Efficacy of Aspirin and Low-Dose Rivaroxaban in Chronic Limb-Threatening Ischemia Under Different Comorbid Conditions

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Abstract

Background: Chronic limb-threatening ischemia (CLTI) in patients with diabetic angiopathy and peripheral atherosclerotic disease is associated with severe thrombotic burden, endothelial dysfunction, impaired distal perfusion, and high risk of restenosis after infra-popliteal revascularization. The coexistence of diabetes mellitus and atherosclerosis further increases vascular complications and negatively affects long-term limb outcomes.

Aim: The aim of the study was to evaluate the effectiveness of aspirin combined with low-dose rivaroxaban in comparison with other antithrombotic regimens in patients with chronic limb-threatening ischemia under different comorbid conditions.

Materials and Methods: A total of **120 patients** with infra-popliteal peripheral arterial disease and chronic limb-threatening ischemia were included in the study.

Patients were divided into **four treatment groups (30 patients each)** according to postprocedural antithrombotic regimen:

- **Group I:** aspirin + clopidogrel
- **Group II:** aspirin + rivaroxaban 20 mg once daily
- **Group III:** aspirin + rivaroxaban 2.5 mg twice daily
- **Group IV:** aspirin + clopidogrel + rivaroxaban 2.5 mg twice daily

Additional subgroup analysis was performed according to comorbid background:

- isolated diabetes mellitus
- combined diabetes mellitus and atherosclerosis
- isolated atherosclerosis

Outcomes included thrombotic events, reocclusion, repeated intervention, ABI, primary patency, and restenosis.

Results

In patients with isolated diabetes mellitus or isolated atherosclerosis, differences between treatment groups were relatively modest.

The most pronounced differences were observed in patients with **combined diabetes mellitus and atherosclerosis**.

In this subgroup, **Group III demonstrated the best results**:

- **ABI: 0.80 ± 0.13**
- **Primary patency: 86.7%**
- **Restenosis: 10.0%**
- **Thrombotic events: 6.7%**

In contrast, **Group IV showed the highest thrombotic burden (50.0%)**, while **Group I demonstrated the lowest ABI and primary patency**.

Conclusion

The combination of **aspirin and low-dose rivaroxaban** demonstrated the most favorable vascular outcomes, particularly in patients with coexistence of diabetes mellitus and atherosclerosis, where thrombotic burden is highest.

Keywords: Chronic limb-threatening ischemia; diabetes mellitus; atherosclerosis; adual pathway inhibition; peripheral arterial disease; infra-popliteal intervention;

Introduction

Chronic limb-threatening ischemia (CLTI) represents the most advanced clinical stage of peripheral arterial disease and is associated with high risks of limb loss, recurrent vascular intervention, and cardiovascular mortality [1,2,3].

In patients with **diabetes mellitus**, infra-popliteal arterial involvement is particularly frequent because of diffuse distal arterial disease, microvascular dysfunction, endothelial injury, and chronic inflammatory activation [4,5,6].

The coexistence of **atherosclerosis and diabetes mellitus** substantially increases vascular complexity by combining macrovascular stenotic lesions with diabetes-related microcirculatory impairment, resulting in reduced distal perfusion, delayed tissue healing, and increased thrombotic burden[7,8].

Peripheral endovascular revascularization has become one of the principal treatment strategies for limb salvage in patients with infra-popliteal disease.

However, despite technical restoration of blood flow, long-term outcomes remain limited by:

- thrombotic complications
- reocclusion
- restenosis
- repeated intervention
- limb loss

The postprocedural thrombotic risk is especially high in diabetic patients because of:

- platelet hyperreactivity
- endothelial dysfunction
- activation of coagulation pathways
- impaired fibrinolysis

Traditional dual antiplatelet therapy remains widely used after peripheral intervention, but recent evidence suggests that **dual pathway inhibition**, combining antiplatelet and anticoagulant therapy, may provide superior vascular protection[9].

Low-dose rivaroxaban combined with aspirin has demonstrated favorable results in major vascular trials, particularly in patients with peripheral arterial disease.

Nevertheless, data remain limited regarding the comparative effectiveness of different antithrombotic regimens in patients with different comorbid backgrounds, especially under conditions of combined **diabetes mellitus and atherosclerosis[10]**.

The present study aimed to evaluate the effectiveness of different antithrombotic treatment strategies after infra-popliteal revascularization and to determine whether the benefit of aspirin combined with low-dose rivaroxaban becomes more pronounced under different comorbid vascular conditions[11].

Special attention was given to patients with coexistence of **diabetes mellitus and atherosclerosis**, where both platelet activation and thrombin generation are biologically intensified[12].

Aim of the Study

The aim of the present study is to evaluate the effectiveness and safety of different antithrombotic and anticoagulant treatment strategies after peripheral arterial revascularization in patients with chronic limb-threatening ischemia caused by diabetic angiopathy.

The study aims to determine the optimal pharmacological management strategy that ensures reduction of thrombotic and reocclusive complications, improvement of long-term revascularization outcomes, limb preservation, and prolongation of patient survival.

Special attention is paid to the comparative analysis of antiplatelet therapy and dual-pathway treatment[antiplatelet plus anticoagulant therapy) in diabetic patients under conditions of coexistence and absence of atherosclerosis. This approach will allow formulation of evidence-based recommendations for optimal post-revascularization management.

Study Population

The study included **120 patients** hospitalized with different clinical forms of chronic arterial insufficiency of the lower extremities.

All patients had peripheral arterial disease with hemodynamically significant lesions of the infra-popliteal segment.

The mean age of the study group was **64.8 ± 8.7 years**, reflecting the higher prevalence of the disease in elderly age groups(Table1).

Sex distribution was as follows:

- **male — 68.3%**
- **female — 31.7%**

The predominance of male patients corresponds to the epidemiological characteristics of peripheral arterial disease, since atherosclerotic vascular lesions are more frequently observed in men.

A significant proportion of patients had the following comorbid conditions:

- arterial hypertension
- diabetes mellitus
- dyslipidemia
- coronary artery disease

chronic kidney disease

Table 1 – Characteristics of Patients

Parameter	**Number (n=120)**	**Percentage (%)**
Age (mean ± standard deviation)	64.8 ± 8.7 years	—
Age distribution		
45–54 years	18	15.0%
55–64 years	36	30.0%
65–74 years	44	36.7%
≥75 years	22	18.3%
Sex distribution		
Male	82	68.3%
Female	38	31.7%
Comorbid conditions		
Arterial hypertension	94	78.3%
Type 2 diabetes mellitus	71	59.2%
Dyslipidemia	83	69.2%

Coronary artery disease	49	40.8%
Chronic kidney disease	21	17.5%
Smoking	67	55.8%

Patient Grouping

A total of **120 patients** included in the study were divided into **four equal study groups** according to the antithrombotic treatment regimen, with **30 patients in each group**.

This stratification was performed to enable comparative evaluation of the effectiveness of different antithrombotic strategies during the postprocedural period after endovascular intervention of the infra-popliteal segment.

During patient allocation, not only the prescribed antithrombotic treatment but also the underlying pathological background was taken into account, since it significantly influences both progression of vascular lesions and revascularization outcomes.

The main underlying diseases were classified into **three principal categories**:

- **Type 2 diabetes mellitus**
- **Combination of diabetes mellitus and atherosclerotic vascular lesions**
- **Isolated atherosclerotic vascular disease**

The study demonstrated that the most frequent clinical background was the **combined form of diabetes mellitus and atherosclerosis**, accounting for nearly half of the study population.

This distribution is clinically expected, since infra-popliteal arterial lesions occur particularly frequently in patients with multiple vascular risk factors.

According to antithrombotic regimens, the study groups were formed as follows (Table 2):

- **Group I:** dual antiplatelet therapy — **aspirin + clopidogrel**
- **Group II: aspirin + rivaroxaban 20 mg once daily**
- **Group III: aspirin + low-dose rivaroxaban (2.5 mg twice daily)**
- **Group IV:** triple therapy — **aspirin + clopidogrel + low-dose rivaroxaban**

Table 2 - Distribution of Patients According to Antithrombotic Regimen and Underlying Disease (n = 120)

Antithrombotic Regimen	**Diabetes Mellitus**	**Atherosclerosis + Diabetes**	**Atherosclerosis**	**Total**
Aspirin + Clopidogrel	10	14	6	30
Aspirin + Rivaroxaban 20 mg once daily	9	15	6	30
Aspirin + Rivaroxaban 2.5 mg twice daily	8	14	8	30
Aspirin + Clopidogrel + Rivaroxaban 2.5 mg twice daily	9	16	5	30
Total	**36**	**59**	**25**	**120**

Subgroup Analysis According to Comorbid Conditions

Within the study framework, an additional analysis of **120 patients** was performed according to underlying comorbid conditions.

For evaluation purposes, three principal subgroups were identified:

- patients with **isolated diabetes mellitus** (**n = 34**)
- patients with **combined diabetes mellitus and atherosclerosis** (**n = 52**)
- patients with **isolated atherosclerotic vascular lesions** (**n = 34**)

The effectiveness of antithrombotic treatment was assessed within all four therapeutic regimens.

Patients with Isolated Diabetes Mellitus

In patients with isolated diabetes mellitus, improvement of hemodynamic parameters was observed in all four treatment groups (Table 3, Diagram 1,2).

In **Group I**, thrombosis occurred in **1 patient**, reocclusion in **1 patient**, and repeated intervention was required in **1 case**.
The mean **ABI** in this group was **0.73**, while **primary patency reached 79.4%**.

In **Group II**, one case of thrombosis and one case of reocclusion were also recorded. The mean **ABI was 0.75**, and **primary patency reached 82.3%**.

In **Group III**, **no thrombotic event was observed**. Only **one patient required repeated intervention**. The mean **ABI reached 0.77**, while **primary patency was 85.2%**.

In **Group IV**, thrombosis was observed in **2 patients**, reocclusion in **1 case**, and the mean **ABI was 0.74**.

These findings indicate that among patients with isolated diabetes mellitus, **Group III demonstrated the most favorable vascular outcomes**, particularly due to the absence of thrombotic complications and the highest primary patency rate.

Table 3. Patients with isolated Diabetes Mellitus

Treatment Group	**Number of Patients (n)**	**Thrombosis n (%)**	**Reocclusion n (%)**	**Repeated Intervention n (%)**	**Mean ABI ± SD**	**Primary Patency (%)**
Group I	9	1 (11.1%)	1 (11.1%)	1 (11.1%)	0.73 ± 0.11	79.4
Group II	9	1 (11.1%)	1 (11.1%)	0 (0%)	0.75 ± 0.10	82.3
Group III	8	0 (0%)	0 (0%)	1 (12.5%)	0.77 ± 0.09	85.2
Group IV	8	2 (25.0%)	1 (12.5%)	0 (0%)	0.74 ± 0.12	80.1

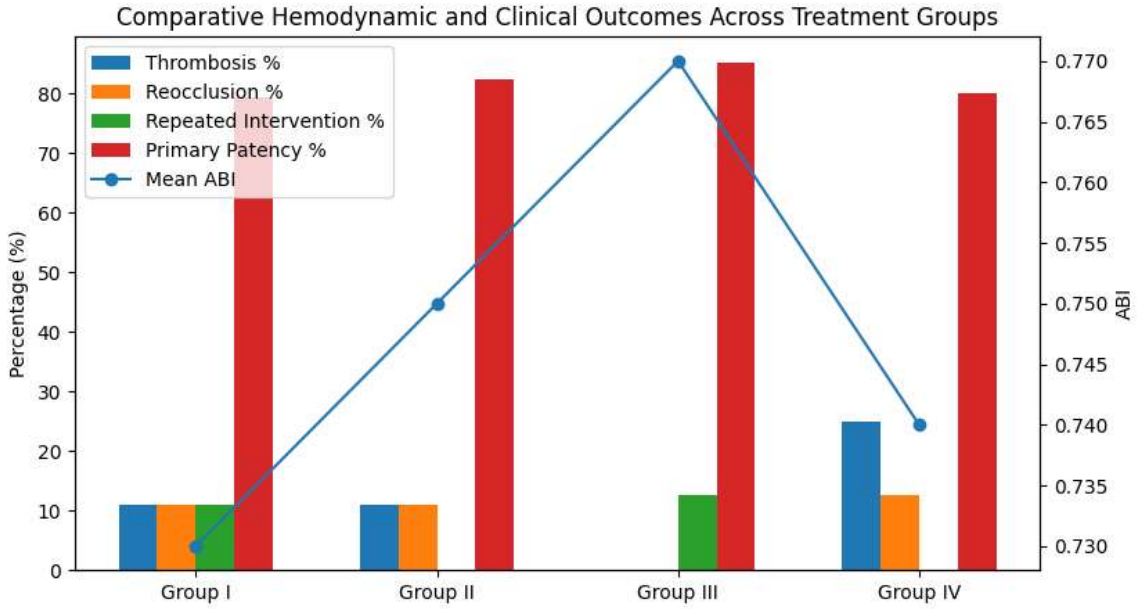

Diagram 1 – Patients with Isolated Diabetes Mellitus

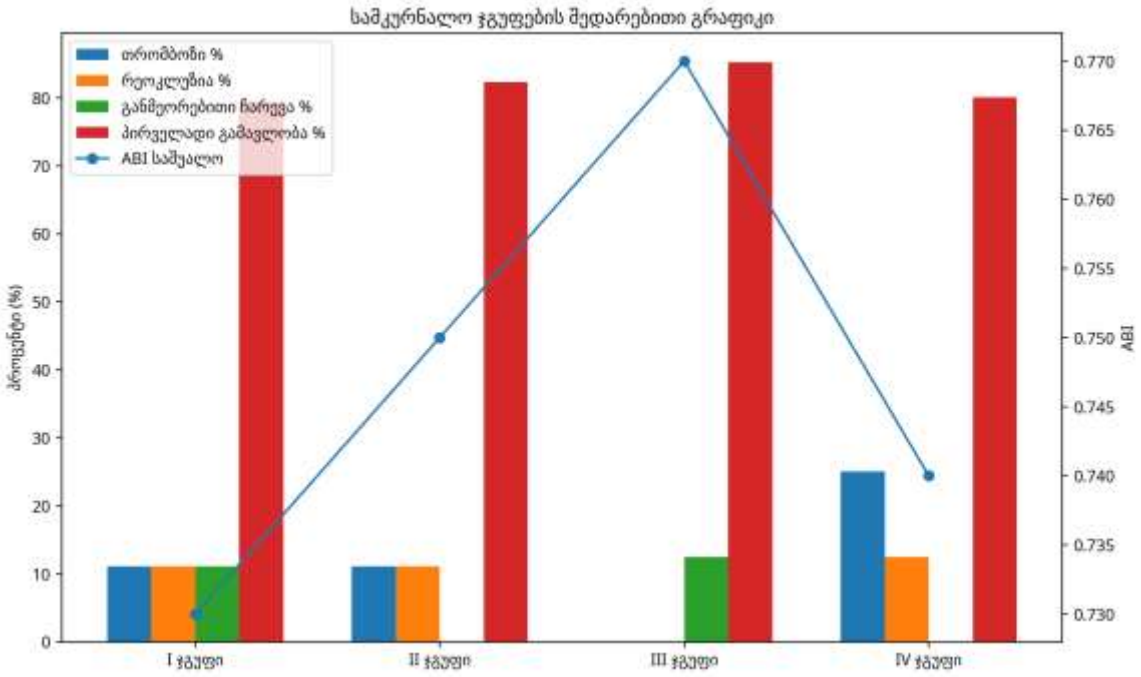

Diagram 2 – Patients with isolated Diabetes Mellitus

Patients with Isolated Atherosclerotic Lesions

In patients with **isolated atherosclerotic vascular lesions**, clinical outcomes were distributed relatively evenly across all four treatment groups (Table 4, Diagram 3).

In **Group I**, thrombosis was observed in **1 patient**, the mean **ABI was 0.74**, and **primary patency reached 81.2%**.

In **Group II**, the mean **ABI reached 0.76**, **primary patency was 83.5%**, and thrombosis was observed in **1 case**.

In **Group III**, comparatively better results were again recorded: the mean **ABI was 0.78**, **primary patency reached 85.0%**, and **no thrombotic event was observed**.

In **Group IV**, the mean **ABI was 0.75**, **primary patency reached 82.0%**, and thrombosis was observed in **1 patient**.

These findings indicate that although outcomes were generally comparable across groups, **Group III again demonstrated the most favorable vascular profile**, characterized by the highest ABI, highest primary patency, and absence of thrombotic complications.

Table 4. patients ith isolated Atherosclerosis

Treatment Group	**Number of Patients (n)**	**Thrombosis n (%)**	**Mean ABI ± SD**	**Primary Patency (%)**
Group I	9	1 (11.1%)	0.74 ± 0.12	81.2
Group II	9	1 (11.1%)	0.76 ± 0.11	83.5
Group III	8	0 (0%)	0.78 ± 0.10	85.0
Group IV	8	1 (12.5%)	0.75 ± 0.13	82.0

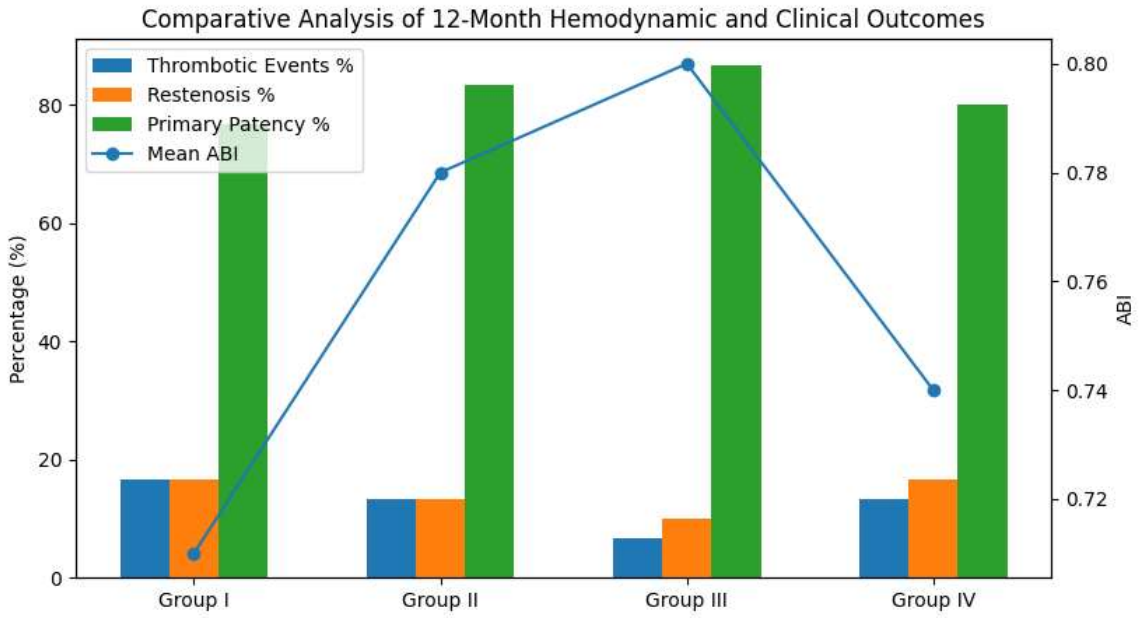

Diagram 3 – patients with isolated Atherosclerosis

Patients with Combined Diabetes Mellitus and Atherosclerosis

The most significant intergroup differences were observed in patients with **coexisting diabetes mellitus and lower extremity atherosclerotic lesions (Table 5, Diagram 4)**.

In **Group I**, thrombosis was observed in **3 patients**, reocclusion in **2 cases**, repeated intervention in **3 patients**, minor amputation in **3 cases**, and major amputation in **1 case**. Limb salvage was achieved in **26 patients**.

The mean **ABI** in this group was **0.71**, **primary patency reached 76.7%**, and **restenosis frequency was 16.7%**.

In **Group II**, thrombosis occurred in **2 patients**, reocclusion in **1 case**, repeated intervention in **2 patients**, minor amputation in **2 cases**, and major amputation in **1 case**. Limb salvage was achieved in **27 patients**.

The mean **ABI** in this group was **0.78**, **primary patency reached 83.3%**, and **restenosis frequency was 13.3%**.

In **Group III**, the most favorable outcomes were achieved.

Thrombosis was observed in only **1 patient**, reocclusion in **1 case**, repeated intervention in **2 patients**, minor amputation in **1 case**, and major amputation in **1 case**.

Limb salvage was achieved in **28 patients**.

At **12 months**, the mean **ABI reached 0.80 ± 0.13**, **primary patency was 86.7%**, **restenosis frequency was 10.0%**, and **thrombotic events accounted for 6.7%**.

In **Group IV**, thrombosis was observed in **4 patients**, reocclusion in **1 case**, repeated intervention in **3 patients**, minor amputation in **2 cases**, and major amputation in **1 case**.

Limb salvage was achieved in **27 patients**.

The mean **ABI** in this group was **0.74**, **primary patency reached 80.0%**, and **restenosis frequency was 16.7%**.

These findings demonstrate that **Group III provided the best overall vascular and clinical outcomes in patients with combined diabetes mellitus and atherosclerosis**.

The superiority of this regimen was reflected by:

- lowest thrombotic burden
- highest ABI
- highest primary patency
- lowest restenosis frequency
- best limb salvage rate

This suggests that **aspirin combined with low-dose rivaroxaban provides the greatest benefit under conditions of combined diabetic and atherosclerotic thrombotic burden**.

Table 5. **Patients with Combined Diabetes Mellitus and Atherosclerosis**

Treatment Group	**Number of Patients (n)**	**Thrombosis n (%)**	**Reocclusion n (%)**	**Repeated Intervention n (%)**	**Mean ABI ± SD**	**Primary Patency (%)**
Group I	9	3 (33.3%)	2 (22.2%)	3 (33.3%)	0.71 ± 0.11	76.7
Group II	9	2 (22.2%)	1 (11.1%)	2 (22.2%)	0.78 ±	83.3

					0.10	
Group III	8	1 (12.5%)	1 (12.5%)	2 (25.0%)	0.80 ± 0.13	86.7
Group IV	8	4 (50.0%)	1 (12.5%)	3 (37.5%)	0.74 ± 0.12	80.0

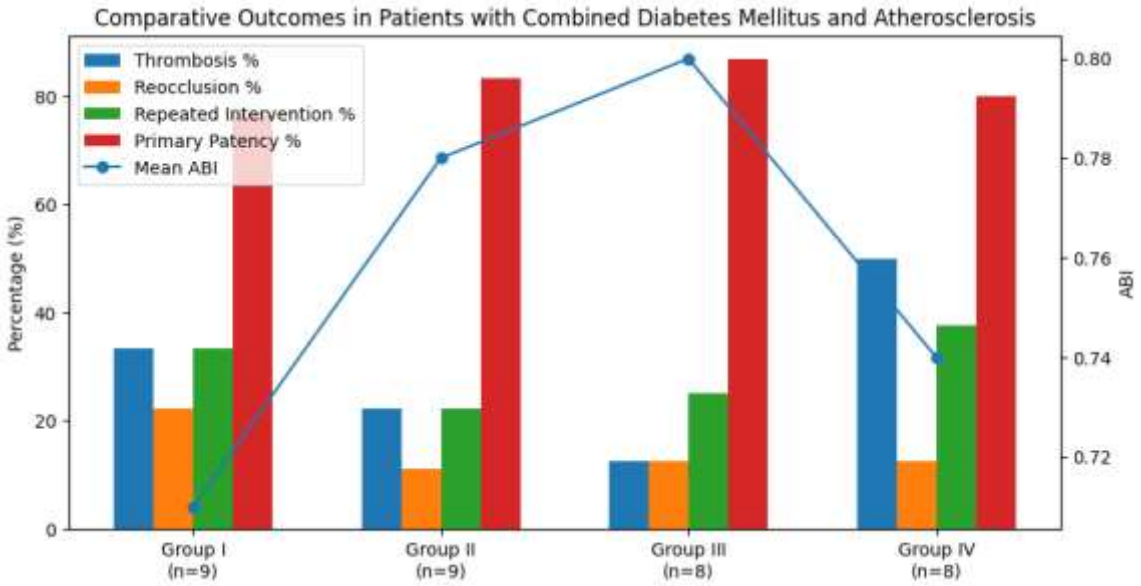

Diagram 4 - **Patients with Combined Diabetes Mellitus and Atherosclerosis**

Thus, the obtained data demonstrate that under conditions of **isolated diabetes mellitus** or **isolated atherosclerotic vascular disease**, differences between the four antithrombotic regimens were relatively modest.

In contrast, in patients with **coexisting diabetes mellitus and atherosclerosis**, the combination of **aspirin and low-dose rivaroxaban** provided the most favorable outcomes, reflected by:

- the highest **ABI values**
- the best **primary patency rate**
- the lowest **restenosis frequency**
- the lowest **incidence of thrombotic events**

These findings indicate that the therapeutic benefit of **dual pathway inhibition becomes most evident under combined diabetic and atherosclerotic thrombotic burden**, where both platelet activation and coagulation pathway activation are simultaneously intensified.

Conclusion

The present study demonstrated that the clinical effectiveness of antithrombotic therapy after infra-popliteal revascularization depends substantially on the underlying comorbid vascular background.

In patients with isolated diabetes mellitus or isolated atherosclerotic lesions, differences between therapeutic regimens remained relatively limited.

However, in patients with coexistence of **diabetes mellitus and atherosclerosis**, the combination of **aspirin and low-dose rivaroxaban (2.5 mg twice daily)** provided the most favorable outcomes.

This regimen was associated with:

- highest ABI values
- highest primary patency
- lowest restenosis frequency
- lowest thrombotic event burden
- best limb preservation profile

These findings suggest that **dual pathway inhibition offers maximal benefit precisely in patients with combined diabetic and atherosclerotic vascular pathology**, where platelet activation and thrombin generation are simultaneously intensified.

Therefore, aspirin combined with low-dose rivaroxaban may be considered the most effective antithrombotic strategy for improving long-term vascular outcomes in high-risk CLTI patients.

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