EXplore the efficacy and safety of once-daily oral riVaroxaban for the prevention of caRdiovascular events in subjects with non-valvular aTrial fibrillation scheduled for cardioversion: X-VeRT

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On behalf of X-VeRT trial committees and Investigators

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Disclosure

- Consultant to: Boston Scientific; Medtronic; St. Jude; Biosense Webster; ELA Sorin; Boehringer Ingelheim; Bayer HealthCare; Abbott; Pfizer
- Speaker's Bureau: Boston Scientific; Medtronic; St. Jude; Biosense Webster; BARD; Sanofi; Boehringer Ingelheim; Bayer HealthCare; Abbott
- Investigator: Medtronic; Biosense Webster; Sanofi; Cameron Health, BARD; Bayer HealthCare; Abbott; Pfizer
- Grants: Boston Scientific; Medtronic; St. Jude; Biosense Webster; BARD; ELA Sorin
- Equity and Intellectual Property Rights: Cameron Health

Study rationale and background

- Cardioversion is a common procedure worldwide used to restore normal rhythm in patients with AF[1]
- Without adequate anticoagulation, the periprocedural risk of thromboembolism with cardioversion is 5–7%[2] (1% for patients receiving a VKA)[3]
- VKAs are the current standard of care before and after cardioversion,[4] with only post hoc analyses supporting use of novel OACs[5–7]

1. Hernandez-Madrid *et al*, 2013; 2. Stellbrink *et al*, 2004; 3. Gallagher *et al*, 2002; 4. Camm *et al*, 2012; 5. Piccini *et al*, 2013; 6. Nagarakanti *et al*, 2011; 7. Flaker *et al*, 2014

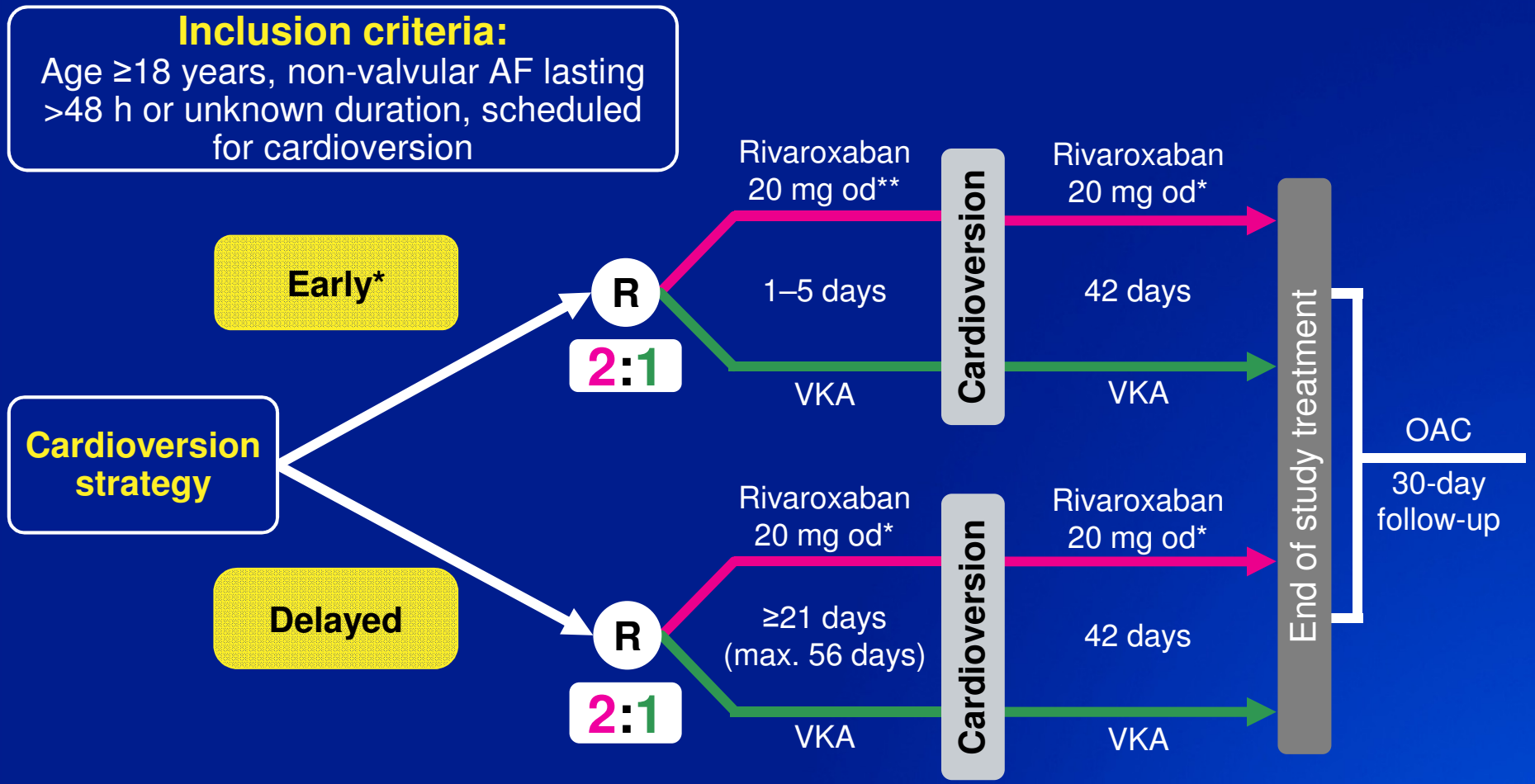
Study objective

- To explore efficacy and safety of once-daily rivaroxaban for the prevention of cardiovascular events* in patients with non-valvular AF scheduled for elective cardioversion compared with dose-adjusted VKAs

*Composite of stroke and TIA, non-CNS systemic embolism (SE), MI and cardiovascular death

Ezekowitz *et al*, 2014; www.clinicaltrials.gov. NCT01674647

Design: randomized, open-label, parallel-group, active-controlled multicentre study



* Protocol recommended only if adequate anticoagulation or immediate TEE;
**15 mg if CrCl 30–49 ml/min; VKA with INR 2.0–3.0

Ezekowitz *et al*, 2014; www.clinicaltrials.gov. NCT01674647

Main exclusion criteria

- Prior acute thromboembolic events, thrombosis, MI or stroke ≤14 days (severe, disabling stroke ≤3 months) or TIA ≤3 days
- Cardiac thrombus, myxoma or valvular heart disease
- Active bleeding or high risk of bleeding
- CrCl <30 ml/min
- Concomitant drug therapies
  - Chronic ASA therapy >100 mg daily or dual antiplatelet therapy
  - Concomitant use of strong inhibitors of both CYP 3A4 and P-gp

Ezekowitz *et al*, 2014

Primary outcomes

Primary efficacy outcome

A composite of:

- Stroke and TIA
- Non-CNS systemic embolism
- Myocardial infarction
- Cardiovascular death

Primary safety outcome

- Major bleeding (ISTH definition)[1]

All endpoints adjudicated by treatment assignment-blinded Clinical Endpoint Committee

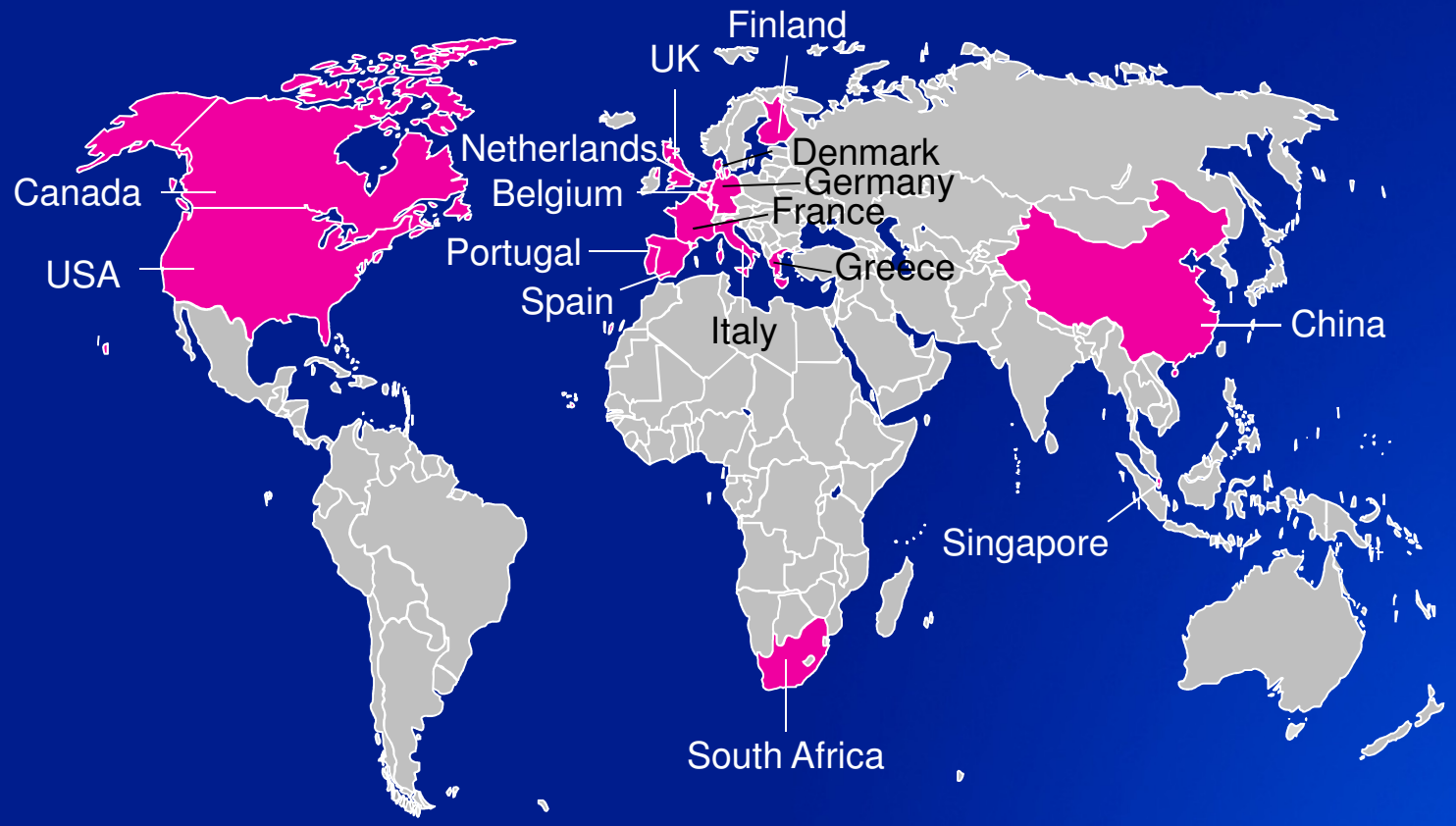
1. Schulman *et al.* 2005

Statistical plan

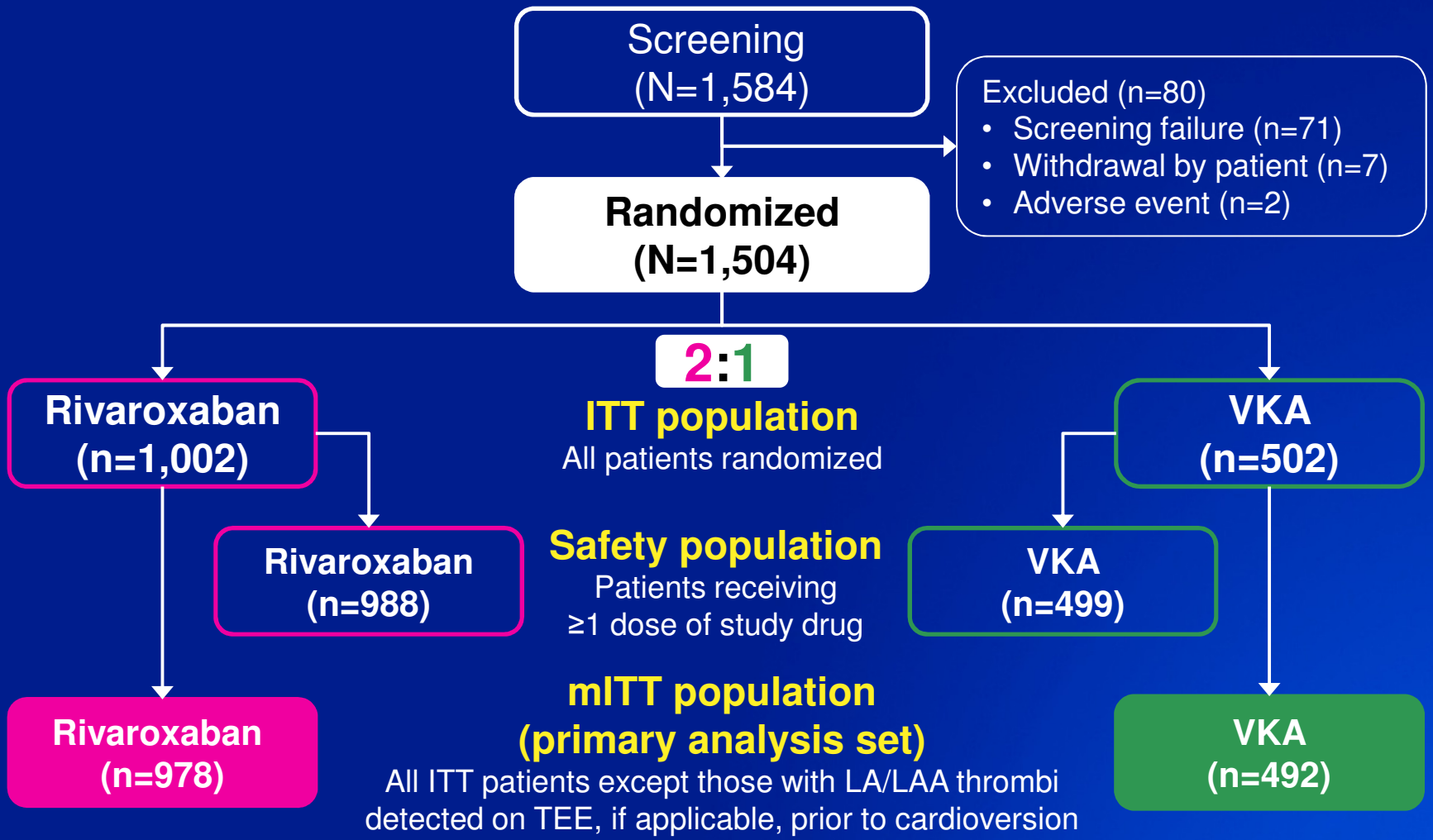
- Sample size to establish non-inferiority of rivaroxaban would be ~25,000–30,000 patients assuming
  - 1% perioperative risk of thromboembolic events with VKA
  - Margin of 1.5 in terms of risk ratio, power 90%
- Trial of this size not feasible
- A descriptive comparison of 1,500 patients would give clinically meaningful information
- Statistical analyses are descriptive with estimates of incidence risks and risk ratios for outcome events including 95% confidence intervals

X-VeRT: participating countries

- **1,504 patients** randomized from **141 centres** across **16 countries**
  - Recruitment began October 2012; database closed in February 2014



Study population



Baseline demographics

	Rivaroxaban (n=1,002)	VKA (n=502)	Total (N=1,504)
Age, mean (SD), years	64.9 (10.6)	64.7 (10.5)	64.9 (10.5)
Female, %	27.4	26.9	27.3
$CHADS_2$ score, mean (SD)	1.3 (1.0)	1.4 (1.0)	1.4 (1.1)
CHA_2DS_2VASc score, mean (SD)	2.3 (1.6)	2.3 (1.6)	2.3 (1.6)
Hypertension, %	65.0	68.7	66.2
Congestive heart failure, %	19.7	14.9	18.1
Previous stroke/TIA or SE, %	6.7	9.8	7.7
Diabetes mellitus, %	20.3	20.5	20.3
Type of AF, %*			
First-diagnosed	23.8	21.1	22.9
Paroxysmal	17.2	22.7	19.0
Persistent	55.9	50.0	53.9
Long-standing persistent	3.0	5.2	3.7

*Data missing in 7 patients. Renal function: 92.5% of patients had CrCl ≥50 ml/min
ITT population

Results

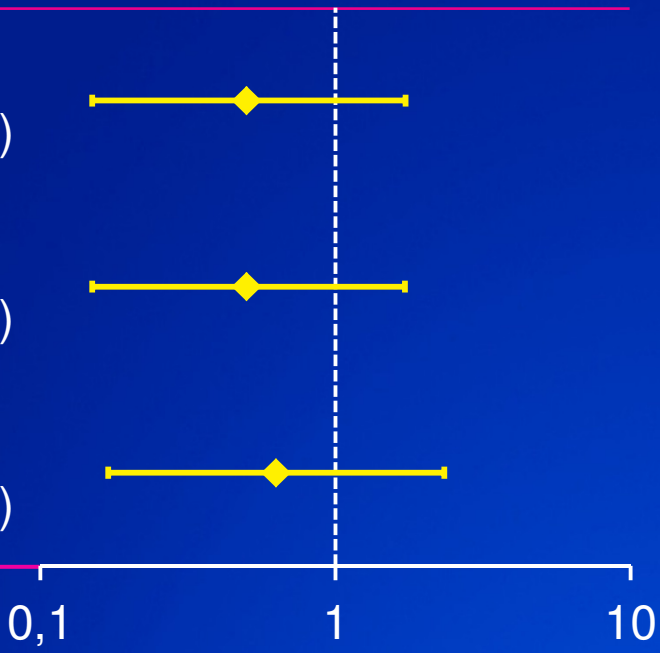
Primary efficacy outcome

	Rivaroxaban (N=978)		VKA (N=492)		Risk ratio (95% CI)
	%	n*	%	n*	
Primary efficacy outcome	**0.51**	**5**	**1.02**	**5**	**0.50 (0.15–1.73)**
Stroke	0.20	2	0.41	2	
Haemorrhagic stroke	0.20	2		0	
Ischaemic stroke		0	0.41	2	
TIA		0		0	
Non-CNS SE		0	0.20	1	
MI	0.10	1	0.20	1	
Cardiovascular death	0.41	4	0.41	2	

*Number of patients with events; patients may have experienced more than one primary efficacy event
mITT population

Primary efficacy outcome

	Rivaroxaban % n*/N	VKA % n*/N	Risk ratio (95% CI)
mITT population	0.51 5/978	1.02 5/492	0.50 (0.15–1.73)
ITT population	0.50 5/1002	1.00 5/502	0.50 (0.15–1.72)
Safety population (on-treatment)	0.51 5/988	0.80 4/499	0.63 (0.17–2.34)



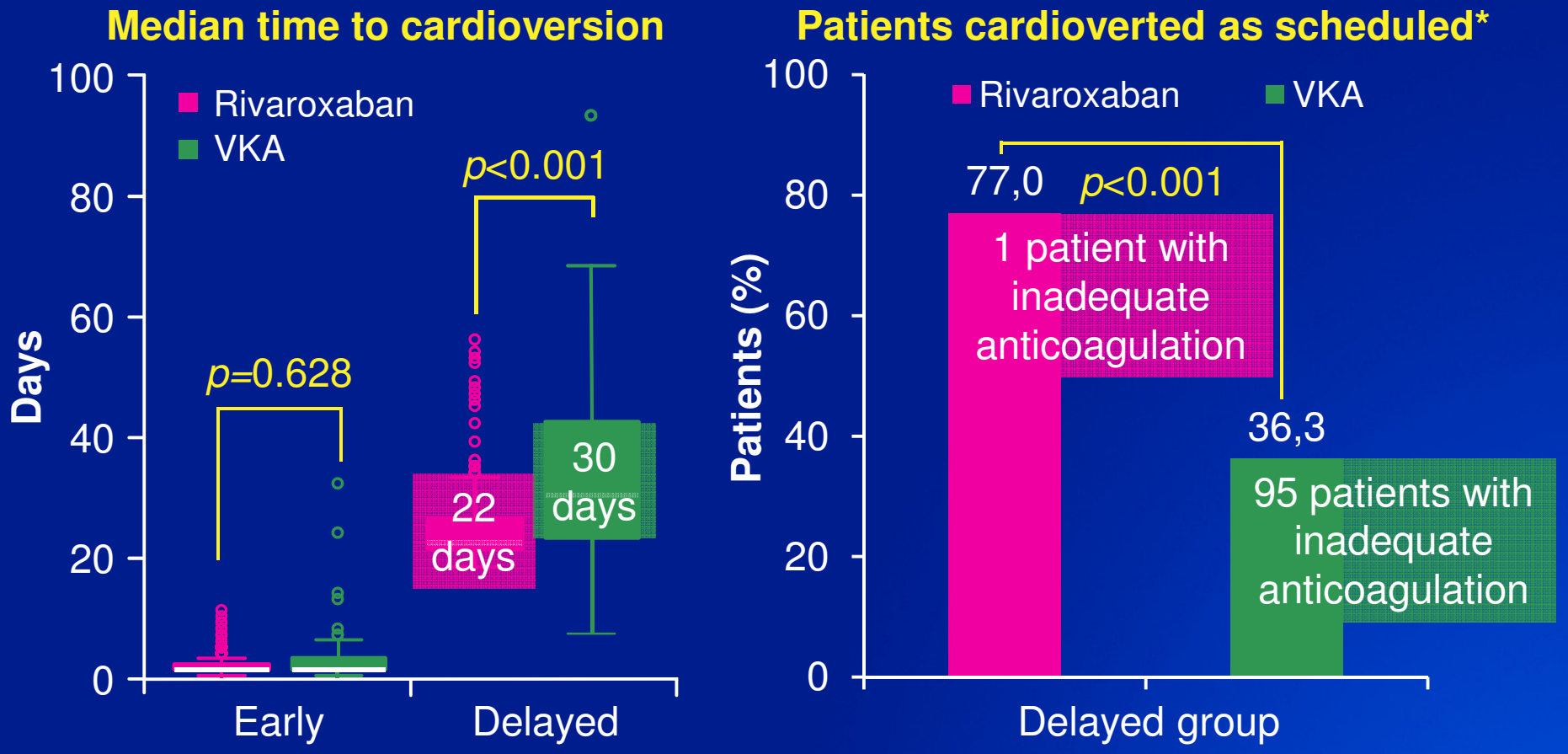
*Number of patients with events

Principal safety outcome

	Rivaroxaban (N=988)		VKA (N=499)		Risk ratio (95% CI)
	%	n*	%	n*	
Major bleeding	**0.61**	**6**	**0.80**	**4**	**0.76 (0.21–2.67)**
Fatal	0.1	1	0.4	2	
Critical-site bleeding	0.2	2	0.6	3	
Intracranial haemorrhage	0.2	2	0.2	1	
Hb decrease ≥2 g/dl	0.4	4	0.2	1	
Transfusion of ≥2 units of packed RBCs or whole blood	0.3	3	0.2	1	

*Number of patients with events; patients may have experienced more than one primary safety event
Safety population

Time to cardioversion by cardioversion strategy



*Reason for not performing cardioversion as first scheduled from 21–25 days primarily due to inadequate anticoagulation (indicated by drug compliance <80% for rivaroxaban or weekly INRs outside the range of 2.0–3.0 for 3 consecutive weeks before cardioversion for VKA)

Limitations

- X-VeRT was underpowered and thus exploratory in nature for the comparison between rivaroxaban and VKAs
  - However, the 95% upper confidence limits of incidences for rivaroxaban in efficacy (1.17%) and safety (1.27%) suggest a reassuring efficacy and safety profile
- Open-label randomization
  - Blinded adjudication of outcome events (PROBE)

Summary

- First prospective, randomized trial of a novel OAC in patients with AF undergoing elective cardioversion
- Low and similar incidence of primary efficacy outcome events between the treatment arms
- Similar incidence of major bleeding
- Time to cardioversion was similar (early strategy) or significantly shorter (delayed strategy) using rivaroxaban compared with VKA

Conclusion

- Oral rivaroxaban 20 mg once daily appears to be an effective and safe alternative to VKA, and allows prompt elective cardioversion in patients with AF

List of study committees

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FASTTRACK
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Rivaroxaban vs. vitamin K antagonists for cardioversion in atrial fibrillation

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