Association between Bilateral Infarcts Pattern and Detection of Occult Atrial Fibrillation in Embolic Stroke of Undetermined Source (ESUS) Patients with Insertable Cardiac Monitor (ICM)

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Background and Aims: Increasingly, insertable cardiac monitors (ICM) have been used to detect Atrial Fibrillation (AF) in patients with cryptogenic stroke or embolic strokes of undetermined source (ESUS). We aim to examine the characteristics of these patients who were subsequently found to have AF. *Methods:* We studied 83 consecutive patients who were comprehensively evaluated using neuroimaging and vessel imaging (computed tomography angiography, magnetic resonance angiography, or transcranial and extracranial Doppler sonography) to have met the previously established ESUS criteria. All 83 patients had ICM implanted between 2015 and 2017. All patients were followed up for at least 1 year, with a median follow-up period of 1.5 ± .5 years. We compared the baseline clinical, laboratory, echocardiographic, neuro-imaging profiles, and clinical outcomes in terms of functional recovery, recurrent stroke, and mortality in patients with and without detected AF. *Results:* AF detection rate in this ESUS cohort was 12% over the study period. Patients with detected AF were associated with bilateral infarcts pattern at presentation (30% versus 5.5%, $P = .035$). Infarcts involving multiple vascular territories was not significantly associated with the detection of AF. There were no significant differences in the other clinical characteristics and outcomes between the AF group compared to the group without detected AF. Echocardiographic parameters including left ventricular ejection fraction and left atrial diameter were also not shown to be significantly different. *Conclusion:* Our study found that a neuroimaging profile of bilateral infarcts was associated with AF detection using insertable cardiac monitor in ESUS patients. Larger prospective studies are needed to validate our findings.

Key Words: Ischemic stroke—ESUS—cryptogenic—loop recorder—implantable—atrial fibrillation

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Introduction

Amongst stroke patients in Singapore, Atrial Fibrillation (AF) has emerged dominantly as a key modifiable risk factor, with population studies seeing a significant increase in proportion of stroke patients with AF from 16.0% in 2007 to 20.6% in 2016.[1] In parallel, the introduction and use of Insertable Cardiac Monitors (ICM) could result in better detection of AF in patients with cryptogenic stroke or Embolic Stroke of Undetermined Source (ESUS). Without a conclusive diagnosis of AF, the management of patients with ESUS remains unclear. ESUS patients represent 20% of acute ischemic stroke (AIS) patients, but the role of anticoagulation in this population has not been clearly established.[2] Most recently, New Approach Rivaroxaban Inhibition of Factor Xa in a Global Trial versus ASA to Prevent Embolism in Embolic Stroke of Undetermined Source showed that rivaroxaban was not superior to aspirin for this population of patients and was associated with an increased risk of major bleeding.[3] In a similar approach, the strategy of empirical anticoagulation using dabigatran was also not found to be superior when compared to aspirin.[4]

In recent years, an implantable loop recorder (ILR) combined with remote monitoring (Reveal LINQ, Medtronic Inc, Minneapolis, MN) had been available as an investigative tool in our institution for patients with ESUS to better detect occult paroxysmal AF. In the CRYSTAL-AF[5] study, AF was detected in 12.4% of patients on ICMs after 12 months of follow-up. The study also found that ICMs have significantly higher detection rates compared to conventional methods such as Holter monitoring in picking up occult AF. Similarly, our institution's experience paralleled the CRYSTAL-AF study, where we reported an AF detection rate at 6 months of 12.9% and 15.2% at 12 months.[6] Upon detection of AF, patients in our institution were then evaluated for suitability and all eligible patients had initiation of anticoagulation therapy.

This retrospective study aims to evaluate the clinical characteristics and stroke profiles of ESUS patients who were detected to have underlying occult AF at our center. In doing so, we intend to evaluate risk factors and associations of AF detection in ESUS patients, and potentially identify a high-risk profile which could be strongly considered for ICM placement.

Methodology

Between January 2015 and December 2017, patients with a diagnosis of cryptogenic AIS referred for ILR implantation in our center were studied. This was a single-center, observational study. The diagnosis of AIS was evaluated by a clinical neurologist and confirmed by Computed Tomography and/or Magnetic Resonance Imaging scans of the brain. The mechanism of the stroke was classified by the Trial of ORG 10172 in Acute Stroke Treatment system.[7]

Amongst cryptogenic stroke patients referred for ILR implantation, we identified 83 patients who completed evaluation and fulfilled the criteria for ESUS. ESUS patients were defined as patients with ischemic strokes that were not lacunar, were not associated with extracranial or intracranial vessel atherosclerosis causing more than 50% luminal stenosis in arteries supplying the area of ischemia or with identified risk factors for a cardiac source of embolism (AF, left ventricular thrombus, mechanical prosthetic cardiac valve, or severe mitral stenosis) and had no other secondary cause of stroke found.[8] The methods used to evaluate potential ESUS patients include the use of multiple neuroimaging modalities such as Computed Tomography angiogram, MR angiogram, or transcranial and extracranial Doppler sonography (TCD & ECD). The 2D-echocardiography and 24 hour inpatient cardiac telemetry or Holter monitoring was also performed to exclude risk factors for a cardiac source of embolism as mentioned above. We included 7 patients who were found to have positive TCD with bubble study, of which 3 patients had Spencer grade 4 and above shunt.

Eighty-three patients underwent insertion of a Medtronic Reveal LINQ (Medtronic Inc, Minneapolis, MN) ILR. The median time between index stroke and ILR implantation was 48.5 days (IQR 8-189). Following ILR implantation, patients were monitored via remote monitoring using the Medtronic CareLink system. The ILR device had an inbuilt proprietary algorithm which used a Lorenz scatter plot of R-R intervals to make the diagnosis of AF. The detected episode of AF was flagged as an event, of which a notification is subsequently sent to a physician via a remote monitoring system. All AF episodes detected were then verified by qualified cardiac electrophysiologists. The patients were followed up for at least 1 year, with a median follow-up period of 1.5 ± .5 years. Patients found to have AF were then considered for lifelong anticoagulation therapy.

To study possible risk factors associated with AF detection in ESUS patients, the baseline clinical, laboratory, echocardiographic, and neuroimaging of these patients were collected. These included age, gender, estimated glomerular filtration rate, fasting glucose, HbA1c, low-density lipoprotein cholesterol, history of cardiovascular risk factors, left ventricular ejection fraction, left atrial diameter, and stroke characteristics (location and vascular territories involved). We defined multiple vascular territory infarctions according to the Trial of ORG 10172 methodology.[9] Noncontiguous infarct lesions observed to be in 2 or more vascular territories were classified as involving multiple territories, but uninterrupted lesions visible in contiguous vascular territories were not.[9] Bilateral infarcts were defined as either (i) bilateral, single, or multiple infarcts involving the bilateral anterior circulation, or (ii) unilateral, single, or multiple infarcts involving the anterior circulation on 1 side and posterior circulation on the contralateral side. Bilateral posterior circulation

infarcts alone were not classified as bilateral infarcts. Clinical outcomes in terms of functional recovery measured by modified Rankin score at 3 months, recurrent strokes and mortality were also studied.

Informed consent for the ILR implantation procedure from all participants was obtained prior to the conduct of the study. Ethics approval for this study had been obtained from the relevant Institutional Review Board.

Statistical Methods

We compared the characteristics and outcomes of patients with detected occult AF and those without using appropriate statistical analyses. We presented the numerical variables as mean and standard deviation and categorical variables as percentages. Numerical predictors were analyzed by using a 2-sample *t* test or Mann-Whitney *U* test where applicable. Categorical variables were evaluated using the chi-square test or Fisher's exact test where applicable. Associations were presented as adjusted odds ratios with corresponding 95% confidence intervals. Statistical analyses were performed using IBM SPSS Statistics version 20. A *P* value of less than .05 was considered significant for this study.

Results

Over the 3-year study period, 10 out of 83 patients (12.0%) with ESUS and ILR insertion were found to have AF. The median time from ILR implantation to AF detection was 144 days (IQR 21-680). The median time between index stroke and AF detection on ICM was 237 days (IQR 95-718). The median duration of the AF detected on ILR was 32 minutes, with the range of (IQR 3.9-282). In 1 patient, ILR also detected multiple significant sinus pauses, where the patient subsequently underwent pacemaker insertion. All 10 patients in the AF group were started on anticoagulation therapy. Nine patients were started on Apixaban, while the remaining 1 patient was on Rivaroxaban.

We found that patients with detected AF were associated with bilateral infarcts pattern at presentation compared to unilateral infarct (30% versus 5.5%, $P = .035$). Otherwise, the AF group did not differ significantly in terms of age (60.9 ± 11.9 versus 62.0 ± 13.0, $P = .816$), gender (60% versus 78.1%, $P = .210$) or baseline clinical characteristics like the prevalence of diabetes, hypertension, or hyperlipidaemia compared to the group without detected AF. On initial echocardiography, left atrial diameter (39.2 ± 5.4 mm versus 37.6 ± 5.7 mm, $P = .411$) was also not shown to be significantly different. Infarcts involving multiple vascular territories was not significantly associated with the detection of AF (30% versus. 12.3%, $P = .154$). Clinical outcomes were similar between the ESUS group with AF and those without detected AF in terms of functional outcome measured by measured by modified Rankin score, recurrent stroke events, and all-cause mortality (Table 1).

Discussion

In terms of neuroimaging parameters, we identified bilateral infarcts pattern as a predictor of AF detection in this ESUS cohort. To our knowledge, this is the first study that reports such an association, where 30% of ESUS patients with detected AF on ICM had imaging findings of bilateral infarcts. This marker of bilateral infarcts pattern, in addition to other established predictors of AF detection in ESUS in the literature, may help clinicians stratify patients more accurately and guide the need for insertable cardiac monitoring and further management accordingly.

A similar study by Ricci et al evaluated the characteristics of ESUS patients with underlying AF and found that older age and moderate to severe left atrial enlargement were predictors of AF detection on follow-up with ESUS.[10] Separately, a study conducted by Israel et al found that older age and higher CHADSVASc scores were associated with detection of AF in ESUS patients.[11] However, the authors also suggested that the differences of older age and higher CHADSVASc scores were too small to be sufficient to positively predict or negatively exclude the presence of AF in ESUS.[10] In contrast, our study did not identify older age, higher CHADSVASc scores, or enlarged left atrial diameters to be significant predictors of AF detection in our ESUS cohort.

In addition, our study findings concur with previous published literature that other imaging patterns typically associated with cardioembolic stroke (eg Middle Cerebral Artery and Posterior Cerebral Artery territory infarction) did not reliably predict AF detection.[11] Interestingly, even though we found bilateral infarcts to be associated with AF, multiple vascular territory infarcts were not. A recent study highlighted the "Three Territory Sign" (TTS) (bilateral anterior and posterior circulation infarct lesions) as a radiographic marker of stroke that was more frequently observed in malignancy-related ischemic stroke, than AF-related ischemic stroke.[12] In our study, the majority of patients with multiple vascular territory infarcts were 2 territory in nature, where only 2 patients had bilateral anterior and posterior circulation infarct lesions or TTS. Both these patients with TTS did not have an underlying malignancy and AF was also not detected. Interestingly in the group without detected AF, less than half of the patients with multiple territory infarcts had bilateral infarcts. The remaining had unilateral, single, or multiple infarcts involving the anterior circulation plus posterior circulation. This relatively high number of patients with unilateral multiple territory infarcts may have been contributed by selection bias where physicians could have been more likely to offer ILR implantation to patients with these infarct characteristics, as they had a higher

Table 1. *Comparing clinical profiles and outcomes of patients with or without AF detected on implantable loop recorder (ILR) with embolic stroke of undetermined source (ESUS)*

Parameter	AF detected (n = 10)	AF not detected (n = 73)	Mean difference/ odds ratio	*P* value
Clinical and laboratory				
Age (years)	60.9 ± 11.9	62.0 ± 13.0	−1.1 (−10.2-8.0)	.816
Gender (Male)	60%	78.1%	.6 (.2-1.3)	.210
eGFR (mL/min)	82.8 ± 19.1	89.0 ± 17.9	−6.2 (−19.8-7.4)	.363
Fasting glucose (mmol/L)	5.4 ± .6	7.4 ± 7.5	−1.9 (−7.7-3.8)	.496
HbA1c (%)	6.1 ± .9	6.7 ± 1.8	−.6 (−2.1-.8)	.396
LDL-C (mmol/L)	3.1 ± .7	2.9 ± 1.2	.2 (−.5-1.0)	.586
Hypertension	90%	68.5%	4.1 (.5-34.6)	.159
Diabetes mellitus	20%	39.7%	.4 (.1-1.9)	.308
Hyperlipidaemia	70%	71.2%	.9 (.2-4.0)	.936
Previous CVA	20%	23.6%	.8 (.2-4.2)	1.000
CHA_2DS_2-VASc Score	2.7 ± 1.6	2.7 ± 1.8	−.0 (−1.2-1.2)	.974
Time from stroke to ILR implantation (days)	79 ± 77	150 ± 264	−71 (−239-96)	.399
Echocardiography				
LV ejection fraction (%)	65.8 ± 1.8	60.2 ± 9.0	5.6 (−.1-11.3)	.053
LA diameter (mm)	39.2 ± 5.4	37.6 ± 5.7	1.9 (−2.2-5.4)	.411
Infarct characteristics				
Anterior cerebral artery territory	0%	5.5%	-	-
Middle cerebral artery territory	60%	60.3%	1.0 (.3-3.8)	.987
Posterior cerebral artery territory	20%	20.5%	1.0 (.2-5.0)	1.000
Other vertebrobasilar artery territory	40%	24.7%	2.0 (.5-8.0)	.444
Bilateral infarcts	30%	5.5%	7.4 (1.4-39.9)	.035
Multiple vascular territory infarcts	30%	12.3%	3.0 (.7-14.0)	.154
Clinical outcomes				
Good functional recovery at 3 months (mRS 0-2)	100%	95.8%	-	-
Recurrent stroke	0%	9.6%	-	0.590
Mortality	10%	5.5%	1.9 (.2-19.1)	.483

Abbreviation: CVA, cerebrovascular accident, eGFR, estimated glomerular filtration rate; mRS, modified Rankin score, LV, left ventricle, LA, left atrium.

suspicion of occult AF. Larger prospective studies are necessary to investigate the utility of multiple vascular territory infarcts as a neuroimaging marker of AF prediction.

Regarding incidence, we found that the rate of AF detection was 12% after a median 1.5 ± .5 years of follow-up in our cohort of ESUS patients, which is comparable to findings from the CRYSTAL-AF study, which reported a 12.4% detection rate on 1 year follow-up.[5] Our study also found that patients with AF detected on ICM also appeared to have a lower incidence of recurrent strokes (10% versus 16.9%, $P = 1.000$) when compared to patients who were not identified with AF, although this did not reach statistical significance. These findings could suggest the importance of anticoagulation therapy as all 10 patients in the AF group were prescribed anticoagulation therapy, but we are unable to draw definitive conclusions in view of the small sample size, lack of statistical significance, and retrospective nature of our study.

Limitations

This is a single-center retrospective study in Asia with a relatively small number of patients and its results may not be representative of a larger population, nor are we able to determine causality. Thus, a larger prospective study is required to validate our findings. In addition, the overall accuracy of Reveal LINQ ILR in detecting AF or non-AF episodes was 99.4%, and the AF burden measured by ICM was highly correlated with Holter (Pearson Coefficient .995)[13] and this may account for a small number of undetected AF episodes. Furthermore, we cannot be entirely certain that the cause of the index AIS was due to a cardio-embolic mechanism from underlying AF, especially since the median time between index AIS and ILR implantation was approximately 1.5 months. Nonetheless, we believe that detecting AF and starting anticoagulation therapy may be beneficial for these patients.

Conclusion

In conclusion, our study found that a neuroimaging profile of bilateral infarcts was associated with AF detection using ICM in ESUS patients. Larger prospective studies are needed to validate our findings.

Conflicts of Interest

The authors have no conflicts of interest to disclose.

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