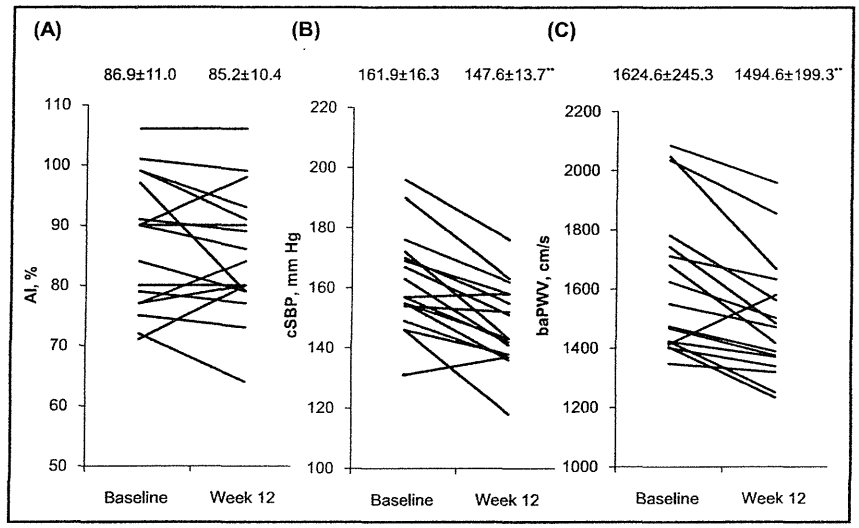

FIGURE 4. (A) Augmentation index (AI), (B) central systolic blood pressure (cSBP), and (C) brachial-ankle pulse wave velocity (baPWV) at baseline and after 12 weeks of aliskiren-based therapy (week 12) (n=17). $^{**}P<.001$ from baseline.

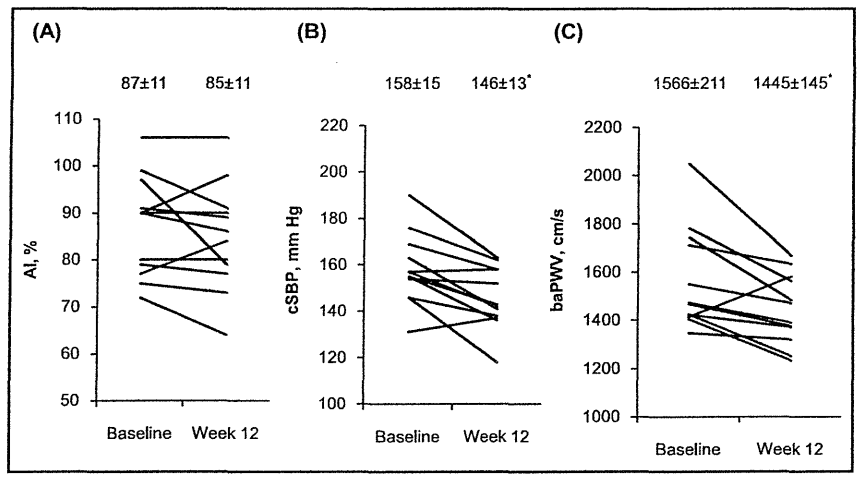

FIGURE 5. (A) Augmentation index (AI), (B) central systolic blood pressure (cSBP), and (C) brachial-ankle pulse wave velocity (baPWV) at baseline and after 12 weeks of aliskiren monotherapy (week 12) (n=12). $^{*}P<.05$ from baseline.

as monotherapy or when used in combination with RAS blockers, have been reported to effectively reduce central BP to a greater extent than peripheral BP, as reported in the Conduit Artery Function Evaluation (CAFE) study.[6,40] With respect to the possible beneficial effects of aliskiren on vascular function, accumulating experimental evidence has shown the beneficial effects of aliskiren on atherosclerosis and plaque stability. A previous study conducted leukocyte adhesion assays in vivo and in vitro using a novel real-time imaging system and showed that treatment with aliskiren significantly suppressed the leukocyte-endothelial interaction, a crucial step in vascular inflammation.[41] In another previous study, treatment with aliskiren had protective effects on endothelial function via improvement in nitric oxide bioavailability and protected against atherosclerotic changes in Watanabe heritable hyperlipidemic rabbits.[42] Other animal studies also revealed a prominent role for macrophage-derived renin in the development of atherosclerotic vascular changes[43] and showed that renin inhibition by aliskiren resulted in striking reductions of pathological vascular change and atherosclerotic lesion size in genetically atherosclerosis-susceptible mice.[43–45]

Further, a previous clinical study showed that aliskiren improved the parameters of systemic vascular function, including arterial stiffness and endothelial function in diabetic patients,[46] and, recently, a significantly greater reduction in central BP was observed with aliskiren/HCTZ combination therapy than

amlodipine monotherapy.[47] Given the well-known beneficial effects of CCBs on central hemodynamics as described above, it would be of interest if there were improvements in the vascular function parameters also on those patients who were treated with aliskiren only, without the addition of a CCB. The results of this study demonstrated that aliskiren exerted a beneficial effect on central hemodynamics (cSBP) and arterial stiffness (baPWV) not only in overall study patients (n=17) but also in patients taking aliskiren monotherapy (n=12).

Concerning the measurement of PWV, the most frequently studied index to date among a variety of PWV measures is carotid-femoral PWV (cfPWV), which is the gold standard and is most widely used in clinical practice.[48] The cfPWV has been used in landmark studies of arterial stiffness conducted in Europe[49,50] as well as in the Framingham Heart Study in the United States.[51] On the other hand, an emerging measure of PWV that has been widely used in Japan and other East Asian countries in the past 10 years is baPWV.[52] Although clinical evidence is still relatively limited, baPWV was an independent predictor for cardiovascular deaths and events in a small cohort of coronary heart disease patients,[53] and baPWV and cfPWV were indices of arterial stiffness that exhibit similar extent of associations with cardiovascular disease risk factors and clinical events in the relatively large community-based research studies from 6 different institutions in Japan and 1 in the United States.[54] Therefore, although this is a relatively short-term trial and it may be difficult to assess the beneficial effects of aliskiren on vascular remodeling beyond BP-lowering effects, the present results suggest potential vascular protective effects of aliskiren in untreated nondiabetic patients with mild to moderate hypertension.

LIMITATIONS

The limitations of the present study include both the small number of patients and the study design. A prospective single-arm trial lacking a placebo control group does not allow for inferences to be made regarding cause and effect. Since the present study compared the parameters at baseline and after the aliskiren-based antihypertensive therapy, the influence of the timing of the therapy could not be fully excluded. Also, there was no mention of recording standards, ie, hours without smoking, meals, and caffeine. Furthermore, although the addition of aliskiren to the ARB losartan proved synergistic in lowering proteinuria in patients with diabetic nephropathy,[55] an increase in adverse events and no apparent benefits among patients randomized to aliskiren in the Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Endpoints (ALTITUDE),[56] which is a randomized, double-blind, placebo-controlled study in high-risk type 2 diabetic patients receiving aliskiren or placebo added to the preceding treatment including ACE inhibitor or ARB, has prompted an early termination of the study. Therefore, the long-term organ protective potential of aliskiren and its superiority over existing therapies remains to be elucidated. Further studies are also necessary to compare the beneficial effects of aliskiren-based therapy on target organ function with those of ACE inhibitor– or ARB-based therapy in hypertension.

CONCLUSIONS

These results suggest that aliskiren as a first-line regimen improves ambulatory BP profile as well as clinic BP and may afford protective vascular effects in patients with untreated mild to moderate essential hypertension and a relatively low renin profile.

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Relationship of Ambulatory Blood Pressure and the Heart Rate Profile with Renal Function Parameters in Hypertensive Patients with Chronic Kidney Disease

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Abstract

Strict blood pressure (BP) control is reportedly important for the management of hypertensive patients with chronic kidney disease (CKD). The purpose of this cross-sectional study was to examine whether the variables of ambulatory BP and the heart rate (HR) profile, central hemodynamics, and arterial stiffness were closely related to the renal function parameters (urine albumin excretion rate [UACR] and estimated glomerular filtration rate [eGFR]) observed in 25 consecutive hospitalized hypertensive patients with CKD. There were significant positive relationships between UACR and 24-hour, daytime, and nighttime ambulatory systolic BP. In addition, there were significant negative relationships between UACR and 24-hour and daytime HR variability. The circulating B-type natriuretic peptide level and hemoglobin A1c were also positively related to UACR. With respect to eGFR, although the 24-hour and nighttime HR variability were positively associated with eGFR, the circulating pentosidine and nighttime HR had a negative relationship with eGFR. On the other hand, central hemodynamics and arterial stiffness did not exhibit any significant association with renal function parameters. These results indicate that ambulatory BP and the HR profile are closely modulated by renal function deterioration. Further studies are needed to investigate the causal relationship between ambulatory BP and the HR profile and renal function parameters in hypertensive patients with CKD.

Keywords: ambulatory BP monitoring, hypertension, chronic kidney disease, HR variability, central BP, arterial stiffness, oxidative stress

INTRODUCTION

Clinical trials have shown that a strict control of blood pressure (BP) is essential to prevent target organ damage and to reduce cardiovascular mortality in hypertensive patients (1,2). Recent evidence has also indicated that the ambulatory BP profile, as well as the clinical BP, is important for a proper estimation of BP control. In particular, ambulatory BP monitoring has allowed both an easier and more accurate determination of the circadian rhythm of BP under different pathophysiological conditions. The circadian pattern of BP in hypertensive patients with chronic kidney disease (CKD) and diabetes has been shown to exhibit a blunted nocturnal decrease in BP, which is associated with autonomic neuropathy and nephropathy in these hypertensive patients (3). The loss of nocturnal BP dipping has been considered to be a risk factor for the progression of nephropathy, and to be of prognostic value with respect to target organ damage and cardiovascular morbidity in these CKD patients (4–6).

The central hemodynamics (i.e., central systolic BP [cSBP] and augmentation index [AI]) and pulse wave velocity (PWV), a marker of large artery stiffness, do not always correlate with the peripheral brachial BP value, but reflects the pressure load in the major organs. Several previous studies showed that these variables (cSBP, AI, and PWV) are related to organ damage more closely than brachial BP (7–10). A recent meta-analysis also showed that cSBP, AI, and PWV are independent risk factors for cardiovascular disease, and that these variables may

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reflect the different conditions of the pathophysiological abnormalities related to arterial stiffness (11,12). Although several studies have reported abnormal central hemodynamics and increased PWV in subjects with end-stage renal disease (6,7), a recent community-based population cohort study showed that the out-of-office ambulatory BP level (24-h systolic BP) may be superior to cSBP in the prediction of cardiovascular mortality (13). Thus, this study aimed to determine whether ambulatory BP profiles, central hemodynamics, and PWV are significantly related to renal function parameters in hypertensive patients with CKD in a cross-sectional design.

SUBJECTS AND METHODS

Subjects

This study was conducted on 25 consecutive hypertensive patients with CKD (stage 2, 5 patients; stage 3, 6 patients; stage 4, 7 patients; and stage 5, 7 patients) who were admitted to our hospital from October 2009 to June 2011. Chronic kidney disease patients on dialysis therapy were excluded. The patients were maintained under stable sodium chloride intake (6 g/d). They underwent ambulatory BP monitoring and measurements of coefficient of variation R–R interval (CVRR), central hemodynamics, and brachial-ankle pulse wave velocity (baPWV). Written informed consent was obtained, in the formal style approved by the Ethics Committee of the Yokohama City University Hospital, before any person was enrolled in this study.

Ambulatory BP and the HR Profile

The ambulatory blood pressure and the heart rate (HR) profile were monitored every 30 minutes with a fully automated device (TM-2425, A&D, Tokyo, Japan), essentially as described previously (14–16). The ambulatory blood pressure monitoring was repeated in patients who had >20% missing values out of the expected number of readings, a >30% error rate for the total readings, or missing values for more than 2 consecutive hours. The following readings were omitted because of technical artifacts: systolic BP >250 mm Hg or <70 mm Hg; diastolic BP >130 mm Hg or <30 mm Hg; pulse pressure >160 mm Hg or <20 mm Hg; systolic differences >60 mm Hg; or diastolic differences >30 mm Hg, compared with the immediately preceding or successive values (17). The patients were instructed to keep a diary to record the time of sleeping, rising, and daytime activities. Therefore, the term "day" and "night" hours in this study reflect the average period during which the subjects were awake/upright and asleep/supine, respectively. Short-term blood pressure variability, which is comprised of the coefficients of variation of the BP values obtained from ambulatory BP monitoring, is defined as the within-subject standard deviation (SD) of all systolic and diastolic readings at 30-minute intervals divided by the mean BP during the course of the measurement period. The heart rate variability, which is comprised of the coefficients of variation of the HR values, is defined as the within-subject SD of all HR values at 30-minute intervals divided by the mean HR (18–23).

Laboratory Measurements

Blood sampling was performed between 8 and 10 am after an overnight fast. After the patients had spent 30 minutes of quiet rest in a recumbent position, blood samples were withdrawn for the measurement of laboratory parameters by routine methods in the Department of Clinical Chemistry, Yokohama City University School Hospital. We calculated the estimated glomerular filtration rate (eGFR) with an application of a revised equation for the Japanese population: eGFR (mL/min/1.73 m^2) = 194 × serum creatinine$^{-1.094}$ × age$^{-0.287}$ × 0.739 (if female) (24).

Central Hemodynamics

The central systolic BP and augmentation index were measured by HEM-9000AI (Omron Healthcare, Kyoto, Japan) using an automatic tonometry probe wrapped onto the wrist to record radial waveforms, which are calibrated against the contralateral brachial BP measured by an arm cuff immediately after tonometry. An algorithm is then applied based on a linear regression model to estimate the cSBP from the "late systolic shoulder" (pSBP2) of the radial pulse waveform, which has been shown to agree closely with cSBP (25–28). The device uses the maxima of the "multidimensional derivatives" on the recorded pressure waveforms to detect the first and second inflection points corresponding to the early and late systolic (pSBP2) pressure readings.

Brachial-Ankle Pulse Wave Velocity

The brachial-ankle pulse wave velocity values were determined with a PP analyzer (model: BP-203RPEII; Nihon Colin, Tokyo, Japan). Pulse volume waveforms were recorded with sensors placed over the right brachial artery and both tibial arteries. The brachial-ankle pulse wave velocity values measured by this method are reported to significantly correlate with the aortic PWV determined by the catheter method (21,22,29).

Coefficient of Variation of R–R Interval

Coefficient of variation of R–R interval was measured (with) using a Cardiofax ECG-1550 (Nihon Kohden, Tokyo, Japan) with the patient in the supine position after 5-minute rest, essentially as described previously (30).

Statistical Analysis

The quantitative data are expressed as the means ± SD. Pearson's correlation coefficient was used for the continuous scale. Spearman's correlation coefficient was used for all other scales. Analysis was performed with IBM SPSS statistics (version 19, IBM SPSS

Statistics, Chicago, IL, USA). A P value < .05 was considered statistically significant.

RESULTS

Baseline Patient Characteristics, Including Ambulatory BP and the HR Profile, Central Hemodynamics, and Arterial Stiffness

Table 1 shows the baseline characteristics of the 25 hypertensive participants with CKD consisting of 5 patients in stage 2, 6 in stage 3, 7 in stage 4, and 7 in stage 5. The mean age was 66.2 ± 11.6 years, and there were 15 males and 10 females. The body mass index was 25.6 ± 4.3 kg/m^2, suggesting that the participants were obese hypertensive patients having moderate-to-severe impairment with albuminuria. The variables of the ambulatory BP and the HR monitoring, central hemodynamics, and arterial stiffness are shown in Table 2.

Variables Related to Renal Function Parameters

As shown in Table 3, there were significant positive relationships between UACR and 24-hour, daytime, and nighttime ambulatory systolic BP. In addition, there were significant negative relationships between UACR and 24-hour and daytime HR variability. Furthermore, the circulating B-type natriuretic peptide (BNP) level and hemoglobin A1c (HbA1c) were positively related to UACR. With respect to eGFR, while the 24-hour and nighttime HR variability were positively associated with eGFR, the circulating pentosidine and nighttime HR had negative relationships with eGFR. On the other hand, neither the central hemodynamics (cSBP, AI) nor the arterial stiffness (baPWV) exhibited any significant association with renal function parameters.

Table 1. Patient characteristics ($N = 25$)

Sex (male/female)	15/10
Age (y)	66.2 ± 11.6
BMI (kg/m^2)	25.6 ± 4.3
Smoking (%)	60
Cerebrovascular disease (%)	20
Coronary artery disease (%)	8
Diabetes (%)	44
Dyslipidemia (%)	64
Medication	
Renin–angiotensin system inhibitor (%)	84
Calcium channel blocker (%)	84
α-Blocker (%)	32
β-Blocker (%)	12
Thiazide diuretic (%)	16
Loop diuretic (%)	32
Metabolism parameters	
Total cholesterol (mg/dL)	190.9 ± 34.2
HbA1c (%)	5.9 ± 1.0
HOMA-R	2.9 ± 2.9
Endocrine parameters	
BNP (pg/mL)	51.5 ± 81.2
PRA (ng/mL/h)	7.5 ± 17.5
Oxidative stress marker	
Pentosidine (ng/mL)	46.1 ± 28.3
Autonomic function	
CVRR (%)	2.1 ± 2.0
Cardiac function	
Ejection fraction (%)	69.1 ± 8.5
LVMI (g/m^2)	175.0 ± 116.2
Renal function	
eGFR (mL/min/1.73 m^2)	33.1 ± 23.1
UACR (mg/gCr)	820.3 ± 1225.2

Abbreviations: BMI – body mass index; BNP – B-type natriuretic peptide; CVRR – coefficient of variation R–R interval; eGFR – estimated glomerular filtration rate; HbA1c – hemoglobin A1c; HOMA-R – homeostasis model assessment ratio; LVMI – left ventricular mass index; PRA – plasma renin activity; UACR – urine albumin excretion rate.

Table 2. Ambulatory BP profile, central hemodynamics, and arterial stiffness

Ambulatory BP profile	
24-h	
Systolic BP (mm Hg)	134 ± 17
Diastolic BP (mm Hg)	79 ± 14
HR (beats/min)	69 ± 10
Systolic BP variability (%)	11.0 ± 3.1
Diastolic BP variability (%)	13.1 ± 4.3
HR variability (%)	12.7 ± 4.1
Daytime	
Systolic BP (mm Hg)	136 ± 16
Diastolic BP (mm Hg)	82 ± 13
HR (beats/min)	71 ± 9
Systolic BP variability (%)	10.2 ± 3.2
Diastolic BP variability (%)	11.8 ± 4.7
HR variability (%)	12.4 ± 4.0
Nighttime	
Systolic BP (mm Hg)	129 ± 21
Diastolic BP (mm Hg)	74 ± 14
HR (beats/min)	65 ± 12
Systolic BP variability (%)	9.1 ± 3.1
Diastolic BP variability (%)	11.4 ± 3.8
HR variability (%)	7.8 ± 3.7
Central hemodynamics	
cSBP (mm Hg)	148 ± 20
AI (%)	80 ± 15
Arterial stiffness	
baPWV (cm/s)	1776 ± 363

Abbreviations: AI – augmentation index; baPWV – brachial-ankle pulse wave velocity; BP – blood pressure; cSBP – central systolic blood pressure; HR – heart rate.
Values are means ± SD.

DISCUSSION

The main finding of this cross-sectional study is that the renal function parameters UACR and eGFR, which are key components of the assessment of the severity of CKD, were associated with the ambulatory BP and the HR profile. On the other hand, parameters of central hemodynamics and arterial stiffness did not exhibit any significant relationship with renal function. These associations between the ambulatory BP profile and renal function status deserve further discussion.

Previous studies have reported strong correlations between the ambulatory BP levels and urinary albumin or protein excretion in both hypertensive patients and CKD patients (31–33). In this study, UACR was

Table 3. Ambulatory BP and other variables related to renal function

Variables	UACR *R* (*P* value)	eGFR *R* (*P* value)
Ambulatory BP profile		
24-h		
Systolic BP (mm Hg)	0. 639 (.001)	NS
Diastolic BP (mm Hg)	NS	NS
HR (beats/min)	NS	NS
Systolic BP variability (%)	NS	NS
Diastolic BP variability (%)	NS	NS
HR variability (%)	−0.555 (.007)	0.474 (.017)
Daytime		
Systolic BP (mm Hg)	0. 542 (.009)	NS
Diastolic BP (mm Hg)	NS	NS
HR (beats/min)	NS	NS
Systolic BP variability (%)	NS	NS
Diastolic BP variability (%)	NS	NS
HR variability (%)	−0.507 (.016)	NS
Nighttime		
Systolic BP (mm Hg)	0.720 (<.001)	NS
Diastolic BP (mm Hg)	NS	NS
HR (beats/min)	0.459 (.031)	−0.418 (.038)
Systolic BP variability (%)	NS	NS
Diastolic BP variability (%)	NS	NS
HR variability (%)	NS	0.520 (.008)
Central hemodynamics		
cSBP (mm Hg)	NS	NS
AI (%)	NS	NS
Arterial stiffness		
baPWV (cm/s)	NS	NS
Other variables		
Age (y)	−0.434 (.043)	NS
BMI (kg/m^2)	NS	NS
Total cholesterol (mg/dL)	NS	NS
HbA1c (%)	0.442 (.040)	NS
BNP (pg/ml)	0.724 (<.001)	NS
Pentosidine (ng/mL)	NS	−0.602 (.004)
CVRR (%)	NS	NS

Abbreviations: AI – augmentation index; baPWV – brachial-ankle pulse wave velocity; BMI – body mass index; BNP – B-type natriuretic peptide; BP – blood pressure; cSBP – central systolic blood pressure; CVRR – coefficient of variation R–R interval; eGFR – estimated glomerular filtration rate; HR – heart rate; NS – nonsignificant; UACR – urine albumin excretion rate; HbA1c – hemoglobin A1c. Values are means ± SD.

positively correlated to 24-hour, daytime, and nighttime systolic ambulatory BP, with the strongest association being that between UACR and nighttime systolic BP. This is consistent with previous studies showing that nocturnal BP is critically important for urinary albumin or protein excretion in both hypertensive and CKD patients (17,34,35). Since the circulating BNP level and HbA1c also showed positive correlations with UACR, the patients with increased UACR are thought to have an increased circulating blood volume with relatively high blood glucose and high BP levels.

The analysis of the relationship between the ambulatory BP and the HR profile and renal function parameters unexpectedly revealed that eGFR was positively correlated to 24-hour and nighttime HR variability. The recent results of the Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) study and meta-analysis of several large-scale cohort studies showed that the preservation of eGFR concomitant with a reduction in albuminuria is important for the management of cardiovascular complications in patients with CKD (36–38). The heart rate variability is a noninvasive measure of autonomic function that actually reflects the beat-to-beat variability in HR. It is best assessed by continuous electrocardiography over a 24-hour period, although shorter-term recordings have also been utilized, as estimated with CVRR in this study.

Utilization of the ambulatory BP monitoring device TM-2425 enabled us to assess HR variability during 24-hour, daytime, and nighttime periods. A lower heart rate variability has been associated with adverse cardiovascular outcomes in settings such as post-myocardial infarction, coronary artery disease, congestive heart failure, diabetes, and end-stage renal disease (39–41). Although it has not been systematically studied in the nondialysis CKD population, a recent study showed that a lower HR variability occurs commonly in advanced stage CKD patients due to cardiac autonomic neuropathy, and this is associated with increased cardiovascular complications and mortality in CKD patients, thereby suggesting an important role of HR variability in both the progression of CKD and the development of cardiorenal syndrome (42).

There is evidence that diabetes and renal dysfunction are associated with persistent oxidative and carbonyl stress, as well as inflammation (38,43). Advanced glycation end products (AGEs) are made up of a protein carbonyl compound which is produced by protein–reactive oxygen species interactions. Furthermore, the elevation of oxidative/carbonyl stress end products, including AGEs, is likely to be, at least partly, responsible for the increased cardiovascular disease in diabetic patients (44,45). Pentosidine, one of the well-defined AGEs, is synthesized through nonenzymatic reactions of pentose, and its formation is closely related to oxidative processes (46). Its relationship with the relative severity of various diseases has been reported (47), and in this study, it was demonstrated that the circulating level of pentosidine was inversely correlated with eGFR.

Finally, although several variables of ambulatory BP monitoring disclosed significant relationships with the key renal function markers UACR and eGFR, central hemodynamics and arterial stiffness did not exhibit any significant association with these renal function markers. However, an interesting recent study demonstrated that the combination of CKD and increased arterial stiffness is a predictor of stroke and cardiovascular disease in hypertensive patients (48), which warrants further large-scale investigation. These results indicate that the ambulatory BP and the HR profile are affected by renal function deterioration and further studies on the causal link in CKD are needed. A limitation of this study is that the cross-sectional analysis of many variables is statistically inadequate with this small patient number.

In conclusion, the results of this study suggest that alteration in the ambulatory BP and the HR profile is closely associated with renal function deterioration in hypertensive patients with CKD, and further studies are needed to examine the influence of this association on the progression of CKD and the development of cardiorenal syndrome, as well as the relation to renal structural abnormalities (49,50).

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Combination Therapy of Angiotensin II Receptor Blocker and Calcium Channel Blocker Exerts Pleiotropic Therapeutic Effects in Addition to Blood Pressure Lowering: Amlodipine and Candesartan Trial in Yokohama (ACTY)

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Abstract

Recent guidelines recommend combination antihypertensive therapy to achieve the target blood pressure (BP) and to suppress target organ damage. This study aimed to examine the beneficial effects of combination therapy with candesartan and amlodipine on BP control and markers of target organ function in Japanese essential hypertensive patients ($N = 20$) who did not achieve the target BP level during the monotherapy period with either candesartan or amlodipine. After the monotherapy period, for patients already being treated with amlodipine, a once-daily 8 mg dose of candesartan was added on during the combination therapy period (angiotensin II receptor blocker [ARB] add-on group, $N = 10$), and a once-daily 5 mg dose of amlodipine was added on for those already being treated with candesartan (calcium channel blocker [CCB] add-on group, $N = 10$). Combination therapy with candesartan and amlodipine for 12 weeks significantly decreased clinic and home systolic blood pressure (SBP) and diastolic blood pressure (DBP). In addition, the combination therapy was able to significantly reduce urine albumin excretion without decrease in estimated glomerular filtration ratio and resulted in significant improvements in brachial-ankle pulse wave velocity, central SBP, and insulin sensitivity. Furthermore, the CCB add-on group showed a significantly greater decrease in clinic and home DBP than the ARB add-on group. The calcium channel blocker add-on group also exhibited better improvements in vascular functional parameters than the ARB add-on group. These results suggest that combination therapy with candesartan and amlodipine is an efficient therapeutic strategy for hypertension with pleiotropic benefits.

Keywords: hypertension, therapy, renal function, central systolic blood pressure, arterial stiffness, insulin resistance

INTRODUCTION

Accumulated results of clinical trials showed that strict control of blood pressure (BP) is essential to prevent target organ damage and to reduce cardiovascular mortality in hypertensive patients (1,2). The angiotensin II receptor blocker (ARB) and dihydropyridine calcium channel blocker (CCB) are the first-line antihypertensive drugs for most patients with hypertension, but monotherapy with either ARB or CCB achieves the target BP recommended by the hypertension guidelines in only a limited number of patients and, thus, combination therapy is required in a majority of patients (3).

This study aimed to examine the beneficial effects of combination therapy with ARB candesartan and CCB amlodipine on BP profile and several target organ functions in Japanese essential hypertensive patients who did not achieve the target BP level according to the Japanese Society of Hypertension Guidelines for the Management of Hypertension during the monotherapy period with either candesartan or amlodipine (4).

SUBJECTS AND METHODS

Study Population and Design

The study participants, aged 26–76 years, were recruited from the Outpatients Department of Internal Medicine, Yokohama City University Hospital (Yokohama, Japan). The entry period was from January 2010 to January

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2011. This study consisted of a 4-week monotherapy period and 12-week combination therapy period. The eligible subjects were mild-to-moderate essential hypertensive patients who were already treated with a once-daily 5 mg dose of amlodipine monotherapy or with a once-daily 8 mg dose of candesartan monotherapy at the initiation of the monotherapy period and did not achieve the target BP level according to the Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH2009) during the monotherapy period (4). The subjects were treated with either monotherapy for more than 4 weeks. After the monotherapy period, for the patients already being treated with amlodipine, a once-daily 8 mg dose of candesartan was added on during the combination therapy period (ARB add-on group), and a once-daily 5 mg dose of amlodipine was added on for those already being treated with candesartan (CCB add-on group). Exclusion criteria included patients who exhibited severe hypertension (clinic systolic BP [SBP] $\geq$ 180 mm Hg and/or diastolic BP [DBP] $\geq$ 110 mm Hg), patients with renal insufficiency (estimated glomerular filtration rate [eGFR] < 30 mL/min/1.73 m^2), women who were nursing or pregnant, and patients with clinically significant heart disease, moderate-to-severe hepatic dysfunction, and known hypersensitivity to any component of the study medications.

Measurements of clinic BP and home BP (HBP) were performed before and 12 weeks after the start of the combination treatment. Venous blood and urine samples for the hematological, biochemical, and renal parameters were drawn and collected in the morning after an overnight fast on the same day the measurements of clinic BP, brachial-ankle pulse wave velocity (baPWV), and central systolic blood pressure (cSBP) were performed. We calculated eGFR with an application of a revised equation for the Japanese population: eGFR (mL/min/1.73 m^2) = 194 $\times$ serum creatinine$^{-1.094}$ $\times$ Age$^{-0.287}$ $\times$ 0.739 (if female) (5). This study was approved by the Ethics Committees of Yokohama City University Hospital, and written informed consent was obtained from every participant.

Clinic BP and Home BP Measurements

Clinic blood pressure was measured in the sitting position after at least 5-minute rest using a sphygmomanometer. Two measurements were taken 1 minute apart, and their average was used for calculation. The home blood pressure measurement was performed using a validated cuff oscillometric device Omron 705IT (HEM-759-E; Omron Healthcare, Kyoto, Japan) according to the Japanese Society of Hypertension Guidelines for the Management of Hypertension (4,6). The patients were instructed to measure their morning HBP (measured after awakening and before breakfast and taking antihypertensive medication) in a sitting position, and the average of morning HBP values for the 3-day period before visiting was calculated.

Central Systolic Blood Pressure and Brachial-Ankle Pulse Wave Velocity

The central systolic blood pressure was measured by HEM-9000AI (Omron Healthcare) using an automatic tonometry probe wrapped onto the wrist to record radial waveforms, which are then calibrated against the contralateral brachial BP measured by an arm cuff immediately after tonometry. An algorithm based on a linear regression model is then applied to estimate cSBP from the "late systolic shoulder" (pSBP2) of the radial pulse waveform, which has been shown to agree closely with cSBP (7–10). The device uses the maxima of the "multidimensional derivatives" on the recorded pressure waveforms to detect first and second inflection points corresponding to early and late systolic (pSBP2) pressures.

The brachial-ankle pulse wave velocity values were determined with a PP analyzer (BP-203RPEII; Nihon Colin, Tokyo, Japan). Pulse volume waveforms were recorded with sensors placed over the right brachial artery and both tibial arteries. The brachial-ankle pulse wave velocity values measured by this method are reported to significantly correlate with the aortic pulse wave velocity (PWV) measured by the catheter method (11–13).

Statistical Analysis

The quantitative data are expressed as means $\pm$ SEM. For the statistical analysis of difference between monotherapy and combination therapy, Wilcoxon signed-rank test was performed, and for the statistical analysis of difference between the ARB add-on group and CCB add-on group, Mann–Whitney's *U*-test was performed, by using SPSS software (version 16.0, SPSS, Chicago, IL, USA). A *P* value of <.05 was considered as statistically significant.

RESULTS

Baseline Patient Characteristics

Table 1 shows the baseline characteristics of the total 20 participants consisting of 10 hypertensive patients (ARB add-on group) precedingly being treated with amlodipine (5 mg/day) and 10 hypertensive patients (CCB add-on group) precedingly being treated with candesartan (8 mg/day) before the start of the combination therapy. Mean age was 62.0 $\pm$ 3.1 years, and the number of males and females was 12 and 8, respectively. Body mass index was 25.6 $\pm$ 1.1 kg/m^2, suggesting that the participants correspond to obese hypertensive patients as a whole.

With respect to BP control, HBP as well as clinic BP did not achieve the target BP level according to the JSH2009 guideline (home SBP/DBP 150 $\pm$ 1/87 $\pm$ 1 mm Hg; clinic SBP/DBP 153 $\pm$ 1/89 $\pm$ 2 mm Hg). Eleven patients were with slightly impaired renal function and albuminuria (urine albumin-to-creatinine ratio [UACR] 373 $\pm$ 124 mg/g-creatinine; eGFR 73.3 $\pm$ 4.6

Table 1. Baseline patient characteristics ($N = 20$)

	Total ($N = 20$)	ARB add-on group ($N = 10$)	CCB add-on group ($N = 10$)	ARB versus CCB
Sex (male/female)	12/8	7/3	5/5	NS
Age (y)	62.0 ± 3.1	63.1 ± 3.1	60.8 ± 5.2	NS
CKD (stage 1 to 3)	11	5	6	NS
Stage 1	4	0	1	
Stage 2	3	2	4	
Stage 3	4	3	1	
Diabetes mellitus	2	1	1	NS
BMI (kg/m^2)	25.6 ± 1.1	25.3 ± 1.1	25.9 ± 1.8	NS
Clinic BP				
SBP (mm Hg)	153 ± 1	152 ± 1	154 ± 1	NS
DBP (mm Hg)	89 ± 2	87 ± 4	91 ± 2	NS
PR (beats/min)	75 ± 1	75 ± 1	74 ± 1	NS
HBP morning				
SBP (mm Hg)	150 ± 1	148 ± 1	151 ± 1	NS
DBP (mm Hg)	87 ± 1	86 ± 1	88 ± 1	NS
Renal function				
UACR (mg/g-Cr)	373 ± 124	374 ± 190	373 ± 150	NS
eGFR (mL/min/1.73 m^2)	73.3 ± 4.6	73.9 ± 7.3	72.6 ± 5.3	NS
Cardiac function				
BNP (pg/mL)	25.9 ± 6.9	13.9 ± 2.4	33.8 ± 9.3	NS
Vascular function				
baPWV (cm/s)	1912 ± 79	1953 ± 122	1871 ± 91	NS
AI (%)	88 ± 4	84 ± 3	92 ± 6	NS
cSBP (mm Hg)	165 ± 4	159 ± 5	171 ± 5	NS
Glucose metabolism				
HOMA-R	3.9 ± 0.5	3.7 ± 0.7	4.1 ± 0.7	NS

Abbreviations: ARB – angiotensin II receptor blocker; CCB – calcium channel blocker; CKD – chronic kidney disease; BMI – body mass index; SBP – systolic blood pressure; DBP – diastolic blood pressure; HBP – home blood pressure; PR – pulse rate; UACR – urine albumin-to-creatinine ratio; eGFR – estimated glomerular filtration rate; BNP – brain natriuretic peptide; baPWV – brachial-ankle pulse wave velocity; AI – augmentation index; cSBP – central systolic blood pressure; HOMA-R – homeostasis model assessment ratio; NS – not significant. Data are shown as means ± SEM or percentages.

mL/min/1.73 m^2) and also with slightly impaired systemic insulin sensitivity (homeostasis model assessment ratio [HOMA-R], 3.9 ± 0.5). Briefly, participants were characterized as middle-aged, obese, mild-to-moderate hypertensive patients with impaired renal function and insulin resistance. There were no significant differences in patient characteristics between ARB add-on group and CCB add-on group at baseline.

Effects of Combination Therapy with ARB and CCB on BP Profile

As a whole, combination therapy with candesartan and amlodipine for 12 weeks significantly decreased clinic SBP and DBP, although the reduction of DBP in the ARB add-on group did not reach a statistical significance (Figure 1A). With respect to changes in clinic BP by combination therapy, the CCB add-on group showed a significantly greater decrease in clinic DBP and a marginally larger reduction of clinic SBP than the ARB add-on group (Figure 1B). Achievement of target BP control, which was defined as BP values less than 130/80 mm Hg in patients with diabetes or chronic kidney disease (CKD) or less than 140/90 mm Hg in those without diabetes or CKD, according to the JSH2009, was attained in an average of 50% of patients in the CCB add-on group and 40% in the ARB add-on group.

Similar to clinic BP, combination therapy with candesartan and amlodipine significantly decreased home morning SBP and DBP (Figure 2A). Again, the CCB add-on group showed a greater reduction of home morning DBP than the ARB add-on group (Figure 2B).

Effects of Combination Therapy with ARB and CCB on Renal Function, Vascular Function, Cardiac Function, and Insulin Sensitivity

Combination therapy with candesartan and amlodipine for 12 weeks significantly decreased UACR (Figure 3A) and there was no significant difference in the decrease in UACR between the ARB add-on group and the CCB add-on group (Figure 3B). In addition, the reduction of UACR by the combination therapy was not accompanied with decline in eGFR in either the ARB add-on group or the CCB add-on group (Figure 3A and B).

Concerning parameters of vascular function, combination therapy with candesartan and amlodipine for 12 weeks significantly improved both baPWV and cSBP as a whole (Figure 4A and B). However, while the CCB add-on group showed significant reductions of baPWV and

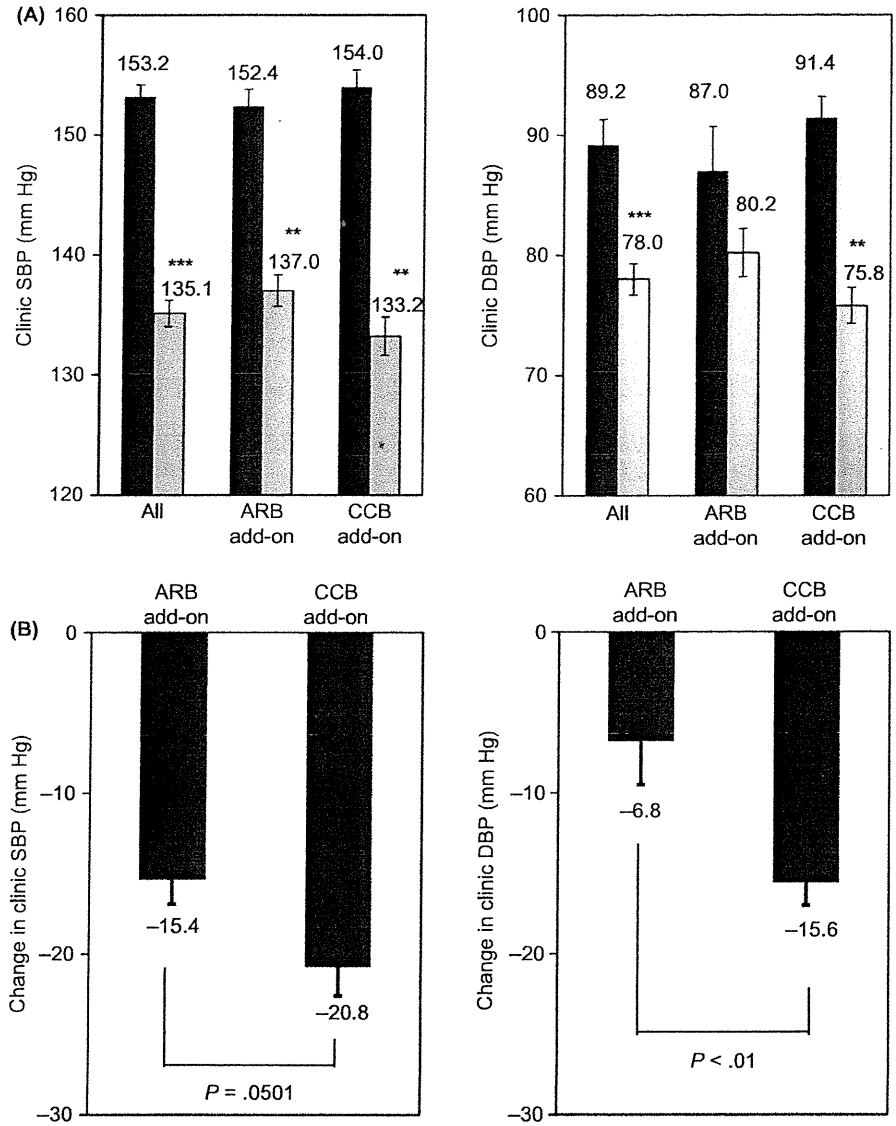

Figure 1. Effects of combination therapy with candesartan and amlodipine on clinic BP profile. (**A**) Effects of combination therapy on clinic SBP and DBP. Black bars indicate values at baseline and gray bars indicate values after 12 wk combination therapy. $^{**}P < .01$, $^{***}P < .001$, 12 wk versus baseline. (**B**) Comparison of change in clinic BP between the ARB add-on group and the CCB add-on group. Values are expressed as means ± SEM.

cSBP, the ARB add-on group failed to exhibit statistically significant improvements in baPWV and cSBP. With respect to cardiac function, the circulating brain natriuretic peptide level was significantly improved only in the CCB add-on group (Figure 4C). Finally, the combination therapy significantly improved HOMA-R and there was no difference in the degree of improvement between the ARB add-on group and the CCB add-on group (Figure 4D).

DISCUSSION

The main finding of this study was that the combination antihypertensive therapy with candesartan and amlodipine successfully decreased clinic BP and HBP in both hypertensive patients precedingly being treated with amlodipine and in those precedingly being treated with candesartan before the start of the combination therapy. In addition, the combination therapy was able to significantly reduce UACR without decrease in eGFR and resulted in significant improvements in vascular function and insulin sensitivity. These pleiotropic effects by combination therapy with candesartan and amlodipine deserve further discussion.

Recent clinical guidelines for hypertensive patients recommend combination therapy such as renin–angiotensin system inhibitors and CCB or diuretics, and in this study, the combination therapy with candesartan and amlodipine was effective for efficient lowering of clinic BP and HBP in Japanese essential hypertensive patients.

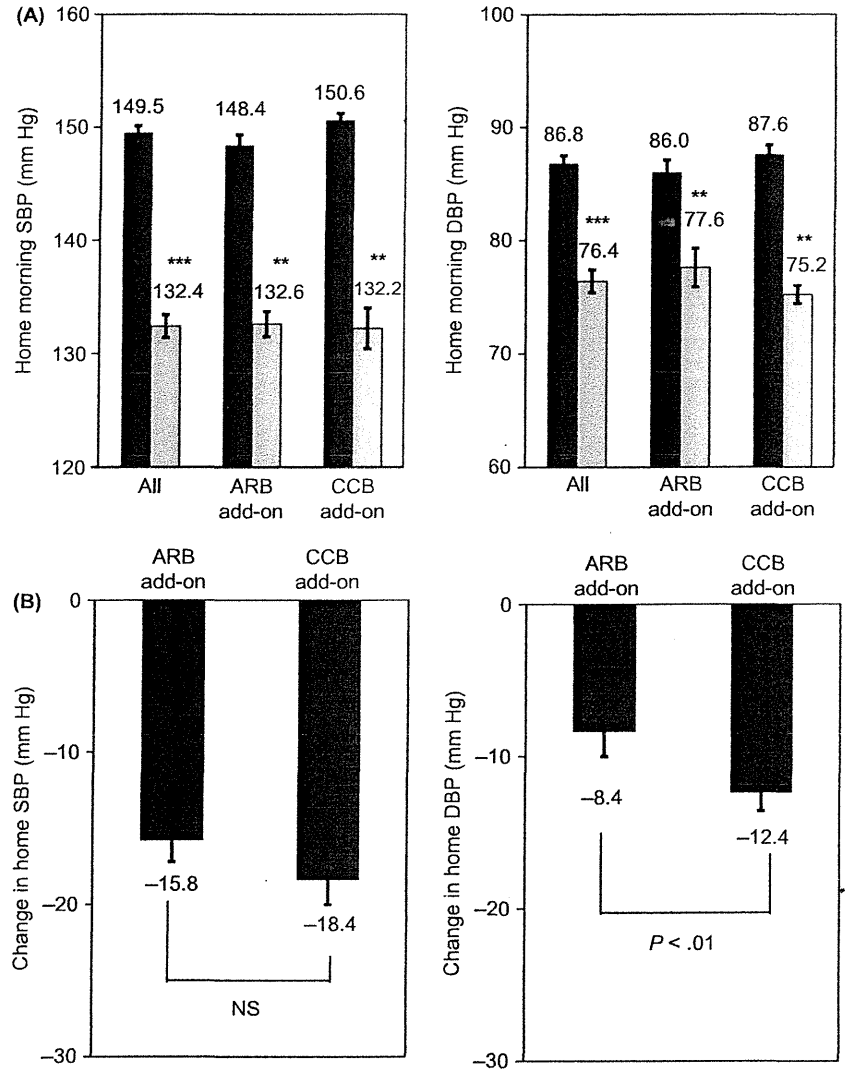

Figure 2. Effects of combination therapy with candesartan and amlodipine on home morning BP profile. (**A**) Effects of combination therapy on clinic SBP and DBP. Black bars indicate values at baseline and gray bars indicate values after 12 wk combination therapy. $^{**}P < .01$, $^{***}P < .001$, 12 wk versus baseline. (**B**) Comparison of change in home morning BP between the ARB add-on group and the CCB add-on group. Values are expressed as means ± SEM.

Interestingly, with respect to BP lowering efficacy, the CCB add-on group exerted greater reductions of clinic BP and HBP than the ARB add-on group, which would be consistent with a previous result of CASE-J trial in Japan showing that the BP level achieved with candesartan treatment was not as low as that achieved with amlodipine treatment (14).

Accumulated evidence indicates that ARB is able to improve albuminuria better than CCB through the reduction of intraglomerular pressure (15). However, the decreases in UACR by combination therapy were comparable in the ARB add-on group and the CCB add-on group in this study. Previous results of VALUE and CASE-J trials showed that the BP lowering effects of the CCB-based regimen were more pronounced than the ARB-based regimen, especially in the early several months period (14,16), and another study demonstrated that the decreases in BP significantly contributed to the decreases in albuminuria by combination therapy with ARB and CCB in CKD patients (17). Since the CCB add-on group showed a significantly greater decrease in clinic DBP and a marginally larger reduction of clinic SBP than the ARB add-on group in this study, the comparable reduction of UACR in the ARB add-on group and the CCB add-on group seems to be consistent with these previous findings.

Analysis of patient characteristics at baseline unexpectedly revealed that substantial participants were complicated with CKD and overt albuminuria. However, the combination therapy with candesartan and amlodipine for 12 weeks succeeded to efficiently suppress albuminuria, irrespective of preceding medication, without further decline in eGFR. This is likely to be an important advantage of the combination therapy with ARB and

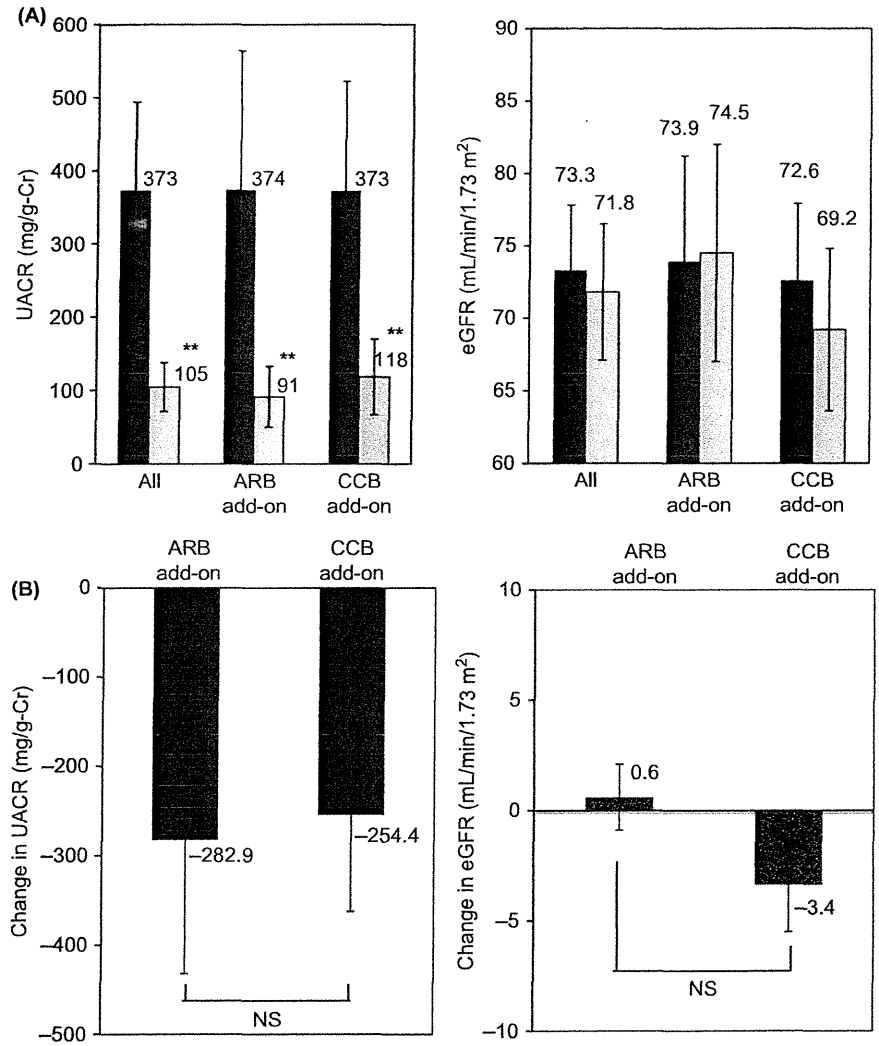

Figure 3. Effects of combination therapy with candesartan and amlodipine on parameters of renal function. (**A**) Effects of combination therapy on urine albumin excretion ratio (UACR) and estimated glomerular filtration ratio (eGFR). Black bars indicate values at baseline and gray bars indicate values after 12 wk combination therapy. $^{**}P < .01$, 12 wk versus baseline. (**B**) Comparison of change in UACR and eGFR between the ARB add-on group and the CCB add-on group. Values are expressed as means ± SEM.

CCB, since several recent epidemiological studies and intervention trials demonstrated that efficient reduction of albuminuria with preserved eGFR is important to inhibit the progression of CKD and to prevent the development of cardiovascular complication (18–20).

The calcium channel blocker add-on group exhibited better improvements in vascular functional parameters such as baPWV and cSBP than the ARB add-on group in this study. A previous study showed that the add-on amlodipine therapy had benefits in terms of the vascular function and vascular structure of hypertensive patients precedingly treated with an ARB, which were independent of its depressor effects but with a concomitant decrease in ambulatory BP variability (21), and a recent study also demonstrated that amlodipine had a stronger inhibitory effect on ambulatory short-term BP variability than indapamide and candesartan in essential hypertensive patients (22). Ambulatory short-term BP variability has been shown to depend on sympathetic vascular modulation and on atherosclerotic vascular changes (23,24). Several previous animal studies showed that exaggerated short-term BP variability without significant changes in mean BP impaired endothelial function by inhibiting NO production and induced chronic cardiovascular inflammation and remodeling (25,26). Ambulatory short-term BP variability is suggested to be clinically relevant by the fact that hypertensive patients with similar 24-hour mean BP values exhibit more severe organ damage when the short-term BP variability is greater (12,13,24,27–30). We also demonstrated that intensified multifactorial intervention, with tight glucose regulation and the use of valsartan and fluvastatin, improved ambulatory BP profile, preserved renal function, and reduced urinary albumin excretion in type 2 diabetic hypertensive patients with overt nephropathy (31).

Recent post hoc and meta-analyses also showed that several parameters of BP variability, such as visit-to-visit

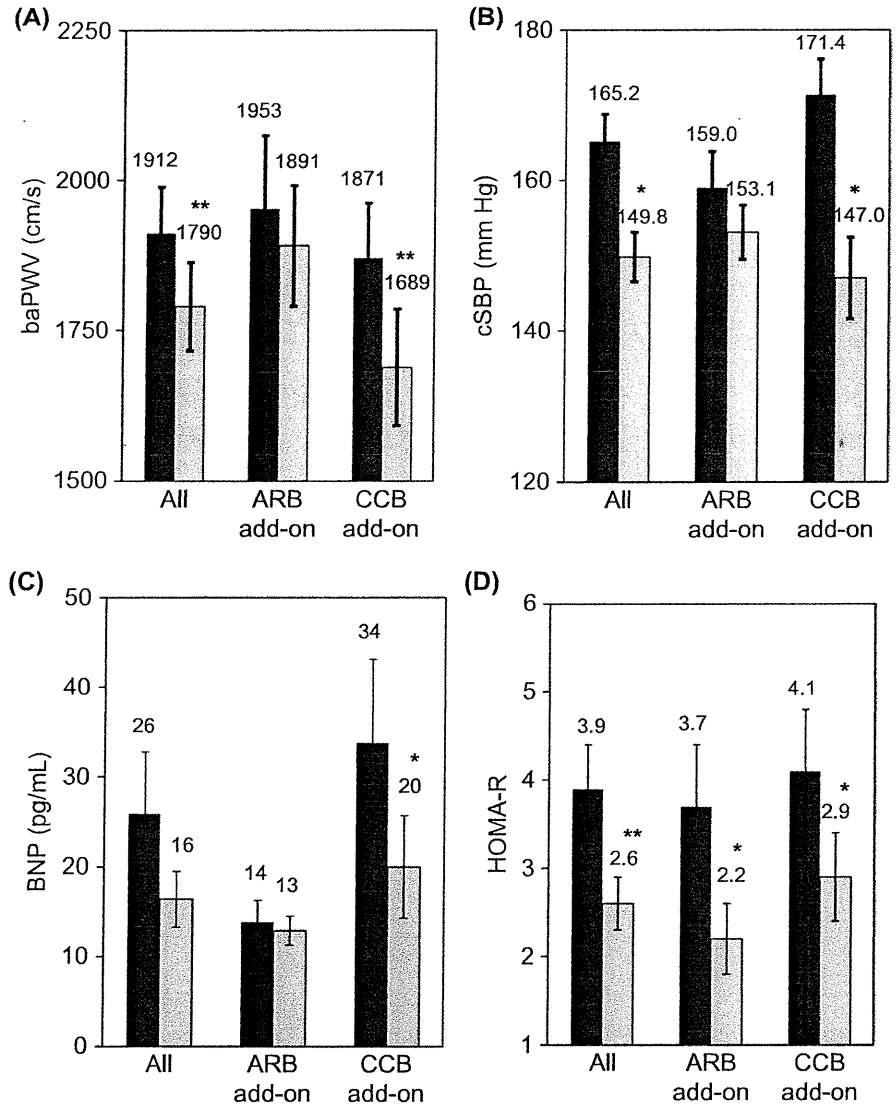

Figure 4. Effects of combination therapy with candesartan and amlodipine on parameters of vascular function, cardiac function, and insulin sensitivity. Effects of combination therapy on brachial-ankle pulse wave velocity (**A**, baPWV), central SBP (**B**, cSBP), brain natriuretic peptide (**C**, BNP), and homeostasis model assessment ratio (**D**, HOMA-R). Black bars indicate values at baseline and gray bars indicate values after 12 wk combination therapy. $*P < .05$, $**P < .01$, 12 wk versus baseline. Values are expressed as means ± SEM.

BP variability and home-measure BP variability in addition to ambulatory BP variability, reflect organ damages and are potential predictors of cardiovascular events, including stroke independently of mean SBP (32–40). Furthermore, these analyses also displayed that CCB is the most effective drug class for reduction of BP variability. Nevertheless, since the clinic BP and HBP lowering effects were larger in the CCB add-on group than in the ARB add-on group in this study, it is still possible that a preferential improvement in vascular function parameters in the CCB add-on group is derived from the better BP control.

In this study the combination therapy with candesartan and amlodipine improved insulin resistance comparably in the ARB add-on group and the CCB add-on group. This observation would be consistent with a previous result showing that CCB reduced glucose intolerance in diabetic mice via different mechanism than ARB, thereby suggesting the clinical possibility that the combination of CCB and ARB could be more efficacious than monotherapy in the treatment of insulin resistance (41). A limitation of this study is the study design. Because the aim of the study was to examine the beneficial effect of combination therapy, the control group should be under monotherapy for strict comparison. However, this study compared the parameters during the period of monotherapy and during the combination therapy. Thus, this study design could not fully exclude the time effect of therapy.

Finally, although only the beneficial effects of combination treatment with ARB and CCB were examined in this study, combination treatment with ARB (or angiotensin-converting enzyme [ACE] inhibitor) and diuretics

is also recommended in the guidelines. Since previous studies reported differential effects between CCB and diuretics when used in combination with ARB on central hemodynamics, arterial stiffness, metabolic profile, and albuminuria in hypertensive patients (5,42–44), further studies are needed to estimate a potential advantage of the ARB + CCB combination over the ARB + diuretics combination for the treatment of hypertension. In conclusion, the results of this study suggest that combination therapy with candesartan and amlodipine is an efficient therapeutic strategy for hypertension with pleiotropic benefits.

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Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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Agonist-Independent Constitutive Activity of Angiotensin II Receptor Promotes Cardiac Remodeling in Mice

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Agonist-Independent Constitutive Activity of Angiotensin II Receptor Promotes Cardiac Remodeling in Mice

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See Editorial Commentary, pp 542–544

Abstract—The angiotensin II (Ang II) type 1 (AT_1) receptor mainly mediates the physiological and pathological actions of Ang II, but recent studies have suggested that AT_1 receptor inherently shows spontaneous constitutive activity even in the absence of Ang II in culture cells. To elucidate the role of Ang II–independent AT_1 receptor activation in the pathogenesis of cardiac remodeling, we generated transgenic mice overexpressing AT_1 receptor under the control of α-myosin heavy chain promoter in angiotensinogen-knockout background (AT_1Tg-AgtKO mice). In AT_1Tg-AgtKO hearts, redistributions of the $G\alpha_{q11}$ subunit into cytosol and phosphorylation of extracellular signal-regulated kinases were significantly increased, compared with angiotensinogen-knockout mice hearts, suggesting that the AT_1 receptor is constitutively activated independent of Ang II. As a consequence, AT_1Tg-AgtKO mice showed spontaneous systolic dysfunction and chamber dilatation, accompanied by severe interstitial fibrosis. Progression of cardiac remodeling in AT_1Tg-AgtKO mice was prevented by treatment with candesartan, an inverse agonist for the AT_1 receptor, but not by its derivative candesartan-7H, deficient of inverse agonism attributed to a lack of the carboxyl group at the benzimidazole ring. Our results demonstrate that constitutive activity of the AT_1 receptor under basal conditions contributes to the cardiac remodeling even in the absence of Ang II, when the AT_1 receptor is upregulated in the heart. (***Hypertension.*** **2012;59:627-633.)** • **Online Data Supplement**

Key Words: ARB ■ cardiac dysfunction ■ fibrosis ■ G protein-coupled receptor ■ inverse agonist

The angiotensin II (Ang II) type 1 (AT_1) receptor is a 7 transmembrane spanning G protein-coupled receptor (GPCR), and the activation of AT_1 receptor is involved in regulating pathophysiological processes of the cardiovascular system. In principle, the AT_1 receptor is activated on binding to Ang II, which is produced systemically or locally after sequential proteolytic processing. However, recent studies demonstrated that the AT_1 receptor inherently shows spontaneous constitutive activity even in the absence of Ang II in cultured cells.[1–3] GPCRs are structurally unstable and show significant levels of spontaneous activity in an agonist-independent manner.[4] In addition, we and others demonstrated that the AT_1 receptor can be activated by mechanical stress independent of Ang II[5–7] through conformational switch of the receptor.[1] These observations have highlighted the inverse agonist activity of AT_1 receptor blockers (ARBs) as a drug-specific property that can inhibit Ang II–independent constitutive activity and mechanical stress-induced receptor activation.[1,2,5,8] In a mouse model, mechanical stress-induced AT_1 receptor activation led to the development of cardiac hypertrophy independent of Ang II, and treatment with inverse agonists for the AT_1 receptor-attenuated cardiac hypertrophy thus formed.[5] However, the pathogenic role of Ang II–independent constitutive activity of the AT_1 receptor and clinical relevance of inverse agonist activity of ARBs against constitutive receptor activation remains to be elucidated in vivo. In several GPCRs, gain-of-function mutations are causative of diseases, but any activating mutations in the

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