JAMA | Original Investigation

Effect of Implantable vs Prolonged External Electrocardiographic Monitoring on Atrial Fibrillation Detection in Patients With Ischemic Stroke
The PER DIEM Randomized Clinical Trial

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IMPORTANCE The relative rates of detection of atrial fibrillation (AF) or atrial flutter from evaluating patients with prolonged electrocardiographic monitoring with an external loop recorder or implantable loop recorder after an ischemic stroke are unknown.

OBJECTIVE To determine, in patients with a recent ischemic stroke, whether 12 months of implantable loop recorder monitoring detects more occurrences of AF compared with conventional external loop recorder monitoring for 30 days.

DESIGN, SETTING, AND PARTICIPANTS Investigator-initiated, open-label, randomized clinical trial conducted at 2 university hospitals and 1 community hospital in Alberta, Canada, including 300 patients within 6 months of ischemic stroke and without known AF from May 2015 through November 2017; final follow-up was in December 2018.

INTERVENTIONS Participants were randomly assigned 1:1 to prolonged electrocardiographic monitoring with either an implantable loop recorder (n = 150) or an external loop recorder (n = 150) with follow-up visits at 30 days, 6 months, and 12 months.

MAIN OUTCOMES AND MEASURES The primary outcome was the development of definite AF or highly probable AF (adjudicated new AF lasting ≥2 minutes within 12 months of randomization). There were 8 prespecified secondary outcomes including time to event analysis of new AF, recurrent ischemic stroke, intracerebral hemorrhage, death, and device-related serious adverse events within 12 months.

RESULTS Among the 300 patients who were randomized (median age, 64.1 years [interquartile range, 56.1 to 73.7 years]; 121 were women [40.3%]; and 66.3% had a stroke of undetermined etiology with a median CHA_2DS_2-VASc [congestive heart failure, hypertension, age ≥75 years, diabetes, stroke or transient ischemic attack, vascular disease, age 65 to 74 years, sex category] score of 4 [interquartile range, 3 to 5]), 273 (91.0%) completed cardiac monitoring lasting 24 hours or longer and 259 (86.3%) completed both the assigned monitoring and 12-month follow-up visit. The primary outcome was observed in 15.3% (23/150) of patients in the implantable loop recorder group and 4.7% (7/150) of patients in the external loop recorder group (between-group difference, 10.7% [95% CI, 4.0% to 17.3%]; risk ratio, 3.29 [95% CI, 1.45 to 7.42]; *P* = .003). Of the 8 specified secondary outcomes, 6 were not significantly different. There were 5 patients (3.3%) in the implantable loop recorder group who had recurrent ischemic stroke vs 8 patients (5.3%) in the external loop recorder group (between-group difference, −2.0% [95% CI, −6.6% to 2.6%]), 1 (0.7%) vs 1 (0.7%), respectively, who had intracerebral hemorrhage (between-group difference, 0% [95% CI, −1.8% to 1.8%]), 3 (2.0%) vs 3 (2.0%) who died (between-group difference, 0% [95% CI, −3.2% to 3.2%]), and 1 (0.7%) vs 0 (0%) who had device-related serious adverse events.

CONCLUSIONS AND RELEVANCE Among patients with ischemic stroke and no prior evidence of AF, implantable electrocardiographic monitoring for 12 months, compared with prolonged external monitoring for 30 days, resulted in a significantly greater proportion of patients with AF detected over 12 months. Further research is needed to compare clinical outcomes associated with these monitoring strategies and relative cost-effectiveness.

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Nonvalvular atrial fibrillation (AF) or atrial flutter is judged as the cause of one-third of all ischemic strokes and the majority of strokes related to cardiac embolism.[1] Among patients with recent ischemic stroke but without evidence of AF on electrocardiographic and Holter monitoring, the guidelines suggest etiologic investigations include additional electrocardiographic monitoring for 2 to 4 weeks.[2,3] This recommendation is based on evidence that evaluation with both external and implantable loop recorders improves the detection of AF in patients with stroke of undetermined etiology. Randomized studies evaluating 30 days of electrocardiographic monitoring after stroke diagnosed new AF in 14% to 16% of patients,[4,5] whereas monitoring with an implantable loop recorder for a longer duration detected AF in 12.4% of patients after 6 months.[6] However, no head-to-head detection rate comparisons of an external loop recorder vs an implantable loop recorder for AF exist.

Prolonged electrocardiographic monitoring studies after stroke have focused on patients with stroke of undetermined etiology.[7] Patients with extracranial or intracranial atherosclerotic lesions and those with isolated subcortical infarcts have not been included in large randomized trials.[4,6] However, determination of stroke etiology is often based on inference without complete certainty because risk factors such as age, obesity, and diabetes are associated with multiple potential infarct mechanisms.[8-10] Regardless of the putative stroke mechanism, detecting new AF after stroke remains clinically important due to risk reduction of recurrent stroke that has been associated with the initiation of oral anticoagulation therapy.[11]

Together, these data support a more pragmatic approach to selecting patients for long-term cardiac monitoring that includes patients with other potential stroke etiologies. Accordingly, the Post-Embolic Rhythm Detection with Implantable vs External Monitoring (PER DIEM) trial was conducted to determine the benefit of monitoring for AF using an implantable loop recorder for 12 months compared with an external loop recorder for 30 days in patients with ischemic stroke without known AF.

Key Points

Question What is the rate of detection of atrial fibrillation with use of an implantable electrocardiographic monitor for 12 months vs use of prolonged external electrocardiographic monitoring for 30 days after an ischemic stroke?

Findings In this randomized clinical trial that included 300 patients, the rate of detection of atrial fibrillation or flutter lasting 2 minutes or longer by 12 months was 15.3% in the implantable loop recorder group vs 4.7% in the prolonged external loop recorder group, a statistically significant difference.

Meaning Among patients with ischemic stroke, implantable electrocardiographic monitoring for 12 months resulted in the detection of more patients with atrial fibrillation compared with prolonged external monitoring for 30 days, although further research is needed to better understand clinical outcomes and cost-effectiveness.

Methods

Study Design

The PER DIEM study was an investigator-initiated, open-label randomized clinical trial of AF detection after ischemic stroke. The study was conducted at 3 hospitals in Alberta, Canada (eTable 1 in Supplement 1). The study design and protocol were reviewed and approved by local human research ethics boards and are available in Supplement 2. The statistical analysis plan appears in Supplement 3. All participants provided written consent before study entry. Enrollment took place between May 2015 and November 2017 and the trial included a 1-year follow-up period.

Study Population and Randomization

Eligible patients were adults aged 18 years or older with an arterial ischemic stroke confirmed by neuroimaging. Patients with resolved symptoms consistent with a clinical diagnosis of transient ischemic attack (TIA) were eligible only if they had evidence of infarction on computed tomographic or diffusion-weighted magnetic resonance imaging of the brain. All clinical and imaging diagnoses were confirmed by a vascular neurologist. Patients were eligible for randomization within 6 months of ischemic stroke if they did not have known AF. Patients were required to have had 12-lead electrocardiographic monitoring at least once after the stroke event, but there were no other requirements regarding stroke etiologic investigations. Patients were excluded if they had previously documented AF, a pacemaker or an implantable cardioverter-defibrillator device that would allow for the detection of AF, or had a stroke workup that already included extended (>7 days) external electrocardiographic monitoring (**Figure 1**).

Patients were randomized using permuted block sizes of 4, 6, or 8. Randomization was stratified by 2 sites (the 2 hospital sites in Edmonton were considered a single study site). The allocation was computer generated and concealed from the investigators and the patients; only the central database programmer was aware of the allocation table (additional details appear in Supplement 3). Study data were collected using the Research Electronic Data Capture tool[12] hosted at the University of Calgary clinical research unit.

Study Procedures

Study enrollment usually occurred at the first outpatient clinic appointment 6 to 8 weeks after stroke and after a review of the completed etiologic investigations. Baseline medical history, concomitant medications, ischemic stroke severity (measured using the National Institutes of Health Stroke Scale score), clinical subtype (using the Oxfordshire Community Stroke Project[13] classification), and presumed etiology (using the Trial of ORG in Acute Stroke Treatment [TOAST][14] classification) based on the results of the investigations performed before enrollment were recorded. The TOAST etiology was independently adjudicated by neurologists (B.H.B. and M.D.H.) specialized in the treatment of patients with stroke; any discrepancies were resolved by consensus.

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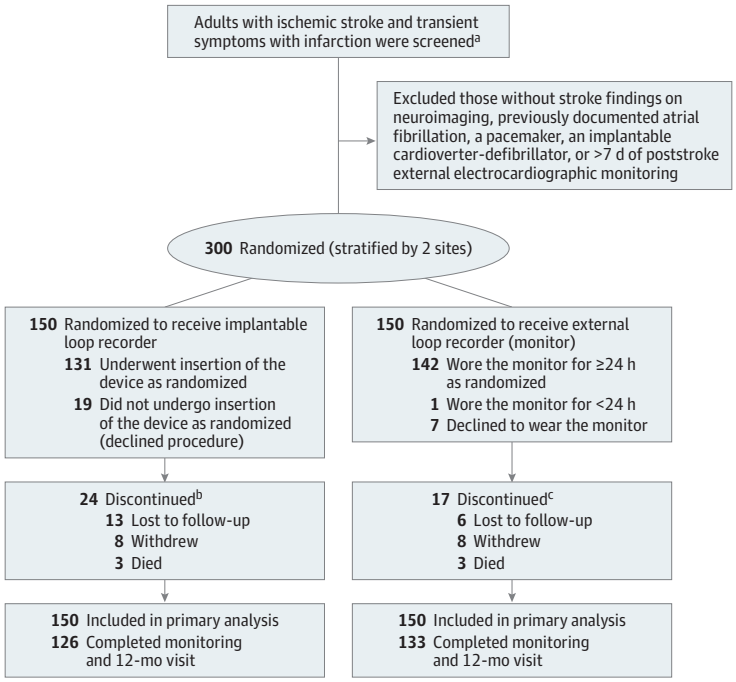
Figure 1. Flowchart of Randomization, Device Allocation, and Follow-up of Patients Enrolled in the PER DIEM Randomized Clinical Trial



PER DIEM indicates Post-Embolic Rhythm Detection with Implantable vs External Monitoring.

[a] The study sites were not required to maintain screening logs thus the total number of patients assessed for study eligibility was not available.

[b] Of the 24 patients, 5 had the device inserted.

[c] Of the 17 patients, 10 completed more than 24 hours of monitoring.

Patients assigned to the external loop recorder group were fitted with a battery-operated SpiderFlash-t (Sorin Group) autotriggered loop recorder and provided a diary to track total hours worn per day and any clinical symptoms. Patients were instructed to wear the external loop recorder as much as possible for 4 weeks. At the end of the monitoring period, stored data were uploaded into proprietary electrocardiographic viewing software and representative strips of any detected arrhythmias were provided in a report for adjudication.

Patients assigned to the implantable loop recorder plus remote monitoring group were scheduled for surgical implantation with a Medtronic Reveal LINQ insertable cardiac monitoring system. The implantable loop recorder device was linked postimplantation to a wireless remote monitoring system (MyCareLink). Patients also were provided with a diary to track clinical symptoms. The implantable loop recorder was programmed with its standard AF detection algorithm as well as for detection of tachycardia (heart rate >230/min minus the patient's age), bradycardia (heart rate <30/min), and pauses lasting longer than 4.5 seconds. The minimum duration of irregular rhythm that the implantable loop recorder will store as AF is 2 minutes, therefore this duration was chosen for both implantable loop recorder and external loop recorder rhythm determination. The device remained implanted for 12 months. At the end of 12 months, patients were given the option of device removal or continued monitoring as long as the device remained active.

For some of the study patients, there was limited availability of the external loop recorders and lack of appointments for insertion of the implantable loop recorders, which delayed the initiation of monitoring after randomization. Investigators and patients were not blinded to monitoring assignment group. Outcome ascertainment including all rhythm diagnoses (external loop recorder and implantable loop recorder) were centrally adjudicated by 2 cardiac electrophysiologists (F.R.Q. and D.V.E.) blinded to all clinical data. The stored electrocardiographic recordings from each device were classified as having definite AF or highly probable AF if there was a good quality recording showing continuously irregular QRS complexes for longer than 2 minutes, with no visible P waves, or with clearly identified fibrillatory atrial activity or atrial flutter waves. For the recordings showing irregular QRS complexes without clearly identified atrial activity because of noise, artifact, or tachycardia, these recordings were classified as possible AF if the electrocardiographic findings could be accounted for by AF or atrial flutter. The final diagnosis was based on a consensus between the 2 raters.

Follow-up study visits were completed without blinding at 30 days, 6 months, and 12 months. New diagnoses of AF, stroke or TIA, intracerebral hemorrhage, other bleeding events, and current use of antithrombotic medications were recorded. Twelve-lead electrocardiographic monitoring was performed at each visit. At 12 months, patients in both study groups were asked to rate overall device satisfaction using a 5-level Likert scale.

Outcome Measures

The primary outcome was the development of definite AF or highly probable AF (adjudicated new AF lasting ≥2 minutes within 12 months of randomization; additional information appears in the eBox in Supplement 1). Only AF events classified as definite or highly probable were considered to have met the

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primary outcome. The initial protocol planned on using a 30-second threshold for defining AF. Due to technical limitations of the implantable loop recorder in reliably capturing AF lasting less than 2 minutes, the temporal threshold for newly detected AF was modified in April 2016 to 2 minutes or longer based on the recommendation of the steering committee and before the adjudication of any device rhythm data. In addition, the steering committee decided to simplify the description of the end point and remove the requirement that new AF had to be clinically actionable. These changes to the primary outcome definition were made before any data were analyzed by the study investigators.

There were 15 prespecified secondary outcomes. Of these 15 outcomes, 8 were analyzed and reported and 7 were not collected or analyzed (eBox in Supplement 1). The 8 prespecified secondary outcome measures were the rate of the composite end point of AF lasting longer than 2 minutes or death, time to event analysis of new AF, recurrent ischemic stroke, TIA, intracerebral hemorrhage, death, device-related series adverse events, and major bleeding (using the definition from the International Society on Thrombosis and Hemostasis[15]) within 12 months.

The prespecified secondary outcomes that included the end point of AF were modified prior to any data analysis to align with the definition of AF for the primary outcome. Other reported outcomes and post hoc analyses included an analysis of group differences for the primary outcome at 30 days, assessment of site × randomized group interaction, group differences in rates of possible AF, the clinical characteristics associated with a diagnosis of new AF, the rates of AF detected by decile of age, the distribution of TOAST classification for patients with or without AF, and a comparison of patient satisfaction with each monitoring strategy.

Data and Safety Monitoring

A clinical events committee reviewed all serious adverse events 12 months after study initiation to ensure that neither group had a disproportionate accumulation of adverse events. The study used approved devices therefore nonserious adverse events were not tracked. No interim analyses were planned.

Statistical Analysis

The detailed statistical analysis plan appears in Supplement 3. The planned sample size provided 85% power to detect a 10% difference in AF detection rates between monitoring groups. We assumed (based on previous studies[16]) cumulative rates of detection for AF of 20% in the implantable loop recorder group and of 10% in the external loop recorder (control) group. This assumption was not based on the minimum clinically important difference but rather the effect size at 12 months seen in previous cardiac monitoring trials after stroke.[5,6] The final sample size of 300 patients included an 8% inflation for crossover (2% with either strategy) or a lost to follow-up rate of 5% in each group. Equal allocation (1:1) to external loop recorder for 30 days or implantable loop recorder plus remote monitoring for 12 months was assumed.

The primary analysis was completed using an as-randomized approach in which all randomized participants were included in the group they were originally allocated regardless of whether they received the cardiac monitoring device or completed the prescribed monitoring. A secondary analysis of the primary outcome was performed on the per-protocol population that was defined as those patients who completed both cardiac monitoring with the assigned study device and the 12-month study visit. Patients who declined the allocated cardiac monitoring device remained in the study and were assessed for a new diagnosis of AF and other outcomes at each study visit. An unadjusted 2-sample comparison of proportions was used to assess the primary outcome. A post hoc analysis compared group differences in the proportion of patients who received AF diagnoses within 30 days and between 30 days and 12 months.

Time to event analysis used the Kaplan-Meier method and a Cox proportional hazards model. A decision was made post hoc to adjust the hazard ratio for age and sex. The proportional hazards assumption was valid based on the Schoenfeld residuals using a global test.[17] Other differences between groups were tested using *t* tests (continuous variables), Mann-Whitney tests (ordinal variables), or Fisher exact tests (categorical variables). There were no missing values for the analyzed baseline variables. Patients who had missing values on the 12-month satisfaction survey were excluded from the between-group comparison.

Factors associated with new AF were examined post hoc using a bivariable analysis that compared baseline demographics and clinical characteristics (sex, hypertension, diabetes, peripheral vascular disease, chronic kidney disease, prior TIA or stroke, coronary artery disease, congestive heart failure, obstructive sleep apnea, CHA_2DS_2VASc [congestive heart failure, hypertension, age ≥75 years, diabetes, stroke or transient ischemic attack, vascular disease, age 65-74 years, sex category] score, TOAST classification, National Institutes of Health Stroke Scale score, and completion of prestudy Holter monitoring) between those patients with or without newly diagnosed AF. Variables significant at the $P < .10$ level were included in a multivariable logistic regression model. The effect of study site on the primary outcome was analyzed post hoc for an interaction with each monitoring device group.

All statistical tests were 2-sided with $P < .05$ considered statistically significant. Due to the potential for type I error from multiple comparisons, the analyses for the secondary outcomes should be considered exploratory. Statistical analyses were completed using Stata version 16.1 (StataCorp).

Results

Participant Characteristics

Between July 2015 and November 2017, 300 patients were randomized (150 to each group). A total of 131 patients (87.3%) in the implantable loop recorder group and 143 patients (95.3%) in the external loop recorder group underwent monitoring with the allocated study device without any crossovers (Figure 1). Of the 300 patients, 273 (131 in the implantable loop recorder group and 142 in the external loop recorder group; 91.0%) completed cardiac monitoring lasting 24 hours or longer. A total

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Table 1. Demographic and Baseline Characteristics of Study Participants

	Implantable loop recorder (n = 150)	External loop recorder (n = 150)
Demographics		
Age, median (IQR), y	65.5 (58.1-73.7)	63.4 (54.7-73.5)
Sex, No. (%)		
Female	61 (40.7)	60 (40.0)
Male	89 (50.3)	90 (60.0)
Medical history, No. (%)[a]		
Holter monitoring prior to enrollment[b]	118 (78.7)	118 (78.7)
Hypertension	93 (62.0)	94 (62.7)
Previous stroke	36 (24.0)	34 (22.7)
Diabetes	30 (20.0)	30 (20.0)
Coronary artery disease	20 (13.3)	23 (15.3)
Current smoker	20 (13.3)	20 (13.3)
Obstructive sleep apnea	14 (9.3)	18 (12.0)
Chronic kidney disease	5 (3.3)	8 (5.3)
Congestive heart failure	2 (1.3)	4 (2.7)
Peripheral vascular disease	6 (4.0)	3 (2.0)
Oral anticoagulation therapy	7 (4.7)	2 (1.3)
CHA_2DS_2-VASc score, median (IQR)[c]	4 (3-5)	4 (3-5)
Index event		
Transient symptoms with infarction[d]	5 (3.3)	4 (2.7)
Time from index event to baseline visit, median (IQR), d[e]	58.5 (30-108)	70.0 (31-110)
NIHSS score at baseline visit, median (IQR)[f]	0 (0-1)	0 (0-1)
Oxfordshire Community Stroke Project[13] classification, No. (%)[g]		
Partial anterior circulation syndrome	84 (56.0)	81 (54.0)
Posterior circulation syndrome	30 (30.0)	30 (30.0)
Lacunar stroke syndrome	26 (17.3)	29 (19.3)
Total anterior circulation syndrome	10 (6.7)	10 (6.7)
TOAST classification, No. (%)[h]		
Stroke of undetermined etiology	101 (67.3)	98 (65.3)
No cause found after complete investigation	87 (58.0)	90 (60.0)
Incomplete investigation	10 (6.7)	6 (4.0)
≥2 causes identified	4 (2.6)	2 (1.3)
Small vessel occlusion	22 (14.7)	26 (17.3)
Large artery atherosclerosis	13 (8.7)	13 (8.7)
Cardioembolism (excluding AF or atrial flutter)	10 (6.7)	9 (6.0)
Stroke of other determined etiology	4 (2.7)	4 (2.7)

Abbreviations: AF, atrial fibrillation; IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale; TOAST, Trial of ORG 10172 in Acute Stroke Treatment.

[a] Collected at the baseline visit and from patient self-report along with chart review for any items requiring further clarification.

[b] Completed 24 hours of monitoring as part of the etiologic work following the index stroke and prior to study enrollment.

[c] This is a risk assessment tool to predict stroke in patients with nonvalvular AF. The CHA_2DS_2-VASc (congestive heart failure, hypertension, age ≥75 years, diabetes, stroke or transient ischemic attack, vascular disease, age 65-74 years, sex category) score range is from 0 to 9, with higher scores indicating a greater annual risk of ischemic stroke.

[d] Symptoms lasting less than 24 hours and evidence of infarction on computed tomographic or magnetic resonance imaging. The remaining patients had an index event that was diagnosed as ischemic stroke.

[e] From the date of diagnosis of the index stroke or transient ischemic attack to the date of the baseline visit. The baseline visit occurred after consent was obtained at study entry and included randomization, collection of medical history, review of etiologic investigations, and completion of study scale measurements.

[f] Scores range from 0 to 42 with higher scores indicating more severe neurological deficits.

[g] A clinical tool that categorizes stroke syndromes into 4 subtypes. The classification was based on a review of clinical information and neuroimaging investigations at the baseline visit.

[h] The TOAST classification was assigned by 2 physicians specializing in the treatment of stroke patients after a review of baseline clinical information and etiologic investigations with discrepancies resolved by consensus.

of 259 patients (86.3%) completed both the assigned monitoring and 12-month follow-up visit and were included in the per-protocol analysis.

The baseline characteristics of the 2 device groups were similar (**Table 1**). The median patient age was 64.1 years (interquartile range, 56.1-73.7 years) and 121 were women (40.3%).

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Table 2. Primary and Secondary Outcomes at 12 Months Compared Between Study Groups

	No. (%)				
	Implantable loop recorder (n = 150)	External loop recorder (n = 150)	Unadjusted risk difference, % (95% CI)	Unadjusted risk ratio (95% CI)	Adjusted hazard ratio (95% CI)[a]
Primary outcome					
Development of definite AF or highly probable AF lasting ≥2 min within 12 mo of randomization	23 (15.3)	7 (4.7)	10.7 (4.0 to 17.3)	3.29 (1.45 to 7.42)	3.36 (1.44 to 7.84)
Secondary outcomes					
AF lasting ≥2 min or death by 12 mo	26 (17.3)	10 (6.7)	10.7 (3.4 to 17.9)	2.60 (1.30 to 5.20)	2.64 (1.27 to 5.49)
Transient ischemic attack[b]	6 (4.0)	2 (1.3)	2.7 (−1.0 to 6.3)	3.00 (0.62 to 14.63)	
Recurrent ischemic stroke[b]	5 (3.3)	8 (5.3)	−2.0 (−6.6 to 2.6)	0.63 (0.21 to 1.87)	
Intracerebral hemorrhage[b]	1 (0.7)	1 (0.7)	0 (−1.8 to 1.8)	1.00 (0.06 to 15.84)	
Death	3 (2.0)	3 (2.0)	0 (−3.2 to 3.2)	1.00 (0.21 to 4.88)	
Initiation of oral anticoagulation therapy in patients with definite AF[c]	23/23 (100)	7/7 (100)			

Abbreviation: AF, atrial fibrillation.

[a] Adjusted post hoc for age and sex.

[b] Determined based on review of patient charts and available computed tomographic or magnetic resonance imaging by 2 independent physicians specializing in the treatment of patients with stroke. Any discrepancies were resolved by consensus.

[c] Data in columns 2 and 3 are expressed as No./total (%).

The median CHA_2DS_2VASc score was 4 (interquartile range, 3-5) and 23.3% of patients had a history of stroke before the index event. The etiologic workup at the baseline visit included at least 1 assessment with a Holter monitor in 78.6% of patients and 66.3% had an index stroke of undetermined etiology. Small vessel occlusion was the next most common TOAST stroke etiology (16.0%). The median time was 64 days (interquartile range, 31-110 days) from the index stroke event to the randomization visit.

Primary Outcome

The primary outcome of development of definite AF or highly probable AF within 12 months was observed in 15.3% (23/150) of patients in the implantable loop recorder group and 4.7% (7/150) of patients in the external loop recorder group (risk ratio [RR], 3.29 [95% CI, 1.45-7.42]; $P = .003$) (**Table 2**). The absolute increase in the number of AF detection events with an implantable loop recorder, relative to an external loop recorder, was 10.7% (95% CI, 4.0%-17.3%). This indicates that approximately 1 additional patient was diagnosed with AF for approximately every 10 patients monitored with an implantable loop recorder instead of an external loop recorder. Additional analyses appear in eTables 2-4 and eFigures 1-3 in Supplement 1.

A post hoc analysis compared group differences in the proportion of patients who received AF diagnoses within 30 days and between 30 days and 12 months. There were 7 (4.7%) new AF diagnoses in the implantable loop recorder group and 5 (3.3%) in the external loop recorder group (between-group difference, 1.3% [95% CI, −3.1% to 5.8%]; $P = .77$). Between 30 days and 12 months, significantly more cases of AF were diagnosed in the implantable loop recorder group compared with the external loop recorder group (16 [10.7%] vs 2 [1.3%], respectively; between-group difference, 9.3% [95% CI, 4.1% to 14.6%]; RR, 8.00 [95% CI, 1.87 to 34.19]; $P = .001$). In the external loop recorder group, there were 2 new AF diagnoses after 30 days based on 12-lead electrocardiographic monitoring completed at the study visits.

A per-protocol analysis included 259 of the 300 patients (86.3%) who completed both the prescribed monitoring and attended the 12-month study visit. The per-protocol analysis was consistent with the primary outcome and showed a significantly higher rate of new AF with the implantable loop recorder (23/126 [18.3%]) compared with the external loop recorder (7/133 [5.3%]) (between-group difference, 13.0% [95% CI, 5.3%-20.7%]; RR, 3.46 [95% CI, 1.54-7.80]; $P = .002$; eFigure 1 in Supplement 1).

Secondary Outcomes

The time from randomization to the first detected episode of AF lasting longer than 2 minutes in the implantable loop recorder group was significantly lower compared with the external loop recorder group (age- and sex-adjusted hazard ratio, 3.36 [95% CI, 1.44-7.84]; $P = .005$; log-rank test, $P = .002$; **Figure 2**). The combined end point of death along with AF detection within 12 months occurred in 26 patients (17.3%) in the implantable loop recorder group compared with 10 patients (6.7%) in the external loop recorder group (between-group difference, 10.7% [95% CI, 3.4%-17.9%]; $P = .007$; adjusted hazard ratio, 2.64 [95% CI, 1.27-5.49]; $P = .009$; eFigures 2-3 in Supplement 1).

There were no significant between-group differences for the secondary outcomes of TIA (6 patients [4.0%] in the implantable loop recorder group vs 2 patients [1.3%] in the external loop recorder group; between-group difference, 2.7% [95% CI, −1.0% to 6.3%]; $P = .28$), recurrent ischemic stroke (5 [3.3%] vs 8 [5.3%], respectively; between-group difference, −2.0% [95% CI, −6.6% to 2.6%]; $P = .40$), intracerebral hemorrhage (1 [0.7%] in each group; between-group difference, 0% [95% CI, −1.8% to 1.8%]), or death (3 [2.0%] in each group; between-group difference, 0% [95% CI, −3.2% to 3.2%]; Table 2).

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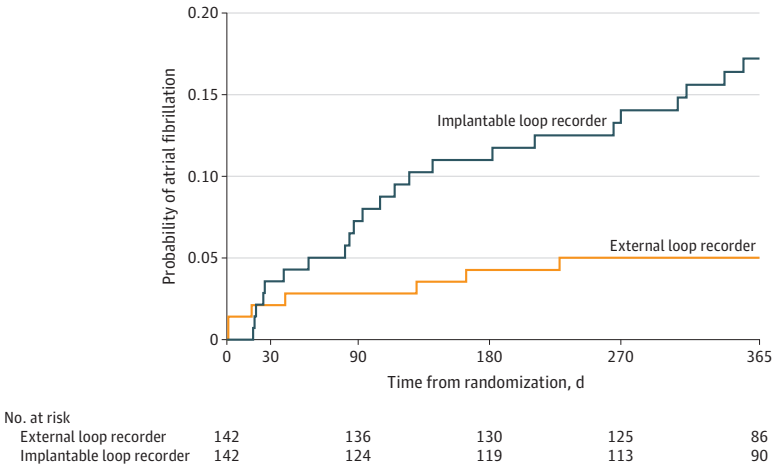
Figure 2. Secondary Outcome of the Probability of New Atrial Fibrillation or Flutter Lasting 2 Minutes or Longer Within 12 Months



No. at risk					
External loop recorder	142	136	130	125	86
Implantable loop recorder	142	124	119	113	90

All patients were included as randomized when calculating survival. Eight patients in each group withdrew immediately after randomization. These patients were censored at day 0. The overall median time at risk was 342 days (interquartile range, 135-258 days). There was a significant difference in the time to detection of new atrial fibrillation or flutter between the groups (age- and sex-adjusted hazard ratio, 3.36 [95% CI, 1.44-7.84], $P = .005$; log-rank test $P = .002$).

Table 3. Reported Serious Adverse Events[a]

	Implantable loop recorder (n = 150)	External loop recorder (n = 150)
Patients with ≥1 serious adverse event, No. (%)	14 (9.3)	4 (3.3)
Description of serious adverse event, No.		
Bacterial peritonitis	1	0
Bladder neck obstruction	1	0
Cardiac amyloidosis	1	0
COPD exacerbation	0	1
Device-related skin erosion	1	0
Femoral fracture	1	0
Gastrointestinal bleeding	1	0
Hepatocellular carcinoma	1	0
High-grade symptomatic atrioventricular block	1	0
Hip fracture	1	0
Lung cancer	1	0
Myocardial infarction	0	2
Pancolitis	1	0
Pneumonia	1	1
Pneumothorax	1	0
Multiple trauma	1	0
Quadriceps tendon rupture	1	0
Recrudescence of stroke deficits	1	0
Renal colic	1	0
Symptomatic sinus bradycardia	2	0

Abbreviation: COPD, chronic obstructive pulmonary disease.

[a] All were reviewed for accuracy by the site principal investigator and the clinical events committee. This listing does not include events that are included as secondary outcomes (eg, transient ischemic attack, stroke, or intracerebral hemorrhage). The study used off-the-shelf approved cardiac monitoring devices and therefore simple adverse events tracking was not deemed necessary.

In a post hoc analysis in which the definition of AF was broadened to include possible AF, detection of AF (≥2 minutes) at 12 months was 20.7% (31 patients) in the implantable loop recorder group and 5.3% (8 patients) in the external loop recorder group (between-group difference, 15.3% [95% CI, 7.9%-22.7%]; RR, 3.88 [95% CI, 1.84-8.15], $P = .001$). All patients with newly diagnosed definite AF or highly probable AF, regardless of study group, were started on oral anticoagulation therapy.

Device-Related Serious Adverse Events

A single device-related serious adverse event was reported. One patient in the implantable loop recorder group experienced skin erosion overlying the device, requiring removal at 2 months without further sequelae. Other serious adverse events appear in **Table 3**.

Post Hoc Outcomes

A post hoc analysis was performed to identify the clinical characteristics associated with a new diagnosis of AF. The only significant features associated with AF detection were older age (RR, 1.03 [95% CI, 1.01-1.06] per year; $P = .002$) and device group (RR, 3.28 [95% CI, 1.45-7.42]; $P = .004$). In a multivariable model adjusting for age, cardiac monitoring after stroke using an implantable loop recorder resulted in a significant increase in the detection of AF lasting longer than 2 minutes (RR, 3.07 [95% CI, 1.36-6.93]; $P = .007$). The estimated rates of AF detection with implantable loop recorder use increased with each age decile from 8.4% for patients aged 20 to 29 years to greater than 50% in those older than aged 90 years (eTable 2 in Supplement 1). The distribution of baseline TOAST classification was not significantly different between patients with or without newly detected AF ($\chi^2_4 = 8.42$, $P = .08$; eTable 3 in Supplement 1). There was no significant site × randomized group interaction ($P = .26$).

There were significant differences in the overall distribution of patient-reported satisfaction with the assigned monitoring strategy at 12 months ($P < .001$); 42.9% (54/126) of patients in the implantable loop recorder group reported being very satisfied with the monitoring strategy compared

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with 20.2% (26/129) in the external loop recorder group (eTable 4 in Supplement 1).

Discussion

Among patients with recent ischemic stroke and no prior evidence of AF, prolonged continuous electrocardiographic monitoring with an implantable loop recorder over 12 months resulted in a significant increase in newly detected AF compared with a conventional 30-day external loop recorder strategy.

The rates of AF detection were not significantly different during the first 30 days of monitoring between groups. Beyond 30 days, new AF diagnoses continued to accumulate in the implantable loop recorder group while there were 2 new AF diagnoses in the external loop recorder group based on 12-lead electrocardiographic monitoring competed at the study visits. All AF diagnoses were clinically actionable, resulting in new prescriptions for oral anticoagulation therapy.

The incidence of AF detection with an implantable loop recorder (15.3%) was comparable with that seen in the Cryptogenic Stroke and Underlying AF trial[6] (12.4% by 12 months) despite the inclusion of all stroke subtypes without known AF. In contrast, the AF detection rate in the external loop recorder group was only 3.3% at 30 days, which is considerably lower than the rate of 16.1% reported in the Event Monitor Belt for Recording Atrial Fibrillation after a Cerebral Ischemic Event (EMBRACE) trial.[4] Differences between the trial results may be related to the definition of AF. The PER DIEM trial used a more rigorous definition of AF that excluded AF events lasting less than 2 minutes and lower probability AF without clearly visible atrial activity, whereas the EMBRACE trial's definition included all episodes of AF lasting 30 seconds or longer. There is currently no universally accepted burden of AF, particularly in the population after stroke. The a priori definition of AF was based on investigator consensus and technical consideration, and neither it nor the more liberal definition used in the EMBRACE trial has been validated. The lower rate of AF in the current trial may also be related to the inclusion of younger patients (mean age, 64.4 years vs 72.5 years in EMBRACE).

Longer-term cardiac monitoring of all patients with stroke and without proven AF would have cost implications. The implantable loop recorders used in this study are single-use devices. Although the PER DIEM trial found a relatively low number needed to monitor to detect AF, it remains unproven whether more widespread adoption of an implantable loop recorder will translate into lower stroke rates and health economic benefits.[18] In this study, the strongest predictor of AF detection was age. Individuals older than aged 80 years with a recent stroke had an estimated rate of AF that approached 50%. Studies are needed to determine if there are subgroups of stroke patients in whom empirical anticoagulation therapy is more cost-effective than extended cardiac monitoring strategies.[19]

Limitations

The study has several limitations. First, the median delay of 2 months between stroke onset and study enrollment may have decreased the rate of detection of AF slightly, although this would be expected to affect both study groups equally.

Second, there was, by design, variability in the investigations that were completed before enrollment. Not all patients had echocardiographic and 24-hour Holter monitoring before they were enrolled in the study. Patients without 24-hour Holter monitoring may have had AF that would have been detected if such monitoring had been completed before study enrollment.

Third, the study was designed with a primary outcome of definite AF lasting 2 minutes or longer because the goal was to identify patients in whom oral anticoagulation therapy was indicated. Even though AF episodes with a shorter duration may be predictive of subsequent AF episodes with a longer duration, this has not been validated.[20]

Fourth, 8.6% of study participants did not complete the prescribed monitoring, which may underestimate the underlying rate of AF. Fifth, phone assessments at 12 and 24 months did not use a validated questionnaire to assess for new stroke events or TIA, which may have resulted in an underestimate of recurrent events.

Conclusions

Among patients with ischemic stroke and no prior evidence of AF, implantable electrocardiographic monitoring for 12 months, compared with prolonged external monitoring for 30 days, resulted in a significantly greater proportion of patients with AF detected over 12 months. Further research is needed to compare clinical outcomes associated with these monitoring strategies and relative cost-effectiveness.

ARTICLE INFORMATION

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