ATRIAL FIBRILLATION
NETWORK

AXAFA – AFNET 5

Hauptergebnis

Apixaban in patients at risk of stroke undergoing atrial fibrillation ablation

Results of the AXAFA – AFNET 5 trial

Anticoagulation using the direct factor **X**a inhibitor apixaban during **A**trial **F**ibrillation catheter **A**blation: Comparison to vitamin K antagonist therapy, NCT02227550

Paulus Kirchhof, Karl Georg Haeusler, Benjamin Blank, Joseph De Bono, David Callans, Arif Elvan, Thomas Fetsch, Isabelle C. Van Gelder, Philip Gentlesk, Massimo Grimaldi, Jim Hansen, Gerhard Hindricks, Hussein R. Al-Khalidi, Tyler Massaro, Lluis Mont, Jens Cosedis Nielsen, Georg Nölker, Jonathan P. Piccini, Tom De Potter, Daniel Scherr, Ulrich Schotten, Sakis Themistoclakis, Derick Todd, Johan Vijgen, Luigi Di Biase

email: p.kirchhof@bham.ac.uk

Main outcomes

Primary outcome:

Composite of death, stroke, or bleeding (BARC 2-5)

The sample size was determined based on a 7.5% absolute non-inferiority margin (1.44 relative margin)

Selected secondary outcomes:

Components of the primary outcome (adjudicated, descriptive)

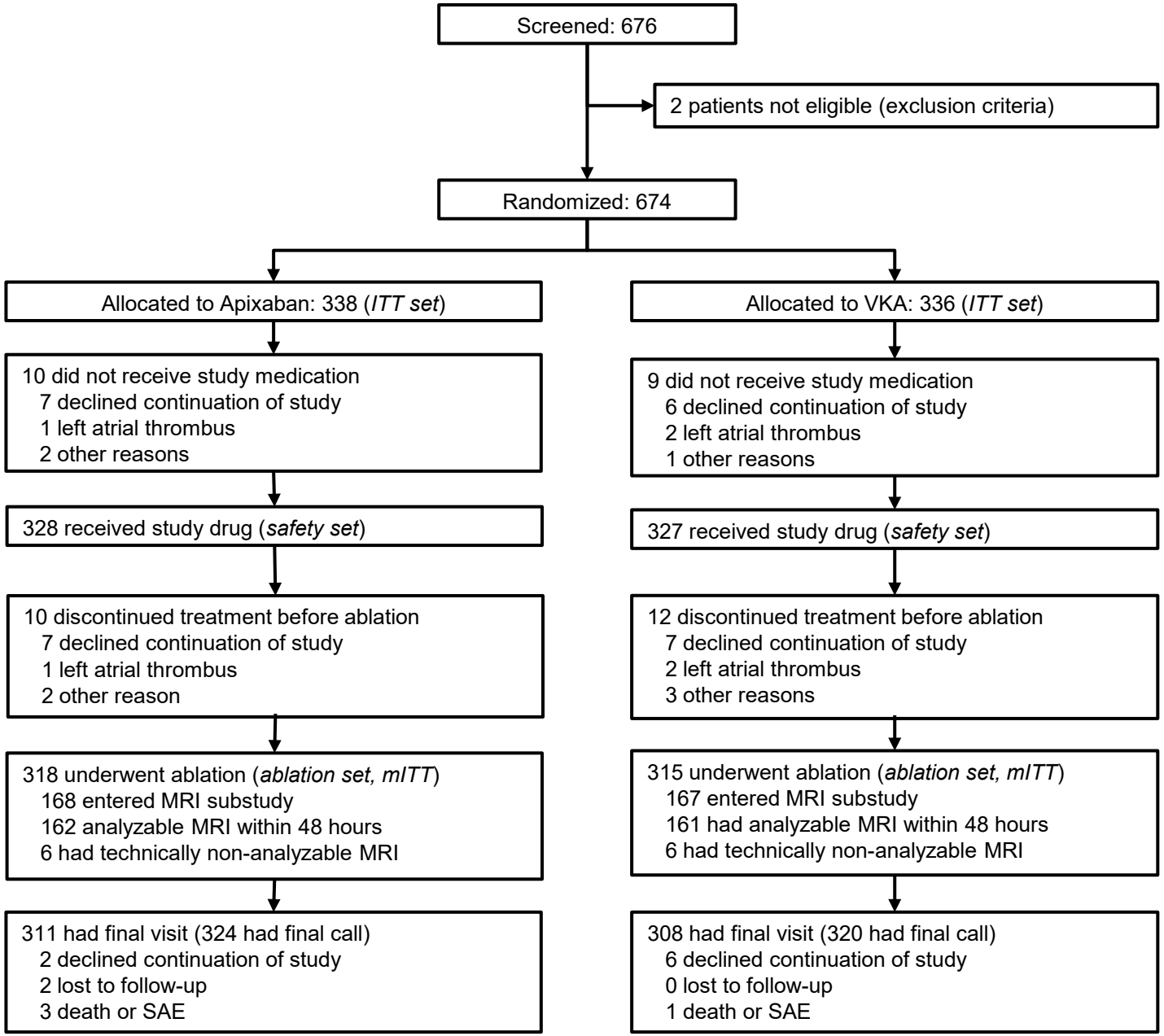
ISTH and TIMI major bleeds (adjudicated, descriptive)

Quality of life (SF-12, Karnofsky scale) at end of study, change compared to baseline

MRI substudy: patients with HR-DWI lesions, number of lesions per patient

Cognitive function at 90 days, change compared to baseline

CONSORT diagram



Baseline characteristics I

	All patients	Apixaban	VKA
Age, median (q1, q3)	64 (58, 70)	64 (57, 70)	64 (58, 70)
Female sex	209 (33%)	100 (31%)	109 (35%)
Persistent or long-standing persistent atrial fibrillation	266 (42.0%)	129 (40.6%)	137 (43.5%)
Body Mass Index, median (q1, q3)	28 (25, 32)	28 (26, 31)	28 (25, 32)
CHA_2DS_2VASc score, mean (SD)	2.4 (1.2)	2.4 (1.2)	2.4 (1.2)
Symptomatic heart failure (NYHA II-IV)	150 (23.7%)	78 (24.5%)	72 (22.9%)
Diabetes mellitus	76 (12.0%)	41 (12.9%)	35 (11.1%)
Prior stroke / TIA	47 (7.4%)	24 (7.5%)	23 (7.3%)
Age ≥ 75 years	56 (8.8%)	28 (8.8%)	28 (8.9%)
Vascular disease	83 (13.1%)	41 (12.9%)	42 (13.3%)
Valvular heart disease	73 (11.5%)	39 (12.3%)	34 (10.8%)

All values are given as median (q1, q3)

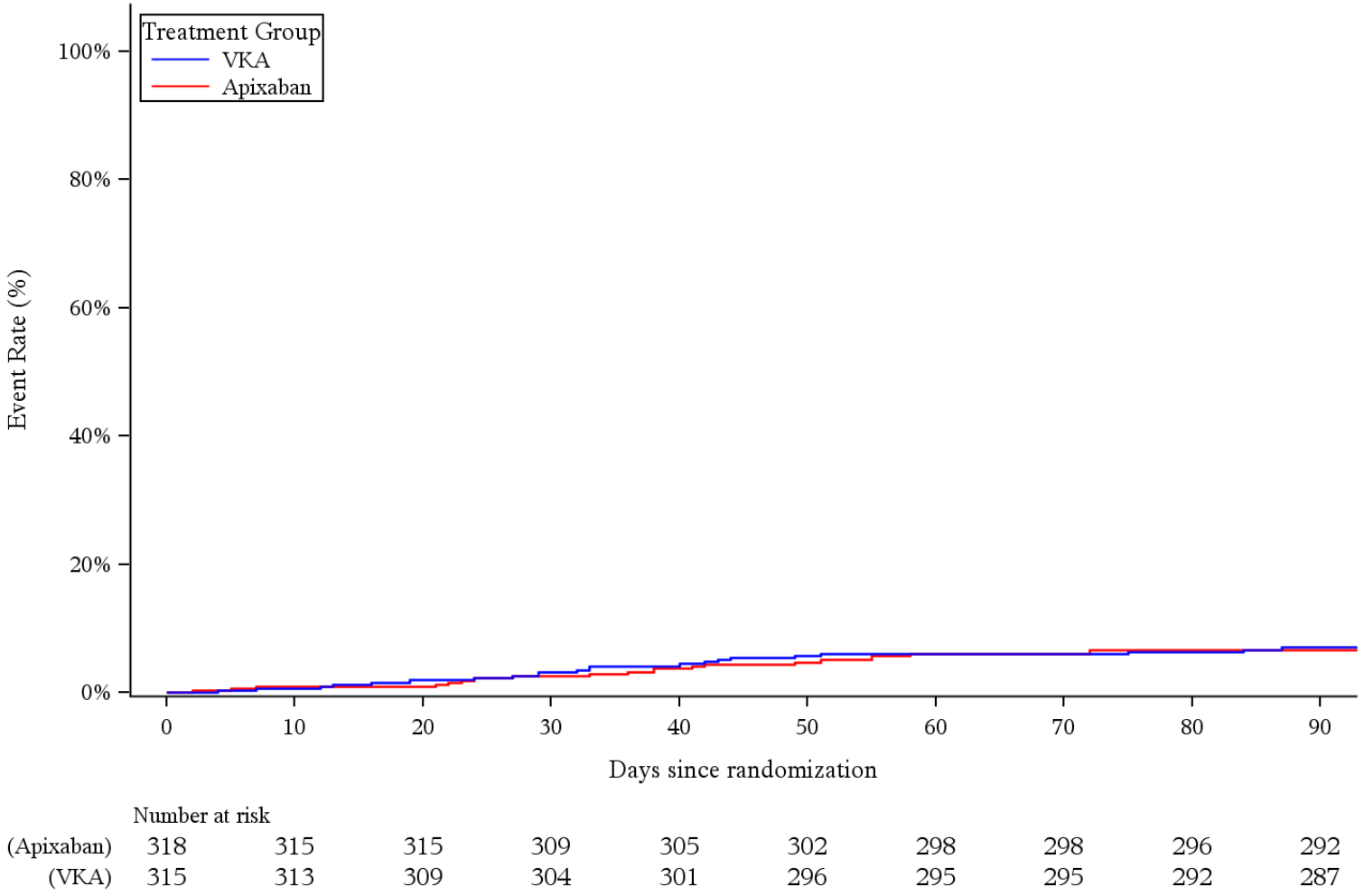
Baseline characteristics II

	All patients n=633	Apixaban n=318 (n=317 5 mg BD, n=1 2.5 mg BD)	VKA n=315 (n=127 warfarin, n=102 phenprocoumon, n=86 acenocoumarol)
SF-12 physical component	45 (38, 51)	44 (38, 51)	45 (38, 52)
SF-12 mental component	50 (43, 58)	51 (43, 58)	50 (43, 57)
Karnofsky scale	90 (80, 90)	80 (80, 90)	90 (80, 90)
Montreal Cognitive Assessment, (MoCA)	27 (25, 29)	27 (25, 29)	27 (25, 29)
At least mild cognitive impairment (MoCA <26)	188 (30.4%)	93 (29.7%)	95 (31.1%)
Quality of Anticoagulation		307/318 patients took all or all but one dose / week	Median TTR 84%

All values are given as median (q1, q3)

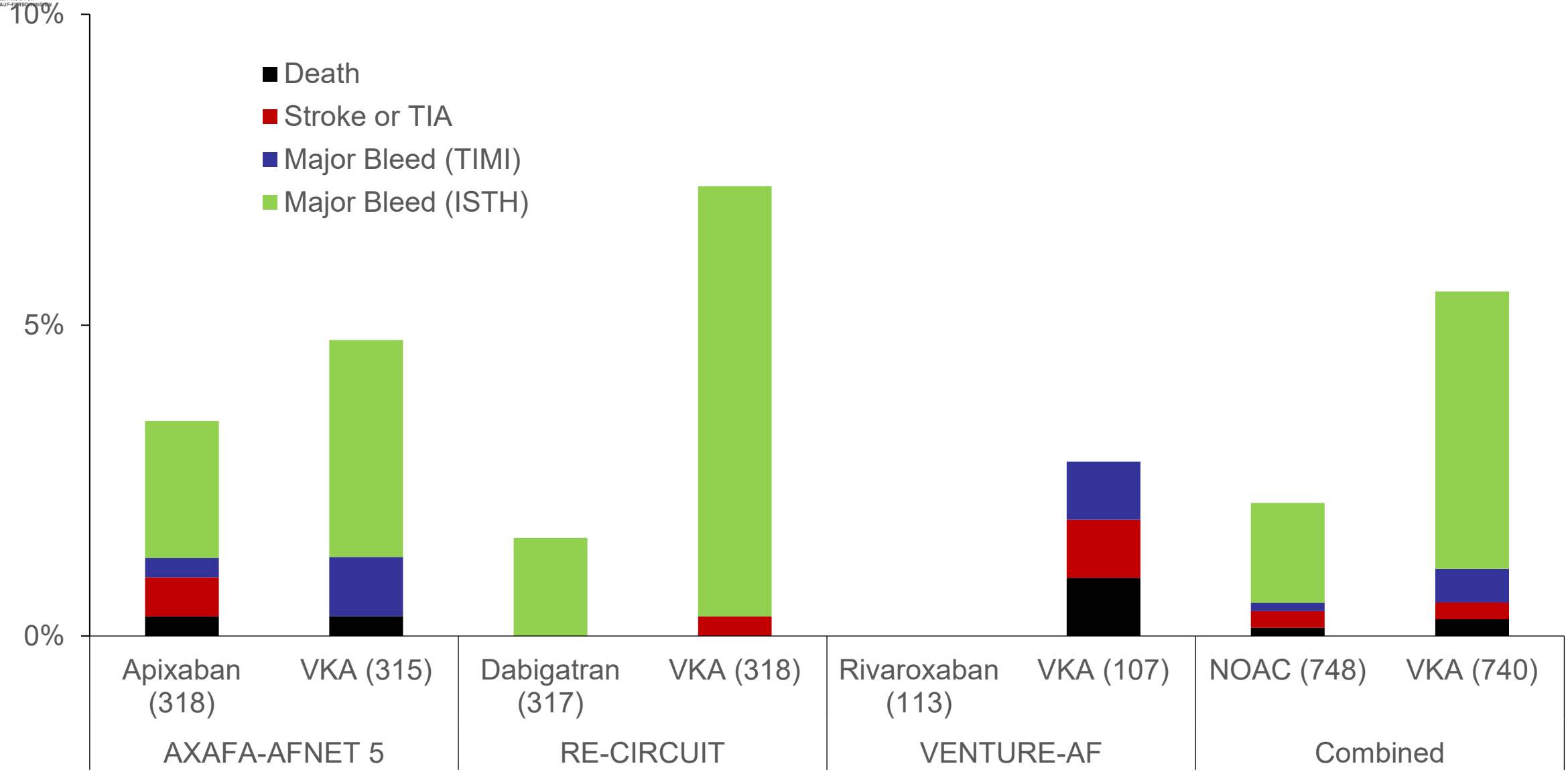
Primary outcome (ablation set)

Difference in primary outcome rate -0.38%; 90% confidence interval -4.0%, 3.3%; non-inferiority p=0.0002). Apixaban was also noninferior to VKA among all randomized patients as assessed by Cox proportional hazards model comparison between treatment groups using a relative non-inferiority margin of 1.44 (hazard ratio=0.88, 90% CI 0.55, 1.41, p=0.042)



	Apixaban	VKA
Patients with primary outcome event: composite of all-cause death, stroke or major (BARC 2 – 5) bleeding	22/318 (6.9%), non-inferiority p=0.0002	23/315 (7.3%)
Death	1 (0.3%)	1 (0.3%)
Stroke or TIA	2 (0.6%)	0
Intracranial hemorrhage	0	1 (0.3%, fatal)
TIMI major bleeding	1 (0.3%)	3 (1%)
ISTH major bleeding	10 (3.1%)	14 (4.4%)
Tamponade	2 (0.6%)	5 (1.6%)

Event rates in AXAFA – AFNET 5, RE-CIRCUIT, and VENTURE-AF (ablation sets)

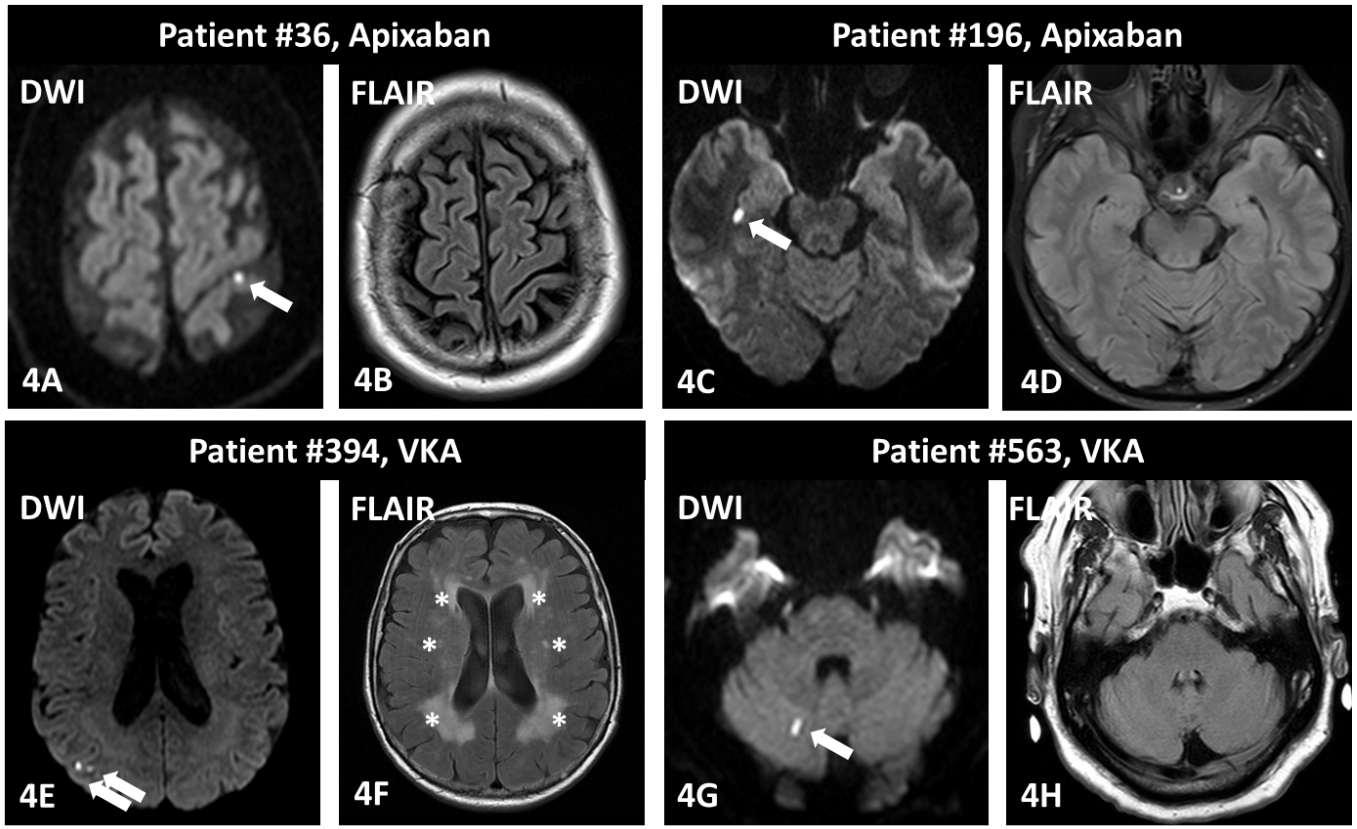


Quality of Life at the end of AXAFA – AFNET 5

	All patients	Apixaban	VKA
SF-12 physical component score	49 (42, 54)	48 (42, 54)	49 (42, 54)
Change in SF-12 physical component score	2.5 (-2.1, 8.1), p<0.001*	2.4 (-2.2, 7.9)	2.8 (-2.0, 8.3)
SF-12 mental component score	54.4 (46.0, 58.6)	54.2 (45.8, 58.3), n=290	54.5 (46.6, 59.7), n=267
Change in SF-12 mental component score	1.2 (-3.2, 8.0), p<0.001*	0.4 (-3.6, 8.0), n=281	1.6 (-2.8, 8.3), n=267
Karnofsky score	100 (90, 100)	100 (90, 100), n=311	100 (90, 100)
Change in Karnofsky score	10 (0, 10), p<0.001*	10 (0, 10), n=311	10 (0, 10), n=308

All values measured at end of study and given as median (q1, q3) or median difference to baseline (q1, q3)

AXAFA – AFNET 5 HD-DWI MRI sub-study



	All patients (n=323)	Apixaban (n=162)	VKA (n=161)	P value
No lesion	239 (74.0%)	118 (72.8%)	121 (75.2%)	0.635
Exactly one lesion	46 (14.2%)	27 (16.7%)	19 (11.8%)	0.211
Exactly two lesions	21 (6.5%)	7 (4.3%)	14 (8.7%)	0.111
More than two lesions	17 (5.3%)	10 (6.2%)	7 (4.3%)	0.463

Cognitive function at the end of follow-up

	All patients	Apixaban	VKA
Cognitive function (MoCA)	28 (26, 29)	28 (26, 29)	28 (26, 29)
Change in MoCA	1.0 (-1.0, 2.0), p<0.001*	0.0 (-1.0, 2.0), n=301	1.0 (-1.0, 2.0), n=296
At least mild cognitive impairment (MoCA <26)	141/607 (23.2%), -7.2%, p=0.005*	75/305 (24.6%) -5.1%	66/302 (21.9%) -9.2%

All values measured at end of study and given as median (q1, q3) or median difference to baseline (q1, q3)

AXAFA – AFNET 5: Strenghts and limitations

Strengths

Large IIT in Europe and US – only one published trial of similar size.

First trial exclusively in patients at risk of stroke undergoing atrial fibrillation ablation.

Excellent time in therapeutic range using locally available VKA (median TTR 84%).

Procedural details close to clinical practice (radio frequency ablation, cryoablation, ablation with or without transesophageal echocardiography or ICE).

Limitations

Sample size only sufficient for a wide non-inferiority margin of the primary outcome.

Open study, but blinded outcome assessment (including MRI reading in core lab).

Cognitive function limited to one test without differentiating functional domains.

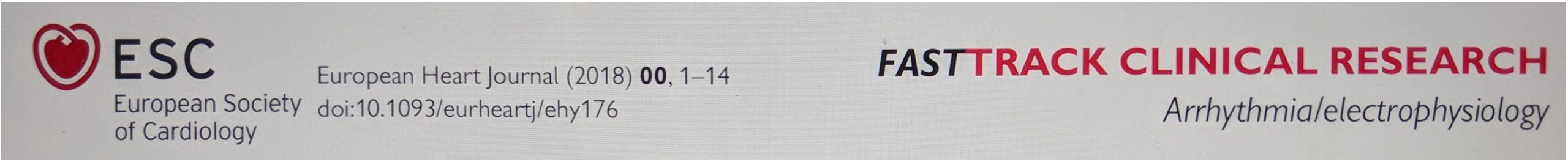
AXAFA – AFNET 5: Conclusions

Continuous apixaban therapy is a safe and effective alternative to VKA in patients at risk of stroke undergoing atrial fibrillation ablation,

including no difference in cognitive function or in MRI-detected acute brain lesions.

Cognitive function appears to improve after atrial fibrillation ablation on continuous anticoagulation with either apixaban or VKA.

More research into the prevention of acute brain lesions after atrial fibrillation ablation is warranted.



supported by European Union, grant agreement No 633196 [CATCH ME]