As contributors to a publicly funded health care system, Canada’s public drug plans must balance the potential benefits of new drugs with ensuring the best value for limited health care budgets. But deciding which drugs to cover, in which situations and for which patients, is never an easy task. CADTH’s Decision Support series provides an overview of relevant drug review issues and highlights sources of evidence to support decision-making. Please refer to the CADTH reports cited for full details on any of the issues discussed.

Acute coronary syndrome (ACS) is a term used for any condition caused by sudden, reduced blood flow to the heart. It most commonly occurs when a coronary artery is partially or completely blocked due to blood clot formation. Partial blockage of blood flow can cause unstable angina (chest pain which comes and goes) and a more complete or total block can cause myocardial infarction (MI); that is, a heart attack. MI can be further defined as ST segment elevation MI (STEMI) or as non-ST segment elevation MI (NSTEMI), depending upon the degree of damage to the heart. STEMI is a more severe heart attack than NSTEMI.

In Canada, patients presenting with symptoms of ACS generally receive immediate dual antiplatelet therapy, typically acetylsalicylic acid (ASA), or aspirin, and clopidogrel (Plavix and generics). Some patients are managed in the acute setting with medications alone, while others may undergo percutaneous coronary intervention (PCI), or “ballooning,” or coronary artery bypass grafting (CABG) (bypass surgery) to reopen the blocked artery. Some patients undergoing PCI may also receive a coronary stent to help keep the artery open. Each year, Canadian hospitals admit 60,000 people with ACS and this number is expected to rise as the Canadian population ages.¹

Health Canada recently approved two new antiplatelet agents — prasugrel (Effient) and ticagrelor (Brilinta) — for use in combination with ASA for the secondary prevention of atherothrombotic events in adults with ACS; in other words, for patients who have experienced unstable angina or MI to prevent stroke or additional MIs. The potential advantages of these new agents over clopidogrel are faster onset of action, and lower variability between patients in the degree of platelet inhibition.

CADTH provides unbiased, evidence-based information to Canada’s decision-makers, who often have tough choices to make about funding health technologies. On the topic of dual antiplatelet therapy in ACS, CADTH has recently published the following reports:
What did the Common Drug Review find?
The Canadian Drug Expert Committee (CDEC), which makes recommendations on drugs for Canada’s publicly funded drug plans, recommends that prasugrel and ticagrelor not be listed at the submitted prices. The specific reasons for these recommendations differed between the two drugs, although in both cases CDEC was not persuaded that the newer agents would have clinical benefits over clopidogrel in Canadian practice.

How do the drugs compare?

Indications: Prasugrel, co-administered with ASA, is indicated for use only in ACS patients who will be managed with PCI. In contrast, ticagrelor and clopidogrel, co-administered with ASA, are indicated in ACS patients managed with medication alone, or managed with PCI and/or with CABG.

Efficacy: The efficacy of prasugrel was compared with standard dose (75 mg daily) clopidogrel in the clinical trial TRITON-TIMI 38, which involved 13,608 patients with ACS undergoing PCI. Following up to 15 months of therapy, the rate at which prasugrel-treated patients experienced the primary composite outcome of MI, stroke, or death from cardiovascular (CV) cause was lower (9.4%) than experienced by clopidogrel-treated patients (11.5%), with a hazard ratio (HR) of 0.8 (95% CI 0.7 to 0.9). CDEC noted that the benefit of prasugrel may not be realized in a Canadian setting due to the timing of antiplatelet therapy in the TRITON-TIMI 38 trial and the dose of clopidogrel used. In the trial, 74% of patients received the antiplatelet loading dose during PCI. Only 2% of patients received the loading dose more than six hours prior to PCI. But in Canada, the majority of ACS patients receive a loading dose of clopidogrel (300 mg to 600 mg) upon hospital arrival. This is important, as the faster onset of action of prasugrel, compared to clopidogrel, has less clinical benefit if patients receive an antiplatelet early in their treatment pathway.

A loading dose of 300 mg of clopidogrel was used in TRITON-TIMI 38, which is a lower dose than is often used in Canadian hospitals. CDEC noted this may have resulted in an overestimation of the comparative efficacy of prasugrel. Recent meta-analyses have shown that a loading dose of 600 mg of clopidogrel provides a reduction in MI, stroke, and CV death, without an increase in major bleeding, compared with a 300 mg clopidogrel loading dose.

The efficacy of ticagrelor was compared with standard dose (75 mg daily) clopidogrel in the PLATO study, which included 18,624 patients with ACS regardless of management strategy (i.e., medical, PCI, or CABG). Following up to 12 months of therapy, the rate at which patients experienced the primary composite outcome of MI, stroke, or CV death was lower for ticagrelor (9.3%) than clopidogrel (10.9%); HR 0.8 (95% confidence interval [CI] 0.8 to 0.9). However, when looking only at the North American patients in the study, there was no statistically significant difference between treatments; HR 1.3 (95% CI 0.9 to 1.7).

New information: In addition to CADTH’s systematic review, a recent network meta-analysis used data from 14 clinical trials (including TRITON-TIMI 38 and PLATO) to indirectly compare prasugrel, ticagrelor, and clopidogrel high-dose (≥150 mg daily) and standard dose (75 mg daily) in patients undergoing PCI. A subgroup analysis was also conducted that focused on trials in patients with ACS. No significant differences between prasugrel, ticagrelor, and high-dose clopidogrel were observed for MI, stroke, CV death, or major adverse cardiac events (MACE) in either the overall analysis or the ACS subgroup. All three strategies were more effective than standard dose clopidogrel. As with all network meta-analyses, differences between trials may introduce bias. In the cited analysis, such differences included dose and timing of antiplatelet loading, dose of ASA, and variation in outcome definitions.
In a recently published paper, prasugrel was compared with standard-dose clopidogrel (75 mg daily) in a new trial (TRILOGY) involving 7,243 ACS patients managed with medication alone. Currently, this use is not an approved indication for prasugrel. The study authors found no significant difference between prasugrel and clopidogrel on the primary composite end point of MI, stroke, or CV death.9

What are the potential harms?
Antiplatelet therapy increases bleeding risk because it reduces clotting. For patients undergoing surgical interventions such as PCI and CABG, bleeding risk is an especially serious consideration.

Bleeds: Bleeding in TRITON-TIMI 38 was assessed using the thrombosis in myocardial infarction (TIMI) criteria. Patients treated with prasugrel had a statistically significantly higher rate of non-CABG-related bleeding (2.4% versus 1.8%), CABG-related bleeding (13.4% versus 3.2%), and life-threatening or fatal bleeding (1.4% versus 0.9%) compared with clopidogrel.6

The percentage of patients with ACS having a major bleed, defined by TIMI criteria, were similar with ticagrelor (7.9%) compared with clopidogrel (7.7%) in the PLATO study.10 However, compared with clopidogrel, ticagrelor-treated patients had a higher frequency of major bleeds unrelated to CABG (2.8% versus 2.2%).6

New information: In the network meta-analysis discussed earlier, some differences were observed regarding bleeding risks. Firstly, prasugrel was associated with a higher risk of major bleeding than ticagrelor and standard dose clopidogrel, but there was no significant difference versus high-dose clopidogrel. The risk of major bleeding was not significantly different between ticagrelor and low-dose or high-dose clopidogrel, nor was there a significant difference between the two doses of clopidogrel.8

Stroke: While the overall risk of stroke was not statistically significantly different between the ticagrelor and clopidogrel arms in PLATO (relative risk [RR] 1.17 [95% CI 0.91 to 1.52]), the incidence of stroke (unknown cause) was higher for ticagrelor-treated patients compared with clopidogrel-treated patients (RR 4.98 [95% CI 1.01 to 22.71]). The risks for other types of stroke (hemorrhagic stroke, non-hemorrhagic stroke) were higher with ticagrelor, but were not statistically different.3

Neoplasms: Analysis of the TRITON-TIMI 38 data by the Food and Drug Administration (FDA) found a statistically significant increase in the incidence of new or worsened neoplasm with prasugrel compared with clopidogrel (2.2% versus 1.6%, P = 0.01; calculated by CDR).2,5 The FDA concluded that the trend may be spurious, but required enhanced surveillance of cancer events in future trials. The Canadian product monograph for prasugrel warns prescribers about the increased frequency of malignancy in the TRITON-TIMI 38 trial and that the causality is currently unknown.11

Breathing difficulties: In PLATO, ticagrelor-treated patients had a higher incidence of dyspnea (breathing difficulties) (12.0% versus 6.5%), and severe dyspnea (0.7% versus 0.4%), compared with clopidogrel.3

What are the costs of treatment?
Costs may vary by jurisdiction. The costs compared by CDEC in December 20113 and June 20122 were:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dose</th>
<th>Daily Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ticagrelor3</td>
<td>90 mg twice daily</td>
<td>$2.96</td>
</tr>
<tr>
<td>(Brilinta)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prasugrel2</td>
<td>10 mg daily</td>
<td>$2.66</td>
</tr>
<tr>
<td>(Effient)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clopidogrel3</td>
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<td>$2.58</td>
</tr>
<tr>
<td>(Plavix)</td>
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<tr>
<td>Clopidogrel2</td>
<td>75 mg daily</td>
<td>$0.66</td>
</tr>
<tr>
<td>(generics)</td>
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Most patients typically continue on dual antiplatelet therapy for up to 12 months following initial treatment. Therapy beyond 12 to 15 months may be considered in some cases; for example, in patients who receive drug-eluting stents (coated with medicine to help keep the artery open).

Who might benefit from the newer agents?

Poor antiplatelet response: Clopidogrel requires activation by the hepatic enzyme CYP2C19. If the function of this enzyme is reduced due to individual genetic variability or concomitant drug interactions, the antiplatelet effects of clopidogrel may be reduced. Indeed, a number of genetic tests to identify carriers of loss-of-effect variants, and phenotypic tests to measure the level of platelet reactivity, are under development to identify poor clopidogrel responders. However, testing for response to clopidogrel is currently not widely performed in Canadian clinical practice. Furthermore, recent systematic reviews have reported that patients predicted to have diminished activation of clopidogrel due to genetic variants of CYP2C19 did not have worse cardiovascular outcomes; thus, the utility of tests to identify such genetic variants is uncertain. At this time, it is also uncertain whether prasugrel or ticagrelor have clinical benefits over clopidogrel regarding reduced cardiovascular events in patients with poor antiplatelet response to clopidogrel.

Following thrombotic events: CDEC considered the possibility that ticagrelor may provide a benefit for patients who experience thrombotic events while taking clopidogrel; however, PLATO did not provide data for this type of patient. Such evidence is also not available for prasugrel.

Following stent thrombosis: CDEC considered that patients who develop stent thrombosis while taking clopidogrel may benefit from switching to prasugrel. In TRITON-TIMI 38, prasugrel-treated patients had a lower incidence of definite or probable stent thrombosis (0.9%) than those receiving clopidogrel (1.9%); HR of 0.5 (0.4 to 0.6). However, there were no data from TRITON-TIMI 38 that allowed the effects of prasugrel to be assessed in clopidogrel-treated patients who have experienced stent thrombosis. Such evidence is also not available for ticagrelor.

Clinical practice guidelines: Several guidelines have been produced in recent years discussing the use of antiplatelet therapy in ACS. The Atlantic Anti-Platelet Initiative guidelines, developed in collaboration with the Atlantic Cardiovascular Society in April 2012, are relevant to a Canadian setting. Essentially, the guidelines recommend that standard dose clopidogrel (75 mg daily) and ASA should continue to be the preferred dual antiplatelet therapy in patients with ACS. These guidelines suggest ticagrelor or prasugrel may be considered for some groups, such as STEMI patients who have not received antiplatelet therapy prior to arrival in the catherization lab for PCI, or ACS patients with NSTEMI or unstable angina at high risk of CV death (as defined by high GRACE or TIMI scores, which assess cumulative risk factors). The evidence on which these guidelines are based ranges from high-quality evidence to very low-quality evidence.

What other clinical issues should be considered?

Pill burden: Ticagrelor requires twice-daily dosing, compared with once daily for clopidogrel and prasugrel. All three drugs should be used with a daily ongoing dose of ASA.

ASA dose: Clopidogrel, ticagrelor, and prasugrel are all indicated for use in combination with ASA. The product monograph for ticagrelor notes that the data from patients in the PLATO trial who received high-dose ASA (> 300 mg daily) do not conclusively demonstrate the efficacy of ticagrelor compared with clopidogrel. Maintenance doses of ASA >150 mg daily are not recommended in combination with ticagrelor.

Drug interactions: Clopidogrel, prasugrel, and ticagrelor are all subject to potential drug interactions. Noteworthy interactions are subsequently discussed.

As clopidogrel requires CYP2C19 activation, use of strong or moderate CYP2C19 inhibitors (such as omeprazole) is not recommended.
Clinical pharmacology data suggest ticagrelor interacts with cytochrome P450 3A4/5 enzymes. Because of that, ticagrelor is contraindicated in patients who are also taking strong CYP3A4 inhibitors (e.g., ketoconazole).

Oral anticoagulants (e.g., warfarin), fibrinolytics, and nonsteroidal anti-inflammatory drugs (NSAIDs) all confer an independent bleeding risk, so should be used with caution in patients who are also receiving clopidogrel, prasugrel, or ticagrelor.

**Preparing for surgery:** For patients undergoing elective surgery and not requiring an antiplatelet effect, prasugrel should be discontinued at least seven days prior to surgery, clopidogrel discontinued five to seven days prior to surgery, and ticagrelor five days prior to surgery.

**Warnings:** Clopidogrel, prasugrel, and ticagrelor should all be used with caution in patients with a propensity for bleeding (due to recent trauma, recent surgery, or other pathological conditions). Prasugrel has a warning against use in patients older than 75 years or those who weigh less than 60 kg due to a higher risk of major bleeding in these patients.

**Contraindications:** All three antiplatelet agents are contraindicated in patients with active bleeding (such as peptic ulcer or intracranial hemorrhage), or in patients with significant liver impairment. Prasugrel is additionally contraindicated in patients with a known history of stroke or transient ischemic attack (TIA). Ticagrelor is contraindicated in patients with a history of intracranial bleeding or in patients who are also taking strong CYP3A4 inhibitors. Refer to product monographs for detailed information.

**References**


12. *Apo-clopidogrel Clopidogrel Tablets USP (equivalent to clopidogrel 75 mg) [product monograph]. Weston (ON): Apotex Inc; 2011 Dec 22.


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