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A Multicenter Retrospective Analysis of Factors Associated With Apixaban-Related Bleeding in Hospitalized Patients With End-Stage Renal Disease on Hemodialysis

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Abstract

Background: In 2014, the United States Food and Drug Administration approved a labeling change for apixaban to include recommendations for patients with severe renal impairment and patients with end-stage renal disease (ESRD) on hemodialysis (HD), though these recommendations are largely based on pharmacokinetic and pharmacodynamic data. **Objective:** Identify variables associated with bleeding events in hospitalized patients with ESRD on HD receiving apixaban. **Methods:** This retrospective, multicenter cohort study evaluated hospitalized patients with ESRD on HD receiving apixaban from January 1, 2013, through March 31, 2016. Correlational analysis and logistic regression were completed to identify factors associated with bleeding. **Results:** A total of 114 adults were included in the analysis. The median length of stay (LOS) was 6.2 (interquartile range = 3.8-11.9) days and bleeding events occurred in a total of 17 patients (15%). A weak correlation was identified for higher cumulative apixaban exposure, increased number of HD sessions while receiving apixaban, and increased hospital LOS ($P < 0.05$; correlation coefficient < 0.40). When controlling for confounders, logistic regression revealed that composite bleeding events were independently increased by continuation of outpatient apixaban (odds ratio = 13.07; 95% CI = 1.54-110.54; $P = 0.018$), increased total daily dose of apixaban (odds ratio = 1.72; 95% CI = 1.20 to 2.48; $P = 0.003$), and total HD sessions while receiving apixaban (odds ratio = 2.04; 95% CI = 1.06-3.92; $P = 0.033$). **Conclusion:** The association between these factors and increased bleeding should prompt concern for long-term anticoagulation with apixaban in patients with ESRD receiving chronic HD.

Keywords

anticoagulation, anticoagulants, dialysis, end-stage renal disease, hematology

Introduction

Patients with end-stage renal disease (ESRD) on hemodialysis (HD) have traditionally received warfarin as the anticoagulant of choice for appropriate conditions. The American College of Cardiology/American Heart Association/Heart Rhythm Society guidelines provide a grade IIa recommendation for use of warfarin in patients with ESRD requiring anticoagulation secondary to nonvalvular atrial fibrillation (NVAF).[1] In addition, the Kidney Disease: Improving Global Outcomes consensus statement on cardiovascular disease recommends against routine oral anticoagulation in patients with NVAF and ESRD secondary to unclear benefits with increased risk of harm.[2] Finally, the CHEST guideline for treatment of venous thromboembolism (VTE) recognizes warfarin as the preferred treatment option in this patient population.[3] No guideline involving anticoagulation management endorses the use of direct-acting oral anticoagulants (DOACs) in patients with ESRD on HD. Warfarin is almost entirely eliminated through hepatic metabolism, and

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its effects can be monitored. Despite limited clinical trial evidence and lack of guideline support, unique circumstances or patient preference may prompt clinicians to consider the use of a DOAC.

Dabigatran, rivaroxaban, and edoxaban have specific recommendations to avoid in patients with ESRD on HD, generally precluding their use.[4-6] Apixaban is a direct factor Xa inhibitor used for anticoagulation in patients with NVAF and in the management of VTE, including deep venous thrombosis (DVT) and pulmonary embolism (PE).[7] Approximately 73% of an apixaban dose undergoes hepatic metabolism to inactive metabolites, with the remaining amount eliminated unchanged via the kidney.[8] This makes apixaban an attractive option compared with the other DOACs in a population with renal impairment. In 2014, the FDA approved a labeling change for apixaban to include recommendations for patients with severe renal impairment (CrCl < 15 mL/min) and patients with ESRD on HD.[7] In general, no dose adjustment is recommended for this patient population. This label extension approval was largely based on a single-dose pharmacokinetic study in 8 patients, which found a 36% higher exposure in patients maintained on HD.[9]

Given the dosing recommendations and pharmacokinetic profile, apixaban may be used in patients with ESRD on HD who require anticoagulation. However, conflicting information exists on the clinical utility in this population.[9-12] We sought to investigate the variables associated with apixaban and bleeding events in hospitalized patients with ESRD on HD.

Methods

Study Design and Patient Cohorts

This was a 2-state, multicenter, retrospective cohort study using data obtained from Indiana University Health (IUH) and Spectrum Health (SH) systems between January 1, 2013, and March 31, 2016. Data from IUH was collected from IUH Methodist Hospital, IUH University Hospital, IUH North Hospital, IUH West Hospital, and IUH Arnett Hospital. Data from SH was collected from SH Butterworth Hospital and SH Blodgett Hospital. Prior to data collection, this study was approved by the respective institutional review boards.

Patients aged 18 years or older were included if they received 2 or more consecutive apixaban doses while they were inpatients and were also receiving chronic, scheduled HD. Prior inpatient receipt of other anticoagulants was permitted only if the conversion to apixaban followed the package insert recommendations.[7] The analysis included apixaban continuation from the outpatient setting prior to admission or newly started during the index hospital stay. Participants were excluded if they received inconsistent HD as a result of improving renal function (acute HD), were receiving continuous renal replacement therapy, were converted inappropriately from another anticoagulant based on package insert recommendations, were classified as outpatient status, or did not receive consecutive apixaban dosing except temporary holding for procedures. Figure 1 represents the participants identified and excluded from each health system.

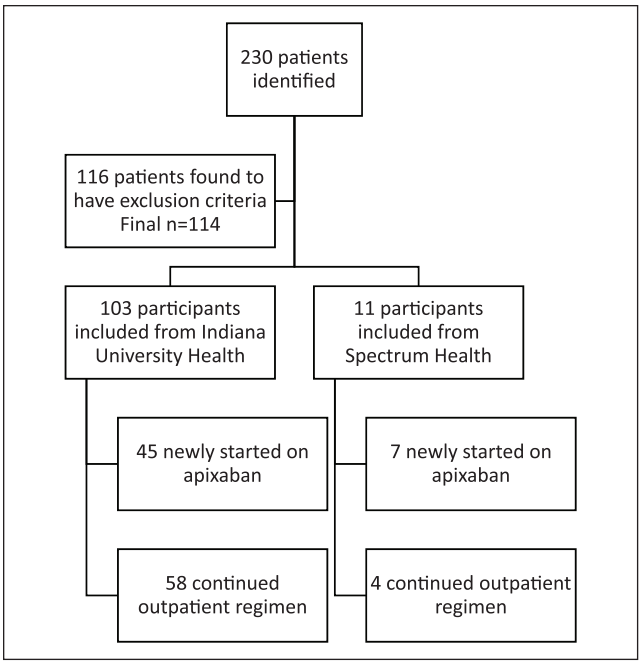

Figure 1. Participants meeting inclusion/exclusion criteria.

Study Outcomes

All participants who met inclusion criteria were categorized into bleeding and no bleeding cohorts and needed to be receiving apixaban at the time any bleeding was identified. Bleeding was characterized as International Society of Thrombosis and Haemostasis (ISTH) major bleeding (fatal bleeding, symptomatic bleeding into a critical area or organ [intracranial, intraspinal, intraocular, retroperitoneal, pericardial, or intramuscular with compartment syndrome] and/or bleeding causing a hemoglobin decrease of ≥2 g/dL or requiring blood transfusion ≥2 units), clinically relevant nonmajor bleeding (CRNMB), or any bleeding regardless of severity.[13,14] CRNMB was defined as bleeding events that did not fulfill ISTH criteria of major bleeding but required medical intervention by a health care professional, led to hospitalization or increased level of care, or prompted in-person evaluation.[14]

Based on the presence or absence of bleeding when evaluated by individual and combined ISTH criteria, CRNMB, or any bleeding, correlational analyses were performed based

on age, gender, weight (kg), body mass index (BMI), new start or continuation of apixaban, apixaban total daily dose (mg), apixaban cumulative inpatient exposure (total mg), concurrent aspirin during apixaban use, cumulative aspirin exposure (mg) during apixaban use, concurrent interacting medications (CYP450 3A4, P2Y12, or P-glycoprotein inhibitors), all-cause mortality, number of inpatient HD sessions during apixaban use, missed HD sessions, absence or presence of prior bleeding events, presence of liver injury (aspartate aminotransferase/alanine aminotransferase greater than 3 times the upper limit of normal), and hospital length of stay (LOS).

Statistical Analysis

The Stata/SE version 13.0 (StataCorp, College Station, TX) Statistics/Data Analysis program utilized the Fisher's exact test for categorical data, the Student's *t*-test for continuous data, and the Pearson correlation coefficient to assess the strength and direction of the association between 2 variable sets.[15] The α value 0.05 was used for statistical significance. For statistically significant correlations, weak (correlation coefficient < 0.4), moderate (correlation coefficient = 0.4-0.6), or strong (correlation coefficient > 0.6) correlations described the strength of each relationship. Logistic regression with odds ratio and 95% CIs were used to determine which variables were significantly influencing the likelihood of bleeding while simultaneously controlling for a host of potential confounders.

Table 1. Baseline Demographics (n = 114).

Categorical Variables	Overall Frequency (%)
Female	66 (58%)
Weight <60 (kg)	29 (25%)
BMI <25 kg/m^2	39 (34%)
BMI ≥30 kg/m^2	45 (39%)
New apixaban start	52 (46%)
Concomitant aspirin use	66 (58%)
Concurrent interacting medications[a]	66 (58%)
Prior bleeding event	13 (11%)
Missed ≥1 HD sessions during hospital stay	4 (4%)
Liver injury (ALT or AST >3× ULN)	1 (1%)
Indication (patients may have had >1 indication)	
Nonvalvular atrial fibrillation (NVAF)	75 (66%)
History of DVT and/or PE	29 (25%)
Acute DVT (without diagnosed PE)	11 (10%)
Venous thromboembolism prophylaxis without known prior event	11 (10%)
Continuous Variables	**Median (Interquartile Range)**
Age (years)	64 (52.25-73)
Weight (kg)	76 (59-92)
BMI (kg/m^2)	27 (22-33)
Apixaban total daily dose (mg)	5 (5-10)
Apixaban total inpatient exposure (mg)	25 (12.5-50)
Total HD sessions	2 (1-4)
Total hospital length of stay (days)	6.2 (3.8-11.9)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; DVT, deep venous thrombosis; HD, hemodialysis; NVAF, nonvalvular atrial fibrillation; PE, pulmonary embolism; ULN, upper limit of normal.
[a]Concurrent interacting medications included CYP450 3A4, P2Y12, or P-glycoprotein inhibitors.

Results

A total of 230 patients were identified from the medical records and were screened for inclusion/exclusion criteria. Of those, 116 were excluded, leaving a total of 114 patients to be included in the analysis. The median LOS of the population studied was 6.2 (interquartile range = 3.8-11.9) days. Table 1 summarizes the baseline characteristics among all apixaban recipients. Overall, bleeding events occurred in 17 patients or 15% of the population and were included in the composite bleeding event cohort (IUH, 14 patients; SH, 3 patients). Among these 17 patients, 7 met ISTH major bleeding criteria and 5 met CRNMB criteria (all 12 IUH admissions). The remaining 5 patients experienced other documented bleeding events that did not fulfill ISTH major bleeding or CRNMB criteria. Of the 17 patients who experienced a bleeding event, 7 (41%) were receiving a reduced apixaban total daily dose (2.5 mg twice daily) at the time of a bleeding event and the remainder were receiving higher doses. Notably, 6 of the 114 patients (5%) received an apixaban dose of 10 mg twice daily at some point during their hospitalization (for acute VTE treatment). Of those, 3 (50%) experienced a bleeding event, although none were classified as ISTH major bleeding. Overall, 4 (4%) patients died during hospitalization, all at an IUH facility, but none experienced bleeding events in the presence of apixaban, and apixaban-related bleeding was not determined to be the cause of their death.

Table 2 summarizes the correlation between continuous variables and the absence or presence of any bleeding event during inpatient apixaban use. A higher cumulative apixaban exposure ($P = 0.03$), number of HD sessions while receiving apixaban ($P < 0.01$), and hospital LOS ($P < 0.01$) were each weakly correlated (correlation coefficient < 0.4) with any bleeding event in the presence of apixaban. No statistically significant associations were found among age, gender, weight, BMI, any bleeding history prior to admission, ≥1 missed inpatient HD session(s), liver injury, concurrent aspirin use and exposure, other concurrent interacting medications, or apixaban indication ($P > 0.05$, for all interactions). Additionally, the same comparisons using the ISTH and CRNMB criteria independently did not suggest any significant correlations ($P > 0.05$, for all interactions).

The variables in the regression model that incorporated apixaban total daily dose, apixaban total exposure, apixaban indication, age, gender, weight, BMI, number of HD

Table 2. Comparison of Continuous Variables Between No Bleeding and Bleeding Events.[a]

	No Bleeding (n = 97), Median (IQR)	Any Bleeding (n = 17), Median (IQR)	*P* Value	All Bleeding Correlation Coefficient
Age (years)	64 (52-73)	66 (53-73)	0.67	—
Weight (kg)	76 (59-92)	76 (68-96)	0.18	—
BMI (kg/m^2)	27 (22-33)	28 (25-37)	0.14	—
Apixaban total daily dose (mg)	5 (5-10)	9.5 (5-10)	0.23	—
Apixaban total exposure (mg)[b]	25 (12.5-45)	50 (15-80)	0.03	0.20
Aspirin total exposure (mg)	162 (0-486)	162 (0-486)	0.40	—
Total HD sessions[b]	2 (1-3)	3 (2-5)	<0.01	0.27
Total hospital length of stay (days)[b]	5.5 (3.5-10.5)	13.1 (6.2-16)	<0.01	0.28

Abbreviations: BMI, body mass index; HD, hemodialysis; IQR, interquartile range.
[a]Data expressed as median (IQR).
[b]Statistically significant.

Table 3. Logistic Regression Explaining Bleeding Events.

	Odds Ratio	95% CI	*P* Value
Apixaban total daily dose (mg)[a]	1.72	1.20-2.48	0.003
Apixaban total exposure (mg)	0.97	0.93-1.01	0.055
Indication: venous thromboembolism	0.74	0.07-7.93	0.805
Indication: nonvalvular atrial fibrillation	11.54	0.84-157.96	0.067
Age (years)	1.00	0.94-1.07	0.899
Gender (female)	1.43	0.32-6.33	0.640
Weight (kg)	1.02	0.99-1.06	0.203
BMI >30 kg/m^2	0.21	0.02-1.88	0.161
Total HD sessions[a]	2.04	1.06-3.92	0.033
Continuation of apixaban[a]	13.07	1.54-110.54	0.018
Concurrent aspirin use	1.56	0.29-8.25	0.604
Aspirin total exposure (mg)	1.00	0.99-1.01	0.387
Concurrent interacting medications[a,b]	0.14	0.03-0.79	0.026
Total hospital length of stay (days)	1.14	0.99-1.31	0.059

Abbreviations: BMI, body mass index; HD, hemodialysis.
[a]Indicates statistical significance.
[b]Concurrent interacting medications included CYP450 3A4, P2Y12, or P-glycoprotein inhibitors.

sessions, continuation of outpatient apixaban, concurrent aspirin use and exposure, other concurrent interacting medications (CYP450 3A4, P2Y12, or P-glycoprotein inhibitors), and total hospital LOS accounted for 31% of the explained variance in bleeding events ($P < 0.01$). Table 3 describes the results of a logistic regression model, and Figure 2 shows the Forest plot of odds ratio of each variable in predicting a bleeding event. Specifically, the likelihood of bleeding was increased by the continuation of outpatient apixaban (odds ratio = 13.07; 95% CI = 1.54-110.54; $P = 0.018$), increase in the apixaban total daily dose (odds ratio = 1.72; 95% CI = 1.20-2.48; $P = 0.003$), and total HD sessions while receiving apixaban (odds ratio = 2.04; 95% CI = 1.06-3.92; $P = 0.033$). Concurrent interacting medications was associated with a reduced chance of bleeding (odds ratio = 0.14; 95% CI = 0.02-0.79; $P = 0.026$).

Discussion

To our knowledge, this retrospective cohort analysis is the first study to evaluate bleeding events in the setting of multidose apixaban use confined to hospitalized participants with ESRD on scheduled HD. Correlational analyses revealed weak associations between higher cumulative inpatient apixaban exposure, increased number of HD sessions while receiving apixaban, and increased hospital LOS and apixaban-related bleeding. On one hand, these associations could possibly be a result of longer duration of apixaban exposure leading to bleeding events. On the other hand, bleeding events may have led to longer LOS, increased HD sessions, and apixaban exposure. When controlling for confounding variables, regression analysis results suggest that the risk of any bleeding event is predicted by the continuation of outpatient apixaban, an increase in the apixaban total

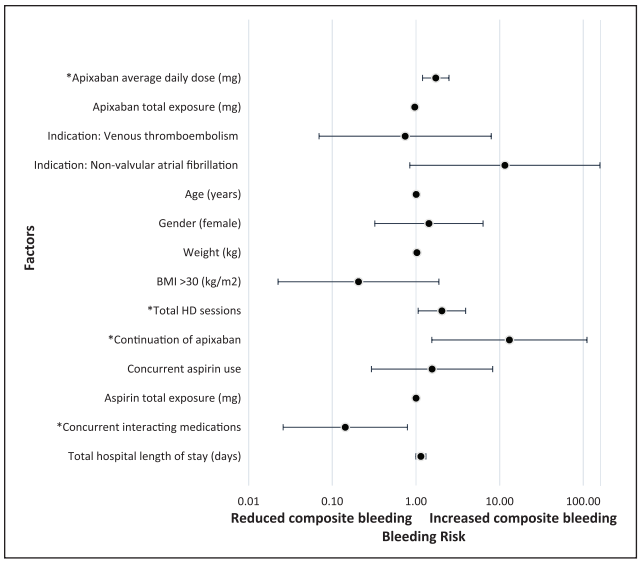

Figure 2. Odds ratio of logistic regression of factors explaining bleeding events.
Abbreviations: BMI, body mass index; HD, hemodialysis.

daily dose, and increased number of HD sessions while receiving apixaban. Even in the presence of a host of potential confounding influences, HD patients were at a greater risk of any bleeding event in relation to apixaban exposure. This is likely a result of a chronic accumulation (continuation of outpatient apixaban) or increased acute exposure (higher daily dose). In either scenario, increased inpatient HD session total during apixaban use did not appear to reduce the potential for a bleeding outcome and was actually associated with increased risk for bleeding. Although less than other DOACs, apixaban is still somewhat reliant on renal excretion (27%) for elimination, and only 7% of the drug is removed after a single 4-hour HD session.[8] Therefore, it is likely that exclusive hepatic metabolism of apixaban in our patient population was unable to compensate for the minimal removal by HD, which could have led to subsequent accumulation with prolonged hospitalization and bleeding events. Taken in sum, these factors support the potential for apixaban to accumulate in patients with ESRD on HD and induce bleeding.

Overall, 66 patients (58%) were on at least 1 medication that could have potentially interacted with apixaban. The most common was amiodarone (26 patients, 39%), and 8 patients (12%) were receiving a concomitant P2Y12 inhibitor. Of those, 33 patients (50%) were receiving a reduced dose of 2.5 mg twice daily. Interestingly, we observed a reduced chance of bleeding in patients who were on potentially interacting medications. It is possible that this trend was observed because of dose adjustments leading to less exposure of apixaban, clinically irrelevant pharmacokinetic interactions (no patient was on strong dual inhibitors of CYP450 3A4 and P-glycoprotein), relatively few pharmacodynamic interactions with P2Y12 inhibitors, potential difference in risk factors in patients on these medications, or more likely, chance.

Patients with ESRD on HD are at increased risk for bleeding at baseline as a result of uremia-induced platelet dysfunction, repeated vascular access cannulation, dialysis membrane interactions, high blood pressures, and heparin administration during dialysis.[8] Additionally, these patients may experience a 2-fold increased risk of major bleeding when anticoagulated with warfarin, despite it having minimal renal clearance.[16] Similarly, we anticipated an association between prolonged apixaban use and an increased bleeding incidence in this patient population because of its pharmacokinetic properties and original studies indicating a 36% increase in drug exposure after 1 dose in patients with ESRD and given the minimal clearance by HD.[8,9] Our study found a clinically relevant increased bleeding concern in this specific patient population when interpreted in the context of a median hospital LOS of 6.2 days. This can be explained partly by increased bleeding risk at baseline in this patient population in addition to acute illness, which can contribute to bleeding and potentially increased LOS, leading to a higher chance of observing a bleeding event, although a bleeding event may have precipitated the need for a longer LOS. Given the bleeding association with these identified variables, this study extends beyond the original single-dose pharmacokinetic study that demonstrates increased exposure in the ESRD population to a more clinical application.[9]

Another recent pharmacokinetic study evaluated multidose apixaban (both 2.5 mg twice daily and 5 mg twice daily) concentrations in 7 stable patients with ESRD on HD.[17] The investigators found that the 2.5-mg dose resulted in similar area under the concentration-time curve from 0 to 24 hours as for patients with preserved renal function for stroke prevention in NVAF and noted supratherapeutic concentrations when patients received the 5-mg dose. They also noted significant accumulation of the drug from day 1 to day 8; however, they did not evaluate clinical outcomes. One patient did have a minor bleeding event when taking apixaban 5 mg twice daily. Interestingly, the observed variables associated with bleeding events in our study also support this accumulation theory, although we did not directly monitor drug concentrations, and our study was done in hospitalized, potentially unstable patients. Nevertheless, the factors independently associated with bleeding by the logistic regression model in our study (continuation of outpatient apixaban, increased total daily dose, and increased number of HD sessions) should be considered along with pharmacokinetic studies when evaluating anticoagulant options and dosing for hospitalized patients with ESRD receiving chronic HD. Future studies with longer durations and larger cohorts are needed to provide a more accurate characterization of long-term bleeding rates, primarily in the ambulatory HD population.

Because of the inpatient focus, the abbreviated duration represents one study limitation. The variables correlated with increased bleeding were observed up to hospital discharge. Therefore, it remains plausible that a lower bleeding rate may be observed in an outpatient, nonacute setting. Conversely, similar or potentially increased bleeding rates may result from apixaban accumulation in this chronic ESRD on HD patient population, especially considering the observed increase in bleeding events when patients continued apixaban from an outpatient setting. Another limitation is the relatively small patient population to evaluate variables associated with increased bleeding risk, which could be influenced by outliers. However, our study is novel and hypothesis generating and provides initial insight that will hopefully alert prescribers and practitioners of variables to be aware of when electing to use apixaban for anticoagulation in the patient population and promote future research.

A recent study comparing the safety and efficacy of apixaban and warfarin in 146 patients with severe renal impairment showed no significant differences in bleeding rates or stroke.[12] However, this study only included a total of 40 patients (27.4%) with ESRD on HD and did not analyze this subgroup separately. The LOS of the apixaban population in the study was 6.3 days (similar to our study with 6.2 days). It is possible that no difference in bleeding between groups was observed because of the majority of those patients having at least some residual renal function potentially leading to less cumulative apixaban exposure. However, the overall bleeding rates observed in this study were slightly higher than in the current investigation, potentially because of different baseline characteristics and risk for bleeding. Although our study did not directly compare bleeding rates with those for warfarin, it did identify risk factors for bleeding in this patient population. In patients treated with apixaban with normal or near-normal renal function, as in the ARISTOTLE and the AMPLIFY trials, overall bleeding rates were observed in 2356 of 9088 patients (25.9%) and 415 of 2676 patients (15.5%), respectively.[18,19] Although the bleeding rates observed in those trials were higher, this is easily explained by the longer duration of those studies (1.8 years and 6 months, respectively), and it is likely that our patient population would experience bleeding rates that exceeded those observed in ARISTOTLE and AMPLIFY if our study duration was extended. Regardless, the risk factors identified by our study are important considerations when electing to prescribe apixaban to a patient with ESRD on HD and selecting a dose. Pharmacodynamic monitoring of apixaban with antifactor Xa concentrations has been previously reported and may be considered based on the clinical scenario.[10]

Existing data suggest that warfarin increases bleeding risk, including hemorrhagic stroke, and mortality without reducing all-cause stroke risk in patients with atrial fibrillation and ESRD on HD.[20,21] These observations are likely multifactorial but include alterations in hemostasis, leading to increased hemorrhagic and thrombotic complications in the ESRD population as well as labile INR control in patients with ESRD (time in therapeutic range in the 40%-50% range).[21,22] The altered risk to benefit ratio of anticoagulation in these patients coupled with expert group opinions may lead prescribers to withhold anticoagulation altogether in patients with NVAF and ESRD on HD.[2] Our study did not directly evaluate efficacy of apixaban because of the short duration. Despite unknown efficacy, DOACs are becoming increasingly popular, even in patients with ESRD on HD. One study indicated that among 100 000 patients with concomitant diagnoses of any chronic kidney disease stage and NVAF, 11.6% of patients with ESRD were prescribed a DOAC (10.4% apixaban).[8] These prescribing trends along with the bleeding concerns observed in our short-term study highlight the importance and need for long-term, head-to-head studies to adequately evaluate the efficacy and safety implications of apixaban use in the ESRD patient population on HD.

Despite these results and previous research, apixaban will likely continue to be the DOAC used most in ESRD because it has the least percentage of renal elimination in its class. Betrixaban, another DOAC currently undergoing clinical trials, undergoes only 5% to 7% renal elimination and represents a possible alternative to warfarin or other DOACs in the future.[23] As the safety and efficacy profile of apixaban in ESRD continues to emerge, increased monitoring should be used, and a potential dose reduction based on recent pharmacokinetic data, such as 2.5 mg by mouth twice daily, may be considered, especially in patients at a high risk of bleeding with NVAF.[17] It is unclear what the optimal dosing in patients with an acute DVT or PE would be.

Conclusion

The weak association between continuation of outpatient apixaban, higher daily apixaban dosage, and number of HD sessions during apixaban use with increased bleeding should prompt concern and highlights the need for additional evaluation in the ESRD population receiving chronic HD, particularly given the increasing use in this population. Future research should focus on including larger patient populations over longer periods to more accurately capture bleeding rates. Additional head-to-head trials comparing warfarin and apixaban are needed to evaluate a true difference in both long-term safety and efficacy in the HD population. Until additional apixaban research convincingly supplants warfarin, it should remain the drug of choice in patients with ESRD on HD who require anticoagulation. If patients have a contraindication to or preference to avoid warfarin, apixaban may be considered with laboratory and clinical monitoring and potentially reduced doses based on indication, especially with long-term use.

Authors' Note

At the time the study was initiated, Dane Shiltz, PharmD, BCPS, and Taylor Steuber, PharmD, BCPS, were affiliated with Indiana University Health and Butler University College of Pharmacy and Health Sciences and have since relocated to their respective institutions during the additional study period and manuscript development.

Declaration of Conflicting Interests

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

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