Anticoagulation: Cardioversion and Ablation

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Disclosures

Honoraria:

- Daiichi-Sankyo
- Bayer
- BMS/Pfizer
- Boehringer Ingelheim
- Astra Zeneca
- Berlin Chemie

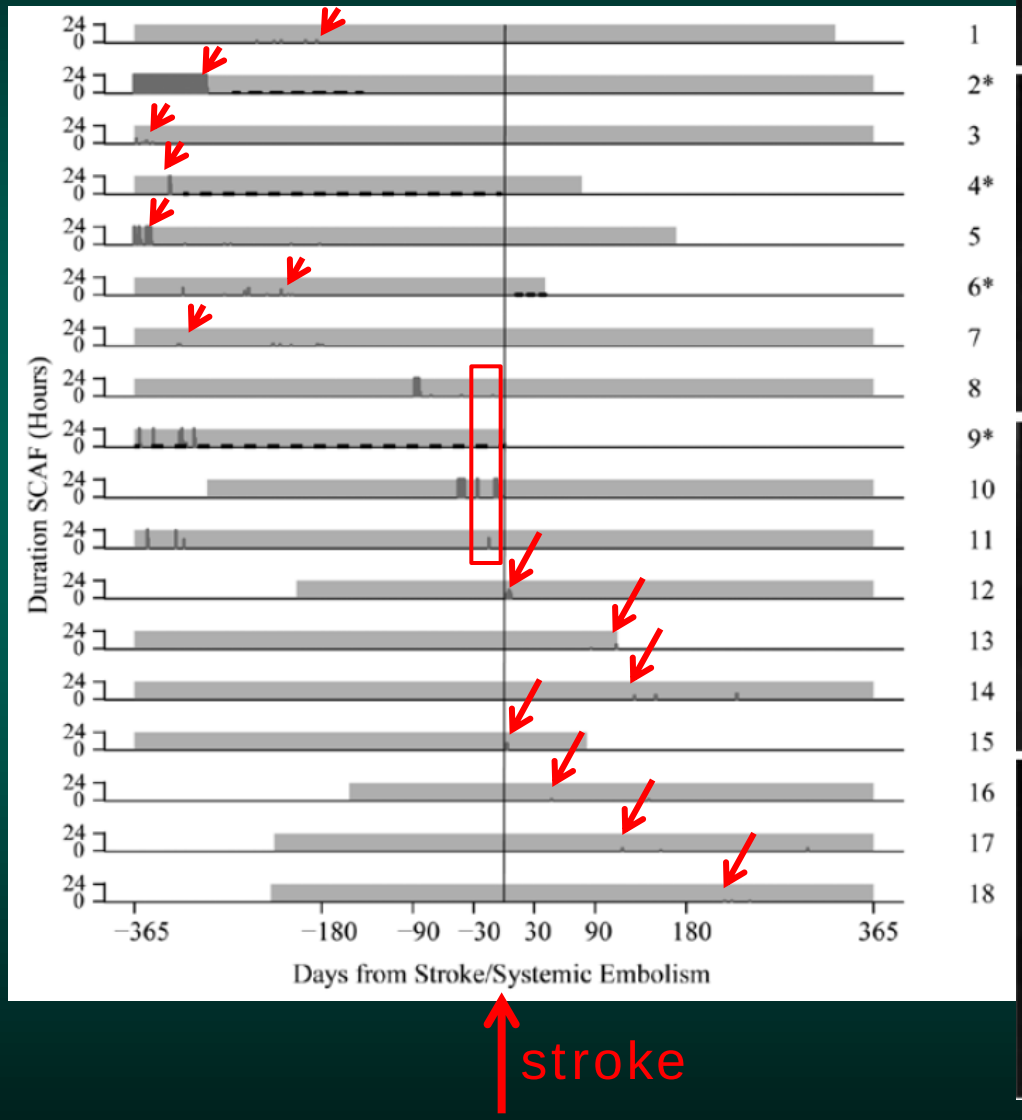
Temporal disconnect between subclinical AF and embolic events

Virchow's trias

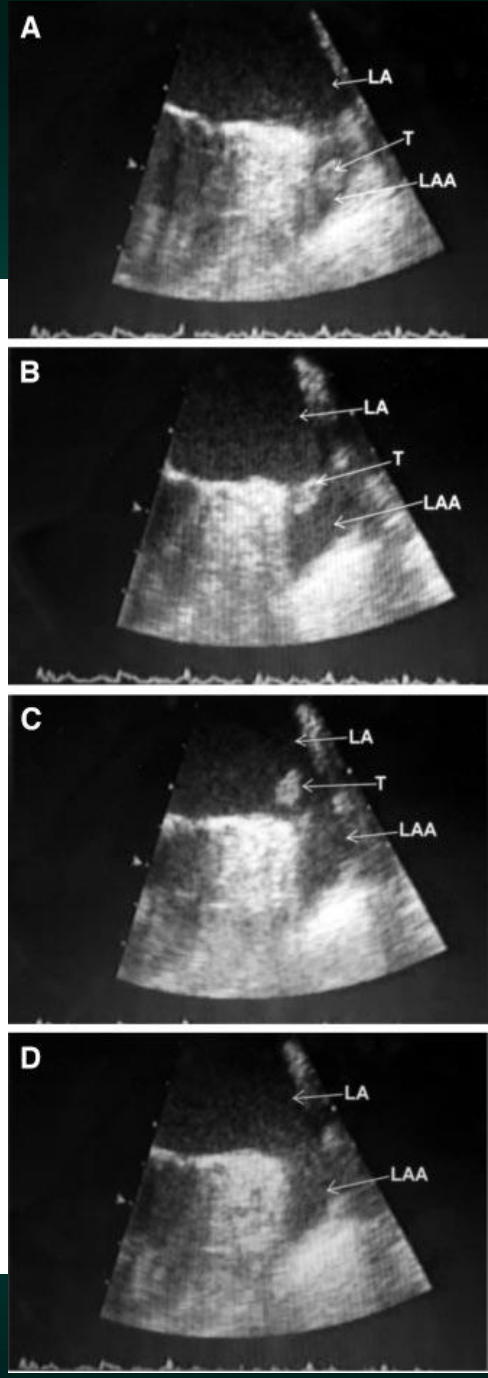
1. Slow blood flow
2. Increased blood coagulation
3. Vascular wall abnormalities

AF monitoring

VKA therapy



Brambatti M, et al. Circulation 2014 ASSERT Study



Parekh et al. Circ 2006

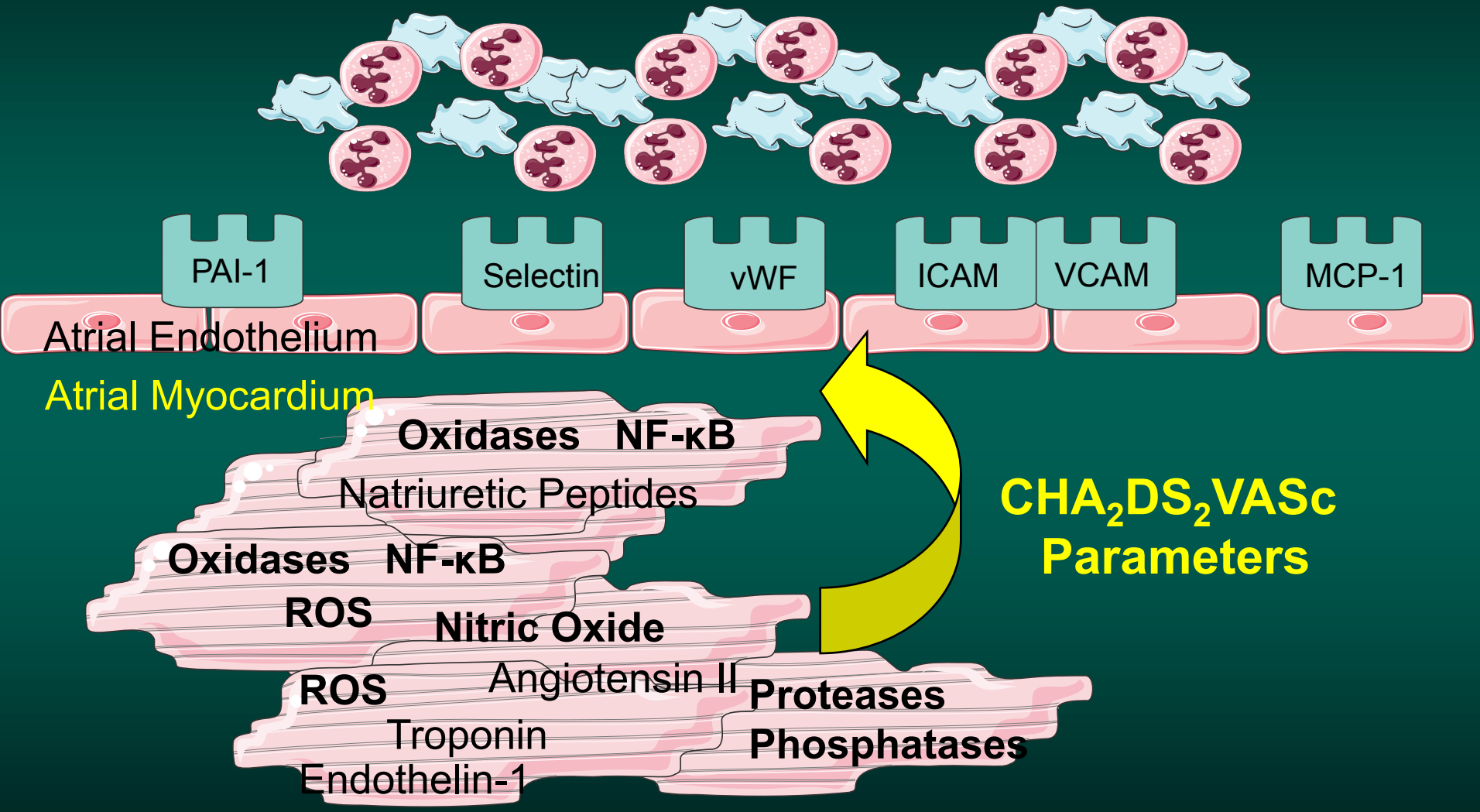
EHRA/HRS/APHRS/SOLAECE Expert Consensus on

Atrial Cardiomyopathies:

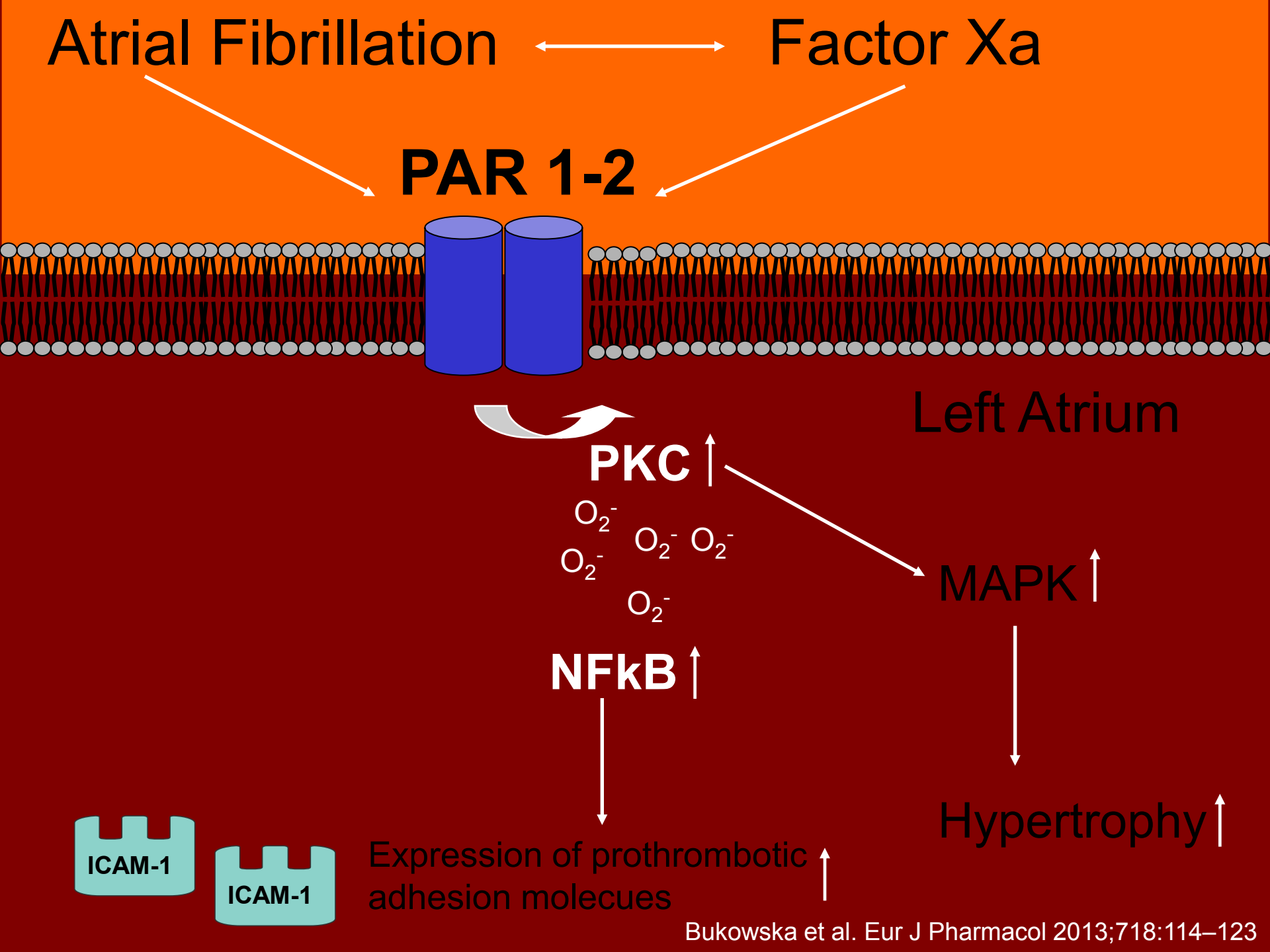
Definition, Characterization and Clinical Implication

Goette et al. EUROPACE 2016
Goette et al. Heart Rhythm 2016

Atrial Cardiomyopathies:
„Thrombogenic Endocardial Remodeling“

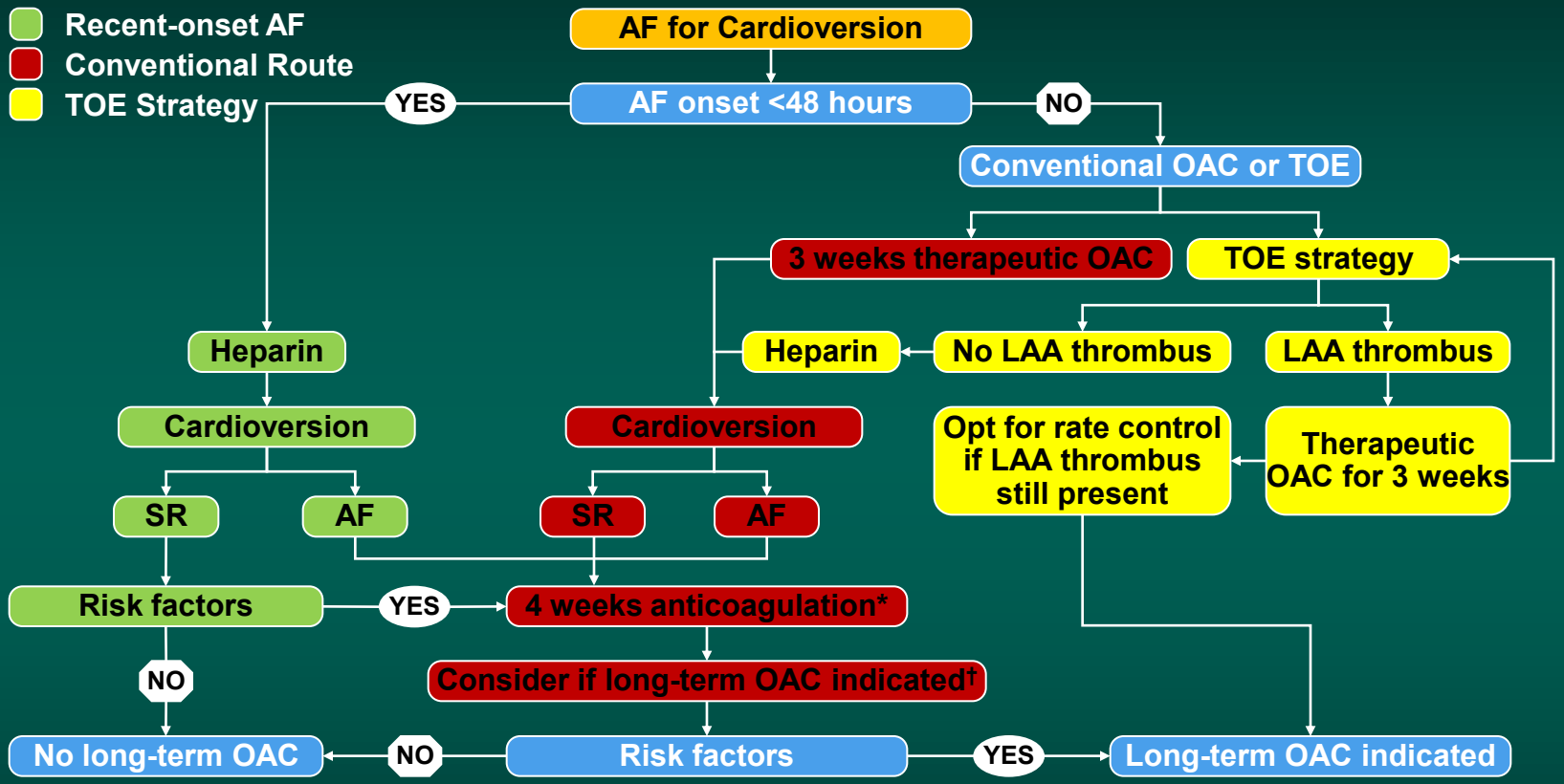


Goette A, et al. EUROPACE 2016



Bukowska et al. Eur J Pharmacol 2013;718:114–123

Cardioversion Strategy in AF



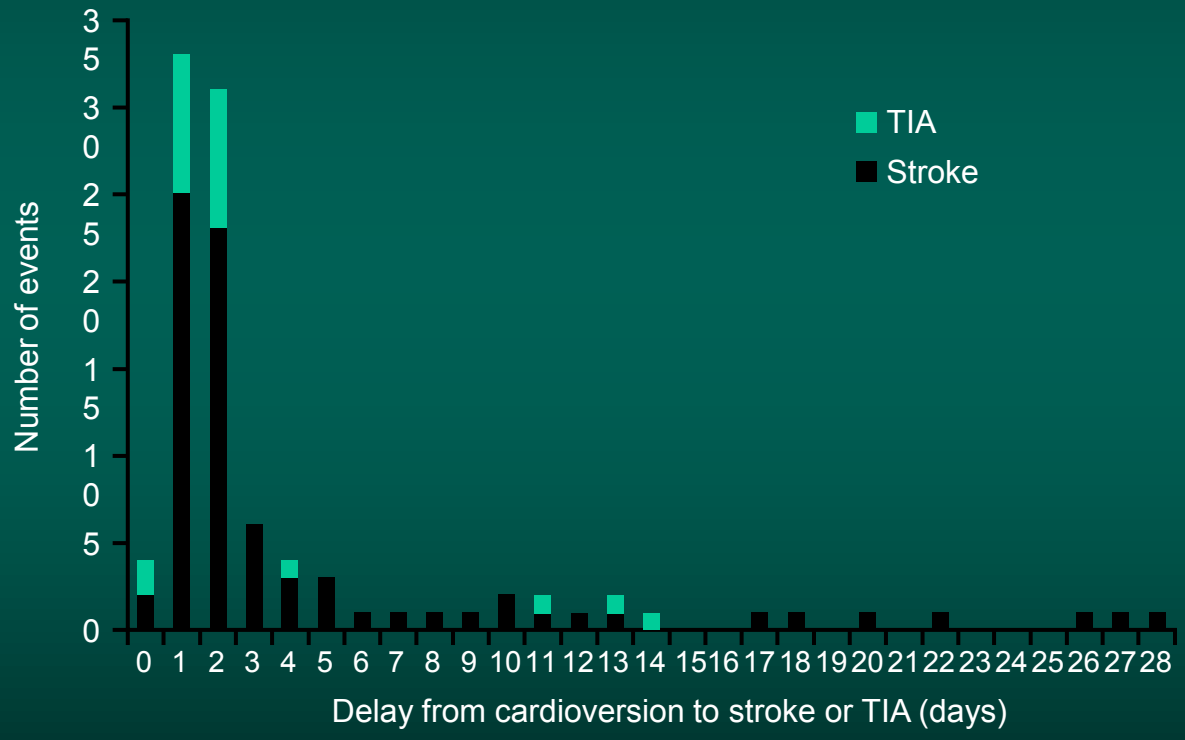
*Anticoagulation should normally be continued for 4 weeks after a cardioversion attempt except when AF is recent onset and no risk factors are present
†Long-term OAC if stroke risk factors and/or risk of AF recurrence/presence of thrombus

AF=atrial fibrillation; LAA=left atrial appendage; OAC=oral anticoagulant; SR=sinus rhythm; TOE = transoesophageal echocardiography

ESC AF Guidelines. Eur Heart J 2010;31:2369–2429

Strokes after cardioversion of atrial fibrillation – the FibStroke study

Palomäki et al. Int J Cardiol 2016;203:269-73



3677 consecutive AF patients suffered 3252 strokes and 956 TIA episodes during 2003–2012

Post- cardioversion strokes accounted for 6.4 % of strokes in patients with paroxysmal/persistent AF

Most post-cardioversion strokes occur in patients not using oral anticoagulation before cardioversion of acute AF

Reported Incidences of Embolic Events After Electrical and Chemical Cardioversion From Atrial Fibrillation

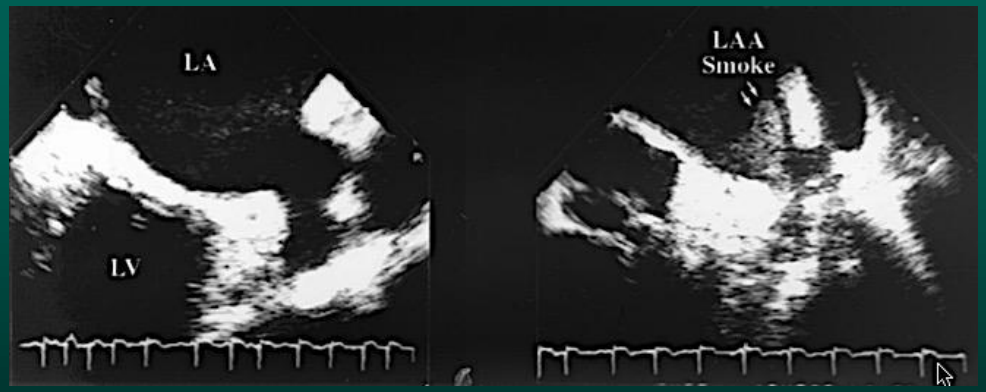
Klein et al. J Am Coll Cardiol 2001;37:691–704

Study		AC Rx	Percent embolism
Electrical cardioversion			
Lown (1963)	50	Some	1.7
Killip (1963)	62	In 45%	0.0
Morris (1964)	70	In 6%	3.4
Oram (1964)	100	Some	1.9
Hurst (1964)	121	No	1.3
Morris (1966)	108	Some	2.5
Korsgren (1965)	138	Yes	0.0
Halmos (1966)	175	No	0.4
Selzer (1966)	189	No	2.1
Lown (1967)	350	In 29%	0.9
Resnekov (1967)	204	Some	0.6
Hall (1968)	142	In 39%	0.8
Radford (1968)	156	In 17%	0.0
Aberg (1968)	207	Most	0.7
Bjerkelund (1969)	437	Yes	1.1
McCarthy (1969)	149	Some	1.6
Henry (1976)	37	Some	5.6
Roy (1986)	152	In 72%	1.3
Arnold (1992)	454	Most	1.3
			1.4±1.3*
Chemical cardioversion			
Sokolow (1956)	177	Some	1.3
Goldman (1960)	400	No	1.5
Freeman (1963)	100	Yes	0.0
Rokseth (1963)	274	Yes	1.6
Carlsson (1996)	1,152	Some	0.26
Mitchell (1997)	110	Some	2.7
			1.2±1.0*

*Mean value ±SD
AC = anticoagulation; Rx = treatment

Studies of TEE-Guided Approach to Cardioversion of Atrial Fibrillation, Including the Incidence of Thrombus by TEE and Recorded Embolic Events

Study	N	Atrial thrombi	Embolic events
Orsinelli (1993)	39	9 (23%)	1 (2.56%)
Stoddard (1995)	206	37 (18%)	0
Klein (1997)	126	7 (23%)	0
Weigner (1998)	466	64 (13.9%)	1 (0.21%)
Grimm (1998)	417	28 (7%)	0
Corrado (1999)	123	11 (9%)	0
ACUTE (2000)	619	79 (13.6%)	5 (0.81%)
Total	1,996	235 (11.8%)	7 (0.35%)



Klein et al. J Am Coll Cardiol 2001;37:691–704

Precardioversion (left) and postcardioversion (right) images of the left atrial appendage (LAA) using TEE. After DC cardioversion, left atrial appendage function diminishes and spontaneous echocardiographic contrast intensifies.

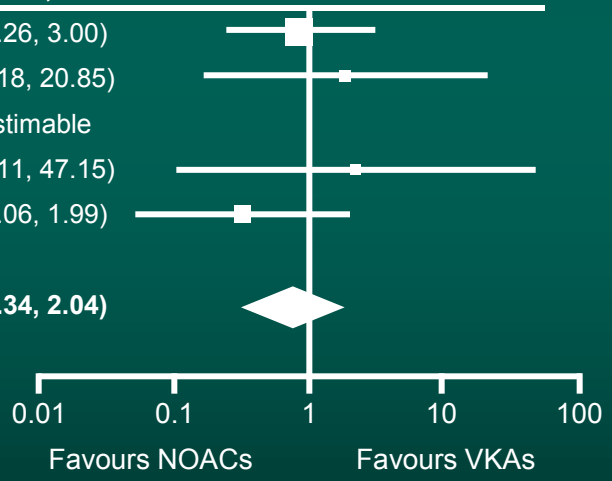
Meta-analysis of Cardioversion of AF with NOACs vs Warfarin

3949 patients undergoing 4900 cardioversions for AF in 5 trials of NOAC vs warfarin

	Favours NOACs		VKAs			Risk ratio
Study or subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**
RE-LY	7	1319	4	664	52.7%	0.88 (0.26, 3.00)
ROCKET-AF	2	138	1	132	13.9%	1.91 (0.18, 20.85)
ARISTOTLE	0	331	0	412		Not estimable
ENGAGE-AF	2	251	0	114	8.6%	2.28 (0.11, 47.15)
X-VeRT	2	1002	3	502	24.8%	0.33 (0.06, 1.99)
Total (95% CI)		**3041**		**1824**	100.0%	**0.84 (0.34, 2.04)**
Total events	13		8			

Heterogeneity: Tau^2= 0.00; Chi^2= 1.91, df = 3 (P=0.59); I^2 =0%

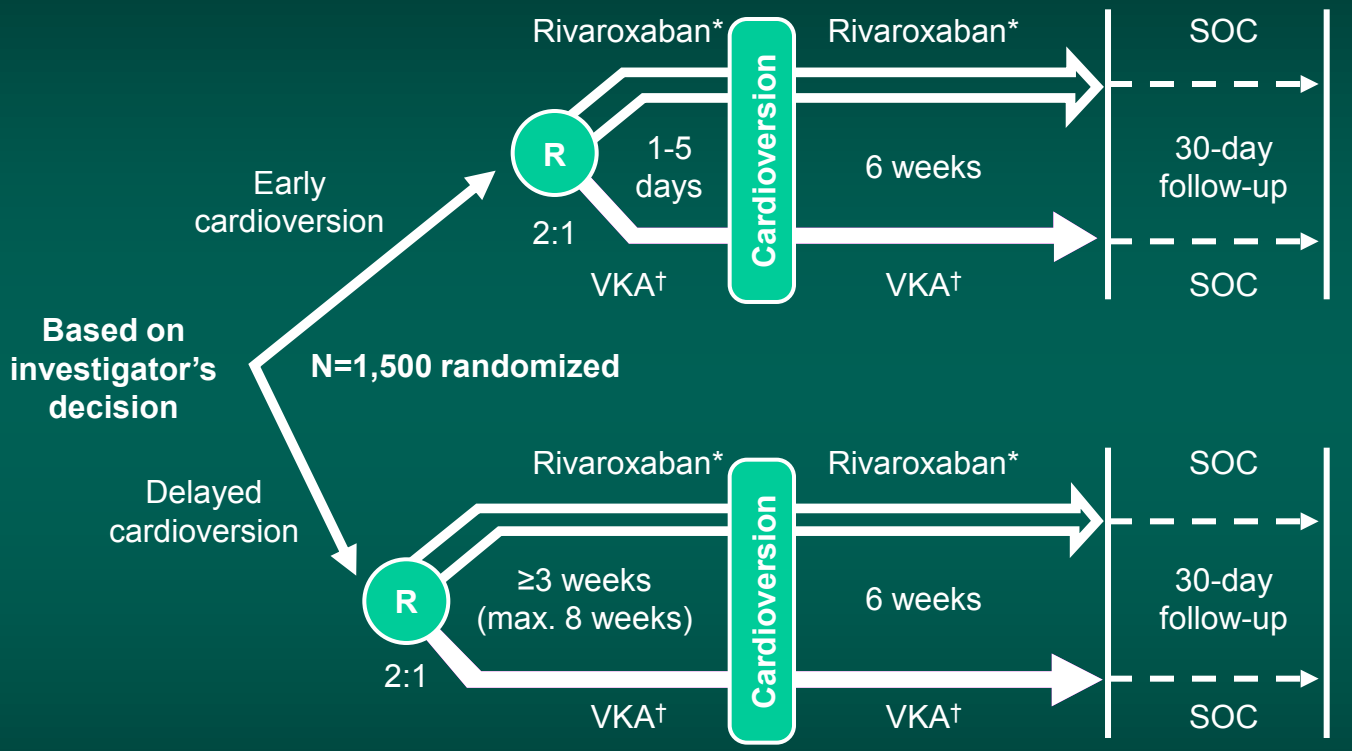
Test for overall effect: Z= 0.39 (P= 0.70)



Renda G et al. Am J Med 2016 in press (DOI:10.1016/j.amjmed.2016.05.007)

XVERT: Rivaroxaban

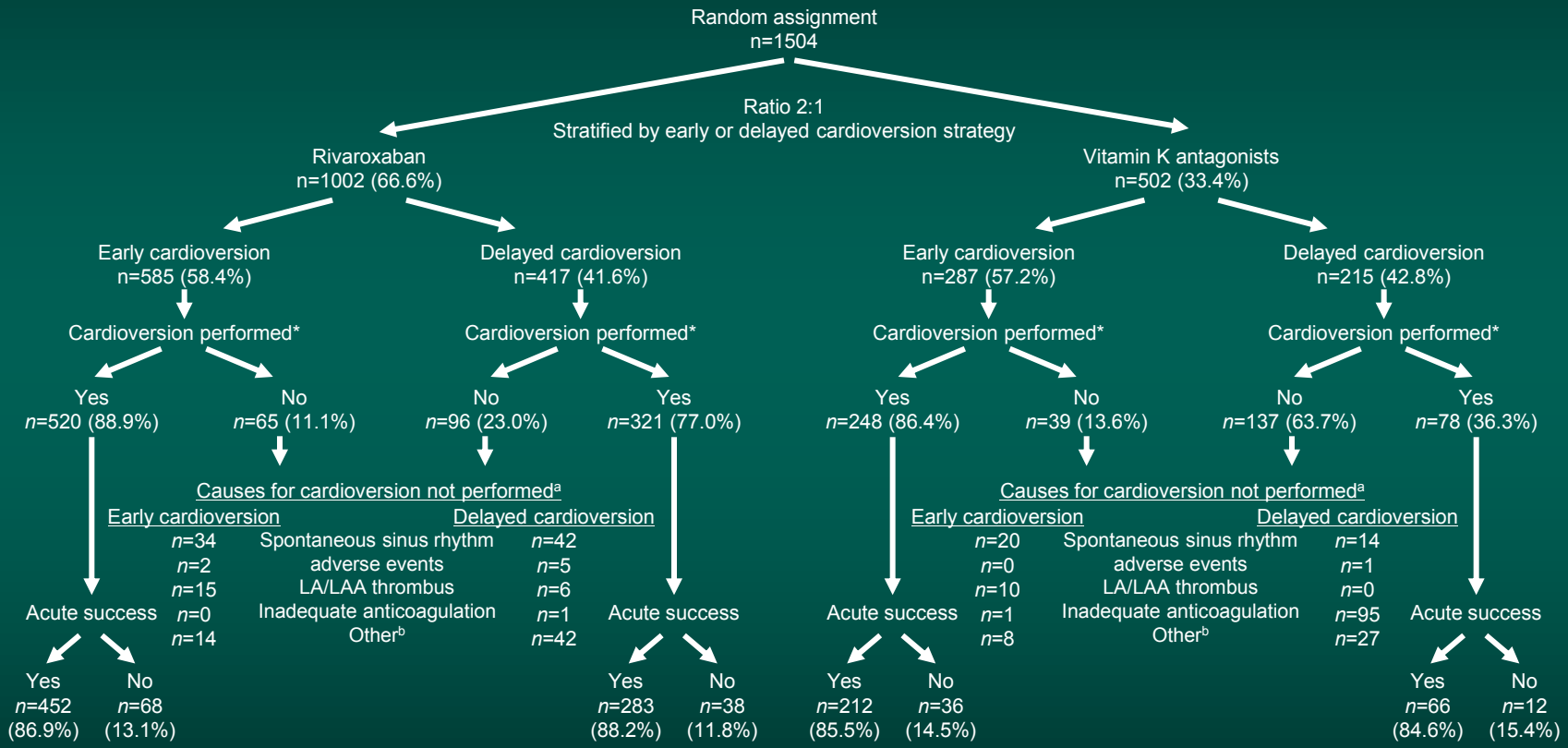
Study Population:
Patients with non-valvular AF lasting >48 hours or of unknown duration and scheduled for electrical or pharmacologic cardioversion



*20 mg once daily (15 mg once daily if creatinine clearance 30–49 mL/min)
†International normalized ratio 2.0 to 3.0

Ezekowitz et al. Am Heart J 2014;167:646–652

XVERT: Rivaroxaban



Cappato R, et al. Eur Heart J 2014

XVERT: Rivaroxaban

	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 ≥ 2g/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

Cappato R, et al. Eur Heart J 2014

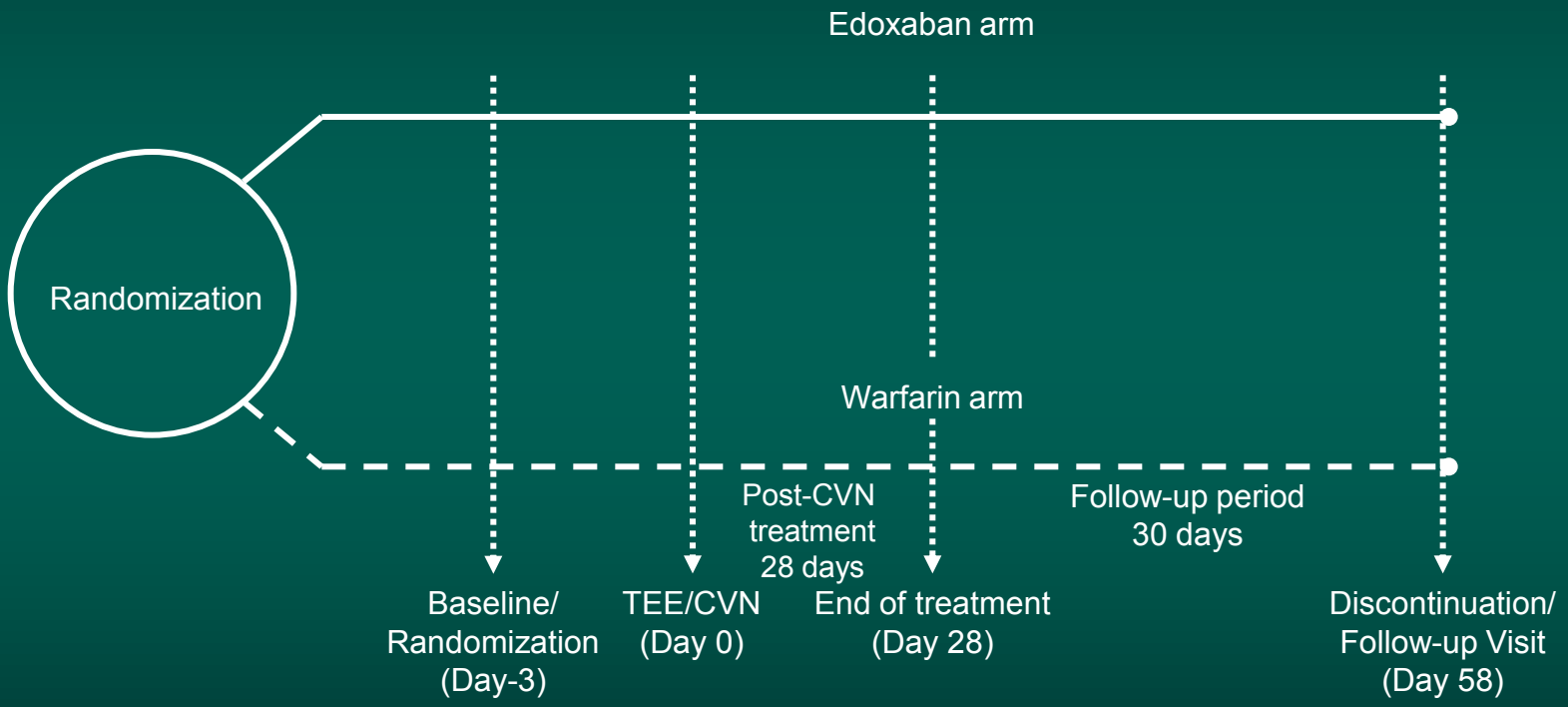
Edoxaban vs Enoxaparin/Warfarin in Subjects Undergoing Cardioversion of Atrial Fibrillation

The Randomized ENSURE-AF Study

Andreas Goette, Jose L. Merino, Michael D. Ezekowitz, Dmitry Zamoryakhin, Michael Melino, James Jin, Michele F. Mercuri, Michael A. Grosso, Victor Fernandez, Naab Al-Saady, Natalya Pelekh, Bela Merkely, Sergey Zenin, Mykola Kushnir, Jindrich Spinar, Valeriy Batushkin, Joris R. de Groot, Gregory Y. H. Lip

The Lancet 2016

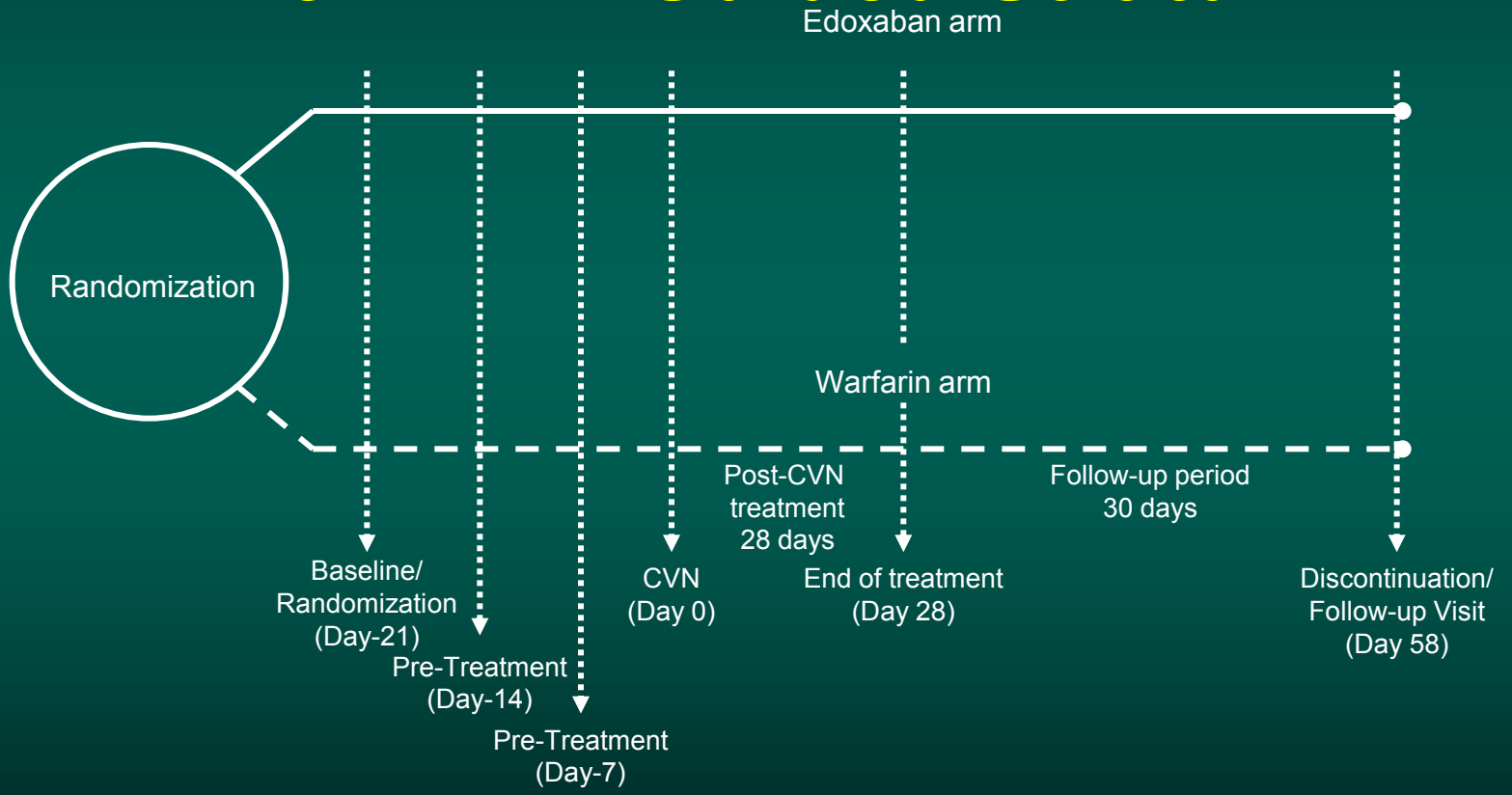
ENSURE AF: Flow Diagram for TEE-Guided Stratum



CVN=Cardioversion;
TEE=Transesophageal echocardiography

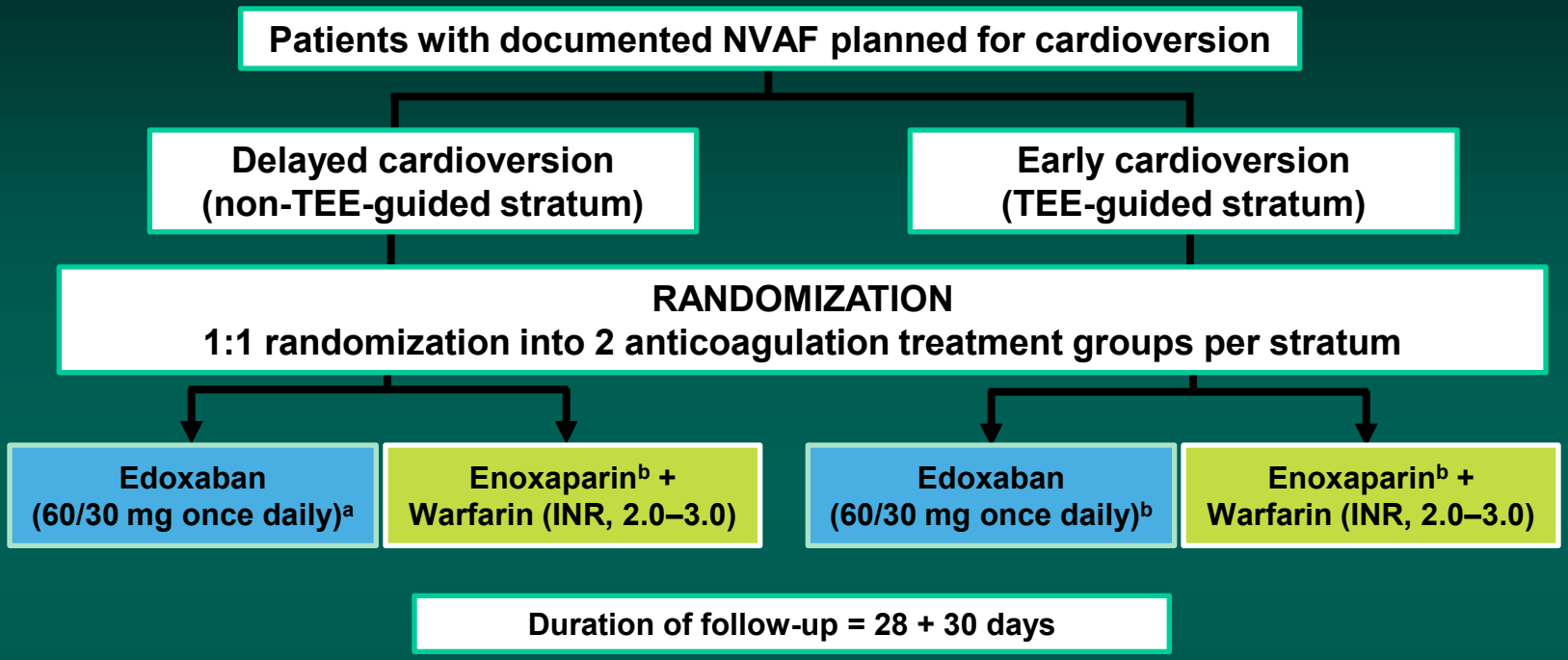
Lip G, et al. Am Heart J 2015

ENSURE AF: Flow Diagram for Non-TEE-Guided Stratum



Lip G, et al. Am Heart J 2015

Overall Study Design

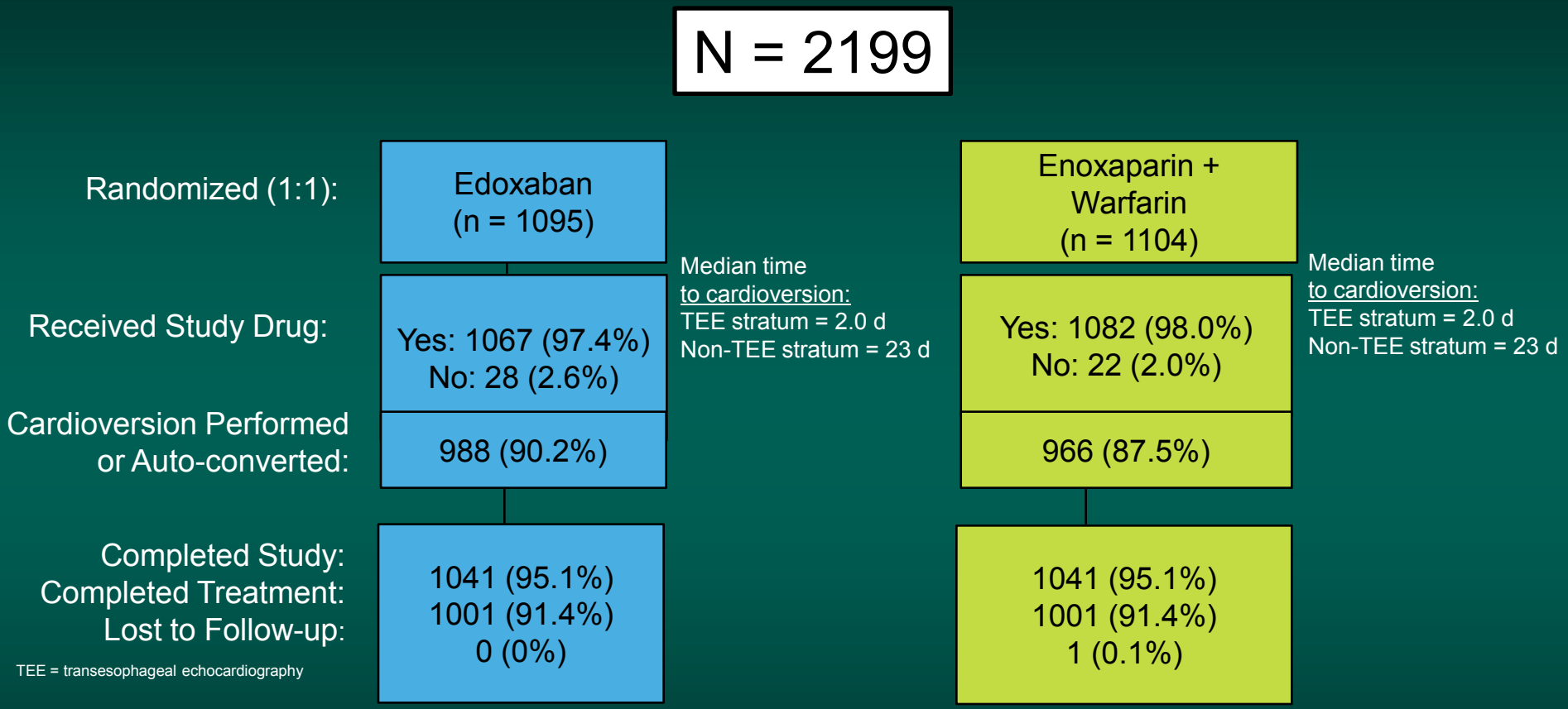


[a] Patients meeting ≥1 of the following criteria: CrCl ≥15 mL/min and ≤50 mL/min; low body weight (≤60 kg); or concomitant use of P-gp inhibitors (with the exception of amiodarone)
[b] Patients with INR at randomization ≥2 did not require enoxaparin
CrCl = creatinine clearance; INR = international normalized ratio; NVAF = nonvalvular atrial fibrillation; TEE = transesophageal echocardiographyet al. LANCET 2016

Lip GY, et al. *Am Heart J.* 2015;169:597-604

Goette A, et al. LANCET 2016

Patient Disposition



TEE = transesophageal echocardiography

Goette A, et al. LANCET 2016

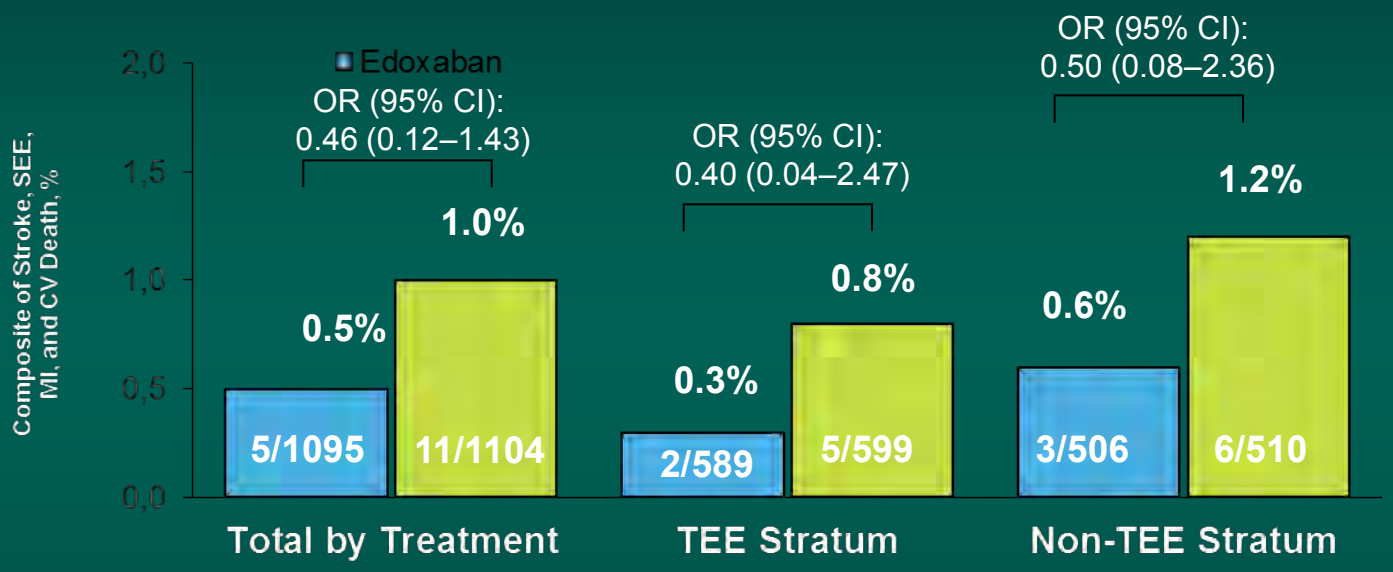
Baseline Demographics

	Total by Treatment		TEE Stratum		Non-TEE Stratum	
	Edoxaban (n = 1095)	Enoxaparin + Warfarin (n = 1104)	Edoxaban (n = 589)	Enoxaparin + Warfarin (n = 594)	Edoxaban (n = 506)	Enoxaparin + Warfarin (n = 510)
Age (y), mean	64.3	64.2	64.9	64.5	63.6	63.8
Male, n (%)	721 (65.8)	722 (65.4)	385 (65.4)	389 (65.5)	336 (66.4)	333 (65.3)
BMI (kg/m^2), mean	30.6	30.7	30.4	30.4	31.0	31.0
CHA_2DS_2-VASc, mean	2.6	2.6	2.7	2.7	2.5	2.5
Paroxysmal AF (≤7 days), n (%)	208 (19.0)	207 (18.8)	138 (23.4)	132 (22.2)	70 (13.8)	75 (14.7)
Persistent AF (>7 days, <1 y), n (%)	887 (81.0)	890 (80.6)	451 (76.6)	458 (77.1)	436 (86.2)	432 (84.7)
Anticoagulant experienced, n (%)	791 (72.2)	808 (73.2)	426 (72.3)	440 (74.1)	365 (72.1)	368 (72.2)
Medical history, n (%)						
Congestive heart failure	476 (43.5)	484 (43.8)	258 (43.8)	259 (43.6)	218 (43.1)	225 (44.1)
Coronary artery disease	181 (16.5)	197 (17.8)	89 (15.1)	111 (18.7)	92 (18.2)	86 (16.9)
Diabetes	218 (19.9)	197 (17.8)	115 (19.5)	105 (17.7)	103 (20.4)	92 (18.0)

AF = atrial fibrillation; BMI = body mass index; CHA_2DS_2-VASc = Congestive heart failure, Hypertension, Age ≥75, Diabetes mellitus, and prior Stroke or TIA or thromboembolism, Vascular disease, Age 65–74 years, Sex category; TEE = transesophageal echocardiography; TIA = transient ischemic attack

Goette A, et al. LANCET 2016

Primary Efficacy[a]



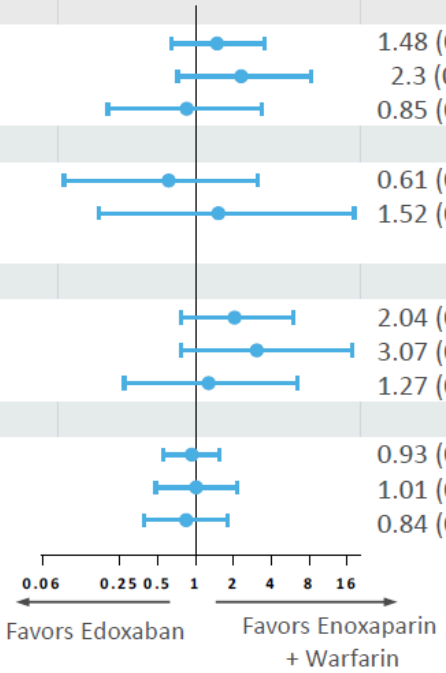
[a] Composite of stroke, SEE, MI, and CV mortality assessed in the ITT population during overall period

CI = confidence interval; CV = cardiovascular; ITT = intent-to-treat; MI = myocardial infarction; OR = odds ratio; SEE = systemic embolic event; TEE = transesophageal echocardiography;
TTR = time in therapeutic range

Goette A, et al. LANCET 2016

ENSURE-AF Adjudicated Safety Outcomes[a]

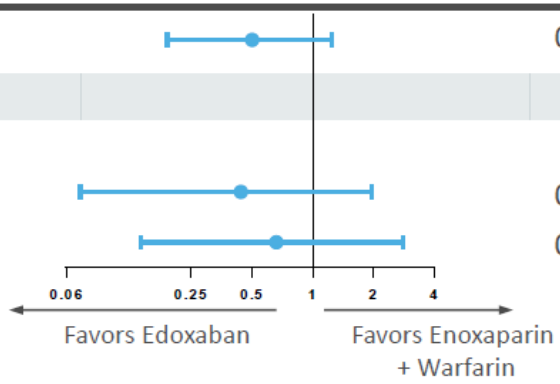
	Event Rate, % (n/N)		Edoxaban vs Enoxaparin + Warfarin	
	Edoxaban	Enoxaparin + Warfarin		OR (95% CI)
First Major or CRNM Bleeding				
Total by Treatment	1.5 (16/1067)	1.0 (11/1082)		1.48 (0.64–3.55)
TEE Stratum	1.9 (11/570)	0.9 (5/577)		2.3 (0.72–8.31)
Non-TEE Stratum	1.0 (5/497)	1.2 (6/505)		0.85 (0.20–3.35)
Major Bleeding				
Total by Treatment	0.3 (3/1067)	0.5 (5/1082)		0.61 (0.09–3.13)
TEE Stratum	0.5 (3/570)	0.3 (2/577)		1.52 (0.17–18.27)
Non-TEE Stratum	0	0.6 (3/505)		NC
CRNM Bleeding				
Total by Treatment	1.3 (14/1067)	0.6 (7/1082)		2.04 (0.77–6.00)
TEE Stratum	1.6 (9/570)	0.5 (3/577)		3.07 (0.76–17.70)
Non-TEE Stratum	1.0 (5/497)	0.8 (4/505)		1.27 (0.27–6.45)
Any Bleeding				
Total by Treatment	3.0 (32/1067)	3.2 (35/1082)		0.93 (0.55–1.55)
TEE Stratum	3.0 (17/570)	2.9 (17/577)		1.01 (0.48–2.13)
Non-TEE Stratum	3.0 (15/497)	3.6 (18/505)		0.84 (0.39–1.79)



Goette A, et al. LANCET 2016

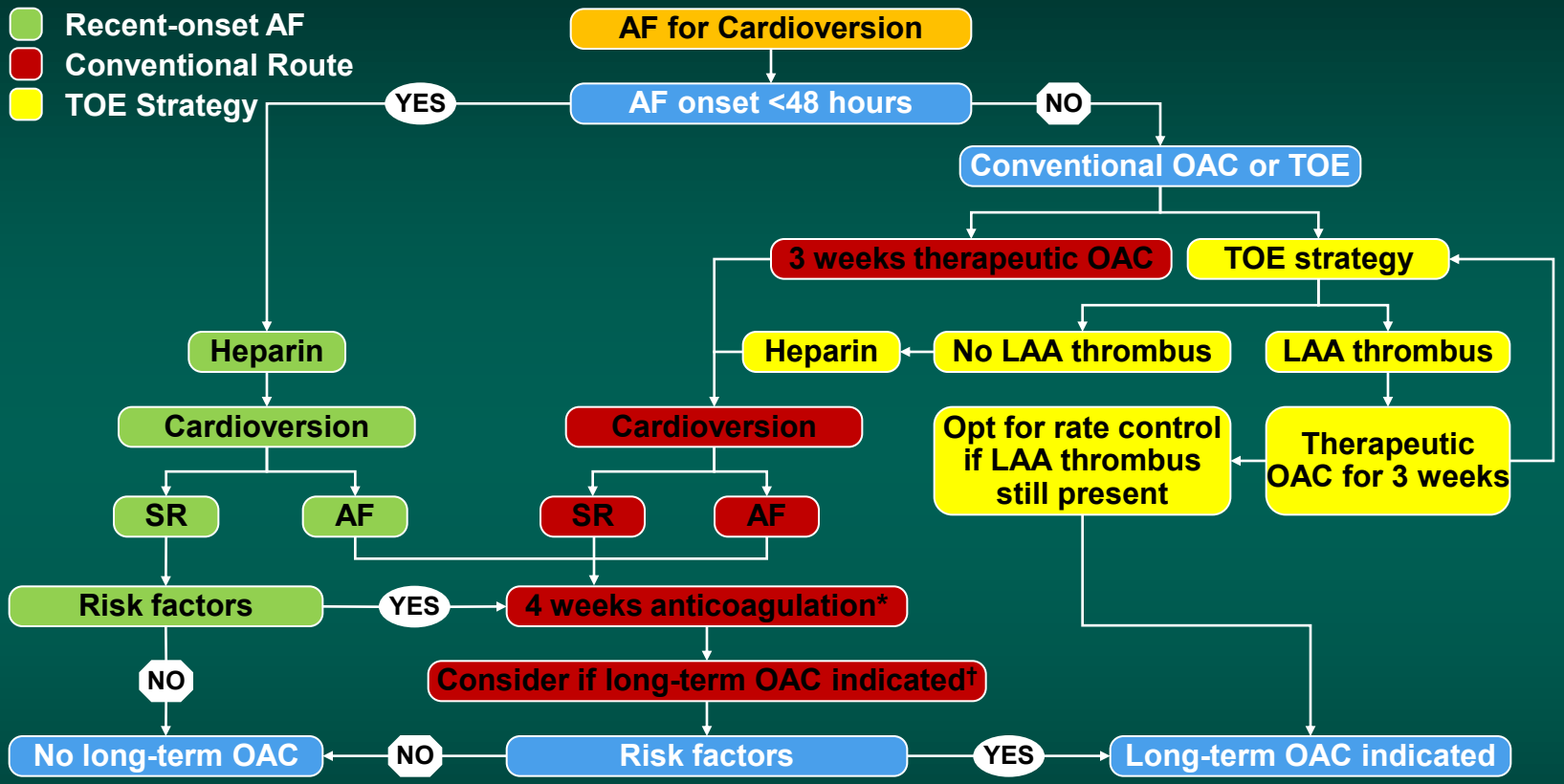
ENSURE-AF Net Clinical Outcome[a]

	Event Rate, % (n/N)		Edoxaban vs Enoxaparin + Warfarin	OR (95% CI)
	Edoxaban	Enoxaparin + Warfarin		
Overall	0.7 (8/1095)	1.4 (16/1104)		0.50 (0.19–1.25)
By CrCl, mL/min				
≤50	0 (0/83)	2.63 (2/76)		NC
>50–<80	0.99 (3/304)	2.22 (7/315)		0.44 (0.07–1.95)
≥80	0.62 (4/643)	0.94 (6/636)		0.66 (0.14–2.79)



Goette A, et al. LANCET 2016

Cardioversion Strategy in AF



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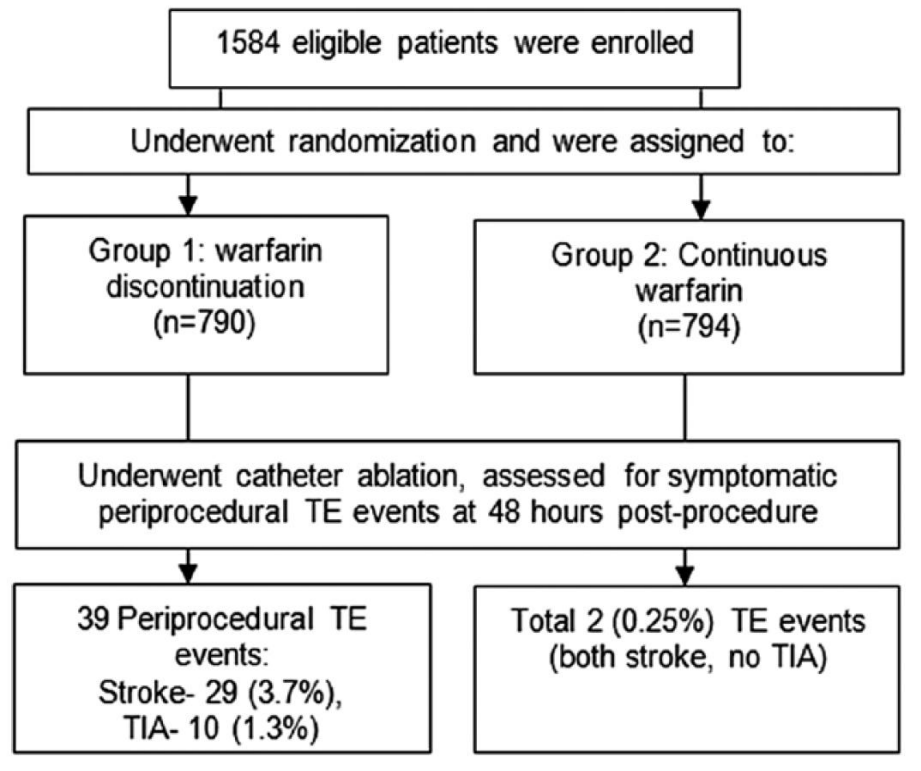
AF=atrial fibrillation; LAA=left atrial appendage; OAC=oral anticoagulant; SR=sinus rhythm; TOE = transoesophageal echocardiography

ESC AF Guidelines. Eur Heart J 2010;31:2369–2429

COMPARE:
Continuous vs interrupted VKA



8 major bleeds (0.8%)	3 major bleeds (0.4%)
7 pericardial effusions (0.9%)	2 pericardial effusions (0.5%)
174 minor bleeds (22%)	22 minor bleeds (4%)

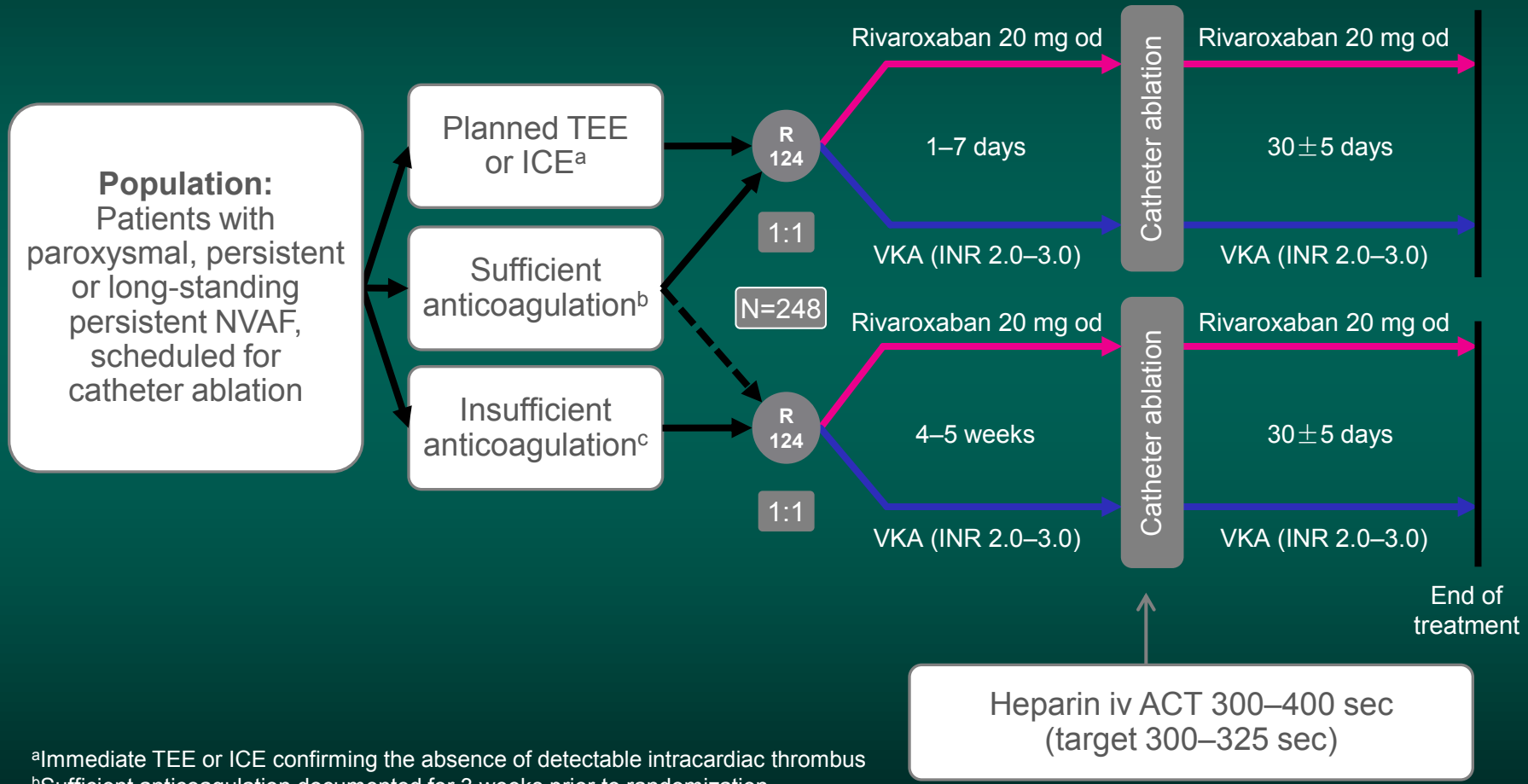
Di Biase L, et al. *Circulation.* 129:2638-2644 (2014)

VENTURE AF:
Study Objectives

To determine whether the use of uninterrupted rivaroxaban is associated with a safety profile that is similar to that of uninterrupted VKA in patients undergoing ablation for NVAF

Naccarelli GV *et al, J Interv Card Electrophysiol* 2014;41:107–116

VENTURE AF Design: Randomized, Open-label, Active-controlled Multicentre Study



[a]Immediate TEE or ICE confirming the absence of detectable intracardiac thrombus
[b]Sufficient anticoagulation documented for 3 weeks prior to randomization
[c]These patients were randomized to receive study drug for 4-5 weeks prior to the procedure
Please refer to the slide notes for the full details of the footnotes

Naccarelli GV *et al, J Interv Card Electrophysiol* 2014;41:107–116

VENTURE AF

VENTURE AF: Key Inclusion and Exclusion Criteria

Key inclusion criteria*	Key exclusion criteria#
◆ Scheduled for catheter ablation for NVAF ◆ Prior paroxysmal (<1 week) or persistent (>1 week and <1 year or requiring pharmacological or electrical cardioversion) or long-standing persistent (≥1 year) NVAF ◆ Suitable for anticoagulant therapy and catheter ablation	◆ Prior stroke, TIA or non-convulsive status epilepticus ≤6 months ◆ Prior major bleeding or a thromboembolic event ≤12 months ◆ Major surgery ≤6 months before screening/planned during study ◆ MI ≤2 months or CABG surgery ≤6 months ◆ Non-cardiac or reversible NVAF ◆ CrCl ≤50 ml/min‡

*Including but not limited to; #any other exclusion criteria in conjunction with the local product information and any other contraindication listed in the local labeling for rivaroxaban or the comparator have to be considered; ‡owing to the small size of the study, patients with a CrCl ≤50 ml/min were excluded to avoid the need for separate data analysis in two different patient cohorts

Naccarelli GV *et al, J Interv Card Electrophysiol* 2014;41:107–116

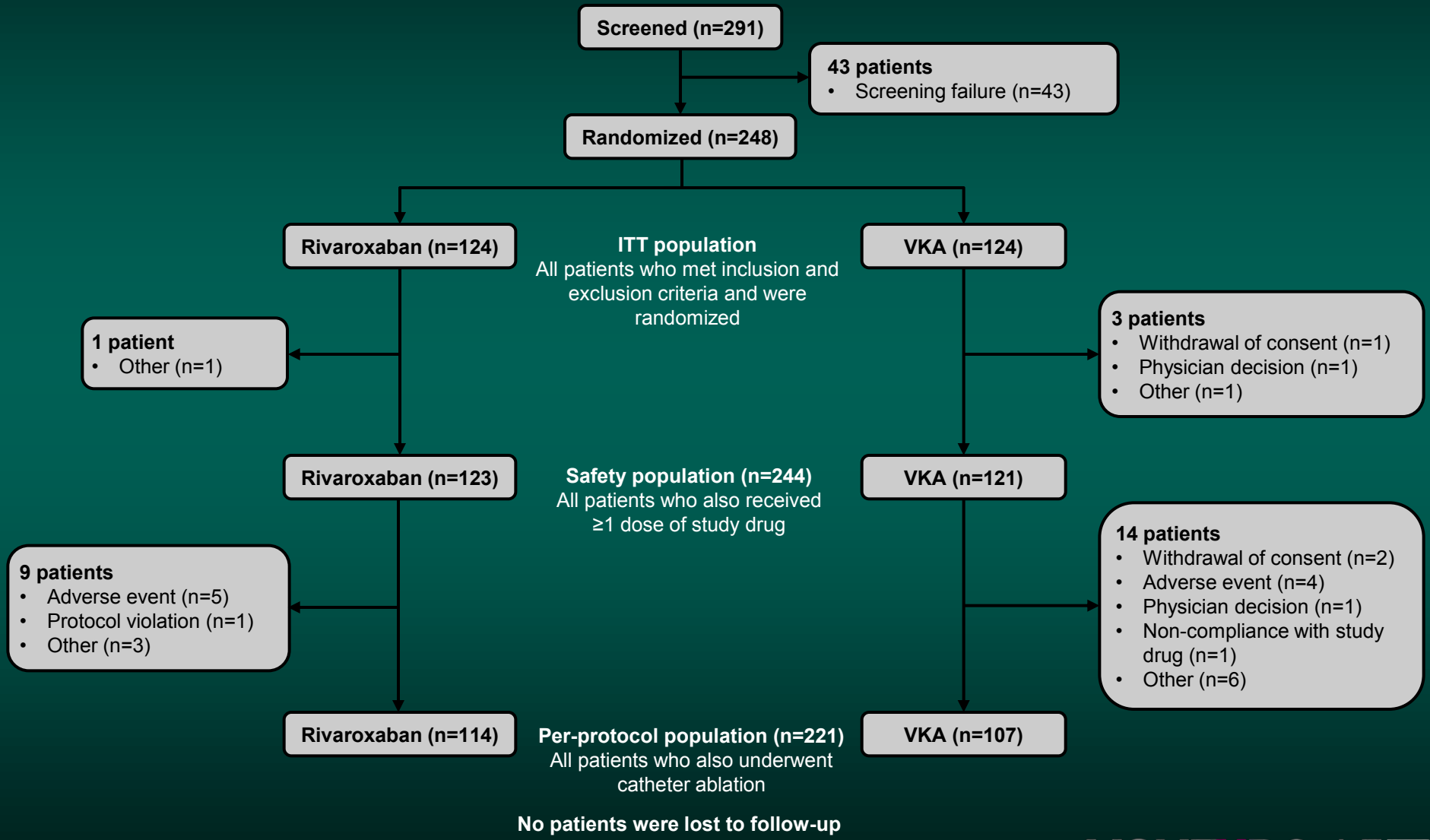
VENTURE AF

Ablation

Prior to CA, patients randomized to rivaroxaban received a once-daily dose of 20 mg orally, preferentially with the evening meal. Patients randomized to VKA received a VKA regimen based on local standards of care (recommended INR 2.0–3.0). Patients were required to receive continuous oral anticoagulation for at least 3 weeks prior to ablation (delayed CA strategy) or for 1 to 7 days (early CA strategy) if an immediate transoesophageal echocardiography (TOE) or intracardiac echocardiography (ICE) demonstrated the absence of an intra-cardiac thrombus. During CA, patients received intravenous unfractionated heparin to achieve a target activated clotting time (ACT) of 300 to 400 s. After CA, the next post-ablation rivaroxaban dose was administered at least 6 h following establishing haemostasis. The next dose of VKA was administered in accordance with the usual care. After CA, the administration of study drug was continued for 30 ± 5 days after CA and the subsequent anticoagulation regimen was determined by the patient's clinician.

VENTURE AF

VENTURE AF: Patient Flow



Cappato R *et al. Eur Heart* J 2015; doi:10.1093/eurheartj/ehv177 [E-Pub ahead of print]

VENTURE AF: Patient Demographics*

	Rivaroxaban (n=124)	VKA (n=124)
Age, years, mean (SD)	58.6 (9.9)	60.5 (10.5)
Male, n (%)	86 (69.4)	90 (72.6)
Paroxysmal AF, n (%)	95 (76.6)	87 (70.2)
Prior cardioversion, n (%)	47 (37.9)	54 (43.5)
Prior catheter ablation, n (%)	11 (8.9)	11 (8.9)
CHF, n (%)	12 (9.7)	9 (7.3)
Hypertension, n (%)	59 (47.6)	57 (46.0)
Diabetes mellitus, n (%)	8 (6.5)	14 (11.3)
Prior stroke/TIA/embolism, n (%)	0	3 (2.4)
Vascular disease, n (%)	22 (17.7)	25 (20.2)
$CHADS_2$ score, mean (SD)	0.7 (0.7)	0.8 (0.9)
CHA_2DS_2-VASc score, mean (SD)	1.5 (1.3)	1.7 (1.4)
Beta-blocker, selective, n (%)	65 (52.4)	61 (49.2)
Antiarrhythmic, class IC, n (%)	51 (41.1)	49 (39.5)
Antiarrhythmic, class III, n (%)	30 (24.2)	39 (31.5)
Previous VKA use, n (%)	36 (29.0)	37 (29.8)
Previous Rivaroxaban use, n (%)	23 (18.5)	29 (23.4)
Previous Dabigatran use, n (%)	12 (9.7)	10 (8.1)

ITT population; **p*-values for interaction were not significant

Adapted from Cappato R *et al. Eur Heart* J 2015; doi:10.1093/eurheartj/ehv177 [E-Pub ahead of print]

VENTURE AF

VENTURE AF: Heparin Management and ACT Levels

	Rivaroxaban	VKA	Total	*p*-value
	n=114	n=107	N=221	
Patients heparinized, n (%)	114 (100)	107 (100)	221 (100)	
	n=113	n=107	N=221	
Total units of heparin, mean (SD)	13,871 (6516)	10,964 (5912)	12,457 (6383)	<0.001
	n=111	n=106	N=218	
ACT level, mean (SD)	302 (49)	332 (58)	317 (55)	<0.001
	n=114	n=107	N=221	
Protamine for heparin reversal, n (%)	32 (28.1)	27 (25.2)	59 (26.7)	0.634

Cappato R *et al. Eur Heart* J 2015; doi:10.1093/eurheartj/ehv177 [E-Pub ahead of print])

VENTURE AF: Complications During the Study Period

	Rivaroxaban	VKA	Total
Any adjudicated event	26	25	51
	n=123	n=121	N=244
Any bleeding event*	21	18	39
Major bleeding event	0	1	1
Vascular pseudoaneurysm	0	1	1
Non-major bleeding event	21	17	38
Most relevant:			
Arteriovenous fistula	0	1	1
Catheter/puncture site haemorrhage	1	1	2
Haematoma/vessel puncture site haematoma	8	10	18
Vascular pseudoaneurysm	3	1	4
	n=124	n=124	N=248
Any thromboembolic events (composite)#	0	2	2
Ischaemic stroke	0	1	1
Vascular death	0	1	1
	n=114	n=107	N=221
Any other procedure-attributable event†	5	5	10
Pericardial effusion without tamponade	0	1	1

*safety population; #ITT population; †per-protocol population

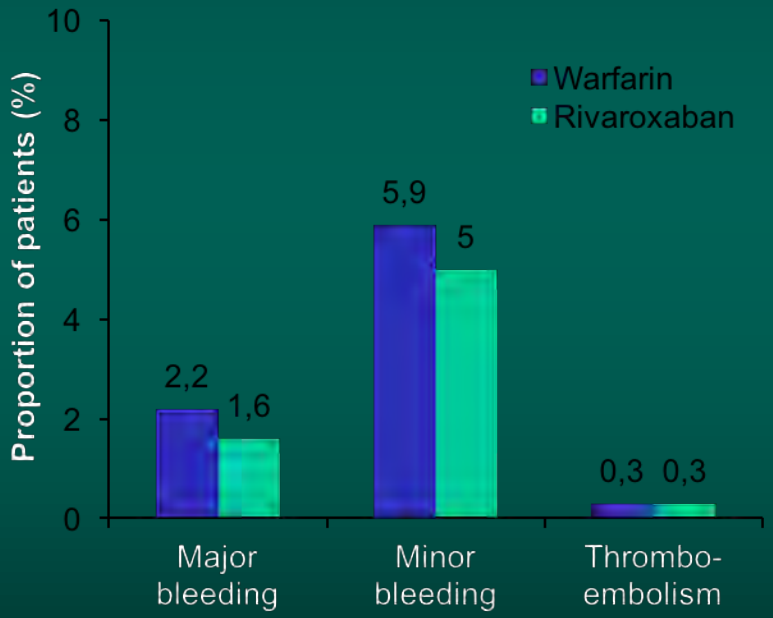
For full list see publication or back-up-slide

Adapted from Cappato R *et al. Eur Heart J* 2015; doi:10.1093/eurheartj/ehv177 [E-Pub ahead of print]

VENTURE AF: Clinical Implications: Rivaroxaban in the Ablation Setting

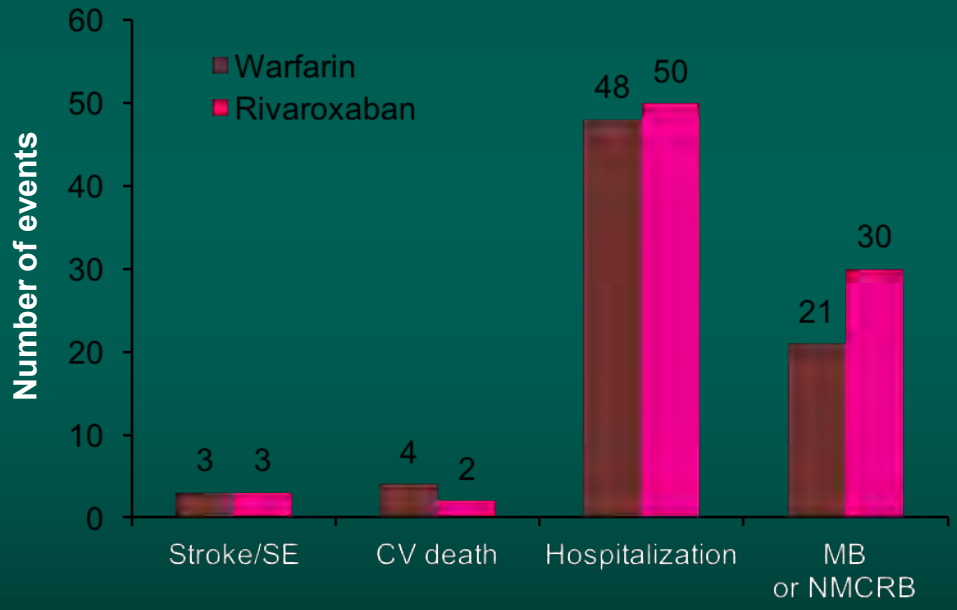
Results of VENTURE AF consistent with real-life studies…

North American registry (n=642)[1]



… and ROCKET AF cardioversion/ablation subanalysis

Outcomes after cardioversion and ablation* (n=321)[2]



*The analysis combined patients undergoing ablation (n=79) with patients undergoing cardioversion (n=285)

1. Lakkireddy D *et al. J Am Coll Cardiol* 2014;63:982–988
2. Piccini J *et al. J Am Coll Cardiol* 2013;61:1998–2006

VENTURE AF

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Uninterrupted Dabigatran versus Warfarin for Ablation in Atrial Fibrillation

Hugh Calkins, M.D., Stephan Willems, M.D., Edward P. Gerstenfeld, M.D., Atul Verma, M.D., Richard Schilling, M.D., Stefan H. Hohnloser, M.D., Ken Okumura, M.D., Ph.D., Harvey Serota, M.D., Matias Nordaby, M.D., Kelly Guiver, M.Sc., Branislav Biss, M.D., Marc A. Brouwer, M.D., Ph.D., and Massimo Grimaldi, M.D., Ph.D., for the RE-CIRCUIT Investigators*

Dabigatran in AF ablation

RESULTS

The trial enrolled 704 patients across 104 sites; 635 patients underwent ablation. Baseline characteristics were balanced between treatment groups. The incidence of major bleeding events during and up to 8 weeks after ablation was lower with dabigatran than with warfarin (5 patients [1.6%] vs. 22 patients [6.9%]; absolute risk difference, –5.3 percentage points; 95% confidence interval, –8.4 to –2.2; P<0.001). Dabigatran was associated with fewer periprocedural pericardial tamponades and groin hematomas than warfarin. The two treatment groups had a similar incidence of minor bleeding events. One thromboembolic event occurred in the warfarin group.

CONCLUSIONS

In patients undergoing ablation for atrial fibrillation, anticoagulation with uninterrupted dabigatran was associated with fewer bleeding complications than uninterrupted warfarin. (Funded by Boehringer Ingelheim; RE-CIRCUIT ClinicalTrials.gov number, NCT02348723.)

Dabigatran in AF ablation

atrial thrombi. The morning dose of dabigatran was taken on the day of the ablation at the patient's usual scheduled time. Ablation was performed with uninterrupted anticoagulation treatment, and anticoagulation was continued for 8 weeks after the procedure. Unfractionated heparin was administered after the placement of femoral sheaths before or immediately after transseptal puncture. During the ablation procedure, achieving and maintaining an activated clotting time of more than 300 seconds was recommended. Dabigatran administration was continued in the evening of the procedure at the scheduled time, with a minimum delay of 3 hours after sheath removal and achievement of hemostasis.

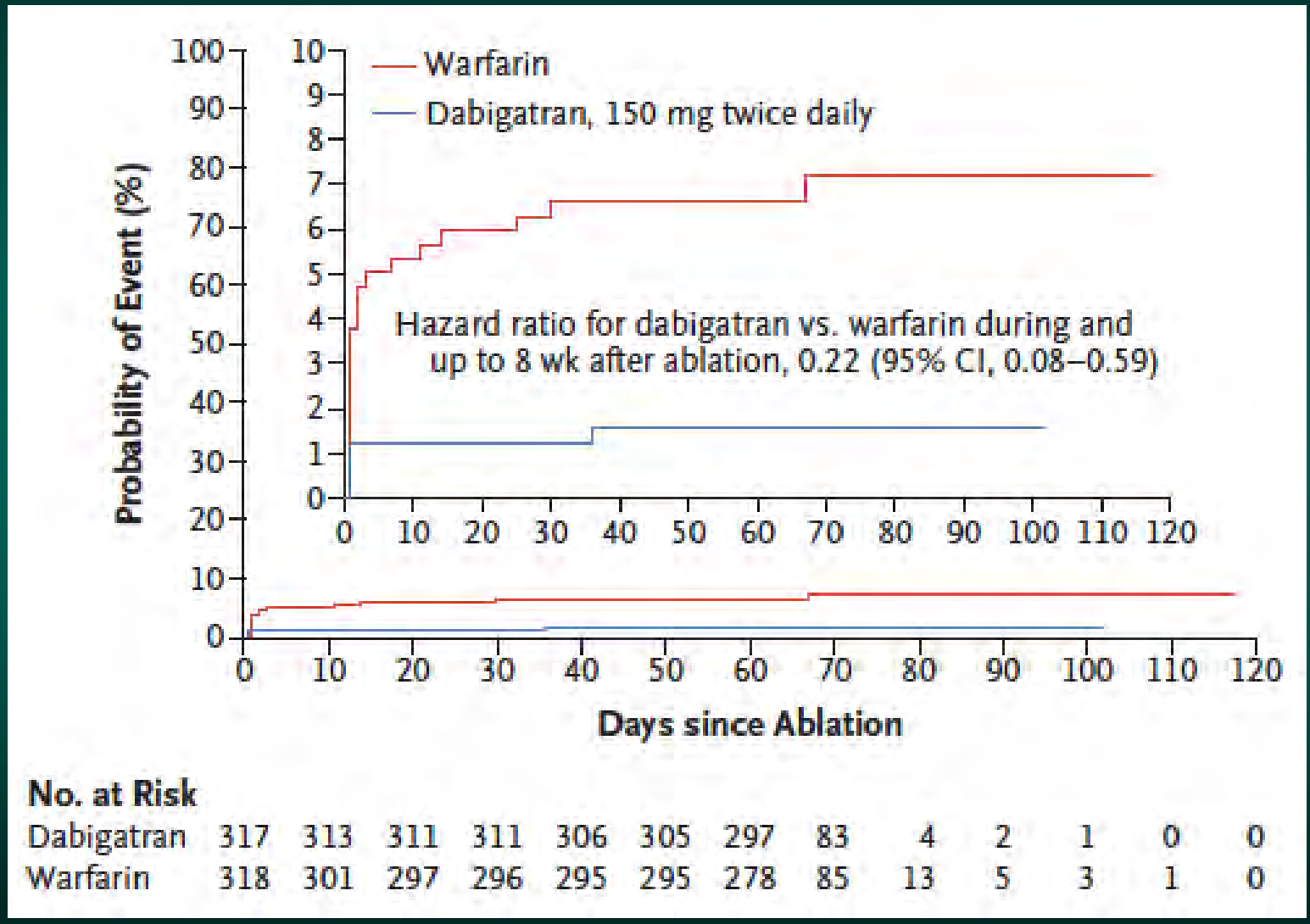
Dabigatran in AF ablation

Table 1. Baseline Demographic and Clinical Characteristics (Ablation Set).*

Characteristic	Dabigatran, 150 mg twice daily (N=317)	Warfarin (N=318)
Age — yr	59.1±10.4	59.3±10.3
Male sex — no. (%)	230 (72.6)	245 (77.0)
Mean body-mass index†	28.5	28.8
Mean CHA_2DS_2-VASc score‡	2.0	2.2
Activated clotting time		
No. of patients analyzed	312	308
Mean — sec	330	342
Medical history — no. (%)		
Congestive heart failure	31 (9.8)	34 (10.7)
Left ventricular dysfunction	25 (7.9)	23 (7.2)
Coronary artery disease	32 (10.1)	48 (15.1)
Percutaneous coronary intervention	16 (5.0)	19 (6.0)
Previous myocardial infarction	10 (3.2)	15 (4.7)
Hypertension	166 (52.4)	177 (55.7)
Previous stroke	10 (3.2)	9 (2.8)
Previous major bleeding or predisposition	3 (0.9)	4 (1.3)
Previous GI bleeding or gastritis	24 (7.6)	21 (6.6)
Renal disease	7 (2.2)	14 (4.4)
Diabetes mellitus	30 (9.5)	34 (10.7)
Atrial fibrillation — no. (%)		
Paroxysmal	213 (67.2)	219 (68.9)
Persistent	86 (27.1)	81 (25.5)
Long-standing persistent	18 (5.7)	18 (5.7)
Medication use — no. (%)§		
Vitamin K antagonists	95 (28.1)	86 (25.4)
Dabigatran	45 (13.3)	36 (10.7)
Rivaroxaban	29 (8.6)	29 (8.6)
Apixaban	21 (6.2)	30 (8.9)
Edoxaban	3 (0.9)	0
NSAIDs	66 (19.5)	78 (23.1)
Proton-pump inhibitors	73 (21.6)	79 (23.4)
Statins	106 (31.4)	101 (29.9)
Beta-blockers	195 (57.7)	204 (60.4)

* Plus–minus values are means ±SD. The ablation set included all randomly assigned patients who had taken at least one dose of trial drug and who had undergone the ablation procedure. GI denotes gastrointestinal, and NSAID nonsteroidal antiinflammatory drug.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ The CHA_2DS_2-VASc score reflects the risk of stroke among patients with atrial fibrillation. Scores range from 0 to 9, with higher scores indicating greater risk.
§ Values are for the treated set (338 patients in each group).

Dabigatran in AF ablation



Dabigatran in AF ablation

Table 2. Adverse Events during the Treatment Period (Treated Set).*

Event	Dabigatran, 150 mg twice daily (N=338)	Warfarin (N=338)	Total (N=676)
		number (percent)	
Any adverse event	225 (66.6)	242 (71.6)	467 (69.1)
Severe adverse event†	11 (3.3)	21 (6.2)	32 (4.7)
Adverse event leading to treatment discontinuation	19 (5.6)	8 (2.4)	27 (4.0)
Serious adverse event	63 (18.6)	75 (22.2)	138 (20.4)
Fatal adverse event	0	0	0
Immediately life-threatening event	1 (0.3)	2 (0.6)	3 (0.4)
Event that resulted in clinically significant or persistent disability or incapacity	0	1 (0.3)	1 (0.1)
Event that required hospitalization	26 (7.7)	34 (10.1)	60 (8.9)
Event that prolonged hospitalization	13 (3.8)	22 (6.5)	35 (5.2)
Other‡	29 (8.6)	27 (8.0)	56 (8.3)

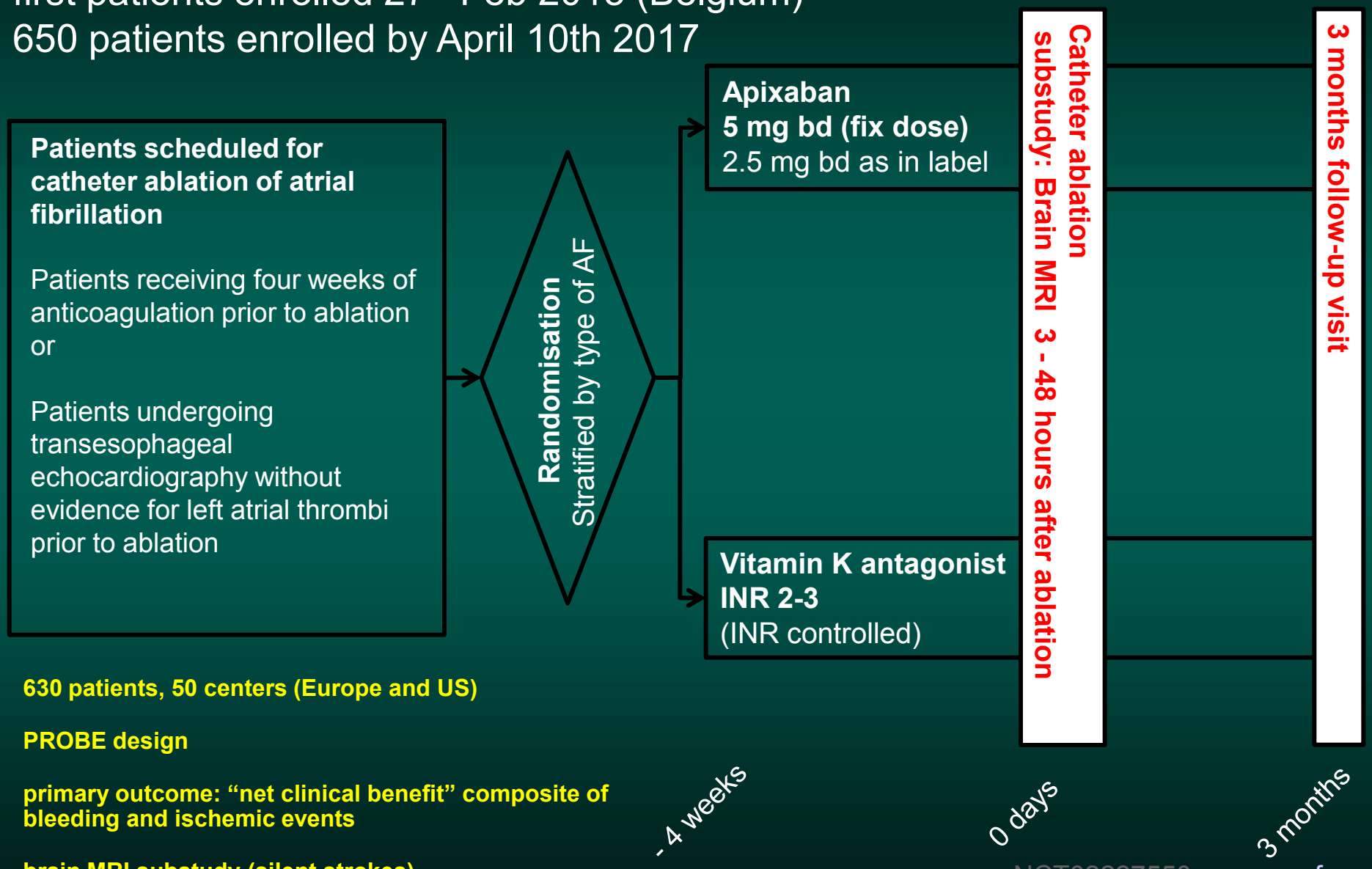
* The treated set included all randomly assigned patients who had taken at least one dose of trial drug. A patient may be counted as having an event that fulfills more than one seriousness criterion. Percentages were calculated with the total number of patients per treatment as the denominator.

† A severe adverse event was defined as an event that is incapacitating or causes an inability to work or perform usual activities.

‡ The "other" category included events deemed to be serious by the investigator in that they were important medical events that, after appropriate medical judgment, may have required medical or surgical intervention to prevent any of the outcomes mentioned previously.

AXAFA – AFNET 5 Study Design

first patients enrolled 27th Feb 2015 (Belgium)
650 patients enrolled by April 10th 2017



630 patients, 50 centers (Europe and US)

PROBE design

primary outcome: "net clinical benefit" composite of bleeding and ischemic events

brain MRI substudy (silent strokes)

NCT02227550. www.axafa.eu

NAOCs work in cardioversion (TEE / non-TEE) and catheter ablation

trials are not powered
not alle subgroups are assessed
recipy for use in clinical practice

etc.

Thank you !

Medizinische Klinik II
St. Vincenz-Krankenhaus Paderborn

AXAFA – AFNET 5: primary outcome

Uninterrupted apixaban vs VKA

650 patients, PROBE design, Europe and US

AFNET

primary outcome: composite of all-cause death, stroke, and major bleeding (BARC 2-5)

Selected secondary outcome parameters

- …
- treatment duration prior to ablation and total time on oral anticoagulation
- Brain MRI lesions (substudy)
- change of cognitive function at end of follow-up