Rivaroxaban versus Warfarin in Treatment of Acute Lower Limb Deep Venous Thrombosis and its Affection on Quality of Life

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Background: Deep vein thrombosis (DVT) poses a considerable burden on the affected patients, which triggers the need for proper management and follow-up. This study aimed to evaluate the outcome of rivaroxaban versus warfarin in the treatment of patients with acute lower limb DVT.

Patients and methods: This is a randomized controlled trial that included patients with ultrasound-proved acute lower limb DVT. Patients were equally randomized to Group A (Treated with warfarin) and Group B (treated with rivaroxaban). All patients received scheduled follow-up visits up to 6 months post-treatment, during which they received clinical examination, routine laboratory analysis, and duplex ultrasound.

Results: Eighty patients were eligible to the study and enrolled in the two study groups. At the 6-month follow-up, the median (IQR) recanalization rate was 100.0% (87.5%–100.0%) in Group A and 100.0% (90.0%–100.0%) in Group B (P = 0.464). Valve incompetence was evident in eight patients in Group A (20.0%) and four patients in Group B (10.0%) (p = 0.211). The Villalta Score (VS) median (IQR) values were 2 (1–3) in Group A and 1 (0–3.5) in Group B (P = 0.340). Regression analysis demonstrated that predictors of 6-month post-thrombotic syndrome (PTS) were the patients' age (OR = 1.46, p = 0.014) and dyslipidemia (OR = 11.6, p = 0.014).

Conclusion: This study highlights the potential benefits of rivaroxaban over warfarin in the management of DVT, with trends suggesting better recanalization rates, lower valve incompetence, and a reduced Villalta score.

Key words: Deep venous thrombosis (DVT), Warfarin, Rivaroxaban, recanalization, post-thrombotic syndrome (PTS).

Introduction

Deep vein thrombosis (DVT) poses a considerable burden on the affected patients, with a risk of 30-day mortality in up to 30% of patients.[1] In addition, approximately a third of patients with DVT will have post-thrombotic syndrome (PTS), and an equal percentage will have recurrence within the next 10 years.[1,2] This DVT-associated impact on human health triggers the need for proper management and follow-up.

Deep vein thrombosis has been traditionally treated with vitamin K antagonists (VKAs), such as warfarin, which overlaps with low molecular weight heparin (LMWH) for at least five days until warfarin begins its anticoagulant therapeutic response, as indicated by normal values of the international normalized ratio (INR) that range from 2 to 3.[3]

At present, direct oral anticoagulants (DOACs) have been growingly used for the treatment of DVT. These new drugs specifically act on either activated factor Xa or thrombin. Among these DOACs, rivaroxaban is currently approved to treat DVT and acts through selective direct and competitive factor Xa inhibition. When factor Xa is activated, the coagulation cascade extrinsic and intrinsic pathways are linked, and this acts as a rate-limiting step in the formation of thrombin. Therefore, inhibition of factor Xa can directly impede the generation of thrombin.[4–7]

Direct oral anticoagulants have shown advantages over VKAs in terms of higher efficacy in the prevention of stroke, a lower rate of major bleeding occurrence, less liability for drug-food interaction, a faster onset of action, and more convenience of use owing to being administered at defined doses without the need for INR monitoring because of their predictable pharmacodynamics and pharmacokinetics. However, rivaroxaban use in DVT treatment is still scarcely addressed, with most research assessing thrombus status through imaging after 3 weeks of anticoagulant use.[8–11] Furthermore, the available research provides conflicting results regarding the effectiveness and safety of rivaroxaban compared to the traditionally used regimen of VKAs and LMWH.

This study aimed to evaluate the outcome of rivaroxaban versus warfarin in the treatment of patients with acute lower limb DVT, with follow-up until 6 months after therapy.

Patients and methods

This is a randomized controlled trial (RCT) that included patients recruited from multiple centers with lower limb acute DVT during the period from

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January 2022 to June 2023. The study was initiated after being approved by the institutional research ethics committee (MD-27-2022) and adhered to the Declaration of Helsinki.

Adult patients who were confirmed to have lower limb DVT by ultrasound duplex examination were eligible for the study. Patients with chronic or limb-threatening DVT, recent cerebral hemorrhage, active peptic ulcer, active bleeding, coagulopathy, thrombocytosis, malignancy, or debilitating systemic conditions were excluded from the study. Pregnant and lactating females were also excluded. Informed written consent was obtained from each included patient.

Sample size calculation

To determine the appropriate sample size for our study, we utilized G*Power version 3.1.9.7 to perform an a priori power analysis. Our objective was to compute the required sample size given an alpha error probability (α) of 0.05 and a power (1-β) of 0.80. We based our calculations on the difference in 6-month patency rates reported in the study by Shnouda et al.[12] According to their findings, the power analysis indicated that a total sample size of 42 participants is required, with 21 participants in each group. This calculation ensures a sufficient power of 0.954 to detect a significant difference between the two proportions at the specified alpha level. The critical z-value for this analysis was 1.645, confirming adequate power to achieve reliable and valid results. To account for potential dropouts and increase the reliability of our results, we have increased the sample size to 80 participants, with 40 participants in each group.

Randomization

The eligible patients were equally randomized into two groups: Group A (The warfarin group) and Group B (The rivaroxaban group). Randomization was done using closed, envelopes were distributed to eligible patients by an independeB.t employer. Opaque envelopes that contained the letter "A" or the letter "B". These envelopes were distributed to eligible patients by an independent employer. After enrolment to their ofoups, the included patients as well as the treating physicians were aware to the medications administered (Non-blinding).

The included patients were subjected to a complete history-taking, dedicated general and local clinical examination, including assessment of lower limb color changes, edema, superficial varicosities, and tenderness, routine laboratory work-up, and duplex ultrasound assessment of the deep venous system's patency, thrombus extent, and valves' involvement.

Treatment regimens

Patients in Group A were treated with warfarin tablets (5 mg once daily) and LMWH (clexane) at a dose of 1 mg/kg twice daily in the first three days to bridge the delayed onset of warfarin. Patients in Group B were treated with rivaroxaban, starting with a dose of 15 mg twice daily for 21 days, then a dose of 20 mg once daily for three months.

Patients in both groups were advised to use elastic stockings and bed rest with limb elevation by 20 degrees during the acute stage.

Patients' follow-up

All patients received scheduled follow-up visits at 2 weeks, 3 months, and 6 months post-treatment, during which they received clinical examination, including the assessment of any potential treatment-related adverse events, underwent routine laboratory analysis, and were screened by duplex ultrasound to monitor recanalization, potential propagation, or early recurrence. The Villalta score (VS) was used to assess the severity of PTS.[13] Patients in Group A were assessed for INR once a week to ensure adequate anticoagulation with an INR range of 2 to 3.

Study outcomes

The study's primary outcomes were the recanalization rate after 6 months of treatment in the two groups and the rate of PTS. The secondary outcomes were the predictors of PTS and the treatment-related bleeding rate.

Statistical analysis

This study's data were analyzed using Jamovi statistical software (Jamovi, Version 2.3, Computer Software, Sydney, Australia). The quantitative data were assessed for normality, then compared with the independent-t test or Mann-Whiteney test accordingly. Qualitative data were compared using the Chi-square test, Fisher's exact test, or Z test for proportion as appropriate. A univariate regression analysis was conducted to determine the predictors for PTS. Independent variables that were found to be significantly predicting PTS were incorporated in a multivariate regression analysis to adjust for confounders. The probability of complete recanalization-free survival was assessed using the Kaplan-Meier test, and the log rank was used to assess the difference between the two groups in the 6-month complete recanalization rate. Statistical significance was set at 0.05.

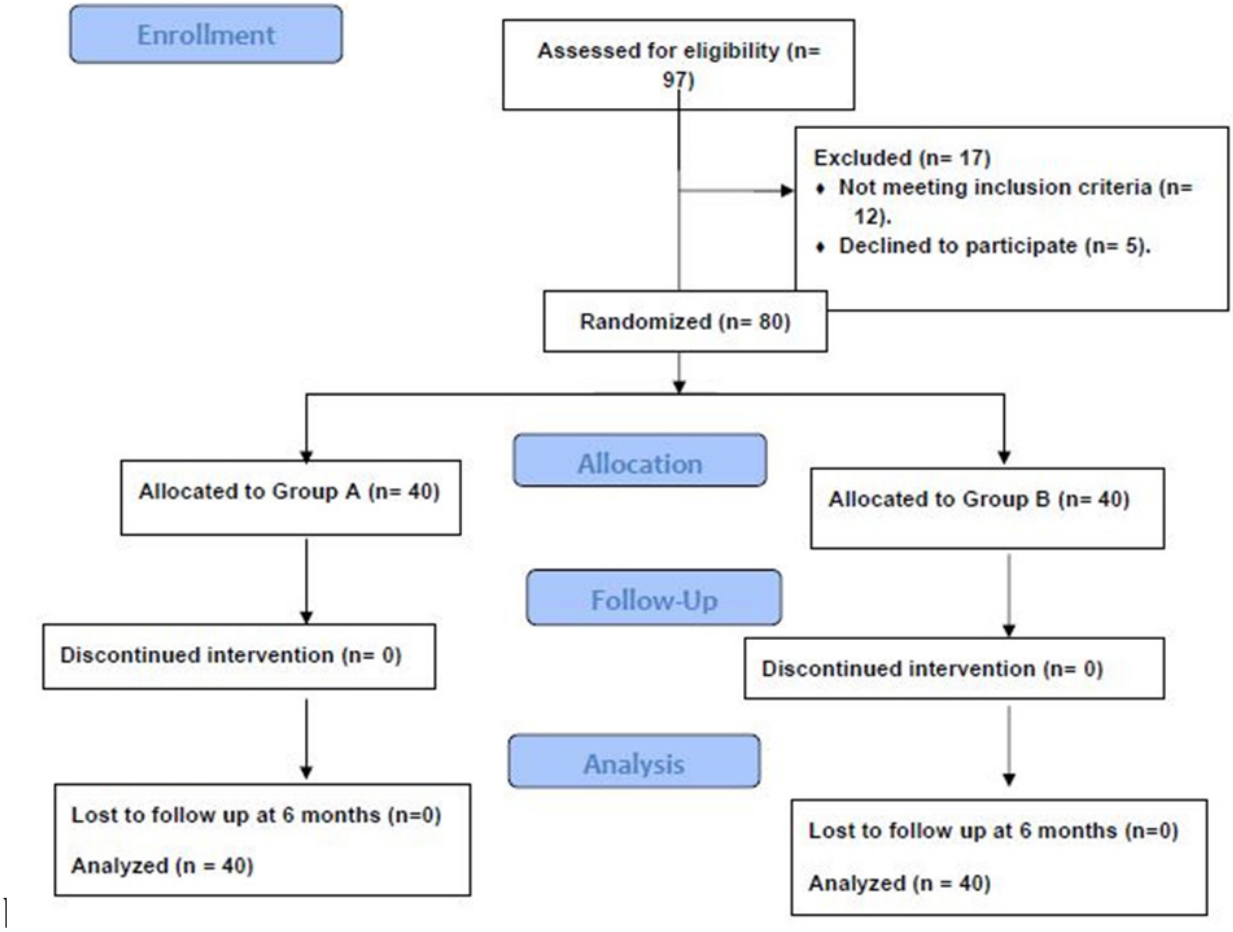

Fig 1: CONSORT flow chart of the study patients.

Results

In this study, ninety-seven patients were initially included, of whom eighty met the eligibility criteria and were finally enrolled in the two study groups with no loss of follow-up **(Fig. 1).**

The patients' ages ranged from 20 to 42 years, with mean values of 23.3 ± 3.08 years in Group A and 24.0 ± 5.02 years in Group B. Most of the patients were males in the two groups (75.0% and 70.0%, respectively).

Smoking was prevalent in 20% and 25% of the two groups, respectively. The mean body mass index (BMI) in Group A was 29.6 ± 1.6 kg/m2 and in Group B was 29.8 ± 1.3 kg/m2, with obesity prevalence rates of 35.0% and 45.0% in the two groups, respectively. No statistically significant differences were found between the two groups in the mean age (p = 0.454), sex distribution (p = 0.617), prevalence of smoking (p = 0.592), mean BMI (p = 0.541), or the prevalence of obesity (p = 0.363) **(Table 1).**

Other risk factors encountered in the study patients were diabetes mellitus, hypertension, dyslipidemia, steroid use, postoperative status, and lower limb varicose veins, with no statistically significant differences in either of them (P > 0.05). DVT was diagnosed as unprovoked in 45% of Group A and 50% of Group B, with no statistically significant difference (P = 0.653) **(Table 1).**

All the included patients had unilateral affection, with more than half of the patients in the two groups having the right side affected (65% in Group A and 55% in Group B, p = 0.363). The affected segments were femoro-popliteal (35.0% in Group A and 35.0% in Group B), popliteal (35.0% in Group A and 30.0% in Group B), calf veins (20.0% in Group A and 30.0% in Group B), and ileo-femoral (10.0% in Group A and 5.0% in Group B). No statistically significant difference was found between the two groups in the distribution of the affected segment (p = 0.655) **(Table 1).**

At the two-week follow-up, recanalization started in two patients of Group A (5%) and six patients of Group B (15%), with no statistically significant difference (p = 0.292). Two patients in Group A (5.0%) showed thrombus propagation from calf veins to the popliteal vein, with no thrombus propagation encountered in Group B (p = 0.311) **(Table 2).**

At the 3-month follow-up, recanalization was evident in all patients in the two groups, with median (IQR) values of 80.0% (57.5%–92.5%) in Group A and 85.0% (67.5%–100.0%) in Group B. However, the difference was statistically insignificant (P = 0.111). Valve incompetence was shown in six patients in Group A (15.0%) and four patients in Group B (10.0%), without statistical significance (P = 0.646). Regarding the VS score, it showed median (IQR) values of 4 (3–7.25) in Group A and 3.5 (3–6.25) in Group B (p = 0.432) **(Table 2).**

As for the 6-month follow-up, the median (IQR) values of the recanalization rate were 100.0% (87.5%–100.0%) in Group A and 100.0% (90.0%–100.0%) in Group B, with no statistically significant difference (p = 0.464). Valve incompetence was evident in eight patients in Group A (20.0%) and four patients in Group B (10.0%), without statistical significance (p = 0.211). The VS score median (IQR) values were 2 (1–3) in Group A and 1 (0–3.5) in Group B (p = 0.340). Eight patients in each group (20.0%) had mild PTS, and two patient in Group B (5.0%) had moderate PTS, with no statistically significant difference in the distribution of PTS (p = 0.597) **(Table 2).**

Assessment of bleeding after treatment showed a higher frequency in Group A (6 cases of minor bleeding; 15.0% vs. two cases in Group B; 5.0%; and two cases of major bleeding; 5.0% compared to none in Group B; 0.0%). The differences didn't reach statistical significance (P = 0.303 and 0.153, respectively) **(Table 2).**

Univariate logistic regression analysis demonstrated that predictors of PTS at the 6-month follow-up were the patients' age (OR = 1.46, p = 0.014) and the presence of dyslipidemia (OR = 11.6, p = 0.014). In the multivariate model, age remained a significant predictor of the 6-month PTS (OR = 1.41, p = 0.034), indicating that older patients are more risky to develop PTS. Dyslipidemia, while still showing a positive association with PTS, is not statistically significant when controlling for age. This means that although dyslipidemia may increase the risk, the evidence is not strong enough to confirm it as an independent predictor within this model **(Table 3).**

Survival analysis to assess the difference between the two groups in the time to achieve complete recanalization did not reveal a statistically significant difference (P = 0.311) **(Fig. 2).**

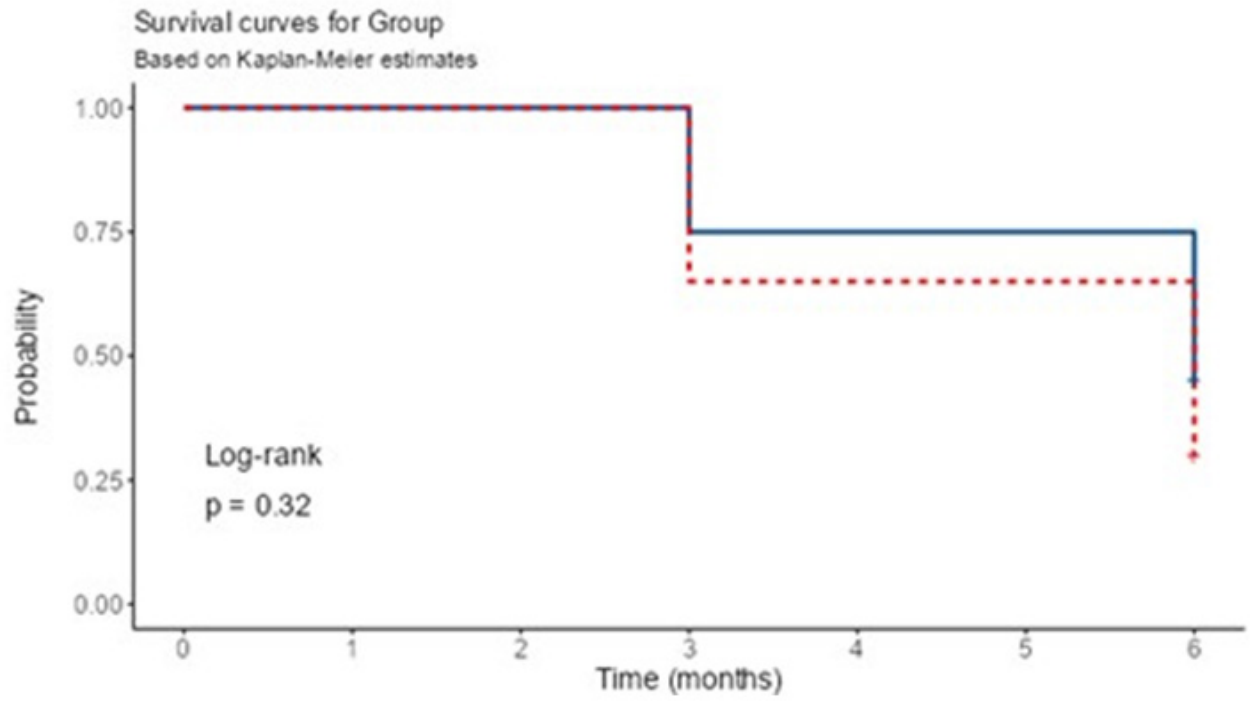

Fig 2: Complete recanalization-free survival in the study patients.

Table 1: Baseline data of the study patients

Variable	Group A (N = 40)	Group B (N = 40)	P-value
Mean Age (years)	23.3 ± 3.08	24.0 ± 5.02	0.454
Sex (Male)	30 (75.0%)	28 (70.0%)	0.617
Smoking Prevalence	8 (20.0%)	10 (25.0%)	0.592
Mean BMI (kg/m²)	29.6 ± 1.6	29.8 ± 1.3	0.541
Obesity Prevalence	14 (35.0%)	18 (45.0%)	0.363
Diabetes Mellitus	0 (0.0%)	2 (5.0%)	0.153
Hypertension	3 (7.5%)	4 (10.0%)	0.689
Dyslipidemia	5(12.5%)	10 (25.0%)	0.153
Steroid Use	0 (0.0%)	2 (5.0%)	0.153
Postoperative Status	3 (7.5%)	0 (0.0%)	0.077
Lower Limb Varicose Veins	3 (7.5%)	6 (15.0%)	0.153
Unprovoked DVT Diagnosis	18 (45.0%)	20 (50.0%)	0.653
Affected side			
Right	26 (65.0%)	22 (55.0%)	0.363
Left	14 (35.0%)	18 (45.0%)	
Affected segment			
Femoro-popliteal	14 (35.0%)	14 (35.0%)	0.655
Popliteal	14 (35.0%)	12 (30.0%)	
Calf Veins	8 (20.0%)	12 (30.0%)	
Ileo-femoral	4 (10.0%)	2 (5.0%)	

Table 2: Baseline data of the study patients

Variable	Group A (N = 40)	Group B (N = 40)	P-value
2-Week Follow-up			
Recanalization	2 (5.0%)	6 (15.0%)	0.292
Thrombus Propagation	2 (5.0%)	0 (0.0%)	0.311
3-Month Follow-up			
Recanalization (%)	80.0% (57.5% - 92.5%)	85.0% (67.5% - 100.0%)	0.522
Valve Incompetence	3 (15.0%)	2 (10.0%)	0.646
VS Score	4 (3 – 7.25)	3.5 (3 – 6.25)	0.432
No PTS	11 (55.0%)	11 (55.0%)	0.277
Mild PTS	6 (30.0%)	7 (35.0%)	
Moderate PTS	3 (15.0%)	2 (10.0%)	
6-Month Follow-up			
Recanalization (%)	100.0% (87.5% - 100.0%)	100.0% (90.0% - 100.0%)	0.464
Valve Incompetence	8 (20.0%)	4 (10.0%)	0.376
VS Score	2 (1 – 3)	1 (0 – 3.5)	0.211
Mild PTS	8 (20.0%)	8 (20.0%)	0.597
Moderate PTS	8 (20.0%)	2 (5.0%)	
Bleeding After Treatment			
Minor Bleeding	6 (15.0%)	2 (5.0%)	0.303
Major Bleeding	2 (5.0%)	0 (0.0%)	0.153

Table 3: Binary logistic regression analysis for the prediction of 6-month PTS

Predictor	Estimate	Odds Ratio	95% Confidence Interval	P-value
Univariate Analysis				
Sex (Male vs. female)	1.34	3.810	[-0.873, 3.548]	0.236
Group (B vs. A)	0.288	1.333	[-1.20, 1.779]	0.705
Age	0.377	1.46	[0.0771, 0.677]	0.014
BMI	0.163	1.17733	[-0.371, 0.698]	0.549
Smoking	-1.02	0.359	[-3.25, 1.206]	0.368
Obesity	0.236	1.267	[-1.26, 1.737]	0.757
Affected side (L vs. R)	0.821	2.273	[-0.686, 2.328]	0.286
Hypertension	19.21	2.20e+8	[-4457.55, 4495.966]	0.993
DM	17.92	6.06e+7	[-4685.10, 4720.942]	0.994
Varicose vein	1.42	4.143	[-0.705, 3.548]	0.190
Steroid use	-16.40	7.57e-8	[-5499.28, 5466.490]	0.995
Dyslipidemia	2.45	11.600	[-5499.28, 5466.490]	0.014
Postoperative	-16.40	7.57e-8	[-5499.28, 5466.490]	0.995
Unprovoked	-0.159	0.853	[-1.65, 1.333]	0.835
Thrombus extent: Iliofem vs. Pop	22.05	3.77e+9	[-12147.037, 12191.139]	0.997
Thrombus extent: Calf vs. Pop	-17.08	3.82e-8	[-6682.365, 6648.203]	0.996
Thrombus extent: Fempop vs. Pop	1.90	6.6667	[-0.417, 4.212]	0.108
Multivariate Analysis				
Intercept	-9.665	6.35e-5	[-17.1608, -2.169]	0.012
Age	0.344	1.41	[0.0262, 0.661]	0.034
Dyslipidemia	1.813	6.13	[-0.5173, 4.144]	0.127

Discussion

Venous thromboembolism (VTE), encompassing DVT and pulmonary embolism, represents a significant medical concern associated with substantial morbidity and mortality worldwide. There is a great deal of disagreement over the best agent for VTE treatment. Despite the growing adoption of DOACs, several research investigations have not yet yielded a definitive result.[14]

This study compared the outcomes of warfarin versus rivaroxaban for the management of DVT, aiming to elucidate the relative merits and considerations associated with each treatment modality. In the initial two-week follow-up assessment, notably, recanalization commenced in more patients in the rivaroxaban-treated group. Two patients within the warfarin-treated group demonstrated thrombus propagation from the calf veins to the popliteal vein during the initial two-week period, contrasting with the absence of similar occurrences within the rivaroxaban-treated group. Despite this discrepancy, statistical analysis revealed non-significant differences. At the 3-month and 6-month follow-ups, a universal achievement of recanalization across all patients was shown, with the rivaroxaban-treated group exhibiting a slightly higher recanalization rate. Similar trends were noted in the assessment of valve incompetence, a critical determinant of PTS development, and the VS scores, demonstrating slightly lower rates of incompetence and lower scores in the rivaroxaban-treated group. The application of survival analysis in this study also confirmed the statistically non-significant shorter timeframe to obtain complete recanalization in patients treated with rivaroxaban.

The assessment of bleeding complications post-treatment is a crucial aspect of evaluating the safety and tolerability of therapeutic interventions for venous thromboembolism. In this study, there was a higher incidence of bleeding events, including both minor and major bleeding episodes, in patients treated with warfarin compared to those treated with rivaroxaban. Nevertheless, statistical analysis failed to demonstrate a significant difference in bleeding rates, suggesting a lack of definitive evidence supporting a differential bleeding risk between both therapeutic interventions.

In agreement with our study findings, the EINSTEIN DVT RCT showed that rivaroxaban was rather equally effective to warfarin in the treatment of DVT, with similar rates of major bleeding.[15] Similar results were concluded by the EINSTEIN PE trial, which concluded similar safety of rivaroxaban compared to warfarin.[16] However, a large systematic review and meta-analysis suggested that rivaroxaban could elevate the risk of gastrointestinal bleeding in

elderly patients.[17]

Our findings were consistent with the study of Houghton et al.,[18] who reported that ivaroxaban was associated with a resolution of DVT that was similar to that of warfarin, with better yet statistically insignificant protection from the propagation of thrombosis and resolution of the thrombus. The results of the J-EINSTEIN RCT were also in alignment with our findings. The trial showed a statistically non-significantly better rate of total thrombus resolution related to the rivaroxaban treatment than that related to the standard therapy.[10]

Other studies, such as a real-world experience documented by Kuznetsov et al.[9] and an RCT performed by de Athayde Soares et al.,[19] demonstrated the evident superiority of rivaroxaban over warfarin in terms of significantly lower rates of PTS occurrence and higher recanalization rates.

The discrepancy in study results, where some studies (Including ours) show the superiority of rivaroxaban over warfarin without statistical significance while others demonstrate statistically significant differences, can be attributed to variations in study design, sample sizes, and patient populations. Differences in patient demographics, comorbidities, and adherence to medication protocols can also impact outcomes.

We believe that despite the non-significant differences found between both treatments in the current study, rivaroxaban is still advantageous by not requiring continuous monitoring of INR levels, which is necessary for warfarin management. This monitoring can be burdensome for patients and healthcare systems, involving frequent clinic visits, laboratory tests, and dose adjustments. Additionally, maintaining the correct INR range can be challenging due to warfarin's numerous interactions with food, medications, and even lifestyle factors, which can affect its efficacy and safety.

The logistic regression analysis conducted in this study, which aimed to identify predictors of PTS at the six-month follow-up, revealed two significant predictors of PTS: patient age and the presence of dyslipidemia. Older patients exhibited a higher likelihood of developing PTS, with each additional year of age associated with a 46% increase in the odds of experiencing this complication. Similarly, the presence of dyslipidemia emerged as a significant predictor, with individuals diagnosed with this condition showing a notably elevated risk of developing PTS. This can be explained by several factors. Aging leads to decreased vascular elasticity and impaired healing, making older individuals more susceptible to venous stasis.[20] Additionally, older patients are more likely to have comorbidities,[21] and longer exposure to risk factors for VTE. Dyslipidemia contributes to endothelial dysfunction and systemic inflammation,[22] both of which impair venous valve function and promote thrombosis, increasing the risk of PTS.[23] The combination of advanced age and dyslipidemia may have a synergistic effect, compounding the risk factors and exacerbating the likelihood of developing PTS more than either factor alone. Upon conducting multivariate analysis to account for potential confounding factors, the significance of predictors shifted. Age retained its status as a significant predictor of PTS at the six-month mark, with each year increment still associated with a 41% increase in the odds of PTS occurrence. Conversely, the association between dyslipidemia and PTS, while still evident, lost statistical significance in the multivariate model when controlling for age. This indicates that while dyslipidemia may indeed confer an increased risk of PTS, its effect may be mediated or confounded by age-related factors.

This study is strengthened by its design, which is an RCT, with insights into their relative efficacy and safety profiles. The inclusion of multiple follow-up assessments (At 2 weeks, 3 months, and 6 months) allowed for a comprehensive evaluation of the treatment outcomes over time. The use of logistic regression analysis to identify predictors of post-thrombotic syndrome (PTS) offered a nuanced understanding of risk factors.

The study, however, has some limitations that should be acknowledged. These include the relatively small sample size. Additionally, it is a single-centered study, which could affect the generalizability of the findings.

Conclusion

This study highlights the potential benefits of rivaroxaban over warfarin in the management of DVT, with trends suggesting better recanalization rates, lower valve incompetence, and reduced VS scores. However, these differences did not reach statistical significance. The identification of age and dyslipidemia as significant predictors of PTS underscores the importance of considering patient-specific factors in treatment decisions. While rivaroxaban shows promise, further large-scale studies are needed to definitively establish its superiority and to better understand the nuances of its safety and efficacy compared to warfarin.

Statements and declarations

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Statement for informed consent: Informed consent was obtained from all individual participants included in the study.

Statement for conflict of interest: The authors declare that they have no conflict of interest.

Ethical approval: This study has been approved by the appropriate institutional research ethics committee.

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