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The therapeutic advantage of combination antihypertensive drug therapy using amlodipine and irbesartan in hypertensive patients: analysis of the post-marketing survey data from PARTNER (Practical combination therapy of Amlodin and angiotensin II Receptor blocker; Safety and efficacy in patients with hypertension) study

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Abstract

Two-thirds of hypertensive patients need a combination antihypertensive therapy to achieve the target blood pressure (BP). The PARTNER (Practical combination therapy of Amlodin and angiotensin II Receptor blocker; Safety and efficacy in paTieNts with hypERtension) study is a prospective specific clinical use survey examining the efficacy and safety of 12-week treatment with amlodipine (AML) and Angiotensin II Receptor Blocker (ARB) in 5900 hypertensive patients. The current analysis was performed as to the BP control, adverse reactions, and the effects on laboratory data in patients treated with the combination of AML and irbesartan (IRB), namely the patients added AML to already taking IRB (AML add-on group, $n = 1202$) and the patients added IRB to AML (IRB add-on group, $n = 1050$). Both study groups showed distinct decreases in office BP at 4 week ($p < 0.001$) and the antihypertensive effects were sustained to 12 week ($p < 0.001$). The percentage of patients achieving BP < 140/90 mmHg was ~70% in either group. Proteinuria and estimated glomerular filtration rate (eGFR) were significantly improved in hypertensive patients with baseline eGFR <60 ml/min/1.73 m^2. Serum uric acid was reduced either by adding AML or IRB, and the reductions were prominent in patients with serum uric acid >7 mg/dl. The incidence of adverse reactions was as few as 1.11% and there were no severe adverse reactions which hampered the continuation of combination therapy. In conclusion, combination antihypertensive therapy with AML and IRB effectively lowers BP without particular safety problems, reduces serum uric acid especially in patients with hyperuricemia and exhibits renoprotective effects in patients with chronic kidney disease.

Keywords

Amlodipine, angiotensin II receptor blocker, calcium channel blocker, combination therapy, irbesartan, uric acid

History

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Introduction

Hypertension is a serious risk factor for stroke and cardiovascular events. To reduce the risk of such events, the Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH2014) (1), emphasized the importance of strict 24-h control of blood pressure (BP) and recommended the use of antihypertensive drugs that were tailored to the conditions of individual patients. However, BP control may be insufficient for some patients, as previous studies in Japan have indicated that antihypertensive goals were achieved in ≤40% of patients receiving a single antihypertensive drug (2,3). JSH2014 recommended combination therapy using multiple drugs for patients who fail to achieve treatment goals with a single antihypertensive drug, and for high-risk patients with grade 2 or 3 hypertension.

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Regarding the choice of antihypertensive drugs, a long-acting calcium channel blocker (CCB) and an angiotensin II receptor blocker (ARB) are often used for combination antihypertensive therapy in Japan. Combined use of CCBs and ARBs, which have different mechanisms of action, should produce greater antihypertensive effects and less adverse reactions, as compared to individual drug treatment in a high dose. In addition, the use of fixed-dose combination drugs improves patient's compliance because of the need to take a less number of tablets and this can improve long-term BP control (4). Several CCB and ARB combinations have been introduced for clinical use in Japan since 2010. In December 2012, AIMIX tablets containing a combination of amlodipine (AML) and irbesartan (IRB) were approved in Japan.

AML is a CCB with a long half-life (~36 h), allowing once-a-day dosing for the treatment of hypertension (5,6). A number of clinical studies have shown that AML exerted certain antihypertensive effects and alleviated cardiovascular organ injuries such as left ventricular hypertrophy (7). In addition, a number of large-scale clinical trials (5,6) have shown that

AML exerted preventive effects against cardiovascular disease along with BP reduction. On the other hand, IRB is an ARB that binds tightly to the angiotensin II type 1 receptor, and also provides antihypertensive efficacy over a 24-h period with once-daily administration (8). It has been shown that IRB inhibited the progression of nephropathy in hypertensive patients with type 2 diabetes through the effects that were not solely attributable to the BP changes (9,10).

Thus, the combination therapy of AML and IRB would be expected to exhibit beneficial effects in addition to the antihypertensive effect by each drug. Since there is insufficient clinical experience of AIMIX treatment, it would be useful to collect information on the efficacy and safety of this combination therapy with AML and IRB in a post-marketing clinical setting. We therefore conducted the analysis of the data from subjects treated with AML and IRB combination in the PARTNER study.

Methods

Patients included in the analysis

The PARTNER study was carried out by Dainippon Sumitomo Pharma Co., Ltd. as a specific clinical use survey, in compliance with Good Post-marketing Study Practice. The target number of patients was 6000. Chief Professor Toshihiko Ishimitsu (Department of Cardiology and Nephrology, Dokkyo Medical University) served as a medical expert for this survey and engaged in sub-analysis planning and considered the results. Dainippon Sumitomo Pharma performed the sub-analysis based on Toshihiko Ishimitsu's direction. The survey was conducted from July 2011 to October 2013. The detailed PARTNER study protocol has been described previously (11). Briefly, a total of 6058 patients were registered, however, 158 were excluded because of protocol violation, neglect of visits or insufficient data collection, and 5900 had fulfilled the study protocol. ARB was added to AML ($n = 3198$) or ARB was added to AML ($n = 1511$) or both were simultaneously started ($n = 1191$), and the combination therapy was continued for 3 months. From these participants, the following patients were extracted to examine the efficacy and safety of AML and IRB combination.

Two groups of patients were included in this analysis: (1) patients where AML was added on to existing treatment with IRB (AML add-on group, $n = 1202$) and (2) patients where IRB was added on to existing treatment with AML (IRB add-on group, $n = 1050$). In each group, the combination therapy was continued for 12 weeks.

Data collection

The background variables recorded for each patient included the presence/absence and details of complications, age, height, body weight and duration of hypertension. Medication information relating to AML and IRB was recorded for each patient, including the daily dosage, daily dosing frequency, dosing period and continuation status at 12 weeks. Concomitant drug usage was also recorded, including the presence/absence of concomitant drugs, the names of concomitant drugs, daily dosage and dosing period(s). Office BP was measured by a sphygmomanometer at each visit with the patient in the sitting position after >10 min of rest. In addition, the information as to the occurrence of adverse effects was obtained. From the laboratory measurements performed before the combination therapy and at the end of study period, we collected the data of serum K, creatinine and uric acid. The estimated glomerular filtration rate (eGFR) was calculated from the serum creatinine level and age by the following equation (12): $\mathrm{eGFR} = 194 \times \mathrm{Age}^{-0.287} \times \mathrm{sCr}^{-1.094}$ ($\times 0.739$ for female).

Statistical analysis

Data were analyzed by Fisher's exact test (for 2×2 tables) or chi-squared test. The Cochran–Armitage test was employed for categories of sequential nature. Quantitative data such as BP, heart rate (HR) and laboratory parameters were analyzed by paired *t*-test. Factor-wise analysis of the mean magnitude of change in systolic BP (SBP) was performed using the Wilcoxon rank sum test or the Jonckheere test (if it involved categories of a sequential nature). Data were expressed as mean ± SD. The significance level was set at 5% (two-tailed). Treatment safety was monitored by recording the presence/absence and details of adverse events using MedDRA/J (Ver. 16) to code adverse reactions, followed by data analysis using preferred terms.

Results

Baseline characteristics

Table 1 shows the baseline characteristics of all the 2252 participants, including 1202 patients in the AML add-on group and 1050 patients in the IRB add-on group. The sex ratio, the mean patient age and body mass index were comparable in the two groups. The mean values of SBP, diastolic BP (DBP) and HR were not significantly different between the two groups. As for the severity of hypertension, grade I hypertension (140–159/90–99 mmHg) was most frequently observed in 46.2% of patients. Qualitative urinary protein data were available in 698 patients, and 112 patients were positive for proteinuria (+ or more). Calculation of eGFR from serum creatinine was possible in 900 patients, and the eGFR value was <60 ml/min/1.73 m^2 in 210 patients. As many as 1287 patients (57.1%) had complications in addition to hypertension. The most frequent complication was dyslipidemia (29.6%), followed by diabetes mellitus (15.3%). The proportion of diabetic patients at baseline was significantly lower in the AML add-on group than in the IRB add-on group.

Antihypertensive medications given to the participants are listed in Table 2. The average dose of AML was higher and the average dose of IRB was higher in the AML add-on group than in the IRB add-on group. Only 176 patients (7.8%) used another antihypertensive drug, in addition to AML and IRB. The other antihypertensive drug used most frequently was a diuretic (3.9%).

Treatment efficacy

Among 1124 patients on the AML add-on group and 962 patients in the IRB add-on group, serial BP data were

Table 1. Baseline characteristics of the study subjects.

	Total ($n = 2252$)	AML add-on group ($n = 1202$)	IRB add-on group ($n = 1050$)	p Value
Sex (male/female)	1124/1128	604/598	520/530	N.S.
Age (year)	65.2 ± 13.1	64.8 ± 12.9	65.5 ± 13.4	N.S.
Body mass index (kg/m^2)	24.6 ± 4.1	24.6 ± 4.1	24.6 ± 4.1	N.S.
Habitual smoking	343 (15.2%)	175 (14.6%)	168 (16.0%)	N.S.
Systolic BP (mmHg)	155.0 ± 16.7	155.6 ± 16.6	154.2 ± 16.8	N.S.
Diastolic BP (mmHg)	87.7 ± 12.6	88.5 ± 12.4	86.8 ± 12.7	N.S.
Heart rate (bpm)	75.0 ± 11.0	74.5 ± 11.4	75.6 ± 10.8	N.S.
BP classification				
Normal	70 (3.1%)	32 (2.7%)	38 (3.6%)	N.S.
High-normal	159 (7.1%)	72 (6.0%)	87 (8.3%)	N.S.
Grade I	1041 (46.2%)	552 (45.9%)	489 (46.6%)	N.S.
Grade II	604 (26.8%)	341 (28.4%)	263 (25.0%)	N.S.
Grade III	238 (10.6%)	137 (11.4%)	101(9.6%)	N.S.
eGFR (ml/min/1.73 m^2)	73.2 ± 21.1	73.9 ± 22.4	72.4 ± 19.7	N.S.
≥60	690 (30.6%)	365 (30.4%)	325 (31.0%)	N.S.
<60	210 (9.3%)	104 (8.7%)	106 (%10.1)	N.S.
N.A.	1352 (1352%)	733 (61.0%)	619 (59.0%)	N.S.
Urinary protein (qualitative)				
Negative (− or ±)	586 (26.0%)	299 (24.9%)	287 (27.3%)	N.S.
Positive (+ or more)	112 (5.0%)	51 (4.2%)	61 (5.8%)	N.S.
N.A.	1554 (69.0%)	852 (70.9%)	702 (66.9%)	N.S.
Complication				
Dyslipidemia	667 (29.6%)	365 (30.4%)	302 (28.8%)	N.S.
Diabetes mellitus	345 (15.3%)	213 (17.7%)	132 (12.6%)	0.001
Hyperuricemia	143 (6.3%)	74 (6.2%)	69 (6.6%)	N.S.
Cerebrovascular disease	93 (4.1%)	51 (4.2%)	42 (4.0%)	N.S.
Heart disease	155 (6.9%)	93 (7.7%)	62 (5.9%)	N.S.
Renal disease	99 (4.4%)	57 (4.7%)	42 (4.0%)	N.S.
Hepatic disease	131 (5.8%)	68 (5.7%)	63 (6.0%)	N.S.

Data are the mean ± SD. AML, amlodipine; IRB, irbesartan; BP, blood pressure; eGFR, estimated glomerular filtration rate; N.A., not available; N.S., not significant.

Table 2. Antihypertensive medication given during the study period.

	Total ($n = 2252$)	AML add-on group ($n = 1202$)	IRB add-on group ($n = 1050$)	p Value
Dose of amlodipine (mg/day)	4.6 ± 1.6	4.2 ± 1.6	5.0 ± 1.6	N.S.
Dose of irbesartan (mg/day)	94.3 ± 25.6	97.5 ± 23.6	90.8 ± 27.3	N.S.
Other antihypertensive drugs				
Diuretics	87 (3.9%)	49 (4.1%)	38 (3.6%)	N.S.
β-Blockers	38 (1.7%)	16 (1.3%)	22 (2.1%)	N.S.
α-Blockers	14 (0.6%)	5 (0.4%)	9 (0.9%)	N.S.
CCB other than AML	10 (0.4%)	3 (0.2%)	7 (0.7%)	N.S.
ACE inhibitors	6 (0.3%)	2 (0.2%)	4 (0.4%)	N.S.
Renin inhibitors	6 (0.3%)	3 (0.2%)	3 (0.3%)	N.S.
Other	1 (0.0%)	0 (0.0%)	1 (0.1%)	N.S.

Data are the mean ± SD. AML, amlodipine; IRB, irbesartan; CCB, calcium channel blocker; ACE, angiotensin converting enzyme; N.S., not significant.

obtained in 765 and 708 patients for BP and in 531 and 538 patients for HR, respectively. Among these patients, changes in BP and HR over time are presented graphically in Figure 1. In the AML add-on group, BP dropped prominently at 4 weeks after the start of combination therapy (−18.7/−9.3 mmHg), and remained reduced at 8 weeks (−20.6/−10.1 mmHg) and 12 weeks (−22.1/−10.9 mmHg). BP was significantly lower at each time-point, as compared to pre-therapy levels, indicating a sustained antihypertensive effect for 12 weeks. BP also dropped distinctively in the IRB add-on group at 4 weeks (−15.1/−6.8 mmHg), and remained reduced at 8 (−17.1/−8.0 mmHg) and 12 weeks (−18.6/−8.6 mmHg), similar to the course followed by the AML add-on group. However, the achieved SBP levels were significantly lower in the AML add-on group than in the IRB add-on group at 4, 8 and 12 weeks. In the AML add-on group, HR was not significantly changed at 4 weeks (−0.5 bpm), but was significantly reduced at 8 weeks (−1.2 bpm) and 12 weeks (−1.8 bpm). In the IRB add-on group, HR decreased significantly throughout the combination therapy period (−1.7 bpm at 4 weeks, −2.0 bpm at 8 weeks and −2.1 bpm at 12 weeks.

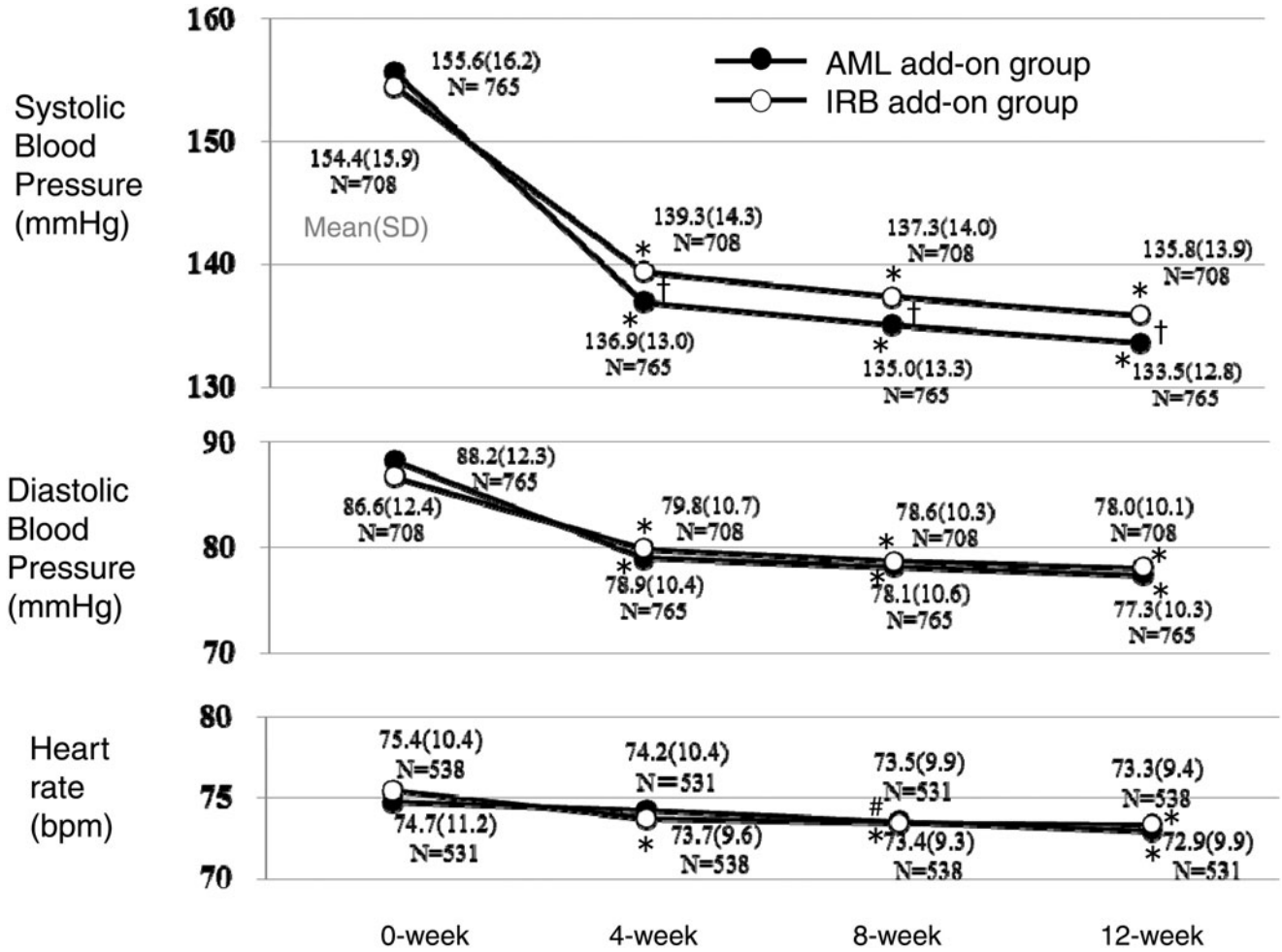

Figure 1. Time-course changes of blood pressure and heart rate in the amlodipine (AML) add-on group and the irbesartan (IRB) add-on group. #$p<0.01$, *$p<0.001$ versus 0 week; †$p<0.01$ between AML add-on group and IRB add-on group.

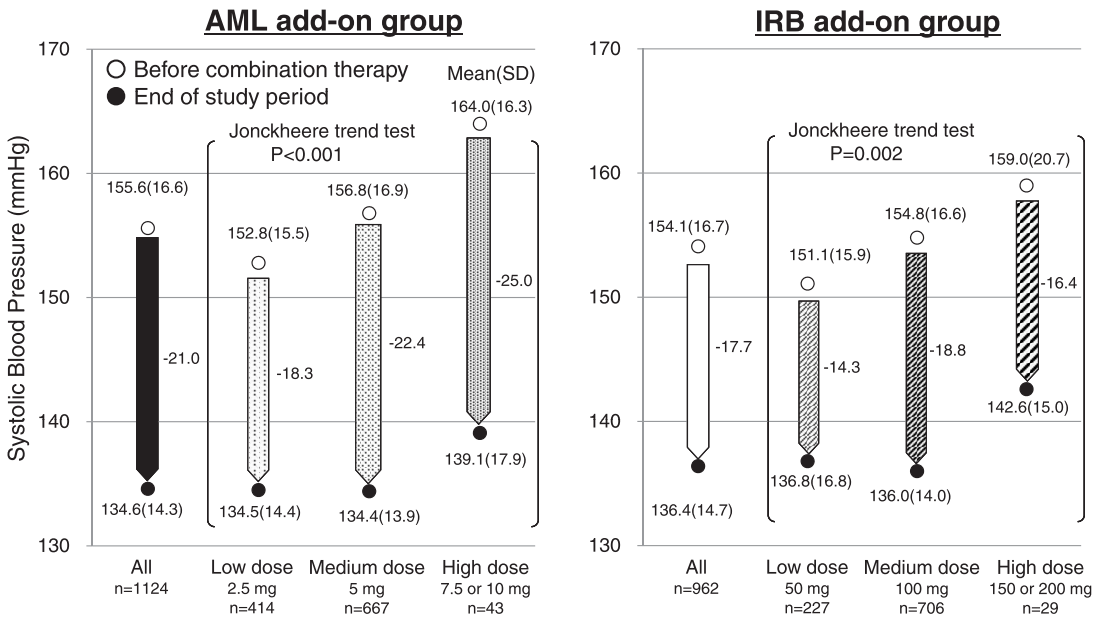

Figure 2. Reductions of systolic blood pressure according to the dose of amlodipine (AML) or irbesartan (IRB) at the end of study period.

Dose dependency of BP reduction

Figure 2 shows changes of SBP in relation to AML or IRB add-on dosage. The patients in the AML add-on group were divided into three groups according to their AML dosage added: low-dose add-on (<2.5 mg, $n = 442$), medium-dose add-on (5 mg, $n = 715$) or high-dose add-on (7.5 or 10 mg, $n = 45$). The patients in the IRB add-on group were also divided into three groups according to their added IRB dosage: low-dose add-on (50 mg, $n = 239$), medium-dose add-on (100 mg, $n = 778$) and high-dose add-on (150 or 200 mg, $n = 33$). At each AML add-on dose level, SBP had decreased prominently by 12 weeks. The magnitude of this decrease differed significantly between groups, with a greater decrease observed at higher AML add-on dose levels ($p < 0.001$, Jonckheere trend test). Significant differences were also observed in the magnitude of the decrease in SBP in the different daily IRB add-on dose groups ($p = 0.002$, Jonckheere trend test), although the magnitude of this effect was similar in the medium- and high-dose add-on groups.

The percentage of patients who achieved a BP of <140/90 mmHg at 12 weeks is shown in Figure 3. Both in the AML add-on group and the IRB add-on group, ~70% patients achieved a BP of <140/90 mmHg. However, the percentage of patients having achieved the BP<140/90 mmHg in the high-dose IRB add-on group was lower by 20% than the high-dose AML add-on group.

Safety

Data on adverse reactions are given in Table 3. The incidence of adverse reactions was as few as 1.11% (25 cases), with major adverse reactions being dizziness (6 cases), hypotension (3 cases), headache (2 cases) and vomiting (2 cases). There was no serious adverse reaction by which the administration of AML or IRB was stopped. When hypotension, dizziness, positional vertigo and malaise were counted as adverse reactions possibly associated with excessive BP reduction, the incidence of these adverse reactions was 0.49% (11 patients). Peripheral edema developed in only one patient from the IRB add-on group. The incidence of adverse reactions did not significantly differ between the AML add-on group and the IRB add-on group.

When the safety was analyzed by AML add-on dose level in the AML add-on group, the incidence of adverse reactions was not significantly different according to the dose of AML. Furthermore, the incidence of adverse reactions possibly associated with excessive BP reduction did not differ

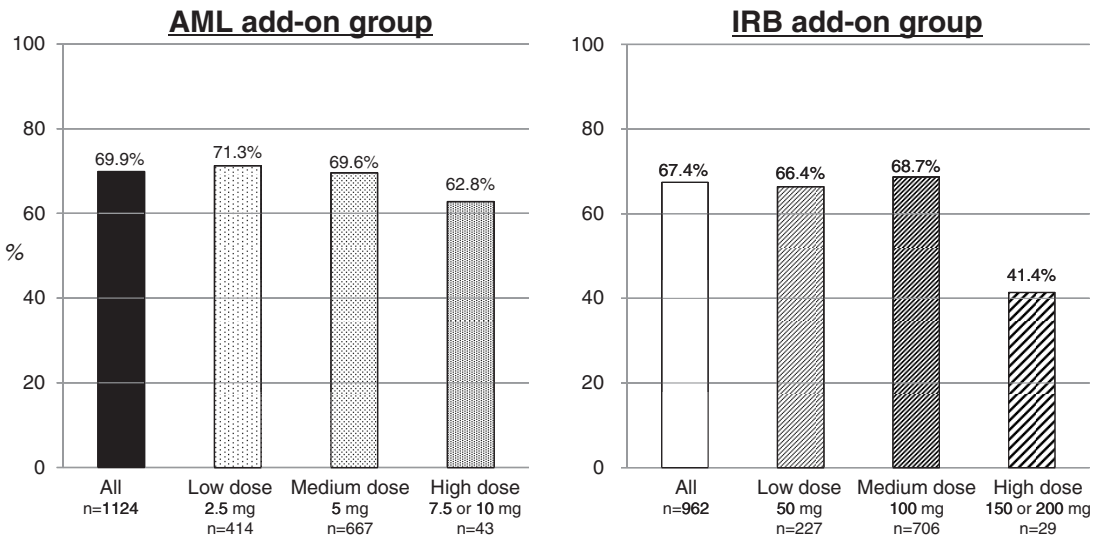

Figure 3. Percentage of the patients achieved the target blood pressure (<140/90 mmHg) at the end of study period.

Table 3. Numbers of patients experienced adverse reactions during the study period.

	Adverse reactions		
	Total	Hypotensive symptom[a]	Periperal edema
Total, $n = 2252$	25 (1.11%)	11 (0.49%)	0 (0.00%)
AML add-on group, $n = 1202$	17 (1.41%)	8 (0.67%)	0 (0.00%)
Low dose (2.5 mg), $n = 442$	8 (1.81%)	4 (0.90%)	0 (0.00%)
Medium dose (5 mg), $n = 715$	8 (1.12%)	4 (0.56%)	0 (0.00%)
High dose (7.5 or 10 mg), $n = 45$	1 (2.22%)	0 (0.00%)	0 (0.00%)
IRB add-on group, $n = 1050$	8 (0.76%)	3 (0.29%)	1 (0.09%)
Low dose (50 mg), $n = 239$	2 (0.84%)	1 (0.42%)	0 (0.00%)
Medium dose (100 mg), $n = 778$	6 (0.77%)	2 (0.25%)	1 (0.12%)
High dose (150 or 200 mg), $n = 33$	0 (0.00%)	0 (0.00%)	0 (0.00%)

[a]Adverse reactions possibly associated with excessive blood pressure reduction such as hypotension, dizziness, positional vertigo and malaise.

significantly between any two of the three AML dose groups. Analysis of the safety by IRB add-on dose level in the IRB add-on treatment group also yielded similar results.

Effects on serum K, uric acid and renal function

Among 1124 patients on the AML add-on group and 962 patients in the IRB add-on group, serial serum K values were obtained in 272 and 271 patients, respectively. The left panel of Figure 4 shows the time-course of the serum K level. The serum K was unchanged in the AML add-on group. On the other hand, in the IRB add-on group, the serum K was minimally but significantly increased by 0.09 mEq/l. However, the change in this parameter was within the normal range and no patients had stopped taking IRB because of hyperkalemia.

Serial serum uric acid values were obtained in 283 patients in the AML add-on group and 291 patients in the IRB add-on group, respectively. In these patients, the serum uric acid level was significantly reduced either in the AML add-on group (5.40 ± 1.43 mg/dl at 0 week and 5.26 ± 1.38 mg/dl at 12 week, $p = 0.011$) and the IRB add-on group (5.47 ± 1.39 mg/dl at 0 week and 5.27 ± 1.44 mg/dl at 12 week, $p = 0.001$) (Figure 5, left panel). This reduction in serum uric acid was especially prominent in patients with a high baseline uric acid at the start of combined therapy (≥ 7 mg/dl) either in the AML add-on group (-0.97 mg/dl, $p = 0.001$) and the IRB add-on group (-0.80 mg/dl, $p < 0.001$) as depicted in the right panel of Figure 5.

Serial eGFR data were available in 317 patients in the AML add-on group and 315 patients in the IRB add-on group, respectively. Figure 6 indicates the time-course of eGFR in these patients. The eGFR of patients with a baseline eGFR ≥ 60 was unchanged either in the AML add-on group or the IRB add-on group. On the other hand, the eGFR was significantly increased at the end of combined therapy in patients with a baseline eGFR of <60 at the start of combination therapy in both the AML and IRB add-on groups ($p = 0.009$ and $p = 0.001$, respectively).

Among 80 patients with baseline eGFR <60 on the AML add-on group and 85 patients with baseline eGFR <60 in the

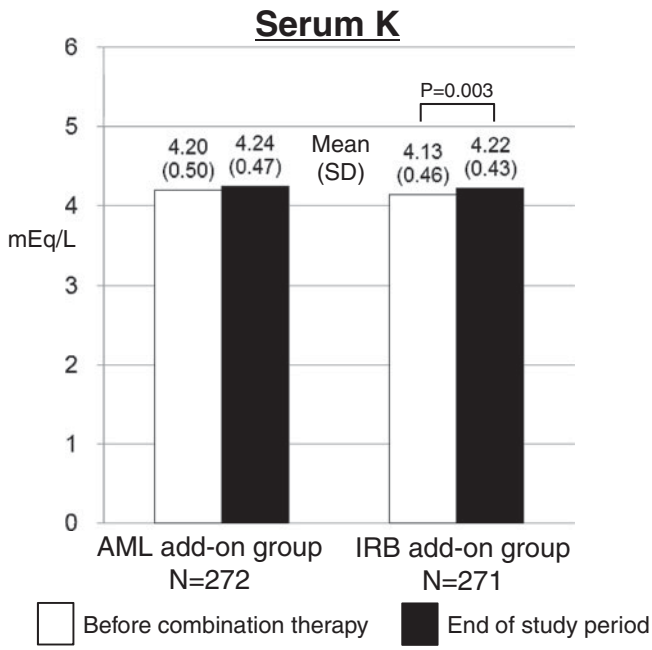

Figure 4. Changes in serum K in the amlodipine (AML) add-on group and the irbesartan (IRB) add-on group.

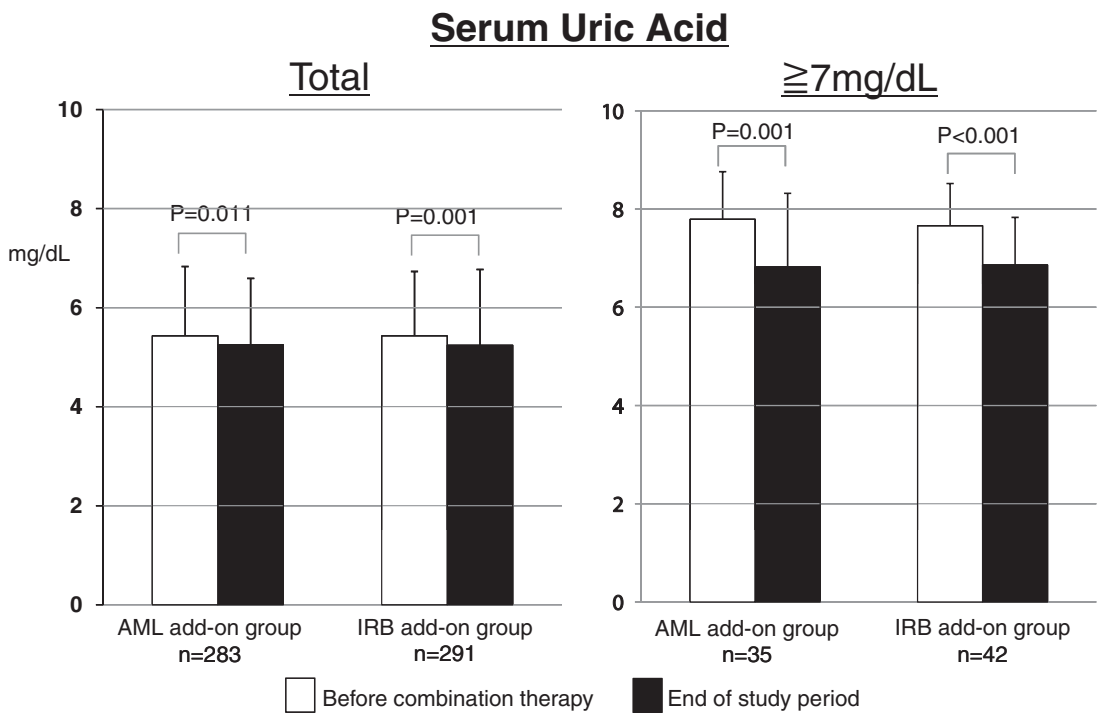

Figure 5. Changes in serum uric acid in the amlodipine (AML) add-on group and the irbesartan (IRB) add-on group (left panel: total subjects and right panel: subjects with serum uric acid ≥ 7 mg/dl).

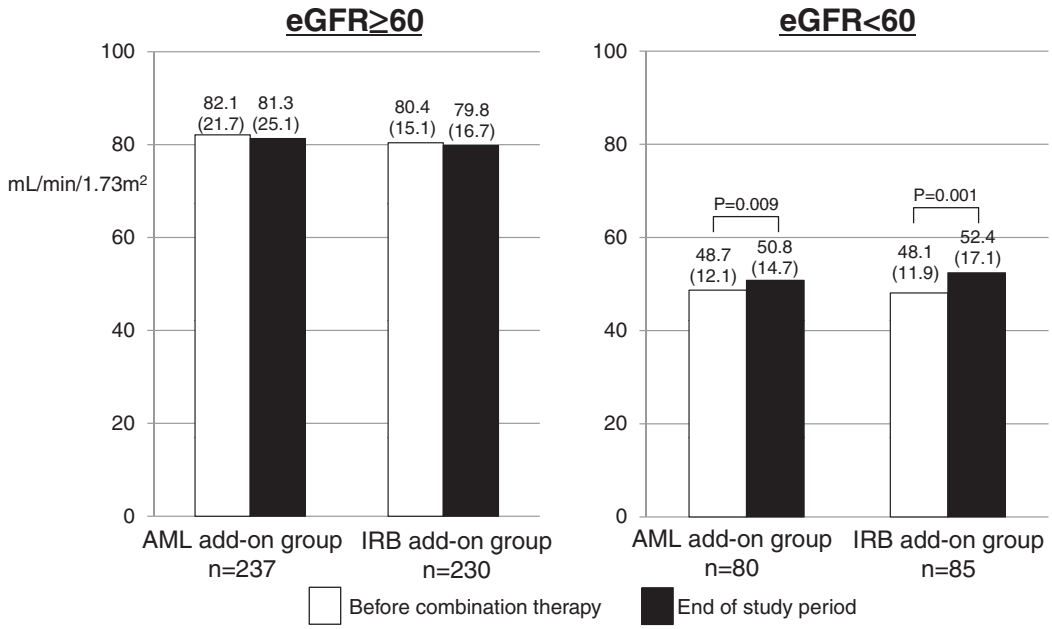

Figure 6. Changes in eGFR in patients with eGFR ≥60 ml/min/m^2 (left panel) and patients with eGFR <60 ml/min/m^2 (right panel). AML, amlodipine; IRB, irbesartan.

IRB add-on group, serial urinary protein data were obtained in 58 and 66 patients, respectively. Figure 7 indicates the time-course of qualitative urinary protein examination in these patients. Proteinuria was significantly improved in patients with a baseline eGFR <60 at the start of combined therapy both in the AML add-on treatment group and the IRB add-on treatment group.

Discussion

In the present study, the analysis was conducted on the efficacy and safety of treatment among the subjects enrolled to the PARTNER Study, extracting the 1202 patients having received AML add-on treatment during IRB therapy and 1050 patients having received IRB add-on treatment during AML therapy. Significant decreases in office BP were observed from 4 weeks onward in the AML add-on group and the IRB add-on group, indicating a sustained antihypertensive effect for 12 weeks. The potential adverse event of tachycardia due to decreased BP was not seen; rather, HR was significantly decreased. Accordingly, combination therapy with AML and IRB was effective for efficient lowering of BP, in the absence of sympathetic nerve stimulation.

Recent research has indicated that the hypotensive effects observed during the combination therapy with AML and IRB were dependent on the dose of AML rather than the dose of IRB (13). In the present study, the AML dosage during AML add-on treatment was higher in patients with higher baseline SBP and these patients showed greater changes in SBP in response to the combination therapy, suggesting that physicians tended to use a higher dose of AML to treat patients with higher SBP levels. The hypotensive effect of the combination therapy was smaller in the IRB high-dose add-on group than in the AML high-dose add-on group. The percentage of patients who achieved a BP of <140/90 mmHg at the end of combined therapy was lower in patients receiving a high IRB dose than in those receiving other IRB doses within the IRB add-on group or each of the AML add-on dose groups. As compared with CCB which directly relaxes vascular smooth muscle, the hypotensive effect of ARB is affected by the intrinsic activity of renin–angiotensin–aldosterone (RAA) system. Therefore, the increase in ARB dose may not be effective in patients with low-RAA system activity. In addition, because the baseline BP was higher in the high-dose IRB add-on group than the other IRB add-on dose groups, a BP of <140/90 mmHg seems less likely to be achieved.

In our analysis of safety, the incidence of adverse reactions was as few as 1.11%. It may be inappropriate to compare this with other previous reports, but the frequency was similar to the incidence of side effects (1.40%) reported in the survey of Japanese elderly hypertensive patients given AML (14). Most of them were assumed to be related to BP reduction and there were no severe adverse effects which forced to stop the combination therapy. Especially, it should be noted that only one patient had experienced peripheral edema, a well-known side effects of CCB, during the combination therapy with AML and IRB. CCB possibly increases the peripheral capillary pressure by dilating the arterioles which allows extravascular leakage of fluid causing edema. On the other hand, the contractive effect of angiotensin II is known to extend to the venous system as well as the arterial system. Therefore, ARB dilates not only the arterioles but also the venules of the peripheral tissues, which alleviates the increase in capillary pressure and reduces the occurrence of edema by CCB (15). Moreover, analysis of the incidence of adverse reactions by daily AML or IRB add-on dose showed that an increased dose did not elevate the incidence of adverse reactions. Thus, the combination therapy with a long-acting CCB and ARB is thought to bring about few chances to cause adverse effects along with BP reduction.

AML add-on group

End of study period

Before combination therapy	-	±	+	++	+++ or more	Total
-	29	1	0	0	0	30
±	4	4	0	0	0	8
+	4	1	3	1	0	9
++	0	0	6	3	0	9
+++ or more	0	0	0	0	2	2
Total	37	6	9	4	2	58

Improved	15	25.9%
Unchanged	41	70.7%
Aggravated	2	3.4%

Signed test P<0.001

IRB add-on group

End of study period

Before combination therapy	-	±	+	++	+++ or more	Total
-	35	0	0	0	0	35
±	3	1	2	0	0	6
+	2	3	1	0	1	7
++	2	1	6	3	1	13
+++ or more	1	0	0	0	4	5
Total	43	5	9	3	6	66

Improved	18	27.3%
Unchanged	44	66.7%
Aggravated	4	6.1%

Signed test P<0.001

Figure 7. Changes in proteiuria in the amlodipine (AML) add-on group and the irbesartan (IRB) add-on group.

Chronic kidney disease (CKD) has recently been identified as a serious risk factor for cardiovascular events and it has therefore received close attention (16,17). JSH2014 defined the goal of antihypertensive treatment as <130/80 mmHg for patients with hypertension complicated by proteinuric CKD, recommending strict BP control for these patients. In the management of hypertensive patients with CKD, it is important to suppress the RAA system and to reduce urinary excretion of albumin and protein, in addition to achieving the target BP. Inhibitors of RAA system such as ACE inhibitors and ARBs have been reported to be effective in dilating the efferent glomerular arterioles and lowering intraglomerular capillary pressure as compared with other classes of antihypertensive drugs (18,19). This effect brings about the reduction of proteinuria which is thought to be associated with renoprotection (20,21). In the present study, eGFR was significantly increased in patients with baseline eGFR <60 ml/min/1.73 m^2 at the end of AML + IRB treatment, and ~30% of these patients showed improvement of proteinuria. The eGFR was significantly increased by the addition of either AML or IRB. CCBs are supposed to increase renal plasma flow and GFR by dilating renal vasculature. On the other hand, it is generally understood that ARBs rather decrease GFR transiently by lowering intraglomerular capillary pressure. However, the increase in GFR by ARB is also observed in J-HEALTH study (22) using losartan in hypertensive patients and the mechanism is not clearly explained. Considering that ARB have been shown to increase renal blood flow (23,24) and AML which preferentially dilates afferent glomerular arterioles was concurrently used, the increase in renal blood flow may have contributed to the GFR increase observed in the present study. In addition, BP reduction itself is possibly correct abnormal renal hemodynamics causing renal dysfunction (25). These results suggest the combination therapy with long-acting CCB and ARB is effective in alleviating renal injuries and dysfunction.

In the present study, either the addition of AML or IRB reduced serum uric acid. This effect was particularly prominent in patients with hyperuricemia. Among ARBs, IRB has been shown to inhibit the expression of URAT1, a uric acid transporter, in the proximal tubules (26). This effect of IRB is supposed to have caused the decrease of uric acid in the IRB add-on group. On the other hand, the decrease of uric acid in the AML add-on group occurred probably because CCBs including AML dilate renal arteries, increase renal blood flow and facilitate the excretion of uric acid (27,28). A number of follow-up studies have indicated that the high serum uric acid level is associated with the increased incidence of cardiovascular events in hypertensive patients (29–31). Moreover, it has been reported that the antihypertensive treatment with a diuretic reduced the incidence of coronary heart disease in elderly patients, however, this preventive effect was negated in patients whose serum uric acid was increased (32). Thus, the reduction of serum uric acid by AML and IRB may be beneficial in inhibiting the occurrence of cardiovascular diseases in hypertensive patients.

The observed results of this study are thought to have some limitations. First, because the study subjects were arbitrary selected from the originally registered patients on the term that IRB was used, the following analyses are subject to the

possibility of influence of selection biases. In addition, considering that the laboratory tests were performed in a limited number of patients, the observed results may not necessarily reflect the representative data of whole group.

In conclusion, the combination therapy with AML and IRB swiftly and certainly lowers BP with a small chance of causing adverse effects. In addition, this combination is advantageous in lowering serum uric acid and is suitable for protecting kidney in CKD patients. The AIMIX tablet containing AML and IRB seems promising in maintaining high adherence and exhibiting the benefits of this combination therapy efficiently.

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References

1. Japanese Society of Hypertension Committee for Guidelines for the Management of Hypertension. The Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2014). Hypertens Res 2014;37:253–387.
2. Mori H, Ukai H, Yamamoto H, et al. Current status of antihypertensive prescription and associated blood pressure control in Japan. Hypertens Res 2006;29:143–51.
3. Ohkubo T, Obara T, Funahashi J, et al. Control of blood pressure as measured at home and office, and comparison with physicians' assessment of control among treated hypertensive patients in Japan: first report of the Japan home versus office blood pressure measurement evaluation (J-HOME) study. Hypertens Res 2004; 27:755–63.
4. Armario P, Waeber B. Therapeutic strategies to improve control of hypertension. J Hypertens 2013;31:S9–12.
5. Ishimitsu T, Minami J, Kawano Y, et al. Amlodipine, a long-acting calcium channel blocker, attenuates morning blood pressure rise in hypertensive patients. Clin Exp Pharmacol Physiol 1999;26:500–4.
6. Ishimitsu T, Minami J, Yoshii M, et al. Comparison of the effects of amlodipine and losartan on 24-hour ambulatory blood pressure in hypertensive patients. Clin Exp Hypertens 2002;24:41–50.
7. Agabiti-Rosei E, Muiesan ML, Rizzoni D, et al. Cardiovascular structural changes and calcium antagonist therapy in patients with hypertension. J Cardiovasc Pharmacol 1994;24:S37–43.
8. Croom KF, Plosker GL. Irbesartan A review of its use in hypertension and diabetic nephropathy. Drugs 2008;68:1543–69.
9. Lewis EJ, Hunsicker LG, Clarke WR, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. N Engl J Med 2001;345:851–60.
10. Parving HH, Lehnert H, Mortensen JB, et al. The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. N Engl J Med 2001;345:870–8.
11. Ishimitsu T, Fukuda H, Uchida M, et al. Interim report on the PARTNER Study: practical combination therapy of amlodipine and angiotensin II receptor blocker; safety and efficacy in patients with hypertension. J Blood Press 2013;20:70–82.
12. 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.
13. Shimada K, Komuro I, Matsubara H, et al. Study of efficacy and safety of irbesartan/amlodipine combination therapy in hypertensive patients uncontrolled on irbesartan or amlodipine monotherapy. J Blood Press 2011;18:1231–43.
14. Fukuda H, Nishimura K, Uchida M, et al. The safety and efficacy of amlodipine in Japanese elderly hypertensive patients. J New Rem Clin 2011;60:1162–88.
15. Makani H, Bangalore S, Romero J, et al. Effect of renin-angiotensin system blockade on calcium channel blocker-associated peripheral edema. Am J Med 2011;124:128–35.
16. Go AS, Chertow GM, Fan D, et al. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med 2004;351:1296–305.
17. Matsushita K, van der Velde M, Astor BC, et al. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. Lancet 2010;375:2073–81.
18. Anderson S. Antihypertensive therapy and the progression of renal disease. J Hypertens Suppl 1989;7:S39–42.
19. Hilgers KF, Mann JF. Role of angiotensin II in glomerular injury: lessons from experimental and clinical studies. Kidney Blood Press Res 1996;19:254–62.
20. Ishimitsu T, Akashiba A, Kameda T, et al. Benazepril slows progression of renal dysfunction in patients with non-diabetic renal disease. Nephrology 2007;12:294–8.
21. Ishimitsu T, Kameda T, Akashiba A, et al. Effects of valsartan on the progression of chronic renal insufficiency in patients with nondiabetic renal diseases. Hypertens Res 2005;28: 865–70.
22. Naritomi H, Fujita T, Ito S, et al. Efficacy and safety of long-term losartan therapy demonstrated by a prospective observational study in Japanese patients with hypertension: the Japan Hypertension Evaluation with Angiotensin II Antagonist Losartan Therapy (J-HEALTH) study. Hypertens Res 2008;31:295–304.
23. Burnier M, Roch-Ramel F, Brunner HR. Renal effects of angiotensin II receptor blockade in normotensive subjects. Kidney Int 1996;49:1787–90.
24. Wuerzner G, Burnier M. Effects of selective angiotensin II and beta1-receptor blockade on renal haemodynamics and sodium handling during orthostatic stress in healthy individuals. J Hypertens Suppl 2006;24:S89–93.
25. Palmer BF. Renal dysfunction complicating the treatment of hypertension. N Engl J Med 2002;347:1256–61.
26. Nakamura M, Anzai N, Jutabha P, et al. Concentration-dependent inhibitory effect of Irbesartan on renal uric acid transporters. J Pharmacol Sci 2010;114:115–18.
27. Thulin T. Calcium antagonists – assessment of side effects. Scand J Prim Health Care Suppl 1990;1:81–4.
28. Lee HY1, Kang HJ, Koo BK, et al. Clinic blood pressure responses to two amlodipine salt formulations, adipate and besylate, in adult Korean patients with mild to moderate hypertension: a multicenter, randomized, double-blind, parallel-group, 8-week comparison. Clin Ther 2005;27:728–39.
29. Alderman MH, Cohen H, Madhavan S, Kivlighn S. Serum uric acid and cardiovascular events in successfully treated hypertensive patients. Hypertension 1999;34:144–50.
30. Verdecchia P, Schillaci G, Reboldi G, et al. Relation between serum uric acid and risk of cardiovascular disease in essential hypertension. The PIUMA study. Hypertension 2000;36:1072–8.
31. Iwashima Y, Horio T, Kamide K, et al. Uric acid, left ventricular mass index, and risk of cardiovascular disease in essential hypertension. Hypertension 2006;47:195–202.
32. Franse LV, Pahor M, Di Bari M, et al. Serum uric acid, diuretic treatment and risk of cardiovascular events in the Systolic Hypertension in the Elderly Program (SHEP). J Hypertens 2000; 18:1149–54.