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« ANTITHROMBOTIC THERAPY IN ENDOVASCULAR PROCEDURES FOR REVASCULARISATION FOR PERIPHERAL ARTERY DISEASE (PAD) »

by

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Abstract

Aim: Managing peripheral arterial disease (PAD) with endovascular interventions remains complex, as evidence guiding optimal post-procedural care is limited. Clinicians often rely on extrapolated data from coronary and cerebrovascular studies, leading to heterogeneous practices. The main challenge is balancing thrombotic prevention with bleeding risk, with various strategies being employed without conclusive evidence of superiority. Surveillance approaches aimed at prolonging intervention durability lack robust data regarding their impact on health resource utilization and cardiovascular outcomes. There is an urgent need for high-quality randomized controlled trials (RCTs) comparing different antithrombotic regimens before, during, and after procedures to establish clear, evidence-based guidelines. The goal is to optimize long-term patency, reduce adverse events, and improve limb salvage rates, ultimately enhancing patient survival and quality of life. This systematic review aims to synthesize the best available RCT evidence to inform clinical decision-making and guide future research directions in PAD management.

Methods: A systematic review of the medical literature was conducted, utilizing PubMed, SCOPUS, and CENTRAL databases, following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) 2020 guidelines. The results were initially filtered automatically and then manually for duplicates. After a manual selection of studies that included both systematic reviews and RCTs, 6 studies remained.

Results: Recent clinical investigations highlight evolving strategies for managing peripheral artery disease (PAD). Bonaca et al. demonstrated that in post-revascularization patients, rivaroxaban combined with aspirin significantly reduced cardiovascular events over three years, with a manageable increase in bleeding risk based on ISTH criteria. Strobl et al. found that six months of dual therapy with aspirin and clopidogrel effectively decreased restenosis rates; however, benefits waned after discontinuation, suggesting potential advantages of extended therapy in high-risk individuals. Moll et al. reported that edoxaban is safe post- EVT, with fewer restenosis or reocclusion events compared to clopidogrel, although differences were not statistically significant. Ambler et al.'s comprehensive review underscored that while antiplatelet monotherapy can reduce non-fatal strokes and cardiovascular deaths in symptomatic patients, it offers limited benefit in asymptomatic cases and carries bleeding risks. Katsanos et al. revealed that among various agents, Clopidogrel monotherapy balances efficacy and safety best, while dual therapy with aspirin and Clopidogrel can reduce major amputations but increases bleeding hazards. Lastly, Megaly et al. showed that cilostazol improves vessel patency and limb preservation after EVT, with benefits unaffected by concomitant

anticoagulation. Collectively, these studies inform the application of antithrombotic therapies in PAD, emphasizing individualized risk-benefit assessments for optimal outcomes.

Conclusion: A solid conclusion is impossible to be made only with the results of this systematic review, so the current guidelines will be presented as a lot more low-level studies are included there, further analyses as well as expert's consensus.

Περίληψη

Στόχος: Η διαχείριση της περιφερικής αρτηριακής νόσου (PAD) με ενδοαγγειακές επεμβάσεις παραμένει πολύπλοκη, καθώς τα στοιχεία που καθοδηγούν την βέλτιστη μετεγχειρητική φροντίδα είναι περιορισμένα. Οι κλινικοί συχνά βασίζονται σε δεδομένα που εξάγονται από μελέτες για στεφανιαία και εγκεφαλικά αγγεία, με αποτέλεσμα η πρακτική να ποικίλλει. Η κύρια πρόκληση έγκειται στην ισορροπία ανάμεσα στην πρόληψη θρομβώσεων και στον κίνδυνο αιμορραγίας, με διάφορες στρατηγικές να εφαρμόζονται χωρίς σαφή αποδείξεις ανωτερότητας. Οι παρακολουθήσεις που αποσκοπούν στην παράταση της αντοχής των επεμβάσεων στερούνται αξιόπιστων δεδομένων σχετικά με την επίδρασή τους στη χρήση πόρων υγείας και στα καρδιαγγειακά αποτελέσματα. Υπάρχει επείγουσα ανάγκη για υψηλής ποιότητας τυχαιοποιημένες ελεγχόμενες μελέτες (RCTs) που θα συγκρίνουν διαφορετικά αντιθρομβωτικά σχήματα πριν, κατά τη διάρκεια και μετά τις επεμβάσεις, ώστε να διαμορφωθούν σαφείς και τεκμηριωμένες κατευθυντήριες γραμμές. Στόχος είναι η βελτίωση της μακροπρόθεσμης διατήρησης της βατότητας των αγγείων, η μείωση των επιπλοκών και η αύξηση των ποσοστών διατήρησης των άκρων, βελτιώνοντας τελικά την επιβίωση και την ποιότητα ζωής των ασθενών. Η παρούσα συστηματική ανασκόπηση επιδιώκει να συνοψίσει τα καλύτερα διαθέσιμα στοιχεία από τις RCTs για την καθοδήγηση της κλινικής πρακτικής και τις μελλοντικές ερευνητικές κατευθύνσεις στη διαχείριση της PAD.

Μέθοδος: Εφαρμόστηκε συστηματική ανασκόπηση της ιατρικής βιβλιογραφίας, χρησιμοποιώντας τις βάσεις δεδομένων PubMed, SCOPUS και CENTRAL, σύμφωνα με τις οδηγίες PRISMA 2020 για την Αναφορά Προτιμώμενων Στοιχείων σε Συστηματικές Ανασκοπήσεις και Μετα-αναλύσεις. Τα αποτελέσματα αρχικά φιλτραρίστηκαν αυτόματα και στη συνέχεια χειροκίνητα για διπλότυπα. Μετά από αυτό, πραγματοποιήθηκε χειροκίνητη επιλογή μελετών που περιείχαν τόσο συστηματικές ανασκοπήσεις όσο και τυχαιοποιημένες ελεγχόμενες μελέτες (RCTs), με αποτέλεσμα να παραμείνουν 6 μελέτες.

Αποτελέσματα: Πρόσφατες κλινικές έρευνες τονίζουν τις εξελισσόμενες στρατηγικές για τη διαχείριση της περιφερικής αρτηριακής νόσου (ΠΑΝ). Ο Bonaca et al. απέδειξε ότι στους ασθενείς μετά από επαναιμάτωση, η ριβαροξάμπάνη σε συνδυασμό με ασπιρίνη μείωσε σημαντικά τα καρδιαγγειακά συμβάματα σε τρία χρόνια, με μια διαχειρίσιμη αύξηση στον κίνδυνο αιμορραγίας βάσει των κριτηρίων ISTH. Ο Strobl et al. διαπίστωσε ότι έξι μήνες διπλής θεραπείας με ασπιρίνη και κλοπιδογρέλη μειώσαν αποτελεσματικά τα ποσοστά επανεμφάνισης στενώσεων, αν και τα οφέλη μειώθηκαν μετά τη διακοπή, υποδεικνύοντας πιθανά πλεονεκτήματα της παρατεταμένης θεραπείας σε άτομα υψηλού κινδύνου. Ο Moll et al. ανέφερε ότι η εδοξαμπάνη είναι ασφαλής μετά τις ενδαγγειακές επεμβάσεις, με λιγότερα συμβάματα επανεμφάνισης στενώσεων ή επαναστένωσης σε σύγκριση με την

κλοπιδογρέλη, αν και οι διαφορές δεν ήταν στατιστικά σημαντικές. Η ανασκόπηση του Ambler τόνισε ότι η μονοθεραπεία με αντιαιμοπεταλιακά μπορεί να μειώσει τις όχι θανατηφόρες εγκεφαλικές ή καρδιαγγειακές θρομβώσεις στους συμπτωματικούς ασθενείς, αλλά έχει περιορισμένα οφέλη σε ασυμπτωματικούς και ενέχει κινδύνους αιμορραγίας. Ο Katsanos et al. αποκάλυψε ότι η μονοθεραπεία με κλοπιδογρέλη διατηρεί την καλύτερη ισορροπία αποτελεσματικότητας και ασφάλειας, ενώ η διπλή θεραπεία με ασπιρίνη και κλοπιδογρέλη μπορεί να μειώσει τους μεγάλους ακρωτηριασμούς αλλά αυξάνει τον κίνδυνο αιμορραγίας. Τέλος, ο Megaly et al έδειξε ότι η σιλοσταζόλη βελτιώνει τη διατήρηση των αγγείων και τη διατήρηση των άκρων μετά τις ενδαγγειακές επεμβάσεις, χωρίς να επηρεάζεται από την ταυτόχρονη αντιπηκτική αγωγή. Μαζί, αυτές οι μελέτες καθοδηγούν την εφαρμογή αντιθρομβωτικών θεραπειών στη ΠΑΝ, τονίζοντας την ανάγκη εξατομικευμένης αξιολόγησης κινδύνου-οφέλους για βέλτιστα αποτελέσματα.

Συμπέρασμα: Ένα σταθερό συμπέρασμα είναι αδύνατον να εξαχθεί αποκλειστικά από τα αποτελέσματα αυτής της συστηματικής ανασκόπησης, επομένως οι τρέχουσες κατευθυντήριες γραμμές θα παρουσιαστούν καθώς συμπεριλαμβάνουν πολλές ακόμα χαμηλού επιπέδου μελέτες, περαιτέρω αναλύσεις και συμφωνίες ειδικών.

Peripheral Artery Disease (PAD) of lower limbs

Peripheral artery disease (PAD) is a prevalent condition that significantly impacts the vascular health of the aging population, with estimates suggesting it affects up to 30% of individuals over 70 and a considerable portion of middle-aged adults with cardiovascular risk factors such as smoking and diabetes. The disease manifests on a spectrum, from asymptomatic cases to severe ischemia, and is associated with heightened risks of major cardiovascular and limb events. Moreover, PAD's coexistence with coronary artery disease (CAD) underscores its systemic nature, elevating the risk for myocardial infarction, stroke, and mortality. Despite its clinical importance, PAD remains underdiagnosed and undertreated, partly due to the limited evidence base guiding specific therapeutic strategies.

Symptomatically, PAD often presents as intermittent claudication—muscular pain precipitated by walking, which subsides with rest—and, in advanced stages, progresses to critical limb ischemia (CLI). The latter is characterized by rest pain, non-healing ulcers, or tissue necrosis—indications of severe ischemia that threaten limb viability. The disease severity is classified using well-established systems such as the Fontaine and Rutherford scales, which delineate stages from asymptomatic to tissue loss, providing guidance for treatment planning [1], [2].

Revascularization remains a cornerstone in managing significant PAD, especially in symptomatic individuals and those with CLI. Percutaneous transluminal angioplasty (PTA), developed in the 1960s and refined through decades, is now a mainstay minimally invasive procedure for restoring blood flow. It involves dilating stenotic or occluded arteries, primarily via balloon catheters introduced through the femoral artery, with adjunctive techniques such as thrombolysis or thromboembolectomy employed for embolic or acute-on-chronic occlusions. Advances in device technology—such as nitinol and drug-eluting stents—have considerably improved long-term patency, especially at the femoropopliteal level, although restenosis due to intimal hyperplasia remains a pertinent challenge [3], [4], [5].

The pathophysiology of revascularization emphasizes the vascular response to injury: rupture of plaques prompts platelet activation and aggregation, fostering thrombus formation and potential early reocclusion. Additionally, denudation of the endothelium and vessel wall manipulation stimulate smooth muscle proliferation—leading to intimal hyperplasia—and contribute to restenosis and late reocclusion. Post-procedural hypercoagulability, evidenced by elevated plasma biomarkers such as D-Dimer and thrombin-antithrombin complexes,

further complicates outcomes, necessitating careful antithrombotic management. [6]

Clinical strategies to prevent re-occlusion and reduce cardiovascular risk are guided by current guidelines, which strongly endorse antiplatelet monotherapy—typically aspirin or clopidogrel—for stabilized PAD patients, aligning with evidence levels that support secondary prevention. However, the role of dual antiplatelet therapy (DAPT), especially after endovascular procedures, remains less definitive, with current recommendations ranging from cautious support to outright discouragement depending on the guideline. The evidence supporting DAPT in the post-revascularization setting is limited, and its application must be individualized, considering both bleeding risk and ischemic potential.

In patients with CLI, prompt revascularization—via endovascular or surgical approaches—is vital for limb preservation. Endovascular techniques, including PTA and stenting, have expanded therapeutic options, offering less invasive alternatives with shorter recovery periods. Nevertheless, despite technical advancements, restenosis rates remain substantial, driven by neointimal hyperplasia and ongoing vessel wall injury[7]. To optimize long-term results, adjunctive pharmacological strategies—such as antithrombotic and antiproliferative therapies—are under active investigation, although definitive evidence guiding their use specifically in CLI patients post-intervention is still evolving [8].

The management of PAD, especially in complex presentations like CLI, requires a multifaceted approach—combining meticulous risk factor modification, appropriate revascularization, and tailored pharmacotherapy. As ongoing research continues to elucidate the nuances of antithrombotic treatment, clinicians must balance the benefits of ischemia prevention against bleeding risks while striving to improve limb salvage rates and reduce systemic cardiovascular events. Future studies aimed at stratifying patients based on risk profiles, as well as evaluating newer device technologies and adjunctive systemic therapies, are essential to refine treatment paradigms and enhance outcomes in this high-risk population.

Antithrombotic drugs

Antiplatelet agents

Acetylsalicylic acid

Aspirin remains a cornerstone in managing peripheral arterial disease (PAD), chiefly due to its antithrombotic properties, which lower cardiovascular event risk. Its application spans primary and secondary prevention, with dosing optimized over years to maximize efficacy and reduce gastrointestinal and bleeding side effects. [9] Standard adult doses range from 75 mg to 325 mg, commonly 81 mg in the US and 300 mg in the UK. Evidence indicates that 75–81 mg daily suffices for effective platelet inhibition, especially in lighter patients under 70 kg; heavier individuals may need slightly higher doses.

Clinical data consistently support routine aspirin use in PAD, especially surrounding vascular interventions. Initiating therapy before procedures provides benefits that extend into the postoperative period. Studies from the early 1990s examining post-angioplasty doses universally concluded that increasing aspirin beyond 100 mg daily does not significantly improve vessel patency or reduce restenosis. For example, a trial comparing 1000 mg and 100 mg daily over two years showed similar patency rates (~62.5%) and no substantial difference in outcomes, with low-dose therapy offering better tolerability. Patients on 100 mg experienced fewer gastrointestinal side effects, leading to better adherence [10].

Aspirin’s mechanism involves irreversible inhibition of COX-1, which decreases thromboxane A2 synthesis and inhibits platelet aggregation. Higher doses might offer additional anti-inflammatory benefits but do not improve vascular outcomes; instead, they increase bleeding risks. Consequently, low-dose aspirin is favoured. Combining aspirin with dipyridamole recently failed to show short-term improvements, supporting the view that higher doses or combination therapy do not confer added benefit.

In summary, low-dose aspirin (~100 mg daily) provides an optimal balance of effectiveness and safety, especially after revascularization procedures. It remains a fundamental element of secondary prevention for PAD, maintaining vessel patency while minimizing adverse effects that could hinder adherence and overall treatment success.

Acetylsalicylic acid as monotherapy for secondary prevention of MACE

Aspirin's efficacy as a single agent in preventing major adverse cardiovascular events (MACE) among patients with established vascular disease has been extensively studied through large reviews and clinical trials. The Antithrombotic Trialists’ Collaboration reported approximately an 18% relative risk reduction with aspirin, equating to about a 1% absolute annual benefit

compared to placebo. However, this meta-analysis encompassed diverse vascular conditions and did not focus solely on peripheral artery disease (PAD), limiting direct applicability to this subgroup.

More specific analyses, such as Berger et al., examined over 3,000 patients with confirmed PAD and observed a trend toward reduced MACE with aspirin, yet the results lacked statistical significance (RR: 0.75; CI: 0.48–1.18). This was largely due to the low event rate within the population, highlighting the challenge of demonstrating clear secondary prevention benefits in PAD[11].

Additional randomized trials offer further insights. The AAA trial, involving 3,350 patients with abnormal ankle-brachial indices (ABI), found no significant difference in mortality, MI, stroke, or revascularization between aspirin and placebo after more than eight years. Notably, about 15% of the placebo group reported self-initiated aspirin use, potentially confounding outcomes. [12]

The CLIPS study, which included patients with claudication and ABI <0.85, showed that aspirin combined with antioxidants significantly reduced fatal and nonfatal vascular events (HR: 0.42). Despite promising results, the limited number of participants restricts the strength of these findings, though they suggest potential benefits in PAD populations[13].

Conversely, the POPADAD trial, involving diabetic patients with asymptomatic PAD (ABI ≤0.99), found no significant reduction in MI, stroke, or amputations over nearly a decade. The addition of antioxidants also failed to show benefits. Thus, in this context, aspirin's protective role remains uncertain [14].

In summary, evidence for aspirin monotherapy in secondary prevention of MACE in PAD is heterogeneous and limited. While some studies suggest benefits in particular subgroups, definitive large-scale trials are lacking. Prescription rates for aspirin in PAD patients without coronary or cerebrovascular disease are often below 36%. Ongoing research and individual risk assessments are necessary to refine its role, and current guidelines advocate tailored, case-by-case decision-making.

P2Y12 Inhibitors

A comprehensive approach to managing platelet aggregation in patients with vascular disease, including peripheral arterial disease (PAD), involves various pharmacologic agents targeting multiple pathways of platelet activation. Central to these are inhibitors of the P2Y12 receptor, a critical nucleotide receptor on platelets. Adenosine diphosphate (ADP) activates platelets through binding to purinergic receptors, mainly P2Y1 and P2Y12, which drive platelet aggregation. Blocking these receptors effectively reduces platelet responsiveness and thrombotic risk.

P2Y12 inhibitors are categorized into two main classes. The first includes thienopyridines—clopidogrel, prasugrel, and ticlopidine—though the latter has been largely phased out due to hematologic side effects such as neutropenia.

These drugs are prodrugs requiring hepatic CYP450 enzyme activation to become active. They irreversibly inhibit P2Y12, ensuring prolonged platelet inhibition. Clopidogrel, widely prescribed in PAD, depends heavily on CYP2C19 for activation, but about 30% of patients possess genetic variants resulting in decreased enzyme activity and responsiveness. Concomitant use of proton pump inhibitors may interfere with clopidogrel activation, although definitive links to adverse outcomes are lacking.

Prasugrel offers advantages over clopidogrel by undergoing a single-step activation, enabling faster onset and more consistent inhibition. It has demonstrated superior efficacy in reducing thrombotic events in coronary artery disease, although its specific benefits in PAD are not well established.

The second family includes non-thienopyridine agents such as ticagrelor and cangrelor. Ticagrelor is a reversible P2Y12 antagonist that does not require hepatic activation, making it less susceptible to genetic variation and offering rapid, potent platelet inhibition unaffected by CYP450 variability[15]. Conversely, cangrelor is administered intravenously, has a very short half-life, and is primarily used in acute settings, rendering it unsuitable for long-term prevention.

Although large trials have validated these agents for preventing major adverse cardiovascular events (MACE)—including myocardial infarction, stroke, and death—such evidence in PAD remains scarce despite the considerable ischemic risk. Therapies should be tailored considering individual patient profiles, including genetic factors, potential drug interactions, and adverse effects, to optimize long-term vascular protection.

Phosphodiesterase Inhibitors

Cilostazol is a key phosphodiesterase (PDE) inhibitor used in managing peripheral arterial disease (PAD). As a PDE3 inhibitor, it rapidly absorbs, reaching peak plasma levels in approximately 2.5 hours, and improves exercise capacity and quality of life in patients with claudication. It also enhances vessel patency after endovascular therapy, reducing restenosis and limb amputation risks. Evidence supports its role as an adjunct in treating femoropopliteal lesions, including in-stent restenosis, mainly through vasodilation that inhibits neointimal hyperplasia and improves endothelial function. Meta-analyses confirm that cilostazol significantly enhances vessel patency and diminishes adverse outcomes, with a safety profile marked by minor side effects such as headache, tachycardia, and diarrhoea. [16]

Despite these benefits, the broader use of cilostazol is constrained by safety concerns associated with PDE3 inhibitors, notably milrinone, which has been linked to increased mortality in congestive heart failure (CHF). Consequently, the FDA has issued warnings about its use in CHF, although current evidence suggests cilostazol does not carry similar risks. Its safety in patients on newer oral anticoagulants (NOACs) remains unestablished, as dedicated studies are lacking.

Cilostazol is not employed after coronary stenting generally because drug-eluting stents (DES) offer superior antiproliferative effects. Nevertheless, its application in peripheral lesions remains valuable, especially for longer lesions with a higher likelihood of occlusion, and subgroup analyses have shown favourable outcomes when combined with DES and second-generation nitinol stents. Additional research is needed to explore its benefits with newer-generation devices, which already demonstrate improved patency and reduced restenosis.

In conclusion, cilostazol is a beneficial adjunct for limb preservation, symptom alleviation, and vessel patency in PAD. Its use should be tailored based on individual risk factors, and more studies are required to optimize its incorporation into advanced endovascular strategies.

Other Antiplatelet agents.

Glycoprotein IIb/IIIa receptor antagonists, such as abciximab, tirofiban, and eptifibatide, are potent antiplatelet agents that inhibit fibrinogen and von Willebrand factor binding on platelets, which is crucial in thrombus formation. Administered intravenously, they have proven benefits in reducing mortality and myocardial infarction (MI) in acute coronary syndrome (ACS) patients, especially during percutaneous coronary interventions (PCI). However, their application in peripheral arterial disease (PAD) is limited due to scarce supporting evidence. Most clinical data originate from coronary artery disease (CAD) contexts involving high-risk ACS patients, where GPIIb/IIIa inhibitors decrease thrombotic complications during PCI. In patients with ACS not undergoing revascularization, the benefit-risk profile remains uncertain, mainly because of the increased bleeding risk associated with these agents' potent effects. As a result, their role outside acute coronary interventions, particularly in PAD, is limited and not well defined.

Vorapaxar binds to protease-activated receptor-1 (PAR-1), inhibiting thrombin-mediated platelet activation. However, its clinical utility remains limited outside specific contexts due to safety concerns[17].

Anticoagulant agents

Unfractionated heparin

Unfractionated heparin (UFH) has long been a fundamental anticoagulant, especially valued for its rapid action in procedures requiring immediate anticoagulation. It functions mainly by activating endogenous antithrombin, which inhibits key coagulation factors such as XIIa, XIa, IXa, Xa, and thrombin [18]. Typically administered as an intravenous bolus (around 100-150 units per kilogram) followed by continuous infusion, UFH’s anticoagulant effect is

monitored via activated partial thromboplastin time (aPTT), though this test has limitations due to potential interference. In intraoperative settings, activated clotting time (ACT) provides a more direct assessment. Despite its widespread use, UFH's variability in effect and challenges in reversal with protamine have led to its gradual replacement by low-molecular-weight heparins (LMWH) and fondaparinux in many practices. However, UFH remains essential in specific contexts, such as emergency revascularizations for acute limb ischemia, where its rapid onset and short half-life (about one hour) allow for precise control. It is also utilized intraoperatively in certain surgeries, like abdominal aortic aneurysm repair, especially when quick reversal is necessary. Although newer agents are favoured for their predictable pharmacokinetics and ease of management, UFH remains vital in acute, complex, and emergent anticoagulation scenarios.

Low molecular weight heparins

Low-molecular-weight heparins (LMWHs), obtained from unfractionated heparin (UFH) through controlled depolymerization, consist of polysaccharide chains averaging around 5 kD. Their primary pharmacodynamic advantage is their selective inhibition of factor Xa over thrombin, due to fewer chains containing the pentasaccharide sequence necessary for high affinity antithrombin binding. This sequence induces a conformational change that enhances anti-Xa activity, whereas inactivation of thrombin requires longer chains (~18 saccharide units), which most LMWH chains lack. As a result, LMWHs possess a higher anti-Xa to anti-IIa activity ratio, with agents like dalteparin, enoxaparin, nadroparin, tinzaparin, and reviparin differing in molecular weight and activity ratios.

Although UFH has traditionally been preferred for extracorporeal membrane oxygenation (ECMO) because of its rapid effect and adjustable dosing, emerging evidence indicates LMWHs may reduce thromboembolic risks while maintaining a similar bleeding profile. Nonetheless, more research is needed to confirm their utility in ECMO. Additionally, LMWHs are widely recommended by the American Society of Clinical Oncology (ASCO) for thromboprophylaxis across various high-risk groups, including hospitalized patients, cancer surgeries, and ambulatory individuals receiving systemic therapies [19].

Pentasaccharides

Pentasaccharides, such as fondaparinux, are synthetic molecules derived from the five-saccharide effector site of heparin, designed to selectively inhibit factor Xa without affecting thrombin (factor IIa). Fondaparinux binds reversibly to antithrombin's activation site, enhancing its ability to block factor Xa. It has high bioavailability and predictable pharmacokinetics after subcutaneous

administration, eliminating the need for routine monitoring. Its half-life of 15–20 hours support once-daily dosing, whereas agents like idraparinux, with longer half-lives of about five days, allow weekly injections.

Clinically, fondaparinux has proven effective in preventing venous thromboembolism (VTE), especially after orthopaedic surgeries, often outperforming low-molecular-weight heparins like enoxaparin, with reductions in VTE rates around 50%. The bleeding risk associated with fondaparinux is increased but remains comparable to enoxaparin, with serious bleeding being rare. Its efficacy extends to treating venous thrombosis and pulmonary embolism, where it performs as well as heparin-based therapies, with similar recurrent thrombosis and bleeding rates [20].

In acute coronary syndrome (ACS), fondaparinux shows comparable efficacy to unfractionated heparin, with some studies indicating lower revascularization rates. Dose-finding studies suggest it can be administered safely across various doses without significant differences in ischemic or bleeding outcomes. The main concern with long acting pentasaccharides is the lack of a specific antidote; although recombinant factor VIIa can reverse their effects, its clinical utility in severe bleeding management remains to be fully established.

Danaparoid

Danaparoid, a low molecular weight heparinoid composed of heparan, dermatan, and chondroitin sulfates, offers significant antithrombotic effects. Its high antifactor Xa to antifactor IIa activity ratio, coupled with a low bleeding risk and minimal impact on fibrinolysis, makes it a favourable agent. Notably, it has a low cross-reactivity rate (~10%) with heparin-induced antibodies, suited for patients with immune-mediated heparin-induced thrombocytopenia (HIT) [21]

Clinical data from extensive international studies show high success rates, particularly in resolving thrombocytopenia, and better thrombus outcomes compared to other anticoagulants like dextran. Its safety profile is characterized by infrequent major bleeding and mortality rates below 15%. Although laboratory testing for cross-reactivity is advised, clinical reactions are rare.

Overall, danaparoid is effective and well-tolerated for HIT management, especially in patients where minimizing bleeding risk and immune reactions are priorities, representing a valuable alternative for anticoagulation.

Vitamin K antagonists

Vitamin K antagonists (VKAs), mainly warfarin, are established anticoagulants that inhibit gamma-glutamyl carboxylase, essential for activating clotting factors II, VII, IX, and X. This suppression reduces the synthesis of functional coagulation proteins, providing anticoagulation. Their effects are delayed by

several days, necessitating overlap with fast-acting agents like heparin during initiation.

Warfarin is rapidly absorbed and primarily metabolized in the liver through CYP2C9, affecting its half-life of 36–42 hours and extensive plasma protein binding, especially to albumin. Individual responses vary due to genetic factors influencing CYP2C9 activity and VKORC1 sensitivity, as well as drug-food interactions, making frequent INR monitoring essential.

Dietary vitamin K, mainly from green vegetables, can impair warfarin's efficacy, while drugs like amiodarone inhibit CYP2C9, increasing bleeding risk. Conversely, agents such as rifampin, carbamazepine, and chronic alcohol intake accelerate metabolism, reducing its effect. Many other medications, including antibiotics and anti-inflammatories, can alter warfarin's efficacy or bleeding risk [22].

VKAs are crucial in preventing stroke in atrial fibrillation, for thromboembolism in arterial and venous thromboses, and in patients with mechanical heart valves, with INR targets varying by condition. In antiphospholipid syndrome, warfarin with higher INR ranges remains standard. Due to its narrow therapeutic window and susceptibility to genetic and environmental influences, warfarin management requires careful oversight and regular laboratory testing to ensure safety and effectiveness.

Direct thrombin inhibitors

Existing anticoagulants have evolved with the development of direct thrombin inhibitors (DTIs), which bind directly to thrombin, inhibiting its role in converting fibrinogen to fibrin and activating platelets. Unlike heparins, DTIs do not depend on cofactors like antithrombin and can inhibit both free and fibrin-bound thrombin, resulting in more consistent effects and fewer interactions.

Currently, four injectable DTIs—lepirudin, desirudin, bivalirudin, and argatroban—are approved in North America for indications such as venous thromboembolism (VTE), heparin-induced thrombocytopenia (HIT), and acute coronary syndromes, especially during procedures like PCI. These agents differ in their pharmacokinetics; some require continuous infusion, while others have short half-lives for rapid modulation [23].

Dabigatran etexilate stands out as a leading oral anticoagulant, converted into its active form in vivo. It offers a predictable, rapid alternative to warfarin, with fixed dosing, minimal food interactions, and a broad therapeutic window. Despite its benefits, it carries a bleeding risk, and no specific antidote is available yet. Supportive measures, including drug discontinuation, surgical intervention, or administration of agents like recombinant factor VIIa, are used in overdose or severe bleeding [24].

Dabigatran was recently approved for stroke prevention in atrial fibrillation, marking a major advance in anticoagulant therapy. As ongoing research continues, these new agents are expected to enhance thromboembolic

disorder management with predictable effects and fewer adverse outcomes than traditional options.

Factor Xa inhibitors

Factor Xa inhibitors, such as rivaroxaban, apixaban, betrixaban, and edoxaban, are oral agents that reversibly target the active site of factor Xa, effectively inhibiting thrombin production from both intrinsic and extrinsic pathways. Because they act proximally in the coagulation cascade, they often require lower doses and tend to have fewer off-target effects, as factor Xa's roles outside coagulation are minimal.

These drugs have predictable linear pharmacokinetics, with rapid absorption and peak plasma concentrations reached within about three hours. Rivaroxaban, at doses of 15–20 mg, is highly bioavailable but must be taken with food to optimize absorption; apixaban and edoxaban can be taken with or without food, with edoxaban's low protein binding allowing potential dialysis.

All are cleared through renal and hepatic pathways, with half-lives between 5 and 13 hours—rivaroxaban being partly excreted unchanged in urine, but its use is contraindicated in severe renal impairment (CrCl <30 mL/min). Apixaban is mainly eliminated via the liver and biliary tract, suitable for dialysis patients, while edoxaban is primarily excreted unchanged by the kidneys. Betrixaban, approved for VTE prophylaxis in hospitalized patients, has a half-life of about 37 hours, allowing once-daily dosing, and is mainly eliminated through P-glycoprotein pathways, making it suitable for patients with renal issues.

All agents interact with the cytochrome P450 system and P-glycoprotein, raising concerns for drug interactions. Reversal agents like andexanet alfa for apixaban and rivaroxaban improve safety, though cost may limit their widespread use [25]. Overall, these drugs are effective and safe alternatives for atrial fibrillation, VTE, and thrombotic conditions, offering convenience over warfarin, especially with the benefit of targeted activity and predictable effects [26].

Bleeding risk evaluation

Numerous bleeding risk prediction tools exist for evaluating individual susceptibility to hemorrhagic events; however, none have achieved widespread validation or integration into clinical practice. The subset of patients at greatest risk of bleeding within this context comprises those with symptomatic lower extremity arterial disease (LEAD), particularly those undergoing interventional procedures.

In the process of drafting a guideline, a collaborative effort led to the development of a novel bleeding risk score, which was internally validated using data from a cohort of 81,930 hospitalized patients treated for LEAD across a spectrum of antithrombotic therapies, including both antiplatelet and anticoagulant agents. This cohort was drawn from a comprehensive German health insurance registry [27]. The resulting score incorporates eight independent predictive variables, facilitating stratification of patients into four categories: low risk, low-to-moderate, moderate-to-high, and high risk. Such stratification could inform antithrombotic therapy decisions, especially when multiple options appear clinically appropriate. It must be emphasized that this model has not yet undergone external validation, and no other risk stratification tools for this specific patient population have been formally validated to date.

More robust validation exists for risk scores used in the context of coronary interventions, such as the Academic Research Consortium High Bleeding Risk (ARC-HBR) [28] and PRECISE-DAPT [29] scores. Nonetheless, these tools lack validation within the PAD population targeted by this guideline.

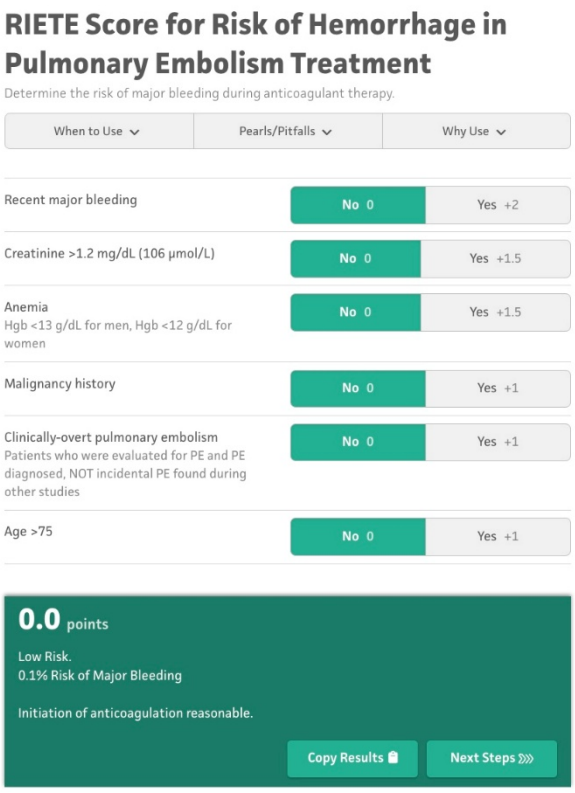
Therefore, although an assessment of bleeding risk is advisable for all LEAD patients considered for antithrombotic treatment, a definitive, validated scoring system cannot yet be recommended. An evaluation of bleeding risk, however, can be valuable for identifying potentially modifiable factors, such as anemia or thrombocytopenia, or reducing the use of agents like non-steroidal anti-inflammatory drugs (NSAIDs). Although current evidence does not definitively demonstrate that correcting these factors decreases future bleeding risk in patients with vascular disease, such considerations remain prudent.

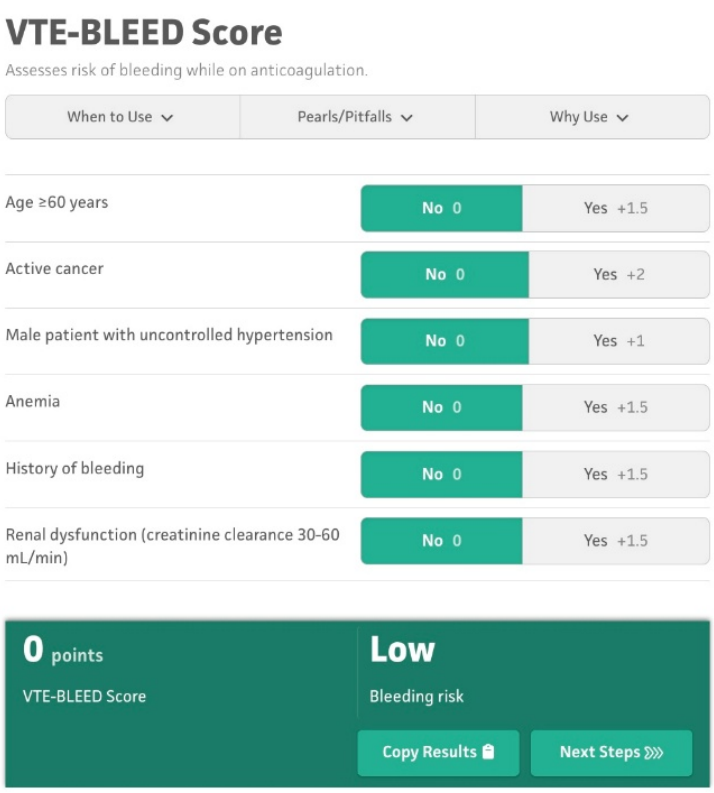
One intervention with evidence supporting its efficacy in reducing bleeding risk among patients on antithrombotics involves the concomitant use of proton pump inhibitors (PPIs), such as pantoprazole. Recent meta-analyses encompassing over 200,000 patients on dual antiplatelet therapy (DAPT) post-percutaneous coronary intervention (PCI) demonstrated that PPI use significantly diminishes gastrointestinal hemorrhage risk (RR 0.32; 95% CI 0.20 to 0.52) without affecting all-cause mortality (RR 1.35; 95% CI 0.56 to 3.23) [30]. The largest contributing trial within a meta-analysis was the

COMPASS study, which randomized patients to pantoprazole 40 mg alongside DAPT. While this regimen did decrease gastroduodenal bleeding (HR 0.52; 95% CI 0.28 to 0.94, p=0.030), the absolute benefit was modest, with a high number needed to treat (NNt=982) [31]. Notably, many high-risk patients in the same study were already receiving PPIs prior to randomization, limiting the generalization of this strategy to all patient populations [32].

Utilization of risk scores may assist clinicians in guiding PPI prophylaxis, especially for those with a history of upper gastrointestinal lesions, which is a key predictor of future bleeding events. Additional modifiable risk factors include cessation of NSAIDs, providing detailed patient counseling regarding bleeding risks, and establishing clear protocols for managing bleeding complications. Balancing anticoagulant management—such as withholding, bridging, or adjusting therapy prior to invasive procedures—is also critical.

Several bleeding risk assessment tools have been proposed for anticoagulation in venous thromboembolism (VTE), including the American College of Chest Physicians (ACCP) risk score [33], VTE BLEED score [34], and REITE score [35]. Although the ACCP score is frequently cited, it lacks comprehensive validation. Furthermore, evidence suggests that patients with venous indications for anticoagulation typically face a lower risk of major bleeding than those with arterial disease.





Perioperative antithrombotic management

The perioperative management of antithrombotic therapy involves patients undergoing surgical or invasive procedures who are concurrently receiving anticoagulant agents, such as vitamin K antagonists (VKAs), direct oral anticoagulants (DOACs), or antiplatelet medications. This clinical scenario is of considerable significance due to the widespread utilization of these pharmacologic agents in the prevention and treatment of various thromboembolic conditions. These include atrial fibrillation, venous thromboembolism (VTE), prosthetic heart valves, coronary artery disease, and peripheral arterial disease. The prevalence of this issue is expected to rise concomitantly with demographic trends, particularly in aging populations where the need for antithrombotic therapy is prevalent and the likelihood of requiring surgical intervention is increased.

Epidemiological data suggest that approximately 15% to 20% of individuals on anticoagulation therapy annually require a surgical or invasive procedure [36], [37], [38]. Furthermore, within the subset of patients with coronary stents, 10% to 15% necessitate surgical intervention within two years following stent implantation [39], [40]. The management of these patients requires careful balancing of thromboembolic risk against bleeding potential, emphasizing the importance of individualized perioperative strategies to optimize outcomes.

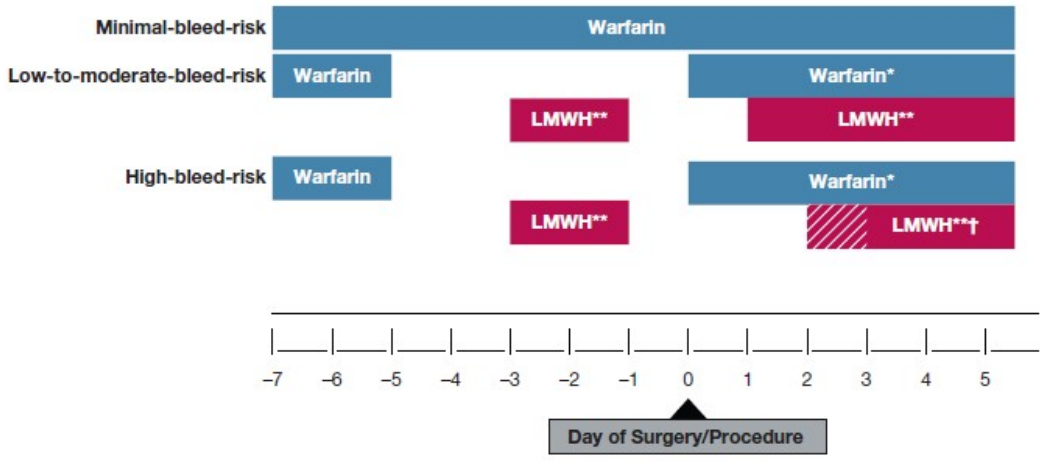
Patients under VKA

The decision regarding the timing of vitamin K antagonist (VKA) discontinuation prior to surgical or invasive procedures aims to achieve a near-normal or normalization of the International Normalized Ratio (INR) at the time of the intervention. This timing is primarily determined by the pharmacokinetics of VKAs, specifically their elimination half-life, which generally ranges from 36 to 42 hours for warfarin, 8 to 11 hours for acenocoumarol, and approximately 96 to 104 hours for phenprocoumon in patients without significant comorbidities such as hepatic impairment, genetic polymorphisms affecting metabolism, or interactions with concomitant medications [41].

For patients whose goal is to normalize the INR following warfarin interruption, a typical period of about five days before the procedure is necessary to reduce anticoagulant effects to a near-zero level. In certain populations, such as elderly individuals or patients with genetic variants that impair warfarin metabolism, or when preoperative INR exceeds 3.5, extending the interruption to six or more days may be warranted. Postoperative resumption of VKA therapy results in a delayed onset of the full anticoagulant effect, with INR levels exceeding 2.0 typically achieved between four to eight days after restarting the medication.

Routine INR monitoring immediately prior to surgery (the day before) or in the first one to two days after the procedure generally is not necessary under standard circumstances. However, specific clinical scenarios—such as a preoperative INR greater than 3.5, known delayed warfarin clearance, or unexpected postoperative bleeding following VKA reinitiation—may warrant targeted laboratory assessment to guide management [42].

In the context of perioperative VKA interruption, heparin bridging has traditionally been employed to reduce the period during which patients are not achieving therapeutic anticoagulation, with the primary aim of decreasing the risk of perioperative arterial thromboembolism (ATE) and recurrent VTE. Nonetheless, this strategy's effectiveness is subject to debate, given the myriad factors contributing to perioperative thromboembolism, including the nature of the surgical procedure itself. Furthermore, the capacity of heparin bridging to influence the complex pathophysiological mechanisms underlying thromboembolic events remains limited.



Legend
*Warfarin can be resumed on the evening of procedure (D0) for most patients, or the day after procedure (i.e., D1) at the patient's usual maintenance dose.
**Bridging suggested for high thrombotic risk populations with full-dose, subcutaneous LMWH (e.g., enoxaparin, 1 mg/kg bid or 1.5 mg/kg daily or dalteparin, 100 IU/kg bid or 200 IU/kg daily), with the last dose given the AM of the day prior to the procedure (i.e., D-1) at half the total daily dose.
†Low-dose LMWH (e.g., enoxaparin, 40 mg daily or dalteparin 5,000 IU daily) can be used for VTE prophylaxis for first 24-72 hours post-procedure, with full dose LMWH resumed 2-3 days post-procedure.

Figure 1 – *Perioperative management of vitamin K antagonists (warfarin). LMWH = low-molecular-weight heparin.*

Patients under Heparin and LMWH

The perioperative approach to patients undergoing heparin bridging therapy relies on a thorough understanding of the pharmacological characteristics of the anticoagulant agents involved, specifically low molecular weight heparin (LMWH) and unfractionated heparin (UFH). LMWH exhibits an elimination half-life of approximately 3 to 5 hours, which guides the timing for discontinuation prior to surgery. Its peak anticoagulant activity occurs within 3 to 4 hours after administration, informing the recommended timing for postoperative initiation of therapy. Conversely, UFH has a dose-dependent elimination half-life averaging around 90 minutes; however, this can range from 30 to 120 minutes depending on the level of anticoagulation at the time of interruption, as measured by activated partial thromboplastin time (aPTT) or anti-factor Xa levels [42].

Currently, there is a lack of study data specifically evaluating the optimal timing for withholding LMWH before surgical procedures and how this impacts bleeding risk or other clinical outcomes. Observational studies assessing LMWH bridging have suggested that bleeding rates are not significantly increased when the last dose is administered approximately 12 hours prior to surgery or roughly 24 hours before the procedure. Further, analyses using surrogate markers of bleeding, such as anti-factor Xa activity, indicate that over 90% of patients who received their final LMWH dose approximately 12 hours before surgery still demonstrated detectable anticoagulant effects at the time of surgery. Notably, about 34% of these patients had anticoagulant levels consistent with therapeutic activity, as indicated by anti-factor Xa levels equal to or exceeding 0.50 IU/mL [41].

Patients under DOACs

The cessation of direct oral anticoagulants (DOACs) prior to elective surgical or invasive procedures can be guided by a pharmacokinetic-based approach, like strategies employed with other anticoagulants. In this approach, the recommended interruption period corresponds to four to five elimination half-lives of the specific DOAC. Given that the half-life of DOACs typically range from 9 to 14 hours, withholding the medication for approximately two full days (which equates to roughly 60 to 68 hours from the last dose) generally ensures that minimal or no residual anticoagulant activity remains at the time of surgery. This interval aims to reduce bleeding risk, particularly in procedures with high hemorrhagic potential [43].

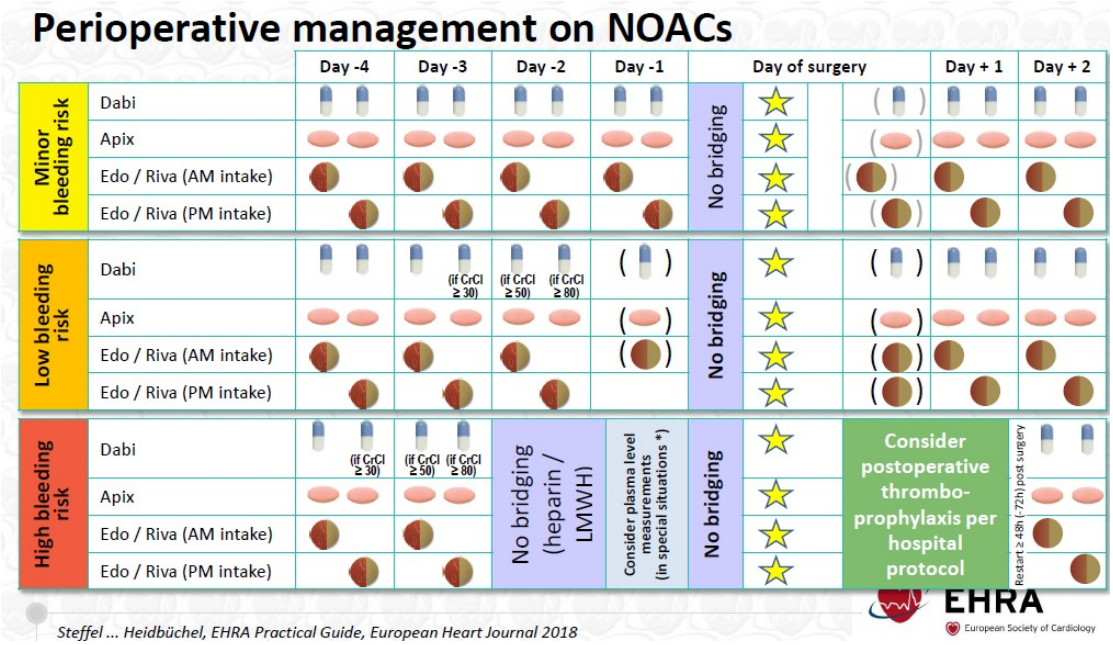
For procedures associated with moderate or low bleeding risk, a shorter withholding period—around 30 to 36 hours, or approximately three half-lives—may be sufficient, resulting in a residual anticoagulant effect that is considered

clinically acceptable for lower-risk interventions. It is important that, in all cases, patients refrain from taking any DOAC on the day of the surgery or procedure.

Several considerations influence this pharmacokinetic interruption strategy. In patients treated with dabigatran who have impaired renal function, specifically, a creatinine clearance (CrCl) below 50 mL/min a longer discontinuation period of three to four days is prudent. This adjustment accounts for the decreased renal clearance of dabigatran, which is primarily eliminated through the kidneys, with approximately 75% to 80% of the drug excreted via this route.

Moreover, some patients may require an even more extended period of DOAC discontinuation prior to surgery, regardless of the specific agent used. This includes patients with severely impaired renal function (CrCl less than 30 mL/min), hepatic dysfunction, or those taking medications that inhibit CYP3A4 or P-glycoprotein pathways, as these medications can interfere with the metabolism and clearance of DOACs.

An alternative approach involves measuring plasma levels of DOACs before surgical procedures, especially in urgent situations where intervention is needed within 24 hours, such as in cases of hip fracture repair. However, routine coagulation tests like the INR or activated partial thromboplastin time (aPTT) are often insufficiently sensitive to reliably detect residual DOAC activity. In such cases, specialized assays—such as anti-factor Xa activity calibrated for apixaban, edoxaban, and rivaroxaban, or dilute thrombin time and ecarin clotting time for dabigatran—may be employed. Although these tests can provide specific information regarding anticoagulant presence, their routine clinical utility remains under investigation, and they may not be widely available or standardized [41], [42].



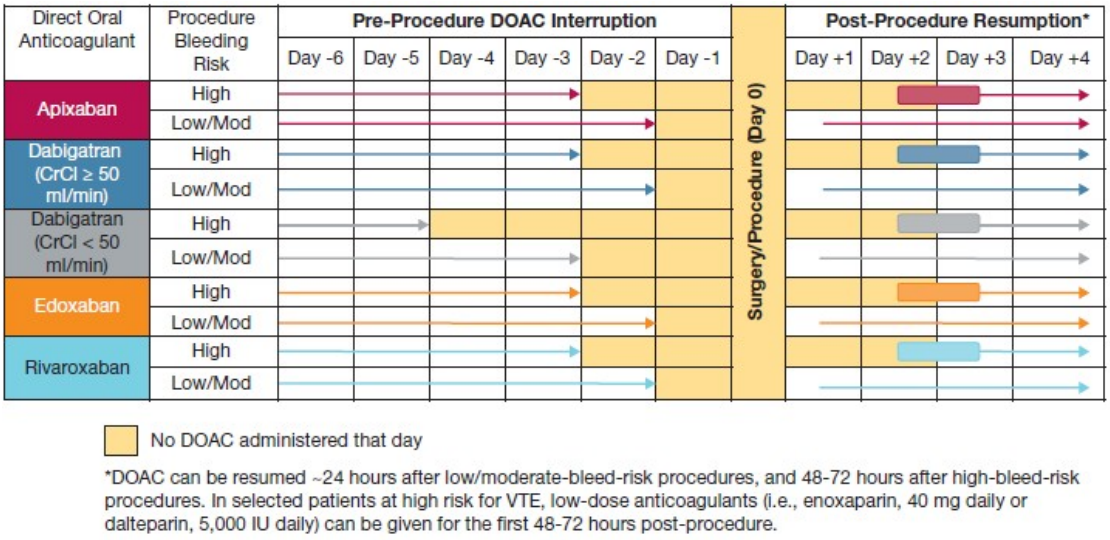


Figure 2 – *Perioperative management of direct oral anticoagulants (DOACs). CrCl = creatinine clearance.*

Perioperative management of NOACs

	Dabigatran		Apixaban - Edoxaban - Rivaroxaban	
	No important bleeding risk and/or adequate local haemostasis possible: perform at trough level (i.e. 12 h or 24 h after last intake)			
	Low risk	High risk	Low risk	High risk
CrCl ≥80 ml/min	≥ 24 h	≥ 48 h	≥ 24 h	≥ 48 h
CrCl 50-79 ml/min	≥ 36 h	≥ 72 h		
CrCl 30-49 ml/min	≥ 48 h	≥ 96 h		
CrCl 15-29 ml/min	Not indicated	Not indicated	≥ 36 h	
CrCl <15 ml/min	No official indication for use			
No bridging with LMWH/UFH				
Resume full dose of NOAC ≥ 24 h post low bleeding risk interventions and 48 (-72) h post high-bleeding risk interventions				
Patients undergoing a planned intervention should receive a written note indicating the anticipated date and time of their intervention and the date and time of the last intake of their NOAC (and any other medication)				

Steffel ... Heidbüchel, EHRA Practical Guide, European Heart Journal 2018

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Patients under antiplatelets

An understanding of the fundamental pharmacologic properties of antiplatelet agents is essential for guiding the timing of their interruption and reinitiation around surgical procedures. When discontinuing aspirin (ASA) and P2Y12 inhibitors such as clopidogrel and prasugrel, it is important to consider that these drugs irreversibly inhibit platelet function. Consequently, a withdrawal period of approximately seven to ten days—corresponding to the lifespan of platelets—is necessary to restore normal platelet activity. In contrast, ticagrelor, which reversibly inhibits platelet function, typically requires a shorter interruption period of at least two to three days to allow for the recovery of platelet function. [41]

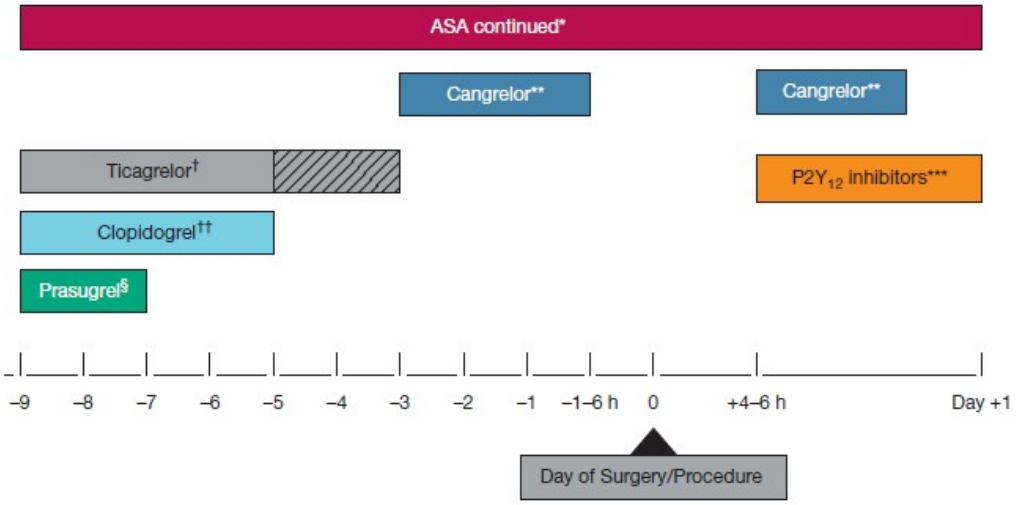
Postoperative reintroduction of antiplatelet therapy results in a rapid onset of maximal effect: within minutes after aspirin ingestion, within two hours following ticagrelor, and approximately four to five days after resuming clopidogrel at a maintenance dose of 75 mg. If a loading dose of clopidogrel is administered, the full antiplatelet effect may be achieved within two to six hours. Additional, less commonly used reversible platelet inhibitors include cilostazol, dipyridamole, and pentoxifylline, which have half-lives ranging from two to ten hours. Vorapaxar, which exerts a prolonged antiplatelet effect, can sustain activity for three to fifteen days after administration. Nonsteroidal anti-inflammatory drugs (NSAIDs) exhibit reversible antiplatelet properties as well, with half-lives varying from two to six hours for agents like ibuprofen, ketoprofen, and indomethacin; around 7 to 15 hours for celecoxib, naproxen, and diflunisal; and approximately 20 hours for meloxicam, nabumetone, and piroxicam.

Limited clinical data exist regarding the optimal duration of aspirin interruption prior to surgery. A small trial involving eighty patients compared four to five days versus ten days of preoperative aspirin withdrawal, yet it was underpowered due to low event rates for cardiovascular and bleeding outcomes. The Prevention of Thromboembolism after Hip Fracture Surgery (PEP) trial, with over 17,000 participants undergoing hip or knee surgeries, demonstrated a reduction in venous thromboembolism (VTE) risk with perioperative aspirin without significantly increasing myocardial ischemia or stroke risk, albeit with a modest increase in major bleeding.[44] Another study involving 220 high-risk patients, initiated seven days before surgery and continued for thirty days, showed a significant reduction in major cardiovascular events with aspirin but was insufficiently powered to detect differences in bleeding.

The POISE-2 trial, a large randomized controlled trial examining aspirin management in over 10,000 patients undergoing major non-cardiac surgery, found that initiating or continuing aspirin perioperatively did not significantly reduce the incidence of non-fatal myocardial infarction or death but did raise

the risk of major bleeding. These findings were complicated by the concomitant use of nonsteroidal anti-inflammatory drugs in a substantial proportion of participants, which could have mitigated the cardioprotective effects of aspirin and contributed to increased bleeding. Smaller, underpowered studies comparing perioperative aspirin interruption with continuation or single preoperative doses have generally reported no significant differences in thromboembolic or bleeding events. [45]

Currently, there are no prospective studies evaluating perioperative management strategies for P2Y12 inhibitors such as clopidogrel, prasugrel, or ticagrelor in non-cardiac surgical settings. Retrospective analyses suggest that ongoing perioperative use of clopidogrel may elevate bleeding risk; however, definitive conclusions regarding optimal timing and safety remain elusive



Legend:
*Based on surgery/procedure bleed risk assessment.
**Routine use not suggested. If used, initiate within 72 hours from $P2Y_{12}$ inhibitor discontinuation at dose of 0.75 mg/kg/min; resume within 6 hours post-procedure for minimum of 48 hours and maximum of 7 days total. Very low quality data for antiplatelet bridging with glycoprotein IIb/IIIa inhibitors (e.g., eptifibatide, tirofiban).
***$P2Y_{12}$ inhibitors can be resumed within 24 hours post-procedure at a maintenance dose.
†For ticagrelor, 3-5 day interruption
††For clopidogrel, 5 day interruption
§For prasugrel, 7-10 day interruption.

Figure 3 – *Perioperative management of antiplatelet drugs. ASA = aspirin.*

Intraoperative antithrombotic management

UFH remains the most widely employed anticoagulant for preventing arterial thromboembolic complications (ATEC) in vascular interventions involving major vessel manipulation, particularly during endovascular and open procedures. Despite its widespread use, there is notable variability in dosing strategies, with many practitioners administering a standard bolus of 5,000 IU regardless of individual patient characteristics or procedural specifics—a practice driven largely by convention rather than evidence-based guidelines.

The anticoagulant effect of UFH is multifactorial and unpredictable at the individual level, owing to its non-linear dose-response relationship and variable pharmacokinetics. Heparin's heterogeneity stems from differences in molecular size, activity, and batch-to-batch variability, which complicates standardization and undermines its predictability. Consequently, monitoring its effect through laboratory parameters such as the activated clotting time (ACT) becomes vital, although routine ACT measurement during NCAP is infrequent compared with cardiac procedures, where it is standard practice.

Current guidelines lack definitive, evidence-based recommendations for optimal heparin dosing or target ACT levels in NCAP. While some protocols suggest maintaining an ACT between 200 and 250 seconds, the evidence supporting these thresholds is sparse, with most data extrapolated from cardiac interventions or observational studies. For example, carotid interventions employ target ACT values ranging from 200 to 300 seconds, depending on the procedure, yet consensus remains elusive. Furthermore, clinical outcomes appear to correlate with achieving certain ACT thresholds; however, definitive randomized trials establishing the optimal ACT range for minimizing ATEC without increasing bleeding risk are lacking. [46]

Several observational studies and registry data suggest that maintaining an ACT below 250 seconds may reduce bleeding complications without compromising thromboembolic protection, whereas higher ACT values (>350 seconds) are associated with increased haemorrhagic events. Nevertheless, the heterogeneity in practice persists, often with practitioners administering fixed doses of UFH without routine monitoring, thereby risking under- or over-anticoagulation [145].

Multicentre prospective trials, such as the MANCO study, have investigated tailored heparin strategies to address these issues. The MANCO trial evaluated three approaches: no additional heparin, fixed-dose heparin aimed at a target ACT of 250 seconds, and weight-based dosing of heparin (100 IU/kg) with subsequent adjustments based on real-time ACT measurements. The results demonstrated that ACT-guided protocols are feasible and safe, with the ability to tailor anticoagulation more precisely, potentially reducing the need for excessive dosing and minimizing bleeding risk [47].

In conclusion, optimal anticoagulation during NCAP remains an unresolved issue. There is an urgent need for randomized controlled trials to define evidence-based target ACT ranges and ideal dosing regimens that balance the prevention of thromboembolic events against bleeding risk. Until such data are available, individualized heparinization guided by ACT measurements appears to be a pragmatic approach, promising enhanced safety and efficacy in vascular interventions.

Protocol

A systematic review of the medical literature was conducted, utilizing PubMed, SCOPUS, and CENTRAL databases, following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) 2020 guidelines. The analysis included RCTs and Systematic Reviews and meta-analyses published up to January 2025, and focused on antithrombotic therapy after endovascular procedures in patients with PAD of lower limbs. Additionally, case reports, case series, and studies involving experimental diagnostic models or not involving human subjects were deemed ineligible. Language was not a criterion for exclusion, provided that an English version of the article was available. Eligible studies underwent a full-text review, adhering to the predefined inclusion and exclusion criteria.

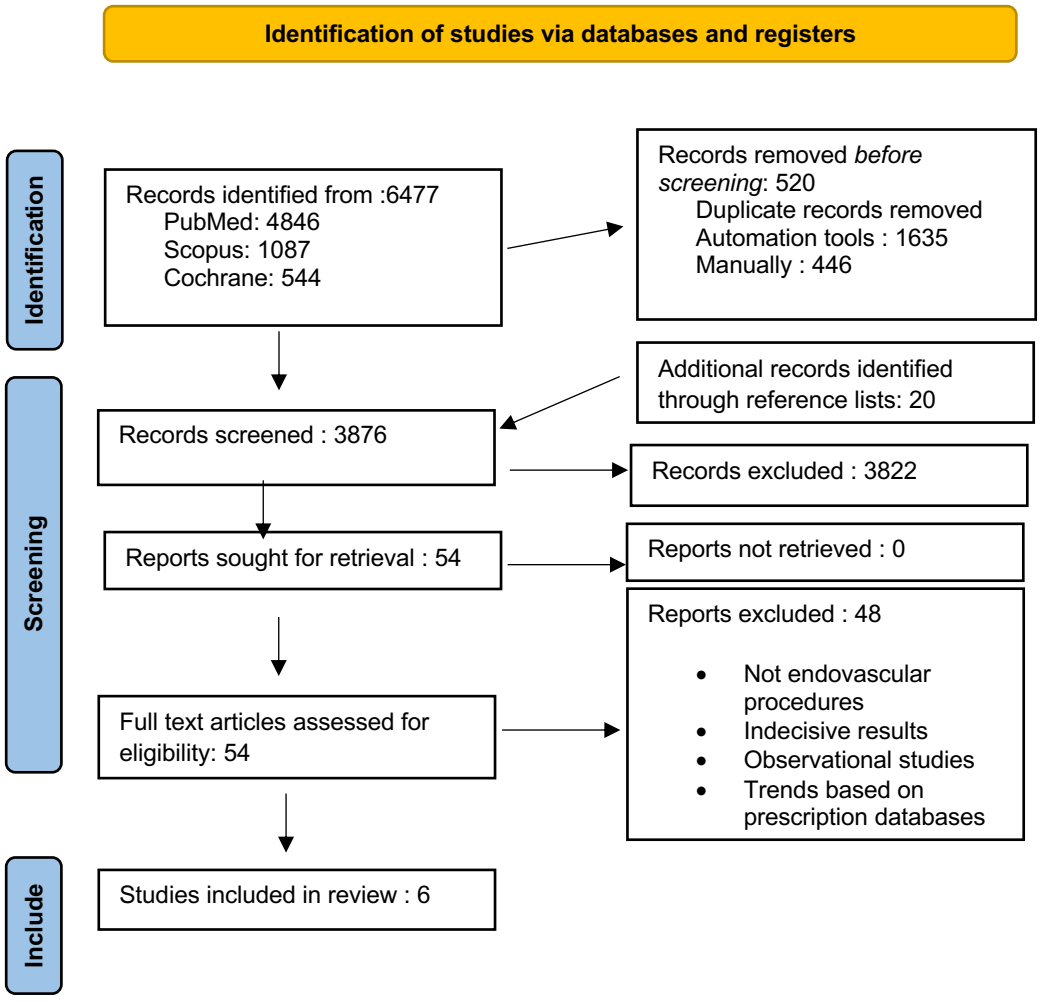


Figure 4. PRISMA 2020 flowchart. Screening process based on the PRISMA 2020 Guidelines for systematic reviews and meta-analyses.

Search strategy

The databases PubMed, SCOPUS, and CENTRAL were systematically searched based on predefined clinically relevant questions established prior to commencing the review, following the P.I.C.O. (patient; intervention; comparison; outcome) model (refer to Supplementary Table S1). A range of terms including “endovascular repair”, “angioplasty”, “stenting”, peripheral endovascular intervention”, “PTA”, “percutaneous transluminal angioplasty”, “endovascular”, “peripheral artery disease”, “PAD”, “CLTI”, “lower limbs”, “extremities”, “antiplatelet therapy”, “SAPT”, “DAPT”, “anticoagulation”, “LMWH”, “heparin”, “VKA”, “antithrombotic”, “vitamin k antagonist”, “acetylsalicylic acid”, “clopidogrel”, “apixaban”, “rivaroxaban”, were employed either individually or in combination under the Expanded Medical Subject Headings (MeSH) filter (see Supplementary Table S1). Duplicate entries were identified and removed using automation tools (EndNote 20.6). Initial screening was based on titles and abstracts, with further evaluation conducted through a full-text review for secondary selection.

P	Patient, population or problem	Patients with PAD (Peripheral Arterial Disease) of lower limbs after endovascular intervention for revascularization.
I	Intervention, prognostic factor or exposure	Antithrombotic drugs (antiplatelets, anticoagulants or combination)
C	Comparison of intervention	Antiplatelet therapy vs Anticoagulation therapy vs combination of them
O	Outcome you would like to measure or achieve	The best combination of antithrombotic drugs that leads to best vessel patency, lower limb amputation, less bleeding events
	What type of question are you asking?	What is the best antithrombotic medication after endovascular procedures for revascularization in patients with PAD
	Type of study you want to find	RCTs, Systematic reviews, meta-analyses

Table 2. P.I.C.O. model

Footnote: P.I.C.O. (patient; intervention; comparison; outcome) model was used to define the clinical questions and clinically relevant evidence in the literature.

Data extraction

A Microsoft Excel spreadsheet extraction tool was created for data extraction purposes. This involved gathering general details such as author, title, publication year, and journal.

Results

Six studies remained after the selection criteria.

In the first RCT by Bonaca et al. patients with peripheral artery disease who had revascularization were treated with rivaroxaban plus aspirin or placebo plus aspirin. Rivaroxaban significantly reduced the risk of major vascular and cardiac events over three years. Although there was an increase in major bleeding according to ISTH criteria, TIMI bleeding rates were similar between groups. Overall, rivaroxaban combined with aspirin lowered the incidence of adverse cardiovascular outcomes with a manageable safety profile.

The second study by Strobl. et al.: showed that six months of dual therapy with aspirin and clopidogrel significantly decreased restenosis rates after intervention. However, this benefit did not persist once clopidogrel was discontinued; restenosis rates at twelve months were similar between groups. Mortality rates were low and not significantly different. The findings suggest that prolonged dual antiplatelet therapy beyond six months may be beneficial for patients at higher risk of restenosis, though further research is needed to confirm this.

The third study was by Moll et al. This randomized study evaluated the safety and potential efficacy of edoxaban, an oral anticoagulant targeting key components of arterial thrombi, in preventing restenosis after femoropopliteal endovascular treatment (EVT). Among 203 patients, those receiving aspirin plus edoxaban (n=101) showed no major or life-threatening bleeding events according to TIMI and ISTH criteria, whereas the clopidogrel group experienced some serious bleeding incidents. Over six months, restenosis or reocclusion occurred less frequently in the edoxaban group (30.9%) compared to the

clopidogrel group (34.7%), though this difference was not statistically significant. Results suggest similar bleeding risks for both regimens, with a possible advantage for edoxaban in reducing restenosis, warranting further investigation.

The fourth study by Ambler et al. This comprehensive review and meta-analysis examined the effectiveness and safety of antiplatelet therapy in peripheral artery disease (PAD). Analyzing 28 meta-analyses with data from over 72,000 patients, the study found that monotherapy reduced non-fatal strokes and, in symptomatic patients, decreased cardiovascular deaths but increased major bleeding risk. In asymptomatic individuals, monotherapy offered limited benefits. Dual therapy increased bleeding complications and showed uncertain benefits for vascular patency. Overall, antiplatelet monotherapy provides minimal clinical advantage, especially in asymptomatic cases, and evidence is lacking regarding post-procedure management, highlighting the need for further research.

The fifth study by Katsanos et al This systematic review and network meta-analysis evaluated different antiplatelet agents for peripheral artery disease (PAD). Analyzing data from 49 randomized controlled trials involving over 34,000 patients, the study found that drugs like aspirin, Cilostazol, Vorapaxar, and Picotamide did not significantly reduce major adverse cardiovascular events (MACE). Conversely, Ticagrelor combined with aspirin, Clopidogrel alone, Ticlopidine, and Clopidogrel with aspirin significantly lowered MACE rates. Dual therapy with Clopidogrel and aspirin also reduced major amputations post-revascularization but increased bleeding risk. Overall, Clopidogrel monotherapy demonstrated the best balance of efficacy and safety for PAD patients.

Finally, the sixth study by Megaly et al. This meta-analysis assessed the effects of cilostazol following endovascular therapy (EVT) for peripheral artery disease (PAD). Analyzing eight studies with nearly 3,846 patients and a follow-up of about 12.5 months, results showed that cilostazol significantly improved primary vessel patency (OR 2.28), reduced target lesion revascularization (OR 0.37), and decreased major amputations (OR 0.15). These benefits persisted

regardless of anticoagulant use, such as warfarin. The findings suggest cilostazol enhances vessel durability and limb preservation after EVT for femoropopliteal and iliac lesions, independently of concomitant anticoagulation therapy.

	Journal	Study Type	PTS	Subject	Primary endpoint /Secondary endpoint	Primary safety outcome
2020	N Eng J Med	RCT	6564	Aspirin + Placebo vs Aspirin + Ricaroxaban 2.5 x 2	Acute limb ischemia, majot amputation, MI, i.Stroke, death	Major bleeding
2011	Eur Radiol	RCT	80	Aspirin + Placebo vs Aspirin + Clopidogrel	Concentrations of platelet activation markers, rate of pts resistance to clopidogrel / Clinical developments 6 months after intervention	
2020	Br J Surg	Review and meta-analysis (28 meta-analyses)	72181	SAPT vs Placebo, DAPT vs SAPT, Antiplatelet vs Anticoagulation	All safety and efficacy outcomes	
2015	PLoS One	Review and meta-analysis	34518	Aspirin,Ticlopidine, Clopidogrel, Tigagrelol, Cilostazol, Picotamide and Voraxapar monotherapy or in combination with Aspirin in PAD pts	Composite rate of MACE, rate of major leg amputations	Rate of severe bleeding events
2019	Vasc. Med.	Meta-analysis of 8 studies (3RCT+5 observational)	3846	Cilostazol vs placebo	Vessel Patency after EVT in femoropopliteal and iliac lesions/major amputation	
2018	J Endovasc Ther	RCT	203	Aspirin + Edoxaban vs Aspirin + Clopidogrel after EVT femoropopliteal	Rate of restonosis/reocclusion	Bleeding (TIMI)

Postoperative management

American Heart Association / American College of Cardiology (AHA/ACC) 2024 GUIDELINES

Peripheral Arterial Disease (PAD) patients frequently present with a history of prior revascularization, either via endovascular or surgical intervention, and evidence suggests they carry a heightened residual risk for cardiovascular and limb-related adverse events. Despite this, current data do not support the routine use of more potent antiplatelet agents or dual antiplatelet therapy outside the context of recent revascularization procedures. Similarly, the deployment of full-dose oral anticoagulation in patients without other indications, such as atrial fibrillation, is generally not justified and may potentially pose harm.

In individuals who have undergone revascularization for PAD, pharmacological strategies that include antiplatelet and antithrombotic agents have demonstrated efficacy in reducing recurrent symptoms and incidences of major adverse limb events (MALE). The decision to initiate or continue such therapies hinges on multiple factors, including the patient's comorbidities—such as coronary artery disease (CAD)—the complexity of the revascularization procedure, and the overall risk profile for major cardiovascular and limb ischemic events versus bleeding complications. The findings from the VOYAGER PAD trial provide further insight; this study illustrated that the combination of low-dose rivaroxaban with low-dose aspirin significantly lowered the incidence of ischemic limb events and the composite primary endpoint in patients without prior stroke or elevated bleeding risk, thereby endorsing adjunctive use of this therapeutic approach in appropriate candidates.

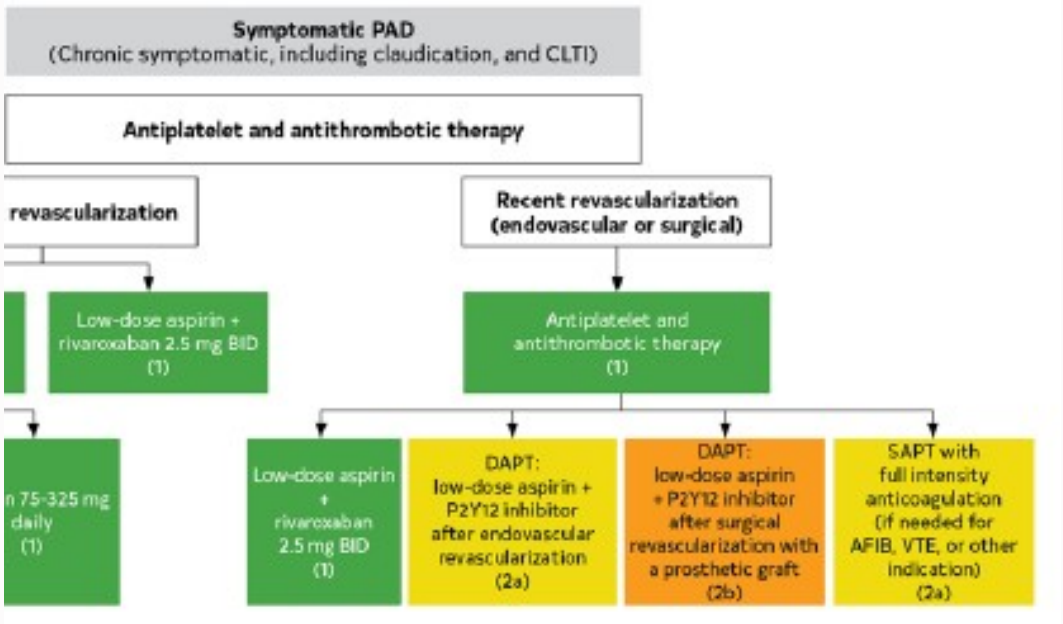
The therapeutic paradigm for dual antiplatelet therapy (DAPT) post-revascularization is primarily extrapolated from data obtained in coronary intervention studies. In the realm of peripheral revascularization, existing evidence supporting DAPT is limited and mainly derived from small-scale trials and meta-analyses, which generally endorse single antiplatelet therapy as a standard, especially considering the absence of large, placebo-controlled trials. Notably, certain revascularization devices, such as drug-eluting stents and drug-coated balloons, have mandated dual antiplatelet therapy for durations spanning from two to six months, owing to the risk of restenosis and thrombosis. Observational data suggest that among patients with critical limb ischemia (CLI), dual therapy may confer additional benefits, although definitive conclusions are yet to be established.

The concomitant use of full-dose oral anticoagulation alongside dual antiplatelet therapy—referred to as "triple therapy"—has been associated with an increased haemorrhagic risk. Recent randomized trials in patients requiring anticoagulation who undergo percutaneous coronary procedures support a strategy favouring single antiplatelet therapy in conjunction with anticoagulation, particularly for those without a high bleeding risk and with indications such as atrial fibrillation or venous thromboembolism. These

findings align with expert guidelines and consensus recommendations, including those issued by the American College of Cardiology (ACC), which emphasize a patient-specific approach when balancing ischemic and bleeding risks in managing anticoagulation and antiplatelet regimens.

In summary, the optimal management of antiplatelet and anticoagulant therapy following vascular revascularization in PAD is an area of active research, with current evidence favouring individualized strategies. Future large-scale, randomized studies are essential to establish definitive guidelines that comprehensively address the nuances of patient selection, device type, procedural complexity, and comorbid conditions to optimize outcomes while minimizing adverse effects.

1	B-R	5. After endovascular or surgical revascularization for PAD, antiplatelet therapy is recommended.[17–9]
1	A	6. After endovascular or surgical revascularization for PAD, low-dose rivaroxaban (2.5 mg twice daily) combined with low-dose aspirin is recommended to reduce the risk of MACE and MALE.[7]
2a	C-LD	7. After endovascular revascularization for PAD, dual antiplatelet therapy with a P2Y12 antagonist and low-dose aspirin is reasonable for at least 1 to 6 months.[8–11]
2a	C-LD	8. After endovascular or surgical revascularization in patients with PAD who require full-intensity anticoagulation for another indication and are not at high risk of bleeding, adding single antiplatelet therapy is reasonable.[12,13]



ESC GUIDELINES

Endovascular management of peripheral artery disease (PAD) has increasingly incorporated pharmacological strategies to optimize outcomes, although high-quality evidence remains limited. Notably, some randomized studies, albeit scarce, have suggested that dual antiplatelet therapy (DAPT), administered for periods ranging from one to three months post-procedure, may contribute to improved vessel patency. However, these studies have not demonstrated a clear reduction in cardiovascular (CV) mortality or major adverse cardiovascular events (MACE) attributable to DAPT, underscoring the need for further validation.

While DAPT appears to enhance vessel patency without significantly elevating bleeding risks, some data indicate a nuanced safety profile. Specifically, the combination of aspirin at a dose of 100 mg daily with low-dose rivaroxaban (2.5 mg twice daily), introduced following revascularization, has been associated with a modest but statistically meaningful reduction in the incidence of major adverse limb events (MALE) and major adverse cardiovascular events (MACE). Importantly, this regimen did not increase the occurrence of thrombolysis in myocardial infarction (TIMI) major bleeding; however, it was linked to a rise in bleeding events classified as major by the International Society on Thrombosis and Haemostasis (ISTH), particularly when clopidogrel was used beyond one month.

Patients suffering from chronic limb-threatening ischemia (CLTI) represent a particularly high-risk cohort for both MACE and MALE. The elevated risk profile underscores the importance of tailored pharmacotherapy that balances the benefits of ischemic protection against the potential for bleeding complications. Given the limited yet evolving evidence base, ongoing research is essential to refine antithrombotic regimens post-revascularization, aiming to optimize limb salvage, reduce recurrent ischemic events, and improve overall survival in this vulnerable population.

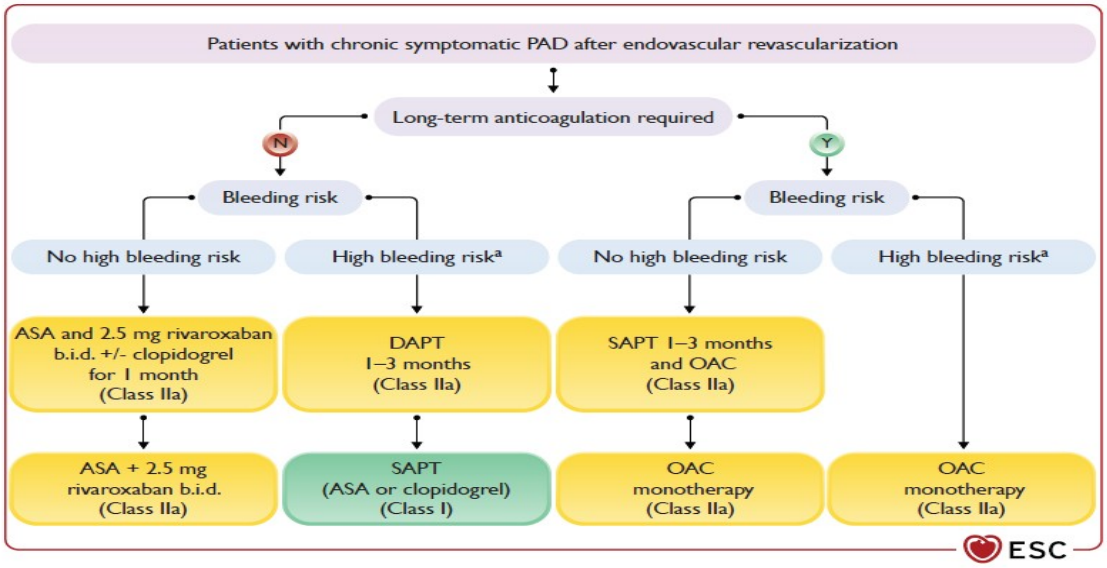


Figure 15 Patients with chronic symptomatic PAD after endovascular revascularization. b.i.d., twice daily; DAPT, dual antiplatelet therapy; OAC, oral anticoagulant; PAD, peripheral arterial disease; ASA, aspirin; SAPT, single antiplatelet therapy [a]High bleeding risk: dialysis or a renal impairment glomerular filtration rate <15 mL/min/1.73 m^2, acute coronary syndrome <30 days, history of intracranial haemorrhage, stroke or TIA, active or clinically significant bleeding.

ESVS GUIDELINES

In the context of endovascular treatment for peripheral arterial disease, the optimal strategy for antithrombotic therapy remains a subject of ongoing investigation, with current evidence primarily extrapolated from studies conducted in coronary and cerebrovascular populations. The combination of aspirin at a standard dose of 100 mg daily with low-dose rivaroxaban (2.5 mg twice daily) has been extensively evaluated in the VOYAGER PAD trial, which enrolled patients at high risk of ischemic events post-revascularization. Notably, the trial's bleeding risk definitions differed slightly from those used in other studies such as COMPASS, and the overall bleeding incidence observed was lower than that reported in broader, real-world cohorts. The primary outcome demonstrated a significant reduction in composite ischemic events over a median follow-up of approximately 28 months, with a notable benefit observed particularly in the surgical subgroup, although the difference was not statistically significant when directly comparing the surgical and endovascular groups.

The trial's population predominantly underwent endovascular procedures for claudication, with the majority (66%) receiving such interventions. Approximately half of the participants also received additional clopidogrel therapy, more frequently so in the post-endovascular subgroup. Subgroup analyses suggested that concomitant clopidogrel did not alter the efficacy of aspirin combined with rivaroxaban but was associated with an increased

incidence of major bleeding as defined by ISTH criteria when used beyond 30 days.

Additionally, a smaller, multicentre, double-blind trial comparing aspirin plus edoxaban with aspirin plus clopidogrel over a three-month period following endovascular intervention found no significant difference in stenosis or re-occlusion rates at six months, nor in the rates of major bleeding complications. These findings highlight the limited comparative evidence available for various antithrombotic regimens in this setting.

A comprehensive network meta-analysis synthesizing current data concluded that while aspirin combined with low-dose rivaroxaban reduced revascularization rates compared with aspirin alone, the paucity of robust evidence for other antiplatelet strategies underscores the difficulty in establishing definitive treatment hierarchies. Consequently, current clinical guidelines offer tailored recommendations, summarized in recent consensus documents, emphasizing individual risk assessment to balance ischemic protection against bleeding hazard in patients undergoing endovascular procedures for lower extremity arterial disease. Overall, the evidence underscores the necessity for further large-scale, well-designed randomized trials to clarify the comparative efficacy and safety profiles of available antithrombotic combinations in this patient population.

Recommendation 33

Patients undergoing endovascular or open arterial surgery may be considered for intra-operative activated partial thromboplastin time, activated partial thromboplastin time ratio, or activated clotting time measurement to guide further doses or reversal of unfractionated heparin.

Class	Level	References
IIb	C	Consensus

Recommendation 34

Patients undergoing endovascular arterial intervention may be considered for a single dose of bivalirudin (0.75 mg/kg) as an alternative to heparin to reduce the risk of peri-operative acute limb events.

Class	Level	References	ToE
IIb	B	Hu *et al.* (2019)[200]	

Recommendation 35

Patients undergoing endovascular intervention for lower extremity arterial disease who are not at high risk of bleeding may be considered for a short course (a minimum of one to maximum six months) dual antiplatelet therapy (aspirin 75 mg plus clopidogrel 75 mg) to reduce the risk of secondary cardiovascular and major adverse limb events.

Class	Level	References
IIb	C	Consensus

Recommendation 31

Patients undergoing endovascular arterial intervention are recommended to have a single bolus of intravenous or intra-arterial unfractionated (50 – 100 IU/kg) or low molecular weight (0.5 mg/kg) heparin to reduce the risk of peri-operative acute limb events.

Class	Level	References	ToE
I	B	Duschek *et al.* (2011)[198]	

Recommendation 36

Patients undergoing endovascular intervention for lower extremity arterial disease who are not at high risk of bleeding should be considered for aspirin (75 – 100 mg once daily) combined with rivaroxaban (2.5 mg twice daily) to reduce the risk of secondary cardiovascular and major adverse limb events.

Class	Level	References	ToE
IIa	B	Bonaca *et al.* (2020)[29]	

Recommendation 37

If clopidogrel (75 mg) is added in exceptional circumstances to aspirin (75 – 100 mg once daily) in combination with rivaroxaban (2.5 mg twice daily) for patients undergoing endovascular intervention for lower extremity arterial disease who are not at high risk of bleeding, it is not recommended for longer than 30 days as the bleeding risk is likely to outweigh the benefit.

Class	Level	References	ToE
III	C	Hiatt *et al.* (2020)[206]	

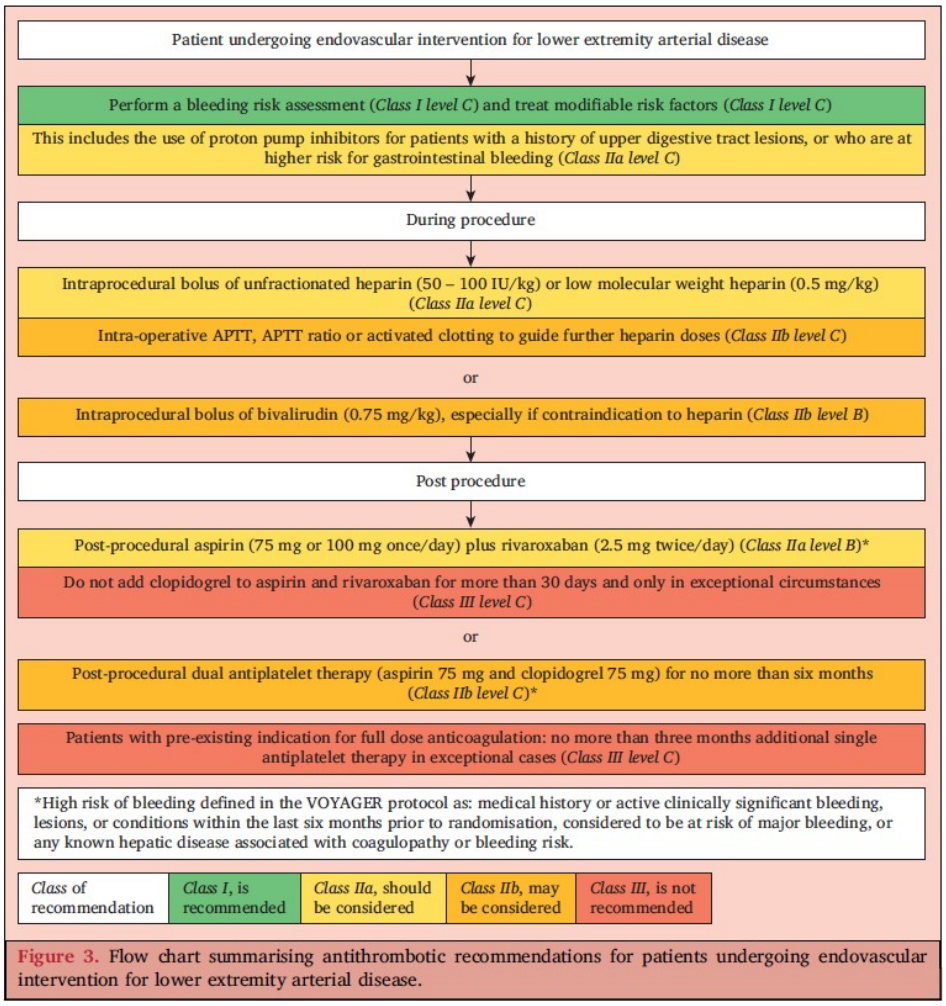


Figure 3. Flow chart summarising antithrombotic recommendations for patients undergoing endovascular intervention for lower extremity arterial disease.

Discussion

Chronic limb-threatening ischemia (CLTI) represents the most severe clinical expression within the spectrum of peripheral arterial disease (PAD). Characterized by critically inadequate blood flow to the lower extremities, CLTI manifests through ischemic rest pain, persistent non-healing ulcers, or gangrenous tissue, signifying advanced disease stages [48,49]. Patients with CLTI face a markedly increased risk of limb loss, with annual amputation rates reported between 15% and 20%, underscoring the urgent need for effective intervention [50].

Beyond the risk of losing a limb, individuals with CLTI are predisposed to major adverse cardiovascular events (MACE) owing to the widespread presence of atherosclerosis affecting coronary and cerebrovascular circulations. Evidence indicates that among PAD patients, those with CLTI are at the highest risk for both cardiovascular mortality and all-cause death, making comprehensive risk reduction strategies imperative [51].

The overarching objectives in managing CLTI encompass dual aims: safeguarding limb function and mitigating systemic cardiovascular risks. Achieving limb salvage necessitates prompt revascularization, undertaken via either endovascular or surgical means, which has proven essential in restoring perfusion [51]. However, the immediate period after revascularization remains perilous, with heightened susceptibility to major adverse limb events (MALE) and MACE [52]. Optimal postoperative care, particularly antithrombotic therapy, is therefore critical to diminish the likelihood of subsequent ischemic complications.

Current guidelines, notably those from the European Society of Cardiology (ESC), endorse a combination of low-dose aspirin (100 mg daily) and rivaroxaban (2.5 mg twice daily) following lower limb revascularization in patients with PAD who do not present a high bleeding risk [53]. For individuals at elevated bleeding risk, a shorter course, typically up to three months—of dual antiplatelet therapy (DAPT) is advised [54]. Nevertheless, it must be emphasized that specific guidelines for antithrombotic treatment in the context of CLTI are lacking, owing largely to limited targeted evidence.

The foundation for the contemporary recommendation on dual pathway inhibition (DPI)—the combination of aspirin and rivaroxaban—stems from the VOYAGER-PAD trial, a large randomized controlled study demonstrating a positive net clinical benefit of DPI over aspirin alone in patients undergoing revascularization for PAD. Notably, this trial included a broad patient population, with only a minority (approximately 23%) presenting CLTI,

highlighting the gap in dedicated evidence for this particularly high-risk subgroup [55].

The scarcity of definitive clinical trial data focusing on antithrombotic regimens specifically for CLTI patients after revascularization has translated into considerable variability across different regions. An international survey conducted by the ESC Working Group on Aorta and Peripheral Vascular Diseases revealed diverse practices, reflecting the uncertainty surrounding optimal management strategies. At present, both current European and surgical guidelines refrain from offering definitive, tailored recommendations for antithrombotic therapy in this subset, leaving clinicians to individualize treatment based on the patient's bleeding risk and clinical profile.

It is increasingly recognized that patients with CLTI may exhibit enhanced platelet activation and a suboptimal response to standard antiplatelet agents, further complicating management. The urgent need for a dedicated, evidence-based scientific statement on antithrombotic strategies in this population has been acknowledged by the ESC Working Groups focused on vascular diseases and cardiovascular pharmacotherapy. This initiative aims to systematically review existing literature with the goal of developing a consensus guide that optimizes secondary prevention, reduces the incidence of MACE and MALE, and advances the clinical care of patients with CLI following revascularization.

In summary, managing CLTI demands an approach that balances ischemia prevention with bleeding risk assessment. Although current evidence guides some aspects of therapy, significant gaps remain, underscoring the necessity for further targeted research to establish clear, evidence-based protocols tailored to this critically vulnerable patient population.

Conclusion

When considering endovascular management of peripheral arterial disease (PAD), optimal antithrombotic strategies remain under active investigation, primarily relying on data from coronary and cerebrovascular studies. The combination of aspirin 100 mg daily with low-dose rivaroxaban (2.5 mg twice daily) has shown benefits in the VOYAGER PAD trial, which involved high-risk post-revascularization patients. Although the trial demonstrated a significant reduction in composite ischemic events, the bleeding risk, though generally acceptable, was somewhat higher than in broader populations, especially when additional clopidogrel therapy was used beyond 30 days.

Most trial participants underwent endovascular procedures, and subgroup analyses indicated that concomitant clopidogrel did not reduce efficacy but increased major bleeding incidences. Smaller studies comparing aspirin with edoxaban to aspirin with clopidogrel showed no significant differences in restenosis or bleeding outcomes, highlighting the limited comparative

evidence for various regimens. A network meta-analysis supports that aspirin combined with low-dose rivaroxaban may reduce revascularization rates compared to aspirin alone, but the overall evidence remains sparse and inconsistent.

Current guidelines advocate for individualized treatment approaches, weighing ischemic benefits against bleeding risks, given the limited robust data. Further large-scale, randomized trials are essential to establish clear, evidence-based recommendations for antithrombotic therapy following endovascular procedures in PAD, aiming to optimize limb salvage, reduce recurrent ischemic events, and improve survival outcomes.

Appendix

Supplementary Table I. Search Strategy

Pubmed Search: ((((((((((((((endovascular repair) OR (EVR)) OR (angioplasty)) OR (stenting)) OR (peripheral endovascular intervention)) OR (PTA)) OR (percutaneous transluminal angioplasty)) OR (endovascular)) OR (endovascular repair[MeSH Terms])) OR (angioplasty, balloon[MeSH Terms])) OR (angioplasty[MeSH Terms])) OR (endovascular stent grafting[MeSH Terms])) OR (drug coated stent[MeSH Terms])) OR (drug eluting stent[MeSH Terms])) AND ((((((((((((peripheral artery disease) OR (PAD)) OR (CLTI)) OR (critical limb threatening ischemia)) OR (critical limb ischemia)) OR (CLI)) OR (lower limbs)) OR (extremities)) OR (peripheral artery disease[MeSH Terms])) OR (critical limb ischemia[MeSH Terms])) OR (lower limbs[MeSH Terms]))) AND ((((((((((((((((((antiplatelet therapy) OR (SAPT)) OR (DAPT)) OR (anticoagulation)) OR (LMWH)) OR (heparin)) OR (VKA)) OR (antithrombotic)) OR (vitamin k antagonist)) OR (acetylsalicylic acid)) OR (clopidogrel)) OR (apixaban)) OR (rivaroxaban)) OR (antiplatelet agents[MeSH Terms])) OR (agents, anticoagulation[MeSH Terms])) OR (agent, antithrombotic[MeSH Terms])) OR (acetylsalicylic acid[MeSH Terms])) OR (rivaroxaban[MeSH Terms])) → **Results: 4846**

CENTRAL search:

ID	Search	Hits
#1	endovascular repair	1070
#2	angioplasty	10720
#3	stenting	6356
#4	peripheral endovascular intervention	503
#5	percutaneous transluminal angioplasty	2804
#6	peripheral artery disease	5539
#7	critical limb threatening ischemia	211
#8	critical limb ischemia	1227
#9	antiplatelet therapy	7141

#10 single antiplatelet therapy 1451

#11 dual antiplatelet therapy 2828

#12 LMWH 1842

#13 antithrombotic therapy 2681

#14 {OR #1-#5} 16134

#15 {OR #6-#8} 6383

#16 {OR #7-#13} 11704

#17 {AND #14-#16} **544 results**

SCOPUS search

ALL((endovascular repair OR EVR OR angioplasty OR stenting OR peripheral endovascular intervention OR percutaneous transluminal angioplasty) AND (peripheral artery disease OR PAD OR CLTI OR CLI OR critical limb ischemia) AND (antiplatelet therapy OR SAPT OR DAPT OR anticoagulation OR dual antiplatelet therapy OR antithrombotic OR acetylsalicylic OR clopidogrel or rivaroxaban OR apixaban)) **1087 results**

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