Management of Home Blood Pressure by Amlodipine Combined With Angiotensin II Receptor Blocker in Type 2 Diabetes

Katsumi Miyauchi, MD; Tsutomu Yamazaki, MD, PhD; Hirotaka Watada, MD, PhD;
Yasushi Tanaka, MD, PhD; Ryuzo Kawamori, MD, PhD; Yutaka Imai, MD, PhD;
Shunya Ikeda, MD, PhD; Akira Kitagawa; Yasuhiro Ono, MD, PhD;
Fumio Murayama, MD, PhD; Jong Bock Choi, MD, PhD; Satoru Suwa, MD;
Dobun Hayashi, MD, PhD; Junji Kishimoto, PhD; Hiroyuki Daida, MD
for the ADVANCED-J investigators

Background: Angiotensin II receptor blocker (ARB) as a first-line drug for hypertension in diabetes often fails to control blood pressure adequately. The objective of the study was to evaluate the effect of amlodipine combined therapy on home blood pressure (HBP) useful for management of hypertension.

Methods and Results: A total of 263 type 2 diabetes with hypertension refractory to standard dose of ARB were randomized to increased ARB regimen (n=132) or amlodipine combination regimen (n=131). The primary endpoint was change in morning HBP at 1 year. The combination regimen significantly lowered morning HBP than the increased ARB regimen (158.2/82.5 mmHg in the combination regimen, 157.3/84.4 mmHg in the increased ARB regimen, at baseline; 142.7/76.3 vs. 155.0/83.1 mmHg, respectively, $P<0.001$ for both, at 8 weeks; 139.6/74.6 vs. 149.1/78.1 mmHg, respectively, $P<0.001$ for systolic and $P=0.010$ for diastolic, at 1 year). The combination regimen showed significantly higher rates of achieving target morning HBP at 8 weeks (11.3% vs. 2.7%, $P=0.015$). In the combination regimen, estimated glomerular filtration rate declined slower, and carotid intima-media thickness decreased in contrast to the increased ARB regimen.

Conclusions: In type 2 diabetes patients with hypertension refractory to standard dose of ARB, the amlodipine combination regimen provides superior antihypertensive effect on HBP to the increased ARB regimen, and beneficial effects on reducing risks of cardiovascular events. (*Circ J* 2012; **76**: 2159–2166)

Key Words: Angiotensin II receptor blocker; Calcium channel blocker; Home blood pressure; Hypertension; Type 2 diabetes

Diabetes mellitus comorbid with hypertension increases the incidence of cardiovascular disease.^{1,2} These patients benefit considerably from the achievement of target blood pressure levels below those generally recommended for hypertensive patients,³ and guideline levels are lower

than those for patients with hypertension alone. Although adequate control of blood pressure in these patients produces a dramatic decrease in the incidence of cardiovascular and cerebrovascular events,^{4–6} few studies have attempted to optimize treatment in those refractory to standard antihypertensive care.

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Department of Cardiology, Juntendo University School of Medicine, Tokyo (K.M., H.D.); Department of Clinical Epidemiology and Systems, Graduate School of Medicine, The University of Tokyo, Tokyo (T.Y.); Department of Medicine, Metabolism & Endocrinology, Juntendo University School of Medicine, Tokyo (H.W., J.B.C.); Department of Medicine, Metabolism and Endocrinology, St. Marianna University, School of Medicine, Kawasaki (Y.T.); Sportology Center, Juntendo University Graduate School of Medicine, Tokyo (R.K.); Department of Planning for Drug Development and Clinical Evaluation, Tohoku University Graduate School, Sendai (Y.I.); Department of Pharmaceutical Sciences, International University of Health and Welfare, Otawara (S.I.); Kanazawa Medical Clinic, Yokohama (A.K.); Department of Medicine, Takagi Hospital, Okawa (Y.O.); Department of Respiratory Surgery, International University of Health and Welfare Atami Hospital, Atami (F.M.); Department of Cardiology, Juntendo University Shizuoka Hospital, Shizuoka (S.S.); Healthcare Center, Nippon Yusen Kaisya, Tokyo (D.H.); and Center for Clinical and Translational Research, Kyushu University Hospital, Fukuoka (J.K.), Japan

Mailing address: Katsumi Miyauchi, MD, Department of Cardiology, Juntendo University School of Medicine, 2-1-1 Hongo, Bunkyo-ku, Tokyo 113-8421, Japan. E-mail: ktmmy@juntendo.ac.jp

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Figure 1. Trial profile. * ≥ 130 mmHg for systolic or ≥ 80 mmHg for diastolic of the mean of the home blood pressure for the latest 5 days during the observation period. †No change of antihypertensive drugs was allowed.

A number of studies have demonstrated that the monitoring only at the clinical visits was insufficient to control blood pressure adequately. Among the results, 1 study identified a discrepancy between screening and ambulatory blood pressure,⁷ while a second showed that the measurement of morning home blood pressure (HBP) has stronger predictive power for mortality than office blood pressure measurement.⁸ Strict control of blood pressure in diabetic patients with hypertension achieves reduction in the risk of deaths, complications related to diabetes, progression of diabetic retinopathy, and deterioration in visual acuity.⁹ These findings both call into question conventional blood pressure monitoring practices and highlight the need for strict hypertensive monitoring in diabetic patients with hypertension.

Thus, we conducted the ADVANCED-J (Amlodipine Versus Angiotensin II Receptor Blocker, Control of Blood Pressure Evaluation Trial in Diabetics) to evaluate the effect of amlodipine combined with the standard dose of angiotensin II receptor blocker (ARB) on HBP for 3 years. We report the 1-year follow-up results of the study (UMIN Clinical trial regis-

try: C000000017).

Methods

The ADVANCE-J study is a prospective, multicenter, randomized study to compare the effect of amlodipine combination regimen on HBP with that of increased dose of ARB for type 2 diabetic patients with hypertension refractory to standard dose of ARB.

Subjects

The protocol of the ADVANCE-J study has been published elsewhere.¹⁰ Briefly, eligible patients were aged 20 years or older with type 2 diabetes mellitus and hypertension refractory to standard dose of ARB for at least 8 weeks, whose mean morning home systolic blood pressure was ≥ 130 mmHg or diastolic blood pressure ≥ 80 mmHg for the latest 5 days of the observation period. Patients were excluded when the patient had secondary hypertension, severe hepatic or renal dysfunction, or history of hypersensitivity to the study drugs. The present

Table 1. Clinical Characteristics of Patients

	Increased ARB (n=132)	Combination (n=131)	P value*
Age (years)	65.1±9.4	65.1±10.0	0.999
Gender, male	85 (64.4)	77 (58.8)	0.349
BMI (kg/m ²)	25.1±3.4	25.4±4.1	0.573
Smokers	27 (20.5)	32 (24.4)	0.440
Duration of hypertension (years)	6.7±7.9	6.8±7.3	0.884
Duration of diabetes (years)	6.0±5.9	8.1±7.4	0.014
Dyslipidemia	57 (43.2)	62 (47.3)	0.499
History of:			
Cerebrovascular disease†	13 (9.9)	11 (8.4)	0.683
Cardiovascular disease‡	21 (15.9)	20 (15.3)	0.886
Cardiac failure	2 (1.5)	3 (2.3)	0.645
Diabetic nephropathy	25 (18.9)	29 (22.1)	0.521
Diabetic retinopathy	32 (24.2)	30 (22.9)	0.798
Diabetic neuropathy	16 (12.1)	20 (15.3)	0.458
ARB at baseline:			
Candesartan	41 (31.1)	38 (29.0)	0.717
Losartan	16 (12.1)	18 (13.7)	0.696
Telmisartan	28 (21.2)	27 (20.6)	0.905
Valsartan	39 (29.5)	41 (31.3)	0.757
Olmesartan	8 (6.1)	7 (5.3)	0.802

Quantitative variables were expressed as mean ± SD.

( ), %. *Comparability was tested by chi-square test for categorical variables, and by 2-sample t-test for quantitative variables; †cerebral hemorrhage and cerebral infarction; ‡angina pectoris and myocardial infarction.

ARB, angiotensin II receptor blocker; SD, standard deviation.

Table 2. Antihypertensive Drugs Added During Study Period (1 Year)

	Increased ARB (n=132)	Combination (n=131)	P value*
Not added	53 (40.2)	89 (67.9)	<0.001
Added†	79 (59.8)	42 (32.1)	
Antihypertensive drugs added†			
α-blocker	50 (37.9)	32 (24.4)	0.017
β-blocker	31 (23.5)	18 (13.7)	0.042
Diuretic	18 (13.6)	4 (3.1)	0.002
Others‡	10 (7.6)	1 (0.8)	0.006
CCB	5 (3.8)	1§ (0.8)	

( ), %. *Comparability was tested by chi-square test; †including drug changed; ‡α2-adrenoreceptor agonist, vasodilator; §a case in which amlodipine was changed to nifedipine.

ARB, angiotensin II receptor blocker; CCB, calcium-channel blocker.

study adhered to the principle of the Declaration of Helsinki. The study protocol was approved by the ethics committee of each participating institute. All patients gave written informed consent prior to participating in the study.

Study Treatment

Patients eligible for the study were randomly allocated to the increased ARB group or the amlodipine combination group. Study drugs were administered once in the morning. Patients received the standard dose of ARB with candesartan 8 mg, losartan 50 mg, telmisartan 40 mg, valsartan 80 mg, or olmesartan 20 mg daily during the observation period. In the increased ARB group, dose of ARB increased to the maximal dose approved, 12 mg, 100 mg, 80 mg, 160 mg, or 40 mg during the study period, respectively. In the combination group, patients received amlodipine of 5 mg/day combined with the standard dose of ARB.

Antihypertensive drugs used concomitantly with ARB dur-

ing the observation period were continued during the study period. In principle, no change of antihypertensive drugs was allowed from allocation throughout the 8-week study period. Diabetes medication was continued in accordance with the guidelines of the Japan Diabetes Society. Patients were advised to adopt positive lifestyle changes, including dietary counseling, smoking cessation, and suitable exercise regimens.

Measurement of HBP

HBP was self-measured using an automated sphygmomanometer (HEM-705IT, OMRON Healthcare Co, Ltd, Kyoto, Japan) with a data transmitter which transferred data to the central data center automatically. Patients were instructed to measure their blood pressure after 5 min of rest in a sitting position after arising and before going to bed.

Treatment group	Baseline	8 weeks		1 year	
	Mean±SD (n)	Mean±SD (n)	P value*	Mean±SD (n)	P value*
Morning home SBP (mmHg)					
Increased ARB	157.3±16.6 (132)	155.0±17.5 (112)	<0.001	149.1±19.9 (86)	<0.001
Combination	158.2±19.2 (131)	142.7±15.8 (106)		139.6±12.2 (91)	
Morning home DBP (mmHg)					
Increased ARB	84.4±11.6 (132)	83.1±11.4 (112)	<0.001	78.1±12.2 (86)	0.010
Combination	82.5±11.8 (131)	76.3±9.6 (106)		74.6±9.5 (91)	
Evening home SBP (mmHg)					
Increased ARB	151.0±21.0 (115)	148.1±20.7 (102)	<0.001	142.6±17.2 (78)	<0.001
Combination	149.8±20.6 (121)	134.1±16.4 (102)		130.8±14.2 (78)	
Evening home DBP (mmHg)					
Increased ARB	77.5±11.6 (115)	75.4±11.4 (102)	<0.001	72.2±11.4 (78)	0.004
Combination	74.9±11.2 (121)	69.0±8.8 (102)		66.3±8.6 (78)	
Office SBP (mmHg)					
Increased ARB	150.9±15.5 (132)	145.9±16.0 (116)	<0.001	140.9±17.9 (106)	<0.001
Combination	152.0±15.7 (131)	134.6±13.4 (114)		133.8±11.8 (102)	
Office DBP (mmHg)					
Increased ARB	83.7±10.3 (132)	80.1±10.5 (116)	<0.001	75.8±12.3 (106)	0.207
Combination	82.7±11.5 (131)	73.7±11.3 (114)		73.5±9.4 (102)	

*Changes between the 2 treatment groups were assessed using analysis of covariance, including treatment groups as the main effect and BP at baseline as covariate.

BP, blood pressure; SD, standard deviation; SBP, systolic BP; DBP, diastolic BP; ARB, angiotensin II receptor blocker.

Figure 2. Achievement of target blood pressure (BP). Target home BP: <125/80mmHg; target office BP, <130/80mmHg. The achievement rates were compared using Fisher's exact test. ARB, angiotensin II receptor blocker.

Clinical Endpoints

The primary endpoint was change in morning HBP at 1 year (Protocol committee amended the protocol on November 18, 2007, before data analysis). Secondary endpoints included changes in morning HBP, evening HBP, and office blood pressure during the study period, and the achievement rates of target blood pressure level (HBP: <125/80mmHg, office blood pressure: <130/80mmHg). Other parameters included changes in HbA_{1c}, B-type natriuretic peptide (BNP), urinary albumin (calculated as creatinine equivalent), and carotid intima-media thickness (IMT). Carotid IMT was scored using the

software, Intima Scope® (SoftMedical Co Ltd, Tokyo, Japan) at the core laboratory of this study, which was organized at the Department of Medicine, Metabolism & Endocrinology, Juntendo University School of Medicine. The core laboratory provided the average IMT, which was the mean value of 60 computer-based points in the 20 mm proximal region to the origin of the carotid bulb.

Statistical Analysis

The target number of patients was estimated to be 300 patients (150 patients in each arm) to detect a difference of 5 mmHg in

Table 4. Changes in Biomarkers and Carotid IMT

Treatment group	Baseline	8 weeks			1 year		
	Mean±SD (n)	Mean±SD (n)	P value*	P value†	Mean±SD (n)	P value*	P value†
HbA _{1c} (%)							
ARB	7.13±0.93 (129)	7.13±0.99 (113)	0.695	0.093	7.16±1.16 (103)	1.000	0.177
Combination	7.25±1.02 (130)	7.39±1.08 (109)	0.142		7.03±0.90 (103)	0.044	
eGFR (ml·min ⁻¹ ·1.73 m ⁻²)							
ARB	72.34±19.14 (129)	72.23±20.51 (111)	0.494	0.832	69.22±19.00 (107)	0.005	0.163
Combination	70.82±18.80 (130)	70.44±19.75 (112)	0.556		69.80±21.85 (105)	0.323	
Average IMT (mm)							
ARB	0.864±0.189 (116)	ND	—	—	0.886±0.177 (75)	0.242	0.073
Combination	0.879±0.180 (115)	ND	—	—	0.872±0.177 (77)	0.172	
	Median [mean] (25–75%), (n)	Median [mean] (25–75%), (n)	P value*	P value†	Median [mean] (25–75%), (n)	P value*	P value†
BNP (pg/ml)							
ARB	25.5 [51.7] (12.4–59.3), (117)	21.6 [59.3] (12.2–81.0), (95)	0.570	0.062	29.8 [65.5] (15.0–82.1), (97)	0.019	0.049
Combination	26.5 [41.0] (13.4–43.2), (122)	20.0 [35.1] (11.6–39.1), (100)	0.002		26.2 [45.5] (12.1–57.6), (91)	0.847	
Urinary albumin (mg/gCr)							
ARB	30.1 [228.4] (12.4–148.7), (131)	29.0 [356.0] (11.1–202.0), (93)	0.343	0.382	24.9 [226.0] (10.2–133.2), (93)	0.253	0.714
Combination	31.8 [268.9] (11.9–97.4), (130)	33.0 [313.7] (11.9–109.7), (104)	0.836		22.0 [297.3] (9.3–100.2), (90)	0.558	

eGFR was estimated using the following equation of the Japanese Society of Nephrology: $\text{eGFR (ml} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}) = 194 \times \text{Serum creatinine}^{-1} - 1.094 \times \text{Age}^{-0.287$ (if female: $\times 0.739$). Average IMT was the mean value of 60 computer-based points in the 20 mm proximal region to the origin of the carotid bulb.

*Change from baseline in each group was assessed using paired t-test. †Changes between the 2 treatment groups were assessed using analysis of covariance, including treatment groups as the main effect and baseline variable as covariate. Log-transformed values were used in statistical tests of BNP and urinary albumin.

IMT, intima-media thickness; eGFR, estimated glomerular filtration rate; ND, not determined; BNP, B-type natriuretic peptide. Other abbreviations as in Table 3.

changes in morning HBP between the 2 groups with 80% power at 2-tailed 5% significant level. Data analyses were carried out on the full analysis set. Changes in blood pressure and other parameters between the 2 groups were compared using analysis of covariance, including treatment groups as main effect and baseline value as covariate. The achievement rates of the target blood pressure levels were compared using the Fisher's exact test. All analyses were performed using SAS statistical software (version 9.2; SAS Institute Inc, Cary, NC, USA).

Results

Patient Characteristics

A total of 316 patients were registered from September 2004 to February 2006. Fifty-three patients were excluded as a result of failure to meet the inclusion criteria, consent withdrawal, lost to follow-up, or miscellaneous reasons during the observation period. Thus, 263 patients were randomly allocated to the increased ARB group (n=132) and the combination group (n=131), all cases for analysis (Figure 1). Baseline patient characteristics were similar between the 2 groups (Table 1), except for the duration of diabetes which was longer in the combination group (P=0.014). In the increased ARB group, more patients received antihypertensive drugs other than the study drugs additionally throughout the 1-year study period (Table 2). Anti-diabetic agents were used comparably in the both groups.

Changes in Blood Pressure

For the primary endpoint, the combination group had significantly lower morning HBP than the increased ARB group at

1 year (P<0.001 for systolic, P=0.010 for diastolic, Table 3), although more patients refractory to the study drugs received antihypertensive drugs additionally in the increased ARB group than the combination group (Table 2). At 8 weeks, the increased ARB group showed almost no change of morning HBP, whereas the combination group had lower morning HBP (intergroup comparison: P<0.001 for systolic and diastolic, Table 3). The combination group showed greater antihypertensive effect than the increased ARB group in evening HBP and office blood pressure during the study period (Table 3). We confirmed that imbalance of the duration of diabetes at baseline did not affect the results with analysis adjusting for the duration of diabetes. The combination group produced significantly higher achievement rates of target blood pressure level than the increased ARB group at 8 weeks (Figure 2). The achievement rates of the morning HBP were less than 10% in the 2 groups at 1 year.

Changes in Biomarkers and Other Parameters

BNP increased at 1 year in the increased ARB group (P=0.019), whereas that in the combination ARB group did not, showing significant difference between the 2 groups (P=0.049, Table 4). Urinary albumin levels did not change significantly in both groups at 1 year. However, the reduction of urinary albumin was positively correlated with the reduction of HBP than that of office blood pressure at 1 year (Table 5). Estimated glomerular filtration rate (eGFR) decreased significantly from baseline in the increased ARB group at 1 year (P=0.005), while that in the combination group decreased but not significantly. The average IMT increase in the increased group from baseline, while that in the combination group decrease, showing tendency

Table 5. Correlation With BP and Urinary Albumin

	Increased ARB group		Combination group	
	r	P value	r	P value
Δ Morning SBP vs. Δ UACR	0.248	0.034	0.406	<0.001
Δ Morning DBP vs. Δ UACR	0.258	0.027	0.360	0.001
Δ Office SBP vs. Δ UACR	0.088	0.404	0.266	0.012
Δ Office DBP vs. Δ UACR	0.080	0.447	0.156	0.146
At 1 year, Morning SBP vs. UACR	0.089	0.456	0.212	0.066
At 1 year, Morning DBP vs. UACR	−0.036	0.764	−0.107	0.359

Δ, [at 1 year]−[at baseline]; r, Pearson's correlation coefficient with log-transformed UACR. UACR, urinary albumin. Other abbreviations as in Table 3.

of significance between the 2 groups at 1 year ($P=0.073$).

Safety

Adverse events were reported in 45 patients (34.1%) of the increased ARB group and in 51 patients (38.9%) of the combination group. The study termination as a result of adverse events occurred in 6 patients (4.5%) and 4 patients (3.1%), respectively. Dizziness was observed in 4 patients in each group. Edema was found in 2 patients of the increased ARB group and in 3 patients of the combination group. Postural hypotension was found in 3 patients of the increased ARB group. Hepatic dysfunction was found in 7 patients in each group. Elevations of serum creatinine were observed more frequently in the combination group (1 patient vs. 7 patients). None of these events had any adverse clinical consequence. Other adverse events were observed comparably between the 2 groups, and each treatment was well tolerated.

Discussion

In these initial 8-week and 1-year data from the ADVANCED-J study, we found that the amlodipine combined with ARB provided significantly greater antihypertensive effect than increased dose of ARB during the study period in type 2 diabetic patients with hypertension. Furthermore, our trial adopted self-measured HBP using an automated sphygmomanometer and an automated data transfer system to obtain more accurate blood pressure measurements as endpoints. To our knowledge, this is the first study to demonstrate the efficacy of combination therapy of antihypertensive drugs on HBP for relatively long-term period in diabetic patients with hypertension.

Blood pressure control in diabetic patients remains a considerable clinical important issue. In particular, these patients are at high risk of cardiovascular events, such as myocardial infarction and stroke.^{1,11} Several large clinical studies demonstrated that adequate control of hypertension in diabetic patients decreased the risk of cardiovascular events.^{4–6} Furthermore, a previous study demonstrated that each 10 mmHg increase in home systolic blood pressure increased the risk of cardiovascular events by 17.2%.¹² The present study showed that the differences in morning systolic blood pressure between the 2 groups were 12 mmHg at 8 weeks and 10 mmHg at 1 year. Our results suggest that significant reduction of HBP with combination of amlodipine and ARB anticipates the possibility of decreasing incidence of cardiovascular events in the future. Advantage of combination therapy by ACCOMPLISH trial¹³ showed that angiotensin II converting enzyme inhibitor (ACEI) and calcium channel blocker (CCB) combination therapy was superior to ACEI and diuretic in clinical outcomes.

The achievement rate of target blood pressure level of am-

lodipine combination therapy was still low in the present study. Most of the participants were treated with only single ARB before the study treatment, although systolic blood pressure was comparatively high. More than half of the participants were aged 65 years and over. Their characteristics might be considered as the factors for not achieving the target blood pressure recommended by the guideline, although other anti-hypertensive drugs were available after 8 weeks. Our result reflected the actual situation of routine care and suggested that it was difficult to control hypertension adequately in diabetic patients with CCB and standard dose of ARB. Clinical evidence also shows that achieving target blood pressure level requires an average of 3.2 different antihypertensive drugs.¹⁴

The reduction of blood pressure in the combination therapy was observed over the short period of 8 weeks, indicating that this therapy provides the clinically beneficial effect. These findings are supported by the VALUE study¹⁵ and the ASCOT-BPLA study,¹⁶ which demonstrated that early normalization of blood pressure is important in sustaining a long-term better control of blood pressure and reducing cardiovascular events in patients with hypertension who are at high risk of cardiovascular events. The difference of blood pressure between the 2 groups did not become small during the study period, even though all antihypertensive drugs were available through the study period, suggesting that it is not easy to control hypertension without CCB and ARB in diabetic patients, although only they are not enough to control hypertension.

Several studies had reported that self-measurement of HBP was useful for detection of insufficient control of blood pressure¹⁷ and it had better prognostic accuracy in terms of both cardiovascular morbidity and mortality than the office measurement.^{12,18} HBP measurements have also been shown to predict the damage of target organ by hypertension better than office measurements.⁸ In fact, our study showed that the reduction of urinary albumin was positively correlated with the reduction of HBP than that of office blood pressure. Of note, we observed the sustained antihypertensive efficacy of combination therapy in which reduction of systolic blood pressure from office measurement was sustained in the evening and the elevation of morning HBP was less in contrast to the increased ARB therapy during the study period. These findings indicate that HBP monitoring and amlodipine combination therapy with ARB should be used in clinical practice, and might provide better prognosis in diabetic patients with hypertension.

The BNP level provides predictive information for future onset of cardiovascular disease.¹⁹ Our study showed that BNP increased significantly in the increased ARB regimen at 1 year, whereas that in the combination regimen did not change, showing the significant difference in the 2 groups. The positive correlation between blood pressure and BNP is well known.²⁰ Our

study did not show the positive correlation of BNP reduction and the reduction of HBP. However, because BNP value and home systolic blood pressure were correlated positively in both groups at 1 year ($r=0.271$, $P=0.017$ for the increased ARB regimen; $r=0.350$, $P=0.002$ for the combination regimen), it was suggested that more potent reduction of HBP might be preferable to avoid the exacerbation of BNP.

The sub-analysis of NICE-Combi study showed that nifedipine and standard dose of candesartan combination regimen reduced urinary albumin excretion than maximal dose of candesartan in hypertensive patients with microalbuminuria with the 8-week treatment.²¹ Our study did not obtain the superiority of combination regimen to increased ARB regimen in reduction of urinary albumin. As one of this reason, it might be considered that urinary albumin level was low; half of patients were categorized into normoalbuminuria in contrast to the NICE-Combi Study. However, it was suggested that adequate management of HBP is important to reduce urinary albumin as a result of their correlation from our results.

In addition, at 1 year, eGFR decreased significantly from baseline in the increased ARB regimen, whereas that in the combination therapy decreased but not significantly. A previous study showed reduced eGFR was independent risk factors for cardiovascular events and mortality rates in patients with diabetes.²² Risk of cardiovascular events was further modified by renal status changes over the first 2 years. End-stage renal disease was too late to improve the outcomes. Therefore, early intervention in early stage was an important strategy for prevention of adverse events. From this point of view, combination therapy at least retarded the progression of renal dysfunction. Furthermore, carotid IMT in the combination group tends to be less than that in ARB group at 1 year. O'Leary et al demonstrated that increases in the thickness of the carotid IMT were directly associated with an increased risk of myocardial infarction and stroke.²³ The estimated cumulative rate of the combined end point for the highest quintile of the combined wall-thickness measure was over 25 percent at 7 years, as compared with a cumulative rate of less than 5 percent for the lowest quintile. These surrogate endpoints also suggested that the combination therapy is more preferable than the increased ARB therapy in the management for hypertension in diabetic patients.

Several limitations of the study warrant mention. First, it was conducted as an open label design. Second, the patients might have become more health-conscious during the course of the study or undertaken other measures that might have influenced the results. However, any such change was likely to have affected both groups equally, and was therefore unlikely to have influenced the results. Third, follow-up data was not available for some patients. However, we also confirmed the efficacy in main analyses with the last observation carried forward analysis. Therefore, we judged the missing data did not affect our overall conclusions.

In summary, these 1-year data from the ADVANCE-J Study indicate that amlodipine combination therapy with ARB produces significant lowering in blood pressure in diabetic patients with hypertension refractory to standard dose of ARB. These findings have significant implications for the care of patients with high risks of cardiovascular events.

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