Rivaroxaban Plus Aspirin vs Dual Antiplatelet Therapy in Endovascular Treatment in Peripheral Artery Disease and Analysis of Medication Utilization of different Lesioned vascular regions

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Article

Keywords:

Posted Date: September 27th, 2023

DOI: https://doi.org/10.21203/rs.3.rs-3340132/v1

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Additional Declarations: No competing interests reported.
Abstract

Background

Peripheral arterial disease (PAD) necessitates administration of anticoagulant or antiplatelet medications. Dual antiplatelet therapy (DAPT) and rivaroxaban show promise in reducing adverse outcomes. Heterogeneity in lower limb artery pathology may calls for personalized treatment strategies.

METHODS

In a single-center retrospective study, pharmacotherapy in peripheral artery disease involved aspirin plus rivaroxaban 5 mg twice daily or aspirin plus clopidogrel 75 mg once daily. The primary efficacy outcome was a composite of Rutherford classification increase, acute limb ischemia, amputation for vascular reasons, target lesion revascularization, myocardial infarction, ischemic stroke, and cardiovascular death. The primary safety outcome was major bleeding, defined according to the Thrombolysis in Myocardial Infarction (TIMI) classification; major bleeding as defined by the International Society on Thrombosis and Haemostasis (ISTH) was a secondary safety outcome. Two subgroups analyzed: suprapatellar and infrapatellar arterial lesion-only patients.

Results

From January 2016 to December 2021, 455 patients received clopidogrel plus aspirin or rivaroxaban plus aspirin after endovascular treatment (EVT). Rivaroxaban group (n=220) had lower primary efficacy outcome incidence (49.1% vs 60.4%, hazard ratio (HR) 0.77, P=0.006), but more TIMI major bleeding events (5.9% vs 2.1%, HR 2.6, P=0.04). ISTH major bleeding events did not significantly differ, though more rivaroxaban patients discontinued medication due to bleeding (10% vs 4.7%, HR 2.2, P=0.03). In suprapatellar subgroup, rivaroxaban group had lower primary efficacy outcome incidence (28.2% vs 45.2%, HR 0.55, P=0.02). In infrapatellar subgroup, no significant difference was found in the occurrence of primary efficacy events between the two groups (58.7% vs 64.8%, HR 0.76, P=0.14).

Conclusion

Rivaroxaban plus aspirin improved outcomes compared to DAPT in lower extremity artery disease. Similar findings were seen in the suprapatellar artery lesion-only group. In the infrapatellar artery lesion-only group, rivaroxaban plus aspirin did not outperform DAPT. Safety-wise, Rivaroxaban plus aspirin had higher bleeding risks and treatment discontinuation compared to aspirin plus clopidogrel.

Introduction

Peripheral arterial disease (PAD) is considered a consequence of systemic atherosclerosis, presenting with cardiovascular symptoms and limb-related events. However, recent evidence indicates that PAD has distinct characteristics compared to coronary and cerebral artery diseases. It carries a higher risk of adverse limb events, including acute limb ischemia and amputation, as well as major cardiovascular
events. These outcomes are often linked to specific high-risk factors unique to PAD.\(^1, 2\). Peripheral arterial disease can cause various symptoms, from intermittent claudication that restricts daily activities to severe forms of limb-threatening ischemia that require revascularization to prevent or limit tissue necrosis \(^3, 4\). While surgical interventions can be successful in treating certain conditions, it has become increasingly evident through treatment experience that relying solely on surgery does not guarantee sustained positive outcomes. Thus, long-term administration of anticoagulant or antiplatelet medications may be necessary to ensure the maintenance of positive results over time \(^5-9\). For many years, antiplatelet therapy has been regarded as the primary treatment option for acute and chronic disorders affecting the coronary and peripheral arteries \(^10-12\). Subsequent research has demonstrated that dual antiplatelet therapy, comprising acetylsalicylic acid and clopidogrel, leads to a decreased incidence of thrombotic events in patients with acute coronary syndromes and those undergoing percutaneous coronary interventions when compared to acetylsalicylic acid monotherapy \(^13, 14\). This observation resulted in a shift in the treatment paradigm. However, subsequent studies have demonstrated that despite treatment with the most potent P2Y12 inhibitors, about one in ten patients experience recurrent thrombotic events within the first year after an acute coronary syndrome event \(^15\). This suggests that other mechanisms beyond platelet function may contribute to thrombosis development \(^13, 16, 17\), questions still remain regarding the most effective antithrombotic therapy for the long-term management of chronic vascular diseases. Dual antiplatelet therapy in peripheral arterial disease is commonly used but lacks strong evidence, primarily relying on observational studies or extrapolation from trials in coronary artery disease, which focused on cardiovascular outcomes and stent thrombosis rather than limb prognosis \(^12, 17, 18\). In clinical practice, the rate of stenosis following percutaneous angioplasty in the femoral popliteal region using conventional treatment (dual antiplatelet therapy) varies from 17% to over 40%, with the probability of stenosis increasing with the length of the lesion \(^19-21\). The treatment effect is significantly unsatisfactory.

Rivaroxaban is a type of selective factor Xa inhibitor used to prevent and treat venous thrombosis, as well as prevent stroke and thromboembolism in individuals with atrial fibrillation \(^22\). In the COMPASS trial, which included a significant number of patients who had undergone lower extremity revascularization, almost 20% of patients in the placebo group experienced a primary composite outcome consisting of acute limb ischemia, major amputation for vascular reasons, myocardial infarction, ischemic stroke, or death from cardiovascular causes within three years. However, the addition of rivaroxaban (2.5 mg twice daily) to aspirin (100 mg once daily) reduced the risk of such outcomes by approximately 15% \(^23\). This combination of rivaroxaban at a dose of 2.5 mg twice daily with aspirin has been approved by several international organizations and is increasingly being utilized and integrated into current international guidelines \(^11, 12\).

Lower extremity vascular diseases represent a significant category of peripheral vascular diseases, with distinct pathological characteristics that can vary across different vascular segments. \(^24, 25\). Our clinical observations indicate that lower limb arterial lesions in the femoral and popliteal arteries exhibit a higher burden of atheromatous plaque, while thrombosis is not the primary cause of limb ischemia. In contrast, infrapopliteal artery lesions are characterized by a more severe thrombotic load but less severe
atherosclerotic pathology. These distinct pathological features suggest different disease progressions, with greater wall damage observed in the femoral and popliteal arteries. Restenosis and vascular access loss after Endovascular Therapy (EVT) primarily result from catheter-induced endothelial injury, leading to platelet activation and coagulation factor activation. (26, 27), Considering the diverse pathological characteristics and varying degrees of tubular wall structural disruption, it may not be appropriate to adopt a uniform postoperative drug strategy.

Methods

Study design

The inclusion criteria for this retrospective study, conducted at a single center, were as follows: age greater than 40 years, clinical evidence of percutaneous transluminal angioplasty for lower extremity atherosclerotic ischemia, including symptoms such as limitation of ambulatory function, intermittent claudication, and ischemic ulceration, imaging evidence of lumen restriction from the iliac to the distal artery within the past year, a history of successful angioplasty without procedural complications, a preoperative Rutherford classification limited to grades 2-5, target lesion segment stenosis greater than 70% or occlusive lesion, and no history of lower extremity arterial revascularization. The exclusion criteria for the study were asymptomatic patients with mild or no intermittent claudication, preoperative extensive ischemic necrosis of the affected limb, use of antiplatelet agents other than clopidogrel or aspirin or anticoagulants other than rivaroxaban, allergy or serious adverse reactions to P2Y12 blockers, severe hepatic disease affecting the anticoagulation pathway and risk of bleeding, renal insufficiency with creatinine clearance less than 30 mL/min, intraoperative angiography suggestive of distal vascular embolism, and a life expectancy of less than 5 years.

The study had primary and secondary endpoints. The primary endpoints included increase in Rutherford classification by at least one grade compared to the post-angioplasty classification, acute limb ischemia, amputation for vascular reasons, target lesion revascularization, myocardial infarction, ischemic stroke, cardiovascular death. The secondary study endpoints included an increase in Rutherford classification by at least one grade over post-angioplasty, acute limb ischemia, amputation for vascular reasons, target lesion revascularization, myocardial infarction, ischemic stroke, death from cardiovascular causes, fatal heart disease, coronary or peripheral arterial thrombotic events, coronary or peripheral artery requiring revascularization.

The primary safety endpoint of the study was major bleeding based on the TIMI criteria, while the secondary safety endpoint was bleeding events following the criteria set by the ISTH (28, 29).

Clinical data were retrospectively collected from inpatient medical records. Prior to surgery, patients received subcutaneous administration of 4000 units of low molecular weight heparin twice daily, except in cases of contraindications. During surgery, local anesthesia, intravenous sedation, and analgesia were provided, along with systemic heparinization. Femoral artery puncture was performed based on the target
lesion location, using appropriate guidewires and catheters. Balloon angioplasty and stenting were performed as deemed necessary. Postoperatively, patients were prescribed either rivaroxaban 5 mg twice daily plus aspirin 100 mg once daily or clopidogrel 75 mg once daily plus aspirin 100 mg once daily orally. Subgroup analysis focused on patients with supra- and infrapopliteal artery lesions to evaluate treatment efficacy and pathological characteristics’ impact. Survival analysis was conducted to assess differences in outcomes and investigate underlying factors. Medication adherence was monitored for at least one year.

The prospective patient follow-up, data acquisition, and organization in this study were conducted with the explicit consent of the participants and received ethical approval from the Institutional Review Board of the First Affiliated Hospital, Chongqing Medical University. The oversight of data integrity and participant safety was entrusted to an independent Data Monitoring Committee comprising researchers impartial to the study’s sponsors. Additionally, a Clinical Events Committee, composed of expert clinicians from the First Affiliated Hospital, Chongqing Medical University, performed blinded assessments to determine bleeding events and clinical outcomes, ensuring unbiased evaluation. Although this study was a low-risk retrospective cohort study, in accordance with the requirements of the Ethics Committee of the First Affiliated Hospital of Chongqing Medical University, we still drafted an informed consent form for patients and confirmed that informed consent was obtained from all participants and/or their legal guardians. This research was conducted in line with the Declaration of Helsinki and involved the analysis of anonymized data.

**Statistic Analysis**

SPSS 26.0 software was utilized for statistical analysis. Continuous variables were assessed using the Kaplan-Meier K-M analysis. Normally distributed data were expressed as mean (± standard deviation) and analyzed with independent samples t-test for between-group comparisons, and paired t-test for within-group comparisons. Non-normally distributed data were presented as median (P25, P75) and compared using Mann-Whitney U test. Categorical variables were reported as n (%) and analyzed using chi-square test or Fisher's exact test. K-M analysis evaluated one-year postoperative patency, while Cox proportional hazards model assessed influencing factors and estimated hazard ratios with 95% confidence intervals. All p-values were two-sided and derived from log-rank test, with significance set at p<0.05.

**RESULT**

**Patients**

528 symptomatic PAD patients (Rutherford category 2–5) were screened for eligibility to participate in the study; of these, 73 did not meet criteria for inclusion. A total of 455 patients satisfying the predetermined inclusion criteria were included in the study (127 women, 328 men; mean age 74.5 ± 9.3 years; range 44-
95 years). And, 220 patients received rivaroxaban plus aspirin, and 235 patients received clopidogrel plus aspirin as postoperative medication as illustrated in Figure 1. Data were collected at two-month intervals during a 12-month follow-up period. Baseline characteristics were balanced between groups and subgroups. Preoperative symptoms included intermittent claudication (60.8%), resting pain (20.8%), and minor tissue loss (18.4%). Comorbidities included diabetes (48.1%), hypertension (59.1%), coronary artery disease (29%), and ACEI/ARB medication use (58.5%). Hyperlipidemia was present in 65.3% of patients at admission, with 65.1% taking statins. Additionally, 57.8% were smokers before admission. Baseline patient characteristics are presented in Table.

Efficacy EndPoints

Primary Efficacy Outcome

Significant differences were observed in the Primary Efficacy Outcome events between the rivaroxaban and dual-antiplatelet groups (Figure 2A). The primary composite efficacy outcome occurred in 108 out of 220 (49.1%) patients receiving rivaroxaban and 142 out of 235 (39.2%) patients receiving dual-antiplatelet therapy (HR 0.70, 95% CI 0.55-0.90, p=0.006) (Table). Significant disparities were observed between the groups in terms of Rutherford classification escalation, a robust indicator of lower limb outcomes, and incidence of target lesion revascularization (TLR). The proportion of patients with a one-year increase in Rutherford grade of at least one level was 35.5% in the rivaroxaban group and 45.1% in the dual-antiplatelet group (HR 0.72, 95% CI 0.54-0.97, p=0.03) (Figure 3). The incidence of TLR events at one year was 16.8% in the rivaroxaban group and 27.8% in the dual-antiplatelet group (HR 0.58, 95% CI 0.38-0.86, p=0.007) (Figure 3). No statistically significant differences were observed between the groups for other efficacy endpoints (Table).

Secondary Efficacy Outcomes

Within one year, 122 patients (55.5%) in the rivaroxaban group and 156 patients (66.4%) in the dual-antiplatelet group experienced secondary efficacy composite outcome events (HR 0.73, 95% CI 0.58-0.93, p=0.01) (Table). The incidence of secondary key efficacy outcome events, which serves as a comprehensive measure of lower limb outcomes, including a one-level increase in Rutherford classification, target vessel recanalization, amputation for vascular reasons, and acute limb ischemia, was lower in the rivaroxaban group (45.9%) compared to the dual-antiplatelet group (56.2%) (HR 0.75, 95% CI 0.58-0.97, p=0.03) (Figure 3). However, no significant differences were observed between the two groups for other secondary outcome events (Table).

Safety EndPoints
The primary safety endpoint event, TIMI major bleeding, occurred in 5.9% of patients in the rivaroxaban group and 2.1% in the dual-antiplatelet group after one year (HR 2.6, 95% CI 0.9-7.3, p=0.04)(Table ). No significant differences were observed in other primary safety outcome events, such as intracranial hemorrhage or fatal bleeding. However, significant differences were observed in the secondary safety outcome of temporary or permanent discontinuation due to bleeding(Table ). After one year, 10% of patients in the rivaroxaban group experienced bleeding leading to discontinuation, compared to 4.7% in the dual-antiplatelet group (HR 2.2, 95% CI 1.1-4.5, p=0.03)(Table ).

Subgroup Analyses

The study compared the efficacy of the anticoagulant rivaroxaban plus aspirin and clopidogrel plus aspirin after surgery for suprapopliteal and infrapopliteal lesions.

In the subgroup analysis of patients with suprapatellar artery lesions, the rivaroxaban group demonstrated a statistically significant decrease in the occurrence of the primary efficacy outcome and secondary efficacy outcome compared to the dual-antiplatelet group. Conversely, in the subgroup of patients with infrapatellar artery lesions, the rivaroxaban group did not exhibit a significant advantage in terms of the primary efficacy outcome(Figure 3). Subgroup analysis showed that the primary composite outcome event occurred in 22 patients (28.2%) in the rivaroxaban group and in 38 patients (45.2%) in the dual-antiplatelet therapy group in the suprapatellar lesion alone group (HR, 0.55; 95% CI, 0.32–0.92; P=0.02)(Figure 2B).

In contrast, in the infrapatellar lesion alone group, the primary composite outcome event occurred in 54 patients (58.7%) in the rivaroxaban group and in 59 patients (64.8%) in the dual-antibody group (HR, 0.76; 95% CI, 0.52–1.09;P=0.14)(Figure 2C), and the difference between the two groups was not statistically significant. For the secondary efficacy composite outcome events, 62 patients (66%) in the rivaroxaban group and 65 patients (71.4%) in the dual-antibody group experienced these events (HR, 0.79; 95% CI, 0.56–1.12;P=0.18)(Table ) in the infrapatellar lesion alone group. In contrast, in the suprapatellar lesion alone group, 27 patients (35.1%) in the rivaroxaban group and 47 patients (55.3%) in the dual-antibody group experienced the secondary critical composite events (HR, 0.56; 95% CI, 0.35–0.90;P=0.02)(Table ).

Discussion

The study findings suggest that the specific pathological characteristics of above-knee and below-knee arterial lesions have a significant impact on the choice of post-EVT medication. In this single-center retrospective study, the combination of rivaroxaban and aspirin demonstrated greater efficacy in preventing adverse limb outcomes in lower extremity atherosclerosis compared to dual antiplatelet therapy. Subgroup analysis confirmed the superiority of rivaroxaban in patients with isolated suprapopliteal artery lesions, while no significant differences were observed for isolated infrapopliteal artery lesions. The addition of low-dose rivaroxaban improved prognostic outcomes for lower extremity atherosclerosis involving the superior knee artery.
The superior and inferior knee arteries demonstrate distinctive postoperative pathological characteristics. Studies investigating the pathological characteristics of above-knee and below-knee vessels in limbs amputated due to chronic limb ischemia have shown that below-knee arteries commonly experience thrombotic lumen occlusion with mild atherosclerosis, whereas above-knee arteries often exhibit lumen occlusion caused by pathological intimal thickening, atherofibrosis, and fibrous calcified lesions. (24, 30). The extent of damage to the vessel wall varies during surgical procedures, including balloon dilation and stent placement, depending on plaque loads and wall pathologies(31, 32). The variability in pathological characteristics may influence the choice of post-EVT drug regimens for distinct vascular regions. Consequently, we opted to create subgroups comprising solely suprapopliteal lesions and infrapopliteal lesions. Our objective was to assess this concept by comparing the effectiveness of the two drug regimens within each subgroup. In the VOYAGER PAD trial, the combination of 2.5 mg of rivaroxaban and 100 mg of aspirin resulted in a significant reduction in major adverse cardiovascular events and major adverse limb events, including major amputations, compared to aspirin alone. This treatment regimen was corroborated by a study involving over 6,500 patients with lower extremity arterial occlusion, confirming its efficacy(33). The VOYAGER PAD trial and this study share the similarity that the combination of rivaroxaban and aspirin as post-EVT medication reduces the occurrence of adverse limb events compared to other treatment approaches. However, unlike the VOYAGER PAD trial, this study conducted subgroup analysis based on the involved vascular regions and found that in cases of isolated below-knee artery lesions, neither treatment approach showed statistical significance in reducing adverse limb events.

Based on the subgroup analysis results, the following inferences are drawn. Thrombin's role is more prominent in stabilizing formed thrombi rather than initiating their formation(34) and platelet significantly contribute to the initiation and progression of atherosclerotic lesions, as well as the eventual development of thrombotic complications (atherothrombosis) following erosion or rupture of atherosclerotic plaques in both suprapopliteal and infrapopliteal arterial lesions(35, 36). While thrombin's role in acute arterial thrombosis is secondary to platelets, primarily involved in thrombus stabilization(34). Thus antiplatelet therapy is crucial in the postoperative management of endovascular treatment (EVT). In the infrapopliteal artery, characterized by narrower diameter, slower blood flow, lower plaque burden, and fewer instances of wall disruption, platelet activation is dominant in thrombus formation(30). Factor Xa, responsible for thrombin formation, also contributes to inflammation, vascular remodeling, plaque progression, and tissue fibrosis(37, 38), which means factor Xa inhibition assumes particular significance in the superior knee artery, characterized by surgically-induced inflammation and severe plaque erosion. Our hypothesis posits that factor Xa plays a more substantial role in the thrombosis and stabilization of suprapopliteal artery lesions in comparison to the less atherosclerotic infrapopliteal artery. Adequate antiplatelet therapy plays a crucial role in the management of infrapopliteal artery lesions. Patients presenting solely with infrapopliteal artery lesions exhibited a comparable prognosis when receiving adequate antiplatelet therapy using either regimen; however, dual antiplatelet therapy without factor Xa inhibition proved less effective than rivaroxaban in the treatment of postoperative EVT patients with superior knee artery lesions.
Given the limited one-year follow-up period in this study, it is plausible that the occurrence of adverse limb events, as utility outcomes, may have been insufficiently captured within the designated timeframe. To enhance the sensitivity of patient outcome assessment, this study incorporated an additional level of Rutherford classification into the utility outcome. This allowed for a more sensitive evaluation of patient prognosis compared to relying solely on adverse limb events, which primarily serve as a staging index for lower extremity arterial disease, further improving the sensitivity of outcome measurement. Previous studies commonly employed adverse limb events, including target lesion revascularization (TLR), acute limb ischemia, and major amputation for vascular causes, as utility outcomes to evaluate the impact of post-endovascular treatment (EVT) medication on lower limb outcomes, and this study did not solely rely on the occurrence of acute limb ischemia and target lesion revascularization (TLR) as indicators of adverse events.

The study revealed a higher incidence of TIMI major bleeding, the primary safety endpoint, in the rivaroxaban group (5.9%) compared to the dual-antiplatelet group (2.1%) after one year (HR 2.6, 95% CI 0.9-7.3, p=0.04). No significant differences were observed in intracranial hemorrhage or fatal bleeding. No significant differences in ISTH major bleeding, a secondary safety outcome, were observed between the two groups. However, the rivaroxaban group had a significantly higher rate of discontinuation due to bleeding (10% vs. 4.7%, HR 2.2, 95% CI 1.1-4.5, p=0.03). These findings suggest an increased risk of major bleeding and treatment discontinuation associated with rivaroxaban use, warranting careful consideration of the benefits and bleeding risks in clinical decision-making. Despite the higher bleeding risk, the rivaroxaban group did not demonstrate significant efficacy superiority over the dual-antiplatelet group in the isolated infrapopliteal artery lesions subgroup, based on the subanalysis results.

**Limitations**

There are several methodological limitations in our trial that warrant discussion. Firstly, it is important to acknowledge that this study served as a proof-of-concept investigation, comparing the efficacy of two postoperative endovascular treatment (EVT) drugs and exploring appropriate dosing strategies for different vascular disease areas. However, the sample size of our study was insufficient for a formal statistical analysis of safety and efficacy, particularly within subgroups. Hence, larger-scale studies are required to validate the findings obtained in this study. Furthermore, as this study is retrospective, despite our efforts to ensure adequate follow-up, it is inevitable that some utility and safety events may have been missed, potentially influencing the final experimental results. Additionally, the results presented within the subgroups are based solely on inferred mechanisms and lack the support of underlying experimental evidence.

**Conclusion**

In patients with symptomatic suprapatellar artery disease who underwent endovascular treatment (EVT), the addition of 5 mg rivaroxaban to twice-daily aspirin reduced composited adverse outcomes, including
increased Rutherford classification, angioplasty, acute limb ischemia, amputation, revascularization, myocardial infarction, stroke, and cardiovascular-related mortality. These findings were consistent in the suprapatellar artery lesion-only group. However, the rivaroxaban plus aspirin regimen did not demonstrate superiority over dual-antiplatelet therapy in the infrapatellar artery lesion-only group. In terms of safety, rivaroxaban plus aspirin showed a higher incidence of major bleeding and more treatment discontinuation due to bleeding compared to aspirin plus clopidogrel.

**Declarations**

**Data Availability**

Due to some patients' reluctance to disclose their personal information, and in adherence to the principle of protecting patient privacy, the dataset generated and analyzed during the current study is not publicly available. However, upon reasonable request, it can be obtained from the corresponding author.

**References**


**Tables**

Table 1. Baseline Characteristics of the Patients.*
<table>
<thead>
<tr>
<th>Variable</th>
<th>Rivaroxaban</th>
<th>DAPT</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (IQR) - yr</td>
<td>77</td>
<td>76</td>
<td>0.40</td>
</tr>
<tr>
<td>Female sex-no. (%)</td>
<td>53 24.1</td>
<td>51 21.7</td>
<td>0.54</td>
</tr>
<tr>
<td>Median body-mass index(IQR)†</td>
<td>25.6(21.8,29.3)</td>
<td>25.6(22.3,28.9)</td>
<td>0.90</td>
</tr>
<tr>
<td>Diabetes-no. (%)</td>
<td>106 48.2</td>
<td>113 48.1</td>
<td>0.98</td>
</tr>
<tr>
<td>Smoking-no. (%)</td>
<td></td>
<td></td>
<td>0.67</td>
</tr>
<tr>
<td>Current</td>
<td>128(58.2)</td>
<td>134(57.0)</td>
<td></td>
</tr>
<tr>
<td>Former</td>
<td>18(8.2)</td>
<td>25(10.6)</td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>74(33.6)</td>
<td>76(32.3)</td>
<td></td>
</tr>
<tr>
<td>Alcohol use-no. (%)</td>
<td></td>
<td></td>
<td>0.16</td>
</tr>
<tr>
<td>Never</td>
<td>129(58.6)</td>
<td>117(49.8)</td>
<td></td>
</tr>
<tr>
<td>Rarely</td>
<td>34(15.5)</td>
<td>42(17.9)</td>
<td></td>
</tr>
<tr>
<td>Currently consumes</td>
<td>57(25.9)</td>
<td>76(32.3)</td>
<td></td>
</tr>
<tr>
<td>Baseline CrCl, mg/dL-no. (%)</td>
<td></td>
<td></td>
<td>0.27</td>
</tr>
<tr>
<td>≤ 50</td>
<td>9(4.0)</td>
<td>20(3.8)</td>
<td></td>
</tr>
<tr>
<td>&gt;50 and &lt;80</td>
<td>91(41.4)</td>
<td>97(41.3)</td>
<td></td>
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<tr>
<td>≥80</td>
<td>120(54.5)</td>
<td>118(50.2)</td>
<td></td>
</tr>
<tr>
<td>&gt;95</td>
<td>41(18.6)</td>
<td>43(18.3)</td>
<td></td>
</tr>
<tr>
<td>Hypertension-no. (%)</td>
<td>127(57.7)</td>
<td>142(60.4)</td>
<td>0.56</td>
</tr>
<tr>
<td>Cardiovascular disease-no. (%)‡</td>
<td>60(27.3)</td>
<td>72(30.6)</td>
<td>0.43</td>
</tr>
<tr>
<td>Carotid artery disease-no. (%)</td>
<td>59(26.8)</td>
<td>72(30.6)</td>
<td>0.37</td>
</tr>
<tr>
<td>Hyperlipidemia-no. (%)</td>
<td>142(64.5)</td>
<td>155(66.0)</td>
<td>0.75</td>
</tr>
<tr>
<td>Cholesterol, mmol/L(IQR)</td>
<td>4.3(3.1,5.5)</td>
<td>4.5(3.5,5.6)</td>
<td>0.15</td>
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<tr>
<td>HDL cholesterol, mmol/L(IQR)</td>
<td>1.4(0.5,2.3)</td>
<td>1.4(0.9,1.9)</td>
<td>0.36</td>
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<tr>
<td>LDL cholesterol, mmol/L(IQR)</td>
<td>2.5(1.0,4.0)</td>
<td>2.5(1.3,3.7)</td>
<td>0.58</td>
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<tr>
<td>Rutherford category-no. (%)</td>
<td></td>
<td></td>
<td>0.90</td>
</tr>
<tr>
<td>2</td>
<td>2(0.9)</td>
<td>3(0.7)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>130(59.1)</td>
<td>274(60.1)</td>
<td></td>
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<tr>
<td>4</td>
<td>43(19.5)</td>
<td>95(20.8)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>45(20.5)</td>
<td>84(18.4)</td>
<td></td>
</tr>
<tr>
<td>Lesion location-no. (%)§</td>
<td>0.62</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------------------------</td>
<td>-----</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Limited to suprapopliteal artery</td>
<td>78(35.9)</td>
<td>84(35.9)</td>
<td></td>
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<tr>
<td>Limited to Infrapopliteal artery</td>
<td>92(42.4)</td>
<td>91(38.9)</td>
<td></td>
</tr>
<tr>
<td>Entire lower extremity arterial</td>
<td>47(21.7)</td>
<td>59(25.2)</td>
<td></td>
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<tr>
<td>Lesion length, cm(IQR)</td>
<td>21.4(8.0,34.8)</td>
<td>23.5(9.5,37.5)</td>
<td>0.13</td>
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<tr>
<td>Lesion severity-no. (%)</td>
<td>0.16</td>
<td></td>
<td></td>
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<tr>
<td>Stenosis</td>
<td>87(39.5)</td>
<td>78(33.2)</td>
<td></td>
</tr>
<tr>
<td>Occlusion</td>
<td>133(60.5)</td>
<td>157(66.8)</td>
<td></td>
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<tr>
<td>Preoperative ABI(IQR)</td>
<td>0.30(0.16,0.44)</td>
<td>0.28(0.16,0.40)</td>
<td>0.37</td>
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<tr>
<td>Postoperative ABI(IQR)</td>
<td>0.78±0.09</td>
<td>0.77±0.09</td>
<td>0.79</td>
</tr>
<tr>
<td>Stent placement-no. (%)</td>
<td>0.17</td>
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<tr>
<td>Bare metal</td>
<td>57(25.9)</td>
<td>45(19.1)</td>
<td></td>
</tr>
<tr>
<td>Drug-eluting</td>
<td>49(22.3)</td>
<td>64(27.2)</td>
<td></td>
</tr>
<tr>
<td>Balloon placement-no. (%)</td>
<td>0.75</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bare</td>
<td>92(41.8)</td>
<td>90(38.3)</td>
<td></td>
</tr>
<tr>
<td>Drug-coated</td>
<td>120(54.5)</td>
<td>136(57.9)</td>
<td></td>
</tr>
<tr>
<td>Residual stenosis(IQR)</td>
<td>13(7,19)</td>
<td>13(9,17)</td>
<td>0.42</td>
</tr>
<tr>
<td>History of vascular angioplasty-no. (%)</td>
<td>43(19.5)</td>
<td>48(21.1)</td>
<td>0.69</td>
</tr>
<tr>
<td>Statin-no. (%)</td>
<td>142(64.5)</td>
<td>154(65.5)</td>
<td>0.82</td>
</tr>
<tr>
<td>ACE inhibitor or ARB-no. (%)</td>
<td>126(57.3)</td>
<td>140(59.6)</td>
<td>0.62</td>
</tr>
</tbody>
</table>

*There were no significant differences between groups. Percentages may not total 100 because of rounding. Continuous data are presented as the means ± standard deviation if it matches normal distribution) or Median(interquartile range)(if it matches skewed distribution).; categorical data are given as the counts (percentage). Percentages were based on the number of subjects in the column heading as the denominator unless specified otherwise. Abbreviations: ACE denotes angiotensin-converting enzyme;ARB angiotensin-receptor blocker, ABI, ankle-brachial index;CrCl, creatinine clearance; HDL, high-density lipoprotein; LDL, low-density cholesterol IQR denotes interquartile range.

†The body-mass index is the weight in kilograms divided by the square of the height in meters.

‡Cardiovascular disease is defined as myocardial infarction, percutaneous coronary intervention, or coronary artery bypass grafting (CABG).
The term "Limited to suprapopliteal artery" denotes suprapopliteal stenosis (>50%) requires endovascular therapy. Under this condition, infrapopliteal stenosis with maintained luminal patency does not require EVT, preserving distal blood flow. The term "Limited to infrapopliteal artery" encompasses arterial stenosis or occlusion that results in interrupted distal limb blood flow, requiring endovascular therapy (EVT). Under this condition, suprapopliteal artery disease typically presents with stenosis degrees below 50%. The term "Entire lower extremity arterial" denotes the pathological condition in which surgical interventions have been performed on both the suprainguinal and infrapopliteal arteries due to stenosis or occlusion.

Tables II and III are available in the Supplementary Files section.

Figures

Figure 1

Enrollment and Outcomes.
Patients may be excluded from the study due to various factors. The category of "Other reasons" for exclusion encompasses patient non-consent, potential non-adherence, subject's recall ambiguity regarding treatment processes and disease progression, as well as the principal investigator's decision to discontinue the patient's participation in the trial.

**Figure 2**

![Graphs showing survival rates and event occurrences for different treatments.]

**A**
- **Rivaroxaban** vs. **BMT**
- HR (95% CI): 0.70 (0.55–0.90)
- P = 0.046

**B**
- **Rivaroxaban** vs. **BMT**
- HR (95% CI): 0.54 (0.32–0.92)
- P = 0.024

**C**
- **Rivaroxaban** vs. **BMT**
- HR (95% CI): 0.75 (0.52–1.09)
- P = 0.13
Kaplan–Meier Analysis of the Primary Composite Efficacy Outcome.

The primary efficacy outcome was a composite of increase in Rutherford classification by at least one grade compared to the post-angioplasty classification, acute limb ischemia, amputation for vascular reasons, target lesion revascularization, myocardial infarction, ischemic stroke, cardiovascular death. The inset shows the same data on an expanded y axis. Kaplan-Meier curve A assesses survival rate without Events for the primary composite efficacy outcome in lower extremity disease, regardless of suprainguinal or infrapopliteal involvement. Curve B focuses on isolated suprapopliteal artery disease, while Curve C examines isolated infrapopliteal artery disease, both for the primary composite efficacy outcome's event-free survival rate.

**Figure 3**

One-year event rates of all efficacy outcomes, as well as the one-year event rates of the primary efficacy composite outcomes within the subgroups of isolated suprapopliteal disease and isolated infrapopliteal disease.
Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Table2and3.docx