidipine group was found compared with the amlodipine group (-25 ± 46 , $51 \pm 60\%$, $P = 0.031$, respectively). These results indicate that benidipine might significantly improve AI and have a greater renal protective effect than amlodipine in patients with advanced renal impairment.

Effects of benidipine and amlodipine on blood pressure: DHP-CCBs including amlodipine are recommended for BP reduction in hypertensive CKD patients on RAS inhibitors.^{6,13} However, in the present study, amlodipine did not provide significant BP reduction and only benidipine provided significant BP reduction. CCBs have been used previously for the treatment of patients given combination therapy consisting of ARB and CCBs. Prior CCB was changed to either amlodipine or benidipine in this study. L-Type CCBs were used for most of the prior therapeutic drugs. Because benidipine is a T/L type CCB, the effects (anti-aldosterone effects, improvement of salt sensitivity¹⁴) induced by T type CCB were added, and a significant decrease in blood pressure was observed. On the other hand, it is thought that the additional effect of a decrease in blood pressure was not observed even if the CCB was changed to amlodipine in the patients who had been given L-type CCBs.

Effect of benidipine on AI values: AI, which is the proportion of reflected pressure waves in pulse pressure waves in systole, is used as a measure of conductive vessel properties. It is difficult, however, to make an accurate assessment unless, in addition to conductive vessel properties, factors that are relevant to left ventricular-vascular interaction via reflection are available. It has been suggested that reductions in blood pressure or heart rate might be sources of error in the assessment of conductive vessels or arterial stiffness based on AI. Analysis of the overall population in the present study found a significant improve-

ment in AI only in the benidipine group, but a significant reduction in SBP was also noted only in the benidipine group. The cause of the lack of a significant reduction in SBP in the amlodipine group is unknown. The mean dose was almost the same in both groups (6.3 ± 2.4 mg/day in the amlodipine group and 7.4 ± 2.8 mg/day in the benidipine group for the overall study population; 6.4 ± 2.4 mg/day in the amlodipine group and 7.3 ± 2.5 mg/day in the benidipine group for the subgroup of patients achieving SBP < 140 mmHg).

A subgroup analysis was performed in patients achieving SBP < 140 mmHg because the analysis of the overall study population found that only the benidipine group showed a reduction in SBP. Both SBP and DBP were significantly reduced in both groups with no differences between the groups. In addition, in this subgroup there was a significant improvement in AI only in the benidipine group. However, there was a slight increase in PR in the amlodipine group, and a significant increase in the benidipine group. The effects of PR on AI were reported by Wilkinson, *et al* in a study of patients with a permanent pacemaker¹⁵ and a study of temporary pacing during cardiac catheterization.¹⁶ These studies found that an increase in heart rate led to a significant decrease in AI. This negative correlation between heart rate and AI was probably due to the following: although the ejection time is shortened in a manner dependent on heart rate with increased heart rate, vascular properties remain unchanged and therefore the reflection time is not greatly affected. Consequently, reflected waves are relatively delayed in a cardiac cycle, leading to a decrease in AI.

The present study, therefore, used a subgroup analysis by studying PR. In the benidipine group, a decrease in AI was noted in both the group with decreased PR (10 of 33 patients, 30.3%) and the group with increased PR (23 of 33 patients, 69.7%), particularly with a significant decrease in AI value in the group with increased PR. In contrast, in the amlodipine group, an increase in AI was noted among patients with decreased PR (11 of 31 patients, 35.5%) with no improvement, whereas a decrease, though not statistically significant, in AI was noted among patients with increased PR (20 of 31 pa-

tients, 64.5%). Thus, it seems that benidipine produces a greater improvement in AI than amlodipine, either with increased or decreased PR. Although it cannot be ruled out that a decrease in AI among patients with increased PR might be secondary to delayed reflected waves, it can be interpreted as a decrease in AI values among patients with decreased PR representing an improvement in vascular properties. Based on these findings, the improvement in AI observed in the benidipine group is thought to be caused not by a decrease in AI associated with just an increase in PR, but by modification effects on vascular elasticity, suggesting that benidipine acts differently from amlodipine. In addition, the percent changes in AI and PR (Figure 3) in the present study had a significant negative correlation in the amlodipine group, but no correlation was seen in the benidipine group, supporting the hypothesis that a significant decrease in AI observed in the benidipine group was not affected by PR.

Takenaka, *et al* reported that benidipine produced a greater improvement in AI than amlodipine, but there was no investigation of the potential effects of PR.⁶⁾ Our study provided additional clear evidence that an improvement in AI with benidipine was not due to the effects of PR, but might represent a direct effect on blood vessels. In addition, a further study comparing the vascular protective effects of benidipine and amlodipine showed that benidipine produced a greater improvement in pulse wave velocity than amlodipine under conditions causing similar blood pressure lowering effects.¹⁷⁾ This report indicates that benidipine has greater antioxidant or anti-inflammatory activity than amlodipine. Benidipine has also been reported to improve vascular endothelial function assessed by flow-mediated dilation.¹⁰⁾ Abe, *et al* reported that benidipine significantly suppresses aldosterone compared with amlodipine,¹⁸⁾ suggesting that these effects may contribute to the effect of benidipine on vascular elasticity.

Renal protective effects of benidipine in patients positive for albuminuria: In general, DHP CCBs block the L-type Ca channel to dilate blood vessels, leading to a lowering of SBP. The L-type calcium channel in renal microcirculation is present in renal glomerular afferent arterioles, but not in efferent arterioles. As CCBs that block only the L-type Ca channel do not dilate efferent arterioles but dilate only afferent arterioles, there are long-term concerns about increased UAE and impaired renal function associated with a relative increase in intraglomerular pressure. Conversely, as the T-type calcium channel is present in efferent arterioles, T/L-type CCBs are expected to dilate both afferent and efferent arterioles to reduce UAE and thereby maintain renal function.^{19,20)} In fact, it has been reported that T/L-type CCBs dilate both renal afferent and efferent arterioles to decrease intraglomerular pressure in patients with nephritis or nephrosclerosis,²¹⁾ with better renal outcomes than those observed for L-type CCBs.²²⁾

The present study compared the L-type CCB amlodipine and T/L-type CCB benidipine in CKD patients with albuminuria. In the amlodipine and benidipine groups in the overall study population, there was no significant improvement in UAE. A subgroup analysis of patients achieving SBP < 140 mmHg showed a significant difference in the percent change in UAE among patients with UAE $\geq$ 300 mg/g Cr between the benidipine ($-25 \pm 46\%$) and amlodipine ($51 \pm 60\%$) groups. No difference in blood pressure was found between the groups, suggesting that there were no benefits of previously reported

renal function amelioration resulting from antihypertensive effects²³⁾ and different effects due to different mechanisms of action, ie, different calcium channels that are intended to be blocked.

As in our study, Fujita, *et al*²⁴⁾ compared the combined therapies of an RAS inhibitor and amlodipine or cilnidipine in hypertensive CKD patients and reported that cilnidipine resulted in a significantly greater decrease in UAE than amlodipine among patients with UAE $\geq$ 300 mg/g Cr. Although our study found no significant differences among patients with mild renal impairment, benidipine resulted in a greater decrease in UAE than amlodipine among patients with advanced renal impairment. This suggests that benidipine was effective, as was observed for cilnidipine.

It is thought that UAE reflects vascular endothelial dysfunction.²⁵⁾ Benidipine has been reported to improve vascular endothelial function in basic and clinical research.^{10,26)} Our study suggested that benidipine might be superior to amlodipine in improving AI and UAE, which may be accounted for by the vascular protective effects of benidipine, including improvement in vascular endothelial function. In our study, no correlation was observed between the percent changes in AI and UAE ($P = 0.706$) in either the benidipine group or amlodipine group ($P = 0.879$). However, drugs with such vascular protective effects can be expected to prevent cardiovascular events. In fact, a study in coronary spastic angina suggested that benidipine was more effective for the prevention of cardiovascular events than other CCBs.⁹⁾ The ultimate goals of hypertension management are the prevention of cardiovascular events and an improvement in outcomes. The present study suggested that the T/L-type CCB benidipine might be a useful option in antihypertensive treatment intended to improve the long-term outcomes of hypertensive CKD patients.

Study limitations: This study has several limitations. First, the number of enrolled patients was small so it did not have enough power to show a significant improvement in renal function in the whole benidipine group, although this study was a randomized control study. Second, there was a possible selection bias because the age of the patient was not a factor in the randomization; therefore, there was a significant difference between the two groups in baseline patient characteristics. Third, this was a single center study, therefore, further larger randomized control trials may be needed to show the efficacy of benidipine to improve renal function in patients with any stage of CKD.

Conclusion: The results of the present study suggest that benidipine might decrease AI significantly and may bring about potentially greater improvements in UAE than amlodipine in patients with advanced renal impairment receiving RAS inhibitors.

DISCLOSURE

Conflict of interest: None

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