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<td><strong>Author(s)</strong></td>
<td>Yasuno, Shinji; Ueshima, Kenji; Oba, Koji; Fujimoto, Akira; Hirata, Masakazu; Ogihara, Toshio; Saruta, Takao; Nakao, Kazuwa</td>
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<tr>
<td><strong>Citation</strong></td>
<td>Diabetes care (2010), 33(5): 1122-1127</td>
</tr>
<tr>
<td><strong>Issue Date</strong></td>
<td>2010-05</td>
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<td><strong>Type</strong></td>
<td>Journal Article</td>
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Kyoto University
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

**Short Title:** Predictive value of pulse pressure for diabetes

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**Word count:** 2998 words including the abstract and entire text.

**Number of tables and figures:** 2 tables and 2 figures.
Abstract and keywords

Objective  Hypertensive patients are at 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 (PP) and the risk of new-onset diabetes in high-risk Japanese hypertensive patients.

Research Design and Methods  The 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 PP 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/m²) 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, PP was an independent predictor for new-onset diabetes (hazard ratio per 1 SD increase 1.44, 95% CI 1.15-1.79), as were male sex, body mass index and additional use of diuretics, whereas age and heart rate were not. Plots of hazard ratios for new-onset diabetes considering both systolic and diastolic
blood pressure (DBP) revealed that a higher PP with a lower DBP, indicating that the increased PP was largely due to increased arterial stiffness, was strongly associated with the risk of new-onset diabetes.

Conclusion

PP 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.

Keywords

Hypertension, Pulse pressure, New-onset diabetes, Arterial stiffness, Microvascular dysfunction.
Introduction

Deaths from cardiovascular (CV) disease, 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 CV 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 CV events (3). Since hypertensive patients are at increased risk of developing diabetes (new-onset diabetes), the two conditions frequently cluster together, and synergistically increase the propensity to CV disease (4). Further, recent study has shown that new-onset diabetes negatively affects the incidence of CV 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 aimed at determining predictors of new-onset diabetes have been reported (6-8).

One independent predictor of CV morbidity and mortality in hypertensive patients is pulse pressure (PP) (9). Although PP derives from the interaction of cardiac ejection (stroke volume) and the properties of arterial circulation (arterial stiffness and
wave reflection), elevated PP 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 between increased arterial stiffness and impaired glucose metabolism, metabolic syndrome and insulin resistance (11-13). These findings suggest a possible association between increased PP and new-onset diabetes, but this association has not been examined in hypertensive patients.

The Candesartan Antihypertensive Survival Evaluation in Japan (CASE-J) trial was designed to compare the long-term effects of the angiotensin II receptor blocker (ARB) candesartan cilexetil and calcium channel blocker (CCB) amlodipine besylate on the incidence of CV 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 less than 140/80 mmHg, and no statistically significant difference was seen in the incidence of primary CV 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 which was aimed at determining whether PP is associated with the risk of new-onset diabetes independent of the effects of antihypertensive treatment and other possible risk factors for diabetes.

**Method**

**Study Design and Treatment Schedule of the CASE-J Trial**

The CASE-J trial was a prospective, multicenter, randomized, open-label, active-controlled, 2-arm parallel-group comparison with response-dependent dose titration and blinded assessment of 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 Helsinki Declaration. 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 (BP) was measured at a clinic in the sitting position. The average of two consecutive measurements of BP on separate visits was used. High-risk was
defined as the presence of any one or more of the following: a) severe hypertension: SBP/DBP ≥ 180/110 mmHg; b) type 2 diabetes (fasting blood glucose ≥126 mg/dL, casual blood glucose ≥200 mg/dL, HbA1c ≥6.5%, 2 h blood glucose on 75 g oral glucose tolerance test (OGTT) ≥200 mg/dL, or current treatment with hypoglycemic agent at baseline); c) a history of stroke or transient ischemic attack more than 6 months prior to screening; d) left ventricular hypertrophy (LVH), angina pectoris, or a history of myocardial infarction more than 6 months prior to screening; e) proteinuria or renal dysfunction (serum creatinine ≥ 1.3 mg/dL); or f) arteriosclerotic peripheral artery obstruction. Exclusion criteria have been reported elsewhere (14,15).

Enrolled patients were randomized 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 angiotensin converting enzyme inhibitors was prohibited.

**Subjects and 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 September 17, 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 been newly started on anti-diabetic agents in the case report form. Written informed consent was obtained from each participating patient before allocation.

**Statistical Analysis**

Data are expressed as mean ± standard deviation (SD) or proportions. Continuous variables were compared using the Student’s t test. Frequency analysis was performed with the $\chi^2$ test. PP was calculated as the difference between SBP and DBP. Multiple Cox regression analysis was used to examine the association between each BP index (SBP, DBP and PP) at baseline and the risk of new-onset diabetes with adjustment for
baseline characteristics (prior antihypertensive treatment, allocated drug, age, sex, body mass index (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 ($PF$), which is calculated as PP divided by mean arterial pressure (MAP), has recently been proposed as a new parameter of the pulsatile component of BP (17). $PF$ is thought to more directly reflect arterial stiffness than PP, since dividing by MAP theoretically cancels out the influence of peripheral vascular resistance. We also evaluated the predictive value of this variable for new-onset diabetes by multiple Cox regression analysis. Since each BP index is affected by aging (10), we also conducted subgroup analyses stratified by age (cut-off point: 65 years old), using the median age at baseline of all included patients. The test for interaction in multiple Cox model was evaluated with the interaction term. In addition, to clarify the significance of PP 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 the SAS version 9.1 (SAS Institute Inc., 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 randomized to a candesartan-based regimen; and more likely to have had a lower DBP, higher PP, and LVH at baseline. At the time of randomization, 1,702 (65.8%) patients without and 65 (67.0%) 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; diuretics, 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 PP (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 previously reported, candesartan-based regimens significantly reduced the risk of new-onset diabetes compared with amlodipine-based regimens (15).

Since PP 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, 95%CI 1.16-1.81, P<0.001). Subgroup analysis stratified by age (cut-off point: 65 years old) revealed that PP remained significantly associated with the risk of new-onset diabetes in both age groups (<65 years old: HR 1.72, 95%CI 1.18-2.49, P=0.004; ≥65 years old: HR 1.34, 95%CI 1.01-1.77, P=0.042; and P for 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 <65 years old: HR 1.20,
95% CI 0.86-1.67, \( P = 0.284 \); ≥65 years old: HR 1.16, 95% CI 0.84-1.59, \( P = 0.374 \); and \( P \) for interaction = 0.780; for DBP <65 years old: HR 1.58, 95% CI 1.10-2.28, \( P = 0.014 \); ≥65 years old: HR 1.32, 95% CI 0.99-1.76, \( P = 0.057 \), and \( P \) for interaction = 0.290).

Because different combinations of SBP and DBP give the same PP value (eg. BPs of 130/60 and 180/110 mmHg both give a PP of 70 mmHg), we evaluated the association of combinations of SBP and DBP with the risk of new-onset diabetes. As shown in Figure 1, a strong association with risk was seen for higher PPs 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 and the risk of new-onset diabetes and found that PP (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 (per 1 SD increase) was significantly associated with the risk of new-onset diabetes in both age groups (<65 years: HR 1.88, 95% CI 1.29-2.73, \( P < 0.001 \); ≥65 years: HR 1.34, 95% CI 1.03-1.74, \( P = 0.027 \); and \( P \) for interaction \( P = 0.057 \)). Since fewer patients developed diabetes with candesartan- than amlodipine-based regimens, we examined the
difference in this effect stratified by quartile of \( \text{PP}_f \). As shown in Figure 2, a trend to an increased incidence of new-onset diabetes with increasing \( \text{PP}_f \) was seen in patients with amlodipine-based regimens, but not in those with candesartan-based regimens (\( P=0.0234 \) for interaction in quadratic term). Candesartan-based regimens significantly suppressed the incidence of new-onset diabetes in the highest quartile of \( \text{PP}_f \). This result was not changed after adjustment for baseline characteristics (data not shown).
**Discussion**

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 PP arising mainly due to a lower DBP, indicating that the increased PP 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 PP, 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 PP may be a surrogate marker for the risk of new-onset diabetes. Supporting this, a higher PP, 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 metabolic disturbance, which is considered a potential mechanism linking metabolic disturbance
to increased CV disease risk (11-13). Arterial properties are impacted both functionally and structurally by many factors, including aging, blood pressure, sympathetic nervous system function, endothelial function, inflammation, bioactive peptides, and other CV 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 non-enzymatic glycation, endothelial dysfunction, inflammation, and local activation of the renin-angiotensin-aldosterone system in pre-diabetics as well as diabetics (18). Indeed, PP$_f$, represented as a parameter of the pulsatile component of BP, was superior to PP in terms of the risk stratification of new-onset diabetes.

Second, increased PP 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
between 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 microcirculation. Accordingly, increased PP, 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 LIFE study, Oki et al reported that in-treatment resolution or continued absence of electrocardiographic LVH was associated with a lower incidence of diabetes (22). Since PP 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 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 (24). In the present study, the suppressive effect of ARB candesartan against new-onset diabetes tended to strengthen as PP 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 assume 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 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 PP 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 PP 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 non-reporting 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 PP with new-onset diabetes in hypertensive patients and may provide useful information in
understanding the underlying mechanism between hypertension and new-onset diabetes. Finally, since 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 conclusion, we found that PP 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 PP and new-onset diabetes in hypertensive patients. Further studies are required to elucidate the significance of PP in new-onset diabetes in hypertensive patients.

Acknowledgements

We thank all collaborating investigators in the CASE-J trial and colleagues at EBM Research Center of Kyoto University for their contributions to the present study.
Conflict of interest

None.

Source of Funding

The CASE-J Trial was funded by EBM Research Center, Kyoto University of Graduate School of Medicine, with an unrestricted grant from Takeda Pharmaceutical Co. and supported by the Japanese Society of Hypertension.
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Figure legends

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

Figure 2. Effect of candesartan and amlodipine on the incidence of new-onset diabetes stratified by quartile of PPf. PPf (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.
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<tr>
<th></th>
<th>Total</th>
<th>NOD (-)</th>
<th>NOD (+)</th>
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<tr>
<td>Number of participants</td>
<td>2,685</td>
<td>2,588</td>
<td>97</td>
</tr>
<tr>
<td>Candesartan*</td>
<td>1,343 (50.0)</td>
<td>1,305 (50.4)</td>
<td>38 (39.2)</td>
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<td>Prior antihypertensive treatment</td>
<td>1,767 (65.8)</td>
<td>1,702 (65.8)</td>
<td>65 (67.0)</td>
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<td>Age (years)</td>
<td>63.7 ± 11.1</td>
<td>63.7 ± 11.2</td>
<td>64.9 ± 10.0</td>
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<tr>
<td>Male*</td>
<td>1,471 (54.8)</td>
<td>1,406 (54.3)</td>
<td>65 (67.0)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)*</td>
<td>24.8 ± 3.6</td>
<td>24.1 ± 3.5</td>
<td>25.2 ± 3.4</td>
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<tr>
<td>SBP (mmHg)</td>
<td>165.0 ± 14.8</td>
<td>165.0 ± 14.8</td>
<td>165.7 ± 16.1</td>
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<td>DBP (mmHg)*</td>
<td>94.3 ± 11.3</td>
<td>94.4 ± 11.3</td>
<td>90.5 ± 11.7</td>
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<td>PP (mmHg)*</td>
<td>70.8 ± 15.8</td>
<td>70.6 ± 15.7</td>
<td>75.2 ± 18.4</td>
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<td>HR (beats/min)</td>
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<td>71.4 ± 10.9</td>
<td>71.2 ± 9.5</td>
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<td>1,136 (43.9)</td>
<td>42 (43.3)</td>
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<tr>
<td>Smoking: Never</td>
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<td>59 (60.8)</td>
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<td>Ever</td>
<td>273 (10.2)</td>
<td>261 (10.1)</td>
<td>12 (12.4)</td>
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<tr>
<td>Current</td>
<td>587 (21.9)</td>
<td>561 (21.7)</td>
<td>26 (26.8)</td>
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<td>Cerebrovascular disease</td>
<td>344 (12.8)</td>
<td>330 (12.8)</td>
<td>14 (14.4)</td>
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<td>LVH*</td>
<td>1,139 (42.4)</td>
<td>1,088 (42.0)</td>
<td>51 (52.6)</td>
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<td>Ischemic heart disease</td>
<td>393 (14.6)</td>
<td>381 (14.7)</td>
<td>12 (12.3)</td>
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<tr>
<td>Proteinuria</td>
<td>548 (20.4)</td>
<td>530 (20.5)</td>
<td>18 (18.6)</td>
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<td>205 (7.6)</td>
<td>196 (7.6)</td>
<td>9 (9.3)</td>
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<tr>
<td>Peripheral vascular disease</td>
<td>37 (1.4)</td>
<td>35 (1.4)</td>
<td>2 (2.1)</td>
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</table>

Data are shown as number of patients (%) or mean ± SD.
NOD, new-onset diabetes; SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; HR, heart rate; Cerebrovascular disease, stroke and transient ischemic attack; LVH, left ventricular hypertrophy.

* P<0.05; NOD(-) vs. NOD(+)**
Table 2. Predictors of new-onset diabetes by multiple Cox regression analysis*

<table>
<thead>
<tr>
<th>Variables, Unit of Increase</th>
<th>HR (95% CI)</th>
<th>P value</th>
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<tr>
<td>PP, per 1SD increase</td>
<td>1.44 (1.15-1.79)</td>
<td>0.001</td>
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<td>Prior antihypertensive treatment, yes</td>
<td>0.97 (0.61-1.54)</td>
<td>0.901</td>
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<td>Allocated drug, candesartan</td>
<td>0.64 (0.42-0.97)</td>
<td>0.037</td>
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<td>Sex, male</td>
<td>1.77 (1.07-2.92)</td>
<td>0.026</td>
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<tr>
<td>Age, per 10 year</td>
<td>1.09 (0.87-1.36)</td>
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<tr>
<td>BMI, per 1 kg/m² increase</td>
<td>1.11 (1.06-1.17)</td>
<td>&lt;0.001</td>
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<td>Heart rate, per 1SD increase</td>
<td>1.01 (0.82-1.23)</td>
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<td>Hyperlipidemia, yes</td>
<td>1.04 (0.68-1.57)</td>
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<td>Smoking ever</td>
<td>1.03 (0.52-2.04)</td>
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<td>Cerebrovascular disease, yes</td>
<td>1.48 (0.80-2.75)</td>
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<td>LVH, yes</td>
<td>1.75 (1.13-2.72)</td>
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<td>Ischemic heart disease, yes</td>
<td>0.91 (0.47-1.76)</td>
<td>0.777</td>
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<tr>
<td>Renal damage, yes</td>
<td>1.10 (0.68-1.79)</td>
<td>0.694</td>
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<tr>
<td>Peripheral vascular disease, yes</td>
<td>1.49 (0.36-6.16)</td>
<td>0.581</td>
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<td>Additional use of diuretics, yes</td>
<td>2.10 (1.25-3.52)</td>
<td>0.005</td>
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<td>Additional use of β-blockers, yes</td>
<td>0.70 (0.40-1.24)</td>
<td>0.226</td>
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<tr>
<td>Additional use of α-blockers, yes</td>
<td>0.63 (0.32-1.24)</td>
<td>0.185</td>
</tr>
</tbody>
</table>

*Adjusted for each variable.

BMI, body mass index; LVH, left ventricular hypertrophy; renal damage, proteinuria and renal dysfunction
Figure 1

Hazard ratio vs. DBP (mmHg)

- Solid line: SBP $\leq 160$
- Dashed line: SBP < 160

- $P=0.003$
- $P=0.041$
Figure 2

Proportion of new-onset diabetes

- **Amlodipine**
- **Candesartan**

P=0.023 for interaction in quadratic term

P=0.034

P=0.473

P=0.696

P=0.522

P=0.021