EUROPEAN HEART HOUSE

Anti-Thrombotic Therapy – Update 2016

Thursday 23 February – Saturday 25 February, 2017

Course Directors:
Raffaele De Caterina (IT), Erik Grove (DK), Steen D. Kristensen (DK), Marco Zimarino (IT)

Faculty :
Giancarlo Agnelli (IT), Jean-Philippe Collet (FR), Kurt Huber (AU), David J. Moliterno (USA), Franz-Josef Neumann (GE), Giuseppe Patti (IT), Bianca Rocca (IT), Helmut Schühlen (GE), Robert F. Storey (UK)

Thrombosis ESC Working Group

EUROPEAN SOCIETY OF CARDIOLOGY®

WE ARE THE ESC

Peri-cardioversion and peri-ablation anticoagulation

Giuseppe Patti
Campus Bio-Medico University of Rome

Thrombosis ESC Working Group

EUROPEAN SOCIETY OF CARDIOLOGY®

What 2016 ESC guidelines recommend

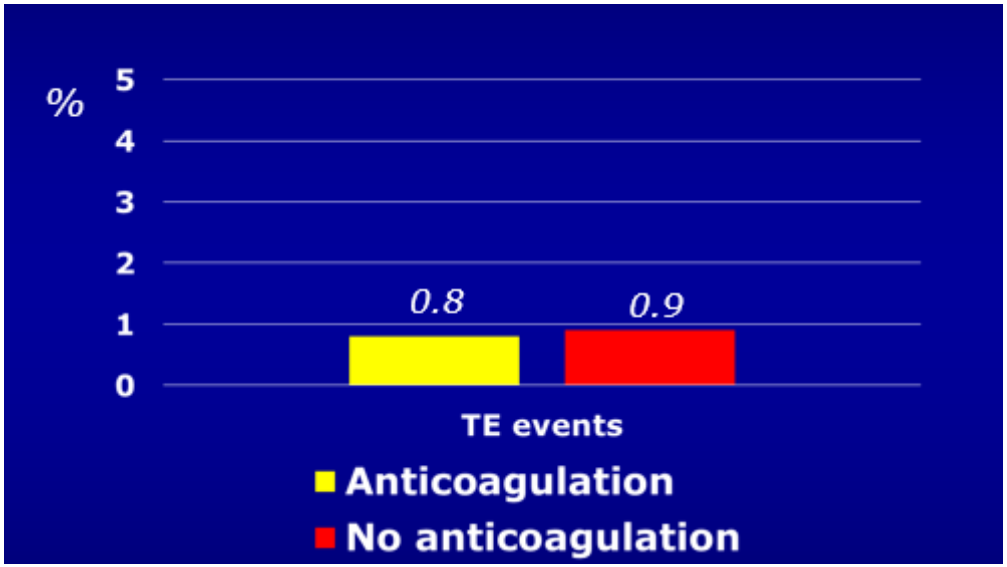
Causes of TE events after cardioversion
1 Preexisting LA thrombosis
2 Atrial stunning causing thrombus formation

30-day incidence of TE events after cardioversion:
- **4-6% without anticoagulation**
- **<1% with anticoagulation**

Patients who have been in AF for longer than 48 h should start OAC at least 3 weeks before cardioversion and continue it for 4 weeks afterwards (in patients without a need for long-term anticoagulation). OAC should be continued indefinitely in patients at risk of stroke. This practice has never been evaluated in controlled trials, but seemed safe in a large observational data set from Finland.[647] When early cardioversion is desired, TOE can exclude the majority of left atrial thrombi, allowing immediate cardioversion.[648,649]

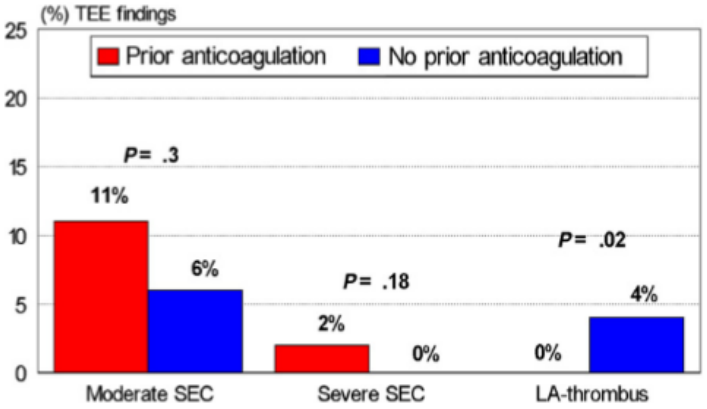
…. Irrespective of CHADS-VASC score

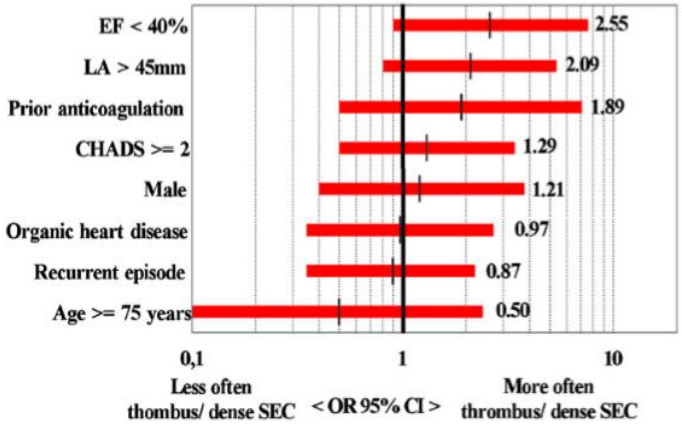
CV and thromboembolic risk in 357 patients with AF duration <48 hrs



Patti G et al. Eur Heart J 2016; Weigner MJ et al. Ann Int Med 1997

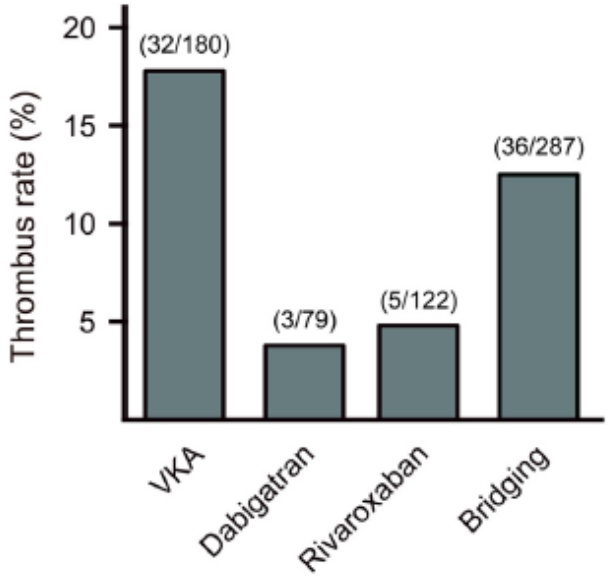
Left atrial thrombosis and dense spontaneous Echo contrast by TEE in patients with <48 hrs atrial fibrillation (N=366)





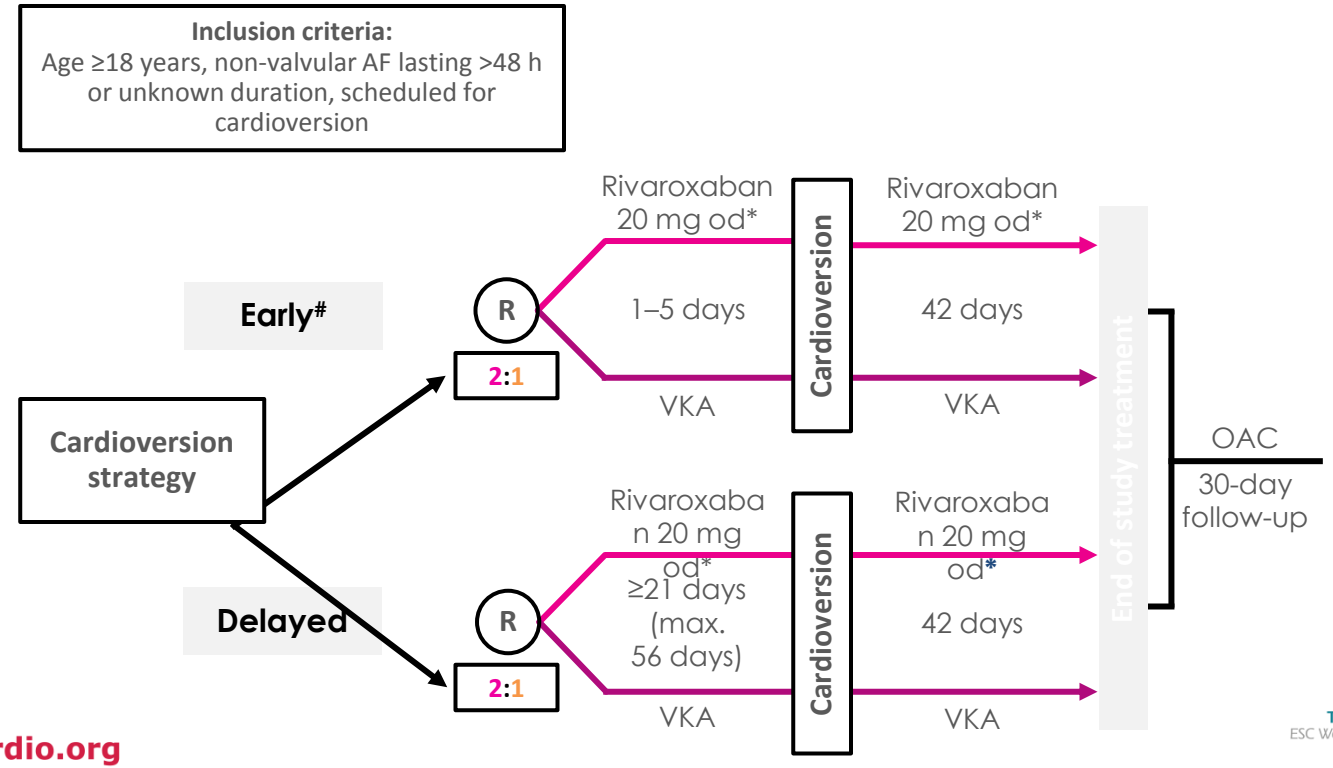
Kleeman T et al. J Am Soc Echocardiography 2009

Prevalence of intracardiac thrombi by TEE in 643 AF patients receiving different anticoagulation regimens and undergoing cardioversion (CHA_2DS_2-VASc score 4, INR ≥2, NOACs for 3 wks)



Zylla MM et al. Am J Cardiol 2015

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

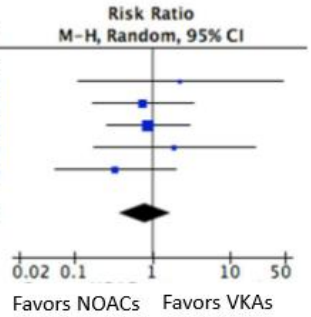


NOACs vs warfarin in AF patients undergoing cardioversion
Meta-analysis from 6CRTs (N=6,148)

STROKE/SE

Study or Subgroup	NOACs Events	NOACs Total	WARFARIN Events	WARFARIN Total	Weight	Risk Ratio M-H, Random, 95% CI
ARISTOTLE	0	331	0	412		Not estimable
ENGAGE-AF	2	251	0	114	6.4%	2.28 [0.11, 47.15]
ENSURE-AF	3	1095	4	1104	26.1%	0.76 [0.17, 3.37]
RE-LY	7	1319	4	664	38.9%	0.88 [0.26, 3.00]
ROCKET-AF	2	138	1	132	10.2%	1.91 [0.18, 20.85]
X-VeRT	2	1002	3	502	18.3%	0.33 [0.06, 1.99]
Total (95% CI)		**4136**		**2928**	**100.0%**	**0.82 [0.38, 1.75]**
Total events	16		12			

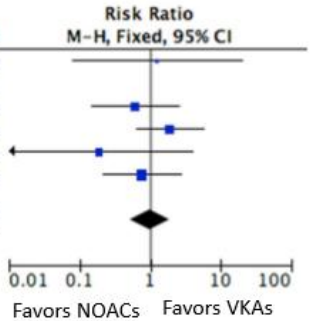
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.92$, df = 4 (P = 0.75); $I^2 = 0\%$
Test for overall effect: Z = 0.52 (P = 0.60)



MAJOR BLEEDING

Study or Subgroup	NOACs Events	NOACs Total	VKAs Events	VKAs Total	Weight	Risk Ratio M-H, Fixed, 95% CI
ARISTOTLE	1	331	1	412	4.7%	1.24 [0.08, 19.82]
ENGAGE-AF	0	251	0	114		Not estimable
ENSURE-AF	3	1067	5	1082	26.1%	0.61 [0.15, 2.54]
RE-LY	15	1319	4	664	27.9%	1.89 [0.63, 5.67]
ROCKET-AF	0	138	2	132	13.4%	0.19 [0.01, 3.95]
X-VeRT	6	988	4	499	27.9%	0.76 [0.21, 2.67]
Total (95% CI)		**4094**		**2903**	**100.0%**	**0.98 [0.51, 1.87]**
Total events	25		16			

Heterogeneity: $Chi^2 = 3.10$, df = 4 (P = 0.54); $I^2 = 0\%$
Test for overall effect: Z = 0.06 (P = 0.95)

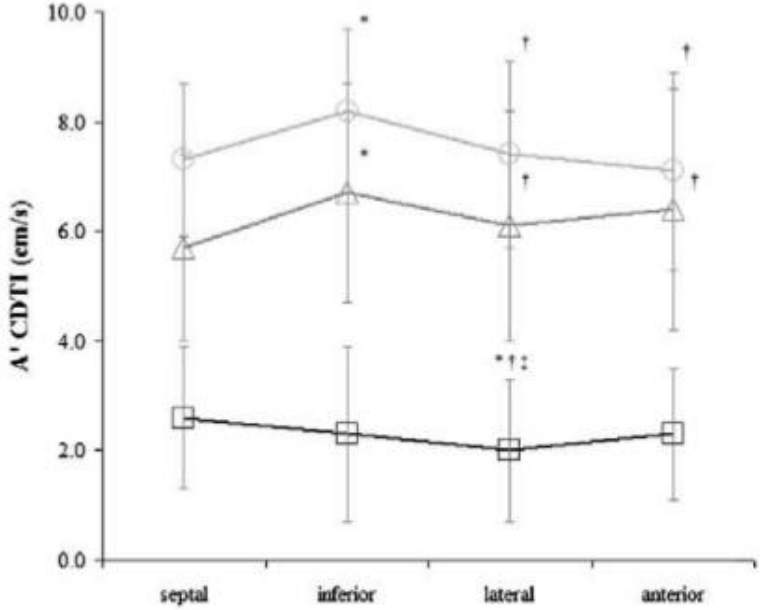


Renda G et al. Am J Med 2016

Potential benefits of NOACs vs warfarin in the setting of cardioversion

- Rapid onset of action (2-4h), short half-life and predictable pharmacokinetics and pharmacodynamics allow a more rapid cardioversion strategy
- Low number of patients failing to achieve adequate anticoagulation pre-cardioversion (no delay)
- Safety
- Reduce costs

Regional atrial contraction by color Doppler tissue imaging in controls and 6-mo after cardioversion or RF ablation



Controls

Cardioversion

Ablation

Boyd AC et al. Am J Cardiol 2009

General recommendations (ESC)

- **All patients undergoing AF catheter ablation should be anticoagulated with a NOAC or a VKA (INR 2-3) for 3 weeks prior to the procedure and up to 8 wks**

- **TEE can be useful before the procedure to rule out LA thrombi**

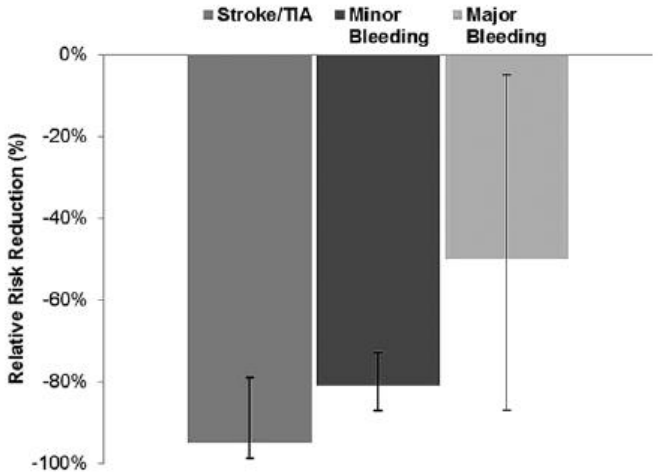
- **In patients with atrial flutter and undergoing right-sided ablation, therapy with VKA or NOAC should not be interrupted and continued for ≥ 4 wks**

- **No need for anticoagulation for left atrial ablation of an accessory pathway or right atrial ablations (excluding atrial flutter) or right ventricular tachicardia ablation**

Interrupped vs uninterrupted warfarin in AF patients undergoing RF ablation

The randomized COMPARE study N=1,584)

Risk reduction in favour of uninterrupted



Di Biase L et al. Circulation 2014

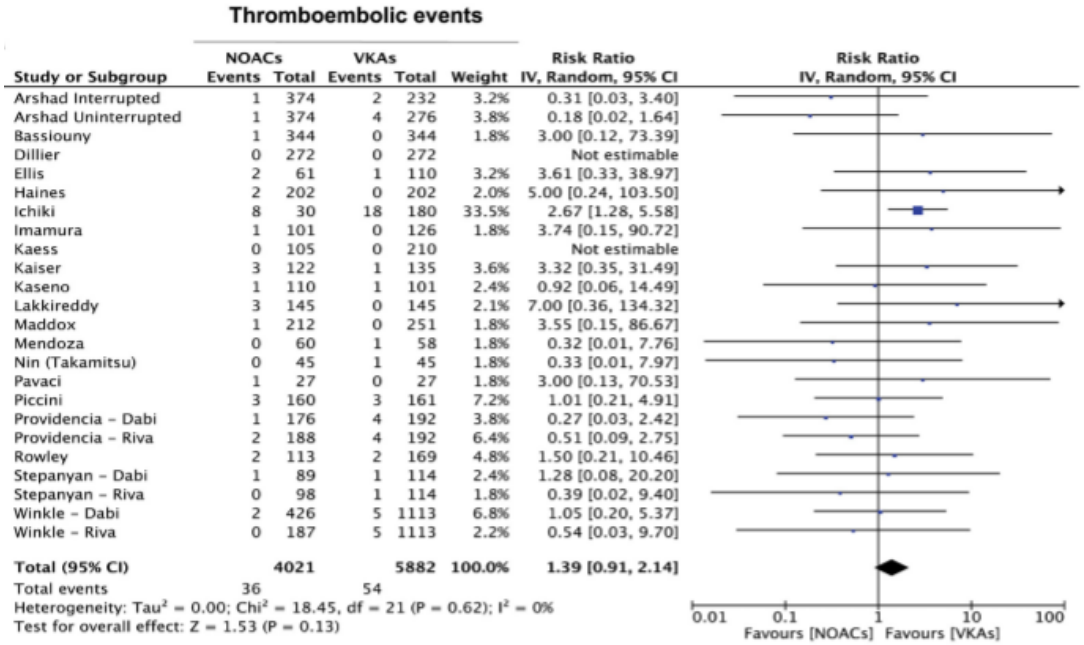
Procedural recommendations (ESC):

- **During the ablation, IV heparin should be administered to achieve an ACT of 300–350s**

- **It seems reasonable to use the same target ACT levels for heparin titration in NOAC-treated patients**

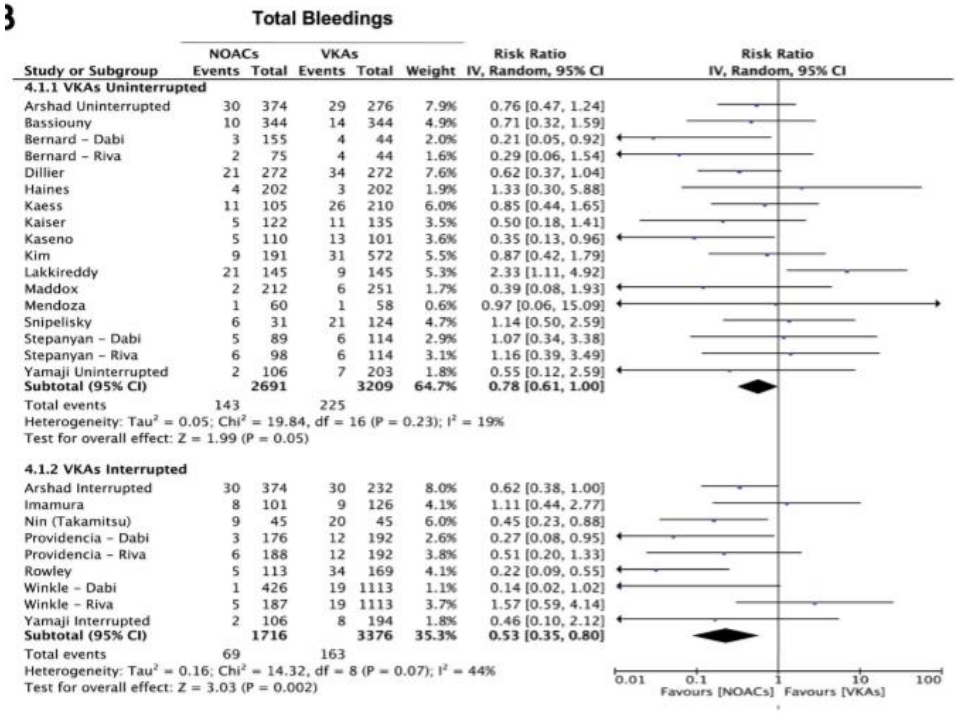
- **Especially with Dabigatran it has been noted that even in patients in whom the last NOAC dose was given in the morning of the procedure, the total need for heparin was higher and the time to target ACT lasted longer than in uninterrupted VKA patients. This likely reflects a difference in whole blood coagulability rather than a direct interaction between NOACs and the ACT test**

Efficacy and safety of NOACs vs warfarin in patients undergoing Radiofrequency catheter ablation of AF (25 studies; 9,881 pts)



Santarpia G et al. PLOS One 2015

Efficacy and safety of NOACs vs warfarin in patients undergoing Radiofrequency catheter ablation of AF (25 studies; 9,881 pts)



Total Bleedings

Study or Subgroup	NOACs Events	NOACs Total	VKAs Events	VKAs Total	Weight	Risk Ratio IV, Random, 95% CI
4.1.1 VKAs Uninterrupted						
Arshad Uninterrupted	30	374	29	276	7.9%	0.76 [0.47, 1.24]
Bassiouny	10	344	14	344	4.9%	0.71 [0.32, 1.59]
Bernard – Dabi	3	155	4	44	2.0%	0.21 [0.05, 0.92]
Bernard – Riva	2	75	4	44	1.6%	0.29 [0.06, 1.54]
Dillier	21	272	34	272	7.6%	0.62 [0.37, 1.04]
Haines	4	202	3	202	1.9%	1.33 [0.30, 5.88]
Kaess	11	105	26	210	6.0%	0.85 [0.44, 1.65]
Kaiser	5	122	11	135	3.5%	0.50 [0.18, 1.41]
Kaseno	5	110	13	101	3.6%	0.35 [0.13, 0.96]
Kim	9	191	31	572	5.5%	0.87 [0.42, 1.79]
Lakkireddy	21	145	9	145	5.3%	2.33 [1.11, 4.92]
Maddox	2	212	6	251	1.7%	0.39 [0.08, 1.93]
Mendoza	1	60	1	58	0.6%	0.97 [0.06, 15.09]
Snipelisky	6	31	21	124	4.7%	1.14 [0.50, 2.59]
Stepanyan – Dabi	5	89	6	114	2.9%	1.07 [0.34, 3.38]
Stepanyan – Riva	6	98	6	114	3.1%	1.16 [0.39, 3.49]
Yamaji Uninterrupted	2	106	7	203	1.8%	0.55 [0.12, 2.59]
Subtotal (95% CI)		**2691**		**3209**	**64.7%**	**0.78 [0.61, 1.00]**
Total events	143		225			
Heterogeneity: $Tau^2 = 0.05$; $Chi^2 = 19.84$, df = 16 (P = 0.23); $I^2 = 19\%$						
Test for overall effect: Z = 1.99 (P = 0.05)						
4.1.2 VKAs Interrupted						
Arshad Interrupted	30	374	30	232	8.0%	0.62 [0.38, 1.00]
Imamura	8	101	9	126	4.1%	1.11 [0.44, 2.77]
Nin (Takamitsu)	9	45	20	45	6.0%	0.45 [0.23, 0.88]
Providencia – Dabi	3	176	12	192	2.6%	0.27 [0.08, 0.95]
Providencia – Riva	6	188	12	192	3.8%	0.51 [0.20, 1.33]
Rowley	5	113	34	169	4.1%	0.22 [0.09, 0.55]
Winkle – Dabi	1	426	19	1113	1.1%	0.14 [0.02, 1.02]
Winkle – Riva	5	187	19	1113	3.7%	1.57 [0.59, 4.14]
Yamaji Interrupted	2	106	8	194	1.8%	0.46 [0.10, 2.12]
Subtotal (95% CI)		**1716**		**3376**	**35.3%**	**0.53 [0.35, 0.80]**
Total events	69		163			
Heterogeneity: $Tau^2 = 0.16$; $Chi^2 = 14.32$, df = 8 (P = 0.07); $I^2 = 44\%$						
Test for overall effect: Z = 3.03 (P = 0.002)						

Risk Ratio IV, Random, 95% CI

0.01 0.1 1 10 100

Favours [NOACs] Favours [VKAs]

Santarpia G et al. PLOS One 2015

❖ **The majority of studies are single-center registries, case-controlled series or post-hoc analyses of prospective studies**

❖ **Available studies enrolled patients populations with different risk profiles**

❖ **No long-term follow-up are available**

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
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)[a]	0	2	2
Ischaemic stroke	0	1	1
Vascular death	0	1	1
	n=114	n=107	N=221
Any other procedure-attributable event[c]	5	5	10
Pericardial effusion without tamponade	0	1	1

Cappato R et al. Eur Heart J 2015

Factors to consider for the timing of last NOAC intake:

- **Kidney function**

- **CHA_2DS_2-VASc score**

- **Experience of the operator**

- **TEE in case of last NOAC intake ≥36 h before the intervention or doubtful adherence to correct NOAC intake in the weeks before ablation**

Restart NOAC 4 hours after sheat removal, if complete haemostasis is achieved and there is no pericardial effusion

Prevention of early bleeding/entry-site complications

- Availability of imaging support to guide transseptal puncture

- Repeated ACT measurements during the procedure (even for ischemic events)

- Vein closure by suture compression after crio-ablation

- No data are available supporting higher safety of coagulation test-guided timing of the procedure

NOACs vs warfarin in AF patients undergoing cardioversion

X-VERT study – Eur Heart J 2014

Sample size and statistical analysis

Assuming the risk for thromboembolic events within 30 days after cardioversion in patients assigned to a VKA is 1%, we estimated that between 25 000 and 30 000 patients would be required to establish that rivaroxaban is non-inferior to VKA at a non-inferiority margin of 1.5 with 90% power and a 2:1 randomization in favour of rivaroxaban. We concluded that a trial of this size was not feasible. Using the post hoc analysis of car-

Classification of operations according to bleeding risk

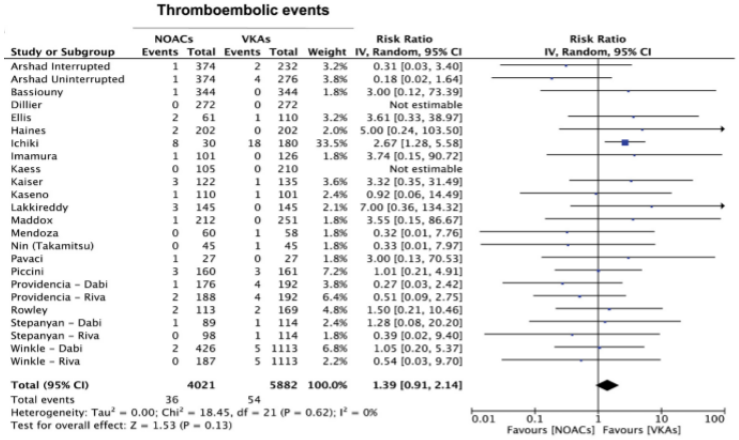
- Interventions not necessarily requiring discontinuation of anticoagulation
  - Dental interventions
    - Extraction of one to three teeth
    - Paradontal surgery
    - Incision of abscess
    - Implant positioning
  - Ophthalmology
    - Cataract or glaucoma intervention
  - Endoscopy without surgery
  - Superficial surgery (e.g. abscess incision, small dermatologic excisions, etc.)
- Interventions with minor bleeding risk (i.e. infrequent or with low clinical impact)
  - Endoscopy with biopsy
  - Prostate or bladder biopsy
  - Electrophysiological study or catheter ablation for right-sided supraventricular tachycardia
  - Non-coronary angiography (for coronary angiography and ACS: see 'Patient with atrial fibrillation and coronary artery disease' section)
  - Pacemaker or ICD implantation (unless complex anatomical setting, e.g. congenital heart disease)
- Interventions with major bleeding risk (i.e. frequent and/or with high impact)
  - Catheter ablation of simple left-sided supraventricular tachycardia (e.g. WPW)
  - Spinal or epidural anaesthesia; lumbar diagnostic puncture
  - Thoracic surgery
  - Abdominal surgery
  - Major orthopaedic surgery
  - Liver biopsy
  - Transurethral prostate resection
  - Kidney biopsy
  - Extracorporeal shockwave lithotripsy (ESWL)
- Interventions with major bleeding risk AND increased thrombo-embolic risk[a]
  - Complex left-sided ablation (PVI; some VT ablations)

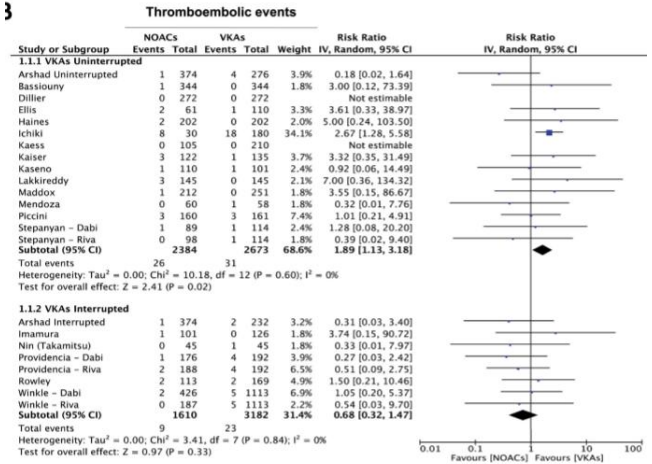
Last NOAC intake before operation

	Dabigatran		Apixaban–edoxaban–rivaroxaban	
	No important bleeding risk and/or adequate local haemostasis possible: perform at trough level (i.e. ≥12 or 24 h after last intake)			
	Low risk	High risk	Low risk	High risk
CrCl ≥ 80 mL/min	≥24 h	≥48 h	≥24 h	≥48 h
CrCl 50–80 mL/min	**≥36 h**	**≥72 h**	≥24 h	≥48 h
CrCl 30–50 mL/min[a]	**≥48 h**	**≥96 h**	≥24 h	≥48 h
CrCl 15–30 mL/min[a]	Not indicated	Not indicated	**≥36 h**	**≥48 h**
CrCl < 15 mL/min	No official indication for use			
There is no need for bridging with LMWH/UFH				

Restart NOAC 4 hours after sheat removal, if complete haemostasis is achieved and there is no pericardial effusion. OAC is continued for 4-12 wks

Efficacy and safety of NOACs vs warfarin in patients undergoing Radiofrequency catheter ablation of AF (25 studies; 9,881 pts)





Santarpia G et al. PLOS One 2015

Thrombosis ESC Working Group

EUROPEAN SOCIETY OF CARDIOLOGY®