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ORIGINAL RESEARCH ARTICLE

A Randomized Controlled Trial Comparing Apixaban With the Vitamin K Antagonist Phenprocoumon in Patients on Chronic Hemodialysis: The AXADIA-AFNET 8 Study

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Background

- Non–vitamin K oral anticoagulants (NOACs) have become the standard therapy for preventing stroke and ischemic thromboembolism in most patients with atrial fibrillation (AF).
- The available trials provide good evidence for the safety and efficacy of NOACs in patients with mild to severe renal failure (chronic kidney disease stage II through IV) but excluded individuals with end-stage kidney disease (ESKD) on chronic hemodialysis.
- Therefore, the effectiveness and safety of non–vitamin K oral anticoagulants in patients on hemodialysis is not well known.

AIM of the study

- To compare the safety and efficacy of the NOAC apixaban (2.5 mg BID) with VKA therapy with phenprocoumon in patients with AF on hemodialysis.
- The researchers' hypothesis was that apixaban is noninferior to VKA.

Methods

- Investigator-initiated, multicenter, PROBE (prospective randomized open blinded end point) outcome assessment trial.
- 39 sites throughout Germany.
- Primary outcome: a composite of all-cause death, major bleeding events, and clinically relevant, nonmajor bleeding in accordance with the International Society of Thrombosis and Hemostasis consensus.
- Secondary outcome: the efficacy of apixaban compared with phenprocoumon regarding prevention of thromboembolic events, assessed as a composite of myocardial infarction, ischemic stroke, all-cause death, and deep vein thrombosis or pulmonary embolism.

Results (I)

- Between June 15, 2017, and May 31, 2022, 97 patients were randomized to treatment with either apixaban (n=48) or VKA (n=49).
- Adherence to apixaban was >80% in 44 of 48 patients; the median time in therapeutic range on VKA was 50.7%.
- A total of 70% of the patients were male, and the average age was 74.7 years (SD 7.9). Mean CHA2DS2-VASc score was 4.5. All randomized patients were treated.
- Baseline characteristics were well balanced between randomized groups.

Results (II)

- Composite primary safety outcome events occurred in 22 patients (45.8%) on apixaban and in 25 patients (51.0%) on VKA (hazard ratio, 0.93 [95% CI, 0.53–1.65];*P*noninferiority=0.157).
- Composite primary efficacy outcome events occurred in 10 patients (20.8%) on apixaban and in 15 patients (30.6%) on VKA (*P*=0.51; log rank).
- There were no significant differences regarding individual outcomes (all-cause mortality, 18.8% versus 24.5%; major bleeding, 10.4% versus 12.2%; and myocardial infarction, 4.2% versus 6.1%, respectively).

Table 2. Follow-Up and Outcomes

Patients with events	All patients (n=97)	Apixaban (n=48)	Phenprocoumon (n=49)	*P* value
Follow-up time, d				0.3360*
Median (Q1 and Q3)	462 (253–702)	429 (174–702)	506 (289–702)	
Range	37–1379	37–1370	101–1379	
Composite primary safety outcome, n (%)†	47 (48.5)	22 (45.8)	25 (51.0)	0.1567[NI] 0.4031[SUP] 0.8060[LR]
On-treatment events	36 (37.1)	18 (37.5)	18 (36.7)	0.2970[NI] 0.5541[SUP] 0.8917[LR]
Composite primary efficacy outcome, n (%)‡	26 (26.8)	10 (20.8)	15 (30.6)	0.5080[LR]
On-treatment events	18 (18.6)	8 (16.7)	10 (20.4)	0.8593[LR]
Safety events, n (%)				
Major bleeding	11 (11.3)	5 (10.4)	6 (12.2)	1.0[Exact]
On-treatment events	10 (10.3)	5 (10.4)	5 (10.2)	1.0 [Exact]
Clinically relevant nonmajor bleeding	19 (19.6)	10 (20.8)	9 (18.4)	0.8026[Exact]
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]
On-treatment events	15 (15.5)	7 (14.6)	8 (16.3)	0.9587[LR]
Secondary events, n (%)				
Cardiovascular 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	NE
Pulmonary embolism	0	0	0	NE
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	NE

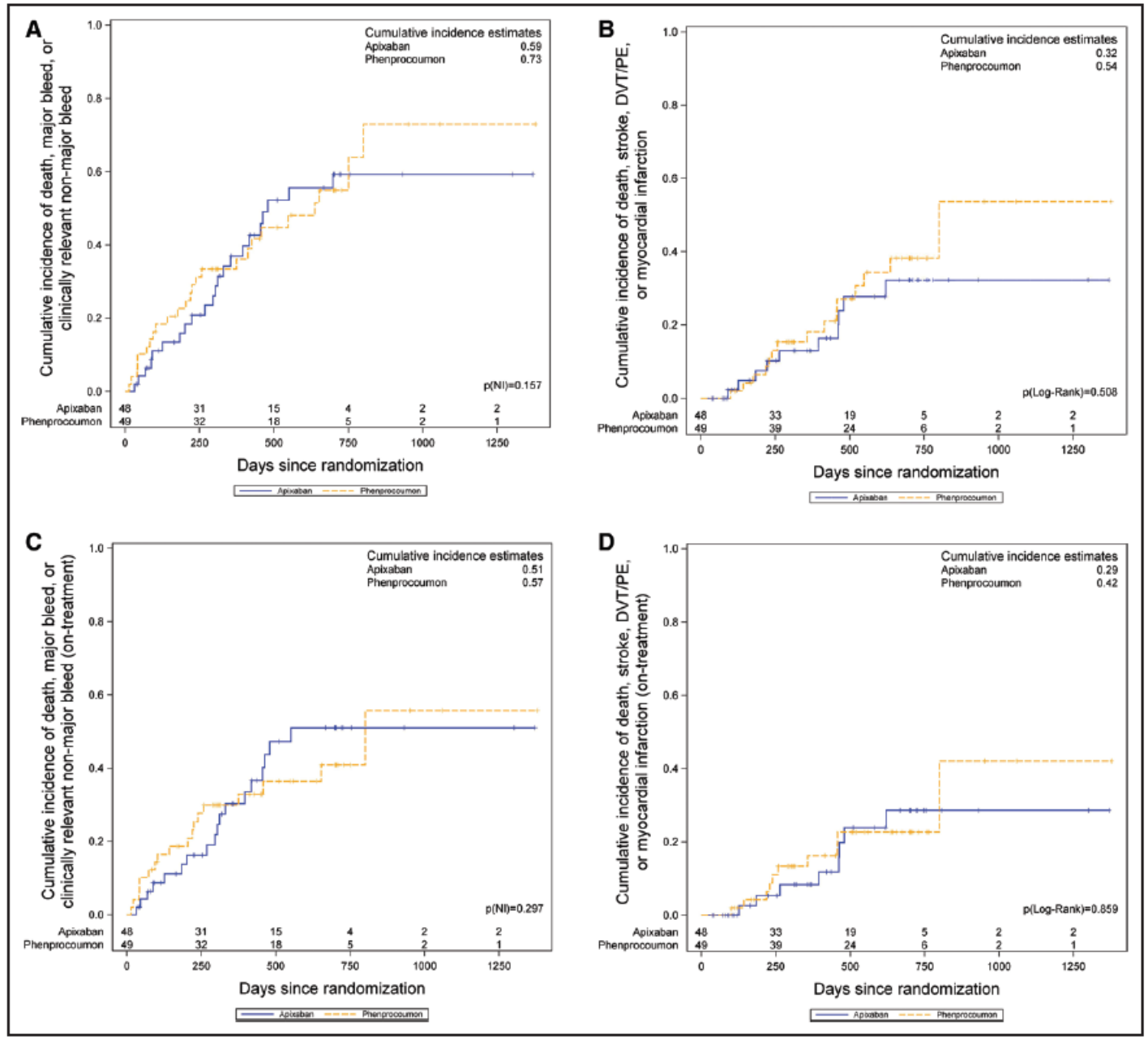

Figure 2. Cumulative incidence of the composite primary safety and efficacy outcome.

Conclusions

- In AXADIA–AFNET 8 trial, treatment with apixaban (2.5 mg BID) showed no apparent differences in safety and efficacy compared with VKA therapy in patients with AF on chronic hemodialysis although the prespecified noninferiority test requirements were not met because of slow enrollment.
- In view of the paucity of randomized trials in this field , these results have clinical implications by providing clinicians with randomized trial data that appear to justify the use of either apixaban or VKA in patients with AF on hemodialysis.
- The study illustrates also that patients on chronic hemodialysis with AF remain at high risk of thromboembolic and bleeding events on OAC, calling for the development of additional interventions to reduce these high event rates in this high-risk population.