Brachial-Ankle Pulse Wave Velocity Predicts All-Cause Mortality and Cardiovascular Events in Patients With Diabetes: The Kyushu Prevention Study of Atherosclerosis

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OBJECTIVE

Whether brachial-ankle pulse wave velocity (baPWV), a noninvasive marker for arterial stiffness, is a useful predictive maker for cardiovascular events in subjects with diabetes is not established. In the present cohort study, we evaluated the benefit of baPWV for the prediction of cardiovascular morbidity and mortality in subjects with diabetes.

RESEARCH DESIGN AND METHODS

A total of 4,272 outpatients with diabetes were enrolled in the Kyushu Prevention Study of Atherosclerosis. Of these, 3,628 subjects, excluding those with an ankle-brachial index of <0.9, were prospectively followed for 3.2 ± 2.2 years. The baPWV at baseline was classified by recursive partitioning (RP) for each end point. We plotted the Kaplan-Meier curves for high- and low-baPWV groups, which were designated based on the cutoff points, and calculated Cox proportional hazards models.

RESULTS

The elevation of baPWV quartiles was significantly correlated to the incidence of coronary artery events, cerebrovascular events, and all-cause mortality. RP revealed baPWVs of 14 and 24 m/s as statistically adequate cutoff points for cardiovascular events and mortality, respectively. High-baPWV classes showed significantly low event-free ratios in Kaplan-Meier curves for all end points and remained independent risks for all-cause mortality and cerebrovascular events, but not for coronary artery events after adjustments for age, sex, BMI, hypertension, hyperlipidemia, smoking, and hemoglobin A_{1c} by Cox proportional hazards models.

CONCLUSIONS

This large-scale cohort study provided evidence that high baPWV is a useful independent predictor of mortality and cardiovascular morbidity in subjects with diabetes.

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Cardiovascular disease, including coronary artery disease and stroke, is the leading cause of death and a major cause of disability among people with diabetes worldwide. In addition to hypertension and dyslipidemia, diabetes is an important risk factor for atherosclerosis; it is commonly associated with abnormalities of coagulation and platelet adhesion and aggregation, increased oxidative stress, and functional and anatomic abnormalities of the endothelium and endothelial vasomotion (1,2). Many subjects with diabetes have evidence of early stage cardiovascular disease, and it is essential that these subjects should be treated early with proven therapies to reduce their risk of future cardiovascular events (3). However, the prognostic values of preceding biological vascular markers for atherosclerosis have not been sufficiently assessed in large-scale diabetes cohorts. Aortic stiffness assessed by pulse wave velocity (PWV) was reported to predict all-cause and cardiovascular mortality and morbidity in subjects with hypertension (4–6), but its technique is too intricate to apply to clinical practice. Brachial-ankle PWV (baPWV), a novel, noninvasive marker for arterial stiffness of peripheral arteries, has been shown to be an independent predictor of coronary artery disease and all-cause mortality in general populations (7,8). In diabetes, baPWV is valued as a useful marker for peripheral vascular sclerosis in combination with the ankle-brachial pressure index (ABI) (9), but its evidence remains a surrogate of direct vascular examinations.

To complicate this issue, arterial stiffness of diabetic arteries increases at an accelerated rate at an earlier age in contrast to that of nondiabetic controls (9–11). In particular, the development of diabetic microangiopathy, including microalbuminuria (12), renal dysfunction (13,14), retinopathy (15), neuropathy (16,17), and evidence of macroangiopathy (18–21), is individually associated with the progression of arterial stiffness. These pathological complexities in subjects with diabetes might necessitate a review of adequate baPWV thresholds that splice the risks of mortality and morbidity. Indeed, our cohorts showed low-quality receiver operating characteristic (ROC) curves of baPWV for all-cause mortality and cardiovascular events in spite of the significant correlation of baPWV to each outcome. Therefore, we derived independent cutoff points of baPWV from recursive partitioning (RP) analysis, targeting the classification of risks of mortality and cardiovascular events in subjects with diabetes.

RESEARCH DESIGN AND METHODS

Subjects

This study was based on data from the Kyushu Prevention Study of Atherosclerosis, a prospective, multicenter survey. Outpatients with diabetes (n = 4,272) and without diabetes (n = 2,166) who were regularly visiting Kyushu University Hospital and its 17 related hospitals as well as Ryukyu University Hospital and its 6 related hospitals were enrolled in this survey from 2001 to 2003. Measurement of height, weight, and systolic and diastolic blood pressure; 12-lead electrocardiography; eye fundus examination; and laboratory tests of blood and urine were carried out at baseline. Medical records included a history of cardiovascular events, current treatment for diabetes, and the use of other medications (including blood pressure–lowering drugs, lipid-lowering drugs, and antithrombotic drugs). The participants provided informed consent, and this study was approved by the ethics committees of the related institutes. Subjects were followed up for 3.2 $\pm$ 2.2 (mean $\pm$ SD) years.

Measurement of baPWV

At baseline, an oscillometric device (form PWV/ABI; Omron Colin Co. Ltd., Komaki, Japan) was used to measure baPWV. Four pneumatic pressure cuffs, two electrocardiogram electrodes, and one microphone for detecting heart sounds were attached at both arms, ankles, and wrists and the left edge of the sternum, respectively, to record the volume waveform for the brachial and ankle arteries. The subjects were kept rest in supine position for at least 5–10 min in fasted condition, avoiding coffee or any exciting beverage or tobacco use before. The examination room was maintained at a standardized temperature. The baPWV was automatically calculated as the length of an arterial segment between the brachium and ankle (which was automatically calculated from the body height) divided by the transit time of the pulse wave. ABI was also automatically calculated by the device as the ratio of systolic blood pressure in the leg to that in the arm on each side. Flow diagram of derivation based on baPWV reliability is shown in Supplementary Fig. 1*A*. First of all, valid ABI was available for 3,991 subjects; 278 subjects were excluded for reasons of safety, such as patients with known severe peripheral arterial disease or diabetic foot, invalid measurement due to incompressible arteries, or withdrawal of consent. Three subjects with known ischemic legs and incompressible arteries, 341 subjects with an ABI of $<$0.9, and 22 subjects with unmeasurable baPWV were also excluded to avoid measurement uncertainty by interference with circulation through the lower legs. The sample data of 3,628 eligible subjects with both ABI and baPWV measured were used for the analyses below.

Clinical Assessment

Retinopathy was assessed by a fundus examination performed by independent ophthalmologists. Clinical proteinuria was defined as a level of $>$1+ using the Albustix method. Diabetic neuropathy was diagnosed by diabetologists based on typical symptoms and physical findings. Hypertension was defined as a systolic blood pressure of $\geq$140 mmHg, a diastolic blood pressure of $\geq$90 mmHg, or the current use of any antihypertensive medication. Hyperlipidemia was determined by a previous history of such or a total cholesterol level of $>$220 mg/dL and/or a triglyceride level of $>$150 mg/dL. Smoking habit was defined as current smoking based on an interview. Initially, hemoglobin A_{1c} (HbA_{1c}) levels were obtained as Japanese Diabetes Society values. Throughout the article, we present the National Glycohemoglobin Standardization Program value calculated as follows: Japanese Diabetes Society value + 0.4 (%) (22) and the International Federation of Clinical Chemistry and Laboratory Medicine mmol/mol units converted using the National Glycohemoglobin Standardization Program converter for HbA_{1c}, available at http://www.ngsp.org/convert1.asp.

End Points

The end points in the present analysis were all-cause mortality and the occurrence of the following major cardiovascular events: coronary artery disease;

fatal and nonfatal myocardial infarction, unstable angina, and cardiovascular disease; and fatal and nonfatal stroke and transient cerebral ischemic attack. Myocardial infarction was defined as an increase in creatine kinase exceeding twofold the upper limit and a new ST elevation in two or more leads. Unstable angina was defined by typical chest pain associated with ischemic electrocardiographic changes and successively documented by provocative tests (treadmill exercise test or/and stress echocardiography, myocardial scintigraphy, or coronary angiography). Transient cerebral ischemic attack was defined by a physician's diagnosis of any sudden focal neurological deficit that cleared completely in <24 h.

Statistical Analysis

Continuous variables are presented as means ± SD or median (lower quartile–upper quartile), and discrete variables are expressed as frequencies and percentages. *P* values for trends of quartiles were calculated using Spearman's rank correlation for continuous variables and the Cochran-Armitage test for categorical variables. The minimum Bayesian information criterion (forward) was used to choose the best model of stepwise multivariable regression for the explanation of log(baPWV) by the following variables: age, sex, BMI, current smoking, HbA_{1c}, log(serum creatinine), uric acid, total cholesterol, log(triglycerides), log (HDL cholesterol), proteinuria, and systolic and diastolic blood pressures. A total of 3,628 subjects were categorized according to the quartiles of baPWV. The risks of a higher-baPWV quartile for all-cause mortality, coronary artery events, and cerebral artery events were calculated by the Cochran-Armitage test for trend. First, an ROC curve with Youden index was analyzed to determine the optimum cutoff point of baPWV for each outcome. Then the RP method developed by SAS Institute Inc. was used alternatively to ROC curve analysis with low quality. Details on the RP method are described in "Monte Carlo Calibration of Distributions of Partition Statistics" found on the JMP website (www.jmp.com). In brief, the splits are determined by maximizing a logworth statistic that is related to the likelihood ratio χ^2 statistic. Mann-Whitney *U* tests for continuous variables or χ^2 tests for categorical variables were used to examine differences between risk groups categorized by RP. An event-free survival curve for each end point was estimated by the Kaplan-Meier method. Cox proportional hazards regression models were also performed to assess the independency of baPWV for the prediction of mortality and cardiovascular events even after adjustment by common risk factors for atherosclerosis (age, sex, BMI, smoking, HbA_{1c} level, and hypertension) or Framingham risk score (FRS) calculated using FRS regression equations provided by British Cardiac Society (23,24). FRS for the prediction of coronary heart disease (including myocardial infarction, coronary heart disease death, angina, and coronary insufficiency) and stroke (including transient ischemic attack) requires the information of time period, age, sex, smoking history (including previous smoker), the presence of diabetes, total cholesterol, HDL cholesterol, systolic blood pressure, and the presence of left ventricular hypertrophy on electrocardiography. Left ventricular hypertrophy was treated as 0 because of lacking data. Time period was set to 5 years. All analyses were performed with JMP version 9 statistical software (SAS Institute Inc., Cary, NC).

RESULTS

Clinical Characteristics

Table 1 describes the demographic and clinical characteristics of the participants. The 3,628 subjects with diabetes and 2,166 control subjects from the Kyushu Prevention Study of Atherosclerosis were compared by univariate and multivariate analysis. The histogram of baPWV (median [quartile 1–quartile 3], 16.7 [14.4–19.8]) did not show a normal distribution (Supplementary Fig. 2). There were significant changes in all parameters except for serum creatinine between control and subjects with diabetes by univariate analysis. The variables most strongly associated with baPWV were determined by forward stepwise selection. In control subjects, log(baPWV) had significant positive correlations to age, uric acid and systolic blood pressure and a negative correlation to BMI when HbA_{1c} and proteinuria were included in explanatory variables of subjects with diabetes with positive coefficient instead of uric acid (Table 2).

Outcome Events

We divided subjects into quartiles of baPWV (quartile 1, 0–14.40 m/s; quartile 2, 14.41–16.69 m/s; quartile 3, 16.70–19.75 m/s; and quartile 4, ≥19.76 m/s), whose characteristics are shown in Supplementary Table 1. The elevation of baPWV quartiles was significantly correlated to all-cause mortality and the incidence of coronary artery and cerebrovascular events (*P* for trend <0.001, respectively) (Fig. 1*A*). However, ROC curves of baPWV for these outcomes presented with low accuracy (area under the curve [AUC] <0.7) for determining the optimal cutoff points (Supplementary Fig. 3). Therefore, according to the best splits of baPWV for coronary artery events (13.3 m/s), cerebrovascular events (14.1 m/s), and all-cause mortality (23.5 m/s) as analyzed by RP, we set the optimal cutoff points for primary outcomes at 14.0 m/s for cardiovascular event risk (ER) and 24.0 m/s for mortality risk (MR). The characteristics of the groups as classified by cardiovascular ER or by MR are shown in Supplementary Table 1. The high-ER group (baPWV ≥14.0 m/s) had significantly higher ages and incidences of male sex, hypertension, hyperlipidemia, retinopathy, nephropathy, and neuropathy and a lower history of smoking and BMI compared with the low-ER group (baPWV <14.0 m/s). Similarly, the high-MR group (baPWV ≥24.0 m/s) had significantly higher ages and incidences of male sex, hypertension, retinopathy, nephropathy, and neuropathy and a lower history of smoking and BMI compared with the low-MR group (baPWV <24.0 m/s); however, no difference in the incidence of hyperlipidemia was shown. Next we compared the incidence rates of primary outcomes between the groups split by MR or ER cutoff points of baPWV during the average 3.2 years of follow-up. Kaplan-Meier curve analyses for all-cause mortality showed that the survival rate of high-MR subjects with a baPWV of ≥24.0 m/s was significantly lower than that of the low-MR group (baPWV <24.0 m/s; $P < 0.001$, log-rank test) (Fig. 1*B*). Identically, event-free survival rates for both coronary artery events and cerebrovascular events of high-ER subjects with a baPWV of ≥14.0 m/s were significantly lower than those of the low-ER group (baPWV <14.0 m/s; $P < 0.001$, log-rank test,

Table 1—Characteristics of subjects with or without diabetes enrolled in the Kyushu Prevention Study of Atherosclerosis

	Control subjects without diabetes (n = 2,166)	Subjects with diabetes (n = 3,628)	P value
Age, years	54 (45–64)	61 (53–69)	<0.001
Sex, male	1,121 (52)	2,166 (60)	<0.001
Current smoking	390 (18)	891 (25)	<0.001
Hypertension	811 (37)	1,841 (51)	<0.001
Hyperlipidemia	552 (25)	1,765 (49)	<0.001
Retinopathy	—	893 (25)	—
Nephropathy	—	811 (22)	—
Neuropathy	—	814 (22)	—
BMI, kg/m^2	23.6 ± 3.6	24.7 ± 4.1	<0.001
HbA_{1c}, % (mmol/mol)	5.3 ± 0.4 (34 ± 4.4)	8.2 ± 2.2 (66 ± 24)	<0.001
Serum creatinine, mg/dL	0.70 (0.60–0.84)	0.70 (0.60–0.88)	0.067
Uric acid, mg/dL	5.6 ± 1.5	5.4 ± 1.6	<0.001
Total cholesterol, mg/dL	207.8 ± 37.6	203.2 ± 40.4	<0.001
Triglycerides, mg/dL	103 (70–156)	125 (87–186)	<0.001
HDL cholesterol, mg/dL	56 (47–69)	50 (42–61)	<0.001
Systolic blood pressure, mmHg	124.5 ± 21.4	136.6 ± 20.4	<0.001
Diastolic blood pressure, mmHg	75.1 ± 12.7	80.7 ± 11.6	<0.001
Proteinuria	55 (3.1)	499 (18)	<0.001
Lower ABI	1.11 ± 0.07	1.10 ± 0.08	<0.001
baPWV (m/s)	14.4 (12.8–17.0)	16.7 (14.4–19.8)	<0.001

Data are presented as number (percentage), mean ± SD, or median (lower quartile–upper quartile) when the distribution was not normal. P values were calculated using Pearson χ^2 test or Mann-Whitney U test.

both) (Fig. 1*B*). Finally, we analyzed the independency of baPWV for the prediction of mortality and cardiovascular events in subjects with diabetes using Cox proportional hazards regression models adjusted by the following risk factors for atherosclerosis: age, sex, BMI, current smoking, HbA_{1c}, and hypertension (Table 3). In our MR model, a baPWV of ≥24.0 m/s was an independent risk factor for all-cause mortality (odds ratio [OR] 1.84; 95% CI 1.13, 2.88) together with age (OR 1.21; 95% CI 1.03, 1.43 for each 10-year increase) and male sex (OR 1.41; 95% CI 1.01, 1.98). In ER models, a baPWV of ≥14.0 m/s was an independent risk factor for cerebrovascular events (OR 1.56; 95% CI 1.03, 2.45) together with age (OR 1.20; 95% CI 1.05, 1.38 for each 10-year increase) and male sex (OR 1.35; 95% CI 1.04, 1.78), similar to the MR model. Meanwhile, it was not an independent risk factor for coronary artery events (OR 1.16; 95% CI 0.82, 1.69) when age (OR 1.34; 95% CI 1.19, 1.51 for each 10-year increase), BMI (OR 1.06; 95% CI 1.03, 1.09 for each 1 kg/m^2 increase), and hypertension (OR 1.30; 95% CI 1.04, 1.65) came up to significant variables. We also tested adjustment for calculated FRS to demonstrate the advantage of baPWV (bottom row in Table 3). Because FRS includes the scores for the prediction of cardiovascular mortality and morbidity risks but not for all-cause mortality, we could apply it only to ER models. The result showed that baPWV had significant risks of both coronary artery events (P = 0.025; OR 1.69; 95% CI 1.06, 2.84) and cerebrovascular events (P = 0.046; OR 1.63; 95% CI 1.01, 2.76) independent of FRS, while FRS (per a point increase) also remains a significant variable for coronary artery events (P = 0.003; OR 1.04; 95% CI 1.02, 1.07) but not for cerebrovascular events (P = 0.621; OR 1.02; 95% CI 0.95, 1.08).

CONCLUSIONS

Our large-scale cohort study aimed to provide evidence that baPWV elevation enables the prediction of mortality and cardiovascular morbidity in subjects with diabetes consistent with the results from previous studies of the general population (7,8) because there have been few studies on the evaluation of baPWV with a focus on subjects with diabetes (25).

The control group has several limitations that it is composed of various populations, including healthy subjects and patients with other metabolic disorders, such as hypertension and hyperlipidemia, and is not age-matched to

Table 2—Comparison of multivariable-adjusted relations of cardiovascular risk factors with baPWV between subjects with and without diabetes

	Control subjects without diabetes		Subjects with diabetes	
Variable	Regression coefficient (SE)*	P value	Regression coefficient (SE)*	P value
Age	0.007 (0.000)	<0.0001	0.008 (0.000)	<0.0001
BMI, kg/m^2	−0.007 (0.001)	<0.0001	−0.007 (0.001)	<0.0001
HbA_{1c}, %	Excluded†	—	0.006 (0.002)	0.0008
Uric acid, mg/dL	0.014 (0.002)	<0.0001	Excluded†	—
Proteinuria	Excluded†	—	0.025 (0.005)	<0.0001
Systolic blood pressure, mmHg	0.005 (0.000)	<0.0001	0.006 (0.000)	<0.0001

*Coefficients represent change in log(baPWV [m]) for an increase in the value of the predictor variables shown. SE is the estimated SE of the coefficient. Forward stepwise selection was used to determine the variables associated with baPWV. †The other variables excluded from the list by the stepwise procedure were sex, current smoking, log(serum creatinine), total cholesterol, log(triglycerides), log(HDL cholesterol), and diastolic blood pressure.

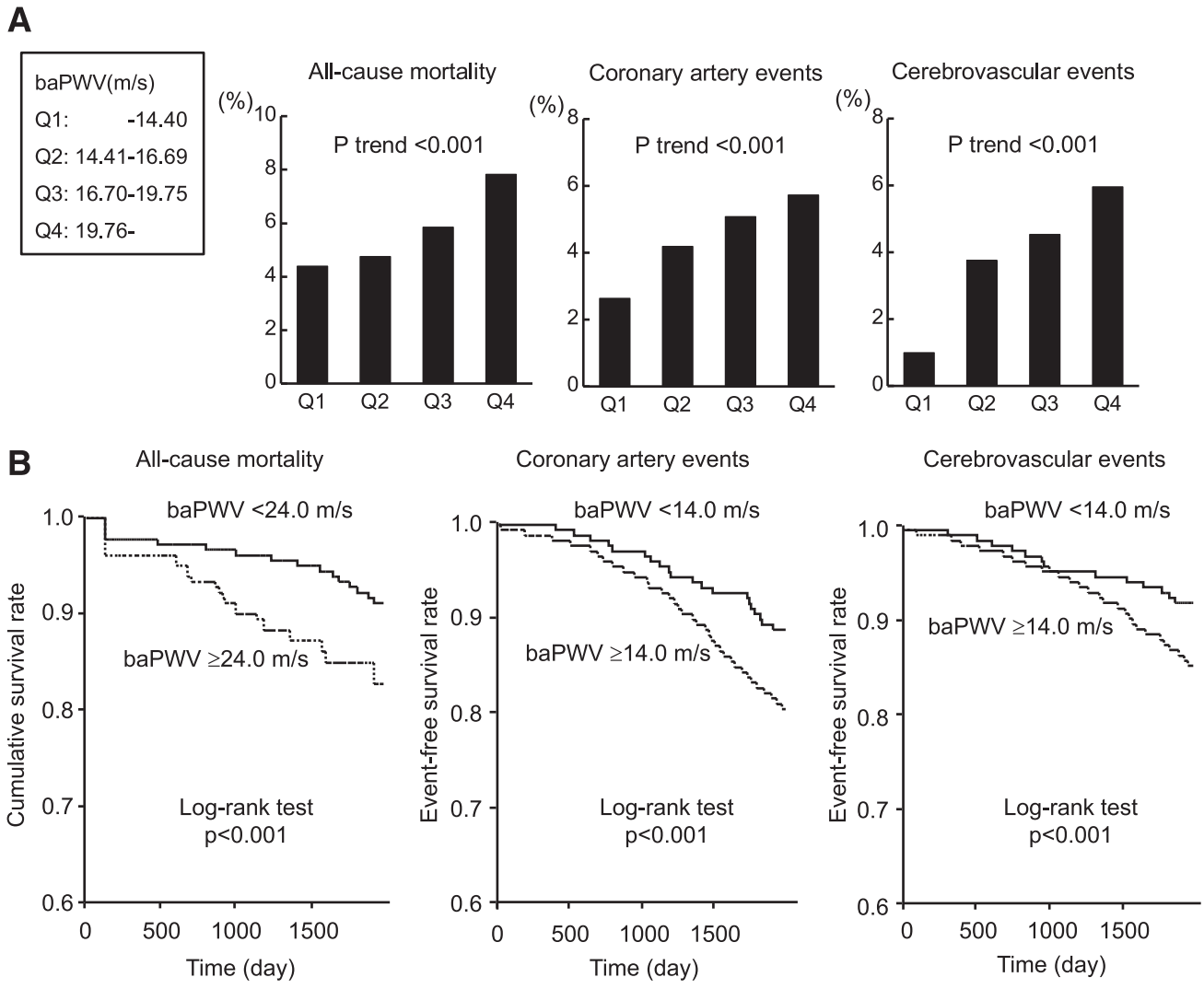

Figure 1—*A*: Incidences of all-cause mortality, coronary artery events, and cerebrovascular events by quartiles of baPWV during the follow-up period. Quartile 1, −14.40 m/s, *n* = 910; quartile 2, 14.41–16.69 m/s, *n* = 905; quartile 3, 16.70–19.75 m/s, *n* = 906; and quartile 4, ≥19.76 m/s, *n* = 907. *P* values for trend were determined by the Cochran-Armitage test. *B*: Kaplan-Meier survival curves for each outcome during the 5-year follow-up period. Comparison of the cumulative survival rate for all-cause mortality and the event-free survival rates for coronary artery events and cerebrovascular events between high baPWV (≥24.0 m/s) and low baPWV (<24.0 m/s). Differences between groups were analyzed using the log-rank test. Q1, quartile 1; Q2, quartile 2; Q3, quartile 3; Q4, quartile 4.

subjects with diabetes. In the control subjects, uric acid along with two common factors, age and systolic blood pressure, was a unique explanatory variable correlated to baPWV, similar to a previous report (26). But uric acid was displaced by HbA_{1c} and proteinuria in subjects with diabetes (Table 2). It implies that both glycemic control and diabetes complications may play an important role in early stage of macrovascular atherosclerotic diseases. As for the inverse correlation of BMI to elevated baPWV, BMI in subjects with diabetes might be affected by outliers, because the coefficient and R^2 of fitted line showing correlation between BMI and baPWV were very small (coefficient = −0.007; R^2 = 0.016). HbA_{1c} and the incidence of diabetic vascular complications were well correlated to the elevation of baPWV and are classic risk factors for arteriosclerosis, aging, and the incidence of hypertension and hyperlipidemia. These findings imply that baPWV is one of the predominant surrogate markers for assessing the cardiovascular ERs in diabetes.

Most importantly, we showed clear positive relationships between baPWV elevation and the incidences of outcome events with statistical significance for trend. To predict mortality and cardiovascular morbidities, we analyzed the ROC curve of baPWV for each end point to set the optimal cutoff point. However, this diabetic cohort showed a very low AUC of the ROC curve for all-cause mortality of <0.6 in contrast to previous reports of the general population, which focused on the prediction of mortality using aortic or carotid-femoral PWV and showed AUCs near 0.7 (27,28). AUCs of the ROC curves for coronary artery events and cerebrovascular events were also low, as shown in Supplementary Fig. 3. Therefore, we used the results of RP analyses instead of these unreliable baPWV thresholds determined by Youden index.

Interestingly, as shown in Fig. 1*A*, the correlation of baPWV stepwise elevation

Table 3—Prediction of risk for all-cause mortality and coronary artery and cerebrovascular events by baPWV

	MR model		ER models			
	All-cause mortality		Coronary artery events		Cerebrovascular events	
Outcomes	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age, for each 10-year increase	1.21 (1.03, 1.43)	0.018	1.34 (1.19, 1.51)	<0.001	1.20 (1.05, 1.38)	0.007
Sex, male	1.41 (1.01, 1.98)	0.041	1.17 (0.93, 1.47)	0.179	1.35 (1.04, 1.78)	0.025
BMI, for each 1 kg/m^2 increase	1.02 (0.98, 1.06)	0.396	1.06 (1.03, 1.09)	<0.001	1.02 (0.99, 1.06)	0.221
Smoking, %	0.81 (0.54, 1.19)	0.293	1.10 (0.85, 1.43)	0.441	1.02 (0.76, 1.37)	0.890
HbA_{1c}, for each 1% increase	1.07 (1.00, 1.15)	0.056	1.00 (0.95, 1.06)	0.972	0.97 (0.91, 1.04)	0.393
Hypertension	1.12 (0.81, 1.55)	0.498	1.30 (1.04, 1.65)	0.024	1.17 (0.90, 1.52)	0.245
High baPWV	≥24.0 m/s		≥14.0 m/s		≥14.0 m/s	
Adjusted for all variables*	1.84 (1.13, 2.88)	0.016	1.16 (0.82, 1.69)	0.391	1.56 (1.03, 2.45)	0.035
Adjusted for modified FRS†	—	—	1.69 (1.06, 2.84)	0.025	1.63 (1.01, 2.76)	0.046

MR is the baPWV split by MR. ER is the baPWV split by cardiovascular ER. Adjusted ORs and 95% CIs were calculated using Cox proportional hazards modeling for individual events. *Adjusted for age, sex, BMI, smoking, HbA_{1c}, and hypertension. †Adjusted for FRS regression equations provided by British Cardiac Society (24).

to the incidence rate of each outcome was not only fitted to a linear correlation, but also accompanied by a lifting point (quartiles 3 to 4 for all-cause mortality and quartiles 1 to 2 for coronary artery events and cerebrovascular events). Because these lifting incidence rates of outcomes were located on low baPWV values for cardiovascular events and a high baPWV value for all-cause mortality, the ROC curves showed severe deviations (Supplementary Fig. 1*B*), leading to the further necessity to find appropriate cutoff points using RP analyses. It implies that the correlations between risks of mortality and cardiovascular events and the baPWV elevation are composed of two factors. The first factor forming a simple linear correlation might be biased by classic risk factors, because raw value of baPWV or the classification by baPWV quartiles did not explain outcomes when adjusted for classic cardiovascular risk factors in multivariate survival models. This bias between simple elevation of baPWV and classic cardiovascular risks might be supported by the recent report that the predictive power of cardiovascular events with high carotid intima-media thickness, but not high baPWV, was improved by the combination with the FRS compared with single intima-media thickness or baPWV in subjects with type 2 diabetes (25). In these respects, we emphasized that the noninvasive measurement of baPWV was useful to not only obtain angiology data, but also formulate an integrated representation of classic risk factors in subjects with diabetes.

The second factor forming a lifting point could be a unique pathological role of arterial stiffness contributing to mortality and cardiovascular morbidity in subjects with diabetes. We studied a relationship between the unique factor of baPWV elevation and cardiovascular risks using appropriate thresholds binarized by RP analyses that provide the statistically strongest split. The very high (baPWV 23.5 m/s) best split for all-cause mortality largely resulted from the fact that subjects with a low ABI (<0.9), who are known to be at severe MR (29,30), were eliminated from analyses because of concern regarding contamination of subjects with erroneous baPWV values due to poor blood flow in the lower extremities. In addition, we previously showed that the prevalence of a low ABI (<0.9), which is considered to increase the risk of development of peripheral arterial disease, was very high in subjects with diabetes (31). Although a substantial number of subjects at risk for mortality had been excluded, this study indicated that severe arterial stiffness contributes to overall death in diabetes. Therefore, at the least, subjects with diabetes with an extremely high baPWV should be carefully treated as having a high MR. On the other hand, the best splits for coronary artery events and cerebrovascular events were low (baPWV of 13.3 and 14.1 m/s, respectively) but provided significant differences in the event-free survival rate between subjects with baPWV of <14.0 and ≥14.0 m/s, inversely indicating that 79.4% of the subjects with diabetes were at high risk of cardiovascular morbidity. After adjustment for classic risk factors for atherosclerosis, high baPWV (≥14.0) remained an independent predictor for cerebrovascular events, but not for coronary artery events. Similar deviations from the median baPWV showing the step-up increment of incidences of mortality and cardiovascular morbidities might have been overlooked in other studies of PWVs. Recently, Turin et al. (8) reported a population-based cohort study showing that the highest-baPWV group (≥17.0 m/s) had a significantly higher MR than the lowest-baPWV group (<14.0 m/s). However, the baPWV classification in that study, which was determined by tertiles of baPWV independently of clinical or statistical meanings of arterial stiffness, suggested only that the threshold of baPWV for mortality was included in the range of baPWV ≥17.0 m/s. To predict cardiovascular morbidities, Sutton-Tyrrell et al. (32) reported that an elevated aortic PWV was useful in healthy elderly subjects. Their Kaplan-Meier survival curves of PWV quartiles for outcome events were separated between the lowest-PWV group (<657.0 cm/s, corresponding to baPWV of approximately 11 m/s in accordance with another report [33]) and the other three groups, also supporting our data. Overall, our data suggest that the thresholds of baPWV to predict risks for mortality and cardiovascular morbidities must be carefully determined, especially in subjects with diabetes.

Hypertension and increased BMI were significant variables confounding

baPWV distinctively for coronary artery events. This implies that vasoconstriction factors, mechanical stress on coronary artery endothelial cells, circulating adipocytokines, coagulation abnormalities, and insulin resistance caused by hypertension and obesity might be more involved in mechanisms of the development of cardiac events in diabetes than a loss of vascular compliance represented by baPWV (34–36). In contrast, high baPWV had adequate power to predict cerebrovascular events, even in the adjusted Cox proportional hazards model. The pathological factors that explain the difference between cerebrovascular and coronary artery events remain to be confirmed in future studies.

However, using the appropriate baPWV cutoff values, we made models for MR and ER prediction and were able to demonstrate the contribution of high baPWV to all-cause death and cardiovascular outcomes independent of classic cardiovascular risk factors. Then we challenged to FRS, the most popular marker for cardiovascular events, with these models. Although we have to consider the limitation that FRS was weakened by the usage of current smoking history and also missing the information of electrocardiography, the results clearly showed that high baPWV was a potent predictive marker for ER independent of FRS.

The current study has certain limitations. First, the low outpatient-based follow-up rate resulted in a short observation period (average of 3.2 years), regardless of the 5-year set follow-up period at baseline, because the cooperative hospitals in this multicenter study covered a wide area throughout the Kyushu islands and had trouble following the subjects. We were also not able to collect enough data of periodic baPWV measurement during follow-up. However, the results of the survival analyses demonstrated the predictive power of baPWV. Second, a history of smoking had a negative correlation to baPWV elevation and was not a significant variable in any Cox proportional hazards model, although smoking is a strong risk factor for vascular atherosclerosis with a positive correlation to baPWV (37–39). Because of this limitation, our definition of smoking history only included current smokers and did not include exsmokers. In clinical practice, patients at high risk for atherosclerosis should be encouraged to stop smoking, as shown by the low rate of current smoking.

We demonstrated that high baPWV could predict all-cause mortality and cardiovascular events in subjects with diabetes. This is the first large-scale cohort study of subjects with diabetes that showed the predictive powers of baPWV for all-cause mortality and cerebrovascular events independent of classic risk factors by using an appropriate cutoff point for each risk. Noninvasive measurement of baPWV is useful for the assessment of macroangiopathy and overall prognosis in subjects with diabetes.

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