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ORIGINAL ARTICLE

Italian Registry in the Setting of Atrial Fibrillation Ablation with Rivaroxaban – IRIS

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ABSTRACT

BACKGROUND: Catheter ablation (CA) of atrial fibrillation is routinely used to obtain rhythm control. Evidence suggest that catheter ablation should be done during uninterrupted oral anticoagulation.
METHODS: Italian Registry in the setting of atrial fibrillation ablation with rivaroxaban (IRIS) is an Italian multicenter, non-interventional, prospective study which enrolled 250 consecutive atrial fibrillation patients eligible for catheter ablation on rivaroxaban. The decision for rivaroxaban management was left to the physician: uninterrupted or shortly interrupted prior to Catheter ablation. Patients received a follow-up visit at 1 month and 12 months after the procedure.
RESULTS: The primary outcome, represented by all-cause death and systemic embolism at 1 month and 12 months was characterized by one transient ischemic attack and one myocardial infarction in the first 30 days. Both events happened in patients with shortly interrupted strategy (P=0.147), and both in patients who underwent radiofrequency ablation (P=0.737). In the primary safety outcome represented by major bleeding we did not register any event in the 12-month follow-up. The secondary outcome constituted by minor bleeding registered 1 event, after the first 30 days since CA.
CONCLUSIONS: IRIS is the biggest real-life data registry regarding CA ablation on rivaroxaban in Italian setting, proving the safety and efficacy of rivaroxaban.

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KEY WORDS: Atrial fibrillation; Catheter ablation; Rivaroxaban.

Atrial fibrillation (AF) is the most frequently encountered arrhythmia, with a prevalence of 1% to 2% in the overall population[1] and it tends to recur in 90% of the cases if not adequately treated.[2, 3] Based on the CHA_2DS_2-VASc score we can conclude that patients affected by AF are

more prone to develop thromboembolic events when compared to the general population, and long-term oral anticoagulation (OAC) is needed in order to prevent stroke. Recent evidence shows that OAC with the use of direct oral anticoagulants (DOACs) should be preferred to vitamin K antagonists (VKa).[3] Catheter ablation (CA) is an interventional approach that has progressively gained ground in the treatment of drug-resistant paroxysmal or persistent AF.[4] Of note, CA for AF carries an intrinsic risk of clinical stroke or silent transient ischemic attack and systemic embolism as well.[5] These adverse events (AEs) are mainly related to thrombus formation provoked by radiofrequency ablation as it promotes the activation of the coagulation cascade due to tissue overheating. However, it is necessary to underline that even the sole placement of intravascular catheters can lead to hyperactivation of the coagulation cascade.[6] Taking this into account and based on the results of the COMPARE Study and previous published studies, CA is nowadays routinely performed without interrupting oral anticoagulants, for this has proven to decrease the risk of thromboembolic complications related to the procedure without increasing bleeding AEs.[7] When compared to VKa, DOACs have proved to be equally effective in the prevention of thromboembolic events but safer as regards the risk of major bleeding.[8-12]Among DOACs, Rivaroxaban directly inhibits the Xa factor and its safety and effectiveness for stroke prevention in patients with AF has been established,[13, 14] even in the context of AF CA. Uninterrupted Rivaroxaban has also been compared to uninterrupted VKa during CA for AF with results showing the same effectiveness level.[15]

The aim of the IRIS (Italian Registry in the setting of AF ablation with rivaroxaban) is the evaluation of safety and effectiveness of Rivaroxaban in the setting of CA for AF using data from a multicenter Italian observational study.

Materials and methods

Trial design and oversight

IRIS, standing for Italian Registry in the Context of Atrial Fibrillation (AF) Ablation with Rivaroxaban, is a comprehensive Italian multicenter study. Its main aim is to assess the safety and efficacy of rivaroxaban during catheter ablation (CA) for AF. This prospective, observational research aligns with the Helsinki Declaration guidelines, received the green light from the Sapienza University of Rome's Ethics Committee, and is listed on ClinicalTrials.gov (NCT04315974). The study, which concluded at the end of 2022, involved sixteen Italian centers skilled in performing CA for AF.

Each participating center contributed by submitting data through an electronic case record form (eCrF). An Italian Clinical Research Organization took the lead in handling the study's administrative, operational aspects, as well as overseeing monitoring and statistical analyses.

Trial participant characteristics

The study population is represented by rivaroxaban-naive AF patients and patients already under treatment with rivaroxaban that were eligible for CA of AF. Rivaroxaban-naïve patients were scheduled for CA after 4 uninterrupted weeks of rivaroxaban assumption except in cases where the presence of atrial thrombi was excluded by transesophageal echocardiogram (TOE). Patients already under chronic treatment with rivaroxaban could go directly to CA. Patients, both men and women, were considered eligible for this study if they were above ≥18 years old, suffering from paroxysmal or persistent AF, and if they were scheduled for elective CA; both rivaroxaban-naïve and patients already assuming rivaroxaban were included. The exclusion criteria were stage 5 chronic kidney disease with estimated glomerular filtration rate (eGFR)<15 mL/min/1.73 m^2 or patients on dialysis.[16] Patients with eGFR up to 15 mL/min/1.73 m^2 were also enrolled in the study given the recent evidence regarding the safety of DOACs in patients with advanced kidney disease.

Enrolment schedule and anticoagulation strategy assignment

For each eligible participant, we arranged an in-office visit to conduct an initial evaluation and obtain signed informed consent. During this baseline assessment, we gathered data on various aspects: demographic details (including birth

date, gender, ethnic background, height, and weight), cardiovascular risk factors, existing cardiovascular and non-cardiovascular conditions, AF patterns, and any previous treatments such as medication, electrical cardioversion, or CA. We also evaluated stroke and bleeding risks using the CHA_2DS_2-VASc and HAS-BLED scoring systems.

The decision on the anticoagulation approach during CA for AF was at the discretion of the physician and was documented as either uninterrupted or briefly interrupted. The uninterrupted method involved continuing anticoagulation therapy despite undergoing CA, while the briefly interrupted strategy meant skipping the anticoagulation dose just before the procedure. The rivaroxaban dosage was tailored following the guidelines in the European Heart Rhythm Association's DOACs Practical Guide.[17] Additionally, standard care procedures like blood tests, 12-lead electrocardiograms, and transthoracic echocardiography were carried out. The scheduling of these tests and assessments is outlined in Figure 1 of our study. For each eligible participant, we arranged an in-office visit to conduct an initial evaluation and obtain signed informed consent. During this baseline assessment, we gathered data on various aspects: demographic details (including birth date, gender, ethnic background, height, and weight), cardiovascular risk factors, existing cardiovascular and non-cardiovascular conditions, AF patterns, and any previous treatments such as medication, electrical cardioversion, or CA. We also evaluated stroke and bleeding risks using the CHA_2DS_2-VASc and HAS-BLED scoring systems.

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Ablation procedure

The choice of the energy source, between radiofrequency, cryo or laser was guided by physicians' experience and center availability. For each AF ablation procedure, we recorded the following data: the number and site of venous/arterial puncture, type of energy, activated clotting time (ACT) during the procedure, overall heparin administered and total duration of the procedure. Major complications during ablation and AEs were reported in the eCRF; AEs are summarized in Table I. The trans-septal puncture was done under fluoroscopy, intracardiac echography or transesophageal guidance, according to center experience. A dose of unfractioned hepa-

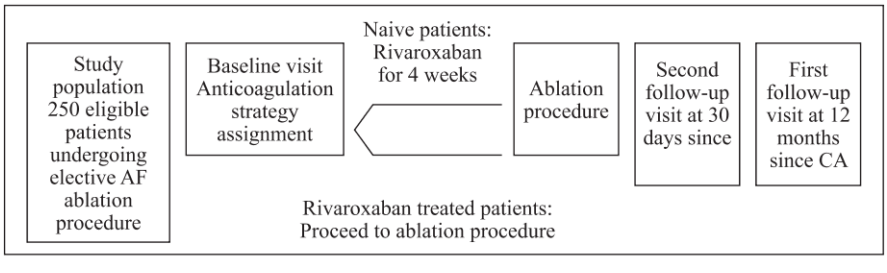

Figure 1.—Trial design.

TABLE I.—*Complications associated with AF ablation.*

Complications
Cardiac tamponade
Cardiac perforation
Pulmonary vein stenosis
Atriesophageal fistula
Atrial Pericardial Fistula
Esophageal injury
Gastric motility/pyloric spasm disorders
Phrenic nerve paralysis
Stroke or TIA
Vascular access complication (hematoma, fistula or pseudoaneurysm)
Myocardial infarction
Pericarditis
Death

AF: atrial fibrillation; TIA: transient ischemic attack.

rin (UFH) calculated on the basis of body weight was administered just before the transeptal puncture, followed by a heparin infusion to maintain an ACT above 300 seconds for the duration of the procedure. The next dose of rivaroxaban was administered at least 6 hours following the procedure, ensuring hemostasis after CA. At the end of the procedure the use of protamine in order to obtain an ACT<250 and remove the sheet was left to physicians' choice.

Radiofrequency ablation

CA was guided by three-dimensional electroanatomical reconstruction of the left atrium with a circular mapping catheter (Lasso; Biosense-Webster, Diamond Bar, CA, USA) and performed with radiofrequency irrigated tip catheters SmartTouch Surround Flow DF Catheter (Biosense Webster, Irvine, CA, USA). Ablation procedure was directed by the Ablation Index, targeting indices of 380 with a 35 W power setting for the posterior and inferior areas. Conversely, for the anterior and superior areas, the target was set at 480 with a 40W power setting. In order to achieve complete isolation of the pulmonary veins (PV), a step-wise approach was chosen: in addition to PV isolation, other lesions were performed according to individual center experience, such as posterior wall isolation or lateral mitral isthmus line or other adjunctive linear ablations. Radiofrequency energy was delivered at the ostium of each PV until the electrical isolation of target PV from the left atrium was reached. Then the electrical isolation of each PVs was assessed testing both for entrance and exit blocks with a circular sensing catheter.

Cryoablation

The cryoablation balloon was introduced in the left atrium by a transeptal puncture and manipulated in the atrial cavity using an intra-lumen guide wire or an integrated circular mapping catheter (aCHieVe™; Medtronic, Dublin, Ireland). After reaching the left atrium the cryoballoon was placed at the ostium of each PV and pushed into the PV in order to occlude it; effective occlusion was assessed with the aid of fluoroscopy and radiopaque contrast agent injection through the balloon's distal tip lumen. A correct occlusion implies the total retention of contrast agent in the PV while any leak suggests incomplete occlusion. Using cryo energy, damage was produced by reaching intracatheter temperatures of -50 °C adjacent to the ostium of each PV without using a mapping system in a "single shot" application. Each cryoablation circle is created by keeping the target temperature for 300 seconds. Generally, two ablation cycles per PV were performed, with a maximum of five. Particular attention was reserved to phrenic nerve function during cryoablation of the right PVs: with the aid of diaphragmatic catheter pacing within the superior vena cava the function of the right phrenic nerve was continuously monitored.

Laser ablation

Using an 8.5 F transseptal sheath (SL0; Abbott, St Paul, MN, USA), a transseptal puncture was carried out. To keep the activated clotting time between 300 and 350 seconds, heparin was administered multiple times. The original transseptal sheath was then replaced with a 12 F steerable sheath (CardioFocus, Marlborough, MA, USA). At the left atrial antrum, the LB was inflated. A circular mapping catheter was utilized for preablation electrical mapping of the pulmonary vein (PV) potentials. The HeartLight X3 catheter (Cardiofocus) was positioned at the ostium of the target PV *via* the deflectable sheath, followed by the inflation of the balloon. The ablation process was conducted with visual guidance. The ablation involved delivering ablative energy in

segments, which included either RAPID mode or manual mode energy delivery, or a mix of the two. The energy output ranged from 5.5 W to 18 W, with each lesion's duration lasting from 20 to 30 seconds. While ablating the right-sided pulmonary veins, phrenic nerve pacing was consistently executed from the superior vena cava. This approach aimed to reduce the likelihood of phrenic nerve damage by closely observing diaphragmatic movements.

Follow-up visits

Participants underwent a thorough follow-up assessment thirty days and once more at twelve months following their catheter ablation (CA) treatment. This assessment included monitoring for significant bleeding events, as categorized by the International Society on Thrombosis and Haemostasis[18] and the Bleeding Academic Research Consortium,[19] as well as non-major but clinically significant bleeding incidents (Table II, III). Additionally, we examined major complications associated with CA (detailed in Table I), adherence to direct oral anticoagulants (DOACs) therapy, use of other medications, any supplementary procedures undertaken, and the occurrence of adverse events (AEs) and serious adverse events (SAEs) (Table IV).

TABLE II.—*Bleeding events definition.*

Variables	Parameters
Major bleeding events	Fatal bleeding Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome Bleeding causing a fall in hemoglobin level of 20 g L^{-1} or more or leading to transfusion of two or more units of whole blood or red cells
Non-major clinically relevant bleeding events	Non-major clinically relevant bleeding is defined as overt bleeding not meeting the criteria for major bleeding but associated with medical intervention, unscheduled contact (visit or telephone call) with a physician, (temporary) cessation of study treatment, or associated with discomfort for the subject such as pain or impairment of activities of daily life

TABLE III.—*Bleeding events BARC Definition.*

Type of bleeding	Description
Type 0	No bleeding
Type 1	Bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a healthcare professional; may include episodes leading to self-discontinuation of medical therapy by the patient without consulting a healthcare professional
Type 2	Any overt, actionable sign of hemorrhage (*e.g.*, more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for type 3, 4, or 5 but does meet at least one of the following criteria: 1) requiring nonsurgical, medical intervention by a healthcare professional; 2) leading to hospitalization
Type 3	
Type 3a	Overt bleeding plus hemoglobin drop of 3 to 5 g/dL (provided hemoglobin drop is related to bleed) any transfusion with overt bleeding
Type 3b	Overt bleeding plus hemoglobin drop 5 g/dL (provided hemoglobin drop is related to bleed) cardiac tamponade bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid). Bleeding requiring intravenous vasoactive agents
Type 3c	Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation, does include intraspinal). Subcategories confirmed by autopsy or imaging or lumbar puncture. Intraocular bleed compromising vision
Type 4	CABG-related bleeding. Perioperative intracranial bleeding within 48 h. Reoperation after closure of sternotomy for the purpose of controlling bleeding. Transfusion of 5 U whole blood or packed red blood cells within a 48-h period. Chest tube output 2L within a 24-h period
Type 5	
Type 5a	Probable fatal bleeding; no autopsy or imaging confirmation but clinically suspicious
Type 5b	Definite fatal bleeding; overt bleeding or autopsy or imaging confirmation

BARC: Bleeding Academic Research Consortium.

In cases where patients experienced atrial arrhythmias like atrial tachycardia, atrial flutter, or AF, efforts were made to reestablish normal sinus rhythm. We documented the length of these arrhythmias, the method of cardioversion used (whether pharmacological or electrical), and any resulting AEs or SAEs. A visual representation of the entire study layout is available in Figure 1.

TABLE IV.—*Adverse and serious adverse events definition and classification.*

Variables	Parameters
Definition of AE	Signs, symptoms, illnesses, or other medical events that develop or worsen in severity during the course of the study They are clinically relevant and their relationship to study medications or procedures cannot be excluded. Note: Disease, signs symptoms, and or laboratory abnormalities already existing at randomization are not considered adverse events unless they show an intensity or frequency exacerbation
Severity of AE	Mild: An AE that is easily tolerated by the subject, causes minimal discomfort and does not interfere with everyday activities Moderate: An AE that is sufficiently discomforting to interfere with normal everyday activities Severe: An AE that prevents normal everyday activities
Definition of SAE	Results in death Is life-threatening Requires or prolongs hospitalization Results in a persistent or significant disability/incapacity May have caused a congenital anomaly or birth defect Is another serious or important medical event (Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life- threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above)

AE: adverse event; SAE: severe adverse event.

Adverse events/serious adverse events and rivaroxaban interruption criteria

AEs and SAEs, as defined in Table I, IV, which occurred during the protocol were registered by the research team at the follow-up visit at 1 month and 12 months. Treatment with Rivaroxaban was interrupted if any of the following conditions occurred: 1) life-threatening or non-life-threatening major bleeding; deterioration of renal function with EGFr<15 mL/min/1.73 m^2; 2) moderate to severe hepatic impairment (Child Pugh Class B or C); 3) pregnancy; 4) surgical interventions with high bleeding risk (according to the European Heart rhythm association DOACs' Practical guide[18]); 5) acute ischemic stroke; and 6) intracranial hemorrhage.

Trial outcomes

Primary outcomes

Our primary outcomes were grossly divided into efficacy and safety outcomes. The primary efficacy outcome was represented by a composite of any incidence of systemic embolism (stroke, transient ischemic attack TIA or myocardial infarction [MI]/peripheral embolism) and all cause-death occurring within the first 30 days and in the 12 months after the CA. Stroke was defined as the rapid onset of a new persistent neurologic deficit attributed to an obstruction in cerebral blood flow and/or cerebral hemorrhage with no overt nonvascular cause (tumor, trauma or infection). Signs or symptoms must persist for at least 24 hours, unless supported by diffusion-weighted magnetic resonance imaging. TIA was defined as neurological symptoms or signs that last no more than 24 hours. Moreover, MI diagnosis was made following current guidelines,[20] systemic arterial embolism was taken into account when there was clear evidence of sudden occlusion of a systemic artery due to an embolic event. Apart from the objective and subjective clinical manifestations, at least one of the following must be present: imaging evidence consistent with arterial embolism, surgical report indicating evidence of arterial embolism, pathological specimens related to embolism removal, or autopsy reports. The primary safety outcome was the occurrence of major bleeding events in the first 30 days after the procedure and in the 12 months of follow-up (Figure 2).

Secondary outcomes

In the secondary outcomes all procedure-related adverse events and non-major, clinically relevant bleeding events occurring in the first 30 days after the procedure and in the 12 months after the procedure were accounted for. In addition, we included supplementary outcomes such as the number of patients undergoing electrical and/or pharmacological cardioversion, the compli-

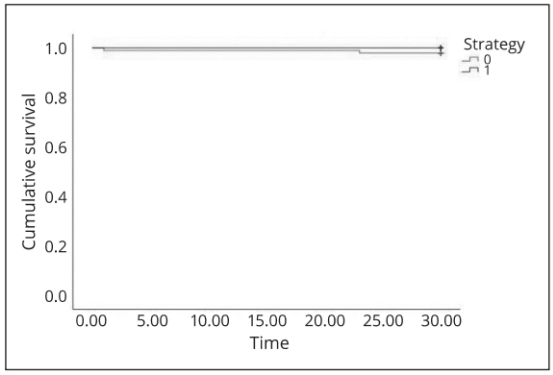

Figure 2.—Kaplan Meier curve showing primary outcome in uninterrupted group and shortly interrupted group. 0: uninterrupted group; 1: shortly interrupted group. 0: uninterrupted group; 1: shortly interrupted group.

ance to study medication counting Rivaroxaban pills from the drug blister at baseline and after12 months, stability of ACT intraprocedurally; a comparison among the uninterrupted and shorty interrupted anticoagulation strategy was also done. Moreover, a comparison between the different types of lesions sets as well as the energy type used and how those may affect the safety of the procedure was performed.

Statistical analysis

For the study protocol we calculated a population of 250 patients: using the Binomial exact test we hypothesize a sample size of 235 to obtain a two-sided 95% confidence interval[21] with a width equal to 0.10, considering an incidence of 0.17 for any ischemic and bleeding events (composite primary endpoint). We derived the incidence of 0.17 from the results of VENTURE AF TRIAL[22] after we corrected for a 5% drop-out rate, we collected a total of 250 subjects. The sample size calculation was performed by using

TABLE V.—*Baseline characteristics.*

Parameters	Total population (N.=250)	Uninterrupted strategy (N.=154)	Shortly interrupted strategy (N.=96)	P value
Age	62 (10)	62.5 (10)	63 (11)	0.442
Male	155	98	57	0.499
Female	95	56	39	0.499
BMI	26.6 (5.6)	26.2 (5.6)	26.6 (5.7)	0.725
Arterial hypertension	128	86	42	0.063
Dyslipidemia	134	85	49	0.375
COPD	34	19	15	0.460
Creatinine	0.9 (0.2)	0.9 (0.2)	0.88 (0.2)	0.475
Chronic kidney disease	18	10	8	0.584
Coronary artery disease	12	7	5	0.811
Heart failure	27	14	13	0.270
Previous stroke/TIA	11	6	5	0.622
Patient already on rivaroxaban	176	107	69	0.686
Patient rivaroxaban naive	74	47	27	0.688
Rivaroxaban 20 mg	233	146	87	0.201
Rivaroxaban 15 mg	17	8	9	0.201
CHA_2DS_2-VASc	2 (2)	2 (2)	3 (2)	0.569
HAS-BLED	0 (1)	0 (1)	0 (1)	0.873
Cardiopathy etiology				
Ischemic cardiomyopathy	12	6	6	0.397
Idiopathic dilatated cardiomyopathy	2	1	1	0.734
Myocarditis	6	3	3	0.554
Hypertensive cardiomyopathy	34	17	17	0.134
Hypertrophic cardiomyopathy	7	4	3	0.805
Infiltrative cardiomyopathy	2	1	1	0.734
Valvular cardiomyopathy	13	7	6	0.554
Congenital cardiomyopathy	2	1	1	0.734
SAPT	46	23	23	0.124
DAPT	10	5	5	0.509
Paroxysmal AF	187	114	73	0.659
Persistent AF	63	40	23	0.721
Permanent AF	0	0	0	N.A.
Prior AF ablation	14	7	7	0.358

BMI: Body Mass Index; AF: atrial fibrillation; TIA: transient ischemic attack; SAPT: single antiplatelet therapy; DAPT: dual antiplatelet therapy; HAS-BLED: hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly, drugs/alcohol concomitantly.

the PaSS software.[23] Statistical analysis was performed using SPSS version 27.0 for MAC (IBM Software, Inc., Armonk, NY, USA). Baseline demographic and clinical characteristics are presented in Table V. Normal distribution of variables was assessed with Kolmogorov-Smirnov Test. Categorical data were described as number and percentage. Continuous variables were expressed as mean and standard deviation or median and interquartile range, as needed. The Student's *t*-Test, χ^2 test, and Fisher's Exact Test were used for comparisons, as needed. Differences between variables with no normal distribution were tested with the Mann-Whitney U Test. When applicable, the Kaplan-Meier method was used to estimate the cumulative event rates in groups of patients managed with shortly interrupted or uninterrupted anticoagulation strategies, and differences in each group were compared using log-rank test. For all tests, a P value less than 0.05 was considered statistically significant.

Results

Patient characteristics

A total of 250 patients were enrolled in our study, everybody already on rivaroxaban or undergoing CA for AF after at least 4 weeks of assuming the medication. The median age was 54.3±4.5 years, 65.2% men. The average CHA_2DS_2-VASc score was 1.87±1.22 and the average HAS-BLED score was 0.43±0.32.

Clinical outcomes

Primary outcomes: 30-day and 12-month follow-up

In the first 30 days after CA, considering both the safety and efficacy aspects of the primary endpoint for all 250 patients, we only registered one TIA which occurred the day after the CA procedure, and one AMI occurring 23 days after the procedure which was treated with percutaneous coronary angioplasty and stent deployment (0.8%). Both events happened in patients with shortly interrupted anticoagulation strategy (P=0.147), and both in patient with RF ablation. We did not register any thromboembolic event for patient with uninterrupted anticoagulation. We did not register any episodes of major bleeding in this period of time both for uninterrupted and shortly interrupted anticoagulation strategy. We did not register any death, systemic embolism or major bleeding in the 12 months of follow-up both for uninterrupted and shortly interrupted anticoagulation strategy. No difference was found in terms of primary outcome event rate among patients managed with shortly interrupted or uninterrupted anticoagulation strategy (log-rank test P=0.073) (Table VI, VII).

TABLE VI.—*Catheter ablation characteristics.*

Parameters	Total population (N.=250)	Uninterrupted strategy (N.=154)	Shortly interrupted strategy (N.=96)	P value
AF recurrence	14	7	7	0.358
Anticoagulation compliance	250	100%	100%	
Basal ACT	150 (48)	150 (10)	149 (42)	0.093
Target ACT	350 (50)	350 (41)	351 (39)	0.111
Heparin given	9000 (6750)	11000 (5000)	9000 (5500)	<0.085
Number of transeptal punctures	1	1	1	N.A.
Intracardiac echocardiography guided transeptal puncture	173	108	65	0.686
Transesophageal guided puncture	18	9	9	0.293
Fluoroscopy guided transeptal puncture	59	30	29	0.052
RF ablation	192	123	69	0.145
Cryo ablation	33	23	10	0.304
Laser ablation	25	8	17	0.001
RF procedure time PVI only	138.7±43.7	139.7±48.8	136.7±23.7	0.516
RF procedure time PVI + posterior wall	148.9±51	149.9±51	148.9±51	0.88
Cryo procedure time	126.6±51	127.6±31	126.9±46	0.89
Laser procedure time	121.3±37.9	121.6±4	122.3±2	0.068
PVI only	224	138	86	0.994
PVI + posterior wall isolation	26	16	10	0.994

AF: atrial fibrillation; ACT: activated clotting time; RF: radiofrequency.

TABLE VII.—*Study outcomes.*

Parameters	Total population (N.=250)	Uninterrupted strategy (N.=154)	Shortly interrupted strategy (N.=96)	P value
Primary composite outcome – 30 days since CA	2	0	2	0.147
All cause death	0	0	0	N.A.
Systemic embolism	2	0	2	0.147
Stroke	0	0	0	N.A.
TIA	1	0	1	0.384
Peripheral embolism (AMI)	1	0	1	0.384
Major bleeding	0	0	0	N.A.
Primary composite outcome – 12 months since CA	0	0	0	N.A.
Death from all causes	0	0	0	N.A.
Systemic embolism	0	0	0	N.A.
Stroke	0	0	0	N.A.
TIA	0	0	0	N.A.
Peripheral embolism	0	0	0	N.A.
Major bleeding	0	0	0	N.A.
Secondary outcomes -30 days since CA	3	3	0	0.288
Procedure-related AEs (cardiac tamponade)	3	3	0	0.288
Minor bleedings	0	0	0	N.A.
Secondary outcomes – 12 months since CA	1	1	0	1
Procedure-related AEs	0	0	0	N.A.
Minor bleedings	1	1	0	1
Groin hematoma	8	5	3	1

CA: catheter ablation; AMI: acute myocardial infarction; TIA: transient ischemic attack; AEs: adverse events.

Secondary outcomes: 30 days since CA

Regarding AEs, 3 cardiac tamponades were observed during the CA procedure; all the 3 cardiac tamponades were treated intraprocedurally with pericardiocentesis, and CA was interrupted. All of these 3 patients were on uninterrupted anticoagulation strategy (P=0.288). No AEs were observed in shortly interrupted patients and no minor bleeding was registered during the first 30 days of follow-up in both strategy of anticoagulation.

Secondary outcome: 12 months since CA

No AEs were registered during the 12 months of follow-up in both anticoagulation strategy. Regarding minor bleedings (bleeding type 1 according to BARC definition), we only observed 1 episode of macrohematuria after 4 months since CA in an uninterrupted patient. Eight patients underwent electrical cardioversion (3.2%): 3 patients underwent electrical cardioversion 4 months after CA (37.5%), 5 patients 6 months after CA (62.5%); six patients (2.4%) (P=0.571). 6 Patients underwent pharmacological cardioversion for AF recurrence, 4 after 5 months since CA (66.6%), 1 patient 6 months after CA (16.6%), 1 patient 7 months after CA (16.6%). All 14 patients that had AF recurrence received PVI only with RF Ablation.

The compliance with the study medication was high, considering that no dose was skipped by any patient. The most adopted strategy for anticoagulation was the uninterrupted assumption of the medication before CA in 154 patients (61.6%) while the shortly interrupted strategy was done in 96 patients (38.4%). Target ACT time was 325.58 sec (DS±36.1).

Regarding the CA lesion sets, IRIS documented that current Italian practice strictly follows the latest ESC guidelines 3: with the use of PVI-only strategy by the majority of electrophysiologists (89.6%, N.=224) with RF and Cryo energy whereas the ablation of non-PV foci was attempted in few cases (26/250, 10.4%) just with RF.

IRIS also documented the tendency of Italian physicians to prefer Radiofrequency over Cryo and laser as the energy source for ablation: no differences in the safety profile regarding AEs and major bleeding have been found.

Discussion

The present study is based on the prospective Italian registry in the setting of AF abla-

TABLE VIII.—*Adverse outcomes at 30days.*

Adverse outcomes at 30 days	XANTUS[26]	VENTURE-AF[21]	IRIS
Major bleeding	5/173 (2.9%)	0/123	0/250
Stroke	2/173 (1.2%)	0/123	0/250
TIA	0/173	Not reported	1/250 (0.4%)
MI	0/173	Not reported	1/250 (0.4%)

MI: myocardial infarction; TIA: transient ischemic attack.

tion with rivaroxaban (IRIS) and intended to evaluate the safety and effectiveness of Rivaroxaban in patients undergoing CA for AF.[24] Our results are consistent with previous study such as XANTUS[25] and VENTURE-AF[21] (Table VIII)[21, 26] showing that: 1) rivaroxaban is both extremely safe and effective, as we did not identify any major bleedings nor any component of our primary outcomes (death from all cause or systemic embolism in the first 30 days since the CA procedure) except one AMI and one TIA; 2) regarding the primary outcome of safety, we did not find any differences in anticoagulation strategies, between uninterrupted or shortly interrupted Rivaroxaban; moreover, we did not register any differences in the type of energy utilized – radiofrequency, cryoablation or laser ablation – when it came to safety; 3) for treatment of AF recurrences, both electrical cardioversion and pharmacological cardioversion were used (8 patients *vs.* 6 patients, P=0.571); 4) the preferred management for anticoagulation therapy in the Italian context is the uninterrupted strategy (154 *vs.* 96 patients); and 5) regarding secondary outcomes, three patients developed cardiac tamponade and one had a minor bleeding event, consisting in macrohematuria. It is important to highlight that the AEs registered can be identified as some of the most frequent complications related to CA itself, independently of anticoagulation therapy, and were completely resolved during the hospital stay.

The statistics of AF have nowadays reached the entity of a pandemic, with 33 million people affected worldwide and numbers constantly rising.[27] Considering the evidence of increased risk of death, morbidity and stroke associated with AF, an aggressive strategy is appropriate to deal with such a severe disease. For this reason, in the last twenty-five years indications for CA have progressively expanded to even overcome antiarrhythmic drugs as first line therapy in certain categories of patients. CA was proved to guarantee a longer maintenance of SR and better quality of life[28, 29] when compared to antiarrhythmic drugs only; moreover, regarding congestive HF[30, 31] patients, CA reduces the risk of adverse outcomes and may improve LVEF. Therefore, AF ablation numbers have risen significantly in the last decade worldwide.[32] Consequently, the incidence of AEs connected to CA has increased in the last years: current data document a 4-10% of patients experiencing complications related to AF ablation, out of which 2 to 3% of them are potentially life threateting.[33] In order to avoid this, considering the possibility of spontaneous cardioversion in AF patients,[34] CA should be reserved for those who will likely benefit from such procedure. Logically the most worrisome aspect of CA for AF is the use of DOACs as they increase the risk of bleeding complications, for instance cardiac tamponade or groin hematoma.[35] CA for AF is associated with a high risk of cardiac tamponade for three intrinsic causes: the need for systemic anticoagulation in order to maintain a proper ACT time, the extensive ablation of atrial tissues which are not as thick as ventricular ones, and the transeptal punctures needed to reach the left atrium.[35]Our intraprocedural cardiac tamponade incidence (3/250, 1.2%),is similar to the one reported in two worldwide surveys of CA for AF, accounting for 1.2-1.3% of all procedures and were all successfully managed with pericardiocentesis.[36, 37] The use of DOACs nowadays represents a common practice thanks to their easy handling and safety:[38] this is also true in patients with a great variety of comorbidities, such as cancer,[39] chronic kidney disease,[40] HIV[41] and heart failure.[42] IRIS has been the first study to assess which is the periprocedural anticoagulant management in the

Italian setting; we documented that the majority of physicians do not interrupt DOACs before the CA procedure, and no major bleeding events were observed in the 30-day nor in the 12-month follow-up. These results match the actual tendencies in EP Labs of uninterrupted DOAC strategy, sustained by strong evidence in literature.[26] Our findings are in line with similar experiences from other countries in terms of outcomes, anticoagulation management and CA workflow[36, 37] thus highlighting the reproducible benefits of Rivaroxaban both for safety and effectiveness. Not a single major bleeding event has been reported in this study confirming the non-inferiority of DOACs over VIT K Inhibitors[38] and the safety profile of Rivaroxaban as well.[13] The IRIS has stated once again the safety and efficacy of DOACs in real practice for patients undergoing AF CA.

Limitations of the study

A limitation of this study was to consider a population from a single country even if patients were enrolled in centers of different parts of Italy. Also, the low rates of periprocedural AEs, and the extremely low incidence of AEs related to DOAC treatment, should require a bigger population in order to obtain a more precise assessment. The lack of a control population represents another weak side of this study.

Conclusions

Rivaroxaban is a safe and effective drug both for patients with AF and for those undergoing CA, in a similar way to other NOACs.[43] The real-world Italian data has proven that CA with rivaroxaban is a safe procedure, regardless of the type of energy used and the lesion box created. CA procedure brings a relevant burden thromboembolic risk in the periprocedural period, consisting mainly silent ischemic strokes;[44, 45] so that the low risk of intraprocedural AEs such as cardiac tamponades, as we observed in our study in the uninterrupted group, represents a worth risk considering the high probability of silent strokes or thromboembolic events during the follow-up period of the shortly interrupted group.

What is known

- Catheter ablation is a safe and effective procedure using every kind of ablation energies, transeptal approaches, ablation targets in every AF settings.
- Xarelto is a safe DOAC in the context of AF, both if shortly interrupted and uninterrupted during catheter ablation.

What is new

- Rivaroxaban is a safe and effective drug both for patients with AF and for those undergoing CA.
- Potential adverse side effects related to catheter ablation procedure or chronic anticoagulant therapy can be easily treated and do not determine long-term side effects.

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Conflicts of interest

The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Authors' contributions

Carlo Lavalle and Giovanni Battista Forleo have given substantial contributions to study conception, Nicola Pierucci and Carlo Lavalle to study design, Marco Valerio Mariani to software development, Carlo Lavalle to study validation, Nicola Pierucci, Marco Valerio Mariani and Vincenzo Mirco La Fazia to data analysis, Carlo Lavalle, Alessio Borrelli, Massimo Grimaldi and Pasquale Notarstefano to data investigation, Agostino Piro, Massimo Grimaldi, Antonio Rossillo and Pasquale Notarstefano to data interpretation, Paolo Compagnucci and Antonio Dello Russo to data curation, Nicola Pierucci and Marco Valerio Mariani to manuscript writing, Francesco Perna, Gemma Pelargonio and Carlo Lavalle to manuscript writing, revision and editing, Carlo Lavalle and Fabio Miraldi to study visualization, Carlo Lavalle and Giovanni Battista Forleo to study supervision. All authors read and approved the final version of the manuscript.

History

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