

Anticoagulation In The Management of CAD and PAD

Atherosclerotic cardiovascular (CV) diseases are a leading cause of death worldwide and accounted for 17.7 million deaths in 2015.¹ Coronary artery disease (CAD) and peripheral arterial disease (PAD) are chronic progressive CV diseases characterized by plaque formation in the walls of the arteries, which become narrowed and hardened, leading to thrombosis and ischemia in the essential parts of the body (ie, brain, heart, or periphery).¹ Patients with established CAD and PAD are at risk of secondary thrombotic events associated with atherosclerotic CV disease, such as myocardial infarction (MI), stroke, and CV-related death (FIGURE 2-5).^{4,5}

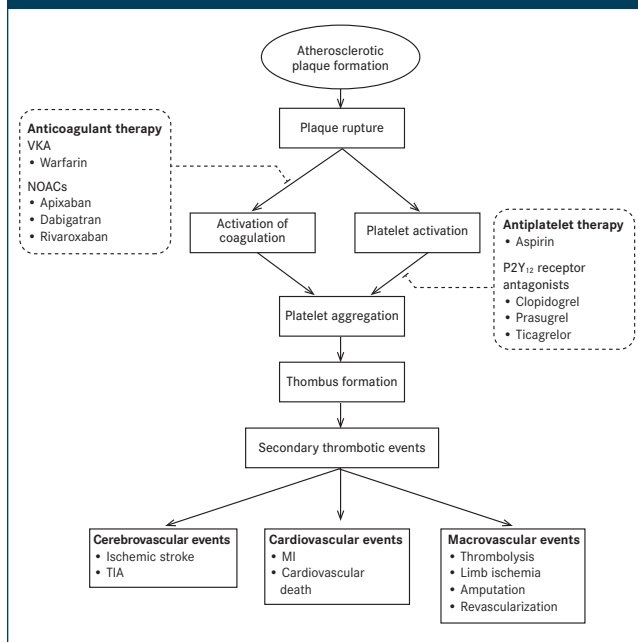
The risk of these secondary events and associated risk factors were evaluated in the international 4-year Reduction of Atherothrombosis for Continued Health (REACH) Registry study.⁶ In a 3-year analysis of patients with symptomatic atherosclerosis (N = 39,675), 29.7% of patients with CAD and 40.4% of patients with PAD experienced at least one of the following CV event outcomes: MI, stroke, vascular death, or rehospitalization for a vascular event not attributed to MI, stroke, or death.⁶

Despite the use of antithrombotic agents and pharmacological management for comorbid conditions in 88% of the REACH Registry population at 4 years of follow up, patients with atherosclerotic disease continued to experience secondary thrombotic events.⁴ Risk factors including hypertension, hypercholesterolemia, type 2 diabetes, obesity, smoking, and prior history of an ischemic event were identified as causes that increase the risk of recurrent ischemic events.⁴ Patients with established atherosclerosis without prior ischemic events (stable disease) are also at risk of subsequent events; 18.3% of patients with atherosclerosis who had experienced a prior ischemic event (MI or stroke) and 12.2% of patients with stable disease had subsequent MI, stroke, or CV death over the 4-year study period.⁴

With the progression of atherosclerosis, atherosclerotic plaque formation can become widespread and affect multiple arterial beds. Nearly 1 in 5 of 19,069 patients with symptomatic atherosclerosis from the REACH Registry in the United States had polyvascular disease or symptomatic disease affecting 2 or more arterial beds.⁷ Compared with single vascular bed disease, patients with symptomatic polyvascular atherosclerosis had a significantly greater 3-year CV event rate (25.5% vs 40.5%; $P < .001$).⁶

Patients with atherosclerosis in the REACH Registry treated with concomitant medical therapy remained at residual risk for secondary thrombotic events in the long-term analysis.⁴ It is important to be aware of guideline-recommended management strategies for secondary prevention of atherosclerosis and determine optimal treatment for reduction of this long-term risk, especially in patients who have elevated risk and may benefit from intensifying therapy.

FIGURE. PREVENTION OF SECONDARY THROMBOTIC EVENTS IN PATIENTS WITH CAD OR PAD²⁻⁵



CAD indicates coronary artery disease; MI, myocardial infarction; NOAC, novel oral anticoagulant; PAD, peripheral arterial disease; TIA, transient ischemic attack; VKA, vitamin K antagonist.

GUIDELINES FOR THE THERAPEUTIC MANAGEMENT OF CAD AND PAD

Current guidelines developed by the American Heart Association and the American College of Cardiology Foundation (AHA/ACCF) recommend lifestyle modifications and pharmacological treatments for the secondary prevention of CV risk in patients with CAD and PAD.²

Antiplatelet Therapy

Long-term pharmacological therapy with antiplatelet agents, such as aspirin or a P2Y₁₂ inhibitor, are recommended by the AHA/ACCF to reduce the incidence of CV events, including MI, stroke, and vascular death in patients with CAD and PAD.² For secondary prevention and risk reduction in patients with CAD, the guidelines recommend treatment with 75 to 162 mg of aspirin daily or 75 mg of clopidogrel daily, as an alternative for patients who are allergic or intolerant to aspirin. Patients with symptomatic PAD of the lower extremity are recommended daily treatment with 75 to 325 mg of aspirin or 75 mg of clopidogrel.² Despite this treatment to prevent CV events, patients

with CAD or PAD have an underlying thrombotic risk and could still have serious or fatal CV events.

Anticoagulant Therapy

While antiplatelet agents are the current standard of therapy, antithrombotic agents such as vitamin K antagonists (VKAs) and novel oral anticoagulants have also been studied in patients with stable CV disease for preventing long-term CV complications. Although VKA treatment has shown benefits in preventing recurrent thrombotic events in patients with established CAD, it has also resulted in major bleeding.^{2,8} Twice-daily treatment with low-dose rivaroxaban (2.5 mg) resulted in a lower rate of composite major adverse cardiac events (MACE) outcomes, including CV death or thrombotic events (MI or stroke), compared with placebo and fewer fatal bleeding events compared with 5 mg of rivaroxaban twice daily.⁹

There is a need for better management options for prevention of secondary major thrombotic events in patients with atherosclerotic CV disease, including CAD and PAD. Results from the Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) trial have suggested the potential role of low-dose rivaroxaban in the management of thrombotic risk among patients with CAD and PAD.¹⁰

CV RISK REDUCTION IN THE COMPASS TRIAL

The international multicenter COMPASS trial investigated the efficacy and safety of rivaroxaban 2.5 mg twice daily plus aspirin 100 mg once daily for the long-term prevention of MACE (composite outcomes of CV death, MI, or stroke) in 27,395 patients with CAD and PAD.¹⁰ The majority of patients enrolled had CAD (90.6%); patients with PAD (27.3%) or thrombotic risk factors, including polyvascular disease or at least 2 additional CV risk factors, were also enrolled.¹⁰ All patients were randomized 1:1:1 to treatment with low-dose rivaroxaban (2.5 mg twice daily) plus aspirin (100 mg once daily), rivaroxaban alone (5 mg twice daily), or aspirin alone (100 mg once daily).¹⁰

Rivaroxaban plus aspirin treatment was more effective than aspirin or rivaroxaban treatment alone in the prevention of the primary MACE outcome.¹⁰ Patients in the rivaroxaban-plus-aspirin treatment arm experienced a 24% reduction in the risk of MACE outcomes compared with patients in the aspirin-alone treatment arm (HR, 0.76; 95% CI, 0.70-1.05; $P < .001$). Reduction in MACE outcomes was largely driven by a 42% decrease in stroke and 22% decrease in CV death.¹⁰

Additionally, treatment with low-dose rivaroxaban-plus-aspirin significantly reduced the risk of secondary composite outcomes that included thrombotic events of ischemic stroke and acute limb ischemia compared with aspirin alone. There was a 26% reduction in

the composite of ischemic stroke, MI, acute limb ischemia, or death from coronary heart disease and a 28% reduction in the composite of ischemic stroke, MI, acute limb ischemia, or CV death ($P < .001$, for both secondary outcomes).¹⁰

The primary safety outcome was a modification of the International Society on Thrombosis and Haemostasis criteria for major bleeding in which any bleeding event requiring medical attention or hospitalization was considered a major bleed.¹⁰ Major bleeding events were mainly associated with differences in bleeding that led to presentation to an acute care facility or hospitalization; major bleeding occurred in 3.1% of the rivaroxaban-plus-aspirin treatment arm compared with 1.9% of the aspirin-alone treatment arm (HR, 1.70; 95% CI, 1.40-2.05; $P < .001$).¹⁰ There was no significant differences between treatment arms in the rates of fatal or intracranial bleeds or symptomatic bleeding into a critical organ.¹⁰

As a result of the superior efficacy of rivaroxaban-plus-aspirin treatment in the reduction of MACE outcomes in the 3-year study (March 2013 through May 2016), the trial was recommended for early termination by the independent data and safety monitoring board.¹¹

ROLE OF THE PHARMACIST

Patients with CAD and risk factors for secondary thrombotic events, such as comorbid diabetes and hypertension, can be more effectively managed with the help of pharmacists to reduce long-term morbidity and mortality. Pharmacists can emphasize the role of nonpharmacological interventions to prevent thrombotic events, such as smoking cessation, healthy diet, physical activity, and weight management.² Additionally, pharmacists should be aware of the residual risk of thrombotic events in patients receiving pharmacological treatment and understand the role of antithrombotic therapy with rivaroxaban for these high-risk patients.

The results from the COMPASS trial provide additional support for the potential role of twice-daily low-dose rivaroxaban (2.5 mg) in the long-term prevention of MACE outcomes in patients with CAD or PAD.¹⁰ In collaboration with the clinical team, pharmacists can assist in appropriately identifying patients at risk of ischemic events who may benefit from anticoagulation therapy. Importantly, pharmacists should understand the multiple indications for rivaroxaban and corresponding dosages, as assistance in dosing rivaroxaban with aspirin may be advised.¹² Patients with high bleeding risks may require close monitoring to prevent major bleeding events, and pharmacists can provide appropriate counseling and support for their long-term therapeutic management.

References are available online at PharmacyTimes.com.