Antithrombotic Therapy for Peripheral Artery Disease in 2018

Connie N. Hess, MD, MHS; William R. Hiatt, MD

Peripheral artery disease (PAD) commonly refers to lower extremity atherosclerosis and is estimated to affect more than 200 million people worldwide. Patients with PAD are at increased risk for major adverse cardiovascular events (MACE) (myocardial infarction [MI], ischemic stroke, and cardiovascular death) and major adverse limb events (MALE) (major amputation and acute limb ischemia). Among patients with symptomatic PAD, annual rates of MACE are 4% to 5%, and rates of MALE are 1% to 2%. These ischemic events are associated with increased platelet and thrombotic activity and are potentially mitigated by antiplatelet therapy, anticoagulant therapy, or both. Based on available evidence, antithrombotic therapies should be individualized based on clinical presentation.

It is useful to categorize patients by clinical history when selecting antithrombotic therapy. These categories are based on the presence of PAD-related symptoms, defined as exertional ischemic leg symptoms including typical intermittent claudication (exertional calf pain that resolves within 10 minutes of rest and does not begin at rest), ischemic exertional leg symptoms that are not classic for intermittent claudication, ischemic rest pain, ischemic ulcers, or history of lower extremity revascularization (Figure). The presence of clinically manifest concomitant coronary artery disease or cerebrovascular disease (ongoing symptoms or a prior ischemic event) also influences the choice of antithrombotic therapy. Most patients with PAD encountered by clinicians do not have clinically manifest coronary or cerebrovascular disease. For example, among 13,885 patients with symptomatic PAD in the EUCLID trial (comparing clopidogrel to ticagrelor), 29.0% (n = 4032) had a history of coronary disease, and 8.2% (n = 1143) had a history of stroke.

The first category consists of patients with PAD with a low ankle-brachial index (ABI) or other noninvasive testing consistent with PAD but no symptoms of PAD and no clinically manifest coronary or cerebrovascular disease. The ABI is the ratio of Doppler-recorded systolic blood pressures in the lower and upper extremities. An ABI of 0.90 or lower is the accepted criterion for the presence of PAD, including asymptomatic patients without ischemic limb symptoms. Despite increased cardiovascular risk and guideline recommendations for aspirin, clinical trial evidence does not support antiplatelet therapy for these asymptomatic patients with PAD who do not have clinically manifest coronary or cerebrovascular disease.

The second category includes patients who have asymptomatic PAD with a history of clinically manifest coronary or cerebrovascular disease. These patients should receive antithrombotic therapy such as aspirin, P2Y12 inhibitors (eg, clopidogrel), or both according to current guidelines for treating acute (ischemic event within the past 12 months) or stable coronary artery or cerebrovascular disease.

The third category consists of patients with symptomatic PAD who do not have clinically manifest coronary or cerebrovascular disease. For these patients, practice guidelines recommend aspirin or

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**Figure. Antithrombotic Therapy in Stable, Symptomatic Peripheral Artery Disease**

1. Confirm patient has peripheral artery disease (PAD) by vascular testing or history of prior lower extremity revascularization
2. Assess if patient has PAD-associated limb symptoms
3. Determine if patient has clinically manifest coronary artery disease (CAD) or cerebrovascular disease
   - PAD alone without clinically manifest CAD or cerebrovascular disease
     - No acute coronary syndrome or percutaneous coronary intervention within the past 12 mo or an acute cerebrovascular ischemic event
   - PAD with clinically manifest CAD or cerebrovascular disease
     - Acute coronary syndrome or percutaneous coronary intervention within the past 12 mo or an acute cerebrovascular ischemic event

**Asymptomatic PAD**
- Do not initiate antithrombotic therapy
- Manage cardiovascular disease risk factors as indicated

**PAD-associated limb symptoms**
- Clotidogrel or ticagrelor monotherapy to prevent MACE
  - Evidence suggests clopidogrel is more effective than aspirin; ticagrelor is an acceptable alternative in patients known to be poor metabolizers of clopidogrel
  - For patients with lower extremity revascularization, evidence supports aspirin monotherapy to maintain procedural patency
- Aspirin (or clotidogrel if aspirin is contraindicated) to prevent MACE
  - For patients taking aspirin and at high risk of cardiac and ischemic limb events, consider adding Ticagrelor if prior (> 12 mo ago) myocardial infarction to prevent MACE and MALE
  - Low-dose rivaroxaban if patient has concomitant CAD to prevent MACE and MALE
  - For patients at high risk of ischemic limb events, consider adding vorapaxar to aspirin or clotidogrel to prevent MALE

MACE indicates major adverse cardiac events (myocardial infarction, ischemic stroke, or cardiovascular death); MALE, major adverse limb events (acute limb ischemia or major amputation).

4 Patients with PAD at highest risk for ischemic limb events are those with a prior history of lower extremity revascularization or more severe disease (ankle-brachial index <0.60).

5 Rivaroxaban 2.5 mg twice daily for this indication is under review by the Food and Drug Administration but is not yet available in the United States.
clopidogrel to reduce MACE, despite a lack of evidence for aspirin in this setting.\textsuperscript{5,6} In contrast, antplatelet agents other than aspirin (P2Y12 inhibitors or ticagrelor), including clopidogrel monotherapy,\textsuperscript{6} reduce MACE in this population (MALE was not studied). In the EUCLID trial, ticagrelor provided similar benefit to clopidogrel monotherapy in preventing MACE.\textsuperscript{2} Therefore, for patients with PAD, who are known to be poor clopidogrel metabolizers, ticagrelor monotherapy can be considered an effective alternative.

The fourth category consists of patients with symptomatic PAD and clinically manifest coronary or cerebrovascular disease. Anti-thrombotic treatment of acute cardiovascular events within the past 12 months should follow guidelines. For symptomatic PAD patients with stable coronary artery or cerebrovascular disease, the benefit of single-drug therapy with aspirin or clopidogrel to reduce MACE risk is well established.\textsuperscript{16} Treatment with dual antplatelet therapy with clopidogrel and aspirin is not more effective than aspirin alone and causes more major bleeding.\textsuperscript{7} In a clinical trial of 21 162 patients with prior MI, adding ticagrelor to aspirin reduced MACE (7.8% vs 9.0% over 3 years; P = .001). Among 1143 patients with MI and PAD, ticagrelor plus aspirin reduced MALE (0.7% vs 0.5% over 3 years; P = .03).\textsuperscript{8}

Rivaroxaban, a direct factor Xa inhibitor, was studied in the COMPASS trial of 27 395 patients with stable coronary artery disease, including 7470 patients with symptomatic PAD and clinically manifest coronary or cerebrovascular disease. Participants were randomized to receive low-dose rivaroxaban (2.5 mg twice daily) plus aspirin, rivaroxaban (5 mg twice daily), or aspirin alone.\textsuperscript{2,9} Overall, rivaroxaban 2.5 mg plus aspirin, but not rivaroxaban 5.0 mg alone, prevented MACE compared with aspirin alone. Among participants with PAD, rivaroxaban 2.5 mg twice daily plus aspirin compared with aspirin alone reduced MACE (5.1% vs 6.9%; P = .005), MALE (0.9% vs 2.4%; P = .004), MALE components of acute limb ischemia (0.8% vs 1.4%; P = .04), and major amputation (0.2% vs 0.7%; P = .01).\textsuperscript{9} The combination of rivaroxaban plus aspirin resulted in increased bleeding compared with aspirin alone. Bleeding was mainly gastrointestinal (1.6% vs 0.7%; P = .03) with few intracranial (0.2% vs 0.4%) or fatal hemorrhages (0.2% vs 0.1%). However, the combined use of low-dose rivaroxaban plus aspirin for PAD has not yet been reviewed by the Food and Drug Administration.

Vorapaxar, a protease-activated receptor-1 antagonist that inhibits thrombin-induced platelet aggregation, was studied in combination with aspirin, clopidogrel, or both in 26 449 patients with history of PAD, MI, or ischemic stroke. In the subgroup of 3787 patients with symptomatic PAD, of whom 57% (n = 2155) had concomitant coronary disease and 14% (n = 513) had a prior ischemic stroke, vorapaxar combined with 1 or 2 additional antplatelet drugs did not significantly reduce MACE (11.3% vs 11.9%; P = .53) but significantly reduced acute limb ischemia (2.3% vs 3.9%; P = .006) and peripheral revascularization (18.4% vs 22.2%; P = .02).\textsuperscript{10} Thus, patients with PAD at high risk for ischemic limb events (those with prior acute limb ischemia or more severe leg disease [ABI<0.60]) may benefit from vorapaxar added to other antplatelet therapies.

In summary, patients with PAD without ischemic limb symptoms or clinically manifest coronary or cerebrovascular disease should have cardiovascular risk factors treated, but current evidence does not support anti-thrombotic therapy. Symptomatic patients with PAD without clinically manifest coronary or cerebrovascular disease should be treated with clopidogrel monotherapy (with ticagrelor as an alternative) to prevent MACE, although aspirin plus clopidogrel is not more effective than aspirin alone and has not been evaluated for preventing MALE. Patients with symptomatic PAD and clinically manifest coronary or cerebrovascular disease should be treated with aspirin or clopidogrel monotherapy. Patients with symptomatic PAD who are at increased risk for ischemic limb events (eg, prior history of acute limb ischemia or ABI<0.60) should be treated with aspirin combined with vorapaxar to reduce MALE, whereas aspirin plus ticagrelor or aspirin plus low-dose rivaroxaban alone reduces MACE and MALE in patients with PAD and clinically manifest coronary artery disease. Adding anti-thrombotic therapies to aspirin is associated with increased risk of major bleeding, necessitating consideration of the net clinical benefit of combination therapies (number of MACE and MALE events avoided relative to major bleeding events caused). The optimal antithrombotic therapy for patients with critical leg ischemia remains unclear and is currently under investigation for patients undergoing lower extremity revascularization.

**REFERENCES**


