# Is Pulse Pressure a Predictor of New-Onset Diabetes in High-Risk Hypertensive Patients?

## A subanalysis of the Candesartan Antihypertensive Survival Evaluation in Japan (CASE-J) trial

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**OBJECTIVE** — Hypertensive patients have an increased risk of developing diabetes. Accumulating evidence suggests a close relation between metabolic disturbance and increased arterial stiffness. Here, we examined the association between pulse pressure and the risk of new-onset diabetes in high-risk Japanese hypertensive patients.

**RESEARCH DESIGN AND METHODS** — The Candesartan Antihypertensive Survival Evaluation in Japan (CASE-J) trial examined the effects of candesartan and amlodipine on the incidence of cardiovascular events in 4,728 high-risk Japanese hypertensive patients. In the present study, we analyzed the relationship between pulse pressure at baseline and new-onset diabetes in 2,685 patients without diabetes at baseline (male 1,471; mean age 63.7 years; mean BMI 24.8 kg/m$^2$) as a subanalysis of the CASE-J trial.

**RESULTS** — During 3.3 ± 0.8 years of follow-up, 97 patients (3.6%) developed diabetes. In multiple Cox regression analysis, pulse pressure was an independent predictor for new-onset diabetes (hazard ratio [HR] per 1 SD increase 1.44 [95% CI 1.15–1.79]) as were male sex, BMI, and additional use of diuretics, whereas age and heart rate were not. Plots of HRs for new-onset diabetes considering both systolic and diastolic blood pressure (DBP) revealed that a higher pulse pressure with a lower DBP, indicating that the increased pulse pressure was largely due to increased arterial stiffness, was strongly associated with the risk of new-onset diabetes.

**CONCLUSIONS** — Pulse pressure is an independent predictor of new-onset diabetes in high-risk Japanese hypertensive patients. Increased arterial stiffness may be involved in the development of diabetes.

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Deaths from cardiovascular disease (CVD), which, as the leading cause of death, accounts for one-third of all deaths globally, are forecast to increase from 17.1 million in 2004 to 23.4 million in 2030 (1). Hypertension is an established risk factor for cardiovascular mortality and morbidity through its effect on several target organs, including the brain, heart, and kidneys (2). Diabetes is also strongly associated with an increased risk of cardiovascular events (3). Because hypertensive patients have an increased risk of developing diabetes (new-onset diabetes), the two conditions frequently cluster together and synergistically increase the propensity to CVD (4). Further, a recent study has shown that new-onset diabetes negatively affects the incidence of cardiovascular morbidity and mortality to the same degree as known diabetes (5). Prevention of new-onset diabetes is therefore an important issue in the management of hypertension, and several studies with the aim of determining predictors of new-onset diabetes have been reported (6–8).

One independent predictor of cardiovascular morbidity and mortality in hypertensive patients is pulse pressure (9). Although pulse pressure derives from the interaction of cardiac ejection (stroke volume) and the properties of arterial circulation (arterial stiffness and wave reflection), elevated pulse pressure is thought to be largely associated with increased arterial stiffness due to aging, arteriosclerosis, or both (9,10), and several recent studies have reported an association among increased arterial stiffness and impaired glucose metabolism, metabolic syndrome, and insulin resistance (11–13). These findings suggest a possible association between increased pulse pressure and new-onset diabetes, but this association has not been examined in hypertensive patients.

The CASE-J trial was designed to compare the long-term effects of the angiotensin II receptor blocker (ARB) candesartan cilexetil and the calcium channel blocker (CCB) amlodipine besylate on the incidence of cardiovascular events in 4,728 high-risk Japanese hypertensive patients (14). Results showed that both treatment-based regimens lowered systolic (SBP) and diastolic blood pressure (DBP) levels to <140/80 mmHg, and no statistically significant difference was seen in the incidence of primary cardiovascular events. However, candesartan-based regimens significantly suppressed the incidence of new-onset diabetes compared with amlodipine-based regimens (15).

Here, we report a subanalysis of the CASE-J trial with the aim of determining whether pulse pressure is associated with the risk of new-onset diabetes independent of the effects of antihypertensive

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treatment and other possible risk factors for diabetes.

## RESEARCH DESIGN AND METHODS

The CASE-J trial was a prospective, multicenter, randomized, open-label, active-controlled, two-arm parallel-group comparison with response-dependent dose titration and blinded assessment of end points conducted in high-risk Japanese hypertensive patients. The trial protocol was approved by the Ethics Committee of Kyoto University Graduate School of Medicine in accordance with the principles of the Declaration of Helsinki. Details of the study and the main results have been reported previously (14,15). In brief, 4,728 high-risk Japanese hypertensive patients aged 20–84 years were randomly assigned to either candesartan- or amlodipine-based regimens. Blood pressure was measured at a clinic with the patient in the sitting position. The average of two consecutive measurements of blood pressure on separate visits was used. High-risk was defined as the presence of any one or more of the following: *1*) severe hypertension (SBP/DBP ≥180/110 mmHg); *2*) type 2 diabetes (fasting blood glucose ≥126 mg/dl, casual blood glucose ≥200 mg/dl, A1C ≥6.5%, 2-h blood glucose on a 75-g oral glucose tolerance test ≥200 mg/dl, or current treatment with a hypoglycemic agent at baseline); *3*) a history of stroke or transient ischemic attack > 6 months before screening; *4*) left ventricular hypertrophy (LVH), angina pectoris, or a history of myocardial infarction >6 months before screening; *5*) proteinuria or renal dysfunction (serum creatinine ≥1.3 mg/dl); or *6*) arteriosclerotic peripheral artery obstruction. Exclusion criteria have been reported elsewhere (14,15).

Enrolled patients were randomly assigned to receive candesartan by oral administration at 4–12 mg/day or amlodipine by oral administration at 2.5–10 mg/day. Patients already under treatment with diuretics, α-blockers, and β-blockers at enrollment were allowed to continue taking these drugs, but the new addition of other ARBs and CCBs or any ACE inhibitors was prohibited.

### Outcome measurement

Of the 4,703 high-risk hypertensive patients analyzed in the CASE-J trial, 2,018 who had diabetes at baseline were excluded, leaving 2,685 patients for inclusion in the present study. New-onset diabetes was prespecified as the end point on 17 September 2005, which was after the beginning but before the completion of the CASE-J trial (15). To detect the occurrence of new-onset diabetes, individual case report forms and adverse-event databases were monitored. 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 newly started antidiabetic agent therapy in the case report form. Written informed consent was obtained from each participating patient before allocation.

### Statistical analysis

Data are expressed as means ± SD or proportions. Continuous variables were compared using Student's *t* test. Frequency analysis was performed with the $\chi^2$ test. Pulse pressure was calculated as the difference between SBP and DBP. Multiple Cox regression analysis was used to examine the association between each blood pressure index (SBP, DBP, and pulse pressure) at baseline and the risk of new-onset diabetes with adjustment for baseline characteristics (prior antihypertensive treatment, allocated drug, age, sex, BMI, heart rate, history of cerebrovascular events, LVH, history of ischemic heart disease, renal dysfunction, peripheral vascular disease, hyperlipidemia, and smoking) as standard covariates and additional drugs (diuretics, α-blockers, and β-blockers) as time-varying covariates. Fractional pulse pressure ($PP_f$), which is calculated as pulse pressure divided by mean arterial pressure, has recently been proposed as a new parameter of the pulsatile component of blood pressure (16). $PP_f$ is thought to more directly reflect arterial stiffness than pulse pressure, because dividing by mean arterial pressure theoretically cancels out the influence of cardiac output and peripheral vascular resistance. We also evaluated the predictive value of this variable for new-onset diabetes by multiple Cox regression analysis. Because each blood pressure index is affected by aging (10), we also conducted subgroup analyses stratified by age (cutoff point: age 65 years), using the median age at baseline of all included patients. The test for interaction in the multiple Cox model was evaluated with the interaction term. In addition, to clarify the significance of pulse pressure for new-onset diabetes, the associations of both SBP and DBP with the incidence of new-onset diabetes were examined by multiple Cox regression analysis with SBP grouped into two categories (SBP <160 mmHg and 160 mmHg ≤SBP) and DBP plotted as a continuous variable. This model was plotted with the middle 80% of the distribution of DBP for each SBP group, and the HR of a DBP of 90 mmHg in the SBP <160 mmHg category was assigned a reference value of 1.0. All statistical tests were two-sided with an α level of 0.05 and were performed using SAS (version 9.1; SAS Institute, Cary, NC).

## RESULTS

### Baseline characteristics

During 3.3 ± 0.8 years of follow-up, 97 patients (3.6%) developed new-onset diabetes. Baseline characteristics of patients with and without new-onset diabetes are shown in Table 1. Patients developing diabetes were more likely to be male and obese, less likely to have been randomly assigned to a candesartan-based regimen, and more likely to have had lower DBP, higher pulse pressure, and LVH at baseline. At the time of randomization, 1,702 (65.8%) patients without and 65 (67.0%) patients with new-onset diabetes were under treatment with antihypertensive drugs (CCB 40.1 vs. 34.0%, $P = 0.229$; ACE inhibitor 13.3 vs. 16.5%, $P = 0.363$; ARB 17.9 vs. 22.7%, $P = 0.229$; diuretic 3.1 vs. 5.2%, $P = 0.255$; β-blocker 12.9 vs. 16.5%, $P = 0.297$; and α-blocker 5.6 vs. 4.1%, $P = 0.542$, respectively).

### Predictors of new-onset diabetes

Multiple Cox regression analysis revealed that pulse pressure (per 1 SD increase) was an independent predictor of new-onset diabetes (HR 1.44 [95% CI 1.15–1.79], $P = 0.001$) (Table 2). In addition, risk was also significantly associated with male sex, BMI, LVH, and concomitant use of diuretics. As reported previously, candesartan-based regimens significantly reduced the risk of new-onset diabetes compared with amlodipine-based regimens (15).

Because pulse pressure was calculated as the difference between SBP and DBP, we conducted separate analyses for SBP and DBP and found that DBP (per 1 SD decrease) was also an independent predictor for new-onset diabetes, whereas SBP (per 1 SD increase) was not (HR for SBP 1.13 [95% CI 0.90–1.41], $P = 0.284$; and HR for DBP 1.45 [1.16–1.81], $P < 0.001$). Subgroup analysis stratified by age (cutoff point: age 65 years) revealed that pulse pressure remained significantly associated with the risk of new-onset diabetes in both age-groups (aged <65 years: HR 1.72 [95% CI 1.18–2.49],

**Table 1—*Baseline characteristics***

| | Total | NOD (−) | NOD (+) |
|---|---|---|---|
| *n* | 2,685 | 2,588 | 97 |
| Candesartan* | 1,343 (50.0) | 1,305 (50.4) | 38 (39.2) |
| Prior antihypertensive treatment | 1,767 (65.8) | 1,702 (65.8) | 65 (67.0) |
| Age (years) | 63.7 ± 11.1 | 63.7 ± 11.2 | 64.9 ± 10.0 |
| Male sex* | 1,471 (54.8) | 1,406 (54.3) | 65 (67.0) |
| BMI (kg/m$^2$)* | 24.8 ± 3.6 | 24.1 ± 3.5 | 25.2 ± 3.4 |
| SBP (mmHg) | 165.0 ± 14.8 | 165.0 ± 14.8 | 165.7 ± 16.1 |
| DBP (mmHg)* | 94.3 ± 11.3 | 94.4 ± 11.3 | 90.5 ± 11.7 |
| Pulse pressure (mmHg)* | 70.8 ± 15.8 | 70.6 ± 15.7 | 75.2 ± 18.4 |
| Heart rate (beats/min) | 71.4 ± 10.9 | 71.4 ± 10.9 | 71.2 ± 9.5 |
| Hyperlipidemia | 1,178 (43.9) | 1,136 (43.9) | 42 (43.3) |
| Smoking | | | |
| Never | 1,825 (68.0) | 1,766 (68.2) | 59 (60.8) |
| Ever | 273 (10.2) | 261 (10.1) | 12 (12.4) |
| Current | 587 (21.9) | 561 (21.7) | 26 (26.8) |
| Cerebrovascular disease† | 344 (12.8) | 330 (12.8) | 14 (14.4) |
| LVH* | 1,139 (42.4) | 1,088 (42.0) | 51 (52.6) |
| Ischemic heart disease | 393 (14.6) | 381 (14.7) | 12 (12.3) |
| Proteinuria | 548 (20.4) | 530 (20.5) | 18 (18.6) |
| Renal dysfunction | 205 (7.6) | 196 (7.6) | 9 (9.3) |
| Peripheral vascular disease | 37 (1.4) | 35 (1.4) | 2 (2.1) |

Data are *n* (%) or means ± SD. *$P < 0.05$, NOD (−) vs. NOD (+). †Stroke and transient ischemic attack. NOD, new-onset diabetes.

$P = 0.004$; aged ≥65 years: 1.34 [1.01–1.77], $P = 0.042$; and $P_{interaction} = 0.152$). However, DBP was significantly associated with risk only in the group aged <65 years, whereas whole SBP was not associated in either age-group (for SBP, aged <65 years: 1.20 [0.86–1.67], $P = 0.284$; aged ≥65 years: 1.16 [0.84–1.59], $P = 0.374$; and $P_{interaction} = 0.780$; for DBP, aged <65 years: 1.58 [1.10–2.28], $P = 0.014$; aged ≥65 years: 1.32 [0.99–1.76], $P = 0.057$; and $P_{interaction} = 0.290$).

Because different combinations of SBP and DBP give the same pulse pressure value (e.g., blood pressures of 130/60 and 180/110 mmHg both give a pulse pressure of 70 mmHg), we evaluated the association of combinations of SBP and DBP with the risk of new-onset diabetes. As shown in Fig. 1, a strong association with risk was seen for higher pulse pressures arising mainly due to a lower DBP. From this result, we hypothesized that patients at high risk of new-onset diabetes had increased arterial stiffness. Accordingly, we next examined the association between $PP_f$ and the risk of new-onset diabetes and found that $PP_f$ (per 1 SD increase) was an independent predictor of new-onset diabetes (HR 1.49 [95% CI 1.21–1.84], $P < 0.001$). In subgroup analysis stratified by age, $PP_f$ (per 1 SD increase) was significantly associated with the risk of new-onset diabetes in both age-groups (aged <65: 1.88 [1.29–2.73], $P < 0.001$; aged ≥65: 1.34 [1.03–1.74], $P = 0.027$; and $P_{interaction} = 0.057$). Because fewer patients developed diabetes with candesartan- than amlodipine-based regimens, we examined the difference in this effect stratified by quartile of $PP_f$. As shown in Fig. 2, a trend to an increased incidence of new-onset diabetes with increasing $PP_f$ was seen in patients with amlodipine-based regimens, but not in those with candesartan-based regimens ($P = 0.0234$ for interaction in the quadratic term). Candesartan-based regimens significantly suppressed the incidence of new-onset diabetes in the highest quartile of $PP_f$. This result was not changed after adjustment for baseline characteristics (data not shown).

**Table 2—*Predictors of new-onset diabetes by multiple Cox regression analysis***

| Variables, unit of increase | HR (95% CI) | *P* value |
|---|---|---|
| Pulse pressure, per 1 SD increase | 1.44 (1.15–1.79) | 0.001 |
| Prior antihypertensive treatment, yes | 0.97 (0.61–1.54) | 0.901 |
| Allocated drug, candesartan | 0.64 (0.42–0.97) | 0.037 |
| Sex, male | 1.77 (1.07–2.92) | 0.026 |
| Age, per 10 years | 1.09 (0.87–1.36) | 0.460 |
| BMI, per 1 kg/m$^2$ increase | 1.11 (1.06–1.17) | <0.001 |
| Heart rate, per 1 SD increase | 1.01 (0.82–1.23) | 0.960 |
| Hyperlipidemia, yes | 1.04 (0.68–1.57) | 0.867 |
| Smoking | | |
| Ever | 1.03 (0.52–2.04) | 0.942 |
| Current | 1.22 (0.72–2.06) | 0.458 |
| Cerebrovascular disease, yes | 1.48 (0.80–2.75) | 0.214 |
| LVH, yes | 1.75 (1.13–2.72) | 0.013 |
| Ischemic heart disease, yes | 0.91 (0.47–1.76) | 0.777 |
| Renal damage, yes* | 1.10 (0.68–1.79) | 0.694 |
| Peripheral vascular disease, yes | 1.49 (0.36–6.16) | 0.581 |
| Additional use of diuretics, yes | 2.10 (1.25–3.52) | 0.005 |
| Additional use of β-blockers, yes | 0.70 (0.40–1.24) | 0.226 |
| Additional use of α-blockers, yes | 0.63 (0.32–1.24) | 0.185 |

Data are HR (95% CI) and are adjusted for each variable. *Renal damage, proteinuria, and renal dysfunction.

**CONCLUSIONS** — In this study, we demonstrated that pulse pressure was a predictor of new-onset diabetes in high-risk hypertensive patients, independent of the effects of antihypertensive treatment and other possible risk factors for new-onset diabetes. Further, a higher pulse pressure arising mainly due to a lower DBP, indicating that the increased pulse pressure resulted largely from increased arterial stiffness, was associated with a higher risk of new-onset diabetes. This finding suggests that increased arterial stiffness, reflected in an increased pulse pressure, may be related to the process of new-onset diabetes in high-risk hypertensive patients, albeit that the mechanism of this association remains to be elucidated.

Two potential interpretations may explain these results. First, increased pulse pressure may be a surrogate marker for the risk of new-onset diabetes. Support-

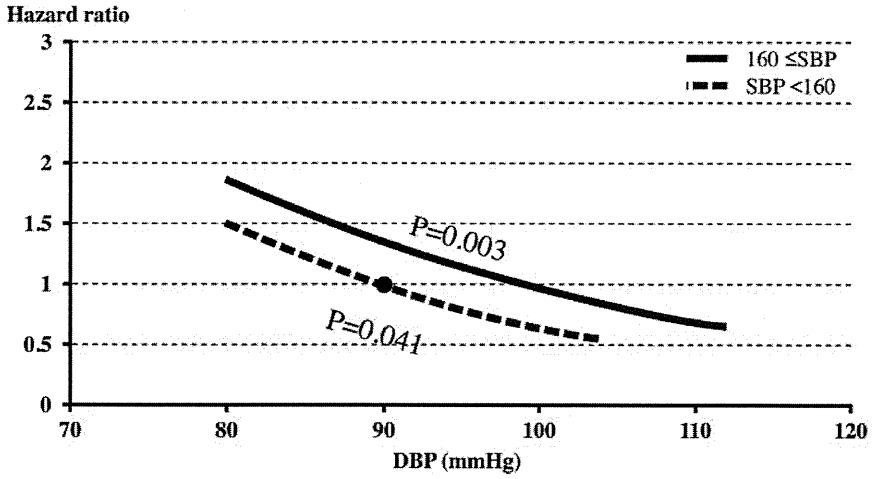


**Figure 1**—*Risk of new-onset diabetes by SBP and DBP at enrollment. HR of DBP of 90 mmHg in the SBP <160 mmHg category was assigned a reference value of 1.0.*

ing this suggestion, a higher pulse pressure, reflecting increased arterial stiffness, was observed in hypertensive patients with metabolic syndrome than in those without (17). Further, accumulating evidence supports the concept of increased arterial stiffness in patients with a metabolic disturbance, which is considered a potential mechanism linking metabolic disturbance to increased CVD risk (11–13). Arterial properties are affected both functionally and structurally by many factors, including aging, blood pressure, sympathetic nervous system function, endothelial function, inflammation, bioactive peptides, and other cardiovascular risk factors. Impaired glucose metabolism, including metabolic syndrome and insulin resistance, usually precedes the development of overt type 2 diabetes (18). Prolonged exposure to hyperglycemic conditions can lead to increased arterial stiffness via collagen cross-linking due to nonenzymatic glycation, endothelial dysfunction, inflammation, and local activation of the renin-angiotensin-aldosterone system in pre-diabetic as well as diabetic individuals (18). Indeed, $PP_f$, represented as a parameter of the pulsatile component of blood pressure, was superior to pulse pressure in terms of the risk stratification of new-onset diabetes.

Second, increased pulse pressure may directly affect glucose metabolism. Recent findings have clarified that microvascular dysfunction may be a cause rather than a consequence of hypertension (19). Microvascular dysfunction may also contribute to impaired insulin-mediated changes in muscle perfusion and glucose metabolism, providing a novel pathophysiological framework for understanding the association among hypertension, obesity, and impaired insulin-mediated glucose disposal (19,20). Microvascular dysfunction is thus a potential mechanism explaining the clustering of hypertension and type 2 diabetes. Interestingly, relations between microvascular function and both aortic stiffness and pressure pulsatility have been reported (21). Abnormalities in peripheral vascular resistance may have deleterious consequences for aortic stiffness, and microvascular dysfunction may in turn be further aggravated by increased transmission of the forward wave into the microcirculation. Accordingly, increased pulse pressure, reflecting increased arterial stiffness, may be both a cause and a consequence of microvascular dysfunction, leading to a "vicious cycle" in impaired glucose metabolism as well as arteriosclerosis (9,19,20).

The present study also revealed that electrocardiographic or echocardiographic LVH at baseline was an independent predictor of new-onset diabetes. In their recent subanalysis of the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) study, Oki et al. (22) reported that in-treatment resolution or continued absence of electrocardiographic LVH was associated with a lower incidence of diabetes. Because pulse pressure was positively related to LVH (23), our study might validate their findings from a different perspective. Interestingly, in another subanalysis of the LIFE study, Olsen et al. (24) found that treatment with the ARB losartan was associated with less peripheral vascular hypertrophy/rarefaction and higher insulin sensitivity than that with atenolol, supporting the hypothesis that microvascular dysfunction in hypertension may induce insulin resistance. In the present study, the suppressive effect of the ARB candesartan against new-onset diabetes tended to strengthen as $PP_f$ increased. These results suggest that ARBs decrease the risk of new-onset diabetes partly via the improvement of microcirculation.

Although the prevalence of diabetes increases with age (25), it remains unclear whether age is a risk factor for new-onset diabetes (6–8). In the present study, age at baseline was not an independent predictor of new-onset diabetes. We assumed that high-risk elderly hypertensive patients who did not have diabetes at baseline were survivors who had avoided the development of diabetes and that their

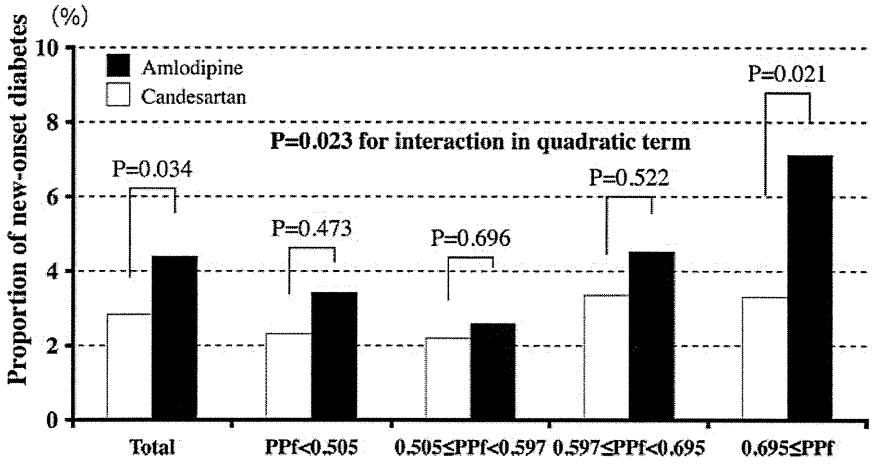


**Figure 2**—*Effect of candesartan and amlodipine on the incidence of new-onset diabetes stratified by quartile of $PP_f$. $PP_f$ (linear and quadratic terms), the allocated drugs, and their interaction terms were entered in multiple Cox regression model. P value was calculated based on the Wald test.*

underlying risk of new-onset diabetes and ability to metabolize glucose may thus have differed from those of younger subjects. We also observed a strong association between pulse pressure and new-onset diabetes in patients aged <65 years, possibly owing to the same mechanism.

Several limitations of this study warrant mention. First, it was conducted as a post hoc analysis. Second, although we found an interesting association between pulse pressure and the risk of new-onset diabetes, the CASE-J trial was not designed to prospectively evaluate this association, and we were consequently unable to elucidate causality, because we did not directly measure parameters of arterial stiffness or collect the data to clarify the underlying mechanism. Third, we were unable to include baseline data regarding glucose metabolism into the multiple Cox regression analysis or information about a family history of diabetes, physical activity, or diet, which are well-known and important risk factors for new-onset diabetes. Fourth, new-onset diabetes was prespecified as the end point just before the completion of the CASE-J trial. Accordingly, there was a possibility of nonreporting bias, because the definition of new-onset diabetes was not in the original protocol and determination of whether new-onset diabetes had occurred depended on the participating investigators' reports. Thus, we may have underestimated the overall incidence of new-onset diabetes. Nevertheless, the present study is the first to examine the association of pulse pressure with new-onset diabetes in hypertensive patients and may provide useful information in understanding the underlying mechanism between hypertension and new-onset diabetes. Finally, because the study population consisted of Japanese patients with high-risk hypertension, the generalizability of our findings to other ethnic groups or general populations may be limited.

In summary, we found that pulse pressure is an independent predictor of new-onset diabetes in high-risk Japanese hypertensive patients. The development of type 2 diabetes may involve increased arterial stiffness, suggesting the importance of the "microvascular dysfunction" theory in the underlying pathophysiological mechanism between hypertension and new-onset diabetes. To our knowledge, this study is the first to report the relation between pulse pressure and new-onset diabetes in hypertensive patients. Further studies are required to elucidate the significance of pulse pressure in new-onset diabetes in hypertensive patients.

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## References

1. World Health Organization. World Health Statistics 2008 [article online], 2008. Available from http://www.who.int/whosis/whostat/2008/en/index.html. Accessed 30 June 2009
2. Cohuet G, Struijker-Boudier H. Mechanisms of target organ damage caused by hypertension: therapeutic potential. Pharmacol Ther 2006;111:81–98
3. Kannel WB, McGee DL. Diabetes and glucose tolerance as risk factors for cardiovascular disease: the Framingham study. Diabetes Care 1979;2:120–126
4. Alderman MH, Cohen H, Madhavan S. Diabetes and cardiovascular events in hypertensive patients. Hypertension 1999;33:1130–1134
5. Verdecchia P, Reboldi G, Angeli F, Borgioni C, Gattobigio R, Filippucci L, Norgiolini S, Bracco C, Porcellati C. Adverse prognostic significance of new diabetes in treated hypertensive subjects. Hypertension 2004;43:963–969
6. Meigs JB, Muller DC, Nathan DM, Blake DR, Andres R, the Baltimore Longitudinal Study of Aging. The natural history of progression from normal glucose tolerance to type 2 diabetes in the Baltimore Longitudinal Study of Aging. Diabetes 2003;52:1475–1484
7. Nichols GA, Hillier TA, Brown JB. Progression from newly acquired impaired fasting glucose to type 2 diabetes. Diabetes Care 2007;30:228–233
8. Gupta AK, Dahlof B, Dobson J, Sever PS, Wedel H, Poulter NR, the Anglo-Scandinavian Cardiac Outcomes Trial Investigators. Determinants of new-onset diabetes among 19,257 hypertensive patients randomized in the Anglo-Scandinavian Cardiac Outcomes Trial–Blood Pressure Lowering Arm and the relative influence of antihypertensive medication. Diabetes Care 2008;31:982–988
9. Dart AM, Kingwell BA. Pulse pressure: a review of mechanisms and clinical relevance. J Am Coll Cardiol 2001;37:975–984
10. Franklin SS, Gustin W 4th, Wong ND, Larson MG, Weber MA, Kannel WB, Levy D. Hemodynamic patterns of age-related changes in blood pressure. The Framingham Heart Study Circulation 1997;96:308–315
11. Henry RM, Kostense PJ, Spijkerman AM, Dekker JM, Nijpels G, Heine RJ, Kamp O, Westerhof N, Bouter LM, Stehouwer CD, the Hoorn Study. Arterial stiffness increases with deteriorating glucose tolerance status: the Hoorn Study. Circulation 2003;107:2089–2095
12. Schillaci G, Pirro M, Vaudo G, Mannarino MR, Savarese G, Pucci G, Franklin SS, Mannarino E. Metabolic syndrome is associated with aortic stiffness in untreated essential hypertension. Hypertension 2005;45:1078–1082
13. Sengstock DM, Vaitkevicius PV, Supiano MA. Arterial stiffness is related to insulin resistance in nondiabetic hypertensive older adults. J Clin Endocrinol Metab 2005;90:2823–2827
14. Fukui T, Rahman M, Hayashi K, Takeda K, Higaki J, Sato T, Fukushima M, Sakamoto J, Morita S, Ogihara T, Fukiyama K, Fujishima M, Saruta T, the CASE-J Study Group. Candesartan Antihypertensive Survival Evaluation in Japan (CASE-J) trial of cardiovascular events in high-risk hypertensive patients: rationale, design, and methods. Hypertens Res 2003;26:979–990
15. Ogihara T, Nakao K, Fukui T, Fukiyama K, Ueshima K, Oba K, Sato T, Saruta T, the Candesartan Antihypertensive Survival Evaluation in Japan Trial Group. Effects of candesartan compared with amlodipine in hypertensive patients with high cardiovascular risks: Candesartan Antihypertensive Survival Evaluation in Japan trial. Hypertension 2008;51:393–398
16. Nakayama Y, Nakanishi N, Sugimachi M, Takaki H, Kyotani S, Satoh T, Okano Y, Kunieda T, Sunagawa K. Characteristics of pulmonary artery pressure waveform for differential diagnosis of chronic pulmonary thromboembolism and primary pulmonary hypertension. J Am Coll Cardiol 1997;29:1311–1316
17. Mulè G, Nardi E, Cottone S, Cusimano P, Incalcaterra F, Palermo A, Giandalia ME, Mezzatesta G, Andronico G, Cerasola G. Relationship of metabolic syndrome with pulse pressure in patients with essential hypertension. Am J Hypertens 2007;20:197–203
18. Stehouwer CD, Henry RM, Ferreira I. Arterial stiffness in diabetes and the metabolic syndrome: a pathway to cardiovascular disease. Diabetologia 2008;51:527–539
19. Serné EH, de Jongh RT, Eringa EC, Ijzerman RG, Stehouwer CD. Microvascular dysfunction: a potential pathophysiological role in the metabolic syndrome. Hypertension 2007;50:204–211
20. Levy BI, Schiffrin EL, Mourad JJ, Agostini

D, Vicaut E, Safar ME, Struijker-Boudier HA. Impaired tissue perfusion: a pathology common to hypertension, obesity, and diabetes mellitus. Circulation 2008; 118:968–976
21. Malik AR, Kondragunta V, Kullo IJ. Forearm vascular reactivity and arterial stiffness in asymptomatic adults from the community. Hypertension 2008;51: 1512–1518
22. Okin PM, Devereux RB, Harris KE, Jern S, Kjeldsen SE, Lindholm LH, Dahlöf B, the LIFE Study Investigators. In-treatment resolution or absence of electrocardiographic left ventricular hypertrophy is associated with decreased incidence of new-onset diabetes mellitus in hypertensive patients: the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) Study. Hypertension 2007;50:984–990
23. Gardin JM, Arnold A, Gottdiener JS, Wong ND, Fried LP, Klopfenstein HS, O'Leary DH, Tracy R, Kronmal R. Left ventricular mass in the elderly. The Cardiovascular Health Study. Hypertension 1997;29:1095–1103
24. Olsen MH, Fossum E, Høieggen A, Wachtell K, Hjerkinn E, Nesbitt SD, Andersen UB, Phillips RA, Gaboury CL, Ibsen H, Kjeldsen SE, Julius S. Long-term treatment with losartan versus atenolol improves insulin sensitivity in hypertension: ICARUS, a LIFE substudy. J Hypertens 2005;23:891–898
25. DECODE Study Group. Age- and sex-specific prevalences of diabetes and impaired glucose regulation in 13 European cohorts. Diabetes Care 2003;26: 61–69

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ORIGINAL ARTICLE
Hypertension and Circulatory Control

# Impact of Left Ventricular Hypertrophy on the Time-Course of Renal Function in Hypertensive Patients

## – A Subanalysis of the CASE-J Trial –

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***Background:*** In this subanalysis of the CASE-J, which was conducted to compare the effects of candesartan and amlodipine in Japanese high-risk hypertensive patients, the association of left ventricular hypertrophy (LVH) with renal function is clarified.

***Methods and Results:*** Patients were divided into 2 groups: 1,082 patients with LVH and 2,119 patients without LVH. The primary endpoint was the change in the estimated glomerular filtration rate (eGFR). The eGFRs were increased from 63.6 to 65.1 $ml \cdot min^{-1} \cdot 1.73 m^{-2}$ in patients with LVH and from 63.6 to 68.5 $ml \cdot min^{-1} \cdot 1.73 m^{-2}$ in those without LVH. The improvement in the eGFR was greater in patients without LVH than in those with LVH (P=0.004). In patients with chronic kidney disease (CKD) patients, the eGFR increased from 52.7 to 60.5 $ml \cdot min^{-1} \cdot 1.73 m^{-2}$ in patients without LVH, but from 53.1 to 57.2 $ml \cdot min^{-1} \cdot 1.73 m^{-2}$ in those with LVH (P<0.001, patients without LVH vs patients with LVH). Furthermore, because the eGFR changed from 76.5 to 75.4 $ml \cdot min^{-1} \cdot 1.73 m^{-2}$ in patients without CKD but with LVH, and from 76.5 to 77.5 $ml \cdot min^{-1} \cdot 1.73 m^{-2}$ in those without either CKD or LVH, the final eGFR was higher in patients without LVH than in those with LVH (P=0.048).

***Conclusions:*** LVH related to the time-course of renal function in Japanese hypertensive patients. (*Circ J* 2010; **74:** 2132–2138)

**Key Words:** Chronic kidney disease; Estimated glomerular filtration rate; Hypertension; Left ventricular hypertrophy

With progressive aging of the population and an increasing prevalence of hypertension and diabetes mellitus, chronic kidney disease (CKD) remains a worldwide public health problem. As many patients with CKD die of cardiovascular (CV) disease before reaching end-stage renal disease, measures against CKD should be undertaken from the viewpoint of improving their prognosis.[1,2]

Left ventricular hypertrophy (LVH) is a manifestation of target organ damage and an independent risk factor for CV morbidity and mortality.[3,4] Several studies have examined the association of renal dysfunction with LVH and have reported that reduced renal function and albuminuria are risk factors for it.[5–7] LVH is thus common in patients with CKD, indicating kidney–heart interaction. To date, however, few studies have examined the impact of LVH on renal function in hypertensive patients.[8,9] Our previous subanalysis of the CASE-J trial reported that cardiac complications, including LVH and ischemic heart disease, were independent predictors of CV events, but not of renal events.[10] In contrast, Boner et al reported that LVH was associated with a significantly increased risk of not only CV events but also the progression of kidney disease in patients with type 2 diabetes and nephropathy.[9] Of 4,703 patients in the CASE-J trial, only 46 (1.0%) experienced a renal event, a much smaller proportion than the 32.9% in the RENALL study, indicating that the CASE-J trial lacked sufficient statistical power to evaluate the impact of LVH on renal events.

In this context, the present study was conducted as a subanalysis of the CASE-J trial aimed at investigating the impact of LVH on the time-course of renal function in high-risk Japanese hypertensive patients.

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**Table 1. Baseline Characteristics of the Study Patients**

| Characteristics | LVH (–) | LVH (+) |
|---|---|---|
| No. of participants | 2,119 | 1,082 |
| Candesartan(%) | 1,071 (50.5) | 537 (49.6) |
| Age (years) | 64.4±10.0 | 63.6±10.3 |
| Men (%)* | 1,065 (50.3) | 687 (63.5) |
| Body mass index (kg/m$^2$)* | 24.6±3.6 | 24.4±3.5 |
| SBP (mmHg)* | 162.7±13.9 | 160.7±13.8 |
| DBP (mmHg)* | 91.1±11.3 | 90.9±10.6 |
| Heart rate (beats/min)* | 72.6±10.8 | 71.3±11.4 |
| Severe HT (SBP ≥180 and/or DBP ≥110 mmHg)* | 448 (21.1) | 120 (11.1) |
| Type 2 diabetes†,* | 1,089 (51.4) | 324 (29.9) |
| Ischemic heart disease (AP and/or OMI) | 299 (14.1) | 134 (12.4) |
| Cerebrovascular disease | | |
| Cerebral hemorrhage* | 52 (2.5) | 12 (1.1) |
| Cerebral infarction* | 155 (7.3) | 48 (4.4) |
| TIA* | 39 (1.8) | 7 (0.6) |
| Renal dysfunction | | |
| Proteinuria* | 471 (22.2) | 171 (15.8) |
| sCr ≥1.3 mg/dl* | 175 (8.3) | 74 (6.8) |
| Vascular disease | | |
| ASO* | 32 (1.5) | 7 (0.6) |

Data are shown as number of patients (%) or mean±SD.
*P<0.05; cardiac risk (–) vs cardiac risk (+).
†Type 2 diabetes mellitus was defined by fasting blood glucose ≥126 mg/dl, casual blood glucose ≥200 mg/dl, hemoglobin $A_{1c}$ ≥6.5%, 2 h blood glucose on 75 g OGTT ≥200 mg/dl, or current treatment with hypoglycemic agent at baseline.
LVH, left ventricular hypertrophy; SBP, systolic blood pressure; DBP, diastolic blood pressure; HT, hypertension; AP, angina pectoris; OMI, old myocardial infarction; TIA, transient ischemic attack; sCr, serum creatinine; ASO, atherosclerosis obliterans; OGTT, oral glucose tolerance test.

## Methods

### Study Design

The CASE-J trial was a prospective, multicenter, randomized, open-label, active-controlled, 2-arm parallel-group comparison study, which evaluated the efficacy of angiotensin receptor blocker candesartan and Ca channel blocker amlodipine in reducing the incidence of CV events in high-risk hypertensive patients.[11,12] The rationale and complete design of the CASE-J trial and main outcome of the primary endpoint have been reported elsewhere.[11,12] 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: (a) severe hypertension: systolic blood pressure (SBP)/diastolic blood pressure (DBP) ≥180/110 mmHg; (b) type 2 diabetes mellitus; (c) history of stroke or transient ischemic attack more than 6 months prior to screening; (d) LVH (SV1+RV5 ≥3.5 mV in electrocardiography (ECG) and/or LV wall thickness ≥12 mm in echocardiography), angina pectoris, or a history of myocardial infarction more than 6 months prior to screening; (e) proteinuria or serum creatinine concentration ≥1.3 mg/dl; and (f) arteriosclerotic peripheral artery obstruction. The exclusion criteria have been reported elsewhere.[11] Enrolled patients were given one of the following medications after randomization, namely candesartan administered orally at a dose of 4–12 mg/day or amlodipine administered orally at a dose of 2.5–10 mg/day. Finally, 4,703 randomly assigned patients were included in the analysis. Mean follow-up period was 3.2 years and follow-up rate was 97.1%.[12]

In the present analysis, we focused on LVH, which was one of inclusion criteria in the trial. Enrolled patients, whose serum creatinine values were available every 6 months during the follow-up period, were divided into 1,082 patients with and 2,119 patients without LVH. Among the 1,082 patients with LVH, 633 met the ECG criteria for LVH, 297 met the echocardiographic criteria, and 152 met both the ECG and echocardiographic criteria. The primary endpoint in this subanalysis was change in estimated glomerular filtration rate (eGFR) in patients with or without LVH. Based on CKD Guidelines of the Japanese Society of Nephrology,[13,14] eGFR was calculated by the following equation:

$$eGFR = 194 \times Cr^{-1.094} \times Age^{-0.28}$$
(×0.739, if female; Cr, serum creatinine)

Further, to evaluate the impact of CKD on the time-course of renal function, the patients were also divided into 2 additional groups, namely those with (n=1,455) and without CKD (n=1,746). Patients at enrollment with positive urinary protein tests by either or both dipstick analysis or an eGFR of $<60\,ml \cdot min^{-1} \cdot 1.73\,m^{-2}$ were defined as having CKD in this study.[15]

### Baseline Characteristics

**Table 1** shows the baseline characteristics of patients with and without LVH in the present analysis. As LVH was one of the inclusion criteria, there were statistical differences in baseline characteristics between the 2 groups. Thus, analyses were adjusted for baseline characteristics as described below.

### Statistical Analysis

Data are expressed as the mean±standard deviation or proportion. We compared continuous variables using the Student's

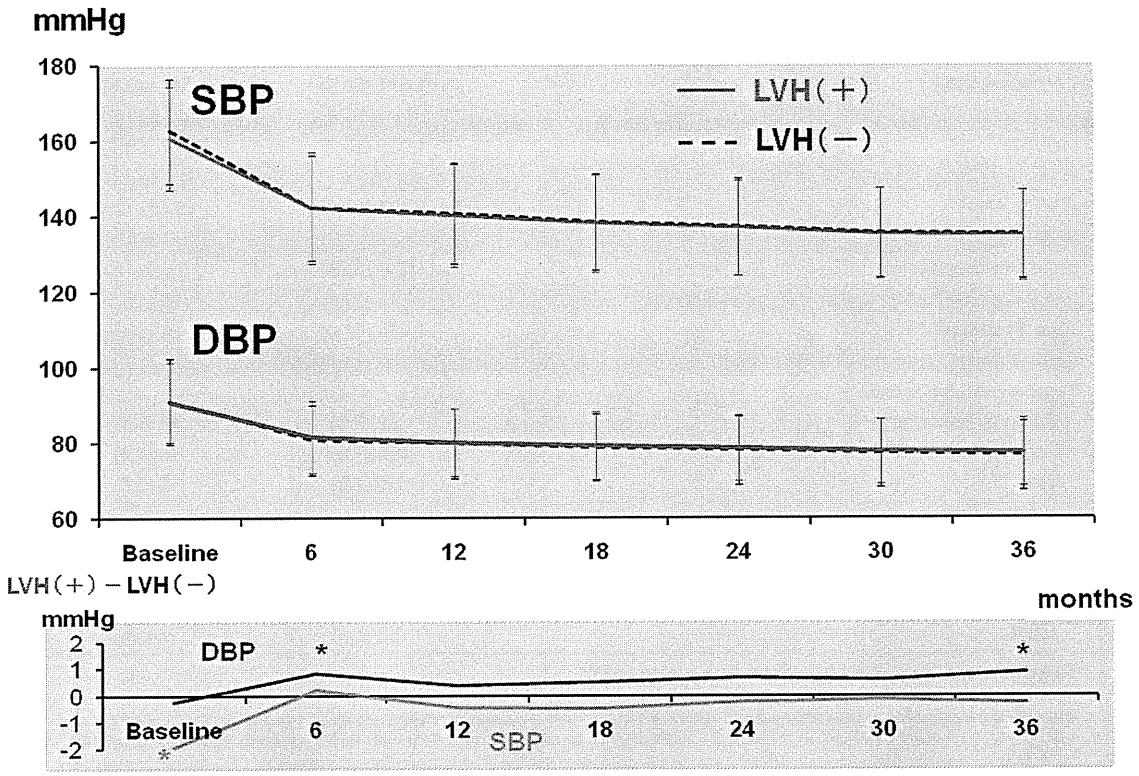


**Figure 1.** Changes in systolic blood pressure (SBP) and diastolic blood pressure (DBP) during the follow-up period. Mean SBP and DBP measured in 2 groups and differences between means. *P<0.05. *P<0.05 LVH (–) vs LVH (+). LVH, left ventricular hypertrophy.

t-test between the 2 groups. Frequency analysis was performed by the $\chi^2$ test.

When we evaluated the time-course of eGFR in patients with and without LVH, we performed a mixed-effect linear regression (PROC MIXED in SAS version 9.1) to account for non-independence of the same participants, and adjusted for baseline eGFR and possible baseline confounders (allocated drug, age, sex, body mass index, SBP, DBP, history of previous antihypertensive treatment, severe hypertension, type 2 diabetes, history of cerebrovascular disease, history of ischemic heart disease, renal dysfunction, and history of vascular disease). Further, we also evaluated the time-course of eGFR in patients with and without CKD, adjusted for possible baseline confounders (allocated drug, age, sex, body mass index, SBP, DBP, history of previous antihypertensive treatment, severe hypertension, type 2 diabetes, history of cerebrovascular disease, history of ischemic heart disease, LVH, and history of vascular disease). We examined the association of the LVH and CKD with the time-course of the eGFR after adjusting for baseline eGFR and possible baseline confounders (allocated drug, age, sex, body mass index, SBP, DBP, history of previous antihypertensive treatment, severe hypertension, type 2 diabetes, history of cerebrovascular disease, history of ischemic heart disease, and history of vascular disease).

Boneferroni correction for multiple comparisons was applied to each analysis. 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 a level lower than 140/80 mmHg in both groups (**Figure 1**). Mean SBP/DBP was 160.7/90.9 mmHg at baseline and 134.9/77.4 mmHg after 3 years in patients with LVH, and 162.7/91.1 mmHg at baseline and 135.2/76.5 mmHg after 3 years in those without LVH. During the follow-up period, there were slight but statistically significant differences in SBP and DBP between the 2 groups (**Figure 1**).

### Association of LVH With Changes in Renal Function

In both groups, the adjusted eGFRs were increased under strict BP control during the follow-up period, from 63.6 to 65.1 $ml \cdot min^{-1} \cdot 1.73\,m^{-2}$ in patients with LVH, and from 63.6 to 68.5 $ml \cdot min^{-1} \cdot 1.73\,m^{-2}$ in those without LVH. This improvement in eGFR was significantly greater in patients without LVH than in those with LVH (P=0.004, **Figure 2**).

Although the adjusted eGFR did not significantly change in patients without CKD, it significantly increased from 53.7 to 60.4 $ml \cdot min^{-1} \cdot 1.73\,m^{-2}$ in those with CKD (P<0.001, **Figure 3**).

When we evaluated the adjusted eGFR among CKD patients with or without LVH, the adjusted eGFR increased from 52.7 to 60.5 $ml \cdot min^{-1} \cdot 1.73\,m^{-2}$ in patients without LVH, but from 53.1 to 57.2 $ml \cdot min^{-1} \cdot 1.73\,m^{-2}$ in those with LVH. Thus, the improvement of eGFR was significantly greater in CKD patients without LVH than in those with LVH (P<0.001,

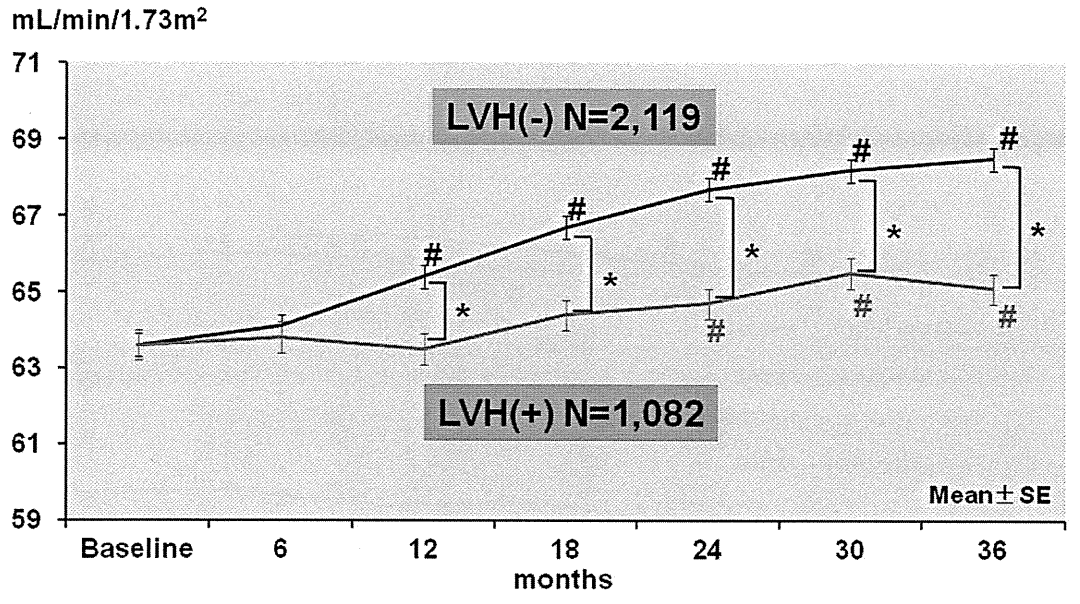


**Figure 2.** Changes in adjusted estimated glomerular filtration rate (eGFR) in patients with and without left ventricular hypertrophy (LVH). #P<0.05 vs eGFR at enrollment, *P<0.05 vs LVH (–).

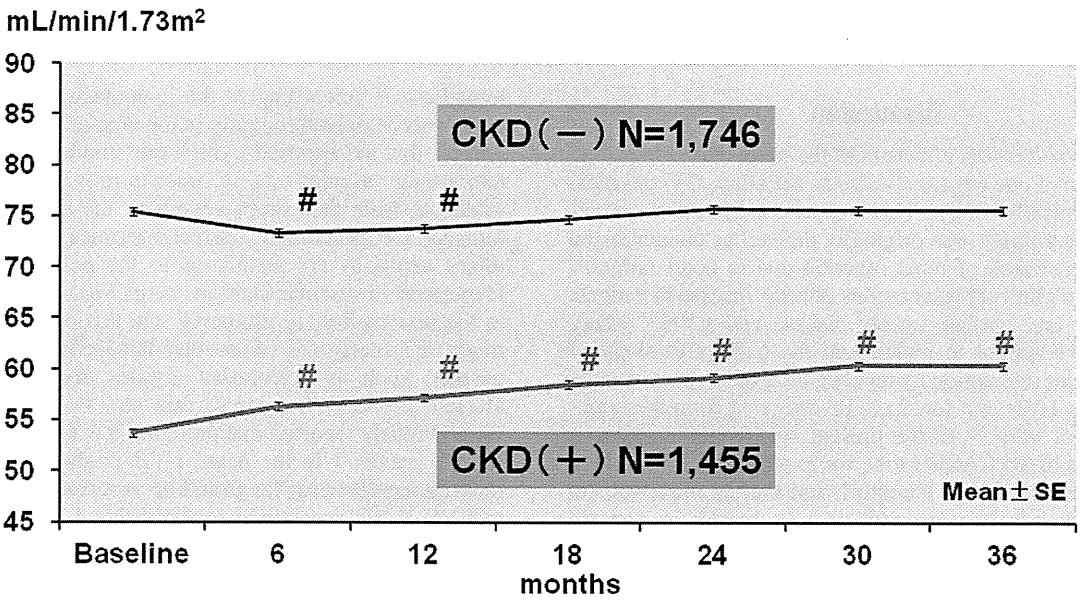


**Figure 3.** Changes in adjusted estimated glomerular filtration rate (eGFR) in patients with and without chronic kidney disease (CKD). #P<0.05 vs eGFR at enrollment.

**Figure 4**). Further, the adjusted eGFR changed from 76.5 to 75.4 ml·min$^{-1}$·1.73 m$^{-2}$ in patients without CKD but with LVH, and from 76.5 to 77.5 ml·min$^{-1}$·1.73 m$^{-2}$ in those without either CKD or LVH. Although the adjusted eGFR did not change notably among the patients without CKD, the final adjusted eGFR was significantly higher in patients without LVH than in those with LVH (P=0.048, **Figure 4**).

When we evaluated the effects of LVH to the time course of eGFR, CV disease were adjusted in our statistical analysis. However, because the participants with heterogeneous CV disease were included in the present study, changes in the eGFR in patients with or without CV disease at baseline were investigated. Then, the complication of LVH deteriorated the improvement of the time-course of the eGFR in patients with or without CV disease at baseline (data not shown).

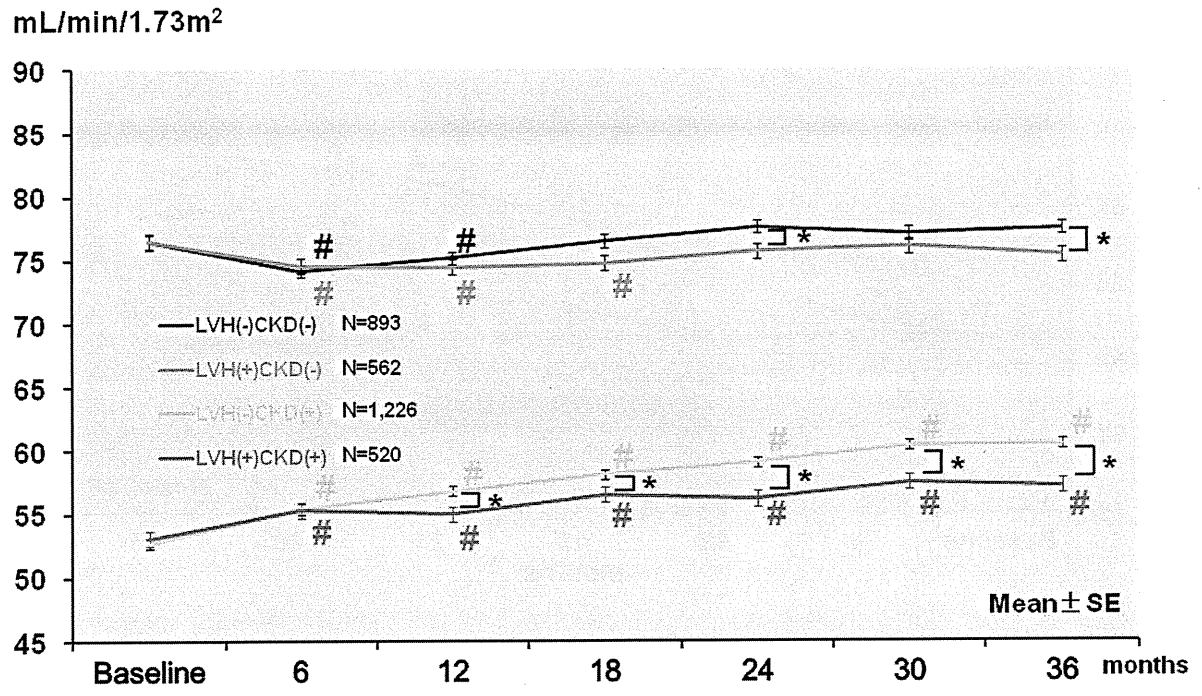


**Figure 4.** Changes in adjusted estimated glomerular filtration rate (eGFR) in patients with and without left ventricular hypertrophy (LVH) and in patients with and without chronic kidney disease (CKD). #P<0.05 vs eGFR at enrollment, *P<0.05 vs LVH (–).

## Discussion

Because hypertension affects both the heart and kidney, and dysfunction of one negatively affects the other, CV and renal disease frequently coexist. This interaction, referred to as 'cardiorenal syndrome', was originally defined as characterized by the aggravation of renal function due to heart failure.[16] The 2 major clinical presentations of heart disease in patients with CKD are coronary artery disease and LVH.[17] Many studies have sought to understand the pathophysiology of kidney–heart interaction by investigating the impact of renal function on LVH, but few have investigated from the opposite point of view.[8,9] In the present study, conducted as a subanalysis of the CASE-J trial, we found that renal function improved under strict BP control, and that its improvement in high-risk hypertensive patients was greater in patients without LVH than in those with LVH.

LVH is an adaptive response that reduces LV wall stress against volume and pressure overload.[18,19] Although originally considered a compensatory and beneficial response to overload, large population studies have provided much evidence that LVH confers an increased risk for CV events.[3,4,20] The mechanism of the close association between LVH and the time-course of renal function is not clear. In the present analysis, achieved DBP levels in patients with LVH were slightly but significantly higher than those without LVH. But, given that the difference in achieved BP levels was small (less than 1 mmHg) and moreover the significant difference of the achieved DBP level was observed only at 2 points (6 months and 36 months), this would not have influenced the difference in the time-course of renal function between the 2 groups.

In this regard, Ito et al recently proposed the 'strain vessel' hypothesis.[21] According to the hypothesis, cerebrovascular events occur most frequently in the area of small perforating arteries that are exposed to high pressure and have to maintain strong vascular tone in order to provide large pressure gradients from the parent vessels to the capillaries. In the kidneys, the glomerular afferent arterioles of the juxtamedullary nephrons are analogous to the perforating arteries. Hypertensive vascular damage occurs first and more severely in the juxtamedullary glomeruli. On this basis, albuminuria might be an early sign of vascular damage imposed on 'strain vessels' such as perforating arteries and juxtamedullary afferent arterioles. Supporting this 'strain vessel' hypothesis, we previously reported that proteinuria is a strong risk factor for CV events.[22] In the heart, LVH might be analogous to renal damage because longstanding exposure to high BP leads to LVH.[23] We previously reported that LVH was strongly associated with the risk of cerebrovascular events (adjusted HR: 2.38; 95%CI: 1.62–3.48; P<0.001).[10] Furthermore, higher urinary albumin excretion has been observed in patients with LVH,[24,25] suggesting that cardiac and glomerular vascular damage might occur concurrently. These findings are consistent with the idea that LVH is analogous to albuminuria. However, de Andrade et al reported that the impairment of volume-sensitive cardiopulmonary reflex control of renal sympathetic nerve activity in spontaneously hypertensive rats correlates better with the magnitude of LVH than the level of arterial pressure.[26] Thus, LVH might have partial direct effects on the time-course of renal function. When we previously evaluated the association of changes in LV mass with time-course of serum creatinine concentrations as another subanalysis of the CASE-J trial, the protection against LVH during antihypertensive treatment might be related to the preservation of renal function.[27] Early detection of LVH

**Table 2. The Dose of Each Antihypertensive Treatment in Patients With or Without LVH During the Follow-up Period**

| | 0.5 year | 1 year | 1.5 year | 2 year | 2.5 year | 3 year |
|---|---|---|---|---|---|---|
| **Patients without LVH** | | | | | | |
| Candesartan (number) | 1,068 | 1,051 | 1,038 | 1,028 | 1,030 | 1,021 |
| Mean dose (mg) | 7.4 | 7.6 | 7.8 | 7.9 | 8.1 | 8.2 |
| Amlodipine (number) | 1,044 | 1,018 | 1,012 | 1,008 | 1,004 | 997 |
| Mean dose (mg) | 5.2 | 5.4 | 5.4 | 5.4 | 5.5 | 5.5 |
| **Patients with LVH** | | | | | | |
| Candesartan (number) | 534 | 521 | 511 | 507 | 508 | 506 |
| Mean dose (mg) | 7.8 | 8.1 | 8.4 | 8.6 | 8.7 | 8.8 |
| Amlodipine (number) | 545 | 536 | 533 | 529 | 529 | 523 |
| Mean dose (mg) | 5.5 | 5.6 | 5.8 | 5.9 | 6.0 | 6.1 |

LVH, left ventricular hypertrophy.

and aggressive BP control might contribute to the prevention of deterioration in renal function.[9,27,28]

In general, the expected decline in eGFR is approximately $1\,ml \cdot min^{-1} \cdot year^{-1}$.[1] In the present analysis, we were surprised to observe an improvement in renal function in CKD patients with or without LVH under strict BP control. To our knowledge, this current study is the first to report an improvement of renal function with antihypertensive treatment. In chronic hypertension, the small arteries of the kidneys, including the afferent arterioles, undergo a number of pathological changes that alter renal autoregulation.[29] The initial response of renal function to a decrease in BP is therefore a decrease in GFR. In this regard, a subanalysis of the REIN study demonstrated the ability of long-term ACE inhibition to effectively prevent progression to end-stage renal disease via the substantial healing of tubular injury as a result of a decrease in urinary protein overload.[30]

Several limitations of the present study warrant mention. First, because the analysis was post-hoc, this cohort should not be regarded as an ordinary epidemiological cohort. Second, hypertensive patients with any of several high-risk factors were enrolled, including LVH, so our evaluation of data for patients with and without LVH required adjustment by respective baseline characteristics owing to their statistical differences. Third, the definition of LVH was based on ECG or echocardiographic criteria. Because echocardiography was only performed when feasible, only a small number of patients underwent the procedure. Fourth, we cannot exclude the possibility that the dose of each allocated drug and the number of concomitant antihypertensive drugs might affect the results in this study. The dose of each antihypertensive treatment in patients with or without LVH during the follow-up period was shown in **Table 2**. In addition, the incidence of the patients with LVH who received concomitant antihypertensive drugs was larger than that of patients without LVH (23.3% vs 17.1% in diuretics, 25.0% vs 16.8% in $\beta$-blockers, and 24.8% vs 19.4% in $\alpha$-blockers; $P<0.001$, respectively). However, because the additional antihypertensive treatments were considered as intermediate variables between LVH and CV events, we did not conduct the statistical adjustment for these factors. Finally, the mean follow-up period of 3.2 years might have been too short to evaluate changes in renal function. The CASE-J trial was extended for 3 years from 2006 as an observational study named CASE-J Ex,[31] which might resolve this issue in the near future.

## Conclusion

In the present subanalysis, we found that renal function in high-risk hypertensive patients improved under strict BP control irrespective of the presence or the absence of LVH. However, the improvement in eGFR was significantly greater in patients without LVH than in those with LVH, particularly among those with CKD. LVH appears to have an adverse impact on the improvement of renal function despite strict BP control. Since early detection and prevention of LVH allows the prevention of deterioration in renal function is still not clear, additional investigation is needed in a future study.

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### Disclosures

K. Ueshima, M. Mukoyama, T. Ogihara, T. Saruta, and K. Nakao have received honoraria for lectures from Takeda Pharmaceutical Co Ltd and Pfizer Japan Inc.

### References

1. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: Evaluation, classification, and stratification. *Am J Kidney Dis* 2002; **39**(Suppl 1): S1–S266.
2. Japanese Society of Nephrology. Chapter 1. Significance of CKD. *Clin Exp Nephrol* 2009; **13:** 192–195.
3. Levy D, Garrison RJ, Savage DD, Kannel WB, Castelli WP. Prognostic implications of echocardiographically determined left ventricular mass in the Framingham Heart Study. *N Engl J Med* 1990; **322:** 1561–1566.
4. Koren MJ, Devereux RB, Casale PN, Savage DD, Laragh JH. Relation of left ventricular mass and geometry to morbidity and mortality in uncomplicated essential hypertension. *Ann Intern Med* 1991; **114:** 345–352.
5. Wachtell K, Olsen MH, Dahlöf B, Devereux RB, Kjeldsen SE, Nieminen MS, et al. Microalbuminuria in hypertensive patients with electrocardiographic left ventricular hypertrophy: The LIFE study. *J Hypertens* 2002; **20:** 405–412.
6. Redón J, Cea-Calvo L, Lozano JV, Fernández-Pérez C, Navarro J, Bonet A, et al. ERIC-HTA 2003 Study Investigators. Kidney function and cardiovascular disease in the hypertensive population: The ERIC-HTA study. *J Hypertens* 2006; **24:** 663–669.
7. Nardi E, Palermo A, Mulè G, Cusimano P, Cottone S, Cerasola G. Left ventricular hypertrophy and geometry in hypertensive patients with chronic kidney disease. *J Hypertension* 2009; **27:** 633–641.
8. Fesler P, Du Cailar G, Ribstein J, Mimran A. Left ventricular remodeling and renal function in never-treated essential hypertension. *J Am Soc Nephrol* 2003; **14:** 881–887.

9. Boner G, Cooper ME, McCarroll K, Brenner BM, de Zeeuw D, Kowey PR, et al; RENAAL Investigators. Adverse effects of left ventricular hypertrophy in the reduction of endpoints in NIDDM with the angiotensin II antagonist losartan (RENAAL) study. *Diabetologia* 2005; **48:** 1980–1987.
10. Ueshima K, Yasuno S, Oba K, Fujimoto A, Ogihara T, Saruta T, et al. The effects of cardiac complications on cardiovascular events in Japanese high-risk hypertensive patients: A subanalysis of CASE-J trial. *Circ J* 2009; **73:** 1080–1085.
11. Fukui T, Rahman M, Hayashi K, Takeda K, Higaki J, Sato T, et al. Candesartan Antihypertensive Survival Evaluation in JAPAN (CASE-J) trial of cardiovascular events in high-risk hypertensive patients: Rationale, design, and methods. *Hypertens Res* 2003; **26:** 979–990.
12. Ogihara T, Nakao T, Fukui T, Fukiyama K, Ueshima K, Oba K, et al, for the CASE-J Trial Group. Candesartan Antihypertensive Survival Evaluation in Japan trial Group. Effects of candesartan compared with amlodipine in hypertensive patients with high cardiovascular risks: Candesartan antihypertensive survival evaluation in Japan trial. *Hypertension* 2008; **51:** 393–398.
13. Japanese Society of Nephrology. Chapter 9: Evaluation method for kidney function and urinary findings. *Clin Exp Nephrol* 2009; **13:** 209–211.
14. Matsuo S, Imai E, Horio M, Yasuda Y, Tomita K, Nitta K, et al. Collaborators developing the Japanese equation for estimated GFR: Revised equations for estimated GFR from serum creatinine in Japan. *Am J Kidney Dis* 2009; **53:** 982–992.
15. Japanese Society of Nephrology. Chapter 2: Definition and classification of CKD. *Clin Exp Nephrol* 2009; **13:** 196.
16. Ronco C, Haapio M, House AA, Anavekar N, Bellomo R. Cardiorenal Syndrome. *J Am Coll Cardiol* 2008; **52:** 1527–1539.
17. Berl T, Henrich W. Kidney-heart interactions: Epidemiology, pathogenesis, and treatment. *Clin J Am Soc Nephrol* 2006; **1:** 8–18.
18. Grossman W, Jones D, McLaurin P. Wall stress and patterns of hypertrophy in the human left ventricle. *J Clin Invest* 1975; **56:** 56–64.
19. Ganau A, Devereux RB, Pickering TG, Roman MJ, Schnall PL, Santucci S, et al. Relation of left ventricular hemodynamic load and contractile performance to left ventricular mass in hypertension. *Circulation* 1990; **81:** 25–36.
20. Jissho S, Shimada K, Taguchi H, Yoshida K, Fukuda S, Tanaka H, et al. Impact of electrocardiographic left ventricular hypertrophy on the occurrence of cardiovascular events in elderly hypertensive patients: The Japanese trial to assess optimal systolic blood pressure in elderly hypertensive patients (JATOS). *Circ J* 2010; **74:** 938–945.
21. Ito S, Nagasawa T, Abe M, Mori T. Strain vessel hypothesis: A viewpoint for linkage of albuminuria and cerebro-cardiovascular risk. *Hypertens Res* 2009; **32:** 115–121.
22. Saruta T, Hayashi K, Ogihara T, Nakao K, Fukui T, Fukiyama K. Effects of candesartan and amlodipine on cardiovascular events in hypertensive patients with chronic kidney disease: Subanalysis of the CASE-J Study. *Hypertens Res* 2009; **32:** 505–512.
23. Komatsu H, Yamada S, Iwano H, Okada M, Onozuka H, Mikami T, et al. Angiotensin II receptor blocker, valsartan, increases myocardial blood volume and regresses hypertrophy in hypertensive patients. *Circ J* 2009; **73:** 2098–2103.
24. Kramer H, Jacobs DR Jr, Bild D, Post W, Saad MF, Detrano R, et al. Urine albumin excretion and subclinical cardiovascular disease: The Multi-Ethnic Study of Atherosclerosis. *Hypertension* 2005; **46:** 38–43.
25. Wachtell K, Palmieri V, Olsen MH, Bella JN, Aalto T, Dahlöf B, et al. Urine albumin/creatinine ratio and echocardiographic left ventricular structure and function in hypertensive patients with electrocardiographic left ventricular hypertrophy: The LIFE study: Losartan Intervention for Endpoint Reduction. *Am Heart J* 2002; **143:** 319–326.
26. de Andrade TU, Abreu GR, Moysés MR, de Melo Cabral A, Bissoli NS. Role of cardiac hypertrophy in reducing the sensitivity of cardiopulmonary reflex control of renal sympathetic nerve activity in spontaneously hypertensive rats. *Clin Exp Pharmacol Physiol* 2008; **35:** 1104–1108.
27. Yasuno S, Ueshima K, Oba K, Fujimoto A, Ogihara T, Saruta T, et al. Clinical significance of left ventricular hypertrophy and changes in left ventricular mass in high-risk hypertensive patients: A subanalysis of the Candesartan Antihypertensive Survival Evaluation in Japan trial. *J Hypertens* 2009; **27:** 1705–1712.
28. Yilmaz BA, Mete T, Dincer I, Kutlay S, Sengül S, Keven K, et al. Predictors of left ventricular hypertrophy in patients with chronic kidney disease. *Ren Fail* 2007; **29:** 303–307.
29. Palmer BF. Renal dysfunction complicating the treatment of hypertension. *N Engl J Med* 2002; **347:** 1256–1261.
30. Ruggenenti P, Perna A, Benini R, Bertani T, Zoccali C, Maggiore Q, et al. In chronic nephropathies prolonged ACE inhibition can induce remission: Dynamics of time-dependent changes in GFR. *J Am Soc Nephrol* 1999; **10:** 997–1006.
31. Ueshima K, Oba K, Yasuno S, Fujimoto A, Sato T, Fukiyama K, et al; Candesartan Antihypertensive Survival Evaluation in Japan Trial Group. Long-term effects of candesartan and amlodipine on cardiovascular mortality and morbidity in Japanese high-risk hypertensive patients: Rationale, design, and characteristics of candesartan antihypertensive survival evaluation in Japan extension (CASE-J Ex). *Contemp Clin Trial* 2009; **30:** 97–101.

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ORIGINAL ARTICLE

# Role of diabetes and obesity in outcomes of the candesartan antihypertensive survival evaluation in Japan (CASE-J) trial

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**The Candesartan Antihypertensive Survival Evaluation in Japan (CASE-J) trial assessed cardiovascular outcomes in high-risk hypertensive patients receiving either candesartan or amlodipine. The aim of this study was to examine the role of pre-existing diabetes or obesity on these outcomes as a sub-analysis of the trial. We examined the influence of pre-existing diabetes on cardiovascular morbidity and mortality using a multivariate Cox regression model. The cardiovascular morbidity and mortality of candesartan and amlodipine were compared between subgroups with or without pre-existing diabetes or by body mass index (BMI) category, and new-onset diabetes was compared by BMI category. Pre-existing diabetes greatly increased the cardiovascular mortality and morbidity, regardless of the allocated drugs. Furthermore, all-cause mortality was significantly higher with amlodipine than with candesartan among patients with BMI $\geqslant 27.5\,kg\,m^{-2}$ (adjusted hazard ratio (HR)=0.32; range=0.13–0.75; $P$=0.009). New-onset diabetes occurred significantly less frequently with candesartan than with amlodipine, with an adjusted HR of 0.66 ($P$=0.043). Furthermore, the increase in new-onset diabetes was dependent on BMI among patients receiving amlodipine, whereas no such dependency was observed for candesartan (interaction $P$=0.016). In conclusion, preexisting diabetes increased the risk of experiencing a cardiovascular event among high-risk Japanese hypertensive patients. Candesartan treatment may suppress all-cause death and reduce the incidence of new-onset diabetes in patients with obesity.**
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**Keywords:** cardiovascular diseases; diabetes; obesity; randomized controlled trial

## INTRODUCTION

Hypertension is often associated with insulin resistance, and hypertensive patients tend to develop type 2 diabetes mellitus (DM), which increases the risk of cardiovascular (CV) events in these patients. Hypertension, insulin resistance, obesity and dyslipidemia frequently occur together in a single individual, and such clustering is recognized as metabolic syndrome. With the prevalence of obesity increasing worldwide, even in Asian nations,[1] researchers have sought to develop treatment options capable of comprehensively addressing these risk factors in hypertensive patients.

As preexisting DM and obesity are thought to be related to the renin–angiotensin system (RAS), considerable interest has been focused on the difference between the treatment effects of angiotensin II receptor blockers (ARBs), angiotensin-converting enzyme inhibitors (ACEIs) and calcium channel blockers (CCBs) with regard to treating hypertensive patients with DM or obesity. Several large randomized clinical trials have found the therapeutic benefits from ARBs,[2] CCBs[3,4] and ACEIs[5] to be superior to beta blocker-based treatments or placebos with regard to reducing mortality and CV events in these patients. The Blood Pressure Lowering Treatment Trialists' Collaboration (BPLTTC) conducted an individual patient-based meta-analysis and concluded that all of the major classes of blood pressure (BP)-lowering agents are capable of producing substantial reductions in short- to medium-term risk associated with the leading causes of death and CV events in patients with diabetes, although small differences in the effects of regimens on macrovascular events cannot be excluded.[6] However, none of the previous trials have analyzed the relationship between obesity and antihypertensive treatment effects on cardiovascular outcomes.

With regard to new-onset DM, the ARB, valsartan, has been shown to suppress incidence of new-onset DM more effectively than the CCB, amlodipine.[7] We recently reported the principal results of the Candesartan Antihypertensive Survival Evaluation in Japan (CASE-J) study, a prospective, multi-center, open-label randomized controlled trial with blinded assessment of end points, which was designed to evaluate the efficacy of candesartan and amlodipine in reducing the

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incidence of CV morbidity and mortality in a Japanese population with high-risk hypertension.[8] Although results ultimately showed no significant difference in incidence of CV events between the two treatments,[9] of particular note among the findings was the fact that the ARB, candesartan, prevented new-onset DM more effectively than amlodipine, thereby raising the possibility that candesartan's treatment effect may be affected by obesity condition, given present knowledge regarding the mechanism of ARB action.

To clarify the role of preexisting DM and obesity in the findings of the CASE-J trial, we evaluated the influence of diabetic status and body mass index (BMI) on trial outcomes and the interaction between these factors and allocated treatments. Preliminary data have been described previously,[9] and here we present a detailed *post-hoc* analysis.

## METHODS

### Study design

As the rationale and complete design of the CASE-J trial have been previously published,[8] relevant details are briefly described below. For the trial, written informed consents were obtained from all patients before enrollment, and the trial protocol was approved by the ethics committee of Kyoto University and undertaken in accordance with the Declaration of Helsinki Principles. The data and safety monitoring board made periodic recommendations to the steering committee regarding the ethical aspects of trial continuation by evaluating each occurrence of a possible adverse event.

The CASE-J trial enrolled eligible Japanese hypertensive patients with, at least, one high-risk factor. High-risk factors in the CASE-J trial were as follows: severe hypertension that is systolic BP (SBP) $\geqslant$180 mm Hg or diastolic BP (DBP) $\geqslant$110 mm Hg on two consecutive visits; type 2 DM (fasting blood glucose $\geqslant$126 mg per 100 ml, casual blood glucose $\geqslant$200 mg per 100 ml, hemoglobin A1c (HbA1c) $\geqslant$6.5%, 2-h blood glucose on 75 g oral glucose tolerance test $\geqslant$200 mg per 100 ml, or currently receiving treatment with a hypoglycemic agent); history of cerebral hemorrhage, cerebral infarction or transient ischemic attack occurring more than 6 months before screening; left ventricular hypertrophy on either echocardiography or electrocardiogram, angina pectoris or history of myocardial infarction occurring more than 6 months before screening; proteinuria or serum creatinine (sCr) $\geqslant$1.3 mg per 100 ml; and symptoms of arteriosclerotic peripheral artery obstruction.

After randomization, patients were allocated to receive either candesartan by oral administration at 4–8 mg day$^{-1}$, increasing up to 12 mg day$^{-1}$ as necessary (or 2 mg day$^{-1}$, increasing up to 8 mg day$^{-1}$ as necessary in patients with renal impairment) or amlodipine by oral administration at 2.5–5 mg day$^{-1}$, increasing up to 10 mg day$^{-1}$ as necessary. Targets for BP control were determined according to practice guidelines developed by the Japanese Society of Hypertension (JSH),[10] as reported previously.[8]

### Outcome measures

Outcome measures evaluated in this analysis were CV event, non-renal CV event, all-cause death, CV death and new-onset DM. In the original CASE-J trial, CV event was the primary end point, which is the first fatal or non-fatal CV event and represented a composite of the following: sudden unexpected death that happened within 24 h without external causes; cerebrovascular events including stroke or transient ischemic attack; cardiac events including heart failure, angina pectoris or acute myocardial infarction; renal events, including sCr $\geqslant$4.0 mg per 100 ml, doubling of sCr (although sCr $\leqslant$2.0 mg per 100 ml in any context was not regarded as an event) and end-stage renal disease; and vascular events, including dissecting aortic aneurysm or arteriosclerotic occlusion of a peripheral artery. As renal pathology in diabetic patients is affected by glycemic control, we also evaluated the incidence of non-renal CV events that excluded renal events from primary CV events. All-cause death and new-onset diabetes were the secondary and pre-specified end point in the CASE-J trial. Event evaluation for CV event and all-cause death was independently performed by the event evaluation committee members, who were blinded to the assigned treatment groups and assessed events according to the protocol criteria. Cases of new-onset DM were defined as patients who were reported to have developed DM as an adverse event or who were on anti-diabetic agents during the course of the study as reported in the case report form.

### Statistical methods

Baseline characteristics were expressed as mean ± s.d. or proportions, and between-groups using the $\chi^2$ test or *t*-test. Analyses were divided into two parts: we first evaluated the influence of preexisting DM at baseline on each end point as a prognostic factor analysis. Here, we conducted multivariate Cox regression analysis with adjustment for allocated drugs, BMI, age, sex, hyperlipidemia, smoking history, high-risk factors in the CASE-J trial (severe hypertension, cerebrovascular history, cardiac complications, renal dysfunction and vascular disease) and antihypertensive drug use at baseline.

We then conducted a comparison with regard to allocated drugs (candesartan *vs.* amlodipine) across subgroups for baseline presence or absence of preexisting DM and the BMI category (<22.0, $\geqslant$22.0–25.0, $\geqslant$25.0–<27.5 and

**Table 1a Baseline characteristics in patients with and without diabetes[a]**

| | *DM (+) at baseline* | | | *DM (−) at baseline* | | |
|---|---|---|---|---|---|---|
| | *Candesartan (N=1011)* | *Amlodipine (N=1007)* | P-*value* | *Candesartan (N=1343)* | *Amlodipine (N=1342)* | P-*value* |
| Age (years) | 63.9 ± 9.5 | 64.1 ± 9.9 | 0.660 | 63.6 ± 11.2 | 63.8 ± 11.7 | 0.684 |
| BMI (kg m$^{-2}$) | 25.1 ± 3.9 | 25.1 ± 3.6 | 0.739 | 24.2 ± 3.5 | 24.0 ± 3.5 | 0.099 |
| Female (%) | 445 (44.0) | 447 (44.4) | 0.866 | 647 (48.2) | 567 (42.3) | 0.002 |
| Severe hypertension[b] (%) | 58 (5.7) | 64 (6.4) | 0.560 | 396 (29.5) | 429 (32.0) | 0.164 |
| Cerebrovascular history[b] (%) | 70 (6.9) | 59 (5.9) | 0.328 | 178 (13.3) | 166 (12.4) | 0.493 |
| Cardiac complications[b] (%) | 291 (28.8) | 313 (31.1) | 0.260 | 716 (53.3) | 710 (52.9) | 0.833 |
| Renal dysfunction[b] (%) | 228 (22.6) | 216 (21.5) | 0.550 | 344 (25.6) | 327 (24.4) | 0.455 |
| Vascular disease (%) | 11 (1.1) | 5 (0.5) | 0.134 | 18 (1.3) | 19 (1.4) | 0.867 |
| Antihypertensive drug use (%) | 712 (70.4) | 686 (68.1) | 0.262 | 900 (67.0) | 867 (64.6) | 0.188 |
| Current or smoking history (%) | 319 (31.6) | 319 (31.7) | 0.952 | 386 (28.7) | 474 (35.3) | <0.001 |
| Hyperlipidemia (%) | 460 (45.5) | 440 (43.7) | 0.415 | 608 (45.3) | 570 (42.5) | 0.144 |
| SBP (mm Hg) | 159.8 ± 12.9 | 160.0 ± 12.5 | 0.690 | 164.5 ± 14.7 | 165.6 ± 14.9 | 0.054 |
| DBP (mm Hg) | 88.3 ± 9.9 | 88.3 ± 10.3 | 0.943 | 94.0 ± 11.2 | 94.5 ± 11.4 | 0.249 |

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; DM, diabetes mellitus; SBP, systolic blood pressure.
[a]Data are shown as the mean ± s.d. or *n* (%) in each category.
[b]Severe hypertension (blood pressure $\geqslant$180 or $\geqslant$110 mm Hg), cerebrovascular event history (history of stroke or transient ischemic attack), cardiac complication (left ventricular hypertrophy, angina pectoris or history of myocardial infarction), renal dysfunction (proteinuria or serum creatinine $\geqslant$1.3 mg per 100 ml).

**Table 1b Baseline characteristics in patients with BMI category[a]**

| | <22.0 kg m$^{-2}$ | | | 22.0–<25.0 kg m$^{-2}$ | | | 25.0–<27.5 kg m$^{-2}$ | | | ⩾27.5 kg m$^{-2}$ | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *Candesartan (N=561)* | *Amlodipine (N=565)* | P-value | *Candesartan (N=813)* | *Amlodipine (N=853)* | P-value | *Candesartan (N=536)* | *Amlodipine (N=527)* | P-value | *Candesartan (N=444)* | *Amlodipine (N=404)* | P-value |
| Age (years) | 67.1 ± 9.9 | 66.4 ± 10.6 | 0.257 | 63.8 ± 9.6 | 64.1 ± 9.7 | 0.419 | 63.5 ± 10.1 | 63.7 ± 10.1 | 0.704 | 59.9 ± 11.9 | 60.4 ± 11.8 | 0.551 |
| BMI (kg m$^{-2}$) | 20.3 ± 1.3 | 20.2 ± 1.4 | 0.384 | 23.5 ± 0.9 | 23.6 ± 0.9 | 0.820 | 26.1 ± 0.7 | 26.1 ± 0.7 | 0.490 | 30.2 ± 2.8 | 30.2 ± 2.8 | 0.875 |
| Female (%) | 299 (53.3) | 267 (47.3) | 0.043 | 337 (41.5) | 342 (40.1) | 0.573 | 250 (46.1) | 205 (38.9) | 0.011 | 206 (46.4) | 200 (49.5) | 0.365 |
| Severe hypertension[b] (%) | 125 (22.3) | 130 (23.0) | 0.771 | 144 (17.7) | 173 (20.3) | 0.182 | 104 (19.4) | 108 (20.5) | 0.656 | 81 (18.2) | 82 (20.3) | 0.448 |
| Preexisting DM (%) | 195 (34.8) | 186 (32.9) | 0.514 | 355 (43.7) | 360 (42.2) | 0.547 | 236 (44.0) | 235 (44.6) | 0.854 | 225 (50.7) | 226 (55.9) | 0.125 |
| Cerebrovascular history[b] (%) | 72 (12.8) | 66 (11.7) | 0.555 | 85 (10.5) | 84 (9.8) | 0.623 | 60 (11.2) | 47 (9.3) | 0.308 | 31 (7.0) | 27 (6.7) | 0.863 |
| Cardiac complications[b] (%) | 238 (42.4) | 260 (46.0) | 0.225 | 372 (45.8) | 385 (45.1) | 0.799 | 216 (40.3) | 231 (43.8) | 0.243 | 181 (40.8) | 147 (36.4) | 0.191 |
| Renal dysfunction[b] (%) | 140 (25.0) | 137 (24.3) | 0.783 | 182 (22.4) | 175 (20.5) | 0.352 | 130 (24.3) | 130 (24.7) | 0.875 | 120 (27.0) | 101 (25.0) | 0.502 |
| Vascular disease (%) | 13 (2.3) | 9 (1.5) | 0.380 | 9 (1.1) | 9 (0.9) | 0.733 | 3 (0.6) | 5 (1.0) | 0.463 | 4 (0.9) | 2 (0.5) | 0.481 |
| Antihypertensive drug use (%) | 377 (67.2) | 378 (66.9) | 0.915 | 540 (66.4) | 536 (62.8) | 0.126 | 385 (71.8) | 374 (71.0) | 0.756 | 310 (69.8) | 265 (65.6) | 0.188 |
| Current or smoking history (%) | 156 (27.8) | 201 (35.6) | 0.005 | 254 (31.2) | 286 (33.5) | 0.319 | 155 (28.9) | 183 (34.7) | 0.042 | 140 (31.5) | 123 (30.5) | 0.733 |
| Hyperlipidemia (%) | 196 (34.9) | 192 (34.0) | 0.736 | 364 (44.8) | 371 (43.5) | 0.599 | 268 (50.0) | 240 (45.5) | 0.146 | 240 (54.1) | 207 (51.2) | 0.412 |
| SBP (mm Hg) | 164.5 ± 13.8 | 165.3 ± 14.0 | 0.348 | 162.1 ± 13.8 | 163.0 ± 14.0 | 0.193 | 162.1 ± 14.3 | 162.3 ± 14.5 | 0.763 | 161.9 ± 14.7 | 162.0 ± 14.2 | 0.413 |
| DBP (mm Hg) | 90.4 ± 11.3 | 91.7 ± 11.1 | 0.106 | 91.3 ± 10.6 | 91.5 ± 11.5 | 0.748 | 91.6 ± 11.3 | 91.7 ± 11.5 | 0.841 | 93.1 ± 11.0 | 92.8 ± 11.0 | 0.725 |

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; DM, diabetes mellitus; SBP, systolic blood pressure.
[a]Data are shown as the mean ± s.d. or *n* (%) in each category.
[b]Severe hypertension (blood pressure ⩾180 or ⩾110 mm Hg), cerebrovascular event history (history of stroke or transient ischemic attack), cardiac complication (left ventricular hypertrophy, angina pectoris or history of myocardial infarction), renal dysfunction (proteinuria or serum creatinine ⩾1.3 mg per 100 ml).

**Table 2 Adjusted HRs of prognostic factors for primary CV events**

| *Baseline characteristics* | *HR*[a] | 95% *CI* | P-*value* |
|---|---|---|---|
| DM (present) | 2.58 | 1.99–3.33 | <.001 |
| Allocated drugs (candesartan) | 0.99 | 0.78–1.26 | 0.922 |
| Age | 1.37 | 1.19–1.57 | <0.001 |
| BMI | 1.16 | 0.98–1.37 | 0.092 |
| Sex (female) | 0.89 | 0.67–1.18 | 0.411 |
| Severe hypertension (yes) | 1.10 | 0.74–1.65 | 0.632 |
| Cerebrovascular history (yes) | 2.04 | 1.47–2.83 | <0.001 |
| Cardiac complications (yes) | 2.21 | 1.72–2.84 | <0.001 |
| Renal dysfunction (yes) | 2.93 | 2.30–3.74 | <0.001 |
| Vascular disease, yes | 1.68 | 0.69–4.10 | 0.255 |
| Antihypertensive drug use at baseline (yes) | 1.42 | 1.05–1.91 | 0.024 |
| Current or former smoker (yes) | 1.02 | 0.77–1.36 | 0.871 |
| Hyperlipidemia (yes) | 0.89 | 0.69–1.15 | 0.368 |

Abbreviations: BMI, body mass index; CI, confidence interval; CV, cardiovascular; DM, diabetes mellitus; HR, hazard ratio.
[a]The HR value was adjusted for all baseline variables listed in Table 2 entering in the multivariate Cox regression model.

⩾27.5 kg m$^{-2}$). The cutoff points of the BMI category (22 kg m$^{-2}$ as normal BMI for the Japanese; 25 kg m$^{-2}$ as upper limit of normal BMI range; and 27.5 kg m$^{-2}$ as the mid-point of the overweight BMI range) were pre-specified before analyzing the data. In the comparison between candesartan and amlodipine, hazard ratios (HRs), 95% confidence intervals (CIs) and *P*-values of the Wald test were also calculated with adjustment for age, sex, smoking history, hyperlipidemia, severe hypertension, cerebrovascular history, cardiac complications, renal dysfunction and antihypertensive drug use at baseline in the multivariate Cox regression model. Interactions of HRs between allocated drugs and the baseline variables of preexisting DM status and BMI (as continuous variable) were also evaluated in the multivariate Cox regression model with interaction terms. All statistical tests were two-sided and performed using SAS version 9.1 (SAS Institute, Cary, NC, USA).

## RESULTS

### Baseline characteristics and medication adherence

Of the 4703 patients that enrolled in the CASE-J trial, 2018 (42. 9%) patients had DM at baseline and 2685 (57.1%) did not. Table 1a summarizes the baseline characteristics by diabetic status at baseline and allocated drug. With regard to between-group comparisons, background characteristics were well balanced between both treatment groups except in regards to sex ratio and smoking history in patients without DM at baseline. The baseline characteristics of the BMI category were shown in Table 1b. There were some statistical differences in sex and current smoking history between two groups in the two BMI categories (<22.0 and ⩾25.0–<27.5 kg m$^{-2}$, respectively), whereas there was no statistical difference in the BMI ⩾27.5 kg m$^{-2}$ category.

Percentages of patients who took more than 80% of the allocated drug and details regarding the distribution of additional drugs during the follow-up period have already been reported in the main results of the CASE-J trial.[9] Regarding drug doses, 59.4% of patients in the candesartan group were taking 8 mg at last follow-up, whereas 23.5% were taking 12 mg and 13.8% were taking 4 mg. In the amlodipine group, 71.6% were taking 5 mg at last follow-up, whereas 14.9% were taking 10 mg and 9.5% were taking 2.5 mg. Mean doses in the candesartan and amlodipine groups were 8.3 and 5.6 mg, respectively.

### Association of diabetic status at baseline with the CASE-J trial outcome

Over 3.3 ± 0.8 mean years of follow-up, primary CV events occurred in 103 (3.8%) patients without DM at baseline (11.8 per 1000 patient-years) and in 165 (8.2%) with DM at baseline (25.5 per

**Table 3 Hazard ratios for each event in patients with and without diabetes**

| | *DM (+) at baseline* | | | | *DM (−) at baseline* | | | | *DM (+) vs. DM (−)* | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| *Events* | *At risk* | *Events* | *Rate*[a] | *95% CI* | *At risk* | *Events* | *Rate* | *95% CI* | *HR*[b] | *95% CI* | P-*value* |
| Primary CV events | 2018 | 165 | 25.5 | 21.8–29.7 | 2685 | 103 | 11.8 | 9.7–14.3 | 2.58 | 2.00–3.33 | <0.001 |
| *Cerebrovascular* | 2018 | 54 | 8.2 | 6.1–10.7 | 2685 | 57 | 6.5 | 4.9–8.4 | 1.49 | 1.01–2.19 | 0.044 |
| *Cardiac* | 2018 | 67 | 10.2 | 7.9–12.9 | 2685 | 23 | 2.6 | 1.7–3.9 | 4.99 | 3.05–8.16 | <0.0001 |
| *Renal* | 2018 | 38 | 5.7 | 4.0–7.8 | 2685 | 8.0 | 0.9 | 0.4–1. 8 | 7.44 | 3.47–16.22 | <0.0001 |
| Non-renal CV events | 2018 | 138 | 21.2 | 17.8–25.1 | 2685 | 96 | 11.0 | 8.9–13.4 | 2.34 | 1.78–3.08 | <0.001 |
| All-cause deaths | 2018 | 89 | 13.3 | 10.7–16.4 | 2685 | 70 | 7.9 | 6.2–10.0 | 2.04 | 1.46–2.87 | <0.001 |
| CV deaths | 2018 | 26 | 3.9 | 2.5–5.7 | 2685 | 21 | 2.4 | 1.5–3.6 | 1.93 | 1.03–3.61 | 0.041 |

Abbreviations: CI, confidence interval; CV, cardiovascular; DM, diabetes mellitus; HR, hazard ratio.
[a]Rate is expressed as incidence per 1000 patient-years.
[b]HR value was adjusted for the potential confounders (allocated drugs, age, body mass index, sex, severe hypertension, cerebrovascular history, cardiac complications, renal dysfunction, antihypertensive drug use at baseline, smoking history and hyperlipidemia).

**Table 4 Comparisons between candesartan and amlodipine for each event for subgroups of diabetes status at baseline**

| | *Candesartan* | | | | *Amlodipine* | | | | *Comparison of treatment groups* | | | *Interaction test* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *At risk* | *Events* | *Rate*[a] | *95% CI* | *At risk* | *Events* | *Rate*[a] | *95% CI* | *HR*[b] | *95% CI* | P-*value* | P-*value* |
| *Primary CV events* | | | | | | | | | | | | |
| DM (−) | 1343 | 54 | 12.5 | 9.4–16.3 | 1342 | 49 | 11.2 | 8.3–14.8 | 1.06 | 0.72–1.58 | 0.744 | 0.565 |
| DM (+) | 1011 | 80 | 24.8 | 19.6–30.8 | 1007 | 85 | 26.3 | 21.0–32.5 | 0.92 | 0.67–1.24 | 0.568 | |
| *Cerebrovascular events* | | | | | | | | | | | | |
| DM (−) | 1343 | 31 | 7.1 | 4.8–10.1 | 1342 | 26 | 5.9 | 3.9–8.7 | 1.13 | 0.67–1.90 | 0.661 | 0.820 |
| DM (+) | 1011 | 30 | 9.1 | 6.1–13.0 | 1007 | 24 | 7.2 | 4.6–10.8 | 1.22 | 0.71–2.10 | 0.466 | |
| *Cardiac events* | | | | | | | | | | | | |
| DM (−) | 1343 | 12 | 2.7 | 1.4–4.8 | 1342 | 11 | 2.5 | 1.2–4.5 | 1.12 | 0.49–2.57 | 0.785 | 0.619 |
| DM (+) | 1011 | 31 | 9.4 | 6.4–13.4 | 1007 | 36 | 10.9 | 7.7–15.1 | 0.87 | 0.54–1.40 | 0.562 | |
| *Renal events* | | | | | | | | | | | | |
| DM (−) | 1343 | 2 | 0.5 | 0.1–1.6 | 1342 | 6 | 1.4 | 0.5–3.0 | 0.31 | 0.06–1.57 | 0.158 | 0.329 |
| DM (+) | 1011 | 17 | 5.1 | 3.0–8.2 | 1007 | 21 | 6.3 | 3.9–9.7 | 0.72 | 0.38–1.37 | 0.320 | |
| *Non-renal CV events* | | | | | | | | | | | | |
| DM (−) | 1343 | 52 | 12.0 | 9.0–15.7 | 1342 | 44 | 10.0 | 7.3–13.5 | 1.16 | 0.77–1.73 | 0.484 | 0.525 |
| DM (+) | 1011 | 68 | 21.0 | 16.3–26.6 | 1007 | 70 | 21.5 | 16.7–27.1 | 0.97 | 0.70–1.36 | 0.879 | |
| *All-cause deaths* | | | | | | | | | | | | |
| DM (−) | 1343 | 33 | 7.5 | 5.1–10.5 | 1342 | 37 | 8.4 | 5.9–11.5 | 0.96 | 0.60–1.54 | 0.853 | 0.775 |
| DM (+) | 1011 | 40 | 11.9 | 8.5–16.3 | 1007 | 49 | 14.7 | 10.8–19.4 | 0.84 | 0.55–1.27 | 0.407 | |
| *CV deaths* | | | | | | | | | | | | |
| DM (−) | 1343 | 11 | 2.5 | 1.2–4.5 | 1342 | 10 | 2.3 | 1.1–4.1 | 1.13 | 0.48–2.68 | 0.783 | 0.818 |
| DM (+) | 1011 | 11 | 3.3 | 1.6–5.9 | 1007 | 15 | 4.9 | 2.5–7.4 | 0.78 | 0.36–1.71 | 0.537 | |

Abbreviations: CI, confidence interval; CV, cardiovascular; DM, diabetes mellitus; HR, hazard ratio.
[a]Rate is expressed as incidence per 1000 patient-years.
[b]HR value was adjusted for the potential confounders (age, body mass index, sex, severe hypertension, cerebrovascular history, cardiac complications, renal dysfunction, antihypertensive drug use at baseline, smoking history and hyperlipidemia).

1000 patient-years). Multivariate Cox regression analysis revealed that DM was an independent predictor of primary CV events (adjusted HR=2.58, 95% CI=1.99–3.33, $P<0.0001$; Table 2), as were aging, cerebrovascular history, cardiac complications, renal dysfunction and antihypertensive drug use at baseline. In addition, DM was significantly associated with risk of each CV event and all-cause death (Table 3).

We then examined the effects of candesartan- and amlodipine-based regimens on the incidences of each event and all-cause deaths among subgroups of diabetic status at baseline, with analysis revealing no significant differences in event incidence between the two treatment regimens, regardless of diabetic status at baseline (Table 4). New-onset DM occurred in 38 (2.8%) patients receiving candesartan-based regimens (8.7 per 1000 patient-years) and in 59 (4.4%) receiving

**Table 5 Comparisons between candesartan and amlodipine for each event for BMI category at baseline**

| | *Candesartan* | | | | *Amlodipine* | | | | *Comparison of treatment groups* | | | | *Interaction test* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *At risk* | *Events* | *Rate*[a] | *95% CI* | *At risk* | *Events* | *Rate*[a] | *95% CI* | *HR*[b] | *95% CI* | | P-*value* | P-*value* |
| *Primary CV events* | | | | | | | | | | | | | |
| BMI <22 | 561 | 37 | 20.9 | 14.7–28.7 | 565 | 33 | 18.1 | 12.5–25.4 | 1.13 | 0.70 | 1.81 | 0.623 | 0.904 |
| BMI ⩾22–<25 | 813 | 31 | 11.6 | 7.9–16.5 | 853 | 48 | 17.4 | 12.8–23.0 | 0.66 | 0.42 | 1.04 | 0.075 | |
| BMI ⩾25–<27.5 | 536 | 37 | 21.6 | 15.2–29.8 | 527 | 28 | 16.4 | 10.8–23.7 | 1.37 | 0.83 | 2.25 | 0.214 | |
| BMI ⩾27.5 | 444 | 29 | 20.6 | 13.8–29.6 | 404 | 25 | 19.1 | 12.3–28.1 | 1.09 | 0.63 | 1.87 | 0.761 | |
| *Non-renal CV events* | | | | | | | | | | | | | |
| BMI <22 | 561 | 34 | 19.1 | 13.2–26.7 | 565 | 25 | 13.6 | 8.8–20.1 | 1.38 | 0.82 | 2.33 | 0.221 | 0.763 |
| BMI ⩾22–<25 | 813 | 28 | 10.5 | 7.2–15.5 | 853 | 41 | 14.8 | 10.6–20.1 | 0.71 | 0.44 | 1.16 | 0.169 | |
| BMI ⩾25–<27.5 | 536 | 33 | 19.2 | 12.8–26.5 | 527 | 24 | 14.0 | 9.0–20.8 | 1.48 | 0.87 | 2.52 | 0.148 | |
| BMI ⩾27.5 | 444 | 25 | 17.7 | 11.4–26.1 | 404 | 24 | 18.3 | 11.7–27.2 | 0.98 | 0.55 | 1.73 | 0.937 | |
| *All-cause deaths* | | | | | | | | | | | | | |
| BMI <22 | 561 | 29 | 15.9 | 10.6–22.8 | 565 | 30 | 16.1 | 10.9–23.0 | 1.00 | 0.60 | 1.67 | 0.997 | 0.102 |
| BMI ⩾22–<25 | 813 | 26 | 9.6 | 6.3–14.0 | 853 | 25 | 8.8 | 5.7–12.9 | 1.11 | 0.64 | 1.92 | 0.722 | |
| BMI ⩾25–<27.5 | 536 | 11 | 6.3 | 3.1–11.2 | 527 | 11 | 6.4 | 3.2–11.4 | 1.08 | 0.46 | 2.52 | 0.854 | |
| BMI ⩾27.5 | 444 | 7 | 4.8 | 1.9–9.9 | 404 | 20 | 15.0 | 9.1–23.1 | 0.32 | 0.13 | 0.75 | 0.009 | |
| *CV deaths* | | | | | | | | | | | | | |
| BMI <22 | 561 | 5 | 2.7 | 0.9–6.4 | 565 | 5 | 2.7 | 0.9–6.3 | 1.03 | 0.29 | 3.58 | 0.969 | 0.170 |
| BMI ⩾22–<25 | 813 | 9 | 3.3 | 1.5–6.3 | 853 | 7 | 2.5 | 1.0–5.1 | 1.44 | 0.53 | 3.89 | 0.474 | |
| BMI ⩾25–<27.5 | 536 | 5 | 2.8 | 0.9–6.6 | 527 | 5 | 2.9 | 0.9–6.8 | 1.02 | 0.29 | 3.65 | 0.977 | |
| BMI ⩾27.5 | 444 | 3 | 2.0 | 0.4–6.0 | 404 | 8 | 6.0 | 2.6–11.8 | 0.34 | 0.09 | 1.28 | 0.110 | |
| *New-onset diabetes* | | | | | | | | | | | | | |
| BMI <22 | 366 | 7 | 5.9 | 2.4–12.1 | 379 | 7 | 5.7 | 2.3–11.8 | 1.09 | 0.38 | 3.13 | 0.868 | 0.016 |
| BMI ⩾22–<25 | 458 | 14 | 9.4 | 5.1–15.8 | 493 | 23 | 14.1 | 9.0–21.2 | 0.67 | 0.34 | 1.32 | 0.250 | |
| BMI ⩾25–<27.5 | 300 | 11 | 11.3 | 5.6–20.2 | 292 | 16 | 17.2 | 9.9–28.0 | 0.64 | 0.29 | 1.39 | 0.258 | |
| BMI ⩾27.5 | 219 | 6 | 8.5 | 3.1–18.5 | 178 | 13 | 23.4 | 12.5–40.0 | 0.35 | 0.13 | 0.94 | 0.036 | |

Abbreviations: BMI, body mass index; CI, confidence interval; CV, cardiovascular; HR, hazard ratio.
[a]Rate is expressed as incidence per 1000 patient-years.
[b]HR value was adjusted for the potential confounders (age, diabetes mellitus, sex, severe hypertension, cerebrovascular history, cardiac complications, renal dysfunction, antihypertensive drug use at baseline, smoking history and hyperlipidemia).

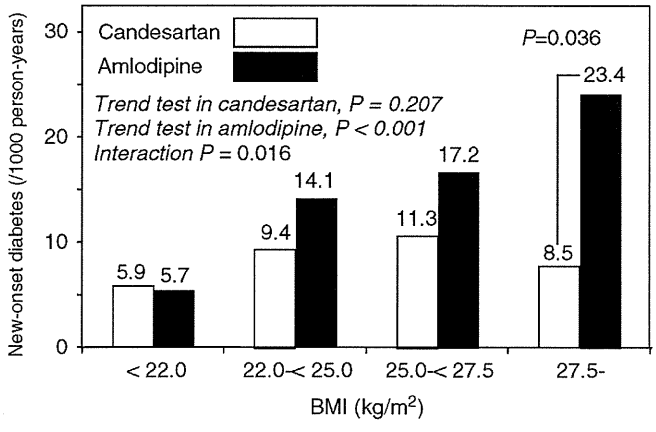


**Figure 1** Relationship between new-onset diabetes and body mass index (BMI) at baseline.

amlodipine-based regimens (13.6 per 1000 patient-years). Multivariate Cox regression analysis also revealed that candesartan suppressed the incidence of new-onset DM to significantly greater degree than amlodipine (adjusted HR=0.66, 95% CI=0.43–0.99, $P$=0.043). This adjusted HR was comparable with the unadjusted one reported previously.[9]

**Association of BMI at baseline with the CASE-J trial outcomes**

The actual number and incidence rate of primary CV events, non-renal CV events, and all-cause death in each BMI category are shown in Table 5. No significant difference in incidence of primary and non-renal CV events was noted between the two treatment regimens in any of the four BMI categories.

With regard to all-cause death, incidence in both regimens was most frequent in the lowest BMI category (<22.0 kg m$^{-2}$). Incidence was similar between treatment regimen groups at BMI <22.0 kg m$^{-2}$; 22.0⩽BMI<25.0 kg m$^{-2}$; and 25.0⩽BMI<27.5 kg m$^{-2}$. However, a statistically significant difference was noted in the incidence among patients in the BMI⩾27.5 kg m$^{-2}$ category, with an adjusted HR of 0.32 (95% CI=0.13–0.75, $P$=0.009). Furthermore, in this category, deaths from both CV (three in the candesartan group and eight in the amlodipine group) and non-CV causes (four in the candesartan group and 12 in the amlodipine group) were more frequent in the amlodipine group than in the candesartan group, although the number of events was small.

Table 5 describes the number of patients with new-onset DM and the adjusted HRs in each category stratified according to BMI at study enrollment. In BMI subgroup analyses, candesartan significantly suppressed new-onset DM in the BMI $\geqslant 27.5\,kg\,m^{-2}$ category (adjusted HR=0.35, 95% CI=0.13–0.94, $P$=0.036) compared with amlodipine. Figure 1 clearly shows that the increase in new-onset DM was dependent on BMI in the amlodipine group, whereas no such dependency was observed in the candesartan group, highlighting the statistically significant interaction between BMI and treatment group (interaction $P$=0.016).

## DISCUSSION

In this analysis, we noted that DM was a strong risk factor for CV events among high-risk Japanese hypertensive patients, in addition to all-cause death, and other outcomes of the CASE-J trial. Furthermore, we showed that the ARB, candesartan, exerted a favorable effect in suppressing new-onset DM among patients with elevated BMI. However, no difference in occurrence of primary CV events was noted between candesartan and amlodipine groups regardless of diabetic status and BMI, albeit these findings had insufficient statistical power.

Previous studies that showed a decrease in the new-onset DM with antihypertensive treatment did not report the influence of BMI on the outcome.[5,7] In our analysis, the incidence of new-onset DM was lower in patients with relatively low BMI than in those with relatively high BMI in the amlodipine group, suggesting that onset of DM is affected by the degree of patient obesity in this group. However, no such dependency was observed in patients receiving candesartan. When we conducted the additional *post-hoc* analysis with quintile cutoff points of the BMI category ($<21.6$, $\geqslant 21.6$–$23.4$, $\geqslant 23.4$–$<25.1$, $\geqslant 25.1$–$<27.2$ and $\geqslant 27.2\,kg\,m^{-2}$), the similar dependency was observed compared with that based on the pre-specified cutoff points of the BMI category (data not shown). These results suggested that candesartan reduced the new-onset DM by preventing the metabolically deleterious effects of increased adiposity in high-risk hypertensive patients.

The average BMI of participants in the CASE-J trial was approximately $25\,kg\,m^{-2}$ among patients diabetic at enrollment and $24\,kg\,m^{-2}$ among non-diabetic patients. As reported previously,[9] patients with a BMI greater than or equal to $27.5\,kg\,m^{-2}$, who were receiving candesartan had a significantly lower risk of all-cause death than those receiving amlodipine, whereas incidence of all-cause death was similar between the two treatment groups among patients occupying lower BMI strata. A U-shaped association between all-cause death and BMI in a Japanese population has been previously reported,[11] and this same relationship was also observed between all-cause death and BMI among patients receiving amlodipine in this study. In contrast, no increase in all-cause death associated with increased BMI was observed for patients receiving candesartan (Table 5); results we interpret to indicate that candesartan treatment reduced the incidence of all-cause death among patients whose BMI was in the highest category, who might otherwise have suffered increased mortality.

The improvement in the insulin resistance observed under antihypertensive treatment has been attributed in part to the direct effect of reduced blood pressure on endothelial function. However, candesartan[12] and enalapril,[13] both suppressed the development of DM in patients with congestive heart failure without hypertension, suggesting that the effect of RAS suppression on the development of DM is not necessarily a direct result of lowered BP. As angiotensinogen is produced by adipose tissue,[14] and angiotensin II has a role in increasing insulin resistance through its effects on adipocyte function,[15] the suppression of new-onset DM by candesartan may well depend on the state of adiposity and therefore be more profound in obese patients, as was observed in the present analysis. Hypertension and impaired glucose homeostasis associated with obesity can be considered a reflection of the pathophysiological process of metabolic syndrome.[16–18] The suppression of both hypertension and glucose intolerance induced by candesartan in this study supports the hypothesis that RAS does indeed have a role in obesity and the development of metabolic syndrome, and results from this and previous studies will aid in development of treatment strategies for pathological conditions associated with obesity, such as metabolic syndrome.

Several limitations to this analysis warrant mention. First, our study was conducted as a *post-hoc* analysis, and therefore there was also a risk that our findings might occur by chance. Second, the number of patients in each subgroup may not have been sufficient to allow for a thorough examination of the relationship between DM (or BMI) and trial outcomes. Third, patients were not vigorously tested for the presence of DM at the end, and diagnosis of new-onset DM relied solely on the attending clinician's decision to prescribe anti-diabetic medications or a report of DM in the adverse event form. According to the National Diabetes Survey in 2002, 69.6% of patients diagnosed as diabetic underwent either drug or insulin treatment.[19] Therefore, although the number of new-onset DM as defined in this study may have underestimated the overall incidence of DM, it is highly probable that a considerable portion of new-onset DM cases were included in the results. Last, we cannot accurately claim that the decrease in new-onset DM observed in this study directly affected the overall CV morbidity and mortality of non-diabetic patients. The recent CASE-J Ex study[20] may provide insights into these and other questions.

In conclusion, this analysis showed that DM increased CV risk among high-risk Japanese hypertensive patients. Candesartan treatment may produce significant suppression of all-cause death and reduced new-onset DM in patients with obesity. Results from this analysis will likely be of long-term benefit to obese hypertensive patients.

## CONFLICT OF INTEREST

OT, NK, UK and ST have received honoraria for lectures from both Takeda Pharmaceutical and Pfizer Japan.

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1 World Health Organisation, International Association for the Study of Obesity, International Obesity Taskforce. *The Asia-Pacific Perspective: Redefining Obesity And Its Treatment.* Health Communications Australia, Sydney, 2000.
2 Dahlöf B, Devereux RB, Kjeldsen SE, Julius S, Beevers G, de Faire U, Fyhrquist F, Ibsen H, Kristiansson K, Lederballe-Pedersen O, Lindholm LH, Nieminen MS, Omvik P, Oparil S, Wedel H, LIFE Study Group. Cardiovascular morbidity and mortality in the losartan intervention for end point reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet* 2002; **359**: 995–1003.
3 Hansson L, Zanchetti A, Carruthers SG, Dahlöf B, Elmfeldt D, Julius S, Ménard J, Rahn KH, Wedel H, Westerling S. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the hypertension optimal treatment (HOT) randomised trial. HOT study group. *Lancet* 1998; **351**: 1755–1762.

4 Tuomilehto J, Rastenyte D, Birkenhäger WH, Thijs L, Antikainen R, Bulpitt CJ, Fletcher AE, Forette F, Goldhaber A, Palatini P, Sarti C, Fagard R. Effects of calcium-channel blockade in older patients with diabetes and systolic hypertension. Systolic hypertension in Europe trial investigators. *N Engl J Med* 1999; **340**: 677–684.
5 Niskanen L, Hedner T, Hansson L, Lanke J, Niklason A, CAPPP Study Group. Reduced cardiovascular morbidity and mortality in hypertensive diabetic patients on first-line therapy with an ACE inhibitor compared with a diuretic/beta-blocker-based treatment regimen: a subanalysis of the captopril prevention project. *Diabetes Care* 2001; **24**: 2091–2096.
6 Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of different blood pressure-lowering regimens on major cardiovascular events in individuals with and without diabetes mellitus—results of prospectively designed overviews of randomized trials. *Arch Intern Med* 2005; **165**: 1410–1419.
7 Kjeldsen SE, Julius S, Mancia G, McInnes GT, Hua T, Weber MA, Coca A, Ekman S, Girerd X, Jamerson K, Larochelle P, MacDonald TM, Schmieder RE, Schork MA, Stolt P, Viskoper R, Widimský J, Zanchetti A. Effects of valsartan compared to amlodipine on preventing type 2 diabetes in high-risk hypertensive patients: the VALUE trial. *J Hypertens* 2006; **24**: 1405–1412.
8 Fukui T, Rahman M, Hayashi K, Takeda K, Higaki J, Sato T, Fukushima M, Sakamoto J, Morita S, Ogihara T, Fukiyama K, Fujishima M, Saruta T, CASE-J Study Group. Candesartan antihypertensive survival evaluation in Japan (CASE-J) trial of cardiovascular events in high-risk hypertensive patients: rationale, design, and methods. *Hypertens Res* 2003; **26**: 979–990.
9 Ogihara T, Nakao K, Fukui T, Fukiyama K, Ueshima K, Oba K, Sato T, Saruta T, Candesartan Antihypertensive Survival Evaluation in Japan Trial Group. Effects of candesartan compared with amlodipine in hypertensive patients with high cardiovascular risks: CASE-J Trial. *Hypertension* 2008; **51**: 393–398.
10 Japanese Society of Hypertension Guidelines Subcommittee for the Management of Hypertension. Guidelines for the management of hypertension for general practitioners. *Hypertens Res* 2001; **24**: 613–634.
11 Tsugane S, Sasaki S, Tsubono Y. Under- and overweight impact on mortality among middle-aged Japanese men and women: a 10-y follow-up of JPHC study cohort I. *Int J Obes (Lond)* 2002; **26**: 529–537.
12 Yusuf S, Ostergren JB, Gerstein HC, Pfeffer MA, Swedberg K, Granger CB, Olofsson B, Probstfield J, McMurray JV, Candesartan in Heart Failure-Assessment of Reduction in Mortality and Morbidity Program Investigators. Effects of candesartan on the development of a new diagnosis of diabetes mellitus in patients with heart failure. *Circulation* 2005; **112**: 48–53.
13 Vermes E, Ducharme A, Bourassa MG, Lessard M, White M, Tardif JC, Studies Of Left Ventricular Dysfunction. Enalapril reduces the incidence of diabetes in patients with chronic heart failure: insight from the studies of left ventricular dysfunction (SOLVD). *Circulation* 2003; **107**: 1291–1296.
14 Karlsson C, Lindell K, Ottosson M, Sjöström L, Carlsson B, Carlsson LM. Human adipose tissue expresses angiotensinogen and enzymes required for its conversion to angiotensin II. *J Clin Endocrinol Metab* 1998; **83**: 3925–3929.
15 Zorad S, Fickova M, Zelezna B, Macho L, Kral JG. The role of angiotensin II and its receptors in regulation of adipose tissue metabolism and cellularity. *Gen Physiol Biophys* 1995; **14**: 383–391.
16 National Cholesterol Education Program (NCEP) Expert Panel on Detection, and Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation* 2002; **106**: 3143–3421.
17 Miyawaki T, Hirata M, Moriyama K, Sasaki Y, Aono H, Saito N, Nakao K. Metabolic syndrome in Japanese diagnosed with visceral fat measurement by computed tomography. *Proc Jpn Acad Ser B* 2005; **81**: 471.
18 Alberti KG, Zimmet P, Shaw J. Metabolic syndrome—a new world-wide definition. A consensus statement from the international diabetes federation. *Diabetes Med* 2006; **23**: 469–480.
19 National Diabetes Survey. Ministry of health, labour and welfare. Accessed 14 April 2009 at http://www.health-net.or.jp/data/menu05/toukei/tonyo_h14.pdf, 2002.
20 Ueshima K, Oba K, Yasuno S, Fujimoto A, Sato T, Fukiyama K, Azuma J, Ogihara T, Saruta T, Nakao K, Candesartan Antihypertensive Survival Evaluation in Japan Trial Group. Long-term effects of candesartan and amlodipine on cardiovascular mortality and morbidity in Japanese high-risk hypertensive patients: Rationale, design, and characteristics of candesartan antihypertensive survival evaluation in Japan extension (CASE-J Ex). *Contemp Clin Trials* 2009; **30**: 97–101.