Rivaroxaban in Arrhythmology from Evidence Based Medicine to Real Life Experience: Patients Undergoing Cardioversion

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Disclosure Statement: Riccardo Cappato

- 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
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- Equity and Intellectual Property Rights: Cameron Health

Novel Oral Anticoagulants in the AF Setting

- Overall effectiveness of novel OACs is non-inferior, and for some endpoints superior, to warfarin
- Compared with VKAs, novel OACs exhibit fewer drug and food interactions and do not require routine coagulation monitoring
- Cardioversion and is associated with an increased risk of thromboembolic complications
  - Most information drawn from phase III studies
  - Prospective studies using guideline-recommended approaches to peri-procedural anticoagulation are needed

Cardioversion and Ablation in Patients with AF

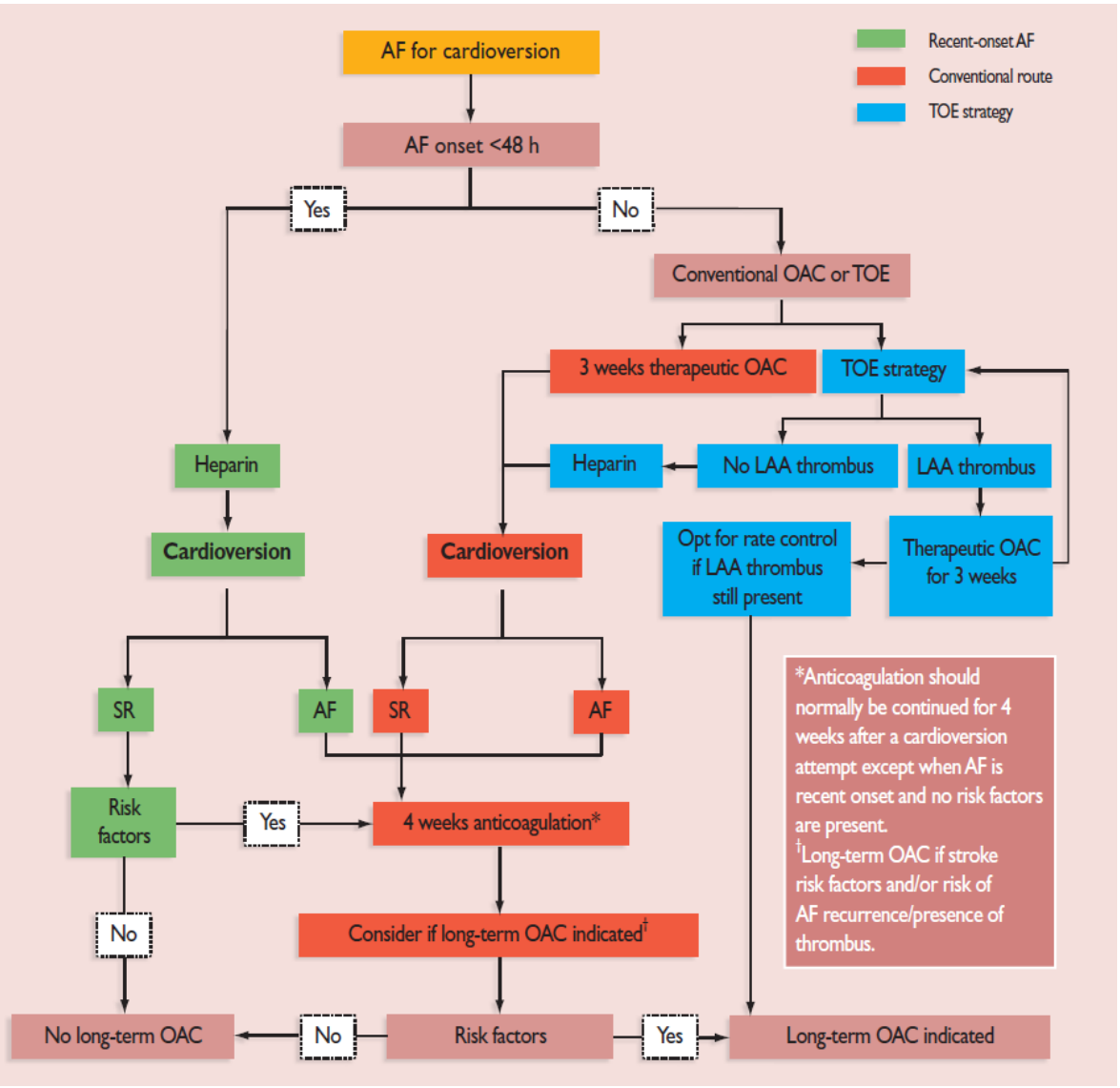
- Cardioversion is a rhythm-control treatment strategy that, if successful, restores normal sinus rhythm
  - Pharmacological (preferred strategy in patients with recent-onset AF; within 48 h)
  - Electrical (preferred strategy when AF is prolonged)
- Associated with an increased risk of thromboembolic complications
  - Risk can be reduced by adequate anticoagulation in the weeks prior to cardioversion or by exclusion of LA thrombi before the procedure

Nonrandomized Trials Comparing Cardioversion in AF Patients With vs Without Anticoagulation

- Cardioversion of AF to sinus rhythm is associated with a risk of thromboembolic events
- The incidence of embolic events after cardioversion is less than 1% if adequate anticoagulation is used

Source	N	Anticoagulation	No anticoagulation	P value
		TE events, n/N (%)		
Bjerkelund and Orning, 1969	437	2/228 (0.8)	11/209 (5.3)	0.016
Weinberg and Mancini, 1989	79	0/51 (0)	2/28 (7)	0.12
Arnold et al, 1992	332	0/153 (0)	6/179 (3.3)	0.026
Total	848	2/432 (0.5)	19/416 (4.6)	-

International Guidelines: Anticoagulation Peri-cardioversion



- According to the current guidelines, subjects with AF (>48 h or unknown period) should receive therapeutic OAC before and after cardioversion
- TEE/TOE strategy could replace 3-week therapeutic OAC prior to cardioversion

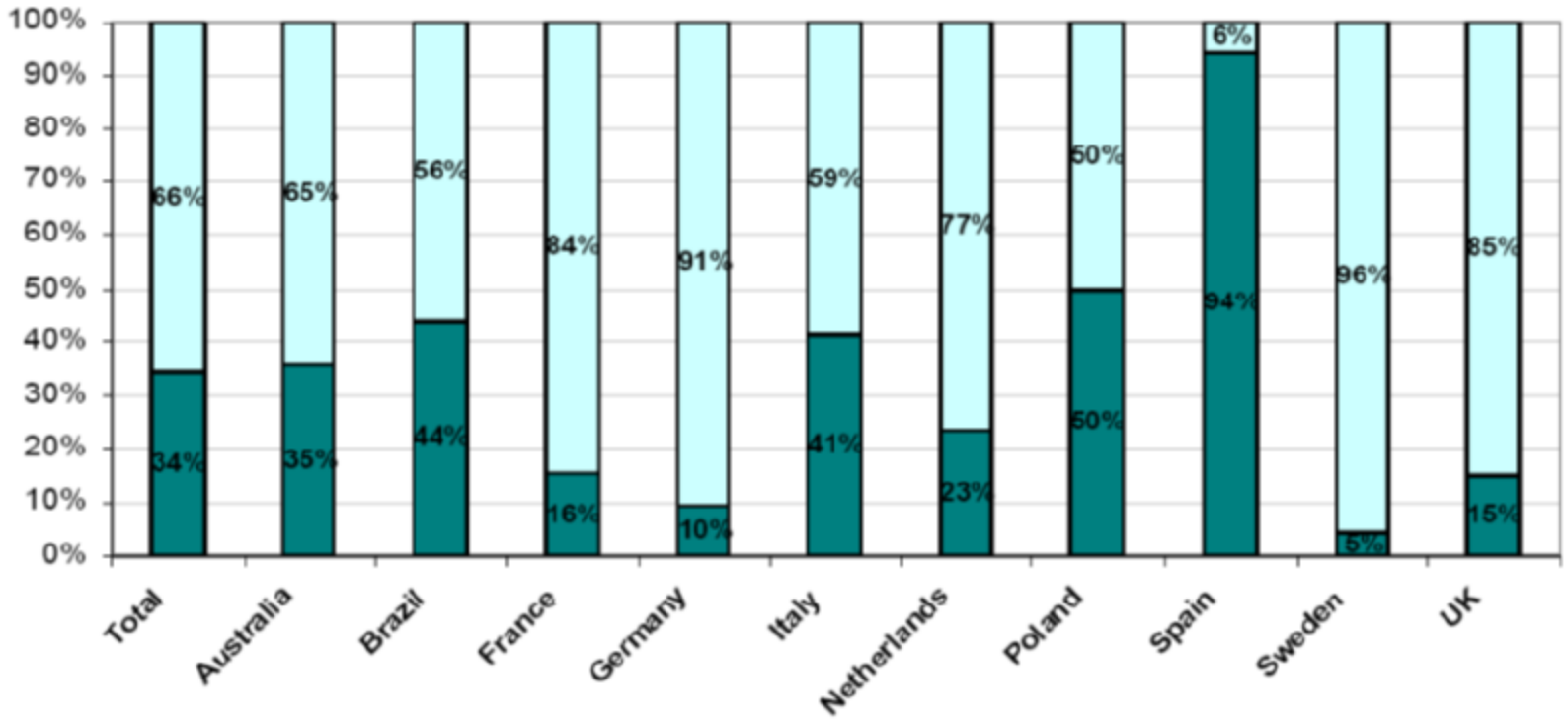
ESC 2010, AHA 2006, ACCP 2011 Guidelines

Real world experience of Cardioversion

RHYTHMAF
International Registry on Cardioversion for Atrial Fibrillation

Electric cardioversion

Pharmacological cardioversion



Crijns et al. Int J Cardiol 2014 Apr 1;172(3):588–94.

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Post-hoc analyses from large trials comparing NOACS with VKA

RE-LY: Outcomes after Cardioversion

- This post-hoc subgroup analysis showed:
  - 1983 cardioversions performed in 1270 patients, not including ablation
  - Stroke/systemic embolism rates in the 30 days following cardioversion were low and similar for both doses of dabigatran and wafarin group, with or without TEE

Groups	D 110mg BID	D 150mg BID	Warfarin	P value
Cardioversions	647	672	664	
- Electrical cardioversion	85.60%	81.90%	83.30%	
TEE before cardioversion	25.50%	24.10%	13.30%	
LA Thrombus Positive	1.80%	1.20%	1.10%	
On study drug ≥ 3 weeks before cardioversion	76.40%	79.20%	85.50%	< 0.01 for both
Stroke and systemic embolism	0.77%	0.30%	0.60%	NS for both
Major bleeding	1.70%*	0.60%**	0.60%	*0.06, **0.99

Nagarakanti et al, 2011

Cardioversion in ROCKET AF

- Total 350 procedures performed, including surgical or catheter ablation, electrical and pharmacological cardioversion

Cardioversion in ROCKET AF During Treatment Period				
	Safety Analysis Set		Safety on-treatment Set*	
Groups	Rivaroxaban	Warfarin	Rivaroxaban	Warfarin
All Cardioversions	177	173	126	132
Primary Efficacy Endpoint	0.56%	0.58%	0	0
- Secondary endpoint 1	0.56%	1.16%	0	0
- Secondary endpoint 2	1.69%	2.31%	0.79%	0
Principal Safety Endpoint	2.26%	8.09%	0.79%	7.58%
Major bleeding	0.56%	2.31%	0	1.52%

Endpoint 1: composite of stroke, systemic embolism, CV death
Endpoint 2: composite of stroke, systemic embolism, CV death, MI

* On study drug ≥ 21 days after procedure

Cardioversion in ARISTOTLE

Outcomes	Warfarin (n=412)	Apixaban (n=331)	Total (n=743)
Stroke or systemic embolism	0	0	0
Myocardial infarction	1 (0.2%)	1 (0.3%)	2 (0.2%)
Major bleeding	1 (0.2%)	1 (0.3%)	2 (0.2%)
Death	2 (0.5%)	2 (0.6%)	4 (0.9%)

Values presented as numbers (percentages).

Flaker et al, 2013

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Prospective randomized analyses from trials comparing NOACS with VKA

X-VeRT: Study Objectives and Treatment

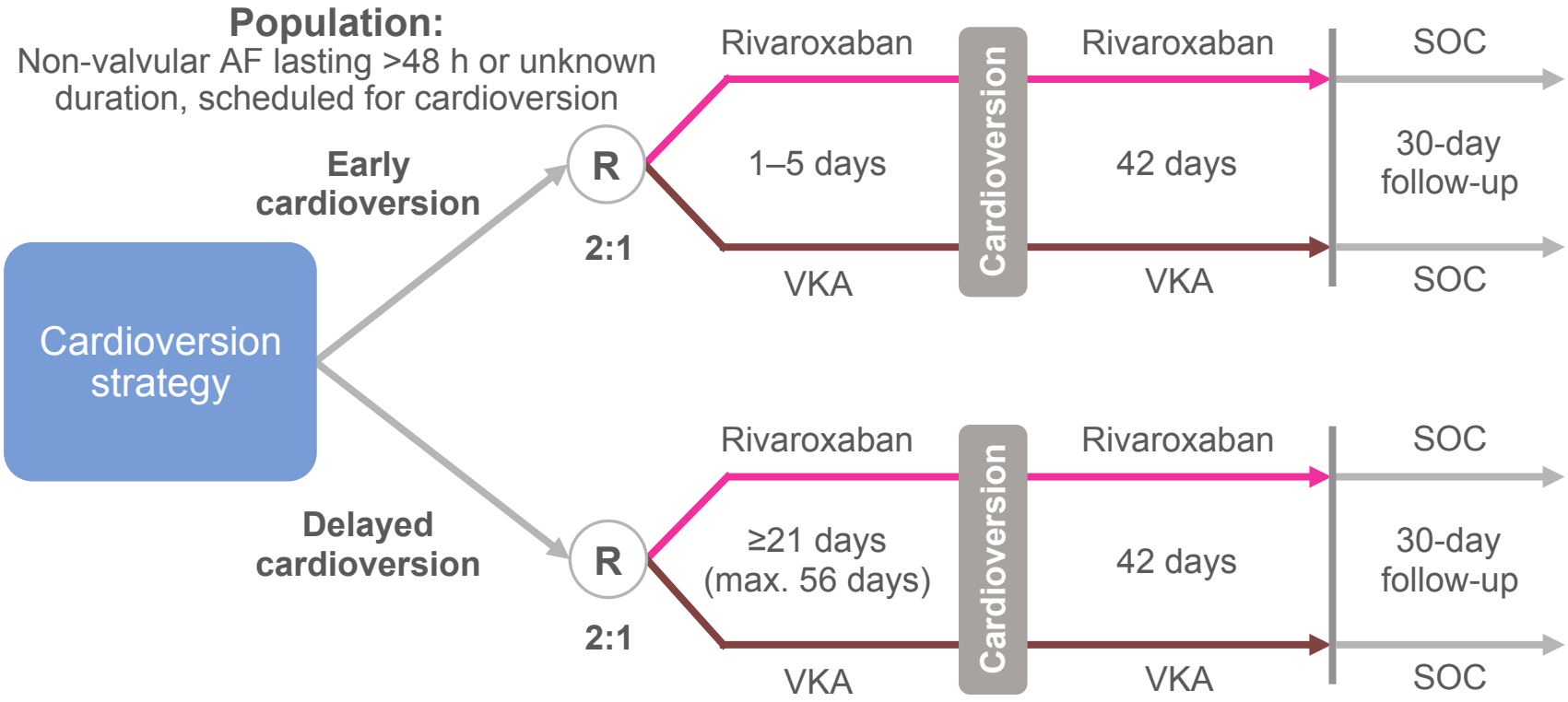
- To explore the efficacy and safety of rivaroxaban compared with dose-adjusted VKA in the prevention of cardiovascular events in patients with non-valvular AF scheduled for early and delayed cardioversion
- Rivaroxaban 20 mg once daily
  - First dose should be started at least 4 hours before cardioversion (OAC-naïve/untreated patients)
  - Dose reduction to 15 mg once daily for patients with moderate renal impairment (CrCl 30–49 ml/min)
  - Compliance of at least 80% for 3 weeks required before cardioversion in the delayed cardioversion group
- VKA with target INR 2.5 (range 2.0–3.0)
  - VKA type according to local treatment standards
  - Weekly INR monitoring required throughout the study to ensure INR within the target range
  - Three consecutive weekly INR measurements >2.0 before cardioversion

Ezekowitz MD *et al*, *Am Heart J* 2014;167:646–652

X-VeRT: Study Design

A randomized, open-label, parallel group, active-controlled multicentre study

- **1504 patients** randomized from **141 centres** across **16 countries**
  Recruitment began October 2012; database closed in February 2014



Ezekowitz MD *et al*, *Am Heart J* 2014;167:646–652; www.clinicaltrials.gov. NCT01674647

X-VeRT: Primary Efficacy Endpoints and Safety Endpoints

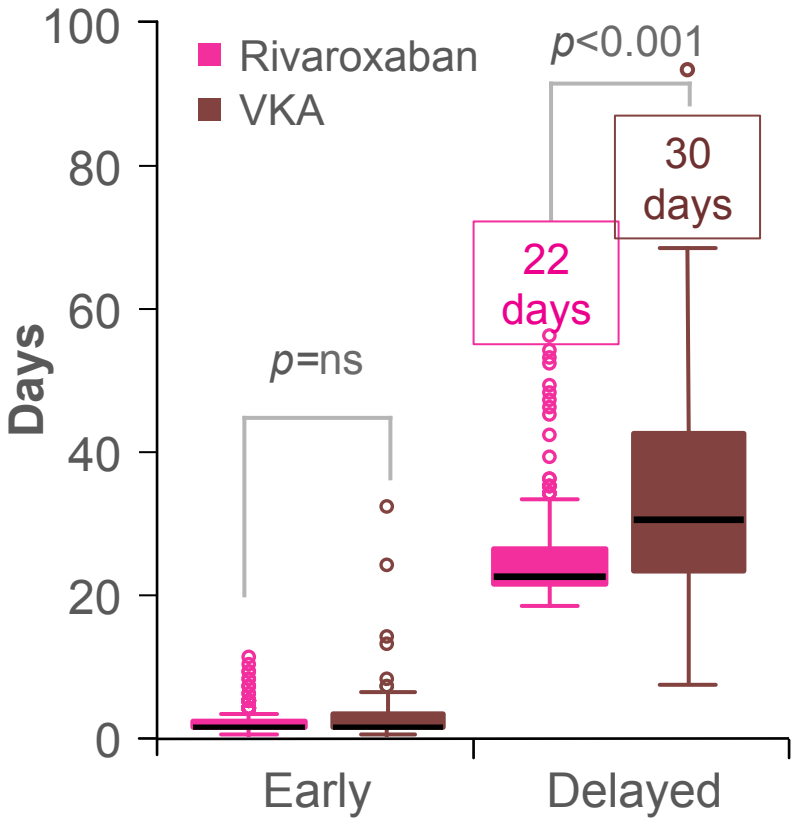
	Rivaroxaban (N=978)		VKA (N=492)		Risk ratio (95% CI)
	%	n	%	n	
Primary efficacy endpoint*	**0.51**	**5**	**1.02**	**5**	**0.50 (0.15–1.73)**
Stroke	0.20	2	0.41	2	
Haemorrhagic stroke	0.20	2		0	
Ischaemic stroke	0		0.41	2	
TIA	0		0		
Non-CNS SE	0		0.20	1	
MI	0.10	1	0.20	1	
Cardiovascular death	0.41	4	0.41	2	
	(N=988)		(N=499)		
Major bleeding#	**0.6**	**6**	**0.8**	**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	
Haemoglobin 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	
Any confirmed bleeding	**8.9**	**88**	**7.2**	**36**	
Non-major clinically relevant bleeding	2.8	28	2.0	10	
Trivial bleeding	6.1	60	5.0	25	

Cappato R *et al, Eur Heart J* 2014;35:3346–3355

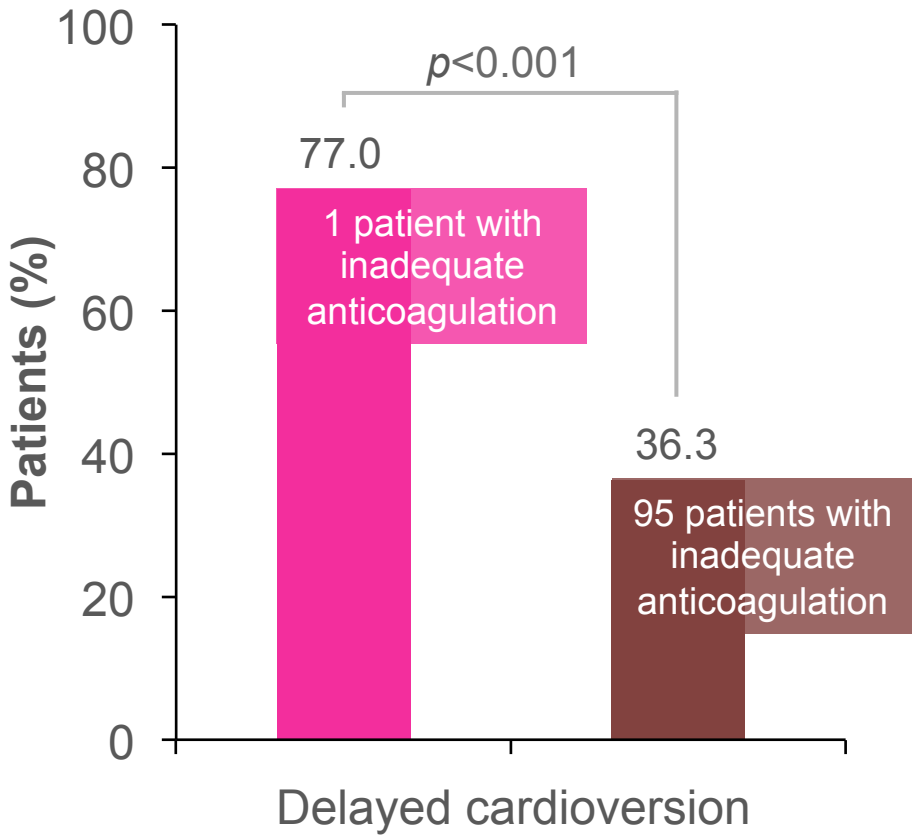
*mITT population for primary efficacy endpoint, #safety population for all bleeding events

X-VeRT: Cardioversion Procedure

Median time to cardioversion



Patients cardioverted as scheduled*



Thin central lines represent median values

*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)

Cappato R *et al, Eur Heart J* 2014;35:3346–3355

X-VeRT Results: Summary

- First completed 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 rivaroxaban and VKA treatment groups
- Similar incidence of major bleeding events
- Time to cardioversion was similar (early strategy) or significantly shorter (delayed strategy) using rivaroxaban compared with VKA
  - A larger proportion of patients were cardioverted in the scheduled time period

Cappato R *et al, Eur Heart J* 2014;35:3346–3355

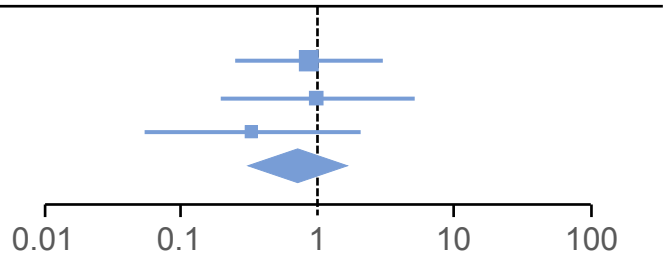
Comparing Novel OACs and Warfarin in AF Patients Who Underwent Cardioversion

Stroke/SE

Study or subgroup	NOAC Event	NOAC Total	Warfarin Events	Warfarin Total	Weight	Odds ratio M-H, Random, 95% CI
ARISTOTLE	0	331	0	412		Not estimable
RE-LY	7	1319	4	664	48.7%	0.88 (0.26–3.02)
ROCKET AF	3	183	3	181	28.4%	0.99 (0.20–4.97)
X-VeRT	2	987	3	492	23.0%	0.33 (0.06–2.01)
Total (95% CI)		**2811**		**1749**	**100.0%**	**0.73 (0.31–1.72)**
Total events	12		10			

Heterogeneity: Tau^2=0.00; Chi^2=0.96; df=2 (p=0.62); I^2=0%

Test for overall effect: Z=0.72 (p=0.47)

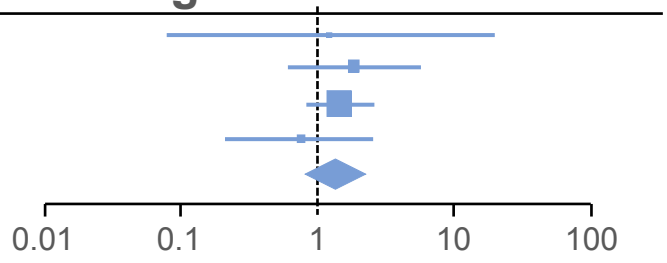


Major bleeding or clinically relevant non-major bleeding

Study or subgroup	NOAC Event	NOAC Total	Warfarin Events	Warfarin Total	Weight	Odds ratio M-H, Random, 95% CI
ARISTOTLE	1	331	1	412	3.0%	1.25 (0.08–19.99)
RE-LY	15	1319	4	664	18.8%	1.90 (0.63–5.74)
ROCKET AF	30	183	21	181	63.9%	1.49 (0.82–2.72)
X-VeRT	6	988	4	499	14.3%	0.76 (0.21–2.69)
Total (95% CI)		**2821**		**1756**	**100.0%**	**1.41 (0.87–2.28)**
Total events	52		30			

Heterogeneity: Tau^2=0.00; Chi^2=1.25; df=3 (p=0.74); I^2=0%

Test for overall effect: Z=1.40 (p=0.16)

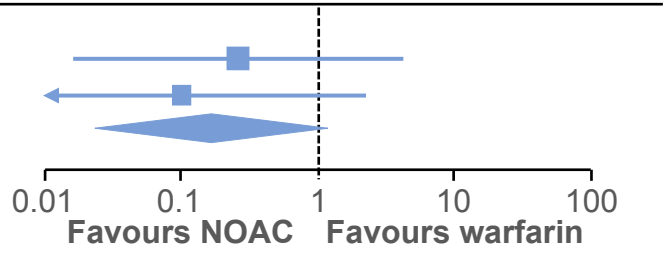


Stroke/SE: TEE prior to cardioversion

Study or subgroup	NOAC Event	NOAC Total	Warfarin Events	Warfarin Total	Weight	Odds ratio M-H, Random, 95% CI
ARISTOTLE	0	86	0	85		Not estimable
RE-LY	1	327	1	87	54.4%	0.26 (0.02–4.26)
X-VeRT	0	410	2	218	45.6%	0.11 (0.01–2.21)
Total (95% CI)		**823**		**390**	**100.0%**	**0.17 (0.02–1.35)**
Total events	1		3			

Heterogeneity: Tau^2=0.00; Chi^2=0.20; df=1 (p=0.66); I^2=0%

Test for overall effect: Z=1.67 (p=0.09)



Cardioversion: electrical or pharmacological

Sen P *et al. Am J Cardiovasc Drugs* 2015; doi:10.1007/s40256-015-0136-1

How Might X-VeRT Change Clinical Practice? Clinical Implications in the Cardioversion Setting

- Based on data from X-VeRT, rivaroxaban can be regarded as an effective and generally safe alternative to VKAs in patients with AF scheduled for cardioversion irrespective of:
  - Early (with or without a TEE-guided approach) or delayed cardioversion strategy
  - Cardioversion strategy (electrical or pharmacological)
- Results demonstrate that rivaroxaban may overcome some limitations of VKA treatment in the setting of cardioversion, including a significant reduction in time to cardioversion

Post Hoc Analysis of X-VeRT Data

- Based on patient population (n=632) in the delayed cardioversion group in X-VeRT
  - Using rivaroxaban in place of warfarin in the delayed cardioversion group could result in cost savings of:
    - £421 per patient in the UK setting
    - €360 per patient in Italy
  - Estimated cost savings equate to over £260,000 in the UK and €228,000 in Italy
    - Equivalent to the cost of approximately 318 and 340 cardioversion procedures, respectively

Hohnloser S *et al, Europace* [in press]

What Has Changed with These Results?

Conclusions

- X-VeRT showed that patients with AF scheduled for cardioversion have a low risk of cardiovascular events or major bleeding if appropriately anticoagulated during the procedure
- Rivaroxaban can be used in:
  - TEE-guided strategy for cardioversion in OAC-naïve or inadequately anticoagulated patients
  - Conventional OAC strategy for cardioversion in OAC-naïve or
    -experienced patients
  - Continued OAC strategy for cardioversion in patients pre-treated with other OACs if switching is required

What Has Changed with These Results?

Conclusions

- Rivaroxaban may overcome certain limitations of VKA treatment in the setting of cardioversion
- Significantly shorter time to cardioversion in rivaroxaban vs VKA treatment groups