

Original Research

Received 09 June 2026

Revised 20 July 2026

Accepted 03 Aug 2026

Natural Resources for Human
Health 2026, Vol. 6 (13s): 1484–1493

KEYWORDS:

CLTI, Peripheral artery disease,
Factor Xa inhibitors, DAPT,
Apixaban, Rivaroxaban,
Angioplasty, infrageniculate.

Outcomes of Factor Xa Inhibitor-based Regimens Versus Dual Antiplatelet Therapy in Managing Infrageniculate Critical Limb Ischemia Post Angioplasty

Abdullah Alhaizaey^{1*}, Mansour Aljaafari¹, Mohammed F. Aboulsaad¹, Awdah Alkhathami², Asma Alyasad², Barrag Alhazmi³, Yahya Almalki⁴, Osama Alahmadi⁵, Ahmed M. Hamed⁶

¹Department of Vascular Surgery, Asser Central Hospital, Abha, Saudi Arabia

²Department of Vascular Surgery, King Khalid University Medical City, Abha, Saudi Arabia

³Department of Vascular Surgery, Armed Forces Hospital, Jazan, Saudi Arabia

⁴Department of Vascular Surgery, Armed Forces Hospital, South Region, Saudi Arabia

⁵Department of Vascular Surgery, King Fahad Hospital, Madina, Saudi Arabia

⁶Department of Vascular and Endovascular Surgery, Faculty of Medicine, Suez Canal University, Egypt

ABSTRACT:

Background: Critical limb-threatening ischemia (CLTI) represents the most advanced stage of peripheral arterial disease and is associated with high rates of limb loss and mortality. Although dual antiplatelet therapy (DAPT) is commonly used following infrageniculate endovascular revascularization, its effectiveness in maintaining vessel patency remains uncertain. Factor Xa inhibitor-based dual pathway inhibition may offer improved outcomes in this high-risk population.

Patients and Methods: This multicenter retrospective cohort study included 145 patients with CLTI (Rutherford class 4–6) who underwent infrageniculate angioplasty between January 2022 and December 2023. Patients were stratified according to post-procedural antithrombotic therapy into three groups: apixaban plus aspirin ($n = 37$), rivaroxaban plus aspirin ($n = 32$), and DAPT with clopidogrel plus aspirin ($n = 76$). The primary outcome was primary patency rate at 12 months. Secondary outcomes included primary-assisted patency, clinical improvement based on Rutherford classification, limb-related outcomes, and safety endpoints including bleeding, hematoma, myocardial infarction, ischemic stroke, and cardiovascular death.

Results: At 12 months, primary patency was significantly higher in the rivaroxaban (75%) and apixaban (72.9%) groups compared with the DAPT group (67.1%) ($p < 0.001$). Primary-assisted patency was also superior in the rivaroxaban (87.5%) and apixaban (83.7%) groups versus DAPT (78.9%) ($p < 0.001$). Clinical improvement was observed in 81% of patients receiving apixaban and 72% receiving rivaroxaban, compared with 9.2% in the DAPT group ($p < 0.001$). Rates of amputation, wound healing, and adverse safety outcomes did not differ significantly among groups.

Conclusion: In patients with CLTI undergoing infrageniculate angioplasty, factor Xa

inhibitor-based regimens combined with aspirin were associated with superior 12-month patency and greater clinical improvement compared with conventional DAPT, without an increased risk of adverse events. These findings support dual pathway inhibition as a promising antithrombotic strategy in this high-risk population.

INTRODUCTION

Over two-hundred million individuals worldwide suffer from peripheral arterial disease (PAD), which has a significant impact on public health since it increases morbidity and mortality [1]. A large percentage of PAD patients are CLTI, the most advanced form of the disease, which is characterised by ischaemic rest discomfort, non-healing ulcers, or gangrene [2]. Patients diagnosed with CLTI face heightened chances of limb amputation, cardiovascular incidents, and mortality. The incidence of CLTI has steadily increased, a critical morbidity driven by global increases in diabetes mellitus, chronic kidney disease, and aging populations [3]. This escalating burden implements the need for effective and durable treatment strategies aimed at improving limb salvage and survival outcomes [3].

Timely revascularization remains the cornerstone of CLTI management. Revascularization can be achieved via open surgical intervention or more commonly in recently through endovascular techniques such as balloon angioplasty and stenting [4]. However, restenosis and thrombosis following these interventions continue to limit long-term success, particularly in infrageniculate arteries where vessel caliber and flow dynamics pose additional challenges [5-7].

Antithrombotic therapy is essential post-revascularization to maintain vessel patency and reduce adverse events. Aspirin and DAPT, typically aspirin combined with clopidogrel, have remained standard pharmacologic strategies in this context [8-9]. Although DAPT has demonstrated efficacy in coronary and cerebrovascular interventions, the benefit in patients with CLI undergoing peripheral angioplasty remains less well defined. Moreover, concerns about bleeding risk and interindividual variability in response, such as clopidogrel resistance, necessitates the need for more effective and individualized approaches [10-11].

Factor Xa inhibitors, including rivaroxaban and apixaban, represent a newer class of oral anticoagulants that selectively inhibit thrombin generation [12]. Their use in PAD has gained attention following the VOYAGER PAD and COMPASS trials, which showed that low-dose rivaroxaban combined with aspirin significantly reduced major adverse cardiovascular and limb events in patients with symptomatic PAD, although with a modest increase in bleeding [13-14]. These findings support the potential benefit of dual pathway inhibition, which targets both platelet aggregation and the coagulation cascade, in the high-risk CLI population.

Ongoing trials, such as the AGRIPPA study, are investigating the efficacy and safety of apixaban plus aspirin compared to traditional DAPT in patients undergoing infrageniculate revascularization [15]. This approach aims to determine whether factor Xa inhibitors can offer superior outcomes by reducing restenosis and thrombotic re-occlusion while maintaining an acceptable bleeding risk.

Given the substantial morbidity associated with CLTI and the limitations of current antiplatelet regimens, exploring alternative or adjunctive strategies like factor Xa inhibition may represent a crucial advance in post-procedural care. Ongoing research will clarify the optimal antithrombotic regimen for improving limb salvage and survival in this vulnerable patient group. Therefore, this multicenter retrospective cohort study aimed to compare the clinical efficacy and safety of dual pathway inhibition using low-dose factor Xa inhibitors (apixaban or rivaroxaban) combined with aspirin versus traditional DAPT (aspirin plus clopidogrel) in patients with CLI undergoing infrapopliteal angioplasty in Saudi Arabia.

PATIENTS AND METHODS

Study design and setting

This is retrospective, multicenter cohort study was conducted across three tertiary vascular centers in the southern region of Saudi Arabia. Adult patients diagnosed with CLTI who underwent percutaneous transluminal infra geniculate angioplasty between January 2022 and December 2023 were enrolled. Data were retrospectively collected from institutional vascular

registries and included demographics, comorbidities, lesion characteristics, procedural details, and clinical outcomes assessed at 12 months.

Each participating center followed a distinct post-procedural antithrombotic protocol. At Asser Central Hospital (Abha), patients received apixaban 2.5 mg twice daily combined with aspirin 100 mg daily. In the Armed Forces Hospital – Southern Region, patients received rivaroxaban 10 mg once daily and aspirin 100 mg daily. Meanwhile, Alhaya National Hospital (Southern Region) administered clopidogrel 75 mg daily and aspirin 100 mg daily (DAPT). Each center consistently adhered to its respective regimen throughout the study period, enabling a structured comparison of factor Xa inhibitor-based dual pathway inhibition versus conventional DAPT in CLI management.

Study population and groups

Eligible patients were stratified into three treatment groups based on the post-angioplasty antithrombotic regimen they received. Group 1 (Apixaban group) was treated with apixaban plus aspirin, Group 2 (Rivaroxaban group) received rivaroxaban plus aspirin, and Group 3 (DAPT group) was administered clopidogrel plus aspirin.

Patients were included if they had symptomatic PAD with Rutherford classification 4 to 6, indicating ischemic rest pain or tissue loss, and had undergone endovascular intervention for infrapopliteal arterial disease. Patients with incomplete follow-up or missing key outcome data were excluded from the study.

Inclusion and exclusion criteria

Patients were included if they had critical limb ischemia; symptomatic PAD with Rutherford classification 4 to 6, with ischemic rest pain or tissue loss, and had undergone endovascular intervention for infra geniculate arterial disease. Patients had no contraindications for anticoagulant or antiplatelet therapy, Patients with incomplete follow-up or missing key outcome data were excluded from the study, although patients with bleeding risk e.g. Hemorrhagic stroke, patients who has sensitivity to the drugs, patients who are known to have resistance to the drugs.

Data collection

The following variables were collected: age, sex, body mass index (BMI), diabetes mellitus, hypertension, cardiovascular disease (CVD), chronic kidney disease (CKD), smoking status, Rutherford classification before and 12 months after angioplasty, lesion location (below-the-knee [BTK] or below-the-ankle [BTA]), lesion severity (stenosis or occlusion), number of prior angioplasties, and the presence of wound healing, major amputation, hematoma, bleeding, myocardial infarction (MI), ischemic stroke, and cardiovascular death.

Outcomes

The primary outcome was primary patency rate (PPR), defined as the proportion of patients who did not require any reintervention within 12 months following the index angioplasty procedure. The PPR was calculated using the formula:

$$PPR = \left(\frac{\text{Number of patients with no reintervention within 12 months}}{\text{Total number of patients}} \right) \times 100$$

Secondary outcomes included the primary-assisted patency rate (PAPR), which was defined as the proportion of patients who underwent early reintervention without complete vessel occlusion, thereby preserving blood flow. This was calculated as:

$$PAPR = \left(\frac{\text{Number of patients with non-occlusive reintervention}}{\text{Total number of patients}} \right) \times 100$$

Additional secondary outcomes assessed limb-related clinical measures, such as the major amputation rate—defined as above-ankle amputation due to vascular cause—and the wound healing rate, defined as complete epithelialization within follow-up. The analysis captured the type and frequency of reintervention, including angioplasty and bypass.

Cardiovascular events included MI, ischemic stroke, and cardiovascular death. Safety outcomes were assessed by monitoring the occurrence of hematoma following angioplasty.

Informed consent

All participants or their legal representatives have provided written informed permission to participate in the research and to have the paper published. Participants' right to privacy has been respected. This study was carried out in accordance with all applicable laws, rules, and regulations in the area where it was conducted. The Aseer Central Hospital granted approval for this research (Approval No. 1055498586).

Statistical analysis

All statistical computations were carried out with SPSS Statistics version 29.0. Continuous variables were analysed for normality and conveyed as mean $\pm$ SD or medians with interquartile ranges, depending on the context. Categorical variables were encapsulated as frequency counts and percentage values. For continuous variables, group comparisons were executed using the independent-samples t-test or the Mann–Whitney U test, and for categorical variables, chi-square or Fisher's exact test was used. Patency rates (both PPR and PAPR) were calculated as proportions of the total cohort, and intergroup differences were tested for statistical significance. Time-to-event analyses, including Kaplan–Meier survival curves for patency outcomes, were conducted, and bar charts depicting adverse events were generated using Python version 3.9 with the matplotlib and seaborn libraries. Statistical significance was set at $p < 0.05$.

RESULTS

Baseline characteristics

A total of 145 patients with CLI underwent infrageniculate angioplasty and were stratified into three groups based on post-procedural antithrombotic regimens (Table I). The mean age differed significantly among groups ($p = 0.02$), with the apixaban group having the highest average age (63 ± 11 years). A significant sex imbalance was observed ($p = 0.02$), with the DAPT group showing a higher proportion of male patients (82.9%) compared to the factor Xa inhibitor groups.

Diabetes and hypertension were highly prevalent across the cohort, with significant differences among groups. The DAPT group had the highest prevalence of diabetes mellitus (88.2%, $p < 0.001$) and hypertension (85.5%, $p = 0.01$). No statistically significant differences were observed in BMI, CKD, or CVD among the groups. Smoking history was more frequently reported in the apixaban and rivaroxaban groups compared to the DAPT group ($p = 0.03$). Lesion severity also varied significantly, with a greater proportion of occlusive lesions in the apixaban and rivaroxaban groups (67.6% and 78.1%, respectively; $p = 0.04$) compared to 92.1% of stenotic lesions in the DAPT group. Patients in the DAPT group had more prior angioplasties ($p = 0.03$) and presented frequently with advanced Rutherford classification scores ($p = 0.02$).

Table (1): Baseline characteristics of the study population

Variable		Overall (column %)	Group 1: Apixaban + ASA (n=37)	Group 2: Rivaroxaban + ASA (n=32)	Group 3: DAPT (n=76)	p-value
Age (mean $\pm$ SD)		60 (10)	63 (11)	59 (9)	58 (10)	0.02*
Gender	Male	107 (73.8%)	22 (59.5%)	22 (68.8%)	63 (82.9%)	0.02*
	Female	38 (26.2%)	15 (40.5%)	10 (31.3%)	13 (17.1%)	
BMI (mean $\pm$ SD)		41 (5)	42 (6)	41 (5)	41 (5)	0.4
Diabetes Mellitus (%)	No	32 (22.1%)	12 (32.4%)	11 (34.4%)	9 (11.8%)	< 0.001*
	Yes	113 (77.9%)	25 (67.6%)	21 (65.6%)	67 (88.2%)	
Hypertension (%)	No	32 (22.1%)	14 (37.8%)	7 (21.9%)	11 (14.5%)	0.01*
	Yes	113 (77.9%)	23 (62.2%)	25 (78.1%)	65 (85.5%)	
Cardiovascular Disease (%)	No	37 (25.5%)	12 (32.4%)	8 (25%)	17 (22.4%)	0.5
	Yes	108 (74.5%)	25 (67.6%)	24 (75%)	59 (77.6%)	
CKD (%)	No	120 (82.8%)	29 (78.4%)	26 (81.3%)	65 (85.5%)	0.6

	Yes	25 (17.2%)	8 (21.6%)	6 (18.8%)	11 (14.5%)	
Smoking History (%)	No	125 (86.2%)	29 (78.4%)	25 (78.1%)	71 (93.4%)	0.03*
	Yes	20 (13.8%)	8 (21.6%)	7 (21.9%)	5 (6.6%)	
Lesion location	BTK	128 (88.3%)	34 (91.9%)	29 (90.6%)	65 (85.5%)	0.5
	BTA	17 (11.7%)	3 (8.1%)	3 (9.4%)	11 (14.5%)	
Lesion severity	Stenosis	25 (17.2%)	25 (67.6%)	25 (78.1%)	70 (92.1%)	0.04*
	Occlusion	120 (82.8%)	12 (32.4%)	7 (21.9%)	6 (7.9%)	
History of Angioplasty	0	32 (22.1%)	7 (18.9%)	10 (31.3%)	15 (19.7%)	0.03*
	1	80 (55.2%)	16 (43.2%)	14 (43.8%)	50 (65.8%)	
	2	28 (19.3%)	11 (29.7%)	8 (25%)	9 (11.8%)	
	3	5 (3.4%)	3 (8.1%)	0	2 (2.6%)	
Rutherford classification	5	103 (71%)	19 (51.4%)	21 (65.6%)	63 (82.9%)	0.02*
	6	42 (29%)	18 (48.6%)	11 (34.4%)	13 (17.1%)	
* Significant, ASA – Acetylsalicylic acid (Aspirin); DAPT – Dual antiplatelet therapy; BMI – Body mass index; BTK – Below-the-knee; BTA – Below-the-ankle; CKD – chronic kidney disease.						

Efficacy outcomes

At the 12-month follow-up, patients in the apixaban and rivaroxaban groups demonstrated significantly better PPR and PAPR compared to those in the DAPT group (Table II). The rivaroxaban group achieved the highest PPR (75%), followed by the apixaban (72.9%) and DAPT (67.1%) groups ($p < 0.001$). Similarly, the rivaroxaban group exhibited the highest PAPR (87.5%), followed by the apixaban (83.7%) and DAPT (78.9%) groups ($p < 0.001$). Although differences in major amputation and wound healing rates did not reach statistical significance, the DAPT group accounted for 80% of all amputation cases and had a higher proportion of patients with poor wound healing.

At 12 months, clinical improvement based on the Rutherford classification was significantly greater in the factor Xa inhibitor groups compared to the DAPT group (Figure 1). Specifically, a substantial proportion of patients in the apixaban (81%) and rivaroxaban (72%) groups achieved downgrading to Rutherford classes 1 through 3, reflecting mild to moderate symptoms and improved limb salvage. In contrast, only 9.2% of patients in the DAPT group reached similar levels of improvement ($p < 0.001$). Notably, no patients in the DAPT group attained class 1, which indicates complete symptom resolution, whereas 8.1% and 12.5% in the apixaban and rivaroxaban groups, respectively, reached this classification. Furthermore, most patients in the DAPT group (76.3%) remained in class 5, and 10.5% persisted in class 6, both of which reflect severe limb-threatening ischemia or ongoing tissue loss.

Table (2): Efficacy outcomes after 1 year of intervention

Outcome		Overall (n=145) (column %)	Group 1: Apixaban + ASA (n=37)	Group 2: Rivaroxaban + ASA (n=32)	Group 3: DAPT (n=76)	p-value
Primary patency rate (%)		70.3%	72.9%	75%	67.1%	< 0.001*
Primary assisted patency rate (%)		82%	83.7%	87.5%	78.9%	< 0.001*
Amputation for vascular reasons (row %)	No	130 (89.7%)	35 (26.9%)	31 (23.8%)	64 (49.2%)	0.07
	Yes	15 (10.3%)	2 (13.3%)	1 (6.7%)	12 (80.0%)	
Wound healing	No	14 (9.7%)	2 (14.3%)	1 (7.1%)	11 (78.6%)	0.1

(row %)	Yes	131 (90.3%)	35 (26.7%)	31 (23.7%)	65 (49.6%)	0.4
Reintervention within 12 months (row %)	No	110 (75.8%)	28 (25.5%)	25 (22.7%)	57 (51.8%)	
	Yes	35 (24.2%)	9 (25.7%)	7 (20%)	19 (54.3%)	
* Significant						

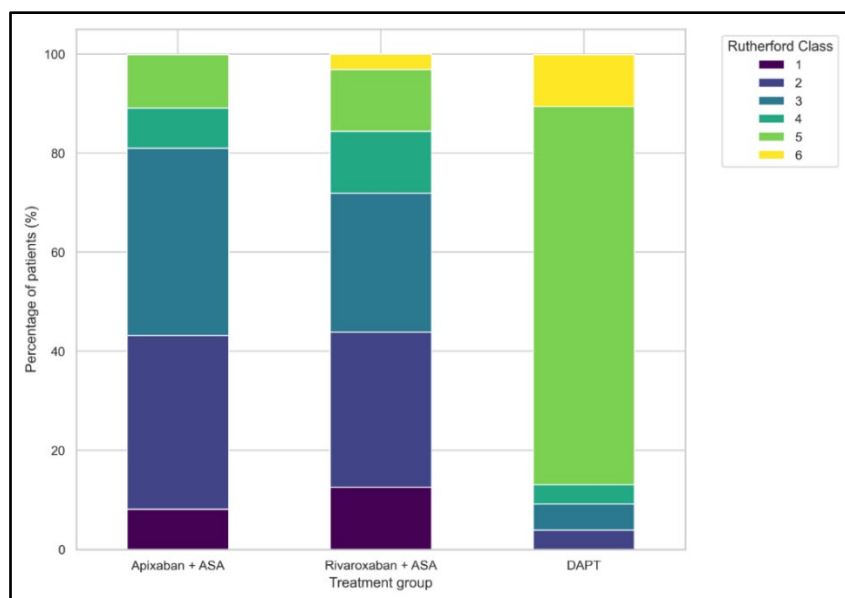


Figure (1): Rutherford classification after 12 months post intervention among the three treatment groups.

Safety outcomes

Safety outcomes, including bleeding, hematoma, MI, ischemic stroke, and CVD, did not differ significantly among the three treatment groups (Table III). The incidence of post-procedural hematoma was higher in the factor Xa inhibitor groups; however, the difference was not statistically significant ($p=0.3$). Although bleeding events occurred more frequently in the DAPT group (52.9%), this difference also lacked statistical significance ($p=0.6$).

Table (3): Safety Outcomes after 1 year of intervention

Outcome		Overall (column %)	Group 1: Apixaban + ASA (n=37)	Group 2: Rivaroxaban + ASA (n=32)	Group 3: DAPT (n=76)	p-value
Hematoma post angioplasty (row %)	No	130 (89.7%)	32 (24.6%)	28 (21.5%)	70 (53.8%)	0.3
	Yes	15 (10.3%)	5 (33.3%)	4 (26.7%)	6 (40%)	
Bleeding from other sources (row %)	No	128 (88.3%)	34 (26.6%)	27 (21.1%)	67 (52.3%)	0.6
	Yes	17 (11.7%)	3 (17.6%)	5 (29.4%)	9 (52.9%)	
Myocardial infarction post angioplasty (row %)	No	138 (95.2%)	36 (26.1%)	31 (22.5%)	71 (51.4%)	0.5
	Yes	7 (4.8%)	1 (14.3%)	1 (14.3%)	5 (71.4%)	
Ischemic stroke (row %)	No	142 (97.9%)	37 (26.1%)	31 (21.8%)	74 (52.1%)	0.5
	Yes	3 (2.1%)	0	1 (33.3%)	2 (66.7%)	
Cardiovascular death (row %)	No	144 (99.3%)	37 (25.7%)	32 (22.2%)	75 (52.1%)	0.6
	Yes	1 (0.7%)	0	0	1 (100%)	

DISCUSSION

This study evaluated and compared the effectiveness and safety of three post-angioplasty antithrombotic strategies: apixaban plus aspirin, rivaroxaban plus aspirin, and DAPT using clopidogrel plus aspirin in patients with CLI. The findings provide important insights into the potential advantages of factor Xa inhibitors when compared to conventional antiplatelet approaches in peripheral vascular disease, particularly in the high-risk CLI population.

In our study, the higher PPR and PAPR observed in the rivaroxaban and apixaban groups suggest that targeting both platelet activation and thrombin generation may be more effective in maintaining vessel patency following infrageniculate angioplasty. These results align with the Bonaca et al. [13] trial, which shown that in patients having lower extremity revascularisation, low-dose rivaroxaban in combination with aspirin decreased the risk of significant adverse cardiovascular and limb events. In this study, 6564 patients were randomised; 3286 were allocated to the rivaroxaban cohort, while 3278 were designated to the placebo cohort; Among patients with PAD who received lower-extremity revascularisation, the administration of rivaroxaban at 2.5 mg twice daily in conjunction with aspirin demonstrated a markedly reduced occurrence of the composite outcome comprising acute limb ischaemia, major vascular-related amputation, myocardial infarction, ischaemic stroke, or mortality due to cardiovascular reasons compared to aspirin monotherapy. The occurrence of TIMI major haemorrhage was not substantially different across the groups. Although that trial included patients with both intermittent claudication and CLI, this study focuses specifically on the CLI subgroup and reinforces the potential benefit of this more severe form of PAD [13].

In a large multicenter trial by Anand et al. [16], patients with PAD were recruited from 602 hospitals, clinics, and community practices across 33 countries on six continents between March 12, 2013, and May 10, 2016. The study included 7,470 patients from 558 centers and compared the outcomes of rivaroxaban plus aspirin versus aspirin alone. The combination regimen significantly reduced the composite endpoint of cardiovascular death, myocardial infarction, or stroke (126 [5%] of 2,492 vs. 174 [7%] of 2,504; hazard ratio [HR] 0.72, 95% CI 0.57–0.90, $p=0.0047$), as well as major adverse limb events, including major amputation (32 [1%] vs. 60 [2%]; HR 0.54, 95% CI 0.35–0.82, $p=0.0037$) [16]. These findings are consistent with our results, further supporting the benefit of combining a Factor Xa inhibitor with aspirin over antiplatelet therapy alone in reducing both cardiovascular and limb-related complications.

Improvements in clinical status, based on the Rutherford classification, further support the efficacy of factor Xa inhibitor-based therapy. A significantly greater proportion of patients in the apixaban and rivaroxaban groups improved to Rutherford class 1 through 3, indicating meaningful symptom relief and enhanced limb salvage. In contrast, very few patients in the DAPT group achieved similar levels of improvement, and the majority remained in classes 5 and 6, reflecting ongoing tissue loss and severe ischemia. This contrast highlights the possibility that traditional DAPT may not be sufficient for managing this advanced stage of disease [15].

Previous large trials such as CHARISMA and EUCLID found limited or no added benefit of DAPT in reducing cardiovascular or limb events among patients with PAD [17-18]. The present findings suggest that in patients with CLI, a population at high risk for both thrombotic and bleeding complications, DAPT may be less effective in promoting long-term vessel patency and functional recovery compared to dual pathway inhibition strategies [19]. The DAPT group also exhibited the highest rate of poor wound healing and accounted for most major amputations despite having a younger mean age. These outcomes likely reflect both the advanced disease stage in this group and potentially less effective thromboprophylaxis from DAPT in the peripheral vascular context.

Significant differences in baseline characteristics must be acknowledged when interpreting the results. For instance, the DAPT group had a higher prevalence of diabetes and hypertension, both known to adversely impact vascular outcomes [20-21]. Although these factors might partly account for the unfavorable results, the consistently superior outcomes in the factor Xa inhibitor groups suggest that treatment selection played a meaningful role in influencing clinical success.

The safety profiles of the three antithrombotic regimens were broadly comparable. Although post-procedural hematoma was slightly more frequent in the factor Xa groups and bleeding events occurred more commonly in the DAPT group, these differences did not reach statistically significant. These findings are consistent with prior studies, such as VOYAGER PAD and COMPASS, which reported that low-dose rivaroxaban conferred a modest increase in bleeding risk, offset by significant clinical benefits [13-14]. Similarly, apixaban has shown a favorable bleeding profile across various vascular and thromboembolic settings, and our findings support its safety in patients with CLI following endovascular procedures [22-23].

Looking ahead, larger randomized controlled trials are warranted to confirm the superiority of factor Xa inhibitor–based regimens over traditional DAPT in patients with CLI undergoing infrageniculate angioplasty. Future research should also explore optimal dosing strategies, long-term limb salvage outcomes, and integration of patient-centered measures such as quality of life and functional recovery. In addition, advances in precision medicine and emerging technologies like artificial intelligence may offer new opportunities for individualized risk stratification, prediction of restenosis, and tailored antithrombotic therapy, thereby further improving outcomes in this high-risk population [24].

LIMITATIONS

Firstly, the relatively small sample size, particularly in the apixaban and rivaroxaban groups, may have reduced the statistical power to detect differences in less frequent outcomes such as bleeding or cardiovascular events. Secondly, the absence of randomization in group allocation introduced potential selection bias, which may have been influenced by clinician preference or unmeasured clinical variables. Thirdly, although the follow-up period was extended to 12 months, longer-term outcomes such as late re-occlusion or delayed adverse events remained unassessed. Fourthly, adherence to prescribed medications and any dose modifications were not monitored, which could have affected treatment efficacy and safety; this is relevant as prior studies, such as an Egyptian multicenter analysis, have shown higher adherence and better quality of life among NOAC users compared to warfarin [25]. Fifthly, variability in lesion characteristics and comorbid conditions, although reflective of real-world CLI populations, may have confounded comparisons across groups. Finally, this study did not evaluate quality-of-life parameters or functional recovery outcomes, which are essential to fully understanding treatment benefits. Larger, randomized controlled trials are needed to validate these findings and to better define the role of dual pathway inhibition in CLI management.

CONCLUSION

This study demonstrated that combining a factor Xa inhibitor (apixaban or rivaroxaban) with aspirin yielded superior clinical outcomes compared to traditional DAPT in patients with CLI undergoing infrageniculate angioplasty. Patients treated with factor Xa inhibitors achieved higher PPR and PAPR, showed greater clinical improvement based on the Rutherford classification, and experienced fewer major amputations despite presenting with more severe lesion characteristics. Safety outcomes were comparable across all groups, with no significant increase in bleeding or cardiovascular events. These findings support the potential benefit of incorporating factor Xa inhibitors into post-procedural antithrombotic regimens to enhance limb salvage and improve vascular outcomes in this high-risk population. Further prospective trials are warranted to confirm these results and establish evidence-based treatment guidelines.

Conflict of interest: None

Financial disclosures: None

REFERENCES

- [1] Stacy Z. Peripheral Arterial Disease and the Pharmacist's Role in Management. *J Clin Pharm Ther* [Internet]. 2023 Jan 1 [cited 2025 Jun 8];2023(1):2352051. Available from: [/doi/pdf/10.1155/2023/2352051](https://doi/pdf/10.1155/2023/2352051)
- [2] Uccioli L, Meloni M, Izzo V, Giurato L, Merolla S, Gandini R. Critical limb ischemia: current challenges and future prospects. *Vasc Health Risk Manag* [Internet]. 2018 May 26 [cited 2025 Jun 10]; 14:63. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC5927064/>
- [3] Duff S, Mafilios MS, Bhounsule P, Hasegawa JT. The burden of critical limb ischemia: a review of recent literature. *Vasc Health Risk Manag* [Internet]. 2019 [cited 2025 Jun 10]; 15:187. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC6617560/>
- [4] Kinlay S. Management of Critical Limb Ischemia. *Circ Cardiovasc Interv* [Internet]. 2016 Feb 1 [cited 2025 Jun 10];9(2): e001946. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC4827334/>
- [5] Aleem S, Parikh P, Bhasin V, Pyo RT. Interventional Approach in Small Vessel, Diffuse, and Tortuous Coronary Artery Disease. *Interv Cardiol (Lond)* [Internet]. 2022 Jun 3 [cited 2025 Jun 10];228–36. Available from: [/doi/pdf/10.1002/9781119697367.ch20](https://doi/pdf/10.1002/9781119697367.ch20)
- [6] Waters RE, Kandzari DE, Phillips HR, Crawford LE, Sketch MH. Late thrombosis following treatment of in-stent restenosis with drug-eluting stents after discontinuation of antiplatelet therapy. *Catheterization and Cardiovascular*

- Interventions [Internet]. 2005 Aug [cited 2025 Jun 10];65(4):520–4. Available from: <https://pubmed.ncbi.nlm.nih.gov/15973673/>
- [7] Wassif H, Welt FGP. Restenosis of Stented Coronary Arteries. SCAI Interventional Cardiology Board Review: Second Edition [Internet]. 2023 Aug 8 [cited 2025 Jun 10];10–5. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK545139/>
 - [8] Thott O, Granath F, Malmstedt J, Wahlgren CM. Editor's Choice – Dual Antiplatelet Therapy Improves Outcome in Diabetic Patients Undergoing Endovascular Femoropopliteal Stenting for Critical Limb Ischaemia. *European Journal of Vascular and Endovascular Surgery* [Internet]. 2017 Mar 1 [cited 2025 Jun 10];53(3):403–10. Available from: <https://www.sciencedirect.com/science/article/pii/S1078588416306438>
 - [9] Mehta N, Samat D. The Balancing Act: A Rational Approach to Postintervention Dual Antiplatelet Therapy. *J Assoc Physicians India* [Internet]. 2024 Nov 1 [cited 2025 Jun 10];72(11):11–3. Available from: <https://pubmed.ncbi.nlm.nih.gov/39563109/>
 - [10] Mehran R, Baber U, Sharma SK, Cohen DJ, Angiolillo DJ, Briguori C, et al. Ticagrelor with or without Aspirin in High-Risk Patients after PCI. *New England Journal of Medicine* [Internet]. 2019 Nov 21 [cited 2025 Jun 10];381(21):2032–42. Available from: <https://www.nejm.org/doi/pdf/10.1056/NEJMoa1908419>
 - [11] Qiao M, Bi Q, Fu P, Wang Y, Song Z, Guo F. Previous hypertensive hemorrhage increases the risk for bleeding and ischemia for PCI patients on dual antiplatelet therapy. *Neurol Res* [Internet]. 2017 Jun 3 [cited 2025 Jun 10];39(6):516–20. Available from: <https://pubmed.ncbi.nlm.nih.gov/28431474/>
 - [12] Hawkins D. Clinical trials with factor Xa inhibition in the prevention of postoperative venous thromboembolism. *Am J Health Syst Pharm* [Internet]. 2003 [cited 2025 Jun 10];60(22 Suppl 7). Available from: <https://pubmed.ncbi.nlm.nih.gov/14650860/>
 - [13] Bonaca MP, Szarek M, Debus ES, Nehler MR, Patel MR, Anand SS, et al. Efficacy and safety of rivaroxaban versus placebo after lower extremity bypass surgery: A post hoc analysis of a “CASPAR like” outcome from VOYAGER PAD. *Clin Cardiol* [Internet]. 2022 Dec 1 [cited 2025 Jun 10];45(12):1143–6. Available from: <https://pubmed.ncbi.nlm.nih.gov/36251249/>
 - [14] Kruger PC, Anand SS, de Vries TAC, Eikelboom JW. Patients with Peripheral Artery Disease in the COMPASS Trial. *European Journal of Vascular and Endovascular Surgery* [Internet]. 2018 Dec 1 [cited 2025 Jun 10];56(6):772–3. Available from: <https://www.ejves.com/action/showFullText?pii=S1078588418305380>
 - [15] Biagioni RB, Lopes RD, Agati LB, Sacilotto R, Wolosker N, Sobreira ML, et al. Rationale and design for the study Apixaban versus Clopidogrel on a background of aspirin in patients undergoing InfraPopliteal angioplasty for critical limb ischemia: AGRIPPA trial. *Am Heart J* [Internet]. 2020 Sep 1 [cited 2025 Jun 10]; 227:100–6. Available from: <https://pubmed.ncbi.nlm.nih.gov/32730905/>
 - [16] Anand SS, Bosch J, Eikelboom JW, Connolly SJ, Diaz R, Widimsky P, et al. Rivaroxaban with or without aspirin in patients with stable peripheral or carotid artery disease: an international, randomised, double-blind, placebo-controlled trial. *The Lancet* [Internet]. 2018 Jan 20 [cited 2025 Aug 24];391(10117):219–29. Available from: <https://pubmed.ncbi.nlm.nih.gov/29132880/>
 - [17] Berger JS, Katona BG, Jones WS, Patel MR, Norgren L, Baumgartner I, et al. Design and rationale for the Effects of Ticagrelor and Clopidogrel in Patients with Peripheral Artery Disease (EUCLID) trial. *Am Heart J* [Internet]. 2016 May 1 [cited 2025 Jun 10]; 175:86–93. Available from: <https://www.sciencedirect.com/science/article/pii/S000287031600034X>
 - [18] Bhatt DL, Fox KAA, Hacke W, Berger PB, Black HR, Boden WE, et al. Clopidogrel and Aspirin versus Aspirin Alone for the Prevention of Atherothrombotic Events. *New England Journal of Medicine* [Internet]. 2006 Apr 20 [cited 2025 Jun 10];354(16):1706–17. Available from: <https://www.nejm.org/doi/pdf/10.1056/NEJMoa060989>
 - [19] Abramson BL, Al-Omran M, Anand SS, Albalawi Z, Coutinho T, de Mestral C, et al. Canadian Cardiovascular Society 2022 Guidelines for Peripheral Arterial Disease. *Canadian Journal of Cardiology* [Internet]. 2022 May 1 [cited 2025 Jun 10];38(5):560–87. Available from: <https://onlinecjc.ca/action/showFullText?pii=S0828282X22001568>
 - [20] Petrie JR, Guzik TJ, Touyz RM. Diabetes, Hypertension, and Cardiovascular Disease: Clinical Insights and Vascular Mechanisms. *Can J Cardiol* [Internet]. 2018 May 1 [cited 2025 Jun 10];34(5):575. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC5953551/>

- [21] Liu Y, Li J, Dou Y, Ma H. Impacts of type 2 diabetes mellitus and hypertension on the incidence of cardiovascular diseases and stroke in China real-world setting: a retrospective cohort study. *BMJ Open* [Internet]. 2021 Nov 29 [cited 2025 Jun 10];11(11): e053698. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC8634005/>
- [22] Agnelli G, Buller HR, Cohen A, Curto M, Gallus AS, Johnson M, et al. Oral apixaban for the treatment of acute venous thromboembolism. *Zeitschrift fur Gefassmedizin* [Internet]. 2013 Aug 29 [cited 2025 Jun 10];10(3):25–6. Available from: <https://www.nejm.org/doi/pdf/10.1056/NEJMoa1302507>
- [23] Budovich A, Zargarova O, Nogid A. Role of Apixaban (Eliquis) in the Treatment and Prevention of Thromboembolic Disease. *Pharmacy and Therapeutics* [Internet]. 2013 Apr [cited 2025 Jun 10];38(4):206. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC3684191/>
- [24] Baklola M, Elmahdi RR, Ali S, Elshenawy M, Mossad AM, Al-Bawah N, et al. Artificial intelligence in disease diagnostics: a comprehensive narrative review of current advances, applications, and future challenges in healthcare. *Annals of Medicine and Surgery* [Internet]. 2025 Jul [cited 2025 Aug 24];87(7):4237. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC12369792/>
- [25] Terra M, Badr A, Baklola M, Hegazy I, Elmanzlawey M, Elrakhawy I, et al. Prevalence of adherence and its impact on quality of life in oral anticoagulant users in Egypt: A cross-sectional study from two Egyptian university hospitals. *BMC Cardiovasc Disord* [Internet]. 2025 Dec 1 [cited 2025 Aug 24];25(1). Available from: <https://pubmed.ncbi.nlm.nih.gov/39922992/>.