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Atrial Mechanical Contraction Predicts Cerebrovascular Risk in Patients With Transthyretin Amyloid Cardiomyopathy and Sinus Rhythm

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ABSTRACT

BACKGROUND Patients with transthyretin amyloid cardiomyopathy (ATTR-CM) remain at risk of cerebrovascular events even when in sinus rhythm (SR), yet the majority of these patients are unrecognized.

OBJECTIVES This study sought to identify patients in SR at high risk of cerebrovascular events.

METHODS We analyzed patients diagnosed with ATTR-CM between January 2003 and December 2023 at the UK National Amyloidosis Centre. Left atrial (LA) function was assessed using speckle-tracking strain echocardiography. Atrial electromechanical dissociation (AEMD) was defined as SR on electrocardiogram with absent left atrial strain contraction (LASc). Patients in SR were stratified according to LASc tertiles. The primary outcome was a cerebrovascular event defined as stroke or transient ischemic attack (TIA), whichever occurred first. The secondary outcome was development of atrial fibrillation (AF). Death was treated as a competing event.

RESULTS The study comprised 2,310 patients with ATTR-CM, of which 873 patients were in SR and not receiving anticoagulation (age 77 years, 82% male, 61% wild type, CHA_2DS_2-VASc 4). AEMD was present in 115 patients (13.2%). Of the patients in SR, over a median of 34 months (Q1-Q3: 18-54 months), 269 patients (30.8%) developed incident AF and 85 (9.7%) experienced stroke/TIA. Patients with baseline AF receiving anticoagulation had a rate of stroke or TIA of 0.7 per 100 person-years. AEMD was associated with a 2.4-fold higher incident AF and 3-fold higher risk of stroke or TIA compared with SR with LA mechanical contraction (8.7 vs 2.5 per 100 person-years, respectively, for stroke or TIA), independent of CHA_2DS_2-based scores and markers of disease severity. Among 758 patients in SR without AEMD, LASc tertiles (<4%, 4%-7%, >7%) exhibited an independent association with 1-year risk of stroke or TIA, with LASc <4% being associated with 10-fold increased risk compared to LASc >7%. This association was consistent after adjustment for NAC stage and prior cerebrovascular events. Adding LASc tertiles to CHA_2DS_2-VASc or CHA_2DS_2-VA significantly improved model fit and risk reclassification at 1 year.

CONCLUSIONS LA dysfunction, particularly AEMD and severely impaired LASc, is associated with increased cerebrovascular events in ATTR-CM. Using LAS analysis may refine risk stratification and help identify patients with ATTR-CM in SR who might potentially benefit from intensified extended rhythm monitoring or prophylactic anticoagulation. (JACC. 2026;■:■-■) © 2026 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

AEMD = atrial electromechanical dissociation

AF = atrial fibrillation

ATTR = transthyretin amyloid

ATTR-CM = transthyretin amyloid cardiomyopathy

ATTRv-CM = p.V142I-associated variant transthyretin amyloid cardiomyopathy

CIF = cumulative incidence function

ECG = electrocardiogram

LA = left atrial

LAMC = left atrial mechanical contraction

LAS = left atrial strain

LASc = left atrial strain contraction

LASr = left atrial strain reservoir

LV = left ventricular

NAC = National Amyloidosis Centre

NRI = net reclassification improvement

NT-proBNP = N-terminal pro-B-type natriuretic peptide

sHR = subdistribution HR

SR = sinus rhythm

TIA = transient ischemic attack

TTR = transthyretin

Transthyretin amyloid cardiomyopathy (ATTR-CM) is a progressive and life-threatening disease caused by the accumulation of misfolded or cleaved transthyretin (TTR) protein in the form of amyloid fibrils within the myocardial extracellular space, with associated disruption in cardiac structure and function.[1] Systemic embolism is relatively common in ATTR-CM, with a reported incidence of 2.2 events per 100 patient-years in contemporary cohorts.[2]

Current guideline thresholds for anticoagulation are based on the CHA_2DS_2-VASc score,[3-5] which was developed and validated exclusively in patients with nonvalvular atrial fibrillation (AF). ATTR-CM patients with sinus rhythm (SR) rarely receive anticoagulation, and the CHA_2DS_2-VASc score is frequently applied in ATTR-CM with AF to guide anticoagulation decisions.[6] However, embolic events have been observed in patients with ATTR-CM even in the absence of AF,[2] underscoring the limitations of applying conventional risk stratification tools to this population.

ATTR amyloid infiltration of the atria impairs atrial systolic contraction and reservoir function[7], increasing the risk of left atrial (LA) thrombus formation.[8,9] With disease progression, patients in SR may have reduced left atrial mechanical contraction (LAMC) or lose effective LAMC entirely, a phenomenon defined as "atrial electromechanical dissociation" (AEMD).[7,9] However, only limited data exist on thromboembolic risk in ATTR-CM, and no studies have specifically examined the association between LA mechanical function and cerebrovascular events.[2,10-14]

The aim of our study was to: 1) characterize the LA phenotype using speckle-tracking strain analysis; 2) evaluate the association between LA function and the risk of stroke or transient ischemic attack (TIA) in a large cohort of patients with ATTR-CM; and 3) identify patients in SR at high risk of cerebrovascular events to help refine clinical decision-making.

METHODS

PATIENT POPULATION. This single-center, longitudinal, observational study was conducted at the National Amyloidosis Centre (NAC), Royal Free Hospital, London, United Kingdom. Data of patients with a diagnosis of ATTR-CM (January 2003 to December 2023) were retrospectively analyzed. Diagnosis of ATTR-CM was established on the basis of heart failure (HF) symptoms together with a characteristic echocardiogram or cardiac magnetic resonance study and either endomyocardial biopsy proof of TTR amyloid or Perugini grade 2 or 3 myocardial uptake on cardiac scintigraphy in the absence of either an abnormal serum free light chain ratio or a monoclonal immunoglobulin in the serum or urine by immunofixation.[15] The TTR gene was sequenced in all patients as previously described.[16] A flowchart of patient selection is shown in Supplemental Figure 1.

The presence of AF was defined by at least 1 of the following: 1) electrocardiogram (ECG) documentation of absolutely irregular RR intervals and no discernible, distinct P waves lasting for at least 30 seconds; 2) documentation of AF on Holter monitoring; or 3) history of pharmacological or direct current

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cardioversion, or AF catheter ablation. Patients with any history of AF were classified in the AF group, irrespective of their rhythm at presentation.

All patients were enrolled into a protocolized clinical follow-up program that consisted of 6 to 12 monthly consultations at the NAC with clinical assessment, laboratory tests, ECG, and echocardiography, including 24-hour Holter monitoring when clinically indicated.

The study was conducted in accordance with the Declaration of Helsinki, and patients provided written informed consent (ref: 06/Q0501/42, Royal Free Ethics Committee, London, United Kingdom).

LA ASSESSMENT. All echocardiograms were retrospectively reviewed by experienced operators and analyzed according to standard international definitions, as previously reported.[17] LA dimensions were reported as parasternal long-axis diameter, and absolute 4-chamber area and volume. LA speckle tracking analysis was performed offline by experienced operators (A.P., B.D.P., L.V., and Z.I.S.) in patients with SR and no history of AF using EchoPAC software version 206 (GE Healthcare), according to the current consensus document.[18] Briefly, a nonforeshortened 2-dimensional apical 4-chamber view was used to define a 3-mm thickened wall region of interest along the LA. The LA contour was extrapolated excluding pulmonary veins and LA appendage. Quality control checking was performed to reject cases with significant (greater than one-third of LA contour) dropout of the atrial wall. Zero baseline was defined as ventricular end-diastole, using the R-R cycle for analysis. LA myocardial deformation was assessed as global longitudinal strain obtained with the endocardial curve of the region of interest.

Left atrial reservoir (LASr), left atrial strain contraction (LASc), and conduit phases were defined as: LASr = peak value at the onset of left ventricular (LV) filling; LASc = peak value at the onset of atrial contraction; and LAS conduit = the difference between LASr and LASc. LA stiffness was calculated as the ratio between E/e′ and LASr, in which e′ is the mean value between lateral and septal e′.

AEMD was defined in presence of normal SR on a same-day surface ECG and absence of atrial contraction on LA strain analysis, as previously reported (Supplemental Figure 1).[7]

In cases where a transmitral A-wave was visible on pulsed-wave Doppler, but the LAS curve showed negligible late-diastolic shortening, the corresponding tracings were jointly reviewed. A mechanical atrial contraction was considered present only when a distinct late-diastolic strain deflection was observed within the expected contraction window on the simultaneously gated strain trace. When a Doppler A-wave was present, but strain amplitude was approaching near-zero, the finding was adjudicated as AEMD, consistent with absent effective mechanical contraction. Minor residual Doppler A-wave signals coexisting with near-zero strain were interpreted as passive transmitral flow or noise rather than active atrial contraction. These cases were categorized as AEMD for the primary analysis. AEMD was adjudicated by an expert operator (L.V.).

STATISTICAL ANALYSIS. Descriptive statistical analyses between the study groups were performed. All continuous variables were tested for normality (Shapiro-Wilk test) and presented as mean ± SD if the distribution was normal or median (Q1-Q3) otherwise. The independent sample *t*-test was used to compare 2 means if the data were normally distributed in each group, and the non-parametric Mann-Whitney *U* test was used to compare the distributions of the 2 groups otherwise. Categorical data are presented as frequencies and percentages, and compared using the chi-square test.

The primary outcome of the study was a composite of stroke or TIA, whichever occurred first. The secondary outcome measure was stroke. Stroke was defined as neurologic impairment due to vascular ischemia, excluding episodes lasting 24 hours or less, which were defined as TIA. Data on cerebrovascular events and AF were collected from NHS Digital via Summary Care Records held within NHS SPINE services—a centralized, nationwide system containing electronic health records from across the United Kingdom—and from official clinical reports generated at scheduled follow-up evaluations. All mortality data were obtained through the UK Office of National Statistics, which is the formal government registry for all deaths throughout the United Kingdom. The censor date was set at December 31, 2024.

All-cause death was treated as a competing event for stroke or TIA and incident AF.[19] Cumulative incidence functions (CIFs) were estimated using the Aalen-Johansen method and reported at 1, 3, and 5 years. Cumulative mortality was estimated using the Kaplan-Meier method at the same time points. Incidence rates for cerebrovascular events and AF were calculated per 100 patient-years, with follow-up censored at the earliest occurrence of the endpoint of interest, death, or the censoring date. Group comparisons were expressed as risk differences (percentage points) and risk ratios, derived from CIF estimates at 1, 3, and 5 years; corresponding 95% CIs were obtained using nonparametric bootstrap

resampling at the patient level (B = 1,000; percentile method). For stroke or TIA (primary endpoint), stroke alone (secondary endpoint, excluding TIA), and incident AF, Fine-Gray subdistribution hazard models (sHRs), using the respective endpoint as the event of interest and treating death as a competing event, were performed. These models provided sHRs for AEMD and LAS indices on the cumulative-incidence scale.

A competing-risk spline analysis was performed to explore the continuous relationship between LASc and cerebrovascular risk. Pseudo-values of the CIF for stroke/TIA at 1, 3, and 5 years (with death as a competing event) were regressed on absolute LASc using restricted cubic splines with knots placed at selected percentiles of the LASc distribution. Predicted CIFs with 95% CIs were plotted across the LASc range, with vertical reference lines at 4% and 7% to reflect the tertile boundaries. Global and nonlinear associations were assessed using Wald tests. The incremental prognostic value of adding AEMD or LASc tertiles to CHA_2DS_2-VASc or CHA_2DS_2-VA was quantified by likelihood-ratio tests comparing nested Fine-Gray models, and by categorical net reclassification improvement (NRI). For NRI, predicted 1-, 3-, and 5-year cerebrovascular risks were obtained from the Fine-Gray models, classified into prespecified categories <5%, 5% to <10%, and ≥10%, and the overall NRI (with standard errors and *P* values) was derived using established asymptotic methods. To assess the clinical utility of incorporating atrial mechanics into risk stratification, decision-curve analysis for stroke or TIA at 1 year was performed in patients without baseline AF (Supplemental Appendix).

Inter- and intraobserver reproducibility on a random sample of 30 echocardiograms was independently analyzed by 2 experienced observers (Z.I.S. and L.V.). For the binary AEMD classification (present/absent), interobserver agreement was quantified using Cohen's κ with 95% CIs. Agreement for continuous LASc was assessed using intraclass correlation coefficients (2-way mixed-effects model, absolute agreement) and Bland-Altman analysis (mean bias and 95% limits of agreement). All statistical analyses were performed using IBM SPSS Statistics 26.0 package and statistical software version 24, Stata Statistical Software: Release 15 (StataCorp), R software version 4.2.2 (R Project for Statistical Computing), and Python. We defined a *P* value <0.05 as statistically significant.

RESULTS

The overall study population comprised 2,310 patients with ATTR-CM (Supplemental Figure 2). The cohort comprised 1,722 patients (74.5%) with wild-type ATTR-CM (ATTRwt-CM), 394 (17.1%) with p.V142I-associated variant ATTR-CM (ATTRv-CM), 141 (6.1%) with p.T80A-associated ATTRv-CM, and 53 (2.3%) with other non-p.V142I, non-p.T80A variant ATTRv-CM genotypes.

Of the total population, 873 patients (37.8%) had no history of AF, were not receiving anticoagulation, were in SR, and had evaluable LAS analysis. They comprised 528 (60.0%) with ATTRwt-CM and 345 (40.0%) with ATTRv-CM. The median age was 77 years, and 82.0% were men. About 7% had a previous stroke or TIA. The median CHA_2DS_2-VASc score was 4 (Q1-Q3: 3-4), and the CHA_2DS_2-VA score 3 (Q1-Q3: 3-4). The median N-terminal pro-B-type natriuretic peptide (NT-proBNP) was 1,830 ng/L (Q1-Q3: 932-3,305 ng/L), and the median estimated glomerular filtration was 64 mL/min/1.73 m^2 (Q1-Q3: 50-78 mL/min/1.73 m^2). They were mostly in NAC stages 1 (64.0%) or 2 (26.0%), and in NYHA functional class I (19.0%) or II (64.0%). The median LV wall thickness was 16 mm (Q1-Q3: 15-18 mm), the median LVEF was 51% (Q1-Q3: 43%-58%), and the median E/e′ was 16.0 (Q1-Q3: 12-20). Median values for LASc, LASr, and LAS conduit were 4% (Q1-Q3: 2%-8%), 11% (Q1-Q3: 7%-15%), and 15% (Q1-Q3: 9%-23%). At diagnosis, beta-blockers, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker/angiotensin receptor/neprilysin inhibitor, mineralocorticoid receptor antagonist, and loop diuretic agents were prescribed in 64.0% (n = 361), 55.0% (n = 446), 35.0% (n = 283), and 65.0% (n = 530), respectively.

Compared with AF patients, patients in SR were younger, less often male, and more frequently had ATTRv-CM. They had fewer previous stroke or TIA, lower NT-proBNP and hs-troponin T levels, more preserved renal function, less severe HF by NYHA functional class, and were more frequently in NAC stage. They had lower LV wall thickness, less severe LV and right ventricular systolic dysfunction, and required less intensive diuretic and neurohormonal therapy. Characteristics of the study population are shown in **Table 1** and Supplemental Table 1.

ASSOCIATION BETWEEN LA FUNCTION AND CEREBROVASCULAR EVENTS. Over a median follow up of 34 months (Q1-Q3: 18-54) months], 5.0% of patients

TABLE 1 Patients Without a History of AF vs Those With a History of AF

	No History of AF (n = 873)	History of AF (n = 1,437)	*P* Value
Age, y	77 (70-82)	80 (75-84)	**<0.001**
Male	716 (82)	1,300 (91)	**<0.001**
Variant ATTR	345 (40)	243 (17)	**<0.001**
Hypertension	346 (42)	514 (37)	**0.042**
Diabetes	141 (16)	225 (16)	0.553
Ischemic etiology	170 (21)	276 (20)	0.624
Previous stroke/TIA	61 (7)	190 (13)	**<0.001**
CHA_2DS_2-VASc score	4 (3-4)	4 (3-5)	**0.001**
CHA_2DS_2-VA score	3 (3-4)	4 (3-4)	**<0.001**
HAS-BLED, approximated	1 (1-2)	2 (2-2)	**<0.001**
Cardiac device	89 (10)	226 (16%)	**<0.001**
NYHA functional class I/II/III/IV	156/535/135/7 (19/64/16/1)	125/928/312/24 (9/67/23/2)	**<0.001**
NAC 1/2/3	555/223/87 (64/26/10)	526/607/277 (37/43/20)	**<0.001**
NT-proBNP, ng/L	1,830 (932-3,305)	3,542 (2,011-6,101)	**<0.001**
hs-troponin T, ng/L	52 (35-78)	60 (42-90)	**<0.001**
eGFR, mL/min/1.73 m^2	64 (50-78)	57 (45-70)	**<0.001**
Therapies at baseline			
Antiplatelet therapy	238 (27)	332 (23)	**0.025**
Oral anticoagulants	0 (0)	1,437 (100)	**<0.001**
Statins	280 (32)	500 (35)	0.180
Loop diuretics	530 (65)	1,071 (77)	**<0.001**
MRA	283 (35)	570 (41)	**0.002**
SGLT2i	59 (7)	116 (8)	0.328
Beta-blocker	361 (64)	840 (61)	**<0.001**
ACEI/ARB	427 (52)	807 (58)	**0.005**
ARNI	19 (3)	36 (3)	0.980
Echocardiographic findings			
IVS, mm	16 (15-18)	17 (15-19)	**<0.001**
PW, mm	16 (15-18)	17 (15-18)	**<0.001**
LVEF, %	51 (43-58)	48 (40-55)	**<0.001**
LV-GLS, %	−11 (−14 to −9)	−10 (13 to −8)	**<0.001**
E/e′	16 (12-20)	14 (10-18)	**<0.001**
LA area, cm^2	25 (21-28)	28 (24-31)	**<0.001**
LAS reservoir, %	11 (7-15)	N/A	—
Absolute LAS contraction, %	4 (2-8)	N/A	—
LAS conduit, %	−15 (−23 to −9)	N/A	—
RA area, cm^2	21 (17-24)	26 (22-30)	**<0.001**
TAPSE, mm	17 (14-20)	14 (10-18)	**<0.001**

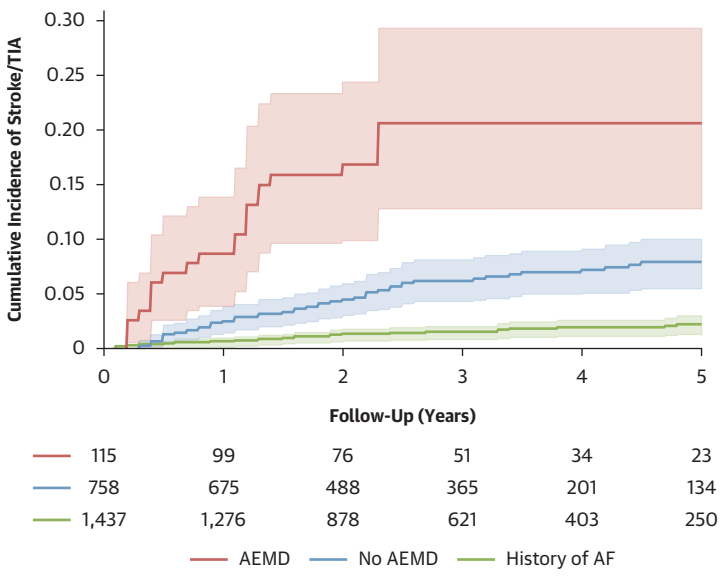
Values are median (Q1-Q3) or n (%). Significant *P* values are reported in **bold**. Percentages were calculated out of the available values.

ACEI/ARB/ARNI = angiotensin-converting enzyme inhibitor/angiotensin receptor blocker/angiotensin receptor/neprilysin inhibitor; AF = atrial fibrillation; eGFR = estimated glomerular filtration rate; GLS = global longitudinal strain; hs = high-sensitivity; ICD = implantable cardioverter-defibrillator; IVS = interventricular septum; LA = left atrial; LAS = left atrial strain; LV = left ventricular; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist; NAC = National Amyloidosis Centre; NYHA = New York Heart Association functional class; PPM = permanent pacemaker; PW = posterior wall; RA = right atrial; SGLT2i = sodium-glucose cotransporter 2 inhibitor; TAPSE = tricuspid annular plane systolic excursion; TIA = transient ischemic attack.

(n =114) experienced the composite outcome of stroke or TIA, defined as the first occurrence of either event. Overall, 3.7% (n = 85) experienced stroke, 1.6% (n = 37) experienced TIA, 30.8% (n = 269) had new documentation of AF, and 58.4% (n = 1,349) died.

Association of AEMD with development of AF and cerebrovascular events. Reproducibility analyses are available in the Supplemental Results. AEMD was present in 115 of 873 patients (13.2%) without baseline AF. Compared with those without AEMD, patients with AEMD had similar age, sex distribution, and prevalence of hypertension, diabetes, ischemic etiology, and prior stroke or TIA. They had features of more advanced cardiac disease with greater median NT-proBNP and hs-troponin T levels, and were more frequently in NAC stages 2 or 3. They

FIGURE 1 AEMD and Risk of Stroke or TIA



Cumulative incidence of stroke/transient ischemic attack (TIA) according to atrial rhythm/mechanical phenotype: baseline atrial fibrillation (AF) (all patients were on anticoagulation), sinus rhythm (SR) with a trial electromechanical dissociation (AEMD), and SR without AEMD. Death was treated as a competing event, and cumulative incidence functions were estimated using the Aalen-Johansen method. Ninety-five percent CIs for the cumulative incidence curves were obtained by nonparametric bootstrap resampling at the patient level, with percentile-based pointwise intervals shown as shaded areas. Numbers of patients at risk at each time point are reported below the plot.

had greater LV wall thickness and E/e′, and had lower LVEF. They had greater use of loop diuretic agents and MRAs (Supplemental Table 1).

AEMD was associated with a substantially higher cumulative incidence of both stroke or TIA, and AF when death was treated as a competing event (**Figure 1**, Supplemental Figure 2). Compared with SR with LAMC, AEMD patients had a 5-year cumulative incidence of stroke or TIA of 21% compared with 8%, and of AF was approximately 50% compared with 30%. Among the 85 patients in this group who had a stroke or TIA, only 10 (11.8%) had AF documented before the cerebrovascular event, and in one-half (n = 5), AF was first detected within 1 month before the stroke or TIA. In Fine-Gray subdistribution hazard models, AEMD was associated with a 3.0-fold higher risk of stroke or TIA (sHR: 2.92; 95% CI: 1.82-4.70; $P < 0.001$) and with a 2.4-fold higher subdistribution hazard of incident AF (sHR: 2.41; 95% CI: 1.81-3.21; $P < 0.001$). In extended Fine-Gray models including CHA_2DS_2-based scores, NAC stage, and prior stroke or TIA, AEMD retained a robust and independent association with stroke or TIA at 1, 3, and 5 years, with sHRs consistently in the 3 to 4 range and significant improvements in risk reclassification compared with score-only models (**Table 2**).

LA strain to predict development of AF and cerebrovascular events. Among patients without baseline AF and AEMD (n = 758), LA strain indices

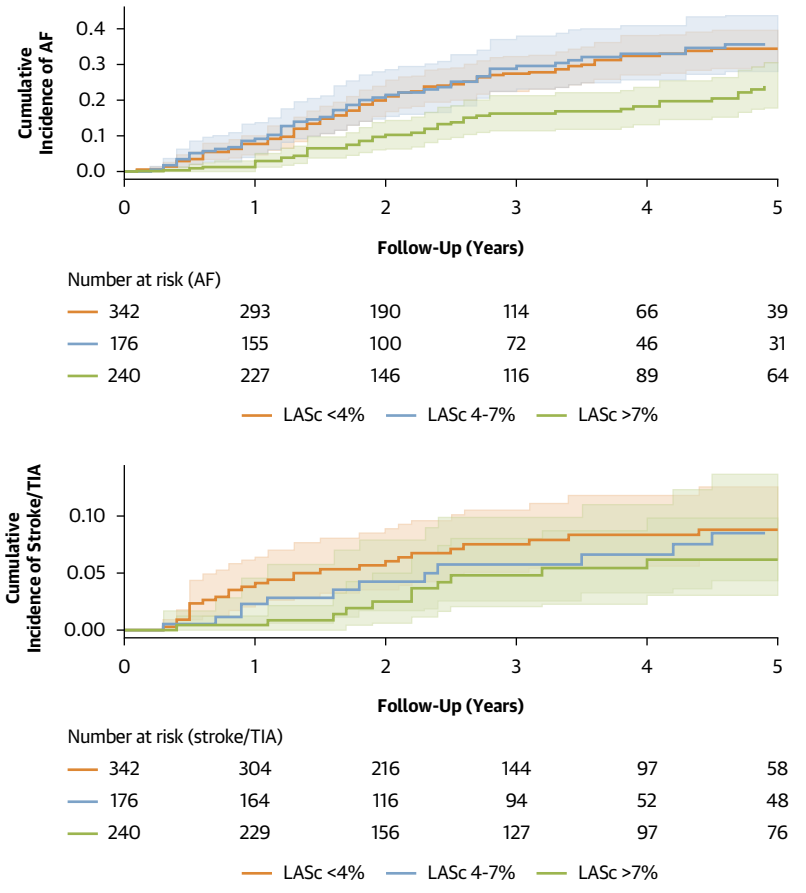
TABLE 2 Prognostic Impact of AEMD on Stroke/TIA in Patients Without Baseline AF

Model	Time, y	sHR (95% CI) for Stroke/TIA With AEMD	*P* Value	LR Chi-Square (1 df)	LR *P* Value	NRI ± SE	NRI *P* Value
AEMD, unadjusted	1	3.66 (1.70-7.87)	0.001	9.21	0.002	0.22 ± 0.09	0.015
CHA_2DS_2-VASc + AEMD		3.77 (1.75-8.11)	0.001	9.59	0.002	0.07 ± 0.01	<0.001
CHA_2DS_2-VA + AEMD		3.64 (1.69-7.83)	0.001	9.15	0.002	0.08 ± 0.01	<0.001
CHA_2DS_2-VASc + NAC stage + history of stroke/TIA + AEMD		3.37 (1.54-7.36)	0.002	7.97	0.005	0.29 ± 0.19	0.13
CHA_2DS_2-VA + NAC stage + history of stroke/TIA + AEMD		3.27 (1.50-7.13)	0.003	7.59	0.006	0.44 ± 0.18	0.015
AEMD, unadjusted	3	3.86 (2.30-6.49)	<0.001	20.68	5.5e-06	0.24 ± 0.06	<0.001
CHA_2DS_2-VASc + AEMD		3.84 (2.29-6.44)	<0.001	20.47	6.0e-06	0.07 ± 0.01	<0.001
CHA_2DS_2-VA + AEMD		3.77 (2.25-6.32)	<0.001	19.93	<0.001	0.08 ± 0.01	<0.001
CHA_2DS_2-VA + NAC stage + history of stroke/TIA + AEMD		3.69 (2.21-6.16)	<0.001	18.96	<0.001	0.59 ± 0.13	<0.001
CHA_2DS_2-VASc + NAC stage + history of stroke/TIA + AEMD		3.52 (2.11-5.86)	<0.001	17.98	<0.001	0.48 ± 0.12	<0.001
AEMD, unadjusted	5	3.22 (1.96-5.27)	<0.001	17.98	<0.001	0.20 ± 0.06	<0.001
CHA_2DS_2-VASc + AEMD		3.21 (1.96-5.26)	<0.001	17.93	<0.001	0.06 ± 0.02	<0.001
CHA_2DS_2-VA + AEMD		3.16 (1.93-5.18)	<0.001	17.51	<0.001	0.33 ± 0.11	0.003
CHA_2DS_2-VASc + NAC stage + history of stroke/TIA + AEMD		3.11 (1.89-5.12)	<0.001	16.83	<0.001	0.43 ± 0.12	<0.001
CHA_2DS_2-VA + NAC stage + history of stroke/TIA + AEMD		3.01 (1.83-4.96)	<0.001	15.96	<0.001	0.40 ± 0.11	<0.001

Fine-Gray subdistribution hazard models for stroke/TIA at fixed time-points (1, 3, and 5 years) in patients without baseline atrial fibrillation, treating death as a competing event. The table reports subdistribution HRs (sHRs) for atrial electromechanical dissociation (AEMD) (present vs absent), with 95% CIs and *P* values; likelihood-ratio (LR) test comparing nested Fine-Gray models with and without AEMD (only applicable to models including CHA_2DS_2-VASc or CHA_2DS_2-VA); and NRI, categorical net reclassification improvement (NRI) based on predicted 1-, 3-, and 5-year stroke/TIA risks derived from the Fine-Gray models and grouped into predefined risk categories (<5%, 5%-<10%, ≥10%).

Abbreviations as in Table 1.

FIGURE 2 LASc and Risk of AF and Stroke or TIA in Patients Without Atrial Electromechanical Dissociation



Cumulative incidence of incident AF (upper panel) and stroke/TIA (lower panel) in patients without a history of AF at baseline and without AEMD, stratified by left atrial strain contraction (LASc) tertiles (<4%, 4%-7%, >7%). Death was treated as a competing event, and cumulative incidence functions were estimated using the Aalen-Johansen method. Ninety-five percent CIs were obtained by nonparametric bootstrap resampling at the patient level, with percentile-based pointwise intervals shown as shaded areas. Numbers of patients at risk at each time point are reported below each panel. Abbreviations as in Figure 1.

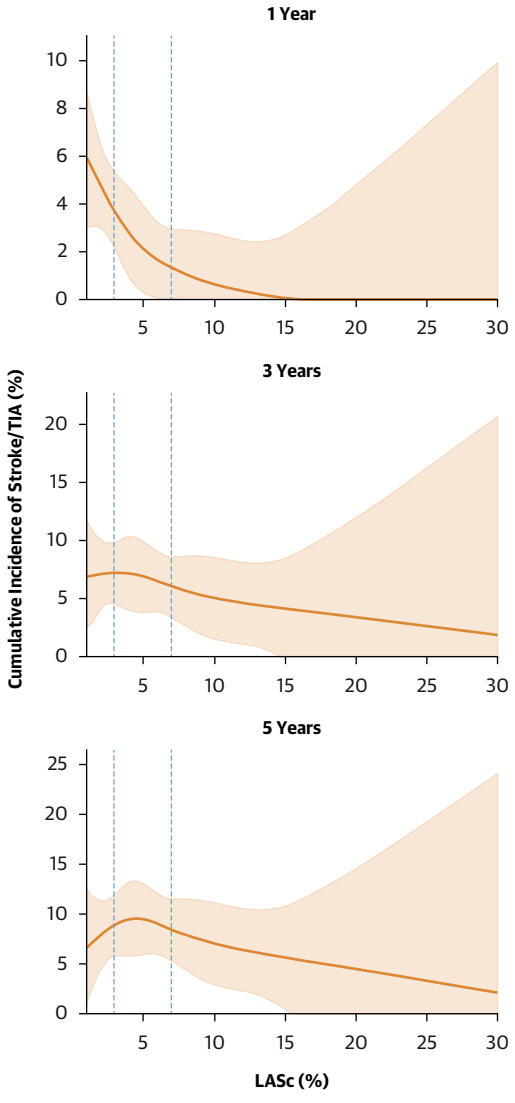
were classified using tertiles to further stratify the risk of cerebrovascular events of AF and stroke or TIA.

When patients were stratified according to LASr tertiles (≤9%, 9%-14.7%, >14.7%), no consistent monotonic gradient was observed in either the cumulative incidence of AF, or stroke or TIA (Supplemental Table 2).

When patients were stratified according to absolute LASc tertiles (<4%, 4%-7%, >7%), there was a gradient in the risk of AF and stroke or TIA across the tertiles, although with overlapping 95% CIs; for stroke or TIA, the gradient was more evident during the first 2 years (**Figure 2**). Spline curves showed the exponential increase in risk of stroke or TIA at 1 year with lower absolute LASc values, and different trends at 3 and 5 years (**Figure 3**). The cumulative incidence of incident AF at 1, 3, and 5 years was 6.1%, 26.1%, and 32.8% for LASc <4%; 10.2%, 30.3%, and 37.2% for LASc 4%-7%; and 3.0%, 16.2%, and 23.8% for LASc >7%, respectively.

LASc tertiles showed a strong and independent association with the 1-year risk of stroke or TIA. After adjustment for CHA_2DS_2-VASc or CHA_2DS_2-VA scores, patients in the lowest tertile (LASc <4%) had an approximately 10-fold higher 1-year risk of stroke or TIA compared with those with LASc >7%. This association remained significant after further adjustment for NAC stage and history of prior stroke or TIA (Supplemental Results). Adding LASc tertiles to CHA_2DS_2-VASc or CHA_2DS_2-VA scores significantly improved model performance and risk

FIGURE 3 LASc and Risk of Stroke or TIA in Patients Without Atrial Electromechanical Dysfunction: Spline Curve Analysis



The vertical dashed lines correspond to the LASc tertile cutpoints (4% and 7%). The 95% CIs are reported as shaded areas. Abbreviations as in Figures 1 and 2.

reclassification at 1 year. The incremental prognostic value at 3 and 5 years was attenuated and no longer statistically significant (Table 3).

DECISION-CURVE ANALYSIS FOR LASc IN ATTR-CM WITH SR. The clinical utility of incorporating AEMD and LASc into risk stratification models based on CHA_2DS_2 scores was assessed in ATTR-CM patients without baseline AF (n = 873; 29 cerebrovascular events within 1 year) (Supplemental Figures 3 to 5). Decision-curve analysis showed that models using CHA_2DS_2-VA alone and CHA_2DS_2-VASc alone both had greater net benefit than default strategies of anticoagulation in all or none of the patients across threshold probabilities between 1% and 10% for 1-year cerebrovascular risk. Adding AEMD to these score-only models further increased net benefit over a wide range of clinically relevant thresholds. At a 2% threshold, the net benefit for CHA_2DS_2-VA alone was 0.014, compared with 0.015 for CHA_2DS_2-VA + AEMD. At a 3% threshold, the net benefit increased from 0.009 with CHA_2DS_2-VA alone to 0.012 with CHA_2DS_2-VA + AEMD (difference 0.003, corresponding to 0.3 additional net correctly treated cerebrovascular events per 100 patients compared with treating none). For CHA_2DS_2-VASc, the net benefit at 3% rose from 0.008 with the score alone to 0.014 with the addition of AEMD (difference 0.006, ie, 0.6 additional net correctly treated events per 100 patients). Incorporating AEMD into CHA_2DS_2-based models yielded a clinically meaningful gain in decision-level performance around the usual anticoagulation thresholds.

SENSITIVITY AND SUBGROUP ANALYSES. The association of AEMD and LASc with stroke or TIA (including stroke as single endpoint) was further confirmed in sensitivity analyses using death as a competing event after excluding subgroups of patients with: 1) history of stroke/TIA at baseline; 2) AF detected within 30 days of stroke or TIA; and 3) AF detected at any time before stroke or TIA (Supplemental Tables 3 to 6). These associations were consistent after adjustment for disease severity markers and across clinically relevant subgroups (Supplemental Results).

DISCUSSION

This large study of over 2,300 patients with established ATTR-CM is the first to demonstrate a clear association between LA mechanical function—quantified by speckle-tracking strain analysis—and the risk of stroke or TIA among patients in SR. Key findings include: 1) LA mechanical dysfunction is common in ATTR-CM, with 13% of patients in SR exhibiting AEMD; 2) AEMD defines an intermediate phenotype characterized by advanced cardiac remodeling and higher natriuretic peptide levels than those with SR and LASc ≤−4.0%, but less atrial dilation and diuretic agent use than patients with AF;

TABLE 3 Prognostic Impact of LASc Tertiles on Stroke/TIA in Patients Without Baseline AF and Without AEMD

Marker	Model	Time, y	sHR LASc <4% vs >7%	95% CI	*P* Value	sHR LASc 4%-7% vs >7%	95% CI	*P* Value	LR Chi-Square (2 df)	LR *P* Value	NRI ± SE (*P* Value)
LASc tertiles	Unadjusted	1	9.91	1.30-75.34	0.027	5.32	0.59-47.63	–	–	–	–
	CHA_2DS_2-VASc		8.52	1.12-65.16	0.039	4.75	0.53-42.54	0.164	7.89	0.019	0.50 ± 0.11 (<0.001)
	CHA_2DS_2-VA		8.71	1.14-66.51	0.037	4.85	0.54-43.47	0.158	8.11	0.017	0.49 ± 0.11 (<0.001)
	CHA_2DS_2-VASc + NAC + stroke/TIA		8.64	1.11-67.11	0.039	4.67	0.52-42.01	0.169	7.64	0.022	0.53 ± 0.11 (<0.001)
	CHA_2DS_2-VA + NAC + stroke/TIA		8.79	1.13-68.24	0.038	4.75	0.53-42.72	0.164	7.76	0.021	0.53 ± 0.11 (<0.001)
LASc tertiles	Unadjusted	3	1.89	0.88-4.07	0.103	1.31	0.52-3.30	–	–	–	–
	CHA_2DS_2-VASc		1.68	0.78-3.62	0.189	1.20	0.47-3.02	0.703	2.05	0.359	0.17 ± 0.13 (0.197)
	CHA_2DS_2-VA		1.74	0.81-3.75	0.159	1.23	0.49-3.10	0.663	2.33	0.311	0.17 ± 0.13 (0.205)
	CHA_2DS_2-VASc + NAC + stroke/TIA		1.83	0.83-4.02	0.132	1.18	0.46-2.98	0.731	2.80	0.246	0.16 ± 0.15 (0.293)
	CHA_2DS_2-VA + NAC + stroke/TIA		1.88	0.86-4.13	0.116	1.22	0.48-3.09	0.675	2.95	0.229	0.15 ± 0.15 (0.301)
LASc tertiles	Unadjusted	5	1.83	0.91-3.68	0.093	1.45	0.64-3.28	–	–	–	–
	CHA_2DS_2-VASc		1.62	0.80-3.28	0.183	1.31	0.58-2.96	0.524	1.90	0.386	0.16 ± 0.12 (0.192)
	CHA_2DS_2-VA		1.67	0.83-3.38	0.154	1.34	0.59-3.03	0.488	2.18	0.336	0.16 ± 0.12 (0.200)
	CHA_2DS_2-VASc + NAC + stroke/TIA		1.72	0.84-3.53	0.141	1.26	0.55-2.86	0.586	2.42	0.299	0.15 ± 0.13 (0.239)
	CHA_2DS_2-VA + NAC + stroke/TIA		1.76	0.86-3.63	0.123	1.29	0.57-2.94	0.542	2.61	0.272	0.18 ± 0.13 (0.159)

Fine-Gray subdistribution hazard models for stroke/TIA at fixed time-points (1, 3, and 5 years) in patients without baseline atrial fibrillation, treating death as a competing event. The table reports incremental prognostic value of LASc tertiles on top of thromboembolic risk scores (likelihood-ratio tests and categorical NRI. Reference category: LASc >7%. LR test is comparing models with and without LASc tertiles (only applicable to models including CHA_2DS_2-VASc or CHA_2DS_2-VA; cells are left blank for unadjusted and clinical models). Categorical NRI is based on predicted 1-, 3-, and 5-year stroke/TIA risks derived from the Fine-Gray models and grouped into predefined risk categories (<5%, 5%-<10%, ≥10%).

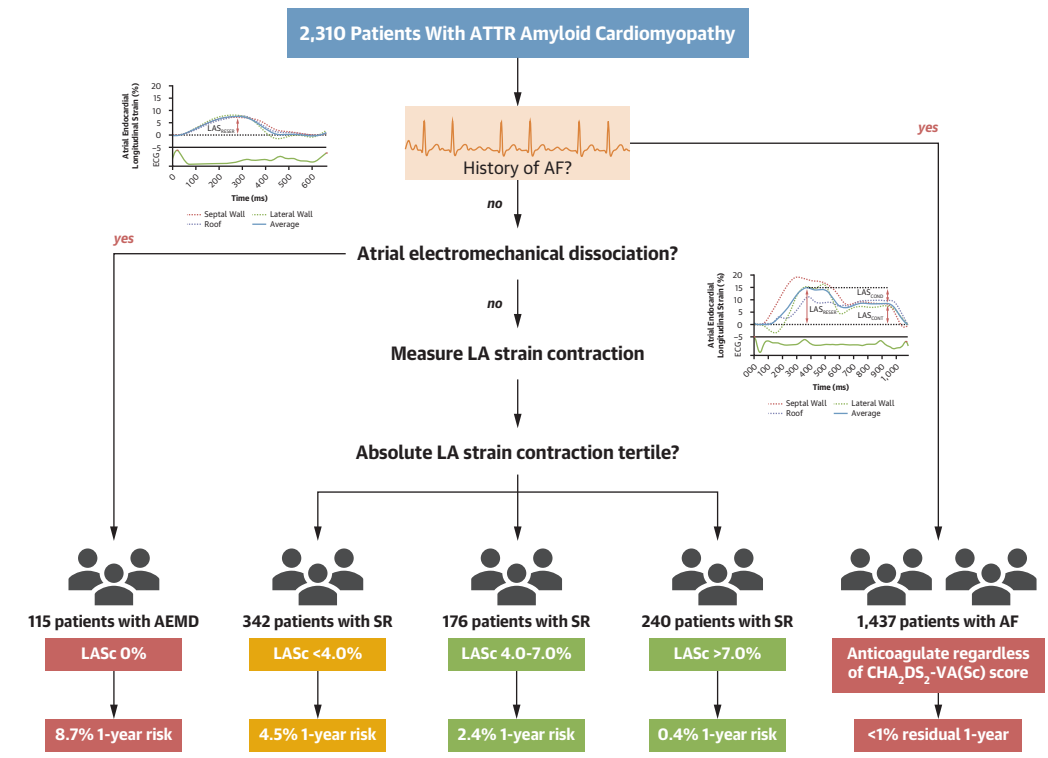
Abbreviations as in Tables 1 and 2.

and 3) worsening LASc was independently associated with an increased risk of cerebrovascular events, with AEMD conveying the highest risk. The predictive value of LASc was consistent across genotypes, disease stages, treatment status, and clinical trial participation. By directly linking atrial mechanics to hard clinical outcomes, this study bridges imaging phenotyping with event risk—a translational connection that has been missing in ATTR-CM.

ATTR-CM provides a unique model in which direct myocardial infiltration by amyloid leads to atrial dysfunction that is mechanical in nature and relatively independent of rhythm disturbances. Progressive amyloid deposition in the LA impairs reservoir, conduit, and contractile function, eventually leading to loss of mechanical contraction despite preserved SR on ECG—manifesting as AEMD.[7] Our study shows that both reduced LA function and AEMD are common in this population and are strongly associated with increased risk of stroke or TIA. These observations highlight atrial myopathy as a clinically meaningful risk phenotype, offering a measurable pathway to identify high-risk patients before AF manifests (**Central Illustration**).

Guideline thresholds for anticoagulation are defined using the CHA_2DS_2-VASc score rather than a fixed absolute risk.[3-5] In the original derivation study,[6] the anticoagulation threshold based on CHA_2DS_2-VASc corresponded to an annual risk of approximately 2.9% for stroke, TIA, or systemic embolism, providing a pragmatic anchor for comparison. In our study, patients in SR with LASc <4.0% had a 1-year cerebrovascular event rate exceeding 2.9% 1-year absolute risk of cerebrovascular events.[6,20,21] This rate rose dramatically to over ~9.0% per year in patients with AEMD, despite these individuals remaining in SR and not receiving anticoagulation therapy. The event rate in patients with AF on anticoagulation therapy was 0.7 per 100 patient-years. Notably, AF patients on anticoagulation typically have higher comorbidity burden and baseline thromboembolic risk, yet their crude event rate was lower than that seen with AEMD or LASc <4%. These findings confirm that impairment in atrial mechanics is a powerful and potentially clinically actionable marker of thromboembolic risk in ATTR-CM, with potential implications, moving beyond a purely rhythm-guided framework

CENTRAL ILLUSTRATION **Atrial Mechanical Contraction Predicts Cerebrovascular Risk in Patients With Transthyretin Amyloid Cardiomyopathy and Sinus Rhythm**



Porcari A, et al. JACC. 2026;■(■):■-■.

AEMD = atrial electromechanical dissociation; AF = atrial fibrillation; ATTR = transthyretin; ECG = electrocardiogram; LA = left atrial; LASc = left atrial strain contraction; SR = sinus rhythm; TIA = transient ischemic attack.

toward a function-informed approach to risk stratification.

Current clinical guidelines for stroke prevention in cardiology are based primarily on the presence of AF or atrial flutter,[22] and the CHA_2DS_2-VASc score remains the standard for guiding anticoagulation in nonvalvular AF.[3,6,23] However, this rhythm-based approach does not account for the underlying atrial mechanical substrate,[2,10,12,24,25] which is particularly relevant in amyloid cardiomyopathy, where LA dysfunction may precede or even occur in the absence of arrhythmia. Our findings, in line with recent data in nonamyloid patients,[26] challenge the assumption that SR implies preserved atrial function or low thromboembolic risk. In fact, the majority of cerebrovascular events in our cohort occurred in patients without known AF at the time of the event. In several cases, AF was diagnosed only months after the stroke or TIA, suggesting that electrical abnormalities may lag behind the onset of mechanical dysfunction.[27] Consistent with this, we also observed that impaired atrial mechanical function predicted subsequent incident AF, reinforcing the concept that mechanical failure precedes electrical instability in ATTR-CM. These observations support the hypothesis that atrial mechanical failure, rather than rhythm disturbance alone, may be the dominant mechanism predisposing to thromboembolism in ATTR-CM. As such, reliance on rhythm status alone for guiding anticoagulation may be inadequate in this population, and could leave a substantial number of high-risk patients untreated.

To address this, we propose a simple, clinically applicable classification based on LASc for risk stratification in patients with ATTR-CM and SR. This classification uses only standard echocardiographic parameters and identifies 2 high-risk groups: patients with AEMD and those with SR and LASc <4.0%. These patients demonstrated cerebrovascular event rates well above the anticoagulation threshold and

represent high-risk SR phenotypes who may warrant consideration in future trials of mechanically guided anticoagulation. Conversely, patients with SR and LASc ≥4.0% had event rates below the 2.9% threshold, suggesting that anticoagulation could be safely withheld in the short term.

Importantly, we emphasize that these thresholds are used only as a conceptual reference for clinicians—not as direct decision cutoffs for anticoagulation therapy in ATTR-CM. Any expansion of anticoagulation use in ATTR-CM must be balanced against bleeding risk, as patients are often elderly, frail, and with competing mortality risks and potentially distinct mechanisms of stroke. Careful patient selection, individualized risk-benefit evaluation, and close monitoring will therefore be crucial to ensure safety and maximize therapeutic benefit.

Overall, our findings suggest that rhythm status alone may be insufficient for thromboembolic risk assessment in ATTR-CM and that atrial mechanical function provides incremental prognostic insight. Rather than defining immediate treatment triggers, LASc and AEMD should be viewed as tools for identifying high-risk phenotypes refining clinical decision-making.

Prospective studies are now needed to validate this approach and determine whether anticoagulation guided by atrial strain parameters can improve outcomes. This work provides the rationale and framework for future mechanics-guided anticoagulation trials—potentially defining a new reference paradigm for evaluating atrial myopathy as a therapeutic target.

STUDY LIMITATIONS. These findings should be interpreted in light of several limitations. Atrial strain was assessed retrospectively, and approximately 10% of cases were excluded due to suboptimal image quality. Nonetheless, this represents the first and largest cohort to date in which LA strain has been systematically evaluated in ATTR-CM, offering novel insights into its clinical relevance, particularly among patients in SR. Strain analysis was performed using a single-vendor platform, and although this ensures internal consistency, it introduces the possibility of limited generalizability due to intervendor variability. Reproducibility was reassessed within this cohort, and consistent with prior studies, atrial strain measurements showed robust interobserver agreement.[28] Given the retrospective design and the inherent difficulty in determining the exact etiology of stroke, we did not attempt to distinguish between cardioembolic and non-cardioembolic events. However, the strong association between reduced LASc and cerebrovascular events supports the hypothesis that the majority of events in this population are of cardioembolic origin. Patients classified as being in SR were not systematically screened for paroxysmal AF using prolonged ECG or Holter monitoring. We recognize that undetected AF may mediate some of the observed events; however, the identification of a high-risk phenotype while patients are in SR remains clinically meaningful. This mechanical signature likely captures both atrial substrate remodeling and the propensity to develop AF or thrombus formation (Supplemental Figure 6). Thus, LA strain and AEMD may serve as upstream indicators of thromboembolic risk rather than substitutes for rhythm monitoring. We could not model incident AF or treatment changes as time-varying covariates. Despite adjustment for established prognostic markers, the presence of residual confounding by unmeasured or incompletely measured markers of disease severity, including dynamic changes in biomarkers, rhythm status and therapies (including antiplatelets and statins), cannot be excluded even after confirming the association of LASc with the risk of stroke or TIA by sensitivity analyses. Serial LASc measurements were not available to track changes in atrial contraction during follow up. Sensitivity analyses restricted to stroke as event of interest were performed to test the association of AEMD and LASc with registry-ascertained events, but were limited by an absolute low number of events at 1 year and are hypothesis-generating. Although our follow-up approach reduced the likelihood of major systematic differences in surveillance between groups, visit-level follow-up intensity by group could not be quantified. Therefore, a degree of surveillance bias, particularly for TIA and AF, cannot be entirely excluded. Finally, this was not a full predictive-modeling study, and LAS-based thresholds were not externally validated; the incremental value of LASc beyond CHA_2DS_2-based scores should therefore be viewed as hypothesis-generating.

CONCLUSIONS

Impaired LA function, particularly AEMD, is common in ATTR-CM and is independently associated with an increased risk of stroke or TIA among patients in SR, irrespective of TTR genotype, disease stage, treatment with disease-modifying therapies, or participation in clinical trials. Because patients with ATTR-CM not in AF rarely receive anticoagulation, these data suggest that they are at substantial increased risk for stroke

and TIA, and thus might benefit from anticoagulation. In the absence of randomized data, assessment of LASc offers a practical and reproducible method to identify high-risk patients in SR.

DATA AVAILABILITY STATEMENT The data underlying this paper cannot be shared publicly due to the privacy of individuals that participated in the study.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: In a large cohort of patients with ATTR-CM, LA AEMD was identified in 13% of patients in SR and was associated with a markedly increased risk of cerebrovascular events. In patients in SR, the 1-year risk increased with worsening LASc, and was highest in those with AEMD (8.7 events/100 patient-years). A simple clinical classification based on AEMD and LASc <4.0% improved identification of patients in SR at high risk of cerebrovascular events within 1 year.

TRANSLATIONAL OUTLOOK: Measurement of LA function using speckle-tracking echocardiographic strain is a novel and feasible approach to identify ATTR-CM patients in SR who are at increased risk of cerebrovascular events. This study supports the integration of LA strain contraction into clinical risk stratification algorithms to guide consideration of preventive anticoagulation in selected patients with ATTR-CM in SR.

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KEY WORDS anticoagulation, atrial mechanical function, prevention, stroke, transient ischemic attack, transthyretin amyloid cardiomyopathy

APPENDIX For expanded Methods and Results sections as well as supplemental figures and tables, please see the online version of this paper.