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ORIGINAL RESEARCH

Predictors of Atrial Fibrillation During Long-Term Implantable Cardiac Monitoring Following Cryptogenic Stroke

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BACKGROUND: Following cryptogenic stroke, guidelines recommend cardiac monitoring for occult atrial fibrillation (AF). We aimed to evaluate predictors of AF during long-term implantable cardiac monitoring.

METHODS AND RESULTS: We studied 293 consecutive patients who underwent implantable cardiac monitor implant (Medtronic LINQ) following hospitalization for cryptogenic stroke at the University of Rochester Medical Center from January 2013 to September 2018. Multivariable Cox proportional hazards regression modeling was used to identify predictors of AF during long-term monitoring. At 36 months of follow-up, the cumulative rate of implantable cardiac monitor–detected AF events was 32% in the total study population. Multivariable analysis identified age ≥70 years as the most powerful predictor of the development of AF events during follow-up (hazard ratio, 2.28 [95% CI, 1.39–3.76]; P=0.001). Replacing age with the CHA_2DS_2-VASc (congestive heart failure, hypertension, age, diabetes mellitus, stroke, vascular disease, age, sex category) score resulted in a weaker association, for which each 1-point increment in the CHA_2DS_2-VASC score was associated with an 18% increased risk of developing AF (95% CI, 1.00–1.38; P=0.047). Consistent results were shown using Kaplan–Meier analysis by age and by the CHA_2DS_2VASc score.

CONCLUSIONS: Cryptogenic stroke patients continue to develop AF episodes during 36 months of implantable cardiac monitoring following the index event. Age is the most powerful predictor of occult AF in this population.

Key Words: atrial fibrillation ■ cryptogenic stroke ■ implantable cardiac monitor

It is estimated that >30% of all ischemic strokes are cryptogenic.[1] The evaluation of ischemic stroke includes, among other tests, prolonged cardiac rhythm monitoring to detect atrial fibrillation (AF). AF episodes following cryptogenic stroke (CS) are frequently asymptomatic and transient and, therefore, may be elusive to diagnosis using periodic electrocardiography alone. If gone undetected, subclinical AF significantly increases the risk of subsequent ischemic stroke.[2] Accordingly, the American Heart Association guidelines advise cardiac monitoring for at least 24 hours following ischemic stroke.[3] In selected patients, additional cardiac monitoring may be performed with a 24-hour Holter monitor, external event recorder, or implantable cardiac monitor (ICM). The International Society for Holter and Noninvasive Electrocardiology and the Heart Rhythm Society expert consensus recommend long-term arrhythmia monitoring using ICMs based primarily on the results of the landmark CRYSTAL AF (Cryptogenic Stroke and Underlying Atrial Fibrillation) trial.[4]

A CHA_2DS_2-VASc (congestive heart failure, hypertension, age, diabetes mellitus, stroke, vascular disease, age, sex category) score is used to predict stroke risk in patients with known AF. However, the CHA_2DS_2-VASc score was also shown to be useful in the selection of patients for ICMs with suspected occult AF.[5–7] In this study, we aimed to identify predictors of ICM-detected AF following CS and to compare the diagnostic yield

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CLINICAL PERSPECTIVE

What Is New?

- The rate of atrial fibrillation (AF) detection during 3 years of continuous implantable cardiac monitoring among patients with cryptogenic stroke approaches one third.
- Age is the most important predictor for new-onset AF following cryptogenic stroke, with a particularly high rate of AF in those aged ≥70 years.
- The CHA_2DS_2-VASc (congestive heart failure, hypertension, age, diabetes mellitus, stroke, vascular disease, age, sex category) score can aid in the identification of patients at high risk of AF but has less predictive value than age.

What Are the Clinical Implications?

- Clinicians should utilize implantable cardiac monitoring for long-term surveillance for AF following cryptogenic stroke because it provides continued incremental value over 3 years after the index event.
- Implantable cardiac monitoring prescription should be implemented especially for patients aged ≥70 years, who represent the highest risk group for AF development following cryptogenic stroke.

Nonstandard Abbreviations and Acronyms

AF	atrial fibrillation
CS	cryptogenic stroke
CHA_2DS_2-VASc	congestive heart failure, hypertension, age, diabetes mellitus, stroke, vascular disease, age, sex category
ICM	implantable cardiac monitor

of the predictive model to the CHA_2DS_2-VASc score to provide measures for appropriate selection of patients for prolonged continuous monitoring following CS.

METHODS

The data that supported the study findings are available from the corresponding author on reasonable request.

Design

We studied 293 consecutive patients who underwent implant of an ICM following hospitalization for CS at the University of Rochester Medical Center between January 2013 and September 2018. Baseline demographic data and information on medical history including comorbidities, laboratory data, imaging results, and prior findings from telemetry and Holter monitoring were collected for all patients. The patients who had AF detected on prior Holter or event monitoring or a history of AF were excluded. The study protocol was approved by the University of Rochester Medical Center institutional review board. The requirement for informed consent was waived.

Study Population

Cryptogenic Stroke

In our medical center, in accordance with the most updated guidelines, patients are classified as having CS if they meet the following criteria; (1) present with acute neurologic symptoms consistent with a transient ischemic attack or stroke and (2) have a negative exhaustive diagnostic workup that includes electrocardiographic and telemetry monitoring, transesophageal echocardiography, laboratory testing for thrombophilia, and imaging studies of the head and neck vasculature often including magnetic resonance imaging.[3] Based on the brain magnetic resonance imaging report, the patient's stroke topology (vascular distribution) was classified as one of the following: embolic lesion(s) in 1 vascular territory; embolic lesions in multiple unilateral vascular territories; embolic lesions in bilateral vascular territories and/or anterior and posterior circulations.

Implantable Cardiac Monitor

All patients enrolled in this study underwent implant of a Medtronic Reveal LINQ ICM. The majority of patients underwent ICM implant during their index stroke hospitalization, and the remainder were scheduled for an ICM implant within 30 days of hospital discharge. The ICM was programmed to detect any AF lasting >2 minutes. All arrhythmia episodes were reviewed and adjudicated by a cardiac electrophysiologist. Patients with ICM-detected new-onset AF were advised to use anticoagulant therapy.

Definition and End Points

The primary outcome measure of this study was ICM-detected AF lasting >2 minutes, which was then classified as new-onset ICM-detected AF. We aimed to identify independent predictors for the development of ICM-detected AF and to compare the predictive model with the CHA_2DS_2-VASc score.

Statistical Analysis

Baseline characteristics among patients with and without ICM-detected AF were compared using the Wilcoxon rank sum test or χ^2 test, as appropriate.

Categorical data are presented as frequency and percentage and continuous variables as mean±SD. Cumulative probabilities of AF by risk factors were displayed according to the Kaplan–Meier method. Event rates were compared using the log-rank statistic. Univariable and multivariable Cox proportional hazards regression models were used to determine predictors of AF. Predictive models were compared with the CHA_2DS_2-VASc score model using the Harrell C-index (concordance index), a goodness-of-fit measure for survival analysis models.[8] Baseline variables having differences with a significance level <0.10 were considered as candidates for multivariable time-to-event AF models, with a *P* value of <0.05 necessary to be included in the final model. However, only age, continuous and dichotomized, was significant at <0.05 and was compared with models using the CHA_2DS_2-VASc score. The cumulative sums of martingale residuals and associated supremum tests were used to assess the proportional hazards assumption of the regression models.

All statistical tests were 2-sided: a *P* value of <0.05 was considered statistically significant. Analyses were carried out with SAS software (v9.4; SAS Institute).

RESULTS

Patient Characteristics

A total of 293 patients underwent ICM implant following CS for long-term arrhythmia monitoring. During mean follow-up of 22±12 months, AF was detected in 74 patients (25%). Table 1 shows baseline characteristics of patients with and without ICM-detected AF. The only statistically significant difference at baseline between the 2 groups was age, which was higher among those who developed AF (72±1 versus 68±13; *P*=0.008, respectively). The majority of the patients in each group had baseline hypertension and were current or past smokers. Most patients had preserved left ventricular function, and about one third were found to have left ventricular hypertrophy on echocardiography. Because the study examined stroke patients, a

Table 1. Baseline Demographics

Baseline Clinical Characteristics	No AF Detected n=219	AF Detected n=74	*P* Value
Age, y	67.5±13.3	72.1±10.8	0.008
CHA_2DS_2-VASc score	4.7±1.5	5.1±1.3	0.079
Female sex, n (%)	94 (43)	31 (42)	0.877
Hispanic, n (%)	8 (4)	3 (4)	1.000
Black, n (%)	15 (7)	5 (7)	0.964
Coronary artery disease, n (%)	48 (22)	20 (27)	0.374
Hypertension, n (%)	163 (75)	56 (75)	0.906
Congestive heart failure, n (%)	13 (6)	6 (8)	0.588
Chronic kidney disease, n (%)	60 (27)	20 (27)	0.988
Diabetes mellitus, n (%)	69 (31)	27 (37)	0.384
Diastolic dysfunction, n (%)	66 (30)	20 (27)	0.588
Supraventricular tachycardia, n (%)	11 (5)	5 (7)	0.568
Moderate or severe valve disease, n (%)	10 (5)	5 (7)	0.543
History of >1 stroke, n (%)	24 (11)	6 (8)	0.506
Current or past smoker, n (%)	112 (51)	44 (59)	0.217
Alcohol use, n (%)	73 (33)	31 (42)	0.177
Hemoglobin A_{1c} >6.5%, n (%)	154 (70)	52 (70)	0.948
Cholesterol >200, n (%)	65 (29)	13 (18)	0.065
HDL >40, n (%)	164 (75)	50 (67)	0.231
LDL <100, n (%)	126 (58)	51 (69)	0.098
Left atrial diameter >4.0 cm, n (%)	66 (30)	28 (38)	0.210
Left ventricular ejection fraction ≥55%, n (%)	204 (93)	70 (94)	1.000
Left ventricular hypertrophy by echo, n (%)	64 (29)	29 (39)	0.104
Prior cardiac monitoring, n (%)	35 (16)	15 (21)	0.361
Prior brain magnetic resonance imaging, n (%)	185 (86)	61 (84)	0.543

Continuous variables: mean±SD; categorical variables: n (% of column total). AF indicates atrial fibrillation; CHA_2DS_2-VASc, congestive heart failure, hypertension, age, diabetes mellitus, stroke, vascular disease, age, sex category; HDL, high-density lipoprotein; and LDL, low-density lipoprotein.

minimum CHA_2DS_2-VASc score of 2 was observed in all patients. The mean CHA_2DS_2-VASc score did not differ significantly between groups (4.7±1.5 versus 5.1±1.3; *P*=0.079).

AF Detection

A high rate of AF was observed throughout the follow-up period. At 36 months, the cumulative probability of new ICM-detected AF was 32% (Figure 1). Following ICM implant, a continuously increasing probability of detecting AF was observed during long-term follow-up. The cumulative probability of new ICM-detected AF at 6, 12, and 24 months was 16%, 20%, and 27%, respectively, suggesting a continuous risk increase throughout follow-up.

Age and the Risk of Developing ICM-Detected AF Following CS

In multivariable regression analysis, the only significant predictor of AF following CS was age >70 years with an estimated hazard ratio of 2.28 (95% CI, 1.39–3.76; *P*=0.001; Table 2). Furthermore, when assessed as a continuous measure, each 5-year increment in age was associated with a corresponding 14% (*P*=0.006) increased risk of developing AF following the index CS event.

Figure 2 shows the probability of AF by age ≥70 and <70 years. A significantly higher rate of ICM-detected AF was observed in patients aged ≥70 compared with those <70 years (log rank *P*<0.001). The cumulative probability of AF at 6 and 12 months among those aged ≥70 years was 3-fold higher than among those who were aged <70 years (6 months: 24% versus 8%, respectively; 12 months: 28% versus 9%).

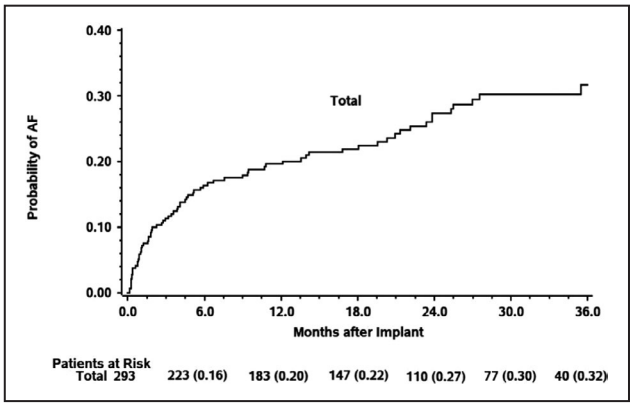

Figure 1. Kaplan–Meier estimates of the cumulative probability of new-onset atrial fibrillation (AF) in the total study cohort.

Figures 1, 2, and 4 show Kaplan–Meier survival curves. The *x*-axis represents the number of patients at risk at each time point, and the percentage of patients with AF is shown in parentheses. The *y*-axis represents the cumulative percentage of patients with AF. The log rank *P* values statistically comparing the 2 groups are shown in Figures 2 and 4.

CHA_2DS_2-VASc Score and the Risk of Developing ICM-Detected AF Following CS

Figure 3 shows the cumulative probability of new-onset AF at 12 months as a function of the CHA_2DS_2-VASc score. An increasing rate of new-onset AF at 12 months was noted with increasing CHA_2DS_2-VASc score. The cumulative probability of ICM-detected AF at 36 months was significantly higher when comparing patients with very high CHA_2DS_2-VASc scores of 6 to 9 with those having lower CHA_2DS_2-VASc scores (44% versus 27;, *P*=0.05; Figure 4).

The Cox regression model showed that a CHA_2DS_2-VASc score of 6 to 9 was associated with a trend for increased risk of ICM-detected new-onset AF compared with patients with a CHA_2DS_2-VASc score of 2 to 5 (hazard ratio, 1.59 [95% CI, 1.00–2.54]; *P*=0.053). Assessing CHA_2DS_2-VASc score as a continuous measure showed that each 1-U increment in the CHA_2DS_2-VASc score was associated with an 18% increased risk of ICM-detected AF (*P*=0.047). When the age ≥70 and CHA_2DS_2-VASc models were compared, the C-statistic was 0.61 for the age model and 0.55 for CHA_2DS_2-VASc model (Table 2), further supporting the fact that age is a more powerful predictor of the development of ICM-detected AF than the CHA_2DS_2-VASc score.

Stroke Topology

In the entire patient population, the majority (58%) of the strokes were embolic lesion(s) in 1 vascular territory. We compared stroke topology on magnetic resonance imaging findings between patients with and without ICM-detected AF and found no statistically significant difference among the presence of embolic lesion(s) in 1 vascular territory, embolic lesions in multiple unilateral vascular territories, or embolic lesions in bilateral vascular territories and/or anterior and posterior circulations (all *P*>0.05%).

DISCUSSION

This large study of CS patients who underwent ICM implant for long-term continuous arrhythmia monitoring provides several important clinical implications for the management of this population. We have shown (1) that a high rate of AF is detected, approaching one third during 3 years of continuous ICM monitoring; (2) that age is the single most important predictor of new-onset AF following CS, with a particularly high rate of AF in those aged ≥70 years; and (3) that although the CHA_2DS_2-VASc score can aid in the identification of patients at high risk of AF, when compared with age as a risk factor, the use of the CHA_2DS_2-VASc score

Table 2. Univariable Model Predicting New-Onset AF

End Point	Hazard Ratio	95% CI	*P* Value	Model C-Statistic
Age as a risk factor				
Age ≥70 vs <70 y	2.28	1.39–3.76	0.001	0.61
Age per 5-y increment	1.14	1.04–1.26	0.006	0.62
CHA_2DS_2-VASc as a risk factor†				
CHA_2DS_2-VASc score 6–9 vs 2–5	1.59	1.00–2.54	0.053	0.55
CHA_2DS_2-VASc per 1-U increment	1.18	1.00–1.38	0.047	0.57

AF indicates atrial fibrillation; CHA_2DS_2-VASc, congestive heart failure, hypertension, age, diabetes mellitus, stroke, vascular disease, age, sex category.
†Findings obtained from separate Cox models.

provided only limited predictive value. Analysis of other demographic, laboratory, and imagining results failed to predict the development of new-onset AF.

The findings of our study show that AF is highly prevalent in the CS patient population. Furthermore, patients aged ≥70 years or who have a very high CHA_2DS_2-VASc score (≥6) are more likely to have occult AF detected on cardiac monitoring. We noted that new AF detection was highest in the first 6 months but continued for as long as 36 months. The American Heart Association and American Stroke Association recommend "prolonged rhythm monitoring," or ≈30 days within 6 months of the stroke.[9] This comes from the EMBRACE (30-Day Cardiac Event Monitor Belt for Recording Atrial Fibrillation After a Cerebral Ischemic Event) trial, which showed that 1 month of cardiac monitoring significantly improved AF detection compared with conventional 24-hour Holter monitoring.[10] Although guidelines recommend "prolonged" monitoring, the optimal duration is unclear. Our study observed a high probability of AF during the first 6 months following stroke.

Patients with CS who were enrolled in the CRYSTAL AF study were found to have a rate of 12% AF detection at 12 months. In our real-world study of CS patients enrolled in a tertiary academic medical center, we identified a higher rate of AF detection at 12 months. The mean age of patients enrolled in our study was older than in CRYSTAL AF, and that could explain the higher detection rate. In our study, when analyzing the cohort of patients by age, we identified a rate of AF detection approaching 30% at 12 months among those aged ≥70 years. A subgroup analysis of CRYSTAL AF showed that patients aged ≥65 years monitored by ICM had a higher rate of AF detection (17% versus 2.5%) at 6 months.[4] Ziegler et al[11] conducted a prospective observational study of patients with CS and found more than twice as much AF (26.6% versus 10.7%; *P*<0.01) in patients >65 years old. Our results further support the finding that age alone is a significant predictor of AF following CS.

The PREDATE AF (Predicting Determinants of Atrial Fibrillation or Flutter for Therapy Elucidation in Patients at Risk for Thromboembolic Events) and REVEAL AF (Incidence of Previously Undiagnosed Atrial Fibrillation Using Insertable Cardiac Monitors in a High-Risk

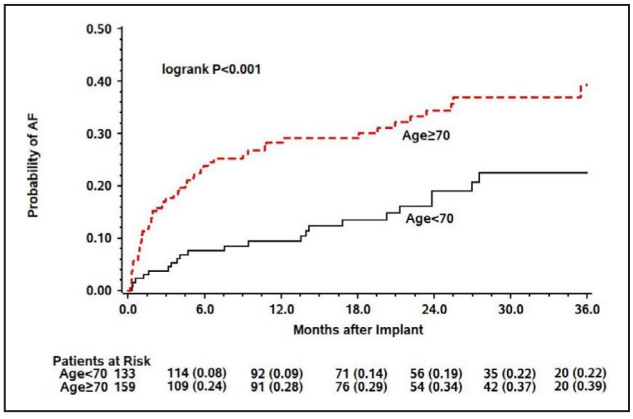

Figure 2. Kaplan–Meier estimates of the cumulative probability of new-onset atrial fibrillation by age <70 vs ≥70 years.

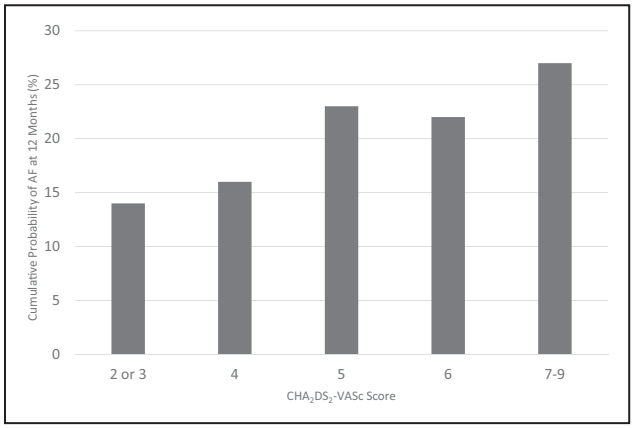

Figure 3. Cumulative probability (%) of new-onset atrial fibrillation at 12 months as a function of CHA_2DS_2-VASc score.
CHA_2DS_2-VASc indicates congestive heart failure, hypertension, age, diabetes mellitus, stroke, vascular disease, age, sex category.

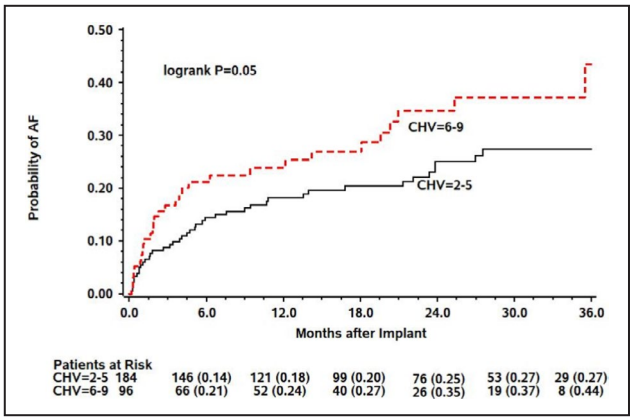

Figure 4. Kaplan–Meier estimates of the cumulative probability of developing atrial fibrillation in patients with CHA_2DS_2-VASc scores of 2–5 vs 6–9.
CHA_2DS_2-VASc indicates congestive heart failure, hypertension, age, diabetes mellitus, stroke, vascular disease, age, sex category.

Population) investigations selected high-risk stroke patients based on CHA_2DS_2-VASc score for ICM implantation to quantify occult AF rates.[5,7] Although the studies detected high AF rates, the specific CHA_2DS_2-VASc scores themselves failed to predict AF. Similarly, our study did not find the CHA_2DS_2-VASc score to be superior to age in predicting AF; therefore, its use alone to risk-stratify CS patients may be inadequate. The CHA_2DS_2-VASc score is a composite score with each variable having different weights. Our data suggest that age ≥70 years is a more powerful risk factor for the development of AF than combined assessment of the components within the CHA_2DS_2-VASc score.

The results of our study favor the clinical practice of ICM for all patients following cryptogenic stroke. Those who are >70 years of age are at increased risk of AF for 6 months, so a 30-day external monitor is insufficient and likely to miss occult AF. Selecting patients for ICM based on other factors should be avoided. Further studies are needed to better risk-stratify CS patients at high risk of AF. However, our data suggest that ICM should be recommended to all post-CS patients >70 years of age. Younger patients (<70 years) in our study also experienced a relatively high rate of ICM-detected AF during long-term follow-up (22% at 3 years). However, event rates were 3-fold higher at 6 and 12 months in the older age group, suggesting that individual risk assessment for implantable cardiac monitoring should be exercised in post-CS patients <70 years of age.

Limitations

Our study has several limitations. First, this study had a single-center retrospective study design; therefore, the results are subject to patient selection and referral bias. However, we included consecutive patients for whom reliable follow-up and arrhythmia data could be obtained. Second, we did not perform a separate and independent adjudication of each arrhythmia event and AF burden. However, our standard protocol for any ICM-detected AF includes review and confirmation by a nurse practitioner trained in interpreting ICM-derived arrhythmia information, following by confirmation of the findings by the treating electrophysiologist. Therefore, the diagnosis of ICM-detected AF is expected to have a very high level of accuracy. Finally, we did not quantify the burden of AF but rather recorded any AF as meeting detection criteria.

CONCLUSIONS

Advanced age is a strong and independent predictor of occult AF after CS. Other factors, including CHA_2DS_2-VASc score, which is used to estimate stroke risk, did not provide incremental predictive value in predicting AF following CS. About one third of patients who experience CS will subsequently have occult AF detected during a 3-year follow-up period. Our data suggest that clinicians should continue to utilize ICMs to provide long-term surveillance for AF following CS, with a focus on the older age group.

ARTICLE INFORMATION

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