Supplementary Methods

Study population

Patients who were diagnosed with cryptogenic stroke and subsequently received an implantable loop recorder (ILR) for screening of atrial fibrillation (AF) at a tertiary care medical center in the United States between March 2015 and March 2022 were eligible for inclusion (n=235). Inclusion criteria consisted of diagnosis of cryptogenic stroke and follow-up for at least 1 year following ILR implantation or diagnosis of AF within 1 year of ILR implantation with interpretable two-dimensional echocardiograms in sinus rhythm. Patients were excluded for missing covariate data (n=34) and lack of adequate follow-up (n=43) resulting in a final cohort of 158 patients.

Exposure variable

All echocardiograms were reviewed by two independent board-certified cardiologists. Phasic left atrial volumes were calculated using biplane method of discs from the apical 2 and 4 chamber views in echocardiograms obtained at time of cryptogenic stroke. Maximum left atrial volume (LAVmax) and minimum left atrial volume (LAVmin) were calculated just before mitral valve opening and mitral valve closure, respectively. The following formula was utilized to calculate left atrial emptying fraction (LAEF): LAEF=[(LAVmax – LAVmin)/LAVmax]×100.

Outcome variables

Development of AF after cryptogenic stroke was the primary outcome of interest and was determined by presence of at least 30 seconds of AF on ILR as noted by independent cardiac electrophysiologists at the author's institution and retrospectively confirmed by the authors. Time to AF development and AF burden were determined retrospectively by the authors. AF burden at the time of AF diagnosis was calculated after a minimum of 7 days and depended on available ILR interrogation reports.

Development of recurrent stroke or transient ischemic attack (TIA) was the secondary outcome of interest and was determined by documentation in the institutional electronic medical record (EMR) by an independent neurology or cardiology provider. Recurrent stroke severity was recorded via the National Institutes of Health Stroke Scale as documented in the institutional EMR. Use of anticoagulation in our cohort included use of apixaban 5 mg twice daily, rivaroxaban 15 mg or 20 mg once daily, dabigatran 110 mg or 150 mg twice daily, or warfarin with a therapeutic international normalized ratio as per EMR review.

Covariates

The covariates included in this study included age, sex, hypertension, coronary artery disease (CAD), prior stroke or TIA, peripheral artery disease, diabetes mellitus, congestive heart failure, and carotid artery stenosis. Comorbid conditions were identified via the following criteria: (1) Hypertension: documented history of hypertension prior to sentinel admission; (2) CAD: documented history of myocardial infarction or presence of coronary artery stenosis >70% on coronary angiography. Coronary calcifications on CT chest were not included as CAD; (3) Prior stroke or TIA: documented history of stroke or TIA prior to sentinel admission. Incidental evidence of prior infarct on computed tomography (CT) or magnetic resonance imaging (MRI) was not included as having history of stroke if the patient did not have clinical symptoms or documentation of stroke prior; (4) Peripheral artery disease: documented history of peripheral arterial disease or history of peripheral arterial stent placement; (5) Diabetes mellitus: documented history of diabetes mellitus or any hemoglobin A1c >6.5%; (6) Congestive heart failure: documented history of heart failure or presence of a left ventricular ejection fraction of <40% on echocardiography prior to sentinel admission; and (7) Carotid artery stenosis: evidence of >70% carotid artery stenosis on CT angiography or carotid Doppler ultrasound. Left atrial maximal volume index was calculated using the following formula: LAVmax/body surface area.

Statistical analysis

Differences between means were determined using the Student's t-test for continuous variables. The chi-squared test or Fisher's exact test were used for categorical variables when appropriate.

The relationship between LAEF and incident AF was explored using a restricted cubic spline adjusted for age, sex, hypertension, CAD, stroke or TIA, peripheral artery disease, diabetes, carotid artery stenosis, congestive heart failure, and left atrial volume index with the knots at 10%, 50%, and 90%.

The association between LAEF and incident AF after cryptogenic stroke was evaluated using Cox proportional hazards models. LAEF was evaluated both as a continuous variable (per 5% decrease) and a categorical variable with categories corresponding to the whole number closest to the bottom 10%, middle 30%, and remaining 60% as reference. Unadjusted cumulative incidence curves were generated for each category. Model 1 included the exposure variable (LAEF) and the following covariates: age and sex. Model 2 added hypertension, CAD, stroke/TIA, peripheral artery disease, diabetes mellitus, carotid artery stenosis, and congestive heart failure. Model 3 added left atrial volume index. Discrimination and calibration for Models 3' (covariates only) and 3 (covariates plus LAEF) were evaluated by calculating the C-statistic and Hosmer-Lemeshow χ^2 statistic.

The association between LAEF and recurrent stroke or TIA af-

ter cryptogenic stroke was evaluated using Cox proportional hazards models. Model A was adjusted for age and sex. Model B was additionally adjusted for hypertension, heart failure, stroke/TIA, peripheral artery disease, diabetes, CAD, carotid artery stenosis, and anticoagulation. Model C was additionally adjusted for left atrial volume index. Model D was additionally adjusted for incident AF.

Supplementary Table 1. Baseline characteristics for primary endpoint

Variable	AF (n=43)	No AF (n=115)	*P*
Mean age (yr)	72.46	69.31	0.14
Male sex	21 (48.84)	54 (46.96)	0.83
Hypertension	31 (72.09)	91 (79.13)	0.35
Coronary artery disease	8 (18.60)	16 (13.91)	0.46
Stroke/transient ischemic attack	8 (18.60)	20 (17.39)	0.86
Peripheral artery disease	9 (20.93)	15 (13.04)	0.22
Diabetes	8 (18.60)	44 (38.26)	0.02
Congestive heart failure	2 (4.65)	10 (8.70)	0.39
Carotid artery stenosis	7 (16.28)	17 (15.65)	0.92
Left atrial volume index (mL/m^2)	36.76±11.54	31.01±11.43	<0.01
Left atrial emptying fraction (%)	48.21±14.87	56.93±13.07	<0.01

Values are presented as n (%) or mean±standard error unless otherwise indicated.
AF, atrial fibrillation.

Supplementary Table 2. Baseline characteristics for secondary endpoint

Variable	Recurrent stroke			No recurrent stroke		
	AF (n=6)	No AF (n=5)	Total (n=11)	AF (n=37)	No AF (n=110)	Total (n=147)
Number of recurrent stroke (on anticoagulation)	6 (4)	5 (0)	11 (4)	-	-	-
NIHSS (on anticoagulation)	0±0 (0±0)	3.6±3.6 (-)	1.8±3.1 (0±0)	-	-	-
Left atrial emptying fraction (%)	44.11±20.69	45.62±19.07	44.79±18.98	49.03±13.82	57.47±12.68	55.28±13.45
Left atrial volume index (mL/m^2)	36.56±9.43	39.79±16.52	38.03±12.51	36.30±12.17	30.72±11.07	32.16±11.59
Carotid artery stenosis	2	0	2	5	18	23
Age (yr)	68.0±9.81	70.40±10.97	69.09±9.89	73.19±11.38	69.26±12.44	70.25±12.26
Female sex	3	2	5	19	59	78
Hypertension	5	3	8	26	88	114
Heart failure	0	1	1	2	9	11
Diabetes	3	3	6	5	41	46
Peripheral artery disease	2	1	3	7	14	21
Coronary artery disease	3	1	4	5	15	20
Stroke/transient ischemic attack	2	0	2	6	20	26

Values are presented as mean±standard error or numbers only.
AF, atrial fibrillation; NIHSS, National Institutes of Health Stroke Scale.

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