ORIGINAL ARTICLE

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)

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Higher doses of angiotensin II receptor blockers (ARBs) are expected to exert more protective effects against cardiovascular diseases. However, the significance of treatment of hypertension with high-dose ARB remains to be defined. The OlmeSartan and Calcium Antagonists Randomized (OSCAR) Study was designed to determine whether high-dose ARB monotherapy is superior to the combination therapy of ARB plus calcium channel blocker (CCB) in the prevention of cardiovascular morbidity/mortality in Japanese elderly high-risk hypertensive patients. The OSCAR study is a multicenter, active-controlled, two-arm parallel group comparison, using the prospective randomized open-blinded end-point method. In the 'Step 1' period, elderly hypertensive patients with diabetes or cardiovascular disease received monotherapy with ARB olmesartan medoxomil at a dose of 20 mg day⁻¹. If the target blood pressure control (less than 140/90 mm Hg) was not achieved by ARB monotherapy, the patients were randomized to receive either (1) the increased dose of olmesartan at 40 mg day⁻¹ (high-dose ARB monotherapy) or (2) the addition of a CCB (amlodipine or azelnidipine) to 20 mg day⁻¹ olmesartan (ARB plus CCB combination) in the 'Step 2' period. The follow-up duration will be 3 years. The primary end points will be the composite of fatal and non-fatal cardiovascular events, and death from any cause. Recruitment for the OSCAR study (around 1200 patients) was completed by the end of May 2007. The OSCAR study is the first large clinical trial comparing the efficacy of high-dose ARB monotherapy with that of an ARB plus CCB combination therapy in elderly high-risk hypertensive patients.

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INTRODUCTION

The renin–angiotensin system, through pleiotropic biological actions of angiotensin II, plays a key role in the pathophysiology of not only hypertension but also of various cardiovascular and renal diseases.¹ Accumulating clinical evidence indicates that angiotensin II receptor blockers (ARBs) are effective for the treatment of not only hyperten-

sion^{2–4} but also of various cardiovascular diseases, including stroke,^{5,6} myocardial infarction,⁷ heart failure,^{8,9} diabetic nephropathy^{10,11} and so on. The Valsartan Antihypertensive Long-Term Use Evaluation¹² study and a subanalysis of the CASE-J (Candesartan Antihypertensive Survival Evaluation in Japan)⁴ study compared the efficacy of ARB valsartan and candesartan, respectively, with that of calcium channel

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blocker (CCB) amlodipine. These two clinical studies provide evidence that these ARBs and amlodipine similarly suppress total cardiovascular morbidity and mortality in high-risk hypertensive patients under strict blood pressure control, indicating that ARBs are as effective as amlodipine for the treatment of hypertension in both Western and Japanese patients. Furthermore, these studies^{4,12} also provide evidence that ARBs prevent the onset of type 2 diabetes in hypertensive patients more than amlodipine, indicating the superiority of ARBs over amlodipine in terms of antidiabetic effect.

Generally, the adverse events of many antihypertensive drugs including CCBs are dose dependent and are far more prevalent at higher doses, which hamper the use of high-dose medication for the treatment of hypertensive patients. In contrast, ARBs, which exert similar antihypertensive efficacy as that of other classes of antihypertensive drugs, have placebo-like tolerability,^{13,14} and ARBs reduce blood pressure of hypertensive patients in a dose-dependent manner with no increase in the incidence of adverse events at their maximal doses.¹⁵ A previous study investigating the renoprotective effects of ARB irbesartan in patients with nephropathy because of type 2 diabetes¹¹ provides evidence that higher doses of irbesartan more potently prevents the progression of diabetic nephropathy in hypertensive patients independent of blood pressure-lowering effects. Therefore, antihypertensive treatment with higher doses of ARBs is supposed to be more effective for treatment of not only hypertension but also for that of cardiovascular and renal diseases. However, the significance of the use of high doses of ARB for treatment of hypertensive patients remains to be defined. Furthermore, it also remains to be determined which therapeutic strategy is more effective for the treatment of hypertensive patients, high-dose ARB monotherapy or the combination of ARB and CCB. Therefore, we designed the OlmeSartan and Calcium Antagonists Randomized (OSCAR) study to compare the efficacy between high-dose ARB and the combination of ARB plus CCB in elderly Japanese patients with high-risk hypertension in terms of prevention of cardiovascular morbidity and mortality.

METHODS

Study organization and management

Organization and members of the committees for the OSCAR study are shown in the Appendix. The responsibilities and activities of these committees are as follows: the Steering Committee is responsible for the study design, makes final decisions about the study, and is also responsible for writing the protocol, the case report forms and informed consent documents, and for revising these documents. The Data and Safety Monitoring Committee is responsible for the evaluation of adverse events and for the interpretation of the results of the interim analysis, and for recommendation to the Steering Committee to stop the study on the basis of the findings of serious adverse events or results of interim analysis. The Endpoint Committee is responsible for the evaluation of the primary and secondary endpoints. Before conducting the study, the Ethics Committee evaluated the ethical and safety aspects of the protocol, and patient explanation documents and informed consent forms at the request of the study representatives. The Ethics Committee is coordinated independently of the other committees and organized with independent experts. Before participating in the study, investigators must be approved by the Ethics Committee of the respective participating medical institutions. If an individual institution was unable to convene its own Ethics Committee, the investigator must have been approved by the Ethics Committee of the OSCAR study.

Eligibility criteria of patients

Inclusion criteria and exclusion criteria are listed in Tables 1 and 2, respectively. Elderly outpatients who fulfilled both criteria (1) and (2) in Table 1 were able to attend the study institution, and those who had at least one of the cardiovascular risk factors (cardiovascular disease or type 2 diabetes) specified in

Table 1 Inclusion criteria for the OSCAR study

- (1) Outpatients aged 65 years or older, and <85 years (at the time of informed consent), of both sex
- (2) Receiving treatment with a single antihypertensive drug in principle, and showing a SBP ≥ 140 mm Hg and DBP ≥ 90 mm Hg at both of two casual blood pressure measurements in the sitting position on two recent clinic visits
- (3) *At least one of the following cardiovascular risk factors:*
 - Type 2 diabetes
 - Cerebral disease
 - History of cerebral infarction, cerebral hemorrhage, subarachnoid hemorrhage or transient ischemic attack (TIA) (at least 6 months before obtaining informed consent)
 - Diagnosis of asymptomatic cerebrovascular disease
 - Cardiac disease
 - Earlier myocardial infarction at least 6 months before obtaining informed consent
 - Angina pectoris or heart failure (NYHA Class I or II)
 - Left ventricular hypertrophy (left ventricular posterior wall thickness ≥ 12 mm on echocardiography or Sv1+Rv5 ≥ 35 mm on electrocardiography before obtaining informed consent)
 - Vascular disease
 - Aortic aneurysm
 - Earlier episode of aortic dissection at least 6 months before obtaining informed consent
 - Arteriosclerotic peripheral artery disease (Fontaine Classification Grade of 2 or worse)
 - Renal disease
 - Serum creatinine of 1.2–2.5 mg per 100 ml for men or 1.0–2.5 mg per 100 ml for women
 - Proteinuria: $\geq +1$ (qualitative) or ≥ 0.3 gram per gram of creatinine (quantitative) estimated in spot urine or 24-h urine corrected for the urinary creatinine value.

Abbreviations: DBP, diastolic blood pressure; NYHA, New York Heart Association; OSCAR, OlmeSartan and Calcium Antagonists Randomized study; SBP, systolic blood pressure.

Table 2 Exclusion criteria for the OSCAR study

- Secondary hypertension or malignant hypertension
- Severe heart failure (NYHA Class III or IV)
- Malignancy requiring treatment
- Serious hepatic or renal dysfunction (that is, serum creatinine > 2.5 mg per 100 ml or need for hemodialysis)
- Difficulty in stopping drugs used for the treatment of hypertension or coronary artery diseases (that is, calcium channel blockers, β -blockers, thiazide diuretics and so on) to switch to the study medication
- History of a serious adverse drug reaction to an angiotensin II receptor blocker or calcium channel blocker
- Any other condition that makes a patient unsuitable for the study in the opinion of the investigator

Abbreviation: NYHA, New York Heart Association.

criterion (3) in Table 1 were eligible for participation in this study. Patients with any of the conditions described in Table 2 were excluded from the study.

Informed consent

The investigator explained the study to each patient, covering the following points: (1) objectives and methods of the study; (2) scheduled participation period and planned number of participants; (3) anticipated clinical benefits and risks; (4) each patient is free to refuse to participate in the study and can

withdraw consent at any time after initiation of the study without any disadvantage; (5) patients will rapidly receive any new information that may affect their willingness to continue participating in the study if such information becomes available; (6) information collected during the study will be used for medical research; (7) measures for the protection of privacy; and (8) follow-up of patients will continue in the case of a cardiovascular event requiring admission to a different hospital for treatment or after withdrawal from the study at the request of the patient. The investigator obtained signed written consent from each patient before participation in the study.

Study drugs

Commercially available drugs are used as the study medications. Olmesartan medoxomil (Olmetec Tablets, Olmetec, Daiich-Sankyo Co. Ltd., Tokyo, Japan) is used as the ARB. Amlodipine besilate (Norvasc Tablets, Norvasc, Pfizer Inc., Tokyo, Japan or Amlodin Tablets, Amlodin, Dainippon Sumitomo Pharma Co. Ltd., Osaka, Japan) or azelnidipine (Calblock Tablets, Calblock, Daiich-Sankyo Co. Ltd.) is used as the CCB. The use of other concomitant drugs for routine medical management (including antiangina drugs like nitrates and nicorandil) is permitted.

Run in and randomization

After receiving the signed informed consent form from a patient and confirming that the patient met the inclusion criteria and did not fit any of the exclusion criteria, the investigator recorded the following specified information on the 'enrollment sheet', and sent the sheet to the OSCAR-Study Data Center by facsimile. After checking the eligibility of the patient on the basis of the enrollment sheet sent by facsimile, the data center randomized the patient to the high-dose ARB group or to the ARB plus CCB group, by a dynamic randomization method that took into account the following factors: sex, age, cardiovascular risk factors and study institution.

Treatment protocol

The treatment protocol is shown in Figure 1. After randomization, any earlier antihypertensive medication was switched to olmesartan at a dose of 20 mg day⁻¹ in the Step 1 period. If blood pressure was not adequately controlled to <140/90 mm Hg by olmesartan at 20 mg day⁻¹, and the treatment was well tolerated, irrespective of the duration of run-in treatment, in the 'Step 2' period, the patients in the high-dose ARB group received the increased dose of olmesartan medoxomil at 40 mg day⁻¹ (the maximum dose approved in Japan), or those in the ARB plus CCB group received a CCB in addition to olmesartan medoxomil at 20 mg day⁻¹. If additional antihypertensive treatment was required during Step 2, another antihypertensive drug could be added, except that ARBs, angiotensin-converting enzyme inhibitors and CCBs were excluded.

Figure 1 Study design of the OlmeSartan and Calcium Antagonists Randomized (OSCAR) study. *Amlodipine or azelnidipine is used as the calcium channel blocker. **If blood pressure control is not adequately achieved, additional antihypertensive drugs may be used, except for angiotensin II receptor blockers (ARBs), angiotensin-converting enzyme inhibitors and calcium channel blockers (CCBs).

Patient follow-up

Data will be collected every 6 months from each patient. All information obtained at the follow-up visits every 6 months, along with information on cardiovascular events, adverse events and investigations into discontinuation/drop-out, if any, will be transmitted to the data center. Enrollment was carried out from June 2005 to May 2007, and follow-up will continue for 3 years on a per-patient basis.

End-point assessment

Primary, secondary and other end points are summarized in Table 3. A cardiovascular event is defined as any treatment-emergent adverse event as listed in terms (1) to (6) in Table 3. The prespecified subgroups to be considered include cardiovascular risk factor, sex, age, body mass index, blood pressure, heart rate, earlier antihypertensive medication, hyperlipidemia, concomitant statin therapy, thrombosis, concomitant anti-thrombotic medication, smoking status, alcohol intake, ECG abnormality, creatinine clearance and estimated glomerular filtration rate. Subgroup analysis according to baseline cardiovascular risk factor (earlier or concurrent cardiovascular disease and concurrent diabetes) was defined as the most important subgroup analysis. The Endpoint Committee will adjudicate, without knowledge of the assigned drugs, all cases of cardiovascular events and death.

Sample size and power of the study

The annual incidence of events conforming to the primary end points was assumed to be 5%, taking into consideration the fact that the participants

Table 3 The OSCAR study outcome/endpoints

Primary endpoints

Composite of fatal and non-fatal cardiovascular events

- (1) Cerebrovascular disease (cerebral infarction, cerebral hemorrhage, subarachnoid hemorrhage, unspecified stroke and transient ischemic attack)
- (2) Coronary artery disease (sudden death, myocardial infarction, angina pectoris and asymptomatic myocardial ischemia)
- (3) Heart failure
- (4) Other arteriosclerotic disease (aortic aneurysm, aortic dissection and atherosclerotic diseases)
- (5) Diabetic complications (nephropathy, retinopathy and neuropathy)
- (6) Deterioration of renal function (doubling of serum creatinine, end-stage renal disease (ESRD; that is, initiation of hemodialysis, and renal transplantation and so on))

All cause death

Secondary endpoints

- (1) Incidence of each cardiovascular event
- (2) Blood pressure (SBP, DBP and mean BP) change from baseline at each assessment during the follow-up period
- (3) Serious adverse events other than the primary endpoints

Other endpoints

- (1) Heart rate change from baseline at each assessment during the follow-up period
- (2) Effect on glucose metabolism
HbA_{1c} change from baseline at each assessment during the follow-up period in the patients with type 2 diabetes
HbA_{1c} change from baseline in the patients with poorly controlled type 2 diabetes
New onset of type 2 diabetes in the patients without type 2 diabetes at the time of screening
- (3) Changes of clinical laboratory tests from baseline at each assessment during the follow-up period
- (4) Subgroup analyses

Abbreviations: DBP, diastolic blood pressure; OSCAR, OlmeSartan and Calcium Antagonists Randomized study; SBP, systolic blood pressure.

would be high-risk patients.¹⁶ Assuming that there would be a relative intergroup difference of 40% in the incidence of events, the required number of participants to have 80% power with $\alpha=0.05$ (two-sided) would be 464 per group.¹⁷ Taking dropouts into consideration, the required number of participants per group was estimated to be 500.

Statistical analysis

Statistical analysis will be performed in the Clinical Education Center at Kumamoto University Hospital and the OSCAR-Study Data Center. Primary analyses will be carried out in compliance with the intent-to-treat principle. For the primary end points, intergroup comparison will be carried out by the stratified log-rank test, stratified by sex, age and cardiovascular risk factors. Using a stratified proportional hazards model, the hazard ratio and 95% confidence interval will be calculated for each treatment group. Time-to-event curves for cardiovascular events will be estimated by the Kaplan–Meier method.

Repeated measures analysis of variance will be used for intergroup comparison to compare the change from baseline at each time of assessment follow-up period in some end-point data including blood pressure, heart rate, HbA1c and laboratory tests. The unpaired *t*-test adjusted by Holm's method¹⁸ will be used for intragroup comparison to avoid multiplicity at multiple time points.

Fisher's exact test will be used for intergroup comparison of the occurrence of serious adverse events other than that of the primary end points.

Prespecified subgroup analyses will be conducted and interactions between factors in each group and subgroup will be investigated.

Single interim analysis will be carried out to judge whether to continue or discontinue the study for ethical reasons. The level of significance will be determined by using the O'Brien–Fleming procedure.¹⁹ For all analyses, the overall level of significance will be $P=0.05$, and two-sided tests will be used. The details will be outlined in the statistical analysis plan.

Data management

Case report forms filled out by the investigators will be collected by the OSCAR-Study Data Center. The OSCAR-Study Data Center will check compliance with the protocol as necessary and will notify the investigators regarding requirements for maintaining the quality of the study. The investigators will keep source documents for essential data (laboratory tests, investigational items and so on). The OSCAR-Study Data Center will conduct centralized monitoring of the participating institutions, visit as necessary and check the source documents and information entered by the investigators.

Trial progress and baseline characteristics of the patients

As shown in Figure 2, a total of 1217 elderly patients diagnosed with high-risk hypertension were recruited and randomized between June 2005 and May 2007.

Figure 2 Trial profile of the OlmeSartan and Calcium Antagonists Randomized (OSCAR) study.

Table 4 Baseline characteristics of the patients

	Total	65–74 years old	75–84 years old
<i>n</i>	1164	655	509
Female (%)	649 (55.8%)	337 (51.5%)	312 (61.3%)
Age (years)	73.6 ± 5.4	69.6 ± 3.0	78.8 ± 2.8
BMI (kg m ⁻²)	24.0 ± 3.6	24.4 ± 3.7	23.6 ± 3.5
SBP (mm Hg)	157.7 ± 12.0	157.2 ± 12.0	158.4 ± 11.9
DBP (mm Hg)	84.9 ± 9.9	86.6 ± 9.6	82.6 ± 9.9
HR (b.p.m.)	73.4 ± 9.6	73.5 ± 9.4	73.3 ± 9.8
<i>Hypertension class</i>			
Mild	704 (60.5%)	411 (62.7%)	293 (57.6%)
Moderate	405 (34.8%)	214 (32.7%)	191 (37.5%)
Severe	55 (4.7%)	30 (4.6%)	25 (4.9%)
Current smoking	115 (9.9%)	84 (12.8%)	31 (6.1%)
Current alcohol use	371 (31.9%)	236 (36.0%)	135 (26.5%)

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; HR, heart rate; SBP, systolic blood pressure.
Values are mean ± s.d.

Finally, 1164 patients will be included in the analysis; a total of 578 patients were randomly assigned to the high-dose ARB group and 586 patients to the ARB plus CCB group.

Tables 4 and 5 summarize the characteristics of the patients at baseline. The mean age of the patients was 73.6 years, and 509 (43.7%) patients were 75–84 years old. Systolic blood pressure and diastolic blood pressure of the patients were 157.7 ± 12.0 and 84.9 ± 9.9 mm Hg, respectively, and the frequencies of mild and moderate hypertension were 60.5 and 34.8%, respectively. About 70% of the patients had a history of cardiovascular disease, including cerebrovascular disease (40.0%), cardiac disease (38.7%) and renal dysfunctions (17.3%). Moreover, 54.0 and 45.0% of the patients had type 2 diabetes and hyperlipidemia, respectively.

DISCUSSION

In the OSCAR study, we enrolled elderly hypertensive patients, because there is much less evidence for the treatment of hypertension in elderly patients than in younger patients. Particularly, evidence for antihypertensive treatment of elderly Japanese patients is scarce. CCBs are generally recommended for the treatment of hypertension in elderly patients, because earlier evidence shows the efficacy of CCBs in such patients.^{20–23} ARBs have also been shown to exert beneficial effects in elderly hypertensive patients, as shown by the Study on Cognition and Prognosis in the Elderly (SCOPE) trial.⁵ Moreover, very recently, a subanalysis of the CASE-J trial²⁴ has shown that ARB candesartan and CCB amlodipine are equally effective in Japanese elderly patients with high-risk hypertension in terms of the prevention of cardiovascular morbidity and mortality, supporting the fact that ARBs as well as CCBs are beneficial as first-line agents for the treatment of hypertension in elderly patients. However, to our knowledge, there is no report of a large clinical trial comparing the efficacy of high-dose ARB monotherapy with the standard dose of ARB plus CCB combination in elderly hypertensive patients in terms of the prevention of cardiovascular morbidity and mortality. Therefore, the OSCAR study is the first clinical trial to investigate the benefit of high-dose ARB therapy on elderly hypertensive patients, and may have much influence on antihypertensive therapeutic strategy for high-risk elderly hypertensive patients.

The target blood pressure for the treatment of elderly hypertensive patients is generally <140/90 mm Hg, as shown by the Japanese and European guidelines for elderly hypertensive patients.^{13,14} Therefore, in the OSCAR study, the target blood pressure used was

Table 5 History of cardiovascular risk of the patients

	Total	65–74 years old	75–84 years old
<i>n</i>	1164	655	509
History of cardiovascular disease	812 (69.8%)	417 (63.7%)	395 (77.6%)
<i>Cerebrovascular history</i>	466 (40.0%)	224 (34.2%)	242 (47.5%)
Stroke	207 (17.8%)	110 (16.8%)	97 (19.1%)
TIA	54 (4.6%)	26 (4.0%)	28 (5.5%)
Asymptomatic cerebrovascular disease	205 (17.6%)	88 (13.4%)	117 (23.0%)
<i>Cardiac history</i>	451 (38.7%)	232 (35.4%)	219 (43.0%)
Myocardial infarction	37 (3.2%)	17 (2.6%)	20 (3.9%)
Angina pectoris	130 (11.2%)	61 (9.3%)	69 (13.6%)
Heart failure	89 (7.6%)	41 (6.3%)	48 (9.4%)
LV hypertrophy	195 (16.8%)	113 (17.3%)	82 (16.1%)
<i>Other vascular diseases</i>	30 (2.6%)	20 (3.1%)	10 (2.0%)
Aortic aneurysm	5 (0.4%)	2 (0.3%)	3 (0.6%)
Aortic dissection	0 (0.0%)	0 (0.0%)	0 (0.0%)
Atherosclerotic disease	25 (2.1%)	18 (2.7%)	7 (1.4%)
<i>Renal dysfunction</i>	201 (17.3%)	100 (15.3%)	101 (19.8%)
Serum creatinine outside normal range ^a	74 (6.4%)	34 (5.2%)	40 (7.9%)
Proteinuria	127 (10.9%)	66 (10.1%)	61 (12.0%)
<i>Hyperlipidemia</i>	524 (45.0%)	316 (48.2%)	208 (40.9%)
<i>Type 2 diabetes</i>	628 (54.0%)	381 (58.2%)	247 (48.5%)

Abbreviations: LV, left ventricular; TIA, transient ischemic attack.

^aMale: 1.2–2.5 mg per 100 ml, female: 1.0–2.5 mg per 100 ml.

140/90 mm Hg. For elderly patients over 75 years of age, the Japanese treatment guidelines for hypertension¹³ recommend both using an intermediate target blood pressure of 150/90 mm Hg and attempting to lower the patient's blood pressure to 140/90 mm Hg, if possible, while closely observing the condition of the patient. However, these targets are not necessarily supported by direct evidence. A consensus regarding the optimal target blood pressure for elderly hypertensive patients, particularly for those aged 75 years or older, has not yet been determined. The recent findings of the subanalysis of the CASE-J trial²⁴ support the idea of using a systolic blood pressure target of <150 mm Hg for hypertensive patients older than 75 years, although the CASE-J trial was not designed to determine the optimal target blood pressure. Interestingly, the baseline characteristics of the patients in the OSCAR study show that 43.7% of the patients were 75 years or older. Thus, the results of the OSCAR study may provide useful information for determining the appropriate target blood pressure for not only elderly hypertensive patients but also for those aged 75 years or older.

In the OSCAR study, we used olmesartan as the ARB. An earlier integrated analysis of safety and efficacy data from seven randomized, double-blind, placebo-controlled, parallel group studies¹⁵ indicate that olmesartan exerts a dose-dependent reduction of systolic blood pressure and diastolic blood pressure, and that olmesartan is as effective in elderly hypertensive patients as it is in younger patients. An earlier randomized double-blind study²⁵ comparing the antihypertensive efficacy of olmesartan with that of amlodipine for mild-to-moderate hypertension shows that olmesartan at the dose of 20 mg day⁻¹ has similar blood pressure-lowering efficacy as that of amlodipine at 5 mg day⁻¹, and that treatment with olmesartan (20 mg day⁻¹) allows more patients to achieve the systolic blood pressure goal of <130 mm Hg and the diastolic blood pressure goal of <85 mm Hg than does treatment with amlodipine (5 mg day⁻¹), thereby indicating

the excellent efficacy of olmesartan on hypertensive patients. Furthermore, in our experimental studies, we have shown that olmesartan potentially prevents hyperplasia of the vascular intima induced by balloon injury,²⁶ prevents hypertensive heart failure by suppressing cardiac hypertrophy and remodeling,²⁷ reverses vascular endothelial dysfunction by reducing oxidative stress and normalizing endothelial nitric oxide synthase,²⁸ and improves insulin resistance, hepatic steatosis and cardiovascular remodeling in type 2 diabetes and obesity.²⁹ Thus, olmesartan is assumed to be a promising antihypertensive agent for the treatment of cardiovascular diseases and metabolic syndrome.

Accumulating clinical evidence indicates that treating hypertensive patients with amlodipine reduces cardiovascular morbidity and mortality, thereby indicating that amlodipine is a useful antihypertensive agent in terms of the prevention of cardiovascular events. Similar to amlodipine, azelnidipine is a dihydropyridine CCB. Interestingly, a comparison between azelnidipine and amlodipine in Japanese hypertensive patients³⁰ has shown that azelnidipine treatment caused significantly lower heart rate than did amlodipine treatment, despite similar blood pressure-lowering effects between azelnidipine and amlodipine. Taken together with the fact that a higher heart rate is a well-known predictor of cardiovascular mortality,^{31,32} this clinical finding of a lower heart rate in azelnidipine treatment than in amlodipine treatment suggests that azelnidipine may be at least as effective as amlodipine in terms of the prevention of cardiovascular events. Furthermore, we have compared the beneficial effects of equihypotensive doses of azelnidipine and amlodipine on hypertensive rats and have shown that azelnidipine treatment exerts a lower heart rate than does amlodipine, and azelnidipine reduces cardiac hypertrophy and remodeling more than amlodipine by a greater reduction of cardiac oxidative stress and inflammation.³³ Our experimental findings show that a lower heart rate results in more protection

against hypertensive cardiac hypertrophy and remodeling. Furthermore, azelnidipine, in combination with an ARB, is shown to exert additional renoprotective effects in hypertensive patients with diabetic nephropathy.³⁴ Thus, azelnidipine is proposed to be a preferable CCB for the treatment of hypertension in terms of the prevention of cardiovascular events. Therefore, in the OSCAR study, we used not only amlodipine but also azelnidipine as CCBs.

In conclusion, the OSCAR study is a multicenter, active-controlled, two-arm parallel group, prospective randomized open-blinded end-point design study, and is the first study to compare the efficacy of high-dose ARB monotherapy with the standard dose of ARB plus CCB combination in elderly patients with high-risk hypertension, in terms of cardiovascular morbidity and mortality. Hence, the results of this study are expected to provide a novel insight into the therapeutic strategy for hypertension in high-risk elderly patients.

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APPENDIX

Membership of Committees.

Steering Committee: Kikuo Arakawa (Chair), Hisao Ogawa, Shokei Kim-Mitsuyama, Tomio Jinnouchi.

End-point Committee: Shuichi Oshima, Yoichiro Hashimoto, Takamichi Nakamura.

Data and Safety Monitoring Committee: Yasuhiro Ogata, Toshiro Yonehara.

Ethics Committee: Takao Hashimoto, Ryo Nagao, Satoshi Asai, Wataru Shimizu, Hideko Agui.

Study Statistician: Kunihiko Matsui.

Study Secretary: Hisao Ogawa.