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Efficacy and safety of Apixaban for the prevention of thrombosis in arteriovenous grafts

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Abstract

This research aims to fill a vital gap in existing studies by evaluating the efficacy and safety of Apixaban, a direct oral anticoagulant, in the prevention of arteriovenous graft (AVG) thrombosis, thereby offering substantial insights into alternative anticoagulant options for hemodialysis patients. Conducted as a multi-center, randomized, double-blind, placebo-controlled trial, this study involved end-stage renal disease (ESRD) patients who had recently received polytetrafluoroethylene grafts. Participants were assigned to receive either Apixaban at a dose of 2.5 mg twice daily or a placebo. The primary outcome measure was the occurrence of graft thrombosis, while secondary outcomes focused on the incidence and severity of bleeding. Analytical methods included Kaplan-Meier estimates, Cox proportional hazards models, and conventional statistical tests. With 96 patients enrolled, the study found that Apixaban significantly reduced the incidence of AVG thrombosis compared to placebo (16.7% vs. 62.5%, $P < 0.0001$). Notably, this reduction in thrombosis incidence was not accompanied by an increase in bleeding events, thus affirming the safety profile of Apixaban as established in prior research. Apixaban is identified as an efficacious alternative to traditional anticoagulants in the prevention of AVG thrombosis among hemodialysis patients, representing a notable advancement in the care of individuals with ESRD. The results of this study support further investigations into the optimal dosing strategies specifically tailored for this patient demographic.

Key Words: Apixaban; arteriovenous graft; thrombosis; hemodialysis; end-stage renal disease; anticoagulants.

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The efficacy of hemodialysis, a critical treatment for end-stage renal disease, is largely dependent on the integrity and reliability of the patient's vascular system, which significantly influences both survival rates and the duration of effective dialysis. Optimal vascular access, ideally combining reliability and minimal complications, tailored to the patient's specific needs, is paramount in hemodialysis.[1] While arteriovenous fistulas (AVFs) are the preferred choice in clinical settings due to their long-term efficacy, arteriovenous grafts (AVGs) are associated with increased risks of fatal infection and all-cause mortality (risk ratios of 1.18 and 1.36,

Table 1. *Inclusion and exclusion criteria.*

Inclusion criteria

1) age>18 years
2) End-stage renal disease on stable hemodialysis treatment (3 weekly sessions of 4 hours)
3) newly placed polytetrafluoroethylene (PTFE) graft.

Exclusion criteria

1. high bleeding risk (HAS BLED score >3)
2. previous history of coagulopathy
3. taking other blood thinners or antiplatelet
4. non-valvular atrial fibrillation
5. persistent thrombocytopenia (platelet count $\leq 50\times10^9$ /L)
6. inability to take oral medications
7. lack of informed consent or inability to give informed consent
8. advanced liver disease
9. acute peptic ulcer disease

respectively).[2,3] Moreover, a 2017 meta-analysis indicated that grafts are more prone to both infectious and noninfectious complications compared to fistulas, with higher incidences of noninfectious access-related complications in grafts (49%) versus fistulas (31.8%).[4] Nonetheless, AVGs are indispensable for patients who are not suitable candidates for AVFs, particularly those with inadequate superficial venous anatomy or multiple unsuccessful AVF attempts.[5]

Thrombosis within vascular accesses, especially AVGs, is a leading cause of access loss in hemodialysis patients and accounts for a substantial portion (65–85%) of permanent access loss cases.[6-8] Alarmingly, more than half of AVGs undergo thrombosis within the first-year post-implantation, often due to neointimal hyperplasia, necessitating salvage procedures in over 75% of cases.[9,10] Thrombosis in dialysis access is typically attributed to the classic Virchow's triad: endothelial injury, stasis, and hypercoagulability.[11] Patients undergoing dialysis are at an increased risk of both bleeding and thrombotic events compared to the general population, complicating the use of anticoagulants due to factors like uremia-induced platelet dysfunction.[12-16]

Historically, vitamin K antagonists (VKAs) have been the primary oral anticoagulants until the advent of direct oral anticoagulants (DOACs), which offer a more predictable and safer profile with efficacy comparable to VKAs and a notable reduction in bleeding risks.[17,18] DOACs have become the preferred choice in the treatment and prevention of deep vein thrombosis, replacing traditional oral and parenteral anticoagulants.[19] Of the DOACs available, Apixaban has been notable for ESRD patients with atrial fibrillation, approved by the US FDA in 2014 based on its pharmacokinetic profile, minimal renal clearance dependency, and limited removal during dialysis.[20,21]

In this study, we conducted a randomized, double-blind, controlled trial to examine the safety and efficacy of Apixaban in preventing graft thrombosis in hemodialysis patients. The primary focus was on the time to graft thrombosis, while secondary emphasis was placed on the incidence of bleeding events.

Materials and Methods

This study was conducted in university-affiliated teaching hospitals equipped with specialized vascular surgery and dialysis units. It focused on patients who had recently received polytetrafluoroethylene (PTFE) grafts for hemodialysis access.

Enrollment was open to individuals who provided informed consent and met the specified inclusion and exclusion criteria, as outlined in Table 1. Participants eligible for the study were required to be over 18 years of age, diagnosed with end-stage renal disease, and on a stable hemodialysis regimen (three weekly sessions of four hours each), with a newly implanted PTFE graft. Exclusion criteria included a high risk of bleeding (HAS-BLED score >3), a history of coagulopathy, current use of other anticoagulants or antiplatelet agents, non-valvular atrial fibrillation, persistent thrombocytopenia (platelet count $\leq 50\times10^9$/L), inability to take oral medications, lack of informed consent, advanced liver disease, and acute peptic ulcer disease.

After confirming graft patency through a physical examination, patients were randomized into two groups using a concealed computer-generated permuted block method in blocks of four. This method ensured the blinding of both participants and research team members to treatment allocation. Participants received either Apixaban (2.5 mg twice daily) or a placebo, meticulously crafted to be identical in form and size to the Apixaban tablets, thus maintaining the integrity of the blinding throughout the study.

Treatment and Follow-Up Protocol

In this study, participant assignment to medication regimens was facilitated via a computer-generated permuted block randomization. The two regimens

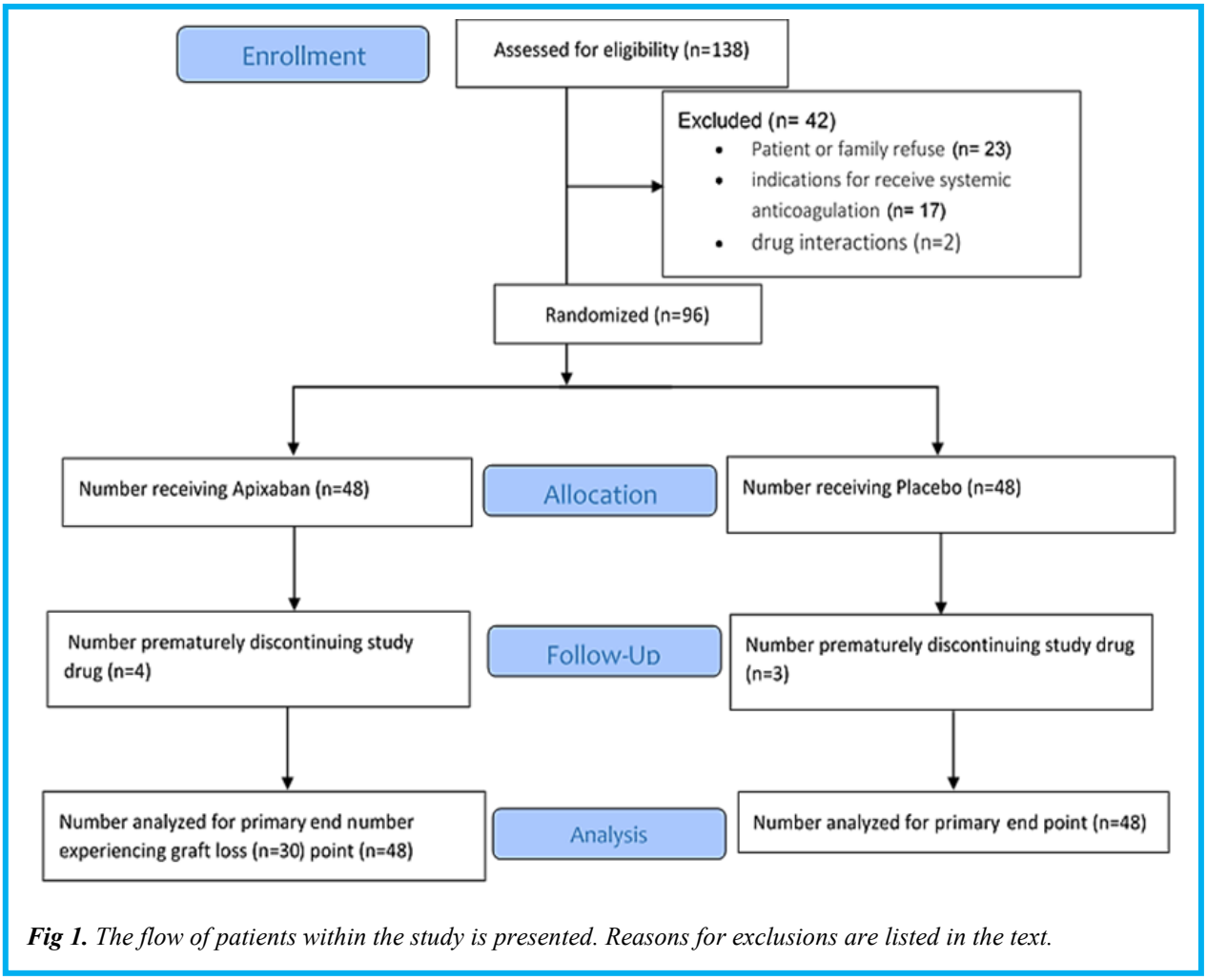

Fig 1. *The flow of patients within the study is presented. Reasons for exclusions are listed in the text.*

consisted of 1) Apixaban, administered at 2.5 mg twice daily, and 2) a placebo, also administered twice daily. The placebo tablets were designed to be identical in form and size to the Apixaban tablets, with the distinction that Apixaban tablets were marked for identification, whereas placebo tablets were not (Figure 1).

Patients continued on their allocated trial regimen as long as clinical benefit was perceived by the investigators, and no severe adverse effects were observed. Management of minor bleeding episodes entailed temporarily suspending the medication until resolution of bleeding. Adherence to the study medication was systematically assessed through pill counts, calculated as: [(number of pills dispensed - number of pills returned) / number of pills prescribed] × 100%. Compliance among participants was further verified by counting the remaining medications, with similar adherence rates observed in both treatment groups.

Patient assessments were conducted three times weekly during their hemodialysis sessions. Additionally, evaluations were performed in outpatient clinics for pre-hemodialysis patients. Consistent medical care within the dialysis center ensured minimal likelihood of missing outcome data. The follow-up period for each patient lasted one year. Thrombosis diagnosis involved palpation and auscultation methods to detect the absence of blood flow or the presence of a thrombus post dialysis needle insertion into the graft, with confirmation by Doppler ultrasound. Data collection commenced at baseline, was repeated two weeks post-graft creation, and thereafter every two months to evaluate graft suitability. Adverse events were meticulously recorded for a period of 30 days following cessation of the trial medication. Upon confirmation of thrombosis by the attending surgeon, the study medication was discontinued.

Outcomes

Primary Outcome

Graft Thrombosis: The principal outcome of this study was the incidence of graft thrombosis, ascertained by clinical personnel who remained blinded to treatment allocations. Graft thrombosis was characterized as a thrombotic event that significantly impeded dialysis functionality or necessitated immediate clinical intervention. In instances where patients underwent renal transplantation or required graft removal due to factors such as infection or restoration of renal function, they were excluded from the study medication, and their data were subsequently censored.

Table 2. *Clinical characteristics and outcome of patients (N=96).*

	Intervention Group			
	Apixaban (N=48)	**Placebo(N=48)**	**Total**	**p-Value**
Age(year), Mean ± SD	61.94 ±14.97	58.69 ±18.92	60.31 ±17.05	0.35
Weight(kg), Mean ± SD	67.62 ±1.88	67.31 ±1.74	67.47 ±1.81	0.40
Gender, n(%)				0.53
Male	30(52.6)	27(47.4)	57(59.4)	
Female	18(46.2)	21(53.8)	39(40.6)	
Smoker, n(%)				0.17
Yes	12(70.6)	5(29.4)	17(17.7)	
Left	10(45.5)	12(54.5)	22(22.9)	
No	26(45.6)	31(54.4)	57(59.4)	
Diabetes, n(%)				0.41
Yes	25(46.3)	29(53.7)	54(56.3)	
No	23(54.8)	19(45.2)	42(43.8)	
Hypertension, n(%)				0.13
Yes	7(35)	13(65)	20(20.8)	
No	41(53.9)	35(46.1)	76(79.2)	
Previous Dialysis(day), Mean ± SD	279.1±804.3	181.04±711.87	230.07±757.10	0.52
Patency Time(Month), Mean ± SD	5.63±2.92	3.67±2.05	4.65±2.70	<0.0001*
Previous graft, n(%)				0.53
Yes	5(41.7)	7(58.3)	12(12.5)	
No	43(51.2)	41(48.8)	84(87.5)	
Bleeding, n(%)				0.01*
Yes	14(29.1)	11(22.9)		
No	34(70.8)	37(77.1)		
Bleeding Type, n(%)				
Major	3(6.25)	1(2.1)		
Minor	11(22.9)	10(20.8)		
Graft site, n(%)				0.33
Upper arm, straight	14(50)	14(50)	28(29.2)	
Forearm, loop	17(42.5)	23(57.5)	40(41.7)	
Forearm, straight	17(60.7)	11(39.3)	28(29.2)	
Thrombosis status, n(%)				<0.0001*
Yes	8(21.1)	30(78.9)	38(39.6)	
No	40(69)	18(31)	58(60.4)	

**. Significant at 0.05*

Secondary Outcome

Incidence of Bleeding: The secondary outcome focused on the incidence and severity of bleeding episodes. Major bleeding events were delineated following the International Society of Thrombosis and Hemostasis (ISTH) guidelines, encompassing clinically significant hemorrhages that were life-threatening, resulted in a hemoglobin decrease of at least 2 g/dL, necessitated a transfusion of a minimum of two units of blood or packed cells, or occurred in critical anatomical regions. Patients encountering such major bleeding events were withdrawn from the study medication, with follow-up continuing until the onset of graft thrombosis, death, or study conclusion.

Additionally, minor hemorrhages, defined as conspicuous bleeding not fulfilling the major bleeding criteria yet requiring clinical intervention, were closely monitored. In cases of minor hemorrhage, patients were advised to recommence the study medication as deemed clinically appropriate. The permanent discontinuation of the study drug was reserved for instances of major or life-threatening bleeding events.

Ensuring Ethical Integrity and Quality in Clinical Research

The study meticulously adhered to high ethical standards, including securing institutional review board approvals and ensuring informed, voluntary participant consent. Participant confidentiality and safety were rigorously protected. Quality control measures included regular training and calibration of staff and equipment, ensuring data integrity and accuracy. Adverse events, especially bleeding episodes, were vigilantly monitored and recorded following established protocols. Additionally, the study protocol was flexible to amendments, with any changes carefully documented and justified to enhance the study's efficacy and maintain scientific integrity.

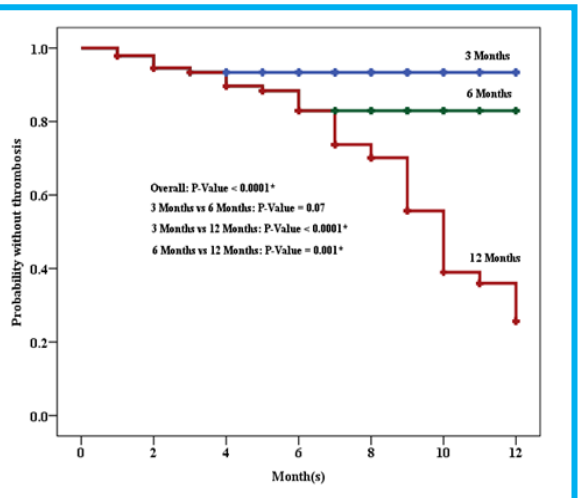

Fig 2. *Comparison of Kaplan-Meier estimates of 3-month, 6 months, and 12-month thrombosis-free graft survival.*

Statistical Analysis

The study utilized a convenience sampling method and a randomized complete block design to ensure balanced allocation and comparability among 96 participants, divided equally into Apixaban and placebo groups. Randomization occurred in blocks of four, resulting in 24 blocks. Data analysis included mean ± standard deviation for continuous variables like age, weight, and prior dialysis duration, and frequencies and percentages for categorical variables such as gender and medical history. The primary endpoint was thrombosis-free graft survival (TFGS), measured from randomization to the first instance of graft thrombosis or failure. TFGS was estimated using the Kaplan-Meier method, with group comparisons via log-rank tests. Both chi-square and independent samples T-tests were used for comparing categorical and continuous variables between groups. Univariate and multivariate Cox proportional hazards models assessed the impact of risk factors and treatment on thrombosis incidence, with a significance level of 0.05. Graphical representations, including Kaplan-Meier curves, aided in visualizing TFGS. All statistical analyses, using SPSS software version 19, were geared towards assessing Apixaban's efficacy in reducing thrombosis risk and its safety regarding bleeding events, aligning with the study's objectives.

Results

From March 2021 to January 2023, a total of 138 patients were evaluated for inclusion in the study. Of these, 96 (69.5%) were successfully randomized into two groups—48 to receive Apixaban and 48 to receive a placebo. The study encountered a decline in participation from 23 patients (16.6%), while 17 patients (12.3%) were already under anticoagulant treatment and 2 patients (1.4%) presented drug interactions with Apixaban at the time of randomization. Post-randomization, clinical treatment commenced accordingly. The demographic and clinical characteristics of the participants are detailed in Table 2. The average age was 60.31±17.05 years, mean weight was 67.47±1.81 kilograms, and the mean duration of prior dialysis was 230.07±757.10 days. The gender distribution included 77 males (59.4%) and 39 females (40.6%), with 17 (17.7%) patients being smokers and 57 (59.4%) non-smokers. Diabetes and hypertension were present as underlying conditions in 56 (56.3%) and 20 (20.8%) patients, respectively.

A thrombosis event was reported in 38 (39.6%) patients. The analysis revealed no significant differences between the Apixaban and placebo groups in terms of age, weight, gender, race, smoking status, diabetes, and hypertension. However, the incidence of thrombosis was significantly lower in the Apixaban group compared to the placebo group (16.7% vs. 62.5%, P-value <0.0001). The rates of thrombosis-free graft survival (TFGS) at 3, 6, and 12 months were 93.4%, 82.9%, and 25.7%, respectively (P-value <0.0001), as illustrated in Figure 2. There were no significant differences in 3-month and 6-month TFGS

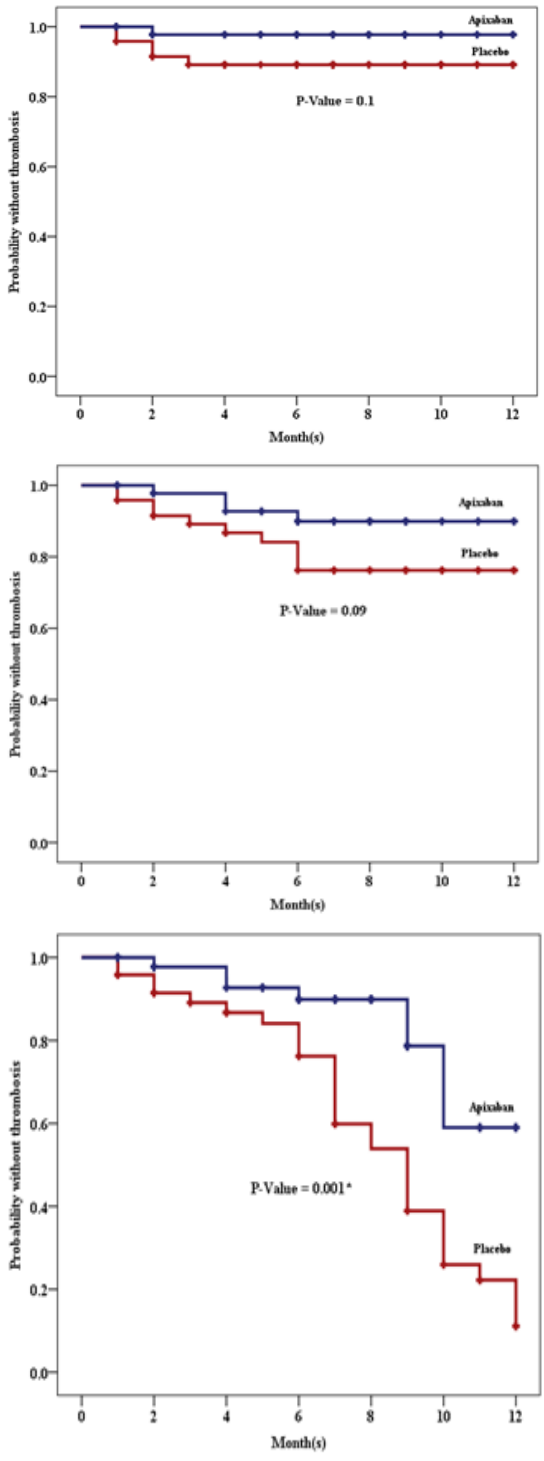

Fig 3. *Top Panel: Comparison of Kaplan-Meier estimates of 3-month thrombosis-free graft survival by group. Medium Panel: Comparison of Kaplan-Meier estimates of 6-month thrombosis-free graft survival by group. Bottom Panel: Comparison of Kaplan-Meier estimates of 12-month thrombosis-free graft survival by group.*

between the groups (Figures 3a and 3b), but a marked difference was observed in 12-month TFGS between the Apixaban and placebo groups (Figure 3c).

The Cox proportional hazard model analysis, as shown in Table 3, indicated that hypertension and intervention group were significant predictors of thrombosis occurrence. After adjusting for other variables in the multivariate model, the risk of thrombosis in patients with hypertension was 2.37 times higher compared to those without hypertension [AHR: 2.37; 95% CI: (1.23–4.77); p-value = 0.009]. Additionally, Apixaban treatment reduced thrombosis risk by 65% compared to placebo [AHR: 0.35; 95% CI: 0.16–0.78; p-value = 0.01]. Notably, a higher incidence of minor bleeding was observed in the Apixaban group compared to placebo.

Adverse Events

In this study, patients treated with Apixaban encountered a total of fourteen bleeding episodes, accounting for 29.1% of the group. These episodes included three major and nine minor incidents. Notably, one major bleeding case involved hematuria, and two others were gastrointestinal (GI) in nature. Each major bleeding episode necessitated the discontinuation of Apixaban, though it is important to highlight that none of these incidents led to fatalities. For minor bleeding episodes, treatment with Apixaban was continued. The average HAS-BLED score, a bleeding risk assessment tool from the Euro Heart Survey, was calculated to be 3.3 for this group.

In the placebo group, twelve patients, representing 25% of the group, experienced bleeding events. This included ten instances of minor bleeding and one major GI bleeding episode. The average HAS-BLED score for the placebo group was 3.1, indicating a comparable level of bleeding risk to the Apixaban group. It is significant to note that there were no reported cases of thrombocytopenia, a condition marked by a low platelet count, at the time of bleeding in either the Apixaban or placebo groups.

Table 3. *Multiple cox regression model for probability without thrombosis (N=96).*

Variables	**Multiple**	
Intervention	**AHR[2](95% CI)**	**p-Value**
Apixaban		0.01*
Placebo(RL[1])	0.35(0.16 - 0.78)	0.01
Hypertension	1	-
Yes		0.009*
No(RL[1])	2.37(1.23 - 4.57)	0.009

Discussion

This investigation provides a novel analysis of Apixaban's effect on arteriovenous (AV) graft thrombosis in patients undergoing dialysis, addressing a gap in current literature on the safety of Apixaban in end-stage renal disease (ESRD) contexts. The study revealed a significant reduction in AV graft thrombosis incidence among these patients compared to a control group, underscoring the need for anticoagulants with both minimal hemorrhage risk and high efficacy.

The quest for effective medical adjuvant therapies to prevent stenosis and thrombosis in AV grafts is of significant interest. Existing studies have explored the use of warfarin, high-dose folic acid, antiplatelet agents, and fish oil for this purpose.[22-24] A specific trial comparing warfarin to placebo, however, did not achieve its aim of reducing AV graft thrombosis and instead heightened complication rates, leading to its discontinuation after 37 months.[25] Our findings align with these results, indicating that Apixaban treatment extends mean patency time significantly more than placebo (5.63 months vs. 3.67 months, $P < 0.0001$).

Comparative analyses of Apixaban and warfarin have shown a safer profile for Apixaban, especially in terms of bleeding risks.[26] This study corroborates these findings, showing no significant difference in bleeding occurrences between Apixaban and placebo groups, aligning with previous research on Apixaban usage in NVAF and VTE patient populations. However, the optimal dosage of Apixaban for ESRD patients remains a contentious topic. Studies by Wang et al.[27] suggest that Apixaban can be administered without dose modification in hemodialysis patients, a conclusion supported by the minimal impact of dialysis on Apixaban levels. Further research by Mavrakanas et al. and Steuber et al. indicates that a lower dosage of 2.5 mg twice daily may improve safety outcomes, while a higher dose may increase risks.[28-29] Our study, adhering to these guidelines, aimed for minimal side effects with its dosing strategy.

The findings of this study have significant implications that extend into clinical practice, suggesting that Apixaban may be a preferred anticoagulant for ESRD patients. This is based on its favorable balance between efficacy and safety, potentially leading to a transformation in treatment protocols and enhanced patient outcomes in managing AVG thrombosis. However, it is important to acknowledge potential biases and confounders in our study's design. Unexplored variables such as patient comorbidities, lifestyle differences, and the various stages of ESRD might have influenced the outcomes. Therefore, future research should encompass a broader range of demographic variables and potential confounding factors to achieve a more comprehensive understanding of Apixaban's effectiveness. To reinforce these initial findings, subsequent studies should involve larger and more diverse patient cohorts. This approach would not only validate Apixaban's efficacy and safety in a wider population but also aid in determining optimal dosing strategies. Ideally, such research should include extended follow-up periods to evaluate the long-term benefits and potential side effects of treatment. Additionally, the broader implications of Apixaban in improving the quality of life for ESRD patients and its impact on healthcare systems warrant further investigation. Future studies should also explore the economic aspects of adopting Apixaban, particularly its cost-effectiveness and implications for resource allocation in healthcare. Despite the insights provided by our study, it is not devoid of limitations. The relatively small sample size limits the ability to definitively ascertain significant differences and make wide-ranging generalizations. Furthermore, the consistent use of a 2.5 mg dosage of Apixaban twice daily for all patients restricts our ability to evaluate the efficacy and safety across different dosing regimens. These limitations necessitate further research to explore these aspects more thoroughly. Caution is advised in interpreting the findings of this study, and these considerations underscore the need for more extensive future research in this area. Taken together, the research findings indicate that Apixaban is effective in preventing arteriovenous graft thrombosis. Nonetheless, it is imperative to recognize the associated risk of bleeding complications, particularly within the end-stage renal disease patient population. Consequently, a thorough evaluation of each patient's individual risk and benefit profile is recommended prior to the initiation of anticoagulant therapy for preventive applications. This approach ensures a tailored and cautious application of treatment, aligning with patient-specific clinical needs and safety considerations.

List of acronyms

AVG - Arteriovenous Graft
CI - Confidence Interval
DOACs - Direct Oral Anticoagulants
ESRD - End-Stage Renal Disease
ISTH - International Society of Thrombosis and Hemostasis
NVAF - Non-Valvular Atrial Fibrillation
PTFE - Polytetrafluoroethylene
RCTs - Randomized Controlled Trials
TFGS - Thrombosis-Free Graft Survival
VKAs - Vitamin K Antagonists
VTE - Venous Thromboembolism

Contributions of Authors

All authors coordinated and supervised all experiments, analysis, draft, wrote, reviewed, and edited the manuscript, contributed to methodology. All authors have read and accepted the final edited typescript.

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Conflict of Interest

The authors declare they have no financial, personal, or other conflicts of interest.

Ethical Publication Statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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