

# Aortic Pulse Wave Velocity Improves Cardiovascular Event Prediction

## An Individual Participant Meta-Analysis of Prospective Observational Data From 17,635 Subjects

Yoav Ben-Shlomo, MBBS, PHD,<sup>1</sup> Melissa Spears, MSc,<sup>1</sup> Chris Boustred, PHD,<sup>1</sup> Margaret May, PHD,<sup>1</sup> Simon G. Anderson, PHD, MBChB,<sup>2</sup> Emelia J. Benjamin, MD, ScM,<sup>3</sup> Pierre Boutouyrie, MD, PHD,<sup>4</sup> James Cameron, MBBS, MD,<sup>5</sup> Chen-Huan Chen, MD,<sup>6</sup> J. Kennedy Cruickshank, MB, MD,<sup>7</sup> Shih-Jen Hwang, PHD,<sup>8</sup> Edward G. Lakatta, MD,<sup>9</sup> Stephane Laurent, MD, PHD,<sup>4</sup> João Maldonado, MD,<sup>10</sup> Gary F. Mitchell, MD,<sup>11</sup> Samer S. Najjar, MD,<sup>9,12</sup> Anne B. Newman, MD, MPH,<sup>13</sup> Mitsuru Ohishi, MD, PHD,<sup>14</sup> Bruno Pannier, MD,<sup>15</sup> Telmo Pereira, PHD,<sup>16</sup> Ramachandran S. Vasan, MD,<sup>17</sup> Tomoki Shokawa, MD,<sup>18</sup> Kim Sutton-Tyrell, DRPH,<sup>13</sup> Francis Verbeke, MD, PHD,<sup>19</sup> Kang-Ling Wang, MD,<sup>6</sup> David J. Webb, MD, DSc,<sup>20</sup> Tine Willum Hansen, MD, PHD,<sup>21</sup> Sophia Zoungas, MBBS, PHD,<sup>22</sup> Carmel M. McEniery, PHD,<sup>23</sup> John R. Cockcroft, BSc, MB,<sup>24</sup> Ian B. Wilkinson, MA, DM<sup>23</sup>

*Bristol, Manchester, London, Edinburgh, Cambridge, and Cardiff, United Kingdom; Boston and Norwood, Massachusetts; Paris, France; Melbourne, Australia; Taipei, Taiwan; Bethesda and Baltimore, Maryland; Glostrup, Denmark; Penacova, Portugal; Washington, DC; Pittsburgh, Pennsylvania; Osaka and Hiroshima, Japan; Coimbra, Portugal; Ghent, Belgium; and Glostrup, Denmark*

- Objectives** The goal of this study was to determine whether aortic pulse wave velocity (aPWV) improves prediction of cardiovascular disease (CVD) events beyond conventional risk factors.
- Background** Several studies have shown that aPWV may be a useful risk factor for predicting CVD, but they have been underpowered to examine whether this is true for different subgroups.
- Methods** We undertook a systematic review and obtained individual participant data from 16 studies. Study-specific associations of aPWV with CVD outcomes were determined using Cox proportional hazard models and random effect models to estimate pooled effects.
- Results** Of 17,635 participants, a total of 1,785 (10%) had a CVD event. The pooled age- and sex-adjusted hazard ratios (HRs) per 1-SD change in  $\log_e$  aPWV were 1.35 (95% confidence interval [CI]: 1.22 to 1.50;  $p < 0.001$ ) for coronary heart disease, 1.54 (95% CI: 1.34 to 1.78;  $p < 0.001$ ) for stroke, and 1.45 (95% CI: 1.30 to 1.61;  $p < 0.001$ ) for CVD. Associations stratified according to sex, diabetes, and hypertension were similar but decreased with age (1.89, 1.77, 1.36, and 1.23 for age  $\leq 50$ , 51 to 60, 61 to 70, and  $> 70$  years, respectively;  $p_{\text{interaction}} < 0.001$ ). After adjusting for conventional risk factors, aPWV remained a predictor of coronary heart disease (HR: 1.23 [95% CI: 1.11 to 1.35];  $p < 0.001$ ), stroke (HR: 1.28 [95% CI: 1.16 to 1.42];  $p < 0.001$ ), and CVD events (HR: 1.30 [95% CI: 1.18 to 1.43];  $p < 0.001$ ). Reclassification indices showed that the addition of aPWV improved risk prediction (13% for 10-year CVD risk for intermediate risk) for some subgroups.
- Conclusions** Consideration of aPWV improves model fit and reclassifies risk for future CVD events in models that include standard risk factors. aPWV may enable better identification of high-risk populations that might benefit from more aggressive CVD risk factor management. (J Am Coll Cardiol 2014;63:636–46) © 2014 by the American College of Cardiology Foundation

From the <sup>1</sup>School of Social and Community Medicine, University of Bristol, Bristol, United Kingdom; <sup>2</sup>Institute of Cardiovascular Sciences, University of Manchester, United Kingdom; <sup>3</sup>National Heart Lung and Blood Institute and Boston University's

Framingham Heart Study, Cardiology Section, Department of Medicine, Boston University School of Medicine, Boston, Massachusetts; <sup>4</sup>INSERM U 970, Paris-Descartes University, Hôpital Européen Georges Pompidou, Assistance Publique

There is considerable interest in refining cardiovascular risk prediction to better target preventative therapy among those individuals considered to be at low or moderate risk according to current guidelines. A number of additional putative cardiovascular biomarkers have been identified, including C-reactive protein, carotid intima-media thickness, and a variety of genetic variants (1,2). However, these factors seem to add little to existing risk estimates, such as that derived from the Framingham Heart Study (1,3,4). Recently, aortic stiffness has emerged (5,6) as a potential additional candidate, and reference values have now been published (7,8).

See page 647

Aortic stiffness can be assessed by using a variety of noninvasive methods. One of the most frequently used methods is carotid-femoral (aortic) pulse wave velocity (aPWV) (9). Data from prospective observational cohort studies indicate that aPWV relates to future cardiovascular risk even after accounting for other accepted cardiovascular risk factors. However, the extent to which aPWV improves risk prediction, whether it does so equally for cardiac and cerebral events, and if it differs by subgroups is unclear because most studies were underpowered to examine these issues. A recent meta-analysis using summary published data found that aPWV predicted cardiovascular events but could not examine subgroup effects at an individual level or calculate the additional prognostic value of aPWV (10).

We undertook a systematic review and used data from both newly published and unpublished cohorts with measures of aPWV and incident cardiovascular disease to conduct an individual participant meta-analysis. Our goal was to address the questions of whether having information on aPWV for both unselected, population-based individuals and patients with manifest disease improved the prediction of future cardiovascular events; whether risk prediction varied according to subgroups; and whether improved risk

prediction was additive to standard risk factors and how this may vary by population.

## Methods

We used the PRISMA 2009 guidelines (11) and undertook a systematic search (details in [Online Appendix 1](#)). The following inclusion criteria were pre-specified: 1) the study had to be a cohort design with a minimum of 1-year follow-up; 2) aortic stiffness had to be assessed by direct measurement of carotid-femoral aPWV; and 3) the study had to be able to provide relevant outcome data, including all-cause mortality, coronary heart disease (CHD) (myocardial infarction or revascularization or as defined by the studies) and stroke events, or CHD and stroke combined (cardiovascular events). Where available, we also tried to differentiate between fatal and nonfatal events, although not all studies collected data on nonfatal events.

Anonymized individual-level subject data were requested for each study, including aPWV, a range of covariates (including age, sex, blood pressure, body mass index, smoking status, lipids, creatinine, and comorbidities), and time to the various endpoint events or censoring.

**Ethics.** Each study obtained appropriate ethical approval from its local research governance body ([Online Appendix 2](#)). The Faculty of Medicine and Dentistry Ethics Committee, University of Bristol, also reviewed the meta-analysis protocol and was satisfied that it met ethical standards.

**Statistical analysis.** Baseline characteristics were summarized for each study sample and reported as mean  $\pm$  SD and number (%) for continuous and categorical variables, respectively. For skewed continuous variables, the median and interquartile range are stated. aPWV varies according to the software algorithm used and the approach to transit distance measurement. Because our main goal was to

### Abbreviations and Acronyms

aPWV = aortic pulse wave velocity

CHD = coronary heart disease

CI = confidence interval

CVD = cardiovascular disease

HR = hazard ratio

PWV = pulse wave velocity

Hopitaux de Paris, Paris, France; <sup>5</sup>Monash Cardiovascular Research Centre, MonashHEART and Monash University Department of Medicine (MMC), Melbourne, Australia; <sup>6</sup>School of Medicine, National Yang-Ming University, Taipei, Taiwan; <sup>7</sup>King's College & King's Health Partners, St. Thomas' & Guy's Hospital, London, United Kingdom; <sup>8</sup>Branch of Population Sciences, Division of Intramural Research, National Heart, Lung and Blood Institute, Bethesda, Maryland; <sup>9</sup>Laboratory of Cardiovascular Science, National Institute on Aging, National Institutes of Health, Baltimore, Maryland; <sup>10</sup>Instituto de Investigação e Formação Cardiovascular, Penacova, Portugal; <sup>11</sup>Cardiovascular Engineering, Inc., Norwood, Massachusetts; <sup>12</sup>MedStar Heart Research Institute, Washington, DC; <sup>13</sup>Center for Aging and Population Health, Pittsburgh, Pennsylvania; <sup>14</sup>Department of Geriatric Medicine, Osaka University, Osaka, Japan; <sup>15</sup>Centre d'Investigations Préventives et Cliniques, Paris, France; <sup>16</sup>Escola Superior de Tecnologia da Saúde de Coimbra, Coimbra, Portugal; <sup>17</sup>National Heart Lung and Blood Institute and Boston University's Framingham Heart Study, Department of Medicine, Boston University, Boston, Massachusetts; <sup>18</sup>Department of Molecular and Internal Medicine, Graduate School of Biomedical Sciences, Hiroshima University, Hiroshima, Japan; <sup>19</sup>Department of Nephrology, Ghent University Hospital, Ghent, Belgium; <sup>20</sup>University/BHF Centre for Cardiovascular Science, Queen's Medical Research Institute, University of

Edinburgh, Edinburgh, United Kingdom; <sup>21</sup>Research Center for Prevention and Health, Glostrup Hospital, Glostrup and Steno Diabetes Center, Glostrup, Denmark; <sup>22</sup>School of Public Health and Preventive Medicine, Monash University, Melbourne, Australia; <sup>23</sup>Clinical Pharmacology Unit, University of Cambridge, Cambridge, United Kingdom; and the <sup>24</sup>Wales Heart Research Institute, Cardiff, United Kingdom. There was no funding supplied for the meta-analysis, but [Online Appendix 1](#) presents details for the individual study funding. Ms. Spears was funded by a National Institutes of Health Research Methods Training Fellowship. Dr. Anderson is a National Institutes of Health Research Clinical Lecturer in Cardiology. Dr. Boutouyrie has received research grants from AtCor and Esaote. Dr. Mitchell is owner of Cardiovascular Engineering, Inc., a company that develops and manufactures devices to measure vascular stiffness; is a consultant for Novartis and Merck; and has received grants from the National Institutes of Health. Dr. Najjar has received research support from HeartWare Inc. Drs. McEniery and Wilkinson are supported by the British Heart Foundation and Cambridge Biomedical Research Centre. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. Dr. Sutton-Tyrell is deceased.

Manuscript received June 19, 2013; revised manuscript received September 13, 2013, accepted September 22, 2013.

examine the relative value of aPWV within a study and then pool these estimates, we used the  $z$ -score of  $\log_e$ -transformed aPWV in the analyses because aPWV values were positively skewed. Thus, effect estimates for each study reflect the change in risk of an outcome for a 1-SD increase in  $\log_e$  aPWV from the average in that population.

Outcome measures were all-cause mortality, cardiovascular mortality, CHD events, stroke, and cardiovascular events (CHD and stroke). For each measure, Cox proportional hazards models were fitted that estimated the hazard ratio (HR) of aPWV: 1) adjusted for age and sex; 2) additionally adjusted for systolic blood pressure; and 3) additionally adjusted for total cholesterol, high-density lipoprotein cholesterol, smoking status, diabetes, and current antihypertensive medication (12). We also repeated these models but replaced systolic blood pressure with pulse pressure. Continuous covariates were expressed as cohort-specific  $z$ -scores. All models were also stratified according to race for 1 study that had a pronounced split in white and African-American populations (details regarding subgroup analysis for ethnicity are given below). We checked whether the association of aPWV with outcomes was linear by visual inspection of graphs of aPWV quintiles against the corresponding HR and formal testing for nonlinearity by using fractional polynomials (13). The proportional hazards assumption was assessed by using tests based on Schoenfeld residuals in models fitted separately to each study.

Models were fitted separately for each study, and the fully- or partially-adjusted estimates pooled by using random effects meta-analysis to account for between-study heterogeneity. Forest plots for each model and outcome show the study-specific effects and the overall pooled estimate, with 95% confidence intervals (CIs) and random effects weightings. In sensitivity analyses, we fitted all models using first, inverse aPWV, and second, the untransformed data but still assessed by using  $z$ -scores within studies. The sensitivity of effects to missing covariate data was examined by repeating analyses using only the 13 studies with all covariates measured (Online Appendix 3). The presence of small study effects and publication bias were examined by using both visual inspection of funnel plots and formal Egger tests. We also considered the influence of each individual study on the pooled meta-analysis effect estimate to examine if any 1 study had undue influence as an outlier.

The protocol pre-specified analyses of the following potential effect modifiers: sex, age group, type of population (healthy vs. disease group), smoking status, renal function measured by the Modification of Diet in Renal Disease (14) estimated glomerular filtration rate ( $\geq 90$  ml/min/1.73 m<sup>2</sup> vs.  $< 90$  ml/min/1.73 m<sup>2</sup>), diabetes, and antihypertensive use at baseline. For each potential effect modifier considered, we estimated the strata-specific effect of aPWV in each study separately. These estimates were pooled across studies, which were then tested to see if the effect of aPWV differed between strata. For type of population (which is a study-level variable), we used meta-regression to test for differences in

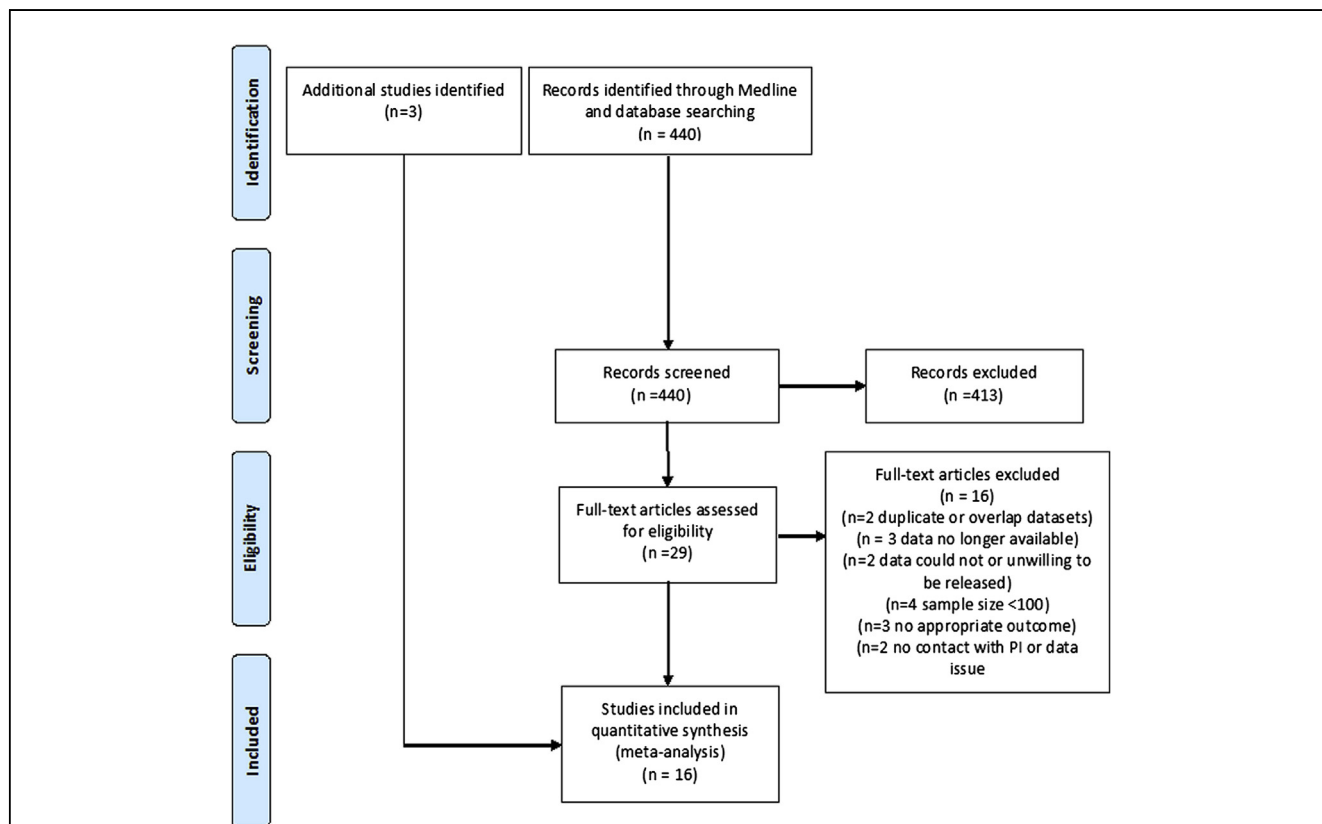
effect of aPWV between clinical and population-based studies. Post-hoc, we also tested for any potential differences in the results dependent on either: 1) the method used to measure distance in calculating aPWV; or 2) the ethnic differences related to participants from the Far East versus European and North American populations (Online Appendix 3).

To compare the discriminatory power of aPWV against simpler hemodynamic measures such as systolic blood pressure, or other established risk factors, the fully adjusted models were fitted with and without  $\log_e$  aPWV. We calculated study-specific measures of discrimination (Harrell's C-index and Royston and Sauerbrei's D measure) and then pooled these statistics weighted by the number of events (15).

We also examined reclassification of subjects to risk groups due to the addition of aPWV to conventional cardiovascular risk factors (net reclassification index) (16). We used reclassification based on 5-year risk because not all studies had sufficient length of follow-up to use the standard clinical cutoff points based on 10-year risk. Risk cutoff points were calculated in each study, based on quartiles of predicted risk from the model without aPWV, considering only those individuals with events. These cutoffs were then applied to the whole study sample. Subjects were ranked according to predicted risk from the models first with and then without aPWV and assigned to low-risk (first quartile), medium-risk (second and third quartiles), and high-risk groups (fourth quartile). Only studies with at least 2 participants experiencing events within 5 years were included in this reclassification exercise. Individuals experiencing an event after 5 years were censored. The number of events available to calculate discrimination statistics is therefore less than the number available to fit the Cox proportional hazards models. Categorizations under the 2 models were cross-tabulated, and the number of subjects moving in the correct direction (up for those experiencing events and down for those not experiencing events) on inclusion of aPWV in the model were counted. The overall percentage of correct reclassifications was combined from those with an event, and those without, across all the studies. We calculated the net reclassification improvement based both on all participants and limited to those at intermediate risk (i.e., in risk quartiles 2 and 3). We also derived the integrated discrimination improvement, which measures improvement in risk prediction on a continuous scale and is independent of the choice of cutoff points for risk categorization. We also undertook a series of sensitivity analyses (Online Appendix 3).

## Results

The flow chart of the selection of papers in the systematic review is shown in Figure 1. From a potential of 29 papers assessed for eligibility, 9 were excluded that were either duplicates or did not meet the eligibility criteria on further examination. An additional 7 studies were unable to supply



**Figure 1** Flow Diagram Illustrating the Process of Study Identification

PI = principal investigator.

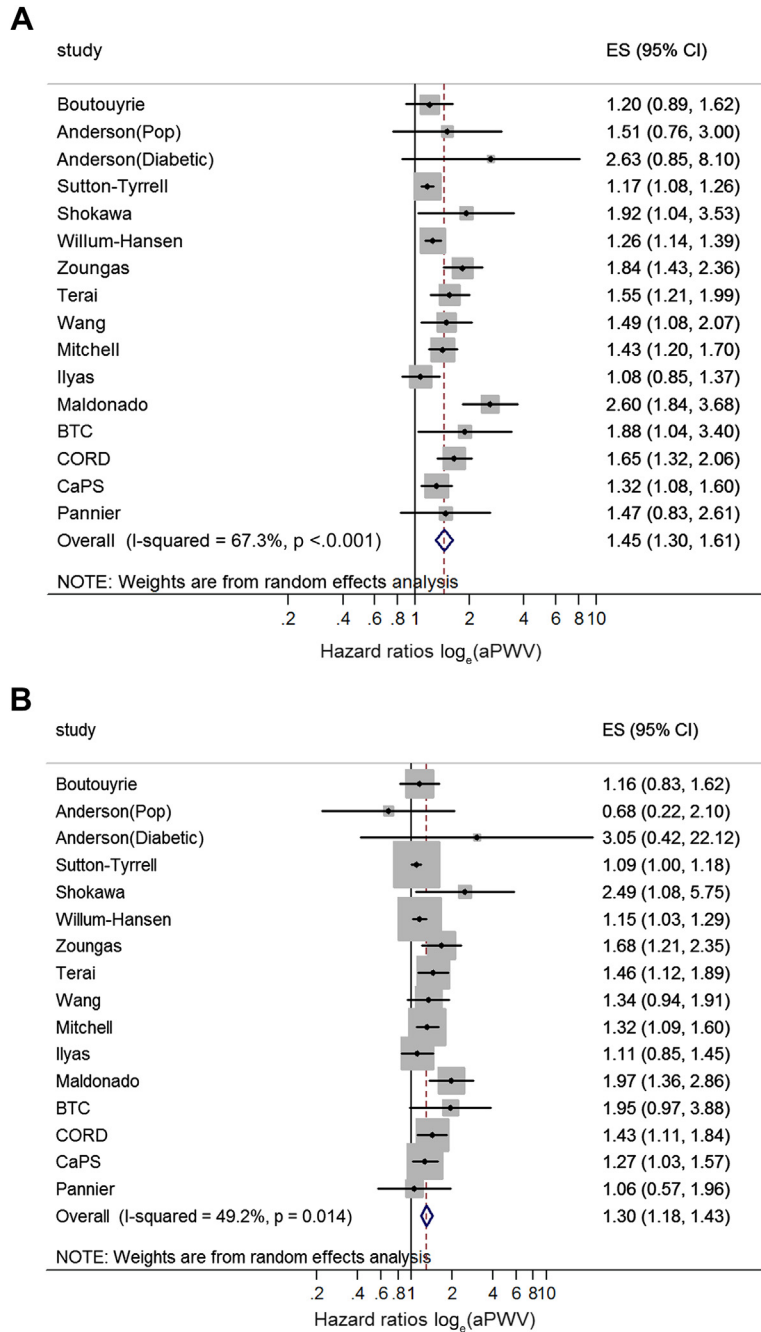
individual participant data (5,17–22). The resulting 13 eligible studies (details given in Online Table 1) for which the original investigators were willing to provide data access were supplemented by 3 additional studies that were not formally published and were identified through other methods (23–37). The study by Cruickshank *et al.* (26) recruited 2 cohorts, a population-based sample and a sample of diabetic patients; therefore, the study was considered as 2 study cohorts in the analyses, resulting in 17 cohorts in the main analysis and comprising 17,635 participants with 1,785 (10%) CVD events.

There was a mix of cohorts, with 8 of the 17 cohorts based on patients with known diseases and the rest from population-based studies. Baseline characteristics of the various cohorts are shown in Online Table 1. Most studies included approximately equal numbers of men and women, except for the Caerphilly Prospective Study (23), which included only men. All except 4 studies had information on all adjustment variables, and all except 5 studies had event rates and follow-up times for all outcome measures. The distribution of raw aPWV measures across the studies is shown in Online Figure 1.

Table 1	Pooled Adjusted Hazard Ratios (95% CIs) of a 1-SD Increase in Log <sub>e</sub> -Transformed aPWV for All-Cause Mortality, CVD Mortality, CHD Events, Stroke Events, and CVD Events		
	Model 1*	Model 2*	Model 3*
CHD events (n = 1,195)	1.35 (1.22–1.50)	1.32 (1.18–1.48)	1.23 (1.11–1.35)
CVD events (n = 1,785)	1.45 (1.30–1.61)	1.37 (1.23–1.52)	1.30 (1.18–1.43)
Stroke events (n = 641)	1.54 (1.34–1.78)	1.37 (1.21–1.54)	1.28 (1.16–1.42)
CVD mortality (n = 395)	1.41 (1.27–1.56)	1.35 (1.20–1.53)	1.28 (1.15–1.43)
All-cause mortality (n = 2,041)	1.22 (1.16–1.27)	1.20 (1.15–1.26)	1.17 (1.11–1.22)

\*Model 1 adjusts for sex and age group; model 2 adjusts for sex, age group, and systolic blood pressure; and model 3 additionally adjusts for other risk factors (cholesterol, high-density lipoprotein cholesterol, smoking status, presence of diabetes, and antihypertensive medication), stratified by race in the Sutton-Tyrell study (27). Not all studies had data on every risk factor.

aPWV = aortic pulse wave velocity; CHD = coronary heart disease; CI = confidence interval; CVD = cardiovascular disease.



**Figure 2** Forest Plot for aPWV and Combined Cardiovascular Events Adjusting for Various Risk Factors

(A) Adjustment for age and sex.  $\log_e$  aortic pulse wave velocity (aPWV) is shown. **Size of box** represents the study-specific weight for the meta-analysis. (B) Adjustment for age, sex, and other cardiovascular risk factors.  $\log_e$  aPWV is shown. Adjusted for age, sex, systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, diabetes, and antihypertensive use. Data from the Baltimore Longitudinal Study of Aging were excluded because there were too few events. **Size of box** represents the study-specific weight for the meta-analysis. BTC = Belgian Transplant Cohort; CaPS = Caerphilly Prospective Study; CI = confidence interval; CORD = Calcification Outcome in Renal Disease; CVD = cardiovascular disease; ES = effect size.

In Cox proportional hazards models,  $\log_e$  aPWV was linearly associated with risk for each of the outcomes, and proportional hazards assumptions were valid. The pooled age- and sex-adjusted hazard ratio (95% confidence interval [CI]) per 1-SD change in  $\log_e$  aPWV was 1.35 (95% CI:

1.22 to 1.50;  $p < 0.001$ ] for coronary heart disease, 1.54 (95% CI: 1.34 to 1.78;  $p < 0.001$ ) for stroke, and 1.45 (95% CI: 1.30 to 1.61;  $p < 0.001$ ) for CVD. **Table 1** shows the HRs for the pooled associations of aPWV with our outcome measures for each of the 3 models. For all outcomes,  $\log_e$

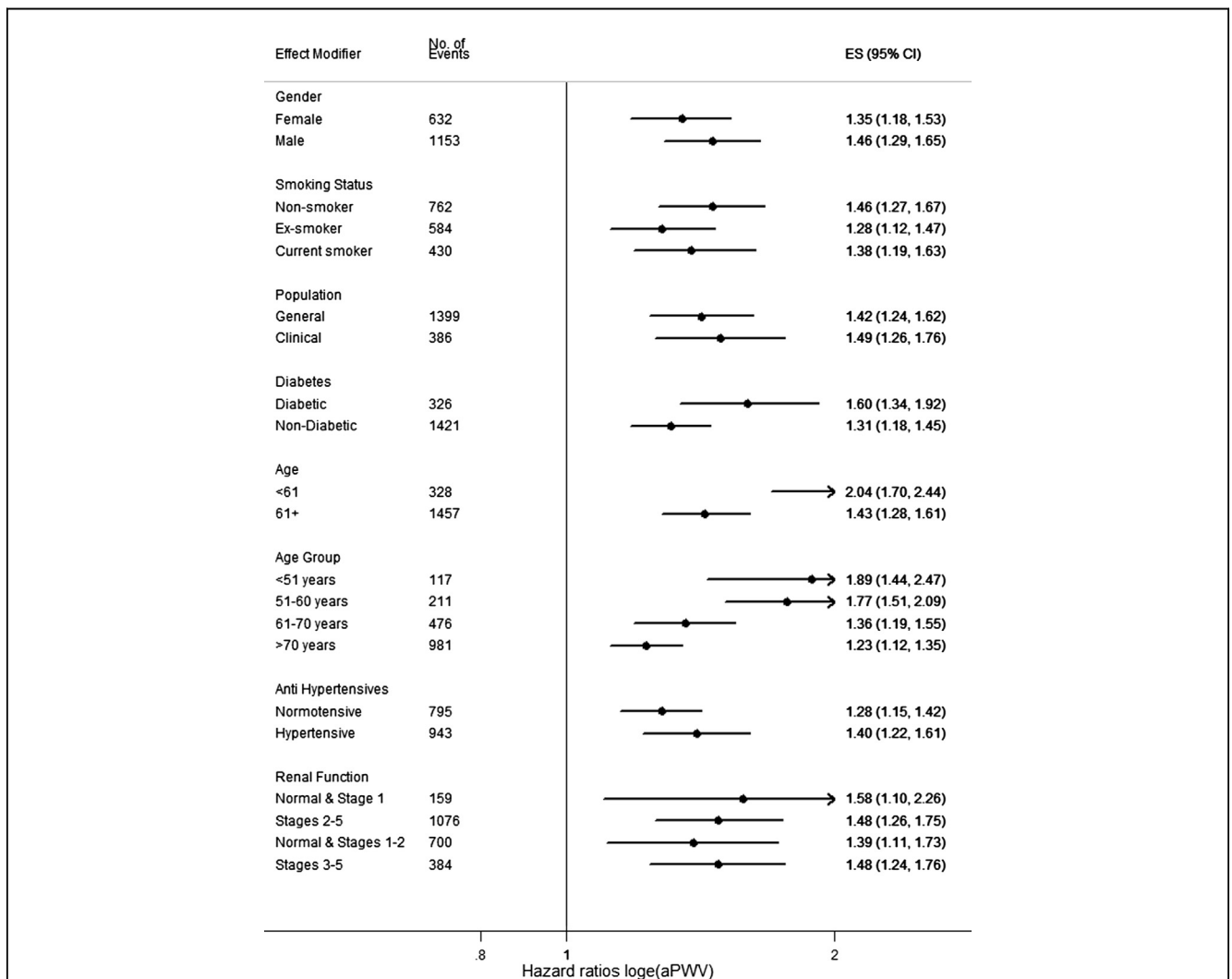


aPWV was strongly associated with increased risk, although additional adjustment resulted in some attenuation. After adjusting for conventional risk factors, aPWV remained a predictor of coronary heart disease (1.23 [95% CI: 1.11 to 1.35];  $p < 0.001$ ), stroke (1.28 [95% CI: 1.16 to 1.42];  $p < 0.001$ ), and CVD events (1.30 [95% CI: 1.18 to 1.43];  $p < 0.001$ ). The study-specific HRs of combined cardiovascular events for aPWV together with the pooled estimate are shown in Figure 2A, adjusted for age and sex, and in Figure 2B, fully-adjusted for all risk factors. Funnel plots and formal Egger tests fitted to estimates from the simple age- and sex-adjusted models indicated limited problems of small study effects, with any differences likely due to some studies having limited numbers of events. There were no overly influential studies.

There was no evidence that the increased risk associated with aPWV was modified by sex, population type, smoking

status, renal function, baseline diabetes, or antihypertensive use. However, aPWV was more strongly related to the risk of CHD ( $p_{\text{interaction}} = 0.001$ ) and stroke ( $p_{\text{interaction}} = 0.004$ ) in younger participants. For example, the hazard ratios decreased with age (1.89, 1.77, 1.36, and 1.23 for 50, 51 to 60, 61 to 70, and >70 years, respectively, for CVD events;  $p_{\text{interaction}} < 0.001$ ). This age effect remained in the fully adjusted models for both CHD and cardiovascular events ( $p = 0.006$  and  $p = 0.03$ , respectively). The results of subgroup analyses for combined cardiovascular events are shown in Figure 3 and in Online Figures 2A to 2D for other outcomes.

Results from the sensitivity analyses that used inverse aPWV and the untransformed aPWV did not materially differ from those using  $\log_e$  aPWV (data not shown). We found that the models that used pulse pressure rather than systolic blood pressure were essentially the same, although



**Figure 3** Forest Plot for aPWV With Cardiovascular Events According to Pre-Specified Subgroups

$\log_e$  aPWV is shown. Data are adjusted for age and sex where applicable. Data from the Baltimore Longitudinal Study of Aging were excluded because there were too few events. Abbreviations as in Figure 2.

the HRs were attenuated for stroke (data not shown) but with clearly overlapping 95% CIs. A change in aPWV of 1 m/s (weighted mean  $10.1 \pm 3.3$  m/s) was associated with an HR for cardiovascular events of 1.07 (95% CI: 1.02 to 1.12) for a male age 60 years who was a nonsmoker, not diabetic, not on any blood pressure medication, and with systolic blood pressure of 120 mm Hg, total cholesterol of 5.5 mmol/l, and high-density lipoprotein cholesterol of 1.3 mmol/l. We found that the fully adjusted HRs were slightly attenuated in the models that were restricted to the studies with a full set of covariate data (data not shown).

The discrimination and reclassification statistics calculated to assess improvement in 5-year risk prediction associated with the inclusion of  $\log_e$  aPWV in models are shown in Table 2. Small differences in C and D statistics and integrated discrimination improvement indicated modest improvement in risk prediction when  $\log_e$  aPWV was added to conventional Framingham risk factors. The integrated discrimination improvement presented evidence of improvements in discrimination for all outcomes when including  $\log_e$  aPWV in the models. However, calculation of the net reclassification improvement for each outcome indicated improvements in reclassification that have some clinical relevance, especially for those at intermediate risk (Table 3).

The net reclassification index for 10-year predicted risk was slightly lower than that for 5-year risk, which may be due to the attenuation of the accuracy of predictions with increasing extrapolation beyond the actual period of observation. We did not find any evidence that any of the results for our various outcomes differed either by the method used to define the distance over which aPWV was calculated or whether the study populations came from the Far East versus Europe or North America. Online Appendix 3 presents results from the sensitivity analysis.

## Discussion

The main finding of the current study is that aortic stiffness, assessed by measurement of aPWV, can predict future cardiovascular events and mortality, even after accounting for other established cardiovascular risk factors. The predictive value of aPWV was stronger in younger versus older subjects but was not modified by hypertension, smoking, sex, diabetes, or kidney disease. Addition of aPWV into risk prediction models also increased the number of participants who were correctly classified, particularly among younger individuals at intermediate risk, and it improved the overall 10-year classification by 13%.

The optimal approach to cardiovascular disease screening and risk stratification remains controversial, with some favoring a strategy based on targeting high-risk individuals (38) and others arguing for a population-based approach (39). The former strategy focuses on measuring traditional risk factors, and the relative cost-effectiveness of such an approach has not been assessed in clinical practice (38).

**Table 2** Improvement in Discrimination and Reclassification of 5-Year Risk Prediction With the Inclusion of  $\log_e$  aPWV as a Risk Factor

	C-Index*			D Measure*			Event Numbers	IDI
	Without $\log_e$ aPWV†	With $\log_e$ aPWV	Change (95% CI) p =	Without $\log_e$ aPWV†	With $\log_e$ aPWV	Change (95% CI) p =		
All-cause mortality	0.7012 (0.6897 to 0.7127)	0.7057 (0.6942 to 0.7172)	0.0046 (0.0010 to 0.0082) p = 0.013	1.2176 (1.1436 to 1.2915)	1.2552 (1.1809 to 1.3292)	0.0375 (-0.0672 to 0.1422) p = 0.483	1,023	0.00589 (0.0033 to 0.0085)
CVD mortality	0.7476 (0.7252 to 0.7699)	0.7566 (0.7342 to 0.7790)	0.0098 (-0.0010 to 0.0207) p = 0.076	1.5031 (1.3341 to 1.6722)	1.7043 (1.4708 to 1.9379)	0.2012 (-0.0871 to 0.4895) p = 0.171	219	0.00632 (0.0024 to 0.0103)
CHD events	0.6780 (0.6630 to 0.6929)	0.6832 (0.6685 to 0.6980)	0.0053 (0.0013 to 0.0093) p = 0.010	1.0734 (0.9777 to 1.1691)	1.1147 (1.0183 to 1.2111)	0.0413 (-0.0945 to 0.1771) p = 0.551	730	0.00366 (0.0010 to 0.0063)
CVD events	0.6797 (0.6669 to 0.6923)	0.6848 (0.6721 to 0.6976)	0.0052 (0.0011 to 0.0092) p = 0.013	1.1436 (1.0649 to 1.2222)	1.1965 (1.1174 to 1.2756)	0.0529 (-0.0586 to 0.1645) p = 0.352	1,060	0.00797 (0.0047 to 0.0112)
Stroke events	0.7243 (0.7054 to 0.7433)	0.7315 (0.7123 to 0.7508)	0.0072 (-0.0003 to 0.0147) p = 0.059	1.3649 (1.2314 to 1.4985)	1.4171 (1.2848 to 1.5494)	0.0522 (-0.1358 to 0.2401) p = 0.587	315	0.00954 (0.0042 to 0.0149)

\*Harrell's C-index and Royston and Sauerbrei's D measure. †Clinical model includes systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, smoking status, diabetes, and antihypertensive medication status. Event numbers for the integrated discrimination improvement (IDI) are reduced due to individuals with no event within 5 years being censored at this point. Abbreviations as in Table 1.

**Table 3**

**Net Reclassification Statistics Showing Percent Change in 5-Year Risk Prediction (and 5- and 10-Year Overall Reclassification) Associated With Including  $\log_e$  aPWV as a Risk Factor in the Fully-Adjusted Model**

	Controls (Event = 0)				Cases (Event = 1)				5-Year Overall Reclassification*	10-Year Overall Reclassification*
	Whole Sample	Clinical Population	General Population	Age ≤61 Yrs	Whole Sample	Clinical Population	General Population	Age ≤61 Yrs		
<b>Whole sample</b>										
All-cause mortality	0.66 (14,125)	1.11 (4,703)	0.44 (9,422)	-0.17 (7,011)	4.30 (1,023)	3.37 (356)	4.80 (667)	4.08 (147)	4.96 (4.11–5.81) (15,148)	1.73 (0.87–2.59) (12,837)
CVD mortality	3.95 (9,275)	0.99 (2,618)	5.11 (6,657)	1.43 (3,975)	8.22 (219)	10.45 (67)	7.24 (152)	16.00 (25)	12.17 (10.68–13.66) (9,494)	8.34 (7.17–9.51) (10,271)
CHD events	0.28 (14,158)	3.05 (3,212)	-0.54 (10,946)	-0.84 (7,158)	4.66 (730)	7.55 (212)	3.47 (518)	8.77 (114)	4.94 (4.00–5.88) (14,888)	3.03 (2.24–3.82) (12,503)
CVD events	0.28 (13,828)	3.06 (3,104)	-0.52 (10,724)	-0.72 (7,092)	5.09 (1,060)	5.31 (320)	5.00 (740)	10.56 (180)	5.37 (4.38–6.36) (14,888)	4.43 (3.53–5.33) (12,503)
Stroke events	-0.04 (13,397)	0.33 (2,142)	-0.12 (11,255)	-0.73 (6,407)	9.52 (315)	8.49 (106)	10.05 (209)	13.79 (58)	9.48 (8.36–10.60) (13,712)	5.60 (4.39–6.81) (10,465)
<b>Intermediate-risk only (quartiles 2 and 3)</b>										
All-cause mortality	5.49 (3,933)	7.69 (1,053)	4.69 (2,880)	9.92 (393)	9.18 (512)	10.67 (178)	8.38 (334)	0 (31)	14.67 (12.63–16.71) (4,445)	6.14 (4.05–8.23) (3,970)
CVD mortality	11.68 (1,970)	15.72 (439)	10.52 (1,631)	17.86 (84)	11.43 (105)	13.33 (30)	10.67 (75)	37.50 (8)	27.17 (29.61–37.73) (2,075)	24.27 (20.65–27.89) (2,164)
CHD events	6.85 (3,929)	13.80 (1,196)	3.81 (2,733)	9.26 (994)	7.92 (366)	7.48 (107)	8.11 (259)	0 (50)	14.77 (12.41–17.13) (4,295)	9.69 (7.61–11.77) (3,346)
CVD events	5.99 (3,774)	15.65 (1,061)	2.21 (2,713)	7.72 (868)	7.97 (527)	4.43 (158)	9.49 (369)	7.25 (69)	13.96 (11.41–16.51) (4,301)	13.05 (10.69–15.41) (3,473)
Stroke events	5.80 (3,740)	8.66 (693)	5.15 (3,047)	8.66 (658)	13.38 (157)	11.32 (53)	14.42 (104)	20.83 (24)	19.18 (16.38–21.98) (3,897)	10.89 (7.97–13.81) (3,141)

Values are risk factor (sample n) unless otherwise indicated. Results shown for the whole sample and those at intermediate risk. \*Values are NRI (95% CI) (n).

NRI = net reclassification index; other abbreviations as in Table 1.

Novel biomarkers may improve risk stratification. However, when these potential biomarkers have been entered into risk prediction models, such as Framingham, they do not seem to improve risk prediction very much beyond that already provided by established risk factors such as blood pressure, blood glucose, and cholesterol. Interest has also focused on markers of tissue or end-organ damage such as carotid intima-media thickness, which has been included in European Society of Hypertension and European Society of Cardiology guidelines (40). However, despite the recommendation in published guidelines, carotid intima-media thickness is rarely measured in routine clinical practice, and its utility remains controversial (3,41,42).

During the last 10 years, a large amount of evidence has accumulated demonstrating that arterial stiffness is an important risk factor for cardiovascular disease. Aortic stiffness can be assessed in a number of ways, but aPWV is regarded as the current gold standard (9) and has the most evidence available linking it to cardiovascular risk. aPWV can be assessed in a routine clinical setting by using

a number of commercially available devices, making it a potentially attractive cardiovascular biomarker. Indeed, assessment of arterial stiffness is included in the latest European Society of Hypertension/European Society of Cardiology guidelines (40), but the American College of Cardiology Foundation and the American Heart Association felt that there was insufficient evidence to recommend measures of arterial stiffness for asymptomatic individuals (43).

Our results confirm those of a previous summary meta-analysis (10) that aPWV predicts future fatal and nonfatal cardiovascular events. We have greatly extended this finding with the addition of new data, the ability to examine important subgroups, and by specifically calculating the prognostic value of aPWV beyond established risk factors. After full adjustment, a 1 m/s increase in aPWV was associated with a 7% increased risk of a cardiovascular events for a 60-year-old man (nonsmoker, not diabetic, not on any blood pressure medication, and with systolic blood pressure of 120 mm Hg, total cholesterol of 5.5 mmol/l, and high-density lipoprotein



cholesterol of 1.3 mmol/l). We have shown that aPWV was a stronger risk factor among younger individuals, although it was still predictive in older individuals. This finding may be because individuals with stiff aortae who are susceptible to cardiovascular disease die younger (“healthy survivor effect”), other risk factors attenuate the effects of aPWV at older ages, and/or systolic pressure is a better surrogate of aortic stiffness in older people than in younger people; therefore, including aPWV in models already containing systolic pressure would be expected to add less predictive value. Indeed, the age-related rise in systolic pressure, and development of isolated systolic hypertension, closely mirrors the age-related rise in aPWV (7,44). Conversely, systolic hypertension in younger individuals seems to be driven predominantly by an elevated cardiac output and stroke volume; as such, systolic or pulse pressure is a poor surrogate for stiffness in the young (45).

Addition of aPWV to the adjusted cardiovascular prediction models only increased the C and D statistics to a modest degree, suggesting that aPWV may not add much to standard risk equations when all participants are analyzed together. However, they are relatively insensitive methods for assessing the potential value of new biomarkers and do not specifically focus on individuals in whom better risk prediction is likely to make an important clinical difference (i.e., those who are at moderate or intermediate risk) (46). Indeed, many current guidelines advocate 10-year cardiovascular risk estimation and the targeting of therapy toward individuals whose estimated risk exceeds a particular threshold. However, refining estimation in those at high or low risk is unlikely to alter management or risk prevention in a substantial way. The performance of aPWV on the net reclassification improvement seems more clinically informative in terms of risk stratification for those at intermediate cardiovascular risk and in younger subjects. However, we have presented data on reclassifying subjects at both low (general population sample) and high (clinical sample) absolute risk for completeness.

Our results also suggest that aPWV may be a suitable target for novel risk reduction strategies. Although we did not investigate the pathophysiological mechanisms underlying cardiovascular disease, previous studies suggest that aPWV attenuation is associated with improved survival (47). The majority of existing drugs do not seem to lower aPWV in a blood pressure-independent manner, but long-term blockade of the renin-angiotensin system (48) and novel agents targeting elastic fiber cross-linking (49) or calcification may afford some benefit. However, these strategies need to be tested directly and remain speculative (50).

**Study limitations.** Almost all of the studies were from white patients or participants from the Far East, limiting the generalizability of these findings to other ethnic populations. A variety of different methods and devices were used to assess aPWV that are known to influence absolute values. However, we tried to minimize methodological

influence by calculating study-specific effects, and our analyses revealed no significant heterogeneity between studies or devices. A sensitivity analysis examining the method used to calculate the distance for the carotid-femoral path failed to find any evidence of heterogeneity. Because we extrapolated the results from some short-term studies to predict 10-year risk, these results should be treated with some caution given the limited long-term data. Our cardiovascular outcome measure was primarily based on myocardial infarction and stroke; therefore, the predictive value of aPWV on heart failure has not been explicitly examined. We tried to include all published studies, but 2 large studies were not included. However, our observations seem consistent with those reported in the excluded studies, and they benefit from a significantly larger sample size than any of the individually published studies. Recently, the Rotterdam study has published its own data on risk prediction (51) and showed a similar 9% reclassification of intermediate-risk group subjects. We were able to include data from several new studies, including 3 unpublished studies, 2 of which have published previous data on their aPWV measures (23,24). All of our estimates come from observational studies, and a previous meta-epidemiological study found that the effects of cardiovascular biomarkers were stronger in such studies compared with randomized controlled trials (52).

## Conclusions

aPWV predicts future cardiovascular risk and improves risk classification, adjusting for established risk factors. Because aPWV can now be reliably and easily measured (53), it may serve as a useful biomarker to improve cardiovascular risk prediction for patients at intermediate risk. However, before its adoption can be recommended, randomized controlled trials using aPWV to guide risk stratification and/or treatment are required to provide convincing evidence that this method has clinical value.

## Acknowledgments

The authors thank their colleagues at the MRC Biostatistics Unit, Cambridge, for their help in modifying the statistical programs they have developed for the Emerging Risk Factors Collaboration. They also thank the 2 anonymous reviewers for their helpful comments. Dr. Pannier wishes to acknowledge the Caisse Nationale d'Assurance Maladie (CNAM), the Caisse Primaire d'Assurance Maladie de Paris (CPAM-Paris), and the Institut National de la Santé et de la Recherche Médicale (INSERM), Paris.

---

**Reprint requests and correspondence:** Dr. Yoav Ben-Shlomo, School of Social and Community Medicine, 39 Whatley Road, Bristol BS8 2PS, United Kingdom. E-mail: [y.ben-shlomo@bristol.ac.uk](mailto:y.ben-shlomo@bristol.ac.uk).

---

## REFERENCES

1. Wang TJ, Gona P, Larson MG, et al. Multiple biomarkers for the prediction of first major cardiovascular events and death. *N Engl J Med* 2006;355:2631–9.
2. Ripatti S, Tikkanen E, Orho-Melander M, et al. A multilocus genetic risk score for coronary heart disease: case-control and prospective cohort analyses. *Lancet* 2010;376:1393–400.
3. Polak JF, Pencina MJ, Pencina KM, O'Donnell CJ, Wolf PA, D'Agostino RB Sr. Carotid-wall intima-media thickness and cardiovascular events. *N Engl J Med* 2011;365:213–21.
4. Danesh J, Wheeler JG, Hirschfeld GM, et al. C-reactive protein and other circulating markers of inflammation in the prediction of coronary heart disease. *N Engl J Med* 2004;350:1387–97.
5. Blacher J, Guerin AP, Pannier B, Marchais SJ, Safar M, London G. Impact of aortic stiffness on survival in end-stage renal disease. *Circulation* 1999;99:2434–9.
6. Laurent S, Boutouyrie P, Asmar R, et al. Aortic stiffness is an independent predictor of all-cause and cardiovascular mortality in hypertensive patients. *Hypertension* 2001;37:1236–41.
7. McEniery CM, Yasmin, Hall IR, Qasem A, Wilkinson IB, Cockcroft JR. Normal vascular ageing: differential effects on wave reflection and aortic pulse wave velocity: the Anglo-Cardiff Collaborative Trial (ACCT 1). *J Am Coll Cardiol* 2005;46:1753–60.
8. The Reference Values for Arterial Stiffness' Collaboration. Determinants of pulse wave velocity in healthy people and in the presence of cardiovascular risk factors: 'establishing normal and reference values.' *Eur Heart J* 2010;31:2338–50.
9. Laurent S, Cockcroft J, Van BL, et al. Expert consensus document on arterial stiffness: methodological issues and clinical applications. *Eur Heart J* 2006;27:2588–605.
10. Vlachopoulos C, Aznaouridis K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis. *J Am Coll Cardiol* 2010;55:1318–27.
11. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* 2009;339:b2535.
12. Thompson S, Kaptoge S, White I, Wood A, Perry P, Danesh J. Statistical methods for the time-to-event analysis of individual participant data from multiple epidemiological studies. *Int J Epidemiol* 2010;39:1345–59.
13. Royston P, Ambler G, Sauerbrei W. The use of fractional polynomials to model continuous risk variables in epidemiology. *Int J Epidemiol* 1999;28:964–74.
14. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med* 1999;130:461–70.
15. The Fibrinogen Studies Collaboration. Measures to assess the prognostic ability of the stratified Cox proportional hazards model. *Stat Med* 2009;28:389–411.
16. Pencina MJ, D'Agostino RB Sr., D'Agostino RB Jr., Vasan RS. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. *Stat Med* 2008;27:157–72;discussion 207–12.
17. Inoue N, Maeda R, Kawakami H, et al. Aortic pulse wave velocity predicts cardiovascular mortality in middle-aged and elderly Japanese men. *Circ J* 2009;73:549–53.
18. Nakano H, Okazaki K, Ajiro Y, Suzuki T, Oba K. Clinical usefulness of measuring pulse wave velocity in predicting cerebrovascular disease: evaluation from a cross-sectional and longitudinal follow-up study. *J Nihon Med Sch* 2001;68:490–7.
19. Blacher J, Safar ME, Guerin AP, Pannier B, Marchais SJ, London GM. Aortic pulse wave velocity index and mortality in end-stage renal disease. *Kidney Int* 2003;63:1852–60.
20. Meaume S, Benetos A, Henry OF, Rudnichi A, Safar ME. Aortic pulse wave velocity predicts cardiovascular mortality in subjects >70 years of age. *Arterioscler Thromb Vas Biol* 2001;21:2046–50.
21. Shoji T, Emoto M, Shinohara K, et al. Diabetes mellitus, aortic stiffness, and cardiovascular mortality in end-stage renal disease. *J Am Soc Nephrol* 2001;12:2117–24.
22. Mattace-Raso FU, van der Cammen TJ, Hofman A, et al. Arterial stiffness and risk of coronary heart disease and stroke: the Rotterdam Study. *Circulation* 2006;113:657–63.
23. McEniery CM, Spratt M, Munnerly M, et al. An analysis of prospective risk factors for aortic stiffness in men: 20-year follow-up from the Caerphilly Prospective Study. *Hypertension* 2010;56:36–43.
24. Najjar SS, Scuteri A, Shetty V, et al. Pulse wave velocity is an independent predictor of the longitudinal increase in systolic blood pressure and of incident hypertension in the Baltimore Longitudinal Study of Aging. *J Am Coll Cardiol* 2008;51:1377–83.
25. Boutouyrie P, Tropeano AI, Asmar R, et al. Aortic stiffness is an independent predictor of primary coronary events in hypertensive patients: a longitudinal study. *Hypertension* 2002;39:10–5.
26. Cruickshank K, Riste L, Anderson SG, Wright JS, Dunn G, Gosling RG. Aortic pulse-wave velocity and its relationship to mortality in diabetes and glucose intolerance: an integrated index of vascular function? *Circulation* 2002;106:2085–90.
27. Sutton-Tyrrell K, Najjar SS, Boudreau RM, et al. Elevated aortic pulse wave velocity, a marker of arterial stiffness, predicts cardiovascular events in well-functioning older adults. *Circulation* 2005;111:3384–90.
28. Shokawa T, Imazu M, Yamamoto H, et al. Pulse wave velocity predicts cardiovascular mortality: findings from the Hawaii-Los Angeles-Hiroshima study. *Circ J* 2005;69:259–64.
29. Willum-Hansen T, Staessen JA, Torp-Pedersen C, et al. Prognostic value of aortic pulse wave velocity as index of arterial stiffness in the general population. *Circulation* 2006;113:664–70.
30. Zoungas S, Cameron JD, Kerr PG, et al. Association of carotid intima-media thickness and indices of arterial stiffness with cardiovascular disease outcomes in CKD. *Am J Kidney Dis* 2007;50:622–30.
31. Terai M, Ohishi M, Ito N, et al. Comparison of arterial functional evaluations as a predictor of cardiovascular events in hypertensive patients: the Non-Invasive Atherosclerotic Evaluation in Hypertension (NOAH) study. *Hypertens Res* 2008;31:1135–45.
32. Wang KL, Cheng HM, Chuang SY, et al. Central or peripheral systolic or pulse pressure: which best relates to target organs and future mortality? *J Hypertens* 2009;27:461–7.
33. Mitchell GF, Hwang SJ, Vasan RS, et al. Arterial stiffness and cardiovascular events: the Framingham Heart Study. *Circulation* 2010;121:505–11.
34. Ilyas B, Dhaun N, Markie D, et al. Renal function is associated with arterial stiffness and predicts outcome in patients with coronary artery disease. *QJM* 2009;102:183–91.
35. Maldonado J, Pereira T, Polonia J, Silva JA, Morais J, Marques M. Arterial stiffness predicts cardiovascular outcome in a low-to-moderate cardiovascular risk population: the EDIVA (Estudo de Distensibilidade Vascular) project. *J Hypertens* 2011;29:669–75.
36. Verbeke F, Marechal C, Van Laecke S, et al. Aortic stiffness and central wave reflections predict outcome in renal transplant recipients. *Hypertension* 2011;58:833–8.
37. Verbeke F, Van Biesen W, Honkanen E, et al. Prognostic value of aortic stiffness and calcification for cardiovascular events and mortality in dialysis patients: outcome of the Calcification Outcome in Renal Disease (CORD) study. *Clin J Am Soc Nephrol* 2011;6:153–9.
38. Khunti K, Walker N, Sattar N, Davies M. Unanswered questions over NHS health checks. *BMJ* 2011;342:c6312.
39. Hingorani AD, Hemingway H. How should we balance individual and population benefits of statins for preventing cardiovascular disease? *BMJ* 2011;342:c6244.
40. Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens* 2013;31:1281–357.
41. Lorenz MW, Schaefer C, Steinmetz H, Sitzer M. Is carotid intima media thickness useful for individual prediction of cardiovascular risk? Ten-year results from the Carotid Atherosclerosis Progression Study (CAPS). *Eur Heart J* 2010;31:2041–8.
42. Lorenz MW, Polak JF, Kavousi M, et al. Carotid intima-media thickness progression to predict cardiovascular events in the general population (the PROG-IMT collaborative project): a meta-analysis of individual participant data. *Lancet* 2012;379:2053–62.
43. Greenland P, Alpert JS, Beller GA, et al. 2010 ACCF/AHA guideline for assessment of cardiovascular risk in asymptomatic adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2010;56:e50–103.

44. Staessen J, Amery A, Fagard R. Isolated systolic hypertension in the elderly. *J Hypertens* 1990;8:393–405.
45. McEniery CM, Yasmin, Wallace S, et al. Increased stroke volume and aortic stiffness contribute to isolated systolic hypertension in young adults. *Hypertension* 2005;46:221–6.
46. Marti R, Parramon D, Garcia-Ortiz L, et al. Improving interMediAte risk management. MARK study. *BMC Cardiovasc Disord* 2011;11:61.
47. Guerin AP, Blacher J, Pannier B, Marchais SJ, Safar ME, London GM. Impact of aortic stiffness attenuation on survival of patients in end-stage renal failure. *Circulation* 2001;103:987–92.
48. Ong KT, Delorme S, Pannier B, et al. Aortic stiffness is reduced beyond blood pressure lowering by short-term and long-term antihypertensive treatment: a meta-analysis of individual data in 294 patients. *J Hypertens* 2011;29:1034–42.
49. Kass D, Shapiro EP, Kawaguchi M, et al. Improved arterial compliance by a novel advanced glycation end-product crosslink breaker. *Circulation* 2001;104:1464–70.
50. Laurent S, Briet M, Boutouyrie P. Arterial stiffness as surrogate end point: needed clinical trials. *Hypertension* 2012;60:518–22.
51. Verwoert GC, Elias-Smale SE, Rizopoulos D, et al. Does aortic stiffness improve the prediction of coronary heart disease in elderly? The Rotterdam Study. *J Human Hypertens* 2012;26:28–34.
52. Tzoulaki I, Siontis KC, Ioannidis JP. Prognostic effect size of cardiovascular biomarkers in datasets from observational studies versus randomised trials: meta-epidemiology study. *BMJ* 2011;343:d6829.
53. Hickson SS, Butlin M, Broad J, Avolio AP, Wilkinson IB, McEniery CM. Validity and repeatability of the Vicorder apparatus: a comparison with the SphygmoCor device. *Hypertens Res* 2009;32:1079–85.

---

**Key Words:** cardiovascular disease ■ meta-analysis ■ prognostic factor ■ pulse wave velocity.

 **APPENDIX**

**For supplemental tables, figures, and other materials on the study protocol, please see the online version of this article.**