GERIATRICS AND GERONTOLOGY SPECIAL SECTION
CLINICAL RESEARCH STUDY
Michael W. Rich, MD, Section Editor

THE AMERICAN JOURNAL of MEDICINE®

Angiotensin II Receptor Blocker-based Therapy in Japanese Elderly, High-risk, Hypertensive Patients

Hisao Ogawa, MD,[a] Shokei Kim-Mitsuyama, MD, PhD,[b] Kunihiko Matsui, MD,[c] Tomio Jinnouchi, MD,[d] Hideaki Jinnouchi, MD,[d] Kikuo Arakawa, MD,[e] for the OlmeSartan and Calcium Antagonists Randomized (OSCAR) Study Group

[a]Department of Cardiovascular Medicine, Kumamoto University Graduate School of Medical Sciences, Kumamoto, Japan; [b]Department of Pharmacology and Molecular Therapeutics, Kumamoto University Graduate School of Medical Sciences, Kumamoto, Japan; [c]Department of General Medicine, Yamaguchi University Hospital, Yamaguchi, Japan; [d]Jinnouchi Clinic, Diabetes Care Center, Kumamoto, Japan; [e]The Second Department of Internal Medicine, School of Medicine, Fukuoka University, Fukuoka, Japan.

ABSTRACT

BACKGROUND: It is unknown whether high-dose angiotensin II receptor blocker therapy or angiotensin II receptor blocker + calcium channel blocker combination therapy is better in elderly hypertensive patients with high cardiovascular risk. The objective of the study was to compare the efficacy of these treatments in elderly, high-risk Japanese hypertensive patients.

METHODS: The OlmeSartan and Calcium Antagonists Randomized (OSCAR) study was a multicenter, prospective, randomized, open-label, blinded-end point study of 1164 hypertensive patients aged 65 to 84 years with type 2 diabetes or cardiovascular disease. Patients with uncontrolled hypertension during treatment with olmesartan 20 mg/d were randomly assigned to receive 40 mg/d olmesartan (high-dose angiotensin II receptor blocker) or a calcium channel blocker + 20 mg/d olmesartan (angiotensin II receptor blocker + calcium channel blocker). The primary end point was a composite of cardiovascular events and noncardiovascular death.

RESULTS: During a 3-year follow-up, blood pressure was significantly lower in the angiotensin II receptor blocker + calcium channel blocker group than in the high-dose angiotensin II receptor blocker group. Mean blood pressure at 36 months was 135.0/74.3 mm Hg in the high-dose angiotensin II receptor blocker group and 132.6/72.6 mm Hg in the angiotensin II receptor blocker + calcium channel blocker group. More primary end points occurred in the high-dose angiotensin II receptor blocker group than in the angiotensin II receptor blocker + calcium channel blocker group (58 vs 48 events, hazard ratio [HR], 1.31, 95% confidence interval, 0.89-1.92; $P = .17$). In patients with cardiovascular disease at baseline, more primary events occurred in the high-dose angiotensin II receptor blocker group (HR, 1.63, $P = .03$); in contrast, fewer events were observed in the subgroup without cardiovascular disease (HR, 0.52, $P = .14$). This treatment-by-subgroup interaction was significant ($P = .02$).

CONCLUSION: The angiotensin II receptor blocker and calcium channel blocker combination lowered blood pressure more than the high-dose angiotensin II receptor blocker and reduced the incidence of primary end points more than the high-dose angiotensin II receptor blocker in patients with cardiovascular disease. The addition of a second antihypertensive agent is more effective at lowering blood pressure than simply doubling the dose of an existing agent.

KEYWORDS: Cardiovascular disease; Clinical trials; Combination therapy; Elderly; High-dose angiotensin II receptor blocker; Hypertension; Type 2 diabetes.

SEE RELATED EDITORIAL p. XXX

Funding: See last page of article.
Conflict of Interest: See last page of article.

Authorship: See last page of article.
This trial was registered with ClinicalTrials.gov, number NCT 00134160.

0002-9343/$ -see front matter © 2012 Elsevier Inc. All rights reserved.
doi:10.1016/j.amjmed.2011.12.010

International[1] and Japanese[2] guidelines indicate that the combination of angiotensin II receptor blocker + calcium channel blocker is one of the preferred combinations for the general hypertensive population. However, there has been no report on large clinical trials investigating the efficacy of angiotensin II receptor blocker + calcium channel blocker combination on cardiovascular events in hypertensive patients, although recent evidence demonstrates that the combination of benazepril (an angiotensin-converting enzyme inhibitor) and amlodipine (a calcium channel blocker) is superior to the combination of benazepril and a thiazide diuretic in reducing cardiovascular events in high-risk hypertensive patients.[3]

The beneficial effects of angiotensin II receptor blockers have been demonstrated in patients with heart failure,[4] myocardial infarction,[5] or diabetic nephropathy.[6] Furthermore, various experimental studies[7,8] indicate that angiotensin II receptor blocker can prevent insulin resistance, vascular endothelial dysfunction, cardiovascular remodeling, stroke, or chronic kidney disease through pleiotropic effects independent of blood pressure lowering. Accordingly, emerging evidence supports the rationale that treatment with an angiotensin II receptor blocker, particularly high-dose angiotensin II receptor blocker treatment, may be a promising therapeutic strategy for prevention of cardiovascular morbidity and mortality in high-risk patients.

On the basis of the above findings, it is important to examine which therapy, high-dose angiotensin II receptor blocker or angiotensin II receptor blocker + calcium channel blocker combination, is more effective for prevention of cardiovascular morbidity and mortality in high-risk elderly hypertensive patients. The purpose of the OlmeSartan and Calcium Antagonists Randomized (OSCAR) study was to compare the efficacy of high-dose angiotensin II receptor blocker versus an angiotensin II receptor blocker + calcium channel blocker combination in the reduction of cardiovascular events and all-cause death in elderly Japanese patients with cardiovascular disease or type 2 diabetes.

CLINICAL SIGNIFICANCE

- The combination of an angiotensin receptor blocker + a calcium channel blocker lowers blood pressure more effectively than a high dose of an angiotensin receptor blocker in Japanese hypertensive, high-risk patients aged 65 to 84 years.
- In patients with cardiovascular disease, combination therapy with an angiotensin receptor blocker + a calcium channel blocker reduces the incidence of the composite of cardiovascular events and noncardiovascular death compared with a high dose of an angiotensin receptor blocker.
- The addition of a second antihypertensive agent is more effective at lowering blood pressure than simply doubling the dose of a single agent.

MATERIALS AND METHODS

Participants

The detailed inclusion and exclusion criteria have been described.[9] Outpatients aged 65 to 84 years of either sex were potentially eligible if they had sitting systolic blood pressure ≥ 140 mm Hg or sitting diastolic blood pressure ≥ 90 mm Hg. Of note, potentially eligible patients also needed to have type 2 diabetes or cardiovascular disease (cerebrovascular disease, cardiac disease, vascular disease, or renal dysfunction). This study was conducted under the Declaration of Helsinki and approved by the institutional review board at each trial site. All patients gave written informed consent.

Measurement of Blood Pressure

In the OSCAR study, we instructed the investigators to follow the Japanese guidelines for treatment of hypertension when measuring the patient's blood pressure by the auscultation method using a mercury or automatic sphygmomanometer.[10]

Study Design

The study design, organization, and management have been described.[9] The design of the OSCAR study was a multicenter, active-controlled, 2-arm parallel group comparison using a prospective, randomized open-label method with blinded end point (PROBE) assessment (**Appendix 1**).[9]

Treatment Protocol

We used a 2-step process (**Figure 1**). In step 1 (run-in period), all the eligible patients received olmesartan (an angiotensin II receptor blocker) monotherapy at a dose of 20 mg/d (a standard dose). If the patients were already receiving antihypertensive treatment, antihypertensive medication was switched to olmesartan alone at a dosage of 20 mg/d. Follow-up visits of the patients were scheduled every 2 to 4 weeks to measure blood pressure. If the target blood pressure control (<140/90 mm Hg) was not achieved by olmesartan (20 mg/d) monotherapy and the treatment was well tolerated, patients were randomized to the treatment arms by a minimization method that took into account the following factors: sex, age, risk factors (cardiovascular disease and type 2 diabetes), and study institution. In step 2, patients received (1) a doubled dose of olmesartan at 40 mg/d (high-dose angiotensin II receptor blocker monotherapy) or (2) a calcium channel blocker (amlodipine or azelnidipine[11]) in addition to 20 mg/d olmesartan (angiotensin II receptor blocker + calcium channel blocker combination). In principle, the dosage of amlodipine was 2.5 or 5 mg/d, and the dosage of azelnidipine was 8 or 16 mg/d. These dosages are most frequently used in Japan. If further additional antihypertensive treatment was required to achieve the target blood pressure during step 2, other antihypertensive drugs (eg, diuretics or beta-blockers) could

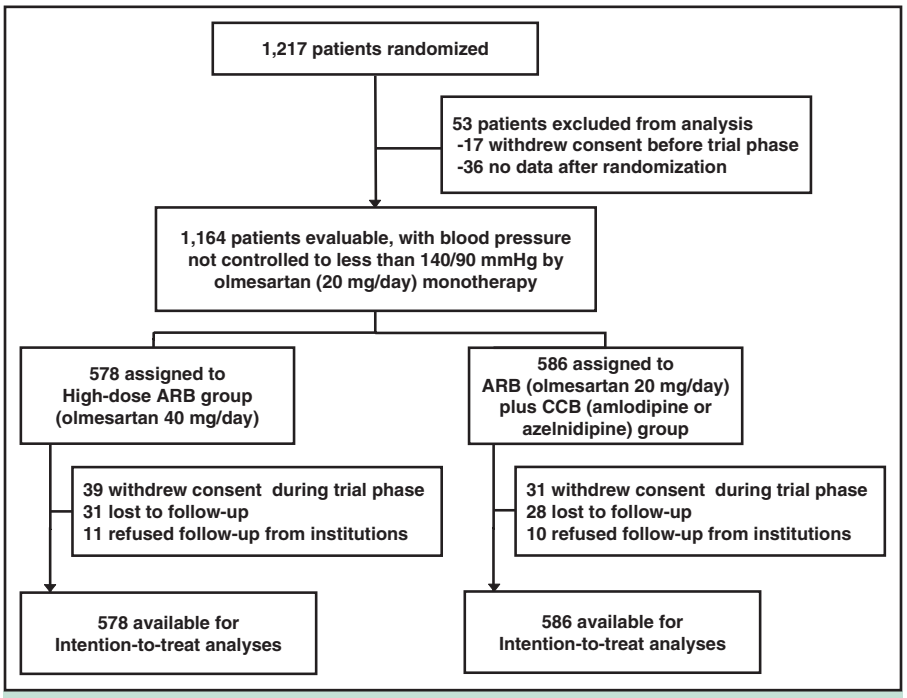

Figure 1 Study profile. ARB = angiotensin II receptor blocker; CCB = calcium channel blocker. The number of patients who entered the olmesartan run-in phase and were excluded prior to randomization was not examined in this study.

be added, but angiotensin II receptor blockers, angiotensin-converting enzyme inhibitors, and calcium channel blockers were prohibited.

Study Outcomes

The primary end point was the time to the first event. The primary end point events were a composite of fatal and nonfatal cardiovascular events (including cerebrovascular disease (cerebral infarction, cerebral hemorrhage, subarachnoid hemorrhage, unspecified stroke, and transient ischemic attack), coronary artery disease (sudden death, myocardial infarction, angina pectoris, and asymptomatic myocardial ischemia), heart failure, other arteriosclerotic disease (aortic aneurysm, aortic dissection, and atherosclerotic diseases), diabetic complication (diabetic neuropathy, retinopathy, and nephropathy), and deterioration of renal function (doubling of serum creatinine, end-stage renal disease as defined by initiation of hemodialysis or renal transplantation), and noncardiovascular death. The secondary end points were incidence of each cardiovascular event, blood pressure change from baseline at each assessment during the follow-up period, and serious adverse events other than the primary end points. The follow-up period was 3 years. Information, including information on cardiovascular events, adverse events, and discontinuation/dropouts, was obtained at follow-up visits every 6 months. The End Point Committee adjudicated, without knowledge of the assigned drugs, all cases of cardiovascular events and death.

Sample Size, Study Power, and Statistical Analysis

Sample size and power of the study were estimated as previously described in detail.[9] Primary analyses were performed in compliance with the intention-to-treat principle. For the primary end points, we compared between groups using the stratified log-rank test stratified by gender, age, and risk factors. By using a stratified proportional hazards model, the hazard ratio (HR) and 95% confidence interval (CI) were calculated for each treatment group. Time-to-first event curves were estimated by the Kaplan-Meier method. Repeated-measures analysis of variance was used to compare between the groups for the change from baseline at each assessment time during the follow-up period for some end point data, including blood pressure. The unpaired *t* test adjusted by Holm's method was used for intergroup comparison to avoid multiplicity at multiple time points. Fisher exact test was used for intergroup comparison of the occurrence of serious adverse events other than those of the primary end points.

Prespecified subgroup analyses based on the presence or absence of cardiovascular disease and of type 2 diabetes at baseline were defined as the most important subgroup analyses. To estimate the heterogeneity of the HR for these prespecified subgroups, we constructed a stratified Cox proportional hazards model that included adjustment for 3 variables: treatment group, subgroups of patients with or without cardiovascular disease, and subgroups of patients with or without type 2 diabetes at baseline; the model also

Table 1 Demographic and Baseline Characteristics of Study Patients

	High-dose ARB (n = 578)	ARB + CCB (n = 586)	*P* Value
Male, n (%)	254 (43.9)	261 (44.5)	.84
Age (y)	73.6 ± 5.3	73.6 ± 5.5	.86
75-84 y, n (%)	254 (43.9)	255 (43.5)	.88
Body height (cm)	154.7 ± 8.8	155.1 ± 9.0	.47
Body weight (kg)	58.3 ± 11.2	57.4 ± 10.6	.14
BMI (kg/m^2)	24.3 ± 3.7	23.8 ± 3.5	.02
BMI ≥ 25, n (%)	227 (39.3)	202 (34.5)	.09
SBP (mm Hg)	158.2 ± 12.6	157.2 ± 11.3	.15
DBP (mm Hg)	85.2 ± 10.1	84.6 ± 9.8	.32
Heart rate (beats/min)	73.9 ± 9.7	72.9 ± 9.4	.09
eGFR ($mL/min/1.73\ m^2$)	66.5 ± 18.6	67.9 ± 18.8	.23
eGFR ≥ 60, n (%)	354 (61.3)	371 (63.3)	.47
Hyperlipidemia	286 (49.5)	270 (46.1)	.24
Serum values			
Creatinine (mg/dL)	0.80 ± 0.26	0.79 ± 0.26	.35
Potassium (mmol/L)	4.3 ± 0.4	4.3 ± 0.5	.59
Total cholesterol (mg/dL)	197.5 ± 34.6	199.9 ± 35.9	.26
HDL cholesterol (mg/dL)	56.0 ± 15.4	57.0 ± 14.9	.30
Fasting plasma glucose (mg/dL)	119.9 ± 47.4	114.6 ± 40.6	.13
Casual plasma glucose (mg/dL)	143.5 ± 54.4	150.7 ± 62	.19
Current smoker, n (%)	62 (10.8)	53 (9.0)	.33
Current alcohol, n (%)	178 (31.0)	193 (33.1)	.45
Drug therapy, n (%)			
Previous antihypertensive treatment			.71
No. of agents			
0	173 (29.9)	169 (28.8)	
1	249 (43.1)	260 (44.4)	
2	126 (21.8)	134 (22.9)	
≥3	30 (5.2)	23 (3.9)	
Oral hypoglycemic agents	224 (38.8)	212 (36.2)	.36
Insulin treatment	32 (5.5)	37 (6.3)	.57
Lipid-lowering agents	213 (36.9)	211 (36.0)	.76
Antiplatelet agents	176 (30.5)	183 (31.2)	.77

ARB = angiotensin II receptor blocker; CCB = calcium channel blocker; BMI = body mass index; BP = blood pressure; eGFR = estimated glomerular filtration rate (men: $194 \times Cr^{-1.094} \times age^{-0.287}$; women: $194 \times Cr^{-1.094} \times age^{-0.287} \times 0.739$); HDL = high-density lipoprotein.

Data are mean ± standard deviation for continuous variables and number (%) for categoric variables. *P* values were calculated using *t* tests for continuous variables and chi-square tests for categoric variables.

used interaction terms between treatment groups and these aforementioned subgroups.[12]

A single interim analysis was carried out, and the Data and Safety Monitoring. Committee judged whether to continue or discontinue the study for ethical reasons. For all analyses, overall significance level was determined as 5%, and 2-sided tests were used.

RESULTS

Demographic and Baseline Characteristics of Study Patients

The trial profile is shown in **Figure 1**. A total of 578 patients were assigned to receive olmesartan 40 mg/day monotherapy (the high-dose angiotensin II receptor blocker group) and 586 patients were assigned to receive the combination of olmesartan 20 mg/day plus amlodipine or azelnidipine (the angiotensin II receptor blocker + calcium channel blocker group). The median follow-up period was 3.0 years, and the follow-up rate was 92.8%.

As shown in **Table 1**, there were no significant differences between the 2 groups in any of the baseline characteristics, except for body mass index (BMI). The difference in BMI was small, and there was no significant difference in body height, body weight, or the proportion of patients with BMI ≥ 25 kg/m^2 between the groups, thereby supporting that the slight difference in BMI might not significantly affect the results of the OSCAR study. The number of subgroup patients with cardiovascular disease was 405 (70.1 %) and 407 (69.5 %) in the high-dose angiotensin II

Table 2 Detailed Data of Baseline Cardiovascular Disease in the Enrolled Patients

	High-dose ARB (n = 578) No. (%)	ARB + CCB (n = 586) No. (%)	*P* Value
With baseline cardiovascular disease	405 (70.1)	407 (69.5)	.82
Stroke	111 (19.2)	96 (16.4)	.21
Transient ischemic attack	26 (4.5)	28 (4.8)	.82
Asymptomatic cerebrovascular disease	106 (18.3)	99 (16.9)	.52
Myocardial infarction	16 (2.8)	21 (3.6)	.43
Stable angina	66 (11.4)	64 (10.9)	.79
Heart failure	41 (7.1)	48 (8.2)	.48
LV hypertrophy	97 (16.8)	98 (16.7)	.98
Aortic aneurysm	1 (0.2)	4 (0.7)	.18
Arteriosclerotic peripheral arterial occlusive disease	10 (1.7)	15 (2.6)	.33
Serum creatinine outside normal range	37 (6.4)	37 (6.3)	.95
Proteinuria	65 (11.3)	62 (10.6)	.72

ARB = angiotensin II receptor blocker; CCB = calcium channel blocker; LV = left ventricular.

Data are number (%). *P* values were calculated using chi-square tests. "Asymptomatic cerebrovascular disease" is defined as cerebrovascular disease without neurologic symptom detected by computed tomography, magnetic resonance imaging, or other diagnostic imaging system, especially for high-risk patients at health checkup.

receptor blocker group and angiotensin II receptor blocker + calcium channel blocker combination group, respectively, whereas the number of subgroup patients without cardiovascular disease (with only type 2 diabetes in the OSCAR study) was 173 (29.9%) and 179 (30.5%) in the high-dose angiotensin II receptor blocker group and angiotensin II receptor blocker + calcium channel blocker combination group, respectively. There were no differences between the groups in the detailed data of baseline cardiovascular disease (**Table 2**).

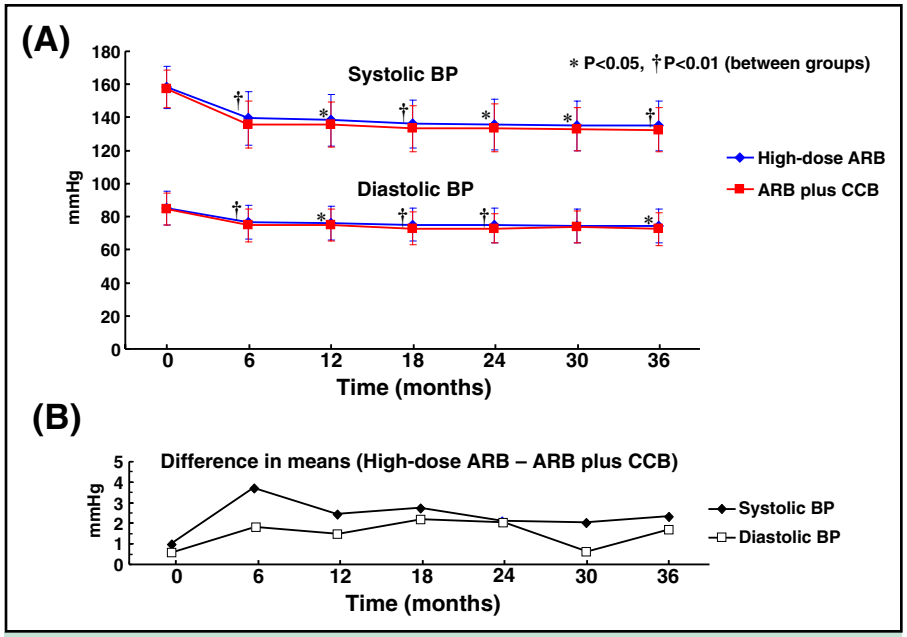

Figure 2 Time course of systolic and diastolic blood pressure in the 2 groups (A) and difference in blood pressure between the 2 groups (B) during follow-up. Blue values show mean systolic and diastolic blood pressure of high-dose ARB group, while red values show those of ARB plus CCB group. BP = blood pressure; ARB = angiotensin II receptor blocker; CCB = calcium channel blocker. * $P < .05$, † $P < .01$ statistically significant difference between the 2 treatment groups at each time point.

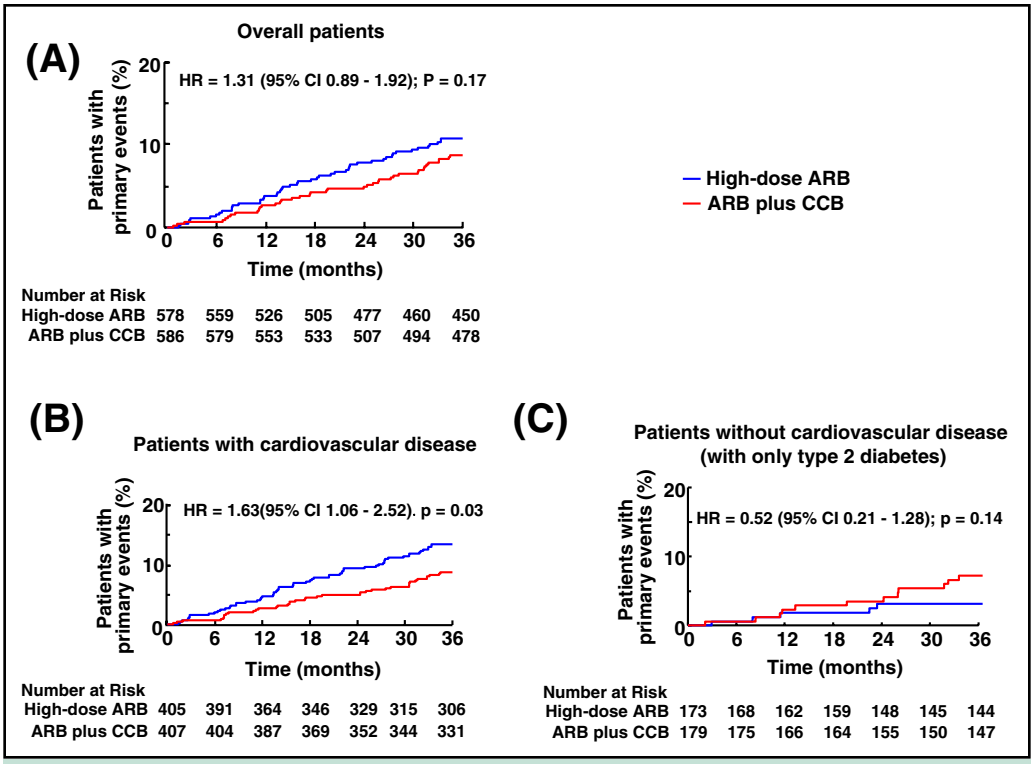

Figure 3 Kaplan-Meier curves for primary composite endpoint during the follow-up period in overall patients (A), patients with cardiovascular disease at baseline (B), and patients without cardiovascular disease at baseline (with only type 2 diabetes) (C). In (A), there were 58 patients with events (10.03%) in the high-dose ARB group, compared with 48 patients with events (8.19%) in the ARB + CCB group. The number of patients with cardiovascular disease in (B) was 405 and 407 in high-dose ARB and ARB + CCB combination groups, respectively, and the number of patients without cardiovascular disease in (C) was 173 and 179 in high-dose ARB and ARB + CCB combination groups, respectively. ARB = angiotensin II receptor blocker; CCB = calcium channel blocker; HR = hazard ratio; CI = confidence interval.

Blood Pressure During Follow-up Period

The percentage of patients who adhered to the protocol treatment at the end of follow-up was 87.5% in the high-dose angiotensin II receptor blocker and 90.3% in the angiotensin II receptor blocker + calcium channel blocker groups, which was not different between the 2 groups ($P = .16$).

At the 6-month follow-up, the percentage of patients who were receiving other approved antihypertensive agents to reach the blood pressure goal was 26.2% in the high-dose angiotensin II receptor blocker group and 12% in the angiotensin II receptor blocker + calcium channel blocker group. At the end of the 3-year follow-up, the percentages were 40.7% and 23%, respectively.

Blood pressure was reduced from baseline levels in a similar fashion in both groups as shown by the group-by-time interaction ($P = .44$ for systolic blood pressure, $P = .24$ for diastolic blood pressure) (**Figure 2**). However, a significant difference between groups was seen over the follow-up period for both systolic and diastolic blood pressures. At 36 months, in the angiotensin II receptor blocker + calcium channel blocker group, compared with the high-dose angiotensin II receptor blocker group, the mean systolic and diastolic blood pressures were lower by 2.4 mm Hg ($P = .03$) and 1.7 mm Hg ($P = .02$), respectively. More patients in the angiotensin II receptor blocker + calcium channel blocker group achieved the target blood pressure of < 140/90 mm Hg compared with the high-dose angiotensin II receptor blocker group (70.5% vs 62.1%, respectively; $P = .003$).

Primary End Point

Only the first event in a patient was counted as a primary end point. The number of primary end points was 58 (10.03 %, 38.1 per 1000 patient-years) in the high-dose angiotensin II receptor blocker group and 48 (8.19 %, 30.1 per 1000 patient-years) in the angiotensin II receptor blocker + calcium channel blocker group. The absolute risk difference was 1.84%, and the HR was 1.31 (95% CI, 0.89-1.92; $P = .17$) (**Figure 3A**). The number needed to treat to prevent 1 primary end point event over a 3-year follow-up period was 54.

Secondary End Point

No significant difference between the 2 groups was found for the incidence of any secondary end point (**Figure 4**).

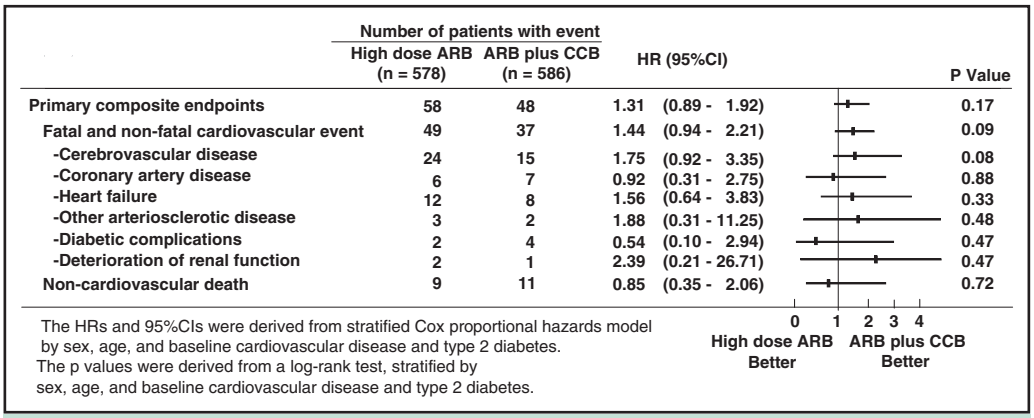

Figure 4 Hazard ratios (HRs) and 95% CIs for the primary composite endpoint and secondary endpoint. ARB = angiotensin II receptor blocker; CCB = calcium channel blocker. The HRs and 95% CIs were derived from a stratified Cox proportional hazards model taking into account sex, age, and baseline cardiovascular disease and type 2 diabetes. The *P* values were derived from a log-rank test, stratified by sex, age, and baseline cardiovascular disease and type 2 diabetes.

Prespecified Subgroup Analysis

The results of a prespecified subgroup analysis according to baseline cardiovascular disease are shown in **Figure 3B and C**. There was a significant interaction between patients with cardiovascular disease and patients without cardiovascular disease (ie, patients with diabetes only) at baseline for the primary outcome ($P = .02$ for interaction). The incidence of primary end point events in patients with cardiovascular disease was 51 in the high-dose angiotensin II receptor blocker group and 34 in the angiotensin II receptor blocker + calcium channel blocker group (HR 1.63, 95% CI, 1.06-2.52; $P = .03$) (**Figure 3**B). In patients without cardiovascular disease, the incidence of primary end point events was 7 in the high-dose angiotensin II receptor blocker group and 14 in the angiotensin II receptor blocker + calcium channel blocker group (HR 0.52, 95% CI, 0.21-1.28; $P = .14$) (**Figure 3**C). On the other hand, there was no significant interaction between patients with diabetes and patients without diabetes for the primary end point ($P = .17$ for interaction).

Comparison of Incidence of Primary End Point Between Patients With and Without Achieved Target Blood Pressure

As shown in **Table 3**, the incidence of the primary end point in the total cohort with achieved target blood pressure was significantly lower than that in the total cohort without achieved target blood pressure, regardless of the existence of cardiovascular disease at baseline.

Adverse Events

The number of serious adverse events, one of the secondary end points in this study, was 47 (8.1%) in the high-dose angiotensin II receptor blocker group and 51 (8.7%) in the angiotensin II receptor blocker + calcium channel blocker

Table 3 Comparison of Incidence of Primary End Point Between Patients With and Without Achieved Target Blood Pressure

Baseline	BP Goal Achieved Events/Patients (%)	BP Goal Not Achieved Events/Patients (%)	*P* Value
Patients with cardiovascular disease			
Total cohort	50/545 (9.2)	35/267 (13.1)	.03
High-dose ARB	27/256 (10.5)	24/149 (16.1)	.09
ARB + CCB	23/289 (8.0)	11/118 (9.3)	.42
Patients without cardiovascular disease			
Total cohort	7/227 (3.1)	14/125 (11.2)	<.001
High-dose ARB	2/103 (1.9)	5/70 (7.1)	.07
ARB + CCB	5/124 (4.0)	9/55 (16.4)	.002

ARB = angiotensin II receptor blocker; CCB = calcium channel blocker; BP = blood pressure.
BP goal was defined as systolic blood pressure < 140 mm Hg and diastolic blood pressure < 90 mm Hg.
P values were calculated using the stratified log-rank test adjusted for age and sex.

group, with no significant difference between the 2 groups ($P = .75$). New cancer diagnosis was not significantly different between the treatment groups (10 [1.7%] in the high-dose angiotensin II receptor blocker group vs 21 [3.6%] in the angiotensin II receptor blocker + calcium channel blocker combination group; $P = .07$).

DISCUSSION

In this study, systolic and diastolic blood pressure levels during the follow-up period were significantly lower in the angiotensin II receptor blocker + calcium channel blocker group than in the high-dose angiotensin II receptor blocker group. More patients achieved the target blood pressure in the angiotensin II receptor blocker + calcium channel blocker group than in the high-dose angiotensin II receptor blocker group. In addition, more patients in the high-dose angiotensin II receptor blocker group required additional antihypertensive medication to achieve the target blood pressure. These findings demonstrate that angiotensin II receptor blocker + calcium channel blocker combination is superior to high-dose angiotensin II receptor blocker in blood pressure-lowering effect in elderly hypertensive patients. Furthermore, the blood pressure results of this study are consistent with previous randomized, double-blind studies showing that the combination of olmesartan with amlodipine or azelnidipine exerted stronger antihypertensive effect than up-titration of olmesartan in Western or Japanese patients.[13,14] Despite lower blood pressure in the angiotensin II receptor blocker + calcium channel blocker group than in the high-dose angiotensin II receptor blocker group, there was no statistically significant difference in the incidence of primary end points between the 2 groups. Although OSCAR was the first large clinical trial comparing the efficacy of high-dose angiotensin II receptor blocker and the combination of angiotensin II receptor blocker and calcium channel blocker, the Valsartan Antihypertensive Long-term Use Evaluation (VALUE)[15] and Candesartan Antihypertensive Survival Evaluation in Japan (CASE-J)[16] trials compared angiotensin II receptor blocker–based therapy and calcium channel blocker–based therapy in the incidence of cardiovascular events in Western and Japanese hypertensive patients, respectively. The VALUE and CASE-J trials provided evidence that blood pressure reduction was greater in calcium channel blocker–based therapy than angiotensin II receptor blocker–based therapy, whereas there was no significant difference in the primary end point of composite cardiovascular events between these therapies.[15,16] Thus, our present findings are similar to the findings of VALUE and CASE-J, although the treatment protocol and the baseline characteristics of the patients significantly differed between the OSCAR study and these previous clinical trials.[15,16]

Of note, the subgroup analysis according to the presence of cardiovascular disease or type 2 diabetes at baseline was planned to be the most important prespecified analysis in the OSCAR study.[9] Of note, for patients with cardiovascular disease, the angiotensin II receptor blocker + calcium channel blocker group had significantly fewer primary end points than the high-dose angiotensin II receptor blocker group, showing that the angiotensin II receptor blocker + calcium channel blocker combination reduces cardiovascular morbidity and mortality in elderly hypertensive patients with cardiovascular disease compared with high-dose angiotensin II receptor blocker. Numerous studies revealed that lowering blood pressure was related to a lower incidence of cardiovascular events in patients with cardiovascular disease.[17] Of note, in this study, the incidence of primary end point in patients who achieved target blood pressure was significantly lower than in those who did not achieve target blood pressure, regardless of the existence of cardiovascular disease at baseline. Thus, in the OSCAR study, the significant difference between the 2 groups in primary outcome for patients with cardiovascular disease seems to be partially attributed to the significant difference in blood pressure between the groups during the follow-up period. However, it cannot be excluded that the angiotensin II receptor blocker + calcium channel blocker combination might provide benefit beyond blood pressure reduction.

On the other hand, in the subgroup of patients without cardiovascular disease (ie, those with type 2 diabetes only), the incidence of primary end points was lower in the high-dose angiotensin II receptor blocker group than in the angiotensin II receptor blocker + calcium channel blocker combination group, although the difference did not reach statistical significance because of the small number of patients. The appropriate statistical method for assessing the heterogeneity of treatment effects among subgroups is a statistical test for interaction.[12] Significant qualitative interaction indicates that the treatment effect is in opposite directions in different subgroups.[18] To examine the possibility, we tested the treatment by subgroup interaction between the subgroups with and without cardiovascular disease and found that it was statistically significant. Therefore, the efficacy of high-dose angiotensin II receptor blocker and angiotensin II receptor blocker + calcium channel blocker combination might differ depending on whether patients have cardiovascular disease (patients without cardiovascular disease have diabetes only in the OSCAR study); this finding is not definitive but may be considered as hypothesis generating.

Study Limitations

The OSCAR study has several limitations. The first limitation is the use of the Prospective Randomized Open Blinded End-point (PROBE) method. The PROBE method has the potential drawback of investigator bias.[19] However, we believe that aggressive treatment for blood pressure control was similarly performed in both groups, as shown by the high percentage of patients who achieved target blood pressure control and good compliance in both groups. Therefore, the use of PROBE design appeared not significantly to affect the main outcomes in this study. The second limitation might be sample size. It is possible that the absence of difference in the primary

outcome in the OSCAR study may be attributed to an underpowered sample size. However, the number of primary end points in the OSCAR study was close to the expected number of events.[9] Therefore, the absence of difference in the primary outcome between the groups seems to be explained by the heterogeneity of treatment effects between 2 subgroups of patients, those with cardiovascular disease and those without as discussed above, although the possibility of insufficient sample size in the OSCAR study cannot be completely excluded.

CONCLUSIONS

In elderly high-risk hypertensive patients, there was no significant difference between the high-dose angiotensin II receptor blocker and angiotensin II receptor blocker + calcium channel blocker groups in the incidence of primary end points. However, the angiotensin II receptor blocker + calcium channel blocker combination lowered blood pressure more than the high-dose angiotensin II receptor blocker and reduced the primary end points more than the high-dose angiotensin II receptor blocker in the patients with cardiovascular disease. Thus, combination therapy may be preferred over monotherapy in selected older adult populations.

References

1. Mancia G, De Backer G, Dominiczak A, et al. 2007 ESH-ESC Practice Guidelines for the Management of Arterial Hypertension: ESH-ESC Task Force on the Management of Arterial Hypertension. *J Hypertens*. 2007;25:1751-1762.
2. Ogihara T, Kikuchi K, Matsuoka H, et al. The Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2009). *Hypertens Res*. 2009;32:3-107.
3. Jamerson K, Weber MA, Bakris GL, et al. Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. *N Engl J Med*. 2008;359:2417-2428.
4. Cohn JN, Tognoni G. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. *N Engl J Med*. 2001;345: 1667-1675.
5. Pfeffer MA, McMurray JJ, Velazquez EJ, et al. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. *N Engl J Med*. 2003;349:1893-1906.
6. Parving HH, Lehnert H, Brochner-Mortensen J, et al. The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. *N Engl J Med*. 2001;345:870-878.
7. Kim S, Iwao H. Molecular and cellular mechanisms of angiotensin II-mediated cardiovascular and renal diseases. *Pharmacol Rev*. 2000;52:11-34.
8. Yamamoto E, Dong YF, Kataoka K, et al. Olmesartan prevents cardiovascular injury and hepatic steatosis in obesity and diabetes, accompanied by apoptosis signal regulating kinase-1 inhibition. *Hypertension*. 2008;52:573-580.
9. Ogawa H, Kim-Mitsuyama S, Jinnouchi T, et al. Rationale, design and patient baseline characteristics of OlmeSartan and calcium antagonists randomized (OSCAR) study: a study comparing the incidence of cardiovascular events between high-dose angiotensin II receptor blocker (ARB) monotherapy and combination therapy of ARB with calcium channel blocker in Japanese elderly high-risk hypertensive patients (ClinicalTrials. gov no. NCT00134160). *Hypertens Res*. 2009;32:575-580.
10. Japanese Society of Hypertension guidelines for the management of hypertension (JSH 2004). *Hypertens Res*. 2006;29(Suppl):S1-105.
11. Kuramoto K, Ichikawa S, Hirai A, et al. Azelnidipine and amlodipine: a comparison of their pharmacokinetics and effects on ambulatory blood pressure. *Hypertens Res*. 2003;26:201-208.
12. Wang R, Lagakos SW, Ware JH, et al. Statistics in medicine–reporting of subgroup analyses in clinical trials. *N Engl J Med*. 2007;357:2189-2194.
13. Chrysant SG, Melino M, Karki S, et al. The combination of olmesartan medoxomil and amlodipine besylate in controlling high blood pressure: COACH, a randomized, double-blind, placebo-controlled, 8-week factorial efficacy and safety study. *Clin Ther*. 2008;30:587-604.
14. Ogihara T, Saruta T, Shimada K, Kuramoto K. A randomized, double-blind, four-arm parallel-group study of the efficacy and safety of azelnidipine and olmesartan medoxomil combination therapy compared with each monotherapy in Japanese patients with essential hypertension: the REZALT study. *Hypertens Res*. 2009;32:1148-1154.
15. Julius S, Kjeldsen SE, Weber M, et al. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomised trial. *Lancet*. 2004;363:2022-2031.
16. Ogihara T, Nakao K, Fukui T, et al. Effects of candesartan compared with amlodipine in hypertensive patients with high cardiovascular risks: candesartan antihypertensive survival evaluation in Japan trial. *Hypertension*. 2008;51:393-398.
17. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA*. 2002; 288:2981-2997.
18. Pocock SJ, Assmann SE, Enos LE, Kasten LE. Subgroup analysis, covariate adjustment and baseline comparisons in clinical trial reporting: current practice and problems. *Stat Med*. 2002;21:2917-2930.
19. Hansson L, Hedner T, Dahlof B. Prospective randomized open blinded end-point (PROBE) study. A novel design for intervention trials. Prospective Randomized Open Blinded End-Point. *Blood Press*. 1992; 1:113-119.

Funding: A grant from the Japan Heart Foundation.

Conflict of Interest: Hisao Ogawa has received grants from the Japan Heart Foundation and consultancy fees/honoraria from Astellas, AstraZeneca, Bayer, Boehringer Ingelheim, Daiichi-Sankyo, Eisai, Kowa, Kyowa Hakko Kirin, MSD, Novartis, Pfizer, Sanofi-Aventis, Schering-Plough, and Takeda. Shokei Kim-Mitsuyama has received consultancy fees/honoraria from AstraZeneca, Astellas, Bayer, Boerhinger Ingelheim, Daiichi-Sankyo, Kyowa Hakko Kirin, Novartis, Pfizer, Takeda, Shionogi, and Servier. All other authors declare that they have no conflict of interest.

Authorship: All authors had access to the data and played a role in writing this manuscript.

Reprint requests should be addressed to: Shokei Kim-Mitsuyama, MD, PhD, Department of Pharmacology and Molecular Therapeutics, Kumamoto University Graduate School of Medical Sciences 1-1-1 Honjyo, Kumamoto 860-8556, Japan.

E-mail address: kimmitsu@gpo.kumamoto-u.ac.jp

APPENDIX 1. OLMESARTAN AND CALCIUM ANTAGONISTS RANDOMIZED STUDY GROUP

Aichi: Kenji Yamada. **Akita:** Goro Namekawa, Yasushi Suzuki, **Aomori:** Kenichi Kimura, Morio Aihara. **Chiba:** Akiko Soyama, Michiko Yonemitsu, Tomotane Shishikura, Toshiyuki Imasawa. **Ehime:** Masahiro Hasui. **Fukuoka:** Hidenori Urata, Hiroshi Ikezono, Masahiko Seki, Masaki Munekiyo, Takatoshi Otonari, Tetsuya Ohtsubo, Yasunori Sawayama, Yoichi Hanaoka, Yoshinori Takajo, Yuji Taira. **Fukushima:** Kuniyoshi Shima. **Gifu:** Hiroyuki Ohbayashi. **Hiroshima:** Kazuya Shigenobu. **Hokkaido:** Chieko Imamoto, Hiromitsu Yokota, Kazuo Yamagata, Kouichi Kanda, Tateo Ogura, Toshio Tsubokura. **Hyogo:** Akira Kosaka, Akira Tabuchi, Masaharu Shigenobu, Takatoshi Taka-

miya, Yasuki Makino, Yoshikazu Irie. **Kagawa:** Hideyasu Kiyomoto, Hirofumi Hitomi. **Kagoshima:** Yasuhiro Hashiguchi, Yoshihiro Fukuoka, Yoshitaka Shintomi. **Kanagawa:** Fusahiro Nonaka, Hiroshi Takeda, Masato Nishimura, Nariaki Kanemoto, Takayuki Furuki. **Kumamoto:** Akira Maki, Akira Sato, Eiichiro Tanaka, Etsuro Tsutsumi, Hajime Shono, Haruo Takeda, Hideaki Jinnouchi, Hirofumi Kann, Hiromi Fujii, Hiroyuki Shono, Hisao Fujimoto, Hisayasu Terazaki, Junichi Matsubara, Kazuhiko Yamada, Kazuhiro Nishigami, Keiichiro Tsuruta, Kenichi Koyama, Kenji Azuma, Koichiro Kataoka, Koji Sasaki, Kouji Honjio, Kunihiro Ohmori, Kunio Idegami, Masakazu Matsukawa, Masamitsu Toihata, Mikiko Suematsu, Motoko Tanaka, Osamu Hashiguchi, Ryo Fukami, Seiko Fujimoto, Shinichi Uemura, Shiro Mimori, Shojiro Naomi, Shouji Maruta, Shuichi Matsuo, Sunao Kojima, Taiji Sekigami, Takashi Fukunaga, Takashi Kudoh, Takashi Ono, Takeshi Koga, Tomio Wakita, Tomohiro Sawada, Toshihiko Sakanashi, Toshihiro Higashi, Yasuhiro Nagayoshi, Yasuhiro Sakamoto, Yoshihiro Kimura, Yuji Miyao, Yutaka Horio, **Kyoto:** Ken Takenaka. **Miyazaki:** Hiroshi Senokuchi, Hirotsugu Ohta, Juniti Miyata, Naoto Yokota, Takeshi Yamamoto. **Nagasaki:** Hiroyuki Oka, Yoshito Tanioka, **Niigata:** Toshihide Shu. **Okayama:** Hirohiko Asonuma, Naoki Kashihara, Naruya Tomita, Takehiko Tokura, Tamaki Sasaki. **Osaka:** Hidenori Koyama, Katsuo Suyama, Kenei Shimada, Masahito Imanishi, Masanori Emoto, Masayuki Hosoi, Masayuki Nagata, Nobuo Wakaki, Shiro Yanagi, Takao Yoshioka, Takeshi Horio, Tetsuya Hayashi. **Saga:** Kazuo Moroe, Shiro Hata. **Saitama:** Hideto Muranaka, Masaru Arai, Shouji Mashiba, Souichirou Ishimoto, Tadahiko Ogasawara, Tomoya Fujino, Tomoyuki Okudaira. **Shimane:** Yuko Yamane. **Shizuoka:** Masako Waki. **Tokushima:** Akira Ota. Kazuto Okagawa, Kenzo Motoki, Takashi Iwase. **Tokyo:** Akihiko Hachiya, Hiromi Takekawa, Kenzo Matsumura, Masato Yamamoto, Minoru Hojo, Shiho Kaku, Tetsuya Taniguchi, Yasunaga Hiyoshi, Yutaka Shimizu. **Yamaguchi:** Hideaki Hanamiya.