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Early atrial fibrillation detection is associated with higher arrhythmic burden in patients with loop recorder after an embolic stroke of undetermined source

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ABSTRACT

Background: After an embolic stroke of undetermined source (ESUS), long-term monitoring is recommended to start an anticoagulation therapy in patients with documented atrial fibrillation (AF). Literature is sparse about the AF burden following an ESUS, although this might have significant implications in terms of clinical management and therapeutic strategy. Our primary aim was to evaluate a possible association between early detection of AF (within 90 days from the ILR implantation) and higher AF burden.

Methods: This is a retrospective single-center study of 129 consecutive patients who received implantable loop recorders (ILRs) after an ESUS for detection of subclinical AF and their AF burden.

Results: Mean age was 70.3 ± 10.4 years old (males: 51.9%). Atrial fibrillation was found in 40.3% of patients. Patients with AF were older, presented a higher CHAD₂S₂-Vasc Score and greater left atrial volume compared with patients without AF. The median AF burden was 1.2%; 59% of patients had the first AF episode within 90 days from the ILR implant while 41% experienced the first episode later than 90 days. The AF burden was significantly higher in the former group. Of note, the univariate analysis showed that only early AF detection was significantly associated with AF burden >1% (OR 20.0; 95% CI 1.68–238.6, $p = 0.01$).

Conclusions: The early AF detection was found to be significantly associated with a higher burden of AF.

1. Introduction

Silent atrial fibrillation (AF) is a well-recognized cause of embolic stroke of undetermined source (ESUS). An appropriate cardiac rhythm monitoring should be performed, for at least 24 h, to tailor the better treatment for prevention of recurrent stroke (antiplatelet or anticoagulant therapy); this includes in-hospital monitoring, ECG-Holter, event recorder and implantable loop recorder. Insertable cardiac monitors (ICMs) are superior to conventional follow-up for detecting subclinical AF after an ESUS [1]; subclinical AF includes atrial high-rate episodes (AHRE) which were confirmed to be AF or atrial flutter by visually reviewed intracardiac electrograms [2]. Continuous monitoring of heart rhythm through cardiac implantable devices led to the concept of AF

burden [3]. There are many ways one can define AF burden, such as the duration of the longest AF episode or total of AF during a certain monitoring period (ex: 24 h); intuitively, the best definition for AF burden is the proportion of time an individual is in AF during a monitoring period, expressed as a percentage [4]. The primary aim of this study was to determine an association between early detection of AF (we chose a cut off of 90 days from the ILR implantation as the ASSERT trial in whom they analyzed patients implanted with a pacemaker or an implantable cardiac defibrillator [5]) and higher AF burden (an arbitrary value of 1% was taken).

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2. Methods

This is a retrospective single-center study including 129 consecutive patients who received implantable loop recorders (ILRs) (Reveal LinQ™ or LinQ II™, Medtronic, MN, USA), after an ESUS, between March 2015 and March 2022. The diagnostic definition of ESUS [6] included 1) stroke detected by computed tomography or magnetic resonance imaging that is not lacunar, 2) absence of extracranial or intracranial atherosclerosis causing $\geq 50\%$ luminal stenosis in arteries supplying the area of ischaemia, 3) no major-risk cardioembolic source of embolism, and 4) no other specific causes of stroke identified (such as arteritis, dissection, migraine/vasospasm, drug misuse).

All patients were followed through remote monitoring for a minimum follow up of 6 months. The AF burden (expressed in percentage) was defined as the proportion of time in AF out of all monitoring time. According to the ASSERT trial [5], a cut off of 90 days from the ILR implantation was used to define early detection of AF.

The cut-off of AF burden was assessed on the basis of two main observations: firstly, the median value of AF burden was 1.2% among patients with AF; secondly, a preliminary ROC curve was made to assess the best cut-off value of AF burden identifying early AF detection and 1% was the best cut-off value. In detail, a burden of AF higher than 1% was found the best cut-off value (AUC 0.827, sensitivity 82.6%, specificity 81.2%) for identifying early AF detection within 3 months.

Continuous data are expressed as mean \pm SD or median and 25th–75th percentiles (interquartile range), as appropriate. Categorical variables are expressed as absolute and relative frequencies. Comparisons of continuous variables were done with a Student *t*-test (or Mann Whitney *U* test, as appropriate) and binomial variables with χ^2 or Fisher test as appropriate. Factors predicting an AF burden higher than 1% were identified by univariable analysis using the logistic regression model; a 2-tailed probability value of <0.05 was deemed significant. Statistical analyses were conducted using the SPSS software (SPSS v22, Chicago, IL).

3. Results

Out of 129 consecutive patients the mean age was 70.3 ± 10.4 years old (67 males, 51.9%); the mean value of left ventricular ejection fraction was $61 \pm 5.8\%$, with a mean follow up of 26.3 ± 12.2 months (median: 23 and IQR: 15; 37) and a mean CHAD₂S₂-Vasc Score was 4.49 ± 1.26 (median: 5 and IQR: 4; 6). Apart from 5 cases (4%) where diagnostic brain imaging was not available, 85 ESUS were secondary to an ischemic injury in the anterior circulation (69%), 29 (23%) in the posterior circulation, 10 (8%) in both anterior and posterior locations. Of note, 52 lesions were located in the right side of the brain (42%), 59 lesions were located in the left side (48%) and 13 in both cerebral sides (10%).

At least one episode of AF was found by ILR in 40.3% of patients (“AF group”: 52 patients, “No AF group”: 77 patients) and each intracardiac electrogram was visually reviewed by two physicians. The Cohen’s kappa coefficient for AF detection (or intraclass correlation coefficient) was 0.92 (95%CI, 0.88–0.97”).

Patients with AF were older (74.6 ± 10.5 vs 67.1 ± 9.2 year-old, $p < 0.001$) and presented higher CHAD₂S₂-Vasc Score (4.80 ± 1.36 vs 4.27 ± 1.15 , $p = 0.02$) and greater left atrial volume (42.0 ± 17.1 vs 31.1 ± 8.1 ml/mq, $p < 0.01$) compared with patients without AF. The AF burden was available and could be assessed only in 39 out of 52 patients with AF episodes. Among 39 patients, the median AF burden was 1.2% (IQR: 0.1%; 14.6%); 23 patients (59%) had the first AF episode within 90 days from the ILR implant compared with 16 patients (41%) which experienced the first episode later than 90 days. The AF burden was significantly higher in the first group (median 3.9% [IQR: 1.2%; 30.9%] vs median 0.1% [IQR: 0.03%; 0.75%]; $p = 0.001$) (Fig. 1). Of note, the univariate analysis (Table 1) showed that only the first AF episode recorded within 90 days was significantly associated with AF burden

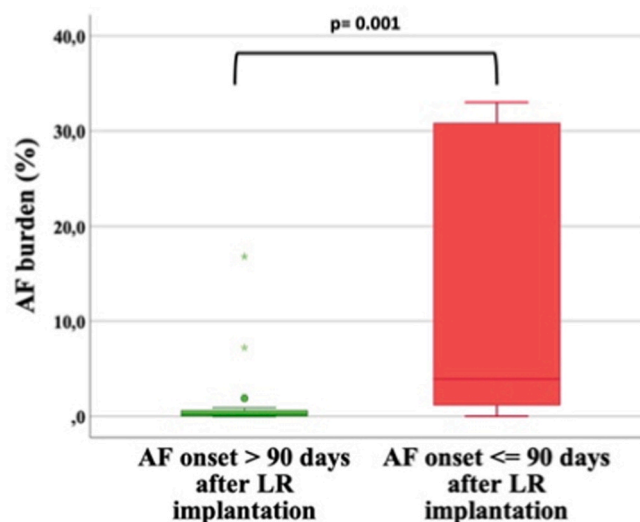


Fig. 1. The picture shows that the AF burden was significantly higher in patients with early detection of AF within 90 days compared with patients with later onset of AF (respectively, median 3.9% [IQR: 1.2%; 30.9%] vs median 0.1% [IQR: 0.03%; 0.75%]; $p = 0.001$). AF: atrial fibrillation. LR: loop recorder.

Table 1

Univariate analysis.

	OR	95% CI	P value
Age	1.020	0.94–1.11	0.65
Male sex	0.55	0.16–1.90	0.36
Left atrial volume	1.11	0.96–1.28	0.14
Arterial hypertension	1.80	0.44–7.31	0.41
Diabetes	1.61	0.28–9.23	0.59
Dyslipidemia	1.01	0.23–4.31	0.90
E/E'	1.14	0.63–2.06	0.66
Left ventricular ejection fraction	1.066	0.92–1.24	0.40
CHAD ₂ S ₂ -Vasc Score	1.62	0.85–3.09	0.14
AF onset within 90 days	20.0	1.68–238.6	0.01
Anterior circulation	1.08	0.22–5.33	0.92
Right cerebral side	0.34	0.08–1.34	0.12

OR: odds ratio. CI: confidence interval. AF: atrial fibrillation.

$>1\%$ (about 7 h for month) (OR 20.0; 95% CI 1.68–238.6, $p = 0.01$).

4. Discussion

In our study, AF was detected by ILR, after an ESUS, in more than one third (about 40%) of patients. Our finding is higher than data reported in literature; for instance, Ungar et al. [7] found subclinical AF in more than a quarter (about 30%) of ESUS patients during a 2-years follow-up period. Our finding of high incidence of AF detection are probably due to an accurate selection of patients who are candidates for ILR implantation and at higher risk of cardioembolic stroke secondary to AF. According to previous studies, increased values of AF burden are associated with higher risk of stroke although the relationship is not well characterized in terms of functional form [4,8]. In addition, higher AF burden seems to be also associated with a greater risk and prevalence of heart failure (HF); the progression from paroxysmal to persistent and permanent forms leads to increased risk of acute decompensation of HF [8]. Suman-Horduna et al. [9] showed that a higher proportion of time spent in sinus rhythm is associated with a greater improvement of NYHA class. In the EURObservational Research Programme-Atrial Fibrillation (EORP-AF) General Pilot Registry, the overall 1-year outcome, in terms of all-cause mortality, of patients with non-paroxysmal AF when compared with paroxysmal AF, was worse; this finding was probably

related to a worse clinical risk profile [10].

Of note, the CASTLE-AF trial [11] compared catheter ablation versus the standard conventional therapy in patients with left ventricular dysfunction and AF; after a median follow up of more than 3 years, patients getting catheter ablation had significantly fewer hospital admissions as well as death from worsening HF. In addition, 63% of patients in the ablation group were in sinus rhythm, as compared with 22% of those in the medical-therapy group ($P < 0.001$). Therefore, longer-duration normal sinus rhythm and lower AF burden might improve outcomes by means of a number of mechanisms, including greater atrial emptying, all of which translate into improved cardiac output. A recent subanalysis confirmed that the AF burden at 6 months was predictive of hard clinical outcomes in HF patients with AF [12].

Moreover, a recent randomized controlled trial (the EAST-AFNET4) [13] about the early treatment of AF for stroke prevention, showed that an early rhythm control strategy was significantly effective in reducing cardiovascular complications (cardiovascular death, stroke, or hospitalization for worsening heart failure or for acute coronary syndrome) compared with usual care only in patients with a high comorbidity burden, defined as a CHA_2DS_2-VASc score ≥ 4 . This data highlights the importance of not withholding rhythm control therapy in patients with recently diagnosed AF and multiple comorbidities.

Apart from AF detection, ILRs provide crucial information such as AF burden severity and its temporal changes and dynamic aspects [14]; according to this data, the clinical management can be adequately tailored for each patient and the proper treatment can be properly chosen. Then, the antiarrhythmic treatment and the rhythm control vs rate control strategy need to be also evaluated according the patients' symptoms.

In the present study we found that an early AF onset, after a cerebrovascular event, is significantly associated with a higher AF burden. As abovementioned, this information might be crucial to optimally manage the therapeutic strategies in order to improve the quality of life of this subset of patients and to minimize the burden of AF itself.

Nevertheless, further studies with a larger sample size including the evaluation of clinical outcomes are necessary to confirm our results.

5. Limitations

The most important limitation of this study is related to its retrospective nature and observational design. A further limitation is the relatively low number of patients included. Moreover, among 52 patients with AF, the arrhythmic burden was available only in 39 patients (75%) because of lack of data.

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Credit author statement

Sofia Capocci: conceptualization, methodology, data curation, writing; **Luca Tomasi:** original draft preparation, supervision, validation; **Cecilia Zivelonghi:** data curation, writing; **Bruna Bolzan:** supervision, review & editing; **Giampaolo Berton:** data curation, software, original draft preparation; **Mattia Strazzanti:** writing, supervision, software; **Elena Franchi:** data curation, supervision; **Ruggero Tomei:** supervision; **Francesca Vassanelli:** methodology, supervision; **Manuel Cappellari:** supervision, review & editing, validation; **Flavio L. Ribichini:** review & editing, validation; **Giacomo Mugnai:** formal analysis,

writing, review & editing, validation.

Declaration of competing interest

The authors report no relationships that could be construed as a conflict of interest.

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