A pharmacist's guide to the 2012 update of the Canadian Cardiovascular Society Guidelines for the Use of Antiplatelet Therapy

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THE INITIAL CANADIAN CARDIOVASCULAR Society (CCS) Guidelines on the Use of Antiplatelet Therapy¹ covered chronic antiplatelet therapy for a number of diseases and patient subgroups. The 2012 Focused Update² specifically addressed the issues of antiplatelet therapy for secondary prevention in the first year after acute coronary syndrome (ACS), percutaneous coronary intervention (PCI), coronary artery bypass grafting (CABG) and the interaction between clopidogrel and proton pump inhibitors (PPIs). The updating of these topics and the prominence of the newer antiplatelet agents in the guidelines make them of particular relevance to pharmacists. The intent of this publication is to highlight components of the guidelines that are most likely to affect the practice of pharmacists and provide practical information to assist pharmacists in managing patients on antiplatelet therapy.

Antiplatelet therapy after acute coronary syndrome

Dual-antiplatelet therapy (DAPT) continues to be the cornerstone of therapy for the continuum of ACS, from unstable angina to ST elevation myocardial infarction managed with either medications alone or a combination of medications and PCI (Table 1, Figure 1). The recommendation that all patients receive acetylsalicylic acid (ASA) 81 mg daily indefinitely remains unchanged.²

Non-ST elevation ACS

In addition to ASA, a second antiplatelet agent should be used in the management of non-ST elevation ACS (NSTEMACS). In patients with moderate- to high-risk NSTEMACS, the guidelines recommend ticagrelor. This is regardless of whether the patient has had PCI, CABG or no intervention. Ticagrelor is recommended over clopidogrel.² Prasugrel is recommended over clopidogrel in NSTEMACS patients undergoing PCI who were not previously treated with any of the P2Y₁₂ inhibitors (i.e., clopidogrel, prasugrel or ticagrelor). The more limited recommendation for prasugrel reflects the study population and manner in which it was used in the TRITON-TIMI 38 trial, the key trial that led to its Health Canada approval.³ Due to a lack of trial comparisons, there are no recommendations for choosing between prasugrel and ticagrelor. For patients who are not eligible for ticagrelor or prasugrel, clopidogrel is recommended. Regardless of the second antiplatelet agent selected, DAPT should continue for 12 months in the setting of NSTEMACS (Table 2).

ST elevation myocardial infarction

Patients with ST elevation myocardial infarction (STEMI) managed with either fibrinolytic therapy or no reperfusion therapy were excluded from the trials studying ticagrelor and prasugrel.^{3,4} For these patients, the second antiplatelet

FIGURE 1 Acute coronary syndrome treatment.

ACS, acute coronary syndrome; STEMI, ST elevation myocardial infarction; NSTEACS, non-ST elevation acute coronary syndrome; PCI, percutaneous coronary intervention

agent in addition to ASA should be clopidogrel, preferably for a period of 12 months, noting that the evidence for continuation of clopidogrel beyond 1 month is limited. However, for patients managed with primary PCI, either prasugrel or ticagrelor in addition to ASA is recommended over clopidogrel for 12 months² (Table 2).

Antiplatelet therapy after PCI for a non-ACS indication

PCI for stable angina or non-ACS indication

A significant number of patients undergo elective PCI, not in the setting of ACS. The newer antiplatelet agents have not been studied in this setting, so clopidogrel with ASA is considered the combination of choice.¹ Patient-specific issues, such as adverse drug reactions or drug interactions, could result in one of the newer antiplatelet agents being a more appropriate choice for an individual patient. However, under many

provincial drug plans, prasugrel and ticagrelor are restricted to patients who have experienced ACS, so pharmacists may need to discuss drug benefit issues with their patients to ensure adherence to therapy.

Stent thrombosis

Stent thrombosis is an infrequent complication following PCI. For patients who have been compliant with clopidogrel and who have gone on to develop stent thrombosis, the guidelines recommend switching to either prasugrel or ticagrelor in combination with ASA, noting that the evidence is of low quality.²

Optimal duration of dual-antiplatelet therapy

The guidelines² broadly recommend 12 months of DAPT following ACS and also following PCI for non-ACS indications. However, there may be specific circumstances under which shorter durations of DAPT may be appropriate (Table 3). For example, the use of triple-antithrombotic therapy (dual antiplatelet and the use of an oral anticoagulant at a therapeutic dose) could be a situation where a practitioner may choose to use a shorter duration of dual-antiplatelet therapy.

Antiplatelet agents

Three antiplatelet agents are referred to in the guidelines for use in combination with ASA. Pharmacists must be aware of the differences between the agents to manage adverse drug reactions, drug interactions and other considerations for individual patients. Various pharmacokinetic and pharmacodynamic characteristics of the agents are outlined in Table 4.

TABLE 1 Glossary

ACS	Acute coronary syndrome is inclusive of both non-ST elevation ACS (NSTEACS) and ST elevation myocardial infarction (STEMI)
NSTEACS	Non-ST elevation acute coronary syndrome is inclusive of both non-ST elevation myocardial infarction and unstable angina, which are differentiated by the lack of heart muscle damage associated with unstable angina
STEMI	ST elevation myocardial infarction is differentiated from NSTEACS by the severity of the ischemia and consequent damage to the heart
PCI	Percutaneous coronary intervention
Primary PCI	Use of PCI as the initial reperfusion strategy for STEMI
Elective PCI	Use of PCI for management of narrowing of a coronary artery, in stable angina, not in the setting of ACS

TABLE 2 Recommendations for dual-antiplatelet therapy²

Indication	Antiplatelet therapy in combination with ASA 81 mg daily	Suggested duration of therapy
NSTEACS patients managed with PCI, CABG or medical management	Ticagrelor 90 mg twice a day over clopidogrel*	12 months*
P2Y ₁₂ -naive NSTEACS patients for planned PCI	Prasugrel 10 mg orally daily over clopidogrel*	12 months*
NSTEACS patients managed with PCI, CABG or medical management who are not eligible for prasugrel or ticagrelor	Clopidogrel 75 mg daily*	12 months*
STEMI patients managed with either fibrinolysis or no reperfusion therapy	Clopidogrel 75 mg daily*	At least 1 month* 12 months [†]
STEMI patients managed with primary PCI	Prasugrel 10 mg daily or ticagrelor 90 mg twice a day over clopidogrel [‡]	12 months [‡]
Stable angina managed with PCI	Clopidogrel 75 mg daily*	12 months*

*Strong recommendation, high-quality evidence.

[†]Conditional recommendation, low-quality evidence.

[‡]Strong recommendation, moderate-quality evidence.

ASA, acetylsalicylic acid; NSTEACS, non-ST elevation acute coronary syndrome; CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; STEMI, ST elevation myocardial infarction.

TABLE 3 Considerations for shorter duration of DAPT

Patient factors	Stent factors
High risk of bleeding	Bare metal stents require a minimum duration of 1 month of DAPT, which could be reduced to 2 weeks in patients at very high risk of bleeding
Need for major surgical procedure	Drug-eluting stents require 12 months of DAPT, but newer generation drug-eluting stents may allow for shorter duration of DAPT, especially in the case of patients at high risk of bleeding

DAPT, dual-antiplatelet therapy.

Adverse effects of antiplatelet agents

Bleeding

All medications are known to have adverse effects, and consideration of the adverse effects within the context of the benefit posed to the patient is foremost in a clinician's mind when initiating drug therapy. The primary adverse effects of antiplatelet therapy involve both minor and major bleeding events. Patients should be educated regarding the potential risk of bleeding and should self-monitor for signs of gastrointestinal bleeding and bruising. The definition of major bleeding is inconsistent between trials but generally includes any intracranial bleeding, bleeding requiring intervention or bleeding

with a significant reduction in hemoglobin.⁸ In the trials assessing the use of antiplatelet therapy in ACS, rates of major bleeding varied between 1.8% and 11.6%, with the differing definitions influencing the variation. In general, the rates of major bleeding are in the range of 2%-3% when ASA is used in combination with a second antiplatelet agent.⁹

The benefits of prasugrel and ticagrelor relative to clopidogrel must be weighed against the increase in the risk of bleeding. Prasugrel was associated with significant increases in major, life-threatening and fatal bleeding in the total study population and increased intracranial bleeding in those with a history of cerebrovascular disease. Prasugrel should not be

TABLE 4 Pharmacokinetic and pharmacodynamic properties of antiplatelet agents⁵⁻⁷

	Clopidogrel (Plavix)	Prasugrel (Effient)	Ticagrelor (Brilinta)
Mechanism of action	Inhibits binding of adenosine-diphosphate (ADP) to platelet P2Y ₁₂ receptor and subsequent ADP-mediated platelet activation	Inhibits binding of ADP to platelet P2Y ₁₂ receptor and subsequent ADP-mediated platelet activation	Binds to the P2Y ₁₂ receptor site and inhibits ADP signaling and receptor conformational change
Maintenance dose	75 mg daily	10 mg daily	90 mg twice daily
Approved indications with concurrent low-dose ASA	<ul style="list-style-type: none"> • MI, stroke, PAD (secondary prevention) • ACS ± PCI • Atrial fibrillation 	ACS undergoing PCI	ACS managed medically or with PCI or CABG
Onset of effect after loading dose	2-5 h	1-1.5 h	1-3 h
% Platelet inhibition at steady state	40%-60%	69%-74%	74%-96%
Duration of platelet inhibition	5-7 days irreversible binding	5-7 days irreversible binding	48-72 h reversible binding
Metabolism	Prodrug (CYP2C19, 3A, 2B6, 1A2)	Prodrug (CYP3A4, 2B6, 2C9, 2C19)	Not a prodrug (CYP3A4)
Pharmacological considerations	Two-step activation required with CYP2C19; CYP2C19 genetic polymorphisms may decrease efficacy	One-step activation dependent on CYP3A4 to active metabolite	No hepatic activation required; metabolism through CYP3A4/5
Precautions and clinical considerations	Efficacy might be reduced when administered with CYP219 inhibitors (i.e., PPI)	<ul style="list-style-type: none"> • Contraindicated with history of stroke or TIA and severe hepatic disease • Caution in patients >75 years and <60 kg • Administration with strong CYP3A4 inhibitors/inducers 	<ul style="list-style-type: none"> • Administration with strong CYP3A4 inhibitors/inducers • Patients at risk of bradycardia events
Most frequent adverse effects	Bleeding, rash	Bleeding, rash (cross-sensitivity with clopidogrel)	Bleeding, dyspnea (12% vs 6.5%)
Cost	\$2.71/day Generic \$0.92/day	\$2.71/day	\$2.96/day

ASA, acetylsalicylic acid; MI, myocardial infarction; PAD, peripheral arterial disease; ACS, acute coronary syndrome; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; PPI, proton pump inhibitor; TIA, transient ischemic attack.

administered to patients with a history of stroke or transient ischemic attack and was not shown to be beneficial in patients 75 years or older and those weighing less than 60 kg.³ The product monograph includes a boxed warning that highlights the bleeding risks in this population

and recommends avoidance in these patients.⁶ Ticagrelor was associated with a higher risk of major bleeding and should be used with caution in patients at a higher risk of bleeding. It is contraindicated in patients with a history of intracranial hemorrhage.⁷

Low-dose ASA (81 mg/day in Canada) is the optimal dose after ACS.² There does not appear to be added benefit for high-dose ASA, and major bleeding is increased in a dose-dependent manner.^{10,11}

Current Canadian antiplatelet guidelines indicate that patients who are receiving ASA or DAPT and develop significant bruising should be assessed with a complete blood count and international normalized ratio (INR), as well as an activated partial thromboplastin time (aPTT) to assess whether the patient has thrombocytopenia or a coagulopathy. In the absence of these, antiplatelet therapy can be continued with clinical observation, whereas in those with thrombocytopenia or a coagulopathy, ASA or DAPT should be stopped pending further investigation. Patients who are receiving DAPT and in whom there is excessive bleeding after a dental procedure should have local pressure applied and use tranexamic acid mouthwash 2 to 4 times daily for 1 to 2 days. Patients receiving ASA or ASA and clopidogrel who develop subconjunctival bleeding should continue therapy and be monitored for bleeding.¹ For any individual patient presenting with bleeding, the risks and benefits of stopping DAPT should be evaluated.

Respiratory reactions

ASA-induced respiratory reactions occur in approximately 0.3% of the general population. These reactions are not IgE mediated but rather due to COX-1 inhibition. Respiratory reactions associated with ASA can occur in up to 5% to 10% of asthmatic patients. Onset is generally 0.5 to 3 hours after ingestion, and symptoms include rhinorrhea, nasal congestion, ocular tearing and conjunctival injection and/or bronchoconstriction. Patients who develop ASA sensitivity need to avoid ASA and other COX-1 nonsteroidal anti-inflammatory drugs (NSAIDs). ASA desensitization can be safely used to reintroduce ASA in patients with a history of a respiratory-induced reaction.^{12,13}

Ticagrelor was associated with an increased risk of mild to moderate and usually transient dyspnea compared with clopidogrel. Dyspnea rarely resulted in treatment discontinuation (0.9% ticagrelor vs 0.1% placebo). In general, ticagrelor-induced dyspnea is mild and self-limiting, and approximately one-third of patients will have spontaneous resolution within 1 week. It is considered reversible upon discontinuation

BOX 1 Canadian Cardiovascular Society guideline system

The Canadian Cardiovascular Society applies the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system to its guideline process. This system categorizes recommendations as strong or conditional and separately rates the level of evidence that supports the recommendation as very low, low, moderate or high quality.

BOX 2 Key educational messages for patients

- Patients should understand that ASA is a lifelong therapy.
- Patients should be aware of the duration of their dual-antiplatelet therapy and appreciate the potential consequences of early discontinuation or nonadherence.
- Patients should know to inform other doctors and health care professionals that they are taking antiplatelet agents and that they should not stop their ASA or antiplatelet agent without speaking with their cardiologist.
- Patients need to be aware of the signs of serious bleeding and understand when they need to seek medical attention.
- Patients need to know to contact a health care professional to ensure appropriate management if they experience side effects that may be due to antiplatelet therapy, rather than just stopping the medication.

of the drug.⁴ Patients reporting new, prolonged or worsened dyspnea while on ticagrelor require appropriate investigation to ensure that other causes are ruled out.⁷ Less than 10% of patients in the PLATO (the PLATelet inhibition and patient Outcomes) trial⁴ had preexisting asthma or chronic obstructive pulmonary disease (COPD). Therefore, there are limited data in these patient groups.

Drug-induced skin eruptions

ASA-induced urticaria or angioedema can occur in approximately 0.07% to 0.2% of the general population but can occur in up to 30% of patients with chronic idiopathic urticaria. Urticaria can occur within 15 minutes of ASA ingestion but may be delayed up to 24 hours. Although desensitization has been used in patients with ASA-induced urticaria, some patients may experience a reaction during the desensitization protocol.¹²

Rash may occur in up to 4% of clopidogrel-treated patients.⁵ The skin eruption usually presents as pruritic macular erythematous confluent rash on the trunk that may become generalized.

BOX 3 Adherence

- Patient education is an important component of adherence.
- Pharmacists should address any cost issues that might affect patient adherence.
- If a patient follow-up/adherence phone system is in place, patients on dual-antiplatelet therapy should be considered a high priority.
- If antiplatelet agents are discontinued for a procedure, patients should receive clear written and verbal directions on when to resume therapy.

BOX 4 Role of the community pharmacist

- Ensure that patients understand the benefit of their medications and how to monitor for adverse effects.
- Identify any potential adherence challenges and assist patients in overcoming these challenges.
- Ensure that patients on dual-antiplatelet therapy are considered a high priority when a patient follow-up/adherence phone system is in place.
- Identify potential issues with multiple prescribers with respect to disruptions in therapy or drug interactions.

It typically presents on day 6 after exposure to clopidogrel. Options for reintroduction include switching to alternative therapies (i.e., ticagrelor), short-term steroids or clopidogrel desensitization.¹⁴ The incidence of rash reported with ticagrelor and prasugrel is 2% and 3%, respectively.¹⁵

Prasugrel bears some chemical similarity to other thienopyridines, and potential exists for cross-reactivity with clopidogrel. In one case series, allergic cross-reactivity following a previous reaction to clopidogrel was observed in 24% of patients with ticlopidine, in 17% of patients with prasugrel and in 7% of patients with both ticlopidine and prasugrel¹⁴ by skin testing. However, there are reports of successful use of prasugrel in patients with a history of clopidogrel allergy.^{16,17}

Other

Ticagrelor was associated with more ventricular pauses (≥ 3 seconds) on Holter monitoring (5.8%) compared with clopidogrel (3.6%) in the PLATO trial. However, this did not result in increased rates of pacemaker insertion, syncope, bradycardia or heart block.⁴ Notwithstanding, caution is warranted in patients with bradycardia, as these patients were excluded from the trial.⁷

Ticagrelor was associated with increases in serum creatinine and uric acid relative to clopidogrel.⁴ Periodic monitoring of renal function and uric acid levels (in patients with gout or at risk of hyperuricemia) may be considered.⁷

Other potential adverse effects of clopidogrel, prasugrel and ticagrelor include nausea, vomiting and diarrhea, which occur in approximately 2% to 5% of patients.⁵⁻⁷

Drug interactions and antiplatelet agents*Pharmacodynamic interactions*

Like most drugs, antiplatelet agents have potential drug interactions through both pharmacodynamic and pharmacokinetic mechanisms. Due to their mechanism of action, all antiplatelet agents result in an increased risk of bleeding when combined with other medications that also increase this risk. One of the most common clinical scenarios is the use of triple therapy, the combination of dual-antiplatelet therapy with oral anticoagulants, in patients with both ACS and atrial fibrillation. Most data for risk of major bleeding in this scenario are with warfarin, rather than the novel oral anticoagulants. Although the data are heterogeneous, the risk of major bleeds appears to be increased 2-fold with triple therapy over dual-antiplatelet therapy in some studies.^{18,19} Pharmacists should be aware of the potential for this pharmacodynamic interaction, especially when multiple prescribers are involved, to ensure appropriate assessment and monitoring.

Pharmacokinetic interactions

Although most practitioners are aware of concerns regarding a potential pharmacokinetic interaction between clopidogrel and the PPIs, as discussed in the Antiplatelet Guidelines,² awareness of the potential pharmacokinetic interactions associated with the newer antiplatelet agents, ticagrelor and prasugrel, is also important. Pharmacokinetic studies of drug interactions with antiplatelet agents are limited, so pharmacokinetic studies of the metabolism of the agents themselves and studies using agents such as rifampin and ketoconazole may be used to predict the magnitude and direction of drug interactions.

Clopidogrel is a prodrug and must undergo a 2-step activation process. It is initially metabolized by hepatic esterases into an inactive moiety.

TABLE 5 Examples of medications that may have pharmacokinetic interactions with newer antiplatelet agents^{*5-7,27,28}

Interaction	Antiplatelet agents		
	Ticagrelor	Clopidogrel	Prasugrel
Drugs that increase effect of antiplatelet agent	Ketoconazole		
	Nefazodone		
	Clarithromycin		
	Ritonavir		
	Atazanavir		
	Cyclosporine		
Drugs that decrease effect of antiplatelet agent	Rifampin	Omeprazole	Ritonavir
	Dexamethasone	Fluvoxamine	
	Phenytoin	Fluoxetine	
	Carbamazepine	Ketoconazole	
	Phenobarbital	Moclobemide	
		Efavirenz	
Drugs affected by antiplatelet agent	Digoxin		

*This table is not a complete list of medications with the potential to interact.

CYP enzymes, predominantly CYP2C19 but also CYP3A4, CYP1A2 and CYP2B6, then create the active thiol derivative. Studies have demonstrated that loss of CYP2C19 activity reduces the effectiveness of clopidogrel, and alterations to this enzyme are the major mechanism for potential drug interactions. Agents that induce CYP2C19 are not felt to be of concern as genetic CYP2C19 rapid metabolizers do not appear to have a significant impact on efficacy.²⁰

PPIs are frequently coadministered with dual-antiplatelet therapy to reduce the risk of gastrointestinal bleeding. Observational data have raised the concern that patients taking both agents are at increased risk of further cardiovascular events.²¹ The rationale is that CYP2C19 is inhibited by certain PPIs, including omeprazole, resulting in less of the active moiety of clopidogrel. This reduction in activity is supported by in vitro platelet studies.¹ However, other studies and observational data associate PPI use with an increased risk of cardiovascular events, even in patients not receiving concomitant clopidogrel.²²⁻²⁴ Two small randomized controlled trials have attempted to address this issue and have found no impact of concomitant administration

on cardiovascular outcomes. However, both trials were small, and the potential risk cannot be completely dismissed.^{25,26} The CCS guidelines strongly recommend that patients receiving DAPT who are at high risk of upper gastrointestinal bleeding receive PPIs for gastroprotection. The accompanying commentary suggests the use of PPIs with minimal effect on CYP2C19, such as pantoprazole.²

Although other potentially interacting agents are not addressed specifically in the guidelines, an in vitro study of the nonnucleoside reverse transcriptase inhibitor efavirenz²⁷ demonstrated that concomitant administration with clopidogrel decreased the area under the curve (AUC) of clopidogrel by 33% through inhibition of CYP2C19 and CYP2C9 bioactivation. Therefore, it is important to consider the potential impact of inhibitors of CYP2C19 when assessing the choice of antiplatelet agent for a specific patient (Table 5).

Prasugrel is also a prodrug. It undergoes a 2-step activation process that begins with rapid hydrolysis in the intestinal lumen. The resulting thiolactone is then converted into the active metabolite. CYP3A4 is primarily responsible

for this conversion, but CYP2B6, CYP2C9 and CYP2C19 also play a role. Concerns regarding potential drug interactions with prasugrel relate to induction or inhibition of CYP3A4 or CYP2B6.²⁰

Despite this potential, the product monograph states that prasugrel can be concomitantly administered with drugs that induce or inhibit cytochrome P450 enzymes. This is based on studies with ketoconazole and rifampin, which are considered strong inhibitors and inducers, respectively. Concomitant administration with ketoconazole did not show an effect on platelet aggregation or the active metabolite's AUC and time to maximum concentration (T_{max}) but did decrease the maximum concentration (C_{max}) of prasugrel by 34% to 46%. A healthy volunteer study with ritonavir, a protease inhibitor that inhibits CYP3A4 and prasugrel, reported a decrease of 40% in the AUC of prasugrel's active metabolite.²⁸ Rifampin administration was not shown to significantly affect the inhibition of platelet aggregation or the pharmacokinetics of prasugrel.²⁹

Ticagrelor does not require metabolic activation. However, its bioavailability is limited (20%-30%) and it is a substrate for P-glycoprotein (Pgp). Pgp inhibition, with an agent such as cyclosporine, resulted in a 2.8-fold increase in ticagrelor's AUC.⁷ Ticagrelor is also a weak inhibitor of Pgp and, therefore, can increase the levels of medications with narrow therapeutic indices that are substrates of Pgp, such as digoxin.⁷ Pgp is, therefore, a potential mechanism for drug interactions. Following absorption, ticagrelor is further metabolized via CYP3A4 into an active metabolite. This metabolite is then conjugated and eliminated. Induction or inhibition of CYP3A4 is also a potential source of drug interactions with ticagrelor. As ticagrelor is transformed by CYP3A4 into a less potent active metabolite, inhibition of CYP3A4 will increase the effect of ticagrelor and the potential for bleeding. Agents such as rifampin that are inducers of CYP3A4 will potentially decrease the effect of ticagrelor and its efficacy.²⁰

For all of the antiplatelet agents, it is important for pharmacists to include drug interactions in their assessment of appropriateness for an individual patient. The majority of pharmacokinetic interactions are based on limited data but should be part of the assessment and may

influence the choice of antiplatelet agent or extent of monitoring.

Perioperative management of antiplatelet agents

As highlighted previously, the majority of patients will continue on dual-antiplatelet therapy for 12 months following ACS or elective PCI. During this period, patients may require CABG or noncardiac procedures. The concern of bleeding in the perioperative period is not as great as for anticoagulants, but the rate of major bleeding associated with antiplatelet therapy is high enough that each individual should undergo assessment.

For those in whom the bleeding risk is determined to be high, these agents must be withheld prior to surgery. The timing of holding these medications depends on their mechanism of action. ASA, clopidogrel and prasugrel all have an irreversible antiplatelet effect. It is recommended that ASA and clopidogrel be held for 5 days prior to surgery and prasugrel for 7 days.^{5,6} Ticagrelor has a reversible antiplatelet effect and should be held for 5 days prior to surgery.⁷ Occasionally, due to the urgency of the surgery, patients will undergo surgery without antiplatelet agents being withheld. In these individuals, pharmacists should monitor for any clinical or laboratory signs of excessive blood loss during the immediate postoperative period. For patients requiring CABG surgery specifically, ASA is not withheld and is given up to and including the day of surgery, particularly in those with a recent ACS. "Bridging therapy" with a short-acting intravenous glycoprotein IIb/IIIa receptor antagonist (e.g., eptifibatide or tirofiban) may be considered in those patients who are unstable and awaiting CABG surgery.³⁰ These agents have usually been stopped at least 4 hours prior to surgery.

Following surgery, it is important to ensure that DAPT is reinitiated where possible. In patients undergoing CABG surgery, ASA will be reinitiated within 6 hours of surgery to prevent graft occlusion. For those patients who were receiving DAPT preoperatively, reinitiation is recommended in those who had recent ACS and should be continued for 12 months. In addition, in those who were receiving DAPT due to stent insertion, DAPT should be reinitiated postoperatively to prevent stent thrombosis, particularly if the stented vessel was not bypassed

TABLE 6 Benefit of antiplatelet agents in acute coronary syndromes^{3,4,10}

Reduction in myocardial infarction, stroke and death				
Drug*	RRR (%)†	ARR (%)†	NNT	Events prevented/ 1000 patients
Clopidogrel and ASA (compared with ASA)	20	2.1	48	20
Prasugrel and ASA (compared with clopidogrel and ASA)	19	2.2	46	22
Ticagrelor and ASA (compared with clopidogrel and ASA)	16	1.9	53	19

*Used in conjunction with acetylsalicylic acid (ASA) 81 to 325 mg oral daily. ASA 81 mg daily recommended with ticagrelor.

†Relative risk reduction (RRR) and absolute risk reduction (ARR) of primary outcome from landmark trials (composite of death, myocardial infarction and stroke).

during surgery. The timing of the reinitiation will vary from patient to patient, but studies have reported that, of those who had DAPT restarted, half resumed therapy within 14 days of surgery. Reinitiation of antiplatelet therapy in non-CABG surgery may be delayed if an epidural or spinal catheter is in place and the patient is deemed high risk for spinal hematoma formation or there would be significant consequences if bleeding did occur (e.g., intraocular bleeding).^{2,31,32}

Patient education

It is important to educate patients on the goals of antiplatelet therapy, which are to reduce the risk of death due to cardiovascular disease, to reduce the risk of future myocardial infarctions and stroke and prevent stent thrombosis for patients who underwent PCI. It is also important that patients have a basic understanding of how exactly these therapies work, their potential adverse effects and the duration of therapy. A useful ACS educational tool that provides both visual and written information can be accessed at www.ccpn.ca.

Providing information in a more quantitative manner can aid in patient education to enhance understanding of the positive impact of antiplatelet therapy, as well as other secondary prevention modalities. In general, the number needed to treat to prevent one major cardiovascular event or death, calculated from the landmark trials for each of these agents, is 46 to 53. It is important to remember that clopidogrel was compared with ASA alone, while prasugrel and ticagrelor were compared with the combination of ASA and clopidogrel. Similarly, the number of events prevented per 1000 patients treated is 19 to 22.^{3,4,10} Table 6 is intended to provide pharmacists with

the necessary tools to put things into perspective for patients.

In addition to efficacy, it is also very important that patients are educated on the safety aspects of dual-antiplatelet therapy. Rates of major bleeding on dual-antiplatelet therapy are reported to be in the range of 2% to 3%.⁹ Patients should seek medical attention if they develop any unexpected, prolonged or excessive bleeding complications such as hematuria, melena, epistaxis or hematemesis.

Adherence and risk of discontinuation

Dual-antiplatelet therapy is a cornerstone of ACS management. Unfortunately, nonadherence has been demonstrated in the use of these agents. Approximately 10% to 30% of patients do not fill their initial prescription for clopidogrel on the day of discharge.^{33,34} Also, in the Canadian setting, adherence to most chronic medications used in the care of patients with cardiovascular disease is approximately 50% to 70% at 1 year.³⁵ In a study by Ho et al.,³⁶ examining 7402 patients discharged from the hospital following stent implantation, a significant increase in death was demonstrated in those having any delay in filling their prescription compared with those who filled their prescription on the day of discharge (14.2% vs 7.9%, $p < 0.001$). Pharmacists have a key role in identifying and resolving adherence problems.

Summary

The CCS guidelines highlight the optimal use of antiplatelet therapy.^{1,2} This article highlights the aspects of those guidelines most relevant to pharmacists to help them care for their patients. ■

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