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 χ^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-

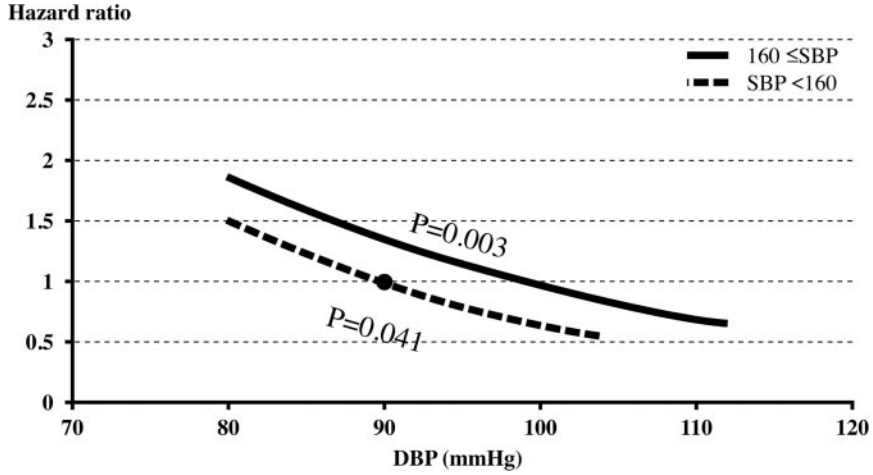

Figure 1—*Risk of new-onset diabetes by SBP and DBP at enrollment. HR of DBP of 90 mmHg in the SBP <160 mmHg category was assigned a reference value of 1.0.*

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

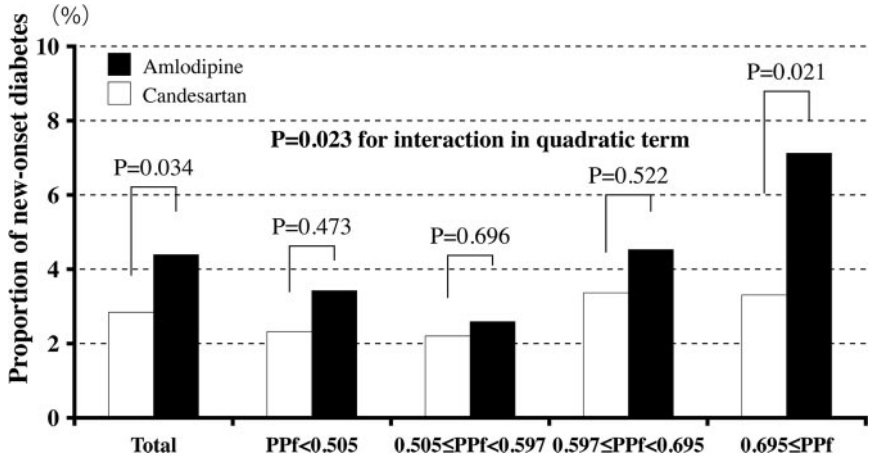

Figure 2—*Effect of candesartan and amlodipine on the incidence of new-onset diabetes stratified by quartile of PP_f. PP_f (linear and quadratic terms), the allocated drugs, and their interaction terms were entered in multiple Cox regression model.* P *value was calculated based on the Wald test.*

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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No potential conflicts of interest relevant to this article were reported.

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