Arterial Stiffness and Cardiovascular Events
The Framingham Heart Study

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Background—Various measures of arterial stiffness and wave reflection have been proposed as cardiovascular risk markers. Prior studies have not assessed relations of a comprehensive panel of stiffness measures to prognosis in the community.

Methods and Results—We used proportional hazards models to analyze first-onset major cardiovascular disease events (myocardial infarction, unstable angina, heart failure, or stroke) in relation to arterial stiffness (pulse wave velocity [PWV]), wave reflection (augmentation index, carotid-brachial pressure amplification), and central pulse pressure in 2232 participants (mean age, 63 years; 58% women) in the Framingham Heart Study. During median follow-up of 7.8 (range, 0.2 to 8.9) years, 151 of 2232 participants (6.8%) experienced an event. In multivariable models adjusted for age, sex, systolic blood pressure, use of antihypertensive therapy, total and high-density lipoprotein cholesterol concentrations, smoking, and presence of diabetes mellitus, higher aortic PWV was associated with a 48% increase in cardiovascular disease risk (95% confidence interval, 1.16 to 1.91 per SD; $P=0.002$). After PWV was added to a standard risk factor model, integrated discrimination improvement was 0.7% (95% confidence interval, 0.05% to 1.3%; $P<0.05$). In contrast, augmentation index, central pulse pressure, and pulse pressure amplification were not related to cardiovascular disease outcomes in multivariable models.

Conclusions—Higher aortic stiffness assessed by PWV is associated with increased risk for a first cardiovascular event. Aortic PWV improves risk prediction when added to standard risk factors and may represent a valuable biomarker of cardiovascular disease risk in the community. **(*Circulation*. 2010;121:505-511.)**

Key Words: aorta ■ arteries ■ cardiovascular diseases ■ epidemiology ■ risk factors

Numerous studies performed in the past decade have identified peripheral pulse pressure, an indirect but widely available measure of arterial stiffness, as a novel cardiovascular disease (CVD) risk factor, although the close correlation between systolic and pulse pressure hinders efforts to distinguish these 2 hemodynamic indices.[1–4] Interest has now shifted to more direct measures of arterial stiffness and central pulsatile hemodynamic load, such as carotid-femoral pulse wave velocity (PWV), central pulse pressure, and augmentation index.[5] Recent studies have demonstrated that carotid-femoral PWV, a direct measure of stiffness of the thoracic and abdominal aorta, is associated with higher CVD event rates in high-risk[6–9] and community-based samples.[10–12] However, several key questions remain. Studies that have evaluated PWV have not applied newer metrics of clinical utility, such as global model fit, discrimination, calibration, and reclassification in models that adjust for standard CVD risk factors. Furthermore, because the heart and brain are exposed to central rather than peripheral pulse pressure, which may differ, central pulse pressure or measures of wave reflection, such as carotid-brachial pressure amplification and augmentation index, may represent incremental or superior measures of vascular risk compared with peripheral pulse pressure or PWV.[13–17] To our knowledge, no prior community-based study has simultaneously compared the utility of PWV, central pulse pressure, and augmentation index for predicting cardiovascular risk. As a result, the relative contributions of these differing pulsatile hemodynamic measures to risk strat-

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ification in the community remain incompletely understood. The present analysis sought to clarify these questions.

Methods

Participants

The design and selection criteria for the Framingham original and offspring cohorts have been detailed previously.[18,19] Participants attending the seventh examination of the offspring cohort (n=3539; 1998–2001) or the 26th examination of the original cohort (n=310; 1999–2001) were eligible for the present investigation. Tonometry measurements were implemented beginning in February 1999 as described previously.[20] Participants were excluded from the present analysis for the following reasons: attended the visit before implementation of tonometry (n=879), bad or incomplete tonometry data (n=209), prior CVD (n=196), or missing covariate or follow-up information (n=333), resulting in a sample of 2232 participants (1299 [58%] women). All protocols were approved by Boston University Medical Center's institutional review board, and participants provided written informed consent.

Clinical Evaluation and Definitions

Medical history, physical examination, and ECG were performed routinely at each Framingham Heart Study examination.[18,19] Blood pressures represent the average of 2 auscultatory blood pressures obtained by the physician on seated participants at the time of each Framingham clinic examination with the use of a standardized measurement protocol. Peripheral pulse pressure was calculated as the difference between systolic and diastolic pressure. Body mass index was calculated by dividing weight in kilograms by the square of the height in meters. Criteria for diabetes mellitus were a fasting glucose level of ≥126 mg/dL (7.0 mmol/L) or use of medications used to treat hyperglycemia.

Outcomes

Major CVD events were defined as fatal or nonfatal myocardial infarction, unstable angina (prolonged ischemic episode with documented reversible ST-segment changes), heart failure, and ischemic or hemorrhagic stroke. Medical records were obtained for all hospitalizations and physician visits related to CVD during follow-up and were reviewed by a committee of 3 investigators; events were adjudicated following written guidelines. Criteria for these cardiovascular events have been described previously.[21,22] Follow-up evaluations were performed on data acquired through December 31, 2007.

Noninvasive Hemodynamic Data Acquisition

Participants were studied in the supine position after resting for ≈5 minutes. Supine brachial systolic and diastolic blood pressures were obtained with the use of an oscillometric device. Arterial tonometry with simultaneous ECG was obtained from brachial, radial, femoral, and carotid arteries with the use of a commercially available tonometer (SPT-301, Millar Instruments, Houston, Tex). All of the recordings were performed on the right side of the body. Transit distances were assessed by body surface measurements from the suprasternal notch to each pulse recording site. Tonometry and ECG data were digitized (1000 Hz) during the primary acquisition and transferred to the core laboratory (Cardiovascular Engineering, Inc, Norwood, Mass) for analyses that were performed blinded to clinical data.

Tonometry Data Analysis

Tonometry waveforms were signal averaged with the ECG R wave used as a fiducial point. Systolic and diastolic cuff blood pressures obtained at the time of the tonometry acquisition were used to calibrate the peak and trough of the signal-averaged brachial pressure waveform. Diastolic and integrated mean brachial pressures were used to calibrate carotid pressure tracings.[23] Calibrated carotid pressure was used as a surrogate for central pressure.[23] Central pulse pressure was defined as the difference between the peak and trough of the calibrated carotid pressure waveform. Carotid-brachial pulse pressure amplification was defined as brachial pulse pressure divided by central pulse pressure. Augmentation index was computed from the carotid pressure waveform as described previously.[24] Carotid-femoral (aortic) and carotid-radial (muscular artery) PWV values were calculated from tonometry waveforms and body surface measurements, which were adjusted for parallel transmission in the brachiocephalic artery and aortic arch with the use of the suprasternal notch as a fiducial point.[25] The carotid-femoral transit path spans the aorta, making carotid-femoral PWV a measure of aortic stiffness. In contrast, the carotid-radial transit path spans the subclavian, brachial, and radial arteries, making carotid-radial PWV a measure of muscular artery stiffness.

Statistical Analysis

The primary goal of the analyses was to determine whether key pulsatile hemodynamic measures were individually or jointly associated with increased risk of a first major CVD event in a model that adjusted for standard CVD risk factors. Baseline characteristics for the entire study sample were tabulated. Aortic PWV was right skewed and was inverse transformed to normalize its variance.

We examined the association between pulsatile hemodynamic measures and time to first major CVD event by using Cox proportional hazards regression, after confirming that the assumption of proportionality was met. Covariates were selected on the basis of components of the Framingham Risk Score[26] and included the following at the baseline examination: age, sex, systolic blood pressure, use of antihypertensive therapy, total and high-density lipoprotein cholesterol concentrations, regular use of cigarettes in the prior year, and presence of diabetes mellitus.

Pulsatile hemodynamic variables that showed significant relations with events in multivariable Cox models were evaluated further to assess prognostic importance. Cumulative probability curves were constructed by using the Kaplan–Meier method, with participant groups segregated according to quartiles of the hemodynamic variable of interest. Predictive value was assessed by using the likelihood ratio test, the Akaike information criterion, and the Schwartz's Bayesian information criterion; the latter 2 tests carry a penalty for the number of variables used in the model and therefore can be compared directly across models with differing numbers of variables.[27] To assess discrimination of events, we compared the C statistic, which is analogous to the area under the receiver operating characteristic curve, for models with and without pulsatile hemodynamic variables included. We also computed net reclassification improvement and integrated discrimination improvement.[28] For the reclassification analysis, we did not use standard clinical cut points based on 10-year risk because we had only 7.8 years of follow-up. Instead, we computed predicted risk for all of the participants using a Cox model that included only the standard risk factors. Using predicted risk from this model, we defined cut points for risk groups based on quartiles of predicted risk in participants who experienced an event within 8 years, resulting in a uniform distribution of events across risk categories. We cross-classified categories of risk on the basis of a model that included standard risk factors against those based on a model that added individual pulsatile hemodynamic variables. Cross-classification was assessed separately in participants who did or did not experience an event. Integrated discrimination improvement is equivalent to the difference in discrimination slopes between new and old models and is analogous to reclassification; however, the calculation is based on continuous rather than empirically thresholded differences in predicted risk in new and old models in individual cases and controls. Thus, integrated discrimination improvement is free of the dependence on choice of risk categories that is inherent in reclassification tables and may be used as an objective indicator of reclassification improvement. To assess calibration, we used the Hosmer-Lemeshow test, which compares observed and predicted risk according to deciles of predicted risk for various models.

To determine whether relations between aortic PWV and CVD events were mediated in part by associated abnormalities in peripheral or central pulse pressure or wave reflection, we additionally adjusted the aortic PWV model for brachial pulse pressure, central pulse pressure, and pulse pressure amplification. To determine whether the relation between hemodynamic measures and CVD

Table 1. Baseline Characteristics of the Sample (n=2232)

Variable	Value
Clinical measures	
Age, y	63±12
Women, n (%)	1299 (58)
Height, cm	167±10
Weight, kg	75±16
Body mass index, kg/m^2	27.2±4.6
Blood pressure, mm Hg	
Systolic	127±20
Diastolic	74±10
Pulse	54±17
Heart rate, bpm	65±11
Total cholesterol, mg/dL	201±36
High-density lipoprotein cholesterol, mg/dL	56±17
Triglycerides, ln (mg/dL)	4.7±0.5
Hypertension treatment, n (%)	717 (32)
Diabetes mellitus, n (%)	179 (8)
Smoker, n (%)	278 (12)
Vascular measures	
Carotid-femoral PWV, m/s*	9.3 (7.8, 11.8)
Inverse carotid-femoral PWV, ms/m	107±31
Carotid-radial PWV, m/s	10.0±1.5
Central pulse pressure, mm Hg	52±17
Carotid-brachial amplification ratio	1.06±0.12
Augmentation index, %	15±13

Values are mean±SD except as noted.
*Median (25th, 75th percentiles).

events differed in older compared with younger participants (segregated by median age) or in men compared with women, we included interaction terms for these variables in separate models that also adjusted for standard risk factors. All of the analyses were performed with SAS version 9.1 (SAS, Cary, NC). A 2-sided $P<0.05$ was considered statistically significant.

Results

Baseline characteristics of the study sample are presented in Table 1. During a median follow-up period of 7.8 (range, 0.2 to 8.9) years, 151 of 2232 participants (6.8%; 77 women) had a first major CVD event composed of 57 fatal or nonfatal myocardial infarctions, 4 episodes of coronary insufficiency, 57 episodes of new heart failure, and 33 strokes.

Cox proportional hazards models for individual pulsatile hemodynamic measures are presented in Table 2. In models that adjusted for standard risk factors, carotid-femoral (aortic) PWV was associated with increased risk for a first major CVD event with a hazard ratio (HR) of 1.48 (95% confidence interval [CI], 1.16 to 1.91; $P=0.002$) per SD lower inverse carotid-femoral PWV, which corresponds to higher aortic PWV. In contrast, carotid-radial (muscular artery) PWV, augmentation index, central pulse pressure, and carotid-brachial pulse pressure amplification were not related to events in risk factor–adjusted models (Table 2). The relation between aortic PWV and events remained significant and essentially unaltered (HR, 1.47 to 1.49; $P<0.003$) when the

Table 2. Cox Proportional Hazards Models for Individual Pulsatile Hemodynamic Measures as Predictors of a Major Cardiovascular Event During the Follow-Up Period

Hemodynamic Measure	HR (LCI, UCI)	*P*
Carotid-femoral (aortic) PWV	1.48 (1.16, 1.91)	0.002
Carotid-radial (muscular artery) PWV	1.07 (0.92, 1.25)	0.77
Augmentation index	0.91 (0.77, 1.07)	0.24
Central pulse pressure	1.00 (0.99, 1.01)	0.98
Pulse pressure amplification	0.86 (0.19, 3.82)	0.84

LCI and UCI indicate lower and upper 95% CIs. HRs are expressed per 1 SD higher value, adjusted for age, sex, total cholesterol, high-density lipoprotein cholesterol, systolic blood pressure, smoking, diabetes mellitus, and hypertension treatment. For carotid-femoral PWV, the inverse transform was used, and results were expressed per 1 SD lower inverse values (which correspond to higher PWV).

model was further adjusted for brachial pulse pressure, central pulse pressure, or carotid-brachial pulse pressure amplification. There were no significant interactions between aortic PWV and median age ($P=0.31$), sex ($P=0.38$), or treatment for hypertension ($P=0.15$) when interaction terms were added to the risk factor–adjusted model. When the model including standard risk factors and aortic PWV was repeated after exclusion of 57 heart failure events, the relation between aortic PWV and events remained significant (HR, 1.95; 95% CI, 1.62 to 2.52; $P=0.015$).

When aortic PWV was added to a base model that included age and sex, measures of model performance improved to a degree that was comparable to adding the full set of standard risk factors to the base model (Table 3). When aortic PWV was added to the risk factor–adjusted model, model fit was improved, as indicated by reductions in log likelihood, the Akaike information criterion, and the Schwartz's Bayesian information criterion; however, the C statistic was unchanged (0.796 to 0.800; $P=0.3$). The Hosmer-Lemeshow test demonstrated excellent calibration (Table 3). Addition of aortic PWV to the standard model resulted in upward reclassification of 6.7% of participants who experienced a CVD event as well as upward reclassification of 1.2% of participants who did not experience an event, yielding an overall net reclassification of 5.5% ($P=0.15$; Table 4). For individuals at intermediate CVD risk (middle 2 quartiles), addition of aortic PWV resulted in upward reclassification of 14.3% of participants who experienced a CVD event and downward reclassification of 1.4% of participants who did not experience a CVD event, yielding a net reclassification of 15.7% ($P=0.03$; Table 4). In the full sample, when aortic PWV was added to the standard risk factor model, the discrimination slope increased from 7.8±12.6% to 8.5±13.3%, resulting in an integrated discrimination improvement of 0.7% (95% CI, 0.05% to 1.3%; $P<0.05$). In participants at intermediate risk, the discrimination slope increased from 1.8±4.5% to 2.7±6.2%, resulting in an integrated discrimination improvement of 0.8% (95% CI, 0.12% to 1.6%; $P=0.02$). Together these findings indicate that addition of aortic PWV to standard CVD risk factors improved model fit and resulted in a well-calibrated model with improved risk discrimination and risk reclassification.

The Figure displays the estimated cumulative incidence of major cardiovascular events. When participants were grouped

Table 3. Measures of Model Fit, Discrimination, and Calibration for Various Cardiovascular Event Models With and Without Carotid-Femoral (Aortic) PWV

	Model Fit			Discrimination	Calibration	
Model	−2 Log Likelihood	Akaike Information Criterion	Schwartz's Bayesian Information Criterion	C Statistic (95% CI)	χ^2	*P*
Age, sex	2155	2159	2165	0.762 (0.723–0.801)	8.7	0.46
Add PWV	2136	2142	2151	0.782 (0.746–0.818)*	2.9	0.97
Age, sex, total cholesterol, high-density lipoprotein cholesterol, systolic blood pressure, smoking, diabetes mellitus, and hypertension treatment	2126	2142	2166	0.796 (0.764–0.828)	4.3	0.89
Add PWV	2116	2134	2162	0.800 (0.768–0.832)†	2.6	0.98

For a description of the tests displayed in the table, please refer to Methods, Statistical Analysis.

*Comparison of C statistics in rows 1 and 2, $P=0.006$.

†Comparison of C statistics in rows 3 and 4, $P=0.3$.

according to quartiles of aortic PWV, the probability of developing a CVD event increased with aortic PWV group. When individuals in the highest (≥11.8 m/s) aortic PWV group are compared with those in the lowest (<7.8 m/s) aortic PWV group after adjustment for age, sex, and standard risk factors, individuals in the highest quartile had an adjusted HR of 3.4 (95% CI, 1.4 to 8.3; $P=0.008$).

Discussion

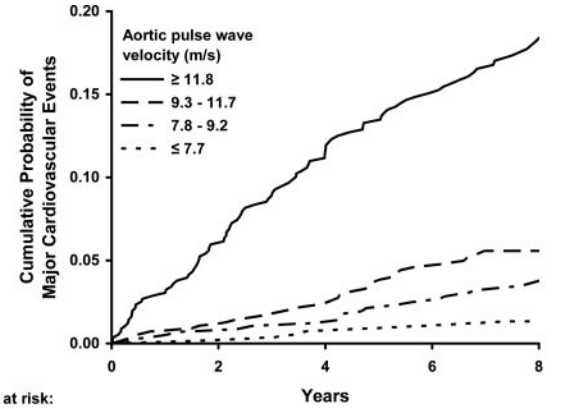
We evaluated relations between carotid-femoral (aortic) PWV, carotid-radial (muscular artery) PWV, central pulse pressure, augmentation index, and carotid-brachial pressure amplification and major CVD events in middle-aged and older participants in the community-based Framingham Heart Study. We demonstrated that per SD increase in carotid-femoral PWV, the adjusted risk of a first major CVD event was significantly increased (HR, 1.48; 95% CI, 1.16 to 1.91). Measures of model fit and discrimination were improved and calibration was extremely good when carotid-femoral PWV was added to standard risk factors. The association between carotid-femoral PWV and excess risk persisted after further adjustment for brachial or central pulse pressure or carotid-brachial pulse pressure amplification. In our community-based sample, carotid-radial (muscular artery) PWV, central pulse pressure, augmentation index, and carotid-brachial pressure amplification were not associated with risk for a major CVD event in models that included standard risk factors. Our results suggest that the adverse association between CVD outcomes and arterial stiffening, as assessed by increased PWV, may be specific to the aorta as opposed to large muscular arteries, like the brachial and radial arteries. Furthermore, we have shown for the first time that the relation between aortic PWV and events is distinguishable from excessive central pressure pulsatility or abnormal wave reflection.

Prior studies have shown that increased carotid-femoral PWV is associated with excess risk in various high-risk[6–9] and

Table 4. Predicted Risk for a CVD Event Before and After Reclassification With Carotid-Femoral (Aortic) PWV in Participants Who Did (A) or Did Not (B) Experience an Event Within 8 Years

	Model With PWV				
A	0%–5%	5%–11%	11%–16%	>16%	Total
Model without PWV					
0%–5%	31*	5	0	0	36
5%–11%	3	29*	3	0	35
11%–16%	0	3	19*	13	35
>16%	0	0	5	38*	43
Total	34	37	27	51	149
B	0%–5%	5%–11%	11%–16%	>16%	Total
Model without PWV					
0%–5%	1376*	51	0	0	1427
5%–11%	48	286*	40	3	377
11%–16%	1	37	55*	36	129
>16%	0	0	19	131*	150
Total	1425	374	114	170	2083

*These values along the diagonal were similarly classified by both models. Values on each row to the right of the value with an asterisk were upwardly classified, and those to the left were downwardly classified by the model that included PWV.



Number at risk: Aortic pulse wave velocity (m/s)					
≥ 11.8	560	513	462	424	161
9.3 - 11.7	555	542	529	502	246
7.8 - 9.2	573	561	551	537	278
≤ 7.7	544	541	535	531	275

Figure. Kaplan–Meier plot of cumulative probability of a first major CVD event when participants were grouped according to quartiles of carotid-femoral (aortic) PWV.

community-based samples.[10–12] In addition, several cross-sectional studies and a limited number of longitudinal studies have suggested that central systolic and pulse pressure and measures of wave reflection may provide incremental CVD risk stratification beyond that provided by standard risk factors including conventional blood pressure recorded in the arm.[5,13–17] Recently published international guidelines have suggested that PWV and central pressure may be useful as guides to therapy. The 2007 European guidelines for the management of hypertension and guidelines for CVD prevention in clinical practice added aortic PWV as a recommended test for assessment of target organ damage.[29,30] The European hypertension guidelines noted that central and peripheral pulse pressure can differ and suggested that central pulse pressure may be a better indicator of risk, although the authors underscored a need for additional prospective data in large-scale studies.[30] The present study extends prior work and clarifies the role of central and peripheral pulse pressure by demonstrating that the adverse effects of increased aortic PWV are not captured by assessing potentially related abnormalities in central or peripheral systolic or pulse pressure. Furthermore, we have shown that after accounting for standard risk factors, including conventional systolic blood pressure assessed in the arm, measures of central pulse pressure and wave reflection do not provide incremental CVD risk prediction in this community-based sample of middle-aged and older people.

In contrast to our findings, a number of prior studies have shown that central systolic and pulse pressure may be better predictors of CVD risk than peripheral values.[13–17] Differences between our study and prior studies may account for differences in findings. In 1 study, supine invasive central pulse pressure was obtained during clinically indicated cardiac catheterization and compared with seated sphygmomanometric peripheral pulse pressure.[17] Thus, the difference in predictive power between central (invasive) and peripheral (noninvasive) pulse pressure in that study may relate to differences in technique. Prior studies have assumed that brachial systolic and diastolic pressures could be applied to the peak and trough of a radial waveform to assess mean arterial pressure, which is required to calibrate the carotid pressure waveform.[14,15] Subsequent work has shown that the implicit assumption of no amplification between brachial and radial arteries is incorrect and confounds the assessment of central pulse pressure.[31] Another study used estimated mean pressure to calibrate a central pressure waveform obtained by using a generalized transfer function[16]; a calibration procedure that uses estimated mean pressure introduces a variable, mean pressure–related error into the calibration of central pressure. In contrast to the foregoing studies, we measured carotid and brachial pressure waveforms directly, calibrated the brachial waveform to brachial cuff pressure, and integrated the calibrated waveform to derive an accurate assessment of mean arterial pressure.

Sample selection may have further contributed to differences in the predictive power of central versus peripheral pulse pressure and pressure amplification in prior studies compared with ours. Prior studies evaluated high-risk groups, including patients with known hypertension and other CVD risk factors,[15] suspected coronary artery disease resulting in cardiac catheterization,[17] and end-stage kidney disease.[14] Another study evaluated a predominantly female sample of American Indians with relatively high prevalences of obesity, diabetes mellitus, and hypertension and an unusually high event rate (13.3% during 4.7 years of follow-up compared with 6.8% during 7.8 years of follow-up in our study).[16] In contrast to the foregoing studies, our panel of stiffness measures was routinely ascertained in an unselected, community-based sample.

The inability of central pulse pressure and measures of wave reflection to provide incremental risk stratification beyond that provided by standard CVD risk factors should be interpreted in light of the strong correlation between central and peripheral systolic and pulse pressure in middle-aged and older adults who are at highest risk for CVD events. To minimize the effects of correlation between central and peripheral pressures, we also evaluated carotid-brachial pressure amplification, which assesses only the relative discrepancy between central and peripheral pulse pressure, and again found no independent relation with events. Our findings suggest that when considered in the context of the broad distribution of values for peripheral systolic and pulse pressure found in middle-aged and older people, knowledge of the modest difference between central and peripheral pulse pressure may not contribute substantively to CVD risk prediction in a sample such as ours. Inability of measures of wave reflection, such as augmentation index, to predict CVD outcomes may relate to the observation that augmentation index and wave reflection are confounded by many factors, including several paradoxical associations between lower augmentation and higher CVD risk factor burden. We have previously shown that with advancing age, the normally compliant aorta stiffens markedly, whereas the relatively stiff muscular arteries remain unchanged. As the properties of the aorta and peripheral muscular arteries become more similar, wave reflection at this interface is reduced and shifted to more distal sites in the arterial system. This "impedance matching" between aorta and large muscular arteries may limit or delay global wave reflection despite the increase in aortic PWV and may thereby facilitate increased transmission of potentially harmful pulsatile energy into the microcirculation.[25,32] Thus, the hypothesis that increas-

ing aortic stiffness should result in progressively premature wave reflection and increasing augmentation, rendering augmentation index a suitable marker for aortic stiffening and associated increased risk, was not evident in our community-based sample.

Several limitations of our study should be considered. We acknowledge that an observational study cannot definitively prove that there is a causal link underlying the association between increased carotid-femoral PWV and increased CVD events. We cannot rule out residual confounding by duration or severity of associated risk factors or unknown risk factors. Furthermore, we had only a modest number of events, and therefore we lacked power to examine threshold models or to analyze specific types of CVD events. In addition, we cannot exclude the possibility that with more follow-up or a larger sample, other vascular measures may have been related to CVD events. We evaluated a middle-aged and older cohort of predominately white study participants, therefore, our results may not be generalizable to younger individuals and other ethnicities. Although carotid-femoral PWV is considered the gold standard measure of aortic stiffness, there are limitations to the measurement. The assessment of transit distance is approximate because of parallel transmission in the aortic arch. In addition, the arterial segment interrogated includes aorta and iliac and femoral arteries, whose properties may change differently with age and risk factor exposure. More specific measures of aortic stiffness may provide superior CVD risk assessment. Strengths of our study include a large, community-based sample with routinely ascertained risk factors and a comprehensive battery of measures of arterial stiffness and wave reflection.

Measurement of PWV is noninvasive, safe, and readily implemented in an office setting with relatively inexpensive equipment and modest training, suggesting that attention should be focused on aortic PWV as a potential novel biomarker of cardiovascular risk. Aortic PWV is strongly associated with CVD risk, is abnormal in a substantial proportion of middle-aged and older people, and is only modestly correlated with standard risk factors, which are desirable attributes of a potential biomarker.[33] Biological correlates and clinical interpretation of aortic PWV values are straightforward in that higher values are directly attributable to excessive aortic wall stiffness and are associated with increasing risk for CVD. In addition, aortic PWV is modifiable, particularly after interventions that target sodium balance (salt restriction, low-dose diuretics) or block the renin-angiotensin system. Reductions in PWV of $\geq$1 m/s are achievable after such interventions even when assessed after a relatively short duration in many studies.[34–37] This magnitude of change could translate into a substantial reduction in CVD risk. Importantly, we have shown previously that the prevalence of elevated aortic PWV increases markedly between 50 and 70 years of age, from a few percent before 50 years of age to nearly 70% after 70 years of age.[20] The combination of aging of the world population, a marked increase in the prevalence of abnormal aortic PWV with age, and a strong relation between aortic PWV and events portends a major increase in the burden of disease potentially attributable to abnormal aortic stiffness. These observations suggest a need to identify and implement effective interventions that limit or reverse arterial stiffening in older people.

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Disclosures

Dr Mitchell is owner of Cardiovascular Engineering, Inc, a company that designs and manufactures devices that measure vascular stiffness. The company uses these devices in clinical trials that evaluate the effects of diseases and interventions on vascular stiffness. The other authors report no conflicts.

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CLINICAL PERSPECTIVE

Various measures of arterial stiffness and wave reflection have been proposed as cardiovascular risk markers; however, no community-based study has compared prognostic utility of pulse wave velocity (PWV), central pulse pressure, and augmentation index. In our study of 2232 Framingham Heart Study participants, after adjustment for risk factors (age, sex, systolic blood pressure, use of antihypertensive therapy, total and high-density lipoprotein cholesterol concentrations, smoking, and presence of diabetes mellitus), a SD increase in carotid-femoral (aortic) PWV was associated with a 48% increase in risk for a first major cardiovascular disease event. Measures of model fit and discrimination were improved when carotid-femoral PWV was added to standard risk factors. In contrast, carotid-radial (muscular artery) PWV, augmentation index, central pulse pressure, and carotid-brachial pulse pressure amplification were not related to events in risk factor–adjusted models. Measurement of PWV is noninvasive, safe, and readily implemented in an office setting with inexpensive equipment and a modest amount of training. Aortic PWV is strongly associated with risk, is abnormal in a substantial proportion of middle-aged and older people, and is only modestly correlated with standard risk factors, suggesting that attention should be focused on aortic PWV as a biomarker of cardiovascular risk. The combination of aging of the world population, increasing aortic PWV with age, and increased risk with higher aortic PWV portends a major increase in the burden of disease potentially attributable to abnormal aortic stiffness. These observations suggest a need to identify and implement interventions that limit or reverse arterial stiffening.