Longitudinal outcomes in cryptogenic stroke patients with and without long-term cardiac monitoring for atrial fibrillation

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BACKGROUND Guidelines recommend a confirmed diagnosis of atrial fibrillation (AF) to initiate oral anticoagulation in cryptogenic stroke (CS) patients. However, the intermittent nature of AF can make detection challenging with intermittent short-term cardiac monitoring.

OBJECTIVE The purpose of this retrospective cohort study was to examine post-CS utilization of cardiac monitoring and associated clinical outcomes.

METHODS Adults with incident hospitalization for CS were identified in the Optum® claims database and assessed for cardiac monitoring received poststroke. Patient were stratified into those with a long-term insertable cardiac monitor (ICM) vs external cardiac monitor (ECM) only. The timing of ICM placement poststroke was treated as a time-dependent covariate. The clinical outcomes of interest were time to AF diagnosis, oral anticoagulation usage, and all-cause mortality.

RESULTS A total of 12,994 patients met selection criteria for the analysis, of whom 1949 (15%) received an ICM and 11,045 (85%) received ECM only. In those who had received an ECM as their first monitoring modality, only 4.4% moved on to receive an ICM for longer-term monitoring. Use of ECM before ICM was associated with a longer time to AF diagnosis (median 336 vs 194 days). Compared to those with ECM only, ICM patients had a significantly lower rate of death (hazard ratio [HR] 0.70; P = .004), and faster time to AF diagnosis (HR 1.50; P <.0001) and anticoagulation initiation (HR 1.57; P <.0001) during follow-up of up to 5 years after CS.

CONCLUSION In a real-world study of CS patients, prolonged cardiac monitoring was associated with higher rates of AF detection and treatment, and higher odds of survival.

KEYWORDS Ambulatory electrocardiography; Atrial fibrillation; Cryptogenic stroke; Insertable cardiac monitor; Oral anticoagulation

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CS/TIA patients who receive an insertable cardiac monitoring (ICM) device vs those who only received a wearable, external cardiac monitoring (ECM) device. Additionally, to provide insight on the patients who ultimately receive ICM, we describe the clinical care pathway before ICM insertion, including the utilization of ECMs and the time delay to ICM monitoring and to AF diagnosis after a CS event.

Methods
This was a real-world retrospective database study leveraging the Optum® (Eden Prairie, MN) de-identified Clininformatics® U.S. claims database, which contains data for privately insured and Medicare Advantage enrollees across the United States from January 1, 2007, to June 30, 2019. Because this was a noninterventional, retrospective, observational study utilizing de-identified data, informed consent was not required from the patient under an institutional review board exemption status. All aspects of this study were conducted in compliance with Health Insurance Portability and Accountability Act of 1996 (HIPAA) regulations and the HIPAA Omnibus Rule of 2013.

Inclusion criteria
Patients were identified based on the presence of a diagnosis code for CS or TIA (International Classification of Diseases [ICD]-9 434.91, 435.9, 434.11; or ICD-10 I63.9) in the primary position during an inpatient hospitalization between January 1, 2007, and June 30, 2019. Although ICD-9 (Ninth Revision) and ICD-10 (Tenth Revision) diagnosis coding does not include explicit codes for CS, these particular codes were selected based on an analysis of the diagnosis codes used during stroke/TIA events in patients who received an ICM for the stated indication of CS (data on file). A record of ≥1 procedures indicative of an acute stroke event (see Supplemental Appendix) was required either 2 days before, during, or within 2 days after the index hospitalization, based on a published algorithm developed by Kaplan et al., evaluating rates of acute stroke and systemic embolism using the same Optum database. The population was limited to patients 18 years of age or older who had ≥12 months of continuous enrollment before their incident CS/TIA hospitalization.

Patients were excluded if any of the following occurred before their index CS/TIA hospitalization: diagnosis of AF or atrial flutter, record of an ablation for AF or atrial flutter, oral anticoagulation usage, mechanical heart valve implant, rheumatic heart disease, mitral stenosis, ischemic or dilated cardiomyopathy, ST-elevation myocardial infarction, end-stage renal disease, previous stroke/TIA, or an ICM implant. Patients also were excluded if they had any of the following procedures within 30 days before to 90 days after their index CS/TIA hospitalization, which could be indicative of a specific stroke etiology (rather than a CS event): carotid artery stenting or endarterectomy, carotid artery stenosis or occlusion, atrial septal defect, or patent foramen ovale closure. Finally, patients with any evidence of other cardiac implantable electronic devices capable of monitoring AF (pacemaker, implantable cardioverter-defibrillator, or cardiac resynchronization therapy device) at any point during baseline or follow-up were excluded as well.

Cohort assignment
For all study participants, the analytic start time (time zero) began with the incident CS/TIA hospitalization. Patients with a record of ICM insertion or after time zero were assigned to the ICM cohort, regardless of whether they received any external monitoring before their ICM insertion. Patients without ICM but with at least 1 ECM were assigned to the ECM cohort. The ECM cohort consisted of those with short-term Holter monitors, event monitors, and mobile cardiac telemetry monitors. Patients with no ambulatory electrocardiographic monitoring (neither ECM nor ICM) were not included in this study, as they may not represent comparable cryptogenic patients.

Data analyses: Patient characteristics
Patient demographics, index hospital stay characteristics, and patient comorbidities (measured by CHA2DS2-VASc score) were summarized for the ICM and ECM cohorts. The CHA2DS2-VASc score is a classification algorithm that is based on ICD-9-10 diagnosis codes, CPT procedure codes, and age at index. Patients are assigned a score derived as follows: 1 point each for any record of congestive heart failure, hypertension, age 65–74 years, female gender, vascular disease, or diabetes mellitus; and 2 points for any record of stroke/TIA or age ≥75 years. For the purposes of the CHA2DS2-VASc score, vascular disease is defined as any 1 or more of the following: coronary artery disease diagnosis, peripheral artery disease diagnosis, coronary artery bypass procedure, percutaneous coronary intervention procedure, or another coronary revascularization procedure. Characteristics of the index hospital stay were
used to estimate the patient’s stroke severity, including length of stay of the index stroke hospitalization in days, intensive care unit (ICU) utilization during the index stroke hospitalization (yes vs no), and discharge status after the index hospitalization to home vs not home (i.e., to a long-term care center or rehabilitation facility).

**Time to events analyses in ICM vs ECM patients**

The 3 main outcomes of interest for this study were time to AF diagnosis, time to oral anticoagulation usage, and time to all-cause mortality. For time to oral anticoagulation usage, a sub-analysis was performed on just those patients who received a diagnosis of AF. In order to estimate time to clinical events (time to AF diagnosis, time to anticoagulation initiation, and time to death), Cox proportional hazard models with a 5-year time horizon were used. A key explanatory variable for this research was whether a patient received an ICM on or after their incident CS/TIA diagnosis (time zero). However, the timing of an ICM implant can vary and may be delayed by varying durations after the index stroke admission (time zero). Therefore, ICM implantation was treated as a time-dependent covariate. Additional covariates incorporated in the Cox models included patient demographics (age, gender, geographic region, and payer type [commercial or Medicare Advantage]); index hospital stay characteristics indicative of stroke severity (length of stay, ICU utilization, and discharge status [home/not home]); and comorbidities as measured by the CHA2DS2-VASc score.

Each time to event model was estimated using the partial likelihood method in SAS. Model adequacy was assessed using residual diagnostics. For testing the proportional hazard assumption, the interaction with time and the independent variables was tested for significance. Additional subanalyses were performed on the time to oral anticoagulation outcome, in which a subset of patients with AF diagnosed during the follow-up period was analyzed separately.

**Characterization of monitoring pathway before ICM**

To further describe the clinical pathway of CS patients who ultimately receive an ICM, before multivariable modeling we explored the pre-ICM usage of ECMs and the time from acute stroke event to ICM insertion and to AF diagnosis. Costs of external monitors were estimated utilizing 2020 U.S. national average Medicare payment rates and incorporating a 125% markup to approximate commercial payment rates.

**Results**

**Patient characteristics**

Figure 1 shows the attrition diagram for the main analyses. Of the 12,944 patients who met inclusion/exclusion criteria, 1949 (15%) received an ICM with a median time to insertion of 26 days, and 11,045 (85%) received ECM only with a median time to ECM assignment of 69 days. Across the ECM cohort, the monitors received were of short-term Holter monitors (43%), long-term Holter monitors (9%), event monitors (32%), and mobile cardiac telemetry monitors (16%). Patients on average received 2.4 (SD 1.1) monitors, for an estimated cumulative 41 days of prescribed monitoring. Table 1 lists patient demographics, index hospital stay characteristics, and CHA2DS2-VASc score (see Table 2 for components of CHA2DS2-VASc score), which were evenly distributed between the ICM and ECM cohorts with an average age of 67 years, slightly more females than males (51% and 55%), and similar mean (± SD) CHA2DS2-VASc score (2.6 ± 1.6 and 2.6 ± 1.6, respectively). Before multivariable adjustment, mean index length of stay (8.8 vs 7.8 days; P = .0015) and frequency of index ICU utilization (49% vs 45%; P = .0006) were higher in the ICM cohort. Patients in the ECM cohort were more often discharged to home (78% vs 72%; P < .0001) compared to those in the ICM cohort.

**Characterization of monitoring pathway before ICM**

Descriptive summary statistics on the clinical care pathway before ICM are presented in Figure 2. Figure 2A shows a
Greater use of ECMs before ICM significantly increased the time from index stroke to ICM, from a median of 0 days in patients with no prior ECMs to 103 days and 210 days in those with 1 or ≥2 prior ECMs, respectively (Figure 2B). Likewise, median time from index stroke to AF diagnosis increased from 194 days to 289 and 336 days, respectively, when either 1 or ≥2 ECMs preceded ICM. This delay in AF diagnosis with ECM patients to ICM patients was largely driven by the delay between ECM and ICM. In patients with 1 ECM before ICM, the median amount of time between monitoring modalities was 70 days, and in patients with ≥2 ECMs before ICM the median time between first ECM and the ICM was 154 days. Overall, of the patients who received ECM as their initial cardiac monitoring modality (11,551), only 506 (4.4%) progressed to longer-term monitoring with an ICM.

### Table 2 Components of the CHA2DS2-VASc score

| CHA2DS2-VASc component | ECM | ICM | P value |
|------------------------|-----|-----|---------|
| Age 65–74 y            | 3335 (30.19) | 646 (33.15) | <.0001 |
| 75+ y                  | 3644 (32.99) | 597 (30.63) | .0430 |
| CHF                    | 390 (3.53)   | 64 (3.28)   | .6304 |
| Hypertension           | 6865 (62.15) | 1202 (61.67) | .7046 |
| Diabetes               | 2874 (26.02) | 496 (25.45) | .6149 |
| Stroke/TIA             | 660 (5.98)   | 133 (6.82)  | .1641 |
| Vascular condition     | 668 (6.05)   | 122 (6.26)  | .7573 |
| Female                 | 6053 (54.80) | 1000 (51.31) | .0043 |

Values are given as n (%) unless otherwise indicated.

CHF = congestive heart failure; ECM = external cardiac monitor; ICM = insertable cardiac monitor; TIA = transient ischemic attack.

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**Table 1 Patient characteristics**

|                | ECM    | ICM    | P value |
|----------------|--------|--------|---------|
| Sample size (n) | 11,045 | 1949   |         |
| Age (y)         | 66.8 ± 13.5 | 66.9 ± 12.6 | .6378 |
| Female          | 6053 (54.8) | 1000 (51.3) | < .0001 |
| Follow-up duration (y) | 3.17 ± 2.64 | 1.92 ± 1.80 | < .0001 |
| Region          |        |        | .0043   |
| Midwest         | 2960 (26.8) | 562 (28.8) |       |
| Northeast       | 1807 (16.4) | 362 (18.6) |       |
| South           | 4360 (39.5) | 797 (40.9) |       |
| West            | 1892 (17.1) | 223 (11.4) |       |
| Unknown         | 26 (0.2)   | 5 (0.3)  |         |
| Payer           |        |        | .0280   |
| Commercial      | 4377 (39.6) | 721 (37.0) |       |
| Medicare Advantage | 6668 (60.4) | 1228 (63.0) | |
| Index cryptogenic stroke hospitalization | | | |
| Length of stay (d) | 7.8 ± 11.6 | 8.8 ± 12.7 | .0015 |
| ICU stay (yes)   | 4942 (44.7) | 954 (49.0) | .0006 |
| Discharge to home (yes) | 8552 (77.7) | 1388 (71.6) | < .0001 |
| Patient comorbidity |       |        |         |
| CHA2DS2-VASc score | 2.6 ± 1.6 | 2.6 ± 1.6 | .228   |

Values are given as mean ± SD or n (%) unless otherwise indicated.

ECM = external cardiac monitor; ICM = insertable cardiac monitor; ICU = intensive care unit.

**Table 3** lists the results of all multivariable modeling for the time to event outcomes. At 5 years after their incident CS/TIA hospitalization, patients receiving ICM had a significantly lower rate of death (hazard ratio [HR] 0.70; P = .004), and faster time to AF diagnosis (HR 1.50; P < .0001) and anticoagulation usage (HR 1.57; P < .0001). Time from the qualifying CS to anticoagulation usage was also faster in ICM patients when the analysis was limited to patients subsequently diagnosed with AF (HR 1.12; P = .029).

**Figure 3** shows the time to anticoagulation following a patient’s CS/TIA hospitalization, with an estimated 51.8% of ICM patients and 31.8% of ECM patients receiving anticoagulation at 5 years.

### Discussion

Our study found that patients receiving ICM after their incident CS/TIA hospitalization had AF detected more quickly and more frequently, had an increase in anticoagulation utilization, and experienced improved survival. These findings are in line with previous studies of implantable continuous cardiac monitoring whereby “silent” AF was detected, which enabled therapeutic interventions for the mitigation of recurrent stroke risk. For example, multiple studies have demonstrated AF detection rates of around 27%–30% after 3 years of continuous monitoring following a poststroke ICM implantation and have shown that under the typical standard of care, only a fraction of those cases would have been caught, suggesting a drastically improved diagnostic yield.1–3,7,17 Direct comparisons of AF detection rates between studies, including this one, are challenging due to differences in follow-up durations, monitoring technologies, and patient demographics.18

An increased rate of AF detection has been associated with longer monitoring periods. The CRYSTAL AF (Cryptogenic Stroke and Underlying AF) trial showed that the rate of AF detection among patients with CS or TIA was 12.4% at 12 months for ICM patients vs 2.0% for standard of care, and at 3 years of follow-up the AF detection rate had increased to 30% in the ICM arm compared to 3.0% in controls.1
Tsivgoulis et al. performed a meta-analysis of 4 studies of prolonged ambulatory electrocardiographic monitoring vs conventional monitoring in CS patients, totaling 1102 patients (including 2 randomized controlled trials [CRYSTAL-AF and FIND-AF [Holter-Electrocardiogram-Monitoring in Patients With Acute Ischaemic Stroke], and 2 controlled observational studies of CS patients). In addition to an increased incidence of AF detection (risk ratio 2.46; 95% confidence interval [CI] 1.61–3.76) and anticoagulant initiation (risk ratio 2.07; 95% CI 1.36–3.17), this pooled analysis also showed a decreased risk of recurrent stroke (risk ratio 0.45; 95% CI 0.21–0.97) during follow-up for patients who underwent prolonged monitoring compared with patients who received conventional cardiac monitoring. A lower
rate of stroke recurrence was also observed in a prospective
nonrandomized clinical trial in Greece.20 The incidence of
stroke recurrence (defined as a new neurological event re-
corded at least 24 hours after hospital discharge and validated
by neuroimaging) in the analysis of consecutively managed
patients was significantly lower in the Reveal LINQ
(Medtronic, Minneapolis) group compared with the
standard-of-care group (4% vs 12%; \(P = .013\)). A similar
result was reported for the propensity score-matched analysis
(ICM 2% vs standard-of-care 9%; \(P < .05\)).20

Our analysis both confirms and extends previous work in
this area by showing that ICM was associated with a 54%
faster time to AF diagnosis and a 57% faster time to oral anti-
cogulation. Additionally, for the first time, our analysis
points to a possible survival benefit from the ICM strategy.
This latter finding could be related to enhanced secondary
prevention of stroke, although given our nonrandomized
study design, the possibility that this finding is due to con-
 founding cannot be excluded. It is possible that patients
with lesser stroke or overall illness severity are more likely
to be prescribed ICMs. However, we found no evidence
that this was so in the measured patient characteristics, which
if anything suggested that the index strokes may have been
more severe in the ICM patients (slightly longer length of
stay and likelihood of ICU admission). The improved sur-
vival of patients receiving ICMs also could be related to other
aspects of their medical care, such as more frequent contact
with providers or receiving treatment in facilities with more
robust aftercare programs following an initial stroke.

Our assessment of care pathways after CS further high-
lights potential advantages of utilizing ICMs earlier rather
than later after CS. Our data clearly demonstrate that patients
managed with external monitors encounter substantial delays
to AF diagnosis and the opportunity for treatment; receive
ICMs much later (or not at all); and in some cases may be
lost to follow-up entirely. Finally, although our observations
indicate that some stroke care pathways include a trial of
ECMs before ICM (likely due in part to the higher upfront
cost of the ICM device), recent cost-effectiveness analysis
found this approach to be overall on average cost-additive
compared to use of an ICM directly after CS, due to the
low likelihood of diagnosis with an initial ECM.21 These
considerations may be important in jurisdictions with con-
strained health care resources, in which short- vs long-term
clinical and economic implications must be weighed. Further
research should focus on assessing economic and clinical im-
lications of stroke monitoring pathways outside the United
States.

### Table 3  Multivariable results: Time to clinical event

| Event                  | Cox regression models | Unadjusted HR | Adjusted HR | Lower CI | Upper CI | \(P\) value |
|------------------------|-----------------------|---------------|-------------|----------|----------|-------------|
| Time to death          | 0.69                  | 0.70          | 0.55        | 0.89     | .0040    |
| Time to AF diagnosis   | 1.51                  | 1.50          | 1.40        | 1.60     | <.0001   |
| Time to anticoagulation| 1.53                  | 1.57          | 1.42        | 1.73     | <.0001   |
| Time to anticoagulation in patients who are diagnosed with AF | 1.11 | 1.12 | 1.01 | 1.23 | .0289 |

All models: ICM is a time-varying covariate. Additional covariates include patient demographics, index hospital stay characteristics indicative of stroke severity (length of stay, intensive care unit utilization, and discharge status home vs not home), and CHA2DS2-VASc score.

AF = atrial fibrillation; CI = confidence interval; HR = hazard ratio; ICM = insertable cardiac monitor.

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**Figure 3** Time to anticoagulation for insertable cardiac monitor (ICM) vs external cardiac monitor (ECM).
Study limitations
The most important limitation is the use of observational data, which is subject to treatment by indication bias. The limitations of this study are consistent with weaknesses in retrospective claims-based analyses, which include the reliance on billing codes and the risk of coding errors. Although we adjusted for a variety of patient characteristics and comorbidities, there may be additional underlying variables that we are not able to account for in claims data. For example, although we adjusted for the available metrics that in our clinical experience are indicative of stroke severity (length of stay, ICU utilization, and discharge status), there may be other important differences in severity that we are not able to capture. Likewise, there may be other external forces affecting these characteristics, such as the availability of health care resources, that are unrelated to the severity of the stroke. Furthermore, the retrospective design of our study and the labeling of the pathologies (CS, TIA, AF) without complete information on diagnosis details (as might be found in an electronic health record) could decrease the significance of the results and their generalizability.

Using commercial claims data, the generalizability of our findings is limited to U.S. patients with commercial insurance. Although our population is primarily of Medicare age, no fee-for-service Medicare patients are represented in our analysis (only Medicare Advantage patients insured through United Healthcare). Additionally, claims-based analyses in the area of CS are limited by the lack of explicit ICD-9 or ICD-10 diagnosis codes for stroke/TIA that remains cryptogenic after initial evaluation. However, we were able to leverage an analysis utilizing Optum linked to ICM device data to identify the 4 diagnosis codes utilized in the vast majority (93.2%) of patients receiving cardiac monitoring for a stated indication of CS (data on file). Due to the complexity and variability in cardiac monitoring pathways, our ECM cohort includes patients receiving a variety of external monitoring modalities (including short- and long-term Holter monitors, event monitors, and mobile cardiac telemetry monitors), which limits the ability to attribute outcomes to any specific monitor type. Finally, we were unable to assess rates of recurrent acute ischemic stroke events due to the lack of needed documentation in claims data, which makes it unreliable to differentiate recurrent events vs follow-up or coding of a previous event in the patient’s history. This research question is better answered utilizing detailed electronic health record data or prospective clinical studies.

Conclusion
One of the important goals of stroke and TIA management is clarifying risk factors for potential stroke recurrence to optimize treatment. Because AF can be infrequent and intermittent in nature, detection can be challenging during the initial evaluation and with short-term monitoring in patients who experience CS. Whether it is cause or consequence of the stroke, AF is a well-established risk factor for recurrent stroke, and initiation of oral anticoagulation is indicated for stroke prophylaxis upon diagnosis of AF. In this study, we found patients with longer-term monitoring had higher rates of AF detection and treatment, and significantly higher odds of survival. Implantable cardiac devices that allow for continuous cardiac rhythm monitoring in patients with CS or TIA may aid in earlier detection of serious underlying disease such as AF, thereby enabling intervention and superior patient outcomes.

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Authorship: All authors attest they meet the current ICMJE criteria for authorship.

Patient Consent: Since this was a non-interventional, retrospective, observational study utilizing de-identified data, informed consent was not required from the patient under an IRB exemption status.

Ethics Statement: All aspects of this study were conducted in compliance with Health Insurance Portability and Accountability Act of 1996 (HIPAA) regulations and the HIPAA Omnibus Rule of 2013.

Data Availability Statement: Analyzable dataset available upon request.

Appendix
Supplementary data
Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hroo.2022.02.006.

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