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

Riccardo Cappato, MD and Michael Ezekowitz, MD, PhD

On behalf of X-VeRT trial committees and Investigators

ESC 2014, Barcelona, Spain

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-aventis; Boehringer Ingelheim; Bayer HealthCare; Abbott
- Investigator: Medtronic; Biosense Webster; sanofi-aventis; 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]
- VKAs are the current standard of care before and after cardioversion,[3] with only post hoc analyses supporting use of novel OACs[4–6]

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

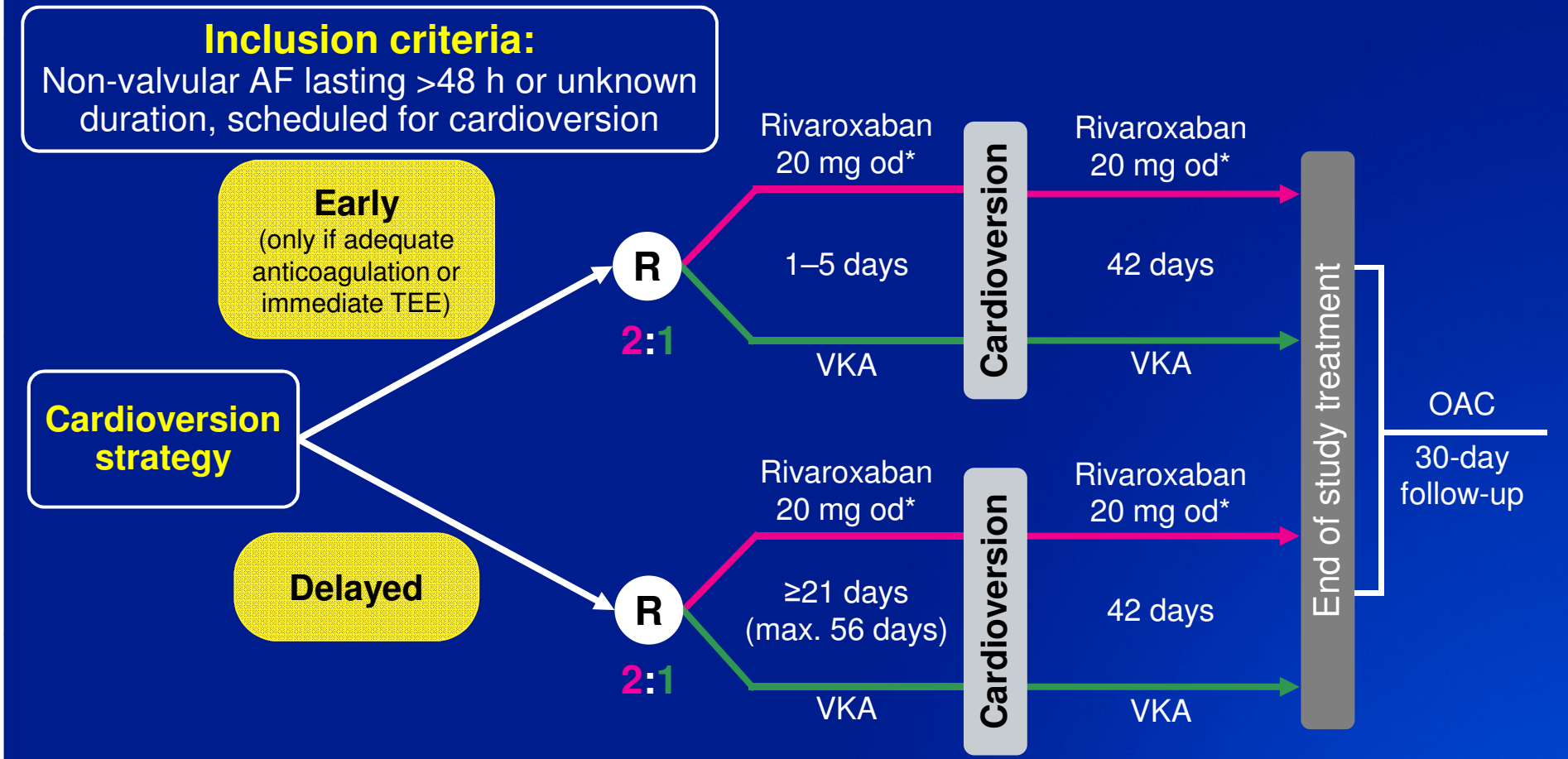
Study objective

- 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



*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 cytochrome P450 3A4 and P-glycoprotein

Ezekowitz *et al*, 2014

Efficacy and safety outcomes

Primary efficacy outcome

A composite of:

- Stroke and TIA
- Non-CNS SE
- MI
- Cardiovascular death

Secondary efficacy outcomes

- Stroke (ischaemic, haemorrhagic)
- TIA
- Non-CNS SE
- MI
- Cardiovascular death
- All-cause mortality
- Composite of stroke and non-CNS SE
- Composite of stroke, non-CNS SE, TIA, MI and all-cause mortality

Primary safety outcome

- Major bleeding (ISTH definition)[1]

Secondary safety outcome

- All bleeding events

All endpoints adjudicated by treatment assignment-blinded Clinical Endpoint Committee

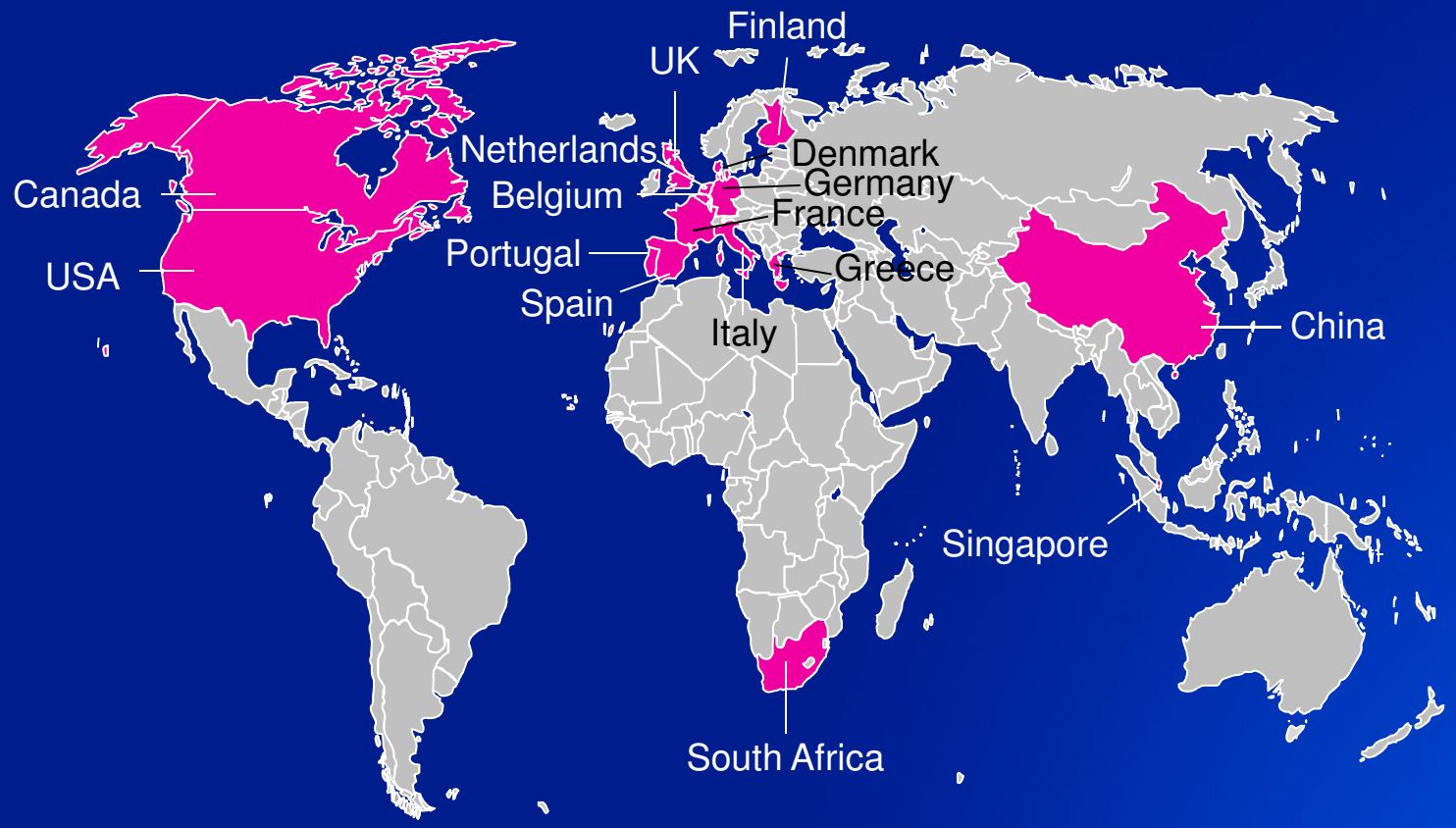
1. Ezekowitz *et al*, 2014; 2. Schulman *et al*, 2005

Statistical plan

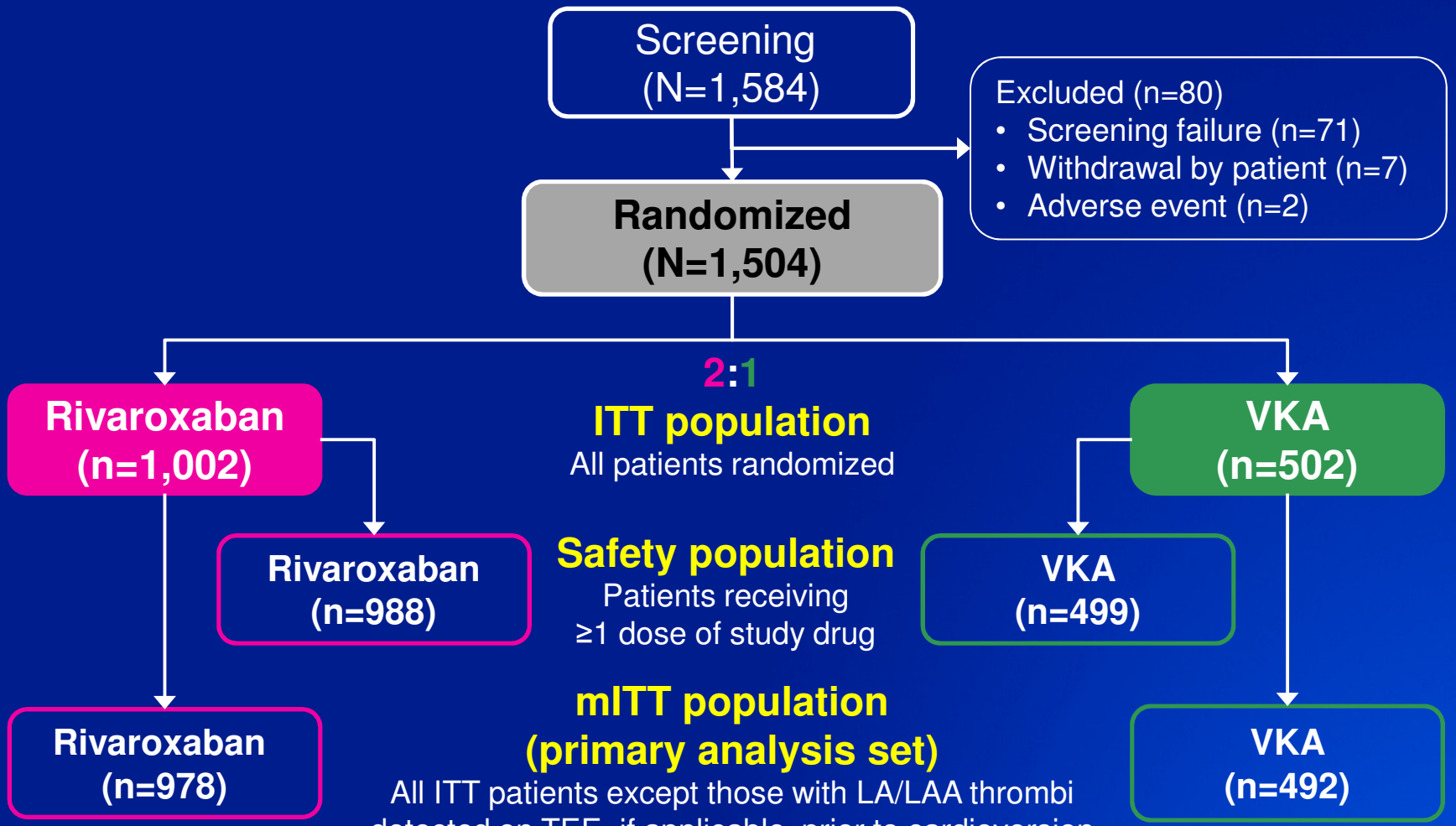
- Sample size to establish non-inferiority would be ~25,000–30,000 patients assuming
  - 1% perioperative risk of thromboembolic events with VKA
  - Margin of 1.5 in terms of risk ratio, power 90%
- Trial of this size not feasible
- A descriptive comparison of 1,500 patients would give clinically meaningful 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=1504)
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

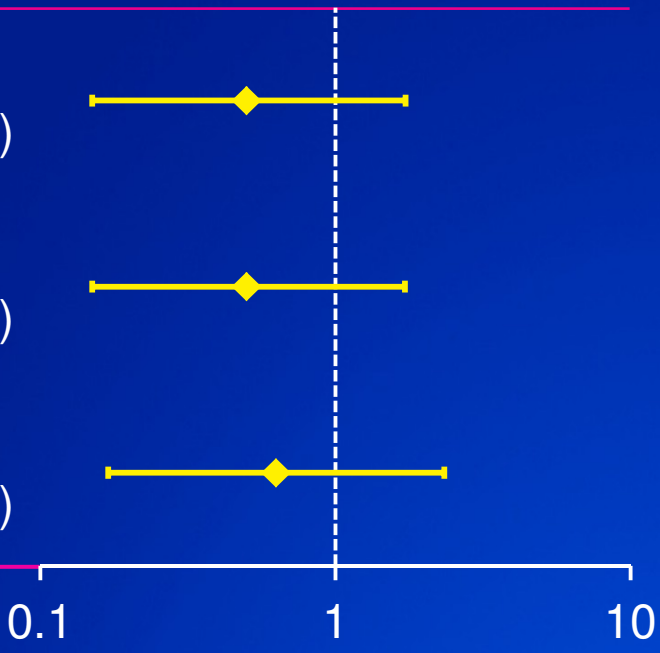
Primary efficacy outcome

	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	

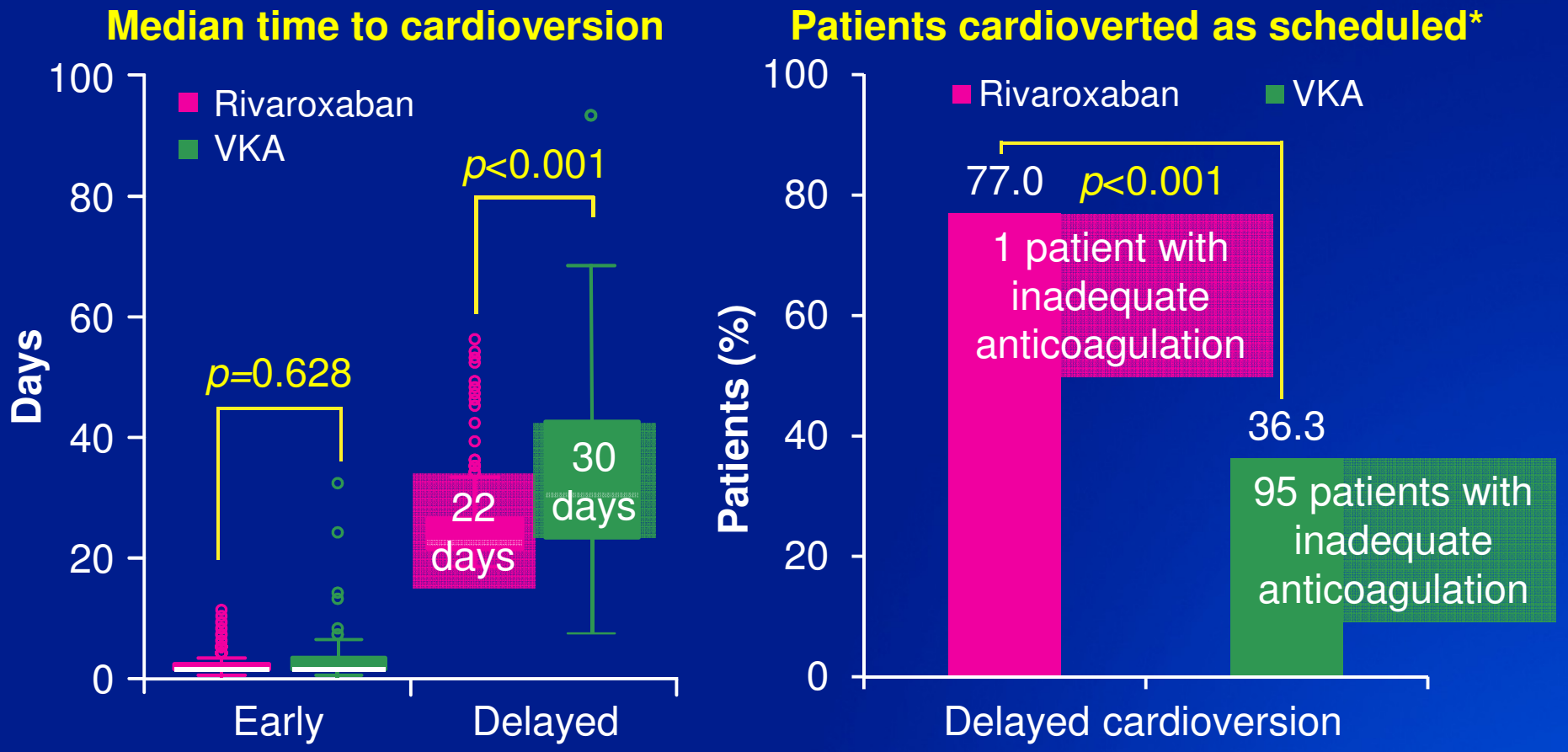
*Number of patients with events
Safety population

Other outcomes

	Rivaroxaban		VKA		Risk ratio (95% CI)
	%	n*	%	n*	
All-cause death#	**0.51**	**5/978**	**1.02**	**5/492**	**0.50 (0.15–1.73)**
Any confirmed bleeding‡	**8.9**	**88/988**	**7.2**	**36/499**	
Non-major clinically relevant bleeding	2.8	28	2.0	10	
Trivial bleeding	6.1	60	5.0	25	

*Number of patients with events
#mITT population; ‡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)

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 groups
- Similar incidence of major bleeding
- Time to cardioversion was similar (early strategy) or shorter (delayed strategy) using rivaroxaban compared with VKA
  - This allowed a larger proportion of patients to be cardioverted in the scheduled time period

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

- **Steering Committee:** Riccardo Cappato, Michael D Ezekowitz (SC co-chairs), Allan L Klein, A John Camm, Chang-Sheng Ma, Jean-Yves Le Heuzey, Mario Talajic, Maurício Scanavacca, Panos E Vardas, Paulus Kirchhof, Stefan H Hohnloser
- **Clinical Event Committee:** Martin Prins (Chair), Harry Büller, Melvin Mac Gillavry, Yvo Roos
- **Data Monitoring Committee:** Alain Leizorovicz (DMC Chairman), Günter Breithardt, Hans-Christoph Diener

List of Investigators

Belgium: H Heidbuchel, P Van de Borne, J Vijgen, E Hoffer, H Striekwold, J Leroy; **Canada:** M Talajic, G Searles, E Lockwood, I Mangat, S Connolly, B Coutu, L Sterns, S Connors; **China:** C Ma, Z Yuan, Z Wang, X Su, B Tang, S Wu, K Hong, Y Zheng; **Denmark:** J Refsgaard, O May, C Torp-Pedersen, G Gislason, H Nielsen; **Finland:** J Airaksinen, S Utriainen, T Paana, P Mustonen, A Hadjikov, H Huikuri, J Koistinen, P Raatikainen, M Lehto; **France:** S Kacet, A Rifai, R Isnard, M Elbaz, E Aliot, L Fauchier, S Ederhy; **Germany**: S Hohnloser, J Vom Dahl, W Haverkamp, A Lind, P Krings, S Willems, T Faber, C Piper, S Schellong, D Bastian, A Bollmann, T Gori; **Greece:** P Vardas, V Vassilikos, D Tziakas,G Andrikopoulos; **Italy:** R Cappato, MM Gulizia, A Capucci, GL Botto, M Grimaldi, S Themistoclakis, F Gaita, L Calò; **Netherlands:** JA Kragten, HJGM Crijns, RW Breedveld, M. Hemels, R Tukkie; **Portugal:** J Primo, M Oliveira, L Brandão, PP Adragão, W Santos, A Botelho, P Mota; **Singapore:** T Ru San, D Foo, H Y Ong, S-C Seow; **South Africa:** J Saaiman, L van Zyl, A Barnard, A Horak, H Cyster, S Dawood, M Essop, J Engelbrecht, T Venter, T Mabin; **Spain:** JM Escudier, L Mont, L Tercedor, I García Bolao, N C Galiano, EG Gasa, E González Torrecilla; **United Kingdom:** D Gorog, R Balasubramaniam (Bala), N Andrews, J Cooke, A Sandilands, A Staniforth, P Davey, I Savelieva; **United States:** J Heilman, S Krueger, N Bedwell, D Smith, I Friedlander, A Meholick, A Splaver, A Aryana, R Sangrigoli, G Larrain, J Robinson, S Zavaro, E Telfer, J Dizon, N Haddad, A Nahhas, J Tiongson, R Downey, M Heiman, S Rao, S Olsen, A Klein, F Navetta, J Norris, W David, A Blanchard, S Mahal, D Henderson, A Slim, A Alfieri, G Pressman, J Banchs, V Bead, B Vakili, W French, R Morris, J Covalesky, V Nguyen, M Marieb, E Polanco, R Vicari, F George Jr, A Seals, A Abdul-Karim, M Koren