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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 have become the standard therapy for preventing stroke and ischemic thromboembolism in most patients with atrial fibrillation (AF). The effectiveness and safety of non–vitamin K oral anticoagulants in patients on hemodialysis is not well known.

METHODS: From June 2017 through May 2022, AXADIA–AFNET 8 (Compare Apixaban and Vitamin K Antagonists in Patients With Atrial Fibrillation and End-Stage Kidney Disease), an investigator-initiated PROBE (prospective randomized open blinded end point) outcome assessment trial, randomized patients with AF on chronic hemodialysis to either apixaban (2.5 mg BID) or the vitamin K antagonist (VKA) phenprocoumon (international normalized ratio, 2.0 to 3.0). The composite primary safety outcome was defined by a first event of major bleeding, clinically relevant nonmajor bleeding, or all-cause death. The primary efficacy outcome was a composite of ischemic stroke, all-cause death, myocardial infarction, and deep vein thrombosis or pulmonary embolism. Our hypothesis was that apixaban is noninferior to VKA.

RESULTS: Thirty-nine sites randomized 97 patients (30% women; mean age 75 years; mean CHA_2DS_2-VASc [congestive heart failure, hypertension, age ≥75 years, diabetes, stroke or transient ischemic attack, vascular disease, age 65 to 74 years, female sex] score, 4.5; baseline characteristics balanced between groups): 48 to apixaban and 49 to VKA. The median follow-up time was 429 days (range, 37 to 1370) versus 506 days (range, 101 to 1379), respectively. Adherence to apixaban was >80% in 44 of 48 patients; the median time in therapeutic range on VKA was 50.7%. 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).

CONCLUSIONS: In this randomized trial comparing apixaban and VKA in patients with AF on hemodialysis with long follow-up, no differences were observed in safety or efficacy outcomes. Even on oral anticoagulation, patients with AF on hemodialysis remain at high risk of cardiovascular events. Larger randomized trials are needed to determine the optimal anticoagulation regimen for patients with AF on hemodialysis.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT02933697.

Key Words: atrial fibrillation ■ randomized controlled trial ■ renal dialysis ■ stroke

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Clinical Perspective

What Is New?

- In this randomized trial, no differences in safety or efficacy were observed between apixaban 2.5 mg BID and vitamin K antagonists in patients with atrial fibrillation on chronic hemodialysis.
- Event rates in patients with atrial fibrillation on hemodialysis remain high on oral anticoagulation, including death or a clinically relevant bleeding event (48.5%) and stroke, myocardial infarction, systemic or pulmonary embolism, or death (26.8%).

What Are the Clinical Implications?

- 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 reduce the very high risk of thromboembolic and bleeding events in this population.

Nonstandard Abbreviations and Acronyms

AF	atrial fibrillation
AFNET	Atrial Fibrillation Network
AXADIA–AFNET 8	Compare Apixaban and Vitamin K Antagonists in Patients With Atrial Fibrillation and End-Stage Kidney Disease
CHA_2DS_2-VASc	congestive heart failure, hypertension, age ≥75 years, diabetes, stroke or transient ischemic attack, vascular disease, age 65 to 74 years, female sex
CKD	chronic kidney disease
CONSORT	Consolidated Standards of Reporting Trials
ESKD	end-stage kidney disease
HR	hazard ratio
INR	international normalized ratio
ITT	intention-to-treat
NOAC	non–vitamin K oral anticoagulant
OAC	oral anticoagulation
PP	per protocol
PROBE	prospective randomized open blinded end point
RENAL-AF	Renal Hemodialysis Patients Allocated Apixaban Versus Warfarin in Atrial Fibrillation
TTR	time in therapeutic range
VKA	vitamin K antagonist

Oral anticoagulation (OAC) by non–vitamin K antagonist oral anticoagulants (NOACs) is the first-line therapy for most patients with atrial fibrillation (AF) to prevent stroke and systemic embolism on the basis of robust data demonstrating equal efficacy with less severe bleeding compared with vitamin K antagonists (VKA).[1,2] Exceptions for therapy with NOACs are patients with mechanical heart valves[1–3] or rheumatic heart disease.[1,2,4] The available trials provide good evidence for the safety and efficacy of NOACs in patients with mild to severe renal failure (chronic kidney disease [CKD] stage II through IV) but excluded individuals with end-stage kidney disease (ESKD) on chronic hemodialysis. Therefore, whether NOACs are safe and effective in patients with AF on hemodialysis is uncertain.[5,6] This is of relevance, as patients on hemodialysis who are initiated on VKA show a high risk of bleeding.[6–9] Moreover, use of VKA accelerates vascular calcifications in patients with CKD and especially those on hemodialysis, thus further contributing to advanced arteriosclerosis.[10] In rare cases, use of VKAs in hemodialysis may lead to the life-threating complication of calciphylaxis.[11] Therefore, alternatives for VKA are of growing interest because with the increasing prevalence of older age, AF, and cardiovascular comorbidities, the group of patients with terminal renal failure is also growing rapidly.[12,13]

Some retrospective and small, prospective, nonrandomized studies in the past suggested that NOACs might be safe and effective in patients on hemodialysis.[14–16] The NOAC apixaban is mainly eliminated by means of metabolization and excretion in the liver, rendering apixaban a suitable NOAC in patients with AF on hemodialysis. The investigator-initiated, multicenter, PROBE (prospective randomized open blinded end point) outcome assessment trial AXADIA–AFNET 8 (Compare Apixaban and Vitamin K Antagonists in Patients With Atrial Fibrillation and End-Stage Kidney Disease) compared the NOAC apixaban (2.5 mg BID) with VKA therapy in patients with AF on hemodialysis.

METHODS

The rationale and design of AXADIA–AFNET 8 was described previously in detail.[17] The primary aim was to compare the safety of the factor Xa inhibitor apixaban with the VKA phenprocoumon in patients with AF on chronic hemodialysis. Phenprocoumon is the most common VKA in Austria, Germany, and Switzerland (>99% of all patients with VKA).

In brief, the trial was conducted in hemodialysis centers in Germany as an investigator-initiated, prospective, parallel-group, single country/national, multicenter phase 3b trial. Because VKA therapy requires repetitive international normalized ratio (INR) measurements to adjust dosage, the study was performed with open-label administration of study drugs. All outcome measures were centrally adjudicated blind to randomization group and anticoagulation therapy.

The trial was conceived, designed, and led by the steering committee (a list of members is provided in the Supplemental Material). The responsible sponsor of the trial was Kompetenznetz Vorhofflimmern eV (AFNET [Atrial Fibrillation Network]; www.kompetenznetz-vorhofflimmern.de), Muenster, Germany. A contract research organization (Proinnovera; Muenster, Germany) and a data management service (GCP-Service; Bremen, Germany) delivered the trial. AXADIA–AFNET8 was financed by Bristol Myers Squibb (Munich, Germany) and Pfizer (Berlin, Germany). The funders did not influence the design, conduct, or interpretation of the trial. All data will be made available upon request after confirmation of regulatory requirements from the sponsor (info@af-net.eu).

Registration, Ethical Approval, and Boards

The trial is registered at EudraCT (Unique identifier: 2015-005503-84) and clinicaltrials.gov (URL: https://www.clinicaltrials.gov; Unique identifier: NCT02933697).

The study protocol was approved by the ethical committee of the Landesaerztekammer (Medical Association) Westfalen-Lippe and the Medical Faculty of the University of Muenster, Germany (reference No. 2016-598-f-A) and by the local ethical boards of all participating sites. Written informed consent was obtained from all patients before study participation, including their consent for long-term follow-up. During the study, all participants were covered by patient insurance contracted with CNA Insurance Company Limited, Cologne, Germany.

A data and safety monitoring board supervised this study (a list of members is provided in the Supplemental Material).

All events that could potentially constitute safety and efficacy outcomes were centrally reviewed and adjudicated by a blinded end point assessment committee (a list of members is provided in the Supplemental Material).

The statistical analysis plan was developed and signed before database lock and unblinding. The full study protocol and statistical analysis plan are available in the Supplemental Material.

Research Hypothesis

The primary goal of this study was to compare the safety of apixaban (2.5 mg BID) with VKA therapy (target range, INR of 2.0 to 3.0). AXADIA was planned in 2013. With regard to the dosage of apixaban within the trial, at that time, no published data were available, nor was the later US Food and Drug Administration label recommending apixaban (5 mg BID) also in patients on hemodialysis. An unpublished pharmacokinetic simulation projected that taking 5 mg BID would lead to higher apixaban exposure, and the lower dose of 2.5 mg BID would lead to a slightly lower apixaban exposure compared with individuals without kidney disease. These considerations, in conjunction with the general high rate of ischemic and bleeding events in hemodialysis, led the steering committee in December 2013 to decide to use apixaban (2.5 mg BID) in the study. The initial hypothesis of the study was that OAC with apixaban would be at least noninferior to VKA therapy in patients with AF on hemodialysis with respect to the safety outcome and effectiveness in stroke prevention would be not inferior.

Patients, Study Design, and Randomization

Adult patients with AF on chronic hemodialysis were centrally and electronically randomized to OAC with apixaban or phenprocoumon in a 1:1 ratio. Key inclusion and exclusion criteria were reported previously[17] and included AF documented on at least 2 ECGs at different days, an increased stroke risk estimated by CHA_2DS_2-VASc score (congestive heart failure, hypertension, age ≥75 years, diabetes, stroke or transient ischemic attack, vascular disease, age 65 to 74 years, female sex) ≥2, and age ≥18 years. Key exclusion criteria included stroke within 3 months of enrollment, hemodialysis for <3 months, moderate or severe aortic or mitral stenosis, conditions other than AF requiring anticoagulation, active endocarditis, planned AF or flutter ablation, active bleeding, serious bleeding <6 months before enrollment, uncontrolled diabetes, history of cancer, and need for chronic aspirin therapy.

The randomization was stratified by 2 conditions: first, patients with a previous ischemic stroke who met the above criteria were included after >3 months if they were not severely handicapped, as indicated by a value of 0 or 1 on the modified Rankin Scale,[18] and were then stratified to assure equal distribution within the groups. Second, randomization was stratified for previous OAC therapy at baseline (anticoagulation-naïve). Patient distribution over these strata is presented in Table S1. The study design and patient allocation were reported in accordance to the CONSORT (Consolidated Standards of Reporting Trials) guideline (patient flow is shown in detail in Figure 1).

Outcomes

The primary outcome measure was 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.[17,19]

Secondary outcomes were 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.[17]

The primary analysis set consisted of all patients who were randomized and received at least one dose of the study drug. A sensitivity analysis compared events on-treatment (ie, while taking study medication or at maximum 2 days after last intake of the study medication). We report descriptive statistics and analysis for all events and for the events on treatment separately.

Statistics

Continuous variables are presented groupwise by mean±SD as well as median and interquartile range (Q1 and Q3). Skewed data were tested by nonparametric Mann-Whitney *U* tests; otherwise, *t* tests were used. Categorical variables are presented by counts and percentages and compared by χ^2 or Fisher exact tests, as appropriate. The primary efficacy outcome as well as the secondary outcomes (events of special interest and thromboembolic events as well as all-cause and cardiovascular mortality) were analyzed in the full analysis set using the intention-to-treat (ITT) principle. The primary analysis population consisted of all patients who were randomized and received at least one dose of the study drug. The full statistical analysis plan is included in the Supplemental Material. Event rates were expressed descriptively and by inferential statistics. No adjustment for multiplicity was provided for these analyses.

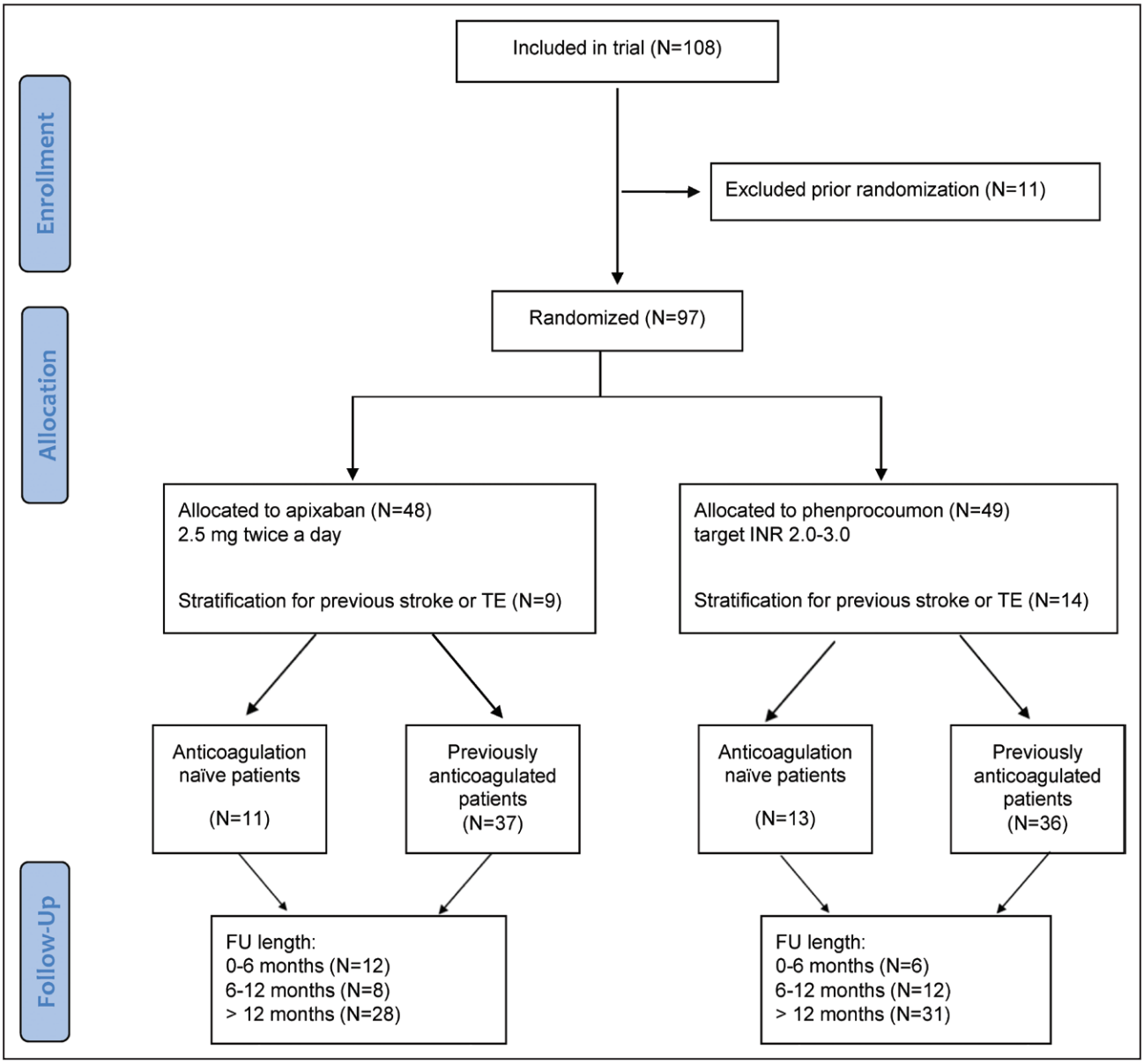

Figure 1. Outline of the AXADIA–AFNET 8 study according to the CONSORT guideline.
The included patients and their allocation to the 2 treatment arms are shown in accordance with the CONSORT (Consolidated Standards of Reporting Trials) criteria. AXADIA–AFNET 8 indicates Compare Apixaban and Vitamin K Antagonists in Patients With Atrial Fibrillation and End-Stage Kidney Disease; FU, follow-up; INR, international normalized ratio; and TE, thromboembolism.

Two primary statistical null hypotheses were tested in a hierarchical multiple comparison procedure, which controls the familywise error rate, with respect to the primary safety outcome:

$H_0^{noninferiority}$: hazard ration (HR) ≥1.25 versus $H_1^{noninferiority}$: HR <1.25 (proof of noninferiority of apixaban)

$H_0^{superiority}$: HR ≥1 versus $H_1^{superiority}$: HR <1 (proof of superiority of apixaban)

HR denotes the corresponding hazard ratio of the apixaban treatment versus phenprocoumon treatment. The multiple 1-sided significance level was set to α=2.5%. The null hypothesis $H_0^{noninferiority}$ was first tested at the local significance level $\alpha(H_0^{noninferiority})$=2.5%. If the initial hypothesis $H_0^{noninferiority}$ could be rejected, subsequently, the hypothesis $H_0^{superiority}$ would be tested on a local significance level of 2.5%. The primary statistical analysis provides confirmatory statistical evidence.

$H_0^{superiority}$ was analyzed in the full analysis set that consists of all randomized patients, including patients with any kind of protocol violations, applying the ITT principle. $H_0^{noninferiority}$ was further analyzed in the per protocol (PP) population, excluding patients with relevant protocol violations. Additional analyses were conducted in the on-treatment population, excluding events that occurred while not receiving study medication. Statistically significant noninferiority was defined as significant differences in both the ITT analysis and the PP analysis. *P* values for the 2 primary null hypotheses were computed using the *z* score, $z=([\ln(HR)-\ln M)]/SE$ (with M as either the noninferiority margin [M=1.25] or the superiority margin [M=1]). Confirmatory evidence was provided by the sequentially rejective testing procedure described previously. All other (2-sided) *P* values ≤0.05 were considered statistically noticeable. For all

time-to-event models, HRs and 2-sided 95% confidence limits were reported. A statistical analysis plan was signed before unblinding of the data and is included in the Supplemental Material.

Sample Size and Power Calculation

AXADIA–AFNET 8 was planned to show noninferiority of the primary safety outcome with 80% power with 64 events. Given the expected combined HR of the composite outcome (HR=0.618), 75 patients would have been sufficient to reach the number of events (on the basis of the log-rank test and the Schoenfeld formula[20]). To adjust for an approximate loss-to-follow-up rate of 30%, 108 patients were planned to be recruited. At the study start in June 2017, the sample size calculation originally included 222 patients to reach a sufficient power for the superiority null hypothesis. After a blind review of recruitment and event rates in 2020, and in view of newly published data,[21] the sample size was changed by an amendment to supply sufficient power for testing the noninferiority null hypothesis. The primary testing strategy and all other aspects of the study design remained unchanged. The data analysis for this article was performed using SAS software (version 9.4, SAS/STAT 14.3; SAS Institute Inc).

RESULTS

Between June 15, 2017, and May 31, 2022, a total of 108 patients were screened in 39 sites throughout Germany. Of these, 97 patients were randomized to treatment with either apixaban (n=48) or VKA (n=49; Figure 1). A total of 70% of the patients were male, and the average age was 74.7 years (SD 7.9). Mean CHA_2DS_2-VASc score was 4.5. All randomized patients were treated. Baseline characteristics were well balanced between randomized groups, including the criteria used for stratification (Table 1 and Table S1). The trial was terminated at the planned maximum duration on July 31, 2022.

Follow-Up

The median follow-up time was 429 days (interquartile range, 174; 702 days) on apixaban therapy and 506 days (interquartile range, 289; 702) on phenprocoumon (Table 2). A total of 60.8% of patients (59/97) were followed up for >12 months after randomization; the maximal follow-up time was 1370 days on apixaban and 1379 days on VKA.

Primary Safety Outcome

Regarding the primary safety outcome, 47 patients (48.5%) had a least one safety event (major bleeding, clinically relevant nonmajor bleeding, or all-cause death). Of these, 22 events occurred in patients randomized to apixaban and 25 events occurred in patients randomized to VKA (Table 2). With respect to on-treatment events, we observed 18 events on apixaban treatment and 18 safety events on VKA treatment (Table 2). The event rate for the composite primary safety outcome in all patients was 36.4 (apixaban 36.1 versus VKA 36.6) per 100 patient-years. The event rate for all-cause mortality in all patients was 16.2 (apixaban 14.8 versus VKA 17.6) per 100 patient-years. There were no differences in all-cause mortality between the 2 groups (apixaban 18.8% versus VKA 24.5%; Table 2).

Outcomes were analyzed by Kaplan-Meier estimates comparing the composite primary safety outcome (Figure 2A) and the composite primary efficacy outcome (Figure 2B); the on-treatment results for both outcomes are shown in Figure 2C and 2D. Cumulative incidences of the composite primary safety outcome in the full analysis set was 59% on apixaban and 73% on VKA (Figure 2A); the on-treatment results were 51% and 57%, respectively (Figure 2C).

The Cox proportional hazard model for the primary safety outcome incorporating all events estimated an HR of 0.931 (95% CI, 0.525–1.651). An assessment of the proportionality assumption of the Cox regression model is presented in Figure S1. This translates into a noninferiority P value of $P_{noninferiority}$=0.157. Thus, noninferiority could not be shown, and the hierarchical testing procedure was stopped. The predefined PP analysis (1 patient excluded because of low CHA_2DS_2-VASc risk [<2] at inclusion) showed a consistent result (HR, 0.895 [95% CI, 0.501–1.599]; $P_{noninferiority}$= 0.130).

We performed another sensitivity PP analysis by excluding 7 patients with protocol violations with respect to treatment switches and one patient with respect to the violated inclusion criterion. This analysis is considered an exploratory sensitivity analysis. Details on the additionally excluded patients can be found in Table S2. The exploratory sensitivity PP analysis showed a consistent result (HR, 0.941 [95% CI, 0.518–1.710]; $P_{noninferiority}$= 0.176; Table S1) with the ITT and the preplanned PP analysis. The Cox proportional hazard model for the on-treatment analysis of the primary safety outcome results in an HR of 1.046 (95% CI, 0.544–2.012; $P_{noninferiority}$= 0.297).

The predefined stratified analyses with regard to previous thromboembolism and anticoagulation-naïve patients showed that without previous thromboembolism in the patient's medical history, apixaban had a similar profile as in the main analysis. Interpretation of the strata with previous thromboembolism was restricted by low power but showed a slight shift of the HR toward favoring VKA (all P>0.05; see Table S1).

Primary Efficacy Outcome

Overall, 26 patients (26.8%) exhibited at least 1 efficacy event (Table 2). Of these, 10 events occurred on apixaban treatment and 15 events occurred on VKA treatment. Most events were cardiovascular deaths (Table 2).

Table 1. Baseline Characteristics

Characteristics	All patients (n=97)	Apixaban (n=48)	Phenprocoumon (n=49)	*P* value*
Male sex, n (%)	68 (70.1)	31 (64.6)	37 (75.5)	0.2399
Age, y				0.9770
Mean (SD)	74.7 (7.9)	74.7 (8.1)	74.8 (7.9)	
Median (Q1, Q3)	77 (69–80)	76.5 (68–81)	77 (70.80)	
Range	57–89	59–89	57–89	
BMI				0.3772
Mean (SD)	28.6 (6.1)	28.0 (5.8)	29.2 (6.4)	
Median (Q1 and Q3)	27.3 (24.3–31.8)	26.9 (24.1–33.1)	27.7 (23.1–31.2)	
Range	18.7–53.0	18.7–40.7	18.99–53.04	
Smoking status, n (%)				0.3531
Never	50 (51.5)	27 (56.3)	23 (46.9)	
Former smoker	42 (43.3)	20 (41.7)	22 (44.9)	
Active smoker	5 (5.2)	1 (2.1)	4 (8.2)	
Coronary heart disease, n (%)				0.1886
No	31 (32.3)	16 (33.3)	15 (31.3)	
One-vessel disease	14 (14.6)	6 (12.5)	8 (16.7)	
Two-vessel disease	6 (6.3)	4 (8.3)	2 (4.2)	
Three-vessel disease	20 (20.8)	6 (12.5)	14 (29.17)	
Main stem stenosis	0	0	0	
Unknown	25 (26.0)	16 (33.3)	9 (18.8)	
Missing information	1	–	1	
Heart valve disease, n (%)	46 (47.4)	27 (56.3)	19 (38.8)	0.0848
Previous MI, n (%)	21 (21.7)	9 (18.8)	12 (24.5)	0.4926
NYHA classification, n (%)				0.4867†
No	0	0	0	
Class I	24 (24.7)	12 (25.0)	12 (24.5)	
Class II	46 (47.4)	20 (41.7)	26 (53.1)	
Class III	24 (24.7)	15 (31.3)	9 (18.4)	
Class IV	3 (3.1)	1 (2.0)	2 (4.1)	
CHA_2DS_2-VASc risk score				0.7856‡
Mean (SD)	4.52 (1.55)	4.50 (1.62)	4.54 (1.49)	
Median (Q1 and Q3)	5 (4–6)	5.00 (3.5–5.0)	4.5 (4–6)	
Range	1–9	1–9	2–7	
Missing	1	0	1	
HAS-BLED risk score				0.7269‡
Mean (SD)	4.20 (1.02)	4.25 (1.02)	4.15 (1.03)	
Median (Q1 and Q3)	4 (3.5–5.0)	4 (3.5–5)	4.0 (3.5–5)	
Range	2–7	3–7	2–7	
Missing	1	0	1	
Days since first dialysis				
Mean (SD)	1687 (2117)	1553 (1329)	1815 (2673)	0.4925‡
Median (Q1 and Q3)	962 (363–2147)	853 (371–2643)	1072 (301–1816)	
Range	2–14128	124–4711	2–14128	
Previous medication, n (%)				
Aspirin	33 (34.0)	16 (33.3)	17 (34.7)	0.8875

(*Continued*)

Table 1. Continued

Characteristics	All patients (n=97)	Apixaban (n=48)	Phenprocoumon (n=49)	*P* value*
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
SGLT2 inhibitor	0	0 (0)	0 (0)	–
Calcium antagonist	21 (21.7)	7 (14.6)	14 (28.6)	0.0944
β-blocker	76 (78.4)	36 (75.0)	40 (81.6)	0.4278
Mineralocorticoid receptor antagonists	0	0 (0)	0 (0)	–
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)	0.10215

ACE indicates angiotensin-converting enzyme; BMI, body mass index; MI, myocardial infarction; NOAC, non–vitamin K oral anticoagulant; NYHA, New York Heart Association; SGLT2, sodium–glucose cotransporter 2; and VKA, vitamin K antagonist.

*Categorical measures were compared by χ^2 test or

†Fisher exact test.

‡Continuous measures were compared by *t* test or Mann-Whitney *U* test.

The event rate for the composite primary efficacy outcome in all patients was 20.1 (apixaban 16.4 versus VKA 22.0) per 100 patient-years. There was no difference in time to primary efficacy outcome between patient groups (Figure 2B); the on-treatment results are shown in Figure 2D.

Cumulative incidences of the composite primary efficacy outcome in the full analysis set was 32% on apixaban and 54% on VKA (Figure 2B); the on-treatment results were 29% and 42%, respectively (Figure 2D).

The Cox proportional hazard model of all events estimated an HR of 0.764 (95% CI, 0.343–1.700; *P*=0.5080). The on-treatment analysis of the efficacy events showed an HR of 0.920 (95% CI, 0.363–2.331; *P*=0.8593) and was thus also consistent with the analysis of all events.

Quality of Anticoagulation

We assessed the quality of anticoagulation by drug accountability for apixaban and the time in therapeutic range (TTR) on the basis of the regular INR controls for phenprocoumon. The TTR was calculated by the Rosendaal method.[22]

In both study arms, all randomized patients started the assigned treatment (ITT). The median therapy duration (first to last intake) was 355.5 days (range, 3 to 1337 days). Of 48 patients randomized to apixaban, 44 adhered to the intake of medication according to protocol; 4 patients missed >20% of the apixaban doses during the therapy. A detailed presentation of the apixaban intake is given in Figure S2. The median time in target range (TTR) in patients randomized to VKA was 50.7% (range, 0 to 100%; Table S3). Three of the 49 patients randomized to VKA never reached the INR target range (INR, 2 to 3) during the study; 14 of 49 patients achieved a TTR >66% during the study. A detailed presentation of the INR values and TTRs is given in Figure S3.

DISCUSSION

In our 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 (Table 2 and Figure 2A through 2D), although the prespecified noninferiority test requirements were not met because of slow enrollment. Our results cannot exclude a clinically relevant difference with the desirable precision because of a lower number of events than planned. The similarity of the observed event rates supports our conclusion. In view of the paucity of randomized trials in this field (Table 3), our 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.

Our results illustrate 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.

Comparison With Other Trials and Studies

When AXADIA–AFNET 8 was initiated, there were neither observational studies nor randomized trials comparing NOACs with VKA in patients with AF on hemodialysis. While our trial was running, 2 other randomized trials comparing NOAC with VKA therapy were started.

RENAL-AF (Renal Hemodialysis Patients Allocated Apixaban Versus Warfarin in Atrial Fibrillation), a US study of apixaban, was stopped early in 2019 after randomizing 154 patients because of severe recruitment problems; the results are published in this issue of *Circulation*.[23] In brief, the patients in the US apixaban trial were an average of 10 years younger and had a slightly lower mean CHA_2DS_2-VASc score of 4.0 compared with 4.5 in our trial. RENAL-AF found no significant differences

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

Exact indicates 2-sided Fisher exact test; LR, 2-sided log-rank test *P* value; NE, not estimable; NI, 1-sided noninferiority *P* value; SUP, 1-sided superiority *P* value; and TIA, transient ischemic attack.

*Tested by a nonparametric Mann-Whitney *U* test.

†Consists of major bleeding, clinically relevant nonmajor bleeding, or all-cause mortality.

‡Consists of myocardial infarction, TIA, all-cause death, deep vein thrombosis, or pulmonary embolism.

between apixaban and VKA regarding safety and efficacy, with 1-year Kaplan-Meier estimates for bleeding of 32% for apixaban and 26% for VKA. RENAL-AF used dosages of 5 mg and 2.5 mg apixaban BID, whereas AXADIA–AFNET 8 only used 2.5 mg of apixaban BID. The number of events is too small to draw conclusions, but rates of major bleeding were high in both AXADIA–AFNET 8 and RENAL-AF. Small differences in bleeding events are most likely attributable to chance in addition to potential differences between treatment with 2.5 mg and 5 mg apixaban BID in the US trial.[23] The pharmacodynamics data reported in RENAL-AF suggest that the 2.5-mg BID dose tested in AXADIA–AFNET 8 results in plasma concentrations that are comparable to those observed in patients without kidney disease, whereas the 5-mg BID dose results in plasma concentrations comparable to those observed in patients with CKD.[23]

Another published trial with 132 patients compared VKA with 10 mg of rivaroxaban and 10 mg of rivaroxaban combined with vitamin K2 in 1:1:1 fashion at 3 Belgian centers.[24] Although in the Belgian trial, the treatment groups were only slightly smaller than in our trial, the investigators found a significantly lower event rate for both bleeding and thromboembolism on rivaroxaban, resulting in HRs of 0.39 and 0.41, respectively: their event rates per 100 patient-years for the primary efficacy outcome were 63.8 in the VKA group, 26.2 in the 10-mg rivaroxaban group, and 21.4 in the 10-mg rivaroxaban plus vitamin K2 group, whereas we observed only 22.0 in the VKA group and 16.4 in the apixaban group. The event rates for all-cause death in the Belgian trial were 33.7 in the VKA group and 28.3 and 30.2 in the 2 rivaroxaban groups, respectively, whereas we observed 17.6 in the VKA group and 14.8 in the apixaban group. Therefore, our event rates in the VKA group were markedly lower than in the Belgian trial, which may be one reason they found a significant benefit for rivaroxaban.[24]

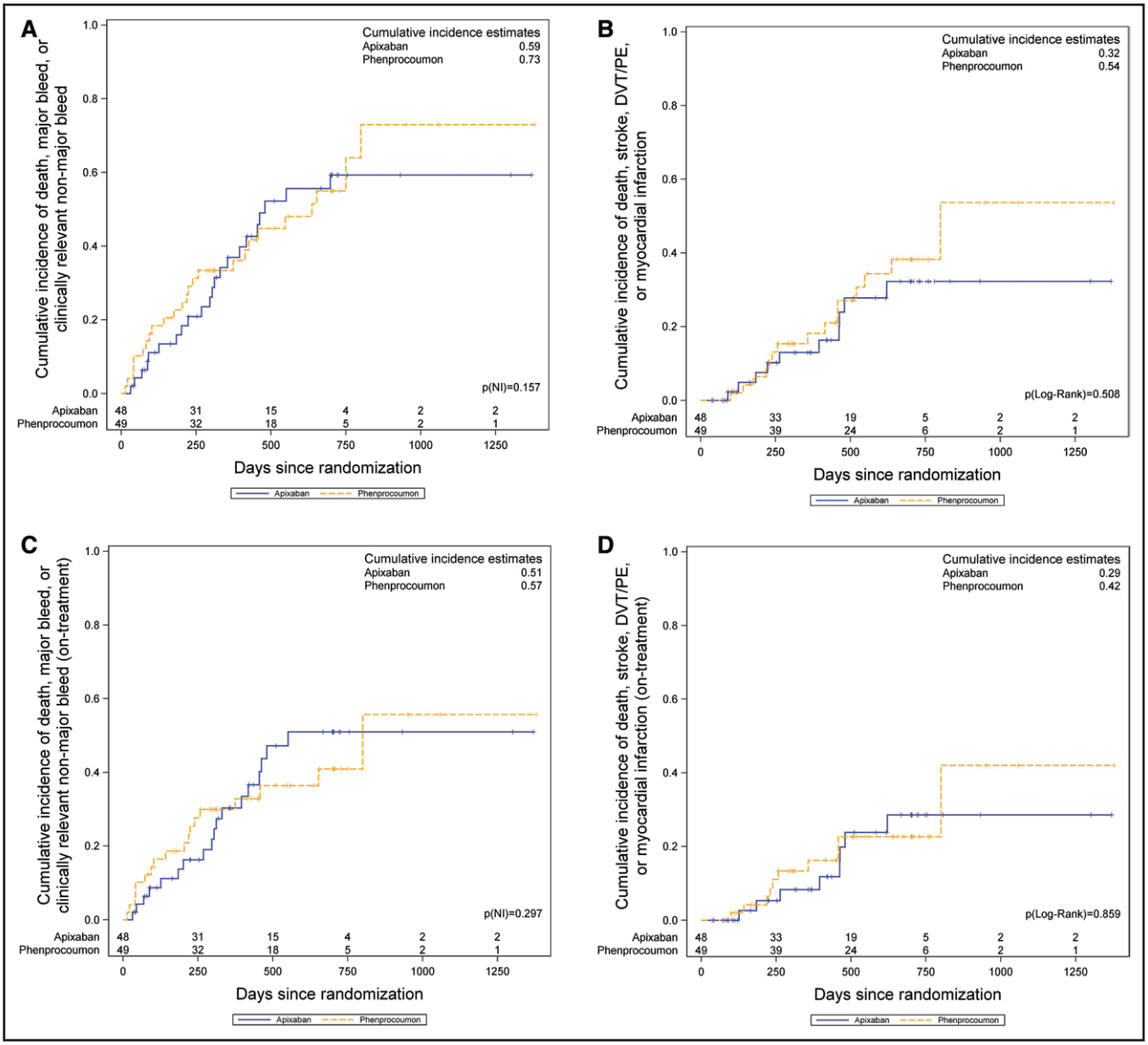

Figure 2. Cumulative incidence of the composite primary safety and efficacy outcome.
A, Cumulative incidence (inverse Kaplan-Meier) for the primary composite safety outcome (major bleeding, clinically relevant nonmajor bleeding, or all-cause death) in the intention-to-treat population. According to the null hypothesis, the 1-sided noninferiority *P* value $P_{noninferiority}$ is given. **B**, Cumulative incidence for the primary composite efficacy outcome (myocardial infarction, ischemic stroke, all-cause death, cardiovascular death, and deep vein thrombosis [DVT] or pulmonary embolism [PE]) is shown and compared with a 2-sided log-rank test. **C** and **D**, The same results for the on-treatment analysis.

Of note, in AXADIA–AFNET 8 and in the other 2 randomized controlled trials,[23,24] the mean TTR in the VKA arm was comparable but low (50.7%, 44%, and 48%, respectively), which is lower than the TTR achieved in patients with remaining excretion by the kidneys, although patients on hemodialysis see their doctors 3 times per week. The low TTR also lends support to the use of NOACs in this population.

The primary safety outcome in AXADIA–AFNET 8 comprised relevant safety events, similar to other trials comparing different anticoagulants. The efficacy outcome in the phase III NOAC studies only counted stroke and systemic embolism. The main efficacy outcome of AXADIA–AFNET 8 combined cardiovascular death, stroke, myocardial infarction, pulmonary embolism, and deep vein thrombosis. This combination of events was chosen by the steering committee because each of these outcomes seems relevant for patients and for health care systems and each can be influenced by anticoagulants.

An overview of the key data of these 2 randomized trials,[23,24] the few retrospective comparisons of NOACs compared with VKA,[14–16,21,25–27] and 2 meta-analyses of the available observational data in patients on hemodialysis[28,29] are summarized in Table 3. Taken together, the 3 randomized controlled trials comparing NOAC therapy with VKA, including our trial, found no evidence

Table 3. Overview of Studies Analyzing Oral Anticoagulation in Patients on Chronic Hemodialysis

Publication	Database	Study design	Treatment	Outcomes
Rivaroxaban vs VKA				
De Vriese et al[24]	132 patients on hemodialysis with AF, February 2015 through January 2019, Belgium	Randomized 1:1:1, 18 months FU	46 patients (34.8%) on 10 mg rivaroxaban, 42 patients (31.8%) on 10 mg rivaroxaban plus vitamin K2, 44 patients (33.3%) on VKA (INR 2–3); TTR: 48% during the first 6 months; subtherapeutic ≈37%, supratherapeutic ≈16%	Primary efficacy outcome: composite of fatal and nonfatal cardiovascular events VKA: 35 patients = 63.8/100 PY 10 mg rivaroxaban: 23 patients = 26.2/100 PY 10 mg rivaroxaban + vitamin K2: 17 patients = 21.4/100 PY HR (rivaroxaban vs VKA), 0.41 (95% CI, 0.25–0.68; *P*=0.0006); HR (rivaroxaban + vitamin K2 vs VKA), 0.34 (95% CI, 0.19– 0.61; *P*=0.0003) Secondary efficacy outcomes: no differences in death from any cause, cardiac death, risk of stroke; all-cause death (*P*=0.66, Fisher exact test); VKA: 32 patients = 33.7/100 PY; 10 mg rivaroxaban: 30 patients = 28.3/100 PY; 10 mg rivaroxaban + vitamin K2: 27 patients = 30.2/100 PY Safety outcome: life-threatening and major bleeding compared with VKA: VKA: 17 patients = 30 events; rivaroxaban: 8 patients = 11 events; rivaroxaban + vitamin K2: 9 patients = 12 events; HR (rivaroxaban vs VKA), 0.39 (95% CI, 0.17–0.90; *P*=0.03); HR (rivaroxaban + vitamin K2 vs VKA), 0.48 (95% CI, 0.22–1.08; *P*=0.08)
Apixaban vs warfarin				
Pokorney et al[23]	154 patients with AF, CHA_2DS_2-VASc score ≥2, ESKD on hemodialysis, candidate for OAC, January 2017–January 2019; trial stopped prematurely because of enrollment challenges	Randomized 1:1, 12 months FU, median FU time 330 days apixaban, 340 days warfarin	82 patients on apixaban, 77 patients (94%) receiving at least 1 dose of apixaban, 55 patients (71%) 2×5 mg, 22 patients (29%) 2×2.5 mg Of the 55 patients with 2×5 mg apixaban, 15 patients (27%) had at least 1 temporary reduction to 2×2.5 mg apixaban 72 patients warfarin (INR 2–3) 69 patients (93%) receiving at least 1 dose of warfarin TTR 44% (IQR, 23%–59%)	Primary outcome: major and clinically relevant, nonmajor bleeding: apixaban, 21 of 82 patients (26%); warfarin, 16 of 72 patients (22%); *P*>0.05 1-year event rates: 32% apixaban, 26% warfarin; HR, 1.20 (95% CI, 0.63–2.30) International Society on Thrombosis and Haemostasis major bleed: apixaban, 9 patients (11%); warfarin, 7 patients (10%) Secondary outcomes: stroke: 2 patients (2%) apixaban vs 2 patients (3%) warfarin; systemic embolism: no events; mortality: 21 patients (26%) apixaban vs 13 patients (18%) warfarin; cardiovascular death: 9 patients (11%) apixaban vs 4 patients (6%) warfarin; apixaban pharmacokinetics are presented
Apixaban vs no anticoagulation				
Mavrakanas et al[25]	2082 patients on dialysis with AF treated with apixaban or no anticoagulation, January 2012–December 2015, United States, US Renal Data System	Retrospective	Propensity score matching 3:1; 1561 patients no anticoagulation, 521 patients apixaban, 207 patients (40%) 2×5 mg, 257 patients (49%) 2×2.5 mg; 57 patients (11%) switched doses	Primary outcome: apixaban vs no anticoagulation; hospital admission for a new stroke (ischemic or hemorrhagic), transient ischemic attack, or systemic thromboembolism: apixaban 13 events, 7.5 events per 100 PY; no OAC: 114 events, 7.0 events per 100 PY; HR (crude), 1.24 (95% CI, 0.69–2.23; *P*=0.47); HR (adj), 1.29 (95% CI, 0.72–2.33; *P*=0.39); subgroup analysis: apixaban 2×5 mg vs no OAC; apixaban: <11 events, 13.6 events per 100 PY; no OAC: 51 events, 7.6 events per 100 PY; HR (crude), 1.80 (0.84–3.86; *P*=0.13); HR (adj), 2.24 (95% CI, 1.03–4.86; *P*=0.04); apixaban 2×2.5 mg vs no OAC: apixaban: <11 events, 5.7 events per 100 PY; no OAC: 50 events, 6.1 events per 100 PY; HR (crude), 1.15 (0.45–2.93; *P*=0.77); HR (adj), 1.11 (95% CI, 0.43–2.85; *P*=0.84) Secondary outcome: apixaban vs no anticoagulation, fatal or intracranial bleeding (major bleeding); apixaban: <11 events, 4.9 events per 100 PY; no OAC: 45 events, 1.6 events per 100 PY; HR (crude), 2.74 (95% CI, 1.37–5.47; *P*=0.004); HR (adj), 2.76 (95% CI, 1.38–5.52; *P*=0.004); subgroup analysis: apixaban 2×5 mg vs no OAC; apixaban: <11 events, 9.8 events per 100 PY; no OAC: 20 events, 1.7 events per 100 PY; HR (crude), 4.33 (1.81–10.35; *P*=0.001); HR (adj), 4.61 (95% CI, 1.91–11.15; *P*=0.001); apixaban 2×2.5 mg vs no OAC; apixaban: <11 events, 2.9 events per 100 PY; no OAC: 20 events, 1.4 events per 100 PY; HR (crude), 2.03 (0.59–7.04; *P*=0.26); HR (adj), 2.02 (95% CI, 0.58–7.04; *P*=0.27)

(*Continued*)

Table 3. Continued

Publication	Database	Study design	Treatment	Outcomes
NOACs vs warfarin				
See et al[26]	12 500 patients with ESKD and AF, June 2012–December 2017, health insurance claims data of the Taiwan National Health Insurance, Taiwan	Retrospective	9263 patients no anticoagulation, 3237 patients anticoagulation, 490 patients (15%) NOAC, 88 patients apixaban, 72 (82%) 2×2.5 mg, 150 patients dabigatran, 138 (92%) 2×110 mg, 19 patients edoxaban, 17 (89%) 30 mg, 233 patients rivaroxaban, 224 (96%) 15/10 mg, 2747 (85%) warfarin 1:1 Propensity score matching 2977 no anticoagulation, 2977 anticoagulation, no TTR given	Outcomes: ischemic stroke/systemic embolism: NOAC 6.67 vs warfarin 5.30 events/100 years; HR 1.21 (95% CI, 0.76–1.92); intracranial hemorrhage: NOAC 1.08 vs warfarin 1.34 events/100 years, HR, 0.78 (95% CI, 0.29–2.10); major bleeding: NOAC 7.07 vs warfarin 7.15 events/100 years, HR, 0.98 (95% CI, 0.64–1.51)
Apixaban vs warfarin				
Ionescu et al[14]	707 patients on hemodialysis initiated on oral anticoagulation for VTE or AF, January 2014–December 2018, United States	Retrospective, multicenter	563 patients (80%) warfarin, 144 patients (20%) apixaban, 92 patients (13%) 2×2.5 mg, 52 patients (7%) 2×5 mg INR values available in 168/173 patients (patients on warfarin with bleeding events) Median INR 2.8, 76 patients (44%) supratherapeutic (INR >3)	Primary event: major or clinically relevant nonmajor bleeding: $P<0.01$; warfarin: 173 patients = 30.7% bleeding rate; apixaban: 24 patients = 16.7% (no difference between dosing); HR, 0.55 (95% CI, 0.35–0.86); with concomitant antiplatelet use, frequencies were similar (31.4% vs 25.0%; $P=0.292$) Secondary event: thrombotic or embolic event (no HR given); warfarin 37 patients = 6.6%; apixaban 7 patients = 4.9% Additional information: nearly all patients (95.4%) were outside the therapeutic range (INR between 2 and 3) >60% of the time; 76 patients (44.0%) had a supratherapeutic value, defined as INR >3
Reed et al[15]	124 patients with ESKD on dialysis receiving apixaban or warfarin, January 2014–October 2016, United States	Retrospective, single-center, FU time 10 months	124 patients, 74 patients apixaban, 59 patients (80%) 2×5 mg, 15 patients (20%) 2×2.5 mg, 50 patients warfarin The study did not assess INR management or TTR for patients on warfarin as it was a retrospective analysis	Indication for anticoagulation: AF: apixaban 29 patients (39%), warfarin 29 patients (58%); VTE: apixaban 45 patients (61%), warfarin 21 patients (42%) Bleeding: apixaban 14 events (3 events in patients on 2×2.5 mg apixaban; these events were clinically relevant nonmajor bleeding events), 18.9%; warfarin 21 events, 42.0%; $P=0.01$; OR, 0.15 (95% CI, 0.05–0.46; $P=0.001$) Major bleeding: apixaban 4 events, 5.4%; warfarin 11 events, 22.0%; $P=0.01$ Recurrent ischemic stroke: none Recurrent VTE: apixaban 2 events, 4.4%; warfarin 6 events, 28.6%, $P=0.99$
Siontis et al[21]	25 523 patients with ESKD and AF undergoing dialysis who initiated treatment with oral anticoagulation, October 2010–December 2015, United States, Medicare beneficiaries included in the US Renal Data System	Retrospective	23 172 (91%) warfarin, 2351 (9%) apixaban (1034 2×5 mg, 1317 2×2.5 mg), matched (1:3 apixaban: warfarin) analysis, 2351 apixaban, 7053 warfarin, no TTR or INR given	Matched cohort: stroke/systemic embolism: apixaban 81 events, 12.4 events per 100 PY; warfarin 373 events, 11.8 events per 100 PY; HR, 0.88 (95% CI, 0.69–1.12; $P=0.29$) Major bleeding, apixaban vs warfarin: apixaban 129 events, 19.7 events per 100 PY; warfarin 715 events, 22.9 events per 100 PY; HR, 0.72 (95% CI, 0.59–0.87; $P<0.001$) Death, apixaban vs warfarin: apixaban 159 events, 23.7 events per 100 PY; warfarin 753 events, 24.9 events per 100 PY; HR, 0.85 (95% CI, 0.71–1.01; $P=0.06$) No difference in intracranial (event rate 3.1 vs 3.5 per 100 PY) or gastrointestinal bleeding (event rate 23.8 vs 23.4 per 100 PY)
Sarratt et al[16]	160 patients with ESKD undergoing hemodialysis who had received apixaban or warfarin for treatment or prevention of VTE	Retrospective, single-center	120 warfarin, 40 apixaban, 23 patients 2×2.5 mg, 17 patients 2×5 mg, INR at inclusion 2.27 (range 0.47–4.07)	Bleeding: no information on analyzed time period; major bleeding: $P=0.338$; apixaban 0 patients, warfarin 7 (5.8%) patients (regarding these 7 patients, admission INRs ranged from 1.29 to >20); clinically relevant nonmajor bleeding: $P=0.116$; apixaban 5 (12.5%) patients, warfarin 7 (5.8%) patients
Wetmore et al[27]	17 156 patients with AF and on dialysis treated with apixaban or warfarin, United States, US Renal Data System database 2013–2018	Retrospective	Apixaban 2×5 mg (label-concordant), 2×2.5 mg (below-label), warfarin	Ischemic stroke/systemic embolism: no difference between groups Major bleeding: label-concordant vs warfarin: HR, 0.67 (95% CI, 0.55–0.81); below label vs warfarin: HR, 0.68 (95% CI, 0.55–0.84); below label vs label-concordant: HR, 1.02 (95% CI, 0.78–1.34) All-cause mortality: label-concordant vs warfarin: HR, 0.85 (95% CI, 0.78–0.92); below label vs warfarin: HR, 0.97 (95% CI, 0.89–1.05)

(*Continued*)

Table 3. Continued

Publication	Database	Study design	Treatment	Outcomes
Reviews and meta-analyses				
Elfar et al[28]	34 516 patients with AF and ESKD on dialysis (5 studies: 2 RCTs and 2 retrospective, 1 prospective)	Meta-analysis: 5 studies	31 472 (91.1%) warfarin, 3044 (8.9%) NOACs, 2473 apixaban, 290 rivaroxaban, 281 dabigatran	Outcome: NOACs vs warfarin Significant differences in systemic embolization: NOACs 102 events (3.39%); warfarin 619 events (1.97%); HR, 1.74 (95% CI, 1.08–2.80; *P*=0.02); minor bleeding: NOACs 47 events (6.78%); warfarin 183 events (2.2%); HR, 1.52 (95% CI, 1.07–2.15; *P*=0.02); death: NOACs 342 events (11.38%); warfarin 1607 events (5.12%); HR, 1.72 (95% CI, 1.16–2.55, *P*=0.006); no significant differences in the incidence of hemorrhagic stroke, major bleeding, hemodialysis access site bleeding, ischemic stroke, or GI bleeding were found between NOACs and warfarin.
Kuno et al[29]	71 877 patients on dialysis and with AF	Meta-analysis: 16 studies, only 2 investigating NOACs	No anticoagulation, apixaban, dabigatran, rivaroxaban, warfarin	Stroke/systemic thromboembolism: OAC vs no anticoagulation; analyzed cohort is composed of no anticoagulation: 28 996 patients included; warfarin: 31 941 patients included; apixaban 5 mg: 1034 patients included; apixaban 2.5 mg: 1317 patients included; apixaban 5 mg: HR, 0.59 (95% CI, 0.30–1.17); apixaban 2.5 mg: HR, 1.00 (95% CI, 0.52–1.93); warfarin: HR, 0.91 (95% CI, 0.72–1.16) Mortality analyzed cohort is composed of no anticoagulation: 17 886 patients included; warfarin: 27 845 patients included; apixaban 5 mg: 1034 patients included; apixaban 2.5 mg: 1317 patients included; apixaban 5 mg vs warfarin: HR, 0.65 (95% CI, 0.45–0.93); apixaban 5 mg vs apixaban 2.5 mg: HR, 0.62 (0.42–0.90); apixaban 5 mg vs no anticoagulation: HR, 0.61 (95% CI, 0.41–0.90); major bleeding analyzed cohort is composed of no anticoagulation: 18 279 patients included; warfarin: 36 757 patients included; apixaban 5 mg: 1034 patients included; apixaban 2.5 mg: 1317 patients included; dabigatran: 281 patients included; rivaroxaban: 244 patients included; warfarin vs apixaban 5 mg: HR, 1.41 (95% CI, 1.07–1.82); warfarin vs apixaban 2.5 mg: HR, 1.40 (95% CI, 1.07–1.82); warfarin vs no anticoagulation: HR, 1.31 (95% CI, 1.15–1.50)

adj indicates adjusted; AF, atrial fibrillation; ESKD, end-stage kidney disease; FU, follow-up; GI, gastrointestinal; HR, hazard ratio; INR, international normalized ratio; NOAC, non–vitamin K oral anticoagulant; OAC, oral anticoagulant; PY, patient-years; TTR, time in therapeutic range; VKA, vitamin K antagonist; and VTE, venous thromboembolism.

that NOAC therapy would be unsafe or less effective than VKA. The majority of the observational studies that included patients not receiving OAC also support the use of OAC in patients with AF and stroke risk factors on hemodialysis (Table 3). For considerations about choosing the reduced apixaban dose in our trial, see the Research Hypothesis in the Methods. RENAL-AF provided pharmacokinetic data from the patients on hemodialysis receiving 2.5 mg BID and 5 mg BID, which shows that the dosage of 2.5 mg BID, as chosen in AXADIA–AFNET 8, was associated with identical plasma levels (steady-state area under the curve, 0 to 12) compared with individuals with normal kidney function receiving 5 mg BID.[23] These results of RENAL-AF viewed in context of the other published data do not provide a substantial signal supporting one or the other NOAC dose.

Strengths and Weaknesses

Strengths of AXADIA–AFNET 8 are the prospective recruitment in 39 hemodialysis centers in Germany, randomized comparison of a standardized NOAC therapy with apixaban (2.5 mg BID) with intensively controlled VKA therapy, and the high event rate. Careful capture of events and central, blind adjudication of events in a rigorous PROBE design is another strength of the data. The adherence to the assigned drug therapy was high in both arms: all patients received the assigned therapy after randomization (only 4 of 48 patients in the apixaban arm showed some deviations). The TTR in the VKA arm was lower (50.7%) than the TTR in large NOAC trials testing anticoagulation in patients not on hemodialysis. This low TTR is a limitation of the trial but also seems to reflect the usual quality of VKA therapy in patients with AF on hemodialysis because it is comparable to the TTR in RENAL-AF (44%),[23] the Belgian trial (48%),[24] and other reports of VKA (Table 3). Thus, VKA therapy seems to be difficult to deliver in patients on hemodialysis despite regular visits with coagulation checks during hemodialysis sessions, as also observed in the 2 other randomized trials.

AXADIA–AFNET 8 was not able to recruit the planned number of patients, requiring an adjustment of the planned number of patients on the basis of a blind review of recruitment and events. The high event rate partially compensated for the slow recruitment, but the study was stopped after reaching the maximal defined duration, observing 48 of the planned 64 events. Because of failure to reach the calculated number of patients and events, our study missed the predefined noninferiority margin for apixaban to VKA regarding safety in the full analysis set (1-sided P_{non-}

$_{inferiority}$=0.1567) and the on-treatment analysis (1-sided $P_{noninferiority}$=0.297; Figure 2A and 2C). Given the observed treatment effect and using the Schoenfeld formula,[20] a total of 177 patients (instead of 64) with a relevant safety event would have been necessary to achieve a CI that would have been able to prove noninferiority. With regard to thromboembolic events, as indicated by the composite primary efficacy outcome, there was no signal for differences between the 2 treatment groups (Table 2 and Figure 2B and 2D).

The trial lacked a third arm with no anticoagulation. Thus, the results cannot clarify whether OAC is indicated in patients with AF on hemodialysis. In view of the high thromboembolic event rate observed in AXADIA–AFNET 8, and in context with observational data (Table 3), the initial design without a third arm remains justifiable.

ARTICLE INFORMATION

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Disclosures

Dr Bauersachs reports consulting/lecture fees from Bayer, Bristol Myers Squibb (BMS), Daiichi-Sankyo, Pfizer, and VIATRIS, all outside the submitted work; and research support by the Bavarian State Ministry of Health. Until 2019, Dr Breithardt received speaker honoraria from BMS and Pfizer; he has been a member of scientific advisory boards for BMS, Pfizer, and Bayer Health Care; and during his chairmanship of the AFNET, this institution has received funding for investigator-initiated trials from various companies (for details, please consult http://www.kompetenznetz-vorhofflimmern.de/en/research). Dr Engelbertz has received travel support from Bayer Vital and Abbott outside the submitted work. Dr Haeusler reports speaker honoraria, consulting fees, lecture honoraria, or study grants from Abbott, Alexion, Amarin, AstraZeneca, Bayer Healthcare, Sanofi, Boehringer Ingelheim, Daiichi Sankyo, Pfizer, Bristol Myers Squibb, Biotronik, Medtronic, Portola, Getemed AG, Premier Research, WL Gore and Associates, SUN Pharma, and Edwards Lifesciences. Dr Hewing has received speaker honoraria from BMS, Pfizer, Novartis, Sanofi, Amgen, Daiichi-Sankyo, Berlin Chemie, Bayer, and Astra Zeneca. Dr Reinecke has received speaker honoraria from NeoVasc, Corvia, BMS, MedUpdate, StremedUp, NephroUpdate, and Pfizer; has acted as a consultant for BMS, Pfizer, and Pluristem, receiving in part also financial compensation for this work; has received research grants from the German Federal Ministry for Education and Research (BMBF); and his division within the University Hospital of Muenster has taken or is still taking in multicenter trials of BARD, Bayer, BIOTRONIK, Novartis, and Pluristem, receiving patient fees and financial compensation for these efforts. Dr Gerß has received honoraria from TESARO, QUIRIS Healthcare, Ecker+Ecker, Dr August Wolff, Roche, University Hospital Schleswig-Holstein, and RWTH Aachen University. Dr Rump has received speaker honoraria from Astellas, Baxter, Bayer, Boehringer, Fresenius, StreamedUp, NephroUpdate, and Novartis; has acted as a consultant for Bayer, Medtronic, Novartis, and ReCor, receiving financial compensation for this work; and his department within the University Hospital of Duesseldorf has taken or is still taking in multicenter trials of Bayer, Oxford University, Medtronic, and ReCor, receiving patient fees and financial compensation for these efforts. Dr Kirchhof has received research support for basic, translational, and clinical research projects from European Union, British Heart Foundation, Leducq Foundation, Medical Research Council (UK), German Centre for Cardiovascular Research, and several drug and device companies active in atrial fibrillation and has received honoraria from several such companies in the past, but not in the past 3 years, and is listed as inventor on 2 patents held by University of Birmingham (Atrial Fibrillation Therapy WO 2015140571, Markers for Atrial Fibrillation WO 2016012783). Dr Wanner does not report conflicts of interest in respect to the current work; outside this area of research, he has received speaker honoraria from Amgen, Boehringer-Ingelheim, Genzyme-Sanofi, and Shire. Dr Goerlich has received research funding from the European Union and the German Jose Carreras Leukemia Foundation for research unrelated to this trial. The other authors do not report any conflicts of interest.

Supplemental Material

Expanded Methods
Tables S1–S3
Figures S1–S3
Participating sites and local principal investigators
Members of the safety monitoring board
Members of the end point assessment committee
Members of the steering committee
Study protocol
Statistical analysis plan

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