Original Article

Renal-Protective Effect of T- and L-Type Calcium Channel Blockers in Hypertensive Patients: An Amlodipine-to-Benidipine Changeover (ABC) Study

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Both strict blood pressure control and efferent artery dilatation are critical in reducing proteinuria, which in turn helps to regulate blood pressure. Benidipine, an L- and T-type calcium channel blocker, has the potential for increased effectiveness compared with L-type–dominant calcium channel blockers such as amlodipine. Therefore, we evaluated blood pressure and proteinuria after changeover from amlodipine to benidipine in poorly controlled hypertensive patients. Fifty-eight hypertensive outpatients undergoing amlodipine treatment and unable to achieve optimal blood pressure as determined by Japanese Society of Hypertension Guidelines for the Management of Hypertention (JSH 2004) were changed over to benidipine treatment. We measured blood pressure and pulse rate and assessed urinary protein excretion before and after changeover. Systolic and diastolic blood pressure dropped from 151/90 mmHg to 140/81 mmHg ($p<0.0001$). Mean blood pressure ($p<0.0001$) and pulse pressure ($p=0.0069$) were also reduced, but pulse rate increased from 75 bpm to 78 bpm ($p=0.0047$). Urinary protein excretion adjusted for urinary creatinine was reduced from 0.35±0.82 to 0.22±0.55 g/g creatinine ($p=0.0119$). The urinary protein reduction was observed only in patients with renin-angiotensin inhibition ($p=0.0216$). By switching from amlodipine to benidipine treatment, more than 80% of patients reduced their blood pressure, and more than 40% achieved optimal blood pressure. Higher urinary protein excretion ($p<0.0001$), lower glomerular filtration rate ($p=0.0011$) and presence of diabetes ($p=0.0284$) were correlated with reduction of urinary proteins during changeover. Taken together, our results suggest that benidipine may have greater efficacy than amlodipine in reducing blood pressure and proteinuria. (*Hypertens Res* 2007; 30: 797–806)

***Key Words*: benidipine, changeover, Japanese Society of Hypertension Guidelines for the Management of Hypertention (JSH 2004), urinary protein excretion, combination with angiotensin II receptor blocker**

Introduction

Chronic kidney disease (CKD) has received considerable attention in the management of lifestyle-related diseases, such as hypertension (*1*). Several recent reports suggest that CKD is an independent risk factor for cardiovascular disease in patients with hypertension (*2*), diabetes mellitus (DM) and so on (*3*). Proteinuria is one of the clinical parameters for diagnosing renal damage, especially glomerular hypertension, and has been reported as a risk factor and predictor for cardiovascular events (*4*). Therefore, reduction of proteinuria is a major

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Table 1. Patient Characteristics

	Before changeover	After changeover	*p* value
Male/Female	36/22		
Age	64.1±12.8		
Diabetes (*n* (%))	18 (31)		
Hyperlipidemia (*n* (%))	22 (38)		
Number taking antihypertensive drugs	2.1±1.0		
Amlodipine only (*n* (%))	17 (29)		
+ARB (*n* (%))	32 (55)		
+ACE inhibitor (*n* (%))	11 (19)		
+β-Blocker (*n* (%))	12 (21)		
+Diuretics (*n* (%))	4 (7)		
+α-Blocker (*n* (%))	4 (7)		
TC	205±29	213±31	n.s.
TG	139±67	157±102	n.s.
HDL-C	58±18	59±18	n.s.
UA	5.6±1.3	5.7±1.5	n.s.
Creatinine	1.0±0.5	1.0±0.5	n.s.
AST	23±9	24±8	n.s.
ALT	23±16	24±13	n.s.
γ-GTP	44±44	52±55	n.s.
FBG	118±48	123±60	n.s.

ARB, angiotensin II receptor blocker; ACE inhibitor, angiotensin converting enzyme inhibitor; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; UA, uric acid; AST, aspartate aminotransferase; ALT, alanine aminotransferase; γ-GTP, γ-glutamyl transpeptidase; FBG, fasting blood glucose.

goal in managing hypertensive patients.

Reduction of glomerular pressure is a principal strategy for reducing proteinuria in hypertensive patients (*5*). To decrease glomerular pressure, blood pressure (BP) must be more strictly lowered and arteriolar resistance in efferent arterioles reduced (*6*, *7*). Angiotensin II type 1 receptors are localized in both afferent and efferent arterioles (*8*), and angiotensin II receptor blockers (ARBs) (*9*) and angiotensin-converting enzyme inhibitors (ACEIs) (*10*) have been shown to reduce proteinuria in several multicenter randomized clinical trials. Based on these results, ARBs and ACEIs were selected as first choice drugs for managing hypertensive patients with CKD in the Japanese Society of Hypertension Guidelines for the Management of Hypertention (JSH 2004).

Calcium channel blockers (CCB) are also useful antihypertensive drugs for reducing BP. There are three types of calcium channels: L-type calcium channels are widely localized to smooth muscle cells of peripheral resistant arteries, N-type channels to those of the brain, and T-type channels to those of the sinus node and brain. In renal tissue, L-type calcium channels are only found in the afferent arterioles, while N-type and T-type calcium channels are localized in both efferent and afferent arterioles (*7*). Amlodipine is a representative CCB that is widely used all over the world (*11*, *12*), blocks L- and N-type calcium channels (*13*) and dilates the afferent arterioles more than the efferent arterioles (*14*). On the other hand, benidipine, a partial T-type CCB, dilates both efferent and afferent arterioles and reduces glomerular pressure (*15*).

Of these two CCBs, benidipine may be more effective at conferring renal protection by reducing glomerular pressure. However, the renal-protective and BP-lowering effects from standard doses of these two drugs have not been compared. Therefore, we designed an amlodipine-to-benidipine changeover (ABC) study to evaluate the effectiveness of benidipine in lowering BP and reducing urinary protein excretion (UPE).

Methods

Study Population and Protocol

Sixty-three hypertensive outpatients at Osaka University Hospital who were administered 5 mg of amlodipine once a day for at least 3 months were recruited for the study. At the time of entry, patients were unable to achieve optimal BP as recommended by JSH 2004 guidelines; JSH 2004 defines hypertension as a systolic BP (SBP) of more than 140 mmHg and/or diastolic BP (DBP) exceeding 90 mmHg and/or administration of antihypertensive drugs. We excluded patients who had suffered a stroke or cardiovascular event within the previous year, those who had congestive heart failure of grade II or higher on the New York Heart Association scale, and those who had more than 3.0 mg/dL of serum creatinine. Use of other hypertensive drugs was permitted, and the

Table 2. Blood Pressure and Pulse Rate at Each Visit

	−6 months	−5 months	−2 months	−1 month	Changeover	1 month	2 months
SBP (mmHg)			151±23	149±21	152±16	138±17***,###,$$$	141±19**,##,$$$
	(146±13)	(144±14)	(144±14)	(144±15)	(150±13)	(135±14)***,##,$	(138±16)**,#
DBP (mmHg)			90±14	89±13	90±11	81±12***,###,$$$	82±12***,###,$$$
	(84±9)	(85±8)	(86±8)	(85±9)	(87±9)	(79±10)***,###,$$$	(80±10)***,##,$$$
MBP (mmHg)			110±16	109±14	111±11	100±12***,###	101±13***,###,$$$
	(105±9)	(105±8)	(106±9)	(105±9)	(108±9)	(97±10)***,###,$$$	(99±11)***,##,$$
PP (mmHg)			60±15	60±15	62±14	57±12#,$$	59±14#
	(62±13)	(60±12)	(58±12)	(59±13)	(63±12)	(56±11)**,$	(59±13)*,$
PR (bpm)			77±10	75±10	75±9	79±11#,$$	77±10$
	(76±10)	(75±10)	(76±9)	(73±9)	(74±9)	(76±11)*,##	(75±10)

Data expressed as mean±SD in parentheses (lower row reflects data of 40 of 58 patients treated with amlodipine 6 months prior to changeover). SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; PP, pulse pressure; PR, pulse rate. *$p<0.05$, **$p<0.01$, ***$p<0.001$ *vs*. −2 months; #$p<0.05$, ##$p<0.01$, ###$p<0.001$ *vs*. −1 month; $$p<0.05$, $$$p<0.01$, $$$$p<0.001$ *vs*. changeover.

doses of these drugs were not changed during the study. Our protocol was approved by the hospital ethics committee, and informed consent was obtained from all subjects 2 months prior to changeover.

We measured BP at the next two visits (1 month prior to changeover and at the time of changeover). The time between visits was approximately 1 month, and three patients with average BP lower than optimal at the time of changeover were excluded. We then modified our treatment of 60 hypertensive patients from 5 mg of amlodipine to 8 mg of benidipine once a day. BP post-changeover was measured at 1 month and 2 months after changeover. Two patients left the study due to headache and dizziness, leaving 58 hypertensive patients for analysis.

Forty of the 58 patients had previously been treated with amlodipine (5 mg daily) for 6 months prior to the study and changeover; we therefore retrospectively obtained an official BP at 5 and 6 months prior to changeover (*i.e.*, at −5 and −6 months) to determine the stability of BP and PR over the course of the study.

Blood Pressure Measurement and Renal Function

BP and pulse rate (PR) were measured twice in the sitting position after 10 min of rest using a BP-103iII sphygmomanometer (Nippon Colin Co., Ltd., Tokyo, Japan), and average BP and PR were automatically calculated. BP and PR measurements were taken three times for each patient and the average BP and PR for the three visits was adopted. All subjects were administered amlodipine or benidipine on the mornings of visits at 2 months prior to changeover (−2 months), at changeover, and at 1 month after changeover; and all subjects were given no drugs on the mornings of visits at 1 month prior to changeover (−1 month) and 2 months after changeover.

To evaluate how the changeover improved renal function, we also measured serum and urinary creatinine and urinary protein at −1 month and 2 months after an overnight fast. We calculated UPE adjusted by urinary creatinine and estimated the glomerular filtration rate (GFR) using the modified Modification of Diet in Renal Disease (MDRD) equation (GFR [mL/min/1.73 m^2] = 186.3 × (serum creatinine)$^{-1.154}$ × (age)$^{-0.203}$ × 0.881 [× 0.742 if female]).

Statistical Analysis

Results are expressed as the mean±SD. Data were analyzed with commercially available statistical software (STATVIEW version 5; Abacus Concepts, Inc., Berkeley, USA). Differences between treatment with amlodipine and benidipine were assessed using the paired *t*-test. Differences between patients with and without renin-angiotensin system (RAS) inhibition and between patients with low and high UPE were assessed by one-factor ANOVA and Fisher's test. A value of $p<0.05$ was considered statistically significant.

Results

Patient Characteristics

Characteristics of the 58 patients completing the changeover study are summarized in Table 1. Seventeen patients were administered only amlodipine, and 41 were also treated with other antihypertensive drugs, such as an ARB ($n=32$, 55%), ACEI ($n=11$, 19%), β-blocker ($n=12$, 21%), diuretics ($n=4$, 7%) or α-blocker ($n=4$, 7%) in addition to amlodipine. Treatment of 58 hypertensive patients was modified from 5 mg of amlodipine to 8 mg of benidipine once a day, and other antihypertensive drugs were not changed during the study. The other common risk factors and liver functions described in Table 1 were not changed during the study.

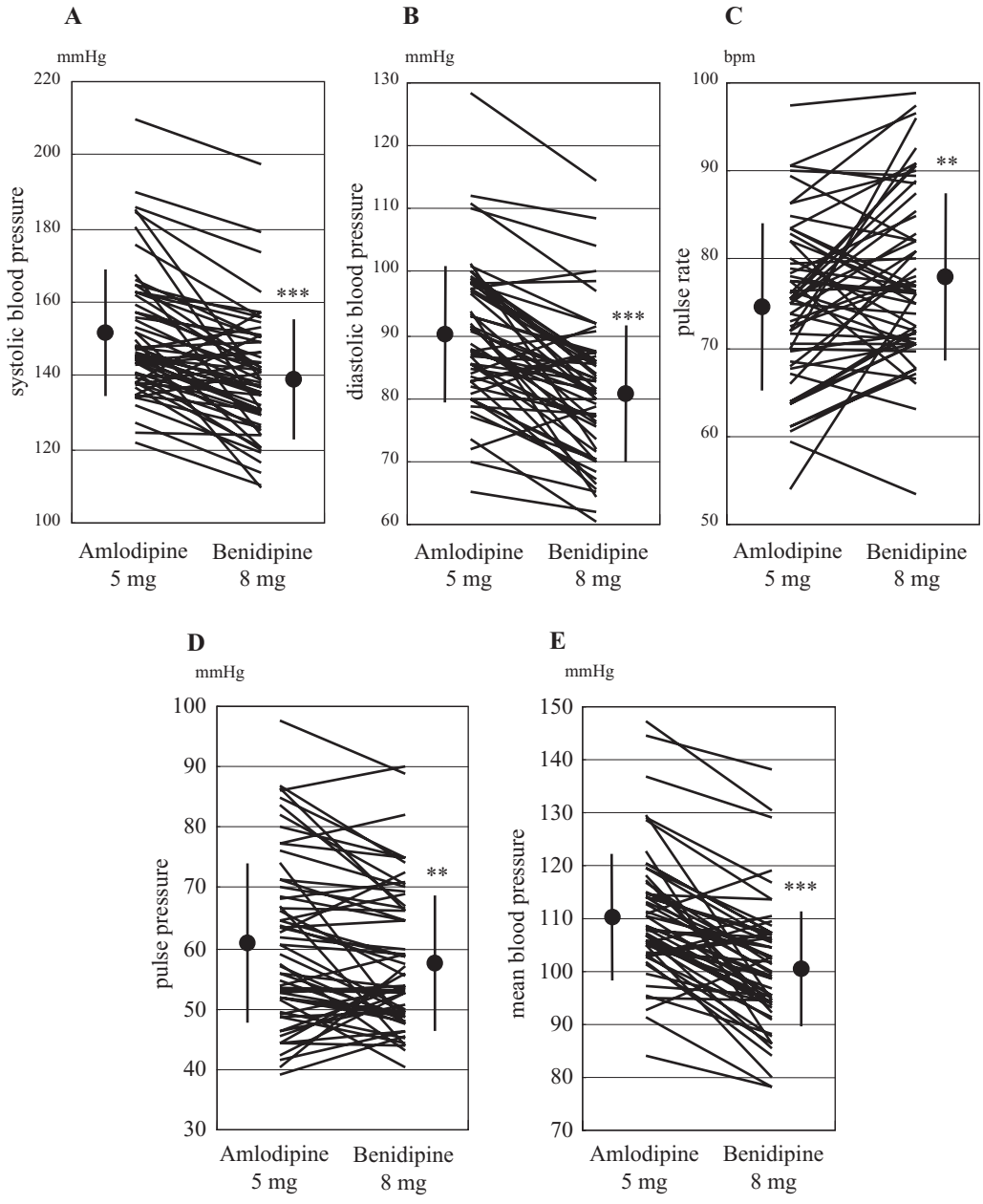

Fig. 1. *Average blood pressure and pulse rate measurements before and after changeover. A: Systolic blood pressure (SBP); B: diastolic blood pressure (DBP); C: pulse rate; D: pulse pressure; E: mean blood pressure. *p < 0.05, **p < 0.01, ***p < 0.0001 vs. during amlodipine administration.*

Blood Pressure and Pulse Pressure at Each Visit

BP and PR did not differ with administration of amlodipine (−2 months, −1 month and changeover) or benidipine (1 month and 2 months) (Table 2). SBP, DBP and mean BP during benidipine administration were significantly lower than those during amlodipine administration. There were no significant differences or changes between BP and PR prior to the changeover (−6 and −5 months compared to −2 and −1 months).

Blood Pressure and Pulse Rate before and after Changeover

To compare BP and PR between before and after changeover, we calculated the average BP and PR from two visits (the visit at −1 month and that at changeover) as representative of the value before changeover (amlodipine administration), and the average BP from two visits (the visit at 1 month and that at 2 months) as representative of the value after changeover (benidipine administration). As shown in Fig. 1, SBP (139.5±16.4

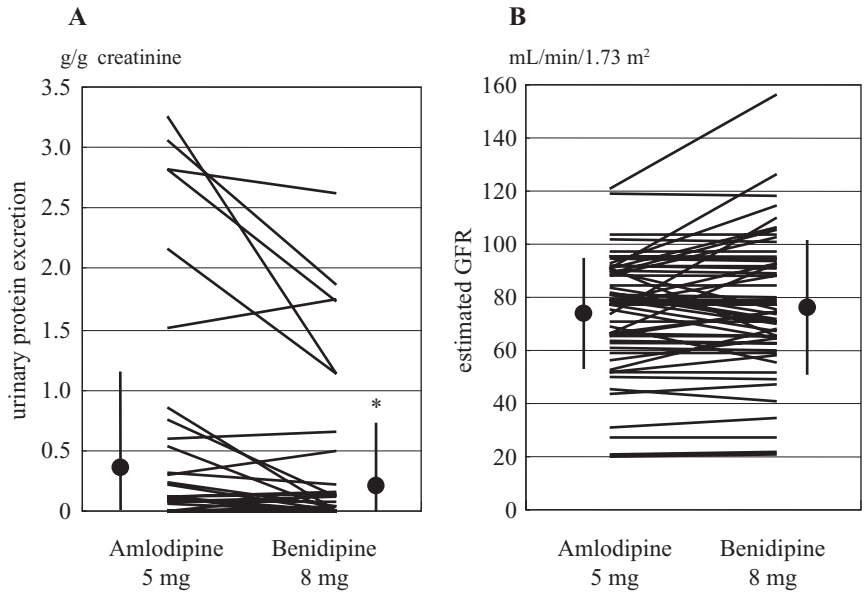

Fig. 2. *Average renal function before and after changeover. A: Urinary protein excretion; B: estimated GFR. *p < 0.05 vs. during amlodipine administration.*

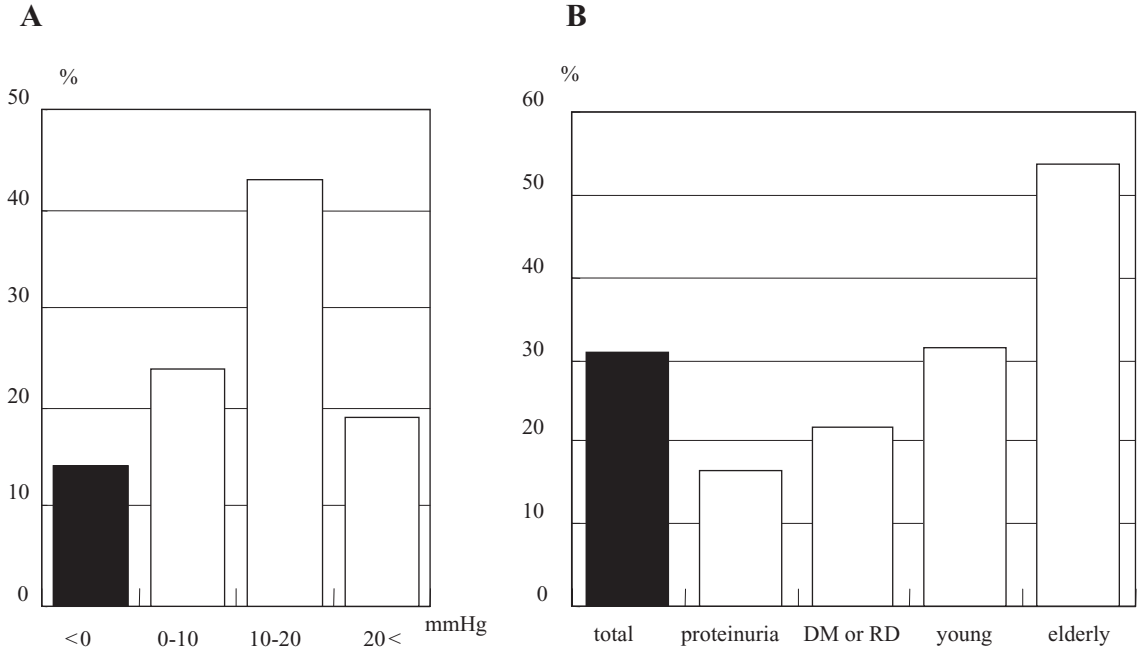

Fig. 3. *Systolic blood pressure reduction and achievement of JSH 2004 guidelines upon changeover to benidipine. A: Reduction of systolic blood pressure (SBP) was measured in patients post-changeover and expressed as a difference in pressure as indicated on the x-axis. B: Achievement of optimal BP levels according to JSH 2004 guidelines was determined in various subgroups as indicated on the x-axis. DM, diabetes mellitus; RD, renal disfunction.*

mmHg) and DBP (81.3±11.1 mmHg) after changeover were significantly reduced compared to those prior to changeover (151.4±17.4 and 90.1±11.1 mmHg, respectively; $p<0.0001$ for both). PR (78.0±9.6 bpm) after changeover was significantly greater than PR before changeover (74.8±9.0 bpm, $p=0.0047$). Pulse pressure (58.2±11.8 mmHg) and mean BP

(100.7±11.9 mmHg) after changeover were significantly reduced compared to the measurements before changeover (61.2±14.0 and 110.5±11.8 mmHg; $p=0.0069$ and $p<0.0001$, respectively).

Renal Function before and after Changeover

We evaluated the effects of changeover on renal function by analyzing UPE and estimated GFR, as shown in Fig. 2. UPE after changeover (0.22±0.55 g/g creatinine) was significantly reduced compared with that before changeover (0.35±0.82 g/g creatinine, $p=0.0119$). However, estimated GFR was not significantly different between before (75.0±21.5 mL/min/1.73 m^2) and after (77.7±25.3 mL/min/1.73 m^2) changeover.

Blood Pressure Reduction Response

To analyze BP reduction upon changeover from amlodipine to benidipine, a histogram was generated based on the SBP values, as shown in Fig. 3A. Eight patients (14%) showed a higher SBP after changeover, 14 (24%) showed an SBP reduction of less than 10 mmHg, 25 (43%) had an SBP reduction of 10–20 mmHg, and 11 (19%) had an SBP reduction of more than 20 mmHg.

Achievement of Optimal Blood Pressure Guided by JSH 2004 Guidelines

The percentage of patients achieving optimal BP, as outlined in the JSH 2004 guidelines, is summarized in Fig. 3B. Overall, 18 of 58 patients (31%) achieved optimal BP. In patients with proteinuria, or more than 1.0 g/day UPE (less than 125/75 mmHg), the frequency was 1/6 (17%); in patients with DM or renal dysfunction (RD), or less than 130/80 mmHg, the frequency was 5/23 (22%); in young patients (less than 65 years) without major complications (less than 130/85 mmHg), the frequency was 5/16 (31%); and in elderly patients (less than 140/90 mmHg), the frequency was 7/13 (54%).

Influences of Renin-Angiotensin System Inhibition

To study the influence of combination with RAS inhibition, we analyzed BP changes and UPE in patients treated with ($n=36$ of 58) or without ($n=22$ of 58) an ARB and/or ACEI (Fig. 4A). The SBP values in the patients with (150.0±16.4 mmHg) and without (153.5±19.0 mmHg) RAS inhibition were significantly reduced upon changeover (139.1±16.1 and 140.1±17.3 mmHg, respectively; $p<0.0001$ for each); similarly, DBP in those with (88.1±9.2 mmHg) and without (93.4±13.3 mmHg) RAS inhibition was also significantly reduced upon changeover (80.0±10.0 and 83.5±12.6 mmHg, respectively; $p<0.0001$ for each). Patients with RAS inhibition (0.46±0.92 g/g creatinine) showed significant reduction in UPE after changeover (0.27±0.63 g/g creatinine; $p=0.0216$). However, UPE inhibition (0.18±0.60 g/g creatinine) was not significantly reduced in patients without RAS inhibition (0.12±0.37 g/g creatinine; $p=0.3143$) (Fig. 4B).

Influences of Urinary Protein Excretion before Changeover

To study the influence of UPE on the effects of the changeover, we analyzed changes in BP in patients with high UPE (≥0.3 g/g creatinine; $n=12$ of 58) compared to low UPE (<0.3 g/g creatinine; $n=46$ of 58). In patients with low UPE, SBP and DBP were significantly reduced (from 155±16 to 138±15 mmHg for SBP and from 90±9 to 80±10 mmHg for DBP; $p<0.0001$ for both); however, in patients with high UPE, the reductions in SBP and DBP did not reach the level of statistical significance (from 154±24 to 146±21 mmHg for SBP and from 90±17 to 86±10 mmHg for DBP; $p=0.0604$ and $p=0.0748$; respectively) (Fig. 5A). UPE was significantly reduced only in patients with high UPE, from 1.6±1.2 g/g creatinine to 1.0 ±0.9 g/g creatinine ($p=0.0118$) (Fig. 5B).

Urinary Protein Excretion Reduction Ratio and Other Factors

To clarify the influence of other factors on the reduction in urinary protein, we calculated the percentage change of UPE levels as a UPE reduction ratio (determined as [UPE before changeover – after changeover]/UPE before changeover). We then analyzed the correlation between this ratio and continuous variables by a single linear analysis, and between this ratio and specific categories by an unpaired *t*-test (Table 3). Higher UPE level before changeover ($p<0.0001$), lower estimated GFR before changeover ($p=0.0011$) and the complication with diabetes ($p=0.0284$) were correlated with significant urinary protein reduction during changeover. In contrast, UPE reduction was not correlated with SBP before changeover in patients who were administrated amlodipine, and UPE reduction was not correlated with SBP reduction during treatment with amlodipine or benidipine.

Discussion

The standard doses of amlodipine and benidipine used in Japan are 5 mg and 8 mg, respectively. Although there has been no direct comparison of the efficacy of these two drugs at these doses, administering 4–8 mg of benidipine once a day has been shown to adequately lower BP (*16–18*). Amlodipine has also been shown to adequately lower BP in a large number of clinical trials (*11*, *12*) and in Japanese hypertensives (*19*, *20*). However, there has been no previous report directly comparing the BP-lowering effects of these two antihypertensive drugs. In the present study, we demonstrated that 8 mg of benidipine once a day resulted in a 12 mmHg greater reduction of SBP and a 9 mmHg greater reduction of DBP than 5

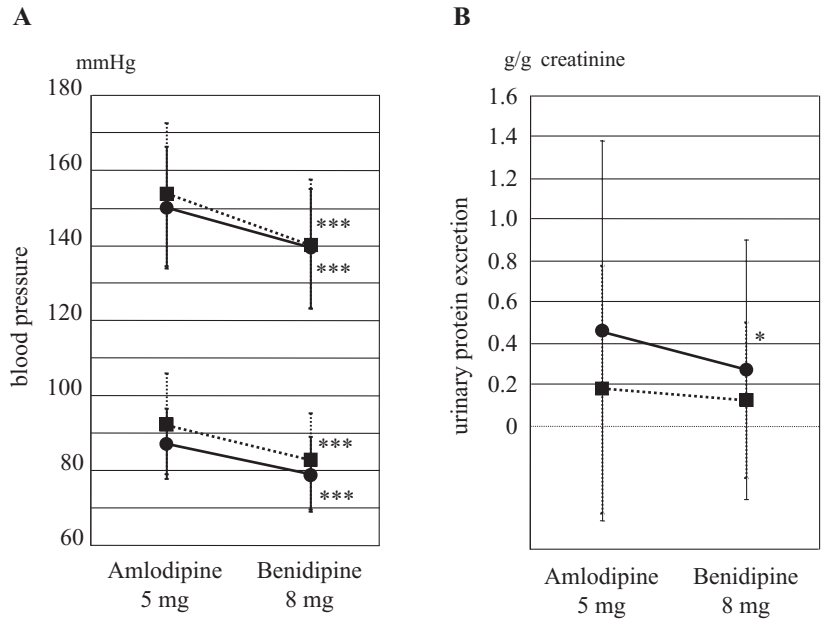

Fig. 4. *Effects of renin-angiotensin inhibition on changeover to benidipine. Measurements were taken as indicated in patients with renin-angiotensin inhibition (represented as a solid line), and in patients without renin-angiotensin inhibition (represented as a dashed line). *p < 0.05, ***p < 0.0001 vs. during amlodipine administration. A: Changes in blood pressure upon changeover in patients with or without renin-angiotensin inhibition. B: Changes in urinary protein excretion in patients with or without renin-angiotensin inhibition.*

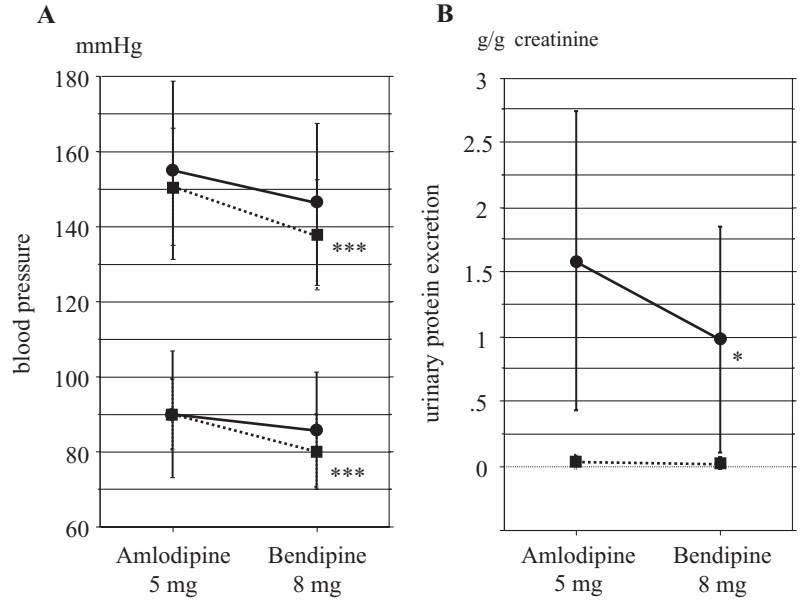

Fig. 5. *Effects of urinary protein excretion levels on blood pressure levels (A) and renal function (B) upon changeover to benidipine. Measurements were taken as indicated in patients with high levels of urinary protein excretion (represented as a solid line), and in patients with low levels of urinary protein excretion (represented as a dashed line). *p < 0.05, ***p < 0.0001 vs. during amlodipine administration.*

Table 3. Comparison of Urinary Protein Excretion Reduction Ratio and Other Factors

	F	*p* value
Sex		0.6106
Age	0.098	0.7556
Diabetes mellitus		0.0284
Hyperlipidemia		0.4572
PreSBP	0.017	0.8979
PreDBP	0.383	0.5387
SBP reduction	0.007	0.9333
SBP reduction ratio	0.015	0.9043
Pre-urinary protein excretion	107.789	<0.0001
PreGFR	11.804	0.0011
RA inhibition		0.2275

PreSBP, systolic blood pressure before changeover; PreDBP, diastolic blood pressure before changeover; SBP reduction, difference of systolic blood pressure between before and after changeover; SBP reduction ratio, difference of systolic blood pressure between before and after changeover per systolic blood pressure before changeover; PreGFR, glomerular filtration rate before changeover; RA inhibition, treatment with renin angiotensin inhibition.

mg of amlodipine once a day. As this study protocol was a changeover rather than a crossover or randomized control protocol, we are not able to directly conclude that benidipine has an advantage over amlodipine. Notably, as shown in Table 2, BP during treatment with amlodipine was very stable; however, after changeover to benidipine, BP was promptly reduced even in the morning without administration. Thus, although a further crossover or randomized study is needed to conclude that benidipine is more effective than amlodipine, our results strongly suggest that treatment with benidipine may reduce BP compared with the current amlodipine protocol.

Several current guidelines for managing essential hypertension (*21*, *22*) and many large multicenter trials (*11*, *12*) suggest that strict reduction of BP is the most important factor in prevention of cardiovascular mortality and morbidity. As an entry criterion for this study we sought hypertensive patients who could not achieve optimal BP even if treated with antihypertensive agents, such as amlodipine treatment at 5 mg per day. In the present study, more than 85% of subjects had reduced BP after the changeover, and more than 60% of subjects and 19% of subjects had BP drops exceeding 10 mmHg and 20 mmHg, respectively. Moreover, achieving optimal BP was an important goal of this study, and by the conclusion of the study, more than 30% of the subjects had achieved optimal BP as defined by JSH 2004 guidelines, and the optimal BP achievement ratio was gradually increased (Fig. 3B). Both the reduction in SBP before changeover and the reduction in SBP after changeover were significantly correlated with higher SBP before changeover (data not shown), indicating that benidipine may be more effective in reducing BP in patients with higher BP than in those with optimal BP.

The present study suggested that treatment with benidipine could reduce UPE more than treatment with amlodipine. Previous reports have suggested that benidipine dilates both efferent and afferent arterioles, whereas amlodipine strongly reduces only afferent arteriolar resistance. To reduce glomerular pressure, strict reduction of systemic BP is also important, and the MDRD study revealed that reduction of mean BP was useful for decreasing UPE (*23*). In the present study, mean BP was significantly lower in patients treated with benidipine. In evaluating other factors which may contribute to UPE reduction (Table 3), we found that while overall BP reduction did not influence UPE reduction, the levels of baseline UPE prior to changeover were significantly correlated with UPE reduction. As shown in Fig. 5A and B, in patients with higher levels of baseline UPE, UPE levels were significantly reduced, but the BP in these patients was not statistically changed. Although we could not verify the efferent arteriolar dilation, one possibility is that this dilation could contribute to the observed UPE reduction, as the systemic BP reduction and reduction of efferent arterioles leads to a marked reduction in glomerular pressure. Taken together, these results suggest that benidipine administration might reduce UPE in patients with higher levels of UPE independent of BP reduction, possibly by efferent arteriolar dilation.

JSH 2004 guidelines recommend combination therapy to achieve optimal BP. Several clinical trials have suggested that treatment with CCBs or ARB/ACEI was effective in preventing cardiovascular events, and combination therapy with CCBs and ARB/ACEI was recommended for hypertensive patients with complications such as CKD, stroke or congestive heart failure. As shown in Figs. 4 and 5 benidipine with an ARB ($n=25$), ACEI ($n=4$) or ARB with ACEI ($n=7$) significantly reduced UPE before and after changeover compared to benidipine treatment alone without RAS inhibition. In the Dahl rat model, reduction of UPE was enhanced when benidipine was used in combination with an ARB (*24*). This effect was observed with benidipine but not with the CCB amlodipine (*25*). The present study assessed these CCB/ARB combinations in humans, showing in addition that higher levels of baseline UPE before changeover were important to reduce UPE during changeover. Patients with high levels of UPE were more likely to receive ARB/ACEI treatment (10 of 12 patients) than patients with low levels of UPE (26 of 46 patients), although the trend did not reach the level of statistical significance. One possible explanation for the statistically significant correlation between UPE reduction and higher baseline UPE may be simply that there was a greater UPE reduction ratio in patients with higher UPE levels. Therefore, the marked UPE reduction in patients treated with benidipine and ARB/ACEI may have been be partially caused by the higher levels of baseline UPE before changeover.

Though our study demonstrates the benefits of benidipine, amlodipine has been proven effective at preventing cardio-

vascular events or total mortality in many multicenter trials (*11*, *12*, *26*). In these studies, amlodipine showed stable, dependable and long-term BP-lowering effects. To achieve long-term survival, strict BP control is the most important factor, and amlodipine is remarkably effective for dependable BP control. We are unable to speculate about the potential effects of increasing the amlodipine dosage from 5 mg a day to 10 mg a day, rather than simply changing to benidipine treatment. In the present study, patients treated with amlodipine showed a stable and controlled BP (prior to changeover), and thus increasing the dosage to 10 mg might result in both a strong, stable BP and a good prognosis.

In the present study, a standard dose of benidipine produced a greater reduction in BP and UPE than did amlodipine. Moreover, benidipine and RAS inhibition collaborated to reduce UPE in patients with essential hypertension, and in particular, benidipine reduced UPE in patients with higher UPE before changeover. Together these data suggest that benidipine, either alone or in combination with RAS inhibition, might be beneficial for managing hypertensive patients, especially those with higher BP.

Study Limitations

The present study included several study limitations. The most important limitation was the study protocol, as only a changeover was performed to compare the two antihypertensive drugs. A subsequent crossover or randomized study will be needed to conclusively compare benidipine and amlodipine treatment. In addition, we preferentially selected subjects with poorly controlled hypertension who were being treated with amlodipine. This selection bias enabled the enrollment of patients who did not respond well to amlodipine. From an ethical standpoint, we could not switch back to amlodipine from benidipine when patients achieved optimal BP. Moreover, multicenter clinical trials to clarify whether benidipine can prevent cardiovascular events are required. The results of the Combination Therapy of Hypertension to Prevent Cardiovascular Events (COPE) trial should be useful for evaluating the efficacy of benidipine (*27*).

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