ATRIAL FIBRILLATION
NETWORK

AXADIA - AFNET 8

Hauptergebnis

Primary results of the safety study assessing oral anticoagulation with apixaban in patients with atrial fibrillation and end-stage kidney disease on chronic hemodialysis treatment (AXADIA – AFNET 8)

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AXADIA – AFNET 8: Hypothesis

Oral anticoagulation with apixaban 2.5 mg b.i.d. has non-inferior safety compared to to vitamin K antagonist therapy (target INR 2-3) in patients with atrial fibrillation on chronic hemodialysis

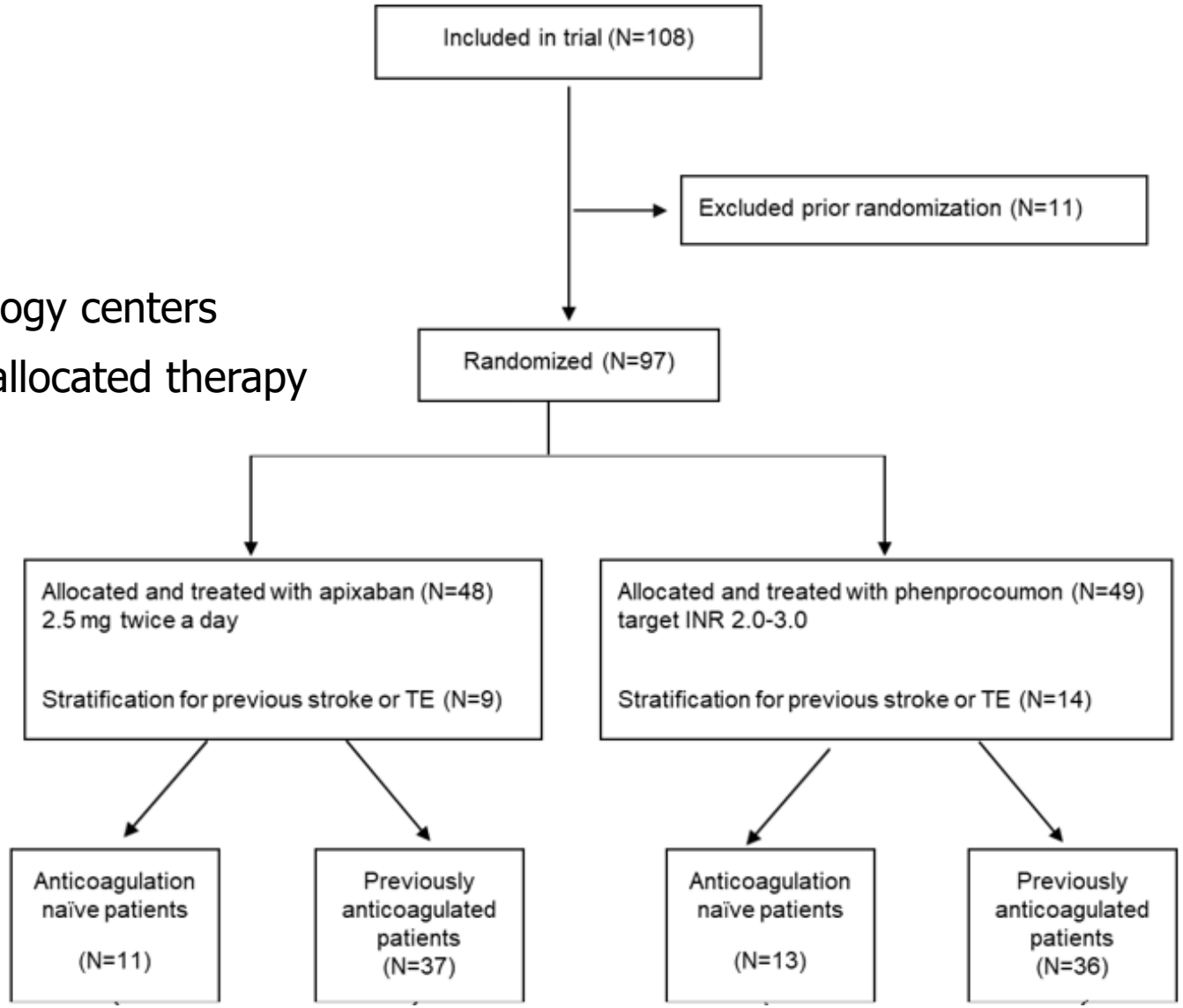
Reinecke H, et al. *BMJ Open* 8:e022690.(2018)

AXADIA – AFNET 8: Enrolment and treatment allocation

39 sites in Germany:

36 hemodialysis centers, 3 cardiology centers

All randomized patients received allocated therapy



429 (range 37-1,370) days

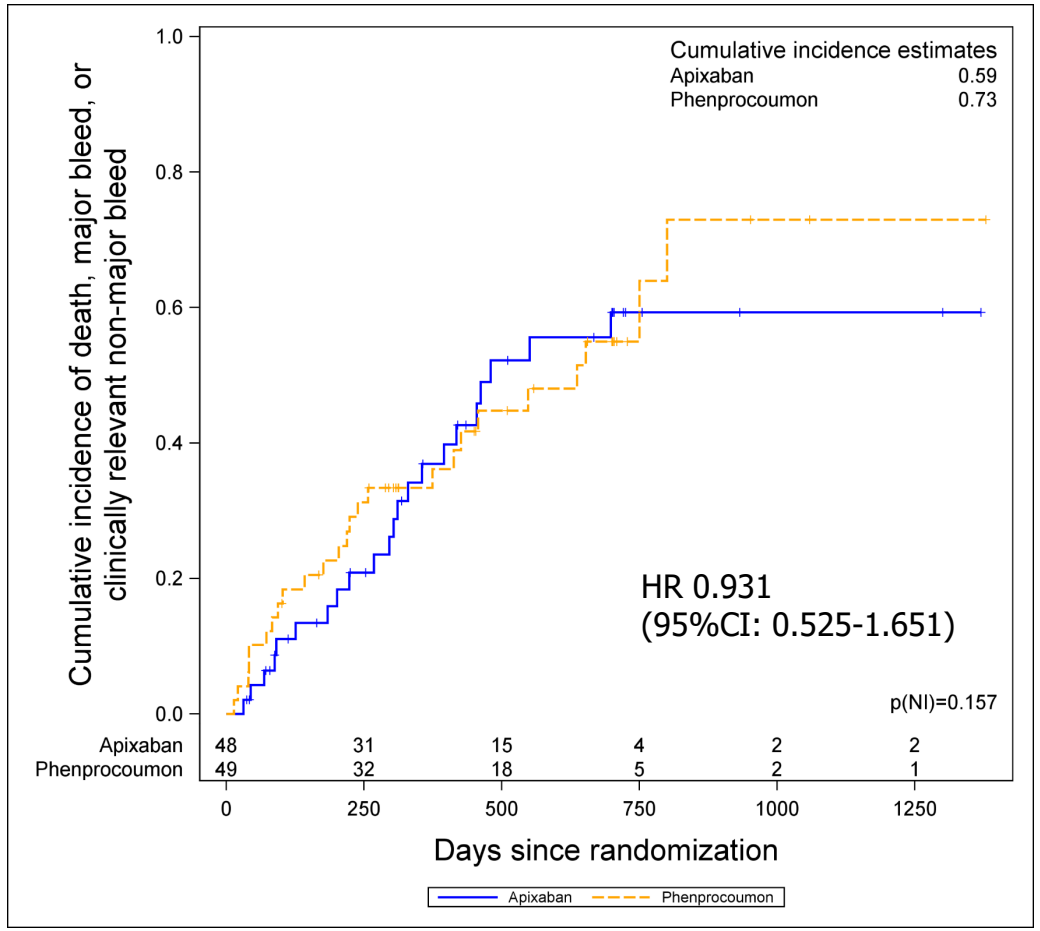
506 (range 101-1,379) days, p=0.34

AXADIA – AFNET 8: Key patient characteristics

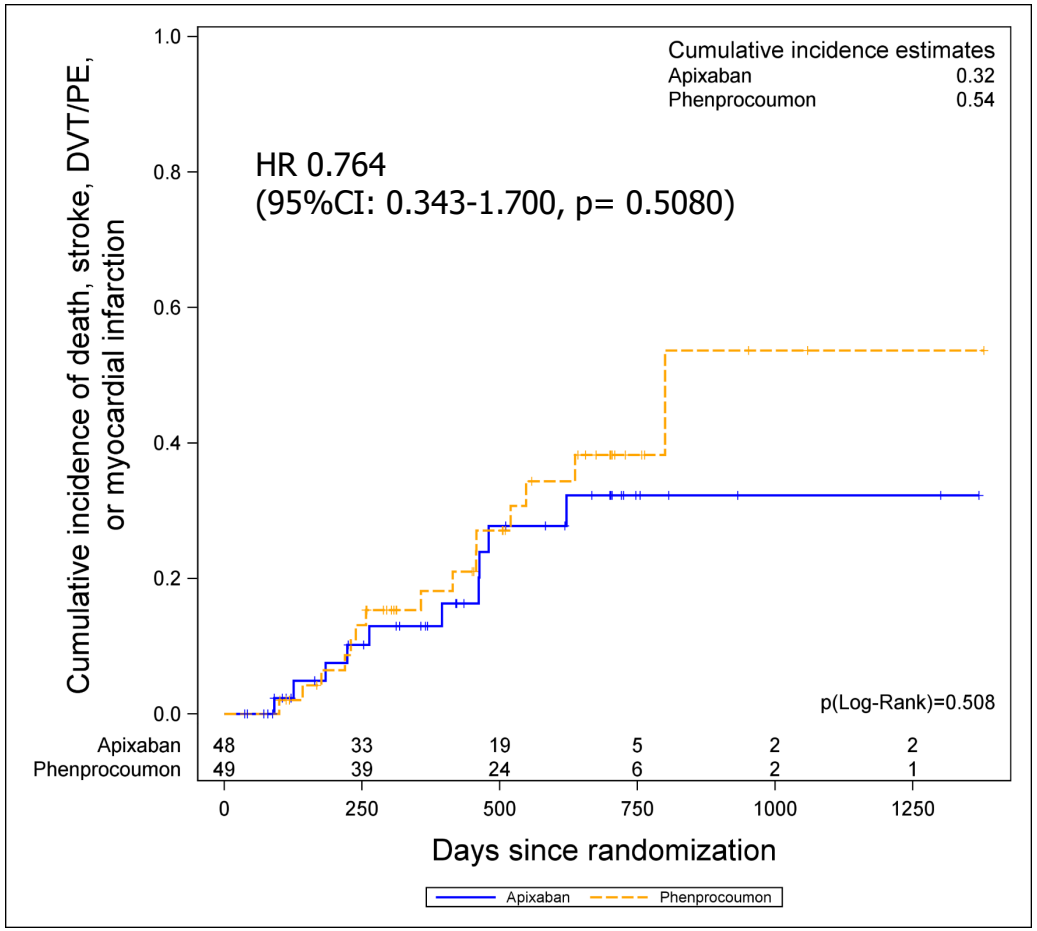
	All patients (N=97)	Apixaban (N=48)	VKA (N=49)	p
Median age in years (Q1, Q3)	77 (69-80)	76.5 (68-81)	77 (70.8)	0.9770
Male sex, n (%)	68 (70.1)	31 (64.6)	37 (75.5)	0.2399
Days since first dialysis **Median (Q1, Q3)** **Range**	962 (363-2147) 2 - 14,128	853 (371-2643) 124-4,711	1,072 (301-1,816) 2-14,128	0.4925
CHA_2DS_2-VASc risk score, median (Q1, Q3)	5 (4-6)	5.00 (3.5-5.0)	4.5 (4-6)	0.7856
HAS-BLED risk score median (Q1, Q3)	4 (3.5-5.0)	4 (3.5-5)	4.0 (3.5-5)	0.7269
Medication at baseline n (%)				
Aspirin	33 (34.0)	16 (33.3)	17 (34.7)	0.8875
Statin	50 (51.6)	21 (43.8)	29 (59.2)	0.1283
ACE inhibitor or Sartan or Sacubitril Valsartan	37 (38.1)	14 (29.2)	23 (46.9)	0.0716
Calcium Channel Antagonist	21 (21.7)	7 (14.6)	14 (28.6)	0.0944
Beta Blocker	76 (78.4)	36 (75.0)	40 (81.6)	0.4278
Diuretic	64 (66.0)	31 (64.6)	33 (67.4)	0.7739
Previous VKA therapy	56 (57.7)	25 (52.1)	31 (63.3)	0.2650
Previous NOAC therapy	11 (11.3)	8 (16.7)	3 (6.1)	0.1015

AXADIA – AFNET 8: Primary outcome, secondary outcome

Primary (safety) outcome, mITT*: death, major or clinically relevant non-major ISTH bleeding



Secondary (efficacy) outcome, mITT*: death, ischemic stroke, systemic embolism or pulmonary embolism



*the mITT population consists of all randomized patients. All randomized patients received at leat one dose of study drug.

AXADIA – AFNET 8: Primary outcome (backup slide)

Patients with events, N (%)	All patients N=97	Apixaban N=48	Phenprocou -mon, N=49	p-value
Follow-up time, days				0.3360*
Median (Q1, Q3)	462 (253-702)	429 (174-702)	506 (289-702)	
Range	37-1,379	37-1,370	101-1,379	
Composite primary safety endpoint†, n (%)	47 (48.5)	22 (45.8)	25 (51.0)	0.1567[NI] 0.4031[SUP] 0.8060[LR]
… thereof, "on-treatment" events	36 (37.1)	18 (37.5)	18 (36.7)	0.2970[NI] 0.5541[SUP] 0.8917[LR]
Composite primary efficacy endpoint††, n (%)	26 (26.8)	10 (20.8)	15 (30.6)	0.5080[LR]
thereof, "on-treatment" events	18 (18.6)	8 (16.7)	10 (20.4)	0.8593[NI]

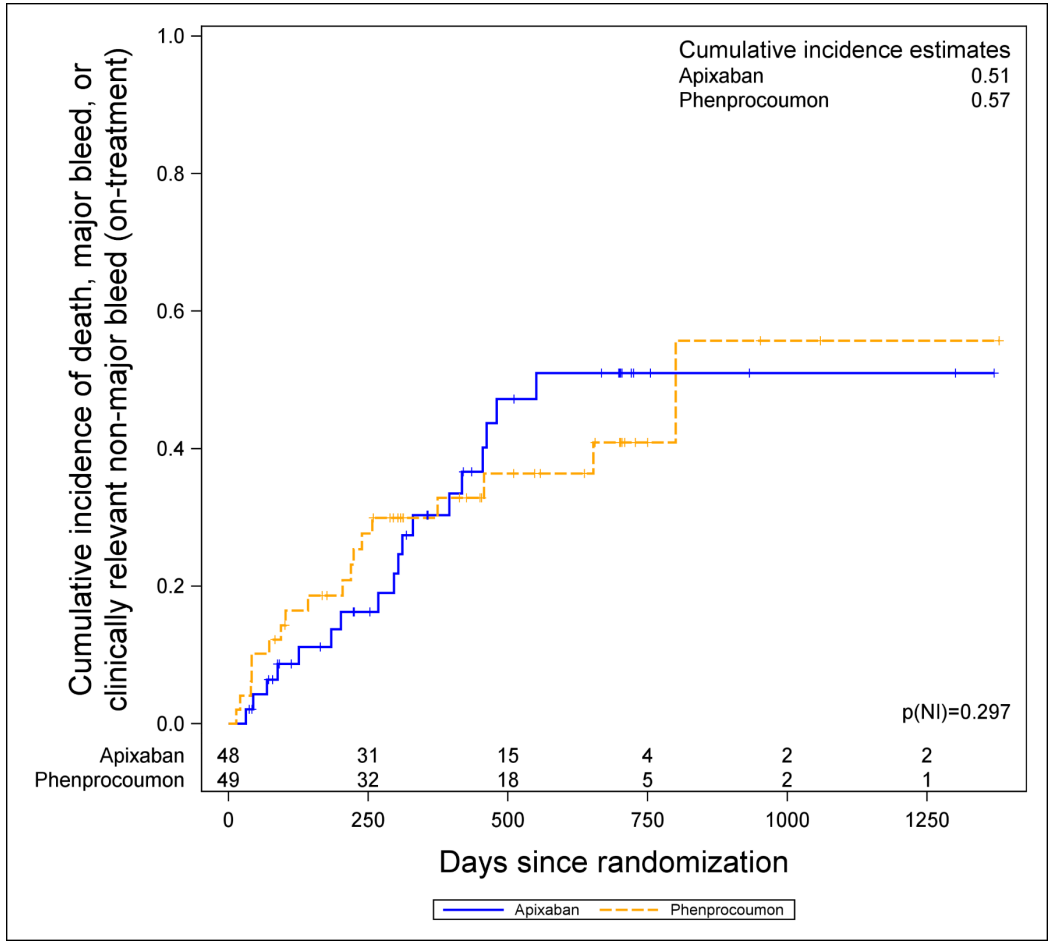
Table 2: Follow-up and outcomes

Patients with events, N (%)	All patients N=97	Apixaban N=48	Phenprocou-mon, N=49	p-value
Safety events, n(%)				
Major bleeding	11 (11.3)	5(10.4)	6 (12.2)	1.0[Exact]
thereof, "on-treatment" events	10 (10.3)	5 (10.4)	5 (10.2)	1.0[Exact]
Clinically-relevant non-major bleedings	19 (19.6)	10 (20.8)	9 (18.4)	0.8026[Exact]
thereof, "on-treatment" events	16 (16.5)	9 (18.8)	7 (14.3)	0.5947[Exact]
All-cause mortality	21 (22.7)	9 (18.8)	12 (24.5)	0.7820[LR]
thereof, "on-treatment" events	15 (15.5)	7 (14.6)	8 (16.3)	0.9587[LR]
Secondary events, n (%)				
Cardio-vascular mortality	12 (13.4)	7 (14.6)	5 (10.2)	0.5529[Exact]
Myocardial infarction	5 (5.2)	2 (4.2)	3 (6.1)	1.0[Exact]
Ischemic stroke / TIA	1 (1.0)	0	1 (2.0)	1.0[Exact]
Deep vein thrombosis	0	0	0	n.e.
Pulmonary embolism	0	0	0	n.e.
Events of special interest, n (%)				
Shunt thrombosis	9 (9.3)	6 (12.5)	3 (6.1)	0.3173[Exact]
Clotted membrane during dialysis	0	0	0	n.e.

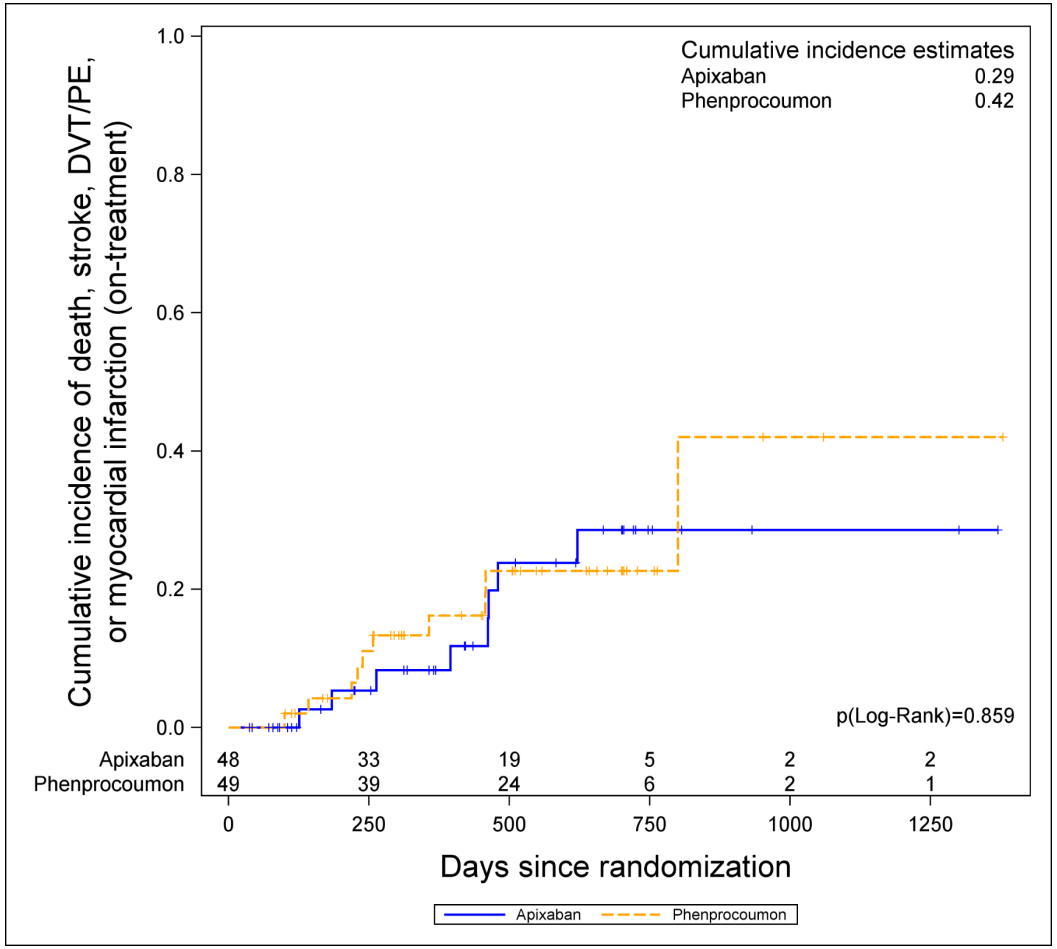
NI indicates one-sided non-inferiority p-value; SUP, one-sided superiority p-value; LR, two-sided log-rank test p-value; Exact, two-sided Fisher's exact test; n.e., not estimable.

AXADIA – AFNET 8: On-treatment (sensitivity) analysis

Primary (safety) outcome, OT*: death, major or clinically relevant non-major ISTH bleeding



Secondary (efficacy) outcome, OT*: death, ischemic stroke, systemic embolism or pulmonary embolism



*OT the on-treatment population consists of the mITT population censored after discontinuation of study drug.

AXADIA – AFNET 8: Individual Outcomes, Adherence

Safety events, n (%)	All patients N=97	Apixaban N=48	VKA, N=49	p
Major bleeding	11 (11.3)	5 (10.4)	6 (12.2)	1.0 Exact
thereof, "on-treatment"	10 (10.3)	5 (10.4)	5 (10.2)	1.0 Exact
Clinically-relevant non-major bleedings	19 (19.6)	10 (20.8)	9 (18.4)	0.8026 Exact
thereof, "on-treatment"	16 (16.5)	9 (18.8)	7 (14.3)	0.5947 Exact
All-cause death	21 (22.7)	9 (18.8)	12 (24.5)	0.7820 LR
thereof, "on-treatment"	15 (15.5)	7 (14.6)	8 (16.3)	0.9587 LR

Secondary events, n (%)	All N=97	Apixaban N=48	VKA, N=49	p
Cardiovascular death	12 (13.4)	7 (14.6)	5 (10.2)	0.5529 Exact
Myocardial infarction	5 (5.2)	2 (4.2)	3 (6.1)	1.0 Exact
Ischemic stroke / TIA	1 (1.0)	0	1 (2.0)	1.0 Exact
Deep vein thrombosis	0	0	0	n.e.
Pulmonary embolism	0	0	0	n.e.
Shunt thrombosis, n (%)	9 (9.3)	6 (12.5)	3 (6.1)	0.3173 Exact
Clotted membrane during dialysis	0	0	0	n.e.

NI indicates one-sided non-inferiority p-value; SUP, one-sided superiority p-value; LR, two-sided log-rank test p-value;Exact, two-sided Fisher's exact test; n.e., not estimable

	Apixaban	VKA
Adherence to apixaban (defined as intake of >80% of medication)	44/48	-
Median TTR in %	-	50.7% (0-100%)

De Vriese AS, et al. *J Am Soc Nephrol* 2:1474-1483. (2021)
Ionescu F, et al. *Eur J Haematol* 106:689-96.(2021)

AXADIA – AFNET 8: Conclusions

In this randomized trial comparing apixaban 2.5 mg bid and VKA in patients with AF on hemodialysis with long follow-up, no differences were observed in safety or efficacy outcomes. Formal non-inferiority could not be shown.

Our data support consideration of apixaban for prevention of cardiovascular complications in patients with atrial fibrillation on chronic hemodialysis, but larger studies are needed.

Additional interventions need to be developed to further reduce the very high risk of thromboembolic and bleeding events in this population.

Circulation

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