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ORIGINAL RESEARCH

Association of Segment-Specific Pulse Wave Velocity With Vascular Calcification: The ARIC (Atherosclerosis Risk in Communities) Study

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BACKGROUND: Pulse wave velocity (PWV) is a noninvasive measure of arterial stiffness and predictor of cardiovascular disease. However, the association between PWV and vascular calcification across different vascular beds has not been fully investigated. This study aimed to quantify the association between PWV and multiterritory calcification and to explore whether PWV can identify individuals with vascular calcification beyond traditional risk factors.

METHODS AND RESULTS: Among 1351 older adults (mean age, 79.2 years [SD, 4.1]) from the ARIC (Atherosclerosis Risk in Communities) study, we measured segment-specific PWVs: heart–carotid, heart–femoral, carotid–femoral, heart–ankle, brachial–ankle, and femoral–ankle. Dependent variables were high calcium score (≥75th percentile of Agatston score) across different vascular beds: coronary arteries, aortic valve ring, aortic valve, mitral valve, ascending aorta, and descending aorta. Quartiles of carotid–femoral, heart–femoral, heart–ankle, and brachial–ankle PWV were significantly associated with coronary artery calcium (eg, adjusted odds ratio [OR] for the highest versus lowest quartile of carotid–femoral PWV, 1.84 [95% CI, 1.24–2.74]). Overall, PWVs were most strongly associated with descending aorta calcification, with significant results for carotid–femoral, heart–femoral, heart–ankle, and brachial–ankle PWV (eg, adjusted OR for the highest versus lowest quartile of carotid–femoral PWV, 3.99 [95% CI, 2.61–6.17]). In contrast, femoral–ankle PWV was inversely associated with descending aorta calcification. Some PWVs improved the discrimination of coronary artery calcium and descending aorta calcification beyond traditional risk factors.

CONCLUSIONS: The associations of PWV with vascular calcification varied substantially across segments, with descending aorta calcification most closely linked to PWVs. Our study suggests that some PWVs, especially carotid–femoral PWV, are helpful to identify individuals with coronary artery calcium and descending aorta calcification.

Key Words: aortic calcification ■ arterial stiffness ■ computed tomography ■ coronary artery calcium ■ pulse wave velocity ■ valvular calcification ■ vascular calcification

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CLINICAL PERSPECTIVE

What Is New?

- Pulse wave velocity (PWV) is a noninvasive measure of arterial stiffness and predictor of cardiovascular disease; however, the associations between PWV and vascular calcification across different vascular beds have not been fully investigated.
- In 1351 older adults from a US community-based cohort, several PWV measures, particularly carotid–femoral PWV, were independently associated with coronary artery calcification and calcification of other vascular beds, such as descending aorta calcification.
- Among different vascular beds, descending aorta calcification was most strongly associated with PWV measures.

What Are the Clinical Implications?

- Our study further supports a unique pathophysiological process across different vascular beds and suggests that some PWV measures, especially carotid–femoral PWV, could help identify individuals with coronary artery calcium or descending aorta calcification.

Nonstandard Abbreviations and Acronyms

ARIC	Atherosclerosis Risk in Communities
baPWV	brachial–ankle pulse wave velocity
cfPWV	carotid–femoral pulse wave velocity
ECC	extracoronary calcium
faPWV	femoral–ankle pulse wave velocity
haPWV	heart–ankle pulse wave velocity
hfPWV	heart–femoral pulse wave velocity
PWV	pulse wave velocity

Arterial stiffness is a pathophysiological process contributing to the development of cardiovascular disease (CVD) and end-organ damage.[1] Among various measures of arterial stiffness, pulse wave velocity (PWV) is most widely used in clinical and research settings.[2] Among PWV measures, carotid–femoral PWV (cfPWV) is considered as a gold standard for the evaluation of arterial stiffness[3] and has been shown to predict CVD risk beyond traditional risk factors.[4] Furthermore, PWV measurement is noninvasive, radiation free, and relatively easy for appropriately trained personnel.[2]

Vascular calcification is another arterial manifestation with prognostic value. Coronary artery calcium (CAC) has been one of the strongest predictors of CVD.[5] The American College of Cardiology and American Heart Association guidelines recommend CAC for guiding CVD preventive therapy (eg, statin) in individuals with intermediate risk based on traditional risk classification.[6] Similarly, extracoronary calcification (ECC) (eg, calcification of the aorta or mitral valve) is also independently associated with CVD.[7–11] However, the measurement of CAC and ECC is usually done by computed tomography (CT) and thus requires radiation in an imaging center.

Reflecting PWV and vascular calcification as measures of arterial wall pathophysiology, several studies have reported positive associations between PWV and CAC.[12–16] However, there are several important knowledge gaps. Most of these studies focused on cfPWV or brachial–ankle PWV (baPWV), and associations of other PWV measures (eg, heart–femoral PWV [hfPWV]) with CAC are uncertain. Few studies have explored ECC and its association with PWV measures. Additionally, PWV may be helpful to identify people with vascular calcification who may benefit from a formal assessment of vascular calcification with CT, but to the best of our knowledge, no studies have formally evaluated whether PWV measures improve the discrimination of having vascular calcification beyond traditional risk factors.

Therefore, the present study aimed to (1) evaluate associations between different PWV measures and different vascular calcification including CAC and (2) assess whether PWV measures improve discrimination of CAC and calcification of other vascular beds beyond traditional risk factors using a community-based cohort, the ARIC (Atherosclerosis Risk in Communities) study.

METHODS

Data of the ARIC study are available through the National Heart, Lung, and Blood Institute Biologic Specimen and Data Repository Information Coordinating Center (https://biolincc.nhlbi.nih.gov/studies/aric/) or from the ARIC study coordinating center at University of North Carolina, Chapel Hill, North Carolina.

Study Population

Details of the ARIC study have been published elsewhere.[17] The ARIC study is a prospective cohort study including 15 792 participants aged 45 to 64 years at visit 1 (1987–1989) from 4 US communities (Forsyth County, NC; Jackson, MS; suburban Minneapolis, MN; and Washington County, MD). The follow-up examination to date included visits 2 (1990–1992), 3 (1993–1995), 4 (1996–1998), 5 (2011–2013), 6 (2016–2017), 7 (2018–2019), 8 (2020), and 9 (2021–2022). ARIC was

approved by the institutional review boards of the participating centers and was conducted according to the principles expressed in the Declaration of Helsinki. All participants provided written informed consent for attending this study.

Electrocardiogram-gated CT scans to assess CAC and ECC were first conducted at visit 7, whereas participants were invited for PWV assessment across visits 6 and 7. Of the 3589 participants at visit 7, we excluded participants who did not undergo CT scan due to clinical history of myocardial infarction (adjudicated definite or probable cases) or coronary revascularization (based on *International Classification of Diseases* [*ICD*] *Ninth* or *Tenth Revision*, as appropriate) (n=1271), those who did not undergo PWV measures either at visits 6 or 7 (n=639), those with missing value in any PWV measures of interest as described below (n=232), those with a missing value in covariates (n=90), and Asian or Native American participants (n=6) due to a small sample compared with Blacks and Whites. A total of 1351 participants were included in the present study (Figure S1). Of these, 784 participants and 567 participants completed PWV evaluation at visits 6 and 7, respectively.

Pulse Wave Velocity

PWV was measured using the VP-1000plus (Omron Healthcare).[18] We analyzed the following PWV measures across different vascular segments in the present study: cfPWV; heart–carotid PWV; hfPWV; heart–ankle (haPWV); baPWV, and femoral–ankle (faPWV). We recorded carotid and femoral arterial pressure waveforms using applanation tonometry sensors at the left common carotid artery and left common femoral artery. Bilateral brachial and posttibial arterial pressure waveforms were also recorded for 10 seconds with cuffs wrapped on both arms and ankles. The details of PWV calculation are in Data S1. Based on anatomy, cfPWV, heart–carotid PWV, and hfPWV are considered to reflect central arterial stiffness, whereas faPWV represents peripheral artery stiffness.[19] Moreover, baPWV and haPWV reflect both central and peripheral arterial stiffness.[20] For baPWV, haPWV, and faPWV, we used the higher value of their bilateral data. All PWV measures were taken at least twice and averaged.

Vascular Calcification

Calcium score was measured by noncontrast, cardiac-gated CT and was calculated using the Agatston method (Agatston score).[21] Calcification was defined as lesions with attenuation ≥130 Hounsfield units (HU) and area ≥1 mm^2 in each slice level. Following the standard approach to obtain the Agatston score, for each calcified lesion, the lesion score was obtained by multiplying the lesion area and the density factor (1 if 130–199 HU, 2 if 200–299 HU, 3 if 300–399 HU, and 4 if ≥400 HU). Then, the total Agatston score was calculated as the sum of all lesion scores.[22] The present study analyzed CAC and other vascular segments or valves as ECC: aortic valve ring, aortic valve, mitral valve, ascending aorta, and descending aorta. The images of coronary arteries and extracoronary arteries were acquired from the level of the pulmonary artery bifurcation to the apex of the heart; thus, aortic arch was not included. Aortic valve calcification was defined as calcification on the aortic valve extending to but not including the aortic root. Aortic valve ring calcification indicates calcification of aortic wall above aortic valve but below coronary arteries. Ascending aorta and descending aorta calcification were measured within the image ranges (ie, aortic arch was not included) (Figure S2).

Covariates

We used covariates from visits 6 or 7 unless specified otherwise, aligning with the timing of the PWV measurement. Educational level was assessed at visit 1 and categorized into basic (less than high school), intermediate (graduated from high school), and advanced (at least some college). Body mass index was defined as weight (in kilograms) divided by height (in meters) squared. Antihypertensive medication use was defined by self-report usage in the past 4 weeks and inspection of medication bottles brought to the visit. Blood pressure was measured by certified technicians with participants in the seated position after a 5-minute rest, and the average of the last 2 of 3 readings was recorded. History of diabetes was based on fasting plasma glucose ≥126 mg/dL, nonfasting glucose ≥200 mg/dL, using medication for diabetes, or self-report of diagnosis by physician. Total and high-density lipoprotein cholesterol were measured using the Olympus high-density lipoprotein cholesterol test. Estimated glomerular filtration rate was computed using the Chronic Kidney Disease Epidemiology Collaboration 2021 creatinine and cystatin C equation.[23] Prior coronary heart disease was defined as self-reported clinical history at visit 1 and then adjudicated events by a physician panel between visit 1 and the relevant visit. Similarly, prior stroke was defined as a self-reported clinical history at visit 1 or adjudicated events during the study follow-up. Prior heart failure was defined as prior hospitalization adjudicated by a physician panel (from 2005 to the relevant visit) or hospitalization with heart failure by *ICD*-based diagnosis (*ICD-9* code 428.X or *ICD-10* code I-50) before 2005. Smoking status and drinking alcohol were categorized as current and noncurrent. Because leg artery stenosis and heart rate may affect PWV measures, we further adjusted for ankle–brachial index and heart rate as covariates

Table 1. Baseline Characteristics According to Quartiles of cfPWV

Variables	Overall n=1351	Quartile 1 n=337	Quartile 2 n=338	Quartile 3 n=338	Quartile 4 n=338
PWV range, cm/s	353–6155	353–1011.5	1012–1196	1196.5–1414.5	1415.5–6155
Age, y	79.2 (4.1)	78.7 (4.0)	78.4 (3.9)	79.5 (4.0)	80.3 (4.4)
Men	527 (39.0)	119 (35.3)	129 (38.2)	137 (40.5)	142 (42.0)
Black	250 (18.5)	49 (14.5)	62 (18.3)	58 (17.2)	81 (24.0)
Body mass index, kg/m^2	27.6 (4.5)	27.7 (4.6)	27.9 (4.8)	27.7 (4.1)	27 (4.4)
Education level					
Basic	115 (8.5)	20 (5.9)	23 (6.8)	37 (10.9)	35 (10.4)
Intermediate	565 (41.8)	133 (39.5)	141 (41.7)	133 (39.3)	158 (46.7)
Advanced	671 (49.7)	184 (54.6)	174 (51.5)	168 (49.7)	145 (42.9)
Current drinker	780 (57.7)	215 (63.8)	205 (60.7)	201 (59.5)	159 (47.0)
Current smoker	81 (6.0)	25 (7.4)	18 (5.3)	19 (5.6)	19 (5.6)
Antihypertensive medication	959 (71.0)	229 (68.0)	226 (66.9)	248 (73.4)	256 (75.7)
Systolic blood pressure, mm Hg	134 (18)	128 (17)	131 (16)	137 (18)	141 (18)
Diastolic blood pressure, mm Hg	67 (11)	67 (11)	67 (10)	68 (11)	68 (11)
Heart rate, bpm	63 (10)	61 (9)	62 (10)	64 (10)	66 (11)
Total cholesterol, mmol/L	4.6 (1.0)	4.7 (1.0)	4.6 (1.0)	4.6 (1.1)	4.6 (1.0)
HDL cholesterol, mmol/L	1.4 (0.4)	1.4 (0.4)	1.4 (0.3)	1.3 (0.4)	1.3 (0.4)
eGFR, mL/min per 1.73 m^2	67.3 (17.5)	69.4 (17.9)	69 (16.8)	65.9 (17.3)	64.9 (17.6)
Diabetes	361 (26.7)	58 (17.2)	74 (21.9)	103 (30.5)	126 (37.3)
Prior coronary heart disease	27 (2.0)	3 (0.9)	5 (1.5)	7 (2.1)	12 (3.6)
Prior heart failure	36 (2.7)	7 (2.1)	9 (2.7)	10 (3.0)	10 (3.0)
Prior stroke	38 (2.8)	8 (2.4)	7 (2.1)	8 (2.4)	15 (4.4)
Ankle–brachial index	1.10 (0.12)	1.09 (0.11)	1.12 (0.12)	1.10 (0.12)	1.08 (0.14)
Field center					
Forsyth County, NC	270 (20.0)	45 (13.4)	61 (18.0)	80 (23.7)	84 (24.9)
Jackson, MS	236 (17.5)	45 (13.4)	58 (17.2)	57 (16.9)	76 (22.5)
Minneapolis, MN	500 (37.0)	162 (48.1)	131 (38.8)	119 (35.2)	88 (26.0)
Washington County, MD	345 (25.5)	85 (25.2)	88 (26.0)	82 (24.3)	90 (26.6)

Continuous variables with mean (SD) and categorical variables with number (percent) are presented. cfPWV indicates carotid–femoral pulse wave velocity; eGFR, estimated glomerular filtration rate; and HDL, high-density lipoprotein.

as sensitivity analyses. The lower ankle–brachial index measure of its bilateral data was used for the analysis, which was simultaneously measured using the same device when PWV was assessed. Heart rate was also simultaneously measured by electrocardiography during PWV measurement.

Statistical Analysis

Because we were interested in PWV measures as predictors of CAC, we treated PWV measures as independent (exposure) variables and CAC/ECC as dependent (outcome) variables. We showed participant characteristics across quartiles of PWV measures. Continuous variables were summarized as mean value with SD, and categorical variables were described as count with proportion.

To assess the association of each PWV measure with CAC and ECC, we ran logistic regression models, with the lowest quartile of each PWV measure as a reference and estimated odds ratio (OR) and 95% CI. We defined CAC and ECC ≥75th percentile Agatston score as high calcification in this analysis. We constructed 3 models to assess the impact of potential confounders: Model 1 unadjusted; Model 2 adjusting for age, sex, race, and field center; and Model 3 further accounting for education level, body mass index, antihypertensive medication use, systolic blood pressure, diabetes, total and high-density lipoprotein cholesterol levels, estimated glomerular filtration rate, prior coronary heart disease, prior heart failure, prior stroke, current drinker, and current smoker. We also modeled each PWV as a continuous variable with restricted cubic spline terms and covariates in Model 3 noted above. We set the median in the lowest quartile as a reference and put 4 knots at 5th, 35th, 65th, and 95th percentiles of each PWV measure.

As sensitivity analysis, we first conducted subgroup analysis using Model 3 by age (<78 versus ≥78 years [median]), sex (men versus women), race (Black

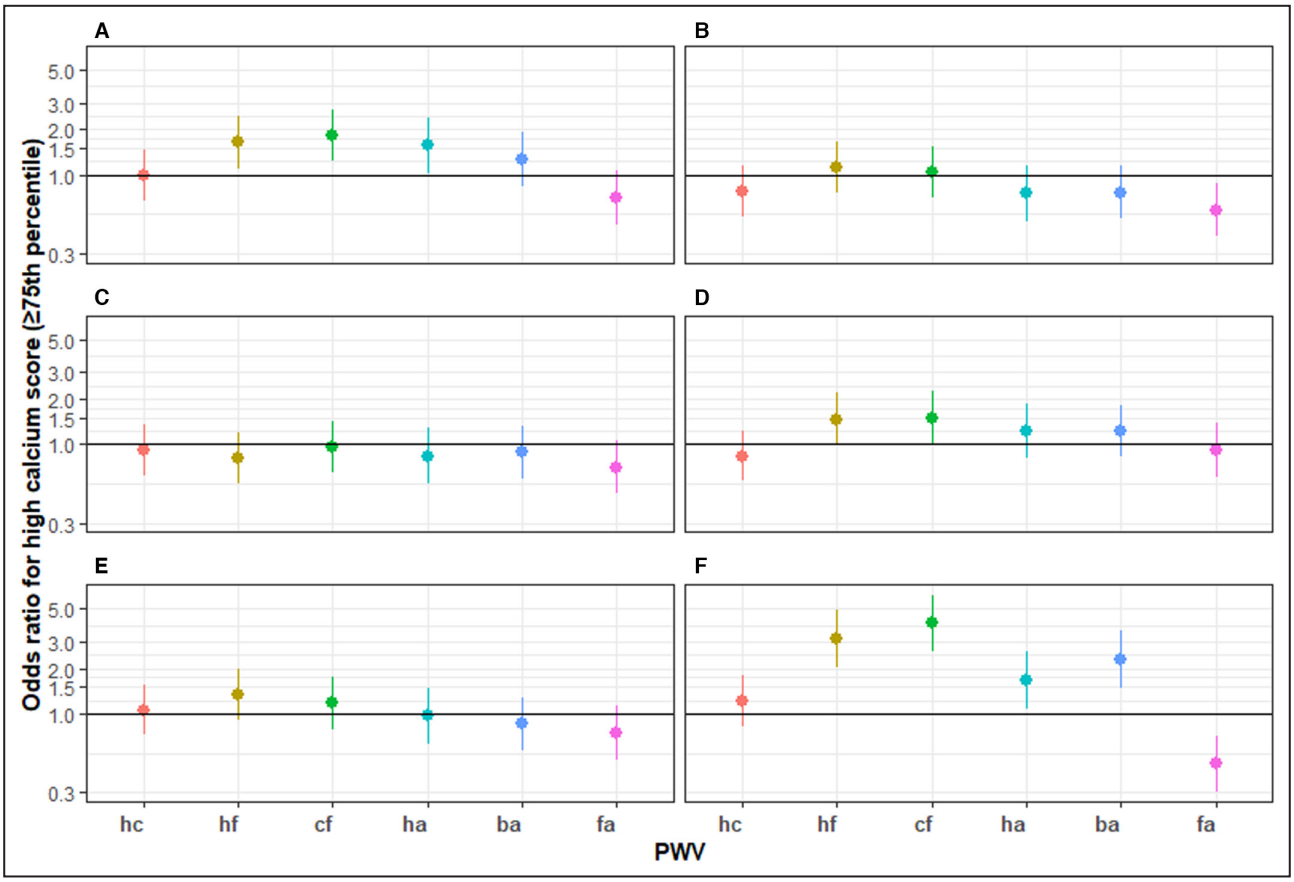

Figure 1. Adjusted odds ratio for different vascular calcification according to different PWV measures (the highest quartile vs the lowest quartile).

Each panel shows odds ratio for calcification of different arteries (**A**, coronary artery; **B**, aortic valve ring; **C**, aortic valve; **D**, mitral valve; **E**, ascending aorta; and **F**, descending aorta) according to different PWV measures (hc-, hf-, cf-, ha-, ba-, and faPWV: the highest vs lowest quartile as reference). Odds ratio was estimated using multivariable logistic regression models adjusted for age, sex, race, field center, education level, body mass index, antihypertensive medication use, systolic blood pressure, diabetes, total and high-density lipoprotein cholesterol levels, estimated glomerular filtration rate, prior coronary heart disease, prior heart failure, prior stroke, current drinker, and current smoker (n=1351). ba indicates brachial–ankle; cf, carotid–femoral; fa, femoral–ankle; ha, heart–ankle; hc, heart–carotid; hf, heart–femoral; and PWV, pulse wave velocity.

versus White), and systolic blood pressure (<133 versus ≥133 mm Hg [median]). To obtain reliable estimates in each subgroup, we modeled relevant PWV measures as a linear term (per 1 SD) and tested interaction using likelihood ratio tests. As noted above, we further adjusted for ankle–brachial index or heart rate as Models 4 and 5. We also excluded subpopulations with conditions influencing PWV measurement such as severe obesity (body mass index ≥40 kg/m^2) (n=11) or peripheral revascularization history before PWV measures (n=7), possible outliers (PWV ≥3 SD above the mean; n=61), or aortic stenosis (n=27), defined as aortic valve peak velocity >2.0 m/s by echocardiography or incomplete assessment (n=25).

Finally, we evaluated whether adding PWV measures improves discrimination of high CAC and ECC beyond traditional CVD risk factors. The base model included predictors in Model 3 described above. We assessed C statistics as a measure of discrimination using logistic regression models. The C statistic between base model and adding PWV measures was compared using the DeLong test. We also assessed Akaike information criterion and Bayesian information criterion for comparing the model performance after adding each PWV measure. Statistical significance was set at $P<0.05$ (2-sided). All analyses were performed using R version 4.2.0 (The R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Baseline Characteristics

Among 1351 participants, the mean age was 79.2 years (SD, 4.1 years), 39% were men, 19% were Black, 27% had diabetes, and 71% were taking antihypertensive medication. Participants with higher cfPWV tended to have higher risk profiles (Table 1). Generally, similar

Table 2. Odds Ratios for High Coronary Artery Calcium Score (≥75th Percentile) According to Quartiles of PWV Measures

PWV measures	Median calcium score (IQI)	Prevalence/participants	Odds ratio (95% CI)		
			Model 1	Model 2	Model 3
hcPWV, cm/s					
Quartile 1, 367–1006	208 (41–629)	81/336	1 (reference)	1 (reference)	1 (reference)
Quartile 2, 1007.5–1204	172 (30–636)	76/338	0.91 (0.64–1.31)	0.88 (0.61–1.28)	0.87 (0.59–1.28)
Quartile 3, 1205–1460	194 (38–666)	85/339	1.05 (0.74–1.50)	0.90 (0.62–1.31)	0.94 (0.64–1.39)
Quartile 4, 1461.5–4994	273 (30–766)	96/338	1.25 (0.89–1.76)	0.90 (0.62–1.30)	0.99 (0.67–1.45)
hfPWV, cm/s					
Quartile 1, 489–1086	154 (24–531)	68/337	1 (reference)	1 (reference)	1 (reference)
Quartile 2, 1087.5–1230	163 (26–545)	66/337	0.96 (0.66–1.41)	0.98 (0.66–1.46)	0.98 (0.66–1.48)
Quartile 3, 1231–1403	240 (46–767)	94/339	1.52 (1.06–2.17)*	1.36 (0.94–2.00)	1.39 (0.94–2.06)
Quartile 4, 1403.5–2573.5	356 (66–870)	110/338	1.91 (1.35–2.72)*	1.68 (1.15–2.45)*	1.65 (1.11–2.48)*
cfPWV, cm/s					
Quartile 1, 353–1011.5	144 (23–514)	70/337	1 (reference)	1 (reference)	1 (reference)
Quartile 2, 1012–1196	143 (16–501)	62/338	0.86 (0.58–1.25)	0.82 (0.55–1.22)	0.79 (0.52–1.19)
Quartile 3, 1196.5–1414.5	210 (42–660)	84/338	1.26 (0.88–1.81)	1.13 (0.77–1.66)	1.05 (0.71–1.56)
Quartile 4, 1415.5–6155	403 (80–920)	122/338	2.15 (1.53–3.05)*	1.99 (1.38–2.89)*	1.84 (1.24–2.74)*
haPWV, cm/s					
Quartile 1, 608.5–1068.5	148 (24–535)	69/336	1 (reference)	1 (reference)	1 (reference)
Quartile 2, 1069–1160.5	210 (37–650)	82/339	1.23 (0.86–1.78)	1.18 (0.81–1.73)	1.21 (0.82–1.79)
Quartile 3, 1160.7–1259	206 (33–648)	81/337	1.22 (0.85–1.76)	1.07 (0.73–1.57)	1.17 (0.78–1.75)
Quartile 4, 1259.5–2064.5	303 (47–777)	106/339	1.76 (1.24–2.51)*	1.36 (0.93–1.98)	1.55 (1.02–2.38)*
baPWV, cm/s					
Quartile 1, 612–1628.5	142 (23–592)	74/335	1 (reference)	1 (reference)	1 (reference)
Quartile 2, 1629.5–1825.5	213 (39–614)	76/340	1.02 (0.71–1.46)	0.98 (0.67–1.44)	0.98 (0.66–1.45)
Quartile 3, 1826–2063.3	192 (30–697)	92/337	1.32 (0.93–1.89)	1.23 (0.85–1.79)	1.28 (0.86–1.91)
Quartile 4, 2064–3908	316 (46–770)	96/339	1.39 (0.98–1.98)	1.30 (0.89–1.89)	1.27 (0.84–1.93)
faPWV, cm/s					
Quartile 1, 595–987.5	286 (41–780)	100/337	1 (reference)	1 (reference)	1 (reference)
Quartile 2, 988.5–1092	185 (41–577)	72/338	0.64 (0.45–0.91)*	0.57 (0.40–0.83)*	0.62 (0.42–0.90)*
Quartile 3, 1092.5–1224.5	165 (27–626)	76/338	0.69 (0.49–0.97)*	0.59 (0.41–0.85)*	0.65 (0.44–0.95)*
Quartile 4, 1225–5748.5	228 (32–697)	90/338	0.86 (0.61–1.20)	0.65 (0.45–0.93)*	0.70 (0.47–1.05)

Model 1 was an unadjusted model. Model 2 was adjusted for covariates: age, sex, race, and field center. Model 3 was further adjusted for covariates other than Model 2: education level, body mass index, antihypertensive medication use, systolic blood pressure, diabetes, total and high-density lipoprotein cholesterol level, estimated glomerular filtration rate, prior coronary heart disease, prior heart failure, prior stroke, current drinker, and current smoker. baPWV indicates brachial–ankle PWV; cfPWV, carotid–femoral PWV; faPWV, femoral–ankle PWV; haPWV, heart–ankle PWV; hcPWV, heart–carotid PWV; hfPWV, heart–femoral PWV; IQI, interquartile interval; and PWV, pulse wave velocity.

*Indicate statistical significance.

patterns were observed across quartiles of other PWV measures, although heart–carotid PWV and faPWV demonstrated somewhat unique characteristics (Tables S1 through S5).

PWV and Vascular Calcification

We observed heterogeneous associations across different PWV measures and the calcification of different vascular beds (Figure 1). For CAC, cfPWV demonstrated the strongest association, followed by hfPWV and haPWV (Figure 1A). Among different vascular beds, descending aorta calcification demonstrated the strongest association with multiple PWV measures (ie, hfPWV, cfPWV, haPWV, and baPWV) (Figure 1F), followed by CAC (Figure 1A) and mitral valve (Figure 1D). Aortic valve ring, aortic valve, and ascending aorta calcifications were not associated with any PWV measures in this analysis. From the perspective of PWV measures, overall, cfPWV (green dots in Figure 1) showed the most robust associations, with significant OR for CAC, mitral valve calcification, and descending aorta calcification. faPWV (pink dots in Figure 1) was inversely associated with vascular calcification, although statistical significance was seen only for descending aorta calcification. Generally, similar patterns

Table 3. Odds Ratios for Descending Aorta Calcification (≥75th Percentile) According to Quartiles of PWV Measures

PWV measures	Median calcium score (IQI)	Prevalence/participants	Odds ratio (95% CI)		
			Model 1	Model 2	Model 3
hcPWV, cm/s					
Quartile 1, 367–1006	415 (51–1431)	85/336	1 (reference)	1 (reference)	1 (reference)
Quartile 2, 1007.5–1204	386 (38–1488)	92/338	1.12 (0.80–1.58)	1.16 (0.81–1.67)	1.21 (0.83–1.78)
Quartile 3, 1205–1460	250 (28–1032)	73/338	0.81 (0.57–1.16)	0.90 (0.62–1.32)	0.98 (0.66–1.45)
Quartile 4, 1461.5–4994	346 (39–1446)	87/337	1.02 (0.72–1.45)	1.05 (0.72–1.53)	1.21 (0.81–1.81)
hfPWV, cm/s					
Quartile 1, 489–1086	138 (11–682)	47/337	1 (reference)	1 (reference)	1 (reference)
Quartile 2, 1087.5–1230	287 (22–905)	63/336	1.45 (0.96–2.19)	1.50 (0.98–2.30)	1.48 (0.95–2.32)
Quartile 3, 1231–1403	475 (55–1777)	109/339	2.92 (2.00–4.32)*	3.04 (2.05–4.56)*	3.02 (1.98–4.65)*
Quartile 4, 1403.5–2573.5	649 (113–1965)	118/337	3.31 (2.28–4.88)*	3.42 (2.30–5.16)*	3.13 (2.02–4.89)*
cfPWV, cm/s					
Quartile 1, 353–1011.5	107 (6–682)	48/337	1 (reference)	1 (reference)	1 (reference)
Quartile 2, 1012–1196	232 (21–796)	47/337	1.00 (0.65–1.54)	1.04 (0.67–1.62)	1.01 (0.64–1.60)
Quartile 3, 1196.5–1414.5	438 (69–1584)	96/337	2.39 (1.63–3.54)*	2.32 (1.56–3.48)*	2.02 (1.33–3.10)*
Quartile 4, 1415.5–6155	927 (221–2633)	146/338	4.58 (3.17–6.70)*	4.56 (3.09–6.82)*	3.99 (2.61–6.17)*
haPWV, cm/s					
Quartile 1, 608.5–1068.5	176 (13–860)	63/336	1 (reference)	1 (reference)	1 (reference)
Quartile 2, 1069–1160.5	314 (35–1336)	83/338	1.43 (0.99–2.07)	1.41 (0.96–2.08)	1.43 (0.95–2.15)
Quartile 3, 1160.7–1259	460 (42–1410)	85/338	1.46 (1.01–2.12)*	1.41 (0.96–2.07)	1.37 (0.90–2.08)
Quartile 4, 1259.5–2064.5	522 (80–1705)	106/337	1.97 (1.38–2.83)*	1.68 (1.15–2.47)*	1.66 (1.07–2.58)*
baPWV, cm/s					
Quartile 1, 612–1628.5	121 (6–741)	49/335	1 (reference)	1 (reference)	1 (reference)
Quartile 2, 1629.5–1825.5	294 (32–1131)	75/338	1.68 (1.13–2.51)*	1.59 (1.06–2.39)*	1.54 (1.01–2.37)*
Quartile 3, 1826–2063.3	409 (36–1474)	88/339	2.06 (1.40–3.06)*	1.78 (1.20–2.68)*	1.63 (1.06–2.52)*
Quartile 4, 2064–3908	725 (153–1906)	125/337	3.41 (2.36–4.99)*	2.59 (1.76–3.85)*	2.29 (1.49–3.55)*
faPWV, cm/s					
Quartile 1, 595–987.5	425 (45–1712)	100/337	1 (reference)	1 (reference)	1 (reference)
Quartile 2, 988.5–1092	380 (42–1320)	79/332	0.77 (0.55–1.08)	0.73 (0.51–1.04)	0.78 (0.53–1.14)
Quartile 3, 1092.5–1224.5	277 (32–1265)	81/343	0.71 (0.50–1.00)	0.57 (0.40–0.83)*	0.56 (0.38–0.84)*
Quartile 4, 1225–5748.5	324 (28–1226)	77/337	0.70 (0.49–0.99)*	0.51 (0.35–0.73)*	0.47 (0.30–0.71)*

Model 1 was an unadjusted model. Model 2 was adjusted for covariates: age, sex, race, and field center. Model 3 was further adjusted for covariates other than Model 2: education level, body mass index, antihypertensive medication use, systolic blood pressure, diabetes, total and high-density lipoprotein cholesterol level, estimated glomerular filtration rate, prior coronary heart disease, prior heart failure, prior stroke, current drinker, and current smoker. baPWV indicates brachial–ankle PWV; cfPWV, carotid–femoral PWV; faPWV, femoral–ankle PWV; haPWV, heart–ankle PWV; hcPWV, heart–carotid PWV; hfPWV, heart–femoral PWV; IQI, interquartile interval; and PWV, pulse wave velocity.

*Indicate statistical significance.

were seen across our 3 models of covariates for CAC (Table 2) and descending aorta (Table 3). For calcification of the other vascular beds, their associations with PWV measures were mostly attenuated after accounting for potential confounders (Tables S6 through S9).

When we modeled PWV measures continuously using restricted cubic splines for CAC and descending aorta calcification specifically, we observed continuous associations of cfPWV above ≈1000 cm/s with CAC and descending aorta calcification (Figure 2), with a sharper gradient for the latter. We observed largely similar patterns for hfPWV, haPWV, and baPWV (Figure S3). faPWV demonstrated an inverse association with both CAC and descending aorta calcification.

We confirmed similar results overall in sensitivity analyses. When we stratified by age, sex, race, and systolic blood pressure, the associations of cfPWV with CAC and descending aorta calcification were largely consistent (Figure 3), although we found statistically significant interactions by systolic blood pressure for descending aorta calcification (greater OR when systolic blood pressure <133 mm Hg versus ≥133 mm Hg, *P*-for-interaction=0.003). The results were consistent or even stronger than the primary analysis when we included ankle–brachial index and heart rate in our

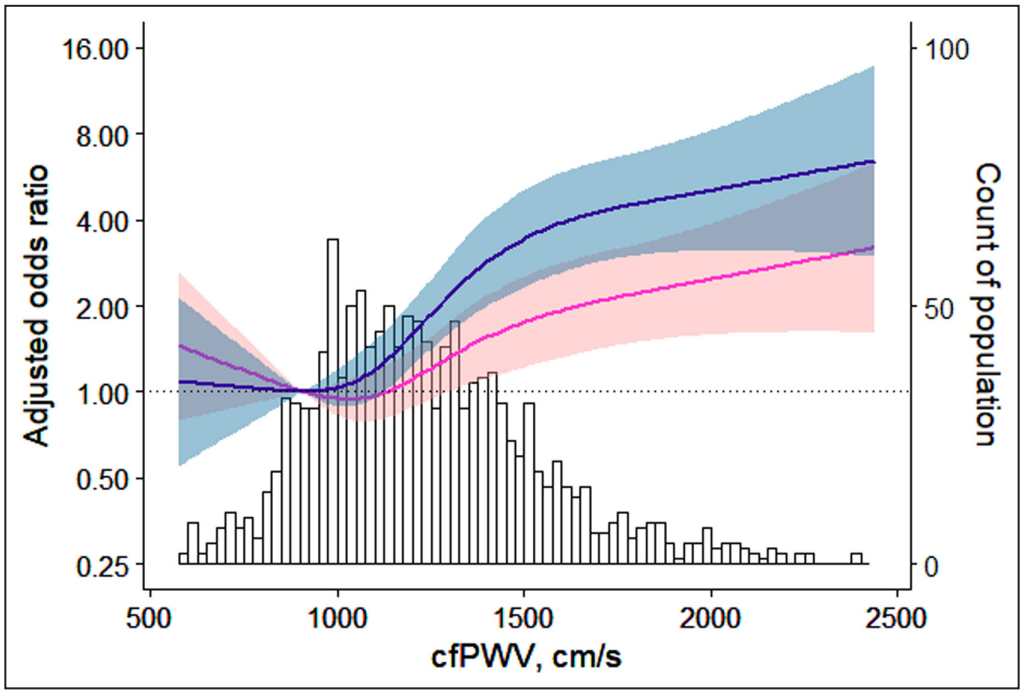

Figure 2. Adjusted odds ratio for high CAC and descending aorta calcification according to cfPWV modeled as restricted cubic spline.

The pink line and light pink shading indicate the odds ratio for high CAC (≥75th percentile) and 95% CI. The blue line and blue shading indicate the odds ratio for descending aorta calcification (≥75th percentile) and 95% CI. Histograms indicate the count of the study population. The reference value is the median of cfPWV in the lowest quartile (910 cm/s). The odds ratio was estimated using multivariable logistic regression models adjusted for age, sex, race, field center, education level, body mass index, antihypertensive medication use, systolic blood pressure, diabetes, total and high-density lipoprotein cholesterol levels, estimated glomerular filtration rate, prior coronary heart disease, prior heart failure, prior stroke, current drinker, and current smoker (n=1351). The figure displays estimates for the range of 0.5 to 99.5 percentiles of cfPWV. CAC indicates coronary artery calcium; and cfPWV, carotid–femoral pulse wave velocity.

models (Figures S4 and S5). Exclusion of participants with severe obesity or prior revascularization, those with PWV measures of possible outliers, and those with aortic stenosis did not alter the results (Figures S6 through S8).

Discrimination of High CAC and Descending Aorta Calcification

The C statistic of high CAC according to the base model (ie, covariates in Model 3) was 0.727 (95% CI, 0.697–0.758) (Table 4). When we added individual PWV measures separately, the largest improvement of discrimination was seen by cfPWV, although it was borderline significant (ΔC statistic 0.008 [95% CI, −0.001 to 0.018]; *P*=0.07) (Table 4). When we added cfPWV with other PWV measures, we observed statistically significant improvement in the C statistic when we simultaneously added hfPWV, cfPWV, haPWV, and baPWV. Among these models, however, the lowest Akaike information criterion and Bayesian information criterion were seen when we added cfPWV to the base model.

For descending aorta calcification, the addition of cfPWV alone to the base model improved the C statistic by 0.021 (95% CI, 0.005–0.037) (Table S10). Further improvement was seen when we combined cfPWV with other PWVs. The lowest Akaike information criterion and Bayesian information criterion for descending aorta calcification were seen when we simultaneously added hfPWV, cfPWV, haPWV, and baPWV to the base model.

DISCUSSION

In this community-based study of older populations with data on PWV measures and calcification of different vascular beds, we observed heterogeneous associations between specific segments of arterial stiffness and vascular beds of calcification. Among PWV measures, cfPWV was most strongly associated with vascular and valvular calcification, followed by hfPWV and haPWV. Interestingly, faPWV was inversely associated with vascular calcification. Among

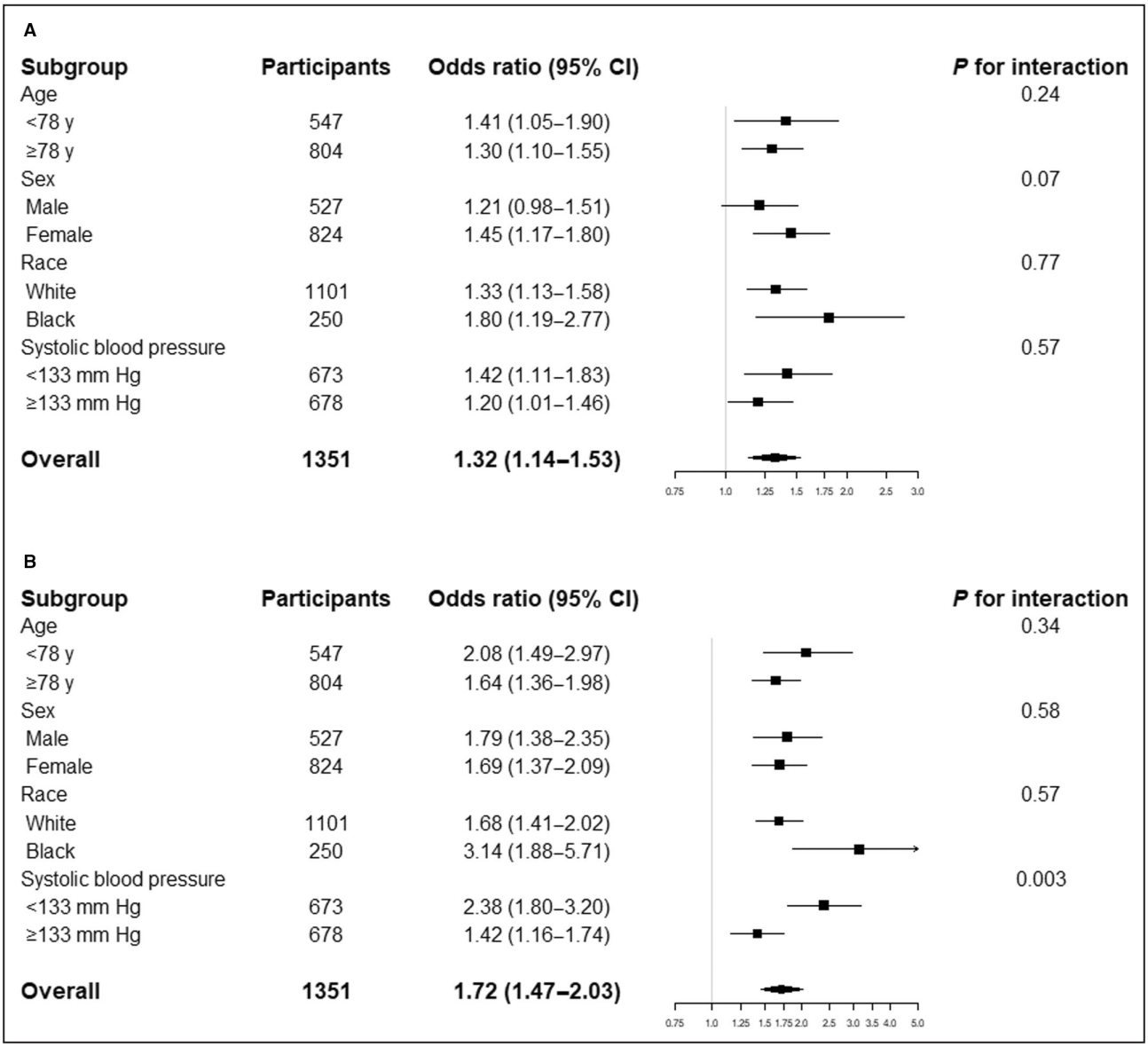

Figure 3. Association of cfPWV with CAC and descending aorta calcification among subgroups.
Adjusted odds ratio for high CAC score (**A**) and descending aorta calcification (**B**) of cfPWV 1-SD increment was stratified according to baseline characteristics (age, sex, race, and systolic blood pressure). Cutoff value of age and systolic blood pressure was each median value. Odds ratio was estimated using multivariable logistic regression model adjusted for age, sex, race, field center, education level, body mass index, antihypertensive medication use, systolic blood pressure, diabetes, total and high-density lipoprotein cholesterol levels, estimated glomerular filtration rate, prior coronary heart disease, prior heart failure, prior stroke, current drinker, and current smoker except for each stratification variable. Interaction was tested using likelihood ratio tests. CAC indicates coronary artery calcium; and cfPWV, carotid-femoral pulse wave velocity.

vascular beds tested, descending aorta calcification was most strongly associated with PWV measures. Some of these PWV measures modestly improved the discrimination of high levels of CAC and descending aorta calcification beyond traditional atherosclerotic risk factors.

There are several studies reporting associations between cfPWV and baPWV with CAC,[12–16] but our study is unique in several aspects. First, we reported that not only cfPWV, but also other PWV measures including hfPWV and haPWV, were associated with high CAC scores. Second, leveraging data on ECC, we found that most PWV measures were associated with different vascular beds tested, with the strongest association with descending aorta calcification. Finally, we rigorously evaluated whether the addition of cfPWV and other PWV measures can improve the discrimination of CAC or descending aortic calcification.

Our observation of cfPWV being most consistently associated with vascular calcification (including CAC)

Table 4. C Statistics for High Coronary Artery Calcium Score (≥75th Percentile) by Adding PWV Measures to Prediction Model Based on Traditional Risk Factors

Predictor	C statistic (95% CI)		AIC	BIC
	0.727 (0.697–0.758)			
Base model	C statistic (95% CI)	C statistic difference from base model (95% CI)	1392.036	1506.626
+hcPWV	0.728 (0.697 to 0.758)	0.001 (−0.001 to 0.002)	1393.559	1513.356
+hfPWV	0.731 (0.701 to 0.761)	0.004 (−0.003 to 0.011)	1386.404	1506.202
+cfPWV	0.736 (0.706 to 0.766)	0.008 (−0.001 to 0.018)	1379.592*	1499.39*
+haPWV	0.728 (0.697 to 0.758)	0 (−0.003 to 0.003)	1392.726	1512.524
+baPWV	0.728 (0.698 to 0.759)	0.001 (−0.003 to 0.004)	1391.985	1511.782
+faPWV	0.728 (0.697 to 0.758)	0 (−0.001 to 0.002)	1393.654	1513.452
+hfPWV, cfPWV, haPWV, and baPWV	0.738 (0.709 to 0.768)*	0.011 (0.001 to 0.021)*	1383.089	1518.512
+hfPWV, cfPWV, haPWV, baPWV, and faPWV	0.738 (0.708 to 0.768)*	0.011 (0.001 to 0.021)*	1384.884	1525.516
+All PWVs	0.738 (0.708 to 0.768)*	0.011 (0.001 to 0.021)*	1386.884	1532.725

Base model includes predictors: age, sex, race, field center, education level, body mass index, antihypertensive medication use, systolic blood pressure, diabetes, total and high-density lipoprotein cholesterol level, estimated glomerular filtration rate, prior coronary heart disease, prior heart failure, prior stroke, current drinker, and current smoker. AIC indicates Akaike information criterion; baPWV, brachial–ankle PWV; BIC, Bayesian information criterion; cfPWV, carotid–femoral PWV; faPWV, femoral–ankle PWV; haPWV, heart–ankle PWV; hcPWV, heart–carotid PWV; hfPWV, heart–femoral PWV; and PWV, pulse wave velocity.

*Statistical significance by the DeLong test or the lowest AIC and BIC.

is in line with previous studies showing the prognostic value of cfPWV superior to other PWV measures[24,25] and further supports cfPWV as a gold standard measure of arterial stiffness.[2] Simultaneously, it is important to recognize that some other PWVs showed similar associations with CAC or descending aorta calcification (eg, hfPWV, haPWV, and baPWV). Importantly, some of these (eg, baPWV) are easier to measure than cfPWV, which requires tonometry sensors at the carotid and femoral and may be uncomfortable for some subjects. Thus, depending on research questions or clinical purpose, some of hfPWV, haPWV, and baPWV may be acceptable as an alternate of cfPWV.[26] Also, the repeatability of each PWV measure should be considered.[27] Furthermore, our discrimination analysis demonstrated additional values of different PWV measures, and thus whenever possible, the comprehensive assessment of multiple PWV measures may be beneficial. Although the amount is small, CAC measure requires radiation in an imaging center. Thus, if some individuals are reluctant to undergo CAC assessment, our study suggests that the PWV assessment in a clinic provides additional information on the probability of having higher CAC beyond traditional risk factors.

All PWV measures tested in the present study, except faPWV, reflect stiffness of the aorta to some degree. Thus, it is not surprising that among vascular beds tested, descending aorta calcification was most strongly associated with PWV measures in our study. Calcification of elastic fibers in the arterial wall contributes to arterial stiffness.[28,29] Although several studies report the association of thoracic aorta calcification (ascending aorta, aortic arch, and descending aorta) with adverse events,[7,10,11,30–32] compared with CAC score, clinical usefulness of descending aorta calcification is less established. If prognostic value of descending aorta calcification beyond CAC is established in the future, cfPWV alone (or in combination with a few other PWV measures) would be helpful to identify individuals who are likely to have descending aorta calcification.

In our study, faPWV showed an inverse association with descending aorta calcification. We have shown a similar inverse association of faPWV with cardiac biomarkers, kidney function, and cardiovascular risk factors previously.[19,33,34] We are not sure why higher faPWV is consistently associated with better clinical phenotypes. These counterintuitive observations may reflect different histology or structure between aorta and peripheral arteries. For example, shorter wave transit time behind higher PWV may have different pathophysiological meanings between an elastic artery like the aorta versus a muscular artery in the periphery. Nonetheless, because faPWV has been much less studied compared with other PWV measures, dedicated investigation on faPWV (eg, whether higher faPWV represent greater leg artery calcification) may help us better understand pathophysiology across different vascular beds.

Our study has several limitations. First, our study included older Black and White participants, and thus, the extrapolation of our results to other age ranges or different racial and ethnic groups needs careful discussion. Second, in some participants, the elapsed time between PWV measurement and

CT scan was >1 year. Third, because the images of vascular beds tested were acquired from the level of the pulmonary artery bifurcation to the apex of the heart, a few other potentially relevant vascular beds (eg, aortic arch, abdominal aorta, leg artery) were not assessed in the present study. Fourth, we are not sure whether our findings are transportable to PWV measures evaluated by different measurement system. Finally, although we did our best to adjust for potential confounders, we cannot deny the possibility of residual confounding due to unmeasured or unknown confounders.

In conclusion, several PWV measures, particularly cfPWV, were independently associated with CAC and calcification of other vascular beds, such as descending aorta calcification, in older adults. Among different vascular beds, descending aorta calcification was most strongly associated with PWV measures tested. Our study further supports unique pathophysiological process across different vascular beds and suggests that some PWV measures, especially cfPWV, could help identify individuals with CAC or descending aorta calcification.

ARTICLE INFORMATION

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Disclosures

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Supplemental Material

Data S1
Tables S1–S10
Figures S1–S8
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