Peripheral Arterial Disease

Thrombosis Canada
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Objective:

To assist in the selection and dosing of antithrombotic agents for patients with peripheral artery disease (PAD), considering the risk of vascular events and bleeding.

Background:

Symptomatic patients with peripheral artery disease often have widespread atherosclerosis and are at risk of both major adverse cardiovascular events (cardiac related deaths, myocardial infarction [MI] and stroke) and major adverse limb events (acute limb ischemia and amputation). Antithrombotic therapy (see summary table) for the prevention and treatment of atherothrombotic complications in patients with PAD is a key component of their management, in addition to aggressive control of risk factors such as dyslipidemia, hypertension, and diabetes, and through the promotion of smoking cessation and regular exercise. While atherosclerosis is an integral part of the pathophysiology of lower extremity PAD, a large proportion of severe vascular occlusions are now known to be caused by thrombotic occlusive disease in the absence of significant atherosclerotic plaque. PAD is therefore considered a disease of 'atherothromboembolism', and often requires antiplatelet therapy, with or without anticoagulant, for optimal treatment.

Indications for Antithrombotic Therapy in PAD:

Symptomatic chronic PAD

Symptomatic patients with chronic PAD, as manifested by intermittent claudication with objective evidence of limb atherosclerosis or a previous vascular intervention (including prior bypass surgery, peripheral angioplasty or prior vascular amputation of the lower extremity), benefit from antithrombotic therapy. Single antiplatelet therapy (ASA or clopidogrel) lowers the risk for major adverse cardiovascular events (MACE) and has long been the standard of care of patients with PAD. In most studies, the dose of ASA varies between 80 and 162 mg, with the ADAPTABLE study showing that higher doses (e.g. 325mg) do not significantly impact MACE or all-cause mortality. For patients allergic or intolerant to ASA, the use of clopidogrel is recommended. The CAPRIE study suggests that clopidogrel may be slightly better than ASA in reducing cardiovascular events in the subgroup of patients with PAD. Ticagrelor has no benefit over clopidogrel in preventing MACE or major adverse limb events (MALE), such as hospitalization for acute limb ischemia, and is discontinued at a higher frequency due to higher rates of side effects.

In the CHARISMA study, adding clopidogrel 75 mg to ASA 75-162 mg did not result in a significant difference in MACE or major bleeding compared to the use of ASA alone in those at high risk of or with established atherosclerosis. While the combination of ASA and clopidogrel led to a 37% lower rate of myocardial infarction in the subgroup with established PAD, there was no significant effect on the risk of other vascular or limb events or of major bleeding. A subanalysis of the PEGASUS trial reported that the combination of

ticagrelor with ASA decreased both MACE and MALE compared with ASA alone in post-MI patients with concomitant PAD, albeit at the cost of excess bleeding; results specific to PAD patients are not definitive due to relatively small patient numbers. In the TRA 2P-TIMI trial, the addition of Vorapaxar, a platelet thrombin receptor antagonist, to a second antiplatelet therapy (primarily ASA) resulted in a reduced rate of acute limb revascularization and amputations in the subgroup of patients with PAD. However, there was no difference in the rates of cardiovascular death, stroke and myocardial infarction, and this combination was associated with an increased risk of severe bleeding events and intracranial hemorrhages. Overall, while dual antiplatelet therapy (DAPT) suggests benefit over single antiplatelet therapy in reducing MACE and MALE, the benefit is marginal and is associated with increased bleeding complications. Therefore, while DAPT can be considered in PAD patients with acute coronary syndrome or post-coronary percutaneous interventions, it is uncommonly utilized in PAD patients in the absence of recent coronary events or peripheral revascularization.

The WAVE trial showed that the addition of warfarin (INR 2-3) to antiplatelet therapy does not reduce major adverse cardiovascular events or severe limb ischemia in patients with chronic PAD and is associated with a 3.4-fold increase in life-threatening bleeding, including increased fatal and intracranial bleeding. Full dose anticoagulation should therefore not be added to antiplatelet therapy for the purpose of decreasing arterial ischemic events for those with chronic stable PAD. There have been no trials evaluating MACE, MALE, or major bleeding outcomes with the combination of full dose direct oral anticoagulants (DOACs) and ASA in patients with chronic PAD. In patients with chronic stable PAD who are on oral anticoagulant therapy with warfarin or a full dose DOAC for another indication (i.e. atrial fibrillation), the addition of an antiplatelet agent is usually not required. While not specifically evaluated in the PAD literature, robust evidence for patients with stable coronary artery disease requiring full dose anticoagulation shows demonstrable harm with the addition of single antiplatelet therapy. Therefore, we caution against the addition of an antiplatelet agent in fully anticoagulated patients with PAD unless it is short term or there has been a recent (<1 year) coronary or peripheral vascular event (with or without revascularization).

In the COMPASS Trial, the combination of low dose rivaroxaban (2.5 mg bid) and ASA as compared to ASA alone reduced both MACE and MALE in patients with chronic stable PAD, conferring a 28% relative risk reduction in cardiovascular death, stroke and myocardial infarction as well as a 46% relative risk reduction in severe limb ischemia leading to an intervention (including major limb amputations). While a significant increase in major bleeding was observed, there was no increase in fatal or symptomatic bleeding into a critical organ (e.g. intracranial hemorrhage). Most major bleeding events were gastrointestinal. Of note, patients with a high risk of bleeding, recent stroke within 1 month, a history of hemorrhagic stroke, or estimated glomerular filtration rate of less than 15 mL/min, and severe heart failure (NYHA III/IV or EF<30%) were excluded from this study. While rivaroxaban alone at 5 mg bid outperformed ASA alone in preventing MALE, it did not reduce MACE and was similarly associated with increased major bleeding, including intracranial hemorrhage.

Patients at particularly high risk of ischemic vascular events derive the greatest benefit with combination low-dose rivaroxaban and ASA. PAD patients with a high-risk limb presentation (HRLP), such as previous revascularization, previous amputation, or Fontaine III/IV status, as well as patients with high-risk comorbidities (HRCM), such as polyvascular disease, diabetes, renal insufficiency (eGFR <60) or heart failure, seem to have the highest risk of vascular events when followed over time. Treatment with rivaroxaban 2.5mg BID in addition to ASA, as compared to ASA alone, yields an absolute risk reduction in MACE or MALE including major amputation of 4.6% for patients with HRLP, 4.4% for patients with HRCM, and 5.2% for patients with both HRLP and HRCM. This is in contrast to a 1.0% absolute risk reduction for patients with neither HRLP or HRCM. Absolute risk increase of major bleeding was <1.0% for all groups. Therefore patients with these HRLP or HRCM should be considered for rivaroxaban 2.5mg BID in addition to ASA.

Health Canada labelling was updated in 2021 for rivaroxaban 2.5mg BID in combination with ASA for the treatment of patients with symptomatic PAD at demonstrated high risk of MALE or MACE, in addition to the initial indication for CAD with or without PAD. Since this time, evidence has continued to support this approach. Sub-analyses of the COMPASS trial displayed a reduction in all-cause mortality in those receiving rivaroxaban and ASA compared to ASA alone, with greater mortality benefits in those with higher baseline risk. Further, an open-label extension of the COMPASS trial displayed that extended combination treatment was associated with similar incidence rates for efficacy and bleeding compared to those seen during the initial study without any new safety concerns. In an indirect treatment comparison that included both the CHARISMA and COMPASS trials, rivaroxaban 2.5mg BID and low dose ASA reduced risk of MACE, cardiovascular death, and stroke in patients with, or at high risk for, chronic coronary artery disease (CAD) and/or PAD compared to clopidogrel combined with low-dose ASA.

Asymptomatic PAD:

There is no evidence that supports the benefit of antiplatelet agents in patients with lone **asymptomatic PAD** or a reduced ABI without symptoms. This absence of a beneficial effect is akin to the role of ASA in primary prevention where the reduced risk of cardiovascular events is counterbalanced by an increased risk of bleeding.

Peripheral limb revascularization:

For patients who undergo **endovascular** or **open revascularization,** rivaroxaban 2.5mg BID in combination with ASA should be utilized unless there is unduly high bleeding risk. Clopidogrel can be added in addition to low dose rivaroxaban and ASA for those who undergo high-risk endovascular stenting. If clopidogrel is added to low dose rivaroxaban and ASA, it should be continued for a maximum of 30 days unless other indications (i.e. coronary revascularization) arise.

The VOYAGER PAD trial, a large population randomized study, randomized 6564 adults who underwent a successful infrainguinal endovascular or surgical revascularization procedure for symptomatic PAD to either ASA and low dose rivaroxaban (2.5mg PO bid) or ASA alone. Clopidogrel was utilized in addition to the randomized intervention at the discretion of the treating medical practitioner. At 3 years, patients treated with ASA and low dose rivaroxaban had a 13% relative risk reduction in the composite outcome of acute limb ischemia, major amputation for vascular causes, myocardial infarction, ischemic stroke, or death from cardiovascular causes when compared to ASA alone. Of note, incidence of all individual components of the primary outcome as well as unplanned index limb revascularization for recurrent ischemia were lowered on ASA and low-dose rivaroxaban, but all-cause mortality was unchanged. There was a nonsignificant 0.78% absolute risk increase in TIMI major bleeding and a significant 1.22% absolute risk increase of ISTH major bleeding on ASA and rivaroxaban. As with COMPASS, there was no excess in severe bleeding, including fatal or intracranial hemorrhage. There was no significant heterogeneity in primary efficacy or bleeding outcomes based on open or endovascular revascularization. Within VOYAGER PAD, the addition of clopidogrel did not affect the efficacy of combination ASA and low-dose rivaroxaban in preventing vascular events compared to ASA alone. Clopidogrel was almost exclusively used in patients undergoing endovascular treatment. Use of clopidogrel for greater than 30 days was found to confer a numerically increased bleeding risk compared to shorter courses of clopidogrel. It is pertinent to note that most of the procedures within VOYAGER PAD were endovascular (65%) and were performed for claudication symptoms (77%), with a smaller proportion for chronic limb ischemia (23%). Regardless of lower extremity revascularization method, combination of rivaroxaban and ASA reduced the primary end point and did not confer any additional safety concerns.

Patients with acute limb ischemia were not well represented, and VOYAGER PAD should therefore not be readily extrapolated to this population of patients.

If ineligible for rivaroxaban (i.e. drug interaction) following **endovascular revascularization**, dual antiplatelet therapy with ASA and clopidogrel should be utilized for 1 to 3 months. If ineligible for rivaroxaban following **open revascularization**, a single antiplatelet agent or full dose oral anticoagulation can be considered. While the overall trial showed no benefit of high intensity warfarin when compared with ASA therapy, a subgroup analysis of the DUTCH BOA trial suggests that oral anticoagulation is more effective in preventing infra-inguinal vein-graft occlusion (but with a significant excess of life-threatening bleeding) while ASA therapy is more effective in preventing non-venous graft occlusion. Addition of clopidogrel or ticagrelor to ASA has not shown clear benefit in optimizing limb patency, but studies addressing DAPT in this setting are small. It is not clear whether complicated distal bypasses or bypasses with synthetic grafts might benefit from temporary DAPT.

Patients presenting with **acute limb ischemia** should be treated with heparin in an emergent manner; thereafter, there is clinical uncertainty as to the optimal acute term antiplatelet +/- anticoagulant regimen to use. A survey of Canadian vascular surgeons demonstrated that ASA combined with full-dose anticoagulation is the most commonly chosen post-operative antithrombotic regimen when concerned for high risk of postoperative graft/stent re-thrombosis. Most acknowledged that clinical equipoise on the topic persists. Patients with acute limb ischemia were not well represented within the VOYAGER PAD trial, though one can consider rivaroxaban 2.5mg BID in combination with ASA as a minimum in patients requiring urgent/emergent revascularization.

Table 1: Summary: Choice of Antithrombotic Therapy in Patients with Peripheral Artery Disease

Indications	Antithrombotic options	Comments
Asymptomatic PAD	Lack of evidence for a proven net-benefit of antiplatelet or anticoagulant therapy.	Manage cardiovascular risk factors. Assess for other clinical indications for antithrombotic therapy (e.g. CAD).
Chronic Symptomatic PAD	ASA in addition to rivaroxaban 2.5mg BID vs. single antiplatelet therapy, depending on high-risk presentation, high-risk comorbidities, bleeding risk and contraindications (see text above)	DAPT may be indicated in patients with acute coronary syndrome or coronary stent implantation.
Elective revascularization		
Endovascular ± Stents	ASA in addition to rivaroxaban 2.5mg BID, with or without short term clopidogrel	The VOYAGER PAD trial showed lower rates of acute limb ischemia, major amputation for vascular causes, myocardial infarction, ischemic stroke, death from cardiovascular causes and unplanned index limb revascularization for recurrent ischemia with ASA and low dose rivaroxaban when compared to ASA alone. The benefit of adding low dose rivaroxaban remained whether clopidogrel was utilized or not. Should clopidogrel be used, it should be continued for a maximum of 30 days unless other extenuating circumstances.
Surgical Revascularization	ASA in addition rivaroxaban 2.5mg BID unless contraindication or other extenuating circumstances. Single antiplatelet therapy (ASA or clopidogrel) or full dose vitamin K antagonist monotherapy in those unable to receive low dose rivaroxaban.	
Emergent Revascularization		
Acute Limb Ischemia or Critical Limb Ischemia	Optimal antithrombotic management is unclear, and more studies are needed. Options include: full-dose anticoagulation in combination with single antiplatelet therapy; ASA in addition to rivaroxaban 2.5 mg BID, with or without short-term use of clopidogrel; or DAPT.	In those with high risk of subsequent adverse limb events, with low bleeding risk, full dose anticoagulation in addition to ASA is the most commonly chosen regimen.

ASA, acetylsalicylic acid; CAD, coronary artery disease; DAPT, dual antiplatelet therapy; DOACs, direct oral anticoagulants; PAD, peripheral artery disease

Dosing:

- The standard daily dose of ASA is 81 mg and the standard dose of clopidogrel is 75 mg.
- The standard dose of ticagrelor is 60 or 90 mg bid.
- Low-dose rivaroxaban dosing is 2.5 mg bid, when used together with low dose aspirin (approved by Health Canada).

Adverse Effects:

The main adverse effect of ASA, seen more at higher doses, is bleeding. While most bleeding occurs within the gastrointestinal tract, there is an increased risk of intracranial bleeding as well. The risk-benefit ratio is generally acceptable in patients with symptomatic PAD. The main adverse effect of clopidogrel is also bleeding, although the rate of severe gastrointestinal bleeding is less than that with ASA. While the combination of ASA and low dose rivaroxaban increases the risk of major bleeding (mostly gastrointestinal),

there is no difference in the risk of critical organ (i.e., intracranial) or fatal bleeds when compared to ASA alone. The combination of full dose anticoagulant and antiplatelet confers further increased bleeding risk. Other sensitives, allergies and intolerances of antithrombotics are rare.

Periprocedural Management:

There is little data on the thrombotic and atherothromboembolic risk in patients with PAD who have antiplatelet therapy interrupted for a surgical or other invasive procedure. The POISE-2 study, which randomized patients already taking ASA and undergoing non-cardiac surgery to either continuing or discontinuing their antiplatelet therapy, reported that continuation does not decrease perioperative MACE but comes at a price of increased major bleeding. A subgroup analysis of patients in POISE-2 undergoing vascular surgery found that withdrawal of ASA therapy did not increase vascular occlusive complications. It is, therefore, reasonable to continue ASA if the procedure is associated with a low risk of bleeding and to stop ASA before the procedure if the bleeding risk of the procedure is anticipated to be high. For patients on clopidogrel for PAD, clopidogrel should be discontinued 5 – 7 days before an invasive procedure. After a procedure, the highest risk of major life-threatening bleeding is 2 days post procedure. A significant reduction in the risk of bleeding occurs by post-procedure day 8 and resumption of antiplatelet therapy is often indicated at this time. However, in high risk patients, physicians may elect to resume antiplatelet therapy before day 8 after weighing the risks of a thrombotic event against the risk of major bleeding.

There is little data on the periprocedural management of low-dose rivaroxaban at 2.5mg BID. While no clinical investigations have been specifically performed to address this question, discontinuing low-dose rivaroxaban 12-24 hours before most surgeries is likely sufficient based on pharmacokinetic data.

Full dose anticoagulation should be managed according to thrombotic risk, surgical bleeding risk, and renal function, as outlined in the Thrombosis Canada Perioperative Management Clinical Guides

Other Relevant Thrombosis Canada Clinical Guides:

- Acetyl Salicylic Acid (ASA)
- Clopidogrel (Plavix®)
- Edoxaban (Lixiana®)
- Rivaroxaban (Xarelto®)
- Ticagrelor (Brilinta®)

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