Detection of Atrial Fibrillation After Central Retinal Artery Occlusion

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BACKGROUND: Central retinal artery occlusion (CRAO) causes sudden, irreversible blindness and is a form of acute ischemic stroke. In this study, we sought to determine the proportion of patients in whom atrial fibrillation (AF) is detected by extended cardiac monitoring after CRAO.

METHODS: We performed a retrospective, observational cohort study using data from the Optum deidentified electronic health record of 30.8 million people cross-referenced with the Medtronic CareLink database of 2.7 million people with cardiac monitoring devices in situ. We enrolled patients in 3 groups: (1) CRAO, (2) cerebral ischemic stroke, and (3) age-, sex-, and comorbidity-matched controls. The primary end point was the detection of new AF (defined as ≥2 minutes of AF detected on a cardiac monitoring device).

RESULTS: We reviewed 884,431 patient records in common between the two databases to identify 100 patients with CRAO, 6,559 with ischemic stroke, and 1000 matched controls. After CRAO, the cumulative incidence of new AF at 2 years was 49.6% (95% CI, 37.4%–61.7%). Patients with CRAO had a higher rate of AF than controls (hazard ratio, 1.64 [95% CI, 1.17–2.31]) and a comparable rate to patients with stroke (hazard ratio, 1.01 [95% CI, 0.75–1.36]). CRAO was associated with a higher incidence of new stroke compared with matched controls (hazard ratio, 2.85 [95% CI, 1.29–6.29]).

CONCLUSIONS: The rate of AF detection after CRAO is higher than that seen in age-, sex-, and comorbidity-matched controls and comparable to that seen after ischemic cerebral stroke. Paroxysmal AF should be considered as part of the differential etiology of CRAO, and those patients may benefit from long-term cardiac monitoring.

Key Words: arrhythmias, cardiac • atrial fibrillation • comorbidity • incidence • ischemic stroke

Central retinal artery occlusion (CRAO) is a rare form of ischemic stroke as recognized in the most recent consensus definition from the American Heart Association/American Stroke Association.1 The prevailing paradigm is that CRAO arises as a result of ipsilateral, stenotic, atherosclerotic plaque.2 However, 60% of people do not have high-grade, ipsilateral carotid stenosis,3 and 30% of people with CRAO do not have even mild ipsilateral carotid disease.4 Atrial fibrillation (AF) is becoming better recognized as a contributor to CRAO risk. In a recent cohort study, we found that 10% of patients with acute CRAO without a clear etiology had AF on a 30-day cardiac event monitor.5 In contrast to cerebral ischemic stroke, the yield of extended cardiac monitoring in the diagnosis of new AF after CRAO is unknown.
Our study was motivated by 3 central observations: (1) the detection of AF after acute cerebral ischemic cryptogenic stroke or TIA continues to increase with extended cardiac monitoring9; (2) there is a high rate of concurrent cerebral ischemia in the presence of CRAO7,8 and an elevated rate of cerebral ischemic stroke in the wake of an episode of CRAO,9 arguing strongly for a common mechanism between the two conditions and; (3) there is a reciprocal relationship between AF and CRAO. CRAO is more common in patients with AF compared with matched controls,10 and patients with CRAO have a higher prevalence of AF than the general population, even after matching for vascular comorbidities.11 Given that AF and CRAO share vascular risk factors, defining an association between the two conditions would not necessarily imply causality. The same principle is observed with cerebral ischemic stroke.

In this study, we aimed to determine the yield of long-term, implantable cardiac monitoring devices for detecting AF after CRAO. Also, we sought to compare the rates of AF detection in patients with CRAO with two control groups: (1) patients matched by age, sex, and vascular comorbidities and (2) patients with cerebral ischemic stroke. Our specific hypothesis was that the diagnosis of CRAO would be associated with a higher rate of AF detection when compared with matched control patients and a similar rate of AF detection compared with patients with recent cerebral ischemic stroke. Additionally, we sought to compare the rates of cerebral ischemic stroke after CRAO with matched controls.

METHODS
Because of contractual arrangements between Medtronic, Inc, and Optum, the data cannot be made available to other researchers for the purposes of reproducing the results or replicating the procedure.

Study Design
We performed a retrospective, observational cohort study using data from the Optum deidentified electronic health record (EHR) database. This is an administrative dataset comprising ~30.8 million patients from 62 health systems in the United States between January 2007 and June 2019. We cross-referenced this with data from the Medtronic CareLink registry, which contains records from 2.7 million patients with implantable cardiac monitoring devices (defined as insertable cardiac monitors [ICMs], cardiac resynchronization therapy devices, or implantable pacemaker/defibrillators). Patients in these two databases were cross-linked by means of arbitrary identifiers. Within this study, the primary exposure variable was CRAO. The outcome variable (defined below) was a new diagnosis of AF. The requirement for informed consent was waived as an exemption was provided by the Institutional Review Board of Rhode Island Hospital/Lifespan (No. 1575882).

Derivation of Clinical Data
Patients with CRAO were identified by an admission with the primary International Classification of Diseases, Ninth Revision (ICD-9), diagnosis code of 362.31 or ICD, Tenth Revision (ICD-10), diagnosis codes of H34.10, H34.11, H34.12, or H34.13. We excluded patients with a preexisting history of AF either detected on extended cardiac monitoring or by the presence of corresponding diagnostic codes (ICD-9 427.31 or ICD-10 I48.91, I48.0, I48.1 or I48.2). Cerebral ischemic stroke was identified by a primary ICD-9 diagnosis code of 433.X, 434.X, or 436.X (previously validated for use in stroke research)12 or ICD-10 diagnosis code of I63.X, I65.X, or I66.X. To improve the specificity of this diagnosis code, we added a number of additional criteria in keeping with a prior publication using this dataset.13 We required that one of the ischemic stroke diagnosis codes be in the primary position, occur after the index date, and that patients also met 1 of 2 further sets of criteria:

1. They underwent mechanical thrombectomy or tissue-type plasminogen activator administration or
2. (a) They underwent neurological testing (computed tomography, magnetic resonance imaging, computed tomography angiography of the neck vasculature, carotid ultrasonography, or coagulation testing) or (b) they underwent administration of antiplatelet agents, prophylactic anticoagulation, or therapeutic anticoagulation and
3. They had relevant diagnostic investigations performed (ECG, Holter monitoring, serum glucose testing, chest radiograph, or echocardiography) or
4. They had hospital critical care time performed during the hospitalization.

Patient Selection
We included adult patients within the Optum EHR who had a preexisting implantable cardiac device in place or a device that was implanted up to 1 year post-index date that was capable of detecting AF. We excluded patients with incomplete data, patients with a history of AF (defined as an ICD-9 or ICD-10 diagnosis code corresponding to AF at any point in their medical record before the index date), and patients with a history of ischemic stroke. Also, we required patients to have EHR data sourced from a provider who was part of an integrated delivery network to increase the reliability of hospitalizations data. To maximize the number of CRAO patients available for analysis, all CRAO patients in the database were screened for inclusion, regardless of the date of their CRAO event.

For a control group, patients were selected via matching against the CRAO cohort in a 10:1 ratio based on age, sex,
and 8 vascular comorbidities (hypertension, hyperlipidemia, type II diabetes, coronary artery disease, congestive heart failure, chronic kidney disease, chronic obstructive pulmonary disease, and obstructive sleep apnea). COPD was included in the matching criteria as it is a known, independent risk factor for AF. The pool of eligible control patients included all patients in the database with a Medtronic device and with daily device data available. For each CRAO patient, all eligible control patients were screened for inclusion criteria at the same index date as the CRAO patient. Control patients were required to meet the same inclusion criteria as of the matched index date, including having no history of cerebral ischemic stroke, no history of AF, EHR data sourced from an integrated delivery network provider, and having an AF-capable device in place or implanted up to 1 year post-index event. Among those that passed all inclusion criteria, 10 control patients were randomly chosen that perfectly matched each of the CRAO patient for age, sex, and the 8 comorbidities listed above as of their index date. In cases where perfect matching between patients was not possible, we allowed an age deviation of up to 5 years or a different status of up to 1 of the 8 matched comorbidities. For example, if one patient in the matched pair has hypertension and the other does not, they must be identical with regard to the presence/lack of the other 7 comorbidities.

The second control group comprised all occurrences of index cerebral ischemic stroke in the database that likewise met all of the same inclusion criteria listed above. For this group, 2 sensitivity analyses were also performed to determine whether results differed for stroke subgroups of interest:

1. Cryptogenic stroke subgroup: index cerebral ischemic strokes in which the first included device was an ICM that was implanted post-index event were assumed to be cryptogenic. Cryptogenic classification was estimated in this way because there are no ICD-9/ICD-10 diagnosis codes that could be used to reliably differentiate cryptogenic stroke from other classifications of cerebral ischemic stroke, and the dataset provided no access to clinical documentation.

2. Matched cerebral ischemic stroke subgroup: because of baseline differences in clinical history and demographics between the CRAO group and the cerebral ischemic stroke group, a cerebral ischemic stroke subgroup that was matched 5:1 against the CRAO group was also analyzed. These patients were matched against CRAO patients using the same procedure as outlined above.

Finally, there was an additional sensitivity analysis performed to examine patients with standalone CRAO, as opposed to CRAO co-occurring with cerebral ischemic stroke or other arterial embolism. CRAO patients were removed that had either a cerebral ischemic stroke event (as defined above) or a diagnosis code for arterial embolism (ICD-9 diagnosis code 444.X or ICD-10 diagnosis code I74.X) within ±5 days of their CRAO index event date. The corresponding matched control patients for the removed CRAO patients were also removed for this sensitivity analysis.

**End Points**

Our primary end point was the detection of new AF ≥2 minutes in duration within one 24-hour period using previously validated AF detection algorithms. The threshold of 2 minutes was chosen as the implantable cardiac monitors used in this study required 2 minutes of AF to permit automatic detection. We applied this threshold across all devices. Our secondary end point was a new diagnosis of cerebral ischemic stroke. This was based on the above validated diagnosis codes corresponding with cerebral ischemic stroke along with additional criteria met for laboratory studies and procedures in their EHR (as described above). This secondary end point was not evaluated in the cerebral ischemic stroke control group due to the ambiguity in the EHR data for distinguishing between recurrent cerebral ischemic stroke and follow-up documentation referencing the index cerebral ischemic stroke.

**Statistical Analysis**

Age, sex, and vascular comorbidities were described via standard descriptive statistics with means and SDs or frequencies as appropriate. We calculated the cumulative incidence of new device-detected AF and new cerebral ischemic stroke and described them via Kaplan-Meier analysis. For cumulative incidence estimates, time to new device-detected AF was measured starting from the later of index event date or device implantation date to account for the difference between patients receiving their device before versus after the index event date. In other words, all estimates of device-detected AF rate are a measure of time since monitoring began rather than time since event. The cumulative incidence of time to new cerebral ischemic stroke was measured from the index event date. Patients were right-censored at the last day of device data availability when estimating device-detected AF incidence and right-censored at the last day of EHR data availability when estimating cerebral ischemic stroke incidence. For comparing cumulative incidence curves, the Fine-Gray proportional hazards model (controlling for age, sex, and vascular comorbidities) was used to calculate hazard ratios (HRs) and 95% CIs while controlling for the competing risk of death.

Statistical analysis was performed with R (Vienna, Austria) and with MatLab (Natick, MA).

**RESULTS**

**Patient Selection**

We identified 884,431 patients with linked data in both the Optum EHR and Medtronic CareLink registry. The process of patient selection within the CRAO group is demonstrated in Figure 1. Of 321 patients with a primary diagnosis code of CRAO and a cardiac monitoring device in situ, 100 were included in the study (full reasons for exclusion are outlined in Figure 1). There were 32,853 patients with a diagnosis code and a hospitalization consistent with cerebral ischemic stroke. Among these, 6559 were included in the study. There were 338,841 patients with daily device data available who were eligible for inclusion as matched controls. Among these, 1000 were selected via the process described above, matching 10:1 against the CRAO group on age, sex, and vascular comorbidities. Of the 1000 matched control patients selected, 68.3% had identical age, sex, and comorbidities as their corresponding CRAO patient, 26.7% had identical sex and comorbidities but differed in age by 1 to 5 years, 3.4% had identical sex and age but differed in their status of exactly 1 comorbidity, and
the remaining 1.6% differed in age by 1 to 5 years and also had exactly 1 differing comorbidity. The demographics of patients in each group are outlined in Table 1.

**Rate of AF Detection**

Figure 2 depicts the Kaplan-Meier analysis of AF detection within the 2-year period post-index event according to the 3 groups. When accounting for loss to follow-up, there was an estimated 33.4% (95% CI, 23.4%–43.4%) cumulative incidence of the detection of AF at 1 year post-CRAO and 49.6% (95% CI, 37.4%–61.7%) at 2 years post-CRAO. For the cerebral ischemic stroke group, these rates were 33.6% (32.4%–34.8%) at 1 year and 43.2% (95% CI, 41.8%–44.7%) at 2 years, and for the matched control group, it was 22.3% (95% CI, 20.4%–24.2%).
Rate of New Ischemic Stroke

Figure 3 depicts the Kaplan-Meier analysis of new cerebral ischemic stroke within the 2-year period post-index event. The cumulative incidence of cerebral ischemic stroke at 2 years post-index event was 9.0% (95% CI, 3.0%–15.0%) for the CRAO group and 3.7% (95% CI, 2.3%–5.0%) for the matched control group. The incidence of new cerebral ischemic stroke in the CRAO group was higher than that observed in the matched controls (HR, 2.85 [95% CI, 1.29–6.29]; \(P=0.009\)).

Cerebral Ischemic Stroke Subgroup Sensitivity Analyses

Figures 4A and 4B depict the Kaplan-Meier analysis of AF detection for the cryptogenic stroke subgroup and the matched cerebral ischemic stroke subgroup, respectively. The majority (77%) of the overall cerebral ischemic stroke group was included in the cryptogenic stroke subgroup, and the data for CRAO and matched control patients remain the same as in Figure 2. In both cases, results were similar to the primary analysis. The estimated cumulative incidence at 2 years post-index was 46.2% (95% CI, 44.6%–47.9%) for the cryptogenic stroke subgroup and 46.7% (95% CI, 41.2%–52.1%) for the matched cerebral ischemic stroke subgroup. In both cases, the CRAO group was still found to have similar rate compared with the stroke groups (CRAO versus cryptogenic stroke: HR, 0.98 [95% CI, 0.70–1.37]; \(P=0.914\)).

Standalone CRAO Subgroup Sensitivity Analysis

For this sensitivity analysis, 19 of 100 of the CRAO cohort were removed that had either cerebral ischemic stroke or other arterial embolism co-occurring with their CRAO. The corresponding 190 matched control patients were also removed from this analysis. Figure IA in the Data Supplement depicts the Kaplan-Meier analysis of AF detection for these subgroups, and the corresponding analysis of new ischemic stroke is depicted in Figure IB in the Data Supplement. In both analyses, the data for the cerebral ischemic stroke groups remain the same as in Figures 2 and 3, respectively. Results remained similar to the primary analysis, although in the case of AF detection, the difference between the CRAO group and the matched control group rose slightly above the 0.05 level of significance. The estimated cumulative incidence of device-detected AF at 2 years post-index was 46.0% (95% CI, 32.8%–59.2%) for the CRAO group and 32.6% (95% CI, 28.6%–36.6%) for the matched control group (HR, 1.45 [95% CI, 0.99–2.14]; \(P=0.058\)). The estimated cumulative incidence of new ischemic stroke at 2 years post-index was 9.8%

Table 1. Demographics and Key Clinical Characteristics of Patients in the CRAO Cohort and 2 Control Groups

<table>
<thead>
<tr>
<th></th>
<th>CRAO (n=100)</th>
<th>Matched control (n=1000)</th>
<th>Cerebral ischemic stroke (n=6559)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y (±SD)</td>
<td>69.0±14.0</td>
<td>69.1±13.9</td>
<td>65.7±13.1</td>
</tr>
<tr>
<td>Women, %</td>
<td>43 (43.0%)</td>
<td>430 (43.0%)</td>
<td>2998 (45.7%)</td>
</tr>
<tr>
<td>Race, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td>7 (7.0%)</td>
<td>83 (8.3%)</td>
<td>913 (13.9%)</td>
</tr>
<tr>
<td>Asian</td>
<td>2 (2.0%)</td>
<td>6 (0.6%)</td>
<td>54 (0.8%)</td>
</tr>
<tr>
<td>White</td>
<td>85 (85.0%)</td>
<td>861 (86.1%)</td>
<td>5273 (80.4%)</td>
</tr>
<tr>
<td>Other/unknown race</td>
<td>6 (6.0%)</td>
<td>50 (5.0%)</td>
<td>319 (4.9%)</td>
</tr>
<tr>
<td>Ethnicity, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>3 (3.0%)</td>
<td>23 (2.3%)</td>
<td>266 (4.1%)</td>
</tr>
<tr>
<td>Non-Hispanic</td>
<td>93 (93.0%)</td>
<td>930 (93.0%)</td>
<td>6050 (92.2%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>4 (4.0%)</td>
<td>47 (4.7%)</td>
<td>243 (3.7%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>73 (73.0%)</td>
<td>730 (73.0%)</td>
<td>4987 (78.0%)</td>
</tr>
<tr>
<td>Diabetes (type II)</td>
<td>28 (28.0%)</td>
<td>272 (27.2%)</td>
<td>2178 (33.2%)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>58 (58.0%)</td>
<td>580 (58.0%)</td>
<td>3986 (60.8%)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>43 (43.0%)</td>
<td>428 (42.8%)</td>
<td>2196 (33.5%)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>14 (1.4%)</td>
<td>144 (14.4%)</td>
<td>1091 (16.6%)</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>16 (16.0%)</td>
<td>148 (14.8%)</td>
<td>948 (14.5%)</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>15 (15.0%)</td>
<td>146 (14.6%)</td>
<td>1156 (17.6%)</td>
</tr>
<tr>
<td>Obstructive sleep apnea</td>
<td>15 (15.0%)</td>
<td>150 (15.0%)</td>
<td>892 (13.6%)</td>
</tr>
</tbody>
</table>

CRAO indicates central retinal artery occlusion.

Types of Device/Characteristics of AF

Table 2 outlines the characteristics of AF detected and the device types in place according to each group. Among CRAO patients, 73% had their first device implanted on or up to 1 year after their CRAO event date, with the other 27% having a prior device already in place. Of those that were implanted within 1 year post-CRAO, the mean number of days between index date and implant was 66.8±82.6. Among CRAO patients with device-detected AF, 31 of 41 (75.6%) had short paroxysmal AF (ie, <6 hours per day), 7 of 41 (17.1%) had nonpersistent AF (6–24 hours per day) and 3 of 41 (7.3%) had persistent AF (ie, episodes lasting ≥7 consecutive days).
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(95% CI, 2.8%–16.7%) for the CRAO group and 4.1% (95% CI, 2.5%–5.8%) for the matched control group (HR, 2.64 [95% CI, 1.14–6.11]; P=0.023).

DISCUSSION

This study demonstrates that extended cardiac monitoring may have an important diagnostic role in patients with CRAO. The rate of device-detected paroxysmal AF in the CRAO population is considerable and is both comparable to the rate in patients with cerebral ischemic stroke and higher than in matched controls. Further, the rate of newly diagnosed AF is higher in this study than in CRYSTAL-AF (Cryptogenic Stroke and Underlying AF Trial), which may reflect the fact that patients in this study were at higher risk of atrial arrhythmias by virtue of their increased age and baseline cardiovascular diagnoses. CRYSTAL-AF included patients with cryptogenic stroke randomized to ICM placement compared with best medical care. By contrast, ASSERT (Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial) included patients with a pacemaker or defibrillator implanted for suspected or diagnosed cardiac disease who are at relatively high risk for AF. Like ASSERT, subjects in our study had at least 1 diagnosed cardiac condition (a property of the Optum database). In patients with CRAO, the rate of recurrent ischemic stroke is also increased when compared with matched controls.

The higher rate of AF in patients with CRAO compared with controls argues for potential causal association between subclinical AF and CRAO in the same way that ASSERT suggested an association between subclinical AF and cerebral stroke.17 Because of close matching between groups, it is unlikely that our findings would otherwise be explained solely by the higher risk of cardiac disease in these patients.

Our study presents a novel finding in the CRAO population. AF should be considered in the differential etiology of CRAO. Long-term (ie, for 2–3 years) cardiac monitoring may be a reasonable option as part of the diagnostic workup in cryptogenic cases of CRAO. Strategies for cardiac monitoring include wearable cardiac monitors as utilized in EMBRACE (30-Day Cardiac Event Monitor Belt for Recording Atrial Fibrillation After a Cerebral Ischemic Event Trial)18 and long-term ICM as utilized in CRYSTAL-AF.6 Although these individual

<table>
<thead>
<tr>
<th>Characteristics of AF</th>
<th>CRAO (n=100)</th>
<th>Matched controls (n=1000)</th>
<th>Cerebral ischemic stroke (n=6559)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any postindex AF detected</td>
<td>41 (41.0%)</td>
<td>282 (28.2%)</td>
<td>2420 (36.9%)</td>
</tr>
<tr>
<td>6–24 h per day</td>
<td>10 (10.0%)</td>
<td>120 (12.0%)</td>
<td>606 (9.2%)</td>
</tr>
<tr>
<td>Persistent AF</td>
<td>3 (3.0%)</td>
<td>45 (4.5%)</td>
<td>143 (2.2%)</td>
</tr>
<tr>
<td>Device type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICM</td>
<td>73 (73.0%)</td>
<td>343 (34.3%)</td>
<td>5347 (81.5%)</td>
</tr>
<tr>
<td>IPG</td>
<td>16 (16.0%)</td>
<td>320 (32.0%)</td>
<td>538 (8.2%)</td>
</tr>
<tr>
<td>ICD</td>
<td>7 (7.0%)</td>
<td>205 (20.5%)</td>
<td>418 (6.4%)</td>
</tr>
<tr>
<td>CRT-P</td>
<td>1 (1.0%)</td>
<td>14 (1.4%)</td>
<td>28 (0.4%)</td>
</tr>
<tr>
<td>CRT-D</td>
<td>4 (4.0%)</td>
<td>128 (12.8%)</td>
<td>268 (4.1%)</td>
</tr>
</tbody>
</table>

Note that device types may sum up to >100% due to patients who had multiple devices of different types in the follow-up period. AF indicates atrial fibrillation; CRAO, central retinal artery occlusion; CRT-D, cardiac resynchronization device-defibrillator; CRT-P, cardiac resynchronization therapy device-pacemaker; ICD, implantable cardioverter-defibrillator; ICM, insertable cardiac monitor; and IPG, implantable pacemaker generator.

Figure 2. Cumulative incidence of new atrial fibrillation (AF) detection via the Kaplan-Meier analysis. CRAO indicates central retinal artery occlusion.
studies were underpowered to detect a reduction in the rate of recurrent stroke with cardiac monitoring, a recent meta-analysis found an association between long-term cardiac rhythm monitoring and both increased rate of anticoagulation initiation and reduced incidence of recurrent stroke. The current study suggests that short-term monitoring alone would fail to detect a significant proportion of patients with underlying AF and, therefore, longer term monitoring may be considered in select patients. The Kaplan-Meier estimate for AF detection at 30 days in patients with CRAO was only 15.1% (95% CI, 8.1%–22.2%) meaning that 70% of patients ultimately diagnosed with AF during the 2 period post-CRAO would have been missed if only 30 days of cardiac event monitoring was performed. Our data build on and broaden the analogy between cerebral ischemic stroke and CRAO—2 conditions in which an urgent, structured workup is necessary to effectuate appropriate secondary prevention strategies.

Our study has a number of strengths. It utilized an innovative approach via large administrative datasets linked with long-term cardiac monitoring data to address a significant and unexplored question in a previously overlooked population. The Optum EHR database includes over 30 million patients, providing the scale needed to effectively study this rare condition (with an incidence of 1.8/100 000 patient years). The large dataset also permitted close matching between the control groups for age, sex, and vascular comorbidities. Another reasonable approach may have been to use propensity score matching; however, the enormous scale of the dataset meant that we were able to achieve the same alignment between groups through selection based on individual comorbidities. Further, we had access to long-term continuous cardiac monitoring data, which allowed us to measure the true incidence of AF in a more robust fashion than relying on diagnosis codes or external monitoring results.

This study should be considered in light of several limitations. First, it is limited by its retrospective nature, which introduces the possibility of selection and misclassification biases. Second, the ICD-9 and ICD-10 codes for CRAO have not been validated before in the context of an administrative database, although there are limited number of diagnosis codes that refer to CRAO within this classification scheme. Third, we chose conservative criteria for the identification of cerebral ischemic stroke, requiring not only a primary diagnosis code corresponding to ischemic stroke but also a set of admission criteria supporting this as the diagnosis. This has the potential to exclude patients with minor stroke or strokes that were rapidly fatal (as such patients may not have undergone further testing or treatment). Fourth, the patients in this study were all at high cardiovascular risk by virtue of their inclusion in this subset of the Optum EHR database and, therefore, likely at higher risk for the development of AF. This database includes cardiovascular patients defined broadly, including any patient with cardiovascular-related diagnosis codes (eg, arrhythmias, coronary disease, syncope, chest pain) or procedure codes (eg, cardiovascular implantable electronic device implants or follow-up). Thus, they may not be representative of a broader population and, in particular, may not generalize to all patients with CRAO. Fifth, the same risk factors that would increase AF burden/lead to AF are the same risk factors that increase risk of emboli that could lead to CRAO/stroke from other sources. We approached this by using an exact matching strategy to ensure that patients were as closely matched as possible by demographics and underlying risk factors. Sixth, for the cryptogenic stroke subgroup sensitivity

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**Figure 3. Cumulative incidence of new cerebral ischemic stroke via the Kaplan-Meier analysis.**

CRAO indicates central retinal artery occlusion.
analysis, while we assumed that ICM placement after an ischemic stroke was performed for the primary reason of determining stroke etiology, it is possible that other reasons may have led the treating provider to place an ICM and that we have erroneously labeled such patients as having cryptogenic stroke. Finally, as with all research on long-term cardiac monitoring after ischemic stroke, we were unable to determine whether AF was causative, incidental, or triggered by concurrent or subsequent cerebral ischemia.

In summary, this study suggests that the rate of paroxysmal AF detection after CRAO is comparable with that seen after ischemic cerebral stroke and higher than in age-, sex-, and comorbidity-matched controls. Patients with CRAO may, therefore, benefit from prolonged cardiac monitoring to detect paroxysmal AF.

**ARTICLE INFORMATION**

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Supplemental Materials
Online Figure I

REFERENCES