

Brachial-ankle pulse wave velocity as a predictor of long-term cardiovascular events in 2174 subjects with type 2 diabetes mellitus

A retrospective cohort study

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Abstract

The prognostic value of arterial stiffness in patients with diabetes mellitus (DM) remains unclear. The aim of this study was to investigate the association between brachial-ankle pulse wave velocity (baPWV) and the occurrence of cardiovascular events in people with DM. A total of 2714 subjects (mean age, 63.6 years; males, 59.3%) with type 2 DM and without documented cardiovascular disease and stroke were analyzed. The primary end-point of this study was composite cardiovascular events of cardiac death, non-fatal myocardial infarction, coronary revascularization and stroke. There were 118 composite events (4.3%) during a median follow-up period of 3.84 years (interquartile range, 1.60–5.52 years). In multivariable Cox regression analysis, higher baPWV (≥ 1672 cm/s) was associated with composite events even after controlling for potential confounders (hazard ratio [HR], 2.00; 95% confidence interval [CI], 1.31–3.07; $P = .001$). Compared to the lowest baPWV tertile, both middle (HR, 1.84; 95% CI, 1.03–3.27; $P = .037$) and the highest (HR, 2.97; 95% CI, 1.69–5.22; $P < .001$) tertile of baPWV were associated with increased risk of cardiovascular events in the same multivariable model. In conclusion, the baPWV was associated with cardiovascular events in people with type 2 DM. Considering the simplicity and convenience of baPWV measurement, baPWV may be useful for risk stratification of people with type 2 DM.

Abbreviations: ABI = ankle-brachial index, baPWV = brachial-ankle pulse wave velocity, BMI = body mass index, cfPWV = carotid-femoral pulse wave velocity, CI = confidence interval, DM = diabetes mellitus, HR = hazard ratio, PWV = pulse wave velocity, RAS = renin-angiotensin system.

Keywords: cardiovascular diseases, diabetes mellitus, prognosis, pulse wave analysis, risk assessment

1. Introduction

Diabetes mellitus (DM), a major chronic disease, not only causes various complications such as nephropathy and retinopathy, but also increases the occurrence of cardiovascular disease.^[1,2] Of note, cardiovascular disease is the most common cause of death in patients with type 2 DM.^[3,4] The global prevalence of diabetes in 2019 was estimated to be 9.3% (463 million) and predicted to increase continuously.^[5] Therefore, prognostic tests that predict future cardiovascular events among people with type 2 DM would be useful for cardiovascular risk stratification and management. Many studies have shown that increased arterial stiffness is associated with the development of future cardiovascular events, independent of traditional cardiovascular risk factors.^[6–10]

Therefore, measurement of arterial stiffness is recommended in some people for risk stratification.^[11] There are several measures of arterial stiffness including pulse pressure, augmentation index and pulse wave velocity (PWV).^[12] Among these indicators of arterial stiffness, PWV is the most widely used in research and clinical fields.^[13,14] Although carotid-femoral pulse wave velocity (cfPWV) is considered the gold standard measure of arterial stiffness,^[14] brachial-ankle pulse wave velocity (baPWV) has been increasingly used because of its simplicity and convenience to measure.^[15] The clinical usefulness of baPWV in the prediction of cardiovascular events and mortality in various populations has been reported in many studies.^[7,16,17] However, studies showing the prognostic value of baPWV in people with diabetes are limited.^[18–20] Furthermore, the relationship between arterial stiffness and

H-LK and WKJ contributed equally to this work.

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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cardiovascular events in people with diabetes remains unclear in other studies.^[7,21] As baPWV is noninvasive and very simple to measure, it is useful for mass screening.^[15] If the prognostic value of baPWV becomes clearer in people with diabetes, it would be useful for risk stratification. Therefore, this study was performed to evaluate the prognostic value of baPWV in people with diabetes.

2. Materials and methods

2.1. Ethical statement

This study was performed with adherence to the declaration of Helsinki. The study protocol was authorized by the Institutional Review Board of Boramae Medical Center (Seoul, Republic of Korea) (Institutional Review Board, number: 10-2021-104). Written informed consent was waived due to retrospective study design and routine nature of information collected.

2.2. Study population

This retrospective, single-center study was performed at a general hospital in a large city (Seoul, South Korea). People with type 2 DM between the ages of 19 and 90 who underwent baPWV measurement from 2008 through 2018 were enrolled in this study. DM was defined on the basis of previous diagnosis of diabetes mellitus, current use of anti-diabetic medications, or fasting blood glucose level over 126 mg/dL in repeated tests. Patients with type 1 DM or other forms of diabetes were excluded. In people with diabetes, baPWV was measured as part of cardiovascular assessment at the discretion of the attending physician. The baPWV measurement was useful in people with diabetes because it also provided information on ankle-brachial index (ABI). Of 2910 participants who were initially screened, 196 with the following conditions were excluded: prior history of documented cardiovascular disease, including coronary revascularization and myocardial infarction as well as stroke, before measurement of baPWV; ABI < 0.9 or > 1.4; uncontrolled arrhythmia; significant valvular heart disease greater than mild degree of regurgitation or stenosis; congenital heart disease, and; presence of pericardial effusion. Finally, 2714 participants were analyzed in this study.

2.3. Clinical data

Baseline clinical information and laboratory results were obtained at the time of the 1st measurement of baPWV. Body mass index (BMI) was calculated as body weight divided by height in square meters (kg/m^2). BMI above and equal to $25 \text{ kg}/\text{m}^2$ was considered as obesity.^[22] Hypertension was defined on the basis of previous diagnosis of hypertension, current use of anti-hypertensive medications or systolic/diastolic blood pressure over 140/90 mm Hg. Dyslipidemia was defined on the basis of previous diagnosis of dyslipidemia, current use of anti-dyslipidemic medications or low-density lipoprotein cholesterol level over 160 mg/dL.^[23] A regular smoker within the last year was defined as a smoker. After overnight fasting for more than 12 hours, laboratory tests were performed for the following parameters: white blood cell count, hemoglobin, creatinine, glucose, glycated hemoglobin, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglyceride and C-reactive protein. The estimated glomerular filtration rate was calculated by the Modification of Diet in Renal Disease Study equation.^[24] Information on concomitant cardiovascular medications, including calcium channel blockers, beta-blockers, renin-angiotensin system (RAS) blockers, diuretics and statins, was also obtained.

2.4. baPWV measurement

The measurement of baPWV has been previously described.^[25,26] PWV was calculated by dividing distance by transit time. The distance from the upper arm to the ankle was estimated by participant's height. The transit time was calculated from the start point of brachial pulse wave to the start of ankle pulse wave. With restriction of smoking and drinking of caffeine-containing beverages on the day of measurement, patient took 5 minutes of rest in the supine position. noninvasive automated volume-plethysmographic apparatus (VP-1000; Colin Co., Ltd., Komaki, Japan) was used for the measurement of baPWV. Blood pressure cuffs were wrapped around the upper arms and ankles, and pulse waves were measured. Both electrocardiographic and phonocardiographic monitoring were performed by attaching leads to both the wrists and the sternum, respectively. We used the average value of right and left baPWV measurements.

2.5. Assessment of cardiovascular events

The primary end-point of this study was composite cardiovascular events of cardiac death, non-fatal myocardial infarction, coronary revascularization and stroke. Cardiac death was defined as death caused by acute myocardial infarction, fatal arrhythmia or heart failure. Unexplained sudden death was also considered cardiac death. Non-fatal myocardial infarction was defined on the basis of electrocardiographic findings, elevated cardiac biomarker and coronary angiography results. Coronary revascularization indicated percutaneous coronary intervention or coronary bypass surgery. Stroke was defined on the basis of neurological symptoms with documented imaging studies. Both ischemic and hemorrhagic strokes were included. Transient ischemic attack and traumatic intracranial hemorrhage were not considered clinical events in this study. Clinical events were identified mainly by medical records. Telephone interview or death data provided by the Ministry of Public Administration and Security of Korea were used in participants who were not followed up clinically within the last 6 months.

2.6. Statistical analysis

Continuous variables are expressed as mean \pm standard deviation and categorical variables are expressed as n (%). Student *t* test was used to compare continuous variable and Pearson Chi-square test or Fisher exact test was used to compare categorical variables between the presence and absence of clinical events. Receiver operating characteristic curve analysis was performed, and Youden index was used to determine the cut-off value of baPWV in the prediction of composite outcome. Cox proportional hazard analysis was performed to determine independent associations between baPWV and composite outcome. Participants were divided in 2 groups according to the cut off value of baPWV and the 3 groups by baPWV tertile. Confounding factors, including age, sex, BMI, heart rate, hypertension, dyslipidemia, cigarette smoking, chronic kidney disease (estimated glomerular filtration rate, $< 60 \text{ mL}/\text{minute}/1.73 \text{ m}^2$) and cardiovascular medications, were controlled during multivariable analysis. Kaplan–Meier event free survival curves were generated with the log-rank test to show differences in event-free survival rates among the subgroups divided by cutoff value and baPWV tertile. A *P* value of $< .05$ was considered statistically significant. All statistical analyses were conducted using SPSS 25 (IMB Corp., Armonk, NY).

3. Results

The baseline characteristics of the total study participants ($n = 2714$) are described in Table 1. Mean age was 63.6 ± 10.4 years and men were predominant (59.3%). The prevalence

Table 1
Baseline characteristics of study participants.

Characteristic	Total (n = 2714)	Event (+) (n = 118)	Event (-) (n = 2596)	P value
Age, yr	63.6 ± 10.4	64.3 ± 9.3	63.6 ± 10.5	.447
Men	1610 (59.3)	73 (61.9)	1537 (59.2)	.565
BMI, kg/m ²	25.3 ± 3.5	25.5 ± 3.6	25.2 ± 3.5	.374
SBP, mm Hg	131 ± 18	132 ± 18	131 ± 18	.472
DBP, mm Hg	77.0 ± 11.1	77.2 ± 11.1	76.9 ± 11.1	.771
Heart rate, per minute	72.8 ± 13.2	69.5 ± 11.7	72.9 ± 13.3	.045
Cardiovascular risk factors				
Obesity (BMI ≥ 25 kg/m ²)	1348 (49.8)	62 (53.4)	1286 (49.6)	.419
Hypertension	1899 (70.0)	92 (78.0)	1807 (69.6)	.053
Dyslipidemia	1700 (62.6)	95 (80.5)	1605 (61.8)	<.001
Cigarette smoking	631 (23.2)	27 (22.9)	604 (23.3)	.923
Laboratory findings				
WBC, per mL	7.8 ± 3.5	8.1 ± 3.5	7.7 ± 3.5	.229
Hemoglobin, g/dL	12.9 ± 2.0	12.8 ± 2.2	12.9 ± 2.0	.542
GFR, mL/min/1.73 m ²	77.3 ± 31.8	73.6 ± 34.1	77.4 ± 31.7	0.240
Fasting glucose, mg/dL	149 ± 59	158 ± 74	148 ± 58	.272
Glycated hemoglobin, %	7.3 ± 1.3	7.2 ± 1.2	7.3 ± 1.3	.602
Total cholesterol, mg/dL	149 ± 40	149 ± 39	149 ± 41	.951
LDL cholesterol, mg/dL	83.4 ± 34.3	86.0 ± 36.5	83.3 ± 34.2	.422
HDL cholesterol, mg/dL	45.4 ± 12.8	44.0 ± 11.4	45.4 ± 12.8	.244
Triglycerides, mg/dL	143.3 ± 94.0	148 ± 92	143 ± 94	.536
C-reactive protein, mg/dL	2.1 ± 5.7	3.1 ± 6.3	2.0 ± 5.7	.065
Concomitant medications				
Calcium channel blockers	381 (14.0)	21 (17.8)	360 (13.9)	.230
Beta-blockers	773 (28.5)	49 (41.5)	724 (27.9)	.001
RAS blockers	1039 (38.3)	56 (47.5)	983 (37.9)	.036
Diuretics	34 (1.9)	0	34 (1.9)	.628
Statins	1555 (57.3)	86 (72.9)	1469 (56.6)	<.001
Antiplatelets	2178 (80.3)	87 (73.7)	2091 (80.5)	.069

Numbers are represented as mean ± SD or n (%).

BMI = body mass index, SBP = systolic blood pressure, DBP = diastolic blood pressure, WBC = white blood cell, GFR = glomerular filtration rate, LDL = low-density lipoprotein, HDL = high-density lipoprotein, RAS = renin-angiotensin system.

of obesity (BMI ≥ 25 kg/m²), dyslipidemia and smoking were 49.8%, 62.6% and 23.2%, respectively. Other major laboratory results were within the normal range except C-reactive protein, which was elevated at a mean value of 2.1 ± 5.7 mg/dL. The proportion of participants taking calcium-channel blockers, beta-blockers, RAS blockers, diuretics and statins were 14.0%, 28.5%, 38.3%, 1.9% and 57.3%, respectively.

There were 118 composite events (4.34%) including 11 cardiac deaths, 15 non-fatal myocardial infarctions, 69 coronary revascularizations and 37 strokes during a median follow-up period of 3.84 years (interquartile range, 1.60–5.52 years). The calculated incidence of composite events was 11.2 per 1000 person-years. The baseline characteristics of the study subgroups divided by the presence or absence of composite cardiovascular events are also shown in Table 1. Participants with events showed a higher prevalence of dyslipidemia than those without. More participants used beta-blockers, RAS blockers and statins in participants with events than without. Other clinical characteristics were similar between the subgroups, regardless of events.

Cutoff value of baPWV predicting composite events was obtained as 1672 cm/s by Youden index in receiver operating characteristic curve (Fig. S1, Supplemental Digital Content, <http://links.lww.com/MD/H913>). There was a significant difference in event-free survival rate between the 2 groups divided by the cutoff value (log-rank, $P < .001$), demonstrated in the Kaplan–Meier survival curve (Fig. 1). The results of univariable and multivariable Cox regression analyses are shown in Table 2. In univariable Cox regression analysis, baPWV ≥ 1672 cm/s and a higher baPWV tertile (middle or highest tertile *versus* lowest tertile) were associated with increased risk of composite cardiovascular events ($P < .005$ for each). In multivariable Cox

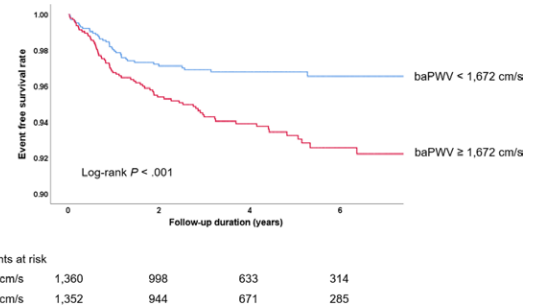


Figure 1. Event free survival rate according to baPWV cutoff value. baPWV, brachial-ankle pulse wave velocity.

Table 2
Independent association of baPWV with clinical outcomes.

Variable	Univariable		Multivariable ^a	
	HR (95% CI)	P	HR (95% CI)	P
Cutoff value of baPWV				
baPWV ≥ 1673 cm/s	1.96 (1.34–2.86)	.001	2.00 (1.31–3.07)	.001
Tertile of baPWV				
Lowest tertile (961–1531 cm/s)	1		1	
Middle tertile (1532–1829 cm/s)	1.79 (1.07–2.98)	.026	1.84 (1.03–3.27)	.037
Highest tertile (1830–3790 cm/s)	2.55 (1.57–4.16)	<.001	2.97 (1.69–5.22)	<.001

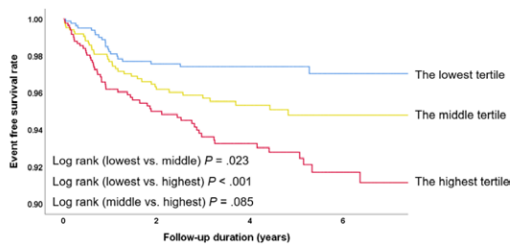
^aFollowing clinical covariates were controlled as potential confounders: age, sex, body mass index, heart rate, hypertension, dyslipidemia, cigarette smoking, chronic kidney disease and cardiovascular medications including beta blocker, renin-angiotensin system blocker and statin. baPWV = brachial-ankle pulse wave velocity, HR = hazard ratio, CI = confidence interval.

regression analysis, baPWV ≥ 1672 cm/s was associated with increased risk of the occurrence of composite cardiovascular events even after controlling for potential confounders (hazard ratio [HR], 2.00; 95% confidence interval [CI], 1.31–3.07; $P = .001$). Compared to the lowest baPWV tertile, both middle (HR, 1.84; 95% CI, 1.03–3.27; $P = .037$) and the highest (HR, 2.97; 95% CI, 1.69–5.22; $P < .001$) tertiles were associated with increased risk of the occurrence of composite cardiovascular events in the same multivariable model. Kaplan–Meier event-free survival curves according to baPWV tertile are demonstrated in Figure 2.

4. Discussion

The major findings of this study are: baPWV of 1672 cm/s was the best cutoff value to predict composite cardiovascular events in people with type 2 DM; baPWV ≥ 1672 cm/s was associated with the occurrence of composite cardiovascular events even after controlling for confounding effects of important clinical covariates, and; when the participants were divided into 3 groups according to baPWV tertile, the middle and highest tertiles also showed increased risk of composite cardiovascular events than the lowest tertile in the same multivariable analysis.

To the best of our knowledge, 2 studies have shown the prognostic value of baPWV in people with diabetes. In Japan, a large-scale cohort study which enrolled 3628 people of the Kyushu prevention study of atherosclerosis with a prospective follow-up of 3.2 years demonstrated significant correlations of baPWV with coronary artery events, cerebrovascular events, and all-cause mortality in people with diabetes.^[18] In another study performed in Korea, which was a multicenter prospective observational study, 2308 people were followed up during



Number of patients at risk	0	2	4	6
The lowest tertile	903	671	431	214
The middle tertile	904	663	432	208
The highest tertile	904	608	441	177

Figure 2. Event free survival rate according to baPWV tertile. baPWV, brachial-ankle pulse wave velocity.

median period of 8.6 years.^[19] This study evaluated the benefits of baPWV as a predictive marker for all-cause and cause-specific mortality in people with diabetes. The interesting finding of this study was that baPWV was correlated not only with all-cause or cardiovascular mortality but also with cancer or other mortality in DM patients. Our study presented similar results providing additional evidence on the prognostic value of baPWV in people with diabetes. Compared to the previous 2 studies,^[18,19] our study has the strengths of minimizing heterogeneity in clinical practice as a single-center study and excluding all people with previous documented cardiovascular disease. There were other study evaluated prognostic impact of baPWV in subjects with type 2 DM which included specific subtype of patients.^[27] This study evaluated 191 subjects with type 2 DM and coronary artery disease, and showed higher baPWV was associated with worse outcome in patients with cardiovascular events.

The pathophysiological mechanism of how arterial stiffness predicts cardiovascular outcome in people with diabetes is uncertain, but the possible explanation could be suggested. Although not limited to people with diabetes, increased arterial stiffness is associated with increased afterload, leading to left ventricular hypertrophy. Also, decreased coronary perfusion in stiffened aorta induces myocardial ischemia. Additionally, shared common risk factors, such as traditional cardiovascular risk factors (old age, high blood pressure, dyslipidemia and smoking), chronic inflammation and endothelial dysfunction is other mechanisms explaining the prognostic value of arterial stiffness in people with type 2 DM.^[15] A relatively limited mechanism in people with diabetes is impedance matching, which means normal stiffness gradient between central and peripheral arteries, is lost in people with diabetes.^[28,29] This may enhance hazardous pressure to microcirculation which causes end organ damage.

The baPWV has many strengths compared to cfPWV.^[15] For the noninvasive assessment of arterial stiffness, cfPWV was considered the gold standard.^[14] However, cfPWV measurement needs more technical skills and causes some discomfort to participant during the palpation of the carotid and femoral arteries. On the contrary, baPWV is simple to measure and convenient to participants by just wrapping blood pressure cuffs around both the upper arms and ankles. Therefore, baPWV is useful especially for mass screening. Clinical usefulness of baPWV has been validated in many studies including meta-analysis.^[7,18,20,25,30,31] With the respect of clinical implication, our results can be more easily applied to real world practice. Because the global incidence and prevalence of DM are continuously increasing and cardiovascular disease is one of the leading causes of death in people with diabetes,^[1,3–5] early prediction of cardiovascular risk is important in people with diabetes. Due to the simplicity and convenience of baPWV measurement, baPWV measurement can be used as an initial test for risk stratification in people with diabetes. Further research is needed on whether baPWV can be used as a treatment monitoring tool or whether treatment targeting baPWV results in improved prognosis in people with diabetes.

There are some limitations in this study. First, we cannot exclude the potential bias originating from retrospective study design and participant enrollment in a single center. The results have limited generalizability. Second, only Korean people were enrolled. In other races, the cutoff value of baPWV may differ or major results could be different. Third, detailed information about DM and its complication was not collected. The results of our study may be affected by the severity of DM. For example, a longer duration of diseased period of DM, the use of insulin or microvascular complications could have influenced arterial stiffness. Fourth, ABI is an indicator of atherosclerosis and is closely related to cardiovascular prognosis in diabetic patients.^[32] Although ABI data could be obtained during the baPWV measurement, ABI was not associated with clinical outcomes in our study. This might be because we exclude patients with low ABI (< 0.9) to improve the reliability of the baPWV value (Fig. S2, Supplemental Digital Content, <http://links.lww.com/MD/H914> and Table S1, Supplemental Digital Content, <http://links.lww.com/MD/H915>). Fifth, although the results of how changes in baPWV affect prognosis may provide additional important information, our study did not have this data. Finally, the area under the curve was not so high to make a decision for a cutoff value. Though the sensitivity and specificity of our cutoff value not satisfactory, the main finding of our results that baPWV is predictive of composite cardiovascular events still has its importance in clinical practice.^[18]

5. Conclusions

A higher baseline baPWV was associated with the occurrence of future cardiovascular events in people with type 2 DM. Considering non-invasiveness and simplicity, the measurement of baPWV may be useful in risk stratification in people with type 2 DM.

Author contributions

Conceptualization: Hack-Lyoung Kim.

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Investigation: Hack-Lyoung Kim and Won Kyeong Jeon.

Methodology: Hack-Lyoung Kim and Won Kyeong Jeon.

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Supervision: Hack-Lyoung Kim.

Writing – original draft: Hack-Lyoung Kim and Won Kyeong Jeon.

Writing – review & editing: Hack-Lyoung Kim.

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