Implantable Cardiac Monitoring in the Secondary Prevention of Cryptogenic Stroke

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Objective: In this study, we sought to evaluate the impact of implantable cardiac monitoring (ICM) in the prevention of stroke recurrence after a cryptogenic ischemic stroke or transient ischemic attack (TIA).
Methods: We evaluated consecutive patients with cryptogenic ischemic stroke or TIA admitted in a comprehensive stroke center during an 8-year period. We compared the baseline characteristics and outcomes between patients receiving conventional cardiac monitoring with repeated 24-hour Holter-monitoring during the first 5 years in the outpatient setting and those receiving continuous cardiac monitoring with ICM during the last 3 years. Associations on the outcomes of interest were further assessed in multivariable regression models adjusting for potential confounders.
Results: We identified a total of 373 patients receiving conventional cardiac monitoring and 123 patients receiving ICM. Paroxysmal atrial fibrillation (PAF) detection was higher in the ICM cohort compared to the conventional cardiac monitoring cohort (21.1% vs 7.5%, $p < 0.001$). ICM was independently associated with an increased likelihood of PAF detection during follow-up (hazard ratio [HR] = 1.94, 95% confidence interval [CI] = 1.16–3.24) in multivariable analyses. Patients receiving ICM were also found to have significantly higher rates of anticoagulation initiation (18.7% vs 6.4%, $p < 0.001$) and lower risk of stroke recurrence (4.1% vs 11.8%, $p = 0.013$). ICM was independently associated with a lower risk of stroke recurrence during follow-up (HR = 0.32, 95% CI = 0.11–0.90) in multivariable analyses.
Interpretation: ICM appears to be independently associated with a higher likelihood of PAF detection and anticoagulation initiation after a cryptogenic ischemic stroke or TIA. ICM was also independently related to lower risk of stroke recurrence in our cryptogenic stroke / TIA cohort.

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Although paroxysmal atrial fibrillation (PAF) appears to be implicated in at least 30% of patients with cryptogenic stroke or transient ischemic attack (TIA),[1] current guidelines from the American Heart Association / American Stroke Association on secondary stroke prevention do not provide firm directions on the optimal screening algorithm for the detection of PAF after an acute ischemic stroke or TIA, whereas this indicates that the clinical benefit of prolonged cardiac monitoring to uncover underlying PAF after an acute ischemic stroke or

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TIA remains uncertain.[2,3] These recommendations highlight that individual randomized controlled clinical trials (RCTs) published to date have not been adequately powered to evaluate the impact of prolonged cardiac rhythm monitoring on stroke recurrence.[4,5]

On the other hand, it has been argued that prolonged cardiac rhythm monitoring with implantable cardiac devices can uncover a substantial proportion of patients with ischemic stroke with PAF, otherwise not detected by conventional short-term or intermittent noninvasive monitoring.[4,5] Furthermore, other international recommendations advocate the use of implantable cardiac monitors in the diagnostic work-up of cryptogenic stroke following initial negative Holter monitoring at baseline.[6,7]

In view of these considerations, we sought to evaluate the impact of implantable cardiac monitoring (ICM) in the prevention of stroke recurrence after a cryptogenic stroke or TIA in a prospective cohort study.

Methods

Population

We prospectively evaluated consecutive patients with cryptogenic ischemic stroke or TIA admitted in the Department of Neurology of the coordinating institution ("Attikon" University Hospital, Athens, Greece) over an 8-year period (2013–2020). Cryptogenic stroke was defined using the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria,[8] and after excluding patients with incomplete evaluation, as previously described.[9–13] All patients underwent investigations with transthoracic and transesophageal echocardiogram where indicated.[9–13] The presence of left atrial enlargement was diagnosed according to the guidelines of the American Society of Echocardiography.[14] All patients received neuroimaging with brain computed tomography (CT) and / or magnetic resonance imaging (MRI) and vascular imaging with the modality left at the discretion of the treating physician (cervical duplex ultrasound, transcranial Doppler, CT angiography and / or magnetic resonance [MR] angiography). All demographics and vascular risk factors were prospectively recorded for all patients using standard definitions, as previously described.[9–13] Stroke severity on admission was assessed with the use of the National Institute of Health Stroke Scale (NIHSS) score by certified neurologists.[9–13]

Strategies of Heart Rhythm Monitoring

All patients recruited during the 8-year period underwent 24-hour Holter echocardiogram (ECG; H12+ digital Holter recorder; Mortara Instrument) during hospitalization as standard of care. In the years 2013 to 2017 patients with a negative 24-hour Holter-ECG investigation during their hospitalization were followed in our outpatient clinic with repeat 24-hour Holter-ECGs at the discretion of treating stroke physicians.[9,10] All ECG recordings from 24-hour Holter monitoring were analyzed by 2 experienced cardiologists in our institution who were blinded to demographics and outcomes of the patients, using dedicated analysis software. Total time in atrial fibrillation (AF) was calculated as the sum of each individual AF episode for patients with multiple episodes during monitoring.[9,10] PAF diagnosis thresholds of 30 seconds and 2 minutes were used for 12-lead ECG and 24-hour Holter-ECGs, respectively, as previously described.[9]

In the year 2017, we implemented the use of an ICM device (Reveal LINQ; Medtronic) for the prolonged outpatient cardiac monitoring of patients with cryptogenic strokes or TIAs and at least one negative 24-hour Holter-ECG during hospitalization. All devices were implanted subcutaneously under local anesthesia in the left chest region by experienced cardiologists in our institution and three other cardiac electrophysiology clinics in tertiary care hospitals in the Athens Metropolitan area (Hippokrateion Hospital, "Georgios Gennimatas" General Hospital of Athens, NIMITS General Hospital of Athens). ICMs were programmed with a validated algorithm for detection of AF episodes lasting at least 2 minutes.[15] Total time in AF was calculated as the sum of each individual AF episode for patients with multiple episodes during monitoring. Experienced cardiologists who were blinded to the clinical outcomes of our patients reviewed all ICM recordings in the 4 participating cardiac electrophysiology clinics. Patients with cryptogenic stroke or TIA who refused to be implanted between 2017 and 2020 were followed in the stroke outpatient clinic of the coordinating institution with repeat 24-hour Holter-ECGs at the discretion of the treating stroke physicians.

Outcomes

All patients were followed for up to 3 years following hospital discharge at the stroke outpatient clinic of our institution by telephone and / or outpatient visits, as dictated by their clinical status and at the discretion of the treating vascular neurologist, as previously described.[9,10] PAF was defined by the presence of a confirmatory ECG, Holter, or ICM recording. If PAF was detected, oral anticoagulation with either a non-vitamin K antagonist oral anticoagulant (NOAC) or a vitamin K antagonist (VKA) was initiated. Stroke recurrence was defined as a new neurological event recorded at least 24 hours after hospital discharge and validated by neuroimaging, as previously described.[13] All outcome events were documented by investigators who were blinded to the heart rhythm monitoring methods that were implemented for each individual.

The primary outcome of interest was the rate of stroke recurrence during the 3-year follow-up between patients receiving conventional cardiac monitoring and patients receiving ICM. Secondary outcomes of interest included: (1) the incidence rates of PAF detection during follow-up, (2) the total duration of PAF, calculated as the sum of each individual AF episode for patients with multiple episodes, (3) the percentage of patients with episodes of a total duration of 6 minutes or less,[16] and (4) the percentage of patients with anticoagulation initiation following PAF detection.

Statistical Analysis

We compared all available clinical characteristics and outcomes of interest between patients receiving ICM or conventional cardiac monitoring (non-ICM) investigation. All binary variables were presented as percentages, whereas continuous variables were expressed with their means and corresponding standard deviations or median values and corresponding interquartile ranges (IQRs), according to the normality of the distribution for each continuous variable. Statistical comparisons between patients receiving ICM and conventional cardiac monitoring were performed with the Pearson's χ^2 test, unpaired *t*-test and Mann–Whitney test, as appropriate.

The likelihood of PAF detection and the risk of stroke recurrence between ICM and conventional cardiac monitoring groups during follow-up were assessed in univariable and multivariable Cox regression proportional hazard models, providing the corresponding unadjusted and adjusted hazard ratios (HRs). As candidate variables for inclusion in the multivariable regression models, we used all baseline characteristics, including cardiac monitoring strategy (ICM vs conventional cardiac monitoring), which were found to yield a p value lower than 0.1 in the initial univariable regression analyses. The resulting multivariable models were finally tested under a 2-sided statistical significance hypothesis with a significance level of 0.05.

Patients receiving ICM were matched 1:1 to patients receiving conventional cardiac rhythm monitoring using a structured, iterative propensity score model with the primary objective to maximize the balance in the distribution of possible confounders between the 2 groups. In the propensity score matching algorithm, all baseline characteristics were included. The corresponding propensity score of the variable ICM was then calculated for each subject and a nearest neighbor matching algorithm was then used to match patients within 0.2*SD of the logit of the propensity score according to the cardiac rhythm monitoring strategy they received. To determine whether the propensity score approach achieved balance in all potential confounders, we compared the baseline characteristics between the 2 propensity score matched groups. We assessed for differences in baseline characteristic and outcomes of interest between the propensity score matched groups using the χ^2 test or the unpaired *t*-test (or Mann–Whitney U test), where appropriate. All statistical analyses were conducted with the Stata Statistical Software Release 13 (StataCorp LP, College Station, TX).

Ethics Approval

The study followed all national and international principles of good clinical and research practice and was approved by the ethics committee of the coordination institution ("Attikon" University Hospital, National and Kapodistrian University of Athens, Athens, Greece). Informed consent for participation in the study was obtained from all patients or guardians of patients.

Results

A total of 373 patients with cryptogenic stroke received conventional cardiac monitoring during the period 2013 to 2017, whereas a total of 123 patients with cryptogenic stroke received investigation with ICM in the consecutive period 2018 to 2020. ICMs were implanted at a median of 30 days (IQR = 16–45 days) after the index stroke onset. Patients receiving ICM presented with less severe neurological deficits ($p < 0.001$) and were more frequently diagnosed to have TIA as an index event ($p < 0.001$) compared to patients receiving conventional cardiac monitoring. However, patients receiving ICM had higher prevalence rates of dyslipidemia ($p = 0.003$), a history of cerebral ischemia ($p < 0.001$), and higher baseline CHA_2DS_2VASC scores (3 [2–4] vs 3 [1–4] $p < 0.001$] compared to those receiving conventional cardiac monitoring. In the echocardiographic evaluation, left atrial enlargement (18% vs 42%, $p < 0.001$) and valvular disease (3% vs 9%, $p = 0.034$) were less prevalent for patients receiving ICM compared to patients receiving conventional cardiac monitoring (Table 1). The mean follow-up duration was 22 ± 8 months. Patients in the ICM group had significantly shorter follow-up (median = 15 months) compared to patients receiving only conventional cardiac monitoring (median = 24 months).

The rate of PAF detection was remarkably higher in the ICM cohort compared to the conventional cardiac monitoring cohort (21.1% vs 7.5%, $p < 0.001$; Fig 1). Patients with detected PAF in the 2 cohorts had comparable total episode durations (10 minutes [IQR = 6–778] vs 22 minutes [IQR = 8–154], $p = 0.986$) and similar rates of episodes with a total duration of 6 minutes or less (34.6% vs 21.4%, $p = 0.280$). The median time from ICM insertion to PAF detection was 118 days (IQR = 21–512 days; Table 2). Figure 2 presents the cumulative probability of PAF detection with elapsed time from ICM implantation. In

TABLE 1. Baseline Characteristics of the Study Population

	ICM (n = 123)	CCM (n = 373)	*p*
Age, mean ± SD, yr	61 ± 12	59 ± 11	0.311
Male sex, (n)	87 (71%)	251 (67%)	0.478
NIHSS admission (median, IQR), points	3 (1–5)	4 (3–9)	<0.001
Ischemic stroke as index event (n)	108 (89%)	373 (100%)	<0.001
Diabetes (n)	20 (16%)	82 (22%)	0.185
Hypertension (n)	95 (79%)	230 (62%)	<0.001
Dyslipidemia (n)	89 (73%)	215 (58%)	0.003
Congestive heart failure (n)	6 (5%)	17 (5%)	0.883
History of stroke/TIA (n)	50 (41%)	74 (20%)	<0.001
History of coronary artery disease (n)	21 (17%)	58 (16%)	0.689
History of antiplatelet pretreatment (n)	7 (6%)	13 (4%)	0.281
Current smoking (n)	49 (43%)	161 (40%)	0.517
History of alcohol abuse (n)	10 (8%)	37 (10%)	0.557
History of peripheral vascular disease (n)	10 (8%)	15 (4%)	0.071
CHA_2DS_2VASC score (median, IQR), points	3 (2–4)	3 (1–4)	<0.001
Left atrial enlargement (n)	22 (18%)	155 (42%)	<0.001
Dilated cardiomyopathy (n)	4 (3%)	5 (1%)	0.164
Valvular disease (n)	4 (3%)	34 (9%)	0.034
Number of Holter repeats (median, IQR)	1 (1–2)	1 (1–2)	0.989

CCM = conventional cardiac monitoring; ICM = implantable cardiac monitoring; IQR = interquartile range; NIHSS = National Institute of Health Stroke Scale; SD = standard deviation; TIA = transient ischemic attack.

multivariable analyses, only ICM implementation (HR = 1.94, 95% confidence interval [CI] = 1.16–3.24), increasing age (HR = 1.02, 95% CI = 1.01–1.04) and the presence of left atrial enlargement (HR = 1.70, 95% CI =1.02–2.82) were independently associated with higher likelihood of PAF detection during follow-up (Table 3).

A total of 49 recurrent strokes (9.9%) were documented during the follow-up period. The distributions of ischemic and hemorrhagic cerebrovascular events among patients with recurrent stroke were 89.8% (n = 44) and 10.2% (n = 5), respectively. During follow-up, patients receiving ICM were found to have significantly higher cumulative rates of anticoagulation initiation (18.7% vs 6.4%, $p < 0.001$) compared with patients receiving conventional cardiac monitoring. We also documented lower incidence rate (0.2 vs 0.5 per 100 patient-days, $p = 0.018$) and cumulative rate (4.1% vs 11.8%, $p = 0.013$; Fig 3) of stroke recurrence in the ICM group. In multivariable analyses, the use of ICM (HR = 0.32, 95% CI = 0.11–0.90), patients' age (HR = 1.08, 95% CI = 1.04–1.13) and a history of congestive heart failure (HR = 3.70, 95% CI: 1.14–12.00) were the only variables that were independently associated with the risk of stroke recurrence during follow-up (Table 4).

Propensity score matching resulted in 2 groups of 96 patients each, which were balanced ($p > 0.1$) for all potential confounding variables (Table 5). Patients receiving ICM were found to have significantly ($p < 0.05$) higher cumulative rates of PAF detection (22% vs 9%), anticoagulation initiation (19% vs 8%), and lower stroke recurrence (2% vs 9%) during follow-up compared to their propensity score matched counterparts receiving noninvasive cardiac rhythm monitoring (see Table 5).

Discussion

Our cohort study showed ICM is independently associated with a 2-fold higher likelihood of PAF detection and

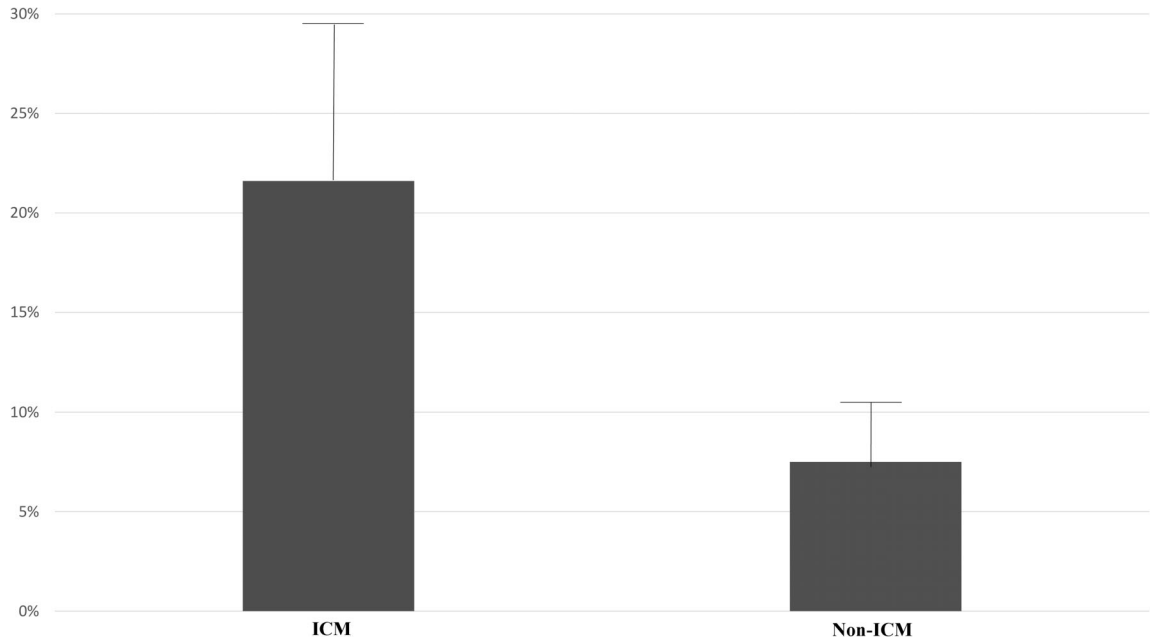

FIGURE 1: Rates of paroxysmal atrial fibrillation between patients receiving implantable cardiac monitoring (ICM) and conventional cardiac monitoring after a cryptogenic stroke or transient ischemic attack.

TABLE 2. Outcomes of the Study Population

	ICM (n = 123)	CCM (n = 373)	*p*
Total follow-up (mo, median, range)	15 (0.5–36)	24 (0.5–36)	<0.001
Cumulative rate of stroke recurrence (n)	5 (4%)	44 (12%)	0.013
PAF detection (n)	26 (21%)	28 (7%)	<0.001
Anticoagulation initiation (n)	23 (19%)	24 (6%)	<0.001
Duration of PAF (minutes, median, IQR)*	10 (6–778)	22 (8–154)	0.986
Duration of PAF ≤ 6 minutes (n)*	43 (35%)	78 (21%)	0.280
Number of AF episodes (median, IQR)*	1 (1–5)	N/A	—
Time from stroke onset to PAF detection (days, median, IQR)*	151 (65–120)	N/A	—
Time from ICM implantation to PAF detection (days, median, IQR)*	118 (21–512)**	N/A	—
Time from stroke onset to ICM implantation (days, median, IQR)	30 (16–45)	N/A	—

*In patients with PAF detection during follow-up, **mean ± standard deviation: 242 ± 293.
AF = atrial fibrillation; CCM = conventional cardiac monitoring; ICM = implantable cardiac monitoring; IQR = interquartile range; N/A = not available; PAF = paroxysmal atrial fibrillation.

a 70% decrease in the risk of stroke recurrence during follow-up of patients with cryptogenic ischemic stroke or TIA. The reduction in the risk of stroke recurrence appears to be mediated through the prompt anticoagulation initiation following PAF detection, which was increased by almost 3-fold in the ICM cohort.

Our results are in accordance with a recent meta-analysis of RCTs and observational studies suggesting that prolonged cardiac monitoring is associated with more than 2-fold higher chance of incident PAF detection and anticoagulation initiation, and a 65% relative risk reduction in stroke recurrence for patients with cryptogenic stroke

TABLE 3. Univariable and Multivariable Cox Proportional Hazard Regression Analyses on the Probability of Paroxysmal Atrial Fibrillation Detection

	Univariable analyses		Multivariable analyses	
	HR (95% CI)	*p*	HR (95% CI)	*p*
Age	1.03 (1.01, 1.05)	0.006	1.02 (1.01, 1.04)	0.040
Male gender	0.81 (0.50, 1.32)	0.406	—	—
NIHSS admission	0.98 (0.93, 1.03)	0.353	—	—
Stroke as index event	1.26 (0.65, 2.43)	0.495	—	—
Diabetes	1.00 (0.57, 1.74)	0.997	—	—
Hypertension	1.83 (1.06, 3.19)	0.031	1.11 (0.59, 2.10)	0.753
Dyslipidemia	1.57 (0.95, 2.61)	0.080	1.16 (0.70, 2.03)	0.589
Congestive heart failure	1.75 (0.75, 4.08)	0.195	—	—
History of stroke/TIA	1.10 (0.68, 1.75)	0.682	—	—
History of coronary artery disease	1.45 (0.83, 2.52)	0.193	—	—
History of antiplatelet pretreatment	1.55 (0.62, 3.87)	0.349	—	—
Current smoking	0.98 (0.67, 1.44)	0.925	—	—
History of alcohol abuse	1.34 (0.66, 2.70)	0.413	—	—
History of peripheral vascular disease	1.43 (0.62, 3.32)	0.404	—	—
Left atrial enlargement	1.49 (0.94, 2.35)	0.089	1.70 (1.02, 2.82)	0.041
Dilated cardiomyopathy	1.49 (0.53, 4.14)	0.446	—	—
Valvular disease	1.02 (0.44, 2.35)	0.968	—	—
CHA_2DS_2VASC score	0.94 (0.81, 1.09)	0.437	—	—
ICM use	1.81 (1.14, 2.89)	0.012	1.94 (1.16, 3.24)	0.012

95% CI = 95% confidence interval; HR = hazard ratio; ICM = implantable cardiac monitoring; NIHSS = National Institutes of Health Stroke Scale; TIA = transient ischemic attack.

or TIA.[17] Our observations parallel the results of another single-center observational study from Spain reporting 70% reduction in risk of recurrent stroke in the ICM compared to the noninvasive cohort.[18]

We also reported a median elapsed time of 4 months between ICM insertion and PAF. This finding further highlights the importance of implantable cardiac monitoring to uncover PAF in cryptogenic stroke, because the duration of prolonged Holter monitoring scarcely exceeds 1 month.[1] In addition, the cumulative probability of PAF detection with elapsed time from ICM implantation presented in Figure 2 resonates to the findings of both Cryptogenic Stroke and Underlying Atrial Fibrillation (CRYSTAL AF) and 30-Day Cardiac Event Monitor Belt for Recording Atrial Fibrillation After a Cerebral Ischemic Event (EMBRACE) trials,[4,5] and highlights further the time-dependent association of cardiac monitoring with the probability of PAF detection. The independent association of ICM duration with the probability of PAF detection was also recently highlighted by a recent systematic review and meta-regression analysis of studies reporting on the incidence of PAF with different cardiac monitoring devices after an acute ischemic stroke or TIA.[19] This meta-analysis reported significant differences in the AF detection rates with respect to ICM duration (< 6 months: 5% [95% CI = 3%–6%]; ≥ 6 and ≤ 12 months: 21% [95% CI = 16%–25%]; > 12 and ≤ 24 months: 26% [95% CI = 22%–31%]; and > 24 months: 34% [95% CI = 29%–39%]).[19]

We found numerically considerable differences in the median durations of PAF detection for patients

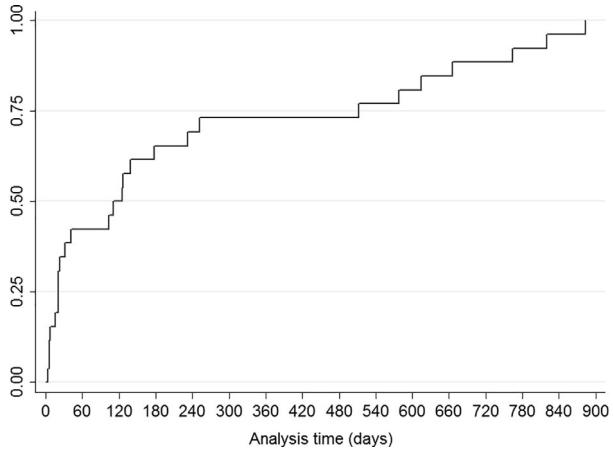

FIGURE 2: Kaplan–Meier curve on paroxysmal atrial fibrillation detection with elapsed time from cardiac monitor implantation.

receiving ICM compared to conventional cardiac monitoring (10 minutes vs 22 minutes) and in the percentages of patients with PAF duration ≤ 6 minutes between the 2 groups (34.6% vs 21.4%). Even though these differences were not found to be statistically significant, due to the limited patient sample size, the increased use of anticoagulants in patients with ICM resulted in significantly lower incidence of stroke recurrence, posing an additional argument against the different clinical relevance of ICM detected versus conventional cardiac monitoring detected PAF. Although there is still no consensus on the minimum PAF duration required to prompt treatment with anticoagulation,[20] we proceeded with anticoagulation initiation for the vast majority of patients with evidence of PAF detected either with implanted or conventional cardiac monitoring independent of the duration of AF episodes. This

TABLE 4. Univariable and Multivariable Cox Proportional Hazard Regression Analyses on the Risk of Stroke Recurrence During Follow-up

	Univariable Analyses		Multivariable Analyses	
	HR (95% CI)	*p*	HR (95% CI)	*p*
Age	1.08 (1.05, 1.11)	<0.001	1.08 (1.04, 1.13)	<0.001
Male gender	0.54 (0.31, 0.96)	0.036	0.84 (0.42, 1.70)	0.632
NIHSS admission	1.06 (1.02, 1.10)	0.007	1.01 (0.96, 1.05)	0.816
Stroke as index event	0.74 (0.13, 4.31)	0.740	—	—
Diabetes	1.05 (0.54, 2.06)	0.881	—	—
Hypertension	2.40 (1.18, 4.87)	0.016	1.99 (0.85, 4.64)	0.111
Dyslipidemia	1.20 (0.66, 2.15)	0.551	—	—
Congestive heart failure	2.58 (1.02, 6.51)	0.045	3.70 (1.14, 12.00)	0.029
History of stroke/TIA	0.73 (0.35, 1.50)	0.392	—	—
History of coronary artery disease	1.67 (0.85, 3.27)	0.136	—	—
History of antiplatelet pretreatment	1.33 (0.41, 4.28)	0.633	—	—
Current smoking	0.80 (0.47, 1.37)	0.421	—	—
History of alcohol abuse	0.55 (0.17, 1.76)	0.314	—	—
History of peripheral vascular disease	1.43 (0.51, 3.99)	0.495	—	—
Left atrial enlargement	2.04 (1.16, 3.58)	0.013	0.82 (0.42, 1.58)	0.554
Dilated cardiomyopathy	3.01 (0.73, 12.48)	0.128	—	—
Valvular disease	1.65 (0.70, 3.89)	0.248	—	—
CHA_2DS_2VASC score	1.23 (1.05, 1.43)	0.009	0.93 (0.71, 1.23)	0.625
ICM use	0.31 (0.12, 0.81)	0.018	0.32 (0.11, 0.90)	0.031

95% CI = 95% confidence interval; HR = hazard ratio; ICM = implantable cardiac monitoring; NIHSS = National Institutes of Health Stroke Scale; TIA = transient ischemic attack.

TABLE 5. Baseline Characteristics and Outcomes of the Propensity Score Matched Groups

	ICM (n = 96)	CCM (n = 96)	*p*
Baseline characteristics			
Age (median, IQR), yr	63 (52–68)	60 (54–65)	0.207
Male sex (n)	69 (72%)	66 (69%)	0.635
NIHSS admission (median, IQR), points	3 (2–6)	3 (2–4)	0.485
Ischemic stroke as index event (n)	96 (100%)	96 (100%)	>0.999
Diabetes (n)	15 (16%)	21 (22%)	0.282
Hypertension (n)	72 (77%)	82 (85%)	0.139
Dyslipidemia (n)	65 (68%)	56 (58%)	0.148
Congestive heart failure (n)	6 (6%)	4 (4%)	0.516
History of stroke/TIA (n)	41 (43%)	38 (40%)	0.660
History of coronary artery disease (n)	18 (19%)	13 (14%)	0.327
History of antiplatelet pretreatment (n)	6 (6%)	3 (3%)	0.306
Current smoking (n)	38 (40%)	39 (41%)	0.883
History of alcohol abuse (n)	8 (8%)	11 (11%)	0.468
History of peripheral vascular disease (n)	9 (9%)	5 (5%)	0.267
CHA_2DS_2VASC score (median, IQR), points	3 (2–5)	3 (2–4)	0.377
Left atrial enlargement (n)	19 (20%)	25 (26%)	0.303
Dilated cardiomyopathy (n)	3 (3%)	2 (2%)	0.650
Valvular disease (n)	4 (4%)	6 (6%)	0.516
Outcomes			
PAF detection (n)	21 (22%)	9 (9%)	0.017
Anticoagulation initiation (n)	18 (19%)	8 (8%)	0.035
Recurrent stroke (n)	2 (2%)	9 (9%)	0.030

CCM = conventional cardiac monitoring; ICM = implantable cardiac monitoring; IQR = interquartile range; NIHSS = National Institute of Health Stroke Scale; PAF = paroxysmal atrial fibrillation; TIA = transient ischemic attack.

decision was based on our previous study that failed to document any association between stroke severity and early outcomes with the duration of PAF in patients with cryptogenic stroke.[9] Furthermore, a recent meta-analysis has provided preliminary evidence underscoring that subclinical device-detected AF may predict clinical AF and increased stroke risk in patients with cardiac implantable electronic devices.[21]

Certain strengths of the present study need to be acknowledged, including the adequate sample of consecutive patients with cryptogenic stroke admitted at a single institution and following the same treatment algorithms and practices for both study periods (before and after the implementation of ICM). We included patients with both cryptogenic stroke and TIA, representing current stroke clinical practice and making our results generalizable to stroke and TIA populations. Even though patients with TIA were included only in the ICM group, and thus we were not able to perform any formal comparisons for patients with TIA in the 2 groups, rates of AF detection (20% vs 27%), oral anticoagulant initiation (18% vs 27%), and recurrent stroke (3% vs 7%) did not differ significantly ($p > 0.1$) between cryptogenic stroke and TIA within the ICM group. Recent international cohort studies indicate that the risk of stroke recurrence is non-negligible for patients after a TIA,[22] whereas the benefit of anticoagulation initiation appears to be comparable to patients with ischemic stroke as an index event.[23] Despite the strengths of our report, certain

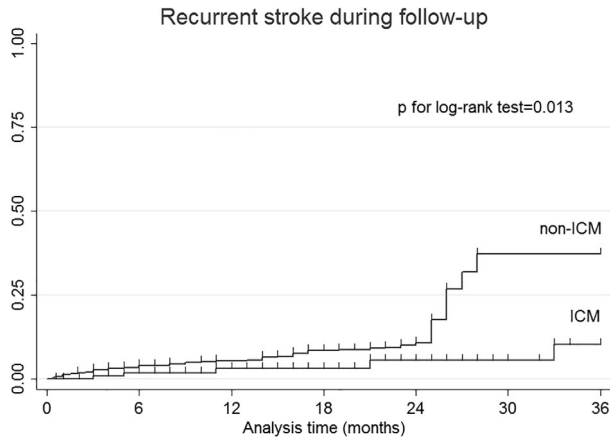

FIGURE 3: Kaplan–Meier curves on the cumulative risk of stroke recurrence during follow-up between patients receiving implantable cardiac monitoring (ICM) and conventional cardiac monitoring after a cryptogenic stroke or transient ischemic attack. Vertical lines designate points of patients exiting the observation period (right censoring).

methodological shortcomings should also be noted. First, patients with cryptogenic stroke were not randomized to receive ICM or noninvasive cardiac monitoring and, therefore, several imbalances in both known and unknown confounders between the 2 groups can be present. Patients receiving ICM had more prevalent vascular comorbidities compared to patients receiving conventional cardiac monitoring. We used both multivariable regression and propensity score matching to account for the substantial number of disparities in baseline characteristics between the 2 groups, with both strategies providing comparable results. Second, patients in the conventional cardiac monitoring cohort had a 2-fold higher prevalence of left atrial enlargement in the echocardiography compared with those in the ICM cohort. Taking into account the association of left atrial enlargement with underlying PAF, as uncovered in our analyses and highlighted in previous studies from our group[10] and other investigators,[24,25] we expect that the true incidence of PAF in the conventional cardiac monitoring cohort would be much higher than that uncovered in the ICM cohort. Third, the prevalence of valvular disease, which also has been independently associated with the probability of PAF detection in patients with cryptogenic stroke,[26,27] was also 3 times higher in patients receiving conventional cardiac monitoring compared to patients receiving ICM. Taking into account the disparities in the aforementioned echocardiographic findings between the 2 cohorts, we consider that the comparative diagnostic yield of conventional cardiac monitoring to ICM for the detection of PAF might be even lower from that presented in our report. Moreover, it should be noted that the association of ICM with lower risk of recurrent stroke was independent of left atrial enlargement, valvular disease, and other potential confounders. Fourth, data on secondary prevention therapies other than anticoagulation initiation, were not collected and, therefore, potential disparities in the 2 groups and residual confounding in the adjusted associations cannot be excluded.

The Detection of Silent Atrial Fibrillation aFter Ischemic StrOke (SAFFO) study and the AF detected by continuous ECG monitoring using implantable loop recorder to prevent stroke in individuals at risk (LOOP) study are two ongoing, multicenter, open-label RCTs that aim to evaluate health benefits, including reduction of recurrent ischemic events and cost-effectiveness, of implantable cardiac monitors in secondary stroke prevention.[28,29] Results from these studies are expected to provide further insight on the target population for ICM, the optimal threshold required for AF definition and further confirm whether prolonged cardiac monitoring with ICM results in lower stroke recurrence through anticoagulant initiation as uncovered by the current cohort study.

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Author Contributions

A.H.K., S.T., and G.T. and contributed to the conception and design of the study. S.T., A.H.K., C.L., K.T., and G.T. contributed to the acquisition and analysis of data. A.H.K. and G.T. contributed to drafting the text and preparing the figures.

Potential Conflicts of Interest

The authors declared no conflict of interest.

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