

Rivaroxaban Plus Aspirin versus Clopidogrel Plus Aspirin after Infrainguinal Endovascular Revascularization: A Narrative Review

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Abstract

The conceptual framework of targeting the coagulation cascade in Peripheral Artery Disease (PAD) is not novel; however, early attempts were marred by unacceptable safety profiles. The introduction of Rivaroxaban represented a profound pharmacological paradigm shift. Unlike Warfarin, which broadly and somewhat unpredictably inhibits the synthesis of multiple vitamin K-dependent clotting factors (Factors II, VII, IX, and X), Rivaroxaban is highly targeted and possesses predictable pharmacokinetics. The COMPASS trial (Cardiovascular Outcomes for People Using Anticoagulation Strategies) was the seminal study that resurrected the "Dual Pathway" theory, proving it could be executed safely and effectively in clinical practice. The VOYAGER PAD trial (Vascular Outcomes Study of ASA Along with Rivaroxaban in Endovascular or Surgical Limb Revascularization for PAD) was specifically designed to determine if DPI could improve outcomes during this acute post-procedural phase. Because VOYAGER PAD compared Rivaroxaban + Aspirin to Aspirin monotherapy (with or without background clopidogrel), a "pure," large-scale randomized control trial specifically comparing Rivaroxaban + Aspirin (DPI) head-to-head against the clinical standard of Clopidogrel + Aspirin (DAPT) is lacking.

Keywords: Peripheral Artery Disease; Rivaroxaban; Clopidogrel; Aspirin; Dual Pathway Inhibition; Dual Antiplatelet Therapy; Infrainguinal Endovascular Revascularization.

Introduction

The conceptual framework of targeting the coagulation cascade in Peripheral Artery Disease (PAD) is not novel; however, early attempts were marred by unacceptable safety profiles.

Before the advent of Direct Oral Anticoagulants (DOACs), clinicians attempted to combine Aspirin with Warfarin (a Vitamin K Antagonist) to suppress the thrombin pathway.

The WAVE Trial (Warfarin Antiplatelet Vascular Events): This landmark multicenter randomized trial evaluated the combination of an antiplatelet agent and an oral anticoagulant (warfarin, targeting an International Normalized Ratio [INR] of 2.0 to 3.0) against antiplatelet therapy alone in patients with PAD ("The Effects of Oral Anticoagulants in Patients with Peripheral Arterial Disease: Rationale, Design, and Baseline Characteristics of the Warfarin and Antiplatelet Vascular Evaluation (WAVE) Trial, Including a Meta-Analysis of Trials," 2006).

The trial was a definitive clinical failure. Adding Warfarin did not significantly reduce the risk of major cardiovascular events (myocardial infarction, stroke, or severe ischemia).

Instead, it led to a devastating twofold increase in life-threatening bleeding, including a high incidence of intracranial hemorrhage.

The failure of the WAVE trial induced a prolonged "blackout period" in vascular medicine, during which systemic anticoagulation was considered excessively dangerous for PAD patients unless explicitly indicated for a concomitant comorbidity, such as Atrial Fibrillation or venous thromboembolism.

Rivaroxaban Pharmacology and the "Vascular Dose" Rationale

The introduction of Rivaroxaban represented a profound pharmacological paradigm shift. Unlike Warfarin, which broadly and somewhat unpredictably inhibits the synthesis of multiple vitamin K-dependent clotting factors (Factors II, VII, IX, and X), Rivaroxaban is highly targeted and possesses predictable pharmacokinetics (R. Singh & Emmady, 2026).

Mechanism of Action

Rivaroxaban is a potent, highly selective, and reversible Direct Factor Xa Inhibitor. By specifically inhibiting Factor Xa, it interrupts the intrinsic and extrinsic pathways of the blood coagulation cascade at a critical bottleneck—the "Amplification Phase." Because one molecule of Factor Xa can catalyze the formation of over 1,000 molecules of thrombin, stopping the process at this specific juncture effectively dampens the "thrombin burst" without completely eliminating basal thrombin generation, which is key to preserving physiologic hemostasis and minimizing catastrophic bleeding (Kubitza et al., 2013).

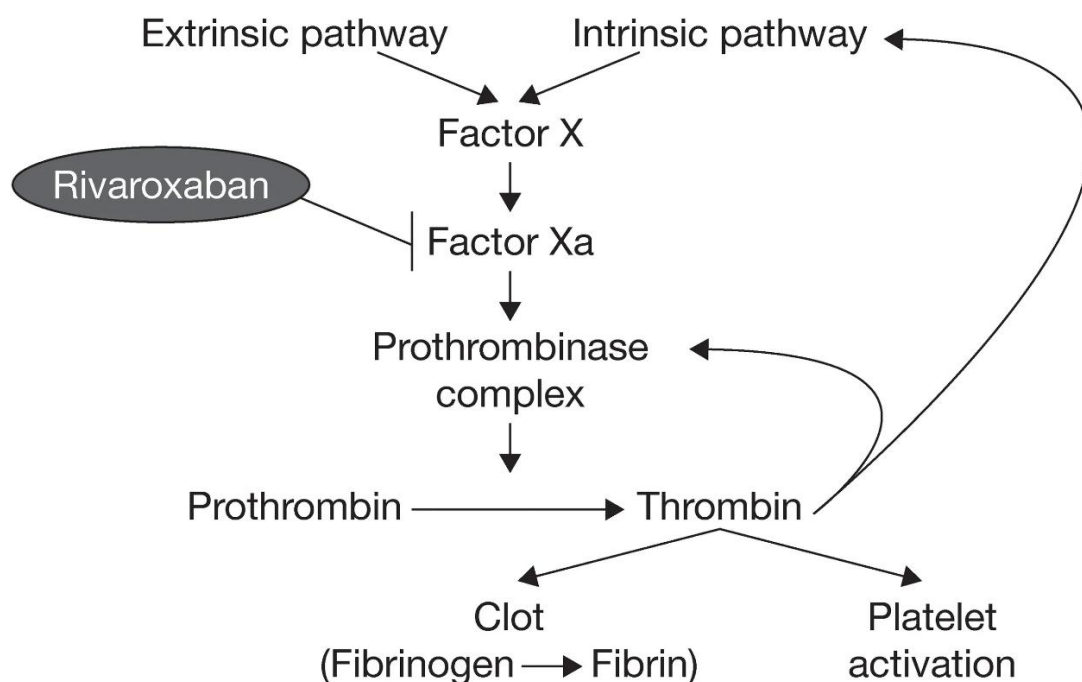


Figure 1. The blood coagulation pathway (Kubitza et al., 2013).

The "Vascular Dose" Concept

A critical distinction in modern antithrombotic therapy—and central to this thesis—is the dosage strategy:

- *The AFib/VTE Dose (15–20 mg OD):*

Administered once daily, this high dose is aimed at the near-total suppression of thrombin to prevent clot formation in the fibrillating atrium or deep veins. This creates high peak plasma concentrations, which correlate with higher bleeding risks (Ablefoni et al., 2019).

The Vascular Dose (2.5 mg BID): Known as "Low-Dose Rivaroxaban," this twice-daily regimen aims to maintain a steady-state trough concentration. It provides a constant "protective ceiling" against acute thrombin spikes in the highly resistant arterial system, while deliberately maintaining a lower peak concentration to drastically minimize the risk of major bleeding (Steffel et al., 2020).

Establishing the Baseline: The COMPASS Trial

The COMPASS trial (Cardiovascular Outcomes for People Using Anticoagulation Strategies) was the seminal study that resurrected the "Dual Pathway" theory, proving it could be executed safely and effectively in clinical practice (Steffel et al., 2020).

This massive, international, double-blind trial randomized over 27,000 patients with stable coronary artery disease (CAD) or PAD to receive Rivaroxaban (2.5 mg BID) plus Aspirin (100 mg OD), Rivaroxaban (5 mg BID) alone, or Aspirin (100 mg OD) alone.

Key Findings in the PAD Subgroup: The PAD subgroup analysis (Anand et al., 2018) yielded practice-changing results.

Dual Pathway Inhibition (DPI) reduced the composite risk of cardiovascular death, MI, and stroke by 24% compared to Aspirin monotherapy.

Even more impressively, the combination therapy reduced Major Adverse Limb Events by 46%, and specifically reduced the need for major amputation by 70%.

Safety: While major bleeding (primarily gastrointestinal) was higher in the combination group compared to Aspirin alone, there was no statistically significant increase in fatal or intracranial bleeding, proving that the 2.5 mg BID dose was inherently safer than historical warfarin regimens.

Evidence in Post-Revascularization Patients: The VOYAGER PAD Trial

While the COMPASS trial proved the benefit of DPI in stable disease, the period immediately following an infrainguinal endovascular intervention represents a much higher-risk "vulnerable window," characterized by intense local inflammation, endothelial denudation, and mechanical thrombogenicity.

The VOYAGER PAD trial (Vascular Outcomes Study of ASA Along with Rivaroxaban in Endovascular or Surgical Limb Revascularization for PAD) was specifically designed to determine if DPI could improve outcomes during this acute post-procedural phase (Bonaca et al., 2020).

The trial randomized 6,564 patients within 10 days of a successful lower extremity revascularization to receive either Rivaroxaban (2.5 mg BID) plus Aspirin or Placebo plus Aspirin.

Primary Outcome:

The study demonstrated a significant 15% relative risk reduction in the primary composite endpoint of acute limb ischemia (ALI), major amputation of vascular etiology, myocardial infarction, ischemic stroke, or cardiovascular death.

The "Limb-First" Benefit:

The most significant driver of this clinical benefit was the profound reduction in Acute Limb Ischemia, which was reduced by 33%. The Kaplan-Meier curves diverged early (within the first 30 days), suggesting that the immediate addition of Rivaroxaban was exceptionally effective at preventing the acute thrombotic occlusion of the newly stented or angioplastied segment.

The "Clopidogrel Interaction" and the Triple Therapy Dilemma

A unique feature of the VOYAGER PAD trial was that investigators were permitted to prescribe a short concomitant course of Clopidogrel at their discretion to prevent early stent thrombosis.

Approximately 50% of the patients randomized in VOYAGER PAD received "Triple Therapy" (Aspirin + Rivaroxaban + Clopidogrel) for a median duration of 29 days.

Ischemic Outcomes: Subgroup analyses revealed that the ischemic benefit of Rivaroxaban was consistent regardless of whether Clopidogrel was utilized.

Crucially, adding Clopidogrel did not provide an additional significant reduction in MACE or MALE beyond the protection already achieved by the Rivaroxaban and Aspirin combination (Bonaca et al., 2020).

However, the prolonged use of Clopidogrel (longer than 30 days) on top of Rivaroxaban and Aspirin significantly and disproportionately increased the risk of major bleeding.

This data strongly suggests that for the vast majority of patients, Dual Pathway Inhibition (Rivaroxaban + Aspirin) is biologically sufficient to protect the intervention. The long-term addition of Clopidogrel (mirroring traditional DAPT) to this regimen adds profound bleeding risk without proportional ischemic reward.

Direct Comparisons: Dual Pathway Inhibition versus Dual Antiplatelet Therapy

Because VOYAGER PAD compared Rivaroxaban + Aspirin to Aspirin monotherapy (with or without background clopidogrel), a "pure," large-scale randomized control trial specifically comparing Rivaroxaban + Aspirin (DPI) head-to-head against the clinical standard of Clopidogrel + Aspirin (DAPT) is lacking.

Conclusion:

Ischemic Outcomes: Subgroup analyses revealed that the ischemic benefit of Rivaroxaban was consistent regardless of whether Clopidogrel was utilized.

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References

1. The effects of oral anticoagulants in patients with peripheral arterial disease: Rationale, design, and baseline characteristics of the Warfarin and Antiplatelet Vascular Evaluation (WAVE) trial, including a meta-analysis of trials. (2006). *American Heart Journal*, 151(1), 1–9. <https://doi.org/10.1016/j.ahj.2005.03.021>
2. Kubitza, D., Perzborn, E., & Berkowitz, S. D. (2013). The discovery of rivaroxaban: translating preclinical assessments into clinical practice. *Frontiers in Pharmacology*, 4. <https://doi.org/10.3389/fphar.2013.00145>
3. Ablefoni, K., Buchholz, A., Ueberham, L. (2019). Initial rivaroxaban dosing in patients with atrial fibrillation. *Clinical Cardiology*, 42(10), 873–880. <https://doi.org/10.1002/clc.23235>
4. Steffel, J., Eikelboom, J. W. (2020). The COMPASS Trial. *Circulation*, 142(1), 40–48. <https://doi.org/10.1161/CIRCULATIONAHA.120.046048>
5. Anand, S. S., Bosch, J., Eikelboom, J. W., Connolly, S. J., Diaz, R., Widimsky, P., Aboyans, V., Alings, M., Kakkar, A. K., Keltai, K., Maggioni, A. P., Lewis, B. S., Störk, S., Zhu, J., Lopez-Jaramillo, P., O'Donnell, M., Commerford, P. J., Vinereanu, D., Ogren, M., Fox, K. A. A., Bhatt, D. L., & Yusuf, S. (2018). Rivaroxaban with or without aspirin in patients with stable peripheral or carotid artery disease: An international, randomised, double-blind, placebo-controlled trial. *The Lancet*, 391(10117), 219–229. [https://doi.org/10.1016/S0140-6736\(17\)32409-1](https://doi.org/10.1016/S0140-6736(17)32409-1)
6. Bonaca, M. P., Bauersachs, R. M. (2020). Rivaroxaban in Peripheral Artery Disease after Revascularization. *New England Journal of Medicine*, 382(21), 1994–2004. <https://doi.org/10.1056/NEJMoa2000052>