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Title: Atrial Fibrillation in Embolic Stroke of Undetermined Source: Role of advanced imaging of left atrial function.

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Abstract

Background: Atrial fibrillation (AF) is detected in over 30% of patients following an embolic stroke of undetermined source (ESUS) when monitored with an implantable loop recorder (ILR). Identifying AF in ESUS survivors has significant therapeutic implications and AF risk is essential to guide screening with long-term monitoring. The present study aimed to establish the role of Left Atrial (LA) function in subsequent AF identification and develop a risk model for AF in ESUS.

Methods: We conducted a single-centre retrospective case-control study including all patients with ESUS referred to our institution for ILR implantation from December 2009 to September 2019. We recorded clinical variables at baseline and analyzed transthoracic echocardiograms in sinus rhythm. Univariate and multivariable analyses were performed to inform variables associated with AF. Lasso regression analysis was used to develop a risk prediction model for AF. The risk model was internally validated using bootstrapping.

Results: Three hundred and twenty-three patients with ESUS underwent ILR implantation. In the ESUS population, 293 had a stroke, whereas 30 had suffered a TIA as adjudicated by a senior stroke physician. AF of any duration was detected in 47.1%. Mean follow-up was 710 days. Following lasso regression with backward elimination, we combined increasing lateral PA (the time interval from the beginning of p wave on surface electrocardiogram to the beginning of A' wave on pulsed wave tissue Doppler of the lateral mitral annulus) (OR 1.011), increasing Age (OR 1.035), higher diastolic blood pressure (DBP) (OR 1.027) and abnormal LA reservoir Strain (OR 0.973) into a new PADS score.

The probability of identifying AF can be estimated using the formula: Model discrimination was good (AUC 0.72). The PADS score was internally validated using bootstrapping with 1000 samples of 150 patients showing consistent results with an AUC of 0.73.

Conclusions: The novel PADS score can identify the risk of AF on prolonged monitoring with ILR following ESUS and should be considered a dedicated risk-stratification tool for decision-making regarding the screening strategy for AF in stroke.

Keywords:

Atrial fibrillation, embolic stroke of undetermined source, ESUS, transient ischaemic attack, prediction model, risk score

Lay Summary

One third of patients with a type of stroke called Embolic Stroke of Unknown Source (ESUS) also have a heart condition called Atrial Fibrillation (AF), which increases their risk of having another stroke. However, we don't know why some patients with ESUS develop AF. To figure this out, we studied 323 patients with ESUS and used a special device to monitor their heart rhythm continuously for up to three years, an implantable loop recorder (ILR). We also looked at their medical history, performed a heart ultrasound, and identified some factors that increase the risk of identifying AF in the future.

- Factors associating with future AF include older age, higher diastolic blood pressure and problems with the coordination and function of the upper left chamber of the heart called left atrium.
- Based on these factors, we created a new scoring system that can identify patients who are at higher risk of developing AF better than the current scoring systems, the PADS score. This can potentially help doctors provide more targeted and effective treatment to these patients, ultimately aiming to reduce their risk of having another stroke.

Main Text

Introduction

Stroke is one of the leading causes of morbidity and mortality in the Western world, affording an increasing financial burden to healthcare systems.[1] The global lifetime risk of stroke in individuals over the age of 25 is estimated at 25%.[2] In approximately one third of patients with ischaemic stroke no immediate cause is identified, classified as Embolic Stroke of Undetermined Source (ESUS).[3,4] With detailed investigations, a significant proportion of patients with ESUS (> 30%) are subsequently identified as having underlying paroxysmal atrial fibrillation (pAF), which may explain the index event.[5,6] Correctly identifying AF in ESUS survivors is vital as it guides clinicians toward initiation of anticoagulation, which reduces stroke recurrence by almost 65%.[7,8]

In the absence of AF, recent trials have suggested that anticoagulation offers no clinical benefit and may be of harm in ESUS survivors.[9,10] However, subgroup analysis of one of these trials has provided evidence that patients with markers for increased risk of AF, may derive benefit from empirical anticoagulation.[11] Therefore, the ability to identify individuals at risk for AF is of vital clinical importance.

Unfortunately, pAF remains challenging to diagnose in practice.[7,12] Long-term monitoring using an implantable loop recorder (ILR) has proven to be the optimal method for screening of pAF.[5,6,13,14] The usefulness of ILR in the context of ESUS is recognized by both the recent American Heart Association (AHA)[15] and European Society of Cardiology (ESC) guidelines.[12] Indeed, implantation of an ILR in all ESUS patients would be an ideal method of identifying AF in this cohort, but this practice is resource-intensive, expensive,

and not yet widely accepted.[16] The recent ESC guidelines acknowledge this, and recommend the use of ILR in a targeted group of stroke patients only, yet the guidance did not provide a method by which suitable individuals should be identified.[12]

Individual risk assessment is therefore a potential method by which patients with a high likelihood of subsequent AF could be targeted for ILR implantation. Several risk scores have been developed and existing risk scores have been utilized to predict AF in patients following an ischaemic stroke or transient ischaemic attack (TIA).[17–19] A significant limitation of the studies attempting to develop AF risk prediction models in an ESUS population is the lack of prolonged cardiac rhythm monitoring with an ILR to diagnose AF, which reduces the sensitivity of the scoring system, as lack of long-term monitoring leads to underestimation of AF episodes. Indeed, none of the risk scores perform sufficiently well in patients with ESUS to be incorporated in the guidelines and are not widely used.[20–29]

Therefore, there is an urgent unmet clinical need for a robust risk-score that can reliably predict the development of AF in an ESUS population and potentially help clinicians target ILR implants more effectively.

We hypothesized that imaging parameters of left atrial (LA) function would be associated with subsequent AF, and combined with other imaging and clinical parameters can help build a risk model to predict AF in patients with ESUS. Such a model could help risk

stratifying ESUS survivors with regards to the AF future risk and thus tailor utilization of ILR monitoring.

Methods

This was a single centre retrospective case- control study. The study was approved by the UK Health Research Authority (16/NW/0527) in 2016 and institutional approval from Cambridge University Hospitals NHS Foundation Trust. The North West-Preston Research Ethics committee waived the need for patient consent for this retrospective study. The study complied with the 1975 Declaration of Helsinki for research and the STROBE guidelines for observational studies were followed.

Study population

We included all adults undergoing ILR implant to screen for AF following a cerebrovascular event of unknown aetiology between December 2009 and September 2019. All patients were prospectively enrolled in a dedicated clinical database, which was retrospectively interrogated. Cerebrovascular events of unknown cause (ESUS) included ischaemic stroke or Transient Ischaemic Attack (TIA; defined as neurological signs resolving within 24 hours). Prior to referral for ILR, all patients had a 12-lead electrocardiogram (ECG) confirming sinus rhythm and underwent a minimum of 24 hours cardiac rhythm monitoring via inpatient telemetry or Holter monitor, which excluded AF. Patients underwent transthoracic, transoesophageal or bubble echocardiography to identify other potential sources of embolism. Patients with patent foramen ovale (PFO),

regardless of the presence of atrial septal aneurysm, were included in the study. We elected to include patients with PFO as this is a common finding occurring in over 25% of the population.[30] Additionally, although its prevalence it higher amongst patient with ESUS the condition itself has not been shown to increase the risk of ischaemic stroke.[31,32] All patients underwent either Carotid Doppler, computed tomography angiography (CTA) or magnetic resonance angiography (MRA) to ensure that there was no significant intracranial or extracranial significant vessel stenosis (>50%) or occlusion in the arterial distribution of the index stroke or TIA. Patients with > 50% stenosis that was not in the arterial distribution of the index event were included in the study. All patients had either brain CT or MRI or both. Referral for ILR was at the discretion of the stroke physicians after completion of the investigations and exhaustive exclusion of other explanations for the index event.

Study variables

Demographic, anthropometric and clinical variables

Demographic and anthropometric data, clinical risk factors, smoking status and alcohol intake were collected from electronic and paper medical records. Additionally, we recorded systolic blood pressure (SBP) and diastolic blood pressure (DBP) at the first clinic visit following index stroke. Medications at discharge for patients admitted with an ESUS or following clinic visit for those referred for outpatient review were also recorded. Results of blood biomarkers at the time of admission with a stroke or review at the outpatient clinic were collected. A summary of the variables collected is shown in **Supplementary Table 1**.

We calculated scores that have previously been used for AF risk prediction including HAVOC,[20,21] CHA_2DS_2VASc,[22,26] HATCH,[26] C_2HEST,[23] Brown ESUS-AF,[24] NDAF[27] as well as HAS-BLED[12,33] and ORBIT risk scores[34] as shown in **Supplementary Table 2.**

Echocardiographic variables

Echocardiograms performed up to one year prior to ILR implantation were included in the analysis. All the echocardiographic images were digitally stored in an Image Vault (GE Vingmed Ultrasound AS, Cambridge, United Kingdom). Analysis was undertaken offline by British Society of Echocardiography accredited cardiologist (PAC) using EchoPac v203.59 (GE), who was blinded to whether patients had subsequent AF or not. Intra- observer variability was assessed using Bland-Altman plot, which did not show any significant variability **(supplementary figure 1a and 1b)**.

Conventional echocardiographic data was obtained in accordance with American Society of Echocardiography and European Association of Cardiovascular Imaging recommendations.[35,36,37,38,39] From the parasternal long-axis view the following parameters were recorded: left ventricular (LV) dimensions and mass, aortic root dimensions and LA diameter. LA volume, LV end-systolic and end-diastolic volumes and LV ejection fraction (LVEF%) were determined using Simpson's biplane method from the apical 4- and 2-chamber views. Diastolic function was described with E wave deceleration

time, E/A and E/E' ratio, based upon the average of the septal and lateral E' values. Atrial electromechanical delay reflecting atrial dyssynchrony was assessed using electrocardiographic P-wave to lateral tissue Doppler A' wave, which will henceforth be referred to as the lateral PA. This was defined as the time interval from the onset of the p-wave on the surface ECG to the onset of the A' wave obtained using pulsed tissue Doppler imaging of the lateral mitral annulus in the apical 4-chamber window **(figure 1).**[40,41] A number of studies have assessed atrial electromechanical delay using tissue Doppler imaging rather than electrophysiological studies.[41–43]

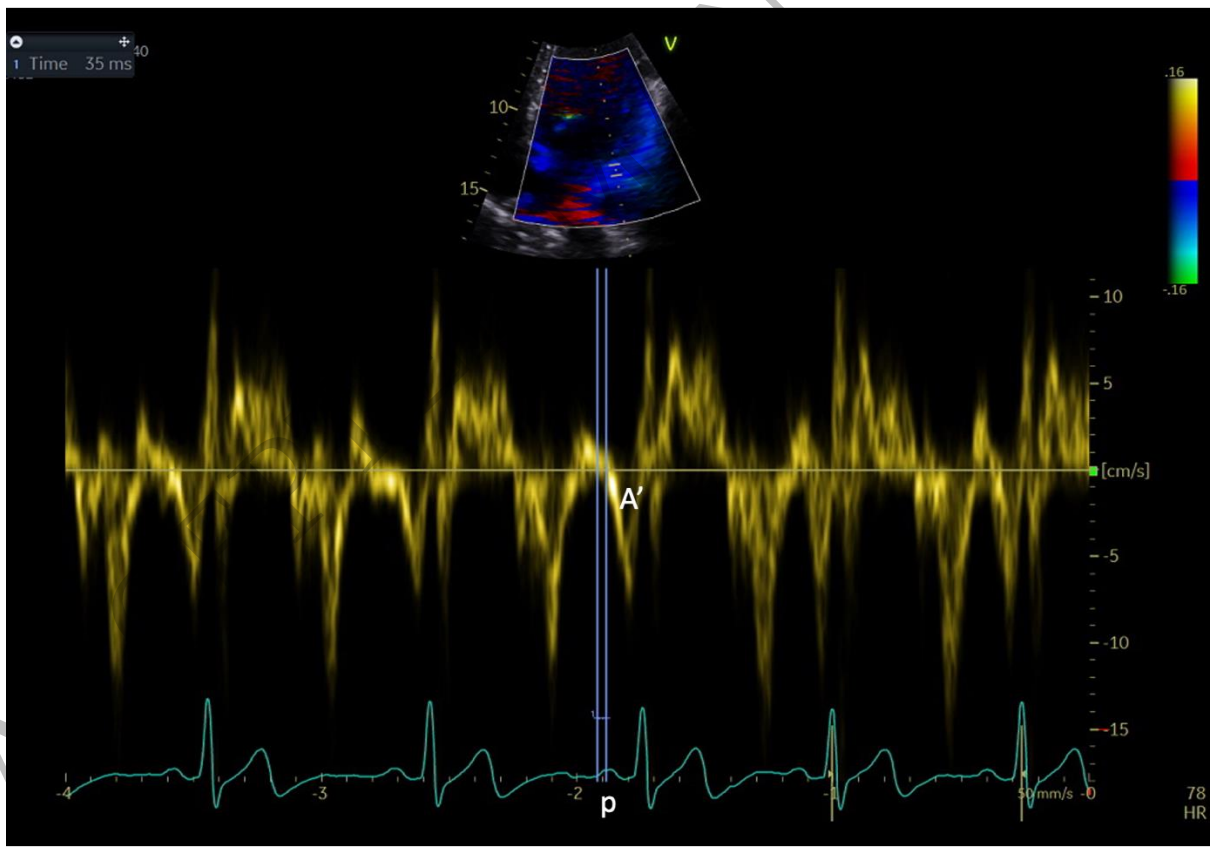

Figure 1 shows the measurement of lateral PA interval by tissue Doppler imaging. Lateral PA was obtained from the lateral mitral annulus in apical 4-chamber view as the time interval from the beginning of p wave on surface ECG to the beginning of A' wave. In this case lateral PA was measured as 35ms.
ECG, electrocardiogram

LA strain was determined using speckle tracking technique from standard grayscale images obtained from the apical 4- and 2-chamber windows and semi-automated software (Echopac, GE). The LA endocardial border was manually traced, and the region of interest was adjusted to optimize the inclusion of the atrial myocardium. The onset of the QRS complex was chosen as the zero-reference point. In each view, the LA was automatically divided into six segments giving time-deformation curves for a total of 12 segments. The average of all 12 segments was used to define three atrial strain parameters including: LA reservoir strain defined as the peak atrial longitudinal strain; LA contractile strain as the value corresponding to the onset of the p-wave on the surface ECG; and LA conduit strain was as the difference between LA reservoir and contractile strain **(figure 2)** [44,45] More positive LA strain values indicated a more favourable strain.

A summary of the additional parameters and how measurements were obtained is shown in **supplementary Table 3**.

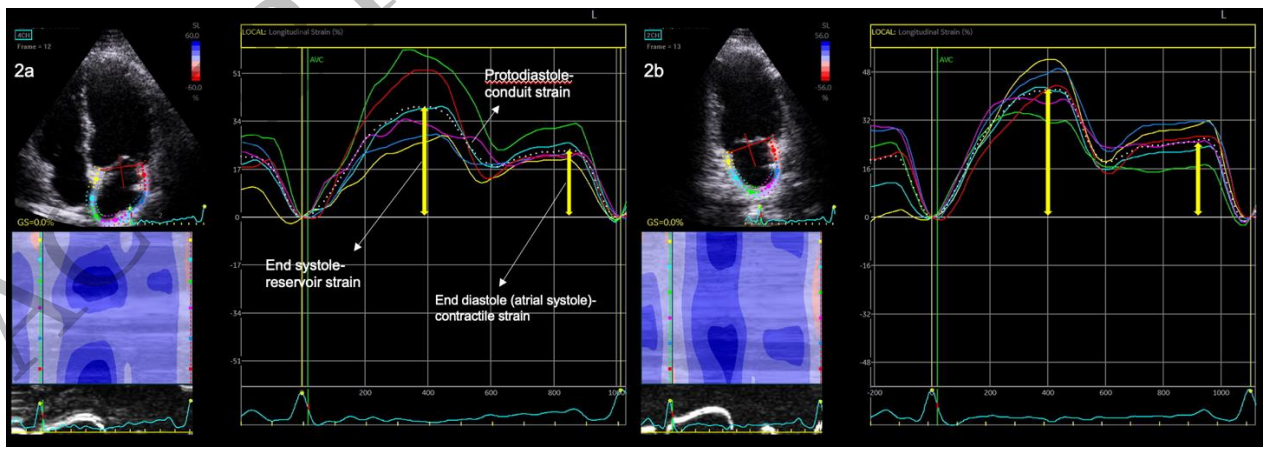

Figure 2 shows an example of LA strain measured using speckle strain analysis. For each apical view the software produces six time-deformation curves corresponding to six atrial segments (coloured traces). The average strain curve is defined for each window (white dotted trace). Three aspects of atrial strain (reservoir, contractile, conduit) are defined and annotated (see main text for details). The average value for reservoir

and contractile strain for all twelve segments is recorded.The conduit strain is calculated as the difference between reservoir and contractile strain.
LA, left atrium

ILR implant

ILRs (Medtronic Reveal XT, Reveal DX and SJM Confirm) were implanted subcutaneously in an appropriately mapped left parasternal position. The Medtronic Reveal LINQ was inserted at 45 degrees relative to the sternum above the fourth intercostal space in the V2-V3 electrode orientation using dedicated incision and insertion tools. The ILRs were programmed with the AF detection algorithm "on", and tachycardia, bradycardia, and patient activated detection on. The ILRs detect AF either by using specific AF detection algorithm, or by recording episodes of tachycardia, bradycardia or pause, which on further inspection are found to be AF. The Reveal LINQ and XT have specific AF detection algorithms.[46,47] Whilst the algorithms detect AF of duration greater than 2 minutes, manual inspection of automatic and patient recorded episodes, allowed for detection of shorter durations of AF. The ILRs were interrogated monthly or whenever the patient activated the device. Until 2012 the ILRs were interrogated in the hospital and thereafter remotely via the Medtronic CareLink ™ monitoring network.

Outcome

The outcome was the detection of any AF or atrial flutter (AFL) of any duration on ILR. There is no of consensus of how much AF is harmful to patients with ESUS. Indeed, even the European Society of Cardiology guidelines are based on expert consensus. As such, we chose any duration of AF as an end-point on the basis that ESUS survivors are a high-

risk cohort for further thromboembolic events. Furthermore, AF begets more AF,[48] and the minimum duration of AF that increases thromboembolic risk is not known at this time. We considered AF and AFL as interchangeable, as the risk of thromboembolism and need for anticoagulation are similar.[49,50]

All auto-triggered and patient triggered episodes on ILR were reviewed by a senior cardiac physiologist and two cardiologists specialized in cardiac arrhythmias and accredited by the European Heart Rhythm Association (PAC, PP) to confirm presence of AF or AFL. In case of disagreement, the traces were reviewed by a third cardiologist for final adjudication. Additionally, we recorded time to ILR implantation and time to detection of first AF episode.

Statistical analysis

Continuous variables are 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 comparisons were made using independent t- test for parametric data and Mann Whitney U test for non-parametric data, after testing for normality. Categorical variables were compared using chi- square test and Fisher's exact test if counts <5. Dichotomous variables with positive events less than 30 were not included in the analysis, due to difficulty in demonstrating homoscedasticity.

To investigate the relationship of all variables with the risk of developing AF, univariate and multivariable logistic regression models were fitted on the original data without imputed values using R statistical software. However, univariate and multivariable regression was only used to inform predictive variables. The final prediction model was based on lasso regression.

Missing Data

We excluded variables with >35% missing data in line with accepted statistical practice.[51,52]We created and analyzed 100 multiply imputed datasets where the missing values were <35%. Incomplete variables were imputed under fully conditional specification, using the default settings of the MICE 3.12 package in R.[53,54] The parameters of substantive interest were estimated in each imputed dataset separately and combined using Rubin's rules. For comparison, we also performed the analysis on the subset of complete cases.

Model selection

Variable selection for the final model was guided by using a lasso model in each of the imputed datasets (library Glmnet in R).[55] In each of the 100 imputed datasets we ran a multivariable model with a lasso (L1) penalty to perform variable selection. Variables that were selected in at least 90 of the100 models were then considered for the final lasso model.

Results

A total of 323 patients were included in the study. The mean follow up was 710 days (standard deviation [SD] 442). Of the 323 patients, 152 (47.1%) were found to have episodes of AF of any duration. Median time from ILR implant to AF detection was 177 days (interquartile range [IQR] 47, 439) and from stroke onset to AF detection 421 days (IQR 261, 677). See **Table 1 and supplementary table 4** for patient demographic data, and clinical and echocardiographic variables both for the entire population and separately for patients with and without post-stroke AF. Table 2 reflects the distribution of the different atrial arrhythmias and presence of symptoms. In short, mean age was 54.7 years (SD 14.8). The AF group was significantly older than the non-AF group (59.3 ± 13.8 versus 50.5 ± 14.4, p <0.0001). One hundred and twenty-six patients were females (39%). Hypertension was a frequent finding in both AF and non-AF cohorts, but blood pressure control was good. LV mass indexed to body surface area was significantly higher amongst patients with AF (p=0.046) reflecting likely the higher rate of hypertension in the AF arm (p=0.019). Moreover, all three aspects of LA strain were significantly more impaired in the AF cohort (all p values <0.05). Of note, 117 patients had a PFO, of whom 47 (40.2%) went on to develop AF, whereas of the 206 patients without a PFO, 105 (51.0%) developed AF (p=0.06).

Among patients with post-stroke AF, 79 (52.0%) had the first episode detected within the first six months of monitoring, 29 (19.1%) at six to 12 months, 30 (19.7%) during the second year of monitoring and 15 (9.9%) after two years of monitoring **(figure 3)**.

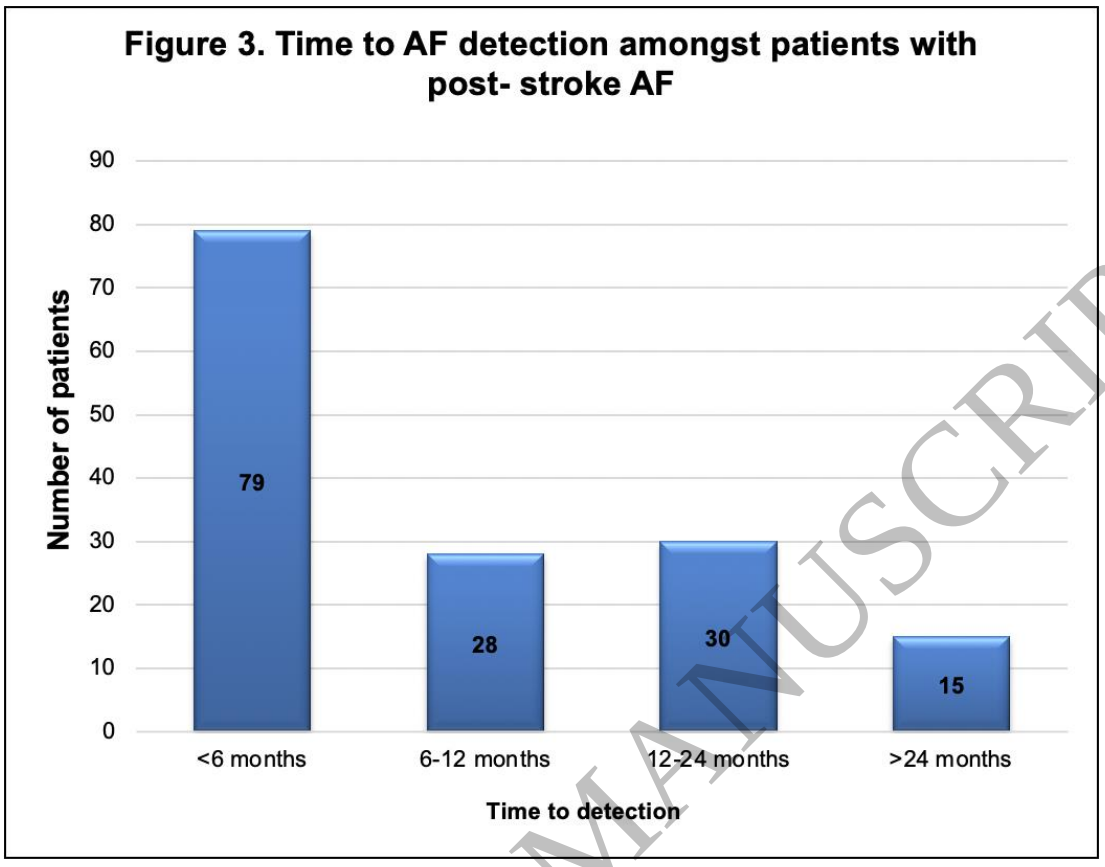

Figure 3 shows time of AF detection in our population, indicating that 107 (70.4%) were shown to have AF within 12 months from implantation.

Risk factors for AF and score development

Univariate analysis is shown in **table 3**. Only variables with p-value <0.1 are included in this table.

Following lasso regression, we combined increasing lateral PA (OR 1.011), increasing age (OR 1.035), higher DBP (OR 1.027) and abnormal LA reservoir strain (OR 0.973) into the new PADS score (Lateral PA, Age, Diastolic BP, LA reservoir Strain) **(table 4)**.

The probability of identifying AF can be estimated using the following formula.

$$Probability\ of\ AF = \frac{e^{-4.06427051+\ln(1.011)lateral\ PA+\ln(1.035)age+\ln(1.027)DBP+\ln(0.973)LA\ reservoir\ strain}}{1+e^{-4.06427051+\ln(1.011)lateral\ PA+\ln(1.035)age+\ln(1.027)DBP+\ln(0.973)LA\ reservoir\ strain}}$$

where age is patient's age, DBP the diastolic blood pressure at first clinic visit following stroke (mmHg), lateral PA the time interval from the beginning of p wave on surface ECG to the beginning of A' wave on pulsed wave Doppler (ms) and LA reservoir strain the left atrial reservoir strain obtained using speckle tracking echocardiography (%).

Using this score, we can estimate the predicted risk for an individual developing/ identifying AF in the next three years (which is the battery life of the ILR) using the formula shown above, and is shown in **supplementary table 5**.

For example, in a patient with ESUS and the following values: Lateral PA 81 ms, Age 64 years, DBP 86 mmHg, LA Reservoir strain 17%, the absolute risk of identifying AF in the next three years is 70.0%. Alternatively, in someone with Lateral PA 40 ms, Age 37 years, DBP 61 mmHg, LA Reservoir strain 45%, the absolute risk of identifying AF in the next three years is 12.3%.

We assessed model discrimination using the area under the curve (AUC) of the Receiver Operating Characteristic (ROC) Curve. The PADS model showed an AUC of 0.72. Furthermore, we internally validated the model using bootstrapping with 1000 samples of 150 patients showing consistent results with an AUC of 0.73.

PADS outperformed all the other scores known to "predict" AF; HAVOC (AUC 0.56), CHA_2DS_2-VASc (AUC 0.58), HATCH (AUC 0.58), C_2HEST (0.58), Brown ESUS AF (0.60) HAS-BLED (0.61) and ORBIT scores (0.55).

Discussion

PADS score development and validation

Our study was conducted to address the pressing need of identifying an appropriate group of post-ESUS patients that would benefit from ILR monitoring. We investigated clinical and echocardiographic parameters for AF and found that the combination of advanced age, increased DBP, increasing lateral PA and impaired LA reservoir strain associates with AF. Most of these factors have been demonstrated to be associated with an increased risk of AF in stroke survivors in other studies. Indeed, advanced age is one of the strongest predictors of AF and has been incorporated in several risk scores targeted to this population.[20,22,24,25,27,56–59] Likewise, elevated DBP reflecting elevated LA pressure is also another risk factor for AF.[60] Additionally, our study showed that increased lateral PA, a marker indicative of atrial electromechanical delay and reflecting LA dyssynchrony is independently associated with AF. This specific relationship has not been reported before amongst ESUS patients. However, increasing lateral PA has been identified as a significant and independent associate of AF amongst 63 patients with pAF and 83 controls.[41] Most importantly, similar to several studies, we found impaired LA function assessed by LA strain to be associated with AF.[61] This is in line with current literature

where LA reservoir strain has been shown to increase predictive value when added to existing risk scores.[60]

Using these variables, we derived and validated the new PADS score, to assess the risk of AF in patients with ESUS, a new score that outperformed all the existing scores in this field, when area under the curve is considered as a performance marker. Moreover, with all ESUS patients recommended to undergo transthoracic echocardiography, the PADS score is a relatively easy score to calculate, with only 4 variables required. Atrial strain is simple, reproducible and validated to calculate, and using manufacturer's strain analysis modules, can, after atrial contouring, automatically produce mean time-deformation curves. For a detailed review of how this can be undertaken please see the article by Voigt et al.[62]

To correctly diagnose the presence of pAF and avoid underestimation of episodes, we used the gold-standard method for AF screening; monitoring with an ILR. We included LA function in our analysis intentionally, as it has been shown in the literature to be a strong and independent predictor of AF, superior to many other variables.[63,64] To our knowledge this is the first study aimed at developing an AF risk prediction model targeted specifically to ESUS patients using ILR and incorporating advanced imaging parameters of LA function.

Usefulness of PADS score

Our risk model provides an estimate of the percentage likelihood of AF within three years of ILR implantation, and individual institutions can tailor this predictive data as they see fit to target their resource most effectively. For example, it can help identify patients at "high", "medium" or "low" risk. Depending on its use, the "high" or "moderate" risk (such as those with an absolute risk of more than 50% according to the authors of the current paper), can be prioritized for an ILR, whilst those with a low risk (e.g. those with <20%) an ILR can be deferred. Using the patient example in **supplementary table 5**, it is clear that the first case with a 70% risk of identifying AF would warrant closer follow up and a low threshold for ILR implantation (if this is not done routinely in the institution the individual presents), whilst the second patient would have a much lower yield in identifying AF had an ILR been implanted. Furthermore, this risk estimation can help inform cost-effectiveness analyses with regards to ILR use, as the use in the moderate and high-risk patients will be more cost-effective than the low-risk patients.

Incidence and duration of Atrial Fibrillation

The incidence of post-stroke AF of any duration in our population is 47.1% and similar to the one reported by Kwong et al, who investigated 9589 patients (age ≥ 40) with cryptogenic stroke or TIA (45.3%). Stroke survivors with AF in this study were identified using international classification of disease codes.[20] It higher though than previously reported by Asaithambi et al, who looked at the prevalence of AF of any duration with ILR monitoring amongst 234 cryptogenic stroke survivors. They found an AF incidence of 29%, but the follow up was shorter comparing to our study.[65] The incidence of AF lasting

>30s in our study was 31.0% and almost identicial to previously reported by cryptogenic stroke and underlying atrial fibrillation (CRYSTAL AF) (30.0%).[6] Our findings with regards to detection rate for AF lasting ≥ 2 minutes (22.6%) are also similar to results published by Ziegler et al. This group examined 1247 patients with cryptogenic stroke and found an incidence of AF lasting ≥ 2 minutes (detected by ILR) of 21.5% at 2 years.[14]

With regards to duration of AF we also feel, similar to Asaithambi et al., that in the context of stroke, AF of any duration is clinically relevant and warrants extensive monitoring to identify longer episodes at the very least, if not consideration of anticoagulation.[65] This is supported by the results of a recent Spanish study, which showed that anticoagulating even short episodes of AF results in a decrease of stroke recurrence, although the study did define AF episodes as being a minimum of 1 minute in duration.[66] In detail, 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 >1min was detected in 58.5% of patients in the ILR group versus 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 versus 37.6% of patients in the control arm. This led to a much lower stroke recurrence rate in the ILR arm, 3.3% versus 10.9% in the conventional arm, indicating that anticoagulating short AF episodes is beneficial.

In contrast, the Atrial Fibrillation Detected by Continuous ECG Monitoring Using Implantable Loop Recorder to Prevent Stroke in High-risk Individuals (The LOOP Study) randomized 6004 individuals aged 70-90 years with at least one risk factors for stroke to

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 versus 12.2% in the control group. Despite a three-times increase in the anticoagulation therapy in the ILR arm (29.7% versus 13.1%), there was no significant reduction in the risk of stroke or system embolism (p=0.11).[67] 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. It is likely, that anticoagulating even short episodes of AF is beneficial and reduces stroke recurrence in patients with ESUS although this would need to be identified in prospective randomized studies.

Future directions

Our risk prediction model also has the potential to identify a group of ESUS patients in sinus rhythm that could benefit from anticoagulation. Further studies are needed in this direction to assess the effectiveness of anticoagulating those at the highest risk of AF.

Study limitations

This was a retrospective case- control single centre study; however, our institute is the regional center for ILR implantation in post-stroke patients and is receiving referrals across a population of over 2 million people. Referrals for ILR were done at the discretion of the treating stroke physician, when they felt that other causes of stroke were excluded, and that the patient warranted a more prolonged search for AF. Therefore, selection bias could have occurred. TTE analysis was performed retrospectively in scans already

obtained and several measurements could not be performed as images were suboptimal. Due to the retrospective nature of the study, where medical records were reviewed and no patient contact was necessary, we have not been able to collect data regarding ethnicity. Moreover, parameters where over 35% of the values were missing were excluded. This included parameters that have previously been identified as strong predictors of AF such as NT-pro BNP and troponin. LA reservoir strain and lateral PA were missing at random in 24% and 32% of cases respectively. This was within our *a priori* cut-off for multiple imputation, but a lower degree of missing data might have provided more accurate results. During the study period, the institution practice was to explant the ILR following AF detection, which precluded accurate analysis of AF burden. Although we have internally validated our risk model, we have not been able to provide external independent validation. Validating the PADS model in an unselected population of ESUS patients would be useful.

On the other hand, strengths of our study include it being the first study aimed at developing a risk prediction model in patients specifically following ESUS incorporating TTE parameters of LA function. In addition, we used long-term monitoring with an ILR for AF detection, proving to be the best method with the highest diagnostic yield. We also included all adults diagnosed with stroke or TIA referred for an ILR to our institution, having no age limit in the inclusion criteria.

Conclusion

We have developed and internally validated the PADS risk prediction model to assess the individual risk of AF in post-stroke survivors. We incorporated imaging parameters of LA function and diagnosed AF using ILRs. This score outperformed existing AF prediction risk scores. PADS score can thus be utilized as a risk-stratification tool for decision-making in relation targeting ILR implant to identify AF in ESUS survivors. In addition, it may provide the ability to target anticoagulation in a suitable group of stroke patients at high risk of future AF who are currently in sinus rhythm.

Disclosures

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Authorship

PAC, JP, PJP and VSV contributed to the conception and design of the work. PAC, RC, LR, KK, EAW, TM, VT and VSV contributed to the acquisition, analysis, or interpretation of data for the work. UB and AP did the statistical analysis for the project. PAC, RC and VT drafted the manuscript. LR, UB, AP, TM, EAW, KK, JP, PJP and VSV critically revised the manuscript. All gave final approval and agreed to be accountable for all aspects of work ensuring integrity and accuracy.

Data Availability

Available from the corresponding author upon request

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Table 1. Baseline characteristics.				
Variable	**All patients (n 323)**	**AF (n 152)**	**No AF (n 171)**	**P value****
Demographic and anthropometric variables				
Age, mean (SD)	54.7 (14.8)	59.4 (13.9)	50.5 (14.4)	<0.001
Female, n (%)	126 (39.0)	60 (39.5)	66 (38.6)	0.872
BMI, mean (SD)	27.76 (4.7)	27.44 (4.6)	28.05 (4.8)	0.242
Clinical variables				
CCF, n (%)	1 (0.3)	0 (0)	1 (0.6)	0.319
HTN, n (%)	131 (40.6)	72 (47.4)	59 (34.5)	0.019
CAD, n (%)	22 (6.8)	9 (5.9)	13 (7.6)	0.548
Diabetes, n (%)	38 (11.8)	19 (12.5)	19 (11.1)	0.699
Cancer, n (%)	20 (6.2)	15 (9.8)	5 (2.9)	0.015
SBP, mean (SD)	129.0 (17.6)	132.1 (16.8)	126.2 (17.9)	0.013
DBP, mean (SD)	74.7 (10.6)	76.56 (10.7)	73.1 (10.2)	0.004
>50% stenosis in a major extracranial/ intracranial vessel, n (%) *	16 (5.0)	11 (7.2)	5 (2.9)	0.075
HTN treatment, n (%)	128 (39.6)	69 (45.4)	59 (34.5)	0.046
Statins, n (%)	266 (82.3)	132 (86.8)	134 (78.4)	0.046
Lymphocytes (10^9 cells/l), mean (SD)	2.0 (1.0)	1.8 (0.7)	2.1 (1.2)	0.073
neutrophil/lymphocyte ratio, median (IQR)	2.5 (1.8, 3.6)	2.7 (1.9, 3.8)	2.3 (1.7, 3.5)	0.035
Platelet/lymphocyte ratio, median (IQR)	123.1 (95.3, 173.3)	131.7 (101.5, 175.0)	117.6 (92.1, 166.7)	0.046
eGFR (ml/min/1.73 m^2), mean (SD)	89.9 (24.5)	85.5 (22.34)	93.7 (25.8)	0.005
CRP (mg/dL), median (IQR)	2.0 (1.0, 6.0)	2.0 (1.0, 6.0)	2.0 (1.0, 5.2)	0.374
Alkaline phosphatase (U/l), median (IQR)	81.0 (67.0, 101.0)	86.0 (71.0, 104.0)	78.0 (65.0, 96.0)	0.033
Echocardiographic variables				
LV mass indexed (g/m^2), mean (SD)	83.8 (19.0)	86.0 (19.6)	81.3 (18.1)	0.046
LVEF biplane (%), median (IQR)	61.1 (57.9, 65.0)	60.7 (57.9, 64.2)	61.9 (57.3, 65.2)	0.166
LV GLS (%), mean (SD)	16.3 (3.4)	16.2 (3.1)	16.4 (3.7)	0.756
Average S' wave (cm/s), mean SD	8.7 (1.9)	8.5 (2.0)	8.9 (1.8)	0.100
E wave deceleration time (ms), median (IQR)	217.0 (187.0, 254.0)	222.0 (191.0, 263.0)	210.0 (180.0, 239.0)	0.007
E/A ratio, median (IQR)	0.9 (0.8, 1.2)	0.9 (0.7, 1.2)	1.0 (0.8, 1.3)	0.022
Septal E' wave (m/s), mean (SD)	7.7 (2.5)	7.2 (2.2)	8.2 (2.7)	0.002

Lateral E' wave (cm/s), mean (SD)	10.3 (3.5)	9.9 (3.3)	10.7 (3.7)	0.073
Lateral PA (ms), mean (SD)	74.7 (19.7)	78.2 (20.4)	71.4 (18.5)	0.011
LAV maximum indexed (ml/m^2), median (IQR)	25.3 (21.1, 30.8)	26.3 (21.5, 32.2)	24.2 (20.8, 28.9)	0.079
LAV min indexed (ml/m^2), median (IQR)	10.8 (8.7, 13.4)	11.3 (9.3, 14.0)	10.6 (8.2, 13.0)	0.018
LA reservoir strain (%), mean (SD)	27.5 (9.1)	25.3 (7.3)	29.7 (10.1)	<0.001
LA contractile strain (%), mean (SD)	15.0 (5.9)	13.4 (4.4)	14.9 (5.1)	0.018
LA conduit strain (%), median (IQR)	12.1 (8.8, 17.1)	11.2 (8.3, 15.0)	13.2 (9.5, 19.1)	0.003
Existing scores				
HAVOC, median (IQR)	1 (0,3)	2 (0,3)	1 (1,3)	0.041
CHA_2DS_2-VASc, median (range)	3 (3,4)	4 (3,5)	3 (3,4)	0.004
HATCH, median (IQR)	2 (2,3)	3 (2,3)	2 (2,3)	0.003
C_2HEST score, median (IQR)	0 (0,1)	1 (0, 1)	0 (0,1)	0.004
Brown ESUS AF, median (IQR)	0 (0,1)	0 (0,1)	0 (0,0)	<0.001
NDAF, median (IQR)	3 (1,3)	3 (1,3)	3 (1,3)	0.215
HASBLED, median (IQR)	2 (2,3)	3 (2, 3)	2 (2,3)	<0.001
ORBIT, median (IQR)	1 (1,1)	1 (1,2)	1 (1,1)	0.245

AF, atrial fibrillation; BMI, body mass index; CAD, coronary artery disease; CCF, congestive cardiac failure; cm, centimetre; CRP, C reactive protein; DBP, diastolic blood pressure; dL, decilitre; eGFR, estimated glomerular filtration rate; GLS, global longitudinal strain; HTN, hypertension; IQR, interquartile range; kg, kilogram; l, litre; LA, left atrium; LAEF, left atrial emptying fraction; LAV, left atrial volume; LVEF, left ventricular ejection fraction; LVIDd, left ventricular internal diameter in end-diastole; LVIDs, left ventricular internal diameter in systole; m, meter; m^2 squared meter; mg, milligram; ms, millisecond; s, second; SBP, systolic blood pressure; SD, standard deviation; U, international units

* not in the arterial distribution of the index event

**Quoted P value is for the difference between the AF and non AF groups

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Table 2. Atrial arrhythmia characteristics

Rhythm	Number of patients with arrhythmia	Number of episodes	Number of patients with symptomatic episodes
Atrial fibrillation	114	375	10 (8.8%)
Atrial flutter	38	188	5 (13.2%)

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Table 3. Univariate analysis.			
Variable	**Lower CI**	**OR**	**Upper CI**
Age	1.03	1.04	1.06
HTN	1.09	1.71	2.67
SBP	1.01	1.02	1.03
DBP	1.01	1.03	1.06
HTN treatment	1.01	1.58	2.47
Statins	1.01	1.82	3.30
Lymphocytes	0.57	0.77	1.03
eGFR	0.98	0.99	1.00
CRP	1.00	1.02	1.05
Alkaline phosphatase	1.00	1.01	1.02
LV mass indexed	1.00	1.01	1.03
E wave deceleration time	1.00	1.01	1.01
E/A ratio	0.21	0.42	0.83
Septal E' wave	0.76	0.84	0.94
Lateral E' wave	0.87	0.94	1.01
Average S' wave	0.78	0.90	1.02
Lateral PA	1.00	1.02	1.03
LAV maximum indexed	1.00	1.03	1.06
LAV minimum indexed	1.02	1.08	1.14
LA reservoir strain	0.92	0.95	0.97
LA contractile strain	0.89	0.94	0.99
LA conduit strain	0.89	0.92	0.97
CI, confidence interval; CRP, C reactive protein; DBP, diastolic blood pressure; dL, decilitre; eGFR, estimated glomerular filtration rate; HTN, hypertension; LA, left atrium; LAV, left atrial volume; OR, odds ratio; s, SBP, systolic blood pressure * not in the arterial distribution of the index event			

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Table 4. PADS risk prediction model.			
Variable	**Low CI**	**OR**	**High CI**
Lateral PA	1.00	1.01	1.03
Age	1.02	1.04	1.05
DBP	1.00	1.03	1.05
LA reservoir strain	0.94	0.97	1.00
CI, confidence interval; DBP, diastolic blood pressure; LA, left atrium; OR, odds ratio			

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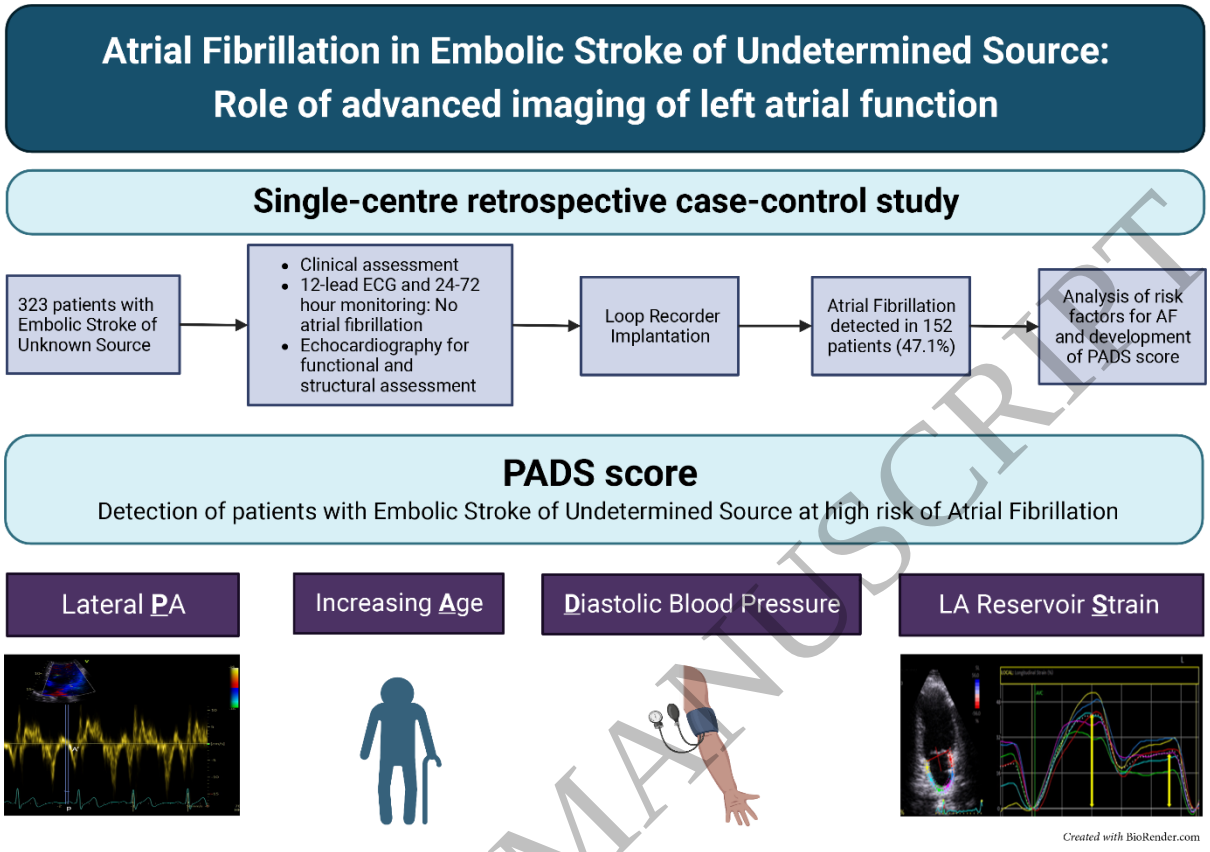

Graphical Abstract
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