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Rivaroxaban vs. vitamin K antagonists for cardioversion in atrial fibrillation

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Aims X-VeRT is the first prospective randomized trial of a novel oral anticoagulant in patients with atrial fibrillation undergoing elective cardioversion.

Methods and results We assigned 1504 patients to rivaroxaban (20 mg once daily, 15 mg if creatinine clearance was between 30 and 49 mL/min) or dose-adjusted vitamin K antagonists (VKAs) in a 2:1 ratio. Investigators selected either an early (target period of 1–5 days after randomization) or delayed (3–8 weeks) cardioversion strategy. The primary efficacy outcome was the composite of stroke, transient ischaemic attack, peripheral embolism, myocardial infarction, and cardiovascular death. The primary safety outcome was major bleeding. The primary efficacy outcome occurred in 5 (two strokes) of 978 patients (0.51%) in the rivaroxaban group and in 5 (two strokes) of 492 patients (1.02%) in the VKA group [risk ratio 0.50; 95% confidence interval (CI) 0.15–1.73]. In the rivaroxaban group, four patients experienced primary efficacy events following early cardioversion (0.71%) and one following delayed cardioversion (0.24%). In the VKA group, three patients had primary efficacy events following early cardioversion (1.08%) and two following delayed cardioversion (0.93%). Rivaroxaban was associated with a significantly shorter time to cardioversion compared with VKAs ($P < 0.001$). Major bleeding occurred in six patients (0.6%) in the rivaroxaban group and four patients (0.8%) in the VKA group (risk ratio 0.76; 95% CI 0.21–2.67).

Conclusion Oral rivaroxaban appears to be an effective and safe alternative to VKAs and may allow prompt cardioversion.

Name of the trial registry Clinicaltrials.gov; Trial registration number: NCT01674647.

Keywords Cardioversion • Oral anticoagulant • Stroke • Thromboembolism

Introduction

Atrial fibrillation (AF) is the most frequently encountered sustained cardiac arrhythmia, with a prevalence of about 1% in the general population.[1] In symptomatic patients, pharmacological or electrical cardioversion can be used to rapidly restore sinus rhythm.[1] However, there is a peri-procedural risk of thromboembolic events associated with cardioversion, with stroke rates between

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5 and 7% in non-anticoagulated patients.[2–4] Vitamin K antagonist (VKA) therapy, although never validated in controlled clinical trials, reduces the peri-procedural incidence of thromboembolic events to between 0.5 and 1.6%.[4,5] Current European Society of Cardiology and American Heart Association/American College of Cardiology/Heart Rhythm Society guidelines recommend at least 3 weeks of effective anticoagulation before cardioversion, followed by at least 4 weeks of anticoagulation after the procedure.[1,6] The use of transesophageal echocardiography to rule out left atrial (LA) thrombus plus heparin and VKA treatment immediately before, during, and for at least 4 more weeks after cardioversion is effective to expedite cardioversion.[6]

Novel oral anticoagulants are alternatives to VKAs for long-term stroke prevention in patients with non-valvular AF.[7–10] In addition, recent post hoc analyses have found dabigatran, rivaroxaban, and apixaban to be as safe and effective as VKA treatment in the setting of cardioversion when the pre-cardioversion anticoagulation time period is long.[11–14] This study was designed to explore prospectively the efficacy and safety of once-daily rivaroxaban compared with dose-adjusted VKA treatment (with or without heparin), in anticoagulation-naïve or -experienced patients undergoing elective cardioversion.

Methods

X-VeRT (eXplore the efficacy and safety of once-daily oral riVaroxaban for the prevention of caRdiovascular events in patients with non-valvular aTrial fibrillation scheduled for cardioversion) was a multinational, randomized, open-label, parallel-group phase IIIb study of patients with haemodynamically stable non-valvular AF of >48 h or of unknown duration. Details of the study protocol have been published previously.[15] Briefly, patients scheduled for cardioversion were randomly assigned to rivaroxaban or VKA therapy in a 2:1 ratio. The decision regarding early cardioversion (a goal of between 1 and 5 days of rivaroxaban or usual VKA therapy before the procedure) or delayed cardioversion (rivaroxaban or VKA for 3–8 weeks prior to the procedure) was made by the local investigator**.** Randomization to rivaroxaban or VKA treatment was performed using an Interactive Voice and Web Response System.

Patients and treatment regimens

Patients aged 18 years or older scheduled for elective electrical or pharmacological cardioversion were eligible for the trial. Patients could be naïve to oral anticoagulation or could have been previously anticoagulated with a VKA or novel oral anticoagulant. The main exclusion criteria were haemodynamically significant mitral valve stenosis, prosthetic heart valves, known LA thrombi, severe disabling stroke within the previous 3 months, and any stroke or transient ischaemic attack up to 2 weeks or 3 days, respectively, prior to randomization. The study protocol was approved by local ethics committees at participating centres and patients provided written informed consent to participate.

Patients randomized to rivaroxaban received a once-daily dose of 20 mg orally (or 15 mg once daily in patients with creatinine clearance of 30–49 mL/min). Patients randomized to the VKA arm received warfarin or another VKA at the investigator's discretion, based on local standard of care. The target international normalized ratio (INR) was 2.5 (range 2.0–3.0). Investigators had the option to use a parenteral anticoagulant drug in addition to VKA therapy especially prior to cardioversion until the target INR was obtained.

Cardioversion strategies and follow-up

Because of the potential adverse consequences of AF, it is desirable to conduct cardioversion as soon as possible. According to guidelines, an early cardioversion strategy can be followed either when transesophageal echocardiography rules out an LA thrombus or if ≥3 weeks' pre-treatment with therapeutic oral anticoagulation is proven.[1,6] In the early cardioversion strategy group in X-VeRT, rivaroxaban or a VKA was given with a goal of between 1 and 5 days before planned cardioversion and continued for 6 weeks post-cardioversion.[15] In patients randomized to rivaroxaban, medication was started at least 4 h before cardioversion. Patients with a LA thrombus detected during the study did not undergo cardioversion. In these patients, study treatment was stopped and patients were treated according to local standard of care and followed for 30 days. In the delayed cardioversion strategy group, patients were treated with either a VKA or rivaroxaban for at least 3 weeks and up to a maximum of 8 weeks before cardioversion. Oral anticoagulation with a VKA was considered adequate if the INR was maintained in the range 2.0–3.0 for at least three consecutive weeks prior to cardioversion. Oral anticoagulation with rivaroxaban was considered adequate if the pill count was ≥80% for three consecutive weeks prior to cardioversion. Rivaroxaban or the VKA was continued for 6 weeks after cardioversion.

After study termination, patients assigned to rivaroxaban could transition to non-study rivaroxaban (or another novel oral anticoagulant) or to a VKA (if INR ≥2.0) or to VKA plus parenteral anticoagulants. In patients who were treated with a VKA, transition to a novel oral anticoagulant occurred when the INR was ≤3 for rivaroxaban or ≤2.0 for dabigatran or apixaban.

Concurrent medications and procedures

The use of strong inhibitors of both cytochrome P450 3A4 and P-glycoprotein, a VKA or factor Xa inhibitors other than study medication, factor IIa inhibitors, low-molecular-weight heparin or unfractionated heparin unless for short-term bridging of VKA therapy, chronic acetylsalicylic acid therapy >100 mg daily, or dual antiplatelet therapy were not permitted in the study. Strong inducers of cytochrome P450 3A4 could be administered with caution. Patients receiving concomitant treatments that affect haemostasis were to be monitored carefully during the study. Patients at risk of ulcerative gastrointestinal disease or bleeding could receive prophylactic treatment with proton-pump inhibitors. When an invasive or surgical intervention was required, rivaroxaban was discontinued 24 h before the intervention and restarted afterwards as soon as possible.[15] Interruption or restarting of VKA therapy was according to usual practice.

Outcome assessment

Clinical events were adjudicated by an independent, blinded clinical events committee. The primary efficacy outcome was the composite of all adjudicated events classified as stroke or transient ischaemic attack, peripheral embolism, myocardial infarction, and cardiovascular death. Secondary efficacy outcomes included adjudicated all-cause mortality, a composite of stroke, transient ischaemic attack, peripheral embolism, myocardial infarction, and all-cause mortality, and individual components of the primary efficacy end-point.

The primary safety outcome was major bleeding. Major bleeding events were defined according to the International Society of Thrombosis and Haemostasis criteria.[16] The secondary safety end-point was all bleeding events.

Sample size and statistical analysis

Assuming the risk for thromboembolic events within 30 days after cardioversion in patients assigned to a VKA is 1%, we estimated that between

25 000 and 30 000 patients would be required to establish that rivaroxaban is non-inferior to VKA at a non-inferiority margin of 1.5 with 90% power and a 2:1 randomization in favour of rivaroxaban. We concluded that a trial of this size was not feasible. Using the post hoc analysis of cardioversions in the RE-LY trial with dabigatran in 1270 patients as a guide,[11] we decided that a descriptive comparison involving 1500 participants would give clinically meaningful information. The statistical analyses were descriptive. We estimated the risk and risk ratios for outcome events including 95% confidence intervals (CIs). Efficacy analyses were performed using the modified intention-to-treat (mITT) population that excluded patients with a LA thrombus and the intention-to-treat (ITT) population, including all randomized patients. The mITT population was used for the primary efficacy analysis. Safety analyses were performed in the safety analysis population, which included patients who received at least one dose of study medication. The study period for efficacy analyses was defined as the time from randomization until either the date of last dose of study medication plus 2 days (for patients who completed the planned study medication period) or the earlier date of the last planned dose of study medication (e.g. 42 days after cardioversion) and the end of the 30-day follow-up (for patients who prematurely discontinued study medication).

Results

Patient population, treatment assignment, and cardioversion

A total of 1584 patients were screened between 3 October 2012 and 25 September 2013, and 1504 patients were randomized (*Figure 1*) at 141 centres from 16 countries. Overall, 1002 patients were assigned to rivaroxaban and 502 to VKA. Thirty-five patients withdrew consent during the treatment phase, of whom 17 were confirmed alive at the end of follow-up. Of the remaining 18 for whom no further information was available, five were never treated with the study drug.

Thirty-four patients (rivaroxaban: 24; VKA: 10) were not included in the mITT population of 1470 patients (rivaroxaban: 978; VKA: 492; Supplementary material online, *Figure S1*). The characteristics of randomized patients were well balanced between the two treatment groups (*Table 1*). Forty-three percent of patients were experienced to oral anticoagulants, defined as ≥6 weeks of oral anticoagulation. Before randomization, 53 (3.5%) patients had received dabigatran, 88 (5.9%) rivaroxaban, 2 (0.1%) apixaban, and 51.3% (772/1504) VKAs. Fifty percent (504/1002) of patients were to be transitioned from pre-study treatment with VKAs to rivaroxaban, and 5.2% (26/502) of patients were to be transitioned from rivaroxaban to VKA.

Overall, 872 (58%) patients were scheduled to undergo early cardioversion with transesophageal echocardiography performed in 564/872 (64.7%; rivaroxaban: 377; VKA: 187) patients. A total of 632 (42%) patients were scheduled to undergo delayed cardioversion, with transesophageal echocardiography performed in 64/632 (10.1%; rivaroxaban: 33; VKA: 31) patients.

Overall, 1167 patients (77.6%) underwent electrical (97.6%) or pharmacological (2.4%) cardioversion within the target time range of 1–5 days (early) or 21–25 days (delayed cardioversion) after randomization. In the delayed group, 321/417 (77.0%) patients in the rivaroxaban arm compared with 78/215 (36.3%) patients in the VKA arm were cardioverted within the target time range ($P < 0.001$), primarily due to failure to achieve adequate anticoagulation (rivaroxaban: 1 patient, VKA: 95 patients). The acute cardioversion success rate was 86.8% (1013/1167) and was similar by treatment arm [rivaroxaban: 735/841 (87.4%); VKA: 278/326 (85.3%)] as well as by cardioversion strategy, 86.5 and 87.5% in the early and delayed cardioversion groups, respectively.

Patients who could not be cardioverted within the target time ranges continued on study treatment and 115 patients (rivaroxaban: 21; VKA: 94) had cardioversion performed at a later visit during the treatment phase. In 116 (7.7%) patients (rivaroxaban: 76; VKA: 40), spontaneous cardioversion was observed before an interventional cardioversion was performed.

Overall, the time between randomization and cardioversion was similar or shorter in patients assigned to rivaroxaban [early: median = 1 (interquartile range: 1–2) vs. 1 (1–3) days, $P = 0.628$; delayed: 22 (21–26) vs. 30 (23–42) days, $P < 0.001$].

Efficacy outcomes

Primary outcome events were experienced in 10/1470 (0.68%; 95% CI 0.36–1.21%) patients in the mITT population. The cumulative risk for this composite outcome was 5/978 (0.51%; 95% CI 0.20–1.17%) for patients assigned to receive rivaroxaban and 5/492 (1.02%; 95% CI 0.40–2.34%) for patients assigned to receive VKA, with a risk ratio for rivaroxaban to VKA of 0.50 (95% CI 0.15–1.73) (*Table 2*). *Table 3* reports individual outcome events. There were two patients with strokes in each treatment group (rivaroxaban: 0.20%; 95% CI 0.04–0.71%; VKA: 0.41%; 95% CI 0.07–1.41%), one patient with systemic embolism in the VKA group, one patient with myocardial infarction in each treatment arm, and six patients with cardiovascular deaths (four in the rivaroxaban group and two in the VKA group). One additional non-cardiovascular (cancer-related) death was reported in each treatment arm. In the early cardioversion strategy, primary efficacy outcome events occurred in 4/567 (0.71%; 95% CI 0.24–1.76%) rivaroxaban-treated patients and 3/277 (1.08%; 95% CI 0.30–3.06%) VKA-treated patients, whereas in the delayed cardioversion strategy group they occurred in 1/411 (0.24%; 95% CI 0.01–1.29%) patients and 2/215 (0.93%; 95% CI 0.17–3.26%) patients in the rivaroxaban and VKA groups, respectively. Out of the 10 patients who experienced primary efficacy outcome events, nine events occurred within the first 21 days after cardioversion; one patient died before cardioversion. When the outcome events occurred, 9 of the 10 patients were on study treatment; one cardioverted patient discontinued study treatment 10 days after randomization and died 10 days later. The cumulative incidence risk for the composite outcome of stroke, non-central nervous system embolism, transient ischaemic attack, myocardial infarction, and all-cause mortality was 6/978 (0.61%; 95% CI 0.27–1.29%) in patients receiving rivaroxaban and 6/492 (1.22%; 95% CI 0.53–2.51%) in patients receiving VKAs (risk ratio 0.50; 95% CI 0.16–1.55).

In OAC-naïve or untreated patients, the primary efficacy outcome events occurred in 4/565 (0.71%) patients in the rivaroxaban group and 3/273 (1.10%) patients in the VKA group. In patients with prior OAC use, the respective incidences were 1/413 (0.24%) in the rivaroxaban group and 2/219 (0.91%) in the VKA group. Patients undergoing transesophageal echocardiogram (TEE) experienced seven primary efficacy events (four in the rivaroxaban arm, and three in the VKA arm).

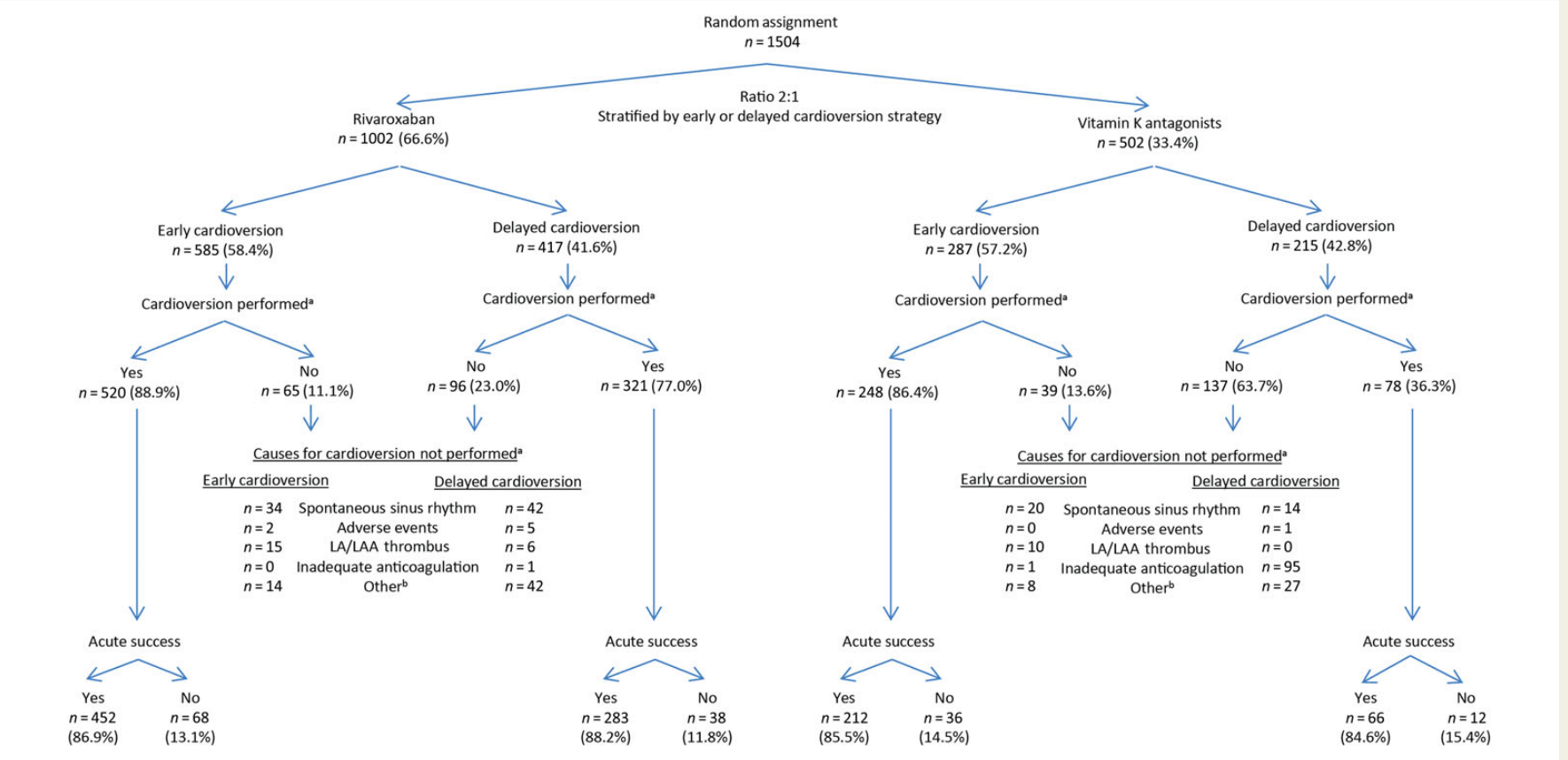

Figure 1 Study patient flow for scheduled cardioversion during the target time period (ITT population). ITT, intention-to-treat; LA, left atrial; LAA, left atrial appendage. [a]As scheduled; for early cardioversion: 1–5 days after randomization; for delayed cardioversion: 21–25 days after randomization. [b]Not further specified.

Table 1 Demographics (ITT population)

	Total by treatment		Early		Delayed	
	Rivaroxaban (n = 1002)	VKA (n = 502)	Rivaroxaban (n = 585)	VKA (n = 287)	Rivaroxaban (n = 417)	VKA (n = 215)
Region, *n* (%)						
Europe	728 (72.7)	364 (72.5)	414 (70.8)	205 (71.4)	314 (75.3)	159 (74.0)
North America	221 (22.1)	111 (22.1)	121 (20.7)	59 (20.6)	100 (24.0)	52 (24.2)
Asia-Pacific	53 (5.3)	27 (5.4)	50 (8.5)	23 (8.0)	3 (0.7)	4 (1.9)
Gender: male, *n* (%)	727 (72.6)	367 (73.1)	426 (72.8)	203 (70.7)	301 (72.2)	164 (76.3)
Age (years): mean ± SD	64.9 ± 10.6	64.7 ± 10.5	65.3 ± 10.4	65.3 ± 10.6	64.4 ± 10.8	64.0 ± 10.3
BMI (kg/m^2): mean ± SD	30.09 ± 5.83	30.19 ± 6.07	29.75 ± 5.82	29.82 ± 6.24	30.55 ± 5.81	30.69 ± 5.82
Creatinine clearance,[a] *n* (%)						
<30 mL/min	0	1 (0.2)	0	0	0	1 (0.5)
30–≤50 mL/min	68 (6.8)	30 (6.0)	50 (8.5)	17 (5.9)	18 (4.3)	13 (6.0)
50–<80 mL/min	310 (30.9)	176 (35.1)	174 (29.7)	114 (39.7)	136 (32.6)	62 (28.8)
≥80 mL/min	616 (61.5)	289 (57.6)	355 (60.7)	152 (53.0)	261 (62.6)	137 (63.7)
Medical history, *n* (%)						
Prior stroke	34 (3.4)	21 (4.2)	18 (3.1)	14 (4.9)	16 (3.8)	7 (3.3)
Prior non-CNS SE	10 (1.0)	11 (2.2)	4 (0.7)	6 (2.1)	6 (1.4)	5 (2.3)
Prior TIA	23 (2.3)	17 (3.4)	15 (2.6)	7 (2.4)	8 (1.9)	10 (4.7)
Congestive HF	197 (19.7)	75 (14.9)	124 (21.2)	52 (18.1)	73 (17.5)	23 (10.7)
NYHA class III/IV	48 (4.8)	9 (1.8)	33 (5.6)	8 (2.8)	15 (3.6)	1 (0.5)
Arterial hypertension	651 (65.0)	345 (68.7)	398 (68.0)	196 (68.3)	253 (60.7)	148 (68.8)
Diabetes mellitus	203 (20.3)	103 (20.5)	125 (21.4)	68 (23.6)	78 (18.7)	35 (16.3)
Vascular disease	134 (13.4)	56 (11.2)	98 (16.8)	32 (11.1)	36 (8.6)	24 (11.2)
MI	90 (9.0)	33 (6.6)	62 (10.6)	17 (5.9)	28 (6.7)	16 (7.4)
Atrial fibrillation, *n* (%)						
First diagnosed	238 (23.8)	106 (21.1)	104 (17.8)	52 (18.1)	134 (32.1)	54 (25.1)
Paroxysmal	172 (17.2)	114 (22.7)	124 (21.2)	85 (29.6)	48 (11.5)	29 (13.5)
Persistent	560 (55.9)	251 (50.0)	339 (57.9)	135 (47.0)	221 (53.0)	116 (54.0)
Long-standing persistent	30 (3.0)	26 (5.2)	17 (2.9)	12 (4.2)	13 (3.1)	14 (6.5)
$CHADS_2$ score, *n* (%)						
0	239 (23.9)	105 (20.9)	119 (20.3)	52 (18.1)	120 (28.8)	53 (24.7)
1	381 (38.0)	203 (40.4)	235 (40.2)	118 (41.1)	146 (35.0)	85 (39.5)
≥2	382 (38.1)	194 (38.6)	231 (39.5)	117 (40.8)	151 (36.2)	77 (35.8)
CHA_2DS_2-VASc score, *n* (%)						
0 (or 1, if female only)	147 (14.7)	65 (12.9)	67 (11.5)	31 (10.8)	80 (19.2)	34 (15.8)
1 (except for female alone)	215 (21.5)	118 (23.5)	128 (21.9)	66 (23.0)	87 (20.9)	52 (24.2)
≥2	640 (63.9)	319 (63.5)	390 (66.7)	190 (66.2)	250 (60.0)	129 (60.0)
OAC experienced,[b] *n* (%)	424 (42.3)	220 (43.8)	280 (47.9)	130 (45.3)	144 (34.5)	90 (41.9)
Antiplatelet agents	289 (28.8)	153 (30.5)	157 (26.8)	90 (31.4)	132 (31.7)	63 (29.3)
ASA	266 (26.5)	142 (28.3)	145 (24.8)	87 (30.3)	121 (29.0)	55 (25.6)
Clopidogrel	21 (2.1)	9 (1.8)	13 (2.2)	5 (1.7)	8 (1.9)	4 (1.9)
Antiarrhythmic drugs, *n* (%)	813 (81.1)	407 (81.1)	471 (80.5)	237 (82.6)	342 (82.0)	170 (79.1)
Amiodarone	181 (18.1)	100 (19.9)	129 (22.1)	62 (21.6)	52 (12.5)	38 (17.7)
Dronedarone	13 (1.3)	8 (1.6)	7 (1.2)	7 (2.4)	6 (1.4)	1 (0.5)
Flecainide	50 (5.0)	22 (4.4)	32 (5.5)	14 (4.9)	18 (4.3)	8 (3.8)

Continued

Table 1 *Continued*

	Total by treatment		Early		Delayed	
	Rivaroxaban ($n = 1002$)	VKA ($n = 502$)	Rivaroxaban ($n = 585$)	VKA ($n = 287$)	Rivaroxaban ($n = 417$)	VKA ($n = 215$)
Propafenone	15 (1.5)	5 (1.0)	8 (1.4)	3 (1.0)	7 (1.7)	2 (1.0)
Others, classes I and III[c]	2 (0.2)	1 (0.2)	2 (0.3)	1 (0.3)	0	0

ASA, acetylsalicylic acid; BMI, body mass index; CNS, central nervous system; HF, heart failure; ITT, intention-to-treat; MI, myocardial infarction; NYHA, New York Heart Association; OAC, oral anticoagulant; SD, standard deviation; SE, systemic embolism; TIA, transient ischaemic attack; VKA, vitamin K antagonist.
[a]Creatinine clearance calculated by Cockcroft–Gault formula.
[b]OAC experienced: oral anticoagulant use for 6 weeks or longer prior to first study medication intake.
[c]Disopyramide, dofetilide, or quinidine.

Table 2 **Number of patients with outcome events**

	Total by treatment			Early		Delayed	
	Rivaroxaban	VKA	RR (95% CI)	Rivaroxaban	VKA	Rivaroxaban	VKA
Efficacy, *n* (%)[a]	$n = 978$	$n = 492$		$n = 567$	$n = 277$	$n = 411$	$n = 215$
Primary end-point	5 (0.51)	5 (1.02)	0.50 (0.15–1.73)	4 (0.71)	3 (1.08)	1 (0.24)	2 (0.93)
Stroke	2 (0.20)	2 (0.41)		2 (0.35)	1 (0.36)	0	1 (0.47)
Haemorrhagic stroke	2 (0.20)	0		2 (0.35)	0	0	0
Ischaemic stroke	0	2 (0.41)		0	1 (0.36)	0	1 (0.47)
TIA	0	0		0	0	0	0
SE	0	1 (0.20)		0	1 (0.36)	0	0
MI	1 (0.10)	1 (0.20)		1 (0.18)	0	0	1 (0.47)
Cardiovascular death	4 (0.41)	2 (0.41)		3 (0.53)	2 (0.72)	1 (0.24)	0
All-cause death	5 (0.51)	3 (0.61)		3 (0.53)	3 (1.08)	2 (0.49)	0
Safety, *n* (%)[b]	$n = 988$	$n = 499$		$n = 575$	$n = 284$	$n = 413$	$n = 215$
Major bleeding	6 (0.61)	4 (0.80)	0.76 (0.21–2.67)	3 (0.52)	3 (1.06)	3 (0.73)	1 (0.47)
Fatal	1 (0.10)	2 (0.40)		1 (0.17)	2 (0.70)	0	0
Critical site	2 (0.20)	3 (0.60)		2 (0.35)	2 (0.70)	0	1 (0.47)
ICH	2 (0.20)	1 (0.20)		2 (0.35)	0	0	1 (0.47)
Hb decrease ≥2 g/dL	4 (0.40)	1 (0.20)		1 (0.17)	1 (0.35)	3 (0.73)	0
Transfusion ≥2 units RBCs or whole blood	3 (0.30)	1 (0.20)		1 (0.17)	1 (0.35)	2 (0.48)	0

Cumulative incidence risk for adjudicated outcomes from randomization up to the date of last study medication plus 2 days. Per protocol, study treatment was to be continued up to 42 days after cardioversion.
CI, confidence interval; CV, cardiovascular; Hb, haemoglobin; ICH, intracranial haemorrhage; MI, myocardial infarction; N/A, not applicable; RBC, red blood cells; RR, risk ratio; SE, systemic embolism; TIA, transient ischaemic attack; VKA, vitamin K antagonist.
[a]mITT population.
[b]Safety population.

In the ITT population, the same 10 patients as in the mITT population experienced adjudicated primary efficacy outcomes because no outcome events were observed in patients excluded due to an LA thrombus (Supplementary material online, *Table S1*). This resulted in a marginally lower estimated risk of the primary efficacy outcome in the larger ITT population (0.50; 95% CI 0.15–1.72). The results were consistent across a large number of pre-specified subgroups. Of 1415 patients (0.28%), 4 experienced a primary outcome event during post-treatment follow-up.

Safety outcomes

Major bleeding occurred in 6/988 (0.61%; 95% CI 0.26%–1.27%) patients in the rivaroxaban group and 4/499 (0.80%; 95% CI 0.27–2.00%) patients in the VKA group (risk ratio 0.76; 95% CI 0.21–2.67) (*Table 2*). Intracerebral bleeding occurred in two (0.2%) patients in the rivaroxaban group and one (0.2%) patient in the VKA group. Fatal bleeding was reported in one (0.1%) patient in the rivaroxaban group and two (0.4%) patients in the VKA group. In patients scheduled for early cardioversion, the incidence of

Table 3 Adjudicated individual efficacy outcome events

Adjudicated event(s)	Age/ gender	NYHA class III/IV	Relevant medical history	$CHADS_2$ score	CHA_2DS_2-VASc score	Cardioversion strategy	Cardioversion performed/ number of attempts/success	Cardioversion type[b]	Days after randomization	Days before(−)/ after(+) cardioversion	TEE performed	
Rivaroxaban group[a]												
Sudden unexpected death	69/M	No	CHF/HTN/liver disease/ bladder cancer	2	3	Early	Yes/1/yes	E	7	+6	Yes (no thrombus)	
MI/CV death	76/M	No	HTN/stroke/syncope/renal disease/pacemaker	4	5	Early	Yes/1/yes	E	6 (MI) 7(death)	+1 (MI) +2 (death)	Yes (no thrombus)	
Stroke/intracerebral bleed, non-fatal[c]	79/M	No	DM/gastric ulcer/prostate cancer/angina pectoris/ sarcoidosis	2	3	Early	Yes/2/yes	E	18	+15	Yes (no thrombus)	
Stroke/intracerebral bleed, fatal[c]	69/F	No	HTN/ischaemic stroke/ CHD/cardiomyopathy/ breast cancer	3	5	Early	Yes/−/yes	P	21 (stroke) 23 (death)	+16 (stroke) +18 (death)	Yes (no thrombus)	
CV death/CHF	89/M	No	Pacemaker/hypothyroid/HF	1	2	Delayed	−/−/−	None	33	–	–	
All-cause death/lung cancer	70/M	No	Lower urinary tract symptoms	0	1	Delayed	Yes/1/yes	E	79	+58	–	
Adjudicated event(s)	**Age/ gender**	**NYHA class III/IV**	**Relevant medical history**	**$CHADS_2$ score**	**CHA_2DS_2-VASc score**	**Cardioversion strategy**	**Cardioversion performed/ number of attempts/success**	**Cardioversion type[b]**	**Days after randomization**	**Days before (−)/ after (+) cardioversion**	**TEE performed**	**INR at time of event**
VKA group												
All-cause death/lung cancer[c]	79/M	No	HTN/prostate cancer/ pulmonary squamous cell carcinoma	2	3	Early	Yes/2/yes	E	26	+26	Yes (no thrombus)	1.2
Ischaemic stroke, non-fatal	76/M	No	HTN/RBBB	2	3	Early	Yes/2/yes	E	4	+2	Yes (no thrombus)	–
Non-CNS SE/CV death/all-cause death (autopsy documented, fatal[c])	72/M	No	HTN/complex aortic plaque/ PAD/dyslipidaemia/left leg above knee amputation; aortobifemoral bypass	2	4	Early	Yes/1/yes	E	9	+9	Yes (no thrombus)	7.4
CV death	63/M	Yes	CHF/MI/cardiomyopathy/ pacemaker	1	2	Early	Yes/−/no	P	21	+19	Yes (no thrombus)	–
Ischaemic stroke, non-fatal	55/M	No	HTN	1	1	Delayed	Yes/1/yes	E	32	+4	–	–
MI, non-fatal	58/M	No	Chronic obstructive pulmonary disease / Crohn's/renal disease/ GERD/fatty liver	0	0	Delayed	Yes/2/no	E	48	+13	–	1.7

AF, atrial fibrillation; CHD, coronary heart disease; CHF, congestive heart failure; CV, cardiovascular; HD, heart disease; HTN, hypertension; INR, international normalized ratio; MI, myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction; NYHA, New York Heart Association; RBBB, right bundle branch block; SE, systemic embolism; TEE, transesophageal echocardiogram.

[a]20 mg once daily, down-titrated to 15 mg once daily if creatinine clearance 30–49 mL/min.

[b]Cardioversion type: E, electrical; P, pharmacological.

[c]Event also qualified as major bleeding (refer to *Table 4*).

Table 4 **Adjudicated individual major bleeding events on treatment**

Adjudicated event(s)	Age/ gender	NYHA class III/IV	Relevant medical history	$CHADS_2$ score	CHA_2DS_2-VASc score	Cardioversion strategy	Cardioversion performed/ number of attempts/success	Cardioversion type[a]	Days after randomization	Days before (−)/after(+) cardioversion	TEE performed	
Rivaroxaban group												
Major intracerebral bleed, non-fatal[b]	79/M	No	DM/gastric ulcer/prostate cancer/angina pectoris/ sarcoidosis	2	3	Early	Yes/2/yes	E	18	+15	Yes (no thrombus)	
Major GI bleed, non-fatal	54/M	No	HTN/DM/anaemia	2	2	Early	Yes/3/yes	E	3	+3	–	
Major intracerebral bleed, fatal[b]	69/F	No	HTN/ischaemic stroke/ CHD/cardiomyopathy/ breast cancer	3	5	Early	Yes/–/yes	P	21	+16	Yes (no thrombus)	
Major GI bleed, non-fatal	72/F	No	CHF/CAD	3	6	Delayed	Yes/1/yes	E	13	−8	–	
Major GI bleed, non-fatal	79/F	No	HTN/TIA/gastric ulcer/ GI bleed	4	6	Delayed	Yes/1/yes	E	64	+12	–	
Major vaginal bleed, non-fatal	51/F	No	Cholecyst-ectomy/atrial septal defect/right eye amaurosis	0	1	Delayed	–/–/–	None	4	–	–	
Adjudicated event(s)	**Age/ gender**	**NYHA class III/IV**	**Relevant medical history**	**$CHADS_2$ score**	**CHA_2DS_2-VASc score**	**Cardioversion strategy**	**Cardioversion performed/ number of attempts/success**	**Cardioversion type[a]**	**Days after randomization**	**Days before (−) /after (+) cardioversion**	**TEE performed**	**INR at time of event**
VKA group												
Major pulmonary bleed/lung cancer, fatal[b]	79/M	No	HTN/prostate cancer/ pulmonary squamous cell carcinoma	2	3	Early	Yes/2/yes	E	24	+24	Yes (no thrombus)	5.3
Major vitreous haemorrhage, non-fatal	54/M	No	HTN	1	1	Early	Yes/1/yes	E	31	+30	–	–
Major GI bleed, fatal[b]	72/M	No	HTN/complexaortic plaque/PAD/left leg above-knee amputation/ dyslipidaemia/ aortobifemoral bypass	2	4	Early	Yes/1/yes	E	9	+9	Yes (no thrombus)	7.4
Major subdural haematoma, non-fatal	62/M	No	HTN	1	1	Delayed	Yes/1/yes	E	58	+36	–	1.8

AF, atrial fibrillation; DM, diabetes mellitus; HTN, hypertension; INR, international normalized ratio; NYHA, New York Heart Association; PAD, peripheral artery disease; TIA transient ischaemic attack; TEE, transesophageal echocardiography; VKA, vitamin K antagonist.

[a]Cardioversion type: E, electrical; P, pharmacological.

[b]Event also qualified as efficacy outcome events (refer to *Table 3*).

major bleeding was 3/575 (0.5%) patients in the rivaroxaban group and 3/284 (1.1%) patients in the VKA group (*Table 4*). The risk of the secondary safety outcome (any confirmed bleeding events) was similar between the two treatment arms (8.9 and 7.2% for the rivaroxaban and VKA groups, respectively). Patients undergoing TEE experienced four primary safety events (two in the rivaroxaban arm, and two in the VKA arm).

Treatment-emergent serious adverse events were reported in 8.8% of patients in total, of which 1.1% were assessed to be drug related. No clinically important differences in the overall cumulative incidence of adverse events and serious adverse events by treatment assignment or by cardioversion strategy were observed.

Discussion

X-VeRT is the first completed prospective trial of a novel oral anticoagulant in patients with AF undergoing elective cardioversion. Rivaroxaban administered *de novo*, or as ongoing therapy, or as a replacement for VKAs or another anticoagulant agent was associated with thromboembolic and bleeding risks that were low and similar to those observed with VKA treatment. This observation applied to both the early and delayed cardioversion strategies. A net clinical benefit outcome (the composite of stroke, non-central nervous system systemic embolism, transient ischaemic attack, myocardial infarction, cardiovascular death, and major bleeding) occurred in 6/978 (1.06%) patients receiving rivaroxaban and 5/492 (1.81%) patients receiving VKA (risk ratio 0.49; 95% CI 0.14–1.69). In the delayed cardioversion group, rivaroxaban allowed cardioversion after a shorter treatment period (mean 25 days) compared with VKAs (mean 34 days) because of the inability to achieve adequate anticoagulation prior to cardioversion in the VKA group at 3 weeks (95 patients compared with 1 patient in the rivaroxaban group). In the early cardioversion group, rivaroxaban administered at least 4 h before cardioversion provided effective and safe anticoagulation. Results were consistent across all analysis sets (mITT, ITT, and safety) and in prespecified subgroups.

The use of VKAs before and after cardioversion is the current standard practice endorsed by guideline recommendations.[1,6] A major obstacle to using a VKA is the observation that >3 weeks are required to achieve stable therapeutic INR values.[17] This finding was confirmed in this study. The pharmacological characteristics of the novel oral anticoagulants are particularly useful in the setting of elective cardioversion. Their rapid onset of action (2–4 h), short half-life, and predictable pharmacokinetics and pharmacodynamics allow a more rapid cardioversion strategy. This study adds to the data from phase III clinical trials from which post hoc analyses using the direct thrombin inhibitor dabigatran,[11] or direct factor Xa inhibitors rivaroxaban and apixaban,[12,13] were conducted. In the RE-LY post hoc analyses, the largest to date, the frequencies of stroke and major bleeding within 30 days after cardioversion were found to be low on chronic treatment with dabigatran similar to those observed with warfarin.[11] Similar findings were found in the other post hoc analyses involving apixaban and rivaroxaban.[12,13]

X-VeRT was underpowered to provide statistically rigorous results and was thus exploratory in nature. Several findings, however, substantiate the strength of the results of X-VeRT. The estimated risk ratios consistently indicated a trend towards lower incidences of thromboembolic events and major bleeding events in favour of rivaroxaban in the total population as well as in the early and delayed cardioversion subgroups (*Table 2*). The 95% upper confidence limits of incidences for thromboembolic events (1.17%) and major bleeding events (1.27%) in the rivaroxaban arm correspond to efficacy and safety incidences, which are well within the range of those reported in previous series of VKA-treated patients.[4,5] The risks for efficacy events in the rivaroxaban arm were much lower than those reported in the absence of anticoagulant therapy (5–7%).[18] The practical advantage of using rivaroxaban was demonstrated by the short time to cardioversion and the low number of patients failing to achieve adequate anticoagulation pre-cardioversion at 3 weeks in the delayed cardioversion group. When considering the results, it should be noted that the study was conducted in a heterogeneous real-world population. The open-label randomization used here could have introduced a bias in the reporting and/or adjudication of outcome events. In order to reduce this bias, several validated procedures, including blinded evaluation of outcome events, were employed, as previously reported in RE-LY.[7] A similar proportion of patients (15.6% in the rivaroxaban arm and 20.3% in the VKA arm) discontinued drug treatment owing to suboptimal compliance.

In summary, oral rivaroxaban appears to be an effective and safe alternative to VKA and may allow prompter cardioversion.

Supplementary material

Supplementary Material is available at *European Heart Journal* online.

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