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Evaluation of Standard Versus Reduced Dose Apixaban for the Treatment of Venous Thromboembolism in Patients with Severe Renal Disease (ESRD-VTE)

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Abstract

Background—There are no clear dosing recommendations when using apixaban for venous thromboembolism (VTE) treatment in patients with severe or end-stage renal disease; clinical trials excluded patients with a creatinine clearance (CrCl) less than 25 mL/min or on dialysis. This study compares bleeding rates in patients with severe or end-stage renal disease taking standard versus reduced dose apixaban for VTE treatment.

Materials and Methods—This was a multicenter, retrospective cohort study using electronic medical records between January 1, 2013, and August 31, 2021. This study included patients 18 years or older who had severe or end-stage renal disease when prescribed apixaban for VTE treatment. Severe or end-stage renal disease was defined as at least one of the following: CrCl <25 mL/min, SCr >2.5 mg/dL, CKD stage 4 or 5, or on dialysis. The primary endpoint was rate of clinically relevant bleeding within six months of starting apixaban. Secondary endpoints were VTE recurrence within six months of starting apixaban, time to clinically relevant bleed, and time to VTE recurrence.

Results—A total of 203 patients were included in the final analysis (n=125 on 5mg; n=78 on 2.5mg). Clinically relevant bleeding rate was significantly higher in the standard dose group (14.4% vs 3.8%, p=0.02). Rates of VTE recurrence appear similar (6.4% vs 7.7%, p=0.21).

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Conclusions: A reduced dose of apixaban may be considered when treating VTE in patients with severe or end-stage renal disease.

Keywords

anticoagulation; apixaban; renal disease; venous thromboembolism; dialysis

Introduction

Chronic kidney disease (CKD) affects approximately 15% of the United States' adult population [1]. Patients with CKD stage 4, defined as an estimated glomerular filtration rate (eGFR) of 15–30 mL/min, have an increased incidence of venous thromboembolism (VTE) compared to those with adequate renal function due to decreased levels of endogenous anticoagulants and an impaired fibrinolytic system. Consequently, the incidence of VTE increases in patients with end stage renal disease (ESRD) who are receiving renal dialysis [2,3]. The preferred treatment of VTE has historically been vitamin K antagonists (VKAs), such as warfarin; however, direct-acting oral anticoagulants (DOACs), such as apixaban (Eliquis; Bristol-Meyers Squibb; New York, NY, USA), have increasingly been recommended over VKAs for the first 3 months of treatment as reflected in the 2021 CHEST guidelines [4]. In patients without severe renal disease, evidence has shown superior efficacy and a favorable safety profile with DOACs compared to VKAs [5,6]. The use of DOACs has also superseded warfarin due to their fixed dosing regimens, minimal laboratory monitoring requirements, and immediate onset of therapeutic effect. However, the 2021 CHEST guidelines do not provide specific recommendations for patients with severe or end-stage renal disease [4].

Aside from warfarin, apixaban is the only oral anticoagulant approved by the US Food and Drug Administration (FDA) for use in patients with ESRD on hemodialysis (HD) for the treatment of acute VTE. However, its extended approval in this patient population was based solely on limited pharmacokinetic data, as many clinical trials excluded patients with severe or end-stage renal disease. Based on the outcomes of AMPLIFY evaluating apixaban in the treatment of VTE in patients with adequate renal function (CrCl ≥25ml/min), the FDA-approved dose of apixaban is 10 mg twice daily for seven days, followed by a maintenance dose of 5 mg twice daily. Criteria for reduced apixaban dosing only exists for the indication of stroke prevention in patients with non-valvular atrial fibrillation (NVAF), with a manufacturer label recommendation to reduce the maintenance dose to 2.5 mg twice daily in patients who meet at least two of the following: age ≥80 years old, actual body weight ≤60 kg, or serum creatinine (SCr) ≥1.5 mg/dL [7].

Despite having an increased thrombotic risk compared to the general population, patients with severe or end-stage renal disease are also more susceptible to bleeding due to several factors, including uremic platelet dysfunction, anemia, and intermittent use of heparin with dialysis. AMPLIFY, a pivotal trial that led to the FDA approval of apixaban for VTE treatment, demonstrated comparable efficacy and a significant reduction in the risk of major bleeding compared to therapeutic enoxaparin transitioned to warfarin. Notably, patients with CrCl <25mL/min or SCr >2.5mg/dL were excluded [8]. Recent evidence has demonstrated

significantly lower bleeding rates with apixaban compared to warfarin in patients with ESRD, suggesting that apixaban may be a safer option in the setting of severe or end-stage renal disease for both NVAF and VTE [9,10,11]. However, the optimal apixaban dosing strategy with respect to safety and efficacy for the treatment of VTE in severe or end-stage renal disease remains unknown.

In addition to having increased risk of bleeding at baseline, patients with severe or end-stage renal disease who take apixaban for an extended duration experience accumulation and increased serum concentrations of the medication due to its partial renal elimination [12]. For these reasons, physicians may elect to prescribe an off-label, reduced dose of apixaban when treating VTE in patients with severe or end-stage renal disease. Current literature lacks robust safety and efficacy data directly comparing the standard apixaban dose of 5 mg twice daily and the off-label, reduced dose of apixaban 2.5 mg twice daily for the treatment of VTE in patients with severe or end-stage renal disease. It is unclear if the standard apixaban dose poses an increased risk of bleeding compared to the reduced dose in this patient population, especially when the duration of VTE treatment exceeds three months. The objective of this study was to compare the clinically relevant bleeding rate between standard and reduced dose apixaban for the treatment of VTE in patients with severe or end-stage renal disease at large, academic medical centers. We hypothesized that patients who received the standard apixaban dose would have a significantly higher rate of bleeding compared to those who received the reduced dose.

Materials and Methods

Study Design

This was a retrospective cohort study conducted at four large academic medical centers within the University of California (UC) health system; UC Davis Health, UC Irvine Health, UC San Diego Health, and UC San Francisco Health, between January 1st, 2013, and August 31st, 2021. Patients were eligible for inclusion if they were at least 18 years of age, prescribed at minimum a one-month supply of apixaban for the treatment of VTE and met one of the following criteria for severe or end-stage renal disease: CrCl <25 mL/min, SCr >2.5 mg/dL, diagnosis of CKD stage 4 or 5 (ESRD), or on HD. Initial VTEs were systematically confirmed by provider notes and categorized as either a ‘deep vein thrombosis/pulmonary embolism’ (DVT/PE) or ‘other clinically relevant VTE’ (Appendix A). Patients were excluded if they were pregnant or were transitioned to a non-apixaban anticoagulant during the 6-month follow-up period. Patients were also excluded if they had lack of follow up or documentation during the six months after starting apixaban. Lack of follow up was defined as patients who did not return for care or evaluation (e.g., due to death, relocation, etc.) or had no additional encounters documented during the 6-month period from date of apixaban initiation. This study was granted approval or deemed exempt by the Institutional Review Board (IRB) at each institution.

Data Collection

Data were extracted from electronic medical records using manual chart review and were collected and managed using REDCap (Research Electronic Data Capture) electronic

data capture tools hosted at UCSF [13,14]. REDCap is a secure, web-based software platform designed to support data capture for research studies, providing 1) an intuitive interface for validated data capture; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for data integration and interoperability with external sources.

The following baseline patient information was collected: sex, age, weight, CKD stage, serum creatinine, apixaban therapy regimen (loading and maintenance dose), VTE Bleed Score components (antiplatelet regimen, active cancer diagnosis, presence of uncontrolled hypertension, anemia, history of major bleeding), date of bleed, type of bleed encounter, date of VTE recurrence, and type of VTE. International Classification of Diseases Ninth or Tenth Revision, Clinical Modification (ICD-9-CM and ICD-10-CM) codes documented at the index hospitalization were used to identify patients for inclusion (Appendix B).

Outcome Measurements

The primary outcome was the rate of clinically relevant bleeding during anticoagulation with apixaban, including all major and clinically relevant non-major bleeds (CRNMB) as defined by the International Society on Thrombosis and Haemostasis (ISTH) criteria [15]. Secondary outcomes were rate of VTE recurrence during anticoagulation with apixaban, time to clinically relevant bleed, and time to VTE recurrence. All bleed and VTE events were identified by chart review of encounters with a health care professional (phone call, office visit, emergency department visit, or hospitalization), where bleeding or VTE were primary reasons for contact. The follow-up period was 6 months after initiation of apixaban in the setting of VTE treatment.

Statistical Analysis

The effect size was estimated using previously reported bleed rates from the RENAL-AF trial and an analysis conducted by Steuber et al [16,17]. We expected to see an absolute difference in bleed rate of 13% between the standard dose group and reduced dose group (25% vs 12%). The required sample size to meet power was calculated to be n=278 (n=139 per treatment group) with an alpha of 0.05 and a beta of 0.20. Descriptive statistics were used to characterize patient demographics, baseline characteristics, and types of bleeds. Statistical analysis was performed by SAS® software version 9.4 for Windows® (SAS Institute Inc. Cary, NC, USA) software. Normality was assessed using histograms. An independent sample student's t-test was used to compare the mean duration of apixaban, the mean VTE bleed score, the mean time to bleed, and the mean time to VTE between the standard dose group and the reduced dose group. Chi-square test was used to compare the proportion of patients who received a full apixaban loading dose of 10 mg twice daily for 7 days between two groups. A Fisher's exact test was used to compare the types of encounters in patients who had bleeding events between two groups. A multiple logistic regression analysis was conducted modeling the rate of clinically relevant bleeding and the rate of VTE recurrence, controlling for antiplatelet medication and weight. Kaplan-Meier curve was constructed to visualize differences in the time to bleed between dosage groups. The log rank test was performed to assess significance.

Results

A total of 863 patients who received at least one month of apixaban for the treatment of VTE between January 1st, 2013, and August 31st, 2021, were screened for inclusion. Of these, 578 patients did not meet inclusion criteria and 82 patients were excluded due to lack of documentation or follow up. For final analysis, there were 125 patients in the standard dose group and 78 patients in the reduced dose group (Figure 1). Our final sample did not meet power for our estimated effect size. We proceeded with our analysis so as to obtain better estimates of the effect sizes in our patient population.

Demographics

Baseline characteristics were largely similar between groups, but we did note that more patients in the standard dosing group received a full apixaban loading dose of 10 mg twice daily for 7 days (44 (35.2%) vs 2 (2.6%), p<0.01) (Table 1). The mean duration of apixaban was similar between groups (148.2 ± 56.9 vs 151.4 ± 51.2 days, p=0.69), and the mean VTE-BLEED score was approximately 4.5 in both groups (p=0.92). Of all included patients, 67 (33.0%) met criteria for reduced dose apixaban according to the stroke prophylaxis indication for atrial fibrillation; in the standard and reduced dose groups, 29.6% and 38.5% met these criteria for reduced dose, respectively. A larger percentage of patients in the reduced dose group were concurrently on antiplatelet medication, but this was not statistically significant (38.4% vs 48.7%, p=0.19).

Primary Outcome

The rate of clinically relevant bleeding was higher in the standard apixaban dose group (14.4% vs 3.8%. p=0.02) (Figure 2). Of the 21 patients who experienced clinically relevant bleeding, 12 required hospital admission (Table 2). Three patients in the standard dose group met ISTH major bleeding criteria. Bleeding event types that occurred in the standard dose group include the following: dialysis catheter site, epistaxis, hematemesis, hematochezia, hematuria, hemoperitoneum, hemoptysis, melena, nephrostomy tube, peripherally inserted central catheter (PICC), rectal hemorrhoids, urethral, and vaginal. Bleeding event types in the reduced dose group included gingival, hematuria, and hip wound. Of the 21 patients who experienced clinically relevant bleeding, 38% met NVAF reduced dose criteria.

Secondary Outcomes

The rate of VTE recurrence was 6.4% (n=8) in the standard dose group and 7.7% (n=6) in the reduced dose group, (p=0.78) (Figure 3). The mean time to clinically relevant bleed was significantly shorter in the standard dose group (32.7 vs 105.3 days, p<0.01) (Figure 4). The mean time to VTE was similar between groups (101.1 vs 98.3 days, p=0.92). The Kaplan-Meier curve showed good separation between the reduced and standard dose treatments for the VTE outcome, however, this did not reach the level of statistical significance (p=.05).

Discussion

Our results suggest that reduced dose apixaban may result in a significantly lower rate of clinically relevant bleeding compared to standard dose apixaban, with similar rate of

recurrent VTE, in patients with severe or end-stage renal disease requiring VTE treatment. To our knowledge, this is the largest study to evaluate apixaban dosing strategies for VTE treatment in patients with severe or end-stage renal disease and provides novel information with clinical implications for practice.

Previous studies have evaluated apixaban in patients with severe renal disease; however, these studies lack sufficient detail on optimal dosing strategies in this population. A recently published study evaluating apixaban for VTE in 68 hospitalized patients with ESRD receiving renal replacement therapy reported a 13.2% rate of major bleeding but did not evaluate the impact of dosing strategy [18]. While we agree with the authors' conclusion that the use of apixaban in this patient population should occur following shared decision making, our findings may support consideration of reduced dose apixaban as a potential safe and effective option.

Identifying safe anticoagulation strategies for patients with severe or end-stage renal disease remains a challenge as this population is at both increased risk of bleeding and thrombosis. In general, assessing bleed risk can be difficult given the lack of evidence to support specific risk factors that carry more weight than others. The percentage of patients who met criteria for reduced dose apixaban in our study, according to the NVAF indication, was very similar between the entire study population and 21 patients who experienced clinically relevant bleeding (33% vs 38%). This suggests utilizing NVAF criteria for dose reduction for VTE may not be appropriate, and our findings suggest severe, or end-stage renal disease alone may warrant a reduced apixaban dosing strategy in this population.

Current literature in patients with severe or end-stage renal disease has largely compared rates of major bleeding between DOACs and warfarin but lack guidance on optimal apixaban dosing strategies. A literature review in 2021 included a total of 9 case-control, cohort, and randomized controlled trials that evaluated DOACs versus active comparators in patients with CKD stage 5 or ESRD [19]. Safety and efficacy data for VTE were limited to one retrospective review, which found a significant difference in major bleeding (apixaban 5.4%, warfarin 22.0%; p=0.01) and did not assess apixaban dosing strategies [20]. A large cohort study has since been published which evaluated the rate of major bleeding between apixaban and warfarin for VTE treatment in dialysis patients [21]. Their findings were similar and suggest that apixaban may be safer, but also did not explore optimal apixaban dosing.

In addition to being the first study to closely compare standard versus reduced apixaban dosing strategies for VTE, our study also brought to light other considerations regarding the safety of apixaban in this population. Much of the existing literature in patients with severe or end-stage renal disease has largely focused on rates of major bleeding between DOACs and warfarin to suggest apixaban as the safer option; however, major bleeding is less common than CRNMB. We applied a definition of "clinically relevant bleeding" to account for both CRNMB and major bleeding in our study. Not only may patients be discouraged to continue therapy after a non-major bleeding event, but non-major bleeding events often result in hospital admission or emergency department visits. Our study identified a majority of the bleeding events led to hospitalization, but a very small percentage of those qualified

as major bleeding. Although major bleeding is an acceptable endpoint measure for safety, a comprehensive assessment of bleeding may better guide dosing strategy.

Furthermore, many patients will require anticoagulation for more than three months (many patients with provoked VTEs are on therapy for three to six months), increasing the risk for apixaban accumulation. In our study, we used a six-month follow-up period to account for this, which is longer than most previously published studies. Although six months may not be sufficient for our secondary endpoint, previous literature suggests VTE recurrence may stabilize within the initial six months [22]. While bleeding events occurred much sooner after treatment initiation in the standard dose group, we found the bleeding risk persisted with five patients (23.8%) experiencing a bleed after the first 90 days. Two of the three patients in the reduced dose group experienced a non-major bleed after 100 days of therapy. Although the study was not powered for the VTE recurrence outcome, this consideration of favorable tolerability and safety with reduced dose apixaban is further supported by the similar rates of recurrence between the groups.

Overall, our study reports similar bleeding rates compared to previously published data on apixaban in patients with severe or end-stage renal disease, which are notably higher than the landmark trials that excluded these patients. However, there are several key differences between our study and the existing literature. A 2017 multicenter analysis of 114 hospitalized patients with ESRD solely on HD reported that apixaban-related bleeding events, regardless of severity, occurred in 14.9% of the study population [17]. While this study reported a higher likelihood of bleeding with increased apixaban total daily dose, it was not designed to directly compare bleed rates based on dosing strategy, and a large majority of patients were on apixaban for NVAF. Of the 17 patients who experienced a bleed, 7 (41.2%) were receiving apixaban 2.5 mg twice daily, a much higher proportion than what our study reported for the reduced dose group. However, it was reported that 5 out of the 17 patients who experienced a bleed did not meet criteria for ISTH major bleeding or CRNMB, and the delineation of types of bleed events for standard and reduced dose groups was not presented. Baseline bleeding risk was not reported either, which could introduce bias if patients on a reduced dose in this study had significantly higher risk of bleeding.

Despite the strengths of our study, it is not without some limitations. We were unable to meet power for our estimated effect size and believe larger sample sizes may be helpful to confirm the bleed and VTE recurrence rates we found in our study population. Additionally, we did not collect any pharmacokinetic data, such as anti-Xa levels, which may provide a more objective assessment of the impaired clearance of apixaban in patients with severe or end-stage renal disease; however, the use of this type of monitoring has not been validated. Due to the retrospective nature of this study, patients' adherence to their prescribed apixaban regimens was not evaluated. We did collect data from external health care facilities who share electronic health record information with our institutions; however, this was not inclusive of all in-state institutions or any out of state, so bleeding and recurrent VTE events could have been underrepresented. Additionally, other than concurrent antithrombotic medications, there were no data collected on concurrent drug-drug interactions with apixaban, such as azole antifungals which may significantly increase serum concentrations of apixaban, or selective serotonin reuptake inhibitors (SSRIs) which

may exhibit antiplatelet effects. There was a higher proportion of patients with CKD 5 in our study, and we did not analyze outcomes between the CKD 4 and 5 cohorts. A substantial number of patients diagnosed with CKD 5 in our study may have been on dialysis during the follow up period, but this was not delineated during data collection, which impairs our ability to accurately compare the serum creatinine and creatinine clearance at baseline between groups. Lastly, we defined a full loading dose as apixaban 10 mg twice daily for 7 days and did not consider other loading strategies in our baseline characteristics. This limits our ability to evaluate loading strategies in this patient population.

Conclusion

While future studies are needed to create more definitive recommendations for dosing of apixaban for treatment of VTE in patients with severe or end-stage renal disease, the use of apixaban in these settings is likely to continue given the relative ease of administration and monitoring, as well as its status as the only oral anticoagulant FDA approved for treatment of VTE in patients with ESRD on HD. The results of this study demonstrate a lower bleeding rate associated with reduced dose apixaban, which suggests that patients with severe or end-stage renal disease should be evaluated carefully for consideration of this dosing scheme, especially in the setting of additional risk factors for bleeding.

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Appendix A.: Indication for initiating apixaban

- DVT/PE: n=198 (97.5%)
- Other clinically relevant VTE

Appendix B.: ICD Codes for Eligibility Screening

- End-Stage Renal Disease (Diagnosis) [ICD-10 Group]
- Dependence on renal dialysis (ICD-10-CM: Z99.2, ICD-9-CM: V45.11)
- Chronic kidney disease, stage 4 (severe) (ICD-10-CM: N18.4, ICD-9-CM: 585.4)
- VTE Diagnoses [ICD-10 Group]
- Other venous embolism and thrombosis (I82.*) [ICD-10 Group], ICD-9-CM: 453
- Pulmonary embolism (ICD-10-CM: I26.*) [ICD-10 Group]
- Chronic pulmonary embolism (ICD-10-CM: I27.82, ICD-9-CM: 416.2)
- Personal history of other venous thrombosis and embolism (ICD-10-CM: Z86.718)

Appendix C.: Bleeding events

- Standard dose group: vaginal bleeding, hematemesis post-mitral clip procedure, melena, post-operative groin site oozing, urethral bleeding post-kidney transplant, rectal bleeding from external hemorrhoids, dialysis catheter site, dialysis catheter site, GI bleed, hemoptysis, hematochezia, hemoperitoneum, hematuria, excessive bruising and vaginal bleeding, bleeding from dialysis shunt, bleeding into nephrostomy tube, epistaxis, iliopsoas hematoma, bleeding from PICC line, hematochezia
- Reduced dose group: bleeding from hip wound, hematuria, bleeding from mouth after teeth cleaning

References

[1]. Centers for Disease Control and Prevention. Chronic Kidney Disease in the United States, 2021. Atlanta, GA: US Department of Health and Human Services, Centers for Disease Control and Prevention; 2021.

[2]. Wattanakit K, Cushman M, Stehman-Breen C, et al. Chronic kidney disease increases risk for venous thromboembolism. J Am Soc Nephrol. 2008;19(1):135–140. doi:10.1681/ASN.2007030308 [PubMed: 18032796]

[3]. Wattanakit K, Cushman M. Chronic kidney disease and venous thromboembolism: epidemiology and mechanisms. Curr Opin Pulm Med. 2009;15(5):408–412. doi:10.1097/MCP.0b013e32832ee371 [PubMed: 19561505]

[4]. Stevens SM, Woller SC, Baumann Kreuziger L, et al. Executive Summary: Antithrombotic Therapy for VTE Disease: Second Update of the CHEST Guideline and Expert Panel Report. Chest. 2021;160(6):2247–2259. doi:10.1016/j.chest.2021.07.056 [PubMed: 34352279]

[5]. Ruff CT, Giugliano RP, Braunwald E, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. Lancet. 2014; 383:955–962. [PubMed: 24315724]

[6]. van der Hulle T, Kooiman J, den Exter PL, et al. Effectiveness and safety of novel oral anticoagulants as compared with vitamin K antagonists in the treatment of acute symptomatic venous thromboembolism: a systematic review and meta-analysis. J Thromb Haemost. 2014;12:320–328. [PubMed: 24330006]

[7]. Eliquis. Package insert. Bristol-Myers Squibb/Pfizer; 2021

[8]. Liu X, Johnson M, Mardekian J, et al. Apixaban reduces hospitalizations in patients with venous thromboembolism: An analysis of the apixaban for the initial management of pulmonary embolism and deep-vein thrombosis as first-line therapy (AMPLIFY) trial. Journal of the American Heart Association, 2015. 4(12). 10.1161/jaha.115.002340

[9]. Stanifer JW, Pokorney SD, Chertow GM, et al. Apixaban Versus Warfarin in Patients With Atrial Fibrillation and Advanced Chronic Kidney Disease. Circ Res. 2020;141(17):1384–1392. doi:10.1161/CIRCULATIONAHA.119.044059

[10]. Schafer JH, Casey AL, Dupre KA, et al. Safety and Efficacy of Apixaban Versus Warfarin in Patients With Advanced Chronic Kidney Disease. Ann Pharmacother. 2018;52(11):1078–1084. doi:10.1177/1060028018781853 [PubMed: 29871510]

[11]. Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011;365(11):981–992. doi:10.1056/NEJMoa1107039 [PubMed: 21870978]

[12]. Mavrakanas TA, Samer CF, Nessim SJ, et al. Apixaban Pharmacokinetics at Steady State in Hemodialysis Patients. J Am Soc Nephrol. 2017;28(7):2241–2248. doi:10.1681/ASN.2016090980 [PubMed: 28302754]

[13]. Harris PA, Taylor R, Thielke R, et al. Research electronic data capture (REDCap) – A metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform. 2009;42(2):377–81. [PubMed: 18929686]

[14]. Harris PA, Taylor R, Minor BL, et al. The REDCap consortium: Building an international community of software partners. J Biomed Inform. 2019. doi:10.1016/j.jbi.2019.103208

[15]. Schulman S, Kearon C. Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. J Thromb Haemost. 2005;3(4):692–694. doi:10.1111/j.1538-7836.2005.01204.x [PubMed: 15842354]

[16]. Stanifer JW, Pokorney SD, Chertow GM, et al. Apixaban Versus Warfarin in Patients With Atrial Fibrillation and Advanced Chronic Kidney Disease. Circ Res. 2020;141(17):1384–1392. doi:10.1161/CIRCULATIONAHA.119.044059

[17]. Steuber TD, Shiltz DL, Cairns AC, et al. A Multicenter Analysis of Factors Associated With Apixaban-Related Bleeding in Hospitalized Patients With End-Stage Renal Disease on Hemodialysis. Ann Pharmacother. 2017;51(11):954–960. doi:10.1177/1060028017717282 [PubMed: 28643524]

[18]. Chen J, Nguyen S, Ruegger M, et al. Evaluation of outcomes with apixaban use for venous thromboembolism in hospitalized patients with end-stage renal disease receiving renal replacement therapy. J Thromb. 2022. doi:10.1007/s11239-022-02650-4

[19]. Starr JA, Pinner NA, Mannis M, et al. A review of direct oral anticoagulants in patients with stage 5 or end-stage kidney disease. Ann Pharmacother. 2021;56(6),691–703. doi:10.1177/10600280211040093 [PubMed: 34459281]

[20]. Reed D, Palkimas S, Hockman R, et al. Safety and effectiveness of apixaban compared to warfarin in dialysis patients. Res Pract Thromb Haemost. 2018;2(2),291–298. doi:10.1002/rth2.12083 [PubMed: 30046731]

[21]. Wetmore JB, Herzog CA, Yan H, et al. Apixaban versus Warfarin for Treatment of Venous Thromboembolism in Patients Receiving Long-Term Dialysis. Clin J Am Soc Nephrol. 2022;17(5):693–702. doi:10.2215/CJN.14021021 [PubMed: 35470214]

[22]. Schulman S, Rhedin A, Lindmarker P, et al. A Comparison of Six Weeks with Six Months of Oral Anticoagulant Therapy after a First Episode of Venous Thromboembolism. N Engl J Med. 1995; 332:1661–1665. doi:10.1056/NEJM199506223322501 [PubMed: 7760866]

[23]. Klok FA, Barco S, Turpie AG et al. Predictive value of venous thromboembolism (VTE)-BLEED to predict major bleeding and other adverse events in a practice-based cohort of patients with VTE: results of the XALIA study. Br J Haematol. 2018;183(3):457–465. doi:10.1111/bjh.15533 [PubMed: 30123981]

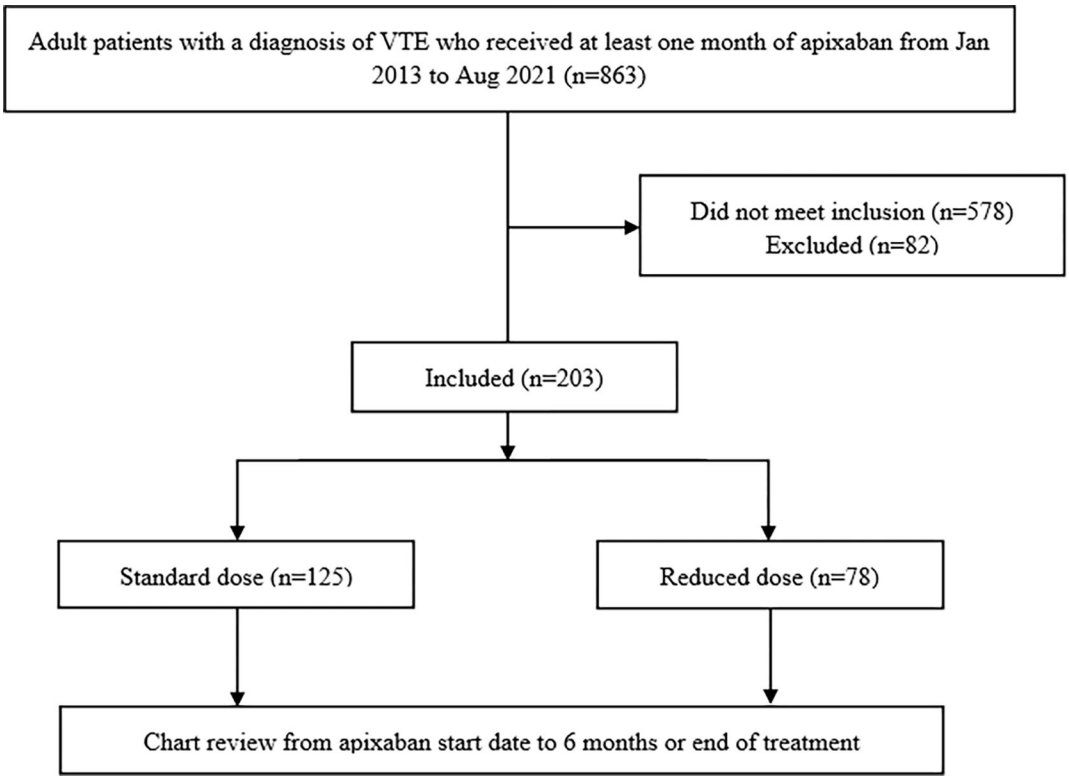

Figure 1.
Patient Enrollment

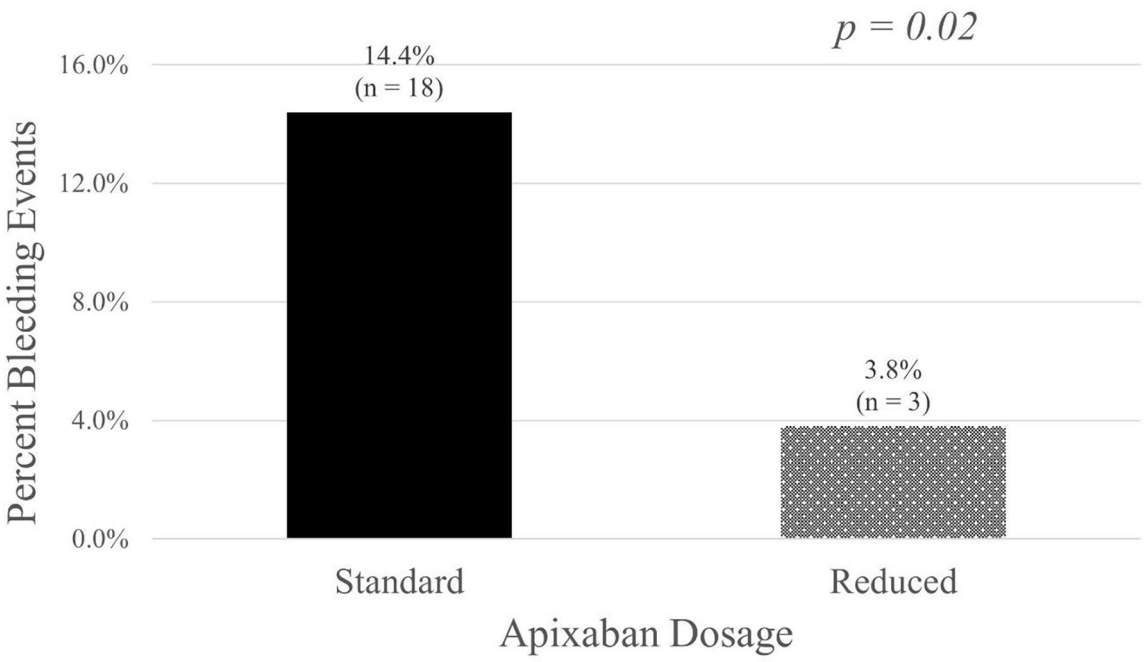

Figure 2.
Percent bleeding events by apixaban dosage

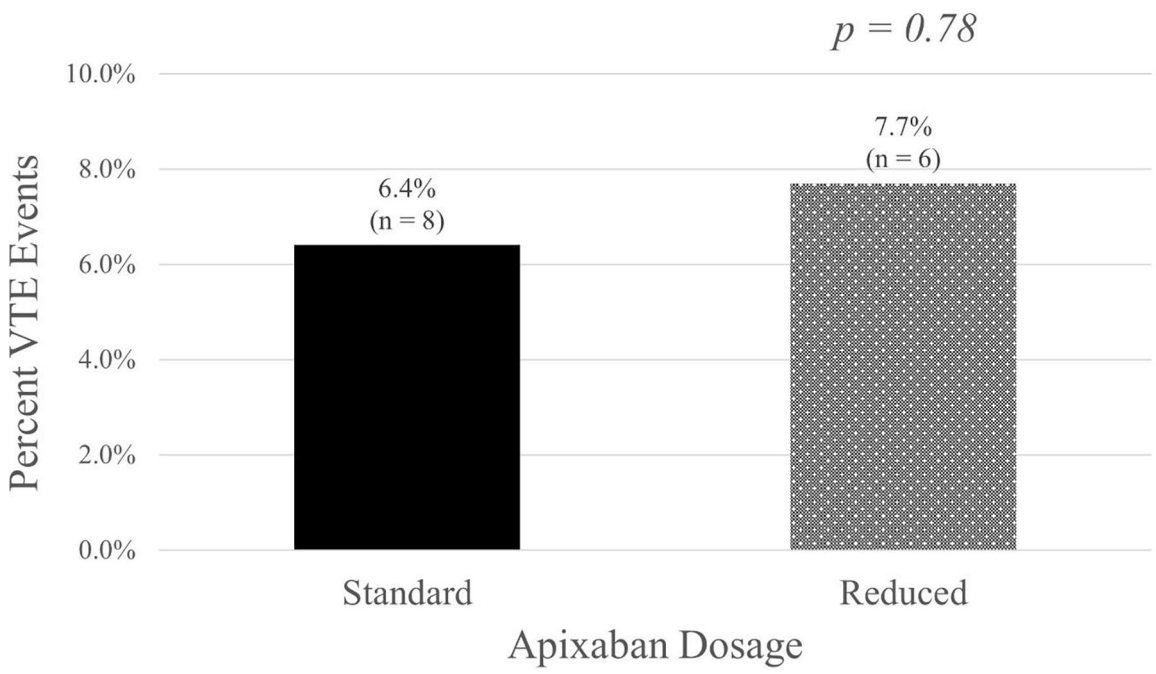

Figure 3.
Percent VTE events by dose

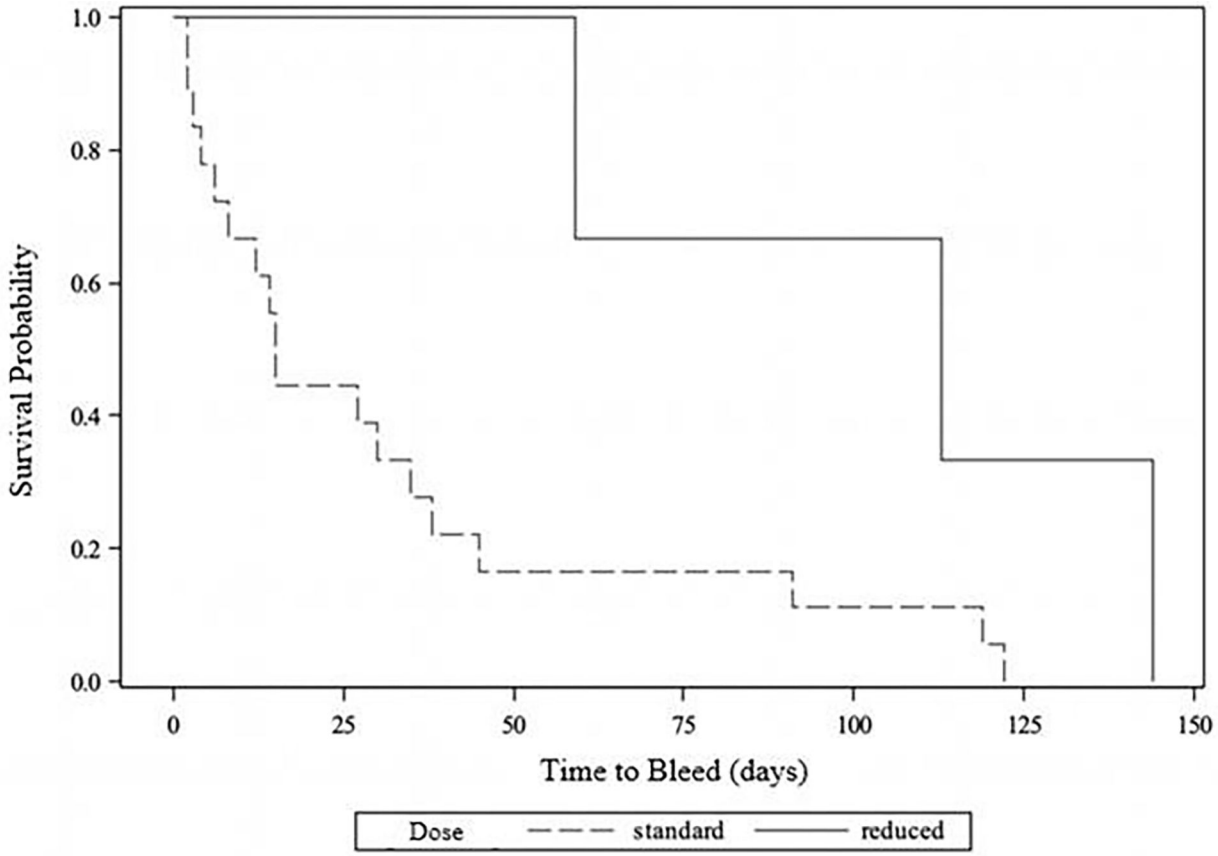

Figure 4.
Kaplan-Meier curve: log rank test (p<.01) for time to bleed by dose

Table 1.

Baseline characteristics

	Standard (n=125)	Reduced (n=78)	*p-value*
Male, n (%)	62 (49.6)	37 (47.4)	0.77
Age (years), mean [SD]	60.2 [18.9]	61.0 [16.8]	0.77
Weight (kg), mean [SD]	79.8 [24.2]	75.2 [19.5]	0.14
CrCl (mL/min) [a], mean [SD]	22.8 [20.0]	18.3 [16.1]	0.01
SCr (mg/dL), mean [SD]	5.2 [3.3]	5.75 [4.7]	0.36
CKD 4 (CrCl 15–29 mL/min), n (%)	53 (42.4)	28 (35.9)	0.46
CKD 5 (CrCl <15 mL/min), n (%)	72 (57.6)	49 (62.8)	0.46
Apixaban loading dose [b], n (%)	44 (35.2)	2 (2.6)	<0.01
Concurrent antiplatelets, n (%)	48 (38.4)	38 (48.7)	0.19
Apixaban treatment duration (days), mean [SD]	148.2 [56.9]	151.4 [51.2]	-
<3 months, n (%)	24 (19.2)	12 (15.4)	-
3–6 months, n (%)	101 (80.8)	66 (84.6)	-
VTE Bleed Score [c], mean [SD]	4.51 [1.2]	4.53 [1.4]	0.92
Active Cancer, n (%)	11 (8.8)	10 (12.8)	0.48
Uncontrolled hypertension, n (%)	48 (38.4)	29 (37.2)	0.88
Anemia, n (%)	108 (86.4)	66 (84.6)	0.83
History of Bleed, n (%)	28 (22.4)	15 (19.2)	0.72
Age ≥60 years, n (%)	71 (56.8)	44 (56.4)	>0.99
CrCl ≤60 mL/min, n (%)	125 (100)	78 (100)	-

[a]Creatinine Clearance (CrCl) calculated with Cockcroft-Gault equation using the actual body weight and serum creatinine (SCr) measured in closest proximity to the initiation of apixaban.

[b]Defined as apixaban 10 mg twice daily for 7 days

[c]VTE-BLEED score [23] calculated from the following variables recorded closest to apixaban start date: SBP ≥140 mmHg at baseline [1 point], anemia defined by Hgb <130 g/L (men) and <120 g/L (women) [1.5 points], history of bleeding (major or non-major clinically relevant bleeding) [1.5 points], age ≥60 years [1.5 points], and renal dysfunction CrCl ≤60 ml/min [1.5 points]

Table 2.

Characteristics of bleeding events and patients who experienced them (n=21)

	Standard (n=18)	Reduced (n=3)
Bleeding events		
Required hospital admission, n (%)	10 (47.6)	2 (9.5)
Met ISTH major bleed criteria, n (%)	3 (16.7)	0 (0)
Time to bleed (days), mean [SD]	32.7	105.3
Age (years), mean [SD]	64.5 [18.2]	55.7 [22.9]
>80 years, n (%)	5 (27.8)	1 (33.3)
Weight (kg)	76 [22.8]	94 [9.1]
<60 kg, n (%)	5 (27.8)	0 (0)
Apixaban indication[a] DVT/PE, n (%)	14 (77.8)	2 (66.7)
CKD 5 (CrCl <15 mL/min), n (%)	11 (61.1)	2 (66.7)
Concurrent antiplatelets, n (%)	6 (33.3)	1 (33.3)
Apixaban loading dose[b], n (%)	9 (50)	0 (0)
Apixaban treatment duration (days), mean [SD]	150.4 [61.9]	145.3 [68.5]
VTE Bleed Score[c], mean [SD]	4.7 [1.3]	4.5 [1.3]

[a] Apixaban indication (Appendix A)

[b] Defined as apixaban 10 mg twice daily for 7 days

[c] VTE-BLEED score [23] calculated from the following variables recorded closest to apixaban start date: SBP ≥140 mmHg at baseline [1 point], anemia defined by Hgb <130 g/L (men) and <120 g/L (women) [1.5 points], history of bleeding (major or non-major clinically relevant bleeding) [1.5 points], age ≥60 years [1.5 points], and renal dysfunction CrCl ≤60 ml/min [1.5 points]