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Original

Comparisons of Increasing Calcium Channel Blocker dose and Adding Thiazide Diuretic in Hypertensive Patients Given Medium-dose Angiotensin II Receptor Blocker and Amlodipine

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SUMMARY

We compared the efficacies of 2 prescriptions, one of a medium-dose angiotensin II receptor blocker (ARB) with high-dose of calcium channel blocker (CCB) and another of medium-dose of ARB with medium-dose of CCB and a thiazide diuretic in 22 hypertensive patients who did not achieve the target blood pressure level with the combination of medium-dose of ARB and medium-dose of CCB. A randomized crossover study was performed giving a fixed combination of 100 mg irbesartan with 10 mg amlodipine or a fixed-dose combination of 100 mg irbesartan with 5 mg amlodipine added by 1 mg trichlormethiazide for 12-16 weeks each. The blood pressure measured in hospital was comparable between the high-dose CCB period (130/77 mmHg) and the thiazide period (130/79 mmHg). The morning and the evening blood pressures measured at home were also comparable in the high-dose of CCB and the thiazide periods, while the evening heart rate was higher in the thiazide period than in the high-dose CCB period. As for the laboratory data, hemoglobin A1c (+0.2%, p=0.013), serum nonHDL cholesterol (+12 mg/dL, p=0.047) and serum uric acid (+0.8 mg/dL, p=0.001) were significantly higher in the thiazide period than in the high-dose CCB period. On the other hand, urinary albumin excretion (−28.8%, p=0.026) and estimated glomerular filtration rate (−5.8%, p=0.012) were significantly lower in the thiazide period than in the high-dose CCB period. In the combination drug therapy of hypertension, the increase of CCB dose is preferable in preserving renal function and in avoiding adverse effects on metabolisms of glucose, lipid and uric acid.

Key words : angiotensin II receptor blocker, calcium channel blocker, diuretic, uric acid, fixed-dose combination, hypertension

INTRODUCTION

High blood pressure facilitates the progression of arteriosclerosis which increases the incidence of cardiovascular diseases such as stroke and coronary heart disease. Hypertension is also a major risk factor for developing a cardiovascular organ damages such as heart failure and renal dysfunction. The population of elderly people is increasing and these cardiovascu-

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lar disorders greatly impairs the activity and life prognosis of elderly people. Therefore, it is obvious how important it is to control the blood pressure to an optimal range and prevent the occurrence of cardiovascular organ damages, considering that hypertension is most prevalent lifestyle-related diseases.

Among the classes of antihypertensive drugs, angiotensin II receptor blockers (ARB) and calcium channel blockers (CCB) are widely used because both drugs rarely cause adverse side effects. In addition, the inhibition of renin-angiotensin-aldosterone (RAA) system is supposedly protective against the development of cardiovascular tissue and organ injuries[1,2]. On the other hand, CCB exhibit certain and potent hypotensive effect by dilating arterioles directly. Therefore, these two classes of antihypertensive drugs are often combined when the target blood pressure is not achieved by monotherapy. However, few patients do not reach the target blood pressure by this combination and need further intensified antihypertensive drug therapy. While CCB generally lower blood pressure dose-dependently by dilating arterioles, the hypotensive effects of renin-angiotensin system inhibitors (RASI) such as angiotensin-converting enzyme (ACE) inhibitors and ARB depend on the intrinsic activity of RAA system to a greater or lesser extent, and the increase in drug dose do not necessarily yields corresponding blood pressure reduction. Therefore, increasing the dose of CCB is supposedly preferable to intensify the hypotensive effect when ARB and CCB are combined. Otherwise, the addition of other classes of antihypertensive drugs with different hypotensive mechanism should be considered to achieve effective blood pressure reduction. Especially, the addition of diuretics is expected to synergistically enhance the hypotensive effects of RASI[3].

In the present study, we compared the therapeutic effects of combination antihypertensive therapy including high-dose of CCB or a thiazide diuretic in hypertensive patients requiring multiple antihypertensive drugs for adequate blood pressure control.

METHODS

There were 22 hypertensive subjects enrolled in this study whose blood pressure did not achieve the target level by taking fixed-dose combination of medium-dose of ARB (irbesartan 100 mg) and medium-dose of CCB (amlodipine 5 mg) for three months or more. The target blood pressure was <130/80 mmHg for patients with diabetes mellitus or chronic kidney disease and <140/90 mmHg for other patients. Patients whose serum creatinine was 2.0 mg/dL or higher were not included because thiazide diuretics are contraindicated to these patients. We also excluded patients with severe hypertension exceeding 180/110 mmHg or secondary causes of hypertension other than stage 1-3 chronic kidney disease. The background characteristics of study subjects are shown in Table 1. Three patients with diabetes mellitus were given antidiabetic drugs such as biguanides (n=2), α-glucosidase inhibitors (n=1) and glinides (n=1). Lipid-lowering drugs (statins) and antihyperuricemic drugs (allopurinol and febuxostat) were given to seven and three patients, respectively. In addition, six patients were taking antiplatelet drugs such as aspirin. The doses of these drugs were unchanged throughout the study.

Table 1 Baseline characteristics of the study subjects

Age, years	62.7±12.5
Gender, male/female	12/10
Body mass index, kg/m^2	27.7±5.0
Systolic blood pressure, mmHg	147.2±6.8
Diastolic blood pressure, mmHg	86.2±8.6
Heart rate, bpm	73.2±11.9
Duration of hypertension, years	13.0±8.1
Complications	
Chronic kidney disease	9 (41%)
Diabetes mellitus	3 (14%)
Dyslipidemia	8 (36%)
Hyperuricemia	7 (32%)
Cardiovascular disease	2 (9%)

Data are the mean±SD.

The patients had been given fixed-dose combination of 100 mg irbesartan and 5 mg amlodipine. Which was changed to fixed-dose combination of 100 mg irbesartan and 10 mg amlodipine, or added 1 mg of trichlormethiazide. Each regimen was taken once daily after breakfast for 12-16 weeks, according to a randomized crossover design. The sequence of treatment periods with high-dose of CCB and thiazide combination therapy was randomized. In hospital blood pressure was measured with a sphygmomanometer in the

Table 2 In hospital blood pressure, heart rate and body weight at the ends of high-dose CCB and thiazide combination periods.

Variable	High-dose CCB	Thiazide	P value
SBP, mmHg	130.1±12.4	129.8±11.6	0.807
DBP, mmHg	77.4±9.8	78.7±10.2	0.164
Heart rate, bpm	73.8±13.0	74.5±12.7	0.457
Body weight, kg	71.0±14.2	70.7±14.6	0.346

Data are the mean±SD. CCB：calcium channel blocker, SBP：systolic blood pressure, DBP：diastolic blood pressure.

sitting position after resting for at least 20 min at each visit every 4 weeks. Blood pressure at home was measured consecutively for 7 days before each visit using an arm-cuff oscillometric automatic manometer within 1 hour of awakening (before drug administration) as morning blood pressure and before going to bed as evening blood pressure, and the mean values were obtained. The patients used their own manometers equipped with arm cuffs.

After overnight, fasting blood samples were collected in the sitting position after resting for more than 20 minutes on the final day of each treatment period. In addition to the routine blood chemistry and blood cell counts, plasma B-type natriuretic peptide (BNP) was assayed using chemiluminescent enzyme immunoassay. The estimated glomerular filtration rate (eGFR) was calculated from the serum creatinine level and age by the following equation[4]：$eGFR = 194 \times Age^{-0.287} \times sCr^{-1.094}$ ($\times 0.739$ for females). Urine samples were collected on the final day of each treatment period. Urinary albumin was measured by an immunoturbidimetric method and corrected using the urinary creatinine level.

The study protocol was in accordance with the recommendations of the World Medical Association for biomedical research involving human subjects and was approved by the institutional review board. Informed consent was obtained from all subjects after explaining the study objective and design.

Clinical data were expressed as means±standard deviations (SD). Values between the 2 periods were compared by paired t-test, however, Wilcoxon signed-rank test was applied for the data with skewed distribution. A P value of less than 0.05 was considered to be statistically significant.

RESULTS

All the 22 patients showed good adherence to the therapy and fulfilled the whole study periods. Table 2 shows the in hospital blood pressure and heart rate at the ends of high-dose of CCB and thiazide combination therapy periods. Body weight was not significantly different between the two treatment periods. There were no significant differences in blood pressure and heart rate between the two treatments periods. As compared with the baseline period treated by fixed combination of medium-dose of ARB and medium-dose of CCB. The increased CCB dose and the thiazide addition comparably lowered blood pressure by −17/−9 mmHg and −17/−8 mmHg, respectively, without affecting the heart rate. Significant difference was not observed in the heart rate between the two treatment periods. Figure 1 shows at home blood pressure in the morning and the evening. Similar to the blood pressure measure in hospital, the blood pressure measured at home in the morning and the evening did not have significant difference between the two treatment periods. However, the heart rate in the evening was significantly higher in the thiazide period than in the high-dose CCB period.

Table 3 shows the laboratory data examined at the end of each treatment period. Among the hematological parameters, hematocrit was slightly higher in the thiazide period than in the high-dose CCB period. Among the blood chemistry data, the serum levels of urea nitrogen, creatinine and uric acid were significantly higher in the thiazide period than in the high-dose CCB period. Serum K was not significantly different between the two treatment periods. Although the plasma glucose and serum high-density lipoprotein

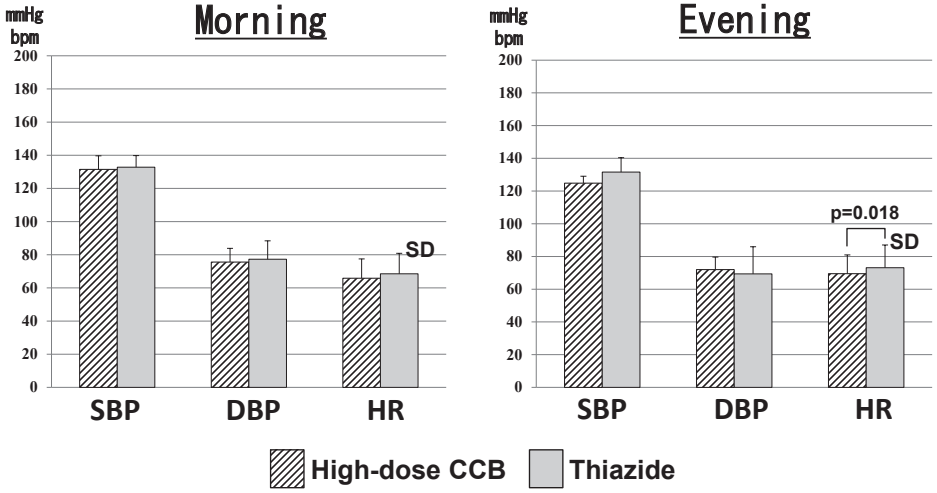

Figure 1 Average home blood pressure and heart rate during the last week of the high-dose CCB period and the thiazide combination period. Data are mean ± SD. CCB : calcium channel blocker.

Table 3 Laboratory data at the ends of high-dose CCB and thiazide combination periods.

Variable	High-dose CCB	Thiazide	P value
Blood cell counts			
White blood cell, $\times 10^3/mm^3$	6.81 ± 1.96	6.79 ± 1.69	0.997
Red blood cells, $\times 10^6/mm^3$	4.48 ± 0.59	4.55 ± 0.58	0.093
Blood hemoglobin, g/dL	13.8 ± 1.5	14.0 ± 1.5	0.189
Hematocrit,%	41.6 ± 4.5	42.6 ± 4.2	0.027
Platelet, $\times 10^3/mm^3$	239 ± 54	253 ± 58	0.085
Blood chemistry			
Aspartate transaminase, U/L	24 ± 12	25 ± 15	0.601
Alanine transaminase, U/L	28 ± 25	29 ± 27	0.625
Total protein, g/dL	7.1 ± 0.3	7.1 ± 0.4	0.657
Albumin, g/dL	4.2 ± 0.3	4.2 ± 0.4	0.930
Na, mEq/L	142 ± 1	141 ± 2	0.208
K, mEq/L	4.2 ± 0.4	4.2 ± 0.3	0.999
Urea nitrogen, mg/dL	15.8 ± 5.1	17.6 ± 4.8	0.021
Creatinine, mg/dL	0.92 ± 0.29	0.97 ± 0.27	0.020
Uric acid, mg/dL	5.8 ± 1.6	6.6 ± 1.5	0.001
HDL-cholesterol, mg/dL	53 ± 14	52 ± 13	0.590
nonHDL-cholesterol, mg/dL	135 ± 23	147 ± 34	0.047
Hemoglobin A1c (NGSP), %	5.8 ± 0.6	6.0 ± 0.7	0.012
Plasma glucose, mg/dL	113 ± 17	117 ± 27	0.374
Plasma BNP, pg/mL	24.2 ± 20.8	23.4 ± 19.4	0.725

Data are the mean ± SD. CCB : calcium channel blocker, HDL : high-density lipoprotein, NGSP : National Glycohemoglobin Standardization Program, BNP : B-type natriuretic peptide.

(HDL) cholesterol were not significantly different between the two periods, hemoglobin A1c and serum nonHDL-cholesterol were higher in the thiazide period than in the high-dose CCB period. Plasma BNP, which is supposed to reflect cardiac ventricular stress, was not significantly different between the two treatment periods.

The eGFR and the urinary albumin excretion of the

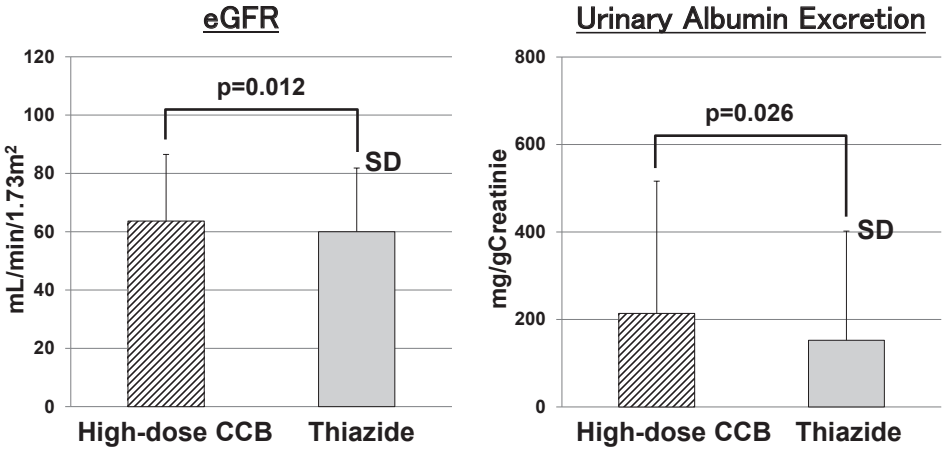

Figure 2 Estimated glomerular filtration rate (eGFR, left panel) and urinary albumin excretion (right panel) at the ends of high-dose CCB and thiazide combination periods. Data are mean ± SD. CCB : calcium channel blocker.

study subjects at the end of each treatment period were depicted in Figure 2. The eGFR was higher in the high-dose CCB period than in the thiazide period, while the urinary albumin excretion was lower in the thiazide period than in the high-dose CCB period.

DISCUSSION

The blood pressure level of 140/90 mmHg or higher is generally recognized as hypertension. The latest versions of guidelines for the management of hypertension recommend the target blood pressure to be lower than this[5~7]. In addition, high-risk hypertensive patients complicated by diabetes mellitus or CKD presenting proteinuria are recommended to lower their blood pressure <130/80 mmHg in order to prevent cardiovascular events and renal failure. However, there is not an apparent threshold level from which higher blood pressure is associated with the increase in cardiovascular diseases. Meta-analyses of prospective observational studies have indicated that there is a linear relationship between blood pressure and the risk of cardiovascular diseases such as stroke and myocardial infarction[8]. This relationship also exists even in the normal blood pressure range below 140/90 mmHg down to 115/75 mmHg. Moreover, in the recent Systolic Blood Pressure Intervention Trial (SPRINT), the intensive treatment hypertensive patients with target SBP less than 120 mmHg showed lower rates of cardiovascular events and death than in the standard treatment group targeted less than 140 mmHg[9]. Therefore, stricter target blood pressure level such as 130/85 mmHg may be preferable in order to achieve better prevention of cardiovascular diseases in hypertensive patients. In the real world clinical practice, however, generally half of the hypertensive patients under antihypertensive treatment do not achieve even the target blood pressure level of 140/90 mmHg. For that reason intensification of antihypertensive drug therapy such as increasing the dose and combination of multiple agents is needed.

In the present study, we enrolled hypertensive patients who did not reach target blood pressure level by the combination of medium-doses of ARB and CCB, and compared the therapeutic effects of increased dose of CCB or an addition of thiazide diuretic as the next step to achieve target blood pressure. Consequently, blood pressure in hospital was comparably lowered in either treatment period. In addition, also the morning and evening blood pressure at home did not significantly differ between the two treatment periods. Therefore, the high-dose of CCB and thiazide diuretic addition are thought to bring about comparable duration of antihypertensive effects. Amlodipine used in this study is a long-acting CCB with plasma half-life of more than 24 hours and has been shown to be effective in lowering blood pressure over 24 hours[10~12]. The addition of diuretic has been also shown to elongate the hypotensive effects of

other antihypertensive drugs by reducing the necessity to maintain high blood pressure level to excrete Na during nighttime and changing the non-dipper pattern into dipper[13]. In other words, diuretics are thought to correct inappropriate renal excretion of Na which contributes to the non-dipping pattern of blood pressure change.

Even if the in hospital blood pressure is controlled in normal range, diurnal blood pressure changes such as morning surge and the lack of nocturnal dipping are known to raise the risk of cardiovascular organ injuries[14,15]. In this context, out of hospital blood pressure values obtained by ambulatory blood pressure monitoring (ABPM) or blood pressure measurement at home have been shown to yield better prediction than that of the blood pressure in hospital for the incidence of target organ damages and cardiovascular diseases[16~18]. Therefore, the long duration of antihypertensive effect yielded by high-dose of long-acting CCB or thiazide addition is expected to be beneficial in preventing cardiovascular complications and improving the prognosis of hypertensive patients.

With regard to the heart rate, the evening heart rate was higher in the thiazide period than in the high-dose CCB period, although the heart rate in hospital did not differ between the two periods. It is speculated that the reduction in blood volume by diuresis may have resulted in the sympathetic nerve activation. Considering that the chronic activation of sympathetic nerve system and the increase in heart rate have been shown to be associated with the increased risk of cardiovascular diseases[19,20], thus the use of high-dose of CCB may be preferable to the addition of diuretic in the combination antihypertensive drug therapy aiming to improve the prognosis of hypertensive patients.

Two drugs or more are often required in order to achieve the target blood pressure. In the combination drug therapy of hypertension, addition of diuretics is effective in reinforcing the hypotensive effects of other vasodilating drugs. However, the long-term use of thiazide diuretics often causes unfavorable side effects such as hypokalemia, hyperuricemia, hyperglycemia and dyslipidemia. In this respect, the combination of RASI is expected to exert opposite influences on the metabolism of K, glucose and lipids thereby cancel the adverse effects of diuretics to some degree[21,22]. Especially, in vitro studies have indicated that irbesartan activates peroxisome proliferator-activated receptor-gamma (PPAR-γ), a transcription factor of nuclear hormone receptor, which has actions such as improving insulin resistance and reducing inflammatory cytokines[23]. In the present study, serum K did not differ between the high-dose CCB and the thiazide periods, however, hemoglobin A1c, nonHDL-cholesterol and uric acid were higher in the thiazide period than in the high-dose CCB period. Therefore, the effects of irbesartan supposedly was not potent enough to negate the adverse effects of trichlormethiazide on glucose and lipid metabolism. RASI are generally neutral as for the production and excretion of uric acid, however, irbesartan has been shown to facilitate uric acid excretion by inhibiting URAT-1, a transporter of uric acid reabsorption in the renal tubules and reduce serum uric acid[24,25]. However, this effect of irbesartan seems modest in clinical practice, considering that the serum uric acid was significantly higher in the thiazide period than in the high-doseCCB period in the present study.

In the long-term treatment of hypertension, not only lowering blood pressure but also reducing proteinuria or albuminuria is associated with prevention of organ injuries and cardiovascular events, thereby improving the prognosis[26]. On the other hand, it has been also shown that the incidence of cardiovascular events increased in patients whose renal function had decreased during antihypertensive therapy[27]. However, in the antihypertensive drug therapy, the reduction of proteinuria is not necessarily associated with the preservation of renal function. It is assumed that the increased intraglomerular capillary pressure, glomerular hypertension, promotes glomerulosclerosis and renal dysfunction. The decrease in intraglomerular capillary pressure is expected to reduce proteinuria on the one hand, but may also reduce GFR on the other hand. In this respect, eGFR was favorably maintained by CCB compared with diuretics in the INSIGHT study[28,29]. The ACCOMPLISH study compared the therapeutic effects of combination therapy with an ACE inhibitor plus diuretic and the combination of an ACE inhibitor plus CCB in high-risk hypertensive patients. As for the indices of renal injury, the

CCB combination was less effective in reducing urinary albumin but better preserved eGFR than the diuretic combination[30,31], which is in accordance with the results of this study. In the ACCOMPLISH study, the hard endpoints such as doubling of serum creatinine and cardiovascular events were fewer in the CCB combination than in the diuretic combination. Thus, it may be surmised that the combination of RASI with CCB is preferable to the combination of RASI with diuretic in terms of improving the long-term prognosis. However, considering that the continuation of albuminuria and high GFR may be associated with glomerular hypertension, further follow-up seems to be needed for the evaluation of long-term renoprotective effects by antihypertensive drug therapy.

In summary, we compared the therapeutic effects of antihypertensive therapies using high-dose of CCB or adding thiazide diuretic in patients with insufficient blood pressure control with the fixed-dose combination of medium-dose of ARB and medium-dose of CCB. Both combination therapies comparably lowered blood pressure, however, the addition of thiazide was more likely to cause sympathetic nerve activation and unfavorable influences on the metabolism of glucose, lipids and uric acid than the high-dose of CCB combination. In the combination drug therapy of hypertension including RASI, it is suggested that the increase of CCB dose has advantages over the addition of thiazide diuretic in improving the long-term prognosis by avoiding adverse effects of antihypertensive drugs.

REFERENCES

1) Maggioni AP : Efficacy of Angiotensin receptor blockers in cardiovascular disease. Cardiovasc Drugs Ther **20** : 295-308, 2006.
2) Ibrahim MM : RAS inhibition in hypertension. J Hum Hypertens **20** : 101-108, 2006.
3) Townsend RR, Holland OB : Combination of converting enzyme inhibitor with diuretic for the treatment of hypertension. Arch Intern Med **150** : 1175-1183, 1990.
4) Matsuo S, Imai E, Horio M, et al : Revised equations for estimated GFR from serum creatinine in Japan. Am J Kidney Dis **53** : 982-992, 2009.
5) Mancia G, Fagard R, Narkiewicz K, et al : 2013 ESH/ESC Guidelines for the management of arterial hypertension : the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). J Hypertens **231** : 1281-1357, 2013.
6) James PA, Oparil S, Carter BL, et al : 2014 evidence-based guideline for the management of high blood pressure in adults : report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA **311** : 507-520, 2014.
7) 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 **37** : 253-390, 2014.
8) Lewington S, Clarke R, Qizilbash N, et al : Age-specific relevance of usual blood pressure to vascular mortality : a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet **360** : 1903-1913, 2002.
9) SPRINT Research Group : A Randomized Trial of Intensive versus Standard Blood-Pressure Control. N Engl J Med **373** : 2103-2116, 2015.
10) 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 **26** : 500-504, 1999.
11) 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 **24** : 41-50, 2002.
12) Ishimitsu T, Kobayashi T, Honda T, et al : Protective effects of an angiotensin II receptor blocker and a long-acting calcium channel blocker against cardiovascular organ injuries in hypertensive patients. Hypertens Res **28** : 351-359, 2005.
13) Uzu T, Kimura G : Diuretics shift circadian rhythm of blood pressure from nondipper to dipper in essential hypertension. Circulation **100** : 1635-1638, 1999.
14) Kario K. Morning surge in blood pressure and cardiovascular risk : evidence and perspectives. Hypertension **56** : 765-773, 2010.
15) Ohkubo T, Hozawa A, Yamaguchi J, et al : Prognostic significance of the nocturnal decline in blood pressure in individuals with and without high 24-h blood

pressure : the Ohasama study. J Hypertens **20** : 2183–2189, 2002.
16) Sega R, Facchetti R, Bombelli M, et al : Prognostic value of ambulatory and home blood pressures compared with office blood pressure in the general population : follow-up results from the Pressioni Arteriose Monitorate e Loro Associazioni (PAMELA) study. Circulation **111** : 1777–1783, 2005.
17) Ohkubo T, Imai Y, Tsuji I, et al : Home blood pressure measurement has a stronger predictive power for mortality than does screening blood pressure measurement : a population-based observation in Ohasama, Japan. J Hypertens **16** : 971–975, 1998.
18) Kikuya M, Ohkubo T, Asayama K, et al : Ambulatory blood pressure and 10-year risk of cardiovascular and noncardiovascular mortality : the Ohasama study. Hypertension **45** : 240–245, 2005.
19) Palatini P, Casiglia E, Julius S, Pessina AC. High heart rate : a risk factor for cardiovascular death in elderly men. Arch Intern Med **159** : 585–592, 1999.
20) Hozawa A, Ohkubo T, Kikuya M, et al : Prognostic value of home heart rate for cardiovascular mortality in the general population : the Ohasama study. Am J Hypertens **17** : 1005–1010, 2004.
21) Gillespie EL, White CM, Kardas M, et al : The impact of ACE inhibitors or angiotensin II type 1 receptor blockers on the development of new-onset type 2 diabetes. Diabetes Care **28** : 2261–2266, 2005.
22) Derosa G, Cicero AF, D'Angelo A, et al : Telmisartan and irbesartan therapy in type 2 diabetic patients treated with rosiglitazone : effects on insulin-resistance, leptin and tumor necrosis factor-alpha. Hypertens Res **229** : 849–856, 2006.
23) Schupp M, Janke J, Clasen R, et al : Angiotensin type 1 receptor blockers induce peroxisome proliferator-activated receptor-gamma activity. Circulation **109** : 2054–2057, 2004.
24) Burnier M, Roch-Ramel F, Brunner HR : Renal effects of angiotensin II receptor blockade in normotensive subjects. Kidney Int **49** : 1787–1790, 1996.
25) Nakamura M, Anzai N, Jutabha P, et al : Concentration-dependent inhibitory effect of irbesartan on renal uric acid transporters. J Pharmacol Sci **114** : 115–118, 2010.
26) Ibsen H, Olsen MH, Wachtell K, et al : Reduction in albuminuria translates to reduction in cardiovascular events in hypertensive patients : losartan intervention for endpoint reduction in hypertension study. Hypertension **45** : 198–202, 2005.
27) Hayashi K, Saruta T, Goto Y, et al : Impact of renal function on cardiovascular events in elderly hypertensive patients treated with efonidipine. Hypertens Res **33** : 1211–1220, 2010.
28) Brown MJ, Palmer CR, Castaigne A, et al : Morbidity and mortality in patients randomised to double-blind treatment with a long-acting calcium-channel blocker or diuretic in the International Nifedipine GITS study : Intervention as a Goal in Hypertension Treatment (INSIGHT). Lancet **356** : 366–372, 2000.
29) de Leeuw PW, Ruilope LM, Palmer CR, et al : Clinical significance of renal function in hypertensive patients at high risk : results from the INSIGHT trial. Arch Intern Med **164** : 2459–2464, 2004.
30) Jamerson K, Weber MA, Bakris GL, et al : Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. N Engl J Med **359** : 2417–2428, 2008.
31) Bakris GL, Sarafidis PA, Weir MR, et al : Renal outcomes with different fixed-dose combination therapies in patients with hypertension at high risk for cardiovascular events (ACCOMPLISH) : a prespecified secondary analysis of a randomised controlled trial. Lancet **375** : 1173–1181, 2010.