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ORIGINAL STUDY

Prognostic value of arterial stiffness in menopausal women

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Abstract

Objective: Because menopausal women have an increased cardiovascular risk, risk stratification is very crucial in this population. This study aimed to verify the prognostic value of arterial stiffness in menopausal women.

Methods: We retrospectively analyzed 2,917 menopausal women (age >55y) without overt cardiovascular disease who underwent brachial-ankle pulse wave velocity measurement. The primary endpoint was a composite of clinical events, including all-cause death, nonfatal myocardial infarction, coronary revascularization, and stroke, hereafter referred to as major adverse cardiovascular events. Propensity score matching and inverse probability-treatment weighting analysis were used to balance differences in baseline participant characteristics.

Results: The mean participant age was 66.8 ± 7.7 years. During a median follow-up period of 4.0 (interquartile range of 1.9-6.3) years, the primary outcome was noted in 56 cases (1.9%). Pulse wave velocity was significantly higher in participants with the primary outcome than in those without (1,947 ± 388 vs 1,690 ± 348 cm/s; $P < 0.001$). For every 100 cm/s increase in pulse wave velocity, the hazard ratio for the primary endpoint increased by 1.15 times (95% confidence interval, 1.08-1.22; $P < 0.001$) in multivariable Cox regression analysis. A pulse wave velocity > 1,613 cm/s was associated with increased risk of the primary endpoint in the same multivariable analysis (hazard ratio, 3.06; 95% confidence interval, 1.40-6.68; $P = 0.005$). The results were consistent after propensity score matching and inverse probability-treatment weighting analysis.

Conclusions: Elevated brachial-ankle pulse wave velocity was associated with the occurrence of major adverse cardiovascular events in menopausal women without cardiovascular disease and may represent a useful screening tool.

Key Words: Arterial stiffness – Cardiovascular disease – Menopause – Prognosis – Pulse wave velocity.

The protective effect of estrogen on the cardiovascular system has been clearly demonstrated and is mediated via several potential mechanisms, including 1) improvement in cholesterol profiles, 2) inducement of vasodilation, 3) increase in nitric oxide production, 4) improvement in endothelial cell function, 5) exertion of anti-inflammatory and antioxidant effects, and 6) inhibition of the proliferation of vascular smooth muscle cells.[1,2] Thus, reduced blood estrogen levels are associated with a significantly increased cardiovascular risk in menopausal women.[2,3] Indeed, many studies have reported that menopausal women have a higher incidence of cardiovascular events than men of the same age.[4-6] The prevalence of coronary artery disease in women is 14% for those ages <45, but it rapidly increases to 48%, 65%, and 79% forthose ages >55 every 10 years, that is, at 55, 65, and 75 years, respectively.[7] Therefore, it is important to promptly identify women who are expected to be at high risk after menopause and provide early personalized treatment.

Arterial stiffness is known to be an important risk factor for cardiovascular events and mortality.[8-10] Although the prognostic value of arterial stiffness has been confirmed in the general population and in patients with various diseases, few studies have directly compared the association between increased arterial stiffness and long-term prognosis in menopausal women. Consequently, this study aimed to verify the prognostic importance of arterial stiffness in menopausal women.

METHODS

Study population

Between October 2008 and June 2018, we retrospectively reviewed the medical records of 3,063 menopausal women (age >55y) without documented cardiovascular disease or

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stroke who underwent brachial-ankle pulse wave velocity (baPWV) assessment at a tertiary referral center. The measurement of baPWV is a common examination performed during cardiovascular evaluation for patients visiting our cardiovascular center. However, some patients may not undergo baPWV evaluation owing to the following reasons: 1) patient refusal and 2) inadequate patient conditions for the measurement, such as hand tremor, amputated extremities, arterio-venous fistula, or peripheral arterial occlusive disease. To increase the reliability of the baPWV value, participants with the following conditions were excluded ($n = 146$): (1) ankle-brachial index >1.4 or <0.9, (2) atrial fibrillation or other uncontrolled arrhythmias, (3) dysfunction of heart valves greater than a mild degree, (4) pericardial effusion more than minimal, and (5) congenital heart disease. Finally, 2,917 women were recruited in this study. This study complied with the provisions of the Declaration of Helsinki as revised in 2013. The study protocol was approved by the Institutional Review Board (approval number, 10-2021-103). The requirement for informed consent was waived owing to the retrospective study design.

Data collection

Clinical data, including body mass index, and information on the history of hypertension and diabetes mellitus were collected. Obesity was defined as a body mass index of $\geq 25\ kg/m^2$.[11] Hypertension was defined based on a diagnosis of hypertension, current prescription of antihypertensive medications, or systolic/diastolic blood pressure of $\geq 140/90$ mmHg. Venous blood samples were obtained from the antecubital vein after overnight fasting for approximately 12 hours. The following blood sample parameters were evaluated on the same day of baPWV measurement: common blood cell count, including white blood cell count and hemoglobin; creatinine; lipid levels including triglyceride, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol; serum glucose and glycated hemoglobin; and C-reactive protein. Glomerular filtration rate (GFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation.[12] Left ventricular (LV) ejection fraction was assessed using the biplane Simpson method based on the apical view of transthoracic echocardiography. Past medication history was identified, which included information on renin-angiotensin system inhibitor, beta-blocker, calcium channel blocker, and statin use.

baPWV measurement

On the day of baPWV measurement, participants were prohibited from consuming alcohol, smoking cigarettes, and consuming caffeine-containing beverages. Regularly administrated drugs were continued without interruption. baPWV was measured after an approximate 5-minute period of bed rest. The examinations were conducted in a silent enclosed space under constant temperature and humidity. baPWV was conducted using a commercially available device (VP-1000 analyzer: Colins, Komaki, Japan).[13,14] The pressure waveforms of the brachial and tibial arteries were acquired after wrapping the blood pressure cuff around both upper arms and ankles with plethysmographic and oscillometric pressure sensors. Time intervals between pressure waveforms of the brachial and tibial arteries (pulse transit time) were examined, and baPWV was calculated automatically with a height-based formula to estimate arterial path length. We used the mean of the right and left baPWV values for analysis. baPWV was conducted by one experienced operator. The coefficient of variation of the intraobserver variability for baPWV measurement was 5.1% in our previous study.[15]

Clinical events

The primary endpoint, major adverse cardiovascular event (MACE), was a composite of clinical events consisting of all-cause death, nonfatal myocardial infarction, coronary revascularization, and stroke. Cardiovascular death included sudden cardiac death and death resulting from acute myocardial infarction, heart failure, stroke, cardiovascular procedures, cardiovascular hemorrhage, or other cardiovascular causes. Unexplained sudden death was also considered cardiac death. Myocardial infarction was defined based on clinical symptoms, electrocardiogram findings, elevated cardiac troponin, and occlusive artery lesions confirmed on coronary artery imaging. Coronary revascularization was defined as undergoing percutaneous coronary intervention and coronary bypass surgery. Stroke was defined as sudden neurological deficits examined by neurologists and as a defect confirmed via brain imaging. Data on clinical events were obtained mainly through medical chart reviews, and clinical events of participants who did not visit our hospital for more than 6 months were assessed through telephone interviews. For those who could not be contacted by telephone, we requested data from the National Statistical Office of Korea to ascertain their death.

Statistical analysis

Data are presented as numbers (percentages) for categorical variables and as mean ± standard deviation for continuous variables. The participants were stratified into two groups according to MACE for univariable comparison. Means were compared using the Student t test for continuous variables, and the prevalence was compared using the chi-square test between the two groups for categorical variables. Multivariable Cox regression analyses were performed to identify the association between baPWV and MACE. Variables with $P < 0.10$ in the univariable analyses were included as independent variables in the multivariable analysis. The receiver operating characteristic (ROC) curve with area under curve analysis and the Youden index was used to acquire the baPWV cutoff value for predicting MACE.[16] We performed Kaplan-Meier survival curve analysis to determine the cumulative incidence according to baPWV and conducted comparisons using the log-rank test. Propensity score (PS) matching analysis and inverse probability of treatment weighting (IPTW) analysis using calculated PS were performed to

TABLE 1. *Baseline clinical characteristics of study participants*

Characteristic	With MACE ($n = 56$)	Without MACE ($n = 2,861$)	P value
Age, y	68.7 ± 7.4	66.8 ± 7.7	0.065
Weight, kg	58.6 ± 7.6	58.8 ± 8.8	0.86
Height, cm	152.4 ± 4.8	153.3 ± 5.7	0.24
Body mass index, kg/m^2	25.3 ± 3.1	25.0 ± 3.4	0.62
Body mass index ≥25 kg/m^2	25 (44.6)	1,332 (46.6)	0.88
Systolic blood pressure, mmHg	133.7 ± 19.3	132.3 ± 18.7	0.59
Diastolic blood pressure, mmHg	75.1 ± 11.0	76.3 ± 10.6	0.41
Heart rate, per minutes	71.1 ± 11.8	69.8 ± 12.0	0.44
Hypertension	30 (53.6)	1,403 (49.0)	0.59
Diabetes mellitus	24 (42.9)	675 (23.6)	0.001
Cigarette smoking	3 (5.4)	105 (3.7)	0.76
Wight blood cell, × 10^3/μL	7.44 ± 4.90	6.71 ± 3.10	0.29
Hemoglobin, g/dL	12.3 ± 1.8	12.9 ± 1.6	0.008
GFR, mL/min/1.73 m^2	71.8 ± 28.0	82.4 ± 19.9	0.008
Glucose, mg/dL	135.3 ± 51.6	119.5 ± 38.5	0.043
Glycated hemoglobin, %	6.6 ± 0.8	6.4 ± 1.1	0.31
Total cholesterol, mg/dL	151.8 ± 40.1	163.5 ± 37.9	0.027
LDL cholesterol, mg/dL	87.4 ± 37.8	93.5 ± 33.0	0.20
HDL cholesterol, mg/dL	50.9 ± 15.1	51.7 ± 12.8	0.67
Triglyceride, mg/dL	108.6 ± 67.5	122.9 ± 64.1	0.12
Left ventricular ejection fraction, %	65.2 ± 11.0	66.2 ± 8.0	0.53
RAS blocker	18 (32.1)	778 (27.2)	0.50
Beta-blocker	19 (33.9)	511 (17.9)	0.004
Calcium channel blocker	10 (17.9)	648 (22.6)	0.49
Statin	34 (60.7)	1,206 (42.2)	0.008

Numbers are expressed as mean ± standard deviation or n (%). GFR, glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MACE, major adverse cardiovascular event; RAS, renin-angiotensin system.

balance covariates between participants with and without MACE. The PS-matched cohort was generated with 15:1 nearest neighbor matching using a 0.01 caliper width using the ``MatchIt'' package of R (R foundation for Statistical Computing, Vienna, Austria). Weights for participants with MACE were the inverse of PS and those for participants without MACE were the inverse of (1-PS), and the weights were stabilized using the trimming technique.[17] A standardized mean difference in covariates below 0.10 in the matched population indicated balance between the two groups. A P value less than 0.05 indicated statistical significance. All statistical analyses were performed using SPSS 25.0 (IBM Corp., Armonk, NY) and R version 4.0.3.

RESULTS

Baseline clinical characteristics and clinical outcomes

The mean follow-up duration was 4.0 ± 2.7 (median, 4.0; interquartile range, 1.9-6.3) years. MACE was observed in 56 cases (1.9%): 33 cases of all-cause death, including eight cases of cardiac death; two cases, nonfatal myocardial infarction; 26 cases, coronary revascularization; and 24 cases, stroke. The mean age of the study participants was 66.8 ± 7.7 years, and their baseline clinical characteristics according to MACE are shown in Table 1. The prevalence of diabetes mellitus was higher in participants with MACE than in those without. Regarding laboratory findings, the hemoglobin level, GFR, and total cholesterol level were lower and the glucose level was higher in participants with MACE than in those without. Among cardiovascular medications, beta-blocker and statins were prescribed more frequently for participants with MACE. In addition, baPWV was significantly higher in participants with MACE than in those without (1,947 ± 388 vs 1,690 ± 349 cm/s; $P < 0.001$) (Fig. 1).

Prognostic value of baPWV

Multivariable Cox regression analyses revealed an independent association between baPWV and MACE (Table 2). In multivariable analyses, the following variables with P value < 0.10 in the univariable analyses (Supplementary Table 1,

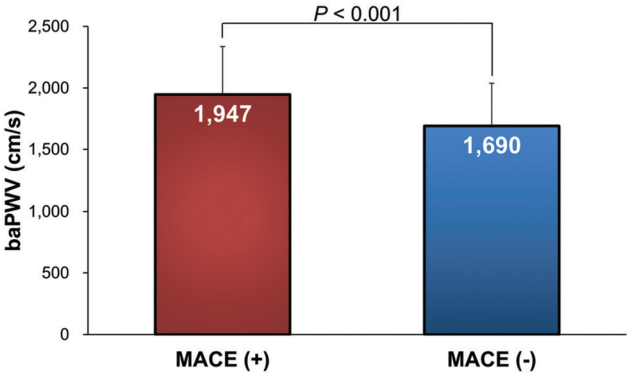

FIG. 1. Mean and standard variation of baPWV according to groups with and without MACE. baPWV, brachial-ankle pulse wave velocity; MACE, major adverse cardiovascular events.

TABLE 2. *Independent association between baPWV and MACE in several different models*

Models	HR (95% CI)	*P* value
Multivariable Cox model		
baPWV, per 100 cm/s	1.15 (1.08-1.22)	<0.001
baPWV, per 500 cm/s	1.98 (1.45-2.71)	<0.001
baPWV, per 1 tertile[a]	2.21 (1.45-3.38)	<0.001
baPWV ≥ 1,613 cm/s	3.27 (1.58-6.75)	<0.001
PS-matching model		
(baPWV, per 100 cm/s)	1.11 (1.05-1.18)	0.001
Stabilized IPTW model (baPWV, per 100 cm/s)	1.13 (1.08-1.18)	<0.001

baPWV, brachial-ankle pulse wave velocity; CI, confidence interval; HR, hazard ratio; IPTW, inverse probability treatment weighting; MACE, major adverse cardiovascular event; PS, propensity score.
The following variables were controlled in each multivariable cox regression, PS-matching, and IPTW model: age, diabetes mellitus, hemoglobin, glomerular filtration rate, glucose, total cholesterol, beta-blocker, and statin.
[a]the lowest tertile, 857-1,505 cm/s; middle tertile, 1,506-1,766 cm/s; and the highest tertile, 1,767-4,515 cm/s.

http://links.lww.com/MENO/A900) were controlled as potential confounders: age, diabetes mellitus, hemoglobin level, GFR, glucose level, total cholesterol level, beta-blocker, and statin. When baPWV increased by 100 cm/s and 500 cm/s, the hazard ratio (HR) for MACE increased by 1.15 (95% confidence interval [CI], 1.08-1.22; $P < 0.001$) and 1.98 (95% CI, 1.45-2.71; $P < 0.001$) times, respectively. When baPWV was subdivided into tertiles, the middle (HR, 4.11; 95% CI, 1.39-12.19; $P = 0.011$) and highest (HR, 6.76; 95% CI, 2.28-20.09; $P = 0.001$) tertiles of baPWV were associated with an increased incidence of MACE when compared with the lowest baPWV tertile. ROC curve analysis demonstrated that a baPWV cutoff value (=1,613 cm/s) predicted MACE with 83.9% sensitivity and 52.4% specificity ($P < 0.001$) (Supplementary Fig. 1, http://links.lww.com/MENO/A900). A high baPWV(≥1,613 cm/s) was associated with an increased risk of MACE (HR, 3.27; 95% CI, 1.58-6.75; $P < 0.001$). KaplanMeier survival curves demonstrated a significantly different cumulative incidence of MACE according to the baPWV cutoff value (Fig. 2A) and tertiles (Fig. 2B) (log-rank $P < 0.001$ for each). The results were concordant in each component of MACE (Supplementary Fig. 2 and Supplementary Table 2, http://links.lww.com/MENO/A900).

Prognostic value of baPWV in PS matching and IPTW models

We performed PS matching and IPTW analyses to correct baseline differences between the groups with and without MACE. After PS matching with a 15:1 ratio, 840 matched participants without MACE were compared with 56 participants with MACE. The mean standardized difference in variables used in PS matching and IPTW analyses was lower than 0.10 after matching (Supplementary Table 3 and Supplementary Fig. 3, http://links.lww.com/MENO/A900). In a Cox regression model, a baPWV increase of 100 cm/s was a significant predictor of MACE after adjustment in PS matching (HR 1.11; 95% CI, 1.05-1.18; $P = 0.001$) and stabilized IPTW (HR 1.13; 95% CI 1.08-1.18; $P < 0.001$) models (Table 2). baPWV ≥ 1,613 cm/s remained associated with a higher cumulative incidence of MACE in the KaplanMeier survival curves for two models (Fig. 3A, B) (log-rank $P = 0.003$ and $P < 0.001$, respectively).

DISCUSSION

The present study showed that baPWV was associated with MACE in menopausal women without overt cardiovascular disease. In multiple Cox regression analyses, the prognostic value of baPWV was significant even when we classified participants based on their baPWV measurement in four different ways: (1) per 100 cm/s increase, (2) per 500 cm/s increase, (3) per tertile, and (4) with a cutoff value obtained via ROC curve analyses. In particular, a 100 cm/s increase in baPWV was associated with a 15% increase in MACE risk, and the risk doubled with a 500 cm/s increase in baPWV. The cutoff value for MACE in menopausal women was 1,613 cm/s in our study. The result was also concordant after sophisticated statistical methods (PS and IPTW) were used to adjust the different baseline characteristics as confounding factors between participants with and without MACE. To the best of our knowledge, our study is the first to suggest that baPWV is an independent risk factor for cardiovascular events in menopausal women.

As mentioned earlier, increased arterial stiffness was an independent risk factor for poor cardiovascular outcomes in the general population.[9,10] There is clear evidence that arterial stiffness increases after menopause.[18] Angeli et al[19] examined 886 menopausal women with hypertension and demonstrated that 24-hour pulse pressure measured through ambulatory blood pressure monitoring, one of the indicators for arterial stiffness, was associated with cardiovascular outcomes. Using the brachial/carotid pulse pressure ratio, menopausal women had impaired pulse pressure amplification compared with age-matched men, mainly owing to increased aortic stiffness, and the parameter was associated with an increased cardiovascular risk.[20] A recent study suggested that abruptly increased arterial stiffness measured using the carotid-femoral pulse wave velocity (cfPWV) was observed within 1 year of the final menstrual period.[21] According to a study of 3,149 women who underwent medical checkups including baPWV, menopause was an independent factor for amplifying aging-

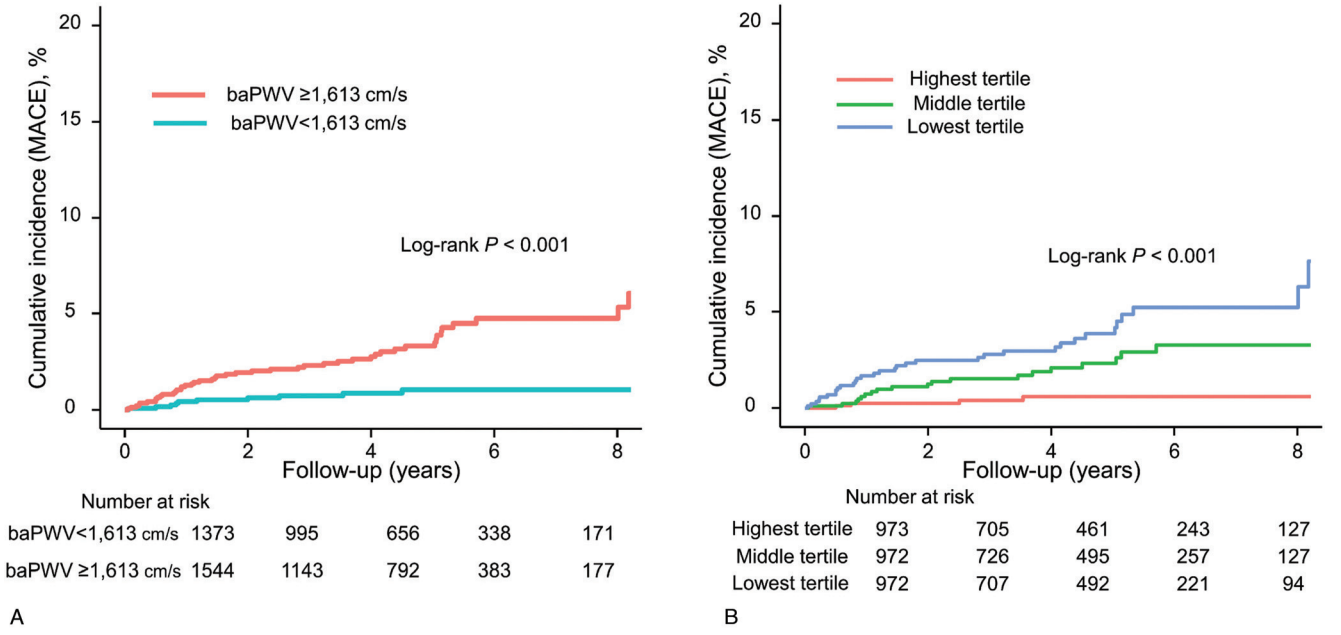

FIG. 2. Kaplan-Meier curves for the cumulative incidence of MACE in the total population. Kaplan-Meier curves for the cumulative incidence of MACE in the **(A)** group with baPWV <1,613 cm/s, which was the cutoff value for MACE calculated using the Youden index, versus those with ≥1,613 cm/s and **(B)** in the baPWV tertile groups: the lowest tertile, 857-1,505 cm/s; middle tertile, 1,506-1,766 cm/s; and highest tertile, 1,767-4,515 cm/s. baPWV, brachial-ankle pulse wave velocity; MACE, major adverse cardiovascular events.

related arterial stiffness, and menopausal women had a steeper slope of the curve with an increase in arterial stiffness.[22] However, there have been few large studies in the literature that have evaluated the predictive ability of baPWV for cardiovascular events in menopausal women. Although not a direct comparison, baPWV more strongly correlated with various cardiovascular disease risk scores in middle-aged and older women than in men of a similar age.[23] This trend was also observed in other ethnic groups limited to menopausal women.[24] A meta-analysis of 18 studies suggested that a 100 cm/s increase in baPWV was associated with a 12% increase in MACE incidence.[25] Our study also showed a similar but numerically higher risk (15%) of MACE per 100 cm/s; this small discrepancy might be owing to the different clinical characteristics of the study populations. We believe that our study will help in screening and managing asymptomatic menopausal women without overt cardiovascular disease using baPWV, which is a noninvasive and easily measurable parameter for estimating arterial stiffness in clinical practice.[26,27]

Suggested mechanisms

The pathophysiology underlying the association of increased arterial stiffness and worse clinical outcome in menopausal women has not been confirmed. However, several possible mechanisms may explain this association. Increased arterial stiffness has more influence on LV diastolic function and geometry in older women than in younger women and men.[28-30] Given that both LV diastolic dysfunction[31] and LV hypertrophy[32] are independent risk factors for worse cardiovascular outcomes, a stronger vascular-ventricular interaction in older women could be suggested as an important underlying mechanism. Coronary microvascular dysfunction is prevalent in older women, and it has been suggested that reduced coronary flow reserve due to increased arterial stiffness is another factor associated with worse cardiovascular prognosis.[33] Based on our results, it can be assumed that the increased arterial stiffness leads to increased LV afterload, oxygen demand, and energy consumption, which sequentially reduce the coronary flow reserve and make it more susceptible to ischemia, resulting in a poor cardiovascular prognosis.[33] Increased arterial stiffness in women, but not in men, is associated with increased coronary plaque volume and calcification, which is another possible mechanism.[34] Although not limited to older women, increased arterial stiffness aggravates subendocardial ischemia by lowering coronary blood flow, and increased pulse pressure negatively affects the integrity of the blood-brain barrier, which can lead to coronary and cerebrovascular events. Shared cardiovascular risk factors, such as high blood pressure, hyper-glycemia, inflammation, oxidative stress, and endothelial dysfunction may be other important mechanisms explaining the association between increased arterial stiffness and worsened cardiovascular outcomes.[26]

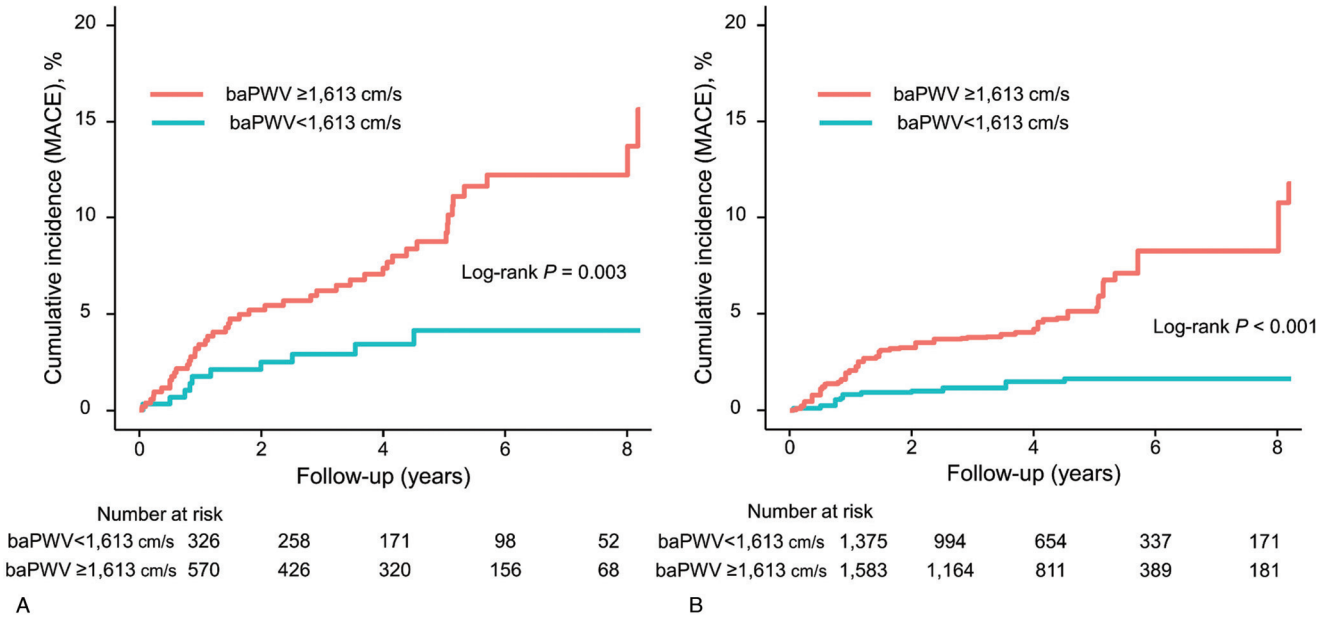

FIG. 3. Kaplan-Meier curves for the cumulative incidence of MACE in the adjusted cohorts. Kaplan-Meier curves for the cumulative incidence of MACE in the **(A)** propensity score-matched cohort with a 15:1 ratio and **(B)** stabilized IPTW cohort. Lowest tertile, 857-1,505 cm/s; middle tertile, 1,506-1,766 cm/s; and highest tertile, 1,767-4,515 cm/s. baPWV, brachial-ankle pulse wave velocity; IPTW, inverse probability-treatment weighting; MACE, major adverse cardiovascular events.

Clinical implications

Menopausal women have an increased cardiovascular risk; therefore, it is important to promptly identify and manage high-risk women, and baPWV can be useful as a screening tool in this setting. Although cfPWV has been considered the gold standard method for the noninvasive measurement of arterial stiffness, it has shortcomings such as technical difficulties and patient inconvenience during the measurement. More specifically, cfPWV measurement requires palpation of the carotid and femoral pulse, which may be difficult in the obese population, and the participant may feel uncomfortable during the acquisition of the pulse wave of the femoral artery.[26,35] Compared with cfPWV, baPWV is easier and simpler to measure because it only requires wrapping of the blood pressure cuffs on both upper arms and ankles. Therefore, baPWV may be more appropriate as a screening tool in a large number of participants.[26] Additionally, a study showed that baPWV had a strong positive correlation with cfPWV ($r = 0.73$) and showed similar performance to that of cfPWV for predicting coronary artery disease and stroke.[36] The Study of Women's Health Across the Nation Heart ancillary study using cfPWV showed an increase in arterial stiffness during perimenopause, but it did not reveal a direct association with prognosis.[21] This study showed that arterial stiffness was an important predictor of cardiovascular events even after strict adjustment of associated variables including age with several statistical methods. Many efforts have been made to improve arterial stiffness in menopausal women,[37,38] and baPWV can be used to assess the effectiveness of treatment strategy to improve arterial stiffness.

Study limitations

Apart from the retrospective design, there are some limitations to this study. First, a selection bias may have occurred because the baPWV measurement was performed by the attending physician. Additionally, patients who refused to undergo baPWV assessment were not included in this analysis. However, we attempted to reduce biases using robust statistical techniques. Second, we intended to identify the natural course of the low- to intermediate-risk women without a history of overt cardiovascular disease; thus, the incidence of MACE was lower. Third, the definition of menopause was based on age; women were considered menopausal if they were over 55 years of age. Although this method seems arbitrary, most Korean women ages >55 years are menopausal.[39] Moreover, there was a lack of information on hormone therapy, age at menopause, and causes of menopause in this study. Fourth, although baPWV has several strengths, cfPWV is the gold-standard noninvasive measure of arterial stiffness and has undergone more validation.[40]

Studies on the role of cfPWV in menopausal women would provide more insightful data, and more validation studies of baPWV as a risk stratification tool, in addition to its noninferiority when compared with cfPWV, for menopausal women will be needed. Finally, since our study only targeted Korean menopausal women without documented

cardiovascular disease, caution is needed when applying the results to other populations.

CONCLUSIONS

Elevated baPWV was associated with MACE in menopausal women without cardiovascular disease, and baPWV may be a useful screening tool for estimating MACE risk in menopausal women. Further studies are needed to validate the clinical utility of baPWV as a risk stratification tool in menopausal women.

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