Effects of Candesartan Compared With Amlodipine in Hypertensive Patients With High Cardiovascular Risks

Candesartan Antihypertensive Survival Evaluation in Japan Trial

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Abstract—The Candesartan Antihypertensive Survival Evaluation in Japan Trial was designed to compare the long-term effects of the angiotensin II receptor blocker candesartan and the calcium channel blocker amlodipine on the incidence of cardiovascular events, represented as a composite of sudden death and cerebrovascular, cardiac, renal, and vascular events in high-risk Japanese hypertensive patients. We conducted a prospective, randomized, open-label study with blinded assessment of the end point in 4728 Japanese hypertensive patients (mean age: 63.8 years; mean body mass index: 24.6 kg/m²). Patients were followed for an average of 3.2 years. Blood pressure was well controlled with both treatment-based regimens (systolic blood pressure/diastolic blood pressure: 136.1/77.3 mm Hg for candesartan-based regimens and 134.4/76.7 mm Hg for amlodipine-based regimens after 3 years). Primary cardiovascular events occurred in 134 patients with both the candesartan- and amlodipine-based regimens. The 2 treatment-based regimens produced no significant differences in cardiovascular morbidity or mortality in the high-risk Japanese hypertensive patients (hazard ratio: 1.01; 95% CI: 0.79 to 1.28; \( P = 0.969 \)). In each primary end point category, there was no significant difference between the 2 treatment-based regimens. New-onset diabetes occurred in fewer patients taking candesartan (8.7/1000 person-years) than in those taking amlodipine (13.6/1000 person-years), which resulted in a 36% relative risk reduction (hazard ratio: 0.64; 95% CI: 0.43 to 0.97; \( P = 0.033 \)). We disclosed that candesartan-based and amlodipine-based regimens produced no statistical differences in terms of the primary cardiovascular end point, whereas candesartan prevented new-onset diabetes more effectively than amlodipine. (Hypertension. 2008;51:1-6.)

Key Words: antihypertensive therapy ■ hypertension ■ cardiovascular diseases ■ angiotensin II ■ calcium channel blockers ■ clinical trials

Angiotensin II receptor blockers (ARBs) and calcium channel blockers (CCBs) have proven to be important advances for the treatment of hypertension. These agents have been shown to be as effective or sometimes better than other antihypertensive drugs in terms of cardiovascular morbidity and mortality and associated adverse events. Clinical trials have shown significant effects from treatment with CCBs or angiotensin-converting enzyme inhibitors for preventing cardiovascular morbidity and mortality in high-risk populations. In the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) Trial, the ARB valsartan was compared with the CCB amlodipine in Europe and the United States. The VALUE Trial concluded that the main outcome (cardiac disease) did not differ between the groups, whereas unequal reductions in blood pressure may have accounted for the observed differences between the groups in the cause-specific outcomes. Thus, it is still unclear whether there are differences in the efficacies of ARBs and CCBs.

The event rates of cardiovascular disease in Japan differ from those in Europe and the United States. Mortality from ischemic heart disease in Japan is one third of that in the United States, and mortality from cerebrovascular disease in Japan is ≈1.5 times higher than that in the United States. These differences may be partly explained by differences in the lifestyles of Japanese and Western populations, which are reflected in body mass index (BMI) (mean BMI: 23 to 25 kg/m² and 28 to 30 kg/m², respectively). In this context, the Candesartan Antihypertensive Survival Evaluation in Japan (CASE-J) Trial was designed to evaluate the efficacies of the ARB candesartan cilexetil and the CCB amlodipine besylate for reducing the incidences of cardiovascular morbidity and mortality (primary and secondary end points), as

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This trial has been registered at www.clinicaltrials.gov (identifier NCT00125463).

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well as new-onset diabetes (prespecified end point) in high-risk Japanese hypertensive patients.

Methods

Study Design

The CASE-J Trial was a prospective, multicenter, randomized, open-label, active-controlled, 2-arm parallel-group comparison in Japan with a response-dependent dose titration and blinded assessment of the end points in high-risk hypertensive patients. The random assignment, data collection, and analyses were performed by the EBM Research Center of Kyoto University. The rationale and complete design of CASE-J Trial have been published elsewhere.12 In addition, the end point of new-onset diabetes was prespecified at the 28th Annual Meeting of the Japanese Society of Hypertension on September 17, 2005.

The Ethics Committee at the Kyoto University Graduate School of Medicine approved the CASE-J Trial protocol according to the principles of the Helsinki Declaration. After obtaining informed consent, the patients were randomly assigned to the treatment groups. Enrolled patients were given 1 of 2 medications: candesartan cilexetil or amlodipine besylate. The former was administered orally at a dose of 4 to 8 mg/day. When the patient’s blood pressure (BP) did not reach the targets for controlled BP, the dose was increased to 12 mg/day. The latter was administered orally at a dose of 2.5 to 5.0 mg/day and was increased to 10.0 mg/day when necessary. Once a patient was given the assigned medication, the use of other ARBs, CCBs, and all of the angiotensin-converting enzyme inhibitors was prohibited. Patients already being treated with diuretics, α-blockers, β-blockers, or α- and β-blockers before enrollment were allowed to continue taking these medications. According to the guideline proposed by Japanese Society of Hypertension, ≥2 consecutive BP measurements were taken from each patient in a sitting position at a clinic.13 The targets for the control of BP were as follows: <60 years old, systolic BP (SBP)/diastolic BP (DBP) <130/85 mm Hg; 60 to 69 years old, SBP/DBP <140/90 mm Hg; 70 to 79 years old, SBP/DBP <150/90 mm Hg; and ≥80 years old, SBP/DBP <160/90 mm Hg.13

Population and Treatment

Patients with high-risk hypertension (SBP ≥140 mm Hg or DBP ≥90 mm Hg in patients <70 years old or SBP ≥160 mm Hg or DBP ≥90 mm Hg in patients ≥70 years old) were enrolled in the study. As reported previously,12 high-risk patients were defined by the presence of any of the following factors: (1) severe hypertension (SBP ≥180 mm Hg or DBP ≥110 mm Hg); (2) type 2 diabetes mellitus; (3) a history of stroke or transient ischemic attack ≥6 months before the screening; (4) left ventricular hypertrophy, which was defined by the thickness of the left ventricular posterior wall or the interventricular septum wall ≥12 mm on echocardiography or SV1+RV5 ≥35 mm on electrocardiography, angina pectoris, or a history of myocardial infarction ≥6 months before the screening; (5) proteinuria or a serum creatinine concentration ≥1.3 mg/dL; or (6) arteriosclerotic peripheral artery obstruction. The exclusion criteria have also been reported elsewhere.12 The event evaluation was performed independently by the event evaluation committee, which was blinded to the assigned treatment groups and adjudicated according to the protocol criteria. Adverse events and prespecified safety parameters were monitored by the data and safety monitoring board. The CASE-J Trial was closed on January 1, 2006.

Outcome Measures

The primary end point, which was the first fatal/nonfatal cardiovascular event, the secondary end points, and the prespecified end point are listed in Table 1. For the analysis of new-onset diabetes, we excluded all of the patients with type 2 diabetes mellitus at baseline from the analysis. Individual case report forms and adverse-event databases were monitored for any information reporting that the patients began to use antidiabetic drugs and/or for newly apparent cases of type 2 diabetes.

Table 1. Outcome Measures

<table>
<thead>
<tr>
<th>Primary end points (composite of the following events)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sudden death: unexpected death that happened within 24 hours without external causes</td>
</tr>
<tr>
<td>Cerebrovascular events: stroke or transient ischemic attack</td>
</tr>
<tr>
<td>Cardiac events: heart failure, angina pectoris, or acute myocardial infarction</td>
</tr>
<tr>
<td>Renal events: serum creatinine concentration ≥4.0 mg/dL, doubling of the serum creatinine concentration (however, creatinine ≥2.0 mg/dL is not regarded as an event), or end-stage renal disease</td>
</tr>
<tr>
<td>Vascular events: dissecting aortic aneurysm or arteriosclerotic occlusion of a peripheral artery</td>
</tr>
</tbody>
</table>

Secondary and prespecified end points

All-cause deaths

New-onset diabetes

Discontinuance of treatment because of adverse events

Statistical Methods

Based on previous results from studies of CCBs14,15 the CASE-J Trial was designed to detect a 40% relative risk reduction in the cardiovascular incidence rate in patients taking candesartan-based regimens with a 2-sided α level of 0.05 and 90% power.16 Assuming a 20% loss to follow-up, we required a minimum of 3,200 patients in total, and each patient was enrolled during a 1.5-year period and was followed for ≥3 consecutive years. An interim analysis was conducted 1 year after the completion of enrollment (December 2003). An O’Brien-Fleming spending function was used to adjust the α level.17

The incidence proportions were calculated using the Kaplan–Meier method and were compared with a log-rank test stratified by diabetic status at baseline. The hazard ratio (HR) and 95% CI were also estimated using Cox regression analysis. The P value and CI were adjusted for sequential testing of the results of the primary end point. These analyses were performed based on the intention-to-treat principle. If there were inequalities in BP levels during the follow-up, the imbalance in the BPs was adjusted using Cox regression analysis with SBP or DBP as the time-dependent covariate.

Exploratory subgroup analyses were prespecified to assess the primary, secondary, and prespecified results corrected for the baseline characteristics (diabetes; sex; age; SBP and DBP; systolic hypertension; BMI; CCB; angiotensin-converting enzyme inhibitor or ARB use before starting the CASE-J Trial; creatinine clearance; and history of cerebrovascular events, cardiac events, or renal events). Cox regression analysis was used to identify the treatment effect in these subgroups. Cox regression analysis was also used to identify the clinically relevant interactions between the treatment and these subgroups.

The safety population was grouped according to the treatment actually received. Differences in the frequency of adverse events were analyzed with the χ2 test. All of the statistical tests were 2-sided with an α level of 0.05 and were performed using SAS version 9.1 (SAS Institute) and East 4.1 (Cytel).

Results

Study Profile and Baseline Characteristics

Between September 2001 and December 2002, 4,728 patients with a mean age of 63.8 years and a mean BMI of 24.6 kg/m² were assigned to the 2 treatment-based regimens. As shown in Figure 1, 4,703 randomly assigned patients were included in the analysis, and 136 patients (2.9%) were lost to follow-up. Table 2 summarizes the characteristics of the patients at baseline. There was a statistical difference between the sex ratios for the 2 treatment-based regimens (46.4% and 43.2% of the subjects were female for the candesartan-based regimens and
amlodipine-based regimens, respectively), whereas there were no differences in terms of the other clinical parameters.

**Duration of Follow-Up and Adherence to the Treatment**
For both treatment-based regimens, the mean follow-up periods were 3.2 years, and the median values were 3.4 years. The fifth to 95th percentile interval of the follow-up periods was 0.9 to 4.1 years for the candesartan-based regimens and 1.0 to 4.2 years for the amlodipine-based regimens. The study accumulated 15 175 person-years of follow-up (7563 person-years and 7612 person-years for the candesartan- and amlodipine-based regimens, respectively). The percentages of patients who received 80% of the allocated drugs during the follow-up were 96.5% and 96.0% in the candesartan- and amlodipine-based regimens, respectively. The percentage of the candesartan-treated patients who received other antihypertensive drugs was larger than that of the amlodipine-treated patients (54.5% and 42.7%, respectively; \( P < 0.001 \); Table 3). After 3 years, the mean number of antihypertensive drugs used, including the allocated drugs, was 1.54 for patients treated with candesartan-based regimens and 1.37 for those treated with amlodipine-based regimens.

**Table 2. Baseline Characteristics of Trial Participants**

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Candesartan (n=2354)</th>
<th>Amlodipine (n=2349)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td>1092 (46.4)</td>
<td>1014 (43.2)</td>
</tr>
<tr>
<td>Age</td>
<td>63.8 ± 10.5</td>
<td>63.9 ± 10.6</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>24.6 ± 3.7</td>
<td>24.5 ± 3.6</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>162.5 ± 14.2</td>
<td>163.2 ± 14.2</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>91.6 ± 11.0</td>
<td>91.8 ± 11.4</td>
</tr>
<tr>
<td>Current smokers</td>
<td>489 (20.8)</td>
<td>536 (22.8)</td>
</tr>
<tr>
<td>Severe hypertension: SBP ≥180 mm Hg or DBP ≥110 mm Hg</td>
<td>454 (19.3)</td>
<td>493 (21.0)</td>
</tr>
<tr>
<td>Type 2 diabetes mellitus*</td>
<td>1011 (42.9)</td>
<td>1007 (42.9)</td>
</tr>
<tr>
<td>History of cerebrovascular events‡</td>
<td>248 (10.5)</td>
<td>225 (9.6)</td>
</tr>
<tr>
<td>History of cardiac events§</td>
<td>1007 (42.8)</td>
<td>1023 (43.6)</td>
</tr>
<tr>
<td>History of renal events$</td>
<td>572 (24.3)</td>
<td>543 (23.1)</td>
</tr>
<tr>
<td>Arteriosclerotic peripheral arterial obstruction</td>
<td>29 (1.2)</td>
<td>24 (1.0)</td>
</tr>
</tbody>
</table>

Data are shown as the No. of patients (%) or the mean ± SD.

*Type 2 diabetes mellitus was defined by fasting blood glucose levels ≥126 mg/dL, casual blood glucose levels ≥200 mg/dL, HbA1c ≥6.5%, 2-hour blood glucose levels in the 75-g oral glucose tolerance test ≥200 mg/dL, or current treatment with a hypoglycemic agent at baseline.

†History of cerebrovascular events includes cerebral hemorrhage, cerebral infarction, and transient ischemic attack.

‡History of cardiac events includes left ventricular hypertrophy, angina pectoris, and myocardial infarction.

§History of renal events includes proteinuria and serum creatinine levels ≥1.3 mg/dL.

The fifth to 95th percentile interval of the follow-up periods was 0.9 to 4.1 years for the candesartan-based regimens and 1.0 to 4.2 years for the amlodipine-based regimens. The study accumulated 15 175 person-years of follow-up (7563 person-years and 7612 person-years for the candesartan- and amlodipine-based regimens, respectively). The percentages of patients who received >80% of the allocated drugs during the follow-up were 96.5% and 96.0% in the candesartan- and amlodipine-based regimens, respectively. The percentage of the candesartan-treated patients who received other antihypertensive drugs was larger than that of the amlodipine-treated patients (54.5% and 42.7%, respectively; \( P < 0.001 \); Table 3). After 3 years, the mean number of antihypertensive drugs used, including the allocated drugs, was 1.54 for patients treated with candesartan-based regimens and 1.37 for those treated with amlodipine-based regimens.

**Table 3. No. of Patients Using Additional Drugs Throughout the Follow-Up Period**

<table>
<thead>
<tr>
<th>Additional Drugs</th>
<th>Candesartan (n=2354), n (%)</th>
<th>Amlodipine (n=2349), n (%)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antihypertensive drugs</td>
<td>1262 (54.5)</td>
<td>1003 (42.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diuretics</td>
<td>580 (24.6)</td>
<td>323 (13.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>610 (25.9)</td>
<td>391 (16.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>α-, and β-Blockers</td>
<td>524 (22.3)</td>
<td>397 (16.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Others</td>
<td>100 (4.2)</td>
<td>47 (2.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Antianginal</td>
<td>1050 (44.6)</td>
<td>1032 (43.9)</td>
<td>0.644</td>
</tr>
<tr>
<td>Antidiabetics (including insulin)</td>
<td>874 (37.1)</td>
<td>900 (38.3)</td>
<td>0.402</td>
</tr>
<tr>
<td>Antithrombotics</td>
<td>652 (27.7)</td>
<td>620 (26.4)</td>
<td>0.314</td>
</tr>
<tr>
<td>Antiarrhythmic</td>
<td>264 (11.2)</td>
<td>280 (11.9)</td>
<td>0.450</td>
</tr>
</tbody>
</table>

*P values were obtained using \( \chi ^2 \) tests.
Effects on BP

The SBP and DBP were well controlled in the CASE-J Trial. SBP/DBP was 162.5/91.6 mm Hg (SD: 14.2/11.0) at baseline and 136.1/77.3 mm Hg (SD: 12.9/9.6) after 3 years for candesartan-based regimens. SBP/DBP was 163.2/91.8 mm Hg (SD: 14.2/11.4) at baseline and 134.4/76.7 mm Hg (SD: 12.1/9.3) after 3 years for amlodipine-based regimens (Figure 2). Both the SBP and DBP were significantly lower in amlodipine-treated patients compared with candesartan-treated patients; after 3 years, the SBP and DBP were 1.7 mm Hg ($P<0.001$) and 0.6 mm Hg ($P=0.028$) lower in the amlodipine-treated patients, respectively.

Primary Outcome

Primary cardiovascular events occurred in 134 patients with both the candesartan- and amlodipine-based regimens. The 2 treatment-based regimens produced no significant difference in cardiovascular morbidity or mortality in the high-risk hypertensive patients (HR: 1.01; 95% CI: 0.79 to 1.28; $P=0.969$; Figure 3). In each primary end point category, there was no significant difference between the 2 treatment-based regimens (Figure 4). The HR for primary composite end point after an adjustment for the baseline characteristics (sex, age, CCB use, angiotensin-converting enzyme inhibitor or ARB use, creatinine clearance rate, and history of cerebrovascular, cardiac, and renal events) was 1.00 (95% CI: 0.78 to 1.27), and HRs after an adjustment using Cox regression analysis with SBP and DBP as the time-dependent covariates were 0.98 and 1.02 (95% CI: 0.77 to 1.25 and 0.80 to 1.30), respectively. The primary result did not change after these adjustments. In addition, we also evaluated the time-specific interval risk ratios of cardiovascular events every 6 months. There were no statistically significant time-specific interval risk ratios between the 2 treatment-based regimens.

Secondary and Prespecified Outcomes

For the secondary end points, 73 candesartan-treated patients (9.4/1000 person-years) and 86 amlodipine-treated patients (11.1/1000 person-years) died during the follow-up period. Neither the all-cause death rates nor the death rates because of cardiovascular events differed significantly between the 2 regimens. At baseline, 1343 candesartan-treated patients (mean age:
Candesartan Amlopidine Hazard Ratio (95% CI) P Value

Primary composite endpoint 134 (5.7) 134 (5.7) 1.01 (0.79-1.28) 0.969
Sudden death 11 (0.5) 15 (0.6) 0.73 (0.34-1.60) 0.434
Cerebrovascular events 61 (2.6) 50 (2.1) 1.23 (0.85-1.78) 0.282
- Stroke 60 (2.5) 47 (2.0) 1.28 (0.88-1.88) 0.198
- TIA 2 (0.1) 4 (0.2) 0.50 (0.09-2.73) <0.001
Cardiac events 43 (1.8) 47 (2.0) 0.92 (0.61-1.39) 0.680
- Heart failure 20 (0.8) 16 (0.7) 1.25 (0.65-2.42) 0.498
- Angina pectoris 8 (0.3) 14 (0.6) 0.57 (0.24-1.36) 0.201
- AMI 17 (0.7) 18 (0.8) 0.95 (0.49-1.84) 0.870
Renal events 19 (0.8) 27 (1.1) 0.70 (0.39-1.26) 0.320
- Creatinine abnormality 19 (0.8) 26 (1.1) 0.73 (0.40-1.31) 0.287
- ESRD 4 (0.2) 10 (0.4) 0.40 (0.13-1.29) 0.112
Peripheral vascular events 11 (0.5) 7 (0.3) 1.57 (0.61-4.05) 0.348

Discussion
The CASE-J Trial demonstrates no statistically significant difference between candesartan-based and amlopidine-based regimens in terms of the primary composite end point in high-risk Japanese hypertensive patients, although the BP level achieved with candesartan treatment was not as low as that achieved with amlopidine; the differences in SBP and DBP were 1.7 and 0.6 mm Hg after 3 years, respectively. Because BP is a crucial prognostic factor for cardiovascular events, the influence of BP differences on the primary composite end point is not negligible. When we adjusted for the imbalance in SBP or DBP levels using Cox regression analysis, we obtained similar results. Accordingly, it is likely that the failure to achieve similar levels of BP control did not influence the outcomes of the CASE-J Trial. Furthermore, it is notable that the BP levels achieved in the CASE-J Trial (<140/80 mm Hg) were lower than those reported in previous antihypertensive trials.3,8,18 These findings suggest that strict BP control is important for the treatment of high-risk hypertensive patients.

The CASE-J Trial also shows that the incidence of new-onset diabetes was significantly lower in patients treated with candesartan-based regimens compared with patients treated with amlopidine-based regimens. The relative risk reduction for new-onset diabetes was 36% in the CASE-J Trial, although the incidence of new-onset diabetes in the amlopidine-treated patients in the CASE-J Trial (13.6/1000 person-years) was approximately one third of that in VALUE Trial (41.1/1000 person-years).8 The mean BMI for patients without diabetes in the CASE-J Trial was 24.1 kg/m², whereas that in VALUE Trial was 28.0 kg/m².19 In addition, the relative risk reduction of new-onset diabetes in the CASE-J Trial was 48% in the subgroup with BMI ≥25 kg/m², in which the mean BMI (27.7 kg/m²) was similar to that in the VALUE Trial. The more favorable effect profile of candesartan in the CASE-J Trial compared with that of valsartan in the VALUE Trial may be explained by the smaller patient population taking additional diuretics in the CASE-J Trial, as well as the potentially beneficial effects of candesartan. Because the number of patients with diabetes and metabolic syndrome is increasing in Eastern coun-
tries as well as in Western countries, the beneficial effect of the ARB candesartan for the prevention of new-onset diabetes should prove to be valuable.

To evaluate the efficacy of drugs that are widely used all over the world, clinical trials should be designed to examine patient outcomes for various races in many countries. In the VALUE Trial, the largest percentage of the randomly assigned patients was from the United States and European countries, whereas only 3.5% of the patients in the VALUE Trial were from Asian countries.8,20 The event rates of cardiovascular disease and the severity of obesity in Asian countries such as Japan (mean BMI in the CASE-J Trial: 24.6 kg/m²) differ from those in Western countries (mean BMI in the VALUE Trial: 28.6 kg/m²).20 As far as we know, there is no published evidence about the efficacy of ARBs in mildly obese populations. The outcome of the CASE-J Trial provides useful information about Asian populations that have similar genetic predispositions and lifestyles as the Japanese population.

**Perspectives**

The CASE-J Trial indicates that, with strict BP control, there is no significant difference between candesartan-based and amloidipine-based regimens in terms of the primary cardiovascular end point in high-risk hypertensive patients. Nevertheless, the ARB candesartan is more effective than the CCB amloidpine for the prevention of new-onset diabetes.

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**References**


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