Usefulness of Rhythm Monitoring Following Acute Ischemic Stroke

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We characterized monitor utilization in stroke survivors and assessed associations with underlying clinical atrial fibrillation (AF) risk. We retrospectively analyzed consecutive patients with acute ischemic stroke 10/2018-6/2019 without prevalent AF and assessed the 6-month incidence of monitor utilization (Holter/ECG, event/patch, implantable loop recorder [ILR]) using Fine-Gray models accounting for the competing risk of death. We assessed for predictors of monitor utilization using cause-specific hazards regression adjusted for the Cohorts for Heart and Aging Research in Genomic Epidemiology AF (CHARGE-AF) score, stroke subtype, and discharge disposition. Of 493 patients with acute ischemic stroke (age 65±16; 47% women), the 6-month incidence of monitor utilization was 36.5% (95% CI 31.7, 41.3), and 6-month mortality was 13.6% (10.4, 16.8). Monitoring was performed with Holter/event (n = 107; 72.3%), ILR (n = 34; 23.0%) or both (n = 7; 4.7%). Monitoring was more likely after cryptogenic (hazard ratio [HR] 4.53 [3.22, 6.39]; 6-month monitor incidence 70.6%) and cardioembolic (HR 2.43 [1.28, 4.62]; incidence 47.7%) stroke, versus other/undocumented (incidence 22.7%). Among patients with cryptogenic stroke, the 6-month incidence of ILR was 27.5% [18.5, 36.5]. Monitoring was more likely after discharge home (HR 1.80 [1.29, 2.52]; incidence 46.1%) versus facility (incidence 24.9%). Monitoring was not associated with CHARGE-AF score (HR 1.08 per 1-SD increase [0.91, 1.27]), even though CHARGE-AF was associated with incident AF (HR 1.56 [1.03, 2.35]). In conclusion, rhythm monitors are utilized after one-third of ischemic strokes. Monitoring is more frequent after cryptogenic strokes, though ILR use is low. Monitor utilization is not associated with AF risk. **(Am J Cardiol 2021;147:44−51)**

Atrial fibrillation (AF) is a well-recognized risk factor for ischemic stroke, and AF-related strokes are typically severe.[1,2] Recognizing AF as the underlying mechanism of stroke is important, as oral anticoagulation substantially reduces risk of recurrent stroke.[3−5] AF is frequently subclinical, however, and detected only after extended rhythm monitoring.[6−8] As a result, current guidelines provide a Class IIa recommendation (moderate strength and good quality evidence) for extended rhythm monitoring ("approximately 30 days") within 6 months following cryptogenic stroke (i.e., strokes with no apparent mechanism).[9] However, rhythm monitoring is costly, can be invasive, and most patients who receive monitoring ultimately do not have AF.[8] Furthermore, limited data suggest that ambulatory monitors are utilized in only a minority of patients after stroke,[10,11] and the effect of factors such as AF-related co-morbidity or stroke subtype on monitor use remain unclear. A better understanding of after-stroke monitor utilization and its determinants may therefore identify opportunities to optimize monitoring yield and appropriateness. In this study, we retrospectively assessed monitor utilization within consecutive patients presenting to a single large tertiary care hospital with acute ischemic stroke and no previous history of AF. We quantified overall monitor utilization and predictors of monitor deployment, including stroke subtype and co-morbidities predictive of AF.[12]

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Methods

The data supporting the current study contains protected health information and cannot be shared publicly. Relevant data processing scripts will be made available upon reasonable request to the corresponding author.

We retrospectively analyzed consecutive patients discharged from the stroke service of Massachusetts General Hospital, a tertiary referral center serving the New England region of the United States, following hospitalization for acute ischemic stroke between October 2018 and June 2019. Given our intent to characterize monitor utilization to detect undiagnosed AF, we excluded patients with prevalent AF or AF first detected during their hospitalization. To assess for heterogeneity in monitor utilization by provider, as well as the association between clinical risk of AF and rhythm monitoring, we also excluded patients whose hospitalizations spanned transitions between stroke service attending physicians, and patients with incomplete data for calculation of the CHARGE-AF score. Patient flow through the study is depicted in Figure 1. This study was approved the local Mass General Brigham Institutional Review Board.

AF-related clinical factors were ascertained after discharge from the index stroke admission by clinical abstractors. Age, gender, and self-reported race were obtained from the electronic health record (EHR) demographic data. Self-reported ethnicity was not collected. Height, weight, systolic and diastolic blood pressure were obtained from initial neurological exam documentation. If weight was not documented, we accepted any weight in the EHR within 1 year of stroke. If height was not documented, we accepted any height in the EHR. The presence of smoking (current or not current), chronic hypertension, diabetes, history of myocardial infarction, and history of heart failure were obtained from the initial neurological history and physical exam. Discharge disposition (home vs rehabilitation facility) was obtained from the index discharge summary.

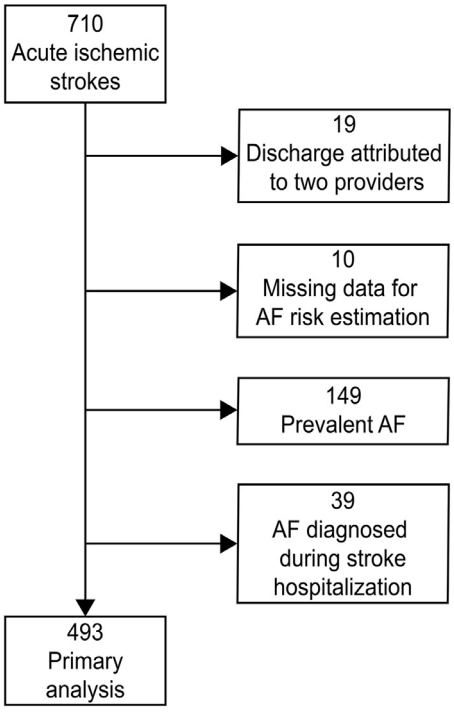

Figure 1. Patient flow diagram. A total of 710 patients were discharged from the acute stroke service at Massachusetts General Hospital during the study period and were therefore potentially eligible for analysis. After applying the listed exclusion criteria in sequence, the primary analysis sample comprised 493 patients with acute ischemic stroke and no prior history of AF.

We estimated AF risk using the linear predictor of the Cohorts for Heart and Aging Research in Genomic Epidemiology AF (CHARGE-AF) score, a well-validated AF prediction instrument.[12–14] For the purposes of calculating CHARGE-AF, the coefficient associated with white race was applied to patients of self-reported white race and not to patients of other races.[13,15] Score components and weights are shown in Supplementary Table 1. Since many anti-hypertensive agents have multiple indications, we substituted the diagnosis of hypertension for anti-hypertensive medication use in the CHARGE-AF score, as performed previously.[13] Given that the calibration of predicted AF risk estimates obtained using CHARGE-AF has not been assessed in an after-stroke setting, we did not attempt to convert CHARGE-AF to predicted absolute AF risk.

All patients were admitted to a dedicated stroke unit and underwent routine assessment for ischemic stroke etiology including continuous telemetry monitoring and electrocardiograms. Stroke subtypes were assigned in accordance with the classification schema utilized by the American Heart Association Get with the Guidelines Stroke initiative[16] by clinical abstractors who manually reviewed physician notes available at the time of discharge from the index stroke hospitalization to extract the treating neurologist's clinical impression of stroke subtype (see the Supplementary Appendix).[16] We collapsed the outlined ischemic stroke classification schema into 3 parent categories: cardioembolic, cryptogenic, and other/undocumented.

The primary outcome was cardiac monitor utilization at 6 months from stroke admission, defined as any of the following: (1) 24-48 hour Holter/ECG monitor, (2) 2-4 week event/patch monitor, or (3) implantable loop recorder (ILR). We utilized a 6-month timeframe for the primary outcome given current guidelines recommending extended monitoring within 6 months for patients with cryptogenic stroke,[9] and assessed other timeframes in secondary analyses. We accounted for death as a competing risk given the mortality associated with acute ischemic stroke.[2] Secondary outcomes included monitor utilization at 3 months and 12 months. In exploratory analyses, we also assessed incident AF at 12 months and recurrent stroke at 12 months. Monitor utilization, mortality, incident AF, and recurrent stroke were adjudicated by manual review of EHR data spanning from stroke admission to death or last encounter (defined as any inpatient encounter or outpatient office visit) by 3 clinical adjudicators blinded to stroke subtype and clinical AF risk. The median follow-up time in the EHR from stroke admission to death or last encounter was 5.1 months (quartile 1: 0.53, quartile 3: 8.7).

In all survival analyses, follow-up time began at stroke admission and ended at a monitoring event, death, or last encounter. To assess for associations between clinical

factors and 6-month monitor utilization, we fit multivariable Cox proportional hazards models with death treated as a censoring event and CHARGE-AF score, stroke subtype, and discharge disposition as covariates. We assessed for potential non-linearity in the association between the CHARGE-AF score and monitor utilization using fractional polynomials.[17] Given no evidence of non-linearity, we utilized the CHARGE-AF score as a linear variable in all models. The proportional hazards assumption was verified by inspecting scaled Schoenfeld residuals. We assessed heterogeneity in monitor utilization across providers by calculating the intra-class correlation coefficient and standard deviation (SD) of monitoring incidence across providers.

We estimated the cumulative incidence of any monitoring with treatment of death as a competing risk. We plotted the 6-month crude cumulative incidence of monitoring stratified by discharge disposition and stroke subtype, and the 6-month crude cumulative incidence of monitoring stratified by tertile of CHARGE-AF score. To estimate monitoring incidence across strata of interest while accounting for the effects of clinical factors, we used Fine-Gray models to predict stratum-specific incidence estimates for an average profile of other covariates included in our multivariable model.

In secondary analyses, we plotted the cumulative incidence of ILR use and fit additional Cox proportional hazards models with ILR utilization as the outcome of interest. To assess the association between covariates and the cumulative incidence of monitoring, we also conducted a subdistribution hazards analysis by fitting a Fine-Gray model with the same predictors.[18] Temporal trends of monitoring were evaluated by fitting additional Cox proportional hazards models including (1) month of discharge, and (2) quarter of discharge, and assessing whether models including calendar time had improved model fit as compared with models not including calendar time, using the likelihood ratio test. To assess whether AF risk factors were associated with incident AF or recurrent stroke, we fit Cox proportional hazards models with (1) incident AF, and (2) recurrent stroke, as outcomes of interest and CHARGE-AF score as the sole predictor.

We considered a 2-sided p value <0.05 to indicate statistical significance. All analyses were performed using R v3.6[19] and SAS v9.4 (SAS Institute, Cary North Carolina).

Results

Of 710 patients discharged after acute ischemic stroke during the study period, 149 (21.0%) had a previous diagnosis of AF, 39 (5.5%) developed incident AF prior to discharge, 19 (4.1%) were seen by multiple providers and 10 (1.4%) had inadequate data for AF risk estimation, resulting in 493 patients in the primary analysis (Figure 1). The mean age (±SD) was 65±16 years and 47.5% were female. Other baseline characteristics are listed in Table 1. Characteristics of patients meeting exclusion criteria are shown in Supplementary Table 2.

At 6 months, the cumulative incidence of any monitoring was 36.5% (95% CI 31.7, 41.3) and the cumulative incidence of death was 13.6% (95% CI 10.4, 16.8) over median follow-up 1 month (interquartile range 0.2-5.9). Of the monitors utilized, the vast majority were Holter/patch/event monitor (n = 107; 72%), followed by ILR (n = 34; 23%) or both (n = 7; 5%). In multivariable Cox regression, monitor utilization was higher for cryptogenic and cardioembolic stroke subtypes (vs other/undocumented), and higher among patients discharged home (vs facility). There was no significant association between CHARGE-AF score and monitor utilization (Table 2). Association results were similar using the Fine-Gray model (Supplementary Table 3). Across the 11 stroke providers, the variation in monitor utilization was not explained by variation between providers as opposed to variation between patients within providers (intra-class correlation coefficient 0.01; SD of monitoring incidence across providers 6%).

Table 1
Baseline characteristics

Variable (N = 493)	Mean ± standard deviation or N (%)
Age (years)	64.5 ± 16
Female	234 (48%)
White	354 (72%)
Black	119 (24%)
Asian	20 (4%)
Active smoker	86 (17%)
Height (cm)	167 ± 12
Weight (kg)	80 ± 39
Systolic blood pressure (mmHg)	157 ± 32
Diastolic blood pressure (mmHg)	83 ± 17
Diabetes mellitus	115 (23%)
Heart failure	23 (5%)
CHARGE-AF	12.8 ± 1.9
Stroke mechanism	
Cardioembolic	29 (6%)
Cryptogenic	130 (26%)
Other/undocumented	334 (68%)

The cumulative incidence of any monitoring in the overall sample, as well as the adjusted cumulative incidences of monitoring stratified by stroke mechanism and discharge disposition are shown in Table 3 and depicted in Figure 2. Unadjusted cumulative incidence curves stratified by stroke mechanism and discharge disposition are shown in Supplementary Figure 1. The adjusted cumulative incidence of any monitoring at 6 months was 70.6% (95% CI 59.7, 79.0) for patients with cryptogenic stroke and 46.1% (95% CI 37.8, 54.1) for patients discharged home. In contrast, the adjusted cumulative incidence of monitoring was 22.7% (95% CI 17.8, 27.9) for patients with other/undocumented stroke subtype. The cumulative incidence of monitoring was similar across tertiles of AF risk using the CHARGE-AF score (adjusted cumulative incidence range 31.4-35.7%, Table 3 and Figure 3). Discharge home was more frequent among patients with cryptogenic stroke (50%), as opposed to cardioembolic (41%) or other/undocumented stroke subtypes (46%) (Supplementary Figure 2). The predicted 6-month cumulative incidence of any cardiac monitoring as a function of clinical AF risk is shown in Supplementary Figure 3.

Of 41 total ILRs placed, 33 (81%) were placed prior to discharge from the stoke hospitalization. At 6 months, the cumulative incidence of ILR utilization was 9.8% (95% CI 6.8, 12.7) (Supplementary Figure 4). Most patients who

Table 2
Cumulative incidence of any monitoring at 6 months

Stratification	Stratum	6-month cumulative incidence of any monitor (%)	
		Unadjusted	Adjusted*
Overall		36.5 (31.7-41.3)	-
According to stroke subtype	Cryptogenic	69.6 (60.2-79.0)	70.6 (59.7-79.0)
	Cardioembolic	49.5 (25.7-73.2)	47.7 (25.6-66.9)
	Other/undocumented	23.3 (18.1-28.4)	22.7 (17.8-27.9)
According to discharge disposition	Home	46.6 (39.0-54.1)	46.1 (37.8-54.1)
	Facility	28.3 (22.2-34.3)	24.9 (19.2-31.0)
According to level of AF risk†	Low	36.1 (27.7-44.5)	31.4 (24.6-38.4)
	Intermediate	35.3 (26.9-43.7)	33.8 (28.5-39.2)
	High	37.9 (29.6-46.2)	35.7 (28.9-42.5)

* Adjusted for covariates in multivariable model by Fine-Gray regression modeling
† Defined as tertiles of clinical AF risk using CHARGE-AF score[26]

received an ILR had a cryptogenic (n=29; 39%) rather than cardioembolic (n = 3; 27%) or other/undocumented stroke subtype (n = 9; 14%) (Supplementary Figure 5). In Cox proportional hazards models assessing ILR utilization, cryptogenic stroke was very strongly associated with ILR utilization (HR 8.65 vs other/undocumented, 95% CI 4.09, 18.32). The cumulative incidence of ILR among patients with cryptogenic strokes was 27.5% (95% CI 18.5, 36.5). Of 29 ILRs placed among patients with cryptogenic stroke, 22 (76%) were placed prior to discharge from the index stoke hospitalization. No significant association was observed between CHARGE-AF score and ILR use (HR 1.09 per 1-SD increase, 95% CI 0.78, 1.51) (Supplementary Table 4).

At 12 months, 20 patients developed incident AF (cumulative incidence 6.6%, 95% CI 3.5, 9.6; 5 [25%] first detected using monitoring) and 32 patients had a recurrent stroke (cumulative incidence 11.0%, 95% CI 6.7, 15.4) (Supplementary Figure 6). Of the 20 incident AF events, 8 (40%) occurred after strokes not classified as cardioembolic or cryptogenic, of whom only 3 (38%) received monitoring within 12 months (Supplementary Table 5). Of the 32 recurrent strokes, 22 (69%) occurred after strokes not classified as cardioembolic or cryptogenic, of whom 11 (50%) received monitoring within 12 months (Supplementary Table 5). Increasing CHARGE-AF score was strongly associated with incident AF (HR 1.56 per 1-SD increase, 95% CI 1.03, 2.35). We did not observe a significant association between CHARGE-AF score and recurrent stroke (HR 1.24, 95% CI 0.88, 1.75), though precision was limited. The cumulative incidences of AF and recurrent stroke stratified by tertile of CHARGE-AF score are shown in **Figure 3** and Supplementary Figure 7. There was no evidence of temporal trends in monitor deployment (p = NS for models including time). The cumulative incidence of monitor utilization was 32.2% (95% CI 27.6, 36.7) at 3 months and 39.3% (95% CI 33.7, 44.9) at 12 months (Supplementary Figures 8-9).

Table 3
Multivariable-adjusted associations with any monitor utilization at 6 months

Factor	Hazard ratio for any monitor (95%CI)	p*
Stroke subtype		<0.01
Other/unknown	reference	
Cardioembolic stroke	2.43 (1.28, 4.62)	
Cryptogenic stroke	4.53 (3.22, 6.39)	
Discharge home (vs facility)	1.80 (1.29, 2.52)	<0.01
CHARGE-AF score (per 1 SD increase)	1.08 (0.91, 1.27)	0.33

* p-value for association between relevant factor and any monitor utilization at 6 months using Cox proportional hazards regression

Discussion

Within nearly 500 patients with acute ischemic stroke and no prior history of AF, we found that about one-third received extended or ambulatory cardiac monitoring within 6 months. Monitor utilization varied substantially according to stroke subtype – over 70% of patients with cryptogenic stroke (i.e., with a guideline-based indication for monitoring[9]) received some form of rhythm monitor, but less than 40% received an ILR. Patients discharged home, as opposed to a rehabilitation facility, were more likely to receive a monitor. Although AF risk was strongly predictive of incident AF within the year following stroke, we did not observe an association between AF risk and monitor utilization.

Our results extend previous findings by providing a precise and nuanced assessment of after-stroke monitor utilization. In a report by Lip et al.[10] without information on stroke subtype or disposition status, only 10% of patients had ambulatory ECG monitoring within 1 year. In a second study, again without information on stroke subtype, Edwards et al.[11] found that 31% of patients received Holter monitoring after stroke or transient ischemic attack, and <1% received prolonged monitoring with event monitors or ILR. Although we observed slightly higher overall monitoring rates, we observed that among patients with cryptogenic stroke – patients in whom extended monitoring ("~30 days") is guideline-recommended[9] – nearly one-third did not receive monitoring, and patients who did receive monitoring most commonly received Holter or event monitors only, as opposed to ILR.

Our results suggest that stroke subtype and discharge disposition are important factors influencing real-world monitor deployment. In the Ontario Stroke Registry, predictors of monitoring included milder strokes, transient

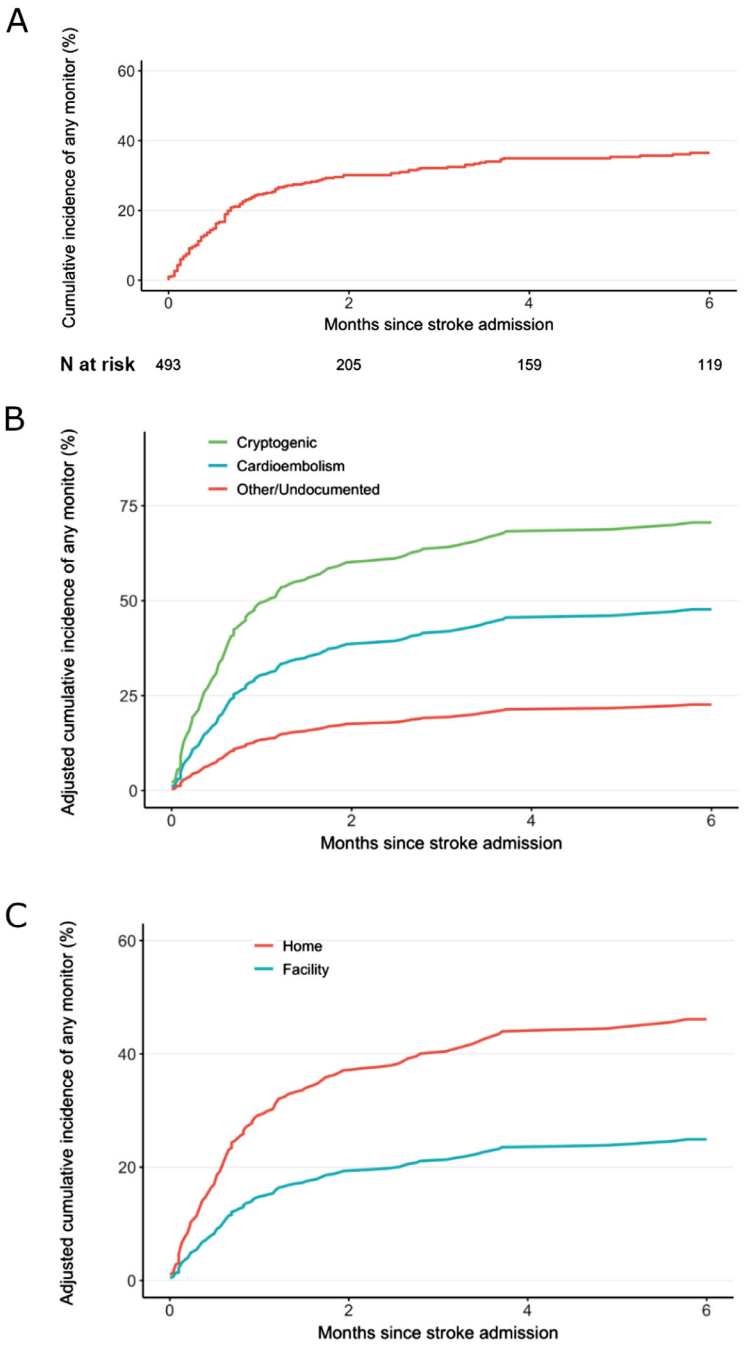

Figure 2. Cumulative incidence of monitor utilization overall and stratified by stroke subtype and discharge disposition. Panel A depicts the cumulative incidence of monitor utilization within the entire sample. Panel B depicts the cumulative incidence of monitor utilization stratified by stroke subtype with adjustment for discharge disposition and clinical AF risk. Panel C depicts the cumulative incidence of monitor utilization stratified by discharge disposition with adjustment for stroke subtype and clinical AF risk.

ischemic attack (as opposed to stroke), pre-event independence, and younger age.[11] In the current study, we found that patients presenting with cryptogenic and cardioembolic strokes were more likely to receive monitoring. Since AF is not uncommonly detected even after strokes with a suspected non-cardioembolic etiology,[20] however, efforts to increase monitor utilization after non-cardioembolic events among patients at elevated AF risk may be reasonable. Indeed, we observed that just under half of incident AF events occurred among patients with strokes not classified as cardioembolic or cryptogenic, and less than 40% of such patients received monitors. The Stroke-AF trial will soon report on the 12-month incidence of ILR-detected AF following stroke of presumed large vessel atherosclerotic or lacunar mechanism.[21] Future work is needed to assess whether our observation of lower monitor utilization among patients discharged to a rehabilitation facility represents an opportunity to improve care transitions, versus reasonable deferral of monitoring among patients receiving ongoing evaluation or with poor prognosis.

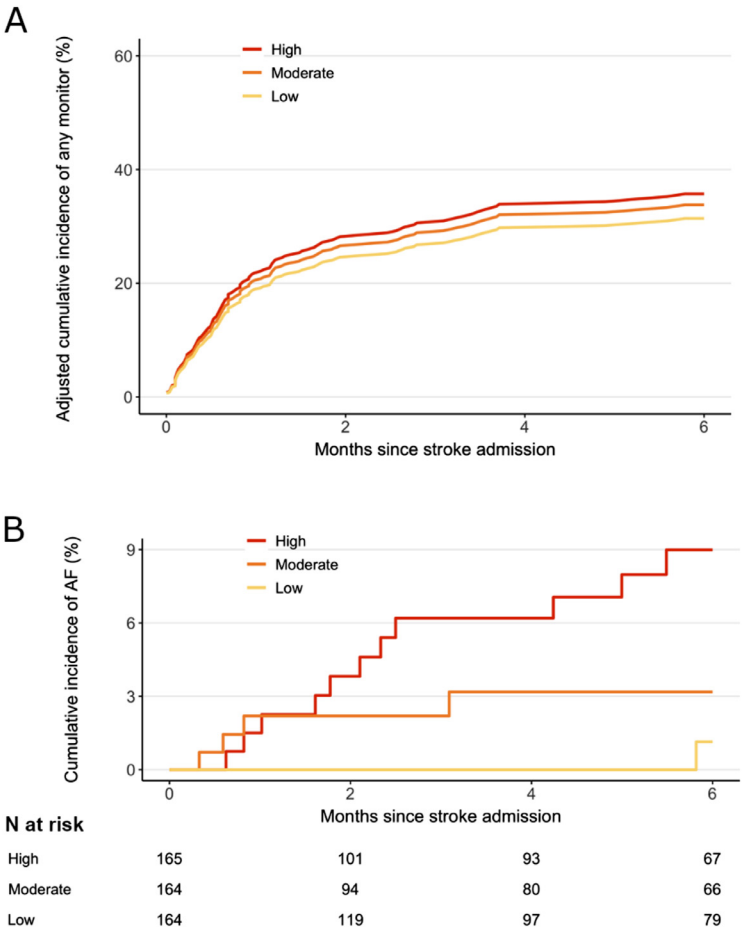

Figure 3. Cumulative incidence of monitor utilization and incident AF stratified by clinical AF risk
Panel A depicts the 6-month cumulative incidence of monitor utilization stratified by tertile of CHARGE-AF score, with adjustment for stroke subtype and discharge disposition. Panel B depicts the 6-month cumulative incidence of AF stratified by tertile of CHARGE-AF score. Yellow denotes the low risk tertile, orange depicts the medium risk tertile, and red depicts the high risk tertile.

Our findings demonstrate that clinical AF risk does not appear to influence contemporary monitor utilization practice. AF risk at the time of stroke has been associated with a cardioembolic mechanism and predicts the subsequent diagnosis of AF.[22,23] We similarly observed that a higher CHARGE-AF score was predictive of incident AF within the year after stroke. Nevertheless, we did not observe an association between CHARGE-AF and likelihood of receiving a monitor. Although AF risk does not appear to be associated with monitor utilization at present, incorporation of AF risk information may improve the efficiency of monitor deployment and health outcomes by increasing the likelihood of diagnosing AF promptly among patients at elevated risk, while avoiding the costs and potential harms associated with invasive or prolonged monitoring in patients less likely to have undiagnosed AF.[24] Planned future work will investigate whether a decision support intervention utilizing EHR notifications conveying predicted AF risk information at the time of stroke results in improved calibration of monitor utilization to AF risk.

Our study should be interpreted in the context of its design. First, our study was retrospective, which introduces bias. Specifically, our ability to appropriately classify outcomes not resulting in EHR-based documentation within our hospital or its 6 networked institutions is limited. Likewise, diagnostic testing was driven by clinical indication, which may lead to misclassification. Second, stroke subtypes were assigned based on the impression of the treating neurologist, rather than blinded adjudication. Third, modest sample size and follow-up limits our ability to detect differences in incident AF or recurrent stroke on the basis of monitor utilization. Fourth, we did not directly assess the effects of stroke severity on monitor utilization, and we did not ascertain whether certain patients did not undergo monitoring due to a clinical judgment that an AF diagnosis would not alter management or prognosis. However, our models were adjusted for discharge disposition and the competing risk of death, which are both surrogates for stroke severity. Fifth, although other AF risk instruments exist,[13,25] we utilized CHARGE-AF since it has been validated in multiple settings and consistently demonstrates favorable performance.[12–14,25] Sixth, our study represents the experience of a single academic hospital and regional stroke referral center. As a result, our results may not generalize to other settings or populations.

In conclusion, in a consecutive sample of nearly 500 strokes, in whom the rate of incident AF at 1 year was

nearly 7%, we found that just over one-third receive cardiac monitoring at 6 months. Although patients with cryptogenic strokes were more likely to receive monitoring, there remains an opportunity to increase monitor utilization in accordance with consensus guidelines. Clinical AF risk does not appear to be associated with monitor utilization despite being a strong predictor of future AF.

Disclosures

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Author Contributions

Shaan Khurshid: Conceptualization, Methodology, Data Curation, Writing − Original Draft; **Xinye Li**: Conceptualization, Methodology, Formal Analysis, Writing − Original Draft; **Jeffrey Ashburner**: Writing − Review and Editing; **Ana Trisini Lipsanopoulos**: Conceptualization, Resources, Project Administration; **Priscilla Lee**: Data Curation; **Aimee Lin**: Data Curation; **Darae Ko**: Conceptualization, Methodology, Writing − Review and Editing; **Patrick Ellinor**: Methodology, Writing − Review and Editing; **Lee Schwamm**: Methodology, Data Curation, Writing − Review and Editing; **Emelia Benjamin**: Methodology, Writing − Review and Editing; **Steven Atlas**: Methodology, Writing − Review and Editing; **Daniel Singer**: Methodology, Writing − Review and Editing; **Christopher Anderson**: Conceptualization, Methodology, Writing − Review and Editing, Supervision; **Ludovic Trinquart**: Conceptualization, Methodology, Formal Analysis, Writing − Review and Editing, Supervision; **Steven Lubitz**: Conceptualization, Methodology, Writing − Review and Editing, Supervision.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2021.01.038.

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