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AORTIC-BRACHIAL ARTERIAL STIFFNESS GRADIENT AND CARDIOVASCULAR RISK IN THE COMMUNITY: THE FRAMINGHAM HEART STUDY

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Abstract

A recent study reported that the aortic-brachial arterial stiffness gradient, defined as carotid-radial/carotid-femoral pulse wave velocity (PWV ratio), predicts all-cause mortality better than carotid-femoral pulse wave velocity (CFPWV) alone in dialysis patients. However, the prognostic significance of PWV ratio for cardiovascular disease (CVD) in the community remains unclear. Accordingly, we assessed the correlates and prognostic value of the PWV ratio in 2114 Framingham Heart Study participants (60±10 years; 56% women) free of overt CVD. Mean PWV ratio decreased from 1.36±0.19 in participants aged <40 years to 0.73±0.21 in those aged ≥80

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Disclosures

Gary F. 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 remaining authors report no conflicts.

years. In multivariable linear regression, older age, male sex, higher BMI, diabetes, lower HDL cholesterol, higher mean arterial pressure, and higher heart rate were associated with lower PWV ratio (P<0.001 for all). During a median follow-up of 12.6 years, 248 first CVD events occurred. In Cox regression models adjusted for standard CVD risk factors, 1-SD changes in CFPWV (hazard ratio 1.33, 95% confidence interval 1.10–1.61) and PWV ratio (hazard ratio 1.32, 95% confidence interval 1.09–1.59) were associated with similar CVD risks. Models that included conventional CVD risk factors plus CFPWV or PWV ratio gave the same c-statistics (c=0.783). Although PWV ratio has been reported to provide incremental predictive value over CFPWV in dialysis patients, we could not replicate these findings in our community-based sample. Our findings suggest that the prognostic significance of PWV ratio may vary based on baseline CVD risk, and CFPWV should remain the criterion standard for assessing vascular stiffness in the community.

Keywords

Cardiovascular Disease; Epidemiology; Risk Factors; Hypertension; High Blood Pressure; Arterial Stiffness

Introduction

Under physiological conditions, the arterial vasculature is characterized by a progressive increase in stiffness from the aorta and large elastic arteries towards the peripheral muscular conduit arteries, often labeled as the arterial stiffness gradient.[1, 2] However, this gradient is not by any means invariable as stiffness of the aorta tends to increase with age, whereas the relationship between peripheral muscular arteries and advancing age is not as pronounced.[1, 3–5] In fact, upper limb muscular artery compliance may even decrease with age in women and in individuals with diabetes.[6, 7] Age-related changes in vasculature thereby result in a reduction, or even a reversal of the physiological arterial stiffness gradient in most individuals.[1, 5]

Increased aortic stiffness, most commonly measured as the carotid-femoral pulse wave velocity (CFPWV), is a strong predictor of cardiovascular disease (CVD) both in patient and population-based cohorts.[8–11] In contrast, it is unclear if muscular conduit artery stiffness, often measured in the arm as the carotid-radial pulse wave velocity (CRPWV), is associated with cardiovascular morbidity.[2, 12–14] Although CRPWV has been largely overshadowed in research and clinical practice by CFPWV because of its limited prognostic value, recent research suggests that CRPWV may, after all, also have an important role in CVD risk prediction. Specifically, a recent study by Fortier and colleagues reported that an increased aortic-brachial arterial stiffness gradient (defined as the ratio of CFPWV and CRPWV) was a better predictor of all-cause mortality than CFPWV per se.[14]

Fortier et al. and the authors of an accompanying editorial speculated that the finding of a clinically significant interaction between elastic and muscular arteries could open a new area for future research, and both agreed that the role of the arterial stiffness gradient as a cardiovascular risk factor needs validation in the community.[14, 15] Therefore, we evaluated if the aortic-brachial arterial stiffness gradient incrementally predicts CVD beyond

conventional CFPWV in community-dwelling participants in the Framingham Heart Study Offspring cohort.

Methods

Participants

The Framingham Heart Study Offspring cohort consists of the children of individuals in the Original Framingham cohort, along with their spouses.[16] The baseline characteristics and more detailed study protocol for the Framingham Offspring cohort have been previously published.[16] We included participants who attended the seventh examination cycle of the Framingham Offspring cohort (n=3539; 1998–2001) in the present investigation. Due to a delayed start, tonometry measurements were implemented in 2660 of 3539 participants during the study cycle beginning in February 1999. We excluded participants who had incomplete tonometry data (n=372) or prevalent CVD (n=174) from the present analysis resulting in a final study sample of 2114 participants. The study was conducted according to the Declaration of Helsinki. All study protocols were reviewed and approved by Boston University Medical Center's Institutional Review Board, and participants provided written informed consent.

Clinical Evaluation and Definitions

The participants provided medical history and underwent physical examination and assessment of CVD risk factors.[16] The participants were using their normal CVD medications at the time of PWV measurements. We assessed participants for self-reported cigarette use in the year preceding the examination and diabetes mellitus (fasting glucose level of ≥126 mg/dL or the use of hypoglycemic medications). In addition, we measured blood pressure (mean of 2 auscultatory values measured by a physician with a mercury column sphygmomanometer on seated participants using a standardized protocol), body mass index, serum total cholesterol levels, and high-density lipoprotein (HDL) cholesterol concentrations. Sitting blood pressure was measured approximately 30–180 minutes before tonometry. We derived heart rate from a 10 second 12-lead ECG recording.

CFPWV, CRPWV and PWV ratio

Arterial tonometry measures with simultaneous ECG recording were acquired from the radial, femoral, and carotid arteries after more than 5 minutes of rest in the supine position, as described previously.[17, 18] All recordings were performed on the right side of the body. Transit distances were estimated by measuring the body surface distance from the suprasternal notch to each pulse recording site. CFPWV and CRPWV 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. We also derived supine mean arterial pressure from integration of the brachial waveform calibrated with oscillometric blood pressure at the time of tonometry. We inverted CFPWV to reduce heteroscedasticity and multiplied by −1 to restore directionality of the association. CRPWV was normally distributed and therefore included in the models without transformation. We defined the aortic-brachial arterial stiffness gradient as a PWV ratio, i.e., CRPWV divided by CFPWV. This approach underscores the youthful

design of the arterial system, i.e., arterial stiffness should normally increase when moving distally in the arterial system. We used the skewed variable as the denominator, which resulted in a normal distribution for PWV ratio.

Outcomes

The primary outcome was incidence of major CVD disease events, a composite endpoint of cardiovascular death, fatal or nonfatal myocardial infarction, unstable angina (prolonged ischemic episode with documented reversible ST-segment changes), stroke, and heart failure. Medical records were obtained for all hospitalizations and physician visits related to CVD disease during follow-up and were reviewed by an adjudication panel consisting of 3 investigators. Criteria for these CVD events have been described previously.[19]

Statistical Methods

We used sex- and 5-year age-specific medians as cutoff points to define high and low PWV. We assessed baseline characteristics in groups cross-classified by high/low CFPWV and CRPWV. We chose this approach to clarify if any potential relation between PWV ratio and CVD outcomes is driven by the numerator (CRPWV) versus the denominator (CFPWV) of the ratio. In addition, we opted to use age- and sex-specific cutoffs instead of a single cutoff because of the strong relationship between age and CFPWV to avoid categorizing individuals in a higher PWV category mainly based on their age. We compared pairwise differences in characteristics between the four groups using two sample t-tests and chi-squared tests. We applied Bonferroni correction on the pairwise comparisons to account for multiple testing. We examined correlates of PWV ratio using Pearson's correlation and linear regression. We included age, sex, body mass index, diabetes mellitus, smoking, serum total cholesterol, HDL cholesterol, mean arterial pressure (diastolic pressure + 1/3 × pulse pressure), and heart rate as the predictors. Continuous variables were standardized for comparability. We also assessed incidence of CVD events in groups cross-classified by high versus low CFPWV and CRPWV using cumulative incidence plots, log-rank tests, and multivariable-adjusted Cox models, with low CFPWV/high CRPWV as referent. We examined the relation of CFPWV, CRPWV, and PWV ratio as continuous variables with CVD outcomes using multivariable-adjusted Cox regression models. We calculated c-statistics for the models to assess model discrimination.[20] We adjusted all multivariable models for age, sex, body mass index, diabetes mellitus, smoking, serum total cholesterol, HDL cholesterol, mean arterial pressure, and heart rate. Further, we examined the relations of CFPWV, CRPWV, and PWV ratio with CVD outcomes in subgroups by sex, age, diabetes, antihypertensive therapy, and CFPWV level. Interactions between the continuous exposure variable and subgroup were tested by entering a product term into the models. A 2-sided value of $P<0.05$ was considered statistically significant. All analyses were performed with Stata software version 13.1 (StataCorp, College Station, Texas, USA).

Results

Characteristics for the overall study sample and in sub-groups cross-classified by high versus low CFPWV and CRPWV are reported in Table 1. In general, participants with high CFPWV had more adverse CVD risk profiles than those with low CFPWV. In turn, after

classification by CFPWV, individuals with high and low CRPWV had relatively similar CVD risk profiles. CFPWV increased whereas CRPWV remained fairly stable with older age (Figure 1). Consequently, PWV ratio was 1.36±0.19 in participants aged <40 years to 0.73±0.21 in those aged ≥80 years.

The correlation coefficient between CFPWV and CRPWV was 0.38 (P<0.001). Univariate and multivariable correlates of PWV ratio are reported in Table 2. In univariate analyses, all variables were associated with lower PWV ratio, except sex and serum total cholesterol. In multivariable linear regression with all variables included, older age, male sex, higher BMI, diabetes, lower HDL cholesterol, mean arterial pressure, and higher heart rate were associated with lower PWV ratio (P<0.001 for all). These variables explained 52% of variation in PWV ratio.

During follow-up (median 12.6 years), 248 first CVD events occurred. Figure 2 illustrates the cumulative incidence of CVD events in groups cross-classified by high versus low CFPWV and CRPWV.. The CVD incidence rates and both unadjusted and adjusted hazards ratios increased from low CFPWV to high CFPWV whereas further cross-classification by CRPWV had only a small effect on the hazard ratios (Table S1). Compared with individuals having low CFPWV and high CRPWV, multivariable-adjusted risk of CVD events was not significantly increased in participants having low CFPWV and low CRPWV (hazard ratio [HR] 1.19, 95% confidence interval [CI] 0.76–1.87). In turn, participants having high CFPWV and high CRPWV had a similar risk of CVD events (HR 1.61, 95% CI 1.04–2.47) compared with those having CFPWV and low CRPWV (HR 1.61, 95% CI 1.01–2.57).

When the prognostic significance of CFPWV, CRPWV, and PWV ratio were assessed as continuous variables, only CFPWV (HR 1.33 per 1-SD increase, 95% CI 1.10–1.61) and PWV ratio (HR 1.32 per 1-SD decrease, 95% CI 1.09–1.59), but not CRPWV CRPWV (HR 0.99 per 1-SD increase, 95% CI 0.86–1.13) reached statistical significance in multivariable-adjusted Cox models (Table 3). C-statistics of the models that included CFPWV or PWV ratio were the same (c=0.783). In a sensitivity analysis, we included supine mean arterial pressure derived from integration of the brachial waveform calibrated with blood pressure at the time of tonometry, instead of sitting auscultatory mean arterial pressure, in the models (Table S2). This did not materially change the results as the multivariable-adjusted HRs for CFPWV, CRPWV, and PWV ratio were 1.23 (95% CI, 1.01–1.51), 0.93 (95% CI, 0.81–1.08), and 1.27 (95% CI, 1.05–1.54), respectively. C-statistics for models with CFPWV or PWV ratio were 0.784. We also investigated if the prognostic significance of CFPWV, CRPWV, and PWV ratio differed between subgroups by sex, age, diabetes, antihypertensive therapy, and CFPWV level (Table 4). In these analyses, CRPWV was not significantly associated with CVD outcomes in any subgroup. The only significant interaction was observed for CFPWV and age (<70 years versus ≥70 years). In the subsample of 427 individuals aged ≥70 years with 109 incident cardiovascular events, the hazard ratios for CVD events per 1-SD increases in CFPWV and CRPWV, and per 1-SD decrease in PWV ratio were 1.39 (95% CI, 1.06–1.82), 0.90 (95% CI, 0.73–1.12), and 1.54 (95% CI, 1.16–2.04), respectively (Table 4).

Discussion

In our investigation, we demonstrated that the aortic-brachial arterial stiffness gradient, defined as the ratio between CRPWV and CFPWV, is significantly related to cardiovascular outcomes in the community. However, PWV ratio provides no incremental predictive value for CVD events over common cardiovascular risk factors and CFPWV. In our lower-risk community-dwelling population, we could not replicate the previous findings that underscored the prognostic importance of the PWV ratio in dialysis patients.[14]

The aortic-brachial arterial stiffness gradient is a relatively new concept in arterial research.[21] The stiffness gradient hypothesis is based on previous observations, which have shown that under normal conditions, when aortic stiffness is lower than that of medium-sized muscular conduit arteries, partial pressure wave reflections are generated at the transition of these segments, resulting in attenuated pulse pressure transmission.[17, 22–24] However, the aortic-brachial arterial stiffness gradient is reversed with aging in most individuals when aortic stiffness increases considerably while peripheral muscular artery stiffness experiences only minor or nonexistent increases.[1, 3–5] This reversal of the stiffness gradient, in turn, has been shown to be associated with less distal reflection and attenuation of the forward pressure wave when it is transmitted to the microcirculation, potentially leading to increased organ damage.[14, 21] The transmission of excessive forward pressure may be especially detrimental for high-flow organs such as the brain or the kidney. Indeed, at least two studies have shown that increased arterial stiffness by itself is associated with transmission of increased flow pulsatility into and the brain and kidneys, leading to structural brain damage, microalbuminuria, and kidney injury.[25, 26]

Although the stiffness gradient hypothesis is an interesting concept, our findings do not support the notion that measurement of the aortic-brachial arterial stiffness gradient ratio provides additional prognostic value over conventional CFPWV in the community, or in subgroups. Our findings have no direct implications for the validity of the concept, but primarily demonstrate that the loss of stiffness gradient is essentially all attributable to the increase in CFPWV rather than a decrease in CRPWV. To our knowledge, only one published study has previously investigated the prognostic significance of arm/aorta PWV ratio. In this publication, Fortier et al. assessed the relation of aortic-brachial arterial stiffness gradient and all-cause mortality in 310 adult patients on dialysis.[14] In contrast to our findings, the authors found that the unadjusted hazard ratio for all-cause mortality related to 1-SD increase in PWV ratio was 1.43 (95% CI 1.24–1.64) while the hazard ratio for a 1-SD increase in CFPWV was 1.29 (95% CI, 1.11–1.50). PWV ratio resulted in a model c-statistic of 0.694 while the c-statistic for a model that included CFPWV was only 0.627. In addition, only PWV ratio, but not CFPWV, CRPWV, or augmentation index (a measure of wave reflection and arterial stiffness), was significantly associated with outcomes after adjustment for other classical cardiovascular risk factors.[14] The discrepancy between our findings and those of Fortier et al. on PWV ratio and CVD outcomes may be explained by several factors. First and foremost, our study included a community-based sample whereas Fortier's included only dialysis patients, a highly selected group of patients with multiple comorbidities, such as hypertension, diabetes, inflammation, and anemia.[27] In the long term, these patients undergo significant arterial remodeling that is already observed

in early-stage chronic kidney disease.[28] And in the short-term, both fluid overload and hemodialysis have been shown to have drastic effects on arterial stiffness.[29, 30] Another possible cause for the inconsistent results is that the stiffness gradient hypothesis may oversimplify the interaction between the aorta and muscular conduit arteries. The vascular system does not solely consist of two tubes attached to each other. Furthermore, previous results have been somewhat mixed even among dialysis patients as in a study by Pannier et al., only aortic stiffness, but not peripheral muscular artery stiffness, predicted cardiovascular mortality.[2] In summary, our observations do not support the use of PWV ratio for CVD risk assessment in the community. We cannot, however, exclude the possibility that PWV ratio might provide incremental predictive value over CFPWV in the elderly. In individuals aged ≥70 years the HRs for CVD events per 1-SD increase in CFPWV and per 1-SD decrease in PWV ratio were 1.39 and 1.54, but with widely overlapping confidence intervals. Given these findings, additional larger studies of older individuals are warranted to better assess the predictive value of the PWV ratio in the elderly.

We observed that higher age, male sex, higher BMI, diabetes, lower HDL cholesterol, higher mean arterial pressure, and higher heart rate were associated with lower PWV ratio. In the study by Fortier et al., only higher age, diabetes, history of CVD, and lower hemoglobin were related to PWV ratio in a multivariable regression analysis.[14] However, the findings of Fortier et al. were limited by their smaller study sample and lack of some relevant clinical variables. However, all of these factors have also been found to be correlates of CFPWV, the apparent main driver of PWV ratio.[17, 31] We could not therefore find any correlates that are specific to PWV ratio.

Our study has several strengths that merit comment. For example, our study was performed with a moderately-sized population sample of community-dwelling individuals, which enhanced generalizability and made subgroup analyses feasible. In addition, in contrast to the only previous prognostic study, data were available on CVD outcomes and all relevant cardiovascular risk factors.[14] Our study also has certain limitations, such as a study sample consisting mainly of middle-aged to older adults of European descent. The extent to which our results are generalizable to other racial or ethnic groups, or to elderly individuals with multiple comorbidities, remains unknown, and warrants further study. In addition, the number of CVD events in some of the groups cross-classified by high/low CFPWV and CRPWV was relatively modest. Nevertheless, the findings from these analyses were consistent with those that modeled PWV ratio as a continuous variable. Furthermore, we cannot exclude residual confounding.

Perspectives

Our results confirm that CFPWV and PWV ratio are associated with CVD events. Although a recent previous study had reported that PWV ratio might provide incremental predictive value over CFPWV in dialysis patients, we could not validate these findings in a community setting.[14] In fact, nearly all of the prognostic significance of PWV ratio in the general population seems to be driven by CFPWV. Based on our results, CFPWV should remain the criterion standard for assessing vascular stiffness in the community.[32]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Novelty and Significance

What is New

- A recent study reported that the aortic-brachial arterial stiffness gradient, defined as the ratio of carotid-radial and carotid-femoral pulse wave velocity, is a better predictor of all-cause mortality than carotid-femoral pulse wave velocity in dialysis patients.
- The role of the arterial stiffness gradient as a cardiovascular risk factor has not been validated in the community.

What is Relevant?

- The arterial stiffness gradient provided no incremental predictive value for cardiovascular events over common cardiovascular risk factors and carotid-femoral pulse wave velocity in a lower-risk community-dwelling population.

Summary

- Carotid-femoral pulse wave velocity should remain the criterion standard for assessing vascular stiffness in the community.

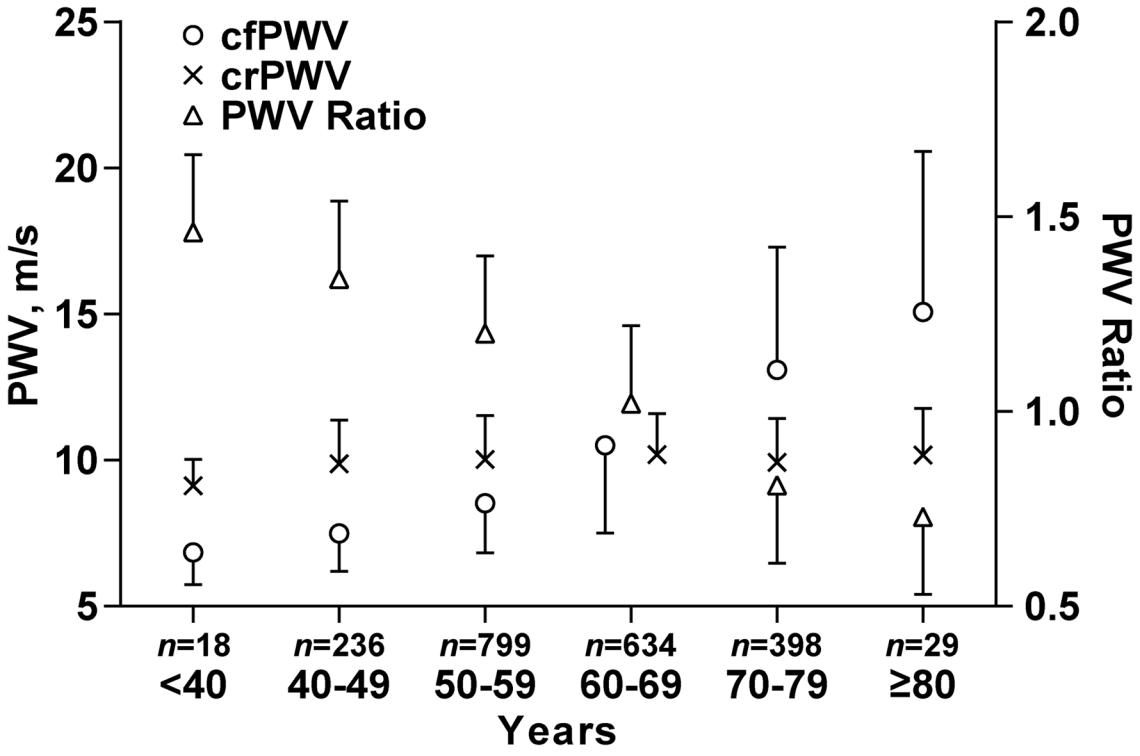

Figure 1.

Mean carotid-femoral pulse wave velocity, carotid-radial pulse wave velocity, and pulse wave velocity ratio in 10-year age groups. Vertical bars indicate standard deviation. PWV, pulse wave velocity; CFPWV, carotid-femoral pulse wave velocity; CRPWV, carotid-radial pulse wave velocity.

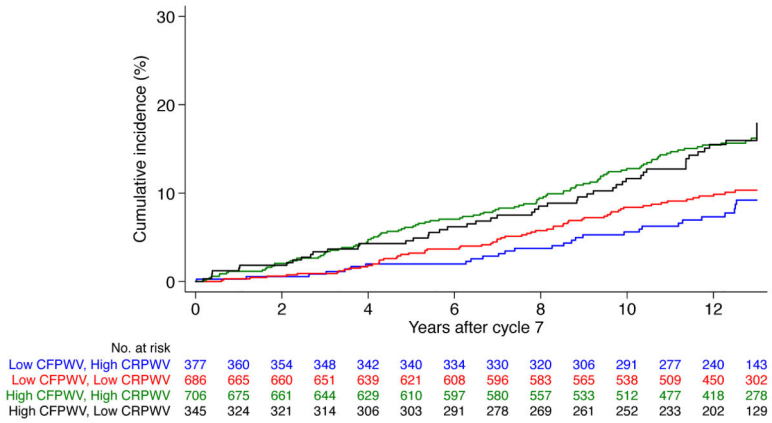

Figure 2.

Cumulative incidence of cardiovascular events in groups classified by high versus low carotid-femoral and carotid-radial pulse wave velocity (truncated at 13 years after baseline). CFPWV, carotid-femoral pulse wave velocity; CRPWV, carotid-radial pulse wave velocity.

Table 1

Baseline characteristics in groups cross-classified by high versus low carotid-femoral and carotid-radial pulse wave velocity.

Characteristic	Overall	Low CFPWV and High CRPWV (1)	Low CFPWV and Low CRPWV (2)	High CFPWV and High CRPWV (3)	High CFPWV and Low CRPWV (4)
n	2114	377	686	706	345
Age, y	60.4±9.5	60.7±9.2	60.4±9.6	60.2±9.7	60.7±9.5
Women, %	56.4	59.4	55.5	55.0	58.0
BMI, kg/m^2	27.4±4.6	26.2±3.9^{3,4}	26.6±4.2^{3,4}	28.2±4.8^{1,2}	28.4±5.0^{1,2}
Diabetes mellitus, %	8.8	4.5^{3,4}	5.4^{3,4}	12.5^{1,2}	12.5^{1,2}
Current Smoker, %	13.5	14.3	13.7	14.3	10.7
Cholesterol, mmol/l	5.2±0.9	5.2±0.9	5.2±0.9^{3}	5.3±1.0^{2,4}	5.2±1.0^{3}
HDL cholesterol, mmol/l	1.4±0.4	1.5±0.5^{3,4}	1.5±0.4^{4}	1.4±0.5^{1}	1.4±0.4^{1,2}
Systolic BP, mmHg	127±19	122±16^{3,4}	119±16^{3,4}	134±20.3^{1,2,4}	131±19^{1,2,3}
Diastolic BP, mmHg	74±10	74±9^{2,3}	70±9^{1,3,4}	79±10.3^{1,2,4}	74±9^{2,3}
MAP, mmHg	91.8±11.3	89.9±9.7^{2,3,4}	86.7±9.5^{1,3,4}	97.2±11.8^{1,2,4}	92.9±9.8^{1,2,3}
Heart rate, bpm	65±11	63±10^{3}	62±10^{3,4}	68±11^{1,2,4}	65±10^{2,3}
BP-lowering therapy, %	30.7	22.3^{3,4}	25.1^{3,4}	36.3^{1,2}	39.4^{1,2}
Diuretics, %	2.8	2.1	1.9	3.8	2.9
Beta-blockers, %	13.8	9.8^{4}	14.3	12.7^{4}	19.4^{1,3}
ACE-inhibitors, %	12.7	9.0^{4}	10.6^{4}	14.2	17.7^{1,2}
ARBs, %	2.3	3.5	1.5	2.1	2.9
CCBs, %	8.8	5.3^{4}	7.4^{4}	9.5	13.6^{1,2}
CFPWV, m/s	9.9±3.4	8.5±1.6^{3,4}	8.1±1.6^{3,4}	12.0±4.1^{1,2,4}	11.0±3.1^{1,2,3}
CRPWV, m/s	10.0±1.5	10.8±0.9^{2,3,4}	8.8±0.9^{1,3,4}	11.3±1.1^{1,2,4}	9.1±0.8^{1,2,3}
PWV ratio	1.08±0.3	1.32±0.2^{2,3,4}	1.13±0.2^{1,3,4}	1.01±0.3^{1,2,4}	0.9±0.2^{1,2,3}

CFPWV, carotid-femoral pulse wave velocity; CRPWV, carotid-radial pulse wave velocity; BMI, body mass index; HDL, high density lipoprotein; BP, blood pressure; MAP, mean arterial pressure; ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; CCB, calcium-channel blocker; PWV; pulse wave velocity. Values are mean±SD for continuous variables or % for categorical variables. Superscript numbers indicate significant difference compared with category 1, 2, 3, or 4 (P<0.05 with Bonferroni-corrected two-sample t-test or chi-squared test).

Table 2

Univariate and multivariable correlates of lower PWV ratio.

	Univariate			Multivariable (Model R^2=0.52)	
Characteristic	**β±SE**	***P* value**	**R^2**	**β±SE**	***P* value**
Age, y	0.18±0.004	<0.001	0.44	0.17±0.004	<0.001
Female Sex	0.02±0.01	0.052	0.002	0.05±0.01	<0.001
BMI, kg/m^2	0.05±0.006	<0.001	0.03	0.03±0.005	<0.001
Diabetes mellitus	0.20±0.02	<0.001	0.04	0.08±0.02	<0.001
Current Smoking	−0.08±0.02	<0.001	0.01	0.006±0.01	0.61
Cholesterol, mmol/l	0.002±0.006	0.69	0.0001	−0.003±0.004	0.44
HDL cholesterol, mmol/l	−0.03±0.006	<0.001	0.01	−0.02±0.005	<0.001
MAP, mmHg	0.07±0.006	<0.001	0.06	0.04±0.004	<0.001
Heart rate, bpm	0.05±0.005	<0.001	0.03	0.03±0.004	<0.001

Coefficients for all continuous variables are reported per 1-SD increase. The variables were included one at a time in the univariate models while all variables were simultaneously included in multivariable model. BP, blood pressure; PWV; pulse wave velocity; HDL, high density lipoprotein; MAP, mean arterial pressure.

Table 3

Risk of cardiovascular events per 1-SD increase in carotid-femoral or carotid-radial pulse wave velocity, and per 1-SD decrease in pulse wave velocity ratio.

	CFPWV			CRPWV			PWV ratio		
Model	**HR (95% CI)**	***P* value**	**Model c-statistic**	**HR (95% CI)**	***P* value**	**Model c-statistic**	**HR (95% CI)**	***P* value**	**Model c-statistic**
Unadjusted	2.27 (2.00–2.59)	<0.001	0.731	1.15 (1.02–1.30)	0.03	0.546	2.22 (1.95–2.54)	<0.001	0.716
Adjusted for MAP	2.31 (2.01–2.65)	<0.001	0.732	1.04 (0.91–1.19)	0.60	0.588	2.17 (1.90–2.49)	<0.001	0.718
Multivariable-adjusted	1.33 (1.10–1.61)	0.004	0.783	0.99 (0.86–1.14)	0.85	0.780	1.32 (1.09–1.59)	0.004	0.783

CFPWV, carotid-femoral pulse wave velocity; CRPWV, carotid-radial pulse wave velocity; HR, hazard ratio; CI, confidence interval; MAP, mean arterial pressure. Multivariable-adjusted model is adjusted for age, sex, body mass index, smoking status, diabetes mellitus, heart rate, total cholesterol, mean arterial pressure, and HDL cholesterol.

Table 4

Risk of cardiovascular events per 1-SD increase in carotid-femoral or carotid-radial pulse wave velocity, and per 1-SD decrease in pulse wave velocity ratio in subgroups by age, sex, and carotid-femoral PWV level.

	CFPWV		CRPWV		PWV ratio	
Subgroup	**HR (95% CI)**	***P* for interaction**	**HR (95% CI)**	***P* for interaction**	**HR (95% CI)**	***P* for interaction**
Sex						
Men (n=921, 130 events)	1.24 (0.95–1.63)	0.63	0.89 (0.73–1.08)	0.24	1.32 (1.02–1.70)	0.83
Women (n=1193, 115 events)	1.46 (1.10–1.93)		1.10 (0.90–1.34)		1.36 (1.02–1.81)	
Age						
<60 Years (n=1053, 56 events)	1.50 (0.98–2.30)	0.88	0.96 (0.71–1.28)	0.24	1.50 (1.02–2.20)	0.37
≥60 Years (n=1061, 189 events)	1.79 (1.49–2.17)		0.95 (0.80–1.12)		1.82 (1.51–2.18)	
Age						
<70 Years (n=1687, 136 events)	1.95 (1.56–2.44)	0.02	1.07 (0.88–1.29)	0.051	1.77 (1.43–2.19)	0.29
≥70 Years (n=427, 109 events)	1.39 (1.06–1.82)		0.90 (0.73–1.12)		1.54 (1.16–2.04)	
CFPWV						
Low (n=1063, 91 events)	--	--	0.95 (0.74–1.23)	0.55	--	--
High (n=1051, 154 events)	--		0.91 (0.75–1.09)		--	
Diabetes Mellitus						
Yes (n=185, 52 events)	1.22 (0.98–1.52)	0.19	1.01 (0.87–1.18)	0.63	1.19 (0.97–1.47)	0.15
No (n=1929, 193 events)	1.94 (1.23–3.08)		0.91 (0.65–1.27)		2.06 (1.30–3.26)	
BP-lowering therapy						
Yes (n=648, 136 events)	1.26 (0.93–1.69)	0.46	1.05 (0.85–1.30)	0.27	1.19 (0.89–1.57)	0.17
No (n=1466, 109 events)	1.27 (0.99–1.64)		0.99 (0.82–1.21)		1.28 (0.98–1.67)	

CFPWV, carotid-femoral pulse wave velocity; CRPWV, carotid-radial pulse wave velocity; HR, hazard ratio; CI, confidence interval, BP, blood pressure. Models are adjusted for age, sex, body mass index, smoking status, diabetes mellitus, heart rate, total cholesterol, mean arterial pressure, and high-density lipoprotein cholesterol (age was omitted from the subgroup analyses by age).