Journal of Thrombosis and Thrombolysis
https://doi.org/10.1007/s11239-019-02028-z

Safety outcomes of apixaban in patients with nonvalvular atrial fibrillation and severe renal impairment

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Abstract

Apixaban is prescribed for stroke prevention in nonvalvular atrial fibrillation (NVAF) in patients with varying degrees of renal dysfunction. While pharmacokinetic data support apixaban in severe renal impairment, clinical safety outcomes data are limited. This retrospective cohort analysis was conducted to evaluate the safety of apixaban in patients with NVAF and renal impairment. A total of 340 patients with NVAF receiving apixaban 5 mg or 2.5 mg twice daily were included for analysis; 287 preserved renal function (pRF: CrCl ≥ 25 ml/min and SCr ≤ 2.5 mg/dl) and 53 impaired renal function (iRF: CrCl < 25 ml/min and/or SCr > 2.5 mg/dl). The primary endpoint was major bleeding in patients taking apixaban 5 mg. Secondary endpoints included major bleeding with apixaban 2.5 mg and minor bleeding in both groups. There was no difference in major bleeding events in the 5 mg pRF group (4.41%) versus iRF group (3.57%) ($P = 0.66$). Similar rates occurred between the 2.5 mg pRF and iRF groups. Minor bleeding events were similar regardless of renal function. The incidence of bleeding in the 5 mg group was 11.45% with pRF versus 10.71% with iRF ($P = 0.6$). In the 2.5 mg group, bleeding incidence was 10% with pRF versus 16% with iRF ($P = 0.47$). There were no observed differences in bleeding between groups with pRF or iRF, regardless of apixaban dose. Because patients with severe renal impairment were excluded from original trials, this study contributes clinical safety outcomes to the limited data for use of apixaban in this patient population.

Keywords Apixaban · Direct oral anticoagulant · Anticoagulation · Atrial fibrillation · Renal function · Safety

Highlights

- Limited data exists for clinical safety outcomes of apixaban use in patients with nonvalvular atrial fibrillation (NVAF) and severe renal impairment, though guidelines now recommend apixaban or warfarin in this population.
- This retrospective analysis compared the safety outcome of bleeding rates between apixaban doses and differing renal function. Patients were considered to have impaired renal function with a creatinine clearance (CrCl) < 25 ml/min and/or serum creatinine (SCr) > 2.5 mg/dl, including hemodialysis.
- In patients with NVAF taking apixaban 5 mg twice daily, there was no observed difference in major bleeding outcomes between impaired renal function and preserved renal function groups. Results were similar for minor bleeding and bleeding outcomes for patients taking apixaban 2.5 mg.

A portion of this research was presented at the 2017 ASHP Midyear Conference; December 2017; Orlando, FL as well as at the 2018 Southeastern Residency Conference; April 2018; Athens, GA. Final results were presented at the ACCP Annual Global Conference; October 2018; Seattle, WA.

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Published online: 04 January 2020

- Though a small study, these results contribute clinical safety outcomes to the limited data for use of apixaban in this patient population excluded from original trials and support the guideline recommendations.
- Larger, prospective studies are needed to further define the safety of apixaban in patients with severe renal impairment.

Background

Apixaban is a direct oral anticoagulant (DOAC) approved for stroke prevention in patients with nonvalvular atrial fibrillation (NVAF) [1]. The urinary elimination of apixaban (27%) compared to dabigatran, rivaroxaban, and edoxaban with renal excretion of 80%, 36%, and 50% respectively, makes it an appealing choice among the DOACs for renally impaired patients [1–4]. Patients with end-stage renal disease (ESRD) were excluded from the ARTISTOTLE trial; however, current prescribing information states that no dose adjustment is required for this population based on pharmacokinetic data [1, 5]. One study concluded that the area under the curve was increased after a single 5 mg dose in patients with ESRD on hemodialysis (HD) [6]. Conversely, data from a multi-dose pharmacokinetic study suggest 5 mg twice daily results in drug accumulation in HD [7]. Despite conflicting data, the recommended dosage of apixaban for NVAF is 5 mg twice daily, reduced to 2.5 mg with two of the following: serum creatinine (SCr) > 1.5 mcg/dl, age > 80 years old, or body weight < 60 kg. No recommendation is made to avoid or reduce apixaban dose based on renal function alone, although providers may empirically reduce the dose.

Prior to 2018, guidelines from American Heart Association, American College of Cardiology and the Heart Rhythm Society (AHA/ACC/HRS) and CHEST recommended warfarin over DOACs for stroke prevention in NVAF and ESRD. With recent updates, both guidelines now support the use of either apixaban or warfarin at approved doses for NVAF and ESRD, including HD [8, 9]. The 2019 AHA/ACC/HRS guidelines cite a study by Siontis et al. [10] analyzing safety and efficacy of apixaban in NVAF patients undergoing dialysis. This large, retrospective cohort study concluded that apixaban was associated with significantly lower major bleeding risk compared to warfarin, yet time in therapeutic range (TTR) of international normalized ratio (INR) was not reported [10].

Though pharmacokinetic data are available for apixaban, limited clinical data exist examining safety in patients with ESRD and/or HD. Sarratt and colleagues compared safety outcomes of warfarin to apixaban in patents with ESRD [11]. The retrospective cohort study analyzed bleeding rates of HD patients on warfarin or apixaban for venous thromboembolism treatment or prophylaxis. While the study was not powered for statistical significance and TTR was not reported, more major bleeding events occurred in patients with warfarin compared to apixaban [11]. Schafer and colleagues investigated the safety and efficacy of warfarin versus apixaban in patients with chronic kidney disease (CKD) stages 4 and 5, including HD [12]. This retrospective study examined major bleeding events following initiation of apixaban or warfarin. At 6 to 12 months, more major bleeding was seen in the warfarin group with a reported TTR of 78.7% [12]. The results support the findings of the Sarratt et al. study [11], concluding that apixaban may have less major bleeding risk than warfarin in ESRD patients. However, these studies did not focus on apixaban dosing and bleeding event correlation with renal function and dose [11, 12]. Additionally, the study conducted by Siontis et al. [10] determined there was no difference in major bleeding comparing apixaban doses in patients undergoing dialysis, yet minor bleeding was not assessed and patients without dialysis were not included [7]. With the limited studies available assessing apixaban safety in renal impairment, further safety data is warranted to determine bleeding risk in this population. The purpose of this study was to determine clinical safety of apixaban 5 mg twice daily for patients with NVAF and severe renal impairment compared to patients with preserved renal function.

Methods

This single-center, retrospective, institutional review board-approved cohort study was conducted at a 625-bed academic medical facility. Patients admitted between May 31, 2013 and November 30, 2017 were screened for inclusion. Patients were included if they were 18 years of age or older with documentation of receiving apixaban 5 mg or 2.5 mg twice daily for NVAF (regardless of dose appropriateness based on age, weight, and SCr) as a preadmission medication for a minimum of 48 h (due to the 12-h half-life of apixaban). Patients were excluded if admitted with a documented bleed attributed to trauma, or to other anticoagulant, antiplatelet therapy, or nonsteroidal anti-inflammatory (NSAID) therapy. Additional exclusion criteria were dual antiplatelet therapy with apixaban, documented history of hypercoagulable state, apixaban use for indications other than NVAF, and if an apixaban dosage change was required during admission. Hypercoagulable state was defined as documentation of: antiphospholipid syndrome, factor V Leiden, deficiency of protein C, protein S, antithrombin, or plasminogen, or unknown cause. All data were collected using REDCap (Research Electronic Data Capture) database [13].

The primary study outcome was major bleeding events in patients receiving apixaban 5 mg for NVAF with impaired renal function (iRF) (CrCl < 25 ml/min and/or SCr >

2.5 mg/dl including HD) compared to patients with preserved renal function (pRF) (CrCl ≥ 25 ml/min and SCr ≤ 2.5 mg/dl). In previous studies, patients with CrCl < 25 ml/min and/or SCr > 2.5 mg/dl have been excluded, leading to the group descriptions of pRF versus iRF [5]. A major bleeding event was defined as an acute overt bleed plus: hemoglobin decrease of 2 g/dl or more, transfusion of 2 or more units of packed red blood cells or fresh frozen plasma, bleed in one or more critical sites, or fatal bleed [14]. Secondary outcomes included the incidence of major bleeding events in patients receiving apixaban 2.5 mg, the incidence of clinically relevant non-major bleed or minor bleed in both dosage groups, and bleed incidence of patients receiving apixaban dosage inconsistent with labeling. Non-major bleeding or minor bleeding criteria included bleeding affecting hemodynamics or resulting in hospitalization, unexpected hematoma or excessive wound hematoma, epistaxis, gingival bleeding, hemoptysis, hematuria, gastrointestinal bleeding, rectal bleeding, other events leading to intervention, or a change in treatment choice due to bleed [15]. Major and minor bleeding criteria were consistent with the International Society on Thrombosis and Haemostasis, Inc. definitions [14, 15]. Bleeding events were determined by chart review of study inclusion patient encounter. Chart documentation and medication reconciliation (over-the-counter and prescription) were reviewed to identify medications with potential to significantly interact with apixaban. These included antiplatelet agents, NSAIDs, anticoagulants, and P-glycoprotein and CYP3A4 inducers and inhibitors. CrCl was calculated using the Cockcroft-Gault equation and actual body weight (ABW) was used if the patient weighed less than ideal body weight (IBW). IBW was used if less than ABW, unless ABW was 130% greater than ideal, and if so, adjusted body weight (AdjBW) was used. In addition to baseline demographics and pertinent laboratory values, hospital length of stay, CHA_2DS_2VASc and HAS-BLED scores, and apixaban dosage were collected. CHA_2DS_2VASc score provides a clinical risk estimation of stroke in patients with atrial fibrillation [16]. HAS-BLED score provides a clinical risk estimation of bleeding in patients with atrial fibrillation [17].

Based on a previous study [11] it was determined that 255 patients would be required for the primary endpoint to achieve 80% power using a 2-sided alpha of 0.05 to detect a 20% difference in bleeding events between groups. Predicted enrollment of the pRF and iRF groups was 4:1 to maximize power with the expectation that 1:1 allocation would not be plausible. Primary and secondary outcomes were analyzed using Chi-squared or Fisher's exact test. Continuous variables were analyzed using the Mann–Whitney U test or Independent t-test. Analyses were performed using SPSS software, version 23 (SPSS, Inc., IBM;Armonk, NY).

Results

Of the 717 patients screened, 340 met inclusion criteria; 287 pRF and 53 iRF. The primary reason for exclusion was duration of apixaban use less than 48 h (Fig. 1). Among patients with pRF, 227 (79.1%) were receiving apixaban 5 mg compared to 28 (52.8%) with iRF. (Fig. 1). The ratio of 4:1 was not maintained and instead resulted in an 8:1 ratio of apixaban 5 mg pRF versus iRF. Baseline demographics are listed in Table 1. Significant differences existed between groups in baseline hemoglobin, albumin, length of hospital stay, and HAS-BLED score groups of low (0–2) and medium (3–4). The overall average HAS-BLED score was 2 in the pRF

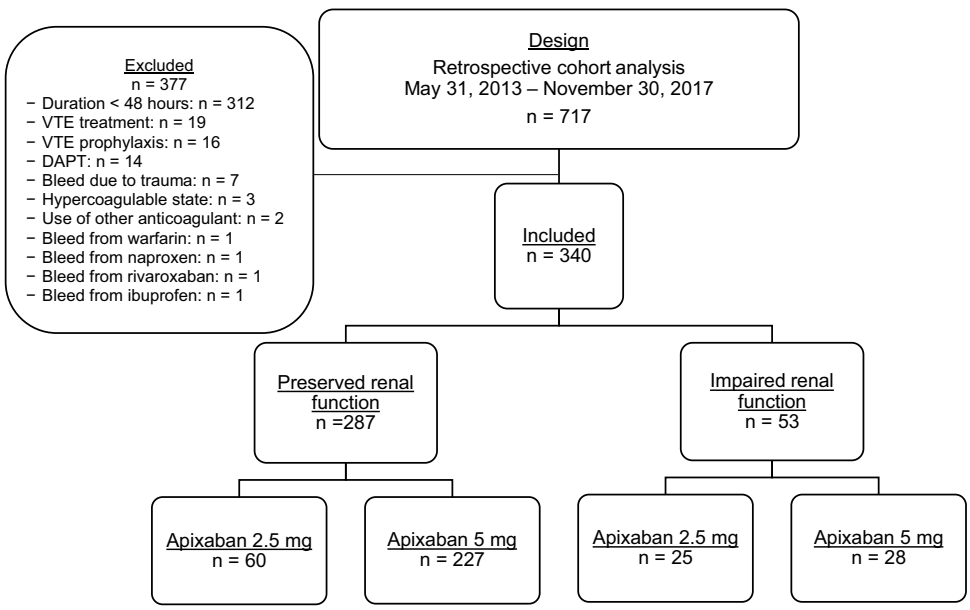

Fig. 1 Methodology

Table 1 Baseline demographics

	Preserved (n = 287)	Impaired (n = 53)	*P value*
Age, years (mean ± SD)	73.71 ± 9.99	74.23 ± 11.24	0.736
Female, n (%)	148 (51.57)	34 (64.15)	0.092
Albumin, g/dl (mean ± SD)	3.7 ± 0.59	3.48 ± 0.52	0.009
Platelet count × 10^3 (median [IQR])	222 [172–283]	218 [144–279]	0.136
Hemoglobin, g/dl (mean ± SD)	12.4 ± 2.3	10.2 ± 1.9	< 0.0001
Length of stay, days (median [IQR])	4 [2–7]	6 [3–11]	0.0029
CHA_2DS_2VASc (mean ± SD)	5 ± 1.65	5 ± 1.55	0.257
HAS-BLED, n (%)			
Low, 0–2	175 (60.98)	20 (37.74)	0.0017
Medium, 3–4	102 (35.54)	30 (56.6)	0.0038
High, 5–9	10 (3.48)	3 (5.66)	0.448
Apixaban 5 mg, n (%)	227 (79.09)	28 (52.83)	–
Apixaban 2.5 mg, n (%)	60 (20.91)	25 (47.17)	–
Serum creatinine, mg/dl (median [IQR])	1.08 [0.85–1.36]	3.19 [2.48–4.7]	–
CrCl ABW, ml/min (median [IQR])	67.92 [48.52–92.76]	20.59 [13.44–27.09]	–
CrCl IBW, ml/min (median [IQR])	49.67 [37.4–63.54]	17.05 [10.32–19.85]	–
CrCl AdjBW, ml/min (median [IQR])	56.39 [42.39–72.54]	18.91 [12.19–22.88]	–
Chronic kidney disease, n (%)	84 (29.27)	43 (81.13)	–
Hemodialysis, n (%)	–	19 (35.85)	–
Renal transplant history, n (%)	5 (1.74)	1 (1.89)	–

ABW actual body weight, *AdjBW* adjusted body weight, *CrCl* creatinine clearance, *IBW* ideal body weight, *IQR* interquartile range, *SD* standard deviation

group and 3 in the iRF group. The mean CHA_2DS_2VASc score was 5 in both the pRF and iRF groups. The mean SCr was 3.19 mg/dl and 1.08 mg/dl in the iRF and pRF groups, respectively (Table 1).

Study results are included in Table 2. Analysis of the primary outcome of major bleeding events revealed no significant differences in patients with pRF compared to iRF who received apixaban 5 mg. Numerically, there were similar major bleeding events in the pRF group compared to the iRF group (4.41 vs. 3.57%, $P = 0.66$) with similar results with apixaban 2.5 mg (10 vs. 16%, $P = 0.47$). Additionally, regardless of dose, overall bleeding events were numerically similar between groups; major bleeding 5.22% vs 5.66% and minor bleeding 11.15% vs 13.21% (pRF vs. iRF respectively). Use of at least one concomitant NSAID or antiplatelet medication was documented in each group, except the apixaban 5 mg iRF group (Table 2). Two of the minor bleeding events in the pRF group occurred in patients with documentation of receiving a concomitant CYP3A4 inhibitor (dronedarone and verapamil). Two patients in the apixaban 2.5 mg iRF group who experienced a minor bleeding event were undergoing hemodialysis.

Table 3 summarizes results of the secondary endpoint analyzing bleeding rates in patients on apixaban doses

Table 2 Apixaban bleeding rates

Apixaban 5 (mg)	Preserved (n = 227)	Impaired (n = 28)	*P value*
Major bleed: n (%)	10 (4.41)[a]	1 (3.57)	0.66
Minor bleed: n (%)	26 (11.45)[b]	3 (10.71)[c]	0.60
Apixaban 2.5 (mg)	Preserved (n = 60)	Impaired (n = 25)	*P value*
Major bleed: n (%)	5 (8.33)[c]	2 (8)[c]	0.96
Minor bleed: n (%)	6 (10.0)[c]	4 (16)[d]	0.47

[a]aspirin n = 5, meloxicam n = 1

[b]aspirin n = 8, meloxicam n = 2, ibuprofen n = 1

[c]aspirin n = 2

[d]aspirin n = 3

Table 3 Bleeding rate for differing doses

	Lower than recommended (n = 48)	Higher than recommended (n = 13)
Major bleed[a]: n (%)	4 (8.3)	0
Minor bleed[b]: n (%)	5 (10.4)	0

[a]Major bleed definition: acute overt bleed plus one of the following: hemoglobin decrease ≥ 2 g/dl, transfusion of ≥ 2 units packed red blood cells or fresh frozen plasma, bleed in ≥ 1 critical site (intracranial, intraocular, intra-articular, retroperitoneal, intraspinal, pericardial, or intramuscular with compartment syndrome), or fatal bleed

[b]Minor bleed definition: any of the following: bleed affecting hemodynamics or resulting in hospitalization, unexpected hematoma or excessive wound hematoma, epistaxis, gingival bleeding, hemoptysis, hematuria, gastrointestinal bleeding, rectal bleeding, other events leading to intervention, or a change in treatment choice due to bleed

inconsistent with labeling. None of the patients on an apixaban regimen higher than approved labeling (n = 13) experienced a bleeding event. Of those patients treated with an apixaban regimen lower than approved dosage (n = 48), four (8.83%) experienced a major bleed and five (10.4%) experienced a minor bleed.

Discussion

Though updated guidelines for anticoagulation in patients with NVAF and severe renal impairment recommend apixaban, limited safety data exist in this population. This study is one of few to demonstrate no difference in bleeding rates with recommended apixaban doses regardless of renal function. Though the difference in major and minor bleeding events was not statistically significant, these data support the safe use of apixaban in patients with severe renal impairment at approved doses. Additionally, the overall major bleeding rate in iRF patients (5.66%) regardless of apixaban dose is similar, or lower, compared to previous reports with comparable baseline average HAS-BLED score [10, 12, 18, 19].

Published data assessing the safety of apixaban in patients with NVAF and renal impairment use warfarin as the comparator or only analyze patients undergoing dialysis. Previous studies suggest that compared to warfarin, apixaban demonstrates less major bleeding risk for ESRD patients, without consideration of dose [11, 12]. Our study is one of the first to compare different apixaban doses in patients with NVAF and renal impairment with or without dialysis and suggests there is no difference in major bleeding events with recommended doses and iRF. This study supports the clinical safety of apixaban 5 mg twice daily in patients with iRF.

For the secondary endpoints of major bleeding events with apixaban 2.5 mg, minor bleeding events, and bleeding events in patients on dosages different than approved labeling, results were similar among all groups with similar rates of bleeding. Only two of the 53 total iRF patients experienced a bleeding event with hemodialysis (3.77%) and the documented dose was apixaban 2.5 mg twice daily. This finding contrasts with the study conducted by Steuber et al. [20] that found an association between apixaban 5 mg twice daily and increased bleeding with patients on HD, yet agrees with the safety outcomes of Siontis et al. [10] demonstrating similar major bleeding events between doses for patients undergoing dialysis. The results of the study also provide clinical support for the pharmacokinetic studies indicating that dose adjustment of apixaban is unnecessary in patients with renal dysfunction. While Mavrakans et al. [4] concluded that twice daily apixaban led to accumulation in patients requiring HD, this is not reflected clinically in our small study, or others [4, 7, 11, 12].

As discussed above and seen frequently in practice, providers may empirically reduce the dose of apixaban based on renal function alone to reduce bleeding risk. Though statistical analysis was not conducted, the results of a secondary endpoint demonstrated that patients who were receiving a lower dose than recommended (apixaban 2.5 mg twice daily and one or less of the following: > 80 years old, < 60 kg, or SCr > 1.5 mg/dl) had more bleeding events compared to patients receiving a higher dose than recommended (apixaban 5 mg twice daily and 2 or more of the following: > 80 years old, < 60 kg, or SCr > 1.5 mg/dl). This small patient sample suggests that there may be similar incidence of bleeding between conventional dosing and lower-than-recommended dosing. Also, the empiric dose reduction may be of importance had these patients been receiving standard dose apixaban and already at an increased bleed risk.

Study limitations include the single center, retrospective design. Data collection and interpretation were reliant on electronic health record documentation. Documentation of bleeding events and relationship to apixaban were not always clear, therefore subject to information bias. Heparin use during dialysis limits the ability to attribute the bleed to apixaban alone for the patients undergoing HD. The significant difference in baseline HAS-BLED score between groups is expected since iRF adds a point to the total score, increasing the number of patients with higher HAS-BLED scores in the iRF group. It was predicted that more patients would be in the pRF group and that equal allocation would not be possible due to the population studied, yet this difference was greater than anticipated (8:1). With each degree of unequal allocation, risk of type II error is increased, increasing the number of patients required to reach statistical significance. Therefore, twice as many patients are required to reach statistical significance. Due to the unique endpoints and study practicality, these results provide relevance to a minimally studied patient population. Of the 10 major bleeding events in

patients with pRF, six were receiving concomitant antiplatelet or NSAID therapy compared to one major bleeding event with iRF and no interacting medications. While use of concomitant medications accurately reflects a real-world patient population, it limits the assessment of the relationship between bleeding and apixaban. This retrospective study design could not control for other factors that may increase patients' risk for bleeding.

Overall, though not statistically significant, the numerically similar bleeding rates between groups with varying renal function suggest clinical relevance. There are many patient factors to consider when choosing anticoagulation therapy for NVAF and this safety data continue to support the use of apixaban regardless of renal function. A larger patient population is needed to determine true clinical safety of apixaban within this population and further prospective studies are required to confirm these findings.

Conclusion

Apixaban continues to be widely used for the prevention of stroke in patients with NVAF regardless of renal function. This study contributes clinical safety outcomes to the limited data available for use of apixaban 5 mg twice daily in patients with severe renal impairment. There were no significant differences in major bleeding or minor bleeding when comparing patients with pRF to iRF receiving either apixaban 5 mg or 2.5 mg twice daily. This research provides clinical data for the patient population that has been previously excluded from trials and does not suggest that there is an increase in bleeding events in patients with severe renal impairment compared to preserved renal function when apixaban is used at approved dosages. As renal function is not the only predictor of bleeding events, anticoagulation and dosage selection for patients with NVAF should be patient-specific and risk and benefits should be considered when initiating therapy.

Acknowledgements We would like to thank Dr. Robert E. Heidel, PhD, assistant professor, Division of Biostatistics at the University of Tennessee Graduate School of Medicine for his contributions to the statistical analysis of this study. We would also like to thank Elizabeth Pollard and Sarah Hawkins, pharmacy students at the time of data collection, for their contribution to data collection.

Compliance with ethical standards

Conflict of interest The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article. The authors received no financial support for the research, authorship, and/or publication of this article.

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