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► To cite this version:

Alexis Hermida, Mustafa Zaitouni, Momar Diouf, Pierre-Marc Lallemand, Floriane Fay, et al.. Long-term incidence and predictive factors of thromboembolic events after a cryoballoon ablation for atrial fibrillation. International Journal of Cardiology, 2020, 321, pp.99 - 103. <10.1016/j.ijcard.2020.08.005>. <hal-03493215>

HAL Id: hal-03493215

<https://hal.science/hal-03493215v1>

Submitted on 7 Nov 2022

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Long-term incidence and predictive factors of thromboembolic events after a cryoballoon ablation for atrial fibrillation

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Declarations of interest: none

Keywords: thromboembolic event, cryoballoon pulmonary vein isolation, CHA₂DS₂-VASc Score

ABSTRACT

Background: Long-term outcomes in terms of thromboembolic events (TEs) are poorly described after cryoballoon pulmonary vein isolation (cryo-PVI) for atrial fibrillation (AF). We evaluated the long-term incidence and predictive factors of TE after cryo-PVI.

Methods: All consecutive patients who underwent cryo-PVI for paroxysmal or persistent AF between November 2012 and October 2017 were included. They were prospectively followed for at least 12 months in the ablation center and then by their cardiologist. Data on all ischemic events (stroke, transient ischemic attack (TIA), systemic embolism) were collected.

Results: In total, 450 patients (78% men, median age 61 years) were included. The mean CHA₂DS₂-VASc score was 1.6 ± 1.3 and 26 patients (6%) had a history of stroke/TIA before the procedure. OAT was discontinued for 75 patients (17%) after the procedure, amongst whom 50 (67%) had no indication for long-term anticoagulation. Six patients experienced an ischemic event, all considered as a TE: three strokes, two TIAs, and one acute lower-limb ischemia. The mean follow up was 30 months. Thus, the incidence of TE was 0.53%/year. Three of the six patients who experienced a TE had no recurrence of atrial arrhythmia documented before, at the time, or after the event. All patients who experienced a TE had a class I or class IIa indication for long-term anticoagulation. After multivariate analysis, the CHA₂DS₂-VASc Score ($p = 0.0005$) was a predictor of TEs.

Conclusion: The long-term incidence of TEs after cryo-PVI was 0.53%/year. The CHA₂DS₂-VASc Score was the only independent predictor of TEs.

INTRODUCTION

Periprocedural rates of stroke/transient ischemic attack (TIA) appear to be comparable between cryoballoon ablation and radiofrequency (RF) catheter ablation for atrial fibrillation (AF), ranging from 0.3 to 0.5%. Long-term annual rates of stroke/TIA after RF catheter ablation for AF are well documented and range from 0.13%/year to 2.10%/year¹⁻⁹. However, this rate has not been reported for cryoballoon pulmonary vein isolation (cryo-PVI). In addition, systemic embolisms (acute limb ischemia, renal infarction, etc.) are rarely taken into account to quantify the ischemic risk after AF ablation.

Studies have shown that it is safe for low-risk patients for stroke/TIA to stop oral anticoagulant therapy (OAT) when the sinus rhythm is maintained after catheter ablation for AF.¹⁰⁻¹⁸ Several authors have stated that the CHA₂DS₂-VASc score does not predict the stroke/TIA risk after RF catheter ablation for AF.^{19,20}

We aimed to evaluate the long-term incidence and identify the predictive factors of thromboembolic events (TEs) after one cryo-PVI procedure.

METHODS

Study population

We prospectively included all consecutive patients with paroxysmal or persistent AF undergoing cryo-PVI at the Amiens-Picardie University Hospital between November 2012 and October 2017. Patients provided their signed informed consent to participate in the registry and the study was approved by the local ethics committee (PI2020_843_0056). All patients underwent preprocedural cardiac computed tomography to determine the left atrial volume and assess the pulmonary venous anatomy. The left atrial area and left ventricular ejection fraction were determined by transthoracic echocardiography prior to the cryo-PVI.

AF was classified according to the 2016 ESC Guidelines for the management of atrial fibrillation.²¹ Paroxysmal AF was defined as AF that terminates spontaneously or with intervention within seven days of onset. Persistent AF was defined as continuous AF that is sustained beyond seven days, including episodes that were terminated by cardioversion. Patients with continuous atrial fibrillation lasting > 1 year (long-standing persistent atrial fibrillation) were also included.

Cryoballoon ablation

Cryoballoon ablations were preceded by at least three weeks of OAT and contrast-enhanced multi-slice computed tomography (CT) of the left atrium. The cryoballoon ablation procedure is described in detail elsewhere.²² Briefly, left atrial access was obtained after fluoroscopy-guided transseptal puncture (SL1, St. Jude Medical, St. Paul, MN, USA) under conscious sedation. The sheath was flushed continuously with heparinized saline. One 4-min application was performed with a second-generation cryoballoon (28 or 23mm Advance balloon, Cryocath, Medtronic, MN, USA). An Achieve (Medtronic) intraluminal catheter was used for

all procedures, allowing real-time visualization of the atriovenous block during cryoapplication. A second 4-min cryoapplication was performed if there was persistent atriovenous conduction to achieve a complete block. During cryoablation in the right pulmonary veins, a quadripolar catheter was used to continuously pace the phrenic nerve adjacent to the superior vena cava. Cryoablation was stopped immediately if there was loss of diaphragmatic contraction to avoid subsequent right phrenic nerve palsy.

Follow-up

After ablation, antiarrhythmic drugs were maintained for at least the three-month blanking period. Anticoagulants were continued for the first three months and can be stopped when the risk of thromboembolism is low, the risk of bleeding high, or according to the decision of the referring cardiologist. Patients were followed-up at our institution at 3, 6, and 12 months, with a Holter-monitoring recording at three months and one year. After the first year, patients were followed by the patient's general practitioners and cardiologists. Subsequent information was obtained by phone and/or e-mail.

Recurrence of atrial arrhythmia was defined as an episode of AF or left atrial flutter documented by electrocardiogram (ECG) or Holter-monitoring, occurring after the three-month blanking period and lasting > 30 s.

The status of the anticoagulation therapy was determined at the time of the TE, the time of the first redo procedure for patients with a recurrence of atrial arrhythmia, or at the last follow up for patients without an atrial arrhythmia recurrence, as appropriate.

The indications for OAT were classified according to the recommendations of the 2016 ESC guideline on AF.²¹

Assessment of ischemic events

We collected data on all ischemic events (stroke, TIA, and systemic embolism) that occurred at least 72 h after the procedure. We thus searched for these events in all electronic files of the patients during the entire period of their follow-up and interviewed their general practitioner and/or cardiologist.

Ischemic stroke was defined as an episode of neurological dysfunction caused by focal cerebral, spinal, or retinal infarction.²³ TIA was defined as a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction.²⁴ Cerebral magnetic resonance imaging (MRI) or cerebral CT were used to diagnose the ischemic stroke/TIA. Systemic ischemia was defined as an acute loss of perfusion of a limb or organ, diagnosed clinically, with CT angiography of a peripheral artery and eventually by ascertainment using open surgical or endovascular procedures.

A thromboembolic mechanism was suspected based on specific elements, including the radiological presentation, transthoracic echocardiography (TTE) and transesophageal echocardiography (TEE) data, and carotid imaging.

Statistical analysis

The primary endpoint was the occurrence of a TE after one cryo-PVI procedure. The occurrence of a TE for patients who did not experience such an event was censored at the time of the first redo procedure for patients who had a redo procedure or at the last follow up.

The secondary endpoint was the time to first atrial arrhythmia recurrence, defined as the time from ablation to the first atrial arrhythmia recurrence. Time to first recurrence was censored at the last follow-up for patients in sinus rhythm.

Continuous variables, expressed as the median (interquartile Q1-Q3 range) or mean \pm standard deviation, were compared using an unpaired t-test, Mann Whitney U-test, or Kruskal-Wallis test, as appropriate. Categorical variables are presented as absolute and relative frequencies and were compared using the χ^2 or Fisher exact tests. Categorical variables are expressed as a percentage and were compared using Fisher's exact test.

Prognostic factors for the time to an ischemic event were assessed using a univariable Cox model. A multivariable Cox model adjusted for the CHA₂DS₂-VASc score was fitted after treating the OAT variable as a time-varying covariate (OAT discontinuation is a dynamic variable occurring during follow up). The first-order interaction between OAT and TE recurrence was evaluated to test either a differential effect of OAT discontinuation between patients who recurred and those who did not, or a differential effect of recurrence between patients who discontinued OAT and those who continued.

All tests were two-tailed and the limit for statistical significance was set at $P < 0.05$. Statistical analysis was performed using SPSS for Windows software, version 22.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Patient characteristics (Table 1)

All eligible patients were included. In total, 450 patients were included (mean age = 60 ± 9 years, 78% men). Among them, 242 patients (54%) had paroxysmal AF, 160 (35%) were in persistent AF, and 48 (11%) had long-standing AF. Seventy-one percent had no structural heart disease. The mean CHA₂DS₂-VASc score was 1.6 ± 1.3 and the mean left atrial volume 142 ± 45 ml. Twenty-six patients (6%) had a history of stroke/TIA before the procedure.

Atrial arrhythmia recurrences

Four hundred and thirty-two (96%) patients completed at least one year of follow-up. Eighteen patients were considered as lost of follow up. Two hundred and seventy patients (60%) had no recurrence of atrial arrhythmia after one cryo-PVI procedure, with a median follow-up of 26 months (IQR 39-16). The 24-months freedom from atrial arrhythmia recurrence probability was 59% [56%;65%].

OAT discontinuation (Supplementary Table 1)

OAT was discontinued for 75 patients (17%) and maintained for 375 (83%), who were essentially treated with a direct oral anticoagulant (234 patients; 62%).

Off-OAT patients were younger (54 years vs. 62 years, $p < 0.001$) and had a lower median CHA₂DS₂-VASc score (0 vs. 2, $p < 0.001$) than on-OAT patients. In addition, fewer off-OAT patients were initially in persistent AF (31% vs. 49%, $p = 0.003$) and they had a significantly lower incidence of prior stroke or TIA (0% vs. 7%, $p = 0.01$).

The reasons for discontinuation of OAT were the absence of an indication for long-term anticoagulation therapy (a CHA₂DS₂-VASc score = 0 for men or 1 for women, in the absence of

another stroke risk factor) for 50 patients (67%); patient and/or physician choice, despite a class IIa indication for long-term anticoagulation therapy (CHA₂DS₂-VASc score = 1 for men or = 2 for women), for 14 patients (19%); patient and/or physician choice, despite a class I indication for long-term anticoagulation therapy (CHA₂DS₂-VASc score > 1 for men or > 2 for women), for six patients (8%); and bleeding, despite the presence of a class I or class IIa indication for anticoagulation therapy, for five patients (7%).

The median interval between the cryo-PVI procedure and OAT discontinuation was 299 days (IQR 523-135). The median duration of follow-up after the discontinuation of OAT was 472 days (IQR 837-148).

TEs during follow-up (Figure 1, Table 2)

Six ischemic events, all considered to be of thromboembolic origin, occurred in six different patients, with a mean interval of 15 months after cryo-PVI. Stroke occurred in three patients, TIA in two, and systemic embolism, with a presentation of acute lower-limb ischemia, in one. The mean follow up of the entire population was 30 months. Therefore, the annualized rate of all TEs was 0.53%/year. Risk of TE at 24 months was estimated at 2% [0.4%;3.6%].

Detailed data for the six patients who experienced a TE are presented Table 2.

A thromboembolic origin was established by neurologists based on the absence of stenosis of the extracranial (patients 1 to 5) and intracranial arteries (patients 1, 2, 3 and 4). Patients 1 and 3 showed multiple spots of cerebral infarction. For patients 4 and 5, prior documented or reported recurrences of atrial arrhythmia was a supplementary argument. For patient 6, a thromboembolic origin was determined based on the typical aspect of a

1 thrombus by arterial angiography and a documented AF recurrence one week before the
2 event. Patients 2 and 6 underwent TEE, which did not show a thrombus.

3 Five patients had a class I indication for long-term OAT at the time of the event.
4 Among them, one (patient 4) was off OAT, despite the recurrence of atrial arrhythmia
5 reported two months earlier (no ECG documentation). Two (patients 5 and 6) of the other
6 four patients (on-OAT) had recurrences of atrial arrhythmia documented before the TE, and
7 the cryo-PVI of two (patients 1 and 3) was considered to be successful at the 11- and 22-
8 month follow-ups, respectively.

9 One patient (patient 2) had a class IIa indication for long-term OAT at the time of the
10 TE. He was off OAT and had no documented or patient-reported recurrence of atrial
11 arrhythmia for the 24 months after cryo-PVI.

12 Among the four patients on OAT at the time of the event, all treated by direct oral
13 anticoagulant, one was switched to vitamin K antagonist after the event (patient 1), one was
14 switched to another direct oral anticoagulant (patient 5), one continued to use the same
15 direct anticoagulant and underwent left atrial appendage occlusion (patient 6), and one died
16 one week after the event (patient 3).

17 OAT was reintroduced for the two remaining patients (patients 2 and 4).

18 None of the patients experienced another TE during follow-up.

Predictive factors of TEs

The absence of OAT and the recurrence of atrial arrhythmia were not predictive of a TE after univariate analysis (Table 3). The CHA₂DS₂-VASc Score (HR = 1.76, CI [1.05;2.95], p = 0.0315) was the only predictive factor of a TE after univariate analysis.

After multivariate analysis, the CHA₂DS₂-VASc score (HR = 2.13, CI [1.39;3.26], p = 0.0005) was still a predictor of TE. The effect of discontinuing OAT did not significantly differ between patients who recurred and those who did not (p = 0.1642), based on the interaction between the discontinuation of OAT and recurrence. However, the effect of discontinuing OAT appeared to be stronger for patients who recurred (HR = 73.05, CI [5.58;956.90], p = 0.0011) than for those who did not (HR = 5.00, CI [0.48;51.66], p = 0.18). Moreover, the effect of recurrence was greater for patients who discontinued OAT (HR = 24.5, CI [1.30;464.01], p = 0.0329) than for those who continued treatment (HR = 1.66, CI [0.23;11.92], p = 0.6998).

After multivariate analysis without the two TIAs, the CHA₂DS₂-VASc score (HR = 2.22, CI [1.34;3.67], p=0.0018) was still a predictor of TE. The effect of discontinuing OAT did not significantly differ between patients who recurred and those who did not (p = 0.9516), based on the interaction between the discontinuation of OAT and recurrence.

We also performed the multivariate analysis with CHA₂DS₂-VASc score as a binary variable. The CHA₂DS₂-VASc score ≥ 3 (HR = 15.71, CI [2.12;116.36], p=0.0070) was a predictor of TE. The effect of discontinuing OAT did not significantly differ between patients who recurred and those who did not (p = 0.1739), based on the interaction between the discontinuation of OAT and recurrence.

1 Three additional TEs (two stroke, one acute lower-limb ischemia) occurred after the
2 second procedure. All patients had class I indication for long term OAT and were on OAT. All
3 patients had recurrences of atrial arrhythmia documented before or at the time of the TE. We
4 decided to verify our results by adding these TEs. After multivariate analysis, the CHA₂DS₂-
5 VASc score (HR = 1.63, CI [1.24;2.14], p=0.0004) was a predictor of TE. The effect of
6 discontinuing OAT did not significantly differ between patients who recurred and those who
7 did not (p = 0.5595), based on the interaction between the discontinuation of OAT and
8 recurrence. However, the effect of discontinuing OAT appeared to be stronger for patients
9 who recurred (HR = 6.03, CI [0.51;70.62], p=0.2867) than for those who did not (HR = 2.25, CI
10 [0.23;21.88], p=0.4829). Moreover, the effect of recurrence was greater for patients who
11 discontinued OAT (HR = 6.77, CI [0.34;134.98], p = 0.2101) than for those who continued
12 treatment (HR = 2.53, CI [0.51; 12.70], p = 0.4208).

1 DISCUSSION

2 Our study provides two important findings. First, the long-term rate of a TE after one
3 cryo-PVI procedure was 0.53%/year. Second, the CHA₂DS₂-VASc score is the only independent
4 predictor of TE.

6 Long-term rates of TEs after catheter ablation of AF

7 There are no data concerning the long-term rates of TEs after cryo-PVI. Existing
8 published studies include patients treated by RF-PVI or a mixture of patients treated by RF- or
9 cryo-PVI.

10 It was important to obtain specific data about the TE risk after cryo-PVI, as it has been
11 demonstrated that the overall lesion width is significantly wider with the cryoballoon than
12 with RF.²⁵ We could have thus hypothesized that left atrium contractility would be more
13 impaired after cryo-PVI, with a potentially greater long-term incidence of TE.

14 Published studies should be compared with caution, as they may include not only RF-
15 PVI but other lesions in the left atrium. Sometimes, they include periprocedural events and
16 not only those that are post-procedural. Studies also may not include all types of TE, such as
17 systemic embolism, but only strokes.

18 Overall, our incidence of 0.53%/year with cryoballoon ablation is quite close to data
19 obtained for RF catheter ablation (Supplementary Table 2). Strivatsa *et al.*⁸ found an incidence
20 of 0.37%/year for stroke; Noseworthy *et al.*⁵, 0.43%/year for stroke/TIA; Hunter *et al.*²,
21 0.5%/year for stroke/TIA; Lin *et al.*³, 0.59%/year for stroke/TIA; Friberg *et al.*⁶, 0.70%/year for
22 stroke; and Chao *et al.*¹, 0.87%/year for TE.

23 Only, Kim *et al.*⁹ found a lower incidence of stroke (0.13%/year), which may be
24 explained by lower a CHADS₂ score in their population.

Conversely, Bunch *et al.*⁴ included periprocedural events and found a higher incidence of stroke (1.4% at one year). The population studied by Saliba *et al.*⁷ had a high mean CHA₂DS₂-VASc score (3.6) and they logically found the highest rate of stroke/TIA of 2.10%/year.

Finally, our incidence of 0.53%/year is much lower than would be expected for our population, for which the mean CHA₂DS₂-VASc score was 1.6. Indeed, the estimated stroke risk is 0.66% when the CHA₂DS₂-VASc score = 1 and 1.5% (0.93;2.21) when the CHA₂DS₂-VASc score = 2.²⁶

Management of OAT after cryo-PVI

European²¹ and US guidelines state that it is necessary to continue long-term anticoagulation therapy after AF ablation based on the CHA₂DS₂-VASc score, irrespective of the atrial arrhythmia recurrence status.

Several observational studies have tried to demonstrate that it is safe to interrupt OAT if a stable sinus rhythm is proven, irrespective of the CHA₂DS₂-VASc score for some.

The literature clearly shows that the rate of off-OAT events for patients in supposed sinus rhythm is very low (Supplementary Table 3).^{10–18,20,19} Nademanee *et al.*¹¹, Themistoclakis *et al.*¹², and Yang *et al.*¹⁸ even found a lower rate for patients off OAT than for those on OAT. Riley *et al.*¹⁶ found no difference in stroke risk, regardless of the OAT status for patients with a CHADS₂ = 1 or ≥ 2. Karasoy *et al.*¹⁷ found that the effect of OAT discontinuation was insignificant after multivariate analysis, as did Yang *et al.*¹⁸ We obtained a similar result but, in our study, OAT discontinuation appeared to have a significant impact on TEs for patients who recurred (HR = 73.05, CI [5.58;956.90], p = 0.0011). The effect of OAT discontinuation on TEs for patients who did not recur was substantially lower (HR = 5.00, CI [0.48;51.66], p = 0.18).

Concerning documented recurrences of atrial arrhythmia, Riley *et al.*¹⁶ found 75% of the patients in AF after an ischemic event. Kim *et al.*⁹ and Hunter *et al.*² found that being in sinus rhythm reduced the risk of stroke, after multivariate analysis. On the other hand, Kochhäuser *et al.*¹⁹ found no difference in AF recurrence for patients, with or without stroke, and Liang *et al.*²⁰ found that AF recurrence was not a predictor of stroke/TIA. These two studies did not use Cox Models to reach their conclusions. In our study, the recurrence of atrial arrhythmia was not a predictive factor of TEs after multivariate analysis. However, we logically found a significant effect of recurrence for patients off OAT (HR = 24.5, CI [1.30;464.01], p = 0.0329).

Several studies have examined the role of the CHA₂DS₂-VASc score in the occurrence of TE. Kochhäuser *et al.*¹⁹ find no difference in the CHA₂DS₂-VASc score for patients with or without stroke. Liang *et al.*²⁰ found that the CHA₂DS₂-VASc score did not predict stroke/TIA, in contrast to our results. In our study, all patients who experienced a TE had a class I or class IIa indication for long-term anticoagulation therapy and the CHA₂DS₂-VASc score was a predictive factor of a TE after multivariate analysis. This difference can be explained by the lack of statistical power (small number of events) and again by the different statistical tests used in these two studies. Conversely, Chao *et al.*¹ obtained a result similar to ours, with a hazard ratio of 1.69 (CI 1.32;2.17, p < 0.001) for each incremental increase of the CHA₂DS₂-VASc score predicting stroke/TIA. In the study of Kim *et al.*⁹, the CHA₂DS₂-VASc score was a predictor of stroke after univariate analysis.

1 In conclusion, we propose that a lack of recurrence should not be considered in the
2 decision to stop anticoagulation therapy for a particular individual. Indeed, it is difficult in real
3 life to monitor the recurrence of AF as performed in certain studies. By contrast, the
4 CHA₂DS₂-VASc score should be considered when deciding whether or not to stop
5 anticoagulation therapy, as recommended in current guidelines. To go further, we showed
6 that CHA₂DS₂-VASc score ≥ 3 could be a good cut-off to continue OAT after AF ablation.

7 8 Limitation and strengths

9 Our results are limited by the small number of TEs that occurred. However, this could
10 also be seen as a strength, as it permitted a detailed description of these six events. We
11 provide “safe” data.

12 We thoroughly researched the information concerning the occurrence of the TEs, both
13 prospectively and retrospectively and are confident about full completeness.

14 Our protocol of atrial arrhythmia monitoring after cryo-PVI does not include
15 continuous monitoring but it corresponds to real life, and our conclusions are thus applicable
16 to daily practice.

17 There were no defined instructions concerning OAT discontinuation in this study.
18 Indeed, information provided about the patients who stopped or continued OAT should be
19 considered with caution.

20 The multivariate analysis includes only 6 events. This exploratory analysis and its
21 results should be confirmed on a larger number of events.

1 **CONCLUSION**

2 The long-term rate of a TE after one cryo-PVI procedure was 0.53%/year, comparable
3 to rates found after a RF AF ablation. Atrial arrhythmia recurrences, which are difficult to
4 document, should not be considered in the decision to discontinue OAT, in contrast to the
5 CHA₂DS₂-VASc score, which was the only predictive factor of a TE after multivariate analysis.

6

7 **ACKNOWLEDGEMENTS**

8 The authors thank Helene Duquenne for her help with data acquisition.

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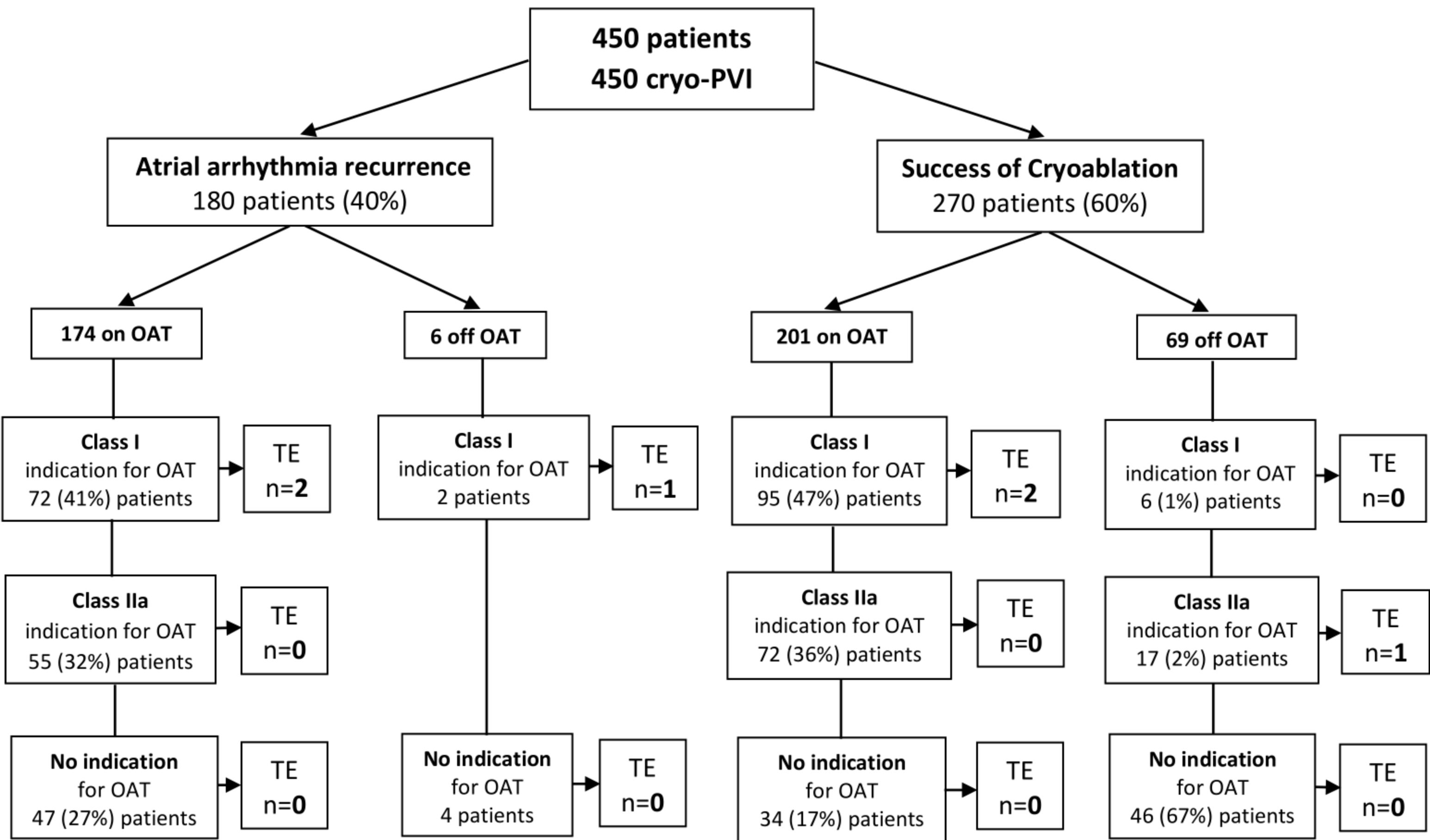
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FIGURE LEGENDS

Figure 1. Thromboembolic events according to the result of cryoablation, and anticoagulation status.



OAT: oral anticoagulant therapy, PVI: pulmonary vein isolation, TE: thromboembolic event.

Figure 1. Thromboembolic events according to the result of cryoablation, and anticoagulation status.

Table 1. Patient characteristics

	All patients (n = 450)
Demographic variables	
Age (years)	60 ± 9
Male, n (%)	349 (78)
Medical history	
Weight (kg)	87 ± 16
Height (m)	1.75 ± 0.09
Body Mass Index (kg/m ²)	29 ± 5
Creatinine Clearance (ml/min)	82 ± 22
Clearance < 60ml, n (%)	59 (13)
COPD, n (%)	19 (4)
Hypertension, n (%)	211 (47)
Diabetes, n (%)	56 (12)
Prior stroke or TIA, n (%)	26 (6)
Heart failure, n (%)	62 (14)
Absence of SHD, n (%)	319 (71)
Coronary artery disease, n (%)	65 (14)
CHA ₂ DS ₂ -VASc Score	1.6 ± 1.3
0	104 (23)
1	138 (31)
2	103 (23)
3	55 (12)
4	38 (8)
5	10 (2)
6	2 (0.4)
Persistent or long-standing persistent AF, n (%)	208 (46)
Previous cavotricuspid isthmus ablation, n (%)	50 (11)
LV and LA parameters	
LVEF (%)	57 ± 11
LVFE < 40%, n (%)	35 (8)
LA Area (cm ²)	24 ± 6
LA Volume (ml)	142 ± 45
Indexed LA Volume (ml)	69 ± 20
PV anatomy	
LSPV diameter (mm)	19 ± 2
LIPV diameter (mm)	17 ± 2
RSPV diameter (mm)	19 ± 5
RIPV diameter (mm)	18 ± 2
Accessory PV n (%)	52 (12)
LCT, n (%)	67 (15)
Atrial arrhythmia recurrence, n (%)	180 (40)
Follow-up (month)	26 (IQR 23)

AF: atrial fibrillation, COPD: chronic obstructive pulmonary disease, LA: left atrium, LCT: left common trunk of pulmonary veins, LSPV: left superior pulmonary vein, LIPV: left inferior pulmonary vein, LV: left ventricle, LVEF: left ventricular ejection fraction, PV: pulmonary veins, SHD: structural heart disease, RSPV: right superior pulmonary vein, RIPV: right inferior pulmonary vein, TIA: transient ischemic attack.

Table 2. Detailed data on patients who experienced a TE.

		Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Patient characteristics	Age, sex	64, M	43, M	78, F	66, M	66, M	65, M
	Type of AF	Paroxysmal	Paroxysmal	Persistent	Paroxysmal	Persistent	Paroxysmal
	CHA ₂ DS ₂ -VASc at cryoablation	3	0	5	2	3	3
	Prior ischemic stroke or TIA	No	No	No	No	Stroke	No
	Atrial arrhythmia recurrence at last consultation or last medical contact, before the TE (type)	- No recurrence documented or reported by patient	- No recurrence documented or reported by patient	- No recurrence documented or reported by patient	+ Recurrence reported by patient 2 months earlier without documentation	+ Asymptomatic paroxysmal AF recurrence documented one month after ablation	+ Paroxysmal AF recurrence documented one week before
TE	Type	Stroke	TIA	Stroke	TIA	Stroke	Lower limb ischemia
	Interval from cryoablation until TE (months)	11	24	22	16	8	10
	CHA ₂ DS ₂ -VASc at the event	3	1	5	2	3	3
	Antiarrhythmic drug at the event	No	No	Amiodarone	No	Flecainide	
OAT status	Discontinuation of OAT before TE (reason)	No	Yes (absence of class I recommendation for anticoagulation)	No	Yes (physician choice)	No	No
	Interval from OAT discontinuation until occurrence of the TE, days	-	180	-	150	-	-
	Type of OAT at time of TE	Rivaroxaban 20mg	- (Aspirin)	Rivaroxaban 20mg	-	Rivaroxaban 20mg	Rivaroxaban 20mg (+ Aspirin)
	Declared therapeutic compliance	Good observance		N/A	-	Good observance	Good observance
	OAT dosage at the time of TE	No	-	No	-	59 ng/ml	50 ng/ml
Assessment at event	Diagnostic imaging (results)	Cerebral MRI (left occipito-parietal infarction; several spots)	Cerebral MRI (normal)	Cerebral CT (left and right anterior cerebral artery infarction)	Cerebral MRI (normal)	Cerebral MRI (left middle cerebral artery infarction)	Arterial angiography (lower extremity bypass graft occlusion)

	Additional tests to establish the origin of the ischemic event (results)	ECG/Holter monitoring (sinus rhythm) MR angiography (absence of intracerebral artery stenosis) TTE (no thrombus, no spontaneous contrast) Carotid imaging (no significant stenosis)	ECG/Holter monitoring (sinus rhythm) CT angiography (absence of intracerebral artery stenosis) TTE/TEE (no thrombus, no spontaneous contrast, no aortic atheroma)	ECG/Holter monitoring (sinus rhythm) TTE (no thrombus, no spontaneous contrast) Carotid imaging (no significant stenosis)	ECG/Holter monitoring (sinus rhythm) MR angiography (absence of intracerebral artery stenosis) TTE (no thrombus, no spontaneous contrast) Carotid imaging (no significant stenosis)	ECG/Holter monitoring (sinus rhythm) MR angiography (left middle cerebral artery occlusion, absence of intracerebral artery stenosis) TTE (no thrombus, no spontaneous contrast) Carotid imaging (no significant stenosis)	ECG/Holter monitoring (sinus rhythm) TEE (presence of spontaneous contrast, grade 2 aortic atheroma, no thrombus)
Therapeutic management		Switch to Vitamin K Antagonist	Introduction of OAT	Death one week after the event	Introduction of OAT	-Thrombolysis -Switch to Apixaban	-Surgery -Continuation of Rivaroxaban -Redo procedure + left atrial appendage occlusion 45 days after the event
Evolution after the TE		-No atrial arrhythmia recurrence documented or reported by patient, off antiarrhythmic -No TE recurrence 45 months after the event	-No atrial arrhythmia recurrence documented or reported, off antiarrhythmic by patient -No TE recurrence 24 months after the event		-Recurrence of atrial arrhythmia reported by patient without documentation, off antiarrhythmic -No TE recurrence 5 months after the event	-No atrial arrhythmia recurrence documented or reported by patient, on flecainide -No TE recurrence 6 months after the event	-Discontinuation of Amiodarone -No atrial arrhythmia recurrence documented or reported by patient -No TE recurrence 43 months after the event

AF: atrial fibrillation, TIA: transient ischemic attack, OAT: oral anticoagulant therapy, MRI: magnetic resonance imaging, CT: computed tomography, ECG: electrocardiogram, TE: thromboembolic event, TTE: trans-thoracic echocardiography, TEE: trans-esophageal echocardiography.

Table 3. Comparison of patients according to the occurrence of TE

	No TE N=444 (98.7%)	TE N=6 (1.3%)	Univariate analysis HR [CI 95%]	P
Demographic variables				
Age (years)	60 ± 9.4	64 ± 11.4	1.04 [0.93;1.16]	0.48
Male, n (%)	344 (77)	5 (83)	0.68 [0.08;5.83]	0.73
Medical history				
Hypertension, n (%)	207 (47)	5 (83)	2.44 [0.44;13.49]	0.31
Heart failure, n (%)	61 (14)	0 (0)		
Diabetes, n (%)	55 (12)	1 (17)	1.61 [0.19;13.83]	0.66
Prior stroke or TIA, n (%)	25 (6)	1 (17)	3.00 [0.47;19.03]	0.24
Absence of SHD, n (%)	314 (71)	5 (83)	2.06 [0.24;17.67]	0.51
Coronary artery disease, n (%)	64 (14)	1 (17)	1.08 [0.13;9.23]	0.94
CHA ₂ DS ₂ -VASc Score	1.6 ± 1.3	2.8 ± 1.3		
0	104 (23)	0 (0)		
1	137 (31)	1 (17)		
2	102 (23)	1 (17)	1.76 [1.05;2.95]	0.0315
3	52 (12)	3 (50)		
4	38 (9)	0 (0)		
5	9 (2)	1 (17)		
6	2 (0.5)	0 (0)		
Class I indication for OAT	175 (39)	5 (83)	8.30 [0.98;70.13]	0.052
Class I or IIa indication for OAT	319 (72)	6 (100)	6.06 [0.27;135.58]	0.25
CHA ₂ DS ₂ -VASc Score ≥ 3	101 (23)	4 (67)	6.69 [1.27;35.36]	0.025
Persistent or long-standing persistent AF, n (%)	206 (48)	2 (33)	0.75 [0.14;4.09]	0.47
Previous cavotricuspid isthmus ablation, n (%)	50 (11)	0 (0)		
LV and LA parameters				
LVEF (%)	57 ± 11	58 ± 6	0.99 [0.96;1.04]	0.88
LVFE < 40%, n (%)	35 (8)	0 (0)		
LA Area (cm ²)	24 ± 6	23 ± 2	1.004 [0.95;1.06]	0.88
LA Volume (ml)	142 ± 45	135 ± 24	0.99 [0.99;1.01]	0.89
Indexed LA Volume (ml/m ²)	69 ± 21	68 ± 10	1.002 [0.98;1.02]	0.81
Follow-up				
Atrial arrhythmia recurrence after 1 cryo-PVI, n (%)	177 (40)	3 (50)	2.26 [0.46;11.21]	0.32
Patients off-OAT, n (%)	73 (16)	2 (33)	3.45 [0.69;16.67]	0.13

AF: atrial fibrillation, COPD: chronic obstructive pulmonary disease, LA: left atrium, LV: left ventricle, LVEF: left ventricular ejection fraction, OAT: oral anticoagulant therapy, SHD: structural heart disease, TE: thromboembolic event, TIA: transient ischemic attack