Insertable cardiac monitor detection of silent atrial fibrillation in candidates for percutaneous patent foramen ovale closure

INSERTABLE CARDIAC MONITOR IN OLDER PATIENTS CANDIDATES TO PERCUTANEOUS PFO CLOSURE (ICM/PFO Registry Study). EFFECTIVENESS IN SILENT ATRIAL FIBRILLATION DETECTION.

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ABSTRACT

Background. An underlying atrial vulnerability or a pre-existing misdiagnosed atrial fibrillation (AF) in some patients (pts) candidates to PFO closure may lead to an unnecessary percutaneous intervention. The ischaemic recurrences after device implantation affect mainly over 55 years old pts, usually in the absence of a significant residual shunt. An improvement in AF detection algorithms may lead to a more accurate clinical selection of pts candidates to PFO closure.

Aim. To define the additional rate of paroxysmal AF detection, through a 6-months prolonged insertable cardiac "loop-recorder" monitoring (ICM), in patients over 55 years old with cryptogenic stroke and candidates to percutaneous PFO closure.

Methods. Pts were candidates to PFO closure in presence of significant right-to-left shunt and one or more of the following high-risk features: permanent right-to-left shunt, atrial septal aneurysm, prominent Eustachian valve, recurrent brain ischemia, previous deep vein thrombosis, thrombophilia. **ICM inclusion criteria**: previous cryptogenic stroke (CS), more than 55 y and one or more of the following AF risk factors: heart failure, hypertension, age older than 65years, diabetes, atrial runs, left atrium dilatation, left ventricle hypertrophy, pulmonary disease, thyroid disease, obesity. **ICM-detected AF threshold**: AF duration of more than 5 minutes was considered clinically meaningful, indicating oral anticoagulation and excluding a percutaneous treatment.

Results. From January 2008 to March 2017, 195 pts older than 55 years and suffering from CS underwent to ICM monitoring. Seventy (36%) pts of this cohort presented a high-risk PFO and were considered candidates to closure. In this group, the 6-months paroxysmal AF detection rate was 11,4% (8/70 pts). In the remaining AF-free cohort, 28 pts (45,2%) underwent to a percutaneous PFO closure (group A) and 34 (54,8%) were medically treated (group B). The following AF detection rate was 14,3% in group A and 0% in group B. The 36-months cumulative AF-free survival was 76%.

Conclusion. An occult pre-existing AF may lead to an unnecessary percutaneous intervention in a significant proportion of pts over 55 years old suffering from a CS. Strict preoperative AF rule-out protocols should systematically be applied in this group of pts. A 6-months prolonged ICM monitoring is advisable, allowing a more appropriate selection of pts.

INTRODUCTION

The percutaneous closure of patent foramen ovale (PFO) as secondary prevention for cryptogenic stroke is emerging as a safe and effective option in patients with high likelihood of PFO-related index event and high risk of recurrence. The results of CLOSE, REDUCE and RESPECT long-term trials, showing a significant reduction in recurrent strokes at the intention-to-treat analysis, confirm this statement [1-3], but the atrial fibrillation (AF) rate up to 6% at the follow up [2] underlies the need of an improvement in the AF rule-out protocols. The reports of an unusually high incidence of AF after percutaneous closure of PFO [4-10] and the remarks that the ischemic recurrences affect mainly the older patients in the absence of a significant residual shunt [11-13], could be the consequence of an occult pre-existing AF.

In the setting of cryptogenic stroke (CS), the exclusion of AF is not an easy task, especially with regard to paroxysmal AF, which may occur without specific symptoms, and is usually under-detected if spontaneous resolution does occur [14]. In a patient with ischemic stroke or TIA, a routine 12-lead-ECG, as well as inpatient cardiac telemetry, or 24-hour Holter monitoring are the usual diagnostic tools used for AF detection. Since paroxysmal AF may have an irregular distribution, they result in under-detection.

The aim of this study is to define the additional rate of paroxysmal AF detection, through a 6-month prolonged insertable cardiac "loop-recorder" monitoring (ICM), in patients over 55 years old with cryptogenic stroke candidates to percutaneous PFO closure.

METHODS

Patients' enrolment

Between January 2008 and March 2017, we prospectively enrolled all consecutive patients older than 55 years discharged from the Stroke Unit of our Institution with the diagnosis of ischemic CS of presumed embolic origin and undergoing ICM monitoring.

An ICM monitoring was performed in the presence of one or more of the following AF risk factors: heart failure, hypertension, age ≥ 65 years, diabetes, atrial runs during inpatient cardiac telemetry

or 24-hour Holter monitoring, left atrium dilatation, left ventricle hypertrophy, pulmonary disease, thyroid disease, obesity.

It has been our institution's policy to perform PFO closure only in patients with high-risk features, as described elsewhere [12, 15]. The pts were candidates to PFO closure if they showed a right-to-left shunt and one or more of the following clinical or anatomical high-risk features: permanent right-to-left shunt, interatrial septum aneurysm (IASA), prominent Eustachian valve, recurrent brain ischemia, previous deep vein thrombosis, thrombophilia not requiring oral anticoagulation.

Definitions and exclusion criteria

Cerebral ischemia was defined as the presence of clinical symptoms evaluated by a neurologist (transient ischemic attack, TIA), or the evidence at CT scan or MRI of one or more cerebral ischemic lesions with cardio-embolic characteristics (silent ischemia), or both (stroke) [16]. Ischemic lesions were considered as embolic when presenting with one or more of the following features: cortical or iuxta-cortical location, multiple lesions or multiple site lesions. Deep and lacunar stroke were excluded.

Cerebral ischemia was defined "cryptogenic" if other causes were excluded after complete clinical and instrumental evaluation. All patients underwent to 12-lead ECG, 48-hours in-hospital continuous telemetry, 24-hours Holter monitoring, transthoracic echocardiography (TTE), cerebral computed tomography (CT) or MRI scans, carotid and vertebro-basilar systems ultrasound or angio-MRI. Vascular malformations, intracranial stenosis and dissections were ruled-out by intracranial-MRI and/or angio-CT. Patients with any episode of AF or with significant atheromasic disease of the ascending aorta or of the carotid vessels, or with intracardiac masses or thrombosis, were excluded.

All patients underwent complete thrombophilia screening to assess the coagulation state. Hypercoagulable states or haematological disorders requiring oral anticoagulation were considered as exclusion criteria.

The shunt was evaluated either with transcranial Doppler (TCD) or TEE. The presence and morphology of PFO was assessed by transesophageal echocardiography (TEE). Presence of right-to-left shunt was assessed basally and after Valsalva manoeuvre release after the injection of bubble contrast. Severe right-to-left shunt was described as either: (a) detection at TCD of uncountable MES in the middle cerebral artery within the first five cardiac cycles after the injection in the

antecubital vein, or (b) assessment by contrast TTE or TEE of uncountable microbubbles passing from the right to the left atrium. IASA was defined as a flapping movement of the interatrial septum during the cardiac cycle, with an excursion ≥ 1 cm [17]. A left atrial dilatation was defined as a volume of more than 29 ml/m2 [18].

Procedures

Implantable loop recorder (ILR). All patients included in the registry were implanted with an ILR (Medtronic Reveal Plus XT 9526; Medtronic Inc., Minneapolis, Minnesota, USA; Medtronic CareLink Network, Medtronic Inc., Minneapolis, Minnesota, USA). This device has a solid-state loop memory capable of storing all significant electrocardiographic events. Data can be transmitted over the telephone or wirelessly. The device was implanted subcutaneously in the electrophysiology laboratory by an interventional cardiologist under local anaesthesia. Before discharge, the device was programmed with semiautomatic activation mode allowing storing of any AF episode longer than 5 min. Moreover, all patients were trained to activate the device in case of palpitations, syncope or recurrence of stroke/TIA. Studies about performance of ILR in detecting atrial fibrillation (Medtronic Reveal XT) report a high sensitivity rate, up to 96% [19]. The specificity of the algorithms for automatic detection of AF showed to be low because of premature atrial or ventricular complexes, myopotential oversensing, sinus arrhythmia or undersensing of R waves, highlighting the importance of human overreading of automatically detected episodes. In our study, the percentage of AF automatic misclassification was about 25% of cases. The manual evaluation was performed to avoid this limitation. All episodes lasting more than 5 min were blinded assessed by two independent observers. When an episode was not clearly classified by the two observers, a third physician reanalysed the recorded ECG.

Interventional PFO closure. The peri- and post-procedural management of the pts treated with percutaneous PFO closure were already described elsewhere [12, 15].

Patient follow-up

Clinical examination, 12-lead ECG and ambulatory ILR control were performed at the enrolment, at 1, 6, 12 months, then yearly and in case of symptoms suggestive of AF or remote AF detection. Following AF detection and diagnosis, therapy was switched from antiplatelet to anticoagulant. The peri-procedural paroxysmal AF, defined as in-hospital detected episode, was not considered an AF

event at follow-up. All data were collected in a dedicated database. Informed, written consent was obtained from all patients. A residual disability impairing the possibility to express an informed consent was an exclusion criteria.

The primary endpoint was the additional rate of paroxysmal AF detection, through a 6-months prolonged ICM monitoring, over the usual AF rule-out protocol (prolonged inpatient cardiac telemetry and/or 24-hour Holter monitoring). Secondary endpoint was the safety of ICM monitoring in terms of ICM-related adverse events (infection, erosion, removal) rate.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation and compared using the Student's t-test. The Chi-square test or Fisher's exact test were performed for categorical variables. Event free survival time during the follow up was assessed with the Kaplan Meier curve. All the tests were two-tailed and a value of $p<0.05$ was considered statistically significant. All analyses were performed using SPSS 20.0 (SPSS, Chicago, IL, USA).

RESULTS

From January 2008 to March 2017, 195 pts suffering CS underwent ICM monitoring. Among these pts, 70 (36%) showed a PFO with high-risk features and were candidates to closure. In this group the prolonged ICM monitoring allowed a 6-months paroxysmal AF detection rate of 11,4% (8/70 patients). The mean number of AF episodes per patient was 8,75 ± 11,32. The maximum AF duration time per patient ranged from 5 minutes to 19 hours.

Among the 62 patients free from AF, 28 (45,2%, group A) underwent percutaneous PFO closure and 34 (54,8%, group B), were medically treated, because of the referring physician's decision and/or patient's refusal. One patient (3%) was lost at follow-up. The following AF detection rate was 14,3% in group A (4 patients) after a mean procedure-to-AF detection time of 6,75 ± 2,06 months and 0% in group B (Figure 1).

The baseline characteristics were not significatively different between pts with and without AF, except for a higher prevalence of atrial septal aneurysm in the AF-free group (56.5% vs. 12.5%; p 0.02), (Table 1).

The mean follow up duration was 18.9 ± 11.9 months. No statistically significant differences were found at follow-up between the two groups regarding bleeding and recurrent stroke rate (Table 2).

The cumulative AF-free survival was 88,4% at 6 months and 73,4% after 36 months (Figure 2).

No patients suffered any side effect (pocket infection or erosion, migration) related to the implanted loop recorder.

DISCUSSION

The main findings of the study are: 1) A 6-months prolonged ICM monitoring allows detecting a significant rate of silent AF in this prespecified group of pts; 2) the loop-recorder monitoring was safe without any detectable side effect.

It is still matter of debate if PFO was "per se" associated with an increased incidence of atrial arrhythmias. Only few dated and small series of unselected patients with IASA reported a relatively high prevalence of atrial tachyarrhythmia (AT), AF and atrial flutter, up to 16%, in patients without any others structural abnormalities and without a known history of hypertension or coronary artery disease [20]. No large-scale clinical studies aimed to confirm these findings are available. The concept of "atrial vulnerability" based on the study of effective refractory periods (ERP), atrial conduction time (latent vulnerability) and inducible sustained AF, has been developed as a reliable predictor of AT and AF [21-22]. Some case–control studies including young patients (≤55 years) with CS and atrial septum abnormalities, defined as PFO, ASA or both, clearly demonstrated a significant higher incidence of inducible sustained AT (from 62% to 75%) and atrial vulnerability (from 45% to 52%) [23-24]. These results suggest that transient AT may occur in the presence of PFO and/or ASA and that the higher embolic risk may be also due to a greater potential for paroxysmal AF. Moreover, some patients with presumed CS submitted to PFO closure, may have AF as an under-detected risk factor for ischemic events. A pre-existing misdiagnosed AF may become clinically evident only after the PFO closure. A reported comparison of two cohorts of patients who

underwent transcatheter PFO closure for CS or other index events, confirmed this hypothesis, demonstrating a significantly higher occurrence of AF in CS patients [9].

Our study demonstrates that in pts with CS older than 55 years and candidates to percutaneous PFO closure, a 6-months ICM monitoring, over the usual AF rule-out diagnostic tools, allows to identify a significant additional proportion (up to 11%) of silent AF. An interventional PFO treatment in this group of pts would be inappropriate. Only few observational case series described the prevalence of AT/AF in patients with PFO and CS candidates to percutaneous closure. The reported rates vary widely from 1.2% to 10%, largely depending on the detection criteria [25]. In the randomized, controlled trial Cristal AF, the ICM long-term monitoring, compared with conventional follow-up, in patients with a recent CS, resulted in a significantly higher rate of detection of AF (8,9% versus 1,4% at 6 months and 12,4% versus 2% at 12 months) [26]. The higher rate of detection of AF with ICM was consistent across all the prespecified subgroups included the presence or absence of PFO, with no significant interactions.

In our study we demonstrate an additional rate of AF after PFO closure (14% of treated pts at a mean procedure-to-AF detection time of 6,75 ± 2,06 months). Different series [4-9] reported the occurrence of new onset AF following transcatheter percutaneous closure, ranging from 3.5% to 15%. The different inclusion criteria, particularly with respect to age, and the various AF detection methods could explain this wide variation. The reported predictors of AF occurrence were larger device size [4-5], older age [6-9] and larger left atrial size [9]. In the randomized controlled trial RESPECT [10], the total incidence of AF did not differ significantly between the closure group and the medical-therapy group (3.0% and 1.5%). Anyway, all these incidence rates appear to be higher than the expected in a general population of healthy subjects with a comparable age [27]. In the randomised controlled study REDUCE [2] the AF rate up at the follow raised up to 6%. It is noteworthy that the vast majority of the reported AF events occurred in the very first months after the procedure. This time-relation suggests that, in patients with an underlying atrial vulnerability, an inflammatory response of the atrial myocardium induced by the PFO closure devices, especially the large one may result in a triggering mechanism for the development of newly diagnosed AF.

In our study, we do not notice any adverse event related to ICM implantation. Conversely, in the Cristal AF trial the ICM removal rate was 2.4%, owing to infection at the insertion site or pocket erosion [26].

We included in our study only pts older than 55 years, given the very low incidence and prevalence of AF in younger patients [27-28] and the remark that the ischemic recurrences affect mainly the older patients in the absence of a significant residual shunt [11-13].

In the Cristal AF trial [26], the number of ICM implanted needed to detect a first episode of AF was 14 for 6 months of monitoring, 10 for 12 months, and 4 for 36 months. In our study, we made a pre-selection of ICM candidates, based on the results of our previous registry [29]. The CHA2DS2-VASc score in AF patients was designed for stroke prediction, but four of its six individual items have been identified to be strongly associated with AF risk prediction: congestive heart failure [30-31], hypertension [32], advanced age [30, 33-34] and diabetes [31, 35]. Atrial runs and LA dilation are also predictors of AF in patients with CS [30, 33, 36-37]. Finally, left ventricular hypertrophy, pulmonary or thyroid disease and obesity are also associated to an increased AF risk [38]. In our study, we selected the candidates to ICM monitoring based on these risk factors, with the aim of reduce the number of ICM needed to detect AF and improve the cost-effectiveness.

The major issue in a patient with PFO and suffering a CS, with an occult AF detected by an extensive ICM rhythm surveillance, is the appropriate selection of the thromboembolic prophylaxis. The duration of AF episodes plays a major role in determining which therapy is more appropriate, but it is still matter of debate, which is the proper time threshold to mandate anticoagulation.

In our study, we considered an ICM-detected AF threshold of at least 5 minutes clinically meaningful, indicating oral anticoagulation and excluding pts from a percutaneous treatment.

The HRS/EHRA/ECAS expert consensus statement on AF ablation suggested that 30 seconds of AF constitutes an AF episode [39]. The rationale for this assumption is that such a brief episode, when detected with an intermittent monitoring, is an indicator of more significant undetected periods of AF. The ICM extensive monitoring do not misses any clinically relevant AF paroxysm, thus the detection of brief episodes may be less critical. In the Mode Selection Trial (MOST), atrial high-rate arrhythmic episodes lasting at least 5 min predicted a higher incidence of the composite outcome of death or nonfatal stroke [40]. Higher duration of AF threshold, as indicated by SOS-AF study (1 hour), TRENDS trial (5.5 hours) and AT500 Registry (24 hours), in our opinion are inappropriate in the context of secondary stroke prevention [41-43]. Patients with CS and PFO, having a CHA2DS2-VASc score of at least two conferred by their prior stroke, are a cohort at elevated risk of recurrences. Therefore, the relevance of transient episodes of AF may be greater in this group than AF detected incidentally in patients without a prior stroke.

The main limitation of this study is its relatively small cohort of pts included and the lack of randomization. On the other hand, to our knowledge, this is the first investigation reported on the efficacy and safety of a prolonged ICM monitoring in patients with CS and candidates to PFO closure. The findings and the rationale of this unique report may have an impact on the daily practice of this particular subgroup of pts.

CONCLUSIONS

An underlying atrial vulnerability or a pre-existing misdiagnosed atrial fibrillation (AF) may lead to an unnecessary percutaneous intervention in pts older than 55 years with CS. An improvement in silent AF detection algorithms by means of a 6-months prolonged ICM monitoring lead to a more accurate clinical selection of CS pts candidates to PFO closure.

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FIGURES

Figure 1.

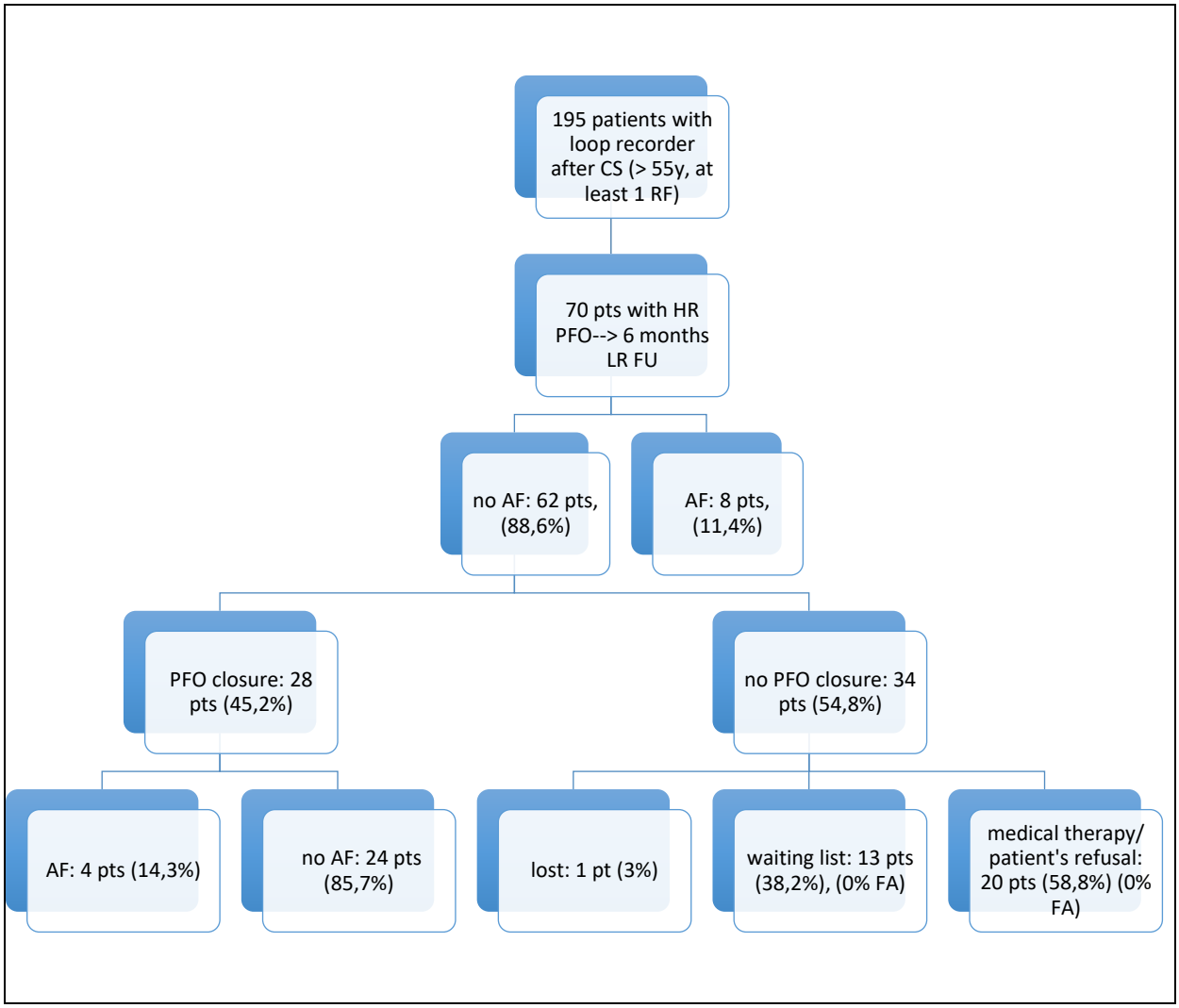
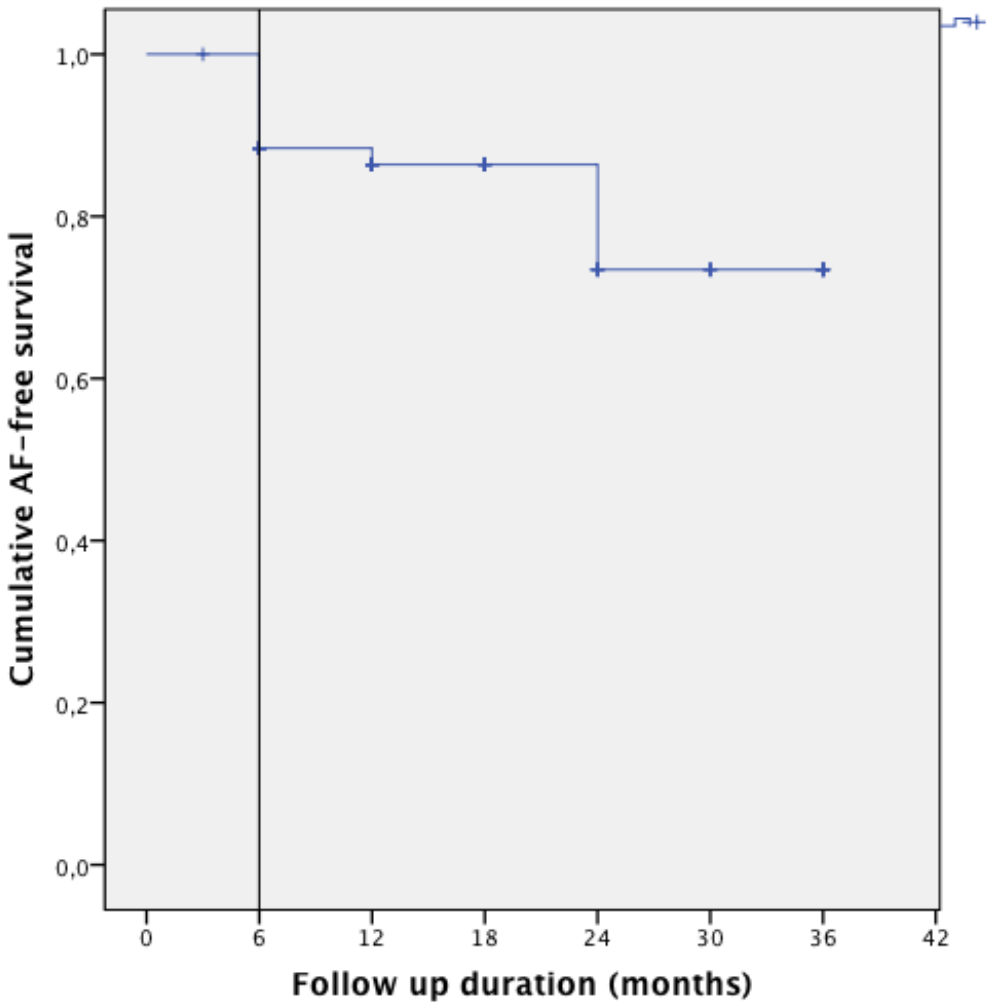


Figure 2.


Cumulative AF-free survival
1,0
0,8
0,6
0,4
0,2
0,0
0
6
12
18
24
30
36
42
Follow up duration (months)

TABLES

	All patients (n = 70)	Absence of atrial fibrillation (n = 62)	Presence of atrial fibrillation (n = 8)	p-value
Male sex	44 (62.9%)	38 (61.3%)	6 (75.0%)	0.45
Age, years	58.9 ± 7.5	58.8 ± 7.5	59.5 ± 8.1	0.71
Hypertension	43 (61.4%)	38 (61.3%)	5 (62.5%)	0.95
Diabetes	5 (7.1%)	5 (8.1%)	0 (0%)	0.41
CHADS2	0.77 ± 0.77	0.77 ± 0.78	0.75 ± 0.70	0.93
CHADSVASC	1.27 ± 0.90	1.27 ± 0.91	1.25 ± 0.89	0.94
HASBLED	0.64 ± 0.70	0.60 ± 0.67	1.00 ± 0.93	0.13
Deep venous thrombosis	1 (1.4%)	1 (1.6%)	0 (0%)	0.72
Trombophilic state	5 (7.1%)	4 (6.5%)	1 (12.5%)	0.53
TCD severe shunt	42 (60.0%)	37 (59.7%)	5 (62.5%)	0.88
TCD pattern • **MIld (<10 MES)** • **Moderate (>10 MES)** • **Severe (> 25 MES)**	 11 (15.7%) 17 (24.3%) 42 (60.0%)	 8 (13%) 17 (27,4%) 37 (59.6%)	 3 (37,5%) 0 5 (62.5%)	0.10
Basal shunt	43 (61.4%)	39 (62.9%)	4 (50.0%)	0.48
Eustachian valve	10 (14.3%)	10 (16.1%)	0 (0%)	0.22
Septal aneurysm	36 (51.4%)	35 (56.5%)	1 (12.5%)	0.02
Recurrent stroke	9 (12.9%)	7 (11.3%)	2 (25.0%)	0.28

Table 1. Baseline characteristics of the study population.

	All patients (n = 70)	Absence of atrial fibrillation (n = 62)	Presence of atrial fibrillation (n = 8)	p-value
Follow up duration, months	18.9 ± 11.9	17.1 ± 10.7	32.7 ± 12.5	0.01
New onset atrial fibrillation		4 (6.6%)	Not applicable	
Oral anticoagulant therapy intake	13 (18.6%)	8 (13.1%)	7 (87,5%)	<0.001
Pulmonary embolism	0 (0%)	0 (0%)	0 (0%)	
Cardiac tamponade	0 (0%)	0 (0%)	0 (0%)	
Bleeding	1 (1.4%)	1 (1.6%)	0 (0%)	NS
Recurrent stroke	1 (1.4%)	1 (1.6%)	0 (0%)	NS
Death	0 (0%)	0 (0%)	0 (0%)	

Table 2. Clinical events at follow up.