ORIGINAL ARTICLE

Long-term effects of candesartan and amlodipine on cardiovascular morbidity and mortality in Japanese high-risk hypertensive patients: the Candesartan Antihypertensive Survival Evaluation in Japan Extension Study (CASE-J Ex)

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In the Candesartan Antihypertensive Survival Evaluation in Japan (CASE-J) trial, comparable efficacy was noted between candesartan and amlodipine in the incidence of cardiovascular (CV) morbidity and mortality during 3.2 years of follow up. Candesartan suppressed new-onset diabetes more effectively than amlodipine. In this observational study, we investigated whether or not the efficacy of the two drugs is sustainable for another 3 years beyond the experimental period of the CASE-J trial. Of the 4728 high-risk hypertensive patients initially enrolled in the CASE-J trial, 2232 agreed to further follow up. The primary endpoint was a composite of CV morbidity and mortality. The distribution of demographic characteristics for the 2232 patients in the CASE-J extension was similar to that in the initial 4703 patients in the CASE-J trial. Both drugs controlled blood pressure well over the relatively long period of time. The incidence of CV events was 15.5/1000 patient years in the candesartan group and 16.3/1000 patient years in the amlodipine group (Hazard ratio (HR)=0.95, 95% confidence interval (CI)=0.77–1.18; $P=0.650$). The incidence of new-onset diabetes was significantly lower in the candesartan group (9.5/1000 patient years) than in the amlodipine group (13.3/1000 patient years), representing a 29% risk reduction for new-onset diabetes (HR=0.71, 95% CI=0.51–1.00, $P=0.0495$). In conclusion, candesartan and amlodipine showed comparable efficacy against CV events beyond the experimental period of the CASE-J trial in high-risk hypertensive patients. In addition, the effects of candesartan on new-onset diabetes observed during the CASE-J trial were sustained in the CASE-J extension. The CASE-J extension, which covered a 3-year extension of follow-up from the original trial, corroborated the results of the CASE-J trial. *Hypertension Research* (2011) 34, 1295–1301; doi:10.1038/hr.2011.120; published online 11 August 2011

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INTRODUCTION

Hypertension is one of the most prevalent diseases in the world today and an independent risk factor for cardiovascular (CV) morbidity and mortality. The purpose of hypertensive treatment is not only to normalize elevated blood pressure (BP), but also to reduce the risk of CV morbidity and mortality. In recent years, we have focused on the clarification and differentiation of effects of antihypertensive agents on the incidence of CV events in addition to their BP-lowering effects.^{1–3}

The Candesartan Antihypertensive Survival Evaluation in Japan (CASE-J) trial was conducted to compare the effects of the angiotensin II receptor blocker (ARB) candesartan and the calcium channel blocker (CCB) amlodipine on the incidence of CV events, represented as a composite of sudden death, cerebrovascular, cardiac, renal and vascular events, in Japanese high-risk hypertensive patients.⁴ The CASE-J trial demonstrated that there was no difference in the incidence of these CV events between candesartan- and amlodipine-based regimens.⁵ This trial further showed that candesartan significantly

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reduced the incidence of new-onset diabetes compared with amlodipine,⁵ and a significantly large decrease in left ventricular mass index was observed in patients with left ventricular hypertrophy receiving the candesartan- vs. the amlodipine-based regimen at the start of the CASE-J trial.⁶ In addition, subanalysis of the trial revealed that candesartan reduced the incidence of CV events, particularly renal events to a greater extent than amlodipine in patients with stage 4 chronic kidney disease.⁷

However, despite extensive evidence supporting candesartan's beneficial effects, no significant difference in the incidence of CV events was noted between the two drug groups in the 3.2 years of follow-up in the CASE-J trial.⁵ As the CV event rate was much lower than we had initially expected in the trial, we hypothesized that the mean 3.2 years of follow-up may have been insufficient to examine the effects of the two drugs on the incidence of CV events, and a longer follow-up period might therefore clarify these effects. From the viewpoint of evidence-based medicine, conducting such a study would provide useful information on the effects of long-term administration of the two drugs, as was carried out in the HOPE and SHEP trials.^{8,9}

The CASE-J extension (CASE-J Ex) was an observational study designed to evaluate the long-term effects of ARB candesartan and CCB amlodipine, incorporating an additional 3-year follow-up of the CASE-J trial.¹⁰ Here, we report the principal results of the CASE-J Ex.

METHODS

Study design

The rationale and design of the CASE-J trial and CASE-J Ex and the primary results of the CASE-J trial have already been published.^{4,5,10} Briefly, the CASE-J trial was a prospective, multicenter, randomized, open-label, active-controlled, 2-arm parallel-group comparison with response-dependent dose titration and blinded assessment of the endpoints. The trial randomized 4728 high-risk Japanese hypertensive patients to candesartan (orally at a dose of 4–12 mg per day)- or amlodipine (orally at a dose of 2.5–10 mg per day)-based regimens. High risk was defined for inclusion as the presence of any one or more of the following: severe hypertension; type 2 diabetes; a history of stroke or transient ischemic attack more than 6 months before screening; left ventricular

hypertrophy, angina pectoris or a history of myocardial infarction more than 6 months before screening; proteinuria or renal dysfunction; or arteriosclerotic peripheral artery obstruction. Exclusion criteria have been reported elsewhere.⁴ Eligible patients were enrolled in the CASE-J trial from September 2001 to December 2002, and follow-up was ended on December 2005. In December 2006, the Steering Committee decided to extend the trial for another 3 years as an observational study named 'CASE-J Ex' to examine the long-term effects of candesartan or amlodipine on the incidence of CV events or new-onset diabetes.

The CASE-J Ex protocol was approved by the Ethics Committee at the Kyoto University Graduate School of Medicine in accordance with the principles of the Helsinki Declaration. All collaborating doctors from the CASE-J trial were also invited to participate in the CASE-J Ex study. From January 2007, patients were re-enrolled after providing written informed consent, with a total of 2232 (1140 in the candesartan group and 1092 in the amlodipine group originally randomized in the CASE-J trial; Figure 1) ultimately opting to continue participating in the study. As shown in Table 1, the background characteristics of the 2232 patients were similar to those of the patients in the CASE-J trial and were well balanced between the two groups except for sex ratio, which was imbalanced in the CASE-J trial, and history of cerebrovascular events. The organizational structure of the CASE-J Ex is the same as that of the CASE-J trial, as previously reported.¹⁰

Patient follow-up and endpoint measurement

Data for medication, physical examination, laboratory test, CV events and adverse events for 2006, 2007 and 2008 were collected at the beginning of 2007, 2008 and 2009, respectively.¹⁰ The follow-up rate of the CASE-J Ex was 97.9%.

The primary endpoint was the first fatal/non-fatal CV event, which included sudden death and cerebrovascular, cardiac, renal and vascular events. The secondary endpoints were all-cause death, CV death and new-onset diabetes. Event evaluation was performed independently by the Event Evaluation Committee, which was blinded to the original treatment allocation, and was adjudicated by the same committee based on the same criteria as was carried out in the CASE-J trial. To detect the occurrence of new-onset diabetes, individual case report forms and adverse-event databases were monitored. As in the CASE-J trial, a case of new-onset diabetes was defined as a patient reported as having developed diabetes on the adverse event form or a patient who had been newly started on anti-diabetic agents in the case report form.

Figure 1 Study profile of the Candesartan Antihypertensive Survival Evaluation in Japan extension (CASE-J Ex).

Table 1 Background characteristics: all patients in the CASE-J trial and CASE-J Ex

Characteristics	CASE-J patients		CASE-J Ex patients		P-value ^a
	Candesartan (n=2354)	Amlodipine (n=2349)	Candesartan (n=1140)	Amlodipine (n=1092)	
Women	1092 (46.4)	1014 (43.2)	560 (49.1)	484 (44.2)	0.021
Age	63.8 ± 10.5	63.9 ± 10.6	63.7 ± 10.3	64.1 ± 10.1	0.387
BMI (kg m ⁻²)	24.6 ± 3.7	24.5 ± 3.6	24.6 ± 3.8	24.4 ± 3.5	0.234
SBP (mm Hg) at enrollment	162.5 ± 14.2	163.2 ± 14.2	162.6 ± 14.1	163.4 ± 13.9	0.204
DBP (mm Hg) at enrollment	91.6 ± 11.0	91.8 ± 11.4	91.8 ± 10.6	91.8 ± 11.3	0.945
Current smokers	489 (20.8)	536 (22.8)	233 (20.4)	234 (21.4)	0.565
Severe hypertension	454 (19.3)	493 (21.0)	226 (19.8)	237 (21.7)	0.274
Type 2 diabetes mellitus ^b	1011 (42.9)	1007 (42.9)	504 (44.2)	472 (43.2)	0.638
History of cerebrovascular events ^c	248 (10.5)	225 (9.6)	127 (11.1)	92 (8.4)	0.031
History of cardiac events ^d	1007 (42.8)	1023 (43.6)	413 (36.2)	419 (38.4)	0.296
History of renal events ^e	572 (24.3)	543 (23.1)	254 (22.3)	243 (22.3)	0.987
Arteriosclerotic peripheral arterial obstruction	29 (1.2)	24 (1.0)	14 (1.2)	13 (1.2)	0.935

Abbreviations: BMI, body mass index; CASE-J Ex, Candesartan Antihypertensive Survival Evaluation in Japan extension; DBP, diastolic blood pressure; SBP, systolic blood pressure.

Data are shown as number of patients (%) or mean ± s.d.

^aThe P-value indicates the results of comparison between the candesartan and amlodipine group in CASE-J Ex patients.

^bType 2 diabetes mellitus was defined as having fasting blood glucose ≥ 126 mg dl⁻¹, casual blood glucose ≥ 200 mg dl⁻¹, HbA1c ≥ 6.5%, 2 h blood glucose on 75 g oral glucose tolerance test (OGTT) ≥ 200 mg dl⁻¹ or current treatment with a hypoglycemic agent at the baseline.

^cHistory of cerebrovascular events includes cerebral hemorrhage, cerebral infarction and transient ischemic attack.

^dHistory of cardiac events includes left ventricular hypertrophy, angina pectoris and myocardial infarction.

^eHistory of renal events includes proteinuria and serum creatinine levels ≥ 1.3 mg dl⁻¹.

The Data and Safety Monitoring Board independently monitored possible adverse events.

Statistical analysis

All analyses of primary and secondary endpoints were performed according to the intention-to-treat principle. The primary analysis was conducted using the database constructed from all data from 4703 patients obtained from the beginning of the CASE-J trial to the end of the CASE-J Ex. (analysis set 1). Sensitivity analysis databases included only data from the 2232 patients who participated in the CASE-J Ex from the beginning of the CASE-J trial to the end of the CASE-J Ex (analysis set 2) and data from the 2161 patients who were event free in the CASE-J trial from the end of the CASE-J trial to the end of the CASE-J Ex (analysis set 3). Our analysis of new-onset diabetes focused only on the 2685 patients who did not have diabetes at baseline. For the safety analysis, the patients who received the allocated drugs at least once during the CASE-J trial or CASE-J Ex period were included.

Survival curves estimated via the Kaplan–Meier method were compared using a log-rank test. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using the Cox regression models. All log-rank tests and Cox regression analyses were stratified by the presence of type 2 diabetes at the start of the CASE-J trial except for comparison of new-onset diabetes. The pre-specified subgroup analysis of new-onset diabetes based on body mass index (BMI) was conducted as in the analysis conducted in the previous report of the CASE-J trial.¹¹ The cut-off points of BMI categories for Japanese were 22 kg m⁻² as normal BMI, 25 kg m⁻² as the upper limit of normal and 27.5 kg m⁻² as the mid-point of the overweight BMI range. Other results were expressed as mean ± s.d. or proportion. Continuous variables were compared using the Student's *t*-test. Frequency analysis was performed using the χ^2 -test. All statistical tests were two-sided with an α level of 0.05 and were performed using SAS version 9.2 (SAS Institute, Cary, NC, USA).

RESULTS

Antihypertensive drugs use

Information on antihypertensive drugs use at the end of the CASE-J trial and every year of the extended follow-up period is shown in Table 2. More than 80% of patients in both groups continued taking their allocated drug throughout the extended follow-up period. The percentage of patients who took additional antihypertensive drugs was

significantly larger in the candesartan group than in the amlodipine group. Approximately 20% of patients took CCBs in the candesartan group and ARBs in the amlodipine group. At the end of the CASE-J Ex, the mean number of antihypertensive drugs used, including the allocated drugs, was 1.63 in the candesartan group and 1.43 in the amlodipine group ($P < 0.001$).

Time course of blood pressure

In the CASE-J trial, systolic/diastolic blood pressure values were 162.5/91.6 mm Hg (s.d.: 14.2/11.0) at baseline and 136.1/77.3 mm Hg (s.d.: 12.9/9.6) after 3 years of treatment in the candesartan group, and those were 163.2/91.8 mm Hg (s.d.: 14.2/11.4) and 134.4/76.7 mm Hg (s.d.: 12.1/9.3) in the amlodipine group.⁵ As shown in Figure 2, respective systolic/diastolic blood pressure (s.d.) values after 4, 5 and 6 years of treatment were 135.1/76.7 (12.8/9.6), 135.4/76.9 (13.0/9.2) and 133.9/75.7 (12.0/9.4) in the candesartan group and 134.5/76.6 (11.7/8.5), 134.3/76.4 (11.7/9.0) and 134.1/75.9 (11.7/8.8) in the amlodipine group. During the extended follow-up period, BP was continuously controlled to a level as low as ~135/75 mm Hg in both groups.

Primary outcome

During the 4.5 ± 1.9 years of follow-up, CV events occurred in a total of 166 patients in the candesartan group (15.5 per 1000 patient years) and 173 in the amlodipine group (16.3 per 1000 patient years), showing no statistically significant difference between the two groups (HR: 0.95; 95% CI: 0.77–1.18; $P = 0.650$; Figure 3). In addition, no statistically significant difference was noted between the two groups in the incidence of sudden death or cerebral, cardiac, renal or vascular events (analysis set 1 of Table 3).

For the sensitivity analysis, we examined the incidence of CV events that occurred from the beginning of the CASE-J trial to the end of the CASE-J Ex in patients who participated in the CASE-J Ex, and which only occurred during the extended follow-up period in patients who were event free in the CASE-J trial. As shown in analysis set 2 of Table 3, CV events occurred in 67 patients in the candesartan group

Table 2 Number of patients who took antihypertensive drugs during the follow-up period

	End of the CASE-J trial		1 year		2 years		3 years	
	CA group (n=1140)	AM group (n=1092)	CA group (n=1140)	AM group (n=1092)	CA group (n=1117)	AM group (n=1072)	CA group (n=1111)	AM group (n=1052)
Allocated drug	1077 (94.5)	1046 (95.8)	1041 (91.3)	953 (87.3)	1013 (90.7)	922 (86.0)	948 (85.3)	871 (82.8)
Concomitant drugs	533 (46.8) ^a	380 (34.8)	584 (51.3) ^a	451 (41.3)	584 (52.3) ^a	464 (43.3)	597 (53.7) ^a	474 (45.1)
Other CCBs	70 (6.1) ^a	13 (1.2)	200 (17.5) ^a	56 (5.1)	235 (21.0) ^a	62 (5.8)	249 (22.4) ^a	73 (6.9)
Other ARBs	17 (1.5)	24 (2.2)	40 (3.5) ^a	136 (12.5)	44 (3.9) ^a	156 (14.6)	55 (5.0) ^a	191 (18.2)
ACE-Is	8 (0.7)	6 (0.6)	14 (1.2)	17 (1.6)	19 (1.7)	22 (2.1)	12 (1.1)	17 (1.6)
Diuretics	227 (19.9) ^a	122 (11.2)	215 (18.9) ^a	120 (11.0)	206 (18.4) ^a	127 (11.9)	209 (18.8) ^a	135 (12.8)
β-blockers	212 (18.6) ^a	162 (14.8)	219 (19.2) ^a	156 (14.3)	207 (18.5) ^a	163 (15.2)	198 (17.8) ^a	144 (13.7)
α-blockers	231 (20.3) ^a	140 (12.8)	171 (15.0) ^a	121 (11.1)	168 (15.0) ^a	112 (10.5)	145 (13.1) ^a	104 (9.9)
αβ-blockers	70 (6.1) ^a	40 (3.7)	37 (3.3) ^a	20 (1.8)	36 (3.2) ^a	20 (1.9)	34 (3.1)	25 (2.4)
Others	36 (3.2) ^a	8 (0.7)	24 (2.1) ^a	11 (1.0)	25 (2.2) ^a	12 (1.1)	18 (1.6)	13 (1.2)

Abbreviations: ACE-Is, angiotensin converting enzyme inhibitors; AM, amlodipine; ARBs, angiotensin II receptor blockers; CA, candesartan; CASE-J Ex, Candesartan Antihypertensive Survival Evaluation in Japan extension; CCBs, calcium channel blockers.

Data are shown as number of patients (%).

^a $P < 0.05$ (χ^2 -tests) vs. AM group.

Figure 2 Time-course of blood pressure (BP) during the entire follow-up period. Data are shown as mean $\pm$ s.d. * $P < 0.05$ vs. amlodipine.

(9.4 per 1000 patient-years) and 74 in the amlodipine group (10.9 per 1000 patient-years) during 6.2 ± 1.0 years of follow-up. No significant difference was noted between the two groups in the incidence of primary CV events and each primary endpoint category. Similar results were also observed in analysis set 3.

Secondary outcomes

Cumulative incidences of secondary endpoints are shown in Figures 4a–c. All-cause and CV death occurred in 114 (10.3 per 1000 patient years) and 29 patients (2.6 per 1000 patient years), respectively, in the candesartan group, and 138 (12.7 per 1000 patient years) and 41 patients (3.8 per 1000 patient years), respectively, in the amlodipine group. No statistically significant difference was noted in the incidence of these endpoints between the two groups (HR: 0.82; 95% CI: 0.64–1.04; $P=0.105$ and HR: 0.70; 95% CI: 0.44–1.13; $P=0.144$, respectively; Figures 4a and b).

New-onset diabetes, incidence of which was significantly different between the two groups in the CASE-J trial, as previously reported,⁵ occurred in 58 patients (9.5/1000 person years) in the candesartan group and 80 (13.3/1000 person years) in the amlodipine group.

Figure 3 Kaplan-Meier curves for the primary composite endpoint throughout the follow-up period.

A 29% reduction in relative risk was observed for the incidence of new-onset diabetes in the candesartan group (HR: 0.71; 95% CI: 0.51–1.00; $P=0.0495$, Figure 4c). In addition, pre-specified subgroup analysis stratified by BMI showed that candesartan significantly reduced the risk of new-onset diabetes in the subgroup with $\text{BMI} \geq 27.5 \text{ kg m}^{-2}$ compared with amlodipine ($P=0.049$, Figure 5). No significant difference was observed in the other subgroups (interaction $P=0.485$).

Safety parameters

During the follow-up period of the CASE-J trial and CASE-J Ex, serious adverse events were reported by the investigators in 211 patients (9.0%) taking candesartan and 233 (10.0%) taking amlodipine, indicating no significant difference in the incidence between the two groups ($P=0.260$). The top-five most-frequent serious adverse events were malignant neoplastic disease (candesartan: 2.9%; amlodipine: 3.6%; $P=0.155$), pneumonia (candesartan: 0.8%; amlodipine: 1.0%; $P=0.348$), aggravation of diabetes (candesartan: 0.6%; amlodipine: 0.8%; $P=0.284$), chest pain (candesartan: 0.5%; amlodipine: 0.6%; $P=0.543$) and bone fracture (candesartan: 0.5%; amlodipine: 0.5%; $P=0.830$).

Table 3 CV events during the extended follow-up period

Outcome	Analysis set 1			Analysis set 2			Analysis set 3		
	Candesartan (n=2354)	Amlodipine (n=2349)	HR (95% CI)	Candesartan (n=1140)	Amlodipine (n=1092)	HR (95% CI)	Candesartan (n=1104)	Amlodipine (n=1057)	HR (95% CI)
CV events	166 (7.1)	173 (7.4)	0.95 (0.77–1.18)	67 (5.9)	74 (6.8)	0.86 (0.62–1.20)	31 (2.8)	38 (3.6)	0.78 (0.48–1.25)
Sudden death	12 (0.5)	21 (0.9)	0.57 (0.28–1.15)	1 (0.1)	6 (0.5)	0.16 (0.19–1.33)	1 (0.1)	3 (0.3)	0.32 (0.03–3.07)
Cerebrovascular events	73 (3.1)	62 (2.6)	1.18 (0.84–1.65)	31 (2.7)	28 (2.6)	1.07 (0.64–1.78)	11 (1.0)	12 (1.1)	0.88 (0.39–1.99)
Stroke	71 (3.0)	58 (2.5)	1.22 (0.87–1.73)	30 (2.6)	25 (2.3)	1.16 (0.68–1.97)	10 (0.9)	11 (1.0)	0.86 (0.37–2.02)
TIA	3 (0.1)	5 (0.2)	0.59 (0.14–2.48)	1 (0.1)	4 (0.4)	0.24 (0.03–2.14)	1 (0.1)	1 (0.1)	0.96 (0.06–15.30)
Cardiac events	54 (2.3)	66 (2.8)	0.81 (0.56–1.16)	24 (2.1)	34 (3.1)	0.68 (0.40–1.15)	11 (1.0)	15 (1.4)	0.70 (0.32–1.52)
Heart failure	25 (1.1)	22 (0.9)	1.13 (0.64–2.00)	9 (0.8)	10 (0.9)	0.87 (0.35–2.14)	5 (0.5)	4 (0.4)	1.18 (0.32–4.40)
Angina pectoris	12 (0.5)	22 (0.9)	0.53 (0.26–1.08)	6 (0.5)	12 (1.1)	0.48 (0.18–1.27)	4 (0.4)	7 (0.7)	0.54 (0.16–1.85)
AMI	20 (0.8)	25 (1.1)	0.80 (0.44–1.43)	10 (0.9)	14 (1.3)	0.75 (0.33–1.69)	2 (0.2)	6 (0.6)	0.31 (0.06–1.54)
Renal events	28 (1.2)	33 (1.4)	0.83 (0.50–1.38)	13 (1.1)	11 (1.0)	1.13 (0.51–2.53)	6 (0.5)	5 (0.5)	1.14 (0.35–3.73)
Creatinine abnormality	28 (1.2)	33 (1.4)	0.89 (0.53–1.48)	13 (1.1)	10 (0.9)	1.25 (0.55–2.84)	6 (0.5)	4 (0.4)	1.42 (0.40–5.03)
ESRD	6 (0.3)	14 (0.6)	0.43 (0.16–1.11)	4 (0.4)	4 (0.4)	1.00 (0.25–4.00)	0 (0.0)	3 (0.3)	—
Vascular events	14 (0.6)	12 (0.5)	1.15 (0.53–2.49)	6 (0.5)	7 (0.6)	0.83 (0.28–2.47)	2 (0.2)	5 (0.5)	0.38 (0.07–1.97)

Abbreviations: AMI, acute myocardial infarction; CI, confidence interval; CV, cardiovascular; ESRD, endstage renal disease; HR, hazard ratio; TIA, transient ischemic attack.

Data are shown as number of patients (%).

Analysis set 1 consists of the data for all patients from the beginning of the CASE-J trial to the end of the CASE-J Ex; analysis set 2, only patients who participated in the CASE-J Ex from the beginning of the CASE-J trial to the end of the CASE-J Ex; analysis set 3, only patients who were event-free in the CASE-J trial during the extended follow-up period.

DISCUSSION

In the CASE-J Ex, BP was continuously controlled to a level as low as ~135/75 mm Hg in both the ARB candesartan and CCB amlodipine groups. Just as in the CASE-J trial, no statistically significant difference was noted in the incidence of primary CV events, all-cause mortality or CV death between the two groups, and the incidence increased in a closely similar manner over time. Of note, however, was the fact that candesartan significantly reduced the incidence of new-onset diabetes compared with amlodipine.

Achieved BP level after 6 years of treatment was 133.9/75.7 mm Hg in the candesartan group and 134.1/75.9 mm Hg in the amlodipine group. The mean number of antihypertensive drugs used, including allocated drugs, was continuously less than 2 in both groups throughout the extended follow-up period, indicating that both drugs have a strong BP-lowering effect in Japanese high-risk hypertensive patients¹² and that this effect is not attenuated even with long-term administration. Achieved BP level in the CASE-J Ex was lower than values achieved in other clinical trials directly comparing the effect of ARB with that of amlodipine on the incidence of CV morbidity and mortality in hypertensive patients.^{3,13,14} No significant difference was noted between the two groups in the incidence of the primary CV events, all-cause death, or CV death under strict BP control in the CASE-J Ex.

This study reinforces the notion that adequate BP control is the most important therapeutic approach for reducing CV risk, irrespective of drug class, in antihypertensive treatment.^{15,16} The primary analysis was conducted using the database constructed from all data from 4703 patients obtained from the beginning of the CASE-J trial to the end of the CASE-J Ex. Of the 4149 patients followed after the CASE-J trial, 2232 agreed to participate in the CASE-J Ex, meaning that data from 1917 patients were censored at the end of the CASE-J trial (Figure 1). To address this issue, we examined background characteristics and noted that the characteristics of the 2232 patients in the CASE-J Ex were similar to those in the CASE-J trial (Table 1).

Further, we performed sensitivity analysis and obtained results similar to those of the primary analysis (Table 3). We therefore assume that censoring data from those 1917 patients at the end of the CASE-J trial did not result in any severe selection bias and that the primary analysis results were acceptable.

Hypertension and diabetes frequently cluster together, substantially increasing the risk of adverse events.^{17,18} The CASE-J Ex confirmed that candesartan was superior to amlodipine in terms of preventing new-onset diabetes, as reported in the CASE-J trial. Interestingly, candesartan inhibited new-onset diabetes more effectively than amlodipine, particularly in obese patients (Figure 5). As angiotensinogen is produced by adipose tissue and angiotensin II increases insulin resistance,^{19,20} these findings suggest that activation of the renin-angiotensin system in the adipose tissues of obese patients may be involved in development of diabetes.^{21,22}

Some observational studies have shown that new-onset diabetes negatively affects the incidence of CV morbidity and mortality to the same degree as known diabetes.^{23,24} Antihypertensive drugs with favorable effects on glucose metabolism are therefore expected to be of more benefit than those without such effects, as prevention against new-onset diabetes during antihypertensive treatment has been suggested to be associated with reduced risk of CV events. However, despite these expected benefits, the prognostic significance of prevention against new-onset diabetes during antihypertensive treatment has not yet been elucidated.

In the CASE-J Ex, we observed no significant difference in the incidence of CV events between the candesartan and amlodipine groups, although significantly reduced incidence of new-onset diabetes was noted in patients who received candesartan vs. amlodipine. Of 2685, only 138 non-diabetic patients (5.1%) developed diabetes during the entire 4.5 ± 1.9 years in the CASE-J Ex. This low incidence of new-onset diabetes may account for our lack of observation of any significant difference in the incidence of CV events between the two drug groups. As shown in observational studies reporting the impact

Figure 4 (a) Kaplan-Meier curves for all-cause death during the entire follow-up period. (b) Kaplan-Meier curves for cardiovascular death throughout the follow-up period. (c) Kaplan-Meier curves for new-onset diabetes throughout the follow-up period.

of new-onset diabetes on CV events, at least a decade of follow-up was needed to note the prognostic significance of new-onset diabetes.^{23,24} Given these findings, the follow-up period may not have been sufficiently long to observe any impact of reduced incidence of new-onset diabetes on the incidence of CV events.

A 14-year follow-up in the SHEP study revealed that in-trial development of diabetes among subjects on placebo (but not those

Figure 5 Subgroup analysis for new-onset diabetes stratified according to body mass index (BMI).

receiving diuretic therapy) was significantly associated with increased CV adverse outcome and total mortality rate.⁹ These findings can be interpreted as indicating that the risk of CV events is substantially reduced by lowering BP in hypertensive patients with new-onset diabetes. As BP was strictly controlled in the CASE-J Ex, assessing the impact of reduced incidence of new-onset diabetes on the incidence of the primary CV events may be difficult. Further studies are necessary to elucidate this issue.

Several limitations to the CASE-J Ex warrant mention. First, as the CASE-J Ex was designed as an observational study, rates of participants taking the originally allocated drugs in the CASE-J Ex were low compared with those in the CASE-J trial. Nevertheless, more than 80% of patients in both groups continued taking their allocated drug throughout the extended follow-up period, a rate which was comparable with values in other clinical trials. Second, the study population consisted only of Japanese patients with high-risk hypertension, and therefore the generalizability of our findings to other ethnic groups or general populations may be limited.

In conclusion, our findings in the CASE-J Ex showed no significant difference between the ARB candesartan and CCB amlodipine groups in the incidence of primary CV events, all-cause mortality and CV death in high-risk hypertensive patients. The superiority of candesartan over amlodipine in reducing new-onset diabetes was sustained in the 3-year-long CASE-J Ex, thereby corroborating the results of the CASE-J trial.

CONFLICT OF INTEREST

Ogihara T, Ueshima K, Nakao K, Matsuoka H and Saruta T received honoraria for lectures from Takeda Pharmaceutical and Pfizer Japan. The other authors have no conflict of interest.

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