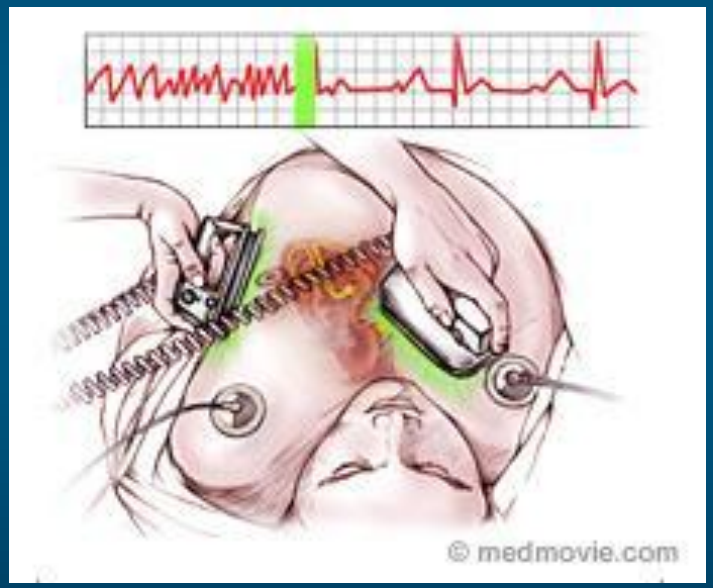
Cardiology Update 2015

Atrial Fibrillation, Cardioversion and NOACs: Practical Considerations and Patient Management

Davos, Switzerland: 8-12th February 2015



NOACS in AF Patients Undergoing Cardioversion

Overview and Latest Data

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Declaration of Interests

Chairman: NICE Guidelines on AF, 2006; ESC Guidelines on Atrial Fibrillation, 2010 and Update, 2012; ACC/AHA/ESC Guidelines on VAs and SCD; 2006; NICE Guidelines on ACS and NSTEMI, 2012; NICE Guidelines on heart failure, 2008; NICE Guidelines on Atrial Fibrillation, 2006; ESC VA and SCD Guidelines, 2015

Steering Committees: multiple trials including novel anticoagulants

DSMBs: multiple trials including BEAUTIFUL, SHIFT, SIGNIFY, AVERROES, CASTLE-AF, STAR-AF II, INOVATE, and others

Events Committees: one trial of novel oral anticoagulants and multiple trials of miscellaneous agents with CV adverse effects

Editorial Role: Editor-in-Chief, EP-Europace and Clinical Cardiology; Editor, European Textbook of Cardiology, European Heart Journal, Electrophysiology of the Heart, and Evidence Based Cardiology

Consultant/Advisor/Speaker: Astellas, Astra Zeneca, ChanRX, Gilead, Merck, Menarini, Otsuka, Sanofi, Servier, Xention, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Pfizer, Boston Scientific, Biotronik, Medtronic, St. Jude Medical, Actelion, GlaxoSmithKline, InfoBionic, Incarda, Johnson and Johnson, Mitsubishi, Novartis, Takeda

Introduction

- Without adequate anticoagulation, the risk of thromboembolism associated with cardioversion is 5–7%[1]
  - VKA therapy, although never validated in clinical trials, was shown to reduce the incidence of thromboembolism to 0.5%[2]
  - Guidelines recommend anticoagulation before and after cardioversion[3–5]
- Novel OACs in patients with AF scheduled for cardioversion
  - Mostly limited to *post hoc* analyses of phase III trials[6–8]
  - One prospective trial has been completed and others are ongoing

1. Stellbrink et al, 2004; 2. Klein et al, 2001; 3. Camm et al, 2012; 4. January et al, 2014; 5. Heidbuchel et al, 2013; 6. Piccini et al, 2013; 7. Nagarakanti et al, 2011; 8. Flaker et al, 2014

Cardioversion in Patients with AF

- Cardioversion is a rhythm-control treatment strategy intended to restore normal sinus rhythm
- Two types of cardioversion:[1]
  - Pharmacological (preferred strategy in patients presenting with recent-onset AF; within 48 hours)[2]
  - Electrical (preferred strategy when AF is prolonged)[2]
- Cardioversion is associated with an increased risk of thromboembolic complications[3]
  - Risk can be reduced by adequate anticoagulation in the weeks prior to cardioversion or by exclusion of left atrial thrombi before the procedure[3]

1. Trappe HJ et al. Dtsch Arztebl Int 2012;109:1–7; 2. Sulke N et al. Heart 2007;93:29–34; 3. Camm AJ et al. Eur Heart J 2010;31:2369–2429

Electrical vs Pharmacologic Conversion of AF: Logistics

	Cardioversion	
	Electrical	Pharmacologic
Patient fasting	yes	no
Anaesthesia required	yes	no
Continuous ECG monitoring	yes	yes
Continuous O_2 monitoring	yes	no
Resuscitation means available	yes	Yes
Thromboprophylaxis	yes	yes

Pharmacological cardioversion may be cost-effective!

TEE-guided Cardioversion

- TEE confirms the absence of a thrombus within the left atrium
  - Recommended as an alternative to 3-week pre-cardioversion anticoagulation[1]
- When early cardioversion is needed:
  - Pre-cardioversion oral anticoagulation is not indicated due to patient choice, or bleeding risks, or when there is high risk of LA/LAA thrombus

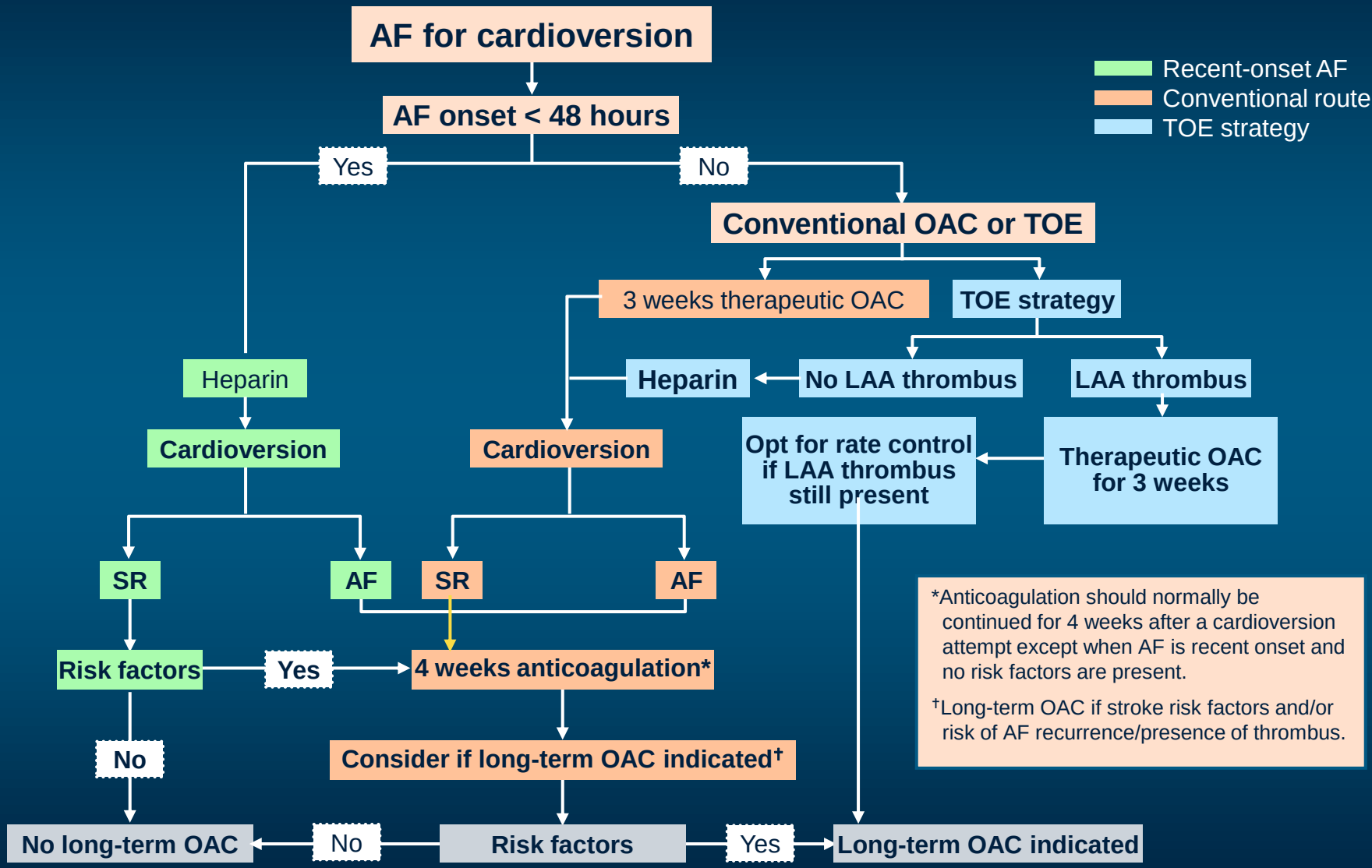
1. Camm AJ et al. Eur Heart J 2010;31:2369–2429

ACUTE (Assessment of Cardioversion Using TEE) study

- Results:
  - No significant difference between the two treatment groups in the rate of
    - Embolic events
    - Death or maintenance of sinus rhythm or in functional status
  - Significantly lower rates of haemorrhagic events in the TEE group
  - Shorter time to cardioversion and greater rate of successful restoration of sinus rhythm in the TEE group
- Conclusions:
  - TEE to guide the management of AF is a clinically effective alternative strategy to conventional therapy

Klein AL et al. N Engl J Med 2001;344:1411–1420

Cardioversion, TOE and Anticoagulation



AF = atrial fibrillation; DCC = direct current cardioversion; LA = left atrium; LAA = left atrial appendage; OAC = oral anticoagulant; SR= sinus rhythm; TOE= transoesophageal echocardiography.

Recommendations for Anticoagulation for CV
ESC/EHRA Focused Update 2010

Recommendation	Class	Level
For patients with AF of 48 h duration or longer, or when the duration of AF is unknown, OAC therapy (is recommended for at least 3 weeks prior to and for 4 weeks after cardioversion, regardless of the method (electrical or oral/i.v. pharmacological)	I	B
In patients at high risk of stroke, OAC therapy with a VKA (INR 2.0–3.0) or a NOAC is recommended to be continued long-term	I	B
As an alternative to anticoagulation prior to cardioversion, TOE-guided cardioversion is recommended to exclude thrombus in LA/LAA	I	B

Features of New Oral Anticoagulants

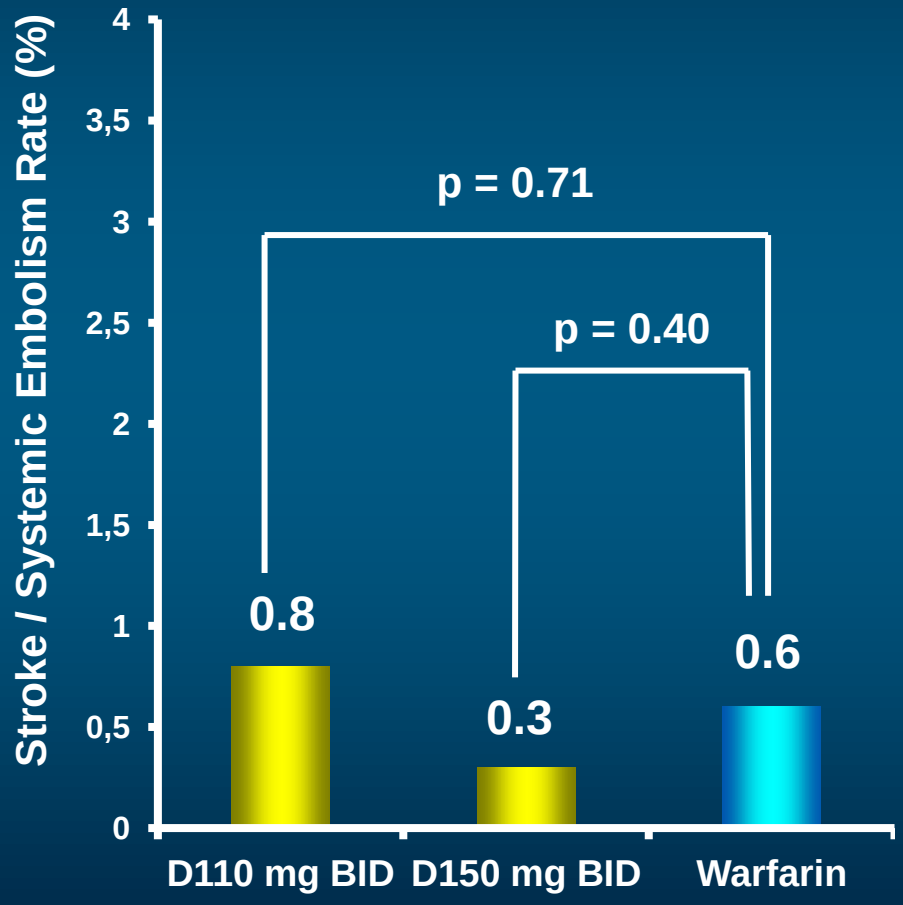
	Dabigatran[1]	Rivaroxaban[2,3]	Apixaban[4]	Edoxaban[5–8]
Target	IIa (thrombin)	Xa	Xa	Xa
Bioavailability, %	3–7	80	50	62
Hours to C_{max}	1–3	2–4	3–4	1–2
Half-life, h	12–17	5–13	12	8–10
Renal clearance, %	80	33	27	50*
Transporters	P-gp	P-gp	P-gp	P-gp
CYP-metabolism, %	None	32%	<32%	<4%
Protein binding, %	35	92–95	87	40–59
Dosing regimen	BID	OD	BID	OD

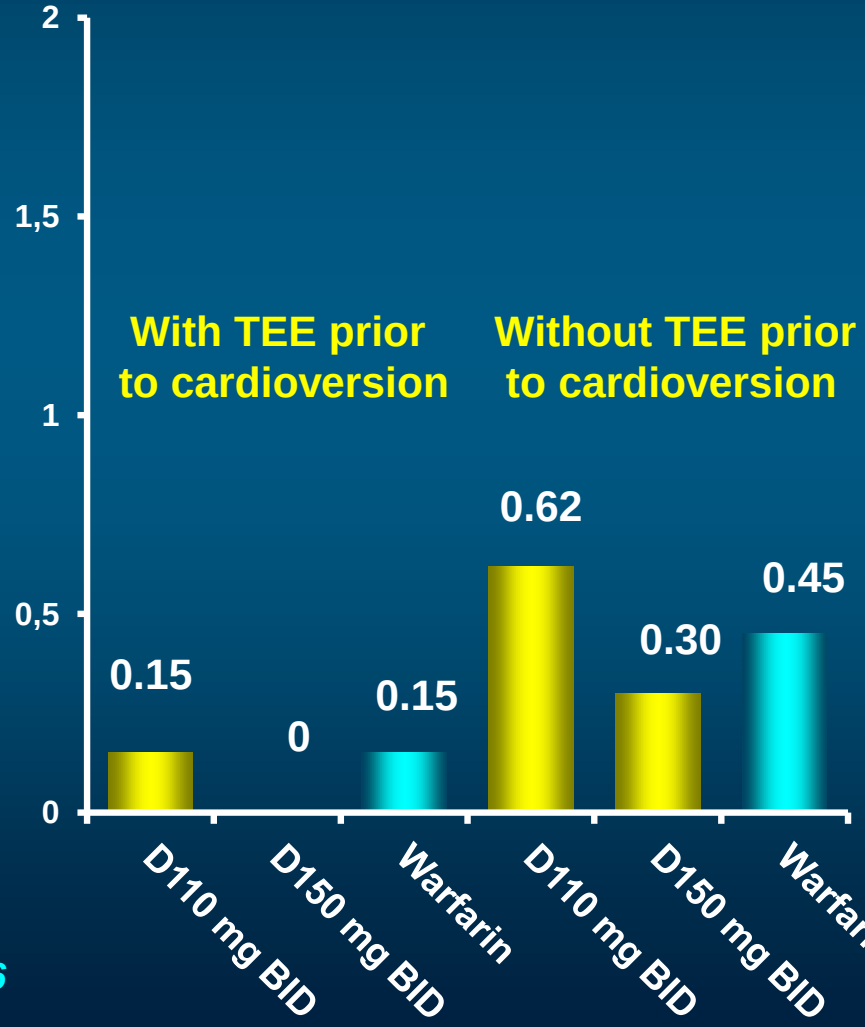
CYP, cytochrome P450; P-gp, P-glycoprotein
*absorbed dose

1.Pradaxa [package insert]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc. 2013
2. Xarelto [package insert]. Titusville, NJ: Janssen Pharmaceuticals, Inc. 2011
3. Weinz et al. Drug Dispos Metab 2009;37:1056–1064
4. ELIQUIS Summary of Product Characteristics. Bristol Myers Squibb/Pfizer EEIG, UK
5. Matsushima et al. Am Assoc Pharm Sci 2011; abstract; 6. Ogata et al. J Clin Pharmacol 2010;50:743–753
7. Mendell et al. Am J Cardiovasc Drugs 2013;13:331–342; 8. Bathala et al. Drug Metab Dispos 2012;40:2250–2255

Dabigatran - Stroke and Systemic Embolism after Cardioversion

1983 cardioversions were performed in 1270 patients

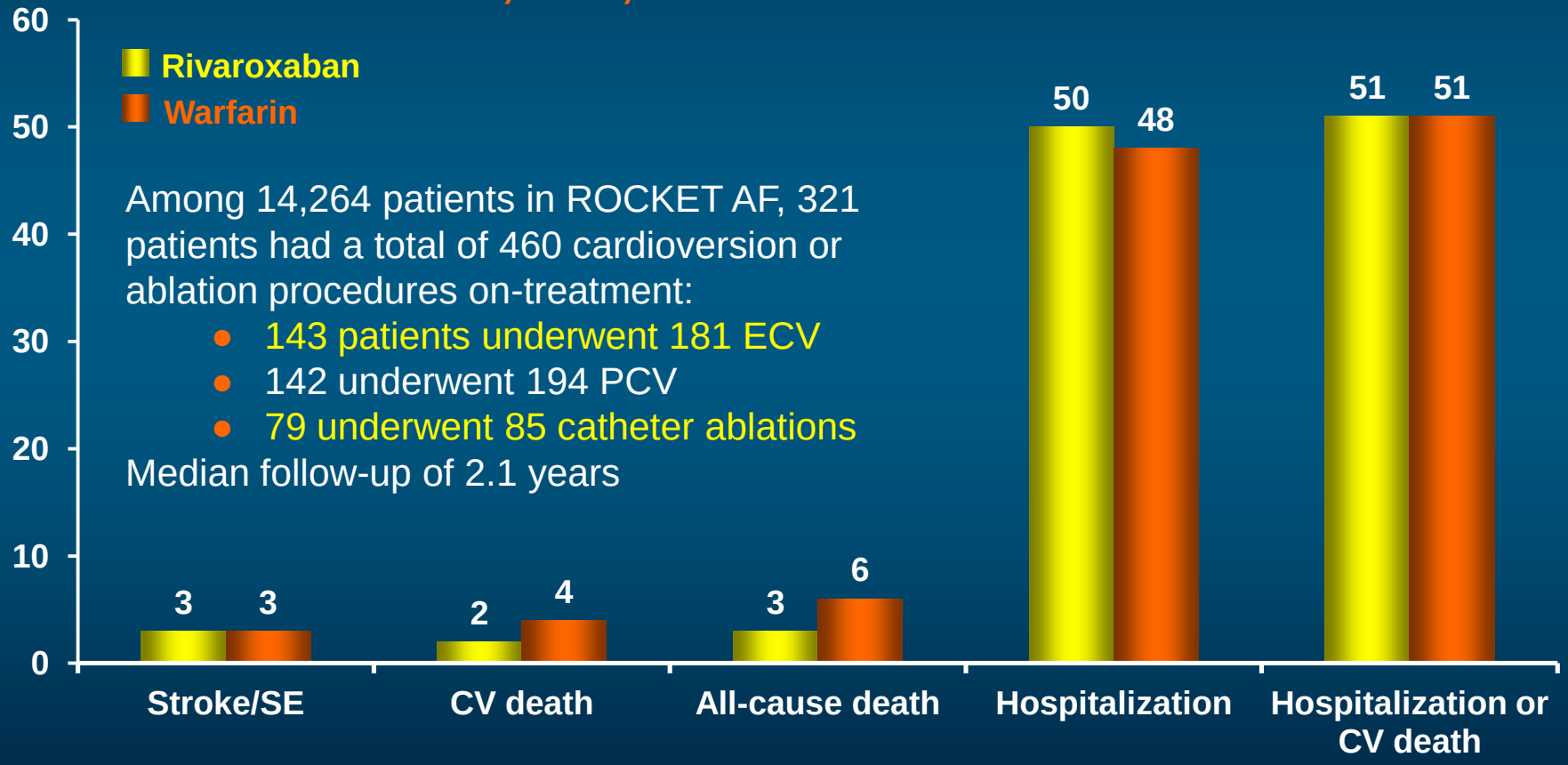




Nagarakanti R et al. *Circulation. 2011;123:131-136*

ROCKET AF
Subanalysis Cardioversion/ablation

Outcomes after ECV, PCV, or catheter ablation



Piccini JP et al. J Am Coll Cardiol 2013;61(19): 1998–2006

ROCKET AF

DCC in ARISTOTLE

Clinical Outcomes After Any Cardioversion, within 30 Days, in Patients Assigned to Either Warfarin or Apixaban

- 743 cardioversions in 540 patients in the trial for a mean of >6 months
- TEE before cardioversion in 27% of cases with no thrombi observed
- Patients remained on their blinded study drug 80% to 85% of the time

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 (0.5)

Values are: n (%)

Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation

Flaker G. et al. J Amer Coll Cardiol 2014; 63: 1082–1087

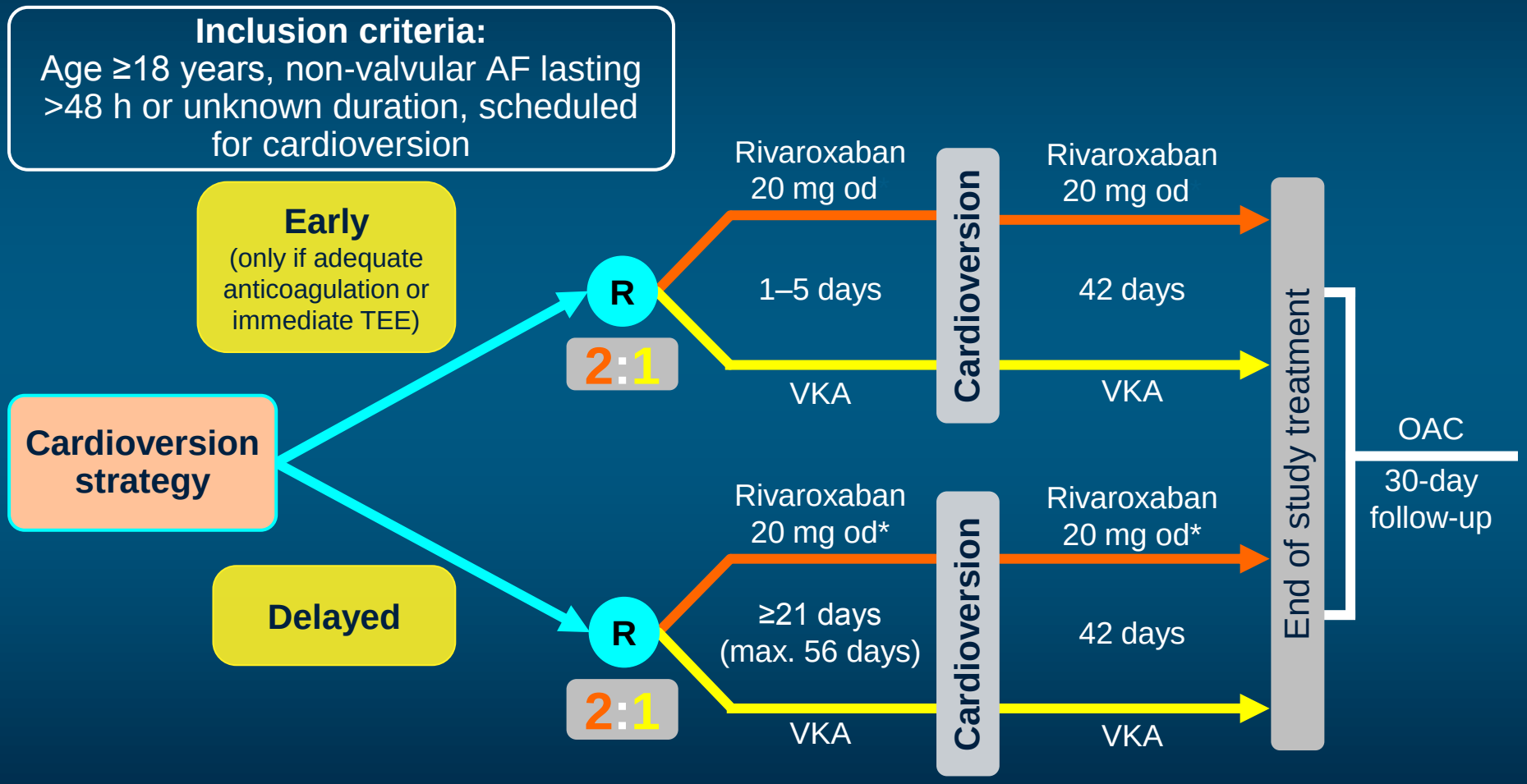
Thromboembolic Complications During Peri-Cardioversion: Pre- and Post-Anticoagulation

Cohorts/ studies	N/n	Anticoagu-lation	Drug	Time frame	Rates of TE, %
Historical	Various	No	N/A	Various	5-7%
Chicago experience	532	Yes	Warfarin	In-hospital	0.56%*
RHYTHM-AF	3940	65%**	Warfarin, heparin	5-70 days	5-70 days: 0.28% > 70 days: 0.1%
RE-LY	1270/1983	Yes, 76-85% for > 3 wks	Warfarin or dabigatran	Enalapril	0.3-0.8%
ROCKET-AF	285/375	Yes	Warfarin or rivaroxaban	30 days	0.6-0.61%***
ARISTOTLE	540/743	Yes, > 6 m; 75% > 1 year	Warfarin or apixaban	90 days	0
ENGAGE-AF	390/645	Yes	Warfarin or edoxaban	30 days	0-0.3%

** inadequate OAC; ** acute AF < 25 yrs; *** composite of TE and death in CV/ablation*

Savelieva I, et al. 2014 [In press]

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

First Prospective Randomized Clinical Trial

European Heart Journal (2014) **35**, 3346–3355
doi:10.1093/eurheartj/ehu367

FASTTRACK
ESC HOT LINE BARCELONA

Rivaroxaban vs. vitamin K antagonists for cardioversion in atrial fibrillation

Riccardo Cappato[1†], Michael D. Ezekowitz[2†*], Allan L. Klein[3], A. John Camm[4], Chang-Sheng Ma[5], Jean-Yves Le Heuzey[6], Mario Talajic[7], Maurício Scanavacca[8], Panos E. Vardas[9], Paulus Kirchhof[10,11,12], Melanie Hemmrich[13], Vivian Lanius[14], Isabelle Ling Meng[13], Peter Wildgoose[15], Martin van Eickels[13], and Stefan H. Hohnloser[16], on behalf of the X-VeRT Investigators

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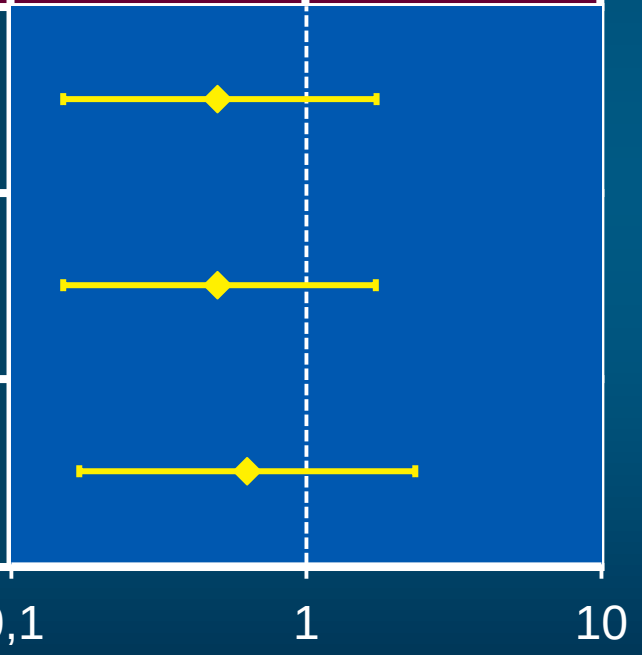
Primary Efficacy Outcome

	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)

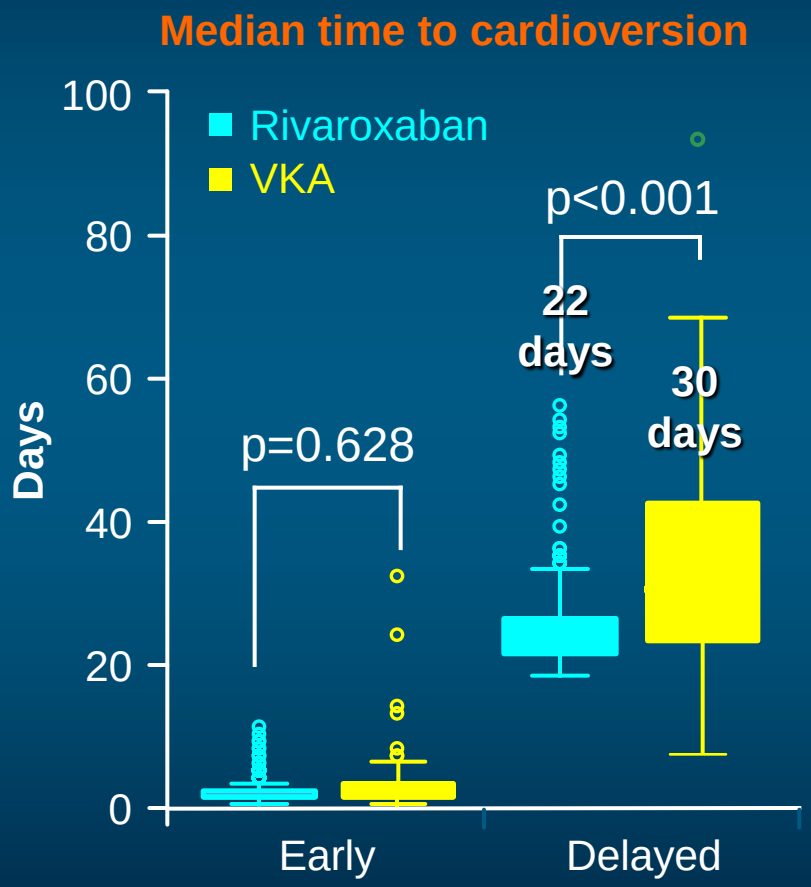


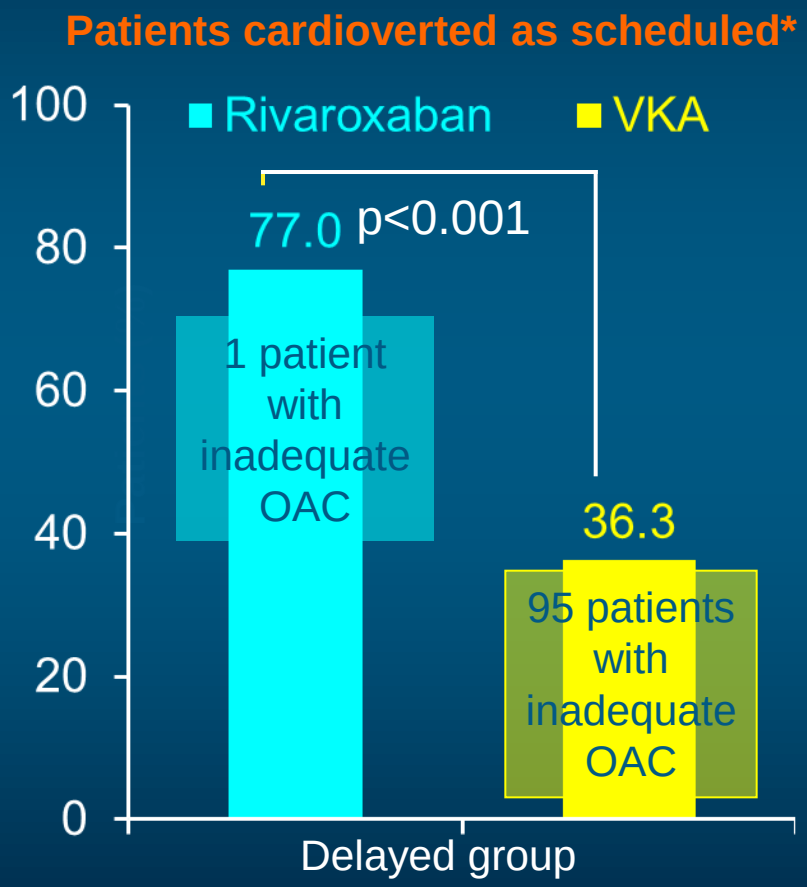
*Number of patients with events

X-VeRT

Cappato R et al. Eur Heart J. 2014 Sep 2. pii: ehu367.

Time to Cardioversion Cardioversion Strategy



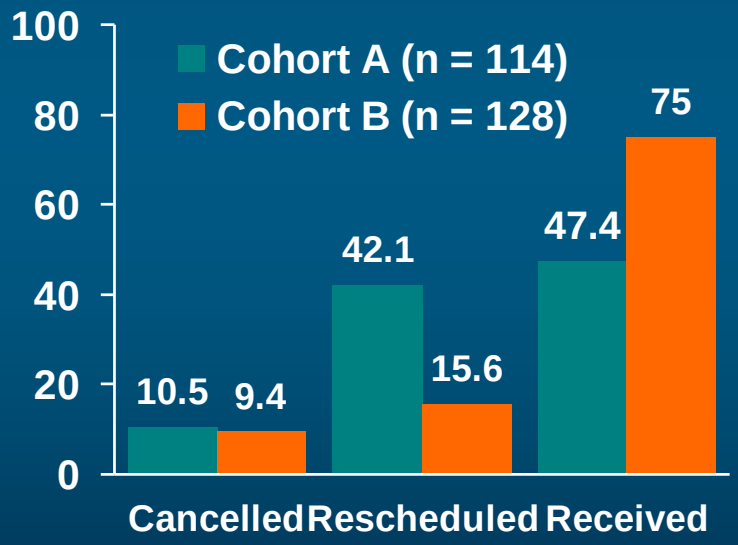


*Reason for not performing cardioversion as first scheduled from 21–25 days primarily due to inadequate anticoagulation (indicated by drug compliance <80% for rivaroxaban or weekly INRs outside the range of 2.0–3.0 for 3 consecutive weeks before cardioversion for VKA)

Cappato R et al. Eur Heart J. 2014 Sep 2. pii: ehu367.

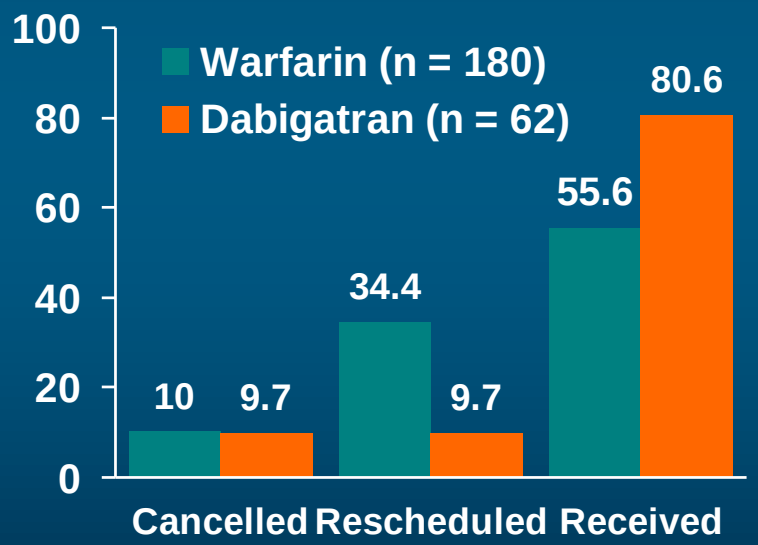
NOAC Use for Cardioversion in Inverness: Cost-Effective?

- 193 patients, 245 DCC, 36 months
- ~ 5000 cancellation in the UK at £722 per DCC; D £75.60/30 days; W £0.86 - 1.67



OR 3.97 (2.06 - 7.53)

OR 0.30 (0.17 - 0.54)



OR 0.20 (0.07 - 0.63)

OR 3.3 (1.39 - 7.11)

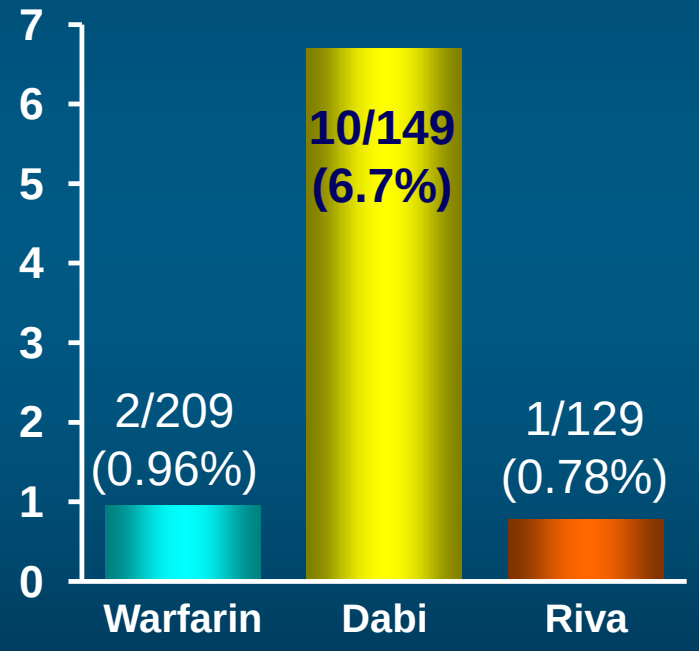
Choo WK, et al. ESC 2014

Incidence of LA Thrombosis

- N = 487 with TEE prior to DCC or ablation
- OAC for at least 30 days prior to TEE
- No differences between groups

Group	Warfarin	Dabi-gatran 150	Rivaro-xaban
n	209	149	129
Age, years	60.1±8.3	60.3±9.6	61.0±9.9
PAF, %	57.4	57	58.1
AF, mos	30.3±15.7	32.1±17.1	29.9±4.8
HTN, %	50.7	52.3	51.2
Stroke, %	5.7	3.4	3.1
CHA_2DS_2-VASc	1.48±1.3	1.63±1.4	1.73±1.3
LA, mm	43.9±7.3	43.3±8.2	43.6±7.4

Presence of LA thrombus, %



D vs W: OR = 4.6 (1.6 - 21), p =0.003
D vs R: OR = 6.2 (1.9 - 31), p = 0.002

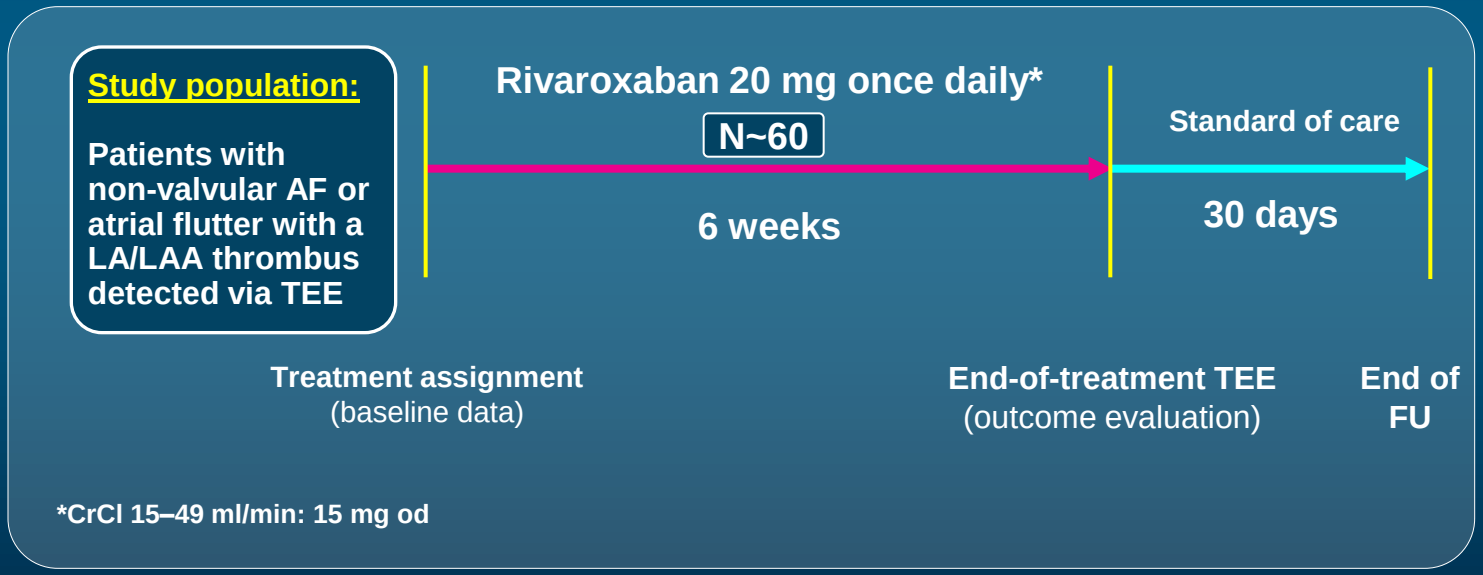
De Biase L, et al. AHA 2013

X-TRA Study Design

Rivaroxaban – Thrombus Accelerated Resolution

Open-label, interventional study

Objective: To explore the efficacy of rivaroxaban 20 mg once daily on the resolution of thrombi in subjects with non-valvular AF or atrial flutter who have a LA/LAA thrombus confirmed by TEE. A retrospective registry in the same centres will provide historical data on standard of care treatment



Primary endpoint:

Complete resolution of LA/LAA thrombus confirmed on TEE at 6 weeks

Study milestones:

FPFV: July 2013
LPLV: Aug 2014
DB: Oct 2014

www.clinicaltrials.gov/01839357

Cardioversion in Patients treated with Novel OACs

- In patients with AF of >48 h duration, OACs should be given for ≥3 weeks before cardioversion
- It is mandatory to ask patients explicitly about adherence over the past weeks and to document their response
  - If compliance can reliably be confirmed, cardioversion seems acceptably safe
- If doubts exist about compliance, consider prior TEE
- Continuous oral anticoagulation for 4 weeks after cardioversion is also mandatory

"We urge for the creation of good prospective registries or even randomized trials on this topic, which is important to facilitate patient management in the future."

Heidbuchel et al, 2013

Trials of Cardioversion on NOACs

Study	N	Drug	Compa-rator	Sponsor	Current State
X-VERT NCT01674647	1504	Rivarovaban	Warfarin	Bayer	Completed Feb 2014, presented at ESC 2014
ARC NCT01747746	60	Rivarovaban	Warfarin	John H. Stroger Hospital	Recruiting since Oct 2012 Completion Oct 2014
NCT01593150	130	Dabigatran	TEE vs no TEE	Odense Uni Hospital	Recruiting since Nov 2011 Completion March 2015
ENSURE-AF NCT02072434	2200	Edoxaban	Warfarin/ Enoxaparin	Daiichi/ Sankyo	Recruiting since March 2014 Completion July 2015
EMANATE NCT02100228	1500	Apixaban	Warfarin	BMS/ Pfizer	Not recruiting, start April 2014 Completion 2016

X-VERT = Explore the Efficacy and Safety of Once-daily Oral Rivaroxaban for the Prevention of Cardiovascular Events in Subjects With Nonvalvular Atrial Fibrillation Scheduled for Cardioversion
ARC = Anticoagulation With Rivaroxaban in Cardioversion
NCT01593150 = Early Versus Late DC-cardioversion of Persistent Atrial Fibrillation: effect on Atrial Remodeling, Inflammatory and Neurohumoral Markers and Recurrence of Atrial Fibrillation
ENSURE-AF = Edoxaban vs. Warfarin in Subjects Undergoing Cardioversion of Atrial Fibrillation
EMANATE = Study Of The Blood Thinner, Apixaban, For Patients Who Have An Abnormal Heart Rhythm (Atrial Fibrillation) And Expected To Have Treatment To Put Them Back Into A Normal Heart Rhythm (Cardioversion)

Savelieva I, et al. 2014 [In press]

Conclusions

- Thrombo-prophylaxis in some form is needed for both pharmacological and electrical cardioversion
- Experience with VKAs demonstrates low rates of thromboembolism peri-cardioversion if full anticoagulation given for 3 weeks before and 4 weeks after cardioversion
- Pre-cardioversion anticoagulation can be omitted if AF less than 48 hours in duration or TEE demonstrates no LA clot
- Post hoc retrospective analyses of major RCTs suggest that NOACs may be as effective as VKAs when used in a similarly
- A prospective study with rivaroxaban (V-VERT) is consistent with this conclusion. Other NOACS are being studied
- Brief NOAC anticoagulation pre-cardioversion is of interest, and is now being investigated