Journal of Cardiovascular Disease Research

ISSN: 0975-3583,0976-2833 VOL 16, ISSUE 6, 2025

A comparative observational study on the effectiveness and safety of acenocoumarol versus apixaban in deep vein thrombosis patients at a tertiary care centre

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ABSTRACT:-

Background: Deep vein thrombosis (DVT) represents a significant manifestation of venous thromboembolism (VTE) and is associated with considerable morbidity and mortality. Anticoagulation remains the cornerstone of DVT management, with vitamin K antagonists (VKAs) and direct oral anticoagulants (DOACs) being the primary pharmacological interventions. Acenocoumarol, a commonly prescribed VKA, and apixaban, a selective direct factor Xa inhibitor, are frequently used. However, comparative real-world data evaluating their relative efficacy and safety remain limited, particularly within the north Indian population.

Materials and methods: A total of 120 patients with confirmed DVT were enrolled and divided into two treatment groups: acenocoumarol (n=60) and apixaban (n=60). Patients were followed up at 0, 14 days, 3, 6, and 9 months. Parameters assessed included pain (numerical pain scale), edema, redness, INR levels, recanalization status (via Doppler), bleeding episodes (classified per ISTH), recurrence, persistence, and complications such as pulmonary embolism and post-thrombotic syndrome.

Results: Apixaban demonstrated faster symptom relief with significantly reduced pain and edema scores by day 14 and 3 months compared to acenocoumarol. Recanalization was more rapid and complete in the apixaban group ($p < 0.033$). Bleeding complications were more frequent in the acenocoumarol group than the Apixaban group (p value < 0.032), although no cases of major bleeding were seen. The recurrence rate was lower in apixaban than in acenocoumarol group (p value - 0.096). Chronic complications were also less prevalent in the

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apixaban group to acenocoumarol group. Side effects and long-term complications were lower in the apixaban group.

Conclusion:- Apixaban was more effective in symptom control, safer in terms of bleeding profile, and associated with better recanalization and fewer recurrences and complications than acenocoumarol. It offers a promising alternative for long-term DVT management, especially in outpatient settings.

Keywords:- Deep vein thrombosis, Venous thromboembolism, Deep vein thrombosis, Acenocoumarol, Apixaban, Anticoagulation, DOAC, VKA, Recanalization, Thrombus burden, Complications

INTRODUCTION

Deep vein thrombosis (DVT) is a pathological condition characterized by the formation of thrombi within the deep venous system, most commonly in the lower extremities. It constitutes a major clinical component of venous thromboembolism (VTE), which also encompasses pulmonary embolism (PE), a potentially fatal complication [1]. The annual incidence of VTE ranges from 1 to 2 per 1,000 individuals in the general population and increases significantly with age [2]. The key objectives in DVT management are to prevent clot extension, PE, recurrent thrombosis, and long-term sequelae such as post-thrombotic syndrome (PTS) [3].

Standard treatment involves anticoagulation therapy, initiated promptly upon diagnosis. Conventional anticoagulants include vitamin K antagonists (VKAs), such as warfarin and acenocoumarol, which act by inhibiting the synthesis of vitamin K-dependent clotting factors II, VII, IX, and X. Although VKAs are effective, their use is complicated by a narrow therapeutic index, variable patient response, food and drug interactions, and the need for frequent INR monitoring [4,5]

To overcome these limitations, direct oral anticoagulants (DOACs) have been developed. These agents offer predictable pharmacokinetics and pharmacodynamics, fewer interactions, and do not require routine monitoring. Among them, apixaban is a selective, reversible inhibitor of activated factor Xa that interferes with the conversion of prothrombin to thrombin, a crucial step in the coagulation cascade [6]. It exerts its anticoagulant effect independently of antithrombin III and targets both free and clot-bound factor Xa [7].

In contrast, acenocoumarol is a coumarin derivative that inhibits vitamin K epoxide reductase, thereby impairing the gamma-carboxylation of coagulation factors. It is rapidly absorbed, has a shorter half-life than warfarin, and requires individualized dosing based on INR values to maintain efficacy while minimizing bleeding risk [8].

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According to recent guidelines by the American Society of Hematology (ASH) and the European Society of Cardiology (ESC), DOACs are now recommended as first-line therapy in most patients with DVT due to their favorable risk-benefit profile [9,10]. However, in resource-limited settings, VKAs like acenocoumarol continue to be used extensively due to cost-effectiveness and availability.[10]

Given the practical differences in monitoring, safety, and pharmacological profiles, this study aims to evaluate the comparative effectiveness and safety of apixaban and acenocoumarol in the real-world management of DVT patients in North India

MATERIALS AND METHODS

This was a prospective, observational study conducted over 12 months in the Department of Vascular Surgery at King George's Medical University (KGMU), Lucknow, a tertiary care centre in North India with institutional ethical approval no. XXI-PGTSC-II A/P53

INCLUSION CRITERION: Patients =/>18 years of age confirmed cases of DVT and who gave consent for the study.

EXCLUSION CRITERION: Pediatric Age group, i.e.,<18 years, Pregnant and lactating females, Patients presenting with Antiphospholipid antibody syndrome, Any known case of Hemophilia and other bleeding disorders, Patients who did not give consent for the study.

Methodology

Based on the estimated incidence of VTE (8%) among hospitalized patients in South Asia, the sample size was calculated using the formula [11]

$$N = [(Z\alpha/2)^2 * P (1 - P)] / D^2$$

This yielded a sample size of approximately 113, which was rounded up to 120 to account for potential loss to follow-up. Patients were allocated equally into two groups 60 received acenocoumarol, and 60 received apixaban. Total sample was divided into two groups – one group was treated with the drug Acenocoumarol 2 mg/day with overlapping of injection heparin (till target INR of 2.0-3.0), Acenocoumarol dose adjusted to achieve INR 2-3, while other group was treated with drug Apixaban (10 mg 1 tab BD for 7 days in initiation phase then 5 mg BD for continuation phase). The choice of anticoagulant was decided by the treating vascular surgeon based on clinical features, patient compliance, and Doppler studies. Participants were evaluated at baseline, day 14, and months 3, 6, and 9. The following parameters were assessed, pain was recorded according to the pain scale [12], edema and Redness recorded according to Clinical grading..DVT was classified based on location as isolated proximal, isolated distal, and blended

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DVT and based on chronology as Acute, subacute, and chronic DVT. Recanalisation and thrombus burden were also seen by colour Doppler in both the groups.Both groups were checked for recurrence and persistence of DVT at follow-up visits and complications like bleeding classified as major or minor based on ISTH criteria [13], pulmonary embolism, secondary varicose vein, chronic ulcers and post thrombotic syndrome.

- **Flow chart of the study**:

Already diagnosed cases of DVT were taken and Screening for Inclusion/Exclusion Criteria

⇩

Day 0:Baseline investigations and doppler study was done for DVT confirmation

⇩

Group A (Treated with Drug Acenocoumarol at 2 mg/day with overlapping of inj. heparin till target INR 2-3)

Group B (Treated with Drug Apixaban 10 mg/day twice daily for 14 days)

⇩

Coagulation profile (Targeted PT/INR 2-3 to be maintained) and clinical signs and symptoms evaluated.

COLOR DOPPLER STUDY checked for DVT (at 14 day)

⇩

Group A: Acenocoumarol started (Dose depending upon the Target INR 2-3)

Group B: Apixaban started at a dose of 5 mg 1 tab BD (no target INR)

⇩

Clinical Assessment(pain, redness and edma) , Check for bleeding manifestations any time during follow-up, unforeseen complications(i.e. acute and chronic), recurrence, and persistence of DVT o be recorded at 14 days,3 ,6 and 9 months

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Statistical Analysis:

- The data was analyzed using MS Excel and Statistical Package for Social Sciences (SPSS 24.0) software
- A P value <0.05 was taken as significant.

OBSERVATIONS AND RESULTS

This study presents a comprehensive comparative evaluation of two commonly used oral anticoagulants—acenocoumarol and apixaban—in patients diagnosed with deep vein thrombosis (DVT). A total of 120 patients were enrolled, equally divided into two treatment groups: 60 received acenocoumarol (Group A) and 60 received apixaban (Group B).

Table 1: Baseline Characteristics of Acenocoumarol (Group 1) and Apixaban (Group 2)

		Group		P value
		Group 1 (60) (Acenocoumarol)	Group 2 (60) (Apixaban)	
Age	<=30	23	15	0.401
	31-40	16	16	
	41-50	9	12	
	51-60	8	8	
	>60	4	9	
	Total	60	60	
Sex	F	16	17	0.584
	M	44	43	
LOCATION OF DVT	DISTAL DVT	42	40	0.891
	PROXIMAL DVT	8	8	
	BLENDED/MIXED DVT	10	12	

Chi-square test was applied to compare baseline demographics, location, and type of DVT between the Acenocoumarol and Apixaban groups.

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The mean age was almost identical in both Groups, and the p-value was insignificant (p-value = 0.401). Additionally, both groups had a nearly equal number of males and females, and the p-value was also insignificant (0.584). Both groups had almost similar numbers of Proximal, Distal, and Blended DVT, and the p-value was insignificant(0.891). both groups had almost a similar number of acute, subacute, and chronic DVT cases, and thus p-value (0.929) was insignificant.

Table 2: Clinical parameters for both Acenocoumarol (Group-1) and Apixaban (Group-2)

Redness		Group		Total	P value
		Group 1 (Acenocoumarol)	Group2 (Apixaban)		
Day0	Present	55	57	112	0.464
	Absent	5	3	8	
Day 14	Present	24	20	44	0.449
	Absent	36	40	76	
3 Months	Present	12	11	23	0.817
	Absent	48	49	97	
6 Months	Present	15	6	21	0.031*
	Absent	45	54	99	
9 Months	Present	6	0	6	0.012**
	Absent	54	60	114	

The chi-square test was applied to assess the association between groups.

p < 0.05 was considered statistically significant

At 6 months,there was a significant difference in redness. 25.0% of Group 1 patients had persistent redness compared to 10.0% in Group 2 (p value= 0.031). At 9 months, 6 (10.0%) patients in Group 1 exhibited persistent redness, while none of the patients in Group 2 had redness (p= 0.012), indicating a significantly better resolution of redness in the Apixaban group.

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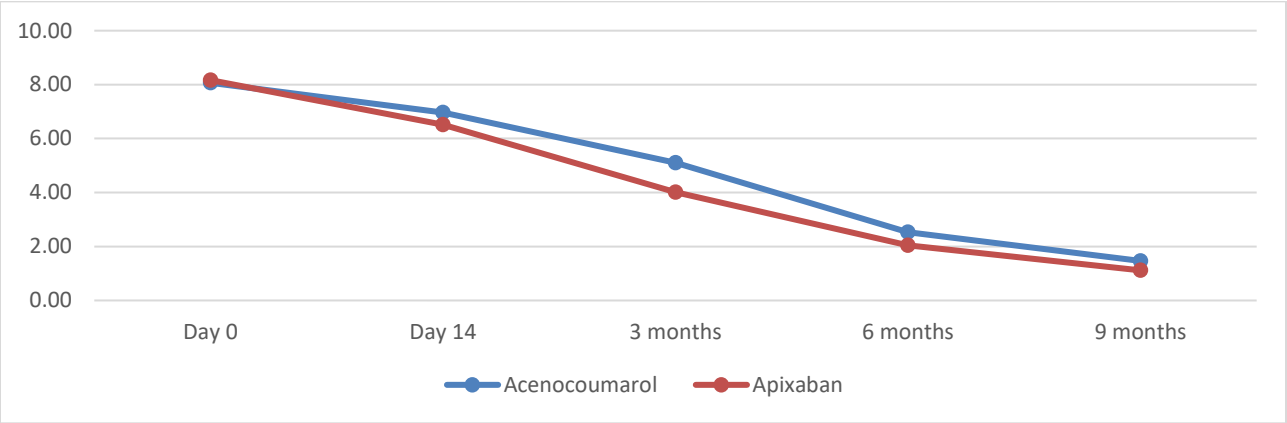
Clinical parameters for both Acenocoumarol (Group-1) and Apixaban (Group-2):

Graph a: Pain-wise distribution across groups

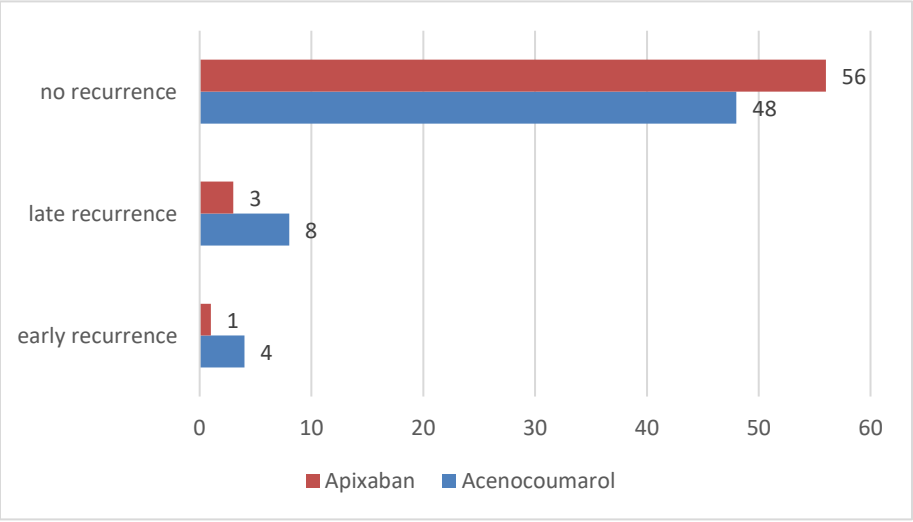


An independent sample t-test was applied to compare the mean pain scores between the Acenocoumarol and Apixaban groups at each follow-up (Day 0, Day 14, 3 months, 6 months, and 9 months). A p-value < 0.05 was considered statistically significant

At baseline (Day 0), pain scores were similar between Group 1 (Acenocoumarol: 8.07 ± 1.35) and Group 2 (Apixaban: 8.17 ± 1.29; p = 0.679). By Day 14, Group 2 showed a significantly greater reduction (6.52 ± 1.02) compared to Group 1 (6.97 ± 1.01; p = 0.016).

At 3 months, the difference widened (Group 1: 5.10 ± 1.08; Group 2: 4.02 ± 1.16; p < 0.001), favoring Apixaban. Further reductions were seen at 6 months (2.53 ± 1.27 vs. 2.05 ± 0.83; p = 0.015) and 9 months (1.47 ± 0.87 vs. 1.12 ± 0.78; p = 0.023)

Graph b: Recurrence for both Acenocoumarol (Group-1) and Apixaban (Group-2)



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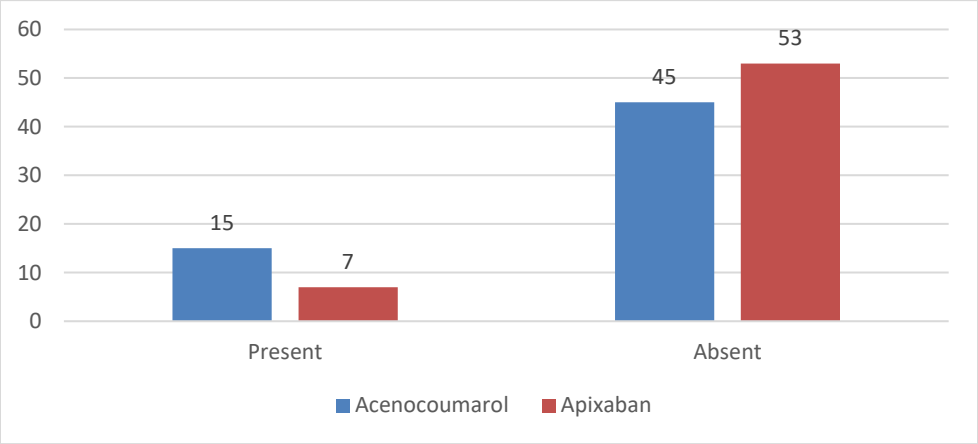
Fisher's exact test of association was used to compare bleeding manifestations between groups due to low event numbers. A p-value < 0.05 indicated statistical significance

Overall, recurrence (early or late combined) was higher in the Acenocoumarol group, but the difference between the groups was not statistically significant (p = 0.096).

Graph c: Persistence wise distribution across Acenocoumarol (Group-1) and Apixaban (Group-2)



Applied Chi2 test of association to assess the persistence of thrombus between groups. Statistical significance was defined as p < 0.05.

A higher proportion of persistence was seen in the Acenocoumarol group 1, the difference did not reach statistical significance (p = 0.059).

Color Doppler findings in both Acenocoumarol (Group 1) and Apixaban (Group 2)

Table 3:Recanalisation for both Acenocoumarol(Group-1) and Apixaban (Group-2)

Recanalization		Group		Total	P value
		Group 1 (Acenocoumarol)	Group 2 (Apixaban)		
Day 14	No	50	45	95	0.381
	Partial	10	14	24	
	Complete	0	1	1	
3 months	No	42	35	77	0.388
	Partial	16	23	39	
	Complete	2	2	4	

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6 months	No	15	8	23	0.232
	Partial	39	43	82	
	Complete	6	9	15	
9 months	No	6	1	7	0.033*
	Partial	8	3	11	
	Complete	46	56	102	

Fisher's exact test of association was used to assess the association between recanalization outcomes and treatment groups due to small expected frequencies. A p-value < 0.05 was considered statistically significant

Recanalization was assessed for both groups based on color Doppler findings. At day 14, 3 month and 6-month patients in the apixaban group showed improvement in recanalisation with more patients having partial and complete recanalisation but differences were not statistically significant. While at 9 months the difference between the two groups was statistically significant (p = 0.033), favoring apixaban for faster and more complete recanalization.

Table 4: Thrombus burden for both Acenocoumarol(Group-1) and Apixaban (Group-2)

Thrombus burden		Group		Total	P value
		Group 1 (Acenocoumarol)	Group 2 (Apixaban)		
Day 14	Increased	2	1	3	0.519
	Decreased	7	11	18	
	Same	51	48	99	
3 months	Increased	1	1	2	0.429
	Decreased	30	37	67	
	Same	29	22	51	
6 months	Increased	1	0	1	0.208
	Decreased	45	52	97	
	Same	14	8	22	
9 months	Increased	0	0	0	0.075*
	Decreased	50	57	110	
	Same	10	3	10	

Applied Fisher's exact test of association to compare changes in thrombus burden between the two groups across time points. p < 0.05 was interpreted as statistically significant

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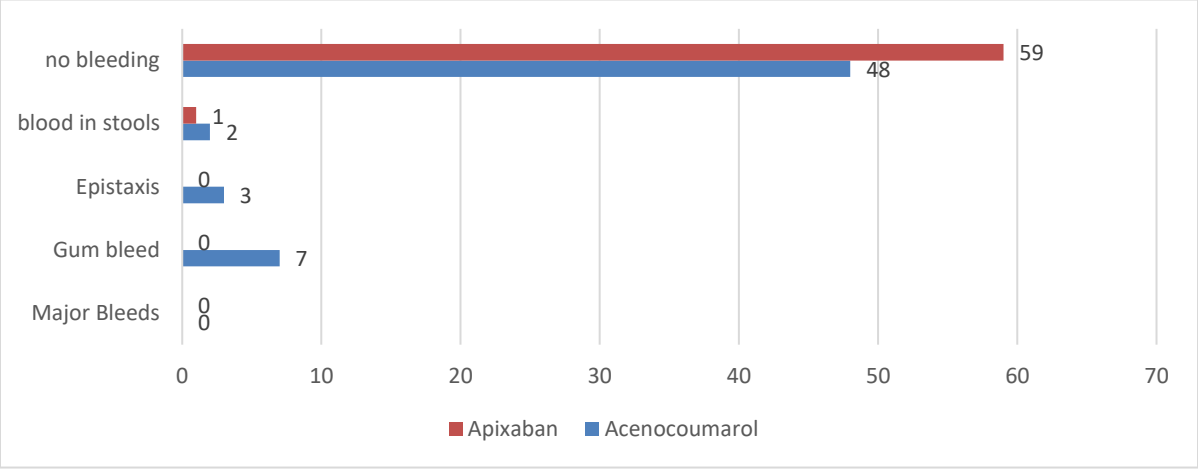
Thrombus Burden was assesed by colour doppler for both the groups. At day 14, 3 and 6 months of follow up thrombus burden was reduced in patients with Apixaban group but there was no significant difference also at 9 month of follow up a favorable trend towards greater thrombus resolution in the apixaban group was seen, the difference did not reach statistical significance (p = 0.075).

Complications in Both Acenocoumarol (Group 1) and Apixaban (Group 2)

Graph d: Bleeding manifestations wise distribution for both Acenocoumarol (Group-1) and Apixaban (Group-2)



Fisher's exact test was applied to compare bleeding manifestations between groups due to low event numbers. A p-value < 0.05 indicated statistical significance

No major bleeding was reported in either group. Minor bleeding manifestations such as gum bleeding (11.7% in Group 1 vs. 0% in Group 2) and epistaxis (5.0% in Group 1 vs. 0% in Group 2) were observed only in Group 1. Blood in stools was reported in 3.3% of patients in Group 1 and 1.7% in Group 2. Overall, 80.0% of Group 1 patients had no bleeding manifestations compared to 98.3% in Group 2, and this difference was statistically significant (p = 0.009).

Amongst other complications none of the patients in either group developed pulmonary embolism during follow-up. In chronic ulcers a higher incidence was observed in the acenocoumarol group compared to the apixaban group, the difference was not statistically significant (p = 0.243). The occurrence of secondary varicose veins was higher among patients receiving acenocoumarol, the difference did not reach statistical significance (p = 0.092).

Graph e: Secondary varicose vein and chronic ulcers wise distribution across both groups

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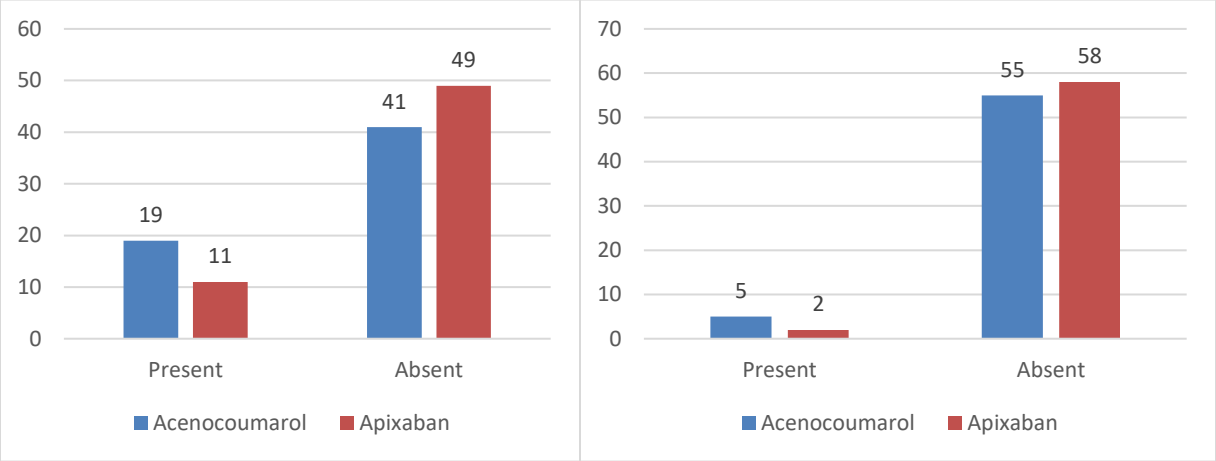

Applied Chi2 test of association to assess the chronic complications occurrence with different anticoagulants used. A p-value < 0.05 indicated significance

Although the occurrence was higher among patients receiving acenocoumarol, the difference did not reach statistical significance for secondary varicose vein (p = 0.092) and chronic ulcers (p = 0.243)

DISCUSSION

In our prospective observational study conducted at a tertiary care center, we compared Acenocoumarol and Apixaban across clinical, symptomatic, and laboratory parameters over a nine-month follow-up period. We took a total of 120 patients, with 60 patients each in group 1(Acenocoumarol) and 2(Apixaban). The mean age of group 1 was 37.2 years, while the mean age of group 2 was 40.9 years. There were 16 females and 44 males in group 1 and 17 females and 43 males in group 2, which were almost similar. both groups were similar in all baseline characteristics. Similar studies, like **Javaid Z et al(2024), Agnelli Giancarlo et al (2013)** had similar baseline characteristics[14][6]. Clinical Parameters like Redness, Pain, and Edema were assessed during the follow-up at days 14, 3,6, and 9 months. Clinical Parameters like Redness, Pain, and Edema were assessed during the follow-up at days 14, 3,6, and 9 months. The apixaban group showed better resolution of redness, particularly at 6 and 9 months. The p-value at 6 and 9 months was 0.03 and 0.01, respectively. Pain scores were significantly reduced in Group 2 patients compared to Group 1, particularly at 9 months. **Einstein-DVT Study (2010)** also showed that Rivaroxaban had non-inferior efficacy concerning the primary outcome with

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enoxaparin–vitamin K antagonist[16]. **Van ES et al (2014)** also demonstrated that DOACs have similar efficacy as VKAs[17].

Apixaban group had a faster and more complete recanalisation and reduced thrombus burden as compared to the acenocoumarol group. **Koehl L Jennifer et al (2020)** showed Apixaban as slightly better than acenocoumarol in reducing thrombus burden[18], while **Hu et al(2024**) compared the VKAs group; there were similar rates of thrombus resolution in the DOACs group at 3 months and 6 months[19].

While major bleeding manifestations were absent in both groups, the apixaban group had significantly fewer minor bleeding manifestations during follow-up. Similarly **Manckoundia et al(2021)**[20], **Einstein-DVT Study(2010)** showed that compared with VKAs, DOACs are associated with a reduced risk of stroke or systemic embolism, intracranial hemorrhage, and major bleeding in older persons.

Limitations of the study were that 120 patients were included; a larger multicenter study would enhance statistical power and external validity. As this was an observational study, the absence of random allocation may have introduced selection bias, potentially affecting the reliability of the results. Randomization could have minimized this bias and strengthened the validity of the findings. While nine months is adequate for primary outcomes, longer follow-up would be better for chronic complications like post-thrombotic syndrome and secondary varicose veins

CONCLUSION

This observational study was conducted over 12 months to compare the efficacy and safety profiles of Acenocoumarol and Apixaban in the treatment of deep vein thrombosis (DVT) among adult patients attending a tertiary care center. A total of 120 patients were enrolled, with 60 patients in each group (Group 1: Acenocoumarol, Group 2: Apixaban).

Baseline characteristics, including age distribution, sex, type of DVT (proximal/distal), and duration (acute/subacute/chronic), were well-matched between the two groups, with no statistically significant differences observed.

Both anticoagulants were effective in reducing the clinical signs and symptoms of DVT, such as pain, edema, and redness, over a nine-month follow-up period. However, patients in the Apixaban group demonstrated more significant reductions in these symptoms from Day 14 onward, suggesting more rapid symptomatic relief.

Apixaban, a direct Factor Xa inhibitor, exhibited superior outcomes in terms of patient compliance, reduced need for laboratory monitoring, and a lower incidence of bleeding

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complications compared to Acenocoumarol, a vitamin K antagonist that requires stringent INR monitoring and frequent dose adjustments. These factors can significantly impact patient compliance and clinical outcomes, particularly in real-world settings

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