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# Aortic Pulse Wave Velocity Is Associated With Measures of Subclinical Target Organ Damage

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**OBJECTIVES** Our goal was to evaluate the associations of central arterial stiffness, measured by aortic pulse wave velocity (aPWV), with subclinical target organ damage in the coronary, peripheral arterial, cerebral, and renal arterial beds.

**BACKGROUND** Arterial stiffness is associated with adverse cardiovascular outcomes. We hypothesized that aPWV is associated with subclinical measures of atherosclerosis—coronary artery calcification (CAC) and ankle-brachial index (ABI) and arteriolosclerosis—brain white matter hyperintensity (WMH) and urine albumin-creatinine ratio (UACR).

**METHODS** Participants (n = 812; mean age 58 years; 58% women, 71% hypertensive) belonged to hypertensive sibships and had no history of myocardial infarction or stroke. aPWV was measured by applanation tonometry, CAC by electron beam computed tomography, ABI using a standard protocol, WMH volume by brain magnetic resonance, and UACR by standard methods. WMH was log-transformed, whereas CAC and UACR were log-transformed after adding 1 to reduce skewness. The associations of aPWV with CAC, ABI, WMH, and UACR were assessed by multivariable linear regression using generalized estimating equations to account for the presence of sibships. Covariates included in the models were age, sex, body mass index, history of smoking, hypertension and diabetes, total and high-density lipoprotein cholesterol, estimated glomerular filtration rate, use of aspirin and statins, and pulse pressure.

**RESULTS** The mean ± SD aPWV was 9.8 ± 2.8 m/s. After adjustment for age, sex, conventional cardiovascular risk factors, and pulse pressure, higher aPWV (1 m/s increase) was significantly associated with higher log (CAC + 1) ($\beta \pm$ SE = 0.14 ± 0.04; p = 0.0003), lower ABI ($\beta \pm$ SE = −0.005 ± 0.002; p = 0.02), and greater log (WMH) ($\beta \pm$ SE = 0.03 ± 0.009; p = 0.002), but not with log (UACR + 1) (p = 0.66).

**CONCLUSIONS** Higher aPWV was independently associated with greater burden of subclinical disease in coronary, lower extremity, and cerebral arterial beds, highlighting target organ damage as a potential mechanism underlying the association of arterial stiffness with adverse cardiovascular outcomes. (J Am Coll Cardiol Img 2011;4:754–61) © 2011 by the American College of Cardiology Foundation

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Arterial stiffness increases with aging (1), and this increase is accelerated in the presence of cardiovascular risk factors such as hypertension and diabetes (2). Greater arterial stiffness has been shown to be an independent predictor of adverse cardiovascular outcomes including mortality (3), myocardial infarction (3), stroke (3), atrial fibrillation (4), cognitive decline (5), and renal dysfunction (6). Aortic pulse wave velocity (aPWV), a robust measure of arterial stiffness, helps to discriminate between patients at low and high risk of adverse cardiovascular outcomes when added to conventional risk factors (7).

Patients with hypertension are predisposed to arteriosclerosis (both atherosclerosis of large vessels and arteriolosclerosis of small vessels) and are at increased risk of target organ damage and related clinical sequelae. Given its adverse effects on the cardiovascular system, arterial stiffness may independently contribute to target organ damage in hypertensives. Moreover, knowledge of potentially reversible (or treatable) arterial function parameters that contribute to the progression of arteriosclerosis in hypertensive individuals could aid in the development of therapies aimed at preventing the clinical sequelae of target organ damage.

Although previous studies assessed the associations of arterial stiffness with arteriosclerosis (8–12), most were limited to 1 or 2 measures of target organ damage. Furthermore, a significant proportion of the available studies included only untreated hypertensive subjects. Whether central arterial stiffness contributes to subclinical small- and large-vessel target organ damage in different arterial beds in treated hypertensive patients remains unclear. To better understand the role of arterial stiffness in target organ damage, we investigated whether aPWV is associated with noninvasive measures of subclinical large- and small-vessel arteriosclerosis, including coronary artery calcification (CAC), the ankle-brachial index (ABI), volume of white matter hyperintensity (WMH) in the brain, and urine albumin/creatinine ratio (UACR) in a cohort enriched for hypertension.

## METHODS

**Study sample.** The study sample consisted of non-Hispanic white participants from the GENOA (Genetic Epidemiology Network of Arteriopathy) study (13), and participants belonged to sibships in which at least 2 family members received a diagnosis of hypertension before the age of 60 years. Between January 2003 and December 2008, 874 participants completed the study protocol. Fifty-one participants with history of myocardial infarction or stroke and 11 participants with technically inadequate aPWV studies were excluded, leaving 812 participants for the final analysis. For analyses related to the ABI, we excluded 17 participants with an ABI >1.4 because the ABI in this range is unreliable due to poorly compressible arteries. The project was approved by the Mayo Institutional Review Board, and participants gave informed consent. Details regarding the assessment of baseline characteristics in the GENOA study cohort were previously described (14). Information regarding age, sex, hypertension, diabetes, body mass index, history of smoking, total and high-density lipoprotein cholesterol, estimated glomerular filtration rate, blood pressure, and medication use was available for all 812 participants.

**Noninvasive assessment of subclinical vascular disease.** The presence and extent of large-vessel damage were assessed in the coronary and peripheral arterial beds. Coronary atherosclerotic burden was assessed by CAC in 791 participants, which was measured with an Imatron C-150 EBCT scanner (Imatron Inc., South San Francisco, California), as previously described (15). A score for each focus of CAC was determined, and the total calcium score was obtained by summing individual foci scores from each of the 4 anatomic sites (left main, left anterior descending, circumflex, and right coronary arteries) (16). The presence of coronary atherosclerosis was defined as a CAC score >0.

**ABBREVIATIONS AND ACRONYMS**

**ABI** = ankle-brachial index

**aPWV** = aortic pulse wave velocity

**CAC** = coronary artery calcification

**DBP** = diastolic blood pressure

**SBP** = systolic blood pressure

**UACR** = urine albumin/creatinine ratio

**WMH** = white matter hyperintensity

Peripheral arterial atherosclerosis was assessed by measuring the participants' ABI, as previously described (17). The lower of the average ABIs from the 2 legs was used in the analyses. The presence of lower extremity atherosclerosis was defined as an ABI ≤0.9. A total of 790 participants had their ABI measured. After excluding the 17 participants with an ABI >1.4, 773 participants were included in ABI analyses.

The presence and extent of small-vessel arteriolosclerosis were assessed in the cerebral and renal arterial beds. Brain WMH volume ($cm^3$), a surrogate for subclinical cerebral arteriolosclerosis, was obtained via cardiac magnetic resonance in 638 participants. All cardiac magnetic resonance scans were performed on Signa 1.5-T CMR scanners (GE Medical Systems, Waukesha, Wisconsin), as previously described (18), and images were centrally

processed at the Mayo Clinic, Rochester, Minnesota. The presence of cerebral arteriolosclerosis was defined as WMH >5.7 $cm^3$, the median value in the study participants.

The UACR (milligrams of albumin/grams of creatinine) was used as a measure of renal glomerular dysfunction. The first voided urine was collected on the morning of the study visit and stored at −80°C until analyzed. Urine albumin and urine creatinine concentrations were measured by standard methods on a Hitachi 911 Clinical Chemistry Analyzer (Roche Diagnostics, Indianapolis, Indiana). The UACR was available for 760 participants. The presence of renal arteriolosclerosis was defined as a UACR >10 mg/g.

**Aortic pulse wave velocity.** Participants were asked to fast for 12 h and withhold vasoactive medications, alcohol, and caffeine for 24 h before the study visit. Arterial tonometry of the right carotid and femoral arteries was performed using the Sphygmocor apparatus (AtCor Medical, Sydney, Australia) with simultaneous electrocardiographic recording, as previously described (19). The mean ± SD intervals (in months) between assessment of each measurement of subclinical arteriosclerosis and subsequent measurement of aPWV were 28.11 ± 19.53 for CAC, 14.4 ± 11.86 for ABI, 13.5 ± 22.3 for WMH, and 28.9 ± 19.4 for UACR.

**Statistical methods.** To reduce skewness, WMH was log-transformed, and UACR and CAC were log-transformed after adding 1. The skewness statistics after transformation were 0.33 for log (CAC + 1), 1.04 for (WMH), and 0.99 for log (UACR + 1), which were within the acceptable range of −2 to +2. Spearman correlation coefficients between aPWV and log (CAC + 1), ABI, log (WMH), and log (UACR + 1) were calculated.

Multivariable linear regression analyses were performed to assess the associations of aPWV with measures of large-vessel atherosclerosis, represented by log (CAC + 1) and ABI, and small-vessel arteriolosclerosis, represented by log (WMH), and log (UACR+1). Analyses were performed for the entire cohort (n = 812) and in the subsets of hypertensives (n = 577) and "ever" smokers (n = 375). We adjusted sequentially for: 1) age and sex (model 1); 2) age, sex, hypertension, diabetes, body mass index, history of smoking, total and high-density lipoprotein cholesterol, estimated glomerular filtration rate, and use of aspirin and statins (model 2); and 3) model 2 variables and pulse pressure (by including systolic blood pressure [SBP] and diastolic blood pressure [DBP] in the model) (model 3). The WMH models were also adjusted for total brain volume. Because SBP is used in the calculation of the ABI, to avoid colinearity, we did not adjust ABI models for SBP and DBP (pulse pressure). In the multivariable models, backward elimination was performed with a criterion of $p < 0.05$ to stay in the model. We investigated potential interactions between aPWV and age, sex, hypertension, and smoking, respectively, in predicting higher CAC, WMH, UACR, and lower ABI.

We also performed multivariable logistic regression analyses, adjusting for relevant covariates as stated previously, to assess whether aPWV was associated with the presence of early target organ damage as reflected by a CAC score >0, an ABI ≤0.9, WMH >5.7 $cm^3$, and a UACR >10 mg/g. Adjusted odds ratios and 95% confidence intervals were calculated to assess the odds of having subclinical target organ damage for each 1 m/s increase in aPWV.

Because our cohort consisted of sibships, we used generalized estimating equations to account for the possible impact of familial correlations. A p value <0.05 was considered to be statistically significant. Statistical analyses were performed with SAS version 8.2 (SAS Institute, Cary, North Carolina).

## RESULTS

The baseline characteristics of the study participants are outlined in Table 1. The mean age of participants was 58.4 years, and 57.6% were women. Hypertension was present in 71.1% of participants, and 11.2% had diabetes. The mean ± SD aPWV was 9.8 ± 2.8 m/s.

Scatterplots depicting the correlations of aPWV with log (CAC + 1) (n = 791), ABI (n = 773), log (WMH) (n = 638), and log (UACR + 1) (n = 760) are shown in Figure 1. aPWV correlated positively with log (CAC + 1), and log (WMH), log (UACR + 1) and inversely with ABI.

After adjustment for age and sex, a higher aPWV was associated with a greater amount of CAC, greater WMH volume, and a lower ABI. These associations remained statistically significant after further adjustment for confounders (Table 2). A statistically significant association of aPWV with CAC and WMH was present even after additional adjustment for pulse pressure (Table 2). After adjustment for age and sex, no statistically significant association was observed between aPWV and UACR (Table 2). We found significant interactions between greater aPWV and older age in the pre-

**Table 1. Baseline Characteristics of the Study Participants (n = 812 Unless Otherwise Specified)**

| | Mean/No. | ± SD, % | Median (IQR) |
|---|---|---|---|
| Age, yrs | 58.4 | 9.7 | 59.09 (51.10–65.33) |
| Men | 344 | 42.4 | |
| Body mass index, kg/m$^2$ | 30.3 | 5.8 | 29.60 (26.33–33.35) |
| Waist circumference, cm | 99.6 | 156.0 | 99.3 (89.2–109.2) |
| Hypertension | 577 | 71.1% | |
| Systolic blood pressure, mm Hg | 130.9 | 16.3 | 129.00 (119.00–142.00) |
| Diastolic blood pressure, mm Hg | 74.6 | 8.7 | 75.0 (69.0–80.0) |
| Total cholesterol, mg/dl | 199.9 | 33.1 | 196.8 (127.0–394.5) |
| HDL cholesterol, mg/dl | 52.7 | 15.5% | 50.0 (24.9–115.3) |
| Statin use | 217 | 26.72% | |
| Antihypertensive use | 546 | 67.2% | |
| ACE inhibitor/ARB use | 262 | 32.2% | |
| Calcium channel blocker use | 104 | 12.8% | |
| Beta-blocker use | 256 | 31.5% | |
| Diuretic use | 291 | 35.8% | |
| Aspirin use | 319 | 39.3% | |
| Diabetes | 91 | 11.21% | |
| Smoking (past or current) | 375 | 46.18% | |
| Estimated glomerular filtration rate, ml/min/1.73 m$^2$ | 65.0 | 13.3 | 65.2 (26.4–113.9) |
| Coronary artery calcification score (n = 791) | 195.9 | 484.1 | 12.04 (0–144.60) |
| Ankle-brachial index (n = 773) | 1.15 | 0.12 | 1.15 (1.01–1.23) |
| White matter hyperintensity volume, cm$^3$ (n = 638) | 7.5 | 6.2 | 5.7 (4.3–7.9) |
| Urine albumin-creatinine ratio, mg/g (n = 760) | 8.2 | 48.5 | 3.1 (0–1177.8) |
| Aortic pulse wave velocity, m/s | 9.8 | 2.8 | 9.1 (7.90–10.98) |
| Coronary artery calcification present | 492 | 60.6% | |
| Ankle-brachial index <0.9 | 27 | 3.3% | |
| White matter hyperintensity volume >5.7 cm$^3$ | 318 | 50% | |
| Urine albumin/creatinine ratio >10, mg/g | 82 | 10.1% | |

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; HDL = high-density lipoprotein; IQR = interquartile range; LDL = low-density lipoprotein.

diction of the ABI (p = 0.002) and WMH (p = 0.0007) and between greater aPWV and smoking in the prediction of WMH (p = 0.0009), suggesting that aPWV was more strongly associated with these phenotypes in older individuals and those with a history of smoking. We did not find a significant interaction between greater aPWV and the presence of hypertension in the prediction of the 4 phenotypes. Thus, results were similar in the subgroup of hypertensives: in fully adjusted multivariable models, greater aPWV was independently associated with greater log (CAC + 1) (n = 556, $\beta \pm$ SE = 0.15 ± 0.04, p = 0.0002); lower ABI (n = 773, $\beta \pm$ SE = −0.005 ± 0.002, p = 0.03 ); and higher log (WMH) (n = 457, $\beta \pm$ SE = 0.03 ± 0.01, p = 0.005) but not with greater log (UACR + 1) (n = 543, p = 0.35 after age and sex adjustment). Among smokers, aPWV was significantly associated with log (CAC + 1) only (n = 366, $\beta \pm$ SE = 0.14 ± 0.04, p = 0.001) after adjustment for the same variables as in model 3.

In the logistic regression analyses for predicting the presence of target organ damage, a 1 m/s increase in aPWV was independently associated with a higher odds of having a CAC score >0 and an ABI ≤0.9 , but not WMH volume >5.7 cm$^3$ or UACR >10 mg/g (Table 3).

## DISCUSSION

In a cohort consisting primarily of treated hypertensive participants, aPWV, a well-established measure of central arterial stiffness, was independently associated with the extent of subclinical target organ damage in coronary, cerebral, and peripheral arterial beds, but not renal arterial beds. Further, aPWV also independently predicted the presence of coronary and lower extremity atherosclerosis. To the best of our knowledge, this is the first study reporting the simultaneous associations of aPWV with subclinical coronary, lower extremity, cerebral, and renal arterial disease in a cohort

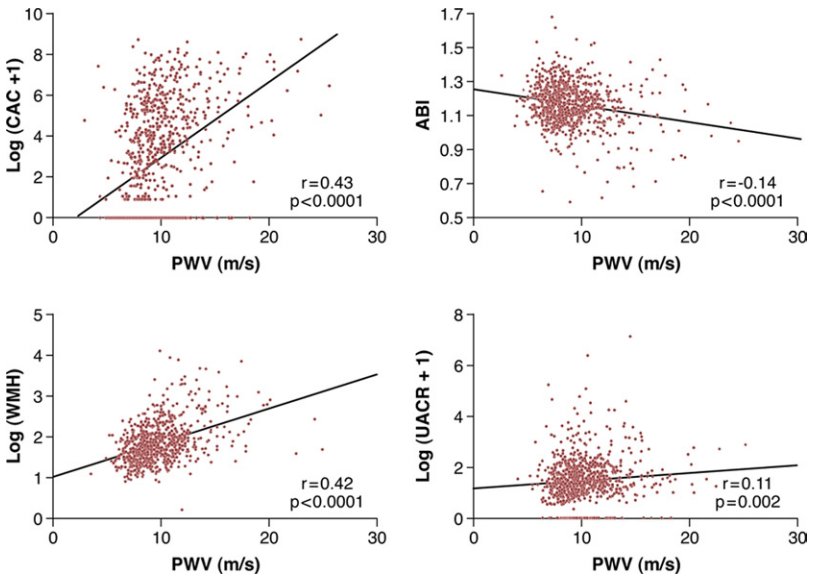


**Figure 1. Correlations of aPWV With Coronary, Lower Extremity, Cerebral, and Renal Arteriosclerosis**

Scatterplot depicting the unadjusted correlations of aortic pulse wave velocity (aPWV) with log (CAC + 1), ABI, log (WMH), and log (UACR + 1). ABI = ankle-brachial index; CAC = coronary artery calcification; UACR = urine albumin/creatinine ratio; WMH = brain white matter hyperintensity volume.

consisting predominantly of treated hypertensive adults.

Arterial stiffness increases with increased SBP. However, in our study, the associations of aPWV with CAC and WMH remained despite adjustment for SBP. Further adjustment for DBP did not alter the association, suggesting that the effects of arterial stiffness on the coronary and cerebral vasculatures are independent of pulse pressure, a readily obtained but crude marker of arterial stiffness. Thus, aPWV appears to be a better predictor of the extent of subclinical target organ damage, providing information beyond what would be obtained by measuring brachial pulse pressure alone.

Measures of arterial stiffness predict adverse cardiovascular events in different populations. In the Framingham Heart Study offspring cohort (20), aPWV was independently associated with cardiovascular events. Similarly, Terai et al. (21) demonstrated that aPWV predicted myocardial infarction or stroke in a cohort of 676 patients with essential hypertension during a mean follow-up of 57 months. A recent meta-analysis including individuals at high and low risk of cardiovascular events (3) corroborated such findings, showing that aPWV was not only significantly associated with an increased risk of adverse cardiovascular events and mortality, but also with all-cause mortality. Associations of aPWV with various markers of subclinical target organ damage have been previously reported (11); however, the study included a small number of patients (n = 178), and, differently from our study, consisted solely of untreated hypertensive individuals. Our work suggests a possible mechanism linking aPWV to

**Table 2. Multivariable Linear Regression Analysis Assessing the Association of aPWV (1 m/s Increase) With CAC, ABI, Brain WMH Volume, and UACR**

| | Log (CAC + 1) (n = 791) | | ABI (n = 773) | | Log (WMH)* (n = 638) | | Log (UACR + 1) (n = 760) | |
|---|---|---|---|---|---|---|---|---|
| | β ± SE | p Value | β ± SE | p Value | β ± SE | p Value | β ± SE | p Value |
| Model 1† | 0.19 ± 0.04 | <0.0001 | −0.005 ± 0.002 | 0.01 | 0.02 ± 0.009 | 0.007 | 0.02 ± 0.02 | 0.28 |
| Model 2‡ | 0.14 ± 0.04 | 0.0002 | −0.005 ± 0.002 | 0.007 | 0.03 ± 0.009 | 0.004 | −0.007 ± 0.02 | 0.96 |
| Model 3§ | 0.14 ± 0.04 | 0.0003 | ‖ | ‖ | 0.03 ± 0.009 | 0.002 | −0.007 ± 0.02 | 0.66 |

*Log (WMH) models were adjusted for total brain volume. †Adjusted for age and sex. ‡Adjusted for model 1 variables plus hypertension, diabetes, body mass index, smoking, estimated glomerular filtration rate, total cholesterol, high-density lipoprotein cholesterol, and use of statins and aspirin. §Adjusted for model 2 variables plus systolic and diastolic blood pressure (pulse pressure). ‖This adjustment was not done for the ABI given the issue of colinearity because systolic blood pressure is used to calculate the ABI.
ABI = ankle-brachial index; aPWV = aortic pulse wave velocity; CAC = coronary artery calcification; UACR = urine albumin-creatinine ratio; WMH = brain white matter hyperintensity.

**Table 3. Logistic Regression Analyses Showing the Odds of Subclinical Target Organ Damage for Each 1 m/s Increase in aPWV**

| | CAC Score >0 | | | ABI <0.9 | | | WMH >5.7 $cm^3$* | | | UACR >10 mg/g | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | OR | 95% CI | p Value | OR | 95% CI | p Value | OR | 95% CI | p Value | OR | 95% CI | p Value |
| Model 1† | 1.23 | 1.12–1.36 | <0.0001 | 1.18 | 1.05–1.33 | 0.008 | 1.03 | 0.94–1.12 | 0.57 | 1.06 | 0.96–1.17 | 0.19 |
| Model 2‡ | 1.17 | 1.06–1.29 | 0.002 | 1.17 | 1.04–1.32 | 0.009 | 1.02 | 0.94–1.12 | 0.59 | 1.03 | 0.94–1.13 | 0.51 |
| Model 3§ | 1.18 | 1.07–1.31 | 0.001 | | ‖ | ‖ | 1.04 | 0.95–1.14 | 0.42 | 1.00 | 0.91–1.11 | 0.92 |

Sample sizes are the same as in Table 2. *Log (WMH) models were adjusted for total brain volume. †Adjusted for age and sex. ‡Adjusted for model 1 variables plus hypertension, diabetes, body mass index, smoking, estimated glomerular filtration rate, total cholesterol, high-density lipoprotein cholesterol, and use of statins and aspirin. §Adjusted for model 2 variables plus systolic and diastolic blood pressure (pulse pressure). ‖This adjustment was not done for the ABI to avoid colinearity because systolic blood pressure is used to calculate the ABI.
CI = confidence interval; OR = odds ratio; other abbreviations as in Table 2.

adverse cardiovascular outcomes via its association with subclinical vascular disease.

The results of our study indicate that aPWV is independently associated with the presence and extent of CAC, and this association was also present in the subsets of hypertensives and smokers. We previously showed that aPWV is independently associated with CAC in a community-based cohort (19), whereas the association of arterial stiffness with CAC has also been explored in different cohorts including the elderly (22), postmenopausal women (23), and patients with diabetes (24) and renal disease (25), confirming a positive association. The present report is the first to demonstrate an independent association of aPWV with CAC in a cohort consisting mainly of treated hypertensive individuals without a history of myocardial infarction or stroke. The association of aPWV with the ABI, a measure of atherosclerosis in the legs, also confirms that arterial stiffness is related to large-vessel atherosclerotic burden. Only 2 previous studies assessed the association of arterial stiffness with the ABI, also demonstrating an inverse association (26,27). However, such studies used brachial-ankle pulse wave velocity, which measures elements of both central and peripheral arterial stiffness rather than aPWV. A possible mechanism leading to the associations of aPWV with coronary and lower extremity subclinical atherosclerosis is that common risk factors (such as age, diabetes, and hypertension) promote both atherogenesis and increased arterial stiffness. Further, inflammation underlies both arterial stiffness (28) and atherosclerosis (29). Additionally, the presence of atherosclerotic plaque itself could lead to increased arterial stiffness (30).

In our study, aPWV was an independent predictor of higher WMH volume in the entire cohort and also in the subgroup of hypertensive participants. aPWV was more strongly associated with WMH in older individuals and those with a history of smoking. The association of arterial stiffness and subclinical cerebral arteriolosclerosis is controversial, and results have varied depending on the population studied. aPWV has been shown to be associated with brain WMH in the elderly (31) and also in hypertensive individuals (12), whereas no association was found in a cohort of young, predominantly normotensive patients (32). Furthermore, WMH appears to correlate with cerebral small-vessel disease and a decline in cognitive function (33). aPWV has also been associated with progressive cognitive dysfunction in elderly individuals (1), suggesting that arterial stiffness may influence the onset of vascular dementia. By decreasing the impedance mismatch between central and peripheral arteries and decreasing the amount of wave reflection, aortic stiffness may impair the pressure-buffering abilities of the arteries and arterioles, resulting in the delivery of a highly pulsatile pressure and augmented flow into the brain microcirculation (34), rendering it more susceptible to vascular damage.

A similar mechanism could be responsible for small-vessel damage in the kidneys due to highly pulsatile pressures associated with aortic stiffness, leading to albuminuria. Although an association between arterial stiffness and microalbuminuria was previously reported (8,11,35,36), we were unable to confirm this in our study. Because a reduction in aPWV resulting from antihypertensive treatment has been shown to decrease the UACR (37), the lack of association may be because the participants in our study had a low UACR (mean = 8.2 mg/g, normal <30 mg/g), their blood pressure was, in general, well controlled, and nearly a third of participants were being treated with either angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, drugs known to decrease microalbuminuria. Moreover, most participants did not have significant renal dysfunction (mean estimated glomerular filtration rate 65.4 ml/min/1.73 $m^2$). Differently from our study, an association between the UACR and arterial stiffness was reported in previous studies that included mainly diabetic pa-

tients (38) or untreated hypertensive patients (8,11,36).

aPWV can be relatively easily measured by arterial tonometry and used in the office setting, highlighting the potential clinical advantages of using aPWV in the assessment and risk stratification of hypertensive patients. Furthermore, measurement of aPWV may aid in better risk stratification of asymptomatic individuals, and therapies aimed at arterial de-stiffening may be used in the hope of preventing onset and/or progression of vascular disease before the development of clinically manifest target organ damage. Arterial de-stiffening can result from weight loss (39), aerobic exercise (39), low-fat, low-sodium diets (40), statins (41), and antihypertensive agents (42).

**Study limitations.** The main strengths of our study are the use of several objective measures of vascular disease in a relatively large cohort, and our ability to assess the association of aPWV with subclinical large- and small-vessel target organ damage. However, the cross-sectional nature of the present study does not allow us to disentangle the temporal association between aPWV and the development of coronary, peripheral arterial, and cerebral target organ damage. Our study population consisted of non-Hispanic white, older, and mostly hypertensive participants. Further studies including other ethnicities, as well as studies including younger, normotensive individuals are necessary to assess whether the effects of arterial stiffness on subclinical vascular disease are race, age, and hypertension dependent. The measurement of target organ damage and aPWV in our study was not contemporaneous; however, this should bias the results against any association. Despite being considered a robust measure of arterial stiffness, a limitation of the aPWV technique is that it does not fully assess the pressure-buffering properties of the ascending aorta and aortic arch.

## CONCLUSIONS

Central arterial stiffness, assessed by aPWV, was independently associated with objective measures of the extent of subclinical coronary and peripheral arterial and cerebral target organ damage as well as the presence of subclinical coronary and lower extremity arterial disease. Our findings suggest that target organ damage may represent a mechanism underlying the association of arterial stiffness and adverse cardiovascular events. Further prospective studies are needed to assess the temporality of the associations between arterial stiffness and target organ damage. Similarly, randomized clinical trials using pharmacological and nonpharmacological arterial de-stiffening therapies will be helpful in establishing whether improvement of arterial stiffness could prevent or slow the progression of target organ damage in hypertensive patients.

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**Key Words:** arterial stiffness ■ arteriosclerosis ■ coronary artery calcification ■ hypertension ■ leukoariosis ■ peripheral arterial disease ■ pulse wave velocity ■ target organ damage.