Effects of Cardiac Complications on Cardiovascular Events in Japanese High-Risk Hypertensive Patients

Subanalysis of the CASE-J Trial

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Background: The Candesartan Antihypertensive Survival Evaluation in Japan (CASE-J) trial compared the effects of candesartan and amlodipine on cardiovascular events in Japanese high-risk hypertensive patients. The present study aimed to clarify the effect of cardiac complications on cardiovascular events in patients enrolled in CASE-J.

Methods and Results: Cardiac complications were defined as left ventricular hypertrophy (LVH) and ischemic heart disease (IHD). The primary endpoint was a composite of sudden death, cerebrovascular, cardiac, renal and vascular events. The study group was divided into 2,030 and 2,673 patients with and without cardiac complications. During 3.2 follow-up years, cardiovascular events occurred for a rate of 13.6 per 1000 patient-years in patients without cardiac complications, and 23.1 per 1000 patient-years in patients with cardiac complications (adjusted hazard ratio (HR): 2.22; P<0.001). Furthermore, LVH was associated with the onset of cerebrovascular events (adjusted HR: 2.38; P<0.001), whereas IHD was associated with the onset of cardiovascular death (adjusted HR: 2.22; P<0.05), especially sudden death and other cardiac events.

Conclusions: Cardiac complications are independent predictors for cardiovascular events in Japanese high-risk hypertensive patients. In particular, LVH is related to cerebrovascular events and IHD is related to cardiac death and other cardiac events. (Circ J 2009; 73: 1080–1085)

Key Words: Coronary heart disease; Hypertension; Hypertrophy; Japanese

Hypertension is one of the major risk factors for cardiovascular (CV) events. Recent advantages of drug treatment are well recognized and lead to better blood pressure (BP) control and prognosis in hypertensive patients. However, the CV events rate is still high in hypertensive patients with other cardiac risks and, moreover, CV risks are known to cluster in hypertensive patients. The importance of identifying complicated CV risk factors has been repeatedly emphasized in national and international guidelines. These guidelines suggest that initiation of antihypertensive treatment, as well as the choice of therapeutic drugs, should be based on a total risk factor evaluation.

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The Candesartan Antihypertensive Survival Evaluation in Japan (CASE-J) trial compared 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. The CASE-J trial disclosed that candesartan and amlodipine equally suppressed total CV mortality and morbidity in high-risk hypertensive patients under strict BP control. Furthermore, primary CV events occurred in 134 patients in each of 2 treatment-based regimens and they were much lower than expected. In this study, we consider the trial as an observational study irrespective of allocated drugs, and clarify the effect of cardiac complications, such as left ventricular hypertrophy (LVH) and ischemic heart disease (IHD), on CV events in Japanese high-risk hypertensive patients.

Methods

Study Design

The CASE-J trial was a prospective, multicenter, randomized, open-label, active-controlled, 2-arm parallel-group comparison study evaluating the efficacy of the ARB, candesartan, and the CCB, amlodipine, for reducing the incidence of CV events in high-risk hypertensive patients. The rationale and complete design of the CASE-J trial have been previously reported. Briefly, 4,728 patients with high-risk hypertension were randomly assigned to either a candesartan- or amlodipine-based treatment regimen. High-risk was defined as the presence of any one of the following factors: (a) severe hypertension: systolic BP (SBP)/diastolic BP (DBP) ≥180/110 mmHg; (b) type 2 diabetes mellitus; (c) history of stroke or transient ischemic attack (TIA) more
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The primary endpoint was the first fatal/non-fatal CV event (a composite of sudden death, which is unexpected death within 24 h without external cause; cerebrovascular events including stroke or TIA; cardiac events including heart failure (HF), AP or acute MI; renal events, including serum creatinine ≥1.3 mg/dl; arterial thrombotic peripheral artery obstruction. The exclusion criteria are also reported elsewhere. After randomization the enrolled patients were given candesartan administered orally at a dose of 2.5–10 mg/day. The target BPs were determined according to the guideline of the Japanese Society of Hypertension. Finally, 4,703 randomly assigned patients were included in the analysis.

Outcome Measurements

The primary endpoint was the first fatal/non-fatal CV event (a composite of sudden death, which is unexpected death within 24 h without external cause; cerebrovascular events including stroke or TIA; cardiac events including heart failure (HF), AP or acute MI; renal events, including serum creatinine concentration ≥1.3 mg/dl; arterial thrombotic peripheral artery obstruction. The exclusion criteria are also reported elsewhere. After randomization the enrolled patients were given candesartan administered orally at a dose of 2.5–10 mg/day. The target BPs were determined according to the guideline of the Japanese Society of Hypertension. Finally, 4,703 randomly assigned patients were included in the analysis.

Baseline Characteristics

In the present study, we focused on the cardiac complications of the inclusion criteria in the CASE-J trial as LVH and IHD, including AP or a history of MI. Enrolled patients were divided into 2,030 patients with cardiac complications (LVH alone, IHD alone, and both LVH and IHD: 1,434, 418, and 178 patients, respectively) and 2,673 patients without cardiac complications. Table shows their baseline characteristics. Of the 1,612 patients with LVH, 927 met the ECG criteria, 463 met the echocardiographic criteria, and 222 met both the ECG and echocardiographic criteria for LVH. When we analyzed the data of patients with or without cardiac complications as an observational study, irrespective of allocated drugs, there were statistical differences between the dichotomized groups in the sex ratio, body mass index (BMI), SBP, DBP, heart rate and complicated risk factors. Next, the analyses were adjusted by baseline characteristics as described below.

Statistical Analysis

Data are expressed as mean±SD or proportions. We compared continuous variables using Student’s t-test. Frequency analysis was performed by χ² test. The cumulative CV events rate was calculated by the Kaplan-Meier method, and the groups were compared with the log-rank test. The hazard ratio (HR) and 95% confidence intervals (CIs) were estimated using Cox regression analysis. We also used the multiple Cox regression analysis to examine the association between the CV events rate and the effects of cardiac complications adjusted by baseline characteristics (allocated drugs, age, sex, BMI, and complicated risk factors). All statistical tests were 2-sided with an alpha level of 0.05, and were performed using SAS version 9.1 (SAS Institute Inc, Cary, NC, USA).

Results

Changes in BP

BP was strictly controlled to <140/80 mmHg in both groups. However, the mean SBP/DBP was 160/79.0 mmHg at baseline and 134.6/76.8 mmHg after 3 years in patients with cardiac complications compared with 164.5/92.5 mmHg at baseline and 135.9/77.2 mmHg after 3 years in patients without cardiac complications. Both SBP and DBP in the patients with cardiac complications were slightly but significantly lower than those without cardiac complications.

Table. Baseline Characteristics of the Study Patients

<table>
<thead>
<tr>
<th></th>
<th>Cardiac complication (–)</th>
<th>Cardiac complication (+)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>2,673</td>
<td>2,030</td>
</tr>
<tr>
<td>Candesartan (%)</td>
<td>1,347 (50.4)</td>
<td>1,007 (49.6)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>63.7±10.5</td>
<td>64.0±10.6</td>
</tr>
<tr>
<td>Men (%)*</td>
<td>1,296 (48.5)</td>
<td>1,301 (64.1)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)*</td>
<td>24.7±2.8</td>
<td>24.4±2.4</td>
</tr>
<tr>
<td>SBP (mmHg)*</td>
<td>164.5±14.3</td>
<td>160.7±13.7</td>
</tr>
<tr>
<td>DBP (mmHg)*</td>
<td>92.5±11.5</td>
<td>90.6±10.7</td>
</tr>
<tr>
<td>Heart rate (beats/min)*</td>
<td>73.3±11.0</td>
<td>71.2±11.3</td>
</tr>
<tr>
<td>Severe HT (SBP ≥180 and/or DBP ≥110 mmHg)*</td>
<td>716 (26.8)</td>
<td>231 (11.4)</td>
</tr>
<tr>
<td>Type 2 diabetes*,*</td>
<td>1,414 (52.9)</td>
<td>604 (29.8)</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebral hemorrhage*</td>
<td>64 (2.4)</td>
<td>22 (1.1)</td>
</tr>
<tr>
<td>Cerebral infarction*</td>
<td>225 (8.4)</td>
<td>99 (4.9)</td>
</tr>
<tr>
<td>TIA*</td>
<td>62 (2.3)</td>
<td>12 (0.6)</td>
</tr>
<tr>
<td>Renal dysfunction</td>
<td>606 (22.7)</td>
<td>299 (14.7)</td>
</tr>
<tr>
<td>Proteinuria*</td>
<td>232 (8.7)</td>
<td>135 (6.7)</td>
</tr>
<tr>
<td>sCr ≥1.3 mg/dl*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascular disease</td>
<td>38 (1.4)</td>
<td>15 (0.7)</td>
</tr>
</tbody>
</table>

Data are number of patients (%) or mean±SD.

*P<0.05; cardiac complication (–) vs cardiac complication (+).

Type 2 diabetes mellitus was defined by fasting blood glucose ≥126 mg/dl, casual blood glucose ≥200 mg/dl, hemoglobin A1c ≥6.5%, 2 h blood glucose on 75-g oral glucose tolerance test ≥200 mg/dl, or current treatment with hypoglycemic agents at baseline.

SBP, systolic blood pressure; DBP, diastolic blood pressure; HT, hypertension; TIA, transient ischemic attack; sCr, serum creatinine; ASO, atherosclerosis obliterans.
at several points during the follow-up period (Figure 1).

**Prognostic Value of Cardiac Complications for CV Events Rate**

During 3.2±0.9 years of follow-up, CV events occurred in 118 (4.4%) patients without cardiac complications at baseline for a rate of 13.6 per 1,000 patient-years and in 150 (7.4%) patients with cardiac complications at baseline for a rate of 23.1 per 1,000 patient-years (adjusted HR: 2.22; 95%CI: 1.73–2.84; P<0.001; Figure 2). In addition, we evaluated the prognostic value of the cardiac complications for each event category. As shown in Figure 3, cardiac complications were associated with the onset of CV death (adjusted HR: 2.14; 95%CI: 1.14–4.02; P=0.018), including sudden death (adjusted HR: 2.79; 95%CI: 1.16–6.70; P=0.022), cerebrovascular events (adjusted HR: 2.27; 95%CI: 1.54–3.35; P<0.001) and other cardiac events (adjusted HR: 2.63; 95%CI: 1.71–4.05; P<0.001), including MI, AP or congestive HF. However, the incidences of renal and vascular events were unaffected by cardiac complications.

Although both complicated LVH and IHD were associated with the CV events rate, there were different effects on
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As shown in Figure 4, LVH was strongly associated with the onset of cerebrovascular events (adjusted HR: 2.38; 95%CI: 1.62–3.48; P<0.001 in LVH, and adjusted HR: 1.25; 95%CI: 0.74–2.12; P=0.401 in IHD), whereas IHD was strongly associated with the onset of CV death (adjusted HR: 1.82; 95%CI: 0.99–3.28; P=0.053 in LVH, and adjusted HR: 2.22; 95%CI: 1.02–3.96; P=0.043 in IHD), especially sudden death (adjusted HR: 1.41; 95%CI: 0.63–3.17; P=0.408 in LVH, and adjusted HR: 4.59; 95%CI: 2.02–10.41; P<0.001 in IHD), and other cardiac events (adjusted HR: 1.44; 95%CI: 0.93–2.21; P=0.100 in LVH, and adjusted HR: 4.20; 95%CI: 2.69–6.55; P=0.001 in IHD). Neither LVH nor IHD was related to the onset of renal or vascular events.

Discussion

The present study extends the clinical implication of cardiac complications such as LVH and IHD in high-risk hypertensive patients. Because the baseline clinical characteristics were different in patients with or without cardiac complications, the HRs for CV events were adjusted by the baseline characteristics. We demonstrated that cardiac complications are an independent predictor for CV events. Moreover, LVH and IHD were independent predictors for CV events. To our knowledge, this is the first report of the separate effect of LVH and IHD on the incidence of CV events, including renal events, analyzed in high-risk hypertensive patients. Although BP lowering was substantial in both groups of patients, the achieved BP was slightly different between them. Because the BP level achieved in patients with cardiac complications was lower than that in the patients without cardiac complications, this result was not caused by inadequacy of BP lowering in patients with cardiac complications.

LVH is an adaptive response that reduces LV wall stress against volume and pressure overload. Although this was originally thought to be a compensatory and beneficial response to normal wall stress, large population studies have provided evidence that LVH confers increased risk for CV events. The reasons why LVH is a powerful predictor for CV events are not yet clear, and there are various mechanisms to explain the relationship between LVH and CV events. Two important concepts have been proposed for the clinical implication of LVH. First, LVH has been predominantly considered a valuable surrogate index for CV events, reflecting longstanding exposure to high BP. Ther-
fore, the complication of LVH indicates advanced atherosclerosis in various organs including the brain and kidneys. The present study results indicated a strong relationship between LVH and the onset of cerebrovascular events. Elevated SBP, which sets up LVH, is associated with a profound increase in the risk of cerebrovascular events. The ARIC study demonstrated that incident stroke was predicted by the echocardiographic LV mass index (LVMI). Another study also revealed that LVH was associated closely with stroke, and that the risk ratio of the LVMI was 1.020 for each 1 g/m² increase. Second, LVH may contribute directly to CV events through pathological changes, including fibrosis and relative ischemia caused by hypertrophy. LVH is related to adverse LV remodeling as a result. We believed that the reason why LVH failed to predict the onset of CV events other than cerebrovascular events is mainly for statistical reasons based on the small numbers in this study. The total number of cerebrovascular events was 111, whereas cardiac events occurred in only 90 cases.

This study indicated that a history of prior IHD is closely connected with CV events. In particular, the adjusted HRs of sudden death and cardiac events, including MI, AP and congestive HF, in patients with IHD was almost 3-fold or more than those in patients with LVH. Because these events are closely related to coronary lesions, the effect of a history of IHD was strong. Conversely, hypertension increases the risk of CV events including stroke, HF and death after MI. Ravigati et al reported that the risk ratio of prior MI was 5.29 for either new stroke or new MI or death in 306 patients with hypertension or diabetes mellitus. Study Limitations

First, because this analysis was post-hoc, the numbers in each category of CV events, particularly renal and vascular events, may not be enough to analyze the effect of cardiac complications on these events. Recently, higher urinary albumin excretion has been observed in patients with LVH suggesting that cardiac and glomerular vascular damage may occur in parallel. Systemic inflammation and endothelial damage are possible mechanisms of the relationship between them. In the present study, however, cardiac complications, both LVH and IHD, failed to predict the onset of renal events. Therefore, we should focus on the time-course of renal function as well as the onset of renal events. Accordingly, the effects of cardiac complications on the kidney remain unknown. Second, in this study, hypertensive patients with any one of the high-risk factors, including LVH and IHD, were enrolled, so when we evaluated the data of patients with or without cardiac complications, the analyses had to be adjusted by the baseline characteristics because of their statistical differences. Third, the definition of LVH consisted of ECG criteria (SV1 + RV5 ≥3.5 mV) and echocardiographic criteria (LV wall thickness ≥12 mm). Because echocardiography is only performed when feasible, there were small numbers of patients who underwent echocardiography. Accordingly, we had to combine different criteria of either ECG or echocardiography. Fourth, 3.2 years of mean follow-up may not be long enough to evaluate the relationship between underlying risks and the incidence of CV events. The CASE-J trial was extended for 3 years from 2006 as an observational study named CASE-J Ex and it may resolve this issue in the near future.

In conclusion, cardiac complications are independent predictors for CV events in Japanese high-risk hypertensive patients, but the clinical implication differs between LVH and IHD. LVH is related to cerebrovascular events and IHD is related to cardiac death, including sudden death and other cardiac events.

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Disclosures

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References

15. Brown DW, Giles WH, Croft JB. Left ventricular hypertrophy as a predictor of coronary heart disease mortality and the effect of hyper-


