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CLINICAL RESEARCH

Rivaroxaban and dabigatran in patients undergoing catheter ablation of atrial fibrillation

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Aims The recent availability of the novel oral anticoagulants (NOACs) may have led to a change in the anticoagulation regimens of patients referred to catheter ablation of atrial fibrillation (AF). Preliminary data exist concerning dabigatran, but information regarding the safety and efficacy of rivaroxaban in this setting is currently scarce.

Methods and results Of the 556 consecutive eligible patients (age 61.0 ± 9.6; 74.6% men; 61.2% paroxysmal AF) undergoing AF catheter ablation in our centre (October 2012 to September 2013) and enroled in a systematic standardized 30-day follow-up period: 192 patients were under vitamin K antagonists (VKAs), 188 under rivaroxaban, and 176 under dabigatran. Peri-procedural mortality and significant systemic or pulmonary thromboembolism (efficacy outcome), as well as bleeding events (safety outcome) during the 30 days following the ablation were evaluated according to anticoagulation regimen. During a 12-month time interval, the use of the NOACs in this population rose from <10 to 70%. Overall, the rate of events was low with no significant differences regarding: thrombo-embolic events in 1.3% (VKA 2.1%; rivaroxaban 1.1%; dabigatran 0.6%; $P = 0.410$); major bleeding in 2.3% (VKA 4.2%; rivaroxaban 1.6%; dabigatran 1.1%; $P = 0.112$), and minor bleeding 1.4% (VKA 2.1%; rivaroxaban 1.6%; dabigatran 0.6%; $P = 0.464$). No fatal events were observed.

Conclusion The use of the NOAC in patients undergoing catheter ablation of AF has rapidly evolved (seven-fold) over 1 year. These preliminary data suggest that rivaroxaban and dabigatran in the setting of catheter ablation of AF are efficient and safe, compared with the traditional VKA.

Keywords Atrial fibrillation • Rivaroxaban • Dabigatran • Vitamin K antagonists • Fluindione • Stroke • Cryoablation • Thromboembolism • Bleeding • Arrhythmia

Introduction

Atrial fibrillation (AF) is the most frequent sustained arrhythmia in clinical practice.[1] Catheter ablation of AF has been established as the most effective therapy for the treatment of symptoms in these patients.[2] However, this procedure is associated with a significant thromboembolic risk during and shortly after the procedure, requiring an effective anticoagulation.[3] Vitamin K antagonists (VKA) have been traditionally used to prevent procedure-related thromboembolism.[4]

Recently, noval oral anticoagulants (NOACs) offering important advantages beyond their easiness of administration, like less interactions and no need of laboratory monitoring, have become available and appear as an attractive alternative in this setting. The impact of the wide availability of these NOACs in preventive anticoagulant treatment of patients that are currently being referred to catheter ablation of AF is currently unknown.

Dabigatran (a direct thrombin inhibitor) has displayed reassuring safety and efficacy data, suggesting that it might be used as an alternative to VKA.[5,6] However, data are almost absent concerning rivaroxaban, another NOAC with a different mechanism of action (a factor Xa inhibitor) which is being increasingly used worldwide.

Aim

We aimed to: (i) observe the change in the pattern of anticoagulant prescription in patients referred for catheter ablation of AF in our

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What's new?

- We demonstrate that the use of the novel oral anticoagulants in patients undergoing catheter ablation of atrial fibrillation has rapidly evolved (seven-fold) over 1 year.
- We provide the largest data to date concerning the safety and efficacy of rivaroxaban in the setting of catheter ablation of atrial fibrillation.
- The incidence of bleeding and thrombo-embolic events was low with all treatment regimens (rivaroxaban, dabigatran, and vitamin K antagonists), with no significant differences being found.

centre since the introduction of the NOAC; (ii) assess the efficacy and safety of dabigatran and rivaroxaban in patients referred for catheter ablation of AF compared with VKA.

Methods

Prospective, non-randomized, single-centre, observational study evaluating the efficacy and safety of different anticoagulation regimens in the setting of catheter ablation of AF.

Study sample

All consecutive patients undergoing catheter ablation of AF from October 2012 to September 2013 in Clinique Pasteur, Toulouse, France, were assessed for possible inclusion in this investigation. All patients with paroxysmal and non-paroxysmal forms, undergoing first or redo procedures and planned for treatment with radiofrequency or cryoballoon ablation were considered eligible.

Participants needed to be on effective oral anticoagulation (VKA, dabigatran, or rivaroxaban) for at least 30 days before the procedure to be considered for inclusion. Patients treated only with antiplatelet agents or subcutaneous heparin before the procedure were excluded from the analysis. On the other hand, if patients had been treated with one of the NOACs and due to intolerance to the drug needed to be changed to a different oral anticoagulant (namely if the changing was already planned before the procedure), they were excluded from the analysis.

Patients treated with VKA before the procedure that were changed to dabigatran and rivaroxaban on the day of the procedure, and those treated with VKA, dabigatran, and rivaroxaban before the procedure, and remaining on the same drug after the procedure were considered eligible for analysis.

Information on baseline $CHADS_2$, CHA_2DS_2-VASc, HAS-BLED, and other clinical data was retrieved. Vascular disease was defined as having at least one of the following: myocardial infarction, peripheral artery disease, or complex aortic plaque.

Computed tomography scan (64-slice Siemens© dual source CT scan) was performed in 24 h prior to the procedure for assessing pulmonary vein and left atrial anatomy and to exclude the presence of thrombi in the left atrial appendage. Transthoracic echocardiography was also performed in all the patients for assessing left atrial dimensions, left ventricle ejection fraction, and the presence of valvular heart disease.

All patients provided an informed consent prior to the procedure. The study complied with the Declaration of Helsinki and the research protocol was approved by the local ethics committee.

Peri-procedural anticoagulation

According to the type of peri-procedural anticoagulation, the study sample was divided into three groups (*Figure 1*): Group A—treated with VKA before and after the procedure; Group B—rivaroxaban or VKA before and rivaroxaban started on the day of the procedure; Group C—dabigatran or VKA before and dabigatran started on the day of the procedure.

Vitamin K antagonists were stopped 5 days before the procedure in all the patients and subcutaneous heparin (either calcium heparin 10 000 IU twice a day (bid) or enoxaparin 1 mg/kg bid, or 0.5 mg/kg bid if chronic kidney disease was present) was started 48 h after.

Dabigatran was interrupted 24–36 h before the procedure. The interruption in patients treated with rivaroxaban occurred 24–48 h before the

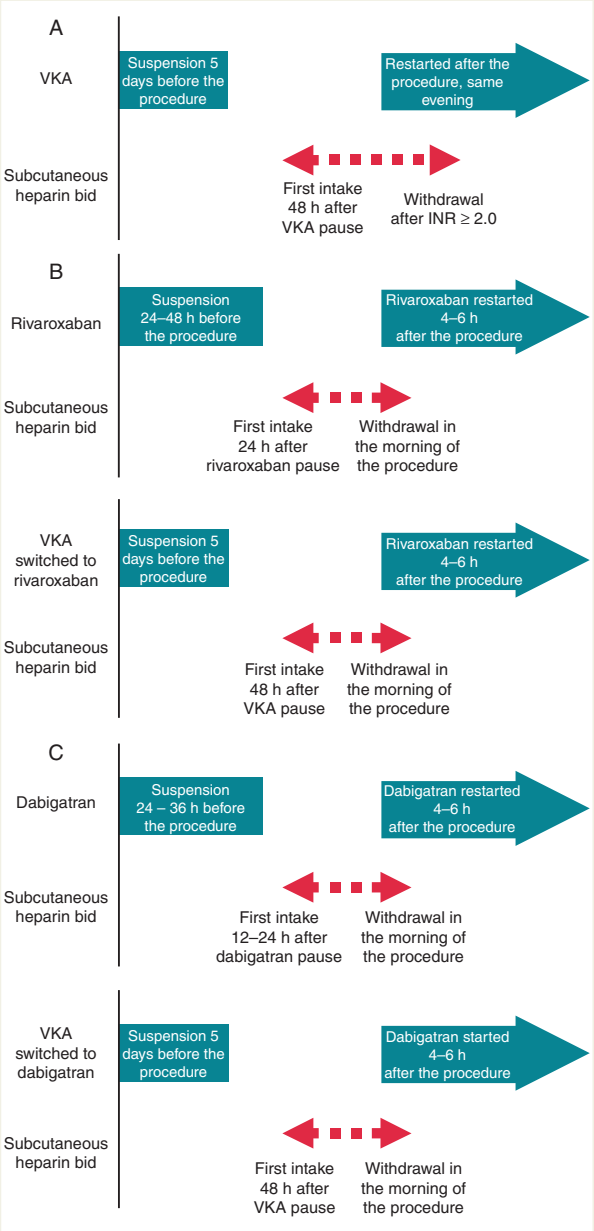

Figure 1 Flowchart illustrating the different treatment regimens and timing of drug interruption and restart, as well as bridging heparin therapy.

ablation. In some patients, an earlier interruption was possible due to the presence of comorbidities (like chronic kidney disease) or physician preference due to other reasons. Subcutaneous heparin was started 24 h after the interruption of rivaroxaban. In patients treated with dabigatran, subcutaneous heparin was started 12 h after suspension of the drug except for patients with estimated glomerular filtration rate below 45 mL/min, where subcutaneous heparin was started only 24 h after dabigatran interruption.

Vitamin K antagonists were restarted in the evening of the procedure. Dabigatran and rivaroxaban were started 4–6 h after the procedure. No protamine was administered at the time of sheath removal. After the procedure, subcutaneous heparin was continued only in patients treated with VKA and until international normalized ratio (INR) values were over 2.0.

Catheter ablation

All patients received general anaesthesia.

Venous punctures were performed: three for radiofrequency procedures (a 8Fr sheath and a 8Fr and 7Fr introducer) and two for cryoballoon ablation (a steerable 12Fr sheath (Flexcath®, Medtronic©, and a 7Fr introducer) and the multipolar irrigated radiofrequency catheter nMARQ™, Biosense Webster©,) (8.5Fr sheath). By using a transfemoral venous approach, a quadripolar catheter was placed in the coronary sinus. A single transseptal puncture was performed under fluoroscopic guidance (with use of transoesophageal echocardiography only if no success was obtained with fluoroscopy). Upon completion of the transseptal puncture, patients received intravenous heparin to maintain an activated clotting time of >300 s.

Patients underwent standard ablation procedures as directed by the operator. These procedures included pulmonary vein isolation with or without additional substrate modification. Ablation catheters used included cryothermic balloon catheter (Arctic Front®, Arctic Front Advance®, Medtronic, Inc.) and open-irrigated catheters: Celsius Thermocool®, EZsteer Thermocool®, SmartTouch®, nMARQ® (Biosense Webster), Tacticath® (St Jude Medical).

Thrombo-embolic and bleeding events

The following safety and efficacy endpoints were assessed, using the criteria proposed by *Sorgente et al.*:[7]

(1) All-cause peri-procedural death.
(2) Thromboembolism—a composite of stroke, transient ischaemic attack (TIA), systemic or pulmonary embolism. A stroke was defined as a sudden focal neurological deficit of presumed cerebrovascular aetiology lasting for >24 h, not due to another identifiable cause and confirmed by computed tomography or magnetic resonance imaging of the brain. If symptoms were short lasting (<24 h) and no evidence of necrosis was found on brain imaging, the event was considered to be a TIA. A systemic embolic event was defined as an abrupt vascular insufficiency associated with clinical or radiological evidence of arterial occlusion in the absence of another likely mechanism (e.g. atherosclerosis, instrumentation, or trauma). A pulmonary embolism was diagnosed when dyspnoea or other suggestive clinical presentation was accompanied by a radiological confirmation of a new pulmonary perfusion of intra-luminal defect, according to the requisites of the latest pulmonary embolism European Society of Cardiology guidelines.[8]
(3) Major bleeding—comprising cardiac tamponade, bleeding necessitating intervention (either thrombin injection or surgery) or transfusion, massive haemoptysis, haemothorax, retroperitoneal bleeding, or any other life-threatening bleed leading to prolongation of hospitalization.
(4) Minor bleeding—defined as puncture site bleeding, thigh ecchymosis or haematoma, pericardial effusion with no haemodynamic compromise, minor gastrointestinal bleeding, *epistaxis*, or any bleeding treated conservatively with no need for transfusion, surgery, or prolonged hospitalization.

We highlight that these criteria for defining major and minor bleeding are strongly based on the *International Society on Thrombosis and Haemostasis*,[9] but adapted to the catheter ablation of AF setting.

Other complications were also reported when the investigators judged that these might possibly be associated with peri-procedural anticoagulation.

Follow-up was obtained for the first 30 days after the procedure for all the patients and was either obtained after an observation of each patient at our centre or by a report from the patient's assistant cardiologist concerning that time period. Patients and their assistant cardiologists were instructed to report to the study centre immediately if any of these events occurred.

Statistical analysis

Comparisons were performed between the different peri-procedural anticoagulation regimens. χ^2 was used for the comparison of nominal variables. One-way analysis of variance (ANOVA), or its non-parametric equivalent, Kruskal–Wallis when appropriate, was used for comparison of continuous variables; the Levene's test was used to check the homogeneity of the variance. Results with $P < 0.05$ were regarded as significant.

When overall significant differences were found in the overall assessment of the three treatment groups, direct comparisons among the different groups were performed. *Post hoc* testing of ANOVA was performed by using the least significant difference test. When the Kruskal–Wallis test was used, *post hoc* was performed using the Mann–Whitney test. When comparing two categorical variables in *post hoc*, the χ^2 test was used, unless the observed value in any of the 2×2 contingency table cells was <5. In this case, the Fisher's exact test was used. The Bonferroni correction was used for estimating the significant *P* value for multiple comparisons. PASW Statistics (SPSS Inc.) version 18.0 was used for descriptive and inferential statistical analysis.

Results

Study sample and anticoagulation

Out of a total of 580 AF ablation procedures performed during the inclusion period, the following 24 were excluded from analysis: 6 due to lack of oral anticoagulation in the previous month (2 patients treated with aspirin, 2 with enoxaparin, and 2 with no thromboprophylaxis); two patients were changed from the NOAC (one rivaroxaban and one dabigatran) into warfarin at the time of ablation due to previously known drug intolerance; 14 patients with intolerance to dabigatran were changed to rivaroxaban and 2 patients with rivaroxaban intolerance changed the treatment to dabigatran.

Of the remaining 556 patients included in the analysis, 192 were included in Group A (treatment with VKA), 188 in Group B (treatment with rivaroxaban), and 176 in Group C (treatment with dabigatran). Vitamin K antagonists were used before the procedure in 86 of the patients (45.7%) treated with rivaroxaban and 68 (38.6%) of those treated with dabigatran (*Figure* 2).

Fluindione was the most frequently used VKA (86% in Group A; 40% in Group B; 32% in Group C). Only a minority of patients were treated with other VKA. Warfarin was used in 20 patients in Group A (10.4%), 8 patients in Group B (4.3%), and 10 patients in Group C (5.7%). Acenocumarol was used in seven patients in Group A (3.6%), two patients in Group B (1.1%), and two patients in Group C (1.1%).

Rivaroxaban 15 mg id was used in three patients before and in seven patients after the procedure. The 20 mg id dosage was used

in all of the remaining patients. Dabigatran 110 mg bid was used in 22 patients before and 17 patients after the procedure. The 150 mg bid dosage was used in all of the remaining patients.

In a small percentage of patients, the NOACs were suspended earlier (4–5 days before the procedure) than described in *Figure 1* (12 patients treated with dabigatran and 17 patients treated with rivaroxaban). This occurred due to physician's preference in the first months of utilization, in procedures that were anticipated to have higher complexity, and in patients with compromised renal function. Despite the small number of patients in this situation, a similar efficacy and safety profile was found in this subset.

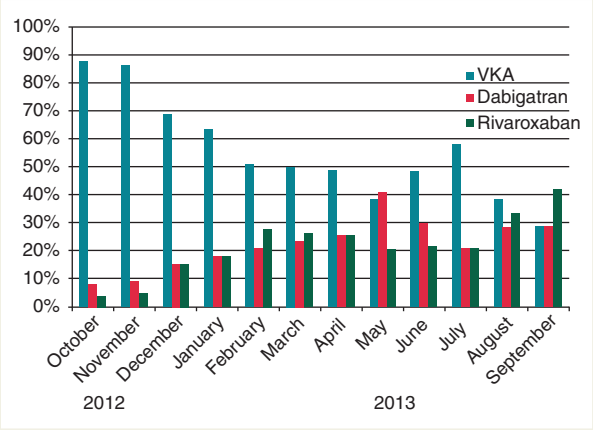

Figure 2 Evolution of the type of anticoagulants used at the arrival of our centre from October 2012 to September 2013 in patients admitted for AF ablation. VKA, vitamin K antagonists.

Some differences were found at baseline among the three different treatment groups (*Table 1*). Patients treated with VKA and rivaroxaban only differed in terms of age (a 3-year difference, with VKA patients being older). Patients treated with rivaroxaban were similar at baseline when compared with those treated with dabigatran, except for a lower bleeding risk (HAS-BLED) in the dabigatran group. Differences at baseline were more pronounced in the VKA vs. dabigatran comparison: higher prevalence of persistent AF, older patients, higher body mass index, higher thrombo-embolic and bleeding risk, more hypertensive patients, and lower baseline haemoglobin in the VKA group.

No differences were found concerning the use of antiplatelet agents before and after the procedure (*Table 2*). All patients treated with VKA before the ablation performed bridging therapy with subcutaneous heparin (mainly calcium heparin). However, in patients suspending rivaroxaban ($n = 27$) and dabigatran ($n = 46$) 24 h or less before the procedure, no subcutaneous heparin bridging was performed. The differences found in the concomitant use of subcutaneous heparin in the different groups are explained by the different half-life of the three agents and consequently the timing of interruption before the procedure.

Table 1 Baseline overall sample and characterization of each treatment group

	Overall ($n = 556$)	VKA ($n = 192$)	Rivaroxaban ($n = 188$)	Dabigatran ($n = 176$)	Overall *P*	Subgroup comparisons
Paroxysmal AF	61.2% (340)	52.6% (101)	63.3% (119)	68.2% (120)	0.007	VKA vs. dabigatran
Age	61.0 ± 9.5	62.9 ± 8.3	60.1 ± 9.9	59.8 ± 9.8	0.002	VKA vs. dabigatran, VKA vs. rivaroxaban
Female gender	25.4% (141)	26.0% (50)	26.1% (49)	23.9% (42)	0.859	
Body mass index	27.6 ± 4.4	28.3 ± 4.6	27.3 ± 4.2	27.2 ± 4.5	0.031	VKA vs. dabigatran
$CHADS_2$	0.8 ± 0.9	0.9 ± 1.0	0.8 ± 1.0	0.5 ± 0.8	0.001	VKA vs. dabigatran
CHA_2DS_2-VASc	1.5 ± 1.3	1.8 ± 1.4	1.5 ± 1.3	1.2 ± 1.2	0.001	VKA vs. dabigatran
HAS-BLED	1.0 ± 0.9	1.1 ± 0.9	1.0 ± 0.9	0.7 ± 0.8	0.001	VKA vs. dabigatran, rivaroxaban vs. dabigatran
Hypertension	39.6% (220)	49.0% (94)	39.4% (74)	30.1% (53)	0.001	VKA vs. dabigatran
Diabetes mellitus	8.8% (49)	10.9% (21)	9.0% (17)	6.3% (11)	0.282	
Previous stroke of TIA	9.4% (52)	10.4% (20)	11.2% (21)	6.3% (11)	0.225	
Glomerular filtration rate (Cockroft–Gault)	74.3 ± 23.7	73.6 ± 27.3	74.1 ± 20.9	75.3 ± 22.3	0.783	
Baseline C-reactive protein (mg/L)	3.7 ± 5.2	3.6 ± 4.7	4.0 ± 5.8	3.4 ± 5.1	0.637	
Baseline haemoglobin (g/dL)	14.7 ± 1.3	14.6 ± 1.3	14.7 ± 1.2	15.0 ± 1.2	0.029	VKA vs. dabigatran
Indexed left atrial volume (mL/m^2)	45.7 ± 16.5	47.6 ± 17.1	45.3 ± 18.1	44.1 ± 13.9	0.172	
Left ventricular ejection fraction (%)	62.4 ± 8.7	61.6 ± 10.2	61.9 ± 8.3	63.9 ± 7.0	0.125	

VKA, vitamin K antagonists; AF, atrial fibrillation; TIA, transient ischaemic attack.
Reference values for haemoglobin: 13.5–17.5 g/dL; C-reactive protein: <3.00 mg/L.
The observed differences were significant for the following subgroup comparisons: VKA vs. dabigatran; VKA vs. rivaroxaban; Rivaroxaban vs. dabigatran.

Table 2 Procedural and medication aspects in the overall sample and each treatment group

	Overall ($n = 556$)	VKA ($n = 192$)	Rivaroxaban ($n = 188$)	Dabigatran ($n = 176$)	Overall *P*	Subgroup comparisons
Antiplatelet agent before the procedure					0.190	
Aspirin	7.0% (39)	9.4% (18)	6.9% (13)	4.5% (8)		
Clopidogrel	0.9% (5)	0.5% (1)	1.6% (3)	0.6% (1)		
Aspirin + clopidogrel	0.4% (2)	1.0% (2)	0%	0%		
Antiplatelet agent after the procedure					0.197	
Aspirin	3.8% (21)	5.7% (11)	3.7% (7)	1.7% (3)		
Aspirin + clopidogrel	0.2% (1)	0.5% (1)	0%	0%		
Subcutaneous heparin bridging					0.001	VKA vs. rivaroxaban, VKA vs. dabigatran, rivaroxaban vs. dabigatran
LMWH	15.1% (84)	6.3% (12)	27.7% (52)	11.4% (20)		
Calcium heparin	71.8% (399)	93.8% (180)	58.0% (109)	62.5% (110)		
Cryoablation	29.5% (164)	33.3% (64)	31.9% (60)	22.7% (40)	0.056	
Redo procedure	22.8% (127)	25.0% (48)	24.5% (46)	18.8% (33)	0.292	
Procedure duration	134.8 ± 47.3	145.3 ± 54.5	132.4 ± 39.1	125.4 ± 44.3	0.001	VKA vs. rivaroxaban, VKA vs. dabigatran
Fluoroscopy duration	24.9 ± 9.7	26.9 ± 10.4	23.8 ± 9.2	23.8 ± 9.0	0.004	VKA vs. rivaroxaban, VKA vs. dabigatran

VKA, vitamin K antagonists; LMWH, low-molecular-weight heparin.
The observed differences were significant for the following subgroup comparisons: VKA vs. rivaroxaban; VKA vs. dabigatran; Rivaroxaban vs. dabigatran.

The length of the procedure was longer in the VKA group than in the NOACs. However, the time difference (when comparing procedures with dabigatran or rivaroxaban vs. VKA) was more pronounced in the dabigatran group (20 min) than in patients treated with rivaroxaban (~10 min).

Safety and efficacy of the different drug regimens

A low overall rate of thrombo-embolic events and complications was observed (*Table 3*). No patients died during the follow-up period. No significant differences in the rate of events were found among the three treatment groups.

An overall low incidence (0.9%) of stroke was reported. Four strokes were observed in the VKA group (2.1%) and another one was observed in a patient treated with rivaroxaban (0.5%) (see Supplementary material online, *Table S4*). These either left no sequels or led to minor disability at the end of the 30-day follow-up period. However, puncture complications filling major bleeding criteria were observed in all the groups, ranging from 1 to 3% of patients. A 1% incidence of pericardial effusion justifying pericardiocentesis or hospitalization/changes in therapy was observed in patients treated VKA and in one patient (0.5%) treated with rivaroxaban. A low incidence (1.4%) of minor bleeding (haematoma) was observed.

One patient treated with dabigatran developed an atrio-oesophageal fistula and one patient treated with VKA presented oesophageal ulceration after cryoballoon ablation (see Supplementary material online, *Table S4*).

The use of cryoballoon ablation was not associated with a significant increase in minor bleeding (2.4 vs. 1.0%; $P = 0.243$) or major bleeding-related puncture complications (1.8 vs. 1.8%; $P = 1.0$), in spite of the larger diameter sheaths required for this technique.

Grouping dabigatran and rivaroxaban in one variable, a similar incidence of thrombo-embolic events (0.8% NOAC vs. 2.1% VKA; $P = 0.205$) and minor bleeding (1.1% NOAC vs. 2.1% VKA; $P = 0.354$) were observed when compared with VKA. Despite the presence of a higher incidence of major bleeding events in the VKA group on univariate analysis (4.2% VKA vs. 1.4% NOAC; $P = 0.038$), after adjusting for all baseline differences, VKA were not independent predictors of major bleeding on multivariate analysis.

Discussion

We present reassuring preliminary data in support of the efficacy and safety of rivaroxaban in the setting of catheter ablation of AF. Furthermore, the low complication rate from patients previously treated with VKA that were changed to the NOAC at the time of catheter ablation of AF seems to provide support to this practice.

Despite the slight differences in some baseline (mainly between the VKA and dabigatran group, impairing possible comparisons between these two agents, which was also not the aim of this work) and intra-procedural aspects, already highlighted in the previous section, our data seem to suggest an overall low event rate with all treatment regimens. Furthermore, similar baseline characteristics allow a legitimate comparison of rivaroxaban with both VKA and dabigatran.

As shown in these data, patients are being referred more frequently to catheter ablation centres under treatment with the NOAC.

Table 3 Events observed during the 30-day follow-up period

	Overall ($n = 556$)	VKA ($n = 192$)	Rivaroxaban ($n = 188$)	Dabigatran ($n = 176$)	P
All-cause mortality	0%	0%	0%	0%	N.A.
Thromboembolism	1.3% (7)	2.1% (4)	1.1% (2)	0.6% (1)	0.410
Stroke	0.9% (5)	2.1% (4)	0.5% (1)	0%	
TIA	0.4% (2)	0%	0.5% (1)	0.6%(1)	
Pulmonary embolism	0%	0%	0%	0%	
Systemic embolism	0%	0%	0%	0%0	
Major bleeding	2.3% (13)	4.2% (8)	1.6% (3)	1.1% (2)	0.112
Puncture complications	1.8% (10)	3.1% (6)	1.1% (2)	1.1% (2)	
Pericardial effusion	0.5% (3)	1.0% (2)	0.5% (1)	0%	
Minor bleeding	1.4% (8)	2.1% (4)	1.6% (3)	0.6% (1)	0.464
Haematoma	1.4% (8)	2.1% (4)	1.6% (3)	0.6% (1)	
Other complications	0.4% (2)	0.5% (1)	0%	0.6% (1)	0.398
Atrio-oesophageal fistula	0.2% (1)	0%	0%	0.6% (1)	
Oesophageal ulcer	0.2% (1)	0.5% (1)	0%	0%	

VKA, vitamin K antagonist; TIA, transient ischaemic attack; N.A., not applicable.

However, if a solid body of evidence has been gathered for dabigatran supporting its use as an alternative to VKA (almost 2000 patients in a recently published meta-analysis[5]), data had been almost absent for rivaroxaban until now. To the best of our knowledge, this is the largest series of patients managed with rivaroxaban in the setting of catheter ablation of AF.

Eitel and colleagues have provided data on 16 patients who underwent AF ablation and were treated with rivaroxaban 20 mg id. However, two of these patients had been treated with subcutaneous low-molecular-weight heparin and one patient had no anticoagulation prior to the procedure.[10]

There is also information from a subanalysis of the 'Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation' (ROCKET-AF) trial, assessing the outcomes after cardioversion and AF ablation. The incidence of stroke or systemic embolism after electrical cardioversion, pharmacological cardioversion, and catheter ablation of AF was 0.93%. However, no specific information exists concerning the 79 patients who underwent 85 AF ablation procedures in the trial, periprocedural drug regimen, and the event rate in each treatment arm.[11]

Further data will certainly be provided by the still ongoing '*A Study Exploring Two Treatment Strategies in Patients With Atrial Fibrillation Who Undergo Catheter Ablation Therapy*' (VENTURE-AF trial), comparing rivaroxaban and warfarin, which estimates an enrolment of 200 patients.[12]

Our data show that some thrombo-embolic events occurred in patients with low risk as illustrated by the $CHADS_2$ and CHA_2DS_2-VASc scores (see Supplementary material online, *Table S4*), which highlights the low acuity of these scores for predicting events in this setting and also suggests that these complications may be more strongly related to the procedure than to the overall baseline thrombo-embolic risk of each patient. Also, it is legitimate to think that the mechanism of thrombus formation after an ablation procedure may be different to that happening naturally in AF and be more related to the extension of left atrial endothelial lesion/denuded left atrial wall. Therefore, it is of utmost importance to assure therapeutic anticoagulation levels right after the procedure.

The overall rate of complications in this sample was low and similar to what has been described in a series of >93 000 procedures from 2000 to 2010, that reported an intra-hospital rate of stroke or TIA of 1.02%, pericardial complications in 1.53%, and vascular complications in 1.52%.[13]

Previously published data suggest that prolonged interruption of dabigatran in this setting may lead to an increase in thrombo-embolic complications.[14] In our sample, the patient who presented a stroke on treatment with rivaroxaban had suspended the drug 4 days before the procedure and despite being on subcutaneous calcium heparin, we wonder if the same principle may also apply to this drug. However, the low rate of events and the low number of patients with a long interruption of rivaroxaban in our sample do not allow the making of such inference.

The overall incidence of atrio-oesophageal fistula after catheter ablation of AF is thought to be rare.[15] Despite the presence of reports of oesophagitis as a possible complication of therapy with dabigatran (out of the context of catheter ablation), due to the presence of tartrate as an excipient,[16] no strong conclusions can be drawn towards a causal effect in the patient presented in our sample, the first reported case of a patient developing an atrio-oesophageal fistula while on treatment with this drug.

In this paper, we assessed the role of the NOACs when used before and after the procedure. However, since 38–45% of patients in the dabigatran and the rivaroxaban groups, respectively, were treated with VKA before the procedure and changed to the NOACs at the time of the procedure, more robust data are provided regarding the post-procedural period. Furthermore, despite the scarcity of data regarding the initiation of a direct thrombin inhibitor or a Factor Xa inhibitor after ablation, this has been proposed in the 2012 Heart Rhythm Society/European Heart Rhythm Association/

European Cardiac Arrhythmia Society Expert Consensus Statement on catheter and surgical ablation of AF.[3]

In our study, we have interrupted the NOACs 24–48 h before the procedure. However, there seems to be a growing trend for shorter interruption times. In some recent investigations, it has been interrupted either the night before the procedure,[17] or even not interrupted at all.[18]

Limitations

Although we report the fist large prospective evaluation of rivaroxaban in the setting of catheter AF ablation, we agree that this investigation has several limitations which need to be discussed. First, our observational and non-randomized single-centre data result from a small sample of patients, but despite this provide the larger body of evidence available until now.

Secondly, subcutaneous calcium heparin and fluindione were used in a relevant number of patients. These drugs are not commonly used in other countries and no direct comparative studies exist in this context with the enoxaparin and warfarin, the drugs most widely used and with larger evidence. However, the European Society of Cardiology 2012 update of the AF guidelines[19] and the recent Venice Consensus on AF ablation[20] refer to VKA as the recommended treatment, not defining if warfarin or other drugs are used. Also, fluindione has been widely used in France for decades (it constitutes 80% of VKA prescription[21]) and no data exist that suggest a higher incidence of events while on this drug. Also, unlike warfarin, fluindione is not a racemic mixture and its longer half-life is thought to help stabilize INR levels.[22] For all these reasons, this point should not be considered as a true limitation but rather a particularity.

Thirdly, unlike other centres where ablation is performed under uninterrupted VKA anticoagulation due to a possible reduction in peri-procedural complications,[23] our centre has been performing these procedures using subcutaneous heparin bridging for over 10 years. However, in the aforementioned Consensus, there is no suggestion or recommendation for choosing uninterrupted VKA over the VKA interruption.[3,20] Furthermore, our practice reflects a local preference, among most French centres, of interrupted VKA, which is also preferred by our anaesthetists. A possible criticism is that we did not compare rivaroxaban with VKA at their best. However, patients treated with the NOAC also suspended treatment at the time of the procedure.

Fourthly, we have used heparin bridging after the interruption of the NOAC. Most available investigations with dabigatran did not use heparin bridging. Therefore, it is not yet known which should be the preferred option, as besides the lack of evidence or comparative trials, no recommendations exist regarding this point.

Fifthly, the baseline differences found in some of the three treatment groups may impair subgroup comparisons as previously mentioned. However, if we look carefully to Supplementary material online, *Table S4*, we can notice that not all seven patients sustaining thrombo-embolic events had a high $CHADS_2$ score: four patients had a CHADS score of 0, two patients a CHADS score of 1, and one patient a score of 3. Similarly, regarding the bleeding complications: for example, in the three observed pericardial effusions, two had a HAS-BLED score of 0 and one had a score of 2.

Lastly, the overall low number of events did not allow assessing the association of the different anticoagulation regimens with the outcomes on multivariate analysis.

Conclusion

Since the introduction of the NOAC, patients are being referred for catheter ablation of AF under treatment with these agents with increasing frequency: from 10 to 70% over a 1-year period.

Our preliminary data suggest that NOAC in the setting of catheter ablation of AF are as efficient and safe, compared with the traditional VKA management.

However, despite being reassuring, these preliminary data need to be replicated in future randomized trials.

Supplementary material

Supplementary material is available at *Europace* online.

Conflict of interest: R.P. was a co-investigator of the ENGAGE-AF TIMI 48 and ATLAS ACS 2-TIMI 51 trials and is speaker and consultant for Boehringer Ingelheim; S.C. is investigator and J.-P.A., N.C., and S.B. are co-investigators of the XANTUS trial. J.M. was investigator of the ATLAS ACS 2-TIMI 5 trial and is speaker/consultant for Bayer Healthcare, Boheringher Ingelheim, and Daiichi Sankyo.

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