The incidence of atrial fibrillation detected by implantable loop recorders: a comparison between patients with and without embolic stroke of undetermined source

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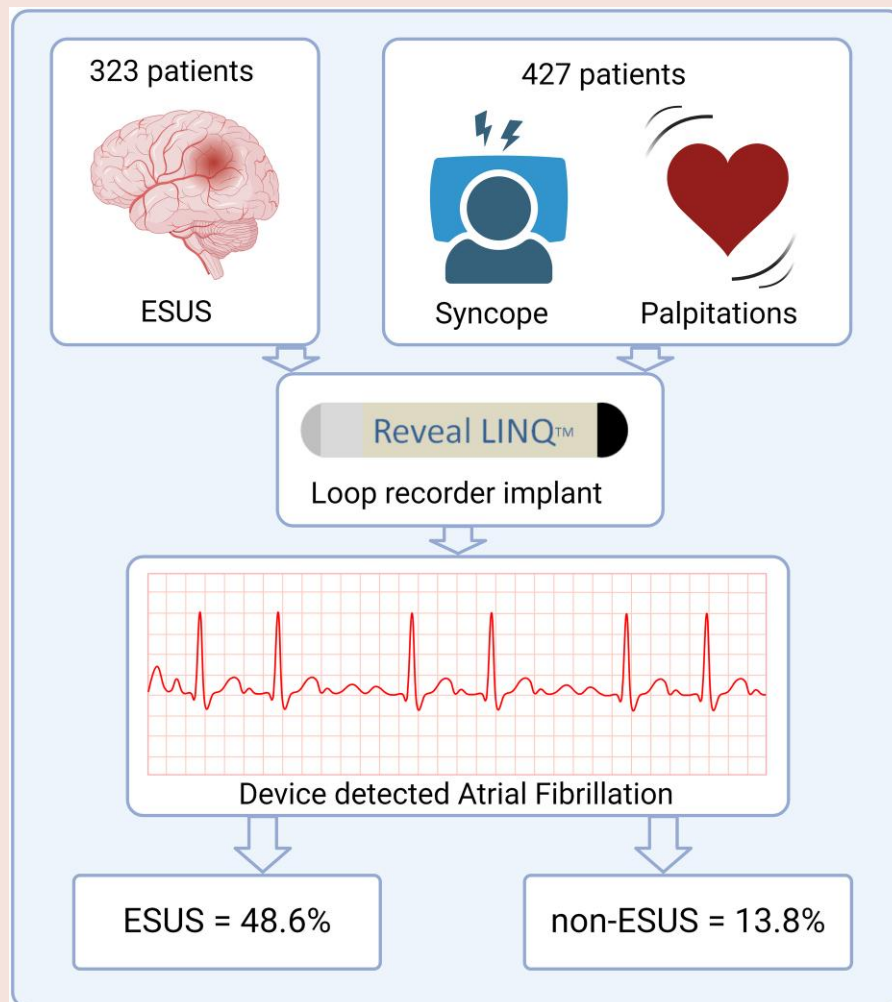|	
Aims	Stroke is the most debilitating outcome of atrial fibrillation (AF). The use of implantable loop recorders increases the detection of AF episodes among patients with embolic stroke of undetermined source. The significance of device-detected AF, or subclinical AF, is unknown. This study aimed to compare the incidence of AF detected by implantable loop recorder in patients with and without embolic stroke of undetermined source.
Methods and results	We retrospectively studied all patients without known AF who were referred to our institution for implantable loop recorder implantation following embolic stroke of undetermined source, syncope, or palpitations from March 2009 to November 2019. The primary endpoint was any detection of AF or atrial flutter by implantable loop recorder. Seven hundred and fifty patients were included and followed up for a mean duration of 731 days (SD 443). An implantable loop recorder was implanted following embolic stroke of undetermined source in 323 and for assessment of syncope, palpitations, or another reason in 427 patients. The incidence of AF was significantly ($P < 0.001$) higher among patients with embolic stroke of undetermined source compared with the non-embolic stroke of undetermined source group; 48.6% vs. 13.8% (for any duration of AF) and 32.2% vs. 12.4% (for AF lasting ≥30 s) both $P < 0.001$. Kaplan–Meier analysis showed significantly higher incidence of AF for incremental durations of AF up to >5.5 h, but not >24 h. This was driven by longest AF durations of <6 min and between 5.5 h and 24 h, suggesting a bimodal distribution. In a multivariable Cox regression analysis, embolic stroke of undetermined source independently conferred an almost 5-fold increase in the hazard for any duration of AF.
Conclusion	The incidence of AF is significantly higher amongst embolic stroke of undetermined source vs. non-embolic stroke of undetermined source patients monitored constantly by an implantable loop recorder. A high number of embolic stroke of undetermined source survivors have short-duration AF episodes. Further work is needed to determine the optimal treatment strategy of these AF episodes in embolic stroke of undetermined source.

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Graphical Abstract

What's new?

- The incidence of atrial fibrillation (AF) is significantly higher in embolic stroke of undetermined source (ESUS) vs. non-embolic stroke of undetermined source (non-ESUS) patients constantly monitored by an implantable loop recorder.
- A large proportion of detected AF in ESUS group was of short duration and significantly higher than the non-ESUS group.
- Patients with ESUS are more likely to have device-detected AF identified during continuous monitoring than other patient cohorts.
- The significance of these short episodes of AF in terms of optimal treatment remains unclear and warrants further investigation.

Introduction

Atrial fibrillation (AF) is a supraventricular arrhythmia characterized by disordered atrial electrical activation, ineffective atrial contraction, and increased risk of thromboembolic stroke. It may be classified as clinical or subclinical AF.[1] Clinical AF is defined by symptomatic or asymptomatic AF on a surface electrocardiogram (ECG) lasting $\geq$30 s.[1] In contrast, subclinical AF and atrial high rate episode (AHRE) refer to individuals with asymptomatic AF in whom a previous diagnosis of clinical AF has not been detected. The AHREs are detected by implantable cardiac devices with an atrial lead and require visual inspection of the device electrogram. Subclinical AF includes either AHRE confirmed to be an atrial arrhythmia [AF, atrial flutter (AFL), or atrial tachycardia] or AF episodes detected by implantable loop recorder (ILR) or wearable monitor, confirmed by visual review of the electrogram or ECG trace.[1] The duration of subclinical AF that is considered significant varies markedly in different studies and ranges from a few seconds to $\geq$24 h.[1–4] Both paroxysmal (pAF) and permanent AF are associated with an increased risk of stroke.[5] Device-detected AF has also been shown to be associated with an increased stroke risk, albeit not as high as that seen in clinical AF.[3,6,7]

Following a diagnosis of embolic stroke of undetermined source (ESUS), AF is detected in a significant proportion of patients when monitored constantly with an ILR.[8–10] Several studies have shown that ILRs

have a higher diagnostic yield for detecting subclinical AF and are superior to routine care, including 7-day monitoring.[10,11] The Cryptogenic Stroke and Underlying AF (CRYSTAL AF) study showed that AF lasting >30 s was detected in 30% of cryptogenic stroke survivors after 3 years of monitoring with an ILR.[8] Similarly, we reported that in patients with unexplained ischaemic stroke, AF was detected by ILR in 25.5%.[9] Studies have suggested that targeting of individuals with predictors of future AF, such as supraventricular premature beats on Holter monitoring or multi-modality approaches, may further improve the detection rate of AF on ILR.[12,13]

However, it is not clear whether short episodes of AF require lifelong anticoagulation. Some studies suggest that only episodes of subclinical AF of over 24 h are associated with an increased risk of stroke or systemic embolism.[3] It is also unknown whether these short episodes seen post-ESUS also occur at a similar frequency in other populations undergoing loop recorder implantation.

This study aimed to compare the incidence of AF, as detected by an ILR, in ESUS survivors with patients receiving an ILR for a different reason in a large single-centre cohort.

Methods

This observational study was approved by the United Kingdom Health Research Authority (16/NW/0527). Institutional approval was given by Cambridge University Hospitals NHS Foundation Trust. The North West Preston Research Ethics committee waived the need for signed consent in view of the retrospective nature of the study. The study is registered at ClinicalTrials.gov (NCT02843516) and complied with the 1975 Declaration of Helsinki for research. Data are available upon reasonable request to the corresponding author for research purposes.

Study population

All adult patients referred for ILR implantation from March 2009 to November 2019 were included in our study. Participants were split into two groups:

- Those who had an embolic stroke of undetermined source and prolonged monitoring who required to screen for AF as the cause of ESUS (ESUS group)
- Those without a history of ESUS, who required monitoring with an ILR for any other reason (such as syncope or palpitations; non-ESUS group)

The diagnosis of ESUS and subsequent referral for prolonged monitoring was performed by a stroke physician or neurologist when extensive investigations with short-term cardiac rhythm monitoring, blood tests, and cardiac and neck imaging failed to show a clear cause of the stroke. In our centre, only ESUS patients in whom the stroke physician felt there was a benefit to AF detection, i.e. they were not already on anticoagulation, and were safe to be commenced on anticoagulation were referred for ILR implantation.

Patients with any history of AF or AFL were excluded from our study.

Clinical variables

Demographic and anthropometric data were collated from the medical notes, along with history of tobacco use and alcohol consumption. Comorbidities, medications, and blood results during the admission due to the index event (stroke, syncope, or palpitations) or review at the outpatient clinic were recorded. CHA_2DS_2-VASc and HASBLED scores were calculated for each patient.

Outcomes

The primary endpoint was newly detected AF or AFL on ILR in the whole population and separately in ESUS and non-ESUS populations.

Supplementary material online, *Table S1*, details the different types of ILR were implanted and programmed. Interrogation of ILR took place every month in patients with ESUS and every 3 months in the non-ESUS patients, or any time there was a patient-activated episode in either group.

Until 2012, ILRs were interrogated in-person in the pacing clinic. Since then, patients transmitted device data remotely via the Medtronic CareLink™ monitoring network.

In our study, we considered AF and AFL together, as the thromboembolic risk, and therefore, the need for anticoagulation is similar.[14,15] Two cardiologists, with a specialist interest in cardiac arrhythmias and holding European Heart Rhythm Association (EHRA) accreditation (P.A.C. and P.J.P.) examined all auto-triggered and patient-triggered ILR episodes to verify presence of AF/AFL. A third cardiologist (V.S.V.) arbitrated if there was no consensus. The longest AF episode for each patient was further classified by duration: < 30 s, ≥30 s, ≥6 min, ≥5.5 h, and ≥24 h.

The different cut-off points of AF duration were chosen based on current literature, published recommendations about duration of AF detected by implantable cardiac devices, and risk of stroke.[2,3,5,7,8,16] The 30-s duration was based on the 2017 EHRA expert consensus statement.[17] The 6-min duration reflects the duration used by the LOOP (implantable loop recorder detection of atrial fibrillation to prevent stroke) study[18] and was subsequently utilized in the ARTESIA (Apixaban for Stroke Prevention in Subclinical Atrial Fibrillation) and NOAH-AFNET 6 (Anticoagulation with Edoxaban in Patients with Atrial High-Rate Episodes) studies.[19,20] The 5.5-h duration was identified by the TRENDS (The relationship between daily atrial tachyarrhythmia burden from implantable device diagnostics and stroke risk) study.[21] The significance of the 24-h duration of AF as a risk for stroke was seen in a substudy of the ASSERT (Subclinical Atrial Fibrillation and the Risk of Stroke) study.[3]

As discussed in Supplementary material online, *Table S1*, the Linq and Reveal XT devices had specific AF detection algorithms. This algorithm utilizes a combination of R-R interval analysis and P-wave 'evidence' scoring, to analyse 2-min intervals of the rhythm recording. In addition, all loop recorders were programmed to detect any tachycardia over 150 b.p.m., any bradycardia with a heart rate less than 40 b.p.m., and any pause of duration greater than 3 s. Atrial fibrillation was identified based on events triggered by the AF algorithm, device alerts due to tachycardia, bradycardia, pauses, or patient-triggered events.

Additionally, we recorded time to first AF detection in both groups.

Statistical analysis

Continuous variables were reported as means [standard deviation (SD)] for parametric data and median [interquartile range (IQR)] for non-parametric data after testing for normality. Categorical variables were reported as proportions. Between groups, two-tailed comparisons were made using independent *t*-test for parametric data and Mann–Whitney *U* test for non-parametric data. Categorical variables were compared using χ^2 test and Fisher's exact test if counts were <5. A $P < 0.05$ was considered statistically significant. Time-to-event analysis was conducted using Kaplan–Meier curves and the log-rank test. Multivariable Cox regression analysis, using the backward conditional method when events outnumbered variables and the forward conditional method when events were less than variables, was utilized to assess for independent risk predictors for AF of specific durations, thus accounting for potential confounders. All analyses were performed using IBM SPSS Statistics for Windows (version 27.0. Armonk, NY) and MedCalc® Statistical Software (version 20.218, Ostend, Belgium).

Results

Study population

Between March 2009 and November 2019, 824 patients were referred to our department for ILR implantation (*Figure 1*). Out of these, 74 were excluded from the study, mostly due to having a known history of AF. In total, 750 patients were included in the study, of whom 323 had an ILR implanted for investigation of unexplained stroke and 427 for investigation of syncope, palpitations, or other reason.

The mean follow-up duration of the whole study population was 731 days (SD 443) and not significantly different between ESUS [741 days (SD 444)] and non-ESUS [723 days (SD 442)] groups ($P = 0.574$). Among ESUS patients ($n = 323$), 1 (0.3%) had a Confirm loop recorder, 1 (0.3%) a Reveal DX, 155 (48.0%) a Reveal XT, and 166 (51.4%) a Reveal Linq implanted. Among the non-ESUS population ($n = 427$),
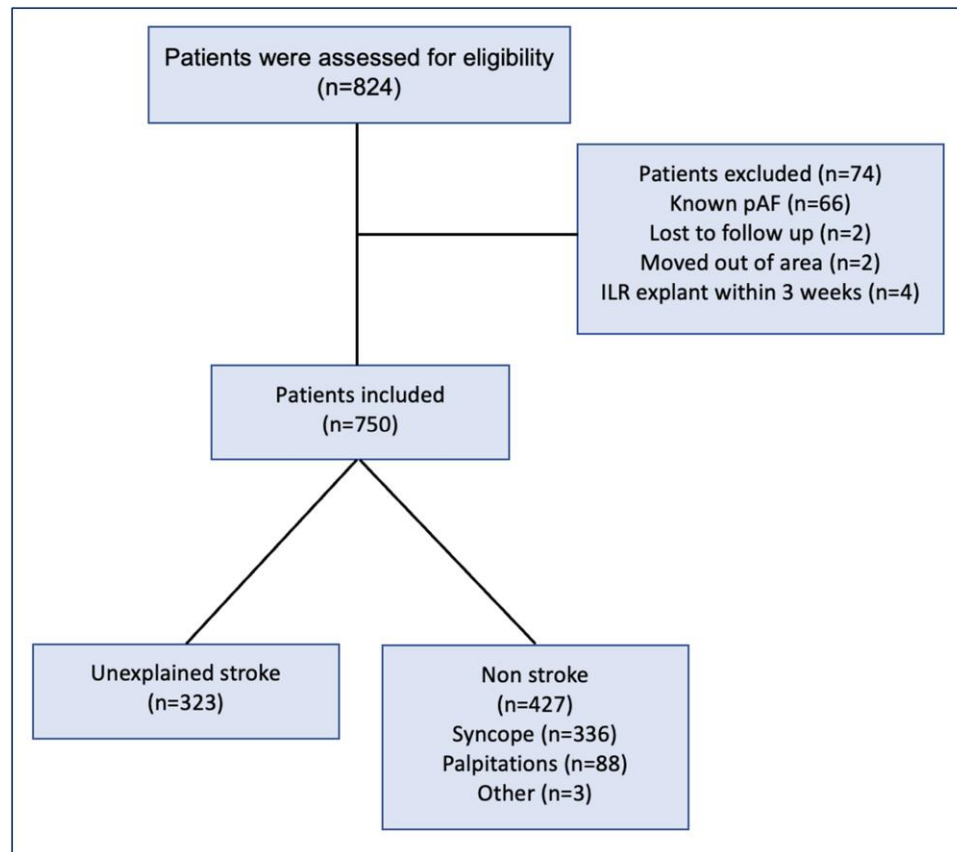
Figure 1 Study protocol. A total of 824 patients were screened for eligibility with 750 selected for inclusion. Most exclusion was due to prior history of atrial fibrillation with a small proportion due to being lost to follow-up. The unexplained stroke (embolic stroke of undetermined source) group comprised 323 patients, whist the non-stroke (non-embolic stroke of undetermined source) group had 427 patients, the majority of whom were being worked up for syncope.

6 (1.4%) had a Confirm loop recorder, 172 (40.3%) a Reveal DX, 75 (17.6%) a Reveal XT, and 174 (40.8%) a Reveal Linq implanted.

Patient characteristics by group are presented in *Table 1*. Patients with ESUS were younger compared with the non-ESUS population (mean age 54.7 years vs. 58.6 years, $P = 0.002$). There were more female patients in the non-ESUS group (55.3% vs.39.0%, $P < 0.001$). Non-ESUS patients had significantly higher incidences of coronary artery disease (CAD), asthma, and chronic obstructive pulmonary disease, while more ESUS patients were current smokers. Patients with ESUS had greater heights and weights, but body mass index (BMI) did not differ significantly between the two groups. The CHA_2DS_2-VASc and HASBLED scores were both significantly higher among the ESUS group.

Detection of atrial fibrillation/atrial flutter

Table 2 shows the incidence of AF/AFL of sequentially increasing longest durations between the ESUS and non-ESUS groups.

Atrial fibrillation/AFL was significantly more common in the ESUS group at all durations except for >24 h.

The median time to detection across the whole population was 180 days (IQR 52–464) with similar times in both the ESUS [182 days (IQR 61–481)] and non-ESUS [172 days (IQR 45–411)] groups ($P = 0.764$). Among patients with AF/AFL of any duration, 50.3% of ESUS and 50.9% of the non-ESUS patients had the first episode of AF/AFL

detected within 6 months of monitoring. The rest had AF/AFL detected after 6 months of monitoring.

The incidence of AF/AFL of any duration increased with time in both ESUS and non-ESUS populations (*Figure 2*), but diagnostic yield tended to plateau at around 3 years of follow-up.

The majority of AF/AFL episodes were detected by standard tachycardia algorithm (49.54%) in the entire study population. Tachycardia detection remained the most useful method even in patients with a Reveal Linq, where 45.5% had AF/AFL detected using tachycardia sensors and 18.8% using the novel AF detection algorithm. Of the patients who had AF detected by the tachycardia algorithm (which is programmed in our centre for heart rates greater than 150 b.p.m.), 71.4% of episodes were over 170 b.p.m. Additionally, out of the 216 patients with AF/AFL, only 26 had symptomatic patient-activated episodes (12.0%). A detailed summary of the AF/AFL detection method by different types of ILR is presented in Supplementary material online, *Table S2*.

Duration of atrial fibrillation and its associated group characteristics

Table 3 shows the percentage of AF/AFL of different durations among the whole population and separately in patients with and without ESUS newly diagnosed with AF/AFL.

Table 1 Baseline characteristics among the entire population and separately in embolic stroke of undetermined source and non-embolic stroke of undetermined source populations

	All (750)	ESUS (323)	Non-ESUS (427)	P-value
Age (years), mean (SD)	56.9 (17.4)	54.7 (14.8)	58.6 (18.9)	**0.002**[a]
Age 65–74 years, n (%)	151 (20.1)	59 (18.3)	92 (21.5)	0.267[b]
Age ≥75 years, n (%)	124 (16.5)	30 (9.3)	94 (22.0)	**<0.001**[b]
Female, n (%)	362 (48.3)	126 (39.0)	236 (55.3)	**<0.001**[b]
CCF, n (%)	8 (1.1)	1 (0.3)	7 (1.6)	0.147[c]
HTN, n (%)	295 (39.3)	131 (40.6)	169 (39.6)	0.551[b]
DM, n (%)	84 (11.2)	38 (11.8)	46 (10.8)	0.670[b]
CAD, n (%)	117 (15.6)	22 (6.8)	95 (22.3)	**<0.001**[b]
DVT, n (%)	16 (2.1)	6 (1.9)	10 (2.3)	0.649[b]
PE, n (%)	19 (2.5)	8 (2.5)	11 (2.6)	0.932[b]
COPD, n (%)	43 (5.7)	9 (2.8)	34 (8.0)	**0.003**[b]
Asthma, n (%)	78 (10.4)	20 (6.2)	58 (13.6)	**0.001**[b]
Cancer, n (%)	62 (8.3)	22 (6.8)	40 (9.4)	0.208[b]
CHA_2DS_2-VASc, median (IQR)	3 (1, 4)	3 (3, 4)	2 (1, 3)	**<0.001**[d]
HASBLED, median (IQR)	2 (1, 3)	2 (2, 3)	1 (0, 2)	**<0.001**[d]
BMI (kg/m^2), median (IQR)	27.2 (24.2, 30.9)	27.1 (24.5, 30.3)	27.3 (24.0, 31.4)	0.624[d]

Statistically significant differences have been highlighted in bold.
CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; ESUS, embolic stroke of undetermined source; g, gram; Hb, haemoglobin; HTN, hypertension; IQR, interquartile range; kg, kilogram; l, litre; m, metre; m^2; metre squared; min, minute; ml, millilitre; mmHg, millimetres of mercury; PE, pulmonary embolism; SD, standard deviation; SBP (systolic blood pressure).
[a]Student's independent t-test.
[b]χ^2 test.
[c]Fisher's exact test.
[d]Mann–Whitney U test.

Table 2 Detection of atrial fibrillation of different durations among embolic stroke of undetermined source and non-embolic stroke of undetermined source populations

	All (750)	ESUS (323)	Non-ESUS (427)	P-value
AF of any duration, n (%)	216 (28.8)	157 (48.6)	59 (13.8)	**<0.001**[a]
AF ≥ 30 s, n (%)	157 (20.9)	104 (32.2)	53 (12.4)	**<0.001**[a]
AF ≥ 6 min, n (%)	86 (11.5)	48 (14.9)	38 (8.9)	**0.011**[a]
AF ≥ 5.5 h, n (%)	34 (4.5)	22 (6.8)	12 (2.8)	**0.009**[a]
AF ≥ 24 h, n (%)	9 (1.2)	6 (1.9)	3 (0.7)	0.184[b]

Statistically significant differences have been highlighted in bold.
AF, atrial fibrillation; ESUS, embolic stroke of undetermined source; h, hours; min, minutes; s, seconds.
[a]χ^2 test.
[b]Fisher's exact test.

Among patients who had AF/AFL detected by the ILR, one-third of ESUS survivors had a longest duration of AF/AFL < 30 s vs. 10% in non-ESUS population (P < 0.001). More than one-third (35.7%) of ESUS patients had AF/AFL lasting between 30 s and 6 min vs. 25.4% of the non-ESUS population with AF (P = 0.153). The other 30.6% of ESUS patients newly diagnosed with AF/AFL had durations lasting >6 min vs. 64.4% of the non-ESUS group (P < 0.001).

Time-to-event analysis

Survival analysis utilizing Kaplan–Meier curves between ESUS and non-ESUS patients was conducted (Figure 2) for varying durations of AF given the uncertainy in duration significance. Comparisons were made using the log-rank test (Table 4). When considered as incremental AF durations, ESUS patients had significantly less AF survival than non-ESUS patients up to longest AF duration of >5.5 h. Atrial fibrillation duration of >24 h was numerically higher, but not significantly different, in ESUS patients.

When the analysis is conducted as AF duration intervals (Table 4), a bimodal distribution of longest AF duration was identified. Patients with ESUS had more 30-s to 6-min and 5.5–24-h durations of AF/AFL. There was no significant difference identified for AF duration intervals between 6 min and 5.5 h.

Multivariable Cox regression analysis

To adjust for potential confounding, multivariable Cox regression analysis was conducted with the previously identified patient demographics
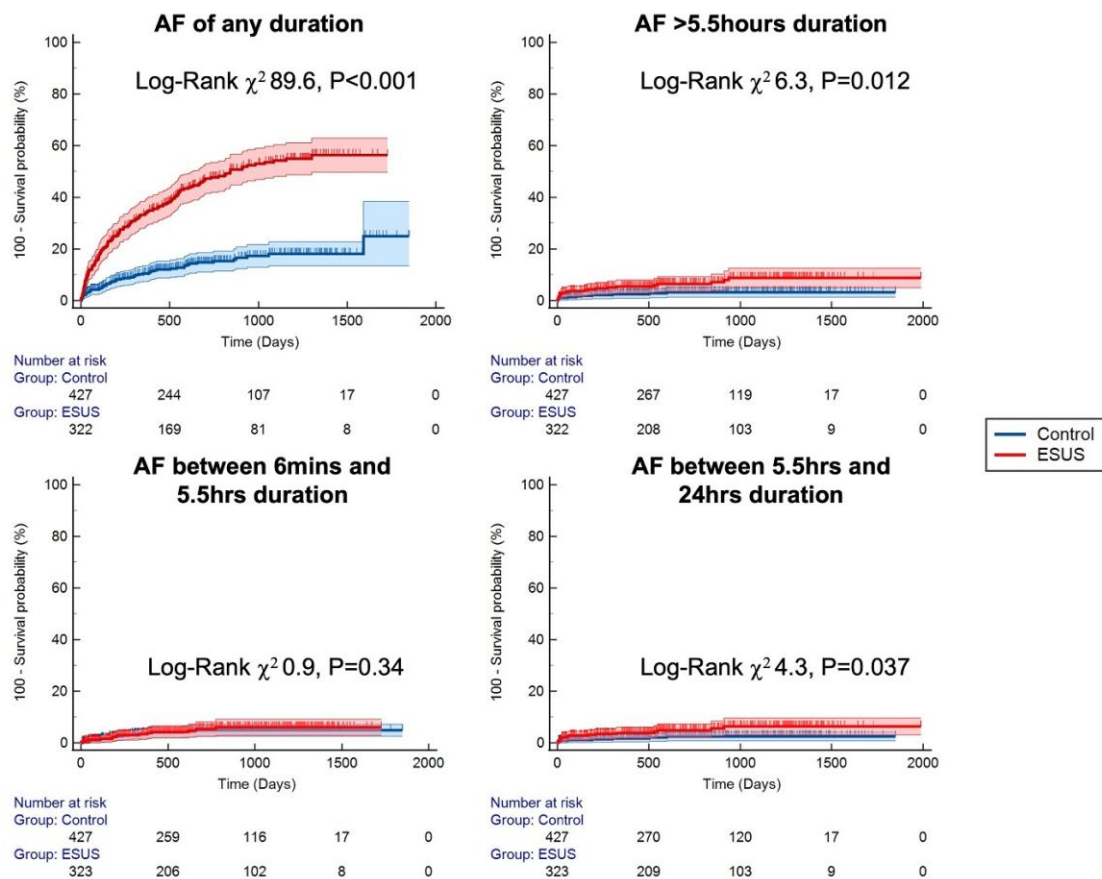
Figure 2 Survival analysis using Kaplan–Meier curves between the non-embolic stroke of undetermined source (control) and embolic stroke of undetermined source (ESUS) groups with 95% confidence intervals shown in respective shading. *Top left*—shows a significant separation between embolic stroke of undetermined source and non-embolic stroke of undetermined source groups for atrial fibrillation/atrial flutter of any duration. Significance persists (*top right*) when longest duration of atrial fibrillation/atrial flutter is >5.5 h albeit with a marked reduction in curve separation. When considered as intervals of atrial fibrillation/atrial flutter duration, there is no difference (*bottom left*) between groups with 6-min to 5.5-h longest duration. However, there is a small but significant difference (*bottom right*) between 5.5 and 24 h.

Table 3 Number of patients with atrial fibrillation according to longest episode among patients newly diagnosed with atrial fibrillation

	All (216)	ESUS (157)	Non-ESUS (59)	*P*-value
AF < 30 s, *n* (%)	59 (27.3)	53 (33.8)	6 (10.2)	**<0.001**[a]
AF 30 s–6 min, *n* (%)	71 (32.9)	56 (35.7)	15 (25.4)	0.153[a]
AF 6 min–5.5 h, *n* (%)	52 (24.1)	26 (16.6)	26 (44.1)	**<0.001**[a]
5.5–24 h, *n* (%)	25 (11.6)	16 (10.2)	9 (15.3)	0.300[a]
≥24 h, *n* (%)	9 (4.2)	6 (3.8)	3 (5.1)	0.707[b]

Statistically significant differences have been highlighted in bold.
AF, atrial fibrillation; ESUS, embolic stroke of undetermined source; h, hour; min, minute; s, second.
[a]χ^2 test.
[b]Fisher's exact test.

for each AF duration interval category (*Table 5*). Embolic stroke of undetermined source was identified as the strongest independent risk factor in AF of any duration, 30-s to 6-min and 5.5–24-h duration with hazard ratios all >3. Monitoring duration was significant in all AF

duration categories, with a small negative association, likely reflecting survivor bias with patients longest monitored at follow-up being less likely to have an event. Established AF risk factors including BMI, age, and history of cancer were identified for short-to-intermediate

Table 4 Log-rank values for atrial fibrillation occurrence of varying duration in Kaplan–Meier analysis between embolic stroke of undetermined source and control groups

AF duration category	χ^2 value	P-value
Any	89.61	<0.001*
<30 s	55.36	<0.001*
>30 s	36.72	<0.001*
>6 min	5.33	0.021*
>1.5 h	4.98	0.026*
>5.5 h	6.26	0.012*
>24 h	1.92	0.165
30 s–6 min	38.90	<0.001*
6 min–1.5 h	0.15	0.701
6 min–5.5 h	0.91	0.34
1.5–5.5 h	0.11	0.744
5.5–24 h	4.33	0.037*

AF, atrial fibrillation.
*P < 0.05.

Table 5 Multivariable cox regression models for the occurrence of atrial fibrillatiom with varying duration (total $n = 750$)

	HR	95% CI for HR	P-value
AF of any duration, 216 events			
ESUS	4.948	3.587–6.825	<0.001*
Monitoring duration (days)	0.998	0.997–0.998	<0.001*
Age (years)	1.029	1.019–1.04	<0.001*
Cancer	1.492	0.964–2.309	0.073
BMI (kg/m^2)	1.025	0.996–1.054	0.09
DVT	0.363	0.112–1.175	0.091
AF 30-s to 6-min duration, 71 events			
ESUS	5.191	2.844–9.472	<0.001*
Monitoring duration (days)	0.998	0.997–0.999	<0.001*
BMI (kg/m^2)	1.070	1.022–1.120	0.004*
Cancer	2.424	1.203–4.885	0.013*
COPD	2.308	0.973–5.476	0.058
AF 6-min to 5.5-h duration, 52 events			
Monitoring duration (days)	0.998	0.997–0.999	0.001*
Cancer	2.424	1.160–5.066	0.019*
Age (years)	1.023	1.003–1.043	0.021*
AF 5.5–24-h duration, 25 events			
Monitoring duration (days)	0.998	0.996–0.999	0.001*
ESUS	3.111	1.300–7.447	0.011*
Age (years)	1.038	1.007–1.070	0.017*
AF > 24-h duration, 9 events			
HTN	10.261	1.261–83.513	0.030*
Monitoring duration (days)	0.998	0.996–1.000	0.045*

AF, atrial fibrillation; BMI, body mass index; CI, confidence intervals; COPD, chronic obstructive pulmonary disease; DVT, deep vein thrombosis; ESUS, embolic stroke of undetermined source; HR, hazard ratio; HTN, hypertension.
*P < 0.05.

durations of AF. A history of hypertension was the main significant risk factor for longer duration (>24 h) of AF.

Discussion

The present study demonstrates that AF, particularly short-duration pAF, is frequently detected among ESUS patients receiving prolonged cardiac monitoring by an ILR. The incidence of AF of any duration in the ESUS population was significantly higher compared with the non-ESUS population (48.6% vs. 13.8%, P < 0.001, and remained greater for longest episodes of AF lasting ≥30 s, ≥6 min, and ≥5.5 h. The incidence of AF with longest duration lasting ≥24 h was not statistically higher in this study of 750 patients. When categorized by duration intervals, rather than sequentially higher durations, a bimodal distribution was demonstrated with ESUS being a strong, independent predictor for AF of longest duration 30 s to 6 min, as well as 5.5 to 24 h.

It is worth noting that the non-ESUS control group in this study was older and more comorbid than the ESUS group, with higher baseline prevalence of coronary disease, chronic obstructive pulmonary disease. These are known risk factors for AF,[22–24] and therefore, it would be expected that the non-ESUS group might have more AF than an entirely healthy cohort. Despite this, the ESUS is still found to have higher rates of AF.

The incidence of AF of any duration in ESUS survivors in our study was higher compared with the study by Asaithambi et al. who examined the incidence of AF of any duration among 234 patients with unexplained stroke. They reported an AF detection rate by ILR of 29%. This difference could be explained by the shorter follow-up (median 536 days) compared with our study (median 691 days). They also excluded patients with severe disabling strokes, and many of their patients elected not to undergo ILR implant, potentially leading to self-selection biases acknowledged by the authors as a limitation. The incidence of AF lasting ≥30 s in our stroke cohort (32.2%) was similar to that of CRYSTAL AF (30%).[8] However, it was slightly higher than previously reported by our group (25%) when 51 patients with cryptogenic stroke were monitored with an ILR. This difference can be explained by the shorter follow-up (mean follow-up 229 vs. 741 days).[9]

In our study, participants were implanted with four different ILR devices with 99.4% of stroke patients receiving a Reveal XT or Linq vs. 58.3% for the non-stroke participants. Comparing just patients with a Reveal XT or Linq (570 patients), we found consistent results, with the incidence of AF being significantly higher in the ESUS patients compared with the non-ESUS group (48.6% vs. 14.9%, P < 0.001). Results therefore appear generalizable to different ILR vendors and detection algorithms.

Although there are a number of studies in the literature about AF incidence by an ILR in the ESUS population,[25] data about AF incidence in the general population are limited. Four studies examined the incidence of AF detected by ILR in high-risk populations. The Asymptomatic atrial fibrillation and Stroke Evaluation in pacemaker patients and the atrial fibrillation Reduction atrial pacing Trial (ASSERT) II reported a 35.2% incidence of AF ≥ 5 min among 256 patients ≥65 years old and one of the following: CHA_2DS_2-VASc score of ≥2, sleep apnoea, obesity, left atrial enlargement, or increased serum N-terminal pro–B-type natriuretic peptide (NT-pro BNP).[26] Similarly, the Predicting Determinants of AF or AFL for Therapy Elucidation in Patients at Risk for Thromboembolic Events (PREDATE AF) found 22.45% incidence of AF ≥ 6 min at 18 months of follow-up among 245 patients with CHA_2DS_2-VASc ≥ 2 (mean 4.6) and mean age 74.3.[27] The REVEAL AF study reported a higher incidence of AF ≥ 6 min at 18 months (29.3%) which increased to 40% at 30 months. However, they included patients with $CHADS_2$ ≥ 3 or 2 with one additional risk factor (CAD, renal impairment, sleep apnoea, or chronic obstructive pulmonary disease).[28] Finally, the randomized controlled trial, the LOOP study, reported that AF ≥ 6 min was detected in 31.8% out of

the 1501 study participants aged ≥70 years and with ≥1 of hypertension, diabetes mellitus, previous stroke, or HF, who had undergone ILR implantation, over a median 64.5 months of follow-up.[29] The reported incidence of AF > 6-min duration is much higher than our findings; however, the inclusion criteria are known to be risk factors for AF, therefore resulting in population enrichment compared with our real-world all-comers results.

Frontera et al., in contrast, looked at the incidence of AF > 30 s among 200 patients undergoing ILR implantation to investigate syncope or palpitations without any selection for AF risk criteria. They reported an AF incidence of 21%, which is higher than our reported incidence of AF > 30 s in the non-ESUS population (12.4%).[30] Comparing their population to our non-ESUS population, a higher proportion of their patients had hypertension, had hyperlipidaemia, had lower eGFR, were current smokers, or were older, which could partially explain the higher incidence of AF.

Another interesting finding of our study is that among patients with AF, a significantly higher proportion of ESUS patients had AF episodes < 6 min (69.4%), compared with the non-ESUS population (35.6%). The incidence of new persistent AF was low in this study. It is well accepted that pAF is more likely to be driven mechanistically by the pulmonary veins, as compared with other atrial substrates. The present study does not inform directly on AF mechanism, but it might be reasonable to hypothesize that the pulmonary veins are more active in ESUS survivors compared with the general cardiology population resulting in higher burdens of short-duration AF.

One of the key questions in the clinical management of ESUS is the significance of device-detected AF in guiding anticoagulation decisions. Despite several recent studies, it remains unclear whether anticoagulation for short AF episodes is beneficial in reducing thromboembolic risk.[31] A Spanish study, showed that anticoagulating even short episodes of AF results in a decrease of stroke recurrence.[32] The investigators randomized 191 ESUS patients aged 50–89 years (mean 75.6) to either conventional monitoring or ultra-early monitoring using ILR following ESUS. AF lasting >1 min was detected in 58.5% of patients in the ILR group vs. 21.3% in the usual care group during 30 ± 10 months of follow-up. Consequently, anticoagulation therapy was initiated in 65.5% in the ILR arm vs. 37.6% of patients in the control arm. This led to a much lower stroke recurrence rate in the ILR arm, 3.3% vs. 10.9% in the conventional arm, suggesting that anticoagulation in short duration AF episodes is beneficial.

In contrast, the LOOP study randomized 6004 individuals aged 70–90 years with at least one risk factor for stroke to a 1:3 ratio of ILR monitoring or usual care. Anticoagulation was commenced if AF lasted ≥6 min was detected. During a mean follow-up of 64.5 months, AF was detected in 31.8% in the ILR group vs. 12.2% in the control group. Despite a three-times increase in the anticoagulation therapy in the ILR arm (29.7% vs. 13.1%), there was no significant reduction in the risk of stroke or systemic embolism (P = 0.11). However, the LOOP investigators examined patients with risk factors for stroke, rather than patients with unexplained stroke—a group recognized to be at higher thromboembolic risk.[33]

A post hoc substudy of the LOOP study has been performed, which looked to explore the impact of rhythm monitoring for AF screening, on severity and aetiology of subsequent stroke.[34] Three main findings were made with respect to rhythm monitoring and AF—that ILR screening was associated a statistically non-significant 31% reduction in disabling or lethal stroke; that patients with AF detected by any means had objectively more severe strokes; and that there appeared to be no benefit on stroke severity to AF screening in individuals with prior stroke. It was suggested that the study might have been underpowered to assess the reduction of severe stroke.

Two major trials have recently been published that assess the potential role of anticoagulation in patients with short episodes of subclinical AF in non-ESUS populations. ARTESIA suggested that in patients with device-detected subclinical AF of durations between 6 min and 24 h, anticoagulation reduced stroke risk but at the cost of increased risk of bleeding when compared with aspirin therapy.[19] In contrast, NOAH-AFNET 6 did not show any beneficial effect for edoxaban with respect to stroke reduction in patients with AHRE > 6 min compared with placebo but was terminated early due to futility and safety concerns due to increased bleeding risk.[20] A study-level meta-analysis by McIntyre et al.[35] concluded that combining both of these large RCTs suggested that therapeutic anticoagulation was associated with a 32% risk reduction in ischaemic stroke, albeit with a 62% increased risk of bleeding. In ESUS populations, neither NAVIGATE-ESUS (Rivaroxaban for Stroke Prevention after Embolic Stroke of Undetermined Source)[36] or RESPECT-ESUS (Dabigatran for Prevention of Stroke after Embolic Stroke of Undetermined Source)[37] demonstrated a benefit to blind anticoagulation of all ESUS patients, when compared with aspirin alone. A subgroup analysis of NAVIGATE ESUS[38] did suggest that a group of patients in the trial, with enlarged left atrium suggestive of increased risk of AF development, benefited from anticoagulation. However, the ATTICUS (Apixaban versus Aspirin for Embolic Stroke of Undetermined Source) trial,[39] which specifically aimed to investigate the use of formal anticoagulation in ESUS patients with features suggestive of atrial cardiopathy, failed to identify any significant difference between apixaban and aspirin use, with respect to stroke prevention. However, the majority of ATTICUS patients were identified based on BNP and P-wave terminal force abnormalities, rather than echocardiographic abnormalities. It therefore seems reasonable, on the basis of ARTESIA trial, subsequent meta-analysis, and NAVIGATE ESUS subgroup analysis, to postulate that careful patient selection may identify groups of ESUS patients whose risk of stroke recurrence is reduced by targeted management of device-detected AF. In our bimodal distribution of ESUS-related AF, the current evidence might therefore support the use of anticoagulation in the 5.5–24-h group but does not inform practice in the <6-min duration group. The use of electrocardiographic[40,41] and multi-modality[13] predictors to identify individuals who are more likely to have AF may aid selection.

Future studies should try and identify a threshold of AF (considering both duration and burden), whereby anticoagulation would be warranted, and try to further investigate the significance of short-duration subclinical AF. Our study may also prompt a randomized controlled trial looking at anticoagulation vs. no anticoagulation of ESUS patients with short runs of sub-clinical AF (SCAF).

One of the controversies that persists around the use of loop recorders in ESUS is whether the device should be replaced if no AF is detected, at the time of battery depletion. Kaplan–Meier analysis in the present study suggests diagnostic yield for any AF plateaus at ~3 years, with stricter requirements for longer durations of AF plateauing earlier. Hence, this study would support a strategy of non-replacement of the loop recorder.

Strengths and limitations

The main strength of our study is the large number of both stroke and non-stroke patients who were monitored continuously for a prolonged period of time with an ILR. This is the first study to compare the incidence of AF between ESUS and non-ESUS patients receiving prolonged cardiac monitoring via an ILR. Aside from the LOOP study, much of the literature on device-detected AF has looked at AF detection using pacemaker devices, or a mixture of devices.[5,6,21,42] Right ventricular pacing has been associated with increased AF incidence, potentially confounding results of pacing studies.[43]

This was a retrospective single-centre study, although our institute is the regional centre for ILR implantation in post-ESUS patients receiving referrals across a population of >2.5 million. Referrals for ILRs were done at the discretion of the treating stroke physician, when they felt other causes of stroke were excluded, and that the patient warranted

prolonged monitoring for AF. Therefore, selection bias may have occurred. Due to its retrospective nature, it was not possible to accurately characterize the natural history of patients with device-detected AF. Implantable loop recorder monitoring was often discontinued when an AF diagnosis was made, especially in the case of ESUS, the CHA_2DS_2-VASc score is higher by nature, and anticoagulation was often started. Moreover, the non-ESUS patients were not representative of a healthy population as they had experienced syncope or palpitations. However, we included all patients undergoing ILR implants for syncope or palpitations, not only the high-risk ones. Indeed, the incidence of AF observed in the non-ESUS population is likely to be an overestimate of that observed in the general population.

This was an observational study with no randomization. As such, confounding factors may affect the results. As discussed, the non-ESUS population were older and had more comorbidities (including coronary artery disease and obstructive lung disease). Given that these are known risks for future AF development, one would have expected any confounding factor to have led to an increased number of AF episodes in the non-ESUS group.

Data were collected over a period of 10 years, during which time there has been a change in ILR technology. Manual verification of recordings has helped to ensure that the results remain relevant. Moreover, despite our growing awareness of device-detected AF, there remains no significant change in its management.

Implantable loop recorder analysis of atrial arrhythmias can be difficult due to baseline artefact precluding accurate P-wave analysis. To minimize this issue, three experienced cardiologists evaluated the strips, utilizing standardized definitions of AF and AFL. Data from the arrhythmia dot plots and the onset and offset of the arrhythmia were also utilized to prevent mis-identification.

In cases where baseline artefact made analysis difficult, the three cardiologists would err on the side of not over-calling possible atrial arrhythmias, to minimize the risk of over-estimating the amount of AF or AFL in the two groups.

This piece of work is hypothesis-generating. Although there is a significantly higher incidence of device-detected AF in ESUS survivors, it still remains unclear as to whether these episodes are prognostically significant. Further randomized studies targeting ESUS patients with subclinical AF are warranted.

Conclusion

The incidence of AF is significantly higher amongst ESUS vs. non-ESUS patients constantly monitored by an ILR. A significantly higher number of ESUS survivors have short episodes of AF. More work is required to understand the significance of these short runs of AF, and whether they require specific therapy. Randomized, multicentre studies are warranted to identify the role of anticoagulation in these patients.

Lead author biography

Dr Chousou, MD, CIED, PhD, is a consultant cardiologist with an interest in heart rhythm management at Addenbrooke's Hospital, Cambridge University NHS Foundation Trust. She completed her medical degree with honours at the University of Athens and her clinical cardiology training within the East of England Cardiology training scheme. She was subsequently awarded a PhD from the University of East Anglia, UK. Her clinical interests are in complex and conduction system pacing, and her research is focused on atrial fibrillation and its prediction, especially in patients who have suffered an embolic stroke of undetermined source.

Data availability

Data are available on request. The data underlying this article will be shared on reasonable request to the corresponding author.

Supplementary material

Supplementary material is available at *European Heart Journal Open* online.

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