Terapia anticoagulante peri-procedurale nei pazienti con fibrillazione atriale sottoposti ad ablazione transcatetere

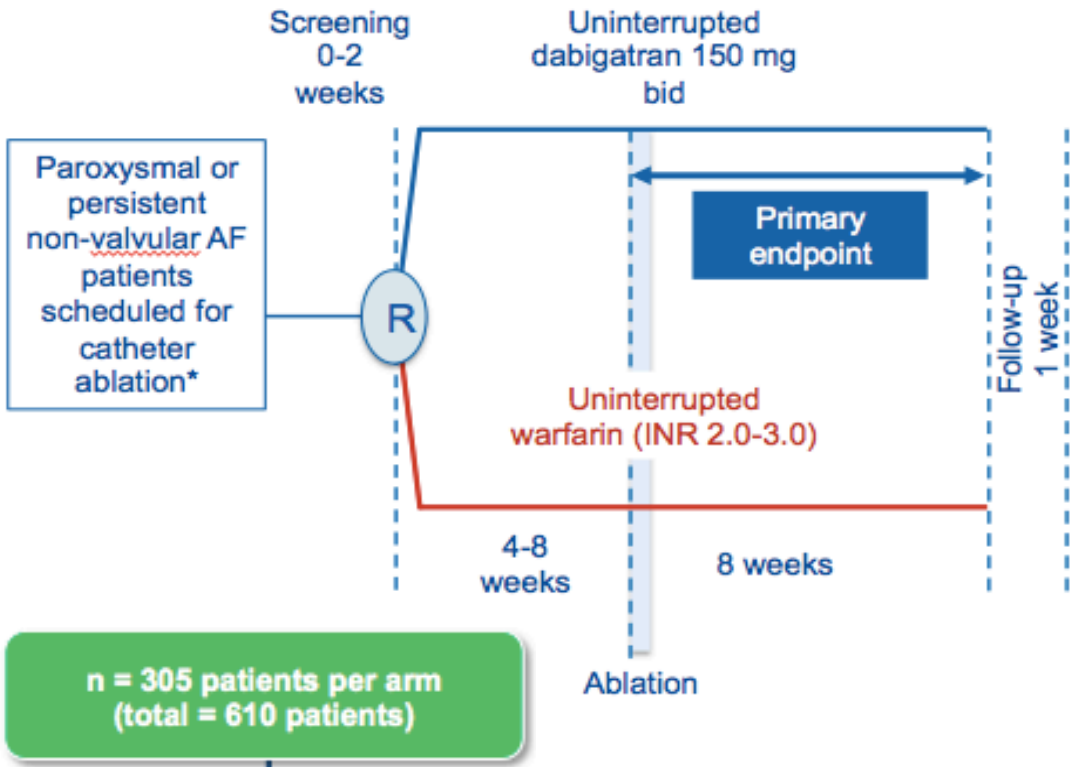
Were Ablation Patients Represented in the NOAC Pivotal Trials?

- RE-LY: The trial design excluded patients with a planned ablation.
- ROCKET AF: 88 patients had ablations during the study; 321 patients were enrolled who had a history of prior ablation.
- ARISTOTLE: The trial design excluded patients with a planned ablation.
- ENGAGE-AF: The trial design excluded patients with a planned electrical or surgical intervention that eliminates anticoagulant use if successful.

RE-CIRCUIT™
Study of peri-procedural anticoagulation in AF ablation

Randomized Evaluation of dabigatran etexilate Compared to warfarIn in pulmonaRy vein ablation: assessment of different peri-proCedUral antIcoagulation sTrategies

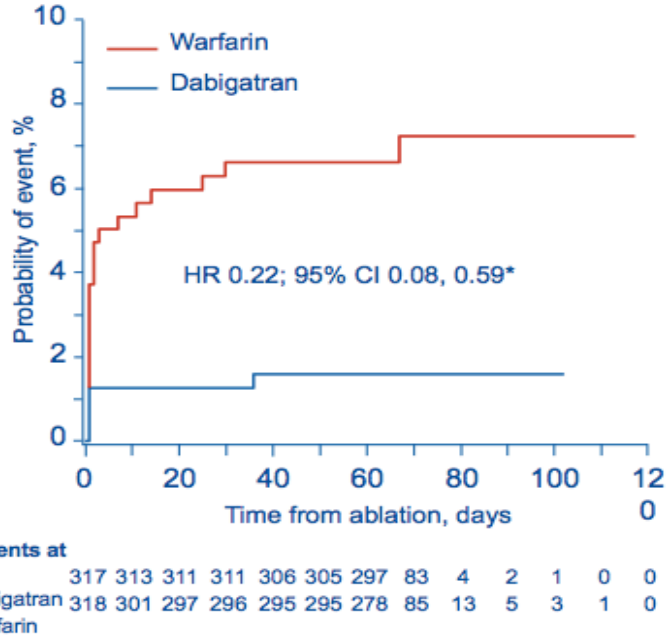
Study Design



- **Primary endpoint:** incidence of adjudicated ISTH MBEs from venous access up to 8 weeks post-ablation†
- **Secondary endpoints** included adjudicated thromboembolic events from venous access to 8 weeks post-ablation†

*And eligible for dabigatran 150 mg bid according to local prescribing information.
†Primary end point assessed from the start of the ablation procedure and up to 8 weeks post-ablation.

Fewer MBEs from the Time of Ablation



Patients at risk													
Dabigatran	317	313	311	311	306	305	297	83	4	2	1	0	0
Warfarin	318	301	297	296	295	295	278	85	13	5	3	1	0

*Cox proportional hazard model and Wald confidence limits.

Results: Secondary Endpoints

Low Rate of Thromboembolic Events

- Stroke: no events
- Systemic embolism: no events
- Transient ischemic attack: dabigatran 0 vs warfarin 1

Minor Bleeding Events Similar Between Treatments

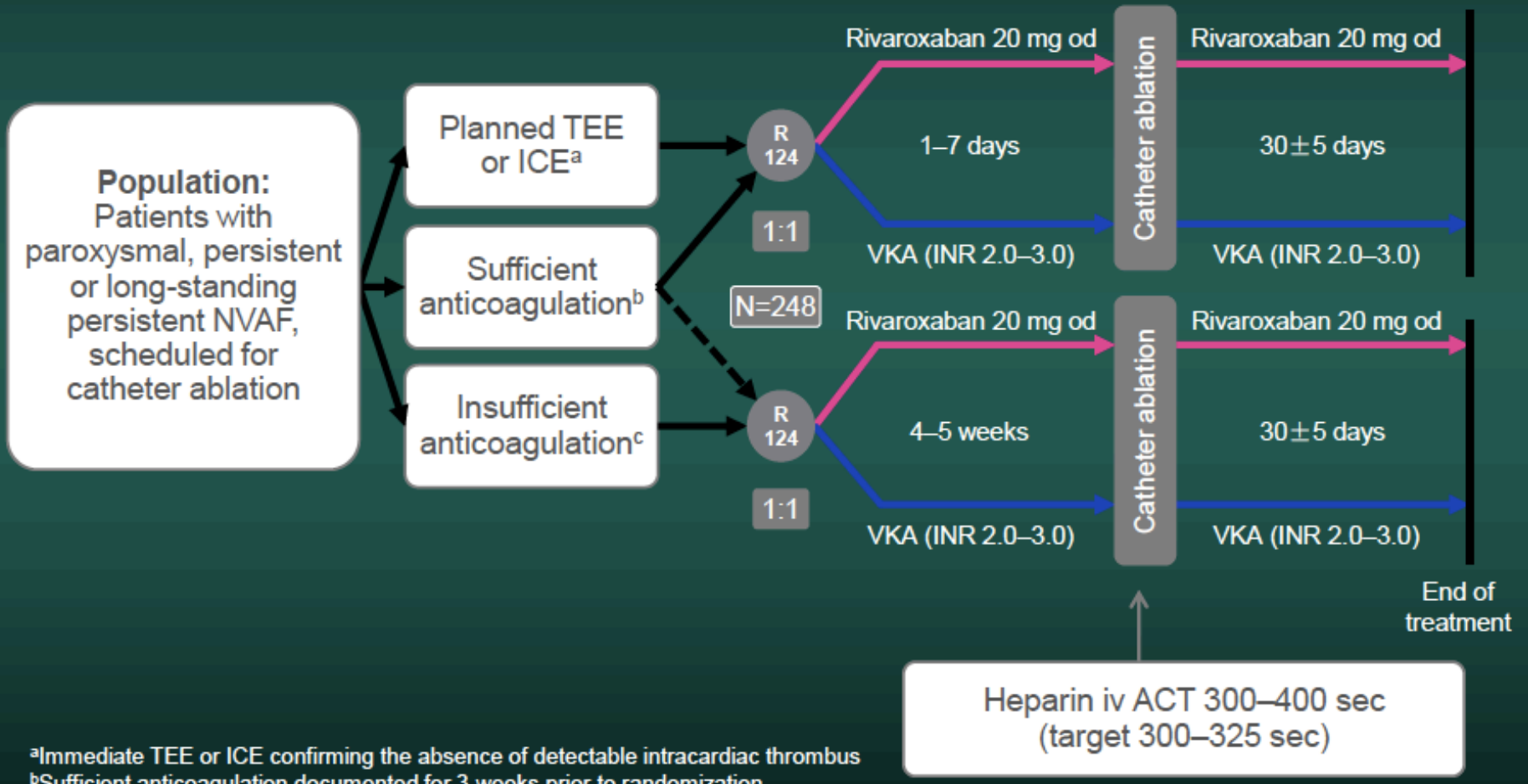
- Dabigatran 59 (18.6%) vs warfarin 54 (17.0%)

Summary

- Performance of AF ablation on uninterrupted dabigatran showed a significantly lower rate of major bleeding compared with performance of AF ablation on uninterrupted warfarin
- Adjudicated major bleeds occurred in five dabigatran treated patients as compared with 22 warfarin-treated patients resulting in an absolute reduction in bleeding risk difference of 5.3% and a relative risk reduction of 77%
- There were no thromboembolic events in either group and one TIA in a patient on warfarin.
- The rates of minor bleeding events were similar in the two groups.
- There were no deaths.

- In conclusion, the results of the RE-CIRCUIT study demonstrate that performance of AF ablation on uninterrupted dabigatran is a better anticoagulation strategy
as compared with performance of AF ablation on uninterrupted warfarin
- The availability of the specific reversal agent idarucizumab, while not needed in any patient in this trial, further supports the adoption of uninterrupted dabigatran as the preferred anticoagulation strategy over uninterrupted warfarin in patients undergoing AF ablation

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

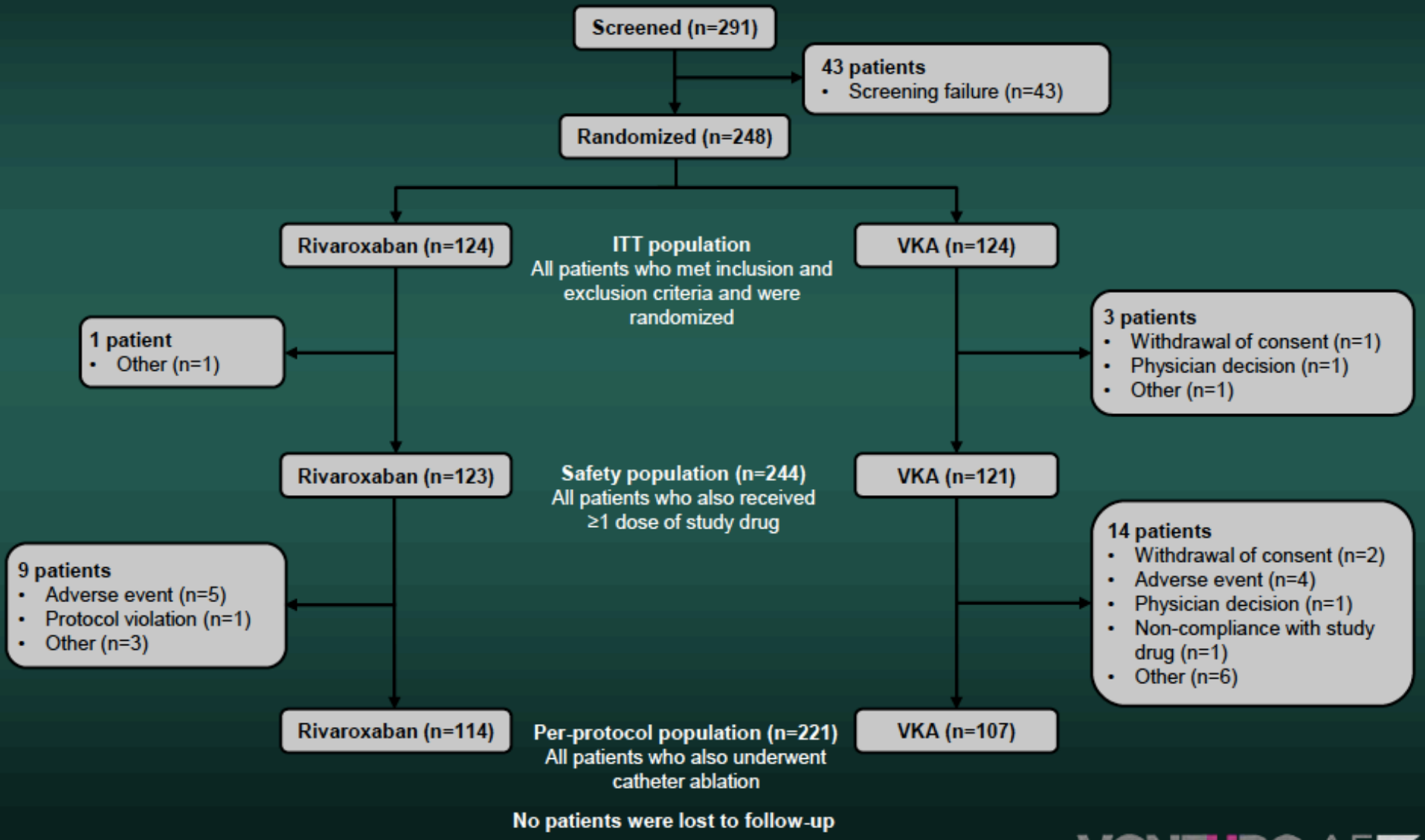


[a]Immediate TEE or ICE confirming the absence of detectable intracardiac thrombus
[b]Sufficient anticoagulation documented for 3 weeks prior to randomization
[c]These patients were randomized to receive study drug for 4-5 weeks prior to the procedure
Please refer to the slide notes for the full details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

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

VENTURE AF

VENTURE AF: Patient Flow



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

VENTURE AF

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

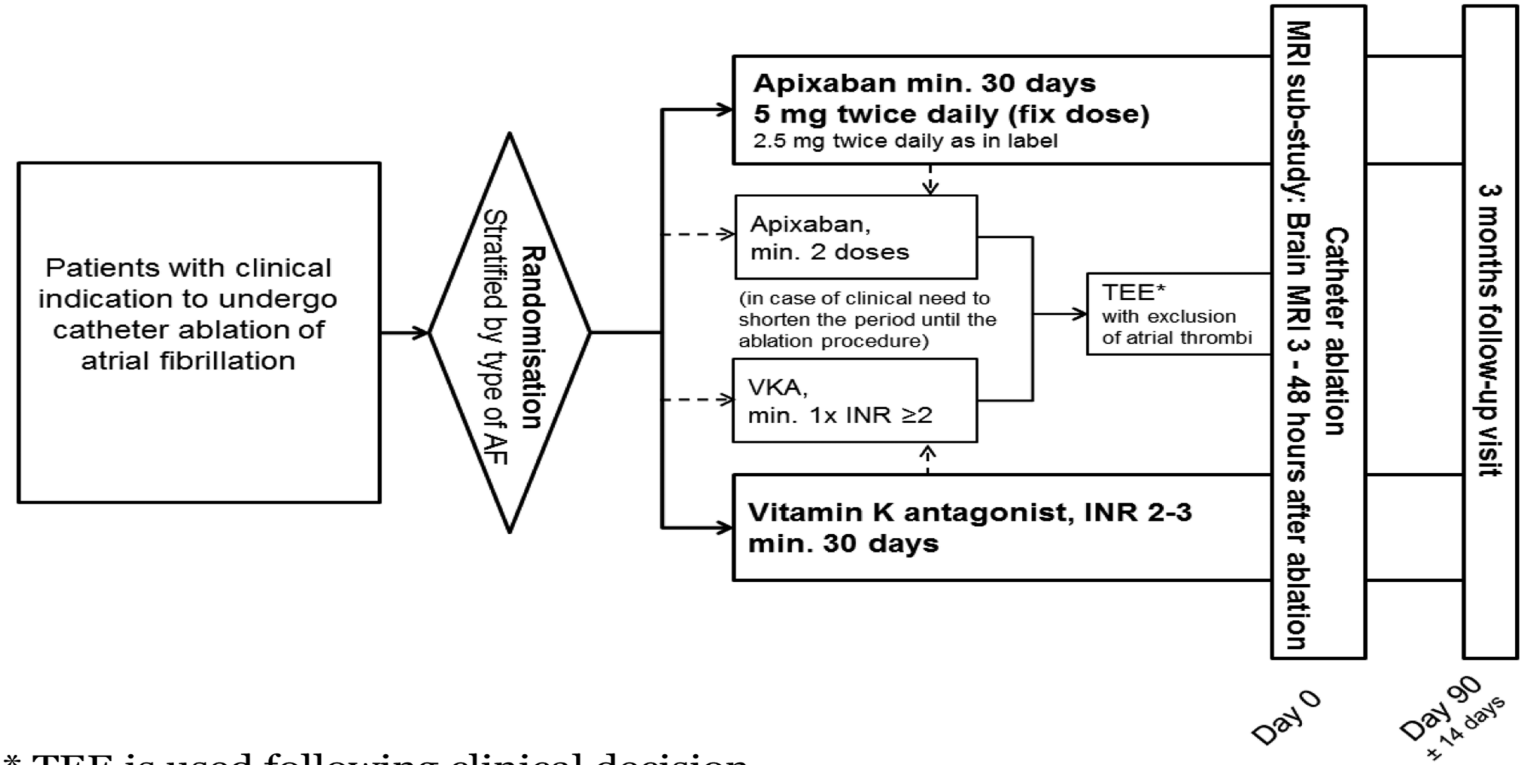
*safety population; #ITT population; †per-protocol population

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]

Rationale and design of AXAFA-AFNET 5:

an investigator-initiated, randomized, open, blinded outcome assessment, multi-centre trial to comparing continuous apixaban to VKA in patients undergoing AF catheter ablation

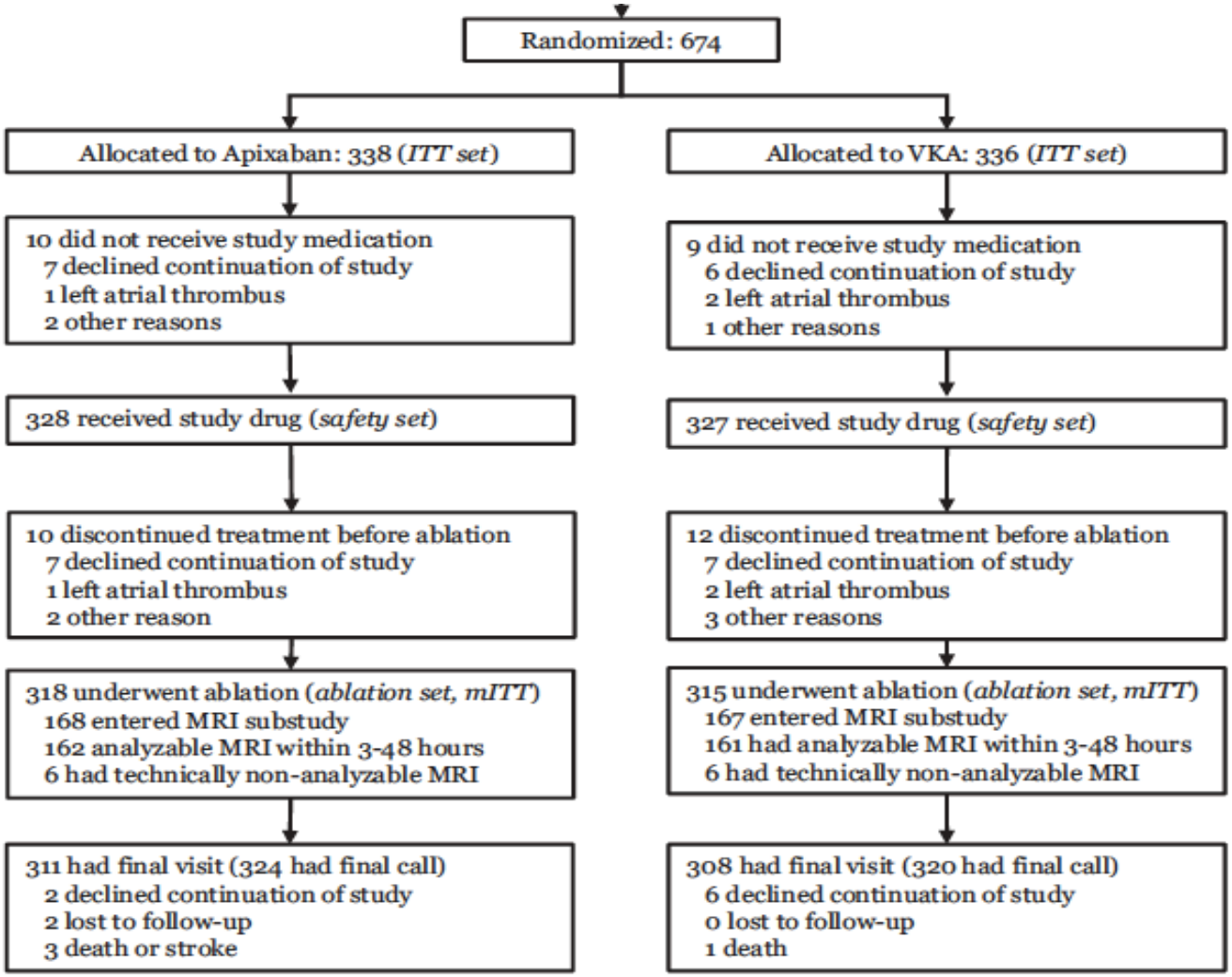


* TEE is used following clinical decision.
Anticoagulation should be effective from randomization until the end of the trial.

Primary outcome: a composite of death, stroke, or bleeding (BARC 2–5)

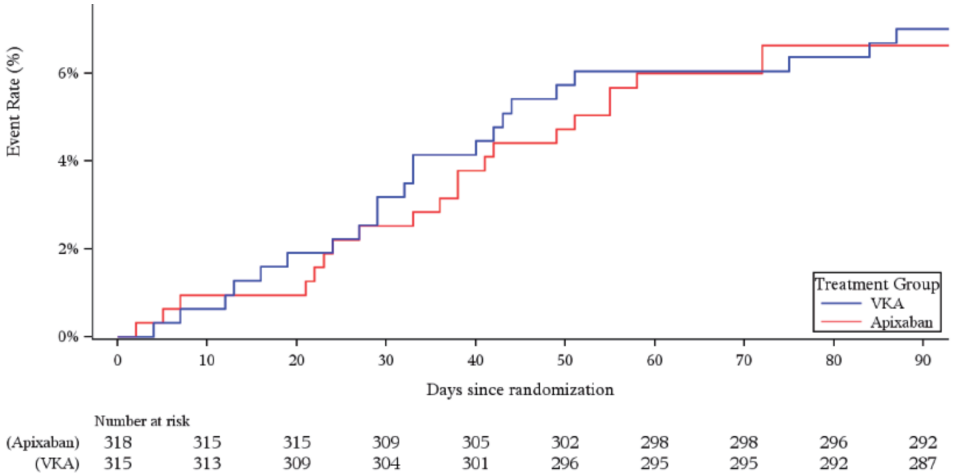
From: Di Biase L et al. Rationale and design of AXAFA-AFNET 5: an investigator-initiated, randomized, open, blinded outcome assessment, multi-centre trial to comparing continuous apixaban to vitamin K antagonists in patients undergoing atrial fibrillation catheter ablation. Europace. 2016;19(1):132-138. doi:10.1093/europace/euw368

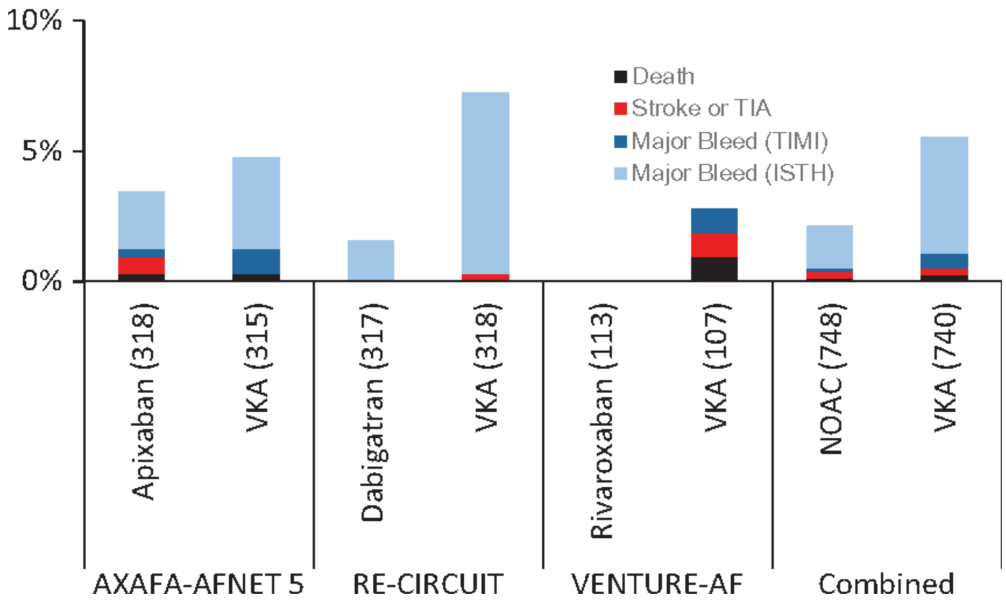
Diagram of the AXAFA – AFNET 5 study



From: Kirchhof P et al., Apixaban in patients at risk of stroke undergoing atrial fibrillation ablation. Eur Heart J. 2018;39(32):2942-2955. doi:10.1093/eurheartj/ehy176

Cumulative outcome events in AXAFA – AFNET 5 in patients undergoing AF ablation at risk of stroke and comparison to event rates in the two other controlled trials comparing continuous NOAC therapy with continuous VKA therapy.





From: Kirchhof P et al., Apixaban in patients at risk of stroke undergoing atrial fibrillation ablation. Eur Heart J. 2018;39(32):2942-2955. doi:10.1093/eurheartj/ehy176

Overview of major bleeding and thromboembolic events in large randomized controlled trials comparing periprocedural NOAC and VKA in patients undergoing catheter ablation of AF

Trial	BARC 3–5 bleedings	ISTH major bleeding	Thrombo-embolic events
RE-CIRCUIT [5] – VKA, N = 318	NA	6.9%	0.3%
RE-CIRCUIT [5] – uninterrupted dabigatran, *N* = 317	NA	1.6%*	0.0%
VENTURE-AF [6] – VKA, *N* = 124	NA	0.8%	0.8%
VENTURE-AF [6] – uninterrupted rivaroxaban, N = 124	NA	0.0%	0.0%
AXAFA [12] – VKA, *N* = 315	4.1%	4.4%	0.0%
AXAFA [12] – uninterrupted apixaban, *N* = 318	2.5%	3.1%	0.6%
ABRIDGE-J [13] – VKA, *N* = 222	NA	5.0%	0.5%
ABRIDGE-J [13] – interrupted dabigatran, *N* = 220	NA	1.4%*	0.0%
AEIOU [21] – uninterrupted apixaban, *N* = 150	1.3%	NA	0.7%
AEIOU [21] – interrupted apixaban, *N* = 145	2.1%	NA	0.7%

*Statistically significant difference in comparison to the VKA group. BARC = Bleeding Academic Research Consortium, ISTH = International Society on Thrombosis and Haemostasis, NA = not available, NOAC = novel oral anticoagulant, TIA = transient ischemic attack, VKA = vitamin K antagonist

De Heide J, J Interv Card Electrophysiol 2018

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https://doi.org/10.1007/s10840-018-0417-0

Minimally interrupted novel oral anticoagulant versus uninterrupted vitamin K antagonist during atrial fibrillation ablation

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Purpose: to compare rates of bleeding and thromboembolic events between minimally interrupted novel oral anticoagulants (NOAC) and uninterrupted vitamin K antagonist (VKA) in patients undergoing atrial fibrillation (AF) ablation.

Methods:

- **Retrospective single-center cohort study** of consecutive patients who underwent AF catheter ablation between January 2013 and April 2017.
- Endpoints included **major bleeding, clinically relevant non-major bleeding and systemic thromboembolic event from the time of ablation through 30 days**. Bleeding events were defined by the Bleeding Academic Research Consortium (BARC) and International Society on Thrombosis and Haemostasis (ISTH).
- A total of **637 patients** were included in the analysis, **520 patients used uninterrupted VKA** and **117 patients minimally interrupted NOAC** (dabigatran: n=68; apixaban: n=30; rivaroxaban: n=14; edoxaban: n=5).

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Table 1 Baseline characteristics

Characteristic	Uninterrupted VKA $N = 520$	Interrupted NOAC $N = 117$	*P*-value
Age (years), mean ± SD	60 ± 10	60 ± 9	0.55
Male sex, n (%)	354 (68)	84 (72)	0.43
Atrial fibrillation, n (%):			0.048
Paroxysmal	392 (76)	86 (74)	
Persistent	116 (22)	24 (20)	
Long-standing persistent	10 (2)	7 (6)	
Hypertension	217 (42)	44 (38)	0.41
Diabetes mellitus	52 (10)	5 (4)	0.05
Coronary artery disease	62 (12)	7 (6)	0.06
Congestive heart failure	20 (4)	2 (2)	0.25
Left ventricular dysfunction	18 (3)	5 (4)	0.58
LA diameter (mm), mean ± SD	42 ± 6	43 ± 7	0.56
CHA_2DS_2-VASc score ≥ 2, n (%)	245 (47)	40 (34)	0.02
HAS-BLED score ≥ 3, n (%)	31 (6)	4 (3)	0.30
Body mass index, mean ± SD (kg/m^2)	27.7 ± 4.1	27.2 ± 3.3	0.23
Technique of catheter ablation, n (%):			0.09
Cryoballoon	100 (19)	33 (28)	
Radiofrequency	402 (78)	83 (71)	
Laser	18 (3)	1 (1)	

LA = left atrium, NOAC = novel oral anticoagulant, VKA = vitamin K antagonist

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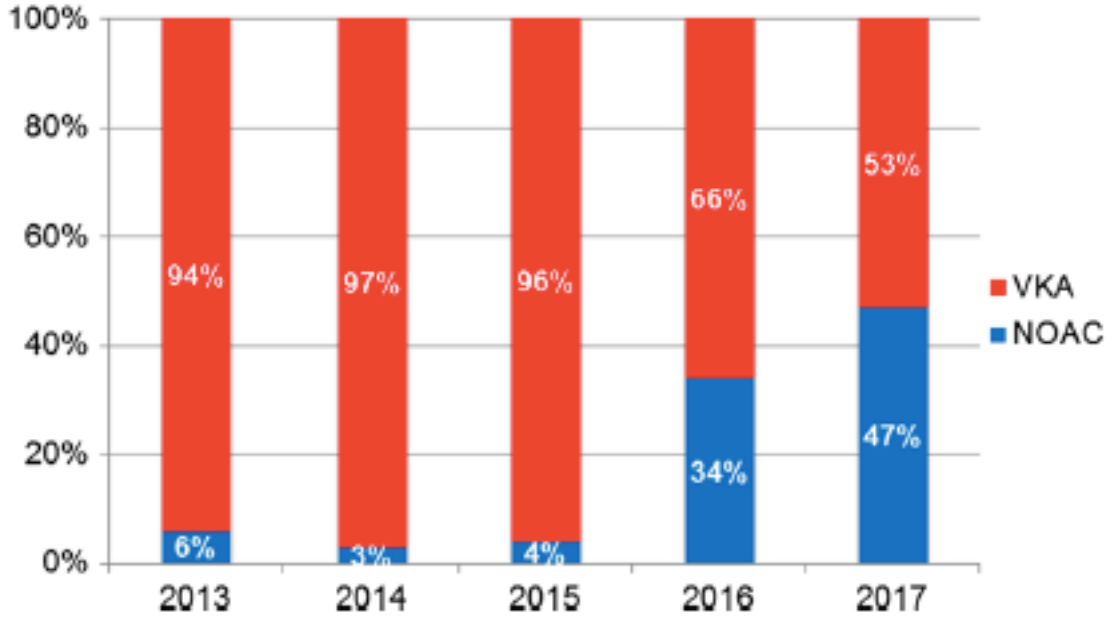

Fig. 1 Proportion of periprocedural NOAC and VKA use over the years

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Table 2 Primary and secondary end points

	Uninterrupted VKA N = 520	Interrupted NOAC N = 117	*P*-value
Primary bleeding endpoints			
BARC 3–5 bleeding, n (%)	22 (4.2)	4 (3.4)	0.70
ISTH major bleeding, n (%)	45 (8.7)	7 (6.0)	0.34
Secondary bleeding endpoints			
Bleeding requiring medical attention that does not fit the criteria for types 3–5 (BARC 2), n (%)	43 (8.3)	3 (2.6)	0.03
Bleeding with hemoglobin drop of 30 to < 50 g/L or requiring transfusion (BARC 3a), n (%)	10 (1.9)	3 (2.6)	0.72
Bleeding with hemoglobin drop of ≥ 50 g/L, or requiring surgery or iv vasoactive agents, or cardiac tamponade (BARC 3b), n (%)	12 (2.3)	1 (0.9)	0.48
BARC 2–5 bleeding, n (%)	65 (12.5)	7 (6.0)	0.04
CRNMB, n (%)	20 (3.8)	–	0.03
ISTH major bleeding and CRNMB, n (%)	65 (12.5)	7 (6.0)	0.04
Primary thromboembolic endpoint			
Stroke, TIA, or other systemic embolism, n (%)	3 (0.6)	–	1.00

BARC = Bleeding Academic Research Consortium, CRNMB = clinically relevant non-major bleeding, ISTH = International Society on Thrombosis and Haemostasis, NOAC= novel oral anticoagulant, TIA = transient ischemic attack, VKA = vitamin K antagonist

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Conclusions:

- The rate of clinically relevant non-major bleeding was lower in patients with a minimally interrupted NOAC strategy compared with those with an uninterrupted VKA strategy.
- The rates of major bleeding and thromboembolic events were similar between groups.
- **The study reinforces the safety and efficacy of a minimally interrupted NOAC strategy as periprocedural anticoagulant in patients undergoing catheter ablation of AF.**

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