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Use of Antiplatelet Agents in Canadian Patients: A Reflection of the 2023 Antiplatelet Guidelines

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Introduction

Antiplatelet agents play a fundamental role in secondary prevention of atherosclerotic cardiovascular disease by reducing the risk of recurrent ischemic events. Over the past decades, developments and refinements in antiplatelet therapy have been made through the commercialization of novel classes (P2Y12 inhibitors, glycoprotein [GP] IIb/IIIa inhibitors), modes of administration (oral and intravenous), and combination strategies (dual antiplatelet therapy [DAPT] of different durations).[1] Recently, concerns have been raised regarding the prognostic impact of bleeding events associated with antiplatelet agents.[2] Consequently, multiple strategies have been studied to optimize the fine balance between ischemic protection and bleeding avoidance with these agents. The 2023 Focused Update of the Guidelines for the Use of Antiplatelet Therapy by the Canadian Cardiovascular Society/ Canadian Association of Interventional Cardiology distilled the most recent evidence on this topic from a Canadian perspective.[3] This review offers insights into the implementation of the guidelines' recommendations in routine clinical practice within the Canadian setting.

Pre-treatment with DAPT Before Coronary Angiography

Patients undergoing percutaneous coronary intervention (PCI) with stent implantation require a combination of acetylsalicylic acid (ASA) and a P2Y12 receptor inhibitor (clopidogrel, ticagrelor, or prasugrel) to inhibit platelet function and prevent stent thrombosis. In theory, obtaining full platelet inhibition at the time of PCI requires administering a P2Y12 receptor inhibitor before the procedure (pre-treatment). However, it is often unknown beforehand if a PCI will be performed at the time of a coronary angiography, therefore pre-treating every patient with a P2Y12 inhibitor leads to unnecessary treatment for many, with an associated risk of bleeding. The new Canadian guidelines provide recommendations regarding pre-treatment for 3 indications of coronary angiography: ST-elevation myocardial infarction

(STEMI), Non-ST-elevation acute coronary syndrome (NSTE-ACS), and stable ischemic heart disease.[3] Routine pre-treatment is suggested for patients with STEMI, and for those with NSTE-ACS with the intent to perform coronary angiography >24 hours after admission (weak recommendation, low-quality evidence). However, pre-treatment is not recommended for those with NSTE-ACS with the intent to perform coronary angiography within <24 hours (weak recommendation, moderate-quality evidence) or for elective patients (weak recommendation, low-quality evidence). For all patients, however, ASA needs to be administered before the procedure and continued afterwards if PCI is performed. A meta-analysis conducted during the development of the guidelines showed that pre-treatment for NSTE-ACS does not reduce the risk of ischemic events (mortality, major adverse cardiac and cerebrovascular events [MACE], and stent thrombosis), but it does increase the risk of major bleeding. The largest study on this topic, the ACCOAST trial, randomized 4,033 participants with non-ST-elevation myocardial infarction (NSTEMI) to receive either prasugrel pre-treatment, or prasugrel at the time of PCI.[4] Pre-treatment increased the risk of major bleeding (2.6% versus 1.4%, p=0.006), without reducing MACE at 7 days (10.0% versus 9.8%, p=0.81). However, the procedure was performed within 24 hours after admission in the ACCOAST trial, similar to most trials in the meta-analysis, except for the Canadian CURE trial.[5] In the Canadian context, PCI is often performed >24 hours after diagnosis of NSTE-ACS. During the waiting period, these patients are at risk of thrombotic complications, which justifies the discrepant recommendations for NSTE-ACS based on the timing of the procedure. Cangrelor, an intravenous P2Y12 inhibitor with rapid onset and offset of action, recently received Health Canada approval to decrease the risk of thrombotic cardiovascular events in patients undergoing PCI who have not received an oral P2Y12 inhibitor or other intravenous antiplatelet agents. Its role remains to be defined in the Canadian context, and it may be addressed in future iterations of the Canadian guidelines.

DAPT for ACS and PCI

Clopidogrel no longer represents the P2Y12 inhibitor of choice for patients admitted to the hospital with an acute coronary syndrome (ACS). Instead, the more potent prasugrel or ticagrelor are recommended as part of DAPT in combination with ASA. Both agents are superior to clopidogrel to prevent recurrent ischemic events, however, there is insufficient head-to-head evidence to support one superior agent over the other. Therefore, neither prasugrel nor ticagrelor is preferred over the other for patients with ACS undergoing PCI (weak recommendation, low-quality evidence). Ticagrelor is more widely available across Canadian provinces than prasugrel. However, it is associated with a 13%-31% rate of dyspnea, leading to drug discontinuation in 1%-7% of patients.[6] It is also administered twice daily, while prasugrel is administered once daily. When contemplating switching from ticagrelor due to side effects, prasugrel should be considered in the right context.

To reduce the risk of major bleeding, without compromising the risk of major adverse cardiovascular events, switching from prasugrel/ticagrelor to clopidogrel after one month is a reasonable alternative based on the TOPIC and TALOS-AMI trials (weak recommendation, moderate-quality evidence).[7,8] Indeed, the risk of recurrent ischemic events is the highest during the first month, and decreases thereafter, making clopidogrel a suitable option. In the TALOS-AMI trial, 2,697 patients with ACS who underwent PCI and were on DAPT with ticagrelor were randomized at 30 days to either continue ticagrelor or to switch from ticagrelor to clopidogrel.[7] The primary endpoint, a composite of cardiovascular death, myocardial infarction, stroke, or bleeding type 2, 3, or 5, according to the Bleeding Academic Research Consortium (BARC) criteria from 1 to 12 months, occurred in 4.6% of participants in the clopidogrel group, and 8.2% of participants in the ticagrelor group (p for superiority=0.0001). There was no significant difference in the risk of cardiovascular death, myocardial infarction, or stroke, between the groups. However, there was a significant reduction in bleeding events with clopidogrel. Of note, patients at high bleeding risk were excluded from the TALOS-AMI trial, suggesting that clopidogrel de-escalation is a suitable strategy that should be considered for all patients, not exclusively those at high bleeding risk. The available evidence is currently not sufficient to recommend dose de-escalations of prasugrel/ticagrelor as part of DAPT to minimize bleeding risk, and therefore no recommendations were issued in the guidelines on this topic.

More recently, studies evaluated the role of ultra-short DAPT durations after PCI (<1 month, and as low as only one day), followed by P2Y12 inhibitor monotherapy (ASA-free strategy).[9,10] This strategy still requires validation before implementation into routine clinical practice, and is currently not recommended.

Patients at high bleeding risk (HBR) represent a particularly challenging population, given that bleeding risk factors often coincide with ischemic risk factors, complexifying decisions about DAPT. A standardized definition of high bleeding risk has been developed by the Academic Research Consortium that can be used in clinical practice to identify these patients **(Table 1)**.[11] This vulnerable subgroup has historically been excluded from randomized controlled trials evaluating DAPT strategies after PCI, contributing

Major Criteria	Minor Criteria
End-stage CKD with eGFR <30 mL/min	CKD with eGFR 30-59 mL/min
Hemoglobin <110 g/L	Hemoglobin 110-129 g/L for men and 110-119 g/L for women
Spontaneous bleeding requiring hospitalization or transfusion within the past 6 months (or at any time, if recurrent)	Spontaneous bleeding requiring hospitalization or transfusion within the past 12 months not meeting the major criterion
• Previous spontaneous ICH (at any time) • Previous traumatic ICH within the past 12 months • Presence of a brain arteriovenous malformation • Moderate or severe ischemic stroke within the past 6 months	Any ischemic stroke at any time not meeting the major criterion
Moderate or severe baseline thrombocytopenia (platelet count <100×10^9/L)	Long-term use of oral NSAIDs or steroids
Anticipated use of long-term OAC	Age ≥75 years
Chronic bleeding diathesis	
Liver cirrhosis with portal hypertension	
Active malignancy within the past 12 months (excluding nonmelanoma skin cancer)	
Nondeferrable major surgery on DAPT	
Recent major surgery or major trauma within 30 days before PCI	

Table 1. Academic Research Consortium (ARC) High Bleeding Risk (HBR) Criteria in Patients Undergoing PCI; *courtesy of Guillaume Marquis-Gravel, MD, MSc*

Abbreviations: CKD: chronic kidney disease; **eGFR:** estimated glomerular filtration rate; **DAPT:** dual antiplatelet therapy; **ICH:** intracranial hemorrhage; **NSAID:** nonsteroidal anti-inflammatory drug; **OAC:** oral anticoagulation; **PCI:** percutaneous coronary intervention

to uncertainty in terms of the safest and more effective approach. More recently, however, the MASTER DAPT trial exclusively enrolled patients considered to be at high bleeding risk after PCI.[12] The 4,434 participants were randomized to either discontinue DAPT after one month, or continue DAPT for at least 5 additional months (for those without concomitant oral anticoagulation [OAC]). The abbreviated DAPT strategy decreased the risk of bleeding without compromising ischemic endpoints. On this basis, the guidelines recommend a 1-3 month DAPT duration (instead of 6-12 months) after PCI for patients at high bleeding risk (weak recommendation, moderate-quality evidence).

Antiplatelet Therapy for Patients with PCI and Atrial Fibrillation Requiring OAC

Patients with atrial fibrillation and an indication of chronic OAC are at a higher risk of bleeding complications with antiplatelet therapy after PCI or myocardial infarction. The AUGUSTUS factorial randomized controlled trial is the only trial which specifically evaluated the role of ASA in these patients, regardless of the type of OAC used.[13] Among the 4,614 participants treated with a P2Y12 inhibitor and an OAC, major or clinically relevant nonmajor bleeding occurred in 16.1% of patients treated with ASA, and in 9.0% of those treated with placebo (p<0.001). The incidence rates of death, hospitalization, and ischemic events were similar between both groups. A meta-analysis conducted during the development of the guidelines, which included 11,156 participants from 6 randomized controlled trials, suggested that dual therapy with OAC + a P2Y12 inhibitor (without ASA) was associated with 23 fewer major bleeding events per 1,000 patients versus triple therapy (OAC + P2Y12 inhibitor + ASA). However, it was associated with 8 more MACE per 1,000 patients. Therefore, in light of the net clinical benefits of dual therapy, it is recommended to stop ASA within 1-30 days after PCI or ACS in patients treated with a P2Y12 inhibitor and concomitant OAC (weak recommendation, moderate-quality evidence). Of note, at the time of PCI, all patients should be treated with ASA, which can be stopped thereafter. The optimal timing for stopping ASA remains unknown. However, in the trials included in the meta-analysis, it was stopped on average between 1.6 to 6.6 days after the index event. Therefore, it is generally reasonable to consider stopping ASA at the time of discharge. Clopidogrel is the most extensively studied P2Y12 inhibitor when used in combination with an OAC and should be preferred for these patients given the uncertainty regarding the safety of ticagrelor and prasugrel in this context. After 12 months, OAC can be continued as a monotherapy, without any antiplatelet agent (weak recommendation, very low-quality evidence), based on the AFIRE randomized controlled trial.[14] In this trial that included 2,236 patients with atrial fibrillation who underwent coronary revascularization >1 year before, OAC monotherapy with rivaroxaban was found to be non-inferior to OAC + single antiplatelet therapy regarding the primary endpoint, which was a composite of stroke, systemic embolism, myocardial infarction, unstable angina requiring revascularization, or death from any cause, which occurred at rates of 4.14% versus 5.75%, respectively; p<0.001 for non-inferiority). OAC monotherapy was also associated with a significant reduction in major bleeding (1.62% versus 2.76%; p=0.01) and all-cause mortality (1.85% versus 3.37%).

ASA for Primary Prevention of Atherosclerotic Cardiovascular Disease

ASA has long been used to prevent atherosclerotic cardiovascular thrombotic events in high-risk patients without established atherosclerotic cardiovascular disease, such as elderly patients and those with diabetes. However, it is no longer recommended routinely in primary prevention, regardless of sex, age, or diabetes (strong recommendation, high-quality evidence).[3] This new recommendation is based on a meta-analysis of 167,587 participants from 14 randomized controlled trials, which showed that while ASA reduces major adverse cardiovascular events in this context, the absolute reduction is low (4 fewer events per 1,000 patients over 5 years). However, this benefit is accompanied by a similar increase in extracranial major bleeding events (5 additional events per 1,000 patients over 5 years). In this context, the net benefits of ASA for primary prevention are neutral. However, the guidelines endorse a patient-centred, informed, shared decision-making process, in which some patients who strongly prefer ischemic risk reduction over bleeding risk avoidance may be considered for ASA in primary prevention. The guidelines include a “Primary Prevention Decision Aid Tool” to support physicians and ensure their patients make the best decision for their specific context.

KeyTake-home Messages

1. Routine pre-treatment with a P2Y12 inhibitor is not recommended for patients undergoing elective coronary angiography or those with a NSTE-ACS who have a procedure planned <24 hours after hospital admission. However, routine pre-treatment is suggested for patients with STEMI or with NSTE-ACS who have a procedure planned >24 hours, which is common in the Canadian context.
2. Prasugrel or ticagrelor are preferred over clopidogrel for patients with ACS treated with PCI to reduce ischemic events, and de-escalating to clopidogrel at 1 month can be considered to reduce bleeding.
3. For patients at high bleeding risk undergoing PCI, an abbreviated DAPT duration (typically 1-3 months) can be considered because it reduces bleeding without compromising ischemic safety.
4. For patients with ACS and/or PCI requiring a concomitant OAC for atrial fibrillation, a dual pathway strategy (P2Y12 inhibitor + OAC) is preferred over triple therapy (P2Y12 inhibitor + OAC + ASA) 1-30 days after the index event. After 12 months, OAC can be continued as monotherapy.
5. ASA is not routinely recommended for primary prevention, but the decision to use it should be based on a patient-centred, informed, and shared decision-making process with the patient.

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