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ABSTRACT

We examined the efficacy of single-pill irbesartan/amlodipine combination-based therapy for 12 weeks in 20 hypertensive chronic kidney disease (CKD) patients, by evaluating self-measured home blood pressure (BP) profile. The single-pill irbesartan/amlodipine combination-based therapy decreased clinic BP and home BP (morning, evening, and nighttime BPs), and improved within-visit clinic BP variability, day-by-day home BP variability (morning and evening), and nighttime home BP variability. Furthermore, the single-pill combination-based therapy reduced albuminuria and exerted improved parameters of vascular function. These results indicate that this single-pill combination-based therapy may exert beneficial effects on clinic and home BP profiles as well as on renal and vascular damages, in hypertension with CKD.

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Albuminuria; arterial stiffness; blood pressure variability; chronic kidney disease; home blood pressure; single-pill combination-based therapy

Introduction

Chronic kidney disease (CKD) patients have been increasing in number, and cardiovascular events are the most common cause of death in these patients. Thus, it would be a considerable advance in the management of this condition to elucidate the mechanisms involved in the renal deterioration and the cardiovascular complication associated with CKD complicated by hypertension and to identify therapeutic approaches to treat them. Accumulated results of clinical trials also showed that strict control of blood pressure (BP) is essential to prevent target organ damage and to reduce cardiovascular mortality in CKD patients with hypertension (1,2). The renin-angiotensin system (RAS) inhibitors, such as angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs), as well as dihydropyridine calcium channel blockers (CCBs) are the first-line antihypertensive drugs for most patients with hypertension and are known to exert efficient BP lowering effects and inhibitory effects on cardiovascular and renal events (3).

Several clinical studies have provided epidemiological evidence of the greater accuracy of home BP monitoring, a measure to estimate out-of-clinic BP, compared with clinic BP monitoring for the prognosis of fatal and nonfatal cardiovascular disease (4). This study aimed to examine the beneficial effects of single pill-based combination-based therapy with irbesartan, an ARB, and amlodipine, a CCB, on home BP profile including day-by-day home BP variability and nighttime home BP variability as well as clinic BP profile including within-visit clinic BP variability, and parameters of renal and vascular function in Japanese hypertensive patients with CKD who did not achieve the target BP level according to the Evidence-based Clinical Practice Guideline for CKD 2013 by the Japan Society of Nephrology (JSN-CKD GL 2013) and the Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2014) (3,5).

Msethods

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and was approved by the ethics committees of Yokohama City University Hospital (B130905055). This study was also registered at the Clinical Trial Registry of University Hospital Information Network (Registration No: UMIN000013213; http://www.umin.ac.jp/ctr/). All of the patients provided written informed consent prior to the start of the study.

Study participants and design

This study consisted of a 2-week run-in period and 12-week single-pill combination-based therapy period. Hypertensive CKD patients who had not been on combination-based therapy

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by a RAS inhibitor (ACEI, ARB, or direct renin inhibitor) and a CCB were eligible for the study if they did not achieve the BP goal (clinic systolic BP ≥130 mmHg and diastolic BP ≥80 mmHg). The estimated glomerular filtration rate (eGFR) was calculated using a revised equation for the Japanese population (6). The exclusion criteria included CKD patients of G5 category or on dialysis, patients who were 19 years old or younger, women who were nursing or pregnant, and known hypersensitivity to any ingredient in the study medications.

After the run-in period, eligible patients were initially given a single pill of irbesartan/amlodipine tablet (AIMIX® LD, irbesartan/amlodipine besylate, 100/5 mg) in the morning (visit of 0 weeks), and the dose of amlodipine in the tablet was titrated up to 10 mg daily (AIMIX® HD, irbesartan/amlodipine besylate, 100/10 mg) 4 or 8 weeks after the treatment (visit of 4 or 8 weeks) to reach the BP target if necessary. In addition, an optional addition of diuretics and α blocker was used to achieve the target BP control 8 weeks after the treatment (visit of 8 weeks) as needed.

Clinic BP and within-visit clinic BP variability

Three BP measurements were taken at 1-minute interval in sitting position, and their average was regarded as the clinic BP. Within-visit clinic BP variability, which has been reported to be associated with the risk of stroke and cardiovascular risk factors (7,8), is defined as the within-patient standard deviation (SD) of three measurements of clinic systolic and diastolic BP (within-visit clinic BP variability, SD) and those divided by the each mean clinic BP (within-visit clinic BP variability, CV%).

Home BP and day-by-day home BP variability

Home BP values were obtained using a validated device (HEM-7080IC; Omron, Kyoto, Japan). Home BP readings were taken in both morning and evening for a 7-day study period before visits of 0 weeks and 12 weeks, and mean home BP was expressed as the average of morning and evening home BPs of 7 measurements maximum, respectively. Day-by-day home BP variability (morning and evening) was defined as SD of home BPs for a 7-day study period before visits of 0 weeks and 12 weeks for each participant (SD, mmHg), and SD divided by home BP (average of morning and evening BPs) (CV, %).

Nighttime home BP and nighttime home BP variability

Omron HEM-7080IC is able to take BP readings at fixed times, and was preset to take nighttime home BP measurements at 0:00, 2:00, 4:00, and 6:00 AM (4 points). The participants were instructed to measure their nighttime home BP for a 7-day study period before the visits of 0 weeks and 12 weeks. The mean nighttime home BP is defined as the average of all readings in the nighttime for the 7-day study period before each visit for each participant (28 measurements maximum). Nighttime home BP variability was defined as SD of nighttime home BP for the 7-day study period before each visit for each participant (SD, mmHg), and SD divided by the nighttime home BP (average of nighttime BPs) (CV, %).

Vascular function analysis

Brachial-ankle pulse wave velocity (baPWV) was determined by a PP analyzer (model: BP-203RPE2; Omron Healthcare, Kyoto, Japan), as described previously (9,10). Central systolic blood pressure (cSBP) and augmentation index (AI) were measured using an HEM-9000AI (Omron Healthcare, Kyoto, Japan), as described previously (11,12). Cardio-ankle vascular index (CAVI) was recorded using a Vasera VS-1500 vascular screening system (VS-1500AN, Fukuda Denshi, Tokyo, Japan) as reported (13).

Laboratory measurements

Blood and urine sampling were performed in fasted state at baseline (visit of 0 weeks) and after a period of 12 weeks treatment (visit of 12 weeks).

Statistical analysis

All data were presented as the mean ± SD or as a percentage. For the statistical analysis of the difference between baseline and 12 weeks of treatment, analysis of variance was compared by paired comparison *t*-test. The analysis was performed using SPSS version 21.0 (IBM Corporation), and a value of $P < 0.05$ was considered statistically significant.

Results

Baseline patient characteristics

Table 1 shows baseline characteristics of a total of 20 hypertensive CKD patients enrolled. Causes of CKD were hypertensive nephrosclerosis (n = 15), chronic glomerulonephritis

Table 1. Baseline characteristics.

Variables	Mean ± SD or %
Age (y)	69.0 ± 10.6
Sex (male/female)	18/2
Body mass index (kg/m^2)	24.2 ± 2.5
Smoking (%)	20
Diabetes mellitus (%)	15
Dyslipidemia (%)	70
Previous cardiovascular disease (%)	5
Clinic Blood pressure:	
SBP (mmHg)	151.6 ± 20.0
DBP (mmHg)	84.3 ± 13.4
Renal function:	
Serum creatinine (mg/dl)	1.38 ± 0.54
eGFR (ml/min/1.73 m^2)	45.1 ± 16.6
UACR (mg/g Cr)	487.4 ± 774.4
Glucose and lipid metabolism:	
Glycated Hemoglobin (%)	6.0 ± 1.0
LDL cholesterol (mg/dl)	117.5 ± 24.4
HDL cholesterol (mg/d)	63.6 ± 17.4
Triglycerides (mg/d)	151.1 ± 111.8
Antihypertensive agents:	
RAS inhibitors (%)	60
Angiotensin II receptor blockers (%)	50
Angiotensin-converting enzyme inhibitors (%)	5
Direct renin inhibitors (%)	5
Calcium-channel blockers (%)	40
Thiazide diuretics (%)	10
β-blockers (%)	10

Values are means ± SD. SBP: systolic blood pressure; DBP: diastolic blood pressure; eGFR: estimated glomerular filtration rate; RAS: renin-angiotensin system.

(n = 3), diabetic nephropathy (n = 1), and polycystic kidney disease (n = 1). Mean age was 69.0 ± 10.6 years, and the number of males and females was 18 and 2, respectively. The RAS inhibitors and CCBs before the combination therapy are as follows: RAS inhibitors: telmisartan (N = 3, 40 mg daily), olmesartan (N = 2, 20 mg daily), azilsartan (N = 2, 20 mg daily), valsartan (N = 2, 160 mg daily), irbesartan (N = 1, 100 mg daily), imidapril (N = 1, 5 mg daily), and aliskiren (N = 1, 150 mg daily); and CCBs: amlodipine (N = 4, the average dose 6.9 ± 2.4 mg daily) and nifedipine coat-core (N = 4, the average dose 25 mg ± 10 mg daily). With respect to BP control at baseline, clinic BP did not achieve the target BP level according to the JSN-CKD GL 2013 and JSH2014 (clinic SBP/DBP 151.6 ± 20.0/84.3 ± 13.4 mmHg) (3,5).

Single-pill irbesartan/amlodipine combination-based therapy was well tolerated in all of the patients without any significant adverse events and none of the enrolled patients discontinued participation in the study. After a period of 12 weeks of treatment, 7 patients (35%) were taking AIMIX® LD (irbesartan/amlodipine besylate, 100/5 mg) and 13 patients (65%) were taking AIMIX® HD (irbesartan/amlodipine besylate, 100/10 mg). Among 13 patients taking the AIMIX® HD tablet, thiazide diuretic or α-blocker was administered as additional antihypertensive medicine (AIMIX® HD/thiazide diuretic, N = 3; AIMIX® HD/α-blocker, N = 1).

Effect of single-pill irbesartan/amlodipine combination-based therapy on clinic BP profile

The single-pill irbesartan/amlodipine combination-based therapy for 12 weeks significantly decreased clinic SBP and DBP (Table 2). In addition, achievement of target BP, defined by JSN-CKD GL 2013 and JSH2014 (3,5), was attained in 85% after the combination-based therapy in spite of 10% achievement at baseline. Furthermore, the combination-based therapy significantly decreased the within-visit SBP and DBP variability (BP-SD and BP-CV) (Table 2).

Effect of single-pill irbesartan/amlodipine combination-based therapy on home blood pressure profile

With regard to control of home BP, single-pill irbesartan/amlodipine combination-based therapy for 12 weeks significantly decreased morning, evening and nighttime home SBP and DBP (Table 3). In addition, the combination therapy significantly decreased the day-by-day home SBP variability (BP-SD and BP-CV) (Table 3). Furthermore, the combination-based therapy significantly improved the nighttime home SBP and DBP variability (SBP-SD, DBP-SD and DBP-CV) (Table 3).

Table 2. Effects of single-pill irbesartan/amlodipine combination therapy on clinic blood pressure profile.

	Baseline	Week 12
Clinic:		
SBP (mmHg)	152 ± 20	125 ± 13**
SBP-SD (mmHg)	5.2 ± 2.0	1.7 ± 0.7**
SBP-CV (%)	3.5 ± 1.4	1.4 ± 0.6**
DBP (mmHg)	84 ± 13	75 ± 9**
DBP-SD (mmHg)	4.1 ± 2.1	1.8 ± 1.0**
DBP-CV (%)	4.7 ± 1.9	2.6 ± 1.4**
Pulse rate (beat/min)	64 ± 10	65 ± 9

Values are means ± SD. SBP: systolic blood pressure; DBP: diastolic blood pressure. *P < 0.05, **P < 0.01.

Table 3. Effects of single-pill irbesartan/amlodipine combination therapy on home blood pressure profile.

	Baseline	Week 12
Morning:		
SBP (mmHg)	150 ± 16	133 ± 12**
SBP-SD (mmHg)	9.0 ± 4.0	5.9 ± 1.9**
SBP-CV (%)	6.0 ± 2.5	4.5 ± 1.5*
DBP (mmHg)	85 ± 10	76 ± 9**
DBP-SD (mmHg)	5.4 ± 2.9	3.7 ± 1.4*
DBP-CV (%)	6.2 ± 2.8	4.9 ± 1.9
Pulse rate (beat/min)	64 ± 11	64 ± 11
Evening:		
SBP (mmHg)	142 ± 16	130 ± 14**
SBP-SD (mmHg)	9.7 ± 3.9	7.2 ± 4.0*
SBP-CV (%)	6.8 ± 2.5	5.4 ± 2.6*
DBP (mmHg)	79 ± 9	72 ± 9**
DBP-SD (mmHg)	5.8 ± 2.9	5.2 ± 4.1
DBP-CV (%)	7.4 ± 3.8	6.9 ± 4.8
Pulse rate (beat/min)	70 ± 12	70 ± 11
Nighttime:		
SBP (mmHg)	136 ± 22	120 ± 13**
SBP-SD (mmHg)	13.3 ± 2.9	10.6 ± 2.9**
SBP-CV (%)	9.9 ± 2.2	8.8 ± 2.2
DBP (mmHg)	75 ± 10	67 ± 7**
DBP-SD (mmHg)	9.6 ± 3.9	7.0 ± 3.9**
DBP-CV (%)	13.0 ± 5.9	10.5 ± 3.1*
Pulse rate (beat/min)	61 ± 10	61 ± 11

Values are means ± SD. SBP: systolic blood pressure; DBP: diastolic blood pressure.
*P < 0.05, **P < 0.01.

Effect of single-pill irbesartan/amlodipine combination-based therapy on renal and vascular function parameters

Single-pill irbesartan/amlodipine combination-based therapy for 12 weeks significantly decreased UACR (Table 4; UACR, 487.4 ± 774.4 vs. 263.6 ± 445.6 mg/g-Cr, P < 0.05). The reduction of UACR by the combination-based therapy was accompanied with decline in eGFR (Table 4; eGFR, 45.1 ± 16.6 vs. 42.9 ± 17.6 ml/min/1.73 m^2, P < 0.01). Concerning the effect on vascular function, the single-pill irbesartan/amlodipine combination-based therapy significantly improved all parameters of vascular function analyzed in the study (Table 4; baPWV, 1950 ± 526 vs. 1668 ± 513 cm/s; CAVI, 9.3 ± 1.2 vs. 8.6 ± 1.1; AI, 87 ± 15 vs. 80 ± 14 %; cSBP, 154 ± 27 vs. 131 ± 19 mmHg, P < 0.01).

Table 4. Effects of single-pill irbesartan/amlodipine combination therapy on renal and vascular function.

	Baseline	Week 12
Renal function:		
Serum creatinine(mg/dl)	1.38 ± 0.54	1.46 ± 0.56**
eGFR(ml/min/1.73 m^2)	45.1 ± 16.6	42.9 ± 17.6*
UACR(mg/g Cr)	487.4 ± 774.4	263.6 ± 445.6*
Vascular function:		
baPWV (cm/s)	1950 ± 526	1668 ± 513**
CAVI	9.3 ± 1.2	8.6 ± 1.1**
AI (%)	87 ± 15	80 ± 14**
cSBP (mmHg)	154 ± 27	131 ± 19**

Values are means ± SD. eGFR: estimated glomerular filtration rate; UACR: urine albumin-to-creatinine ratio; baPWV; brachial-ankle pulse wave velocity; CAVI; cardio ankle vascular index; AI: augmentation index; cSBP; central systolic blood pressure.
*P < 0.05, **P < 0.01.

Assessment of clinic and home BP as factors contributing to improvements in renal and vascular function

In the results of univariate correlation analysis, whereas no significant association was observed between the decreases in clinic SBP, morning home SBP and evening home SBP, and the reduction in log-transformed UACR, there was a significant positive relationship between the decrease in nighttime home SBP and the reduction in log-transformed UACR (Figure 1; R = 0.455, P = 0.044). In addition, there were significant positive associations between the decreases in clinic SBP, morning home SBP, evening home SBP, and nighttime home SBP, and the improvement in baPWV (Figure 2; R = 0.480, 0.716, 0.650, 0.680; P = 0.032, <0.001, 0.002, 0.001).

Furthermore, although there was no significant relation between the decreases in clinic and home BP parameters and the improvement in CAVI (**Supplemental Figure S1**), significant positive correlations between the decreases in clinic BP and nighttime home SBP, and the improvements in AI (**Supplemental Figure S2**; R = 0.584, 0.451; P = 0.007, 0.046) and cSBP (**Supplemental Figure S3**; R = 0.730, 0.445; P < 0.001, = 0.049) were observed. These results indicated a close relationship between reduction in home BP parameters and improvement in baPWV. In addition, there were significant associations between reduction in clinic BP and nighttime home BP, and improvements in AI and cSBP by the combination-based therapy. Among home BP measurements, the decrease in nighttime home BP had significant positive relationships with the improvements in both albuminuria and vascular indices (baPWV, AI, and cSBP).

On the other hand, there were no significant positive correlations between the improvements in variability (CV, %) of clinic SBP, morning home SBP, evening home SBP, and nighttime home SBP, and the improvements in renal and vascular function parameters (**Supplemental Table S1**). In addition, there were no significant correlations between the clinic and home BP values and the improvements in clinic and home SBP variability (SD, CV), other than positive association between the decrease in evening home SBP and the improvement in evening home SBP variability (SD, CV) (**Supplemental Figure S4, Supplemental Figure S5**).

Discussion

The main finding in the present study was that the single-pill irbesartan/amlodipine combination-based therapy may improve home BP profile in addition to clinic BP profile. The single-pill irbesartan/amlodipine combination-based therapy successfully decreased clinic BP so as to improve the achievement of target BP in hypertensive CKD patients already being treated before the study. In addition, the single-pill combination-based therapy was able to efficiently decrease morning, evening, and nighttime home BP. These improvements in clinic and home BP were accompanied with the improvement in within-visit clinic BP variability as well as the improvement in day-by-day

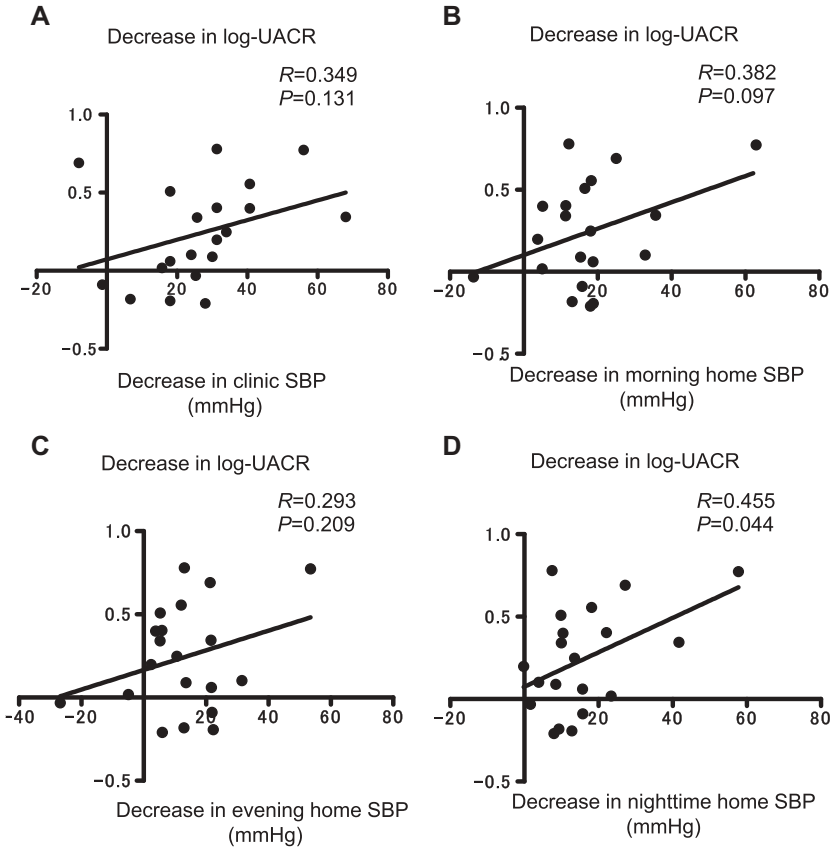

Figure 1. Univariate correlation analysis between the decreases in clinic systolic blood pressure (SBP), morning home SBP, evening home SBP, and nighttime home SBP, and the reduction in natural log-transformed urine albumin-to-creatinine ratio (log-UACR).

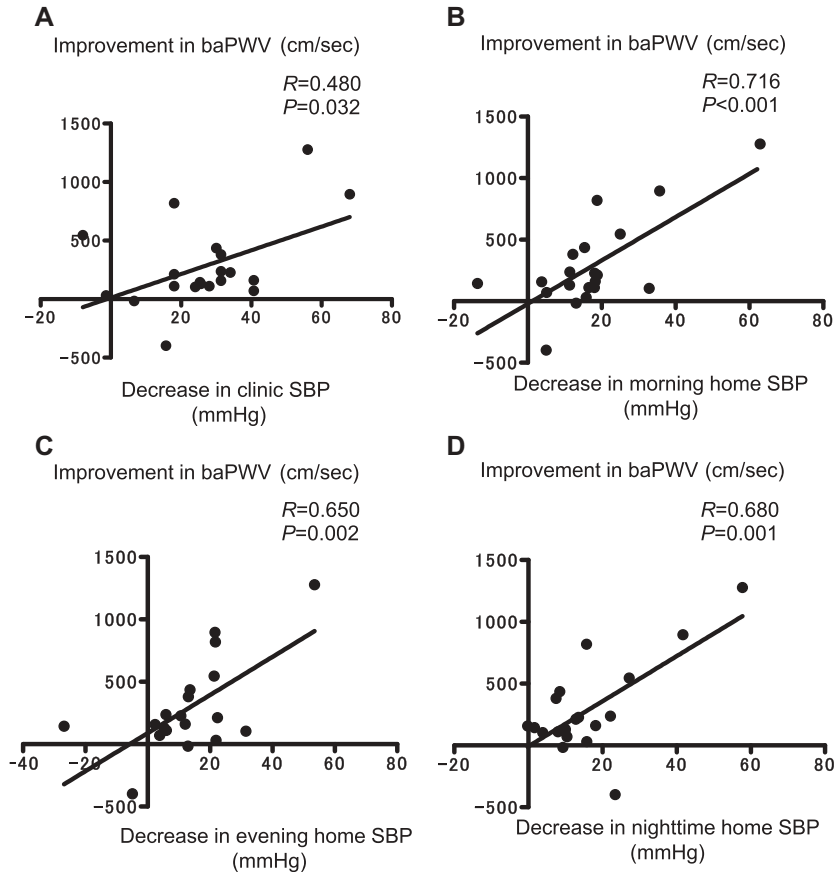

Figure 2. Univariate correlation analysis between the decreases in clinic systolic blood pressure (SBP), morning home SBP, evening home SBP, and nighttime home SBP, and the improvement in brachial-ankle pulse wave velocity (baPWV).

home BP variability (morning and evening) and nighttime home BP variability. Furthermore, the single-pill combination-based therapy significantly reduced albuminuria and exerted beneficial effects on vascular function. These pleiotropic therapeutic effects by the single-pill combination-based therapy with irbesartan and amlodipine on the clinic and home BP profiles and biomarkers of renal and vascular damage deserve further discussion.

Accumulated evidence has shown that ambulatory BP, another measure to estimate out-of-clinic BP, is a superior predictor of future cardiovascular events than clinic BP, and ambulatory nighttime BP is reportedly shown to be a superior predictor of future cardiovascular events than daytime BP (14). Home BP is also reportedly a better predictor of future cardiovascular events than clinic BP, and recently several home BP devices, such as HEM-7080IC used in the present study, capable of measuring automatically nighttime BP have been developed (15). Particularly, in CKD patients the prevalence of nocturnal hypertension is high and increases with disease progression (16), and nocturnal hypertension is reportedly associated with the worsening of albuminuria (17,18) and the increased risks of further renal deterioration and future cardiovascular events (19). Thus, it should be important to measure nighttime BP level and to reduce nighttime BP, in order to inhibit renal deterioration and cardiovascular complication (20). In the present study, the single-pill combination-based therapy with irbesartan and amlodipine was effective for the efficient lowering of home BP including not only morning and evening home BP but also nighttime home BP.

With respect to the renal protective effect, the combination-based therapy significantly reduced albuminuria with concomitant decreases in clinic and home BP levels. In addition, although there was no correlation between the reduction in albuminuria and the decreases in clinic BP, morning home BP, and evening home BP, there was a significant positive relationship of the reduction in albuminuria with the decrease in nighttime home BP, thereby indicating nighttime home BP as a possible target to treat for reducing albuminuria in CKD patients. In addition, the magnitude of the fall of eGFR was approximately 4.9% and far less than 30%, which is the upper limit of acceptable fall due to dilatation of efferent arteriole by the inhibition of post glomerular angiotensin II type 1 receptor (AT1R) (3,5,21). These results suggest this combination-based therapy to be a candidate as a therapy for CKD patients with hypertension including nocturnal hypertension and albuminuria.

The single-pill combination-based therapy also exhibited a significant improvement in vascular functional parameters. With regard to the relation between the decreases in clinic and home BP levels, and the improvement in vascular function parameters by the combination therapy, significant positive associations between the decreases in clinic BP and nighttime home BP, and the improvements in baPWV, AI, and cSBP were noted. Therefore, these results indicated that

not only clinic BP but also nighttime home BP would be important as targets to treat for improving atherosclerosis in CKD patients.

Particularly, among the vascular function parameters examined, baPWV has been intensively studied and identified as a relevant factor for the progression of CKD and cardiovascular events (22,23). Thus, the single-pill combination-based therapy with irbesartan and amlodipine may have an additive beneficial effect on the vasculature so as to improve vascular atherosclerotic changes via improvements in clinic and home BP profile. Although the decrease in nighttime home BP had significant positive relationships with the improvements in both albuminuria and vascular indices (baPWV, AI, and cSBP) among home BP measurements, further investigations are necessary to determine which home BP measurement (i.e. morning, evening, or nighttime home BP), in comparison to clinic BP, would be the most sensitive method for evaluation of target organ damage and prognosis.

Recently parameters of BP variability obtained by clinic BP, home BP, and ambulatory BP measurement are suggested to be associated with target organ damage including CKD and cardiovascular complication (8,24–28). The present study showed that the single-pill combination-based therapy with irbesartan and amlodipine significantly decreased not only clinic BP and home BP but also within-visit clinic BP variability and home BP variability (day-by-day home BP variability and nighttime home BP variability) concomitant with improvements in renal and vascular function. Therefore, this single-pill combination-based therapy may have an additive beneficial effect on the BP variability so as to exert vascular and renal protective effects and warrant further investigation.

Because there were no significant correlations between the mean clinic and home BP values and the improvements in clinic and home SBP variability (SD, CV), other than a positive association between the decrease in evening home SBP and the improvement in evening home SBP variability (SD, CV), the beneficial effects of the combination-based therapy on clinic and home BP variability may be largely independent of BP lowering effects. However, since there were no significant positive correlations between the improvements in clinic and home variability and the improvements in renal and vascular function parameters, further studies are warranted to investigate putative roles of clinic and home BP variability as markers of target organ damage and as prognostic factor.

There are several limitations in the present study. First, as a main problem in the present study, the study design is a single-arm trial but not randomized parallel-group control trial. In addition, the numbers of participants in the study are small. However, a recent study showed the therapeutic advantage of combination therapy of antihypertensive drugs using amlodipine and irbesartan in controlling clinic BP in 5900 Japanese hypertensive patients by analysis of the post-marketing survey data (29), which is consistent with the results of the present study indicating the improved achievement of target BP by this combination-based therapy.

Second, the patient's adherence was not examined in the present study. Since there are several previous studies suggesting that single-pill regimen rather than 2-pill regimen improve the patient's adherence and thus the BP control (30), so as to reduce cardiovascular events (31), the improving effect of the single-pill combination-based therapy with irbesartan and amlodipine on patient's adherence may have an influence on the results of this study. Further studies are needed to estimate the true long-term advantage of the single-pill combination-based therapy with irbesartan and amlodipine in improving BP profile and ameliorating renal and vascular damage. In conclusion, the results of the present study suggest that the single-pill combination-based therapy with irbesartan and amlodipine improves clinic and home BP profile with beneficial effects on renal and vascular damages in hypertension with CKD.

Declaration of Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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