

Outcomes after catheter ablation and cardioversion in patients with non-valvular atrial fibrillation: results from the prospective, observational XANTUS study

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Aims

In patients with atrial fibrillation, catheter ablation and cardioversion carry a risk of peri-procedural thromboembolic events; current guidelines recommend anticoagulation in these settings. This study aimed to report the baseline demographics and clinical characteristics of patients enrolled in the prospective, observational XANTUS study who underwent catheter ablation or cardioversion, and adverse outcomes with each of these procedures in patients treated with rivaroxaban.

Methods and results

Data collected included information on catheter ablation and cardioversion, and adverse outcomes occurring within 30 days of these procedures: incidence of treatment-emergent adjudicated symptomatic thromboembolic events and major bleeding; and cardiovascular and all-cause death. Incidence of these adverse outcomes at 42 days after cardioversion was also analysed. Patients undergoing either procedure had significantly lower mean CHA₂DS₂-VASC and HAS-BLED scores than those who did not, and were more frequently hospitalized at study baseline. Within a period of 30 days after intervention, symptomatic thromboembolic events were reported in 1.2% and 0.6% of patients undergoing ablation or cardioversion, respectively; major bleeding events were reported in 2.9% and 0.4% of patients undergoing ablation or cardioversion, respectively. No patients died within 30 days of intervention. Incidence of symptomatic thromboembolic and major bleeding events remained low at 42 days after cardioversion.

Conclusion

Similar to the results of prospective and non-interventional studies, the low rates of symptomatic thromboembolic events and major bleeding in patients with atrial fibrillation undergoing ablation or cardioversion and treated with rivaroxaban in XANTUS suggest that its use is associated with an acceptable benefit–risk profile in this setting.

Trial registration number

Clinicaltrials.gov: NCT01606995.

Keywords

Atrial fibrillation • Cardioversion • Catheter ablation • Non-vitamin K antagonist oral anticoagulants • Real-world evidence

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What's new?

- The results of the real-world, prospective, observational XANTUS study confirm data from prospective and non-interventional studies in terms of low rates of adverse outcomes, i.e. symptomatic thromboembolic events and major bleeding, in patients with atrial fibrillation treated with rivaroxaban who undergo catheter ablation or cardioversion.
- These results indicate that the use of rivaroxaban is associated with an acceptable benefit–risk profile in patients with atrial fibrillation undergoing ablation or cardioversion.

Introduction

By 2030, it is estimated that there will be 14–17 million patients with atrial fibrillation (AF) in the European Union, with 120 000–215 000 patients newly diagnosed each year.¹ Catheter ablation and cardioversion (pharmacological or electrical) have become the standard of care for re-establishing sinus rhythm in symptomatic patients, especially those with recent-onset AF.^{2,3} Because both catheter ablation and cardioversion carry a risk of peri-procedural thromboembolic events, current guidelines recommend that patients with AF of ≥ 48 h (or unknown) duration receive anticoagulation in the peri-procedural setting, beginning at least 3 weeks prior to the procedure and continuing until 4 weeks post-cardioversion and at least 8 weeks post-ablation.^{2–4} If a transoesophageal echocardiogram demonstrates the absence of thrombi in the left atrium or left atrial appendage, pre-procedural oral anticoagulant (OAC) therapy can be omitted.^{2–4}

Oral anticoagulation with vitamin K antagonists (VKAs) such as warfarin as part of the peri-procedural regimen have been the clinical standard for stroke prevention in patients with AF undergoing catheter ablation or cardioversion,^{2,3} although evidence from randomized controlled clinical trials is limited.⁵ Rivaroxaban and other non-VKA oral anticoagulants (NOACs) are an alternative to VKAs for long-term stroke prevention in patients with AF. NOACs offer well-described benefits over VKAs, including fewer interactions with food and other drugs, fixed dosing regimens, no requirement for routine coagulation monitoring, and a lower risk of intracranial haemorrhage and death.⁶ Growing real-world evidence suggests that the efficacy and safety profiles of these agents observed in the environment of phase III randomized controlled trials translate to unselected patients treated in routine clinical practice.^{7–11}

In addition to the benefits of NOACs in patients with AF, evidence is now emerging for the use of these agents in patients undergoing catheter ablation or cardioversion. Consequently, the 2016 European Society of Cardiology (ESC) guidelines on AF management recommend continuous anticoagulation with NOACs as an alternative to warfarin in patients undergoing catheter ablation,³ based on data from the COMPARE¹² and phase IIIb VENTURE-AF¹³ studies. Additionally, the 2016 ESC guidelines and the 2014 American Heart Association/American College of Cardiology (AHA/ACC) guidelines include a recommendation for the use of the NOACs apixaban, dabigatran, and rivaroxaban in patients undergoing cardioversion,² based on data from *post hoc* analyses of phase III clinical trials^{14–16} and from the phase IIIb X-VeRT study.¹⁷

XANTUS was a prospective, observational study assessing the safety and effectiveness of rivaroxaban in routine, real-world clinical practice in 6784 patients with non-valvular AF.¹¹ XANTUS showed that, in a broad, unselected patient population, the rates of stroke (0.6%) and major bleeding (1.9%) were low in patients receiving rivaroxaban in routine clinical practice.¹¹ Here, we report the baseline demographics and clinical characteristics of patients enrolled in the XANTUS study who underwent catheter ablation or cardioversion, and the outcomes observed in patients treated with rivaroxaban for each of these interventions.

Methods

The design of the international, non-interventional, observational XANTUS study was approved by the European Medicines Agency (EMA) and the study design and main results have been published previously.^{11,18}

Study population and data collection

Participating investigators were asked to screen all AF patients receiving pharmacological treatment for stroke prevention regardless of the prescribed treatment. This screening documentation occurred before eligible and consenting patients signed the informed consent forms and no patient-related data were permitted to be collected from the remaining patients. Eligible patients had a diagnosis of non-valvular AF, were aged ≥ 18 years, started rivaroxaban therapy for the prevention of stroke/non-central nervous system (CNS) systemic embolism (SE) and provided written informed consent.¹⁸ Patients undergoing these procedures were followed for up to 1 year or for 30 days after the end of rivaroxaban therapy. Investigators were asked to collect patient data every 3 months, including information on AF-related procedures such as catheter ablation, synchronized electrical cardioversion, and pharmacological cardioversion, along with all adverse outcomes.¹⁸ In this real-world study, dosing and administration of rivaroxaban, as well as the procedures carried out, were at the sole discretion of the participating investigators and no protocol recommendations existed.

Study outcomes

The data reported in this analysis were the following adverse outcomes occurring within 30 days of a catheter ablation (as in the VENTURE-AF study¹³) or cardioversion procedure: incidence of treatment-emergent adjudicated symptomatic thromboembolic events [stroke, non-CNS SE, transient ischaemic attack (TIA) and myocardial infarction (MI)] and major bleeding [International Society on Thrombosis and Haemostasis (ISTH) definition]; cardiovascular death (independently adjudicated cause); and all-cause death. In addition, the same adverse outcomes occurring within 42 days after the procedure were reported in patients undergoing cardioversion, as in the X-VeRT study.¹⁷ Data on success of interventions were not collected.

Study governance

The study complied with the Declaration of Helsinki and was approved by the appropriate health authorities, independent ethics committees and independent review boards as required.¹⁸ The study was conducted in accordance with good pharmacoepidemiology practice. An independent academic steering committee oversaw the design and conduct of the study. In addition, the committee was responsible for manuscript development, had full access to all data and approved all versions of the manuscript.

Informed consent from the patient included the permission for data collection and analysis. To minimize the risk of loss to follow-up, patients could voluntarily provide an alternative contact to the investigator/independent patient management team in countries where this was permitted. Data management and statistical analyses were overseen by the sponsor, in compliance with good clinical practice (GCP) standards. The lead statistician oversaw programming and validation of the statistical analyses.

Statistical analysis

This *post hoc* analysis of cardioversion and ablation outcomes and demographics was of an exploratory, descriptive nature. *P*-values were determined based on the χ^2 test for categorical variables and *F*-test for continuous variables.

Results

Patient population and ablation and cardioversion procedures

The overall XANTUS safety population included 6784 non-selected patients, of whom 173 underwent catheter ablation and 502 underwent cardioversion. Forty-nine patients underwent both procedures, bringing the number of patients who had at least 1 intervention to 626. *Figure 1* shows patient disposition during the study, with numbers of patients undergoing each of the procedures. Of the 502 patients who underwent cardioversion, 391 underwent electrical cardioversion and 151 pharmacological cardioversion; 40 of these patients underwent both types of cardioversion. In total, 71/173 (41%) patients undergoing catheter ablation and 201/502 (40%) of those undergoing cardioversion did not receive rivaroxaban on the day of the procedure.

Patient demographics and clinical characteristics

Patients who underwent catheter ablation tended to be significantly younger than those who did not (mean age 64.1 years vs. 71.7 years), with higher rates of paroxysmal (52.0% vs. 40.3%) or persistent (19.7% vs. 13.4%) AF rather than an initial diagnosis of permanent AF,

and fewer co-morbidities such as hypertension, diabetes mellitus, or congestive heart failure (CHF) (*Table 1*). In addition, they had a significantly lower mean CHA₂DS₂-VASc score (2.4 vs. 3.4) and a lower mean HAS-BLED score (1.6 vs. 2.0), and were more frequently hospitalized at study baseline (*Table 1*).

When compared with patients who did not undergo cardioversion (electrical or pharmacological), patients undergoing cardioversion were significantly younger (mean age 67.4 years vs. 71.8 years), with a greater likelihood of having newly diagnosed (32.1% vs. 17.4%) or persistent (23.9% vs. 12.8%) AF rather than initial diagnosis of permanent AF, and fewer co-morbidities such as hypertension, diabetes mellitus, prior stroke/non-CNS SE/TIA, or CHF (*Table 2*). This was reflected in the significantly lower mean CHA₂DS₂-VASc score (2.7 vs. 3.4) and lower HAS-BLED score (1.7 vs. 2.0) of patients undergoing cardioversion. These patients were also more frequently hospitalized at study baseline, i.e. before enrolment in XANTUS, than patients who did not undergo cardioversion (*Table 2*).

Outcomes

Within a period of 30 days after the procedure, symptomatic thromboembolic events were reported in 2/173 (1.2%) patients undergoing catheter ablation (2 events adjudicated as stroke) and 3/502 (0.6%) of those undergoing cardioversion (3 events adjudicated as TIA) (*Table 3*). All three symptomatic thromboembolic events in patients undergoing cardioversion occurred in those undergoing electrical cardioversion. Within 42 days of cardioversion, there were 2 additional symptomatic thromboembolic events adjudicated as stroke in 1 patient who had undergone cardioversion. This patient first underwent electric cardioversion, and then catheter ablation 40 days later. She experienced a primary ischaemic stroke with haemorrhagic transformation within 42 days of electric cardioversion, which was adjudicated as both stroke and major bleeding. Two days later, on the day of catheter ablation, she also experienced brain ischaemia, which was also counted for the cardioversion group because it occurred within 42 days of cardioversion.

Major bleeding events at 30 days after intervention occurred in 5/173 (2.9%) patients who had undergone catheter ablation

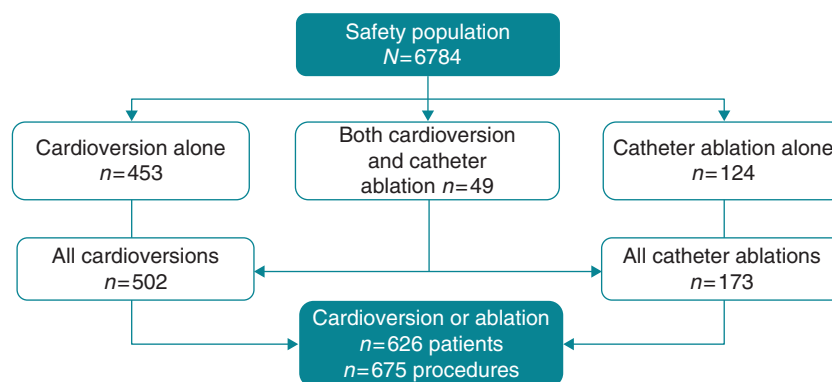


Figure 1 Patient flow in the population of patients who underwent cardioversion or ablation in the XANTUS study.

Table 1 Baseline demographics and clinical characteristics for patients undergoing catheter ablation in the XANTUS study

	Catheter ablation n = 173	No catheter ablation n = 6611	P-value ^a
Age, years, mean (SD)	64.1 (10.48)	71.7 (9.86)	<0.0001
<65 years, n (%)	76 (43.9)	1402 (21.2)	
≥65–≤75 years, n (%)	82 (47.4)	2700 (40.8)	
>75 years, n (%)	15 (8.7)	2509 (38.0)	
Male sex, n (%)	108 (62.4)	3908 (59.1)	0.3851
AF type ^b , n (%)			<0.0001 ^a
First diagnosed	36 (20.8)	1217 (18.4)	
Paroxysmal	90 (52.0)	2667 (40.3)	
Persistent	34 (19.7)	889 (13.4)	
Permanent	12 (6.9)	1823 (27.6)	
Blood pressure ^b , n (%)			
Systolic mmHg, mean (SD)	131.1 (17.59)	134.6 (17.83)	0.0156
Diastolic mmHg, mean (SD)	79.0 (11.98)	79.2 (10.61)	0.7394
Existing co-morbidities, n (%)			
Hypertension	101 (58.4)	4964 (75.1)	<0.0001
Diabetes mellitus	22 (12.7)	1311 (19.8)	0.0201
Prior stroke/non-CNS SE/TIA	24 (13.9)	1267 (19.2)	0.0800
Prior MI	10 (5.8)	678 (10.3)	0.0542
CHF	17 (9.8)	1248 (18.9)	0.0026
Cancer at baseline, n (%)	3 (1.7)	102 (1.5)	0.8406
Anaemia/reduced Hb levels, n (%)	3 (1.7)	200 (3.0)	0.3251
Prior anticoagulation therapy (before study baseline), n (%)	124 (71.7)	5048 (76.4)	0.1533
Concomitant antiplatelet/NSAID use, n (%)	33 (19.1)	1207 (18.3)	0.7835
Hospitalization at study baseline ^{b,c} , n (%)	62 (35.8)	1164 (17.6)	<0.0001
HAS-BLED score ^b , mean (SD)	1.6 (0.98)	2.0 (1.01)	<0.0001
CHADS ₂ score, mean (SD)	1.3 (1.12)	2.0 (1.27)	<0.0001
CHA ₂ DS ₂ -VASc score ^b , mean (SD)	2.4 (1.59)	3.4 (1.69)	<0.0001

AF, atrial fibrillation; CHF, congestive heart failure; CNS, central nervous system; Hb, haemoglobin; MI, myocardial infarction; NSAID, non-steroidal anti-inflammatory drug; SD, standard deviation; SE, systemic embolism; TIA, transient ischaemic attack.

^aDenotes significant interaction between patients undergoing ablation and those not undergoing ablation.

^bDenotes some missing data.

^cPrior to enrolment in XANTUS.

(5 events) and 2/502 (0.4%) of those who had undergone cardioversion (4 events) (Table 3). The number of patients who experienced major bleeding events remained low (3/502; 0.6%) at 42 days after intervention in the cardioversion group (5 events) (Table 3). No patients suffered cardiovascular death or all-cause death in either group at 30 days after the intervention.

Individual data in patients with adverse outcomes

In patients undergoing catheter ablation, the major bleeding events observed were: two pericardial haemorrhages; one anaemia; one groin haematoma; and one haemoptysis with haemoglobin drop. In patients undergoing cardioversion, the major bleeding events observed were: one ruptured aortic aneurysm; one haemorrhagic transformation; and one pericardial effusion. Three patients had treatment interruption in the peri-procedural setting; none of these patients received bridging therapy. Neither of the two patients who suffered an ischaemic stroke had treatment interruption before the procedure. Full narratives for the three TIA events were not written. Further details on the individual data for patients who had a major

bleeding or symptomatic thromboembolic event are summarized in Table 4.

Rates of symptomatic thromboembolic events and major bleeding at 30 days were low both in patients who received rivaroxaban on the day of the intervention and in those who did not receive the medication, as detailed in Supplementary material online, Table S1.

Discussion

This *post hoc* analysis of the XANTUS study provides insights into current treatment patterns, as well as thromboembolic and bleeding events, among non-selected patients undergoing catheter ablation or cardioversion who were treated with rivaroxaban for stroke prevention. Of the overall patient cohort ($N = 6784$), 9% of patients underwent catheter ablation or cardioversion, with 8% of these patients undergoing both procedures. Analysis of the demographics and clinical characteristics showed that, as expected, patients who underwent a procedure were generally younger than those who did not,

Table 2 Baseline demographics and clinical characteristics for patients undergoing cardioversion in the XANTUS study

	Cardioversion n = 502	No cardioversion n = 6282	P-value ^a
Age, mean years (SD)	67.4 (9.80)	71.8 (9.89)	<0.0001
<65 years, n (%)	176 (35.1)	1302 (20.7)	
≥65 to ≤75 years, n (%)	223 (44.4)	2559 (40.7)	
>75 years, n (%)	103 (20.5)	2421 (38.5)	
Male sex, n (%)	320 (63.7)	3696 (58.8)	0.0322
AF type ^b , n (%)			<0.0001 ^a
First diagnosed	161 (32.1)	1092 (17.4)	
Paroxysmal	198 (39.4)	2559 (40.7)	
Persistent	120 (23.9)	803 (12.8)	
Permanent	22 (4.4)	1813 (28.9)	
Blood pressure ^b , n (%)			
Systolic mmHg, mean (SD)	133.6 (18.58)	134.6 (17.77)	0.2474
Diastolic mmHg, mean (SD)	80.2 (11.40)	79.2 (10.58)	0.0387
Existing co-morbidities, n (%)			
Hypertension	348 (69.3)	4717 (75.1)	0.0043
Diabetes mellitus	79 (15.7)	1254 (20.0)	0.0219
Prior stroke/non-CNS SE/TIA	47 (9.4)	1244 (19.8)	<0.0001
Prior MI	46 (9.2)	642 (10.2)	0.4506
CHF	72 (14.3)	1193 (19.0)	0.0101
Cancer at baseline, n (%)	10 (2.0)	95 (1.5)	0.4020
Anaemia/reduced Hb levels, n (%)	7 (1.4)	196 (3.1)	0.0290
Prior anticoagulation therapy (before study baseline), n (%)	341 (67.9)	4831 (76.9)	<0.0001
Concomitant antiplatelet/NSAID use, n (%)	104 (20.7)	1136 (18.1)	0.1418
Hospitalization at study baseline ^{b,c} , n (%)	159 (31.7)	1067 (17.0)	<0.0001
HAS-BLED score ^b , mean (SD)	1.7 (0.96)	2.0 (1.01)	<0.0001
CHADS ₂ score, mean (SD)	1.5 (1.10)	2.0 (1.28)	<0.0001
CHA ₂ DS ₂ -VAsc score ^b , mean (SD)	2.7 (1.59)	3.4 (1.69)	<0.0001

AF, atrial fibrillation; CHF, congestive heart failure; CNS, central nervous system; Hb, haemoglobin; MI, myocardial infarction; NSAID, non-steroidal anti-inflammatory drug; SD, standard deviation; SE, systemic embolism; TIA, transient ischaemic attack.

^aDenotes significant interaction between patients undergoing cardioversion and those not undergoing cardioversion.

^bDenotes some missing data.

^cPrior to enrolment in XANTUS.

Table 3 Number of patients with major bleeding and symptomatic thromboembolic events within 30 days of intervention in patients with non-valvular atrial fibrillation undergoing catheter ablation or cardioversion in the XANTUS study

	Patients with events, n (%)		
	Catheter ablation n = 173	Cardioversion n = 502	Catheter ablation or cardioversion n = 626
Major bleeding ^a	5 (2.9)	2 (0.4)	6 (1.0)
Cardiovascular death	0	0	0
All-cause death	0	0	0
Symptomatic thromboembolic event	2 (1.2)	3 (0.6)	5 (0.8)
Stroke	2 (1.2)	0	2 (0.3)
Primary haemorrhagic stroke	0	0	0
Primary ischaemic stroke	2 (1.2)	0	2 (0.3)
Non-CNS embolism	0	0	0
TIA	0	3 (0.6)	3 (0.5)
MI	0	0	0

CNS, central nervous system; MI, myocardial infarction; TIA, transient ischaemic attack.

^aIncludes procedure-related bleedings and events during rivaroxaban interruption.

Table 4 Individual adverse outcomes occurring in patients undergoing cardioversion or catheter ablation in the XANTUS study

Subject	Procedure	Event	Treatment interruption	Bridging	Description of the event
Female, 75 years old	Electrical cardioversion	Major bleeding	No	N/A	Aortic aneurysm rupture >2 weeks after cardioversion
Female, 70 years old	Electrical cardioversion and catheter ablation	Ischaemic stroke and major bleeding	No	N/A	Primary ischaemic stroke with haemorrhagic transformation after cardioversion, adjudicated as both stroke and major bleeding within 42 days of cardioversion ^a . Second event of brain stem ischaemia on the day of catheter ablation, recorded as stroke within 30 days of catheter ablation and within 42 days of cardioversion
Female, 75 years old	Catheter ablation and electrical cardioversion	Two events of major bleeding (pericardial haemorrhage and pericardial effusion)	Yes—treatment interruption on day before catheter ablation/reintroduced day after procedure at reduced dose of 15 mg once daily	No	First event of pericardial haemorrhage on day of catheter ablation and second event of pericardial effusion on day of cardioversion. Both events adjudicated as major bleeding events
Female, 66 years old	Catheter ablation	Major bleeding	No	N/A	Major bleeding (haemoptysis with haemoglobin drop) on day of catheter ablation; no further details available
Male, 74 years old	Catheter ablation	Major bleeding	No	N/A	Anaemia recorded 20 days after catheter ablation; no further details available
Female, 67 years old	Catheter ablation	Major bleeding	Yes—treatment interruption two days before catheter ablation/reintroduced two days after procedure	No	Haematoma in groin on day after catheter ablation
Male, 68 years old	Catheter ablation	Ischaemic stroke	No	N/A	Ischaemic stroke on day of catheter ablation
Female, 61 years old	Catheter ablation	Major bleeding	Yes—treatment interruption for two days, starting on day of catheter ablation	No	Pericardial haemorrhage on day of catheter ablation

Full narratives for the three events of transient ischaemic attack are not available.

N/A, not applicable.

^aHaemorrhagic transformations of ischaemic stroke were adjudicated as major bleeding in XANTUS.

and had fewer co-morbidities and lower CHA₂DS₂-VASc and HAS-BLED scores.

In line with the overall XANTUS cohort, the numbers of symptomatic thromboembolic events, major bleeding events, and deaths (cardiovascular and all-cause) in this *post hoc* analysis of patients undergoing catheter ablation or cardioversion remained low, and most patients undergoing an intervention did not experience an adverse outcome. All symptomatic thromboembolic events in patients undergoing cardioversion occurred in those undergoing electrical cardioversion, both within 30 and 42 days of the procedure; however, the low number of events in both groups precluded comparison between the two approaches to cardioversion.

Although current ESC guidelines recommend uninterrupted treatment in patients undergoing catheter ablation,³ 41% of patients were recorded as having had treatment interruption on the day of procedure in the observational XANTUS study, which reflects the non-interventional design of the study. An uninterrupted treatment strategy was used in the phase IIIb VENTURE-AF study,¹³ which showed that in patients undergoing catheter ablation, use of uninterrupted oral rivaroxaban was feasible, with low rates of thromboembolic events and major bleeding reported. The risk of bleeding and stroke in patients undergoing catheter ablation or cardioversion in XANTUS appeared numerically higher in patients undergoing catheter ablation compared with

Table 5 Incidence of adverse outcomes after intervention in patients with AF undergoing catheter ablation and/or cardioversion and receiving anticoagulation therapy with rivaroxaban: data across four prospective studies^a

n/N (%)	ROCKET AF ^{b,16} Catheter ablation/ cardioversion	At 30 days		At 42 days		
		XANTUS Catheter ablation/ cardioversion	VENTURE-AF ¹³ Catheter ablation	XANTUS Catheter ablation	X-VerT ¹⁷ Cardioversion	XANTUS Cardioversion
Major bleeding	30/160 (18.75) ^c	6/626 (1.0)	0/123	5/173 (2.9)	6/988 (0.61) ^d	3/502 (0.6)
Cardiovascular death	2/160 (1.25)	0/626	0/124 ^e	0/173	4/978 (0.41) ^f	0/502
All-cause death	3/160 (1.88)	0/626	NR	0/173	5/978 (0.51) ^f	0/502
Symptomatic thromboembolic event	NR	5/626 (0.8)	0/124	2/173 (1.2)	3/978 (0.31) ^f	4/502 (0.8)
Stroke	3/160 (1.88) ^g	2/626 (0.3)	0/124 ^h	2/173 (1.2)	2/978 (0.20) ^f	1/502 (0.2)
Non-CNS embolism	NR	0/626	NR	0/173	0/978 ^f	0/502
TIA	NR	3/626 (0.5)	NR	0/173	0/978 ^f	3/502 (0.6)
MI	NR	0/626	NR	0/173	1/978 (0.1) ^f	0/502

AF, atrial fibrillation; CNS, central nervous system; ITT, intention-to-treat; MI, myocardial infarction; NR, not reported; TIA, transient ischaemic attack.

^aThe rivaroxaban dose was 20 mg once daily, with the ROCKET AF, X-VerT and XANTUS studies also having a 15 mg dose in patients with renal impairment (30–49 mL/min in ROCKET AF and X-VerT; 15–49 mL/min in XANTUS). Dose selection was at the investigator's discretion.

^bEvent rates over a median follow-up of 2.1 years (therefore, this dataset is not directly comparable with other datasets presented in this table).

^cMajor or non-major clinically relevant bleeding.

^dSafety population.

^eVascular death.

^fModified ITT population.

^gStroke/non-CNS systemic embolism.

^hIschaemic stroke.

cardioversion, most likely owing to the more invasive character of catheter ablation.

The phase III, randomized, double-blind ROCKET AF study,¹⁶ as well as the phase IIIb studies VENTURE-AF¹³ and X-VerT,¹⁷ compared rivaroxaban with dose-adjusted VKAs in patients with non-valvular AF. These studies have provided information on outcomes after catheter ablation or cardioversion in patients with non-valvular AF treated with rivaroxaban. The studies had very different designs and populations; in contrast to the prospective, non-interventional XANTUS study, they were performed in selected patients across a limited number of centres and with standard procedures, as for any randomized controlled trial. However, despite these limitations in terms of different designs and populations, a common finding was that the incidence of thromboembolic events after catheter ablation or cardioversion was low, as was the incidence of major bleeding events. In these studies, where a VKA comparator arm was included, the rates were similar in both the rivaroxaban- and VKA-treated groups.

A *post hoc* analysis of the ROCKET AF data showed that the rates of stroke/non-CNS SE (0.93%) or death (cardiovascular or all-cause: 1.25% for both) were low in the first 30 days after catheter ablation or cardioversion in a pooled analysis of patients treated with rivaroxaban or warfarin. Over a median follow-up period of 2.1 years, rates of stroke/non-CNS SE were similar in patients treated with rivaroxaban or warfarin (1.88% vs. 1.86%); the rates of cardiovascular death were 1.25% vs. 2.48%, respectively (all-cause death: 1.88% vs. 3.73%) (Table 5).¹⁶ Interrupted and uninterrupted rivaroxaban strategies were associated with similar outcomes. In XANTUS, similar outcomes were also observed between patients who received rivaroxaban on the day of the intervention and those who did not (see

Supplementary material online, Table S1). Similar *post hoc* analyses of the phase III studies for apixaban (ARISTOTLE)¹⁴ and dabigatran (RE-LY)¹⁵ also showed low rates of thromboembolic events [0% for apixaban, 0.8% (5/647) for dabigatran 110 mg twice daily (bid) and 0.3% (2/672) for dabigatran 150 mg bid for stroke/non-CNS SE] and major bleeding events [0.3% (1/331) for apixaban, 1.7% (11/647) for dabigatran 110 mg bid and 0.6% (4/672) for dabigatran 150 mg bid] in patients undergoing cardioversion at 30 days after the intervention, similar to those observed in XANTUS [0.6% (3/502) and 0.4% (2/502), respectively].

The multinational, randomized, open-label, parallel-group phase IIIb VENTURE-AF study evaluated the safety of uninterrupted rivaroxaban or VKAs in 248 patients with non-valvular AF undergoing catheter ablation. Rates of major bleeding at 30 days after intervention were low in this study, with no thromboembolic events or major bleeding observed in rivaroxaban-treated patients (Table 5), while rates of 1.6% (2/124) and 0.8% (1/121) were seen in VKA-treated patients, respectively. A meta-analysis of multiple observational studies assessing adverse outcomes at 30 days (and up to 11–18 months in 1 study) reported fewer thromboembolic events in patients treated with rivaroxaban compared with those receiving VKA [4/1954 (0.2%) vs. 19/5219 (0.4%)]. For major bleeding after catheter ablation, rates of 1.2% (23/1994) were reported in patients treated with rivaroxaban, compared with 1.7% (90/5406) in those receiving VKA.¹⁹ In the XANTUS study, the proportions of patients treated with rivaroxaban who experienced a symptomatic thromboembolic event or a major bleeding event at 30 days after catheter ablation were 1.2% and 2.9%, respectively, which is higher than the rates observed in VENTURE-AF (Table 5) and in the meta-analysis. The slightly higher event rates observed in this *post hoc* XANTUS analysis

compared with other datasets may be accounted for by the specific procedures used in the patients enrolled in the XANTUS study, which were not defined in a protocol as they were in these other studies because XANTUS was a non-interventional study. Additionally, some patients in XANTUS did not receive treatment on the day of the procedure. Randomized trials of NOACs and VKA in patients with AF undergoing catheter ablation, such as RECIRCUIT²⁰ and AXAFA-AFNET 5,²¹ will provide more precise estimates of the rates of adverse outcomes in these patients.

The X-Vert trial, a prospective, open-label, multinational, randomized phase IIIb study investigating rivaroxaban vs. VKA treatment in the cardioversion setting in patients with haemodynamically stable non-valvular AF of 48 h or unknown duration, showed that rivaroxaban-treated patients had low thromboembolic and bleeding risks at 42 days after cardioversion, similar to those observed in the VKA study arm.¹⁷ In X-Vert, 2/978 (0.2%) patients treated with rivaroxaban had a stroke vs. 2/492 (0.4%) of those treated with a VKA. The proportion of patients treated with rivaroxaban who had a major bleeding event was lower than in those treated with a VKA (0.6% vs. 0.8%) (Table 5).¹⁷ The proportions of patients who experienced a stroke or major bleeding event in X-Vert were similar to those observed at 42 days after cardioversion in XANTUS (0.2% and 0.6%, respectively), suggesting that rivaroxaban is associated with a low risk of thromboembolic events and major bleeding in patients undergoing cardioversion.¹⁷ The prospective, open-label, multi-centre, randomized phase IIIb ENSURE-AF study of edoxaban ($n=1095$) vs. enoxaparin/warfarin ($n=1104$) in patients with AF undergoing cardioversion also showed low rates of the composite of stroke, SE, MI and cardiovascular death [$<1\%$ (5/1095) vs. 1% (11/1104); primary efficacy endpoint] and major and clinically relevant non-major bleeding events [1% (16/1067) vs. 1% (11/1082); primary safety endpoint].²² The rates of stroke and major bleeding were $<1\%$ for both treatment groups (2/1095 vs. 3/1104, respectively; and 3/1067 vs. 5/1082, respectively).²²

Limitations

Limitations exist in the current analysis of the XANTUS study. It is important to note that the findings presented here are from a *post hoc* analysis of prospectively collected clinical data. In the context of this observational study, the procedures were carried out at the sole discretion of the participating investigators; no protocol recommendations existed and no details relating to the procedures were recorded. Additionally, the duration of anticoagulation before an intervention was at the discretion of the investigators, which could have impacted on outcomes. Finally, there was limited information relating to treatment interruption before or after the procedures, as well as at other time points during the study.

With these limitations in mind, however, it is reassuring to note that the use of rivaroxaban in routine clinical practice in patients undergoing cardioversion or ablation was associated with low rates of symptomatic thromboembolic events and major bleeding. The strength of the evidence for rivaroxaban lies in the use of different prospective studies employing different methods for data collection, but with a common feature of all outcomes being centrally adjudicated. The key finding of low rates of symptomatic thromboembolic events and major bleeding across four prospective and non-interventional studies involving patients treated with rivaroxaban

suggests that its use in routine practice is associated with an acceptable benefit–risk profile in patients with AF undergoing catheter ablation and/or cardioversion.

Conclusion

The rates of adverse outcomes (i.e. symptomatic thromboembolic events and major bleeding) were low in this real-life cohort of patients with AF treated with rivaroxaban who underwent catheter ablation or cardioversion as part of the XANTUS study, with no deaths up to 30 days after the procedure. These results were similar to the results of prospective, randomized controlled trials, and observational studies and suggest that the use of rivaroxaban in patients with AF undergoing catheter ablation or cardioversion as part of routine clinical practice may be associated with an acceptable benefit–risk profile.

Supplementary material

Supplementary material is available at *Europace* online.

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