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Aortic Pulse Wave Velocity Improves Cardiovascular Event Prediction

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

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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 ≤50, 51 to 60, 61 to 70, and >70 years, respectively; $p_{interaction} < 0.001$). 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

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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).

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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.

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

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 ± 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

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