Circulation

ORIGINAL RESEARCH ARTICLE

Apixaban for Patients With Atrial Fibrillation on Hemodialysis: A Multicenter Randomized Controlled Trial

Sean D. Pokorney, MD, MBA; Glenn M. Chertow, MD; Hussein R. Al-Khalidi, PhD; Dianne Gallup, MS; Pat Dignacco, BA; Kurt Mussina, MBA; Nisha Bansal, MD; Crystal A. Gadegbeku, MD; David A. Garcia, MD; Samira Garonzik, PharmD; Renato D. Lopes, MD, PhD; Kenneth W. Mahaffey, MD; Kelly Matsuda, PharmD; John P. Middleton, MD; Jennifer A. Rymer, MD, MBA; George H. Sands, MD; Ravi Thadhani, MD; Kevin L. Thomas, MD; Jeffrey B. Washam, PharmD; Wolfgang C. Winkelmayer, MD; Christopher B. Granger, MD; on behalf of the RENAL-AF Investigators

Background

- Atrial fibrillation (AF) is common in patients with chronic kidney disease (CKD), with prevalence estimates ranging from 13% to nearly 50%.
- Evidence of net safety and benefit of anticoagulation for stroke prevention in patients with CKD and AF is lacking because patients with advanced CKD and those with end-stage kidney disease (ESKD) have been excluded from randomized clinical trials of stroke prevention in AF.
- Observational data of apixaban in advanced CKD and ESKD have suggested that apixaban may be a safe and effective alternative to warfarin.

AIM of the study

- To test the hypothesis that apixaban was noninferior to warfarin for safety with respect to major or clinically relevant nonmajor bleeding in patients with AF and ESKD on hemodialysis.

Methods

- The RENAL-AF trial (Renal Hemodialysis Patients Allocated Apixaban Versus Warfarin in Atrial Fibrillation; NCT02942407) is a prospective, randomized, open-label, blinded-outcome evaluation (PROBE) trial.
- Eligible patients had AF, a CHA2DS2-VASc score ≥2, have received chronic hemodialysis therapy for ≥3 months, and were considered by their treating physician to be a candidate for oral anticoagulation.
- Patients were randomly assigned 1:1 to 5 mg of apixaban twice daily (2.5 mg twice daily for patients ≥80 years of age, weight ≤60 kg, or both) or dose-adjusted warfarin (INR 2-3).
- The primary outcome was major or clinically relevant nonmajor bleeding.
- Secondary outcomes included stroke, mortality, and apixaban pharmacokinetics.
- Pharmacokinetic sampling was day 1, day 3, and month 1.

Results (I)

- 154 patients: 82 randomly assigned to apixaban and 72 randomly assigned to warfarin.
- Median follow-up did not differ in both groups: 330 days and 340 days in patients randomly assigned to apixaban and warfarin, respectively.
- Time in therapeutic range (INR, 2.0–3.0) for warfarin-treated patients was 44% (interquartile range, 23%–59%).
- The primary outcome occurred in 21 (26%) patients in the apixaban group and 16 (22%) patients in the warfarin group.
- The 1-year incidence of major or clinically relevant non major bleeding was 31.5% in the apixaban group and 25.5% in the warfarin group.
- There were 9 (11%) major bleeding events in the apixaban group and 7 (10%) major bleeding events in the warfarin group, with 1 intracranial hemorrhage in each group.
- Hemodialysis access site bleeding events were responsible for the majority of the clinically relevant nonmajor bleeds in both the apixaban and warfarin groups.

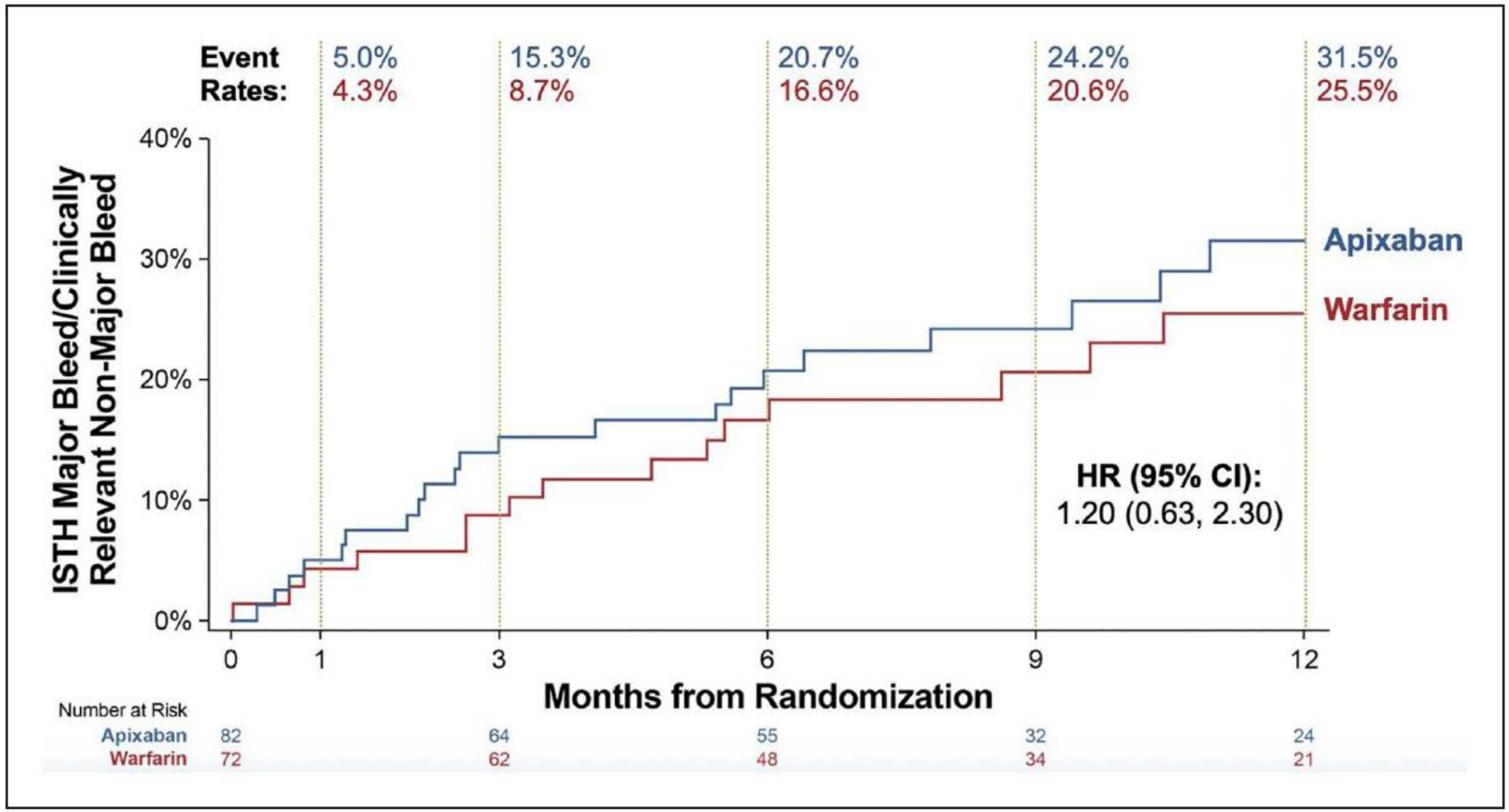

Figure 1. Time to major or clinically relevant nonmajor bleeding.
HR indicates hazard ratio; and ISTH, International Society of Thrombosis and Haemostasis.

Table 2. Primary Safety Outcome on the Basis of Intention-to-Treat Analysis

Primary safety outcome	Apixaban n=82	Warfarin n=72
International Society for Thrombosis and Haemostasis major bleed/clinically relevant nonmajor bleed	21 (26)	16 (22)
Intracranial	1 (1)	1 (1)
Gastrointestinal	2 (2)	6 (8)
Hemodialysis access site	11 (13)	6 (8)
Other	7 (9)	3 (4)
International Society for Thrombosis and Haemostasis major bleed	9 (11)	7 (10)
Intracranial	1 (1)	1 (1)
Gastrointestinal	4 (5)	5 (7)
Hemodialysis access site	1 (1)	0 (0)
Other	3 (4)	1 (1)
International Society for Thrombosis and Haemostasis clinically relevant nonmajor bleed	14 (17)	10 (14)
Intracranial	0 (0)	0 (0)
Gastrointestinal	0 (0)	2 (3)
Hemodialysis access site	10 (12)	6 (8)
Other	4 (5)	2 (3)

Results (II)

- Death was the most common major event, with 21 (26%) patients having died in the apixaban arm and 13 (18%) patients having died in the warfarin arm.
- There were 3 ischemic strokes and 3 deaths related to major bleeding.
- The 1-year event rates for stroke or systemic embolism were 3.0% (95% CI, 0.5%–9.7%) and 3.3% (95% CI, 0.6%–10.5%) in the apixaban and warfarin groups, respectively.

Table 3. Secondary Outcomes Based on Intention-to-Treat Analysis

Secondary outcomes	Apixaban n=82	Warfarin n=72
Stroke, n (%)	2 (2)	2 (3)
Ischemic	1 (1)	2 (3)
Hemorrhagic	1 (1)	0 (0)
Systemic embolism, n (%)	0 (0)	0 (0)
Death, n (%)	21 (26)	13 (18)
Cardiovascular	9 (11)	4 (6)
Noncardiovascular	5 (6)	8 (11)
Undetermined	7 (9)	1 (1)
Major bleeding-related death*	1 (1)	2 (3)

*Major bleed occurred within 30 days of death.

Results (III)

- Data from 50 patients.
- Median steady-state 12-hour area under the curve was 2475 ng/mL×h (10th to 90th percentiles, 1342–3285) for 5 mg of apixaban twice daily and 1269 ng/mL×h (10th to 90th percentiles, 615–1946) for 2.5 mg of apixaban twice daily.
- There was substantial overlap between minimum apixaban blood concentration, 12-hour area under the curve, and maximum apixaban blood concentration for patients with and without a major or clinically relevant nonmajor bleeding event.

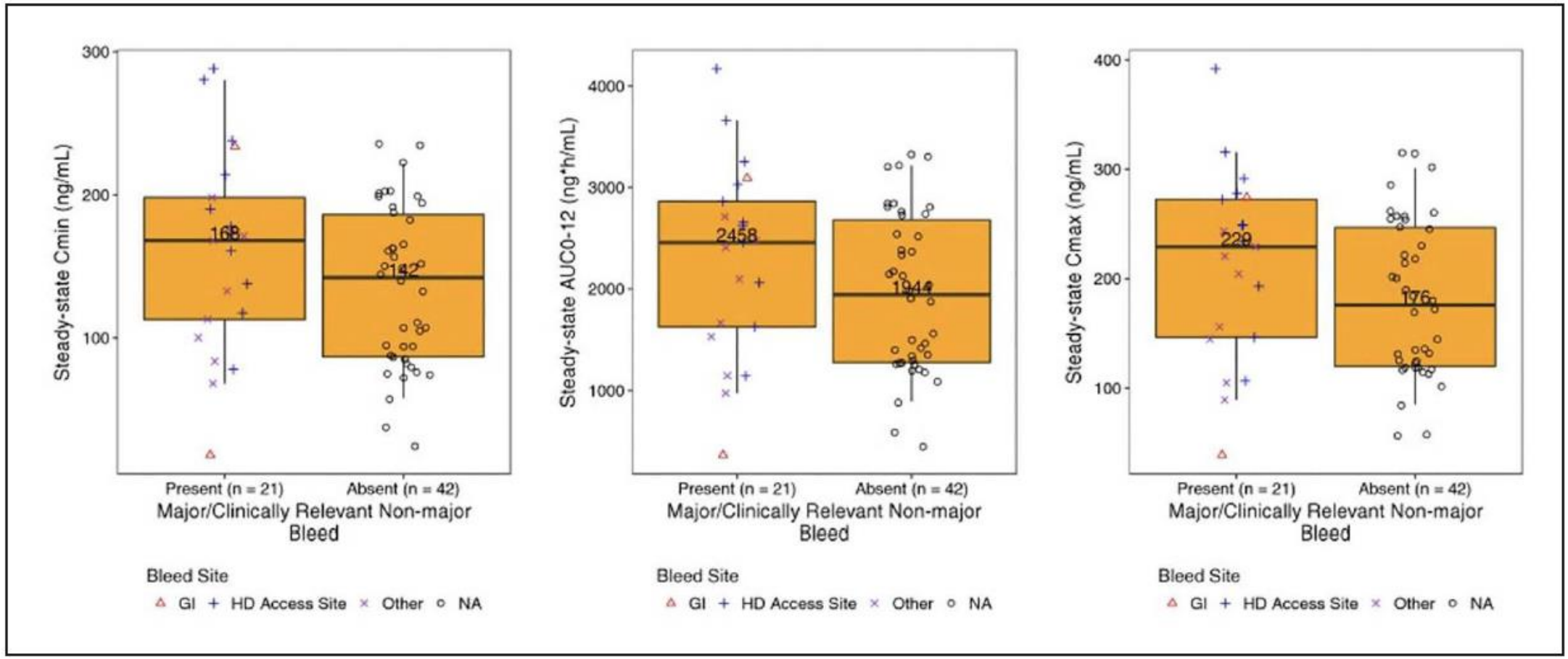

Figure 4. Comparison of pharmacokinetic values among patients with and without a major or clinically relevant nonmajor bleeding event.

Conclusions

- In this trial there was inadequate power to draw any conclusion regarding the rates of major or clinically relevant nonmajor bleeding comparing apixaban and warfarin.
- Among patients with ESKD on hemodialysis, apixaban drug levels did not differ from those observed with standard dosing of apixaban for patients with CKD in previous trials.
- The high mortality registered in the trial underscores the urgent need for improved treatments in this population, although most deaths were not attributable to thrombosis and will not be prevented by improvements in anticoagulant therapy.
- Future studies are needed to evaluate the risks of bleeding versus the benefits of stroke prevention and the effect on all-cause mortality with any anticoagulation in patients with AF and ESKD on hemodialysis.