Anticoagulation in Patients Requiring Antiplatelet Therapy

Thrombosis Canada
Thrombose Canada

Objective:

To provide guidance to clinicians on the management of patients with indications for both antiplatelet and anticoagulant drugs.

Background:

Patients who have an indication for oral anticoagulation (OAC) can develop separate conditions that would normally be treated with antiplatelet agents. Atrial fibrillation (AF) and acute coronary syndrome (ACS), with or without requirement for percutaneous coronary intervention (PCI), overlap in approximately 20% of patients. Other indications for anticoagulation, such as venous thromboembolism (VTE), mechanical prosthetic heart valves and left ventricular (LV) thrombus, may also co-exist with an indication for single or dual antiplatelet therapy (SAPT, DAPT). Recently, low dose rivaroxaban therapy in combination with acetylsalicylic acid (ASA) has demonstrated benefit in patients with coronary artery disease with or without peripheral artery disease.

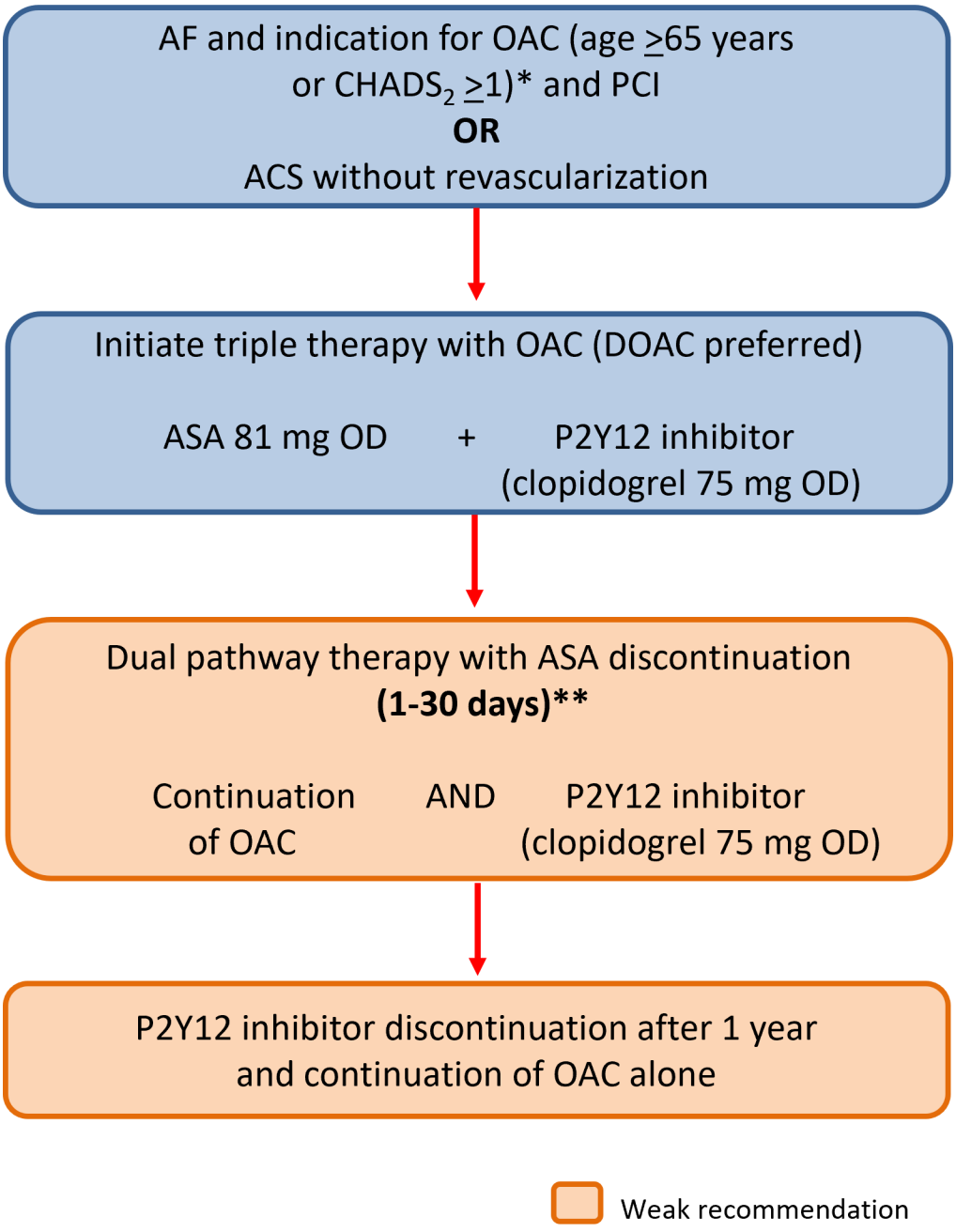
Antithrombotic management of patients requiring combined anticoagulant and antiplatelet therapy necessitates an **individualized consideration of thrombotic risk, including stroke, embolism, stent thrombosis, and ACS, as well as bleeding risk** (see **Tables 1 and 2**). The rationale for combining DAPT (P2Y12 inhibitor + ASA) with warfarin or a direct acting anticoagulant (DOAC) is based on suggested benefits in preventing thrombotic events, but the high rates of associated bleeding are a major concern. Randomized trials have demonstrated reduced bleeding with the use of a P2Y12 inhibitor + DOAC or warfarin (dual pathway therapy) over triple therapy (DAPT + OAC). Although no increased thrombotic risk has been noted with this strategy, individual studies have been underpowered for thrombotic outcomes.

Management strategy for patients with AF and ACS/PCI requiring antiplatelet therapy

A treatment algorithm recommended by the Canadian Cardiovascular Society and Canadian Association of Interventional Cardiology is shown in Figure 1. They recommend that patients with AF + PCI or ACS should first be stratified according to their risk of stroke or systemic embolism based on CHADS2 plus age. Those at low risk (CHADS2 =0 age <65) have no indication for anticoagulation so may be managed in the same way as those without AF. For those with CHADS2 > 0 or age >= 65, triple therapy with OAC, ASA, and clopidogrel should be employed, then ASA should be discontinued between 1 and 30 days taking into consideration the risk of stent thrombosis and bleeding. Those at high risk of stent thrombosis (see Table 1) and at low bleeding risk may experience more benefit from longer durations of triple therapy, while those at low risk of

stent thrombosis and high risk of bleeding (see Table 2) may benefit more from a dual pathway strategy beginning 1 day after PCI.

Figure 1: Antiplatelet strategies in patients with concomitant atrial fibrillation (AF) and percutaneous coronary intervention (PCI) and/or acute coronary syndrome (ACS)



 Patients who do not require OAC for their AF as per the Canadian guidelines for the management of AF would receive dual antiplatelet therapy.
 ASA duration before switching to dual pathway was an average of 1.6-6.6 days after PCI in the large-scale trials.
Redrawn from Bainey KR, et al. Can J Cardiol 2024;40:160-181.

Table 1: Factors Associated with Increased Thrombotic Risk with PCI

Clinical factors	Diabetes mellitus Prior ACS Chronic renal dysfunction Prior stent thrombosis Current tobacco use Multi-vessel disease
PCI factors	Multiple stents implanted Complex bifurcation lesion Total stent length >60 mm Intervention for chronic total occlusion Bioabsorbable vascular scaffold implantation

Table 2: Factors Associated with Increased Bleeding Risk

Need for OAC in addition to DAPT
Advanced age (older than 75 years)
Frailty
Anemia with hemoglobin < 110 g/L
Chronic renal failure (creatinine clearance < 40 mL/min)
Low body weight (<60 kg)
Hospitalization for bleeding within past year
Previous stroke/intracranial bleed
Regular need for NSAIDs or prednisone

Management strategy for patients with VTE and ACS/PCI requiring antiplatelet therapy

For patients with VTE, oral or parenteral anticoagulation should be prescribed as recommended for those who do not require antiplatelet therapy. For patients in whom extended or indefinite oral anticoagulation is required, use of an agent with the potential for dose reduction can be considered (e.g., rivaroxaban to 10 mg

daily or apixaban to 2.5 mg bid when used beyond 6 months). The choice of antiplatelet agent should be focused on minimizing bleeding risk. Clopidogrel is recommended over ticagrelor or prasugrel and the duration of DAPT may be reduced to the shorter recommended periods as outlined above, if it can be done so safely. Patients requiring elective PCI should have the procedure delayed, if possible, until oral or parenteral anticoagulation is no longer required for VTE management or the risk of recurrence with anticoagulant interruption is minimized (see **Clinical Guide:** Venous Thromboembolism Duration of Therapy).

Management strategy for patients with LV thrombus and ACS/PCI requiring antiplatelet therapy

Patients with LV thrombus have a high risk of developing thromboembolic complications, and anticoagulation should be considered in such patients. Meta-analysis of data from small RCTs and larger observational studies suggest similar efficacy and safety of DOACs compared to warfarin for treatment of LV thrombus, albeit with a low degree of certainty. A scientific statement from the American Heart Association found DOACs to be a reasonable alternative to warfarin for this indication, especially for patients in whom time in therapeutic range for warfarin is predicted to be low.

When patients with LV thrombus undergo PCI with or without ACS, triple therapy with OAC, clopidogrel and ASA should be used initially. Of note, in most studies for this indication, DOACs were used at full therapeutic dose without dose reduction even with concomitant use of antiplatelet therapy. As with other indications for triple therapy, depending on bleeding and thrombotic risks, ASA may be discontinued as early as 1-day post PCI or continued up to 6 months. Optimal duration of OAC in these patients is unclear, and decisions regarding continuation of OAC should be made on a case-by-case basis. In general, OAC may be discontinued after 3 months if there has been resolution of the LV thrombus. There is currently insufficient evidence to support the use of prophylactic OAC in patients with anterior wall STEMI to prevent LV thrombus. Given the known increased risk of bleeding and uncertain benefit, triple therapy should be avoided in patients at risk for, but with no history of, LV thrombus.

Management strategy for patients with prosthetic heart valves requiring antiplatelet therapy

In patients with a mechanical heart valve, warfarin is specifically recommended. DOACs are contraindicated. After PCI, the uninterrupted use of warfarin is critical to minimize the risk of valve thrombosis. When patients with mechanical heart valves undergo PCI with or without ACS, triple therapy with OAC, clopidogrel and ASA should be used initially. As with other indications for triple therapy, ASA may be discontinued as early as 1 day post PCI or continued up to 6 months depending on bleeding and thrombotic risk (see **Tables 1 and 2**).

Low dose rivaroxaban and ASA in patients with stable cardiovascular disease or lower extremity revascularization

The risk of recurrent thrombotic events in patients with stable cardiovascular disease remains substantial despite secondary prevention strategies. While the combination of warfarin with standard low dose ASA has been associated with decreased thrombotic event rates, risks of bleeding (including intracranial bleeding)

are increased. The Cardiovascular Outcomes for People with using Anticoagulation Strategies (COMPASS) trial randomized patients with stable atherosclerotic vascular disease to receive rivaroxaban 2.5 mg twice daily plus ASA 100 mg daily, rivaroxaban 5 mg twice daily, or ASA 100 mg daily. The combination of rivaroxaban plus ASA resulted in a 1.3% absolute risk reduction in cardiovascular death, stroke, or nonfatal myocardial infarction (24% relative risk reduction), with a trend toward improved mortality. This benefit was offset by a 1.2% increased absolute risk in major bleeding (70% relative risk increase), without any significant difference between the groups with respect to fatal bleeding or intracranial bleeding. Similar results were seen in a randomized trial focusing on patients with peripheral artery disease who had undergone lower extremity revascularization in the previous 10 days. In this trial, 51% of patients were also treated with clopidogrel post-procedure, and there was a trend for greater bleeding in those treated with clopidogrel for >30 days compared to those with shorter clopidogrel treatment. Given these results, the addition of rivaroxaban 2.5 mg po twice daily to ASA can be considered in patients with stable atherosclerotic vascular disease with a high thrombotic risk that is thought to outweigh the bleeding risks associated with this combination.

Information about the use of low dose rivaroxaban and ASA in patients with peripheral artery disease can be found in **Clinical Guide:** **Peripheral Arterial Disease**.

Long-term use of an antiplatelet agent with concomitant therapeutic dose anticoagulation

Fewer data are available to guide clinicians on which patients could benefit by receiving indefinite use of the combination of low dose ASA with a full dose anticoagulant. Potential scenarios include antiphospholipid antibody syndrome (APS), mechanical heart valves, and atrial fibrillation with stable CAD.

APS: This syndrome is associated with a significantly elevated risk of both arterial and venous thrombosis. Those patients with this syndrome who develop arterial thrombosis have a higher risk of recurrent thrombotic episodes. Guidelines suggest that the addition of ASA to warfarin may be considered in those patients with APS who experience a recurrent arterial or venous thrombosis despite already being on warfarin and in the target INR range (INR 2-3), and may also be considered in those with an index arterial thrombotic event. It is recommended that all such patients be referred to a thrombosis specialist or hematologist (See **Clinical Guide:** **Thrombophilia: Antiphospholipid Antibody Syndrome**).

Mechanical Heart Valves: Older randomized studies reported lower rates of systemic embolism and potentially lower rates of death when ASA was added to warfarin in patients with mechanical heart valves. Experts suggest using this combination in this scenario, especially if the patient is at low risk of bleeding or at a high thrombotic risk. (See **Clinical Guide:** **Mechanical and Bioprosthetic Heart Valves: Anticoagulant Therapy**).

Concomitant AF and stable CAD: Guidelines suggest anticoagulation alone in most patients who have an indication for an anticoagulant (most commonly atrial fibrillation) and are at least 1 year from an ACS or coronary stent implantation. This has been supported by randomized trials that have established warfarin's secondary preventative benefit in stable CAD. In addition, other studies have suggested no difference in the risk of arterial thrombotic events in patients with atrial fibrillation who are on warfarin alone versus combination ASA and warfarin. The AFIRE randomized trial assessed rivaroxaban alone versus the combination of a single antiplatelet agent (70% ASA) with rivaroxaban in Japanese patients with stable CAD and atrial fibrillation. This trial was terminated early due to excess mortality in the combination group. There was less major bleeding, and thrombotic events were not significantly different with rivaroxaban

alone compared to the combination group. Patients with a history of stent thrombosis were excluded from this trial. Consultation with an expert to develop an antithrombotic regimen is suggested in patients who are at high risk for stent thrombosis.

Other relevant Thrombosis Canada Clinical Guides

- Acetylsalicylic Acid (ASA)
- Apixaban (Eliquis®)
- Clopidogrel (Plavix®)
- Dabigatran (Pradaxa®)
- Deep Vein Thrombosis (DVT): Treatment
- Mechanical and Bioprosthetic Heart Valves: Anticoagulant Therapy
- Peripheral Arterial Disease
- Prasugrel (Effient®)
- Pulmonary Embolism (PE): Treatment
- Rivaroxaban (Xarelto®)
- Stroke Prevention in Atrial Fibrillation
- Thrombophilia: Antiphospholipid Antibody Syndrome
- Ticagrelor (Brilinta®)
- Venous Thromboembolism: Duration of Therapy
- Warfarin

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