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Prognostic Value of Brachial-Ankle Pulse Wave Velocity According to Subjects' Clinical Characteristics: Data From Analysis of 10,597 Subjects

Hack-Lyoung Kim ,[1*] **Kyu-Sun Lee** ,[2*] **Hyun Sung Joh** ,[1] **Woo-Hyun Lim** ,[1] **Jae-Bin Seo** ,[1] **Sang-Hyun Kim** ,[1] **Joo-Hee Zo** ,[1] **and Myung-A Kim** [1]

[1]Division of Cardiology, Department of Internal Medicine, Seoul Metropolitan Government-Seoul National University Boramae Medical Center, Seoul National University College of Medicine, Seoul, Korea
[2]Division of Cardiology, Department of Internal Medicine, Daejeon Eulji University Hospital, Daejeon, Korea

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Address for Correspondence:
Hack-Lyoung Kim, MD, PhD
Division of Cardiology, Department of Internal Medicine, Seoul Metropolitan Government-Seoul National University Boramae Medical Center, 5 Boramae-ro, Dongjak-gu, Seoul 07061, Korea.
Email: khl2876@gmail.com

*Hack-Lyoung Kim and Kyu-Sun Lee equally contributed to this work.

ORCID iDs
Hack-Lyoung Kim
https://orcid.org/0000-0002-6703-1472
Kyu-Sun Lee
https://orcid.org/0000-0002-2582-663X
Hyun Sung Joh
https://orcid.org/0000-0003-2020-7028
Woo-Hyun Lim
https://orcid.org/0000-0001-9298-8500
Jae-Bin Seo
https://orcid.org/0000-0001-5347-8313

ABSTRACT

Background: To make good use of the prognostic value of arterial stiffness, it is important to identify the population with the greatest benefit. In this study, we compared the prognostic value of brachial-ankle pulse wave velocity (baPWV) according to various clinical characteristics.
Methods: A total of 10,597 subjects who underwent baPWV measurement (mean age, 61.4 ± 9.5 years; female proportion, 42.5%) were retrospectively analyzed. Major adverse cardiovascular events (MACEs), defined as a composite of cardiac death, non-fatal myocardial infarction, coronary revascularization, and ischemic stroke were assessed during the clinical follow-up period.
Results: In the multivariate analysis, clinical variables with more than 4,000 subjects were selected as grouping variables, which were sex (men and women), age (≥ 65 and < 65 years), body mass index (BMI) (≥ 25 and < 25 kg/m^2), hypertension (presence and absence), estimated glomerular filtration rate (≥ 90 and < 90 mL/min/1.73 m^2), and statin use (user and non-user). During the median clinical follow-up duration of 3.58 years (interquartile range, 1.43–5.38 years), there were 422 MACEs (4.0%). In total study subjects, baseline higher baPWV was associated with increased risk of MACE occurrence (hazard ratio for baPWV ≥ 1,800 cm/s compared to baPWV < 1,400 cm/s, 4.04; 95% confidence interval, 2.62–6.21; P < 0.001). The prognostic value of baPWV was statistically significant regardless of sex, age, BMI, hypertension, renal function, and statin use.
Conclusion: Our results suggest that baPWV is not only effective in specific clinical situations, but can be effectively applied to predict cardiovascular prognosis in various clinical situations.

Keywords: Major Adverse Cardiovascular Event; Pulse Wave Velocity; Prognosis; Risk Factors; Risk Stratification

INTRODUCTION

Arterial stiffness, reflecting structural changes of the arterial wall, is accelerated by aging and cardiovascular (CV) risk factors.[1,2] Recognition of arterial stiffness is clinically important

Sang-Hyun Kim
https://orcid.org/0000-0001-8026-1582
Joo-Hee Zo
https://orcid.org/0000-0003-1417-1049
Myung-A Kim
https://orcid.org/0000-0002-3064-7118

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Disclosure

The authors have no potential conflicts of interest to disclose.

Author Contributions

Conceptualization: Kim HL. Data curation: Kim HL, Joh HS, Lim WH, Seo JB, Kim SH, Zo JH, Kim MA. Formal analysis: Kim HL, Lee KS, Zo JH. Funding acquisition: Kim HL. Investigation: Kim HL, Lee KS, Lim WH, Seo JB, Kim MA. Methodology: Kim HL, Lee KS, Joh HS, Lim WH, Seo JB, Kim SH, Zo JH, Kim MA. Resources: Kim SH, Zo JH, Kim MA. Writing - original draft: Kim HL, Lee KS. Writing - review & editing: Kim HL, Joh HS, Lim WH, Seo JB, Kim SH, Zo JH, Kim MA.

because it has proven to be an independent risk factor for the occurrence of cardiovascular disease (CVD) and mortality.[3,4] There are various methods for measuring arterial stiffness.[5,6] Among them, pulse wave velocity (PWV) is non-invasive and relatively simple to measure, making it widely used clinically or for research purposes.[7] Although carotid-femoral PWV (cfPWV) is considered the gold standard for non-invasively measured arterial stiffness,[6] the use of brachial-ankle PWV (baPWV), which has a simpler measurement method, is increasing, mainly in Asia.[3,7] It is essential to find a specific population that can maximize the prognostic value of PWV. PWV applied to this population will be more helpful in CV prognosis evaluation. In this study, we investigated whether the prognostic value of baPWV differs according to subjects' clinical characteristics. We sought to determine the clinical characteristics with the greatest prognostic value of baPWV.

METHODS

Study population

This is a single-center and retrospective study performed at Seoul Metropolitan Government Seoul National University Boramae Medical Center (Seoul, Republic of Korea). Between January 2008 and June 2018, individuals aged between 40 and 79 years who underwent the measurement of baPWV were eligible for this study. At our hospital, PWV testing is a standard assessment for patients who come to the CV center. The baPWV test not only provides information on arterial stiffness but also gives the ankle-brachial index result simultaneously, making it frequently utilized in predicting CV risk. The final decision on performing baPWV test rests with the attending physician. Some patients might decline the test or, for various reasons, may not be able to undergo it. Initially, 10,716 subjects were screened, but those with the following conditions were excluded (n = 119): 1) uncontrolled blood pressure (systolic blood pressure > 180 mmHg or diastolic blood pressure > 110 mmHg), 2) uncontrolled cardiac arrhythmia, 3) valvular dysfunction > mild degree, 4) congenital heart disease, 5) pericardial effusion, and 6) ankle-brachial index < 0.9. Finally, 10,597 subjects were analyzed in this study.

Clinical data collection

Baseline clinical data were obtained based on when the patient was first tested for baPWV. All study subjects were medically stable at the time of the baPWV measurement. Body mass index (BMI) was calculated as body weight divided by height in square meters (kg/m^2). BMI ≥ 25 kg/m^2 was considered as having obesity.[8] Using an oscillometric device, a trained nurse measures systolic and diastolic blood pressure and heart rate. The information on CV risk factors, including hypertension, diabetes mellitus, dyslipidemia, smoking habits, and atherosclerotic CVD (ASCVD), was obtained by a standardized questionnaire. Hypertension was defined on the basis of previous diagnosis of hypertension, current anti-hypertensive medications, systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg. Diabetes mellitus was defined on the basis of a previous diagnosis by a physician of diabetes mellitus, current anti-diabetic medications, fasting blood glucose level ≥ 126 mg/dL and glycated hemoglobin ≥ 6.5%. Dyslipidemia was defined on the basis of a previous diagnosis of dyslipidemia, current anti-dyslipidemic medications, or low-density lipoprotein cholesterol ≥ 160 mg/dL. A person who smoked regularly within the last year was defined as a smoker. ASCVD included myocardial infarction, coronary revascularization and ischemic stroke. After overnight fasting, blood levels of following laboratory parameters were obtained: white blood cell count, hemoglobin, creatinine, glucose, glycated hemoglobin,

total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglyceride, and C-reactive protein. Estimated glomerular filtration rate (eGFR) was calculated using Modification of Diet in Renal Disease study equation incorporating age, race, sex, and serum creatinine level. Information of concomitant CV medications including antiplatelets, calcium channel blockers, beta-blockers, renin-angiotensin system blockers, and statins was also obtained.

baPWV measurement

The baPWV measurement method has been published elsewhere.[9,10] Briefly, the test subjects restricted smoking, drinking, and caffeine-containing beverage on the day of baPWV measurement but maintained medications that were normally taken on a regular basis. In addition, subjects lay in a quiet room for at least five minutes before testing. baPWV was measured using a commercially available volume-plethysmographic apparatus (VP-1000; Collin Co., Ltd., Komaki, Japan). Electrocardiographic electrodes were applied to both wrists, phonocardiographic electrodes were placed on the edge of the sternum to detect heart sounds, and pneumatic cuffs were wrapped on both upper arms and ankles. PWV was calculated by dividing distance by transit time. The distance between the measurement point of baPWV was estimated by an algorithm using the subject's height. Transit time was calculated from the start point of the brachial pulse wave to the start of the ankle pulse wave. The average value of the left and right baPWV measurements was used for the study. The coefficient of variance for interobserver reliability of baPWV was 5.1% in our laboratory.[9]

Assessment of CV events

The primary endpoint of this study was the major adverse CV events (MACEs), a composite of cardiac death, non-fetal myocardial infarction, coronary revascularization, and ischemic stroke. Cardiac death was defined as death caused by acute myocardial infarction, fatal ventricular arrhythmia, and heart failure. Unexplained sudden death was also considered as cardiac death. Non-fatal myocardial infarction was defined on the basis of electrocardiographic findings, elevated cardiac troponin, and coronary angiographic results. Coronary revascularization indicated percutaneous coronary intervention and coronary bypass surgery. Ischemic stroke was defined on the basis of neurologic signs or symptoms with documented imaging studies. For patients who were unable to follow-up more than six months on medical records, we attempted to obtain the information on the occurrence of CV events as accurately as possible by using telephone contact and national death data. When multiple events occurred, the first event was regarded as the MACE.

Statistical analysis

Categorical and continuous variables were presented as number (%) and mean ± standard deviation, respectively. A multivariable Cox proportional hazard regression model was used to investigate the independent association between baPWV and MACE. baPWV values were categorized into < 1,400 cm/s (n = 3,010; 28.4%), 1,400–1,799 cm/s (n = 5,219; 49.2%), and ≥ 1,800 cm/s (n = 2,368; 22.3%) for the multivariable analysis.[11] We categorized the study patients into two groups based on several clinical factors. Clinical factors with a sample size exceeding 4,000 subjects were selected as grouping variables, which were sex (men and women), age (≥ 65 and < 65 years), BMI (≥ 25 and < 25 kg/m^2), hypertension (presence and absence), eGFR (≥ 90 and < 90 mL/min/1.73 m^2), and statin use (user and non-user). We conducted separate multivariable Cox regression analyses for each group. The following clinical covariates were controlled during the multivariable analyses as potential confounders: age, BMI, hypertension, diabetes mellitus, dyslipidemia, cigarette smoking,

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eGFR, beta-blockers, renin-angiotensin system blockers, and statins. Group variables were not included as independent variables. However, age, BMI, and eGFR were included as group variables as continuous variables. The incremental prognostic value of baPWV to traditional risk factors was assessed using global chi-square value. All *P* values where $P < 0.05$ were considered statistically significant. SPSS version 25.0 (IBM SPSS Statistics, Chicago, IL, USA) was used for statistical analysis.

Ethics statement

The study protocol was approved by the Institutional Review Board (IRB) of Boramae Medical Center (Seoul, Republic of Korea) (IRB number, 20-2021-78), and written informed consent was waived by the IRB due to its retrospective study design and the routine nature of information collected.

RESULTS

Baseline clinical characteristics of study subjects

The baseline clinical characteristics of study subjects (n = 10,597) are demonstrated in **Table 1**. The mean age was 61.4 ± 9.5 years, and the female proportion was 42.5%. The prevalence of hypertension, diabetes, dyslipidemia and previous CVD were 46.4%, 24.0%, 52.9%, and 26.5%, respectively. Major laboratory results were within normal range. The proportions of subjects taking antiplatelets, calcium channel blockers, beta-blockers, renin-angiotensin system blockers, and statins were 41.8%, 16.1%, 24.8%, 34.8%, and 48.5%, respectively.

Table 1. Baseline clinical characteristics of study subjects

Characteristics	Total subjects (N = 10,597)	MACE (+) (n = 422)	MACE (-) (n = 10,175)	*P* value*
Age, yr	61.4 ± 9.5	64.7 ± 9.0	61.3 ± 9.5	< 0.001
Age ≥ 65 yr	4,297 (40.5)	240 (56.9)	4,057 (39.9)	< 0.001
Female sex	4,504 (42.5)	148 (35.1)	4,356 (42.8)	0.002
Body mass index, kg/m^2	24.8 ± 3.2	24.9 ± 3.3	24.8 ± 3.3	0.744
Body mass index ≥ 25 kg/m^2	4,823 (45.5)	187 (44.8)	4,636 (45.7)	0.734
Cardiovascular risk factors				
Hypertension	4,915 (46.4)	250 (59.2)	4,665 (45.8)	< 0.001
Diabetes mellitus	2,548 (24.0)	153 (36.3)	2,395 (23.5)	< 0.001
Cigarette smoking	1,969 (18.6)	116 (27.5)	1,853 (18.2)	< 0.001
Atherosclerotic cardiovascular disease	2,812 (26.5)	189 (44.8)	2,623 (25.8)	< 0.001
Laboratory findings				
Glucose, mg/dL	121 ± 41	137 ± 60	120 ± 40	< 0.001
Glycated hemoglobin, %	6.39 ± 1.12	6.65 ± 1.19	6.38 ± 1.12	0.006
Estimated glomerular filtration rate, mL/min/1.73m^2	85.9 ± 25.1	77.9 ± 32.4	86.3 ± 24.7	< 0.001
Estimated glomerular filtration rate < 90 mL/min/1.73m^2	5,585 (52.7)	250 (60.2)	5,335 (55.2)	0.044
Total cholesterol, mg/dL	166 ± 41	154 ± 47	166 ± 41	< 0.001
Low-density lipoprotein cholesterol, mg/dL	98.1 ± 36.8	95.2 ± 40.8	98.2 ± 36.7	0.120
High-density lipoprotein cholesterol, mg/dL	48.6 ± 13.0	45.2 ± 13.7	48.7 ± 13.0	< 0.001
Triglyceride, mg/dL	134 ± 95	138 ± 90	134 ± 95	0.426
Cardiovascular medications				
Antiplatelets	1,712 (16.2)	96 (22.7)	1,616 (15.9)	< 0.001
Calcium channel blockers	1,706 (16.1)	51 (12.1)	1,655 (16.3)	0.022
Beta-blockers	2,626 (24.8)	167 (39.6)	2,459 (24.2)	< 0.001
Renin-angiotensin system blockers	3,684 (34.8)	184 (43.6)	3,500 (34.4)	< 0.001
Statins	5,137 (48.5)	275 (65.2)	4,862 (47.8)	< 0.001

Numbers are expressed as mean ± standard deviation or number (%).

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Baseline clinical characteristics of study subjects according to MACEs

During the median clinical follow-up duration of 3.58 years (interquartile range, 1.43–5.38 years), there were 422 MACEs (4.0%): 112 non-cardiac deaths (1.1%), 27 cardiac deaths (0.3%), 31 non-fatal myocardial infarctions (0.3%), 175 coronary revascularizations (1.7%) and 77 ischemic strokes (0.7%). The results of comparisons in the baseline clinical characteristics are demonstrated in **Table 1**. Subjects with MACEs were older (64.7 ± 9.0 *vs.* 61.3 ± 9.5 years; $P < 0.001$) and more likely to be male (64.9% vs. 57.2%; $P < 0.001$) than those without MACEs. Subjects with MACEs had more CV risk factors including hypertension, diabetes mellitus, cigarette smoking and prior history of ASCVD ($P < 0.001$ for each) than those without MACEs. In major laboratory findings, the blood levels of glucose and HbA1c were higher, and the blood levels of total cholesterol and HDL-cholesterol were lower in subjects with MACEs compared to those without MACE. eGFR was significantly lower in subjects with MACEs than those without MACEs. CV medications were more frequently prescribed in subjects with MACEs than those without MACEs, except for the lower prescription rate of calcium channel blockers in subjects with MACEs.

Predictive value of baPWV in various subgroups

Table 2 demonstrates the results of multivariable analyses showing the independent association between baPWV with MACE according to subjects' clinical characteristics. In total study subjects, baseline higher baPWV was associated with increased risk of MACE occurrence (hazard ratio for baPWV ≥ 1,800 cm/s compared to baPWV < 1,400 cm/s, 4.04; 95% confidence interval, 2.62–6.21; $P < 0.001$) (**Table 2**). Kaplan-Meier survival curves also show that MACE-free survival rates were significantly different depending on the baPWV groups (log-rank $P < 0.001$) (**Fig. 1**). The prognostic value of baPWV was statistically significant regardless of sex, age, BMI, hypertension, renal function, and statin use Incorporating baPWV information alongside traditional risk factors notably raised the global χ^2 value from 157 to 238 ($P < 0.001$) (**Fig. 2**).

DISCUSSION

The current study evaluates the prognostic value of baPWV for MACEs in subjects who visited a general hospital and underwent CV evaluation. Although we expected the prognostic value of baPWV to be higher in subjects with specific clinical features, the analysis showed that the predictive value of baPWV for MACE was excellent regardless of all the clinical features we focused on. In other words, regardless of sex, age, BMI, hypertension, renal function, and statin use, the MACE predictive value of baPWV was statistically significant in multivariable analyses. To the best of our knowledge, this is the first study to show the prognostic value of baPWV subdivided according to various clinical features.

The prognostic value of the measures of arterial stiffness has been well-documented. Arterial stiffness information has been an important tool for predicting future CV events in normal subjects[12-14] as well as in various patient groups.[15-20] Meta-analyses also confirmed that CV events occurred more frequently in patients with baseline increased arterial stiffness.[3,4] However, few studies have analyzed the prognostic value of arterial stiffness by subdividing it according to the subjects' clinical characteristics. Recently, our group demonstrated that baPWV is an important tool for predicting CV risk, regardless of the patient's risk profile,[21] which aligns with the current study's findings. When using a CV risk prediction tool, it is necessary to apply it differently according to the subject's CV risk or clinical

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Table 2. Multivariable analyses showing the independent association between baPWV with major adverse cardiovascular event according to subjects' clinical characteristics

Variables	HR (95% CI)	*P* value
Total population (N = 10,597)		
baPWV, < 1,400 cm/s	1	-
baPWV, 1,400–1,799 cm/s	2.40 (1.63–3.55)	< 0.001
baPWV, ≥ 1,800 cm/s	4.04 (2.62–6.21)	< 0.001
Male (n = 6,093)		
baPWV, < 1,400 cm/s	1	-
baPWV, 1,400–1,799 cm/s	2.40 (1.63–3.55)	< 0.001
baPWV, ≥ 1,800 cm/s	4.04 (2.62–6.21)	< 0.001
Female (n = 4,504)		
baPWV, < 1,400 cm/s	1	-
baPWV, 1,400–1,799 cm/s	1.75 (0.92–3.32)	0.086
baPWV, ≥ 1,800 cm/s	3.72 (1.91–7.26)	< 0.001
Age ≥ 65 yr (n = 4,297)		
baPWV, < 1,400 cm/s	1	-
baPWV, 1,400–1,799 cm/s	2.75 (1.38–5.47)	0.004
baPWV, ≥ 1,800 cm/s	4.81 (2.42–9.54)	< 0.001
Age < 65 years (n = 6,300)		
baPWV, < 1,400 cm/s	1	-
baPWV, 1,400–1,799 cm/s	2.05 (1.39–3.04)	< 0.001
baPWV, ≥ 1,800 cm/s	3.78 (2.33–6.15)	< 0.001
Body mass index ≥ 25 kg/m^2 (n = 4,823)		
baPWV, < 1,400 cm/s	1	-
baPWV, 1,400–1,799 cm/s	1.86 (1.16–2.99)	0.010
baPWV, ≥ 1,800 cm/s	3.67 (2.18–6.18)	< 0.001
Body mass index < 25 kg/m^2 (n = 5,741)		
baPWV, < 1,400 cm/s	1	-
baPWV, 1,400–1,799 cm/s	2.51 (1.57–4.02)	< 0.001
baPWV, ≥ 1,800 cm/s	4.27 (2.58–7.07)	< 0.001
Hypertension, yes (n = 4,915)		
baPWV, < 1,400 cm/s	1	-
baPWV, 1,400–1,799 cm/s	2.72 (1.58–4.70)	< 0.001
baPWV, ≥ 1,800 cm/s	4.55 (2.58–8.02)	< 0.001
Hypertension, no (n = 5,682)		
baPWV, < 1,400 cm/s	1	-
baPWV, 1,400–1,799 cm/s	1.94 (1.26–2.99)	0.003
baPWV, ≥ 1,800 cm/s	3.95 (2.39–6.53)	< 0.001
GFR < 90 mL/min/1.73m^2 (n = 5,585)		
baPWV, < 1,400 cm/s	1	-
baPWV, 1,400–1,799 cm/s	1.72 (1.08–2.73)	0.022
baPWV, ≥ 1,800 cm/s	3.07 (1.89–4.99)	< 0.001
GFR ≥ 90 mL/min/1.73m^2 (n = 4,491)		
baPWV, < 1,400 cm/s	1	-
baPWV, 1,400–1,799 cm/s	2.72 (1.69–4.38)	< 0.001
baPWV, ≥ 1,800 cm/s	4.61 (2.66–8.00)	< 0.001
Statin use, yes (n = 5,137)		
baPWV, < 1,400 cm/s	1	-
baPWV, 1,400–1,799 cm/s	1.75 (1.18–2.59)	0.005
baPWV, ≥ 1,800 cm/s	3.64 (2.38–5.56)	< 0.001
Statin use, no (n = 5,460)		
baPWV, < 1,400 cm/s	1	-
baPWV, 1,400–1,799 cm/s	3.54 (1.85–6.77)	< 0.001
baPWV, ≥ 1,800 cm/s	4.93 (2.44–9.96)	< 0.001

Separate multivariable Cox regression analyses were performed for each clinical condition. baPWV is one of independent variables in each separate multivariable model. The following variables were controlled during the multivariable analyses: age, body mass index, hypertension, diabetes mellitus, cigarette smoking, ASCVD, eGFR, antiplatelets, beta-blockers, renin-angiotensin system blockers and statins. Group variables were not included as independent variables. However, age, body mass index and eGFR were included as group variables as continuous variables.

baPWV = brachial-ankle pulse wave velocity, HR = hazard ratio, CI = confidence interval, GFR = glomerular filtration rate, ASCVD = atherosclerotic cardiovascular disease, eGFR = estimated glomerular filtration rate.

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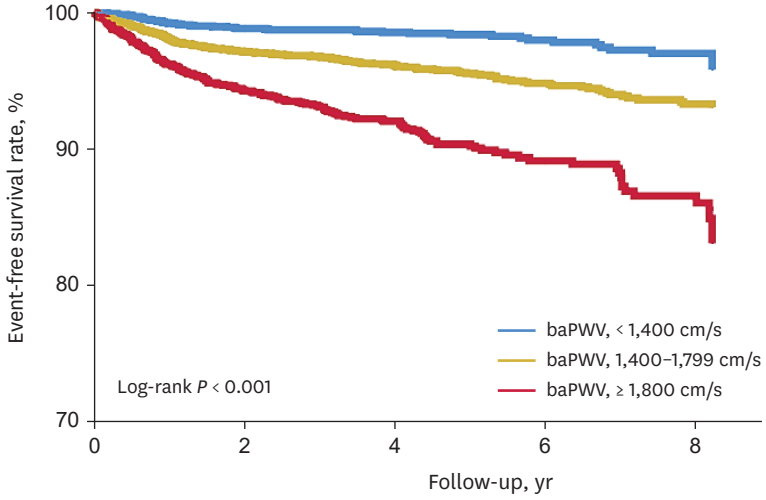

No. of subjects at risk					
baPWV, < 1,400 cm/s	3,010	1,878	1,359	936	454
baPWV, 1,400–1,799 cm/s	5,219	3,112	2,220	1,528	642
baPWV, ≥ 1,800 cm/s	2,368	1,297	811	402	180

Fig. 1. Major adverse cardiovascular event-free survival rate according to baseline baPWV tertile.
baPWV = brachial-ankle pulse wave velocity.

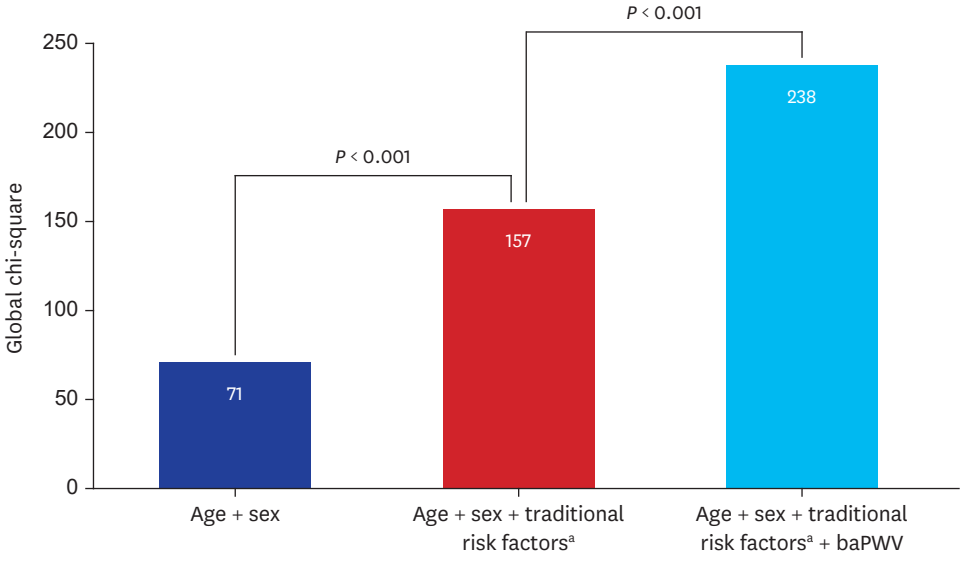

Fig. 2. Incremental prognostic value of baPWV to traditional risk factors.
baPWV = brachial-ankle pulse wave velocity.
[a]Included hypertension, diabetes mellitus, dyslipidemia, cigarette smoking and obesity.

characteristics.[22,23] Moreover, finding clinical factors that can maximize the predictive power of future CV events is very important for the effective use of risk prediction tools. Considering these points, we hypothesized that the predictive power of baPWV would be further increased in subjects with specific clinical features, but the study results differed from our expectations. Although there were some differences, the prognostic value of baPWV was significant in various clinical situations. Our results suggest that baPWV is not only effective in specific clinical situations, but can be effectively applied to predict CV prognosis in various clinical

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situations. Since baPWV measurement is non-invasive and very simple,[7] baPWV would be a very effective tool for mass screening among subjects with various clinical risk factors.

There are several limitations to the current analysis. First, since it is a retrospective and observational study, there are unavoidable limitations, such as selection bias or the possibility of uncorrected confounding variables. Second, we used clinical factors with n > 4,000 as grouping variables for multivariable analyses. Thus, some important clinical factors such as diabetes mellitus, dyslipidemia, and smoking were not considered as grouping variables. Despite analyzing a vast number of patients, a relatively short follow-up period and a low rate of CV events made subgroup analyses challenging. If the count in a group was below 4,000, the results varied due to the need for a comprehensive multivariable analysis. However, the outcomes were more consistent when each group had over 4,000 patients. Third, cfPWV is the gold standard for non-invasively measured arterial stiffness; however, we used baPWV. baPWV included a large portion of the peripheral muscular artery, although muscular arteries may not be relevant for the CV risk assessment.[7] However, from the point of view of mass screening, baPWV is more suitable than cfPWV because it is easier to measure and does not cause discomfort to the subject. baPWV also correlates very well with cfPWV and invasively measured arterial stiffness indicators.[7] Moreover, baPWV has been identified in many studies for its clinical value in predicting CV prognosis, so there is no need to hesitate to use baPWV. Lastly, this study was mainly performed in east Asian population. Therefore, we should be cautious in extrapolating the current results to other ethnicities.

The prognostic value of baPWV for MACE was significant in subjects with various clinical situations. Therefore, baPWV is useful as a risk prediction tool because the measurement is simple and less affected by the subject's clinical features.

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