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Noninvasive Cardiac Event Monitoring to Detect Atrial Fibrillation After Ischemic Stroke

A Randomized, Controlled Trial

Peter Higgins, MRCP; Peter W. MacFarlane, DSc; Jesse Dawson, MD; Gordon T. McInnes, MD; Peter Langhorne, PhD; Kennedy R. Lees, MD

Background and Purpose—Atrial fibrillation (AF) elevates risk of recurrent stroke but is incompletely identified by standard investigation after stroke, though detection rates correlate with monitoring duration. We hypothesized that 7 days of noninvasive cardiac-event monitoring early after stroke would accelerate detection of AF and thus uptake of effective therapy.

Methods—We performed a pragmatic randomized trial with objective outcome assessment among patients presenting in sinus rhythm with no AF history, within 7 days of ischemic stroke symptom onset. Patients were randomized to standard practice investigations (SP) to detect AF, or SP plus additional monitoring (SP-AM). AM comprised 7 days of noninvasive cardiac-event monitoring reported by an accredited cardiac electrocardiology laboratory. Primary outcome was detection of AF at 14 days.

Results—One-hundred patients were enrolled from 2 centers. Within 14 days of stroke, sustained paroxysms of AF were detected in 18% of patients undergoing SP-AM versus 2% undergoing SP ($P<0.05$). Paroxysms of any-duration were detected in 44% of patients undergoing SP-AM versus 4% undergoing SP ($P<0.001$). These differences persisted at 90 days. Anticoagulant therapy was commenced within 14 days in 16% of SP-AM patients versus none randomized to SP ($P<0.01$). This difference persisted to 90 days (22% versus 6%; $P<0.05$).

Conclusions—Routine noninvasive cardiac-event monitoring after acute stroke enhances detection of paroxysmal AF and early anticoagulation. Extended monitoring should be offered to all eligible patients soon after acute stroke. Guidelines on investigation for AF in stroke patients could be strengthened.

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Key Words: anticoagulants ■ atrial fibrillation ■ ischemic attack, transient ■ stroke

Ischemic stroke is the leading cause of adult disability in the developed world and the third leading cause of mortality. Healthcare-related costs are high and effective preventative strategies are crucial in reducing the burden of disease.

Atrial fibrillation (AF) predisposes to the formation of thrombus within the left atrium and consequently to thromboembolic events, typically ischemic stroke. AF independently increases the risk of stroke 5-fold¹ and doubles the risk of recurrent stroke,² the latter irrespective of the etiological mechanism for the incident stroke. AF-related stroke is associated with increased stroke severity, which may be associated with worse outcome.³ AF is common, and prevalence will increase with the aging population.⁴

Oral anticoagulant therapy dramatically reduces the risk of ischemic stroke in patients with AF, particularly those with prior stroke or transient ischemic attack (TIA),⁵ regardless of the underlying etiological mechanism. Moreover, it is substantially more effective than antiplatelet therapy.⁵ New anticoagulant drugs such as the direct thrombin and factor Xa inhibitors may be yet more effective with reduced bleeding complications.^{6,7}

Risk of recurrent stroke is similar with both sustained and paroxysmal AF (PAF) and both forms are optimally treated with anticoagulation.⁸ Accordingly, detection of occult PAF after ischemic stroke is of critical importance to optimize uptake of treatment with oral anticoagulation.⁹

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One in 5 patients with ischemic stroke or TIA will have a history of AF or is revealed to have AF on their initial 12-lead ECG,¹⁰ but further investigation is needed to detect culprit PAF and occult PAF, which confers future risk.¹¹ A recent systematic review suggested that PAF will be detected in an additional 4.6% of patients through routine application of 24-hour Holter monitoring, the conventional modality for investigation,¹² although individual studies have reported widely variable detection rates.¹¹ However, alternative investigation strategies such as extended-duration Holter monitoring, cardiac telemetry, and implantable cardiac-event monitors may increase detection rates but are labor intensive, expensive, and lack a definitive evidence base supporting their routine use.¹³ It is acknowledged that detection rates increase with more prolonged monitoring.¹³

Although detection with prolonged monitoring has been explored in uncontrolled longitudinal studies and selected populations (eg, cryptogenic stroke), no randomized comparisons have been reported for specific investigation strategies in unselected ischemic stroke patients. Clinical guidelines reflect this uncertainty and are diverse in their conclusions regarding investigation. Typically the guidelines refer to repeated 12-lead ECGs or some form of cardiac monitoring for selected patients but generally offer no specific recommendation regarding modality or duration.^{14–17} Some stroke centers may reserve prolonged monitoring for patients with so-called cryptogenic stroke, some regard 24 hours' Holter monitoring as standard, and others may restrict full investigation to patients with cortical or multiple territory infarcts.¹⁸

The optimal investigation strategy, including modality, duration of investigation, and patient subgroup remains undefined, not only for efficacy in the detection of AF, but also cost-effectiveness in healthcare systems. We designed a pragmatic randomized trial to test whether the effectiveness of current guideline-based investigation could be improved, through application of a simple addition to routine approaches.

Aims

We aimed to determine, in a population of patients with recent ischemic stroke or TIA, with no ECG evidence nor history of AF, whether supplementing standard guideline-based investigation with 7 days' cardiac-event monitoring would: (1) increase detection of paroxysms of AF of duration that would justify anticoagulation; (2) increase detection of paroxysms of AF of any duration (including brief episodes of uncertain prognostic significance); and (3) increase use of anticoagulation for prophylaxis of thromboembolism. We also aimed to evaluate whether stroke clinicians without specialist cardiology training could reliably interpret the supplementary cardiac-event monitoring data.

Methods

Study Design

We conducted a randomized controlled trial, comparing standard clinical practice for the detection of AF, against standard clinical practice plus additional cardiac-event monitoring.

Study Population

Patients were eligible within 7 days of transient or persistent symptoms of acute ischemic stroke, provided they had an admission

12-lead ECG demonstrating sinus rhythm and had neither history of AF or atrial flutter nor any irreversible contraindication for long-term anticoagulation (Table I in the online-only Data Supplement). Patients or their legally approved proxy gave written informed consent. The study was approved by the Scotland A Research Ethics Committee.

Sample Size

We calculated that a sample size of 5000 patients gives 95% power to detect a difference between 3% (control) and 5% (intervention) detection rates for AF and 90% power to detect a difference between 2% (control) and 3.5% (intervention) anticoagulation rates. An initial pilot phase of 100 patients was conducted to demonstrate feasibility of early 7-day monitoring and provide estimates of AF detection rate to verify the abovementioned assumptions. On completion of 14- and 90-day follow-up of the 100 participants in the pilot phase, interim analyses of the predefined primary and secondary end points was planned to inform on progression to the larger main study phase.

Randomization and Masking

Enrolled patients were randomized, via an interactive voice response system, to either a control group or intervention study group on a 1:1 basis. Research nursing staff assigned participants to their intervention after randomization. Investigators and patients were aware of study group allocation. This allowed pragmatic management decisions to be made without delay, based on diagnostic information gained through study procedures.

Study Intervention, Data Collection, and End Point Determination

Patients were enrolled from 2 acute stroke services in Glasgow (Glasgow Western Infirmary and Glasgow Royal Infirmary).

Before entry, every patient had a 12-lead ECG that confirmed sinus rhythm. Patients in both groups received standard practice (SP) investigation for the detection of AF, as individually determined at the discretion of the local treating clinical team, consistent with existing guidelines and with national practice.^{14–18} Investigations that afforded the opportunity for AF detection comprised additional 12-lead ECGs (subsequent to the admission 12-lead ECG), 24-hour Holter monitoring, and echocardiography (which, as coupled with cardiac rhythm monitoring, afforded the opportunity for AF detection). 24-hour Holter recordings were reported centrally at the recruiting hospital cardiology laboratory and reviewed thereafter by treating clinicians.

Patients randomized to the intervention group underwent usual SP investigation plus additional monitoring (AM) for the detection of AF (SP-AM). AM comprised 7 days of noninvasive cardiac-event monitoring, performed with the Novacor R-test Evolution 3 device. The device weighs <50 g and garners cardiac rhythm data through 2 electrodes, placed respectively at the sternum and apex. This approximates to a CM5 lead configuration. The R-test device used a loop recording system to capture cardiac rhythm episodes of 30 seconds duration (the maximum period of dysrhythmia recordable with the R-test device settings used in the study), triggered automatically by possible AF recognition. Ten seconds of rhythm preceding and 20 seconds subsequent to the trigger point were captured.

Monitoring commenced immediately after randomization, with interim downloads at 24, 72, and 168 hours to permit interim analysis of any captured events and to avoid losing any detected AF episodes (with a 20-minute memory, the device automatically stores the most prolonged rhythm disturbances preferentially over briefer ones). The SP-AM group also had digital 12-lead ECGs recorded at 24 and 72 hours with a Lexor Cardiolex ECG.

The cardiac-event monitoring and digital ECG data were transferred to a central cardiac electrocardiology laboratory (Glasgow Royal Infirmary) led by 1 of the authors (P.W.M.), for storage and analysis. This is an accredited specialist core laboratory, with extensive experience in ECG reporting and cardiac monitoring data for many international trials. A trained technician established whether the recordings were normal or showed possible evidence of AF, based

on absence of discernible organized atrial activity and irregular ventricular response. Recordings with suspected AF were reviewed by an experienced electrocardiologist (P.W.M.).

End Points

On the basis of core laboratory interpretation, patients identified as having evidence of AF were subsequently categorized as exhibiting either sustained or nonsustained paroxysms of AF. Sustained PAF was diagnosed where AF was recorded for the complete 20-second rhythm strip after event triggering. This definition accords closely with that recommended for diagnosis within clinical trials¹⁹ and clinical practice⁹ and which would justify consideration of formal anticoagulant therapy. Nonsustained PAF included briefer paroxysms of a minimum of 6 conducted ventricular complexes but <20 seconds' duration. Such episodes lack a substantial evidence base in terms of prognostic significance, and there is clinical uncertainty in terms of benefit of anticoagulant therapy. Hereafter, we refer to detection of sustained PAF and any-duration PAF (the latter comprising both sustained and nonsustained PAF patients).

In addition to the external validated reporting of R-test data, local treating clinicians were able to review data captured by the R-test device on a real-time basis as recordings were collected. Local clinician interpretation of the R-test data in this manner facilitated potential adjustment to patient therapy without delay. Local clinician reports were collated to permit comparison with the external laboratory reports.

Follow-up

Patients were reviewed at 14 and 90 days, either through a patient visit or, if this was not possible, through telephonic discussion with the patient and their primary care practitioner together with review of case notes and relevant investigation reports.

The primary end point was the difference in AF detection between patients randomized to receive SP-AM compared with SP alone at 14 days. As noted above, detection of AF was defined as evidence of sustained PAF and any-duration PAF.

Secondary end points were the difference in AF detection at 90 days and the difference in AF-thromboembolic prophylaxis-related anticoagulation (eg, warfarin) between patients randomized to receive SP-AM compared with SP alone at 14 and 90 days.

Data regarding serious adverse events were collected to 14 days. Data regarding relevant clinical end points (TIA, stroke, MI, death) were collected to 90 days.

Though we recorded use of other investigations such as transthoracic or transesophageal echocardiography and vascular imaging, we did not control their use. The study population was neither one of cryptogenic stroke nor enriched according to cortical or multiple territory infarcts. In line with its pragmatic nature, our trial included all patients with sinus rhythm who may eventually benefit from detection of AF.

Statistical Analysis

Analysis was performed on an intention-to-treat basis, with comparison of AF detection (sustained and any-duration) and anticoagulation status by difference in proportions, performed at 14 and 90 days. The Fleiss κ statistic was used to assess agreement between local treating clinicians and the validated core laboratory in R-test reporting of AF (Minitab, version 16). Survival analysis, with the log-rank test was performed for each end point of interest at 90 days (SPSS, version 18). The study design is summarized in Figure I in the online-only Data Supplement.

Results

Interim analysis was performed after 90-day follow-up of 100 patients enrolled from 2 stroke services in Glasgow between May 2010 and September 2011. All 100 patients completed 90-day follow-up. There were no significant differences between the randomized groups in either baseline

characteristics (Table 1) or the investigations performed that comprised SP (Table 2).

The AM was well tolerated, with high completion rates and no associated adverse events (Table 3). The AM cumulative detection rate for evidence of AF, reported through the core ECG laboratory, was: 4/50 (8%; 95% confidence interval [CI], 2.2%–19.2%) for the 2 additional digital 12-lead ECGs; 8/50 (16%; 95% CI, 7.2%–29.1%) for sustained AF with the non-invasive R-test cardiac-event monitoring; 21/50 (42%; 95% CI, 28.2%–56.8%) for any-duration AF with the noninvasive R-test cardiac-event monitoring. Every patient in whom AF was identified by 12-lead ECG at 24 or 72 hours also had sustained PAF episodes identified through R-test noninvasive cardiac-event monitoring.

Sustained and any-duration PAF episodes were each detected more frequently in the SP-AM group compared with the SP group at both 14 and 90 days (Table 4). Ninety-day survival free from sustained and any-duration PAF detection are shown in Figures II and III in the online-only Data Supplement.

Anticoagulant therapy was initiated more frequently in the SP-AM group compared with the SP group at both 14 and 90 days (Table 4). Ninety-day survival free from anticoagulation for AF-related thromboembolism prophylaxis, is shown in Figure IV in the online-only Data Supplement. Ninety-day survival free from anticoagulation for any indication, is shown in Figure V in the online-only Data Supplement.

There was no difference between groups for recurrent stroke, TIA, MI, death, or any combination of these clinical end points (4 combined events in each group). There were no serious adverse events associated with use of the R-test device.

There was excellent agreement between the ECG core laboratory and local clinicians for the presence of sustained paroxysms of AF on the R-test event monitors: 48/50 cases (96%; 95% CI, 86.3–99.5), Fleiss' κ 0.86, $P < 0.00001$. Agreement for the presence of any-duration AF was present in 44/50 cases (88%; 95% CI, 75.7–95.5), Fleiss' κ 0.76, $P < 0.00001$.

Discussion

Guidelines for investigation of ischemic stroke recommend a 12-lead ECG in all patients, Holter monitoring for many, and extended ECG monitoring in cryptogenic stroke, as detection rates are closely related to duration of monitoring. Our trial provides randomized evidence for superior effectiveness of routine early and extended cardiac-event monitoring in all ischemic stroke patients with sinus rhythm, versus existing guideline-based practice. This strategy enhances anticoagulation rates, which should offer improved stroke prevention. Guideline-based practice, as currently implemented in the United Kingdom and elsewhere,¹⁸ is inadequate for the prevention of AF-related recurrent stroke and can readily be improved.

Without routine use of extended cardiac monitoring after stroke, AF will be detected in only 6% to 8% of patients followed for 90 days.²⁰ Extended monitoring increases detection up to 3-fold.^{11,13} The annual risk of stroke recurrence among AF patients treated with antiplatelet drugs is 10% but is readily reduced to 4% with anticoagulation.²¹

Despite this, current guidelines make limited recommendations regarding investigation for AF detection after stroke,

Table 1. Baseline Characteristics

	Mean (SD)			P Value for Difference Between Groups
	Total, N=100	SP Group, n=50	SP-AM Group, n=50	
Age, y	65.8 (12.3)	64.6 (13.3)	67.1 (11.1)	0.32
Ictus to randomization, median (IQR)	1 (1)	1 (2)	1 (1)	0.74*
NIHSS (stroke patients only), median (IQR)	2 (4)	1 (3.5)	1 (4)	0.82*
SBP	154.8 (27.1)	154.4 (25.3)	155.2 (29.0)	0.88
DBP	81.5 (14.5)	81.5 (14.4)	81.5 (14.7)	1.00
HR	77.55 (17.5)	77.5 (16.2)	77.6 (18.8)	0.96
Alcohol units/week, median (IQR)	3 (15)	2.5 (15)	3 (15)	0.71*
Male sex	56% (45.7%–65.9%)	64% (49.1%–77.1%)	48% (33.7%–62.6%)	0.10
Qualifying event stroke	68% (57.9%–77.0%)	66% (51.2%–78.8%)	70% (55.4%–82.1%)	0.67
Qualifying event TIA	32% (23.0%–42.1%)	34% (21.2%–48.8%)	30% (17.9%–44.6%)	0.67
TACS	14% (7.9%–22.4%)	14% (5.8%–26.7%)	14% (5.8%–26.7%)	1.00
PACS	41% (31.3%–51.3%)	42% (28.2%–56.8%)	40% (26.4%–54.8%)	0.84
LACS	33% (24.0%–43.1%)	30% (17.9%–44.6%)	36% (22.9%–50.8%)	0.52
POCS	12% (6.4%–20.0%)	14% (5.8%–26.7%)	10% (3.3%–21.8%)	0.54
IHD	16% (9.4%–24.7%)	16% (7.2%–29.1%)	16% (7.2%–29.1%)	1.00
Hypertension	58% (47.7%–67.8%)	60% (45.2%–73.4%)	56% (41.3%–70.0%)	0.69
Diabetes mellitus	15% (8.6%–23.5%)	22% (11.5%–36.0%)	8% (2.2%–19.2%)	0.09†
Smoker	32% (23.0%–42.1%)	40% (26.4%–54.8%)	24% (13.1%–38.2%)	0.08
Aspirin	55% (44.7%–64.9%)	56% (41.3%–70.0%)	54% (39.3%–68.2%)	0.84
Dipyridamole MR	21% (13.5%–30.3%)	22% (11.5%–36.0%)	20% (10.0%–33.7%)	0.81
Clopidogrel	27% (18.6%–36.8%)	26% (14.6%–40.3%)	28% (16.2%–42.5%)	0.82
Any antiplatelet	75% (65.3%–83.1%)	78% (64.0%–88.5%)	72% (57.5%–83.8%)	0.49
ACE-I	37% (27.6%–47.2%)	38% (24.7%–52.8%)	36% (22.9%–50.8%)	0.84
ARB	8% (3.5%–15.2%)	6% (1.3%–16.5%)	10% (3.3%–21.8%)	0.72†
Thiazide	18% (11.0%–26.9%)	14% (5.8%–26.7%)	22% (11.5%–36.0%)	0.30
CCB	15% (8.6%–23.5%)	14% (5.8%–26.7%)	16% (7.2%–29.1%)	0.78
β-Blocker	17% (10.2%–25.8%)	16% (7.2%–29.1%)	18% (8.6%–31.4%)	0.79
α-Blocker	2% (0.0%–7.0%)	0% (0%–5.8%)	4% (0.0%–13.7%)	0.50†
Statin	58% (47.7%–67.8%)	60% (45.2%–73.4%)	56% (41.3%–70.0%)	0.69
Other lipid modifying	2% (0.0%–7.0%)	4% (0%–13.7%)	0% (0%–5.8%)	0.50†
Hypoglycemic therapy	10% (4.9%–17.6%)	14% (5.8%–26.7%)	6% (1.3%–16.5%)	0.32†

Continuous baseline characteristic values are quoted as mean (SD) unless otherwise stated. Comparison was with 2 sample *t* tests except when a variable did not approximate to the normal distribution, when comparison with the Mann–Whitney test (*) was used. Categorical baseline characteristics are quoted as % (95% CI). Comparison between groups is with difference in 2 proportions. When observed frequencies were low, Fisher exact test (†) was used. A *P* value of <0.05 was considered statistically significant. ACE-I indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CI, confidence interval; DBP, diastolic blood pressure; IHD, ischemic heart disease; IQR, interquartile range; LACS, lacunar anterior circulation syndrome; MR, modified release; NIHSS, National Institutes of Health Stroke Scale; PACS, partial anterior circulation syndrome; POCS, posterior circulation syndrome; SBP, systolic blood pressure; SP, standard practice; SP-AM, standard practice plus additional monitoring; TACS, total anterior circulation syndrome; and TIA, transient ischemic attack.

reflecting a paucity of randomized or controlled evidence evaluating detection strategies. In the UK, no recommendation beyond repeated 12-lead ECGs is made.^{14,15} International guidelines either disregard prolonged monitoring¹⁶ or recommend its use in selected patients only,¹⁷ after inpatient continuous electrophysiological monitoring of unspecified modality and duration.

Consequently, clinical practice varies widely, with limited investigation for AF in many stroke centers. In the UK, only 25% of stroke physicians routinely use any form of prolonged monitoring for AF detection, and 40% rely solely

on the admission 12-lead ECG.¹⁸ Stroke units may lack adequate facilities for routine continuous electrophysiological monitoring, and in the absence of automated analysis software systems, the likelihood of AF detection is remote.²² Outpatient management of TIA and minor stroke patients further limits viability of continuous electrophysiological monitoring.

UK standard practice reflects guidelines in using Holter devices for extended monitoring.¹⁸ Systematic review suggests Holter monitoring will identify AF in only an additional 4.6% of patients,¹² no better than detection rates observed in

Table 2. SP Investigations Affording Opportunity for AF Detection Performed to 14 and 90 Days

	SP Group (n=50)	SP-AM Group (n=50)	P Value for Difference in Proportions Between Groups
12-Lead ECG (14 days)			
14 days	16% (7.1%–29.1%)	12% (4.5%–24.3%)	0.56
90 days	28% (16.2%–42.5%)	18% (8.6%–31.4%)	0.23
24-Hour ECG monitoring			
14 days	16% (7.1%–29.1%)	26% (14.6%–40.3%)	0.22
90 days	60% (45.2%–73.4%)	46% (31.8%–60.7%)	0.16
Echo			
14 days	30% (17.9%–44.6%)	42% (28.2%–56.8%)	0.21
90 days	62% (47.2%–75.3%)	54% (39.3%–68.2%)	0.42
Any-duration PAF detected			
14 days	4% (0.0%–13.7%)	12% (4.5%–24.3%)	0.27*
90 days	10% (3.3%–21.8%)	22% (11.5%–36.0%)	0.10
Sustained PAF detected			
14 days	2% (0.0%–10.6%)	8% (2.2%–19.2%)	0.36*
90 days	8% (2.2%–19.2%)	16% (7.2%–29.1%)	0.36*

Values quoted are % (95% CI). Comparison between groups is with difference in 2 proportions. When observed frequencies were low, Fisher exact test (*) was used. A P value of <0.05 was considered statistically significant. CI indicates confidence interval; PAF, paroxysmal atrial fibrillation; SP, standard practice; and SP-AM, standard practice plus additional monitoring.

groups lacking routine monitoring.²⁰ Extending the duration of Holter monitoring should increase detection but consumes more resources.²³

Standard investigations in our trial reflected wider UK practice: 60% of patients had 24-hour Holter monitoring, especially patients with suspected embolic stroke etiology. The AF detection level of 8% in the SP group was comparable with rates reported in the absence of routine monitoring²⁰ or with 24-hour Holter monitoring.¹²

The AM compared very favorably against rates reported for 24-hour Holter monitoring¹² or repeated 12-lead ECGs²⁴ and achieved similar detection rates to extended-duration Holter monitoring,²³ automated software-assisted continuous electrophysiological monitoring,²⁵ and implantable cardiac-event recorders.²⁶ Thus, guideline-based practice underdetects AF. In contrast, we detected sustained PAF episodes that justify anticoagulation in an additional 16% of patients, within 14

days. This allows initiation of treatment during the period when recurrence risk is highest.

In patients with cryptogenic stroke, in whom simple measures have failed to identify any potential cause, invasive and more costly implantable event recorders with their adherent risks of infection may be justified. They offer greatly extended monitoring periods and high detection rates.²⁶ For the majority of patients, however, our trial suggests that a relatively brief duration of noninvasive monitoring may be sufficient for routine application, with 88% of sustained PAF identified within 72 hours. Excellent reporting agreement between treating stroke physicians and the electrocardiology laboratory facilitates immediacy of clinical decisions and could limit costs. A noninvasive strategy that has few technical failures and no adverse events is an attractive option for routine application in unselected acute patients.

Cost-Effectiveness

Our trial was underpowered to examine rates of recurrent ischemic stroke. Extrapolating from UK first stroke incidence,²⁷ our approach could identify an additional 18432 patients with sustained PAF annually in United Kingdom. Assuming an absolute risk reduction of 6%,²¹ switching all the additionally detected sustained PAF patients from antiplatelet to anticoagulant therapy may prevent 1106 recurrent ischemic strokes. Our anticoagulation rate of 75% was high but even using more typical rates of 39%²⁸ and disregarding availability of direct oral anticoagulants, achievable improvements in detection would prevent 431 UK ischemic strokes per annum.

Any-duration AF was also detected in 40% more patients receiving AM. Extrapolating across the United Kingdom, this would identify an additional 46080 patients annually. However, these brief, nonsustained paroxysms of AF are distinct from sustained PAF. The risk they confer is uncertain,^{29,30} and anticoagulant therapy is of unproven value.³¹ Though permanent and paroxysmal AF share an equal risk of stroke,⁸ we need a large-scale prospective study to evaluate the risk associated with these very brief paroxysms of AF that are now readily detected.

The cost per quality-adjusted life year (QALY) gained by outpatient monitoring for AF detection is estimated at only (US)\$13 000.³² This excludes indirect savings (eg, carers' costs) associated with stroke prevention and was based on only a 4.45% increment in AF detection. Our strategy, which more rapidly achieved a 16% increment in sustained AF, will improve cost-effectiveness.

Table 3. AM Tolerability and PAF Detection According to Individual Regime Components

Modality	Completed Satisfactorily	Any-Duration PAF Detected	Sustained PAF Detected
24-Hour 12-lead ECG	84% (70.9%–92.8%)	8% (2.2%–19.2%)	8% (2.2%–19.2%)
72-Hour 12-lead ECG	82% (68.6%–91.4%)	8% (2.2%–19.2%)	8% (2.2%–19.2%)
24-Hour R-test download	94% (83.5%–98.7%)	18% (8.6%–31.4%)	8% (2.2%–19.2%)
72-Hour R-test download	90% (78.1%–96.7%)	38% (24.7%–52.8%)	14% (5.8%–26.7%)
168-Hour R-test download	82% (68.6 - 91.4%)	42% (28.2%–56.8%)	16% (7.2%–29.1%)

Values quoted are % (95% CI) for one proportion. CI indicates confidence interval; and PAF, paroxysmal atrial fibrillation.

Table 4. Differences Between Groups for Detection of Any-Duration PAF, Sustained PAF and Treatment with Anticoagulation at 14 and 90 Days

End Point	SP Group	SP-AM Group	Difference Between Groups	P Value
Any-duration PAF, 14 days	4% (0.0%–13.7%)	44% (30.0%–58.7%)	40% (25.2%–54.8%)	<0.001*
Any-duration PAF, 90 days	10% (3.3%–21.8%)	48% (33.7%–62.6%)	38% (21.8%–54.1%)	<0.001
Sustained PAF, 14 days	2% (0.0%–10.6%)	18% (8.6%–31.4%)	16% (4.7%–27.3%)	<0.05*
Sustained PAF, 90 days	8% (2.2%–19.2%)	22% (11.5%–36.0%)	14% (0.0%–27.7%)	0.09*
AC for any indication, 14 days	0% (0%–5.8%)	18% (8.6%–31.4%)	18% (7.4%–28.6%)	<0.01*
AC for any indication, 90 days	10% (3.3%–21.8%)	26% (14.6%–40.3%)	16% (1.2%–30.7%)	<0.05
AC for AF TE prophylaxis, 14 days	0% (0%–5.8%)	16% (7.2%–29.1%)	16% (5.8%–26.2%)	<0.01*
AC for AF TE prophylaxis, 90 days	6% (1.3%–16.5%)	22% (11.5%–36.0%)	16% (2.8%–29.2%)	<0.05*

Values quoted are % (95% CI). Comparison between groups is with difference in 2 proportions. When observed frequencies were low, Fisher exact test (*) was used. A P value of <0.05 was considered statistically significant. AC indicates anticoagulation; CI, confidence interval; PAF, paroxysmal atrial fibrillation; SP, standard practice; SP-AM, standard practice plus additional monitoring; and TE, thromboembolic.

Limitations

Generalizability of our trial is limited by the size of our sample and its derivation from only 2 centers; however, equipoise was lost after such striking differences were seen at conclusion of the pilot phase, so that we did not extend sampling more widely.

SP investigations in our centers and across the United Kingdom¹⁸ likely lie toward one end of a spectrum of guideline interpretation,^{14–17} across which healthcare funding approaches may exert an influence. However, the detection rate across our sample from Holter monitoring matches prior reports.¹² We did not use echocardiography or other investigations to screen our patients first for etiological mechanisms; however, indiscriminate transthoracic and transesophageal echocardiography offer low returns,³³ and undirected tests are discouraged in our health service.^{15,17}

Our patients had relatively mild stroke or TIA but they potentially have most to gain from expedited AF detection and treatment. Detection rates could be higher among patients with extensive cortical stroke, although many such patients were ineligible because AF was already present.

Technical limitations of the existing R-test device precluded quantification of the total burden of AF. Improved memory and detection algorithms are now available, which could underpin a registry study of stroke recurrence risk in relation to burden of nonsustained AF episodes.

Conclusions

Our trial offers randomized evidence that routine extended monitoring for AF in unselected patients with acute ischemic stroke delivers clinically meaningful and statistically significant improvements in detection and treatment rates versus current guideline-based practice. Noninvasive cardiac-event monitoring should be routinely adopted as the standard of care in all stroke patients who appear to be in sinus rhythm.

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Disclosures

Dr Dawson has received honoraria and speaker fees from Boehringer Ingelheim and Bayer for lectures on anticoagulation treatment for the prevention of cardioembolic stroke. Professor Langhorne has previously received honoraria and expenses to contribute to nonpromotional educational events related to the management of atrial fibrillation. None of these relate to the content of this article. Professor Lees has held the following positions: Chairman of independent data monitoring committee for DIAS trials (Lundbeck); Plasmin (GRIFOLS); ECASS-IV (Boehringer Ingelheim); ICTUS (Ferrer); NEST-3 (Photothera); ATTEST (University of Glasgow); member of independent data monitoring committee for REVASCAT (Covidien); WAKE-UP (EU FP7). He has received speaker fees from Boehringer Ingelheim. He is Director for the NIHR Stroke Research Network.

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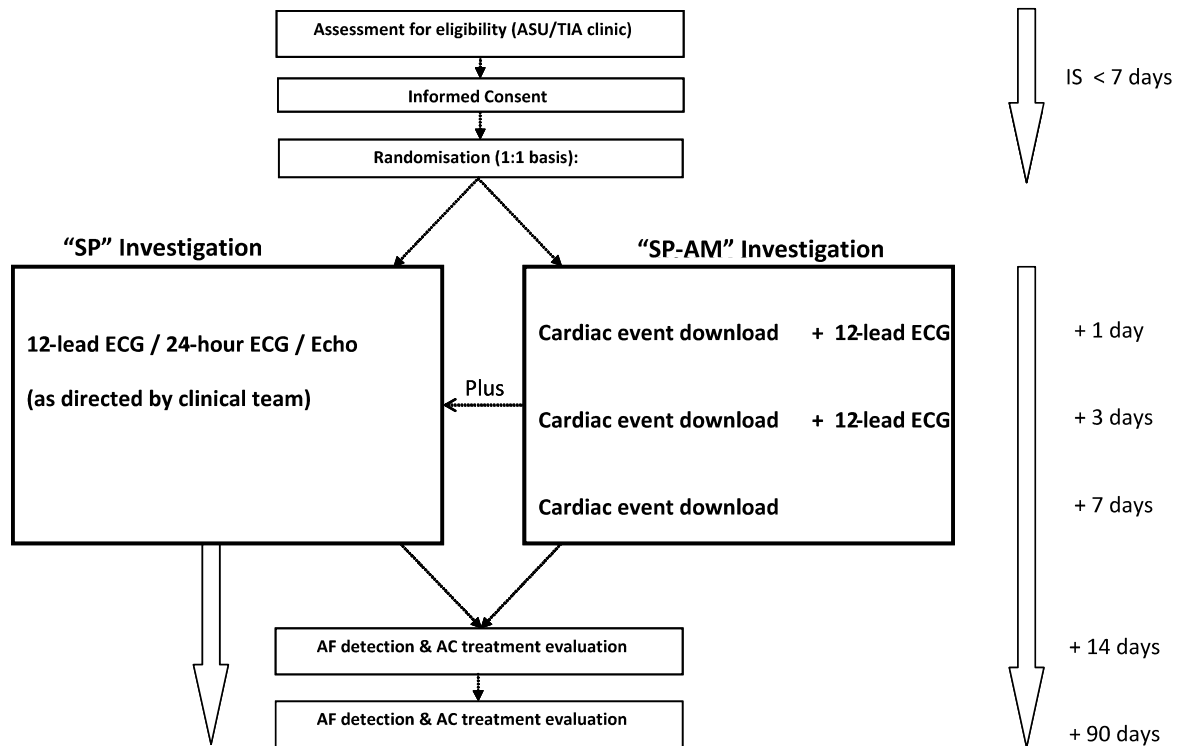
ONLINE SUPPLEMENT

Non-invasive cardiac event monitoring to detect atrial fibrillation after ischaemic stroke: a randomised controlled trial

Table I – Principal eligibility criteria

Inclusion Criteria	Exclusion Criteria
<ol style="list-style-type: none"> 1. Ischaemic Stroke (including transient ischaemic attack (TIA) where symptoms last less than 24 hours). 2. Brain imaging not suggestive of an alternative diagnosis. 3. Sinus rhythm on screening ECG 4. Consent to participate, from patient or approved proxy 5. Randomisation within 7 days of ictus. 	<ol style="list-style-type: none"> 1. Previously documented atrial fibrillation 2. Known durable cardiac source of embolism (e.g. mitral stenosis or left ventricular akinesia), or other absolute indication for indefinite anticoagulation 3. Existing treatment with long term anticoagulation 4. Unlikely to be available for completion of study procedures 5. Clinical decision or expressed refusal to consider long term anticoagulation at a future date if cardio-embolism may be diagnosed 6. Pre-morbid condition or concomitant disease that would render subsequent secondary prevention of stroke inappropriate 7. Cognitive impairment deemed sufficient to compromise capacity to consent or to comply with the protocol. 8. Prisoners.

Figure I – Summary of study design



ASU, acute stroke unit; TIA, transient ischaemic attack; IS, ischaemic stroke, SP, standard practice; SP-AM, standard practice plus additional monitoring; ECG, electrocardiogram; AF, atrial fibrillation; AC, anticoagulation

Figure II - Kaplan-Meier curve illustrating detection of "sustained" PAF episodes to 90 days

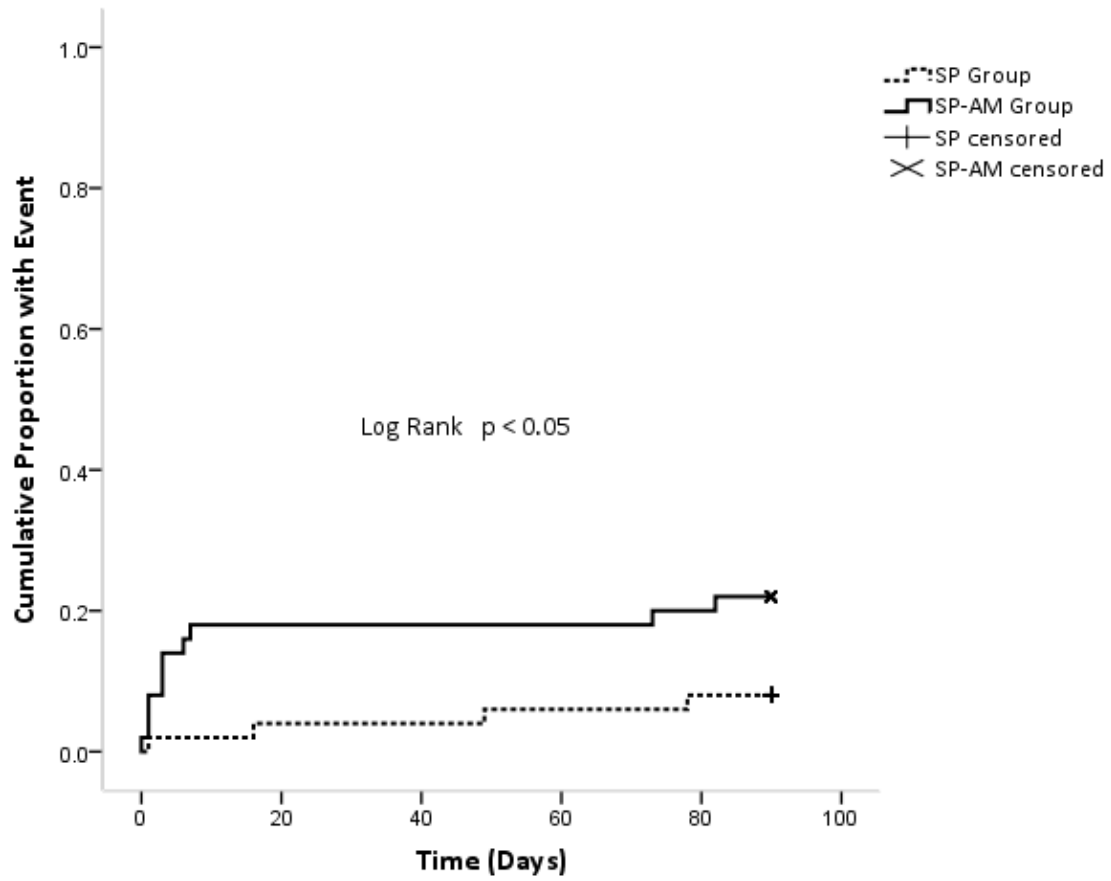


Figure III - Kaplan-Meier curve illustrating detection of “any duration” PAF episodes to 90 days

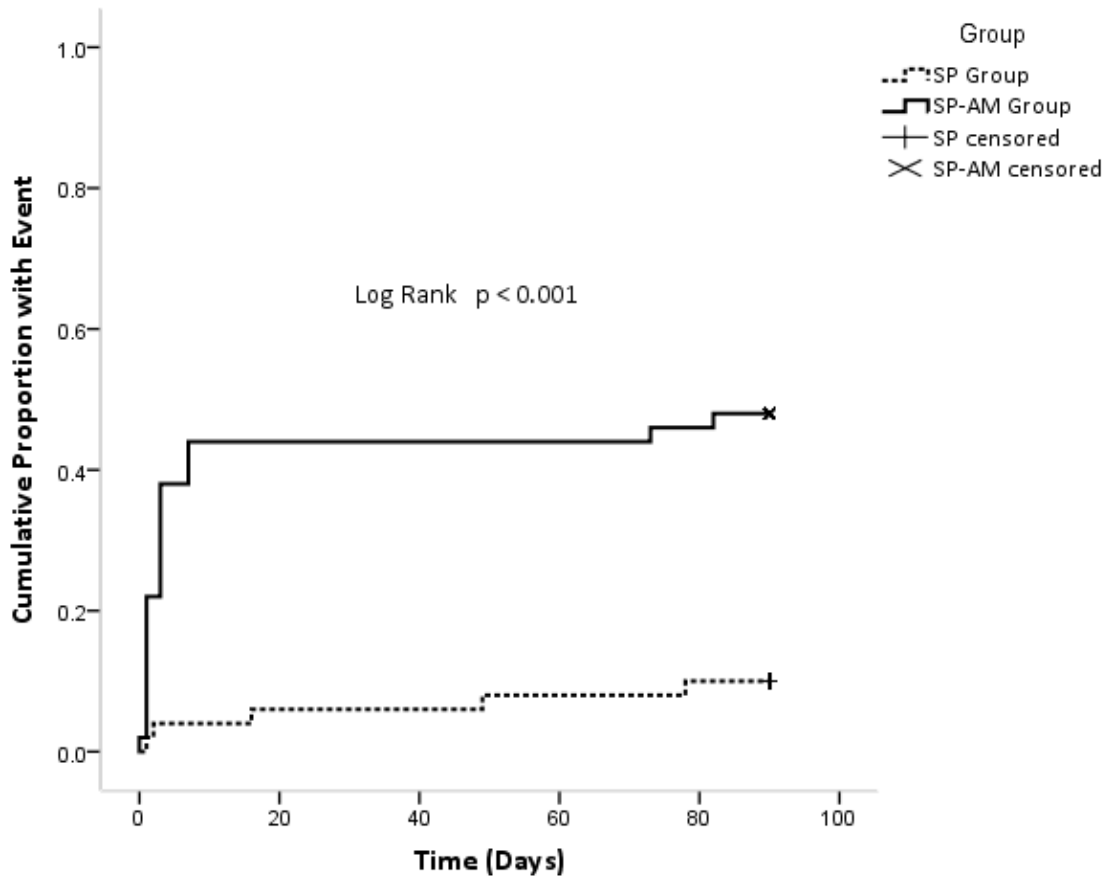


Figure IV - Kaplan-Meier survival curve illustrating initiation of anticoagulation attributable to PAF detection to 90 days

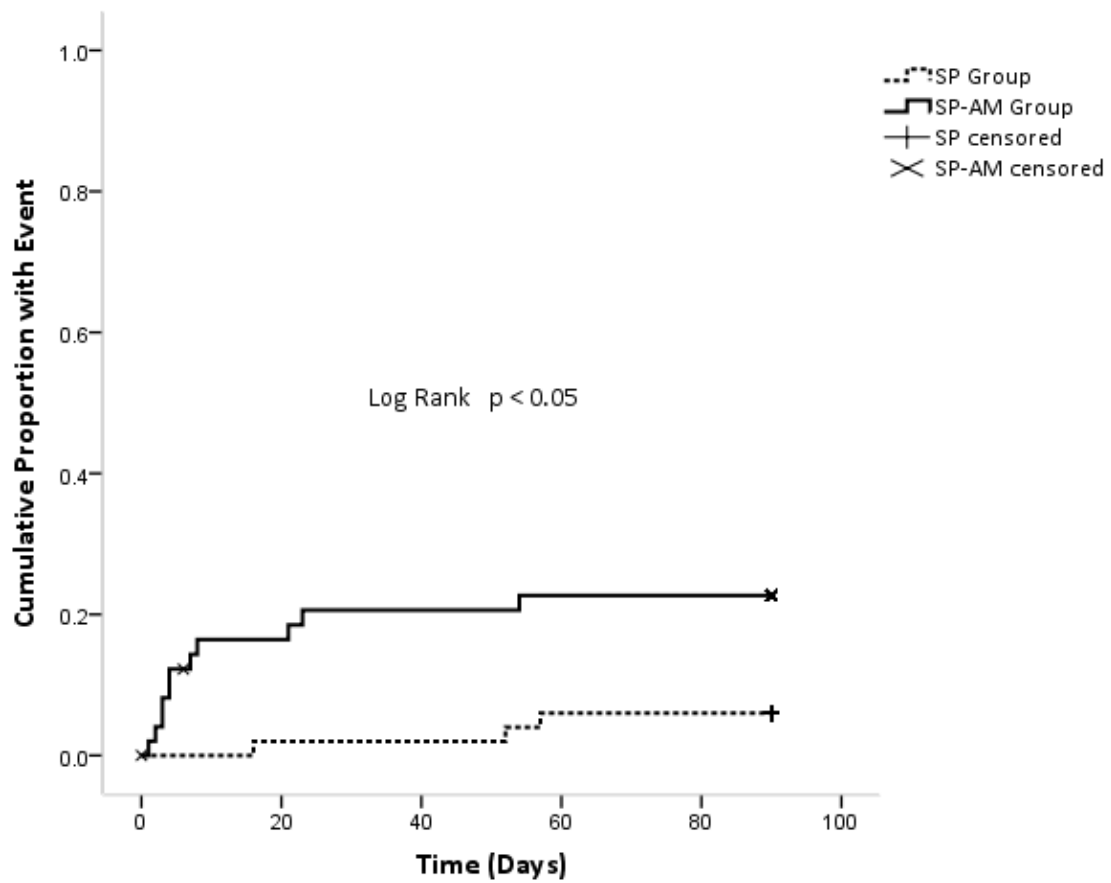


Figure V - Kaplan-Meier survival curve illustrating initiation of anticoagulation for any indication to 90 days

