Stroke

CLINICAL AND POPULATION SCIENCES

Differences in Stroke Recurrence Risk Between Atrial Fibrillation Detected on ECG and 14-Day Cardiac Monitoring

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BACKGROUND: Ischemic stroke and transient ischemic attack (TIA) standard-of-care etiological investigations include an ECG and prolonged cardiac monitoring (PCM). Atrial fibrillation (AF) detected after stroke has been generally considered a single entity, regardless of how it is diagnosed. We hypothesized that ECG-detected AF is associated with a higher risk of stroke recurrence than AF detected on 14-day Holter (PCM-detected AF).

METHODS: We conducted a retrospective, registry-based, cohort study of consecutive patients with ischemic stroke and TIA included in the London Ontario Stroke Registry between 2018 and 2020, with ECG-detected and PCM-detected AF lasting ≥30 seconds. We quantified PCM-detected AF burden. The primary outcome was recurrent ischemic stroke, ascertained by systematically reviewing all medical records until November 2022. We applied marginal cause–specific Cox proportional hazards models adjusted for qualifying event type (ischemic stroke versus TIA), CHA_2DS_2-VASc score, anticoagulation, left ventricular ejection fraction, left atrial size, and high-sensitivity troponin T to estimate adjusted hazard ratios for recurrent ischemic stroke.

RESULTS: We included 366 patients with ischemic stroke and TIA with AF, 218 ECG-detected, and 148 PCM-detected. Median PCM duration was 12 (interquartile range, 8.8–14.0) days. Median PCM-detected AF duration was 5.2 (interquartile range, 0.3–33.0) hours, with a burden (total AF duration/total net monitoring duration) of 2.23% (interquartile range, 0.13%–12.25%). Anticoagulation rate at the end of follow-up or at the first event was 83.1%. After a median follow-up of 17 (interquartile range, 5–34) months, recurrent ischemic strokes occurred in 16 patients with ECG-detected AF (13 on anticoagulants) and 2 with PCM-detected AF (both on anticoagulants). Recurrent ischemic stroke rates for ECG-detected and PCM-detected AF groups were 4.05 and 0.72 per 100 patient-years (adjusted hazard ratio, 5.06 [95% CI, 1.13–22.7]; P=0.034).

CONCLUSIONS: ECG-detected AF was associated with 5-fold higher adjusted recurrent ischemic stroke risk than PCM-detected AF in a cohort of ischemic stroke and TIA with >80% anticoagulation rate.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: atrial fibrillation ■ risk ■ stroke ■ transient ischemic attack

The increasing use of prolonged cardiac monitoring (PCM) in patients with ischemic stroke to look for paroxysmal atrial fibrillation (AF) has led to a better characterization of PCM-detected cardiac arrhythmias. AF detected on 14-day Holter (PCM-detected AF) is defined as any AF found on PCM, including Holter

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Nonstandard Abbreviations and Acronyms

AF	atrial fibrillation
AFDAS	atrial fibrillation detected after a stroke
aHR	adjusted hazard ratio
DELIMIT-AF STROKE	Differences in ECG- Versus Prolonged Cardiac Monitoring-Detected Atrial Fibrillation in STROKE Patients
HS-TnT	high-sensitivity troponin T
IQR	interquartile range
LVEF	left ventricular ejection fraction
MACE	major adverse cardiovascular event
PCM	prolonged cardiac monitoring
TIA	transient ischemic attack

monitoring, external or internal loop recorders, and cardiac implantable electronic devices. Current knowledge about AF-associated ischemic stroke risk derives from large population-based observational studies in which AF diagnosis was based on 12-lead ECG. ECG-detected AF is known to be high-burden and is primarily identified among symptomatic patients seeking medical attention because of specific symptoms or cardiovascular complications (eg, decompensated heart failure or symptomatic arrhythmia). Conversely, PCM-detected AF in patients with ischemic stroke is frequently low-burden[1] and asymptomatic in ≈8 out of 10 patients,[2] suggesting it may be associated with a relatively lower embolic risk compared to ECG-detected AF.[3]

Evidence accrued in the past decade suggests that patients with AF first diagnosed after an ischemic stroke (AFDAS), which is primarily PCM-detected, has a lower prevalence of vascular risk factors, cardiovascular comorbidities, and structural heart disease than those with AF known before stroke occurrence or known AF.[4] Furthermore, the risk of stroke recurrence in patients with AFDAS seems to be 26% lower than in those with known AF.[4] In prior studies, AFDAS cohorts included patients with both ECG-detected and PCM-detected AF, without stratifying the analyses for these specific AF subtypes.[5,6] We previously proposed that ECG-detected AF in patients with an acute ischemic stroke should not be considered AFDAS because ECG-detected AF is more likely to be preexistent.[7] We hypothesized that despite remaining undetected before stroke, ECG-detected AF has a high burden and a similar stroke risk as known AF.[7] Currently, ECG- and PCM-detected AF in patients with ischemic stroke and TIA are used indistinguishably both in clinical practice and research because they have never been compared. However, it is unknown if the risk of recurrent ischemic stroke differs between both types of AF. Another major current knowledge gap is the scarcity of studies providing comprehensive data on AF burden in patients with stroke with PCM-detected AF on 14-day Holter. AF burden is a well-recognized marker of AF-associated stroke risk.[8] Evaluating AF burden will become increasingly important in the context of an increased use of wearable cardiac monitoring technologies and intense cardiac monitoring poststroke. In the present study, we compared the risk of stroke recurrence (primary outcome) among patients with ischemic stroke and transient ischemic attack (TIA) with a first ECG-detected versus PCM-detected AF. Additionally, we compared the risk of major adverse cardiovascular events (MACE, secondary outcome) and death among other tertiary outcomes between both modes of AF detection. We also aimed to provide a detailed description of AF burden for PCM-detected AF on 14-day Holter to help understand the implications of this study's findings in the context of current knowledge.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request and subject to the approval of the London Health Sciences Center Privacy Office and Western University Ethics Review Board.

Study Design and Patient Selection

The DELIMIT-AF STROKE (Differences in ECG- Versus Prolonged Cardiac Monitoring-Detected Atrial Fibrillation in STROKE Patients) is a retrospective registry-based cohort study based on prospectively collected data from consecutive patients with ischemic stroke and TIA included in the London Ontario Stroke Registry. The registry was created in 2017 and consistently collects consecutive information from patients assessed by certified stroke neurologists with suspected ischemic stroke or TIA since 2019, regardless of the final diagnosis. Patients are evaluated in the Emergency Department, the stroke unit, or the secondary stroke prevention clinic. We excluded patients with a known history of AF as documented in medical records, or previous ECGs or cardiac monitoring. Patients with a history of ablation therapy or AF identified in the context of acute illness (eg, cardiac surgery, sepsis, pulmonary embolism) were also excluded. We included consecutive patients with ischemic stroke or TIA who had ECG- or PCM-detected AF. Ischemic stroke was defined as a focal neurological deficit with a matching acute or subacute brain infarct demonstrated on brain computed tomography or magnetic resonance imaging. TIA was defined as transient brain or retinal focal neurological dysfunction without evidence of an acute infarct on ophthalmological evaluation or brain imaging.[9]

Definition of AF

In the London Ontario Stroke Registry, patients assessed in the Emergency Department or admitted to the stroke unit receive at least one 12-lead ECG as a first approach to AF diagnosis. Some Emergency Department patients receive a first ECG and are referred to the secondary stroke prevention clinic. The secondary stroke prevention clinic has a mandate to evaluate

patients within 48 hours of the Emergency Department referral. All patients with a first ECG without AF and high suspicion of ischemic stroke or TIA, undergo PCM. One or more 14-day CardioSTAT™ Holter (Icentia, Quebec, Canada) is applied in the clinic or before hospital discharge if there is no evidence of AF in the initial ECG and during in-hospital cardiac monitoring. The CardioSTAT device has been previously validated for arrhythmia detection in adult patients.[10] ECG recordings are analyzed at a central lab in Quebec, and AF reporting is done blinded to most patients' characteristics. Patients with AF detected by in-hospital telemetry were excluded from this study to allow for direct comparison between ECG- and PCM-detected AF. The latter was defined as any AF lasting ≥30 seconds on 14-day cardiac monitoring.[11] To minimize the risk of immortal time bias, we excluded patients who died in the first 14 days after the ischemic event because the premature death precluded them from receiving PCM. Patients with ECG-detected AF after a PCM-based AF diagnosis were included in the PCM-detected AF group.

Ascertainment of Use of Oral Anticoagulants

Medical records at London Health Sciences Center have a prespecified template for patients with stroke in which there is a medication documentation section, and the use of antithrombotic agents is updated at every stroke consult. We also used a specific section of the electronic medical record in which filled prescriptions are recorded.

Outcomes

The primary outcome was the development of a recurrent ischemic stroke until end of the available follow-up (eg, last visit documented in the electronic medical record by any specialty). Recurrent ischemic stroke was defined as new symptomatic neurological deterioration not attributable to a nonischemic cause with imaging evidence of a new brain infarction.[12] The secondary outcome was the first occurrence of a MACE, defined as acute coronary syndrome, heart failure exacerbation requiring admission, recurrent ischemic stroke, or cardiovascular death. Tertiary outcomes included the individual components of MACE, major bleeding, intracranial bleeding, and all-cause death. Major bleeding was defined according to the International Society on Thrombosis and Hemostasis.[13] Outcomes were blindly adjudicated by a stroke neurologist and a stroke nurse by retrospectively reviewing all hospital encounters in all patients' electronic medical records until the last documented visit. The last revision of electronic medical records was performed in November 2022. London Health Sciences Center University Hospital is a regional stroke center serving a catchment area of 2 million people. As such, stroke recurrences are unlikely to be missed by applying this outcome-ascertaining strategy. Similarly, the same hospital is a primary percutaneous coronary intervention and cardiology referral center, meaning that most MACE events are likely to be captured in the electronic medical records.

AF Burden

PCM-detected AF burden was analyzed as a continuous variable and additionally categorized in strata as done previously: (1) 30 seconds to <6 minutes, (2) 6 minutes to <5.5 hours, (3) 5.5 hours to <24 hours, and (4) ≥24 hours.[14,15] Additionally, 2 measures of AF burden were used: (1) total time spent in AF, and (2) total time spent in AF divided by the net duration of cardiac monitoring.[16] Net monitoring time was calculated by subtracting noninterpretable recording time due to signal noise from the total time of monitoring.

Statistical Analysis

All variables were expressed in medians, interquartile range (IQR), total numbers, and percentages. We compared baseline characteristics between groups by estimating standardized mean differences. We estimated the crude number of events, and we developed cumulative incidence function curves or the primary and secondary outcomes until end of follow-up. We also applied marginal cause–specific Cox proportional hazards models to estimate adjusted hazard ratios (aHR) accounting for competing risk of death.[17] Models were adjusted for variables known to biologically influence outcomes and those with a standardized mean differences >0.20.[18] We generated Schoenfeld residual plots, Pearson correlation of ranked times, and residuals to assess if the ratio of the hazards remained constant over time. Missing values of variables with <20% missing data were resolved by using multiple imputation. A Fully conditional specification method for arbitrary pattern was used (Figures S1 through S6; Table S1).[19]

Study Registration and Ethics Approval

This study is registered in clinicaltrials.gov (https://www.clinicaltrials.gov; Unique identifier: NCT05822791) and has been approved by Western University Ethics Review Board (2023-122969-78477).

RESULTS

Of 429 patients with ischemic stroke and TIA with AF, 45 were excluded due to AF lasting ≤30 seconds and 18 because of a documented death within 14 days poststroke (Figure S7). The final cohort included 366 patients, 218 with ECG-detected AF and 148 with PCM-detected AF. The comparison of patients with and without missing data is shown in Table S1. The mechanisms of the qualifying events for ECG-detected AF were 94.5% cardioembolism and 5.5% undetermined, with >1 cause (1.8% small vessel disease and 3.7% large artery atherosclerosis). The large proportion of cardioembolism in this group is explained by the diagnosis of AF being made soon after stroke onset and before discharge from hospital. Among patients with PCM-detected AF, the suspected causes at the time of initiating PCM were 96.6% cryptogenic, 0.7% small vessel disease, and 2.7% large artery atherosclerosis.

Baseline characteristics were balanced for most variables except for age, type of qualifying event (ischemic stroke or TIA), CHA_2DS_2-VASc score, anticoagulation status at the time of the event, left ventricular ejection fraction, left atrial size, and high-sensitivity troponin T (Table 1). These variables were used for adjusting the regression analyses. Age was not included to avoid

Table 1. Baseline Characteristics

	All patients (N=366)	ECG-detected AF (N=218)	PCM-detected AF (N=148)	SMD
Age, y, median [IQR]	79.2 [71.5–85.5]	80.3 [72.4–86.2]	77.9 [71.0–84.0]	0.16 (–0.05 to 0.37)
Male, n (%)	173 (47.2)	126 (53.4)	69 (46.6)	0.02 (–0.19 to 0.23)
Qualifying event, n (%)				
TIA	75 (20.5)	29 (12.3)	46 (31.1)	0.45 (0.23 to 0.66)
Ischemic stroke	291 (79.5)	207 (87.7)	102 (68.9)	
Follow-up, mo, median [IQR]	17.0 [5.0–34.0]	15.0 [3.0–34.0]	18.0 [6.0–33.0]	0.01 (–0.19 to 0.22)
CHA_2DS_2-VASc, median [IQR]	4.0 [3.0–5.0]	5.0 [4.0–5.0]	4.0 (3.0–5.0)	0.14 (–0.06 to 0.35)
Hypertension, n (%)	264 (72.1)	168 (71.2)	107 (72.2)	0.01 (–0.20 to 0.21)
Dyslipidemia, n (%)	180 (49.2)	111 (47.0)	78 (52.7)	0.12 (–0.09 to 0.33)
Diabetes, n (%)	74 (20.2)	46 (19.5)	33 (22.2)	0.09 (–0.12 to 0.30)
Congestive heart failure, n (%)	21 (5.7)	15 (6.4)	8 (5.4)	0.02 (–0.18 to 0.23)
Coronary arterial disease, n (%)	55 (15.0)	43 (18.2)	18 (12.1)	0.14 (–0.07 to 0.35)
Chronic kidney disease, n (%)	23 (6.3)	19 (8.1)	8 (5.4)	0.06 (–0.15 to 0.27)
Smoking, n (%)	47 (12.8)	29 (12.3)	18 (12.1)	0.03 (–0.17 to 0.24)
Prior stroke, n (%)	42 (11.5)	20 (8.5)	21 (14.1)	0.14 (–0.07 to 0.35)
Anticoagulation,* n (%)	304 (83.1)	179 (82.1)	125 (84.5)	0.21 (0.01 to 0.42)
LVEF, %, median [IQR]	62.5 [57.5 to 67.5]	60.0 [52.5 to 67.5]	62.5 [57.5 to 67.5]	0.20 (0.15 to 0.24)
LAVI, ml/m^2, median [IQR]	36.2 [28.0 to 44.0]	38.3 [28.3 to 45.4]	35.0 [27.2 to 40.6]	0.23 (0.18 to 0.27)
HS-TnT, ng/L, median [IQR]	20.0 [12.0 to 40.0]	21.0 [14.0 to 40.0]	15.1 [10.0 to 27.0]	0.34 (0.09 to 0.58)

AF indicates atrial fibrillation; HS-TnT, high-sensitivity troponin T; IQR, interquartile range; LAVI, left atrial volume index; LVEF, left ventricle ejection fraction; PCM, prolonged cardiac monitoring; SMD, standardized mean difference; and TIA, transient ischemic attack.
*Anticoagulation at the end of follow-up.

collinearity as it is already included in the CHA_2DS_2-VASc score. Reasons for no anticoagulation are shown in the Table S2.

The median net monitoring time for patients with PCM-detected AF was 12 (8.8–14.0) days. The median AF duration was 5.2 (0.3–33.0) hours and the median AF burden was 2.23% (IQR, 0.13–12.25). Only 7 patients had PCM-detected AF lasting >7 days, fulfilling the definition of persistent AF. None of the patients with PCM-detected AF required cardioversion. The median time between the qualifying ischemic stroke or TIA and the diagnosis of ECG-detected and PCM-detected AF were 2 (IQR, 0–18) days and 36.6 (IQR, 24.5–94.5) days, respectively. There were no stroke recurrences in patients with device-detected AF before the monitor was applied. The proportion of PCM-detected AF in each burden strata was 19.0% for 30 seconds to 6 minutes, 32.8% for 6 minutes to 5.5 hours, 19.0% for 5.5 to 24 hours, and 29.2% for >24 hours. Figure 1 shows the measures of AF burden for PCM-detected AF. There were only 5 patients with AF found on an ECG performed after the PCM-based AF diagnosis. The median AF duration among these 5 patients was 135.0 (41.34–273.64) hours, accounting for a median AF burden of 45.0% (8.7–68.39).

The Schoenfeld residuals and Pearson correlation indicated that none of the variables used to adjust the regression model for the primary analysis violated the proportional hazards assumption. The same was true for the global test of the model, suggesting that the risk of recurrent ischemic stroke remained unchanged during the duration of follow-up (Figure S8; Table S3).

After a median follow-up of 17 (IQR, 5–34) months, 18 ischemic stroke events were documented, with an overall crude incidence of recurrent ischemic stroke of 2.7 per 100 person-years (Figure 2). On the multivariable time-to-event analyses, patients with ECG-detected AF had a 5-fold higher adjusted risk of recurrent ischemic stroke than those with PCM-detected AF (aHR, 5.06 [95% CI, 1.13–22.7]; P=0.034; Table 2). The crude incidence of all outcomes is shown in Table S4. A recurrent ischemic stroke occurred in 16 patients with ECG-detected AF (13 receiving anticoagulants) and 2 patients with PCM-detected AF. Among both patients with PCM-detected AF who experienced a recurrent event, AF durations were 204 and 0.6 hours, with a burden of 61.3% and 0.1%, respectively. Both were anticoagulated at the time of recurrence, and only one was noted to be in AF at the time of the recurrence. Stroke recurrence rates in patients with ECG-detected and PCM-detected AF were 4.05 and 0.72 per 100 patient-years, respectively. The mechanisms of recurrent ischemic strokes were cardioembolism (61,1%), small vessel disease (11.1%), large artery atherosclerosis (1.1%), and >1 cause (22.2%).

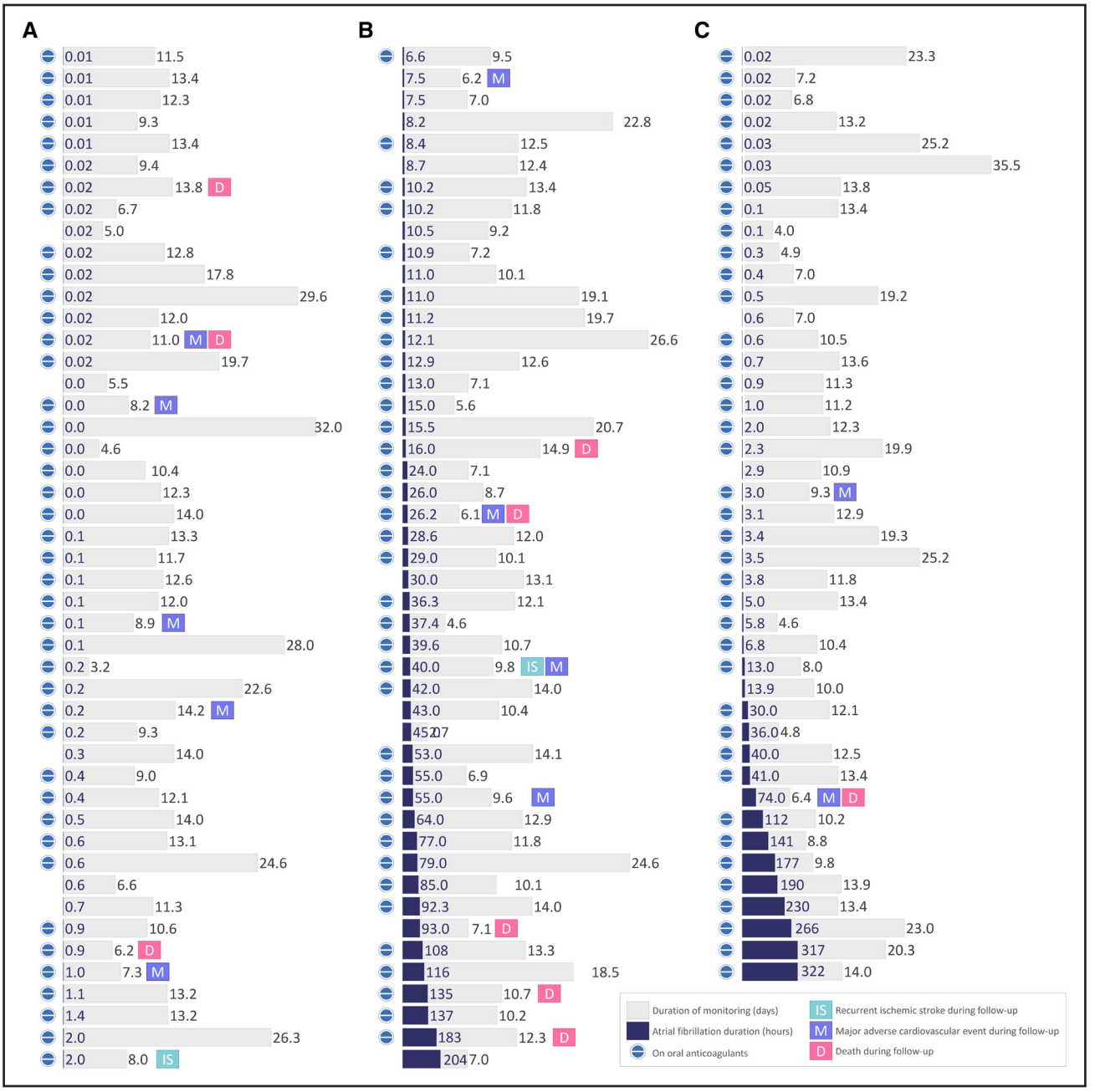

Figure 1. Burden of atrial fibrillation (AF) detected on 14-day Holter.
A and **B**, Patients with ischemic stroke. **C**, Patients with transient ischemic attack. The gray horizontal bar denotes the net duration of cardiac monitoring in days. The blue horizontal line represents the total AF duration in hours. Recurrent ischemic stroke, major adverse cardiovascular events, and all-cause death are shown in green, purple, and pink rectangles labeled IS, M, and D, respectively. Blue circles with a horizontal line represent patients who were on anticoagulants. Data on atrial fibrillation burden was available for 137 of 148 participants with PCM-detected AF (14-day Holter monitoring). AF burden and Holter monitoring are shown with their own and different time scales. The events occurred during follow-up are shown at the end of cardiac monitoring but do not represent a specific time to event.

A total of 49 MACE events occurred during follow-up, for a MACE incidence rate of 7.8 per 100 person-years. The crude incidence of MACE was 9.22 per 100 person-years for ECG-detected AF and 5.71 per 100 person-years for PCM-detected AF (Figure 3A). The risk of MACE did not differ significantly between AF diagnostic modalities (aHR, 1.43 [95% CI, 0.75–2.70]; P=0.27; Table 2). The marginal cause–specific Cox proportional hazards models for individual components of the composite MACE outcome are shown in Table S5. The marginal cause–specific Cox proportional hazards models for major bleeding, intracranial bleeding, and all-cause death are shown in Table S6.

All-cause mortality rate was 7.39 deaths per 100 person-years. The crude incidence of all-cause death was 9.85 per 100 person-years for ECG-detected AF and

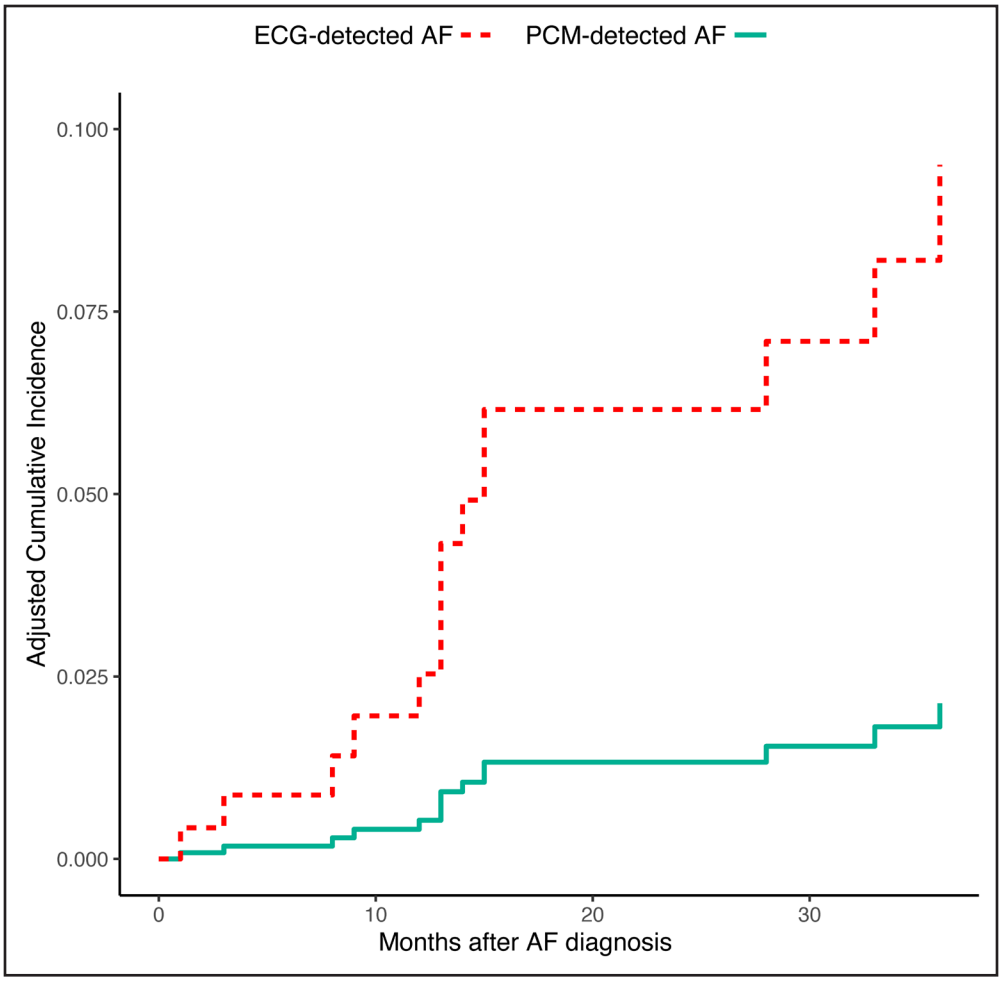

Figure 2. Cumulative incidence function curve for recurrent ischemic stroke.
There were 2 ischemic strokes in the atrial fibrillation (AF) detected on 14-day Holter (PCM-detected AF) group. The other censoring events in the PCM group were congestive heart failure (n=10) and acute coronary syndrome (n=3). ECG-detected-AF indicates atrial fibrillation detected on 12-ECG.

3.83 per 100 person-years for PCM-detected AF (aHR, 2.50 [95% CI, 1.20–5.19]; P=0.015; Figure 3B). None of the remaining tertiary outcomes showed significant differences between AF types (Table 2).

DISCUSSION

In this retrospective cohort study of prospectively collected data including 366 patients with ischemic stroke and TIA newly diagnosed with AF, we found a 5-fold increase in the risk of recurrent ischemic stroke in patients with ischemic stroke and TIA with ECG-detected AF relative to PCM-detected AF, after adjusting for group imbalances and known modifiers of thromboembolic risk, including anticoagulation. Our findings support the hypothesis that significant heterogeneity exists in the clinical profile and thromboembolic risk of ECG-detected and PCM-detected-AF.[4,20]

Despite an overall anticoagulation rate of 83.1% in this study, the crude incidence of recurrent ischemic stroke of 2.7 per 100 patient-years is higher than that reported in pivotal clinical trials of direct oral anticoagulants, in which it ranged between 1.8 and 2.3 per 100 patient-years.[21,22] Patients with ECG-detected AF had an exceedingly elevated stroke recurrence rate, which is not explained by differences in anticoagulation rates between groups since similar proportions of participants received anticoagulants in each group and the time-to-event analysis was adjusted for this variable. Furthermore, only 3 of 16 stroke recurrences were documented in patients with ECG-detected AF who were not receiving anticoagulants at the time of the event. The difference between groups in the primary outcome can be also explained by the low ischemic stroke recurrence rate in the PCM-detected AF group in this cohort, which was one-third of that documented in clinical trials.[21,22] Other variables known to affect stroke risk and showing imbalances between groups (eg, proportion of qualifying ischemic stroke versus TIA) are unlikely to have influenced the results as they were also included in the regression analyses.

Table 2. Marginal Cause–Specific Cox Proportional Hazards Models for Main Study Outcomes

	aHR	95% CI	*P* value
Recurrent ischemic stroke			
ECG-based AF diagnosis	5.06	1.13–22.7	0.034
Qualifying event (TIA)	0.71	0.19–2.61	0.60
Anticoagulation*	0.96	0.27–3.36	0.95
CHA_2DS_2-VASc score	1.18	0.79–1.76	0.43
LVEF†	1.17	0.86–1.60	0.32
LAVI‡	1.05	0.87–1.29	0.60
HS-TnT§	0.99	0.93–1.06	0.81
MACE			
ECG-based AF diagnosis	1.43	0.75–2.70	0.27
Qualifying event (TIA)	1.27	0.65–2.50	0.49
Anticoagulation*	0.87	0.40–1.88	0.72
CHA_2DS_2-VASc score	1.33	1.02–1.73	0.035
LVEF†	1.02	0.87–1.19	0.85
LAVI‡	1.12	1.00–1.26	0.055
HS-TnT§	0.99	0.95–1.03	0.63
All-cause death			
ECG-based AF diagnosis	2.50	1.20–5.19	0.015
Qualifying event (TIA)	0.63	0.27–1.46	0.27
Anticoagulation*	0.24	0.13–0.44	<0.001
CHA_2DS_2-VASc score	1.44	1.11–1.88	0.008
LVEF†	0.96	0.84–1.10	0.54
LAVI‡	0.97	0.87–1.09	0.58
HS-TnT§	1.01	1.00–1.02	0.17

AF indicates atrial fibrillation; aHR, adjusted hazard ratio; HS-TnT, high-sensitivity troponin T; LAVI, left atrial volume index; LVEF, left ventricle ejection fraction; MACE, major adverse cardiovascular event; and TIA, transient ischemic attack.

*Anticoagulation at time of the event or the end of follow-up.

†Per 5% increase.

‡Per 5% increase.

§Per 5 ng/L increase.

The risk of MACE did not differ between groups. We did not find prior studies comparing this outcome in patients with ischemic stroke or TIA with ECG-detected versus PCM-detected AF. Based on the CIs for the HR for this outcome, the lack of difference in MACE is unlikely to be explained by a lack of power, although it cannot be ruled out.

The risk of death from any cause was 2.5-fold higher in patients with ECG-detected than PCM-detected AF. This result should be considered with caution given that all-cause death was a tertiary outcome. We hypothesize that the higher all-cause death observed among patients with ECG-detected AF is possibly associated with a higher prevalence of baseline comorbidities in this group. Since we were not able to reliably capture all comorbidities influencing the risk of death (eg, cancer), this hypothesis requires further investigation. Still, our findings are in line with those of a recent meta-analysis showing no differences in all-cause death between AFDAS and known AF.[4] In the 6 studies included in this meta-analysis, AFDAS diagnoses were primarily ECG-based. The interpretation of other tertiary outcomes in this study is limited due to the low number of events.

Patients with ECG-detected AF were older, had a higher CHA_2DS_2-VASc score, worse left ventricular ejection fraction, and a larger left atrium. These differences in risk profiles, cardiovascular comorbidities, and structural cardiac abnormalities further support that the population with PCM-detected AF is probably overall healthier than that with ECG-detected AF. The differences in baseline characteristics between ECG- and PCM-detected AF in this study are similar to those found between AFDAS and known AF,[3,4] reinforcing that ECG-detected AF resembles more the characteristics of known AF rather than AFDAS, as previously proposed.[7] ECG-detected AF in patients with stroke is probably a preexisting AF that was not diagnosed before the stroke because of patients being asymptomatic or due to insufficient interaction with the health care system (eg, patients not seeking medical attention in the presence of mild AF-related symptoms).

Approximately 30% of PCM-detected AFs lasted >24 hours, suggesting that AFDAS has a high risk of recurrent stroke in at least on third of the cases.[14] Among the remaining 70% of PCM-detected AF, the most frequent duration was 6 minutes to 5.5 hours (32.8%). Due to the low number of recurrent stroke events in the PCM-detected AF group, we were unable to test any relationship between AF burden strata and this outcome. The median AF burden in this study (2.23%, IQR, 0.13–12.25) was lower than in a study of 7-day external monitoring in patients with stroke (4.9%, IQR, 0.9%–10.6%)[23] and higher than in the LOOP study (Atrial Fibrillation Detected by Continuous ECG Monitoring Using Implantable Loop Recorder to Prevent Stroke in High-Risk Individuals) conducted in the general population (0.13%; IQR, 0.03%–1.05%).[24] However, the % in AF burden measures of these 3 studies are only provided as a reference and should not be compared due to their different duration of monitoring and patients' characteristics. Shorter duration of monitoring studies tend to underestimate detection rates and inflate the % in AF measure of burden.[25]

This study has limitations. First, patients who died in the first 14 days of stroke onset were excluded from the study because their premature death may have precluded PCM with 14-day external monitors and anticoagulation therapy, which is a major modifier of thromboembolic risk[2] Second, we only included patients with 14-day external continuous monitoring. Since implantable cardiac monitors have a higher detection yield than shorter-term external monitors,[26] our study possibly missed a significant proportion of AFDAS that may have otherwise been detected with implantable devices. Regardless, our study provides valuable insights into external monitoring poststroke, a widely used technology in clinical practice.[27] Third, although we have established a thorough ascertainment of primary and secondary outcome events, the lack of a systematic prospective

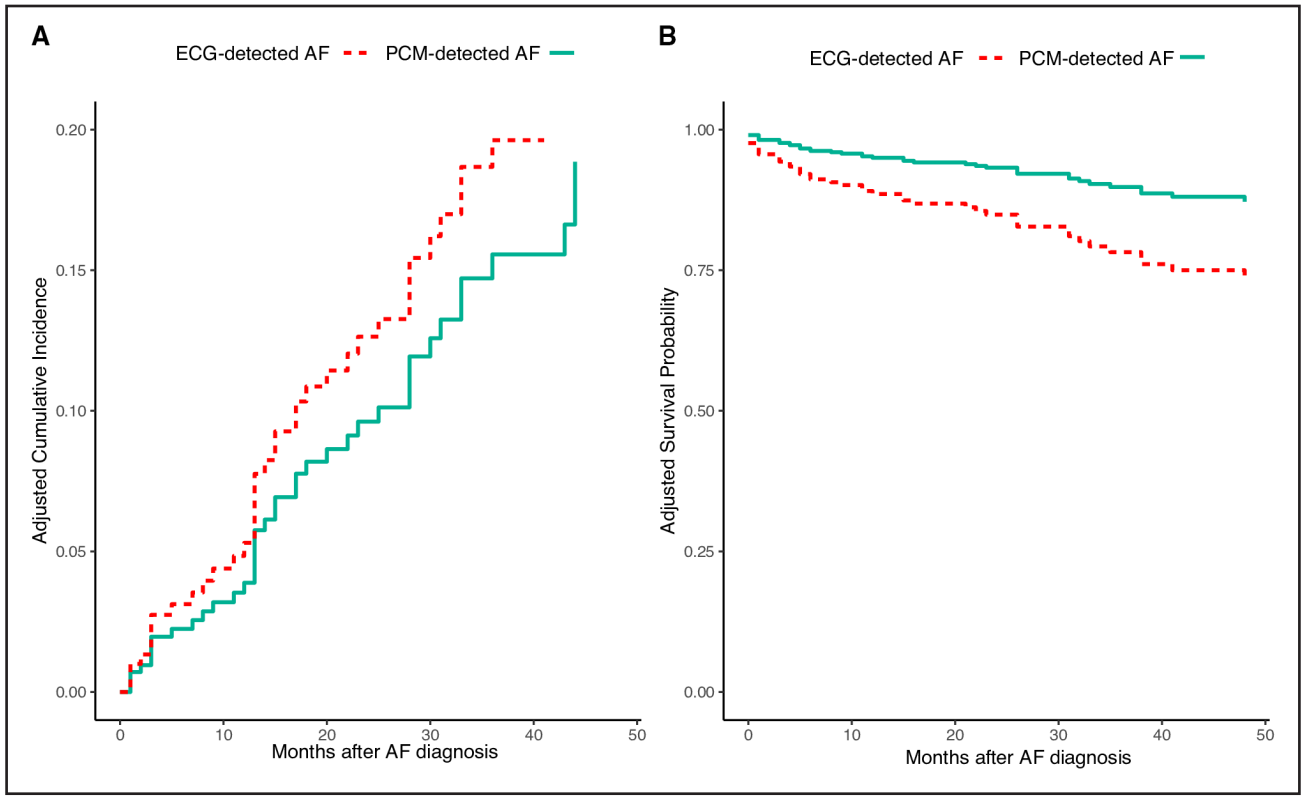

Figure 3. Major adverse cardiovascular events and all-cause death.
A, Cumulative incidence function curve for major adverse cardiovascular events. **B**, Kaplan-Meier curve for all-cause death. AF indicates atrial fibrillation; ECG-detected-AF, AF detected on 12-ECG; PCM, prolonged cardiac monitoring; and PCM-detected AF, AF detected on 14-day Holter.

follow-up may have resulted in missed outcomes. However, this limitation may have affected both study groups equally, with minimal impact on the main results. Fourth, the number of stroke recurrences in this study was low and it could be argued that multivariable analyses can be challenging according to the 10/1 rule of thumb (10 outcomes per 1 variable included in the model). Although it has been suggested that only some extra caution is warranted for plausible and highly significant associations hypothesized a priori, as those of our study,[28] a preplanned sample size calculation may have been performed before conducting the analysis.[29] Fifth, we were unable to report the exact time between AF diagnosis and anticoagulation. However, in our site, stroke neurologists are alerted as soon as a diagnosis of AF is made on PCM and patients are usually started on anticoagulants within the following 72 hours.

In conclusion, our study provides 3 novel insights on AF newly diagnosed in patients with ischemic stroke and TIA. First, PCM-detected AFDAS is associated with a lower risk of stroke and all-cause death than ECG-detected AF. It is important to note that these results should be considered in the context of over 80% of the patients being on anticoagulants at the time of the event. Second, patients with PCM-detected AFDAS have a lower CHA_2DS_2-VASc score, a better left ventricular ejection fraction, and a smaller left atrial size than ECG-detected AF, further supporting that ECG-detected AF should not be considered AFDAS and should be grouped under the category of known AF,[4] since it is likely a high-burden and subclinical preexisting arrhythmia. Third, we herein provided a detailed description of AFDAS burden in patients having 14 days of cardiac monitoring and the 14-day AFDAS burden-associated risk of stroke recurrence in a relatively large cohort of patients receiving anticoagulants. These data can be used as a reference for future studies. These measures of AF burden should be compared only with those of studies with similar durations of monitoring and patients' characteristics. A deeper understanding of the clinical AFDAS phenotypes and their associated thromboembolic risk in patients with different durations of PCM is warranted.

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Supplemental Material

Figures S1–S8
Tables S1–S6

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