Apixaban dosing in non-valvular atrial fibrillation patients with elevated serum creatinine

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Abstract

Introduction

Current guidelines recommend dose reduction in patients with at least 2 of the following criteria: age ≥ 80 years, body weight ≤ 60 kg, or serum creatinine (Scr) ≥ 1.5 mg/dL.[1-2] The use of reduced dose apixaban for non-valvular atrial fibrillation (NVAF) has been seen in common practice in patients with elevated serum creatinine levels. However, data is limited on patients that only meet Scr ≥ 1.5 mg/dL criteria and patients undergoing hemodialysis. This study aims to assess the clinical outcomes for patients with NVAF on apixaban with Scr ≥1.5 mg/dL. It also further compares the impact of reduced dose apixaban in patients on hemodialysis.

Methods

This is a retrospective chart review on the clinical outcomes associated with renal dose adjustments of apixaban for patients with NVAF meeting only 1 criterion, Scr ≥ 1.5 mg/dL. Patients to be included were admitted from January 2022 through December 2022. The primary outcome is bleeding events and systemic embolism on admission. Secondary outcomes include re-admissions and all-cause mortality. Patients were eligible for inclusion if they were taking apixaban for NVAF and had a Scr ≥ 1.5 mg/dL. Patients were excluded if they received apixaban for venous thromboembolism, or had valve replacement.

Results

The study included 301 patients in the final analysis. No statistically significant difference was found for the primary outcomes of bleeding events and systemic embolism in patients that met criteria vs those that did not meet criteria. For secondary outcomes we found a significant difference in all-cause mortality for patients on reduced dose apixaban (6% vs 11%, p = 0.009) . Additionally, similar to other literature, our study found a higher number of bleeding events in patients on reduced dose apixaban and hemodialysis that met criteria for dose reduction vs those that did not meet criteria (18% vs 11%, p = 0.872).

Conclusion

There was no statistical difference seen in the primary outcomes for bleeding events and systemic embolism, regardless if the patient met criteria for dose reduction. A significant difference was found in all-cause mortality in patients that did not meet criteria for dose reduction. No significant differences were found in the subgroup analysis for hemodialysis patients. The results of this study did show the importance of adhering to the dose reduction criteria.

Keywords: atrial fibrillation, apixaban, dose reduction, criteria, serum creatinine

Introduction

The current guidelines for the management of patients with nonvalvular atrial fibrillation (NVAF) with prior stroke, transient ischemic attack, or a CHA_2DS_2-VAS_c score of ≥ 2, recommend the use of oral anticoagulants.[1-2] Apixaban is an oral anticoagulant that works by inhibiting factor Xa, indicated to reduce the risk of stroke and systemic embolism in these patients.[3] The standard dose is 5 mg orally twice daily for patients with NVAF. Dose reduction of 2.5 mg orally twice daily is recommended in patients with at least 2 of the following criteria: age ≥ 80 years, body weight ≤ 60 kg, or serum creatinine (Scr) ≥ 1.5 mg/dL.[4] However, there is limited data in patients undergoing hemodialysis. Some sources suggest no dosage adjustments are necessary in hemodialysis patients unless they are ≥80 years of age or weight ≤ 60 kg.[5-7]

Despite these recommendations, physicians may reduce the dose if only 1 criterion is met, if criteria are close to the cutoff values, or if patients are at an elevated bleeding risk. Currently, there is limited data on the effect of the 2.5 mg twice daily dose of apixaban on clinical outcomes in patients with Scr ≥ 1.5 mg/dL meeting none of the other criteria. The Dignity Health Anticoagulation Policy and Procedure (see Appendix A) indicates that apixaban is an option for patients on hemodialysis if they are ≥80 years of age or weight ≤ 60 kg. An important question that arises is the impact of these clinical practices on the risk of bleeding, stroke, and systemic embolism.

There is conflicting data on the effect of reduced dose apixaban in NVAF patients with only Scr ≥ 1.5 mg/dL. In a study done in 2020 by Inoue H.,et al it was found that the incidence rates of major hemorrhage and thromboembolism events were higher in patients taking reduced dose apixaban.[8] However, in another 2020 trial by Mavrakanas TA., et al there was a higher incidence of fatal or intracranial bleeding and hemorrhagic stroke in patients taking standard dose apixaban.[5] Furthermore, there is limited data in NVAF patients undergoing hemodialysis.[9-10] A recent 2022 study by Wetmore JB., et al found that reduced dose apixaban is not associated with a lower bleeding risk in patients receiving hemodialysis.[6] This begs the question, is dose reduction necessary in hemodialysis patients?

The goal of this project was to evaluate the clinical outcomes at St. Rose Dominican Hospital-Siena Campus for patients with NVAF on apixaban with Scr ≥ 1.5 mg/dL. We further compared the impact of reduced dose apixaban in patients who were also receiving hemodialysis.

Methods

This is a retrospective chart review on the clinical outcomes associated with renal dose adjustments of apixaban for patients with NVAF meeting only 1 criterion, Scr ≥ 1.5 mg/dL. It was conducted by the primary investigator.

Informed consent was waived due to retrospective design of the study. This study was conducted from November 1, 2023 through June 30, 2024. Patients to be included have been admitted from January 1, 2022 through December 31, 2022. Patients included were at least 18 years of age, hospitalized at St. Rose Dominican Hospital-Siena campus, taking apixaban for NVAF, with a Scr ≥ 1.5 mg/dL. Patients to be excluded were receiving apixaban for venous thromboembolism prophylaxis or treatment, or with valve replacement.

The primary outcomes of interest in this study are bleeding events and systemic embolism. Secondary outcomes are re-admissions and all-cause mortality. Patients were divided into 2 study groups, reduced dose apixaban and standard dose apixaban, as seen in diagram 1 below. Each study group was then further divided into patients that meet criteria vs those that do not meet criteria.

Statistical Analysis

Statistical analyses were performed using the chi-square test for nonparametric values. To determine the required sample size for adequate statistical power, power calculations were conducted. Based on assumptions of an 80% power level and a significance threshold of $p < 0.05$, it was estimated that a sample size of 100 patients in each

arm would be needed to detect a 14% difference in the primary outcome.

Diagram 1: Study Groups

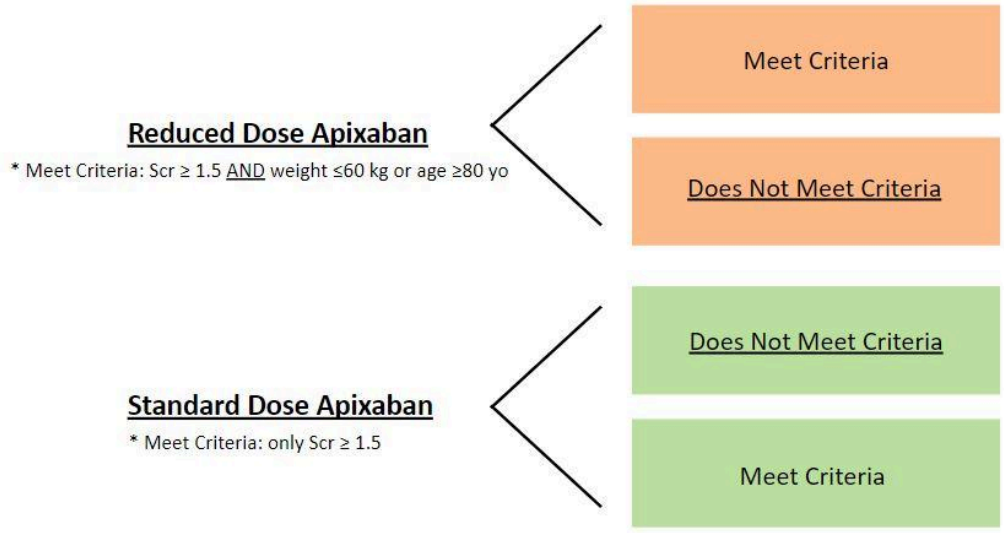

Table 1: Baseline characteristics

	Reduced Dose		Standard Dose	
	Meet Criteria (N = 126)	Does Not Meet Criteria (N = 45)	Does Not Meet Criteria (N = 24)	Meet Criteria (N = 106)
Age – mean yr (SD)	84 (6)	69 (8)	81 (7)	69 (9)
Female – n (%)	47 (37)	12 (27)	7 (29)	25 (24)
Weight – mean kg (SD)	75 (19)	96 (27)	72 (18)	101 (29)
Scr – mean mg/dL (SD)	2.73 (1.5)	4.55 (3)	2.7 (1.9)	2.65 (1.9)
Hemodialysis – n (%)	28 (22)	27 (60)	4 (17)	19 (18)
CHA_2DS_2-VASc score – mean (SD)	5 (1)	5 (2)	5 (1)	4 (2)
HAS-BLED score – mean (SD)	3 (1)	4 (1)	4 (1)	3 (1)
Stroke/TIA – n (%)	22 (17)	16 (36)	8 (33)	31 (29)
Vascular disease – n (%)	54 (43)	20 (44)	10 (42)	49 (46)
Liver disease – n (%)	13 (10)	5 (11)	7 (29)	9 (8)
Prior bleeding – n (%)	12 (10)	1 (2)	1 (4)	5 (5)
Labile INR – n (%)	9 (7)	4 (9)	1 (4)	6 (6)
Other meds: ASA/clopidogrel – n (%)	76 (60)	13 (29)	14 (58)	50 (47)

*CHF, HTN, DM, and alcohol use – similar between the groups

Results

Of the total 1243 charts reviewed, 301 were included in the final analysis of this study. Baseline characteristics, as presented in Table 1, included the average age of 75.8 ± 7.5 years, Scr of 3.16 ± 2 mg/dL, and 77.2% identifying as male. Patients were well-qualified for anticoagulation with a mean CHA_2DS_2-VAS_c score of 5 and had a high bleeding risk with a mean HAS-BLED score of 3.5. Vascular disease, CHF, HTN, DM, and alcohol use were well-balanced between the groups. Approximately 60% of patients that met criteria for reduced dose and did not meet criteria for standard dose were on other medications, like aspirin and clopidogrel, which increased their risk of bleeding.

Our primary outcomes showed no significant difference in bleeding events (13% vs 7%, p = 0.4) and systemic embolism (5% vs 9%, p = 0.2) between reduced dose apixaban groups. However, in patients taking standard dose apixaban, there were more bleeding events in those that did not meet criteria (17% vs 8%, p = 0.07) (Table 2). In terms of secondary outcomes, as shown in Table 3, there were more readmissions in patients that did not meet criteria for dose reduction (58% vs 40%, p = 0.1) and significantly more all-cause mortality (11% vs 6%, p = 0.009). In the standard dose group, there were no significant differences between the two groups.

In the subgroup analysis for patients on hemodialysis, 55 patients met criteria on the reduced dose apixaban. Only 19 hemodialysis patients were on standard dose apixaban, which was insufficient for a logistic regression model. There were no significant differences in bleeding events, systemic embolism, re-admissions, and all-cause mortality in reduced dose apixaban patients on hemodialysis. However, it is worth mentioning, there were more bleeding events in patients that met criteria for dose reduction (18% vs 11%, p = 0.9) than those that did not meet criteria (Table 4).

Table 2: Primary Outcomes

	Reduced Dose		
	Meet Criteria (N = 126)	Does Not Meet Criteria (N = 45)	P-value
Bleeding events – n (%)	16 (13)	3 (7)	0.405
Systemic embolism – n (%)	6 (5)	4 (9)	0.177
	Standard Dose		
	Meet Criteria (N = 106)	Does Not Meet Criteria (N = 24)	P-value
Bleeding events – n (%)	9 (8)	4 (17)	0.071
Systemic embolism – n (%)	7 (7)	5 (21)	0.595

Table 3: Secondary Outcomes

	Reduced Dose		
	Meet Criteria (N = 126)	Does Not Meet Criteria (N = 45)	P-value
Re-admissions – n (%)	51 (40)	26 (58)	0.098
All-cause mortality – n (%)	8 (6)	5 (11)	0.009
	Standard Dose		
	Meet Criteria (N = 106)	Does Not Meet Criteria (N = 24)	P-value
Re-admissions – n (%)	46 (43)	12 (50)	0.386
All-cause mortality – n (%)	6 (6)	0	0.961

Table 4: Subgroup Analysis - Hemodialysis

	Reduced Dose		
	Meet Criteria (N = 28)	Does Not Meet Criteria (N = 27)	P-value
Bleeding events – n (%)	5 (18)	3 (11)	0.872
Systemic embolism – n (%)	1 (4)	2 (7)	0.610
Re-admissions – n (%)	12 (43)	16 (59)	0.338
All-cause mortality – n (%)	2 (7)	2 (7)	0.668

Discussion

The findings of this project emphasize the importance of adhering to the dose reduction criteria. Regardless if the patient met criteria for dose reduction, there was no significant difference in the primary outcomes between the reduced dose apixaban groups. However, in the standard dose apixaban group, there was a higher occurrence of bleeding events in patients that did not meet criteria for standard dose. In addition, all-cause mortality was almost twice as high in patients that did not meet the criteria for dose reduction. Although these results were statistically significant, it is important to note that the cause of mortality was not necessarily due to apixaban. Finally, there were similar readmission rates in patients on standard doses of apixaban.

No significant differences were found in the subgroup analysis for hemodialysis patients on reduced dose apixaban. However, it is important to note that bleeding events were higher in patients on reduced dose apixaban that met criteria for dose reduction (18% vs 11%). Although not statistically significant, this was also seen in the 2022 retrospective cohort study, which further shows that reduced dose apixaban in hemodialysis patients is not associated with a lower bleeding risk.[6]

There were several limitations to this study. Firstly, readmission and mortality rates were not necessarily due to apixaban. As seen in Table 1, these patients had multiple medical conditions that could have led to hospitalization. Furthermore, the baseline characteristics were dependent on the accuracy of the charting. This was a retrospective chart review, which may have been a missed opportunity to further assess medication compliance by the patient. Also, the primacy outcomes were only based on admission notes. This can potentially lead to type 2 error, saying there were no bleeding events or systemic embolism when in fact there was during the patient's hospital stay. Finally, all information was collected using a closed medical system. If a patient were to get admitted to another facility, outside of Dignity Health, the research investigators were unaware.

Conclusion

In conclusion, this study provides insights into the dose reduction criteria for NVAF that only meet criteria for Scr ≥ 1.5 mg/dL. While there was no significant difference observed in the primary outcomes for bleeding events and systemic embolism, these results still show the importance of adhering to the dose reduction criteria. Significant differences in all-cause mortality were seen in patients with reduced dose apixaban that did not meet criteria. Further studies with larger sample sizes are warranted to validate these findings and overcome the limitations identified in this study.

For future research, outcomes may benefit from a medication use evaluation to assess protocol compliance. As seen in this study, about 1 in 3 patients in each study group did not meet criteria for the dose they were on. In addition, looking at a larger sample of patients only on hemodialysis might be beneficial to make stronger conclusions.

Conflicts of Interest

The author has no conflicts of interest to declare.

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References

1. January C, Wann L, Calkins H, et al. 2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for Management of Patients with Atrial Fibrillation. Circulation. 2019;140:e125–e151. doi.org/10.1161/CIR.0000000000000665
2. Lip GYH, Banerjee A, Boriani G, et al. Antithrombotic therapy for atrial fibrillation: CHEST Guideline and Expert Panel Report. Chest.2018;154(5):1121-1201. doi:10.1016/j.chest.2018.07.040
3. Alshehri AM. Stroke in atrial fibrillation: Review of risk stratification and preventive therapy.J Family Community Med. 2019;26(2):92-97. doi:10.4103/jfcm.JFCM_99_18
4. Apixaban (Lexi-Drugs). https://online.lexi.com/lco/action/doc/retrieve/docid/patch_f/3804162. Accessed September 2, 2023.
5. Mavrakanas TA, Garlo K, Charytan DM. Apixaban versus No Anticoagulation in Patients Undergoing Long-Term Dialysis with Incident Atrial Fibrillation. Clin J Am Soc Nephrol. 2020;15(8):1146-1154. doi:10.2215/CJN.11650919
6. Wetmore JB, Weinhandl ED, Yan H, et al. Apixaban Dosing Patterns Versus Warfarin in Patients With Nonvalvular Atrial Fibrillation Receiving Dialysis: A Retrospective Cohort Study. American Journal of Kidney Diseases. 2022; 80(5): 569-579.
7. Buchholz A, Ueberham L, Gorczynska K, et al. Initial apixaban dosing in patients with atrial fibrillation. Clin Cardiol. 2018;41(5):671-676. doi:10.1002/clc.22949.
8. Inoue H, Umeyama M, Yamada T, et al. Safety and effectiveness of reduced-dose apixaban in Japanese patients with nonvalvular atrial fibrillation in clinical practice: A sub-analysis of the STANDARD study. J Cardiol. 2020;75(2):208-215. doi:10.1016/j.jjcc.2019.07.007
9. Siontis KC, Zhang X, Eckard A, et al. Outcomes Associated With Apixaban Use in Patients With End-Stage Kidney Disease and Atrial Fibrillation in the United States. Circulation. 2018;138(15):1519-1529. doi:10.1161/circulationaha.118.035418
10. Wang X, Tirucherai G, Marbury TC, et al. Pharmacokinetics, pharmacodynamics, and safety of apixaban in subjects with end-stage renal disease on hemodialysis. J Clin Pharmacol. 2016;56(5):628-636. doi:10.1002/jcph.628

Appendix A

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St. Rose Dominican

POLICY/PROCEDURE

CATEGORY: Clinical/Pharmacy
SUBJECT: **Anticoagulation Therapy**
ORIGINATED: 06/09 EFFECTIVE: 08/20 SUPERSEDES: 01/18

APIXABAN Renal Impairment Dosing

For *Non-Valvular Atrial Fibrillation*	
IF THE PATIENT MEETS ANY *TWO (2)* OF THE FOLLOWING CHARACTERISTICS:	**ACTION**
▪ Age greater than or equal to eighty (80) years ▪ Body weight less than or equal to sixty (60) kilograms ▪ Serum creatinine greater than or equal to one-point-five (1.5) mg/dL	▶ Reduce dose to 2.5 mg twice daily
IF THE PATIENT MEETS *ONE (1)* OF THE FOLLOWING CHARACTERISTICS *AND* IS ON *HEMODIALYSIS*:	**ACTION**
▪ Age greater than or equal to eighty (80) years ▪ Body weight less than or equal to sixty (60) kilograms	▶ Reduce dose to 2.5 mg twice daily

Policy: Anticoagulation Therapy, Adult