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## ORIGINAL ARTICLE

# Aortic Pulse Wave Velocity as Adjunct Risk Marker for Assessing Cardiovascular Disease Risk: Prospective Study

Carlos A. Valencia-Hernández<sup>1</sup>, Joni V. Lindbohm, Martin J. Shipley, Ian B. Wilkinson, Carmel M. McEnery<sup>1</sup>, Sara Ahmadi-Abhari<sup>1</sup>, Archana Singh-Manoux, Mika Kivimäki<sup>1</sup>, Eric J. Brunner<sup>1</sup>

**BACKGROUND:** Aortic pulse wave velocity is a noninvasive measure of aortic stiffness and arterial aging. Its current value in cardiovascular risk estimation practice is unknown. We aimed to establish whether aortic pulse wave velocity identified individuals with higher risk of incident major adverse cardiovascular events and improved performance of the American Heart Association/American College of Cardiology atherosclerotic cardiovascular disease risk score.

**METHODS:** This prospective analysis included 3837 Whitehall II cohort participants screened in 2008 to 2009, and followed for 11.7 years (mean=10.3, SD=1.81), without history of stroke, myocardial infarction, or coronary heart disease.

**RESULTS:** Mean age of the sample was 65.0 years (SD=5.6), 2831 participants (73.8%) were male and mean atherosclerotic cardiovascular disease risk score was 13.8%. At the end of follow-up, 411 individuals (10.7%) had suffered a major cardiovascular event. Those in the highest aortic pulse wave velocity quartile were at high risk (hazard ratio, 2.99 [95% CI, 2.25–3.97]) and reached the threshold for statin medication (7.5% risk) after 5 years whereas others reached it after 10 years (difference  $P<0.001$ ). The addition of aortic pulse wave velocity to the risk score improved the C statistic (0.68 versus 0.67,  $P=0.03$ ) and net reclassification index (4.6%,  $P=0.04$  and 11.3%,  $P=0.02$ ).

**CONCLUSIONS:** Our results show that aortic stiffness predicted major adverse cardiovascular events in a cohort of elderly individuals, improving the performance of a widely used cardiovascular disease risk estimator. Aortic pulse wave velocity measurement is scalable, radiation-free, and easy to perform. Further studies on its applicability in cardiovascular disease risk assessment in primary care settings are needed. (*Hypertension*. 2022;79:836–843. DOI: 10.1161/HYPERTENSIONAHA.121.17589.) • **Supplemental Material**

**Key Words:** aging ■ arteriosclerosis ■ atherosclerosis ■ blood pressure ■ cholesterol ■ hypertension

American Heart Association/American College of Cardiology guidelines recommend the atherosclerotic cardiovascular disease (ASCVD) Score to guide preventive interventions. The ASCVD score takes age, sex, systolic blood pressure, antihypertensive medications, smoking, total cholesterol, high-density lipoprotein cholesterol, and diabetes status as input, providing an individual 10-year risk estimate for major adverse cardiovascular events (MACE) as output.<sup>1</sup> Within the ASCVD score, chronological age is important, however,

with differing risk factor trajectories<sup>2</sup> and genetic risk categories,<sup>3</sup> individuals of the same age may have a very different atherosclerosis burden.<sup>4</sup>

Carotid-femoral (aortic) pulse wave velocity (aPWV) is surrogate measure of arterial stiffness and an established marker of vascular aging and atherosclerosis.<sup>5,6</sup> There is a dose-response increase in risk of MACE and related mortality as aPWV increases.<sup>7,8</sup> Consistently, aPWV measurement may also be clinically useful for estimating the risk of incident hypertension.<sup>9</sup>

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## NOVELTY AND RELEVANCE

### What Is New?

This research shows that the measurement of aortic stiffness with pulse wave velocity improves the performance of cardiovascular risk stratification tools, especially in risk groups where the decision of initiation of primary prevention therapies might not be clear.

### What Is Relevant?

The results suggest aortic stiffness measurement holds potential to improve cost-effectiveness of cardiovascular disease prevention in primary care.

### Clinical/Pathophysiological Implications?

The improved performance of the combined model predicting cardiovascular events when aortic pulse wave velocity is added to atherosclerotic cardiovascular disease risk score may be explained by better capture of the degree of arterial aging.

## Nonstandard Abbreviations and Acronyms

<b>aPWV</b>	aortic pulse wave velocity
<b>ASCVD</b>	atherosclerotic cardiovascular disease
<b>CAC</b>	coronary artery calcium
<b>HR</b>	hazard ratio
<b>MACE</b>	major adverse cardiovascular events
<b>NRI</b>	net reclassification index

## Study Population

The Whitehall II cohort study recruited 10,308 British Civil servants (67% male) between 1985 and 1988, with a response rate of 73%. Age at baseline ranged from 35 to 55 with a mean age of 44. Participants were asked to attend clinical assessments every 4 to 5 years.<sup>10</sup> aPWV was assessed on 4342 participants at the 2007 to 2009 clinical examination, which was the baseline of this analysis. Participants were followed-up for MACE until 31 March, 2019, for a mean period of 11.7 years. Five hundred five participants were excluded of the analysis due to prevalent CVD or lack of data required to calculate the ASCVD score. The final sample comprised 3837 participants with 411 incident MACE.

It is thus possible that inclusion of an aPWV measurement in risk assessment could improve on performance of the ASCVD score in elderly individuals. Current American Heart Association guidelines for primary prevention recommend measurement of coronary artery calcium (CAC) to support shared decision making on initiation of statin therapy. CAC assessment involves ionizing radiation and is often not available in primary care clinics, a common setting for initiation of preventive medications. Since aPWV measurement using applanation tonometry is quick, affordable, and potentially available in primary care settings, it is reasonable to ask whether it improves the ASCVD score and could be used to improve CVD risk assessment in primary care.

This study aimed to assess whether adjunct measurement of aPWV on a single occasion could improve risk stratification over and above the ASCVD score alone in elderly individuals, and thus improve effectiveness of primary prevention.

## Aortic PWV

Aortic PWV is defined as the travel time of the pulse wave along the aorta. It was measured using the SphygmoCor (Atcor Medical, Australia) applanation tonometer device with the participant in the supine position following standard procedures. The device detects the difference between the peak of the R-wave on ECG and the foot of the pulse waveform at the measurement site. When placed at the carotid artery, the device detects the blood transmission time between the heart and the carotid pulse. Afterwards, the process is repeated at the femoral site. The time of transit was defined as the difference between the heart-carotid and heart-femoral times.

The path length, defined as the distanced travelled by the pulse wave, was measured with a tape measure subtracting the carotid-sternal notch distance from the femoral-sternal notch distance,<sup>11</sup> with the final calculation of aPWV in m/s calculated by dividing the path length over the transit time. Aortic PWV was measured twice, and if the difference in velocity between the 2 measurements was >0.5 m/s, a third measurement was taken. The average of the measurements was used in the analysis. aPWV measurements were repeated in 125 study participants within 60 days to assess the short-term reproducibility. The median intraindividual difference in aPWV was 0.83 m/s (SD, 1.27; interquartile range, 0.43–1.40).

## Major Adverse Cardiovascular Events

MACE is a composite endpoint consisting of nonfatal and fatal stroke, myocardial infarction, definite angina, and

## METHODS

Data, analytic methods, and study materials of this study are available from Prof. Eric J. Brunner on reasonable request (data sharing policy: <https://www.ucl.ac.uk/epidemiology-health-care/research/epidemiology-and-public-health/research/whitehall-ii/>).

cardiovascular death (Table S1). Information about clinical events in the participants of the cohort was extracted from the Hospital Episode Statistics database in the National Health Service Central Registry, where all in- and out-patient admissions to hospitals in the United Kingdom are recorded and clinical events are coded according to the *International Classification of Diseases*, Tenth Revision.<sup>12</sup> The events were retrieved using the unique National Health Service identification number from the participants. To reduce potential inaccuracies, the endpoints used in this study were matched to specific *International Classification of Diseases*-codes.<sup>13</sup>

## Variables Used in the Equation of the ASCVD Score

Baseline ASCVD score was derived using the variables and the equation suggested in American Heart Association guidelines.<sup>14</sup> The participants were categorized according to their ASCVD score in low risk (<5%), borderline risk (5%–7.5%), intermediate risk (≥7.5%–20%), and high risk (≥20%). Data on sociodemographic characteristics, antihypertensive medication, other prescription medications and health behaviors as smoking status (smoker, ex-smoker, non-smoker) were obtained from the self-administered questionnaire. To ascertain that a given drug was prescribed as antihypertensive, hypertension had to be stated as cause.

Blood pressure was measured with the patient in a supine position, after resting for 10 minutes and with the upper right arm exposed, systolic blood pressure and diastolic blood pressure readings in millimeters of mercury were obtained using the oscillometric sphygmomanometer Omron HEM 907. Different cuffs were used according to the size needed by the patient. Two readings were taken with an interval of 1 minute. In the case of a difference greater than 10 mmHg between the 2 measurements, a third measurement was obtained. Height, weight, and other anthropometric measurements were taken with the participants in a standing position. Waist circumference was obtained using a tape measure with participants in mid-expiration and muscles relaxed. Diabetes status was assessed by an oral glucose tolerance test at clinical screening or a self-reported doctor diagnosis, or the use of diabetes medication. Serum total and high-density lipoprotein cholesterol were measured in a blood sample after fasting either overnight or 4 hours after a fat-free breakfast.

## Statistical Analysis

Sociodemographic characteristics were presented as proportions for categorical variables and means with standard deviations for continuous variables.  $\chi^2$  tests or *t* tests were performed to assess differences between participants above and below the intermediate (7.5%) and high (20%) ASCVD thresholds. Cox proportional hazards models were fitted to estimate the association between aPWV, in quartiles or as a continuous variable, and the risk of MACE. Nonlinear effects of aPWV on the risk of MACE were assessed by adding a quadratic term for continuous aPWV, and an interaction term of aPWV by age was added to test whether the effect of aPWV on risk of MACE differed by age. The proportional hazards assumption was tested using the Schoenfeld method of analysis of residuals. For analysis of predictive performance, all variables

included in the Pooled Chained Equations for the calculation of the ASCVD score were included in a Cox proportional hazards model. A further model including also aPWV at baseline was additionally fitted.

Discrimination ability of the models including and not including aPWV was estimated using Harrell C statistic. The C statistic is a rank parameter equivalent to the area under the receiver operating characteristic curve that measures the concordance between the predicted and experienced outcomes.<sup>15</sup> The difference between C statistic scores was calculated using the Somers' D program.<sup>16</sup> Net reclassification index (NRI) analysis after the addition of aPWV to the components of the ASCVD pooled equation was performed using the NRI program in Stata.<sup>17</sup> The thresholds set up for the calculation of NRI were 7.5%, which is the lowest risk limit for recommending the use of lipid-lowering drugs in the presence of a risk enhancer favoring that decision and 20%, which is defined as high ASCVD risk indicating lipid-lowering therapy. Calibration was measured using the Hosmer-Lemeshow test. All statistical analysis was performed using Stata 13.<sup>18</sup>

## RESULTS

There were 3837 participants with mean age 65.0 years free of MACE at baseline with data on all ASCVD components and aPWV. The mean ASCVD score was 13.8%. At baseline, 28.0% of the participants were in the low and borderline (<7.5%) ASCVD risk threshold (Table 1), 51.2% were in the intermediate (≥7.5%–20%), and 20.7% in the high-risk (≥20%) groups. Compared with the intermediate and high ASCVD score risk groups, the group low and borderline group tended to be younger and comprised a higher proportion of female participants. Heart rate and frequency of alcohol consumption were similar across groups. Total cholesterol was marginally lower and use of lipid-lowering medication more frequent in the highest ASCVD score group compared with the lowest.

After a follow-up of 11.7 years, 10.7% of participants suffered MACE. 52.8% of events were nonfatal coronary heart disease, 18.5% nonfatal stroke, 17.8% definite MI, 5.4% other CVD-related mortality (Table S1). The risk of MACE increased across the quartiles of aPWV (Figure), with the highest quartile (aPWV >9.45 m/s) having an unadjusted hazard ratio (HR) of 2.99 (95% CI, 2.25–3.97) compared with the lowest. These associations remained after adjustment for the ASCVD score and endured stratification to intermediate risk group and exclusion of those on lipid-lowering and antihypertensive medications (Table S2). After adjustment for the ASCVD score the HR for the highest quartile was 1.93 (95% CI, 1.41–2.64). The high-risk group reached the threshold for statin treatment in 5 years, while the other quartiles reached it in 10 years and these results remained the same after adjustment to ASCVD score (Table S2 and Figure S1). Using aPWV as a continuous measure, the unadjusted HR was 1.22 (95% CI, 1.17–1.26) for each

**Table 1. Sample Characteristics at Baseline by ASCVD Score Categories (N=3837)**

Characteristic	ASCVD score <7.5% (N=1076)	ASCVD score 7.5%–19.9% (N=1966)	ASCVD score ≥20% (N=795)
	Mean (SD)/N (%)	Mean (SD)/N (%)	Mean (SD)/N (%)
Age	60.7 (3.2)	64.9 (4.7)*	71.2 (4.7)*
Heart rate	62.7 (9.8)	63.7 (10.8)*	65.9 (11.9)*
Sex (male)	438 (40.7)	1678 (85.4)*	715 (89.9)*
Ethnicity (non-White)	69 (6.4)	117 (5.9)*	86 (10.8)*
aPWV, m/s	7.4 (1.3)	8.4 (1.8)*	9.9 (2.2)*
Individuals in the highest PWV quartile, %	80 (7.4)	427 (21.7)*	421 (52.9)*
Body mass index, kg/m <sup>2</sup>	25.4 (4.4)	26.3 (3.7)*	26.7 (3.5)*
Waist circumference, cm	86.5 (11.1)	93.6 (10.6)*	96.5 (10.1)*
Smoker, %	25 (2.3)	145 (7.4)*	65 (8.2)*
Diabetes, %	23 (2.1)	114 (5.8)*	251 (31.6)*
Total cholesterol, mg/dL	206.8 (38.8)	206.6 (38.9)	198.5 (42.9)*
HDL cholesterol, mg/dL	71.1 (17.6)	60.1 (16.0)*	57.1 (16.3)*
Systolic blood pressure, mmHg	119.2 (12.7)	129.3 (13.8)	137.4 (15.4)*
Diastolic blood pressure, mmHg	67.6 (8.6)	71.3 (9.3)*	73.0 (9.7)*
Antihypertensive medication, %	163 (15.2)	520 (26.5)*	390 (49.1)*
Lipid-lowering drugs, %	183 (17.0)	508 (25.8)*	292 (36.7)*

aPWV indicates aortic pulse wave velocity; ASCVD, atherosclerotic cardiovascular disease; HDL, high-density lipoprotein; and PWV, pulse wave velocity.

\* $\chi^2/t$  test for equality of means compared with the reference group (ASCVD <7.5%) <0.05.

1 m/s higher aPWV. After adjustment for ASCVD risk factors, the association attenuated slightly to HR 1.12 (95% CI, 1.07–1.18; Table 2). There was no evidence of nonlinearity ( $P=0.33$ ) or any interaction of aPWV with age ( $P=0.21$ ). The association between aPWV and MACE remained when analyses were adjusted for systolic blood pressure, and when high-risk participants or those using lipid-lowering or antihypertensive medication were excluded (Table S2).

After adding aPWV to the ASCVD score, there was a modest, but meaningful improvement in the C statistic of the model from 0.67 to 0.68 (Table 2). In an analysis including only the intermediate ASCVD group (7.5%–20%) or participants not on lipid-lowering or antihypertensive medications, the improvement in C statistic was similar in magnitude although with a  $P$  value=0.09 (95% CI, –0.004 to 0.048). (Table 3). Internal calibration of the risk prediction model was good (Figure S2). Table 4 shows that including aPWV as additional predictor led 11 (2.7%) extra MACE cases to be reclassified into a higher risk category (improving sensitivity) and 66 (1.9%) extra non-MACE cases to be classified into a lower risk category (improving specificity). The overall net reclassification improvement was 4.6% in

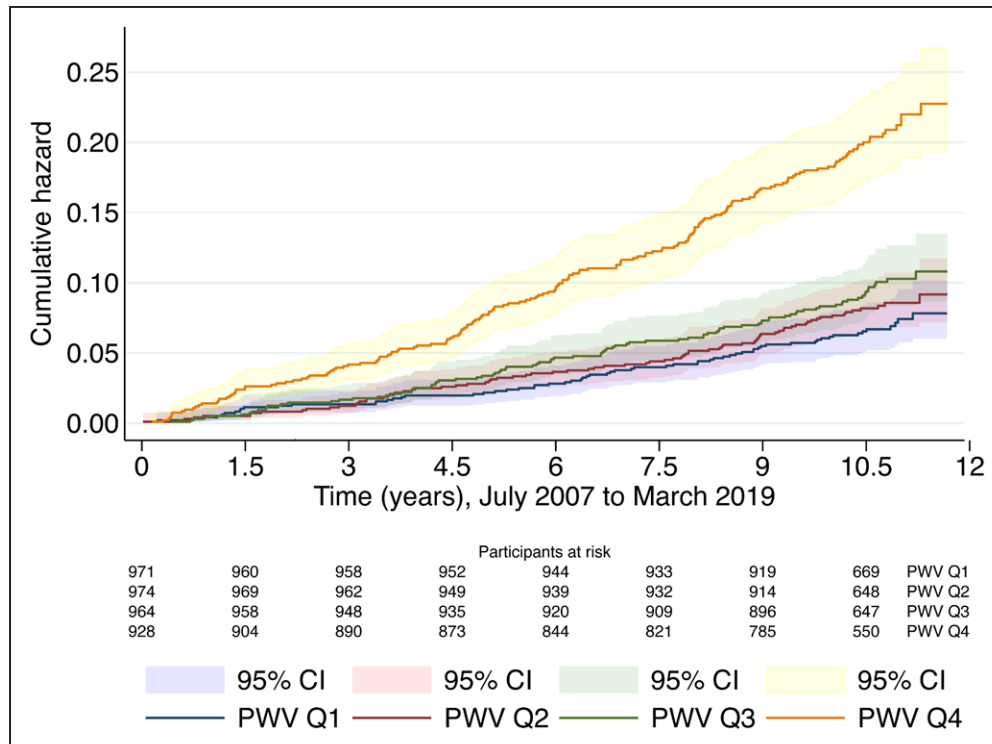
the total sample ( $P=0.04$ ). The NRI increased to 11.3% when those on medication were excluded (Table 5).

## Conclusions

Among healthy elderly men and women, participants with aPWV in the top quartile (>9.45 m/s) reached the high CVD risk threshold within 5 years. This was twice as fast as those in other quartiles, who reached the 7.5% risk level after ≈10 years. Aortic PWV was associated with MACE after adjustment for all ASCVD components and when stratified to intermediate risk group or to those not using lipid-lowering or antihypertensive medications. It also improved performance of the ASCVD score in predicting MACE. The net reclassification improvement after adding aPWV to ASCVD score, was 5% in the whole cohort and 11% in those not on lipid-lowering or antihypertensive medications.

Previous studies have shown that aPWV is independently associated with incident CVD events after adjusting for systolic blood pressure and other cardiovascular risk factors. Our study confirms the additional predictive value of the PWV measurement over and above the information provided by systolic blood pressure.<sup>8,19</sup> Building on pioneer studies showing risk reclassification using aPWV,<sup>20</sup> our study explores the clinical relevance of this reclassification within groups of individuals with intermediate risk. Our study is the first to suggest that aPWV can identify older individuals with accelerated risk progression in a similar way to that achieved with measurement of CAC,<sup>21</sup> and to show that adding aPWV to ASCVD score improves NRI. The improvement in NRI of 5% to 11% is comparable to other strong risk enhancers and suggests that health benefit could be achieved at population as well as clinical level. Earlier studies on improvement of the ASCVD score have shown that adding CAC and family history increased NRI by 12% and 5%, respectively,<sup>22</sup> whereas ankle-brachial index and C-reactive protein did not show improvements. Recently, a polygenic risk score for coronary heart disease was observed to improve NRI in detection of early onset MACE by 4%.<sup>23</sup> Compared with these findings, our results suggest aPWV improves ASCVD score with similar magnitude as other major risk enhancers. This makes it an interesting tool that could be used in primary prevention to detect subclinical atherosclerosis rather than elevated CVD risk alone. These findings hold promise in improving risk stratification in a growing number of elderly individuals with a high ASCVD risk score driven by age and not by underlying atherosclerosis.

Scalability and applicability of applanation tonometry-based aPWV measurement is feasible in primary health care centers where preventive medication is commonly prescribed. Currently, determination of CAC score is the gold-standard recommendation when the treatment



**Figure.** Cumulative hazard for major adverse cardiovascular events (MACE) according to quartiles of aortic pulse wave velocity (aPWV) with 95% CI (411 events in 3837 participants).

Figure shows Kaplan-Meier curves depicting the unadjusted cumulative hazard for Major Adverse Cardiovascular Events in different quartiles of aPWV during the follow-up time, individuals in the highest quartile of aPWV showed higher risk of MACE.

decision of lipid-lowering medication is uncertain.<sup>24</sup> However, CAC measurement is dependent on ionizing radiation and computed tomography scanners are often not available in primary care. The cost per gained quality adjusted life-year using CAC measurements (USD

\$35 000–\$48 000) exceeds the cost-effectiveness recommendations in the United Kingdom,<sup>25</sup> making its use in primary care less feasible. In comparison, aPWV is less expensive, does not rely on ionizing radiation, and can be performed by trained technicians. This stresses the need

**Table 2.** Association of MACE With ASCVD Risk Factors and aPWV and the Predictive Ability of 2 Models Excluding and Including PWV (N=3837, Events=411)\*

	HR	95% CI	P value	C statistic	95% CI	P value
Model 1 (ASCVD components)						
Age	1.08	1.06–1.09	<0.001	0.6680	(0.6423–0.6938)	<0.001
Total cholesterol (per SD)	1.02	0.92–1.13	0.71			
HDL-C (per SD)	0.89	0.79–0.99	<0.05			
Antihypertensive use	1.61	1.30–1.98	<0.001			
SBP (per SD)	1.15	1.04–1.26	<0.01			
Smoker	1.67	1.18–2.35	<0.001			
Incident diabetes	1.14	0.88–1.48	0.319			
Female	0.74	0.57–0.96	<0.05			
Model 2 (ASCVD components+aPWV)						
Model 1+aPWV (m/s)	1.12	1.07–1.18	<0.001	0.6784	(0.6525–0.7044)	<0.001
aPWV (SD)	1.26	1.14–1.38	<0.001			
aPWV (SD-log unit)	1.29	1.16–1.44	<0.001			
Model 2–model 1				0.0104	(0.0012–0.0195)	<0.05

aPWV (m/s) indicates aortic pulse wave velocity at baseline (continuous measure in meters per second); ASCVD, atherosclerotic cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; MACE, major adverse cardiovascular event; PWV, pulse wave velocity; and SBP, systolic blood pressure.

\*Participants with history of MACE at baseline are excluded.

**Table 3. Association Between aPWV and MACE and Discriminant Ability in Subgroups**

Participants with intermediate ASCVD risk score (7.5%–20%; 208 events among 1966 participants)*						
Model 1 (ASCVD components)						
Adjustment	HR	95% CI	P value	C statistic	95% CI	P value
Age	1.05	1.00 to 1.09	<0.05	0.5808	(0.540 to 0.6211)	<0.001
Total cholesterol (per SD)	0.99	0.84 to 1.17	0.92			
HDL (per SD)	0.93	0.78 to 1.09	0.38			
Antihypertensive use	1.56	1.15 to 2.11	<0.01			
SBP (per SD)	1.02	0.86 to 1.20	0.83			
Smoker	1.18	0.69 to 2.00	0.53			
Incident diabetes	1.09	0.63 to 1.89	0.76			
Female	1.02	0.66 to 1.56	0.94			
Model 2 (ASCVD components+aPWV)						
Model 1+aPWV (m/s)	1.13	1.06 to 1.20	<0.001			
aPWV (SD)	1.28	1.13 to 1.45	<0.001	0.6032	(0.5633 to 0.6432)	<0.001
aPWV (SD-log unit)	1.32	1.14 to 1.54	<0.001			
Model 2-model 1				0.0225	(−0.004 to 0.048)	0.09
Participants without lipid-lowering or antihypertensive medication (185 events among 2301 participants)†						
Model 3 (ASCVD components)				0.6463	(0.6077 to 0.6849)	<0.001
Model 4 (model 3+aPWV)				0.6588	(0.6188 to 0.6987)	<0.001
Model 4-model 3				0.0125	(−0.0074 to 0.0324)	0.22

aPWV (m/s) indicates aortic pulse wave velocity at baseline (continuous measure in meters per second); ASCVD, atherosclerotic cardiovascular disease; HDL, high-density lipoprotein; HR, hazard ratio; MACE, major adverse cardiovascular event; and SBP, systolic blood pressure.

\*Participants with history of MACE at baseline and participants with ASCVD <7.5% or >20% are excluded.

†Participant with current use of lipid lowering or antihypertensive medication are excluded.

of further studies on applicability of aPWV in risk stratification in primary care settings.

The magnitude of risk of MACE associated with aPWV in the present study was similar to that reported in the scientific literature. A meta-analysis of studies assessing risk of MACE according to aPWV reported a summary HR of 1.4 per m/s similar to that in the present study (HR, 1.2 per m/s).<sup>8</sup> The Health ABC study obtained an unadjusted

HR for CHD of 1.5 in the highest quartile of aPWV compared with the lowest.<sup>26</sup> In overview, our results appear broadly representative of White ethnic background populations. The magnitude and strength of the association between aPWV and MACE was consistent among low and intermediate risk individuals and nonstatin users. In these subgroups, the performance of aPWV as an ASCVD predictor was at least as good as in the main analyses.

**Table 4. Net Reclassification Improvement for MACE After the Addition of aPWV to ASCVD Risk Factors\***

ASCVD risk factors at baseline	ASCVD risk factors+aPWV				NRI (95% CI)
Subpopulation	<7.5%	7.5%–20%	>20%	Total	
Incident MACE cases					0.027 (−0.016 to 0.070)
<7.5%	67	13	0	80	
7.5%–20%	21	183	33	237	
>20%	0	14	80	94	
Total	88	210	113	411	
No MACE during follow-up					0.019 (0.007 to 0.031)
<7.5%	1322	109	0	1431	
7.5%–20%	176	1456	77	1709	
>20%	0	76	210	286	
Total	1498	1641	287	3426	
Total NRI					0.046 (0.002 to 0.090) P=0.04

aPWV indicates aortic pulse wave velocity; ASCVD, atherosclerotic cardiovascular disease; MACE, major adverse cardiovascular event; and NRI, net reclassification index.

\*Participants with history of MACE at baseline are excluded.

**Table 5. Net Reclassification Improvement for MACE After the Addition of PWV to ASCVD Risk Factors\* (N=2301, Events=185)**

ASCVD risk factors at baseline	ASCVD risk factors+PWV			Total	NRI (95% CI)
	Subpopulation	<7.5%	7.5%–20%		
Incident MACE cases	<7.5%	7.5%–20%	≥20%	Total	0.081 (0.009 to 0.152)
	<7.5%	7.5%–20%	≥20%		
	7.5%–20%	7.5%–20%	≥20%		
	≥20%	7.5%–20%	≥20%		
Total	68	97	20	185	
No MACE during follow-up	<7.5%	7.5%–20%	≥20%	Total	0.032 (0.015 to 0.048)
	<7.5%	7.5%–20%	≥20%		
	7.5%–20%	7.5%–20%	≥20%		
	≥20%	7.5%–20%	≥20%		
Total	1255	809	52	2116	
Total NRI					0.113 (0.039 to 0.187) <i>P</i> =0.02

ASCVD indicates atherosclerotic cardiovascular disease; MACE, major adverse cardiovascular event; PWV, pulse wave velocity; and NRI, net reclassification index.

\*Participants with history of MACE at baseline and participants with lipid lowering and antihypertensive drugs are excluded.

There are 3 main strengths of our study. First is the quality of the data, using aPWV, the gold-standard for measuring arterial stiffness.<sup>27,28</sup> Second, although Whitehall II is an occupational cohort, risk factor estimates are similar to those derived from community-based cohorts,<sup>29</sup> suggesting our results may be extrapolated to the general elderly population. Third, ascertainment of fatal and nonfatal MACE through the use of National Health Service Hospital Episode Statistics means that neither outcomes nor participants were lost over the follow-up.<sup>12</sup> The validity of cardiovascular disease ascertainment using linkage to the UK Hospital Episode Statistics database records is supported by agreement with high resolution disease data collected in the cohort.<sup>30</sup> Also, the quality of the National Health Service Hospital Episode Statistics data is high enough to be used in studies of clinical outcomes.<sup>31</sup> Taking all these factors into account, consideration of aPWV as a risk enhancer to the ASCVD score is an option that could be developed for the improvement of treatment decision making.

Our study has some limitations. We studied only the ASCVD score, although many other risk estimation tools exist.<sup>32</sup> ASCVD score was chosen because earlier studies on other potential risk enhancers for ASCVD score are numerous, which eased the comparison of aPWV to other risk enhancers. In addition, risk algorithms tend to exhibit similar performance after calibration.<sup>32</sup> As an occupational cohort recruiting London-based civil servants in the 1980s, Whitehall II has largely male participants of white ethnicity. Our results would benefit therefore from replication in cohorts with diverse ethnic composition and younger baseline age range. However, the results were consistent in subgroup analyses including younger individuals with lower CVD risk and individuals with no statin medications.

## Perspectives

Among older men and women, adjunct measurement of aPWV on a single occasion modestly improved the performance of the ASCVD score. Due to scalability and cost-effectiveness of aPWV, there is potential gain in cardiovascular prevention in primary care where patient volumes are high. The clinical benefits of aPWV should be evaluated in future research.

## ARTICLE INFORMATION

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## Disclosures

None.

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