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ORIGINAL RESEARCH

Combined Evaluation of Arterial Stiffness and Blood Pressure Promotes Risk Stratification of Peripheral Arterial Disease

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ABSTRACT

BACKGROUND Previous studies have reported the separate association of arterial stiffness (AS) and blood pressure with peripheral arterial disease (PAD).

OBJECTIVES The aim of this study was to investigate the risk stratification capacity of AS on incident PAD beyond blood pressure status.

METHODS A total of 8,960 participants from Beijing Health Management Cohort were enrolled at the first health visit between 2008 and 2018 and then followed until the incidence of PAD or 2019. Elevated AS was defined as brachial-ankle pulse-wave velocity (baPWV) >1,400 cm/s, including moderate stiffness (1,400 ≤ baPWV <1,800 cm/s) and severe stiffness (baPWV ≥1,800 cm/s). PAD was defined as ankle-brachial index <0.9. A frailty Cox model was used to calculate the HR, integrated discrimination improvement, and net reclassification improvement.

RESULTS During follow-up, 225 participants (2.5%) developed PAD. After adjusting for confounding factors, the highest risk for PAD was observed in the group with elevated AS and blood pressure (HR: 2.253; 95% CI: 1.472-3.448). Among participants with ideal blood pressure and those with well-controlled hypertension, PAD risk was still significant for severe AS. The results remained consistent in multiple sensitivity analyses. In addition, baPWV significantly improved the predictive capacity for PAD risk beyond systolic and diastolic blood pressures (integrated discrimination improvement 0.020 and 0.190, net reclassification improvement 0.037 and 0.303).

CONCLUSIONS This study suggests the clinical importance of combined evaluation and control of AS and blood pressure for the risk stratification and prevention of PAD. (JACC: Asia 2023;3:287-297) © 2023 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Peripheral arterial disease (PAD) is a common manifestation of systemic atherosclerosis[1] that occurs most frequently in the arteries of the lower extremity. It is estimated that globally, approximately 202 million people have PAD.[2] Ankle-brachial index (ABI) is a primary noninvasive test to diagnose lower extremity PAD. In healthy subjects, ABI is >1.0, whereas ABI <0.9 is commonly used to

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ABBREVIATIONS AND ACRONYMS

ABI = ankle-brachial index

AS = arterial stiffness

baPWV = brachial-ankle pulse-wave velocity

DBP = diastolic blood pressure

HDL = high-density lipoprotein

HTAS = hypertension with elevated arterial stiffness

HTMAS = hypertension with moderately elevated arterial stiffness

HTNAS = hypertension with normal arterial stiffness

HTSAS = hypertension with severely elevated arterial stiffness

NHTNAS = no hypertension with normal arterial stiffness

PAD = peripheral arterial disease

SBP = systolic blood pressure

diagnose PAD, with estimated diagnostic sensitivity and specificity of 79% and 96%, respectively.[3] Prevalent PAD significantly increases the risk for cardiovascular events and overall death.[4,5]

Studies have shown that people with smoking behavior, hypertension, diabetes, and obesity have a higher prevalence of PAD and a significantly increased risk for adverse cardiovascular events.[6-8] A study revealed that reduced high-density lipoprotein (HDL) cholesterol is significantly associated with a higher risk for cardiovascular events and mortality in patients with PAD.[9] These findings indicate that there are shared risk factors between PAD and cardiovascular diseases. Arterial stiffness (AS) measured at the material or structural level is an important surrogate marker of vascular damage and a strong predictor of cardiovascular disease.[10] Degenerative changes in the intima of large elastic arteries contribute to the loss of arterial elastin and increase of AS. Although most sensitive to effects of blood pressure and aging, AS provides significant clinical value independently.[11,12] In a cross-sectional analysis, AS was independently associated with PAD even when adjusting for several atherosclerotic risk factors, including age.[13] A cohort study reported the relationship between blood pressure parameters and PAD events.[14] AS was also reported to affect the prognosis of patients with PAD.[15] However, the combined effect of AS and blood pressure on incident PAD remains unknown. A recent study revealed that AS status could better predict diabetes onset than hypertension.[16] No study has focused on whether AS could be a risk enhancer for PAD independent of blood pressure.

Therefore, in this study we aimed to explore the combined association of AS and hypertension status with PAD onset using a Chinese cohort and to reveal the clinical importance of joint assessment of AS and blood pressure for the risk stratification and primary prevention of PAD.

METHODS

STUDY POPULATION. Subjects for the present study were recruited from the Beijing Health Management Cohort. Participants underwent annual examinations, including face-to-face questionnaire surveys, physical examinations, and laboratory blood tests, as described in a previous publication.[17]

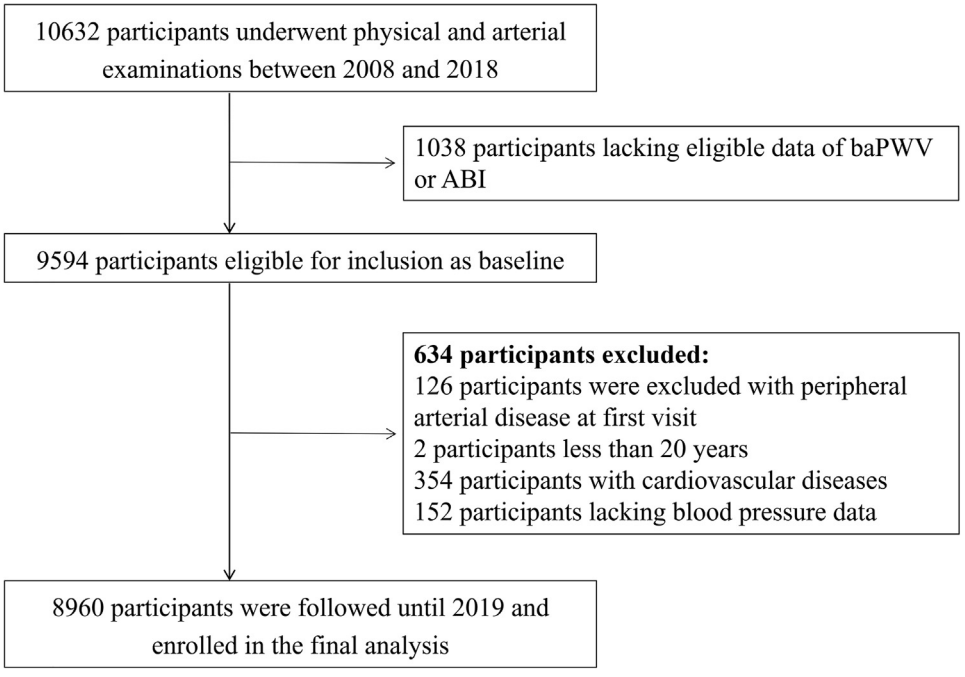
The present study included 10,632 participants who participated in the health examinations and AS measurements for the first time between 2008 and 2018 and were then followed until the onset of PAD or the end of 2019. We excluded participants with missing data for brachial-ankle pulse-wave velocity (baPWV) or ABI at baseline (n = 1,038). In addition, participants with PAD at baseline (n = 126), self-reported cardiovascular disease (n = 354), age <20 years (n = 2), or missing blood pressure information (n = 152) were also excluded (**Figure 1**). This study was in accordance with the principles of the Declaration of Helsinki and approved by the ethics committee of Capital Medical University (2020SY031). All participants provided written informed consent before taking part in this study.

BLOOD PRESSURE MEASUREMENT AND HYPERTENSION DEFINITION. Blood pressure was measured in a sitting position using a mercury sphygmomanometer, and the average of 2 measurements was recorded using systolic blood pressure (SBP) and diastolic blood pressure (DBP). The correlation coefficients between the 2 measurements were 0.988 for SBP and 0.976 for DBP. The difference between the 2 measurements should be <10 mm Hg. Mean arterial blood pressure was calculated as: (SBP + 2 × DBP) / 3. Hypertension was defined as SBP ≥140 mm Hg, DBP ≥90 mm Hg, use of any antihypertensive medication, or self-reported history of diagnosed hypertension.

BaPWV MEASUREMENT AND AS DEFINITION. BaPWV was measured using the Colin BP-203RPE III device (Omron Healthcare). After the patient lay supine for 5 minutes, 4 cuffs were placed on the bilateral brachial and ankle joints, and then the plethysmographic sensor and the oscilloscope pressure sensor were connected, and the maximum value of baPWV on the left and right sides was selected as the systemic AS level, as previously described.[18,19] Normal AS was defined as baPWV <1,400 cm/s and elevated AS as baPWV ≥1,400 cm/s. In addition, we also classified baPWV into 3 categories: normal AS was defined as baPWV <1,400 cm/s, moderately elevated AS as 1,400 ≤ baPWV <1,800 cm/s, and severely elevated AS as baPWV ≥1,800 cm/s according to previous standards.[20,21]

ABI MEASUREMENT AND PAD DEFINITION. ABI is the ratio of blood pressure in the ankle arteries to that in the brachial arteries on the same side of the subject. Using the Colin BP-203RPE III device, the upper limbs and ankles were fully exposed in the supine position, and the subject's bilateral humeral and

FIGURE 1 Flowchart of the Present Study



A total of 8,960 participants from the Beijing Health Management Cohort were included in the present study. ABI = ankle-brachial index; baPWV = brachial-ankle pulse-wave velocity.

ankle arterial SBPs were measured simultaneously; the software then automatically calculated the ABI according to the aforementioned formula. PAD was defined as ABI <0.9 in either lower limb.[22,23] The included participants were free of PAD at baseline and annually followed for PAD onset.

COVARIATES MEASUREMENT AND DEFINITION. Information on age, sex, education, physical activity, smoking status, drinking status, and disease history were collected using a standard questionnaire (Supplemental Appendix). Educational level was categorized as "primary education," "secondary education," and "third education." Physical activity was defined as "≥80 minutes of moderate or vigorous physical activity per week." Smoking status was divided into "current smoking" and "no current smoking" during the past year. Drinking status was divided into "current drinking" and "no current drinking" during the past year. Disease history included self-reported cardiovascular diseases, hypertension, and diabetes. Physical examination parameters included height, weight, heart rate, and waist circumference. Body mass index was calculated as weight (kilograms) divided by the square of height (meters). Biochemical parameters included fasting blood glucose, triglycerides, total cholesterol, HDL cholesterol, and low-density lipoprotein cholesterol. Fasting glucose was defined as glucose concentration before breakfast after overnight fasting (no intake, except water, for at least 8 hours). Diabetes was defined as fasting glucose ≥7.0 mmol/L, self-reported history of diabetes, or self-reported use of antidiabetic medication.

STATISTICAL ANALYSIS. Participants were divided into 4 groups according to joint hypertension and AS status at baseline: 1) no hypertension with normal AS (NHTNAS); 2) no hypertension with elevated AS; 3) hypertension with normal AS (HTNAS); and 4) hypertension with elevated AS (HTAS). Considering the severity of AS, baPWV was classified into 3 categories, and participants were correspondingly divided into 6 groups together with hypertension status (Supplemental Figure 1): 1) NHTNAS; 2) no hypertension with moderately elevated AS; 3) no hypertension with severely elevated AS;

TABLE 1 Baseline Characteristics of the Study Population (N = 8,960)

Age, y	53.41 ± 13.35
Range	22-94
Age group	
≤44 y	2,257 (25.2)
45-59 y	4,293 (47.9)
≥60 y	2,410 (26.9)
Male	2,501 (27.9)
Educational level	
Primary	1,196 (13.3)
Secondary	5,810 (64.8)
Third	1,954 (21.8)
Physical activity	4,228 (47.2)
Current smoking	2,563 (28.6)
Current drinking	5,891 (65.7)
BMI, kg/m^2	25.5 (23.5-27.6)
Obese	1,824 (21.0)
Overweight	6,056 (69.6)
Waist circumstance, cm	88.0 (81.0-94.0)
Heart rate, beats/min	76.0 (69.0-84.0)
MAP, mm Hg	108.7 (98.7-118.3)
LDL cholesterol, mmol/L	3.1 (2.5-3.7)
Triglycerides, mmol/L	1.4 (1.0-2.0)
HDL cholesterol, mmol/L	1.2 (1.1-1.4)
Total cholesterol, mmol/L	4.9 (4.3-5.5)
Fasting glucose, mmol/L	5.4 (5.0-5.9)
Serum uric acid, μmol/L	349.0 (294.0-407.0)
Hypertension	2,617 (29.2)
Use of antihypertensive medication	612 (6.8)
Diabetes	999 (11.1)
Use of hypoglycemic medication	180 (2.0)
ABI, median (range)	1.12 (0.91-1.39)
Ankle blood pressure, mm Hg	139.2 (125.0-155.2)

Values are mean ± SD, n (%), or median (IQR), except as indicated.
ABI = ankle-brachial index; BMI = body mass index; HDL = high-density lipoprotein; LDL = low-density lipoprotein; MAP = mean arterial pressure.

4) HTNAS; 5) hypertension with moderately elevated AS (HTMAS); and 6) hypertension with severely elevated AS (HTSAS). The incidence rate was calculated as the number of incident cases divided by the total follow-up duration (person-years). The cumulative incidence rate was defined as the number of incident cases divided by the total number of participants.

We used the frailty Cox proportional hazards regression models to analyze the risk for PAD across groups. To solve the existence of tied events due to annual follow-up, the Efron method was used in the Cox model. Some participants were from the same working place, which was considered a random term in the frailty Cox model. HRs with 95% CIs were calculated using the NHTNAS group as the reference. Model 1 was unadjusted; model 2 was adjusted for age group, sex, educational level, physical activity, smoking status, and drinking status; and model 3 was further adjusted for body mass index, heart rate, total cholesterol, HDL cholesterol, fasting glucose, and serum uric acid.

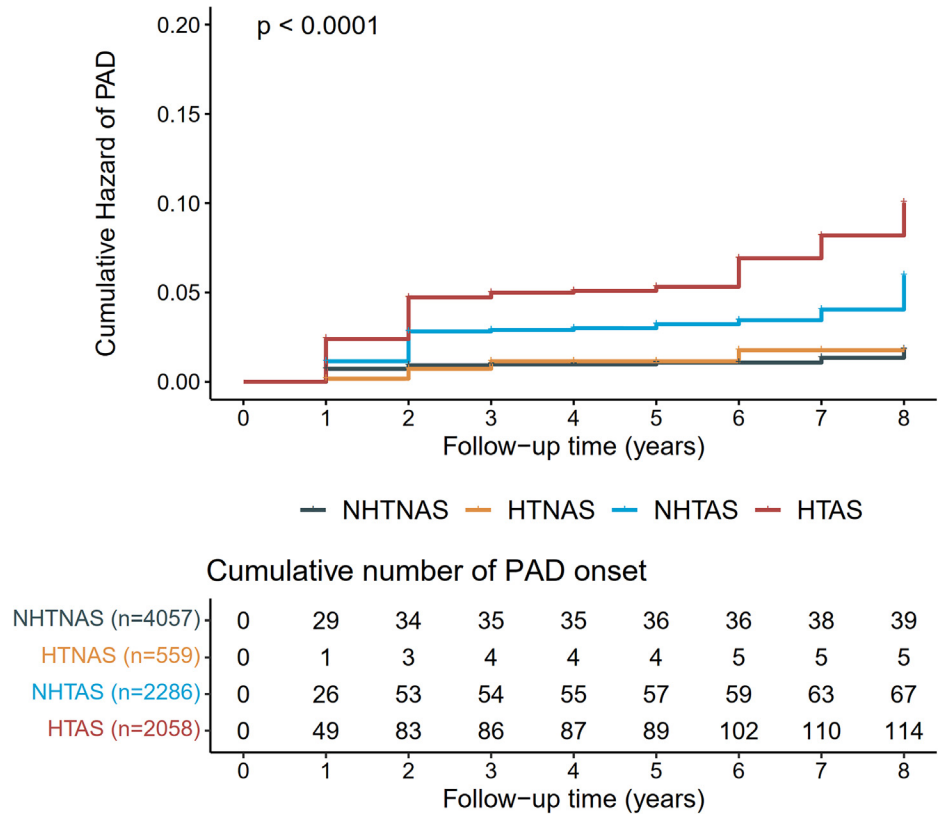
We performed several sensitivity analyses to validate the observed results. First, hypertension was redefined as SBP ≥130 mm Hg, DBP ≥80 mm Hg, use of any antihypertensive medication, or self-reported history of diagnosed hypertension. Second, we excluded participants who developed PAD within the first year of follow-up. Third, we performed analyses on the complete data and multiple imputed datasets (5 iterations) using Markov-chain Monte Carlo. Fourth, we repeated analyses after excluding participants using any antihypertensive medication.

In subgroup analyses, the hypertensive population was divided into a poorly controlled group and a well-controlled group (defined as SBP <140 mm Hg and DBP <80 mm Hg among patients with hypertension).[16] The effect of AS on PAD was then analyzed using the NHTNAS group as a reference. In addition, we analyzed the incremental predictive capacity of baPWV level beyond blood pressure using the C index, integrated discrimination improvement, and continuous net reclassification index, which does not require discrete risk categories and relies on the proportions of individuals with outcome correctly assigned a higher probability and individuals without outcome correctly assigned a lower probability by an updated model compared with the initial model.[24] Integrated discrimination improvement and net reclassification improvement >0 indicates a positive improvement of the original model.[25] All statistical analyses were performed using R version 4.1.0 (R Foundation for Statistical Computing), and a 2-sided *P* value <0.05 was considered to indicate statistical significance.

RESULTS

BASELINE CHARACTERISTICS. Table 1 shows the baseline characteristics of the 8,960 participants. The mean age of the population is 53.41 ± 13.35 years. There were 4,293 participants (47.9%) between 45 and 59 years of age, and 2,501 were men (27.9%). The median ABI at baseline was 1.12, ranging from 0.91 to 1.39. The median value of ankle blood pressure was 139.2 mm Hg (IQR: 125.0-155.2 mm Hg). Characteristics according to joint hypertension and AS status (4 groups) are shown in Supplemental Table 1, and

FIGURE 2 **Kaplan-Meier Curves of PAD in Hypertension and Arterial Stiffness Groups**



Statistical significance was calculated using the log-rank test. The highest risk for peripheral arterial disease (PAD) was observed in the hypertension with elevated arterial stiffness (HTAS) group, emphasizing the clinical importance of combined evaluation of arterial stiffness and blood pressure. HTNAS = hypertension with normal arterial stiffness; NHTAS = no hypertension with elevated arterial stiffness (brachial-ankle pulse-wave velocity ≥1,400 cm/s); NHTNAS = no hypertension with normal arterial stiffness (brachial-ankle pulse-wave velocity <1,400 cm/s).

people in the HTAS group were older, with higher waist circumference, heart rate, mean arterial pressure, and fasting glucose. Supplemental Table 2 shows baseline characteristics according to the 6 groups by hypertension status and AS severity.

COMBINED HYPERTENSION AND AS STATUS WITH PAD ONSET. During follow-up, a total of 225 cases of PAD occurred. Participants in the HTAS group had the highest risk for developing PAD (log-rank $P < 0.0001$) (**Figure 2**). The incidence rates were 3.12, 2.71, 7.64, and 14.05 per 1,000 person-years for the NHTNAS, HTNAS, no hypertension with elevated AS, and HTAS groups, respectively (Supplemental Table 3). In addition, people with severe AS had the highest incidence rate of PAD, regardless of hypertension and blood pressure control status (Supplemental Table 4, Supplemental Figure 2).

After adjusting for confounding factors, the HR for incident PAD was 2.253 (95% CI: 1.472-3.448) for the HTAS group compared with the NHTNAS group, and the remaining 2 groups were not statistically significant. No significant interaction effect of hypertension and AS was observed (P for interaction = 0.700). Among participants without hypertension, the HR was 2.286 (95% CI: 1.288-4.058) for severely elevated AS. In those with hypertension, the HRs were 1.887 (95% CI: 1.173-3.036) and 3.150 (95% CI: 1.942-5.108) for both moderately elevated AS (HTMAS) and severely elevated AS (HTSAS), as shown in **Table 2**. The

TABLE 2 Association of Combined AS and Hypertension Status With Risk for Peripheral Arterial Disease

	Model 1		Model 2		Model 3	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Classification 1						
No hypertension/normal AS (39 of 4,057)	Reference	–	Reference	–	Reference	–
None hypertension/elevated AS (67 of 2,286)	2.672 (1.800-3.968)	<0.001	1.345 (0.874-2.070)	0.178	1.321 (0.853-2.046)	0.213
Hypertension/normal AS (5 of 559)	0.886 (0.349-2.249)	0.800	0.841 (0.331-2.136)	0.715	0.719 (0.256-2.021)	0.531
Hypertension/elevated AS (114 of 2,058)	4.959 (3.444-7.140)	<0.001	2.236 (1.484-3.371)	<0.001	2.253 (1.472-3.448)	<0.001
Classification 2						
No hypertension/normal AS (39 of 4,057)	Reference	–	Reference	–	Reference	–
No hypertension/moderate AS (42 of 1,929)	2.004 (1.295-3.100)	0.002	1.201 (0.753-1.914)	0.442	1.185 (0.738-1.903)	0.482
No hypertension/severe AS (25 of 357)	6.150 (3.719-10.168)	<0.001	2.307 (1.312-4.055)	0.004	2.286 (1.288-4.058)	0.005
Hypertension/normal AS (5 of 559)	0.887 (0.350-2.250)	0.800	0.841 (0.331-2.136)	0.715	0.716 (0.255-2.013)	0.526
Hypertension/moderate AS (45 of 1316)	3.129 (2.037-4.807)	<0.001	1.853 (1.169-2.934)	0.009	1.887 (1.173-3.036)	0.009
Hypertension/severe AS (69 of 742)	8.067 (5.441-11.962)	<0.001	3.118 (1.955-4.972)	<0.001	3.150 (1.942-5.108)	<0.001

The reference group was defined as no hypertension with normal AS (baPWV <1,400 cm/s). Elevated AS was defined as baPWV ≥1,400 cm/s, moderate AS as 1,400 ≤ baPWV <1,800 cm/s, and severe AS as baPWV ≥1,800 cm/s. Classification 1 was stratified by hypertension status and AS status. Classification 2 was stratified by hypertension status and the severity of AS. Model 1 was unadjusted; model 2 was adjusted for age group, sex, educational level, physical activity, smoking status, and alcohol status; and model 3 was further adjusted for body mass index, heart rate, total cholesterol, high-density lipoprotein cholesterol, fasting glucose and serum uric acid.

AS = arterial stiffness; baPWV = brachial-ankle pulse-wave velocity.

results remained consistent when using alternative definitions of hypertension (Supplemental Table 5) and in multiple sensitivity analyses (Supplemental Table 6). In addition, people with hypertension and elevated AS had the severest ABI progression, as shown in Supplemental Table 7.

SUBGROUP ANALYSIS STRATIFIED BY BLOOD PRESSURE CONTROL STATUS. Among participant with well-controlled hypertension, the HRs for the HTAS and HTSAS groups were 2.331 (95% CI: 1.140-4.767) and 5.689 (95% CI: 2.276-14.220), respectively, compared with the NHTNAS group. Of note, among participant with poorly controlled hypertension, the HR for the HTAS, HTMAS, and HTSAS group were significant at 2.584 (95% CI: 1.626-4.108), 2.213 (95% CI: 1.335-3.668), and 3.358 (95% CI: 1.958-5.760), respectively. On the contrary, people with normal AS had similar risk compared with those in the NHTNAS group, regardless of blood pressure control status (**Table 3**). The results remained consistent when using alternative definitions of hypertension (Supplemental Table 8).

INCREMENTAL PREDICTIVE CAPACITY OF AS ASSESSMENT. BaPWV level significantly improved the predictive capacity of incident PAD. The C-index values for separate SBP and DBP for predicting PAD onset were 0.654 (95% CI: 0.607-0.702) and 0.579 (95% CI: 0.530-0.628) and increased to 0.692 (95% CI: 0.646-0.739) and 0.691 (95% CI: 0.643-0.739) with additional AS assessment. The integrated discrimination improvement and net reclassification improvement were 0.020 (95% CI: 0.009-0.038) and 0.037 (95% CI: 0.021-0.061) for SBP and 0.190 (95% CI: 0.096-0.258) and 0.303 (95% CI: 0.214-0.383) for DBP (**Figure 3**). In addition, we found that baPWV and blood pressure levels outperformed baseline ABI for predicting PAD events (Supplemental Figure 3).

DISCUSSION

In this prospective study, we found that participants with elevated AS and hypertension had the highest risk for incident PAD, as summarized in the **Central Illustration**. Among people with ideal blood pressure and the population with well-controlled hypertension, assessment of AS still significantly contributed to the risk stratification of PAD onset. In addition, AS assessment significantly improved the predictive capacity for incident PAD.

ABI is an indicator of arterial stenosis and obstruction in the lower extremities.[26] ABI has good sensitivity and excellent specificity in detecting PAD.[27] ABI is an independent risk factor for the development of cardiovascular diseases and all-cause mortality.[28,29] AS is an indicator of structural and functional changes in vessel walls, causing thickening of artery walls, reduced complacency, and increased rigidity.[30] Previous studies have shown that elevated AS is associated with an increased risk for cardiovascular events such as coronary artery disease, stroke, and end-stage renal disease.[31,32] Husmann

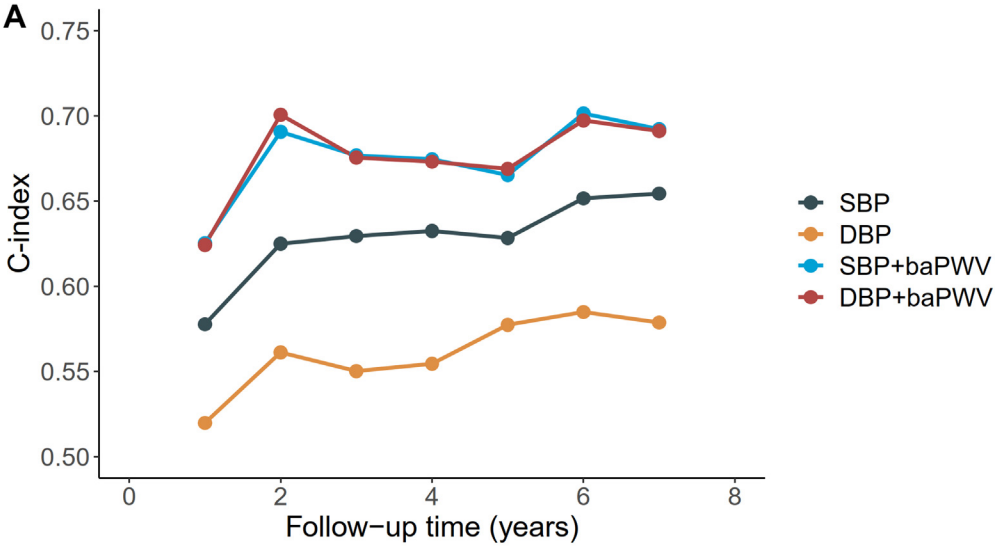
TABLE 3 AS and Peripheral Arterial Disease Stratified by Blood Pressure Control Status in Patients With Hypertension

	Model 1		Model 2		Model 3	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Reference group (39 of 4,057)	Reference	—	Reference	—	Reference	—
Well-controlled hypertension						
Normal AS[a] (0 of 173)		—		—		—
Elevated AS (16 of 328)	4.365 (2.429-7.845)	<0.001	2.549 (1.253-5.186)	0.010	2.331 (1.140-4.767)	0.020
Moderate AS (5 of 237)	1.897 (0.746-4.825)	0.179	1.338 (0.490-3.656)	0.570	1.210 (0.441-3.323)	0.711
Severe AS (11 of 91)	10.746 (5.477-21.085)	<0.001	6.042 (2.457-14.859)	<0.001	5.689 (2.276-14.220)	<0.001
Poorly controlled hypertension						
Normal AS (5 of 386)	1.313 (0.517-3.330)	0.567	1.266 (0.498-3.218)	0.620	1.060 (0.375-3.002)	0.912
Elevated AS (98 of 1,730)	5.143 (3.545-7.463)	<0.001	2.660 (1.718-4.118)	<0.001	2.584 (1.626-4.108)	<0.001
Moderate AS (40 of 1,079)	3.460 (2.225-5.382)	<0.001	2.274 (1.407-3.675)	0.001	2.213 (1.335-3.668)	0.002
Severe AS (58 of 651)	7.787 (5.180-11.708)	<0.001	3.460 (2.071-5.782)	<0.001	3.358 (1.958-5.760)	<0.001

The reference group was defined as no hypertension with normal AS (baPWV <1,400 cm/s). Elevated AS was defined as baPWV ≥1,400 cm/s, moderate AS as 1,400 ≤ baPWV <1,800 cm/s, and severe AS as baPWV ≥1,800 cm/s. Model 1 was unadjusted; model 2 was adjusted for age group, sex, educational level, physical activity, smoking status, and alcohol status; and model 3 was further adjusted for body mass index, heart rate, total cholesterol, high-density lipoprotein cholesterol, fasting glucose, and serum uric acid. [a]No participant developed peripheral arterial disease in this group.

Abbreviations as in Table 2.

FIGURE 3 Predictive Capacity of Blood Pressure and Arterial Stiffness Assessments

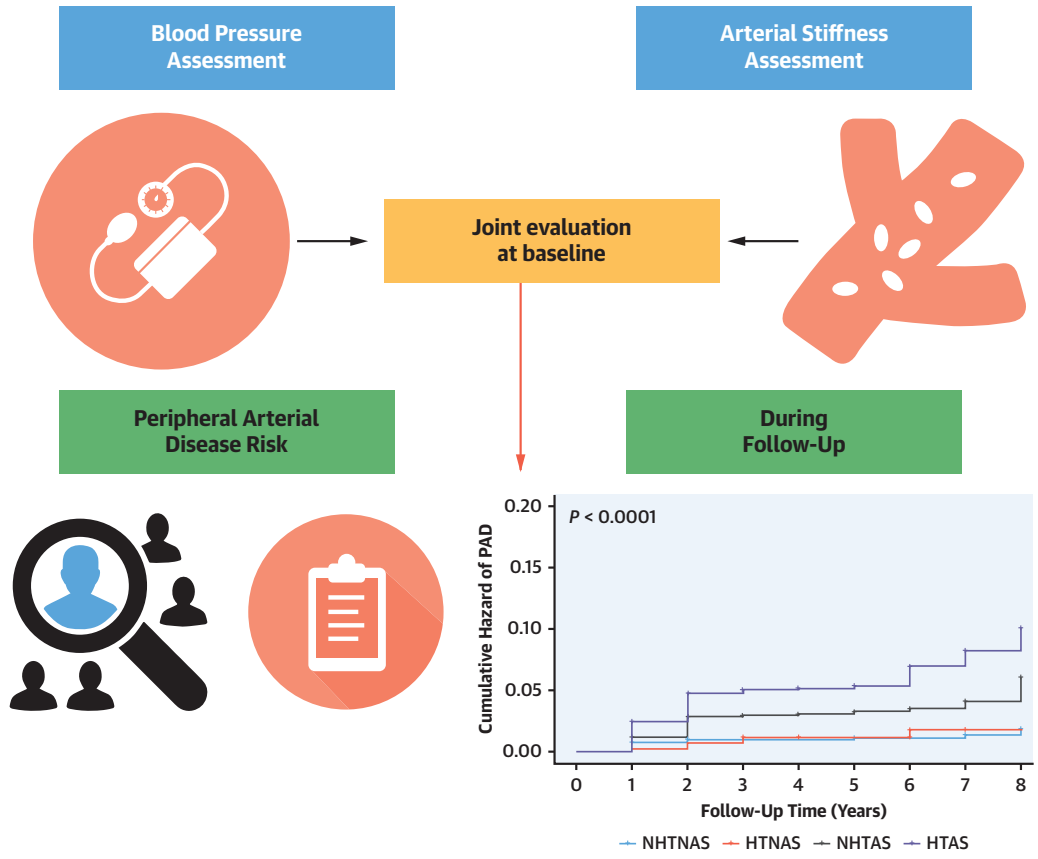


B

	C-index		IDI		NRI	
	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI
SBP	0.654***	0.607 – 0.702				
DBP	0.579***	0.530 – 0.628				
SBP+baPWV [a]	0.692***	0.646 – 0.739	0.020***	0.009 – 0.038	0.190***	0.096 – 0.258
DBP+baPWV [b]	0.691***	0.643 – 0.739	0.037***	0.021 – 0.061	0.303***	0.214 – 0.383

(A) C-index values for predicting peripheral artery disease at different follow-up times. **(B)** Incremental predictive capacity of arterial stiffness beyond blood pressure. Statistical significance was calculated using the DeLong test for C-index comparison and bootstrap for integrated discrimination improvement (IDI) and continuous net reclassification improvement (NRI) comparison. ***$P < 0.001$ ([a]compared with model of systolic blood pressure [SBP], [b]compared with model of diastolic blood pressure [DBP]). baPWV = brachial-ankle pulse-wave velocity.

CENTRAL ILLUSTRATION **Arterial Stiffness, Blood Pressure, and PAD**



Wu Z, et al. JACC: Asia. 2023;3(2):287–297.

A total of 8,960 participants were included in the follow-up and survival analysis. HTAS = hypertension with elevated arterial stiffness; HTNAS = hypertension with normal arterial stiffness; NHTAS = no hypertension with elevated arterial stiffness; NHTNAS = no hypertension with normal arterial stiffness; PAD = peripheral arterial disease.

et al[33] suggested that arterial lumen narrowing and severe ischemia, as late manifestations of PAD, may be regarded as the end stage of increased AS. Two cross-sectional studies showed that patients with PAD had greater AS.[13,34] Moreover, elevated AS may be an indicator of high mortality in patients with PAD with claudication or severe ischemia.[35] On the contrary, a study in middle-aged Japanese men free of PAD reported that decreased AS is related to lower ABI.[19] This could be explained by the fact that AS (eg, baPWV) reflects the stiffening of central and peripheral muscular arteries,[36] which is closely correlated with but different from blood pressure. Central vascular stiffening as a dominant component of baPWV is a strong predictor of cardiovascular diseases and PAD. In our study, elevated AS was associated with a higher risk for developing PAD regardless of hypertension and blood pressure control status, suggesting that early control of AS could contribute to the prevention of PAD. In contrast, studies have reported the association between blood pressure and PAD development. A large British cohort study including 4.2 million adults aged 30 to 90 years showed that a 20 mm Hg increase in SBP was associated with a 63% increased risk for PAD, while a 10 mm Hg increase in DBP was associated with 35% excess risk.[37] Another study involving 12 million people produced consistent results,[38] suggesting that lowering blood pressure could reduce the risk for PAD. In this study, we supplemented evidence about

the combined effect of AS and blood pressure on PAD onset and identified people with extremely high risk for PAD.

There are studies focusing on the relationship between blood pressure and AS. A study based on patients with hypertension showed that poorly controlled blood pressure is a risk factor for severe AS.[39] Lim et al[40] showed that changes in blood pressure are associated with corresponding changes in AS parameters. An increase in blood pressure could cause progressive damage to the elasticity of the arterial wall and result in increased stiffness and lead to increased pressure and pulsatile load on the arterial wall, impairment of endothelial function, and atherosclerosis.[41] These findings suggest that blood pressure could interact with AS and then cause severe impairment of vascular lesions, including lower limb arteries. Our study showed that participants with hypertension and concomitant elevated AS had the highest risk for developing PAD.

Pulse-wave velocity is a noninvasive and simple measurement commonly applied in the risk stratification of cardiovascular diseases. Rapid and accurate evaluation of AS facilitates early intervention and control of vascular lesions.[42] Our findings showed that baPWV could be a risk enhancer of PAD and be potentially used in conjunction with blood pressure. The early control and treatment of AS may prevent the incidence of PAD beyond blood pressure management. Studies have shown that AS is associated with a variety of modifiable factors, such as smoking,[43] alcohol consumption,[44] obesity,[45] insulin resistance,[46] and physical activity.[47] Thus, management of lifestyles and modifiable metabolic risk factors has potential to improve AS.[48,49] Medications can also be used to improve the stiffness of arterial vessels. Randomized controlled clinical trials have shown that antihypertensive drugs (angiotensin-converting enzyme inhibitors, calcium antagonists, beta-blockers, and diuretic agents) not only reduce blood pressure but also improve AS in patients with hypertension.[50] In addition, statins have a protective effect against vascular stiffness, primarily by reducing endothelial dysfunction and improving vascular and myocardial remodeling.[51,52] Pharmacologic and nonpharmacologic intervention for AS is accompanied by gradual repair of vascular function, which can reduce the incidence of cardiovascular disease, including PAD.

STUDY LIMITATIONS. First, we used ABI to define PAD, and lower limb arterial duplex ultrasound and computed tomographic angiography should be considered in further research. Second, AS was defined by measuring baPWV alone, and other AS parameters, such as carotid-femoral pulse-wave velocity and peripheral femoral-to-ankle pulse-wave velocity,[53] were not collected in this study. Thus, we were unable to compare the results of baPWV and other pulse-wave velocity indexes. Third, this was an observational cohort study, and we could not verify the causal relationship of AS status with incident PAD, which warrants further clinical studies to evaluate the effect of combined control of blood pressure and AS.

CONCLUSIONS

Our study revealed that AS is significantly associated with PAD onset beyond blood pressure, suggesting the clinical importance of combined evaluation and control of AS and blood pressure for the risk stratification and early prevention of PAD.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: The present study showed that the highest risk for PAD was observed in patients with elevated AS and blood pressure, emphasizing the clinical importance of combined evaluation of AS and blood pressure for the risk stratification and prevention of PAD.

TRANSLATIONAL OUTLOOK: Future clinical studies are needed to evaluate the effect of joint control of AS and blood pressure on cardiovascular outcomes.

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KEY WORDS arterial stiffness, blood pressure, brachial-ankle pulse-wave velocity, hypertension, peripheral arterial disease

APPENDIX For supplemental tables and figures and the standard questionnaire, please see the online version of this paper.