Relations of Arterial Stiffness and Brachial Flow–Mediated Dilation With New-Onset Atrial Fibrillation

The Framingham Heart Study

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Abstract—The relations of measures of arterial stiffness, pulsatile hemodynamic load, and endothelial dysfunction to atrial fibrillation (AF) remain poorly understood. To better understand the pathophysiology of AF, we examined associations between noninvasive measures of vascular function and new-onset AF. The study sample included participants aged ≥45 years from the Framingham Heart Study offspring and third-generation cohorts. Using Cox proportional hazards regression models, we examined relations between incident AF and tonometry measures of arterial stiffness (carotid–femoral pulse wave velocity), wave reflection (augmentation index), pressure pulsatility (central pulse pressure), endothelial function (flow-mediated dilation), resting brachial arterial diameter, and hyperemic flow. AF developed in 407/5797 participants in the tonometry sample and 270/3921 participants in the endothelial function sample during follow-up (median 7.1 years, maximum 10 years). Higher augmentation index (hazard ratio, 1.16; 95% confidence interval, 1.02–1.32; *P*=0.02), baseline brachial artery diameter (hazard ratio, 1.20; 95% confidence interval, 1.01–1.43; *P*=0.04), and lower flow-mediated dilation (hazard ratio, 0.79; 95% confidence interval, 0.63–0.99; *P*=0.04) were associated with increased risk of incident AF. Central pulse pressure, when adjusted for age, sex, and hypertension (hazard ratio, 1.14; 95% confidence interval, 1.02–1.28; *P*=0.02) was associated with incident AF. Higher pulsatile load assessed by central pulse pressure and greater apparent wave reflection measured by augmentation index were associated with increased risk of incident AF. Vascular endothelial dysfunction may precede development of AF. These measures may be additional risk factors or markers of subclinical cardiovascular disease associated with increased risk of incident AF. (***Hypertension*. 2016;68:590-596. DOI: 10.1161/HYPERTENSIONAHA.116.07650.)** • **Online Data Supplement**

Key Words: arrhythmia ■ augmentation index ■ flow-mediated dilation ■ pulse wave velocity ■ tonometry

Atrial fibrillation (AF) is the most common clinically encountered chronic arrhythmia in adults and is associated with increased risk for stroke and mortality.[1,2] Hypertension[3] and elevated blood pressure[4] are important risk factors for AF.[5] To better understand the causal pathway between hypertension and AF, researchers have examined relations between AF and state-of-the-art measures of arterial stiffness, wave reflection, pulsatile hemodynamic load, and endothelial dysfunction.

Studies have reported that various measures of vascular structure and function[6–9]—including carotid–femoral pulse wave velocity (CFPWV), augmentation index, and central pulse pressure (CPP)—and measures of endothelial dysfunction,[10,11] including arterial flow-mediated dilation (FMD), are associated with higher risk for cardiovascular diseases. In addition, the Framingham Heart Study[12] and the Multi-Ethnic Study of Atherosclerosis[13] identified peripheral pulse pressure, another marker of aortic stiffness, as a risk factor for incident AF. Impaired FMD is a noninvasive surrogate marker of endothelial dysfunction[14] and has been associated, largely in cross-sectional analyses, with atrial arrhythmias, including

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AF, as well as several other manifestations of cardiovascular disease.[10,11,15–19] However, the relative contributions of direct measures of arterial stiffness, pulsatile hemodynamic load, and endothelial dysfunction in relation to incident AF remain unclear in the general population.

To address present gaps in our understanding of how hypertension leads to AF, we sought to evaluate a comprehensive panel of noninvasive measures of vascular function (CFPWV, augmentation index, CPP, FMD, resting brachial artery diameter, and hyperemic flow) in relation to new-onset AF. Our goal was to identify potential upstream intermediate phenotypes or risk factors of incident AF from a large, community-based cohort. We examined the hypothesis that measures of arterial stiffness, pulsatile load, and endothelial dysfunction are associated with incident AF.

Methods

Study Participants

The study design and selection criteria for the Framingham offspring cohort[20] and the third-generation cohort[21] have been detailed. Participant enrollment and eligible samples for the study are shown in Figure S1 in the online-only Data Supplement. Tonometry measures were implemented from February 1999 to January 2008.[22] Ascertainment of brachial artery diameter, hyperemic flow, and FMD began in November 1998 and continued through July 2005.[23] We excluded participants <45 years of age. All protocols were approved by Boston University Medical Center's Institutional Review Board, and participants provided written informed consent.

Risk Factor Definitions

Medical history, physical examination, and ECG were performed routinely at each Framingham Heart Study examination. Blood pressures are the average of 2 auscultatory pressures by Framingham physicians on seated participants during clinic examination with the use of a standardized measurement protocol.[12] Hypertension was defined as systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg or on treatment with an antihypertensive medication. Peripheral pulse pressure was calculated as the difference between systolic and diastolic pressures. Body mass index was calculated by dividing weight in kilograms by the square of height in meters. Criteria for diabetes mellitus were fasting glucose level of ≥126 mg/dL or use of medications used to treat hyperglycemia.[12] Valvular disease was defined as significant systolic murmur (grade 3 or greater out of 6) or any diastolic murmur identified at the Framingham clinic examination.[12]

Medical records were obtained for all hospitalizations and follow-up physician visits related to cardiovascular disease and were reviewed by a committee of 3 investigators; events were adjudicated following written guidelines.[24]

Tonometry Measurements

Arterial tonometry with ECG was obtained from the brachial, radial, femoral, and carotid arteries using a custom transducer (Cardiovascular Engineering, Inc, Norwood, MA).[25] Body surface measurements from suprasternal notch to pulse recording sites were obtained by using a fiberglass tape measure for carotid, brachial, and radial sites and a caliper for the femoral site. Tonometry waveforms were signal-averaged using the electrocardiographic R-wave as a fiducial point. Average systolic and diastolic cuff pressures were used to calibrate peak and trough of the signal-averaged brachial waveform. Diastolic and integrated mean brachial pressures were then used to calibrate carotid waveforms. CFPWV was calculated as described previously.[26] Augmentation index was assessed from the carotid pressure waveform. Augmentation index is the percentage of CPP attributed to reflected wave overlap in systole and has complex relations with aortic stiffness and cardiovascular risk.

Flow-Mediated Dilation Measurements

The brachial artery images and Doppler flow were assessed with a Toshiba SSH-140A ultrasound system and 7.5-MHz linear array transducer (for offspring) or a Philips Sonos 5500 with a 3.0- to 11.0-MHz linear array transducer (for third generation) before and after arterial flow was interrupted for 5 minutes by a cuff placed on the proximal forearm. Using a carrier frequency of 3.75 MHz (for offspring) or 3.6 MHz (for third generation) and an insonation angle of ≈60°, Doppler flow was assessed at baseline and for the initial 15 seconds after cuff deflation to document baseline and peak hyperemic flow. All flow values were corrected for actual insonation angle. Brachial artery baseline (D_{BL}) and 60-second postdeflation diameter (D_{DF}) were measured as described previously. FMD was expressed as relative change from baseline: $FMD\% = (D_{DF} - D_{BL})/D_{BL}$.[27]

Flows were analyzed from the digitized audio data using a semiautomated, signal-averaging approach. Sonographers analyzed diameters and, on a separate occasion, measured flows with no knowledge of clinical status or the corresponding FMD%. Raw flow spectra were displayed, and cardiac cycles with artifacts were excluded by the sonographer. During hyperemia, peak flow timing was confirmed visually, and only beats representing the peak flow response were included in the signal-averaged spectrum. Flow spectra were then signal-averaged (1000-Hz resolution) using the ECG as a fiducial point. The pulsatile flow velocity waveform for the signal-averaged cardiac cycle was established automatically by finding the median flow velocity at each time point in the flow spectrum. Measurement variability of brachial artery diameter and FMD has been reported previously[23] and was comparable to reports from other laboratories.

Definition of AF

Participants were diagnosed with AF if AF or atrial flutter was present on an ECG obtained from outside hospital or physician records or from routine Framingham clinic examination (every 4–8 years in the offspring and third-generation cohorts). The Framingham Heart Study cardiologists confirmed the electrocardiographic interpretation of incident AF.[3]

Statistical Analysis

Pooled participant data were included and analyzed for the tonometry and FMD measures. Baseline characteristics for the study sample were tabulated using mean±standard deviation (SD) for continuous and proportion for categorical variables. Follow-up was censored at 10 years or death, with the final participant censored based on follow-up data collected by December 2013. For participants who had tonometry variables measured at examinations 7 and 8, follow-up after examination 7 was censored at examination 8, followed by a second epoch of follow-up. We used the negative inverse CFPWV (−1000/CFPWV) to limit heteroscedasticity. We used −1000/CFPWV to convert units to ms/m and to restore the directionality of the relations between −1000/CFPWV and aortic stiffness.

We examined the associations between tonometry measures, FMD measures, and risk for new-onset AF using Cox proportional hazards regression models adjusted for age and sex. Hazards ratios were expressed per SD of the vascular measure. Subsequently, we conducted multivariable-adjusted analyses for standard AF-related clinical covariates (age, sex, body mass index, current smoking, diabetes mellitus, hypertension, history of myocardial infarction and heart failure, valvular disease, and heart rate).[28] We checked the proportional hazards assumption by adding a time-dependent covariate for each predictor: an interaction between the predictor and the log event time. Proportional hazards did not hold for age, so we retained an age interaction term in the Cox model. For tonometry analyses, we had repeated observations on some participants. For repeated measurements, we used robust sandwich covariance estimate (COVS[AGGREGATE]) with individuals as clusters. The endothelial function analyses did not have repeated observations on individuals, so we stratified it based on generation variable.

Cumulative probability curves were constructed by using the Kaplan–Meier method, with participant groups segregated according to quartiles of the hemodynamic variables of interest. We tested for effect modification of tonometry and FMD variables of interest with

sex and with age (<60 versus ≥60) by including interaction terms. All analyses were performed using SAS version 9.3. A 2-sided *P* value <0.05 was considered statistically significant.

Results

The clinical characteristics of the study sample are presented in Table 1. Mean age was 61 (limits 45–91) years. During follow-up (median 7.1, maximum 10 years), there were 407 new cases of AF in the tonometry sample and 270 cases in the FMD sample (Table 2). A total of 482 (8.3%) participants died.

The results of Cox models, including hazard ratios for arterial stiffness measures, endothelial function measures, and incident AF, are presented in Table 3. Adjusting for clinical covariates, higher augmentation index, larger brachial artery diameter, and lower FMD were associated with an increased risk of incident AF. An unadjusted analysis using Kaplan–Meier method showed that the cumulative incidence of incident AF was significantly higher for the fourth quartile of CFPWV, augmentation index, CPP, and baseline brachial artery diameter as compared with the lower quartiles, whereas the incidence was significantly higher for the first quartile of FMD and hyperemic flow as compared with the higher quartiles (Figure).

Table 1. Baseline Characteristics of Framingham Offspring and Third-Generation Pooled Participants

Characteristics	Tonometry Sample (N=5797)	Endothelial Function Sample (N=3921)
Clinical		
Age, y	61±10	58±9
Women, n (%)	3185 (55%)	2091 (53%)
Cigarette smoking, n (%)	686 (12%)	549 (14%)
Height, cm	168±10	168±9
Weight, kg	78±17	80±18
Heart rate, bpm	63±10	64±11
Systolic BP, mm Hg*	128±18	126±18
Diastolic BP, mm Hg*	75±10	75±10
Pulse pressure, mm Hg*	52±16	50±15
Hypertension treatment, n (%)	2156 (37%)	1137 (29%)
Diabetes mellitus, n (%)	563 (10%)	352 (9%)
Heart failure, n (%)	40 (1%)	17 (0.4%)
Myocardial infarction, n (%)	184 (3%)	116 (3%)
Tonometry		
CFPWV, m/s	9.78±3.43	
Inverse CFPWV, ms/m	−112±29	
Augmentation index, %	15.4±12.4	
Central pulse pressure (CPP), mm Hg	60±20	
Endothelial function		
Baseline brachial artery diameter, mm		4.2±0.9
Hyperemic flow velocity, cm/s		54±21
Flow-mediated dilation (FMD), %		3.7±3.3

CFPWV indicates carotid–femoral pulse wave velocity.

*The systolic and diastolic pressures were measured by physicians during examination. Pulse pressure was calculated as the difference between systolic and diastolic blood pressure. Values are means±SD for continuous measures or n (%) for binary measures.

A secondary interaction analysis was conducted to analyze the effect modification by age and sex of the primary exposure variables of interest in relation to incident AF. The *P* value for all the exposure variables for age interaction analysis was >0.35, except for CPP (*P*=0.04). A stratified analysis revealed a stronger association of CPP in participants <60 years (versus ≥60 years) of age at the time of the baseline study (hazard ratio 1.78; *P*<0.001). Two thousand eight hundred (48%) participants in the tonometry sample and 1611 (41%) participants in the endothelial function sample had hypertension. Mean duration of presence of hypertension was 3.5 years in examination 7 and 7.0 years in examination 8.

Discussion

Our study demonstrated that greater wave reflection, as measured by augmentation index, was associated with increased risk of incident AF. Higher pulsatile load, as quantified by CPP, was associated with incident AF, despite adjustment for presence of hypertension. We also showed that lower FMD and increased baseline brachial arterial diameter, 2 markers of endothelial dysfunction, were associated with increased risk of AF.

Arterial Stiffness and Pulsatile Load

Elevated pulse pressure, a surrogate marker for increased proximal aortic stiffness, has been associated with advancing age, higher body mass index, and prevalent diabetes mellitus.[29] In addition, elevated pulse pressure predisposes to left ventricular hypertrophy,[30] impaired ventricular relaxation,[31] myocardial infarction,[32] heart failure,[33] and increased left atrial size.[34] A Framingham Heart Study analysis demonstrated that peripheral pulse pressure, but not mean arterial pressure, was associated with incident AF even if adjusted for baseline left atrial diameter and left ventricular mass.[12] A recent multi-ethnic study of atherosclerosis (MESA) analysis also demonstrated the importance of peripheral pulse pressure as a risk factor for AF.[13] However, because the heart and brain are exposed to central rather than peripheral pulse pressure, which may differ, CPP or measures of wave reflection, such as augmentation index, may represent incremental measures of incident AF risk compared with peripheral pulse pressure.[35] We observed that associations between CPP and new-onset AF were significant even after adjusting for hypertension.

Increased CFPWV has been associated with lone AF,[36] increased left atrial diameter,[37,38] and left ventricular diastolic dysfunction.[39] In our study, mean CFPWV was not associated with incident AF. Our findings for CFPWV are similar to the recent multi-ethnic study of atherosclerosis analysis, wherein the authors did not find a significant association between magnetic resonance imaging–measured aortic distensibility and incident AF.[13] Elevated augmentation index has been associated with lone AF recurrence,[40] paroxysmal AF,[41] and elevated Brain-Natriuretic Peptide (BNP) levels in paroxysmal AF.[42] In our study, the association between augmentation index and new-onset AF was significant even after adjusting for hypertension

Table 2. Incidence Rates of AF per 1000 Person-Years

Cohort	Event	Sample	Person-Year	Incidence Rate (95% CI)
Tonometry sample				
Gen3 examination 1	17	1234	11311	1.5 (0.8, 2.2)
Offspring examination 7	202	2117	13756	14.7 (12.7, 16.7)
Offspring examination 8	188	2446	16306	11.5 (9.9, 13.2)
Endothelial function sample				
Gen3 examination 1	18	1272	11638	1.5 (0.8, 2.3)
Offspring examination 7	252	2649	17377	14.5 (12.7, 16.3)

AF indicates atrial fibrillation; and CI, confidence interval.

or other risk factors. Elevated augmentation index might be a marker of concentric left ventricular hypertrophy, which may further explain the association with incident AF.

Episodic increases in pulse pressure in individuals with a stiff aorta may contribute to increased risk of AF, accounting for left atrial size or left ventricular mass.[12] Acute increases in pulsatile load likely increase left atrial distending pressure,[43] cause neurohormonal activation,[44] and lead to generalized cardiovascular inflammatory response,[45] which may contribute to AF development.[46] Importantly, interventions known to reduce pulse pressure, such as blockade of the renin–angiotensin system, have been shown to decrease rates of incident and recurrent AF.[47] The exponential rise in AF incidence with advancing age parallels a rapid age-related increase in aortic stiffness.[12] Our stratified analysis for effect modification by age of the relation between CPP and incident AF showed that at or above age 60 years, the discriminatory value of higher CPP in prediction of incident AF might be attenuated if adjusted for other risk factors. This may be because of increased prevalence of higher CPP above age 60 because of a parallel increase in aortic stiffness with advancing age.

Endothelial Dysfunction

Several AF risk factors, including advancing age,[48,49] diabetes mellitus,[48] hypertension,[50] and smoking,[51] relate to endothelial dysfunction. Endothelial dysfunction, in turn, leads to upregulation of adhesion molecules and downregulation of nitric oxide, key factors in endovascular inflammation, oxidative stress, and cardiac dysfunction.[48] Nitric oxide recently also has been implicated in atrial arrhythmogenesis.[15,16,46] A lower arterial FMD suggestive of vascular endothelial dysfunction is associated with cardiovascular disease.[10] A recent multi-ethnic study of atherosclerosis analysis showed that a lower arterial FMD was associated with incident AF.[19] A recent case–control study, for example, reported that FMD was impaired in participants with persistent AF and improved after restoration of sinus rhythm.[17] A recent multi-ethnic study of atherosclerosis analysis, including 2936 participants (137 with incident AF), showed that lower FMD was associated with higher rates of incident AF.[19] Greater brachial artery diameter has been associated with coronary artery disease, but not AF.[52] Our study showed that both lower FMD and also larger baseline brachial artery diameter were associated with new-onset AF, even after adjusting for other important AF risk factors, including hypertension. Our findings support the notion that impaired endothelial function may contribute to the pathogenesis of AF.

Strengths and Limitations

The strength of our study is the large, prospective, community-based cohort design and long follow-up, as well as rigorous adjudication of all potential cases of new-onset AF. Several limitations of our study should be considered when interpreting our results. The observational nature of our study precludes any causal inference. We cannot exclude residual confounding by duration or severity of associated risk factors or unmeasured common risk factors. We evaluated a middle-aged and older cohort of white study participants. Therefore, our results may not be generalizable to younger individuals or those from nonwhite racial groups. We did not analyze AF or atrial flutter, nor AF subtypes (eg, paroxysmal, persistent, etc.) separately, so cannot comment if the markers of endothelial dysfunction and arterial stiffness were more specific to subclasses of AF. We, as well as others, have observed that atrial flutter and AF share similar epidemiological and pathophysiologic characteristics.[53] We cannot exclude the possibility that some clinically unrecognized cases of AF might have been missed.

Perspectives

We observed that greater wave reflection, as measured by the augmentation index, was associated with higher risk of incident AF. Higher CPP, a marker of greater pulsatile load, was

Table 3. Hazard Ratio for Incident AF per Standard Deviation of Vascular Function Measures

	Age- and Sex-adjusted			Age–Sex–Hypertension Adjusted*			Multivariable-Adjusted		
Variables	HR (CI)	X^2	*P* Value	HR (CI)	X^2	*P* Value	HR (CI)	X^2	*P* Value
–1000/CFPWV	1.18 (1.04, 1.35)	6.33	0.01	1.10 (0.97, 1.26)	2.19	0.11	1.10 (0.96, 1.26)	1.74	0.19
Augmentation index	1.17 (1.03, 1.32)	6.04	0.014	1.15 (1.02, 1.29)	4.90	0.03	1.16 (1.02, 1.32)	5.12	0.02
Central pulse pressure	1.21 (1.08, 1.35)	11.5	<0.001	1.14 (1.02, 1.28)	5.23	0.02	1.11 (0.98, 1.25)	2.93	0.09
Flow-mediated dilation	0.75 (0.63, 0.89)	10.3	0.001	0.79 (0.66, 0.94)	6.90	0.009	0.79 (0.63, 0.99)	4.13	0.04
Baseline brachial arterial diameter	1.38 (1.17, 1.63)	14.2	<0.001	1.34 (1.14, 1.58)	12.21	<0.001	1.20 (1.01, 1.43)	4.16	0.04
Hyperemic flow	0.79 (0.67, 0.94)	7.4	0.007	0.85 (0.71, 1.01)	3.57	0.06	0.87 (0.73, 1.03)	2.65	0.10

AF indicates atrial fibrillation; BMI, body mass index; CFPWV, carotid–femoral pulse wave velocity; CI, confidence interval; and HR, hazard ratio

*Multivariable model included age, sex, height, BMI, diabetes mellitus, current smoking, hypertension, prevalent heart failure, prevalent myocardial infarction, valve disease, and heart rate. Endothelial function analyzes multivariate model additionally adjusted for hyperemic flow. All hazard ratios are expressed per 1 SD higher value for the exposure variable.

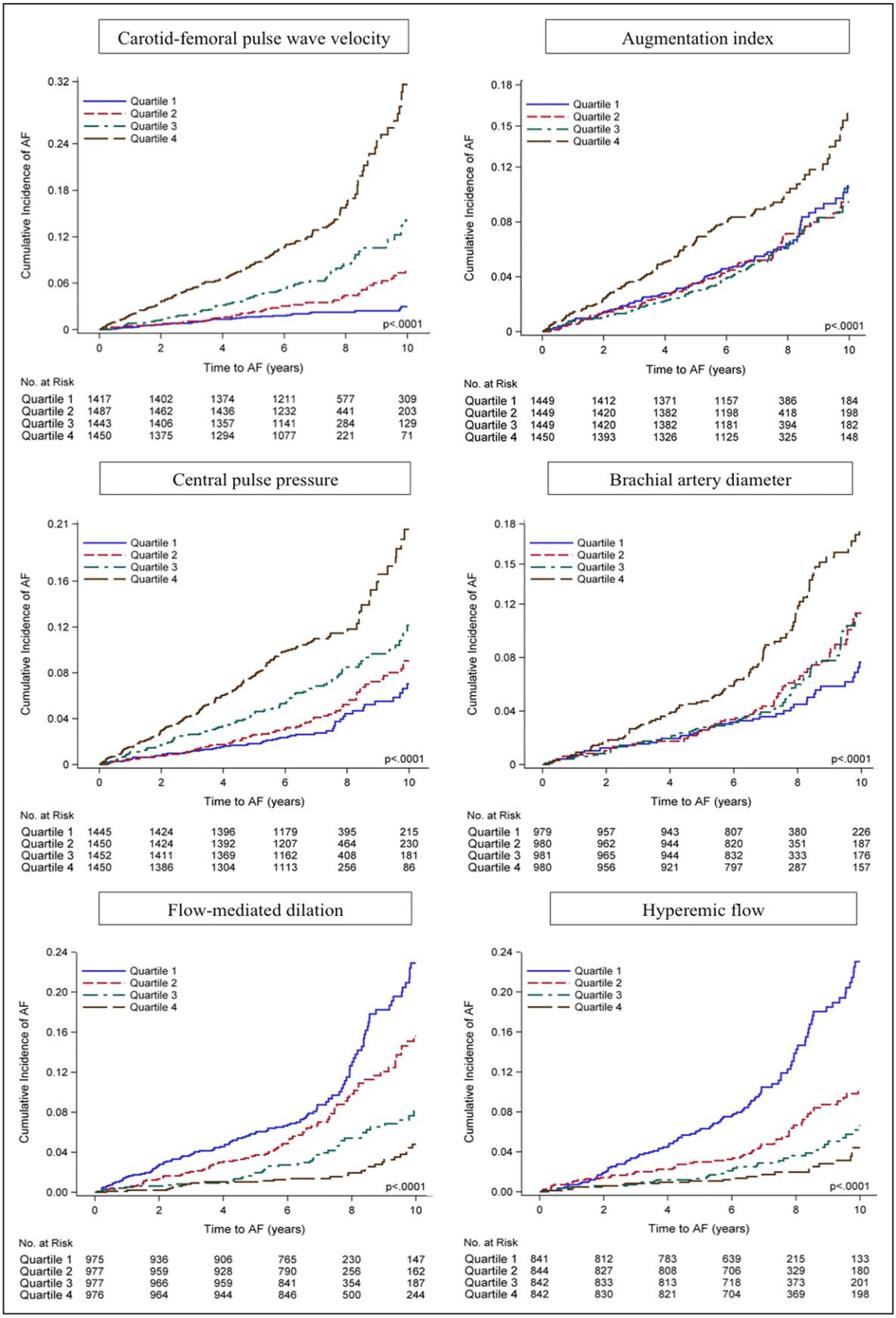

Figure. Kaplan–Meier curve plots for cumulative incident atrial fibrillation (AF) based on quartiles on hemodynamic variables of interest.

associated with incident AF, even after adjustment for hypertension. We also observed that vascular endothelial dysfunction measured by lower FMD and higher baseline brachial arterial diameter was associated with higher risk of incident AF. Future studies should explore whether noninvasive measures of pulsatile load, wave reflection, and endothelial function are intermediate phenotypes of incident AF.

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Novelty and Significance

What Is New?

- This study elucidates the relationship between markers of aortic stiffness, pulsatile load, endothelial dysfunction, and incident atrial fibrillation (AF) in a large, prospective, community-based cohort with long follow-up.
- We showed that greater apparent wave reflection measured by augmentation index was associated with higher risk of incident AF. Higher pulsatile load assessed by higher quartiles of central pulse pressure was associated with incident AF, despite adjustment for presence of hypertension. We also observed that vascular endothelial dysfunction measured by lower flow-mediated dilation and higher baseline brachial arterial diameter was associated with higher risk of incident AF.

What Is Relevant?

- Our findings support the notion that increased pulsatile load and impaired endothelial function may contribute to the pathogenesis of AF.

Summary

To better understand the pathophysiology of AF, we examined associations between noninvasive measures of vascular function and new-onset AF. AF developed in 407/5797 participants in the tonometry sample and 270/3921 participants in the endothelial function sample during follow-up (median 7.1 years, maximum 10 years). Higher pulsatile load assessed by central pulse pressure, and greater apparent wave reflection measured by augmentation index, were associated with increased risk of incident AF. Vascular endothelial dysfunction (assessed by lower flow-mediated dilation and higher baseline brachial arterial diameter) may precede development of AF. These measures may be additional risk factors or markers of subclinical cardiovascular disease associated with increased risk of incident AF.