Evaluation of Apixaban for the Treatment of Nonvalvular Atrial Fibrillation With Regard to Dosing and Safety in a Community Hospital

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Abstract

Background: Apixaban, a direct factor Xa inhibitor, is approved by the US Food and Drug Administration (FDA) for prevention of stroke and systemic embolism in nonvalvular atrial fibrillation. Apixaban's compelling safety and efficacy data, combined with minimal laboratory monitoring, make it an attractive anticoagulant. **Objectives:** To characterize and evaluate the dosing and safety of apixaban for the treatment of nonvalvular atrial fibrillation at a community hospital. **Design/Patients:** A retrospective chart review evaluated patients ≥ 18 years of age who received at least 2 consecutive doses of apixaban from January 1, 2013 to June 30, 2016. Patients with multiple admissions were evaluated for each hospitalization. Patients were excluded if height, weight, or serum creatinine was not documented during hospital admission. Patients who received apixaban for the treatment or prophylaxis of venous thromboembolism were excluded. Prescribing patterns were characterized based on FDA-approved dosing regimens and patient demographics. Safety outcomes included incidences of major, clinically relevant nonmajor, and minor bleeding. **Results:** Of the 707 patients evaluated, 82% received an FDA-approved apixaban regimen. Of the 127 patients (18%) who received an unapproved regimen, 5.5% (7 patients) received an unapproved frequency and 94.5% (120 patients) received an unapproved dose. The majority (98 patients, 81.7%) were underdosed. Composite bleeding rates were 2.7%, with 1.8% major bleeds, 0.7% clinically relevant nonmajor bleeds, and 0.1% minor bleeds. **Conclusions:** The use of apixaban must be monitored in order to ensure FDA-approved dosing regimens are being prescribed and patients are not being underdosed.

Keywords

anticoagulation, apixaban, atrial fibrillation, warfarin, drug utilization review

Background

Thrombotic events, especially ischemic stroke, can occur with any type of atrial fibrillation (ie, paroxysmal, persistent, long-standing persistent, or permanent) and warrants chronic oral anticoagulation for risk prevention in most patients.¹ Previously, the vitamin K antagonist, warfarin, was the only option for oral anticoagulation in the setting of nonvalvular atrial fibrillation (NVAF). Meta-analyses and randomized clinical trials have demonstrated the efficacy of warfarin in the reduction of ischemic stroke and other thromboembolic events in patients with NVAF compared to both aspirin and placebo.^{2,3} However, the efficacy of warfarin has various limitations, including a narrow therapeutic range, numerous drug and food interactions, and cumbersome monitoring requirements.³ The introduction of direct oral anticoagulants (DOACs) came with attractive advantages,

such as predictable pharmacokinetics, rapid onset of action, fewer drug and food interactions, and the lack of routine monitoring requirements. Currently, 4 DOACs are approved by the Food and Drug Administration (FDA) as alternatives to warfarin for patients with NVAF.⁴⁻⁷

Apixaban is a direct factor Xa inhibitor initially approved by the FDA for prevention of stroke and systemic embolism in the setting of NVAF in December 2012. Apixaban has a dosing regimen unique from other

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DOACs.⁴⁻⁷ Rather than requiring dose adjustment based on creatinine clearance (CrCl), apixaban is dose-adjusted for the indication of NVAF based on a combination of at least 2 of the following factors: serum creatinine (sCr) ≥ 1.5 mg/dL (or receiving hemodialysis), age ≥ 80 years, or body weight ≤ 60 kg.^{7,8} The safety and efficacy of apixaban for NVAF is demonstrated in 2 randomized controlled trials, Apixaban in Patients with Atrial Fibrillation (AVERROES) and Apixaban versus Warfarin in Patients with Atrial Fibrillation (ARISTOTLE).^{9,10}

Apixaban's decreased monitoring requirements, wide range of indications, and compelling safety and efficacy data make it an attractive choice of anticoagulation for hospital use. However, unlike other DOACs that are dose adjusted based on CrCl, apixaban has unique dose adjustments based on sCr, age, and weight. The unique dosing recommendations of apixaban could increase the possibility of prescribing unapproved regimens and potentially lead to negative patient outcomes. In a published registry evaluating the dosing of all DOACs, 9.4% of patients were underdosed, 3.4% were overdosed, and 87% were dosed according to US labeling. Receiving non-FDA-approved doses were associated with worse clinical outcomes. Compared to FDA-approved dosing, DOAC overdosing was associated with significantly increased all-cause mortality, while underdosing was associated with a significantly increased association with hospitalization for cardiovascular complications. Additionally, the data suggest that both DOAC under- and overdosing is associated with increased bleeding compared to FDA-approved dosing.¹¹

Since coming to market, a large number of patients have received apixaban for stroke and systemic embolic risk reduction in NVAF. The purpose of this study is to characterize the use and evaluate the dosing and safety of apixaban in patients with NVAF at a community hospital.

Design/Patients

A retrospective chart review was conducted evaluating patients who received apixaban from January 1, 2013, to June 30, 2016. Patients were identified utilizing an electronic database query for active orders for apixaban during the study period. Data were collected at a community hospital in Saint Louis, Missouri, utilizing the hospital's electronic medical record systems. This study was approved by the institutional review board, and informed consent was not required due to the retrospective nature of the study.

All patients 18 years of age or older who received at least 2 doses of apixaban for prevention of stroke and systemic embolism in NVAF were evaluated. Patients were excluded if height, weight, or sCr was not documented during the hospital admission being assessed. Patients who received apixaban for venous thromboembolism (VTE) treatment or prophylaxis were also excluded.

Apixaban regimens were evaluated on the first day of therapy in the hospital based on FDA-approved dosing recommendations to prevent stroke and systemic embolism in NVAF.⁷ FDA package labeling states patients should receive a reduced dose of 2.5 mg orally twice daily for NVAF if 2 of the following characteristics are present: age ≥ 80 years, sCr ≥ 1.5 mg/dL (or receiving hemodialysis), or weight ≤ 60 kg.^{7,8} The first day of therapy for each hospital admission was evaluated regardless of whether the patient received apixaban as a home medication or if apixaban was newly initiated in the hospital. Patients with multiple admissions were evaluated for each hospital stay.

Bleeding was assessed utilizing modified International Society for Thrombosis and Hemostasis (ISTH) definitions for major, clinically relevant nonmajor, and minor bleeding. This is consistent with the definitions utilized in ARISTOTLE.^{10,12,13} Major bleeding was defined as fatal bleeding; and/or symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome; and/or bleeding causing a fall in hemoglobin level of ≥ 2 g/dL or leading to transfusion ≥ 2 units of whole blood or red cells. In order to prevent falsely elevated bleeding rates, a source of bleeding must have been identified in the patient's electronic medical record to confirm a major bleed. Clinically relevant nonmajor bleeding was defined as overt bleeding not meeting criteria for major bleeding but requiring medical intervention or increased level of care. All nonmajor bleeds were considered minor bleeds.^{12,13}

The following parameters were evaluated based on data collected from the patients' medical records: demographics, CHADS₂ score (congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, and prior stroke/transient ischemic attack or thromboembolism), HAS-BLED score (hypertension, abnormal renal or liver function [dialysis, transplant, cirrhosis], history of stroke or bleeding, labile international normalized ratio, age > 65 , concomitant drugs that promote bleeding or excess alcohol), dosing regimen, and bleeding (major, clinically relevant nonmajor, and minor).¹²⁻¹⁵ Descriptive statistics were utilized to characterize the use of apixaban. All analyses were performed with IBM SPSS Statistics for Windows, Version 24.0 (IBM Corp, Armonk, NY).

Results

Of the 1506 patients identified with an order for apixaban from January 1, 2013, to June 30, 2016, 707 were evaluated for the treatment of NVAF. The 799 patients excluded were not evaluated for numerous reasons: 295 were missing height, weight, or sCr prior to receiving the first dose of apixaban; 215 patients received 1 dose; 118 patients were treated for active VTE; 50 patients were treated for

Table 1. Baseline Demographics.

Characteristics	Patients (N = 707)
Age (years), mean $\pm$ SD	75.1 $\pm$ 11.6
Male sex, n (%)	344 (48.7)
Race, n (%)	
Caucasian	603 (85.3)
Black	66 (9.3)
Other	12 (1.7)
Unknown	26 (3.7)
Length of stay (days), median (IQR)	3 (2-6)
Weight, mean $\pm$ SD	86.9 $\pm$ 26.2
Serum creatinine (mg/dL), mean $\pm$ SD	1.5 $\pm$ 1.2
Creatinine clearance (mL/min), mean $\pm$ SD ^a	42 $\pm$ 20.7
CHADS ₂ score	
Median (IQR)	2 (1-3)
0-1, n (%)	188 (26.6)
2-3, n (%)	362 (51.2)
$\geq$ 4, n (%)	157 (22.2)
HAS-BLED	
Median (IQR)	3 (2-3)
$\geq$ 3, n (%)	408 (57.7)
Concomitant antiplatelet therapy, n (%)	377 (53.3)
Aspirin, n (%)	357 (50.5)
Concomitant dual antiplatelet therapy, n (%)	39 (5.5)

Abbreviations: SD, standard deviation; IQR, interquartile range.

^aCalculated with the Cockcroft-Gault equation using admission age and ideal body weight (actual weight was utilized in underweight patients).

reduction in the risk of recurrence of VTE; 40 patients did not have adequate documentation to assess indication; 34 did not receive apixaban during the hospitalization identified; 25 patients were for treated for VTE prophylaxis; and 22 for off-label indications. Baseline demographics are reported in Table 1. Of note, 85.3% of the patients were Caucasian and 48.7% of patients were male. The mean age was 75.1 years, with a mean sCr of 1.5 mg/dL and CrCl of 42 mL/min. The median CHADS₂ score was 2, indicating an annual stroke rate of approximately 4% and a median HAS-BLED score of 3.¹⁴ A HAS-BLED score $\geq$ 3 indicates a potentially high risk for bleeding.¹⁵ It is important to note that while patients with a sCr $>$ 2.5 mg/dL, CrCl $<$ 25 mL/min, or on dialysis were excluded from clinical trials, these patient populations were accounted for in this study and represented approximately 5.1%, 11.9%, and 5%, respectively.⁷⁻¹⁰ Overall, regardless if dosed according to the US FDA labeling recommendations, 39.9% of the patients were $\geq$ 80 years of age, 14% weighed $\leq$ 60 kg, 5% were on dialysis, and an additional 24.3% of patients not on dialysis had a sCr $\geq$ 1.5 mg/dL (Table 2).

Medication regimens and assessment of dosing are reported in Table 2. Overall, 18% of patients (n = 127) did not receive the FDA-approved dose as listed in the package

Table 2. Medication Therapies, Patient Characteristics, and Assessment of Dose.

	Patients (N = 707)
Apixaban home medication, n (%)	361 (51.1)
Apixaban hospital dose, n (%)	
2.5 mg	213 (30.1)
5 mg	491 (69.4)
10 mg	3 (0.4)
Apixaban hospital frequency, n (%)	
Daily	7 (1)
Twice daily	700 (99)
Doses received during hospitalization, mean $\pm$ SD	6.3 $\pm$ 6
Age $\geq$ 80 years of age, n (%)	282 (39.9)
Body weight $\leq$ 60 kg, n (%)	99 (14)
Hemodialysis	35 (5)
Serum creatinine $\geq$ 1.5 mg/dL, mean $\pm$ SD ^a	172 (24.3)
Unapproved regimen, n (%)	127 (18)
Home medication inappropriately continued, n (%)	59 (46.5)
Medication inappropriately initiated in hospital, n (%)	68 (53.5)
Unapproved frequency, n (%)	7 (5.5)
Unapproved dose, n (%)	120 (94.5)
Underdosed	98 (81.7)
Overdosed	22 (18.3)

^aExcludes patients on dialysis.

Abbreviations: SD, standard deviation; IQR, interquartile range.

insert.⁷ Seven patients (5.5%) received an unapproved frequency of once daily. The remaining 120 patients did not receive the FDA-approved dose. Of those patients, 98 patients were underdosed and 22 patients were overdosed. Of the 22 patients who were overdosed, 3 were prescribed 10 mg without a documented presence of VTE, and 19 should have received a reduced dose of 2.5 mg based on their age, body weight, or sCr. There were similar rates of unapproved regimens initiated in the hospital compared to patients admitted with home apixaban regimens (46.5% and 53.5%, respectively, $P = .425$). All 7 patients with unapproved frequencies were taking apixaban at home; however, they were initiated on an unapproved frequency in the hospital. Eleven other patients were incorrectly transitioned from their FDA-approved home regimen to an unapproved dosing scheme while hospitalized.

Patients who were underdosed were significantly more likely to have had apixaban initiated as an outpatient (61.2%) compared to patients who received the FDA-approved dose (49%; $P < .05$; Table 3). Underdosed patients were also significantly more likely to be older (80.2 vs 73.9, $P < .05$), receive dialysis, (13.3% vs 3.8%, $P < .05$), have a higher sCr (2.0 mg/dL vs 1.4 mg/dL, $P < .05$), and have a higher CHADS₂ score (3 vs 2, $P < .05$). There was no significant difference in HAS-BLED score, median 3 ($P = .211$).

Table 3. Underdosed Patients Compared to Patients Who Received the FDA-Approved Dose.

Baseline Demographics	Underdosed (N = 98)	FDA-Approved Dose (N = 580)	P Value
Home medication, n (%)	60 (61.2)	284 (49)	<.05
Age (years), mean $\pm$ SD	80.2 $\pm$ 9.7	73.9 $\pm$ 11.7	<.05
Weight (kg), mean $\pm$ SD	87.4 $\pm$ 25.3	87.3 $\pm$ 26.3	.988
Dialysis, n (%)	13 (13.3)	22 (3.8)	<.05
Serum creatinine (mg/dL), mean $\pm$ SD	2.0 $\pm$ 2	1.4 $\pm$ 1	<.05
Creatinine clearance (mL/min), mean $\pm$ SD	32 $\pm$ 14.1	44 $\pm$ 21.4	<.05
CHADS ₂ score, median (IQR)	3 (2-4)	2 (1-3)	<.05
HAS-BLED, median (IQR)	3 (2-4)	3 (2-3)	.211

Abbreviations: SD, standard deviation; IQR, interquartile range.

Table 4. Apixaban Criteria for Reduced Dose.

	Evaluated Patients ^a (N = 700)	Overdosed—Standard Dose (5 mg) (N = 19)	Recommended Reduced Dose (2.5 mg) (N = 113)
Age $\geq$ 80 years and weight $\leq$ 60 kg, n (%)	46 (6.6)	9 (47.4)	37 (32.7)
Age $\geq$ 80 years and sCr $\geq$ 1.5 mg/dL, n (%)	68 (9.7)	9 (47.4)	59 (52.2)
Body weight $\leq$ 60 kg and sCr $\geq$ 1.5 mg/dL, n (%)	3 (0.4)	1 (5.2)	2 (1.8)
Age $\geq$ 80 years, weight $\leq$ 60 kg, and sCr $\geq$ 1.5 mg/dL, n (%)	15 (2.1)	0	15 (13.3)

Abbreviation: sCr, serum creatinine.

^aPatients with an unapproved frequency were excluded from this evaluation.

Table 4 describes the characteristics that qualified patients for a dose reduction of 2.5 mg taken twice daily. After excluding the 7 patients who were prescribed apixaban with an unapproved frequency (n = 700), nearly 1 in 5 patients (19%) met at least 2 criteria, indicating the need for reduced dosing. The most common combination (9.7%) was age $\geq$ 80 years and sCr $\geq$ 1.5 mg/dL; however, patients $\geq$ 80 years and weight $\leq$ 60 kg were equally as likely to not receive the FDA-approved dose reduction (47.4% who met criteria received the standard 5 mg dose). Patients who met all 3 criteria consistently received the FDA-approved dose with 0% of patients receiving the standard dose. Overall, 19 patients who met criteria for a reduced dose were prescribed the standard dose of 5 mg.

Bleeding events were low with a composite of 2.7% (19 patients). The incidence of major bleeding was 1.8% (13 patients), clinically relevant nonmajor bleeding was 0.7% (5 patients), and minor bleeding was 0.1% (1 patient). The evaluation period spanned 350 363 patient follow-up days with the average patient having a follow-up of 495 days. This translates to 0.054 bleeding events per 1000 patient days. Of patients experiencing a bleed, the median HAS-BLED score was 4, indicating that these patients had a high risk of bleeding. Of the patients who experienced a bleed, 13 were on a single antiplatelet agent (all aspirin 81 mg) while only one patient was on dual antiplatelet therapy (ticagrelor plus aspirin 81 mg). None of the patients who were overdosed or underdosed experienced a bleed. The gastrointestinal tract was the most common bleed site

accounting for 9 of the 19 bleeds. All gastrointestinal bleeds were considered major except one, which met criteria for clinically relevant nonmajor bleeding as the patient did not receive 2 units of packed red blood cells or have a hemoglobin drop $\geq$ 2 g/dL. Hemorrhoids/rectal bleeding was experienced by 3 patients, 2 had hemoptysis, 1 experienced hemarthrosis secondary to fall, 1 had a retinal hemorrhage, 1 had a bleeding ulcer, 1 experienced bleeding after tunneled catheter placed, and 1 experienced bleeding of unknown origin.

Discussion

The results of this retrospective study highlight the challenges clinicians encounter with dosing apixaban in hospitalized patients. Similar evaluations have been conducted at the study institution evaluating dabigatran and rivaroxaban regimens.^{16,17} Dabigatran had the lowest rates of unapproved FDA regimens prescribed in patients with NVAF at 16.6%.¹⁶ The investigators found that in patients utilizing rivaroxaban, 36.9% of patients with NVAF were on an unapproved regimen.¹⁷ In both studies the most common reason for having an inappropriate regimen was overdosing based on renal function.^{16,17}

In contrast to previous evaluations of rivaroxaban and dabigatran, the most common attribute of an unapproved apixaban regimen was underdosing. While it is difficult to confirm physician intent, there are several theories that could explain this prescribing pattern. Apixaban demonstrated

statistically significant lower rates of bleeding compared to warfarin in ARISTOTLE and similar rates to aspirin in AVERROES.^{9,10} Based on the data from clinical trials, clinicians could be utilizing apixaban more often in patients with a higher bleed risk and opting to use the lower dose to further mitigate risk of bleeding. This approach, however, has not been proven to be efficacious nor is it supported by primary literature. The patients in the present study did have a median HAS-BLED score of 3. Additionally, the efficacy of apixaban in patients receiving dialysis has not been established, as these patients were excluded from major clinical trials.^{9,10} The safety of apixaban in patients receiving dialysis has been evaluated; however, the pharmacokinetic study only included 8 patients after receiving 1 dose of apixaban.⁸ The lack of safety and efficacy data extending beyond a single dose could explain the 13.3% of dialysis patients that were underdosed.

Additionally, apixaban has a unique dosing regimen not solely dependent on CrCl as is the case with other DOACs.^{4,7} Clinicians unfamiliar with dosing guidelines may have inappropriately reduced the dose for patients with an elevated sCr, diminished CrCl, or undergoing dialysis, which would only be appropriate if they were also ≥ 80 year of age or weighed ≤ 60 kg.^{7,8} Finally, clinicians could be intentionally prescribing off-label doses based on patients' trending renal function. These findings are consistent with recently published registry data, which indicated that 14% of patients receiving apixaban received unapproved doses. Apixaban had the highest rate of unapproved dosing regimens among DOACs, with the majority of patients being underdosed.¹¹

There are several limitations to this study. This is a single-center, retrospective review at a community hospital that only evaluated patients who received at least 2 consecutive treatment doses of apixaban. The retrospective nature of the study allows for error in data abstraction from the electronic medical records. Patients were not prospectively observed during hospitalization; therefore, physician and nursing documentation was heavily relied upon. This leaves room for bias in the interpretation of medical records and allows for error in documentation at the time of hospitalization and during data abstraction. Regimens were assessed on the first day of apixaban therapy based on age, weight, and sCr; patients' sCr could potentially have worsened or improved, which could alter the assessment of the dose. Modifications to the dosing regimen were not evaluated. Patients were excluded if a height, weight, or sCr was not obtained prior to apixaban initiation in the hospital. This could potentially underestimate the reported bleeding rates because failure to obtain weights in patients administered anticoagulants has been associated with increased rates of hemorrhage compared to patients with documented weights.¹⁸ In addition, the retrospective nature of the study makes it difficult to directly attribute bleeding events to apixaban use unless explicitly stated. Bleeding rates could

potentially be falsely low if patients presented with a bleed to hospitals outside of the study institution's health care system; however, the low rates of bleeding, specifically intracranial bleeding, is consistent with previously published data.¹⁹

As the utilization of DOAC therapy continues to increase, it is important that hospitals implement monitoring systems and provide education to health care providers in order to adhere to the FDA-approved dosing recommendations and improve patient safety for these high-risk medications. Therapeutic interchanges, pharmacist-directed interventions, and other initiatives can be implemented to ensure appropriate use. Based on registry data and the findings discussed above, patients at highest risk for underdosing are older, have renal dysfunction, and have a higher CHADS₂ score.¹¹

In an effort to screen medication orders, the study institution utilizes an automated medication alert system. Alerts are triggered when medication orders breach a set of pre-written rules that may result in an inappropriate medication dose or serious adverse event. Alerts are generated based on laboratory data, renal function, weight, antimicrobial culture results, and other pertinent data; pharmacists then have the opportunity to review the alert and contact the appropriate health care provider if interventions are necessary. Alerts for apixaban dosing are generated when patients' sCr, weight, and/or age violate the prespecified parameters corresponding to FDA-approved dosing.²⁰ While this mode of artificial intelligence is invaluable in facilitating clinical pharmacists to efficiently monitor a large number of orders, fallacies exist. The most conspicuous of these is that in patients for whom sCr or weight is not obtained and documented, alerts cannot be generated. In patients on chronic oral anticoagulation for stroke prevention in NVAF, acute and chronic renal dysfunction is common, particularly in patients with moderate chronic kidney disease and concomitant coronary artery disease.²¹ Recently published data suggest that patients on chronic oral anticoagulation who present with moderate renal failure at baseline (CrCl 30-59 mL/min) should receive more frequent monitoring of sCr to account for changes in CrCl; moderate renal failure at baseline was associated with the highest risk of declining renal function. This highlights the importance of appropriately monitoring for changes in renal function, especially when patients with renally dosed medications are admitted to the hospital.²¹

Conclusions

When utilized according to the FDA-approved recommendations, apixaban has demonstrated superior efficacy and safety to warfarin; however, patients should receive FDA-approved doses to replicate these results. Safe and effective dosing for patient with severe renal dysfunction not studied

in clinical trials continues to be challenging and would best be addressed by further pharmacokinetic and clinical studies. In patients with characteristics corresponding to those studied in clinical trials, opportunities for improvement in the prescribing of apixaban have been identified, particularly those that pertain to dosing the medication according to FDA-approved recommendations and improving clinical and safety outcomes.

Declaration of Conflicting Interests

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