Atrial Cardiopathy and the Risk of Ischemic Stroke in the CHS (Cardiovascular Health Study)

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Background and Purpose—Emerging evidence suggests that an underlying atrial cardiopathy may result in thromboembolism before atrial fibrillation (AF) develops. We examined the association between various markers of atrial cardiopathy and the risk of ischemic stroke.

Methods—The CHS (Cardiovascular Health Study) prospectively enrolled community-dwelling adults ≥65 years of age. For this study, we excluded participants diagnosed with stroke or AF before baseline. Exposures were several markers of atrial cardiopathy: baseline P-wave terminal force in ECG lead V_1, left atrial dimension on echocardiogram, and N terminal pro B type natriuretic peptide (NT-proBNP), as well as incident AF. Incident AF was ascertained from 12-lead electrocardiograms at annual study visits for the first decade after study enrollment and from inpatient and outpatient Medicare data throughout follow-up. The primary outcome was incident ischemic stroke. We used Cox proportional hazards models that included all 4 atrial cardiopathy markers along with adjustment for demographic characteristics and established vascular risk factors.

Results—Among 3723 participants who were free of stroke and AF at baseline and who had data on all atrial cardiopathy markers, 585 participants (15.7%) experienced an incident ischemic stroke during a median 12.9 years of follow-up. When all atrial cardiopathy markers were combined in 1 Cox model, we found significant associations with stroke for P-wave terminal force in ECG lead V_1 (hazard ratio per 1000 μV*ms 1.04; 95% confidence interval, 1.001–1.08), log-transformed NT-proBNP (hazard ratio per doubling of NT-proBNP, 1.09; 95% confidence interval, 1.03–1.16), and incident AF (hazard ratio, 2.04; 95% confidence interval, 1.67–2.48) but not left atrial dimension (hazard ratio per cm, 0.96; 95% confidence interval, 0.84–1.10).

Conclusions—In addition to clinically apparent AF, other evidence of abnormal atrial substrate is associated with subsequent ischemic stroke. This finding is consistent with the hypothesis that thromboembolism from the left atrium may occur in the setting of several different manifestations of atrial disease. **(*Stroke*. 2018;49:980-986. DOI: 10.1161/STROKEAHA.117.020059.)**

Key Words: adult ■ atrial fibrillation ■ cardiomyopathies ■ risk factors ■ thromboembolism

Standard evaluation fails to determine the cause of one third of ischemic strokes.[1] Such cryptogenic strokes often seem to have arisen from distant emboli.[2] Although subclinical atrial fibrillation (AF) is often suspected as the cause of these embolic appearing cryptogenic strokes, fewer than one third of patients with cryptogenic stroke manifest AF even after 3 years of continuous heart rhythm monitoring.[3] Several lines of evidence indicate that some cases of cryptogenic stroke may arise from an atrial cardiopathy that forms a nidus for thrombus formation and embolization even in the absence of AF.[4,5]

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P-wave terminal force in lead V_1 ($PTFV_1$)—a widely accepted marker of left atrial abnormality on 12-lead ECG (ECG)[6]—is associated with stroke[7–10] and radiographic brain infarction[11] in the absence of clinically apparent AF.[12] Left atrial size on echocardiogram is associated with stroke even after adjustment for clinically apparent AF.[13–16] Lastly, N terminal pro B type natriuretic peptide (NT-proBNP)—a marker of ventricular and atrial dysfunction—is associated with stroke independent of clinically apparent AF.[17–19] The association of several markers of atrial dysfunction with stroke, all independent of clinically apparent AF, is consistent with the hypothesis that atrial cardiopathy may cause stroke even in the absence of AF. To further test this hypothesis, we examined the association between various markers of atrial cardiopathy and the risk of stroke.

Materials and Methods

Design

The CHS (Cardiovascular Health Study) prospectively enrolled and continues to follow a community-dwelling cohort of men and women ≥65 years of age. CHS field centers recruited a first cohort of 5201 participants in 1989 to 1990 and a second cohort of 687 participants in 1992 to 1993. These 5888 participants were selected from a random sample of people on Medicare eligibility lists in 4 counties, 1 each in California, Maryland, North Carolina, and Pennsylvania.[20] Participants returned for annual in-person study visits until 1998 to 1999 and again in 2005 to 2006. Throughout follow-up, participants were contacted via semiannual telephone calls, and data were linked with Medicare claims. Institutional Review Boards at the University of Washington and each field center approved this study, and all participants provided written informed consent. CHS provided a suitable opportunity to test our study hypothesis given its prospective design, large sample, availability of multiple measurements of atrial cardiopathy at baseline, annual study ECGs for a substantial part of the follow-up period, and long-term follow-up with careful ascertainment and adjudication of incident stroke. Because of the sensitive nature of the data collected for this study, requests to access the data set from qualified researchers trained in human subject confidentiality protocols may be sent to the corresponding author.

Participants

CHS did not enroll participants who were <65 years of age, could not give consent or answer questions without a surrogate, resided in an institutional setting, were wheelchair dependent, or were receiving active treatment for cancer. For this study, we excluded CHS participants who had experienced a stroke (ischemic or hemorrhagic) or were diagnosed with AF before baseline.

Measurements

The exposures of interest were $PTFV_1$, left atrial dimension, NT-proBNP level, and incident AF. $PTFV_1$ was derived from digital 12-lead ECGs done at the baseline visit. ECGs were obtained on MAC PC ECG machines (Marquette Electronics, Milwaukee, WI) calibrated at 10 mm/mV with a speed of 25 mm/s. P-wave amplitudes and durations were centrally measured at the Wake Forest Epidemiological Cardiology Research Center using a fully automated program (12-SL, version 2001; GE Marquette). $PTFV_1$ was defined as the duration (ms) of the downward deflection (terminal portion) of the median P wave in lead V_1 multiplied by the absolute value of its amplitude (μV).[21] Left atrial dimension was based on M-mode data from echocardiograms performed at baseline for the first cohort of participants and 2 years after baseline for the second cohort.[22] NT-proBNP values were defined based on assays performed on blood stored and frozen at the time of echocardiograms.[23] Incident AF was ascertained from hospital discharge diagnoses, as well as diagnoses from inpatient or outpatient facility claims or physician claims in linked Medicare data throughout follow-up, and 12-lead ECGs at annual study visits through 1998 to 1999. AF identified only by self-report did not meet our definition of incident AF, nor did any AF diagnoses based on inpatient claims or hospital discharge records if accompanied by codes for coronary bypass or valve replacement surgery.[24]

The primary outcome was incident ischemic stroke. The methods for identification and adjudication of strokes in CHS have been published previously.[25] In brief, stroke was defined as the rapid onset of neurological deficit lasting >24 hours or until death, a lesion on computed tomography or magnetic resonance imaging, and no evidence that the symptoms were because of brain trauma, tumor, or infection. Ischemic stroke was further defined as: (1) a focal neurological deficit without evidence of intracranial hemorrhage on computed tomography, magnetic resonance imaging, or cerebrospinal fluid analysis or (2) imaging evidence of brain ischemia in a location compatible with the presenting symptoms. Because our hypothesis was that atrial cardiopathy can cause embolism that is not currently recognized as arising from a cardiac source, a secondary outcome was ischemic stroke subtyped as other, which mostly included ischemic strokes of uncertain cause. We also assessed lacunar strokes, which are typically nonembolic.

We adjusted our models for the following potential confounders: demographic characteristics, such as age, sex, race (black versus other race), and education level (<high school level versus high school or more); cardiovascular disease and risk factors, including body mass index, coronary heart disease, heart failure, diabetes mellitus, antihypertensive medications and systolic blood pressure, high- and low-density lipoprotein and triglyceride levels, and smoking status (never, past, or current). High- and low-density lipoprotein and triglyceride levels were carried forward from study enrollment for the second cohort.

Statistical Analysis

Because of the timing of echocardiographic assessments, the baseline for analyses involving left atrial dimension measurements was 1989 to 1990 for the first cohort and 1994 to 1995 (2 years after study baseline) for the second cohort. Baseline data were summarized separately for CHS participants excluded from our analysis, for those eligible but without all exposures of interest, and for those with all exposures of interest. Baseline characteristics were reported as mean and SD for continuous variables and number and percent for categorical variables.

Cox proportional hazards analysis was used to model the association between the exposures of interest and incident ischemic stroke. Participants were censored at the time of ischemic or hemorrhagic stroke, last follow-up, or death. The 3 atrial cardiopathy markers and a time-varying AF covariate were entered into the model separately and then in combination to test the hypothesis that each marker is associated with stroke independent of the other 3. For models involving only individual atrial cardiopathy markers, we included participants with data on at least that marker. For models involving all markers in combination, we included only participants with data on all markers. In our primary analysis, we included only incident AF diagnoses made before the time of ischemic stroke because in some cases, stroke may trigger AF rather than be caused by AF.[26] Based on prior work, we excluded $PTFV_1$ values >99.9th percentile as outliers, and modeled $PTFV_1$ as a linear variable.[7,9,11] We determined the functional form of left atrial dimension and NT-proBNP with penalized cubic splines before including these variables in the Cox model. Cubic splines were examined to help determine whether transformations of the exposures were appropriate. Because the associations of left atrial dimension with stroke and of log NT-proBNP with stroke were rather linear, we modeled left atrial dimension without transformation and NT-proBNP as log transformed. There was no evidence that modeling those exposures with splines in our main models was necessary. Results for NT-proBNP are for the log-transformed variable. All hazard ratios (HRs) for NT-proBNP in relation to stroke should be interpreted as the change in stroke risk associated with a doubling of

NT-proBNP because we used a log base 2 transformation. In our Cox analyses, model 1 was adjusted for age, race, and sex/gender, and model 2 was additionally adjusted for education, body mass index, coronary heart disease, heart failure, diabetes mellitus, systolic blood pressure, antihypertension medication, high-density lipoprotein level, low-density lipoprotein level, log-transformed triglyceride level, and smoking status.

In secondary analyses, we dichotomized continuous atrial cardiopathy markers using the following previously published cut points: $PTFV_1$ >4000 μV*ms.[27] NT-proBNP >185 pg/mL,[19] and left atrial dimension thresholds corresponding to moderate or severe left atrial dilatation (>4.3 cm for women and >4.7 cm for men).[28] Further secondary analyses were performed with other ischemic stroke and lacunar stroke as outcomes. We also tested 2-way interactions between each of the atrial cardiopathy markers.

We performed several sensitivity analyses. First, we included AF cases diagnosed at the time of stroke in the incident AF variable. Second, we adjusted all models that included left atrial dimension for body surface area. Third, we excluded participants with a left ventricular ejection fraction <45% on their echocardiogram given that NT-proBNP is associated with ventricular and atrial dysfunction. Fourth, we examined the association between the atrial cardiopathy markers and incident stroke while adjusting for the CHA_2DS_2-VASc score.

All statistical tests were 2 tailed, and the threshold of statistical significance was set at α=0.05. Statistical analyses were performed using Stata 12.1 (StataCorp, TX).

Results

Of the 5888 participants in the overall CHS cohort, 93 were excluded from the second cohort because they did not have a 1994 to 1995 clinic visit, 419 were excluded because of prevalent stroke or AF at baseline, and 256 were excluded for missing covariates, leaving 5120 who met our inclusion criteria. Compared with those who were excluded, the 5120 eligible participants were more often women, less often black, had received more formal education, and had a lower burden of vascular risk factors and comorbidities (Table 1). Left atrial dimension was similar in both excluded and eligible participants, but NT-proBNP and $PTFV_1$ were lower in eligible participants (Table 1).

During a median 12.7 years of follow-up, 817 ischemic strokes occurred among these 5120 participants (16.0%). In multivariable models that included 1 atrial cardiopathy marker at a time, we found associations with incident ischemic stroke for $PTFV_1$ (HR per 1000 μV*ms 1.05; 95% confidence interval [CI], 1.02–1.09), NT-proBNP (HR per doubling of NT-proBNP, 1.12; 95% CI, 1.05–1.18), and incident AF (HR, 2.06; 95% CI, 1.75–2.43) but not for left atrial dimension (HR per cm, 1.07; 95% CI, 0.95–1.21; Table 2).

Among the 5120 participants who were eligible for the analysis above, 1397 had missing data on at least 1 atrial cardiopathy marker, leaving 3723 participants for the analysis of all 4 atrial cardiopathy markers in combination (Table 1). During a median 12.9 years of follow-up, 585 ischemic strokes occurred among these 3723 participants (15.7%). When we included all atrial cardiopathy markers together in 1 model, we again found significant associations with incident ischemic stroke for $PTFV_1$ (HR per 1000 μV*ms 1.04; 95% CI, 1.001–1.08), NT-proBNP (HR per doubling of NT-proBNP, 1.09; 95% CI, 1.03–1.16), and incident AF (HR, 2.04; 95% CI, 1.67–2.48) but not for left atrial dimension (HR per cm, 0.96; 95% CI, 0.84–1.10; Table 2).

Table 1. Baseline Characteristics of Cardiovascular Health Study Participants

Characteristics*	Excluded (n=768)	Eligible for Partial Model (n=5120)	Eligible for Full Model (n=3723)
Age, y	75±6	73±6	73±5
Men	369 (48.0)	2126 (41.5)	1483 (39.8)
Black	279 (36.3)	645 (12.6)	520 (14.0)
Did not complete high school	279 (37.2)	1453 (28.4)	1080 (29.0)
Body mass index	27.0±4.9	26.6±4.6	26.7±4.7
Systolic blood pressure, mm Hg	141±22	137±21	137±21
Diastolic blood pressure, mm Hg	73±12	72±11	72±11
High-density lipoprotein, mg/dL	51±16	55±16	55±16
Low-density lipoprotein, mg/dL	125±38	130±35	130±35
Triglycerides, mg/dL	172±147	135±60	135±60
Coronary heart disease	215 (28.0)	952 (18.6)	680 (18.3)
Heart failure	98 (12.8)	195 (3.8)	132 (3.5)
Diabetes mellitus	179 (27.0)	753 (14.7)	621 (16.7)
Antihypertension medication use	415 (64.5)	2320 (45.3)	1721 (46.2)
Smoking status			
Never	344 (45.0)	2335 (45.6)	1744 (46.8)
Former	331 (43.3)	2179 (42.6)	1582 (42.5)
Current	90 (11.8)	606 (11.8)	397 (10.7)
Incident AF	NA	1835 (35.8)	1321 (35.5)
$PTFV_1$, μV*ms	3032±2615	2697±2145	2693±2123
Left atrial dimension, cm	4.2±0.9	3.9±0.7	3.9±0.7
NT-proBNP, pg/mL	706±1544	242±645	233±631

AF indicates atrial fibrillation; NT-proBNP, N-terminal pro-B-type natriuretic peptide; and $PTFV_1$, P-wave terminal force in lead V_1.

*Baseline characteristics are displayed by whether (1) patients were excluded from the analysis; (2) were included in the partial analytic model, which required data on at least 1 atrial cardiopathy marker; or (3) were included in the full analytic model, which required complete data on all atrial cardiopathy markers. Data are presented as mean±SD or n (%).

In tests of interaction using the full model, we found no significant interactions between the atrial cardiopathy markers in relation to incident ischemic stroke.

In the full model containing all 4 atrial cardiopathy markers, we found no associations between any of the markers and ischemic stroke subtypes classified as other (n=262; Table 3) or lacunar strokes. In dichotomized analyses using the full model, we found a significant association with stroke only for NT-proBNP >185 pg/mL (HR, 1.30; 95% CI, 1.08–1.58; Table 3).

Our results were similar in sensitivity analyses (Appendix in the online-only Data Supplement).

Table 2. Associations Between Markers of Atrial Cardiopathy and Incident Ischemic Stroke in Cardiovascular Health Study Participants

Marker	Model 1*	Model 2†
Individual markers		
$PTFV_1$ alone‡ (n=4954)	1.08 (1.04–1.11)	1.05 (1.02–1.09)
Left atrial dimension alone§ (n=4919)	1.15 (1.03–1.29)	1.07 (0.95–1.21)
NT-proBNP alone‖ (n=3992)	1.17 (1.11–1.24)	1.12 (1.05–1.18)
AF alone¶ (n=5120)	2.18 (1.85–2.57)	2.06 (1.75–2.43)
Combined markers#		
$PTFV_1$ (n=3723)	1.05 (1.01–1.09)	1.04 (1.001–1.08)
Left atrial dimension (n=3723)	0.99 (0.87–1.13)	0.96 (0.84–1.10)
NT-proBNP (n=3723)	1.13 (1.06–1.20)	1.09 (1.03–1.16)
AF (n=3723)	2.07 (1.70–2.52)	2.04 (1.67–2.48)

AF indicates atrial fibrillation; NT-proBNP, N-terminal pro-B-type natriuretic peptide; and $PTFV_1$, P-wave terminal force in ECG lead V_1.

*Adjusted for age, race, and sex/gender.

†Adjusted for the variables in model 1 plus education level, body mass index, coronary heart disease, heart failure, diabetes mellitus, systolic blood pressure, treatment with antihypertensive medications, high- and low-density lipoprotein level, log of triglyceride level, and smoking status (never, former, or current).

‡Results are reported as the hazard ratio for the outcome associated with a 1000-μV*ms higher $PTFV_1$ (95% confidence interval).

§Results are reported as the hazard ratio for the outcome associated with a 1-cm larger left atrial dimension (95% confidence interval).

‖Results are reported as the hazard ratio for the outcome associated with a doubling of NT-proBNP (95% confidence interval).

¶Results are reported as the hazard ratio for the outcome associated with incident AF as a time-varying variable.

#In the combined analysis of all markers, only participants with data on all 4 markers were included. In this analysis, model 2 included the other 3 atrial cardiopathy markers, as well as the marker of interest and the other covariates listed above. For example, results for $PTFV_1$ in model 2 of the combined marker analysis are adjusted for left atrial dimension, NT-proBNP, and AF, in addition to demographics and vascular risk factors.

Table 3. Secondary Analyses of Markers of Atrial Cardiopathy and Incident Ischemic Stroke in Cardiovascular Health Study Participants

Analysis	HR (95% CI)*
Dichotomized markers, ischemic stroke end point†	
$PTFV_1$	1.14 (0.95–1.38)
Left atrial dimension	1.01 (0.81–1.27)
NT-proBNP	1.30 (1.08–1.58)
Continuous markers, secondary ischemic stroke end point‡	
$PTFV_1$§	1.01 (0.95–1.07)
Left atrial dimension‖	1.01 (0.82–1.25)
NT-proBNP¶	1.00 (0.92–1.10)
AF#	0.93 (0.64–1.35)

AF indicates atrial fibrillation; CI, confidence interval; HR, hazard ratio; NT-proBNP, N-terminal pro-B-type natriuretic peptide; and $PTFV_1$, P-wave terminal force in ECG lead V_1.

*Model was adjusted for age, race, and sex/gender, education level, body mass index, coronary heart disease, heart failure, diabetes mellitus, systolic blood pressure, treatment with antihypertensive medications, high- and low-density lipoprotein level, log of triglyceride level, and smoking status (never, former, or current), in addition to the other atrial cardiopathy markers.

†Thresholds were 4000 μV*ms for $PTFV_1$, 4.3 cm for women, and 4.7 cm for men for left atrial dimension and 185 pg/mL for NT-proBNP.

‡Ischemic stroke subtyped as other, which included 262 ischemic strokes that were mostly of uncertain cause.

§Results are reported as the HR for the outcome associated with a 1000-μV*ms higher $PTFV_1$ (95% CI).

‖Results are reported as the HR for the outcome associated with a 1-cm larger left atrial dimension (95% CI).

¶Results are reported as the HR for the outcome associated with a doubling of NT-proBNP (95% CI).

#Results are reported as the HR for the outcome associated with incident AF as a time-varying variable.

Discussion

In a large, prospective, longitudinal cohort study, we found that evidence of abnormal atrial substrate, defined more broadly than just clinically apparent AF, was associated with incident ischemic stroke. Although incident AF seemed to be most strongly associated with stroke risk, comparisons are difficult because AF was treated as a time-varying variable and thus likely reflected later stages of atrial cardiopathy than the other markers, which were measured only at baseline. When the continuous variables were dichotomized, the associations with stroke were less robust, but the optimal cut points of these markers in regard to stroke risk are undefined, and dichotomization leads to loss of information for continuous markers.

These findings should be interpreted in the context of other recent findings on atrial dysfunction and stroke risk. $PTFV_1$ has been associated with stroke in several different longitudinal cohort studies.[7–9] The associations in these prior studies were unchanged regardless of adjustment for clinically apparent AF and were most pronounced for cryptogenic or embolic appearing stroke subtypes.[8,9] Our results build on these prior studies by showing that $PTFV_1$ is associated with stroke even after adjustment for other markers of atrial cardiopathy, such as left atrial size and NT-proBNP. $PTFV_1$ may reflect atrial changes, such as fibrosis[29,30] and elevated filling pressures,[31] that are not fully captured by echocardiographic or serum biomarker assessments.

The association between left atrial dilatation on echocardiogram and the risk of stroke, independent of clinically apparent AF, has been less consistent in prior studies. Larger left atrial size has been associated with a heightened risk of recurrent stroke, particularly cryptogenic or cardioembolic stroke, independent of AF.[16] An association between left atrial dilatation and incident stroke, independent of clinically apparent AF, has been noted in several different cohorts, but the association was not consistently seen across sexes and racial groups.[13–15] Left atrial size is strongly associated with AF[32] and with the risk of stroke in patients with AF,[33] but we found no association between left atrial size and ischemic stroke even before adjustment for clinically apparent AF. The reasons for these discordant results are unclear, and further research is required to better elucidate the relationship between echocardiographic left atrial size and stroke.

Elevated NT-proBNP levels can reflect both atrial and ventricular dysfunction. Prior studies have found robust associations between elevated NT-proBNP and stroke even after

adjustment for or exclusion of clinically apparent AF and heart failure,[17–19] suggesting that NT-proBNP may reflect atrial or other pathways associated with thromboembolism independent of AF. We similarly found an association between NT-proBNP and stroke after adjustment for clinically apparent AF and other markers of atrial cardiopathy. This association remained significant in a sensitivity analysis excluding those with a reduced left ventricular ejection fraction, supporting the hypothesis that NT-proBNP reflects thrombogenic atrial changes in addition to its established role in ventricular dysfunction.

Overall, our analysis builds on prior studies by indicating that in addition to clinically apparent AF, other evidence of atrial abnormality is independently associated with ischemic stroke. This finding calls to mind 2 key potential explanations, which are not mutually exclusive. First, these markers of atrial abnormality may serve as surrogates for subclinical AF, which has been associated with stroke in multiple studies.[34,35] Second, our findings are also consistent with the hypothesis that thromboembolism from the left atrium does not necessarily require AF and may occur in the setting of other manifestations of atrial disease.[4] Although the emerging concept of a thrombogenic atrial cardiopathy remains controversial,[36,37] it would explain several currently puzzling aspects of the relationship between AF and stroke, particularly the lack of a strong temporal linkage between AF and subsequent stroke, and may lead to a better mechanistic understanding.[38] In 2 recent studies of patients with implanted cardiac devices, one third of patients with both AF and stroke during the study had no AF documented during many months of heart rhythm monitoring before their stroke and only manifested AF for the first time after the stroke.[39,40] These findings would be less puzzling if left atrial thromboembolism can occur before AF begins. Such a concept would also explain why many cryptogenic strokes appear radiographically to have resulted from embolism, despite the lack of an obvious embolic source,[2] with only one third of these patients manifesting any AF during ≤3 years of poststroke continuous heart rhythm monitoring.[3] Because AF is currently conceived of as a prerequisite, cases of left atrial thromboembolism may currently go unrecognized and thus be classified as cryptogenic strokes.

Our results should be considered in light of the limitations of this study. First, participants did not undergo continuous heart rhythm monitoring to detect subclinical AF. Future studies will be needed to fully isolate the relationship between atrial cardiopathy markers and stroke independent of subclinical AF. Second, given the modest strength of associations between markers of atrial cardiopathy and our outcomes, as well as the multiple exposures tested, these results may simply represent chance findings. However, as discussed above, our results are consistent with findings from several other population-based studies of individual markers of atrial cardiopathy. Third, the characteristics of participants in this analysis differed from those of the overall CHS cohort. However, our results are consistent with the other population-based studies described above, in which data were used from the entire cohort of participants. Fourth, we lacked data on another end point, systemic embolism, which is of relevance to this hypothesis.

Many cases of AF are not diagnosed until a patient has already experienced a stroke.[3,41] Although the incidence of stroke occurring before AF is not high in absolute terms,[42] cardiac embolism causes especially severe strokes[43] and, therefore, represents an important target for reducing the global burden of stroke. Given the proven efficacy of anticoagulant therapy in reducing stroke risk in AF,[44] better efforts are needed to identify patients at risk of thromboembolism before stroke. Our findings suggest that such efforts may require assessment of both atrial rhythm and atrial substrate. Further research will be necessary to determine optimal strategies for assessing atrial rhythm and substrate to permit efficient targeting of anticoagulant therapy for high-risk patients while avoiding unnecessary adverse events from anticoagulation for those at low risk. Because an increasing share of strokes occur as a result of atrial thromboembolism,[45,46] improving our ability to prevent thromboembolic stroke may have a substantial impact on the enormous public health burden of stroke.

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Disclosures

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Atrial Cardiopathy and the Risk of Ischemic Stroke in the CHS (Cardiovascular Health Study)

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SUPPLEMENTAL MATERIAL

Atrial Cardiopathy and the Risk of Ischemic Stroke in the Cardiovascular Health Study

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Supplemental Results

We performed three sensitivity analyses using the full model. First, the associations did not substantially change depending on whether we included only AF diagnosed before stroke or also included AF diagnosed at the time of stroke, except that AF was now more strongly associated with stroke (HR, 2.92; 95% CI, 2.41-3.53). Second, the associations with the echocardiographic findings were not substantially different when adjusting for body surface area in models with left atrial dimension. Third, when excluding participants with a left ventricular ejection fraction <45% or missing (1,338 participants excluded), the association with ischemic stroke remained significant for $PTFV_1$ (HR per 1,000 μV*ms, 1.04; 95% CI, 1.0002-1.08), NT-proBNP (HR per doubling of NT-proBNP, 1.09; 95% CI, 1.03-1.17) and incident AF (HR, 2.07; 95% CI, 1.69-2.53). In addition, our results were similar in an alternative model containing the atrial cardiopathy markers and the CHA_2DS_2-VASc score.