

## Original Article

# Implications of the Antiplatelet Therapy Gap Left With Discontinuation of Prasugrel in Canada

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### ABSTRACT

**Background:** The current Canadian Cardiovascular Society antiplatelet therapy guidelines recommend the use of ticagrelor or prasugrel over clopidogrel as first-line platelet P2Y<sub>12</sub> receptor antagonists for treatment of moderate- to high-risk acute coronary syndromes. Recently, Effient (prasugrel [Eli Lilly Canada Inc, Toronto, Canada]) was discontinued by its distributor in Canada.

**Methods:** Five members of the Canadian Cardiovascular Society antiplatelet therapy 2018 guidelines committee undertook an independent, evidence-based review to outline patients for whom prasugrel should be the optimal P2Y<sub>12</sub> agent and discuss alternative strategies to consider without prasugrel.

**Results:** Several clinical scenarios where prasugrel should be indicated are identified and discussed. Considerations to be undertaken for alternative therapies are summarized, including a review of na-

### RÉSUMÉ

**Introduction :** Dans ses lignes directrices actuelles sur la thérapie antiplaquettaire, la Société canadienne de cardiologie recommande l'utilisation du ticagrélor ou du prasugrel plutôt que l'utilisation du clopidogrel comme antagonistes des récepteurs plaquettaires P2Y<sub>12</sub> de première intention dans le traitement des patients qui présentent un risque modéré à élevé de syndromes coronariens aigus. Depuis peu, le distributeur a cessé la distribution d'Effient (prasugrel) au Canada.

**Méthodes :** Cinq membres du comité des lignes directrices 2018 sur la thérapie antiplaquettaire de la Société canadienne de cardiologie ont entrepris une revue indépendante fondée sur les données probantes pour dresser le profil des patients pour lesquels le prasugrel devrait être la meilleure option parmi les antagonistes des récepteurs P2Y<sub>12</sub> et se pencher sur les traitements alternatifs en l'absence de prasugrel.

Effient (prasugrel [Eli Lilly Canada Inc, Toronto, Canada]), an oral P2Y<sub>12</sub> platelet receptor inhibitor was discontinued from the Canadian market on January 31, 2020, by its distributor on the basis of a business decision. As 1 of only 2 first-line agents for acute coronary syndromes (ACS), this is impactful for patient care in Canada and poses a therapeutic

challenge for clinicians, from family physicians to pharmacists, internists, and cardiologists. This article delves into scenarios in which prasugrel should be the optimal P2Y<sub>12</sub> agent, alternative strategies to consider without prasugrel, and possible contributing factors for its discontinuation in Canada.

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**Ethics Statement:** The paper reflects the authors' analysis in a truthful and complete manner.

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See page 6 for disclosure information.

### Background

Dual antiplatelet therapy using aspirin and a P2Y<sub>12</sub> receptor antagonist is the cornerstone therapy after ACS and percutaneous coronary intervention (PCI). Worldwide, there are 4 available oral P2Y<sub>12</sub> receptor inhibitors—ticlopidine, clopidogrel, prasugrel, and ticagrelor—of these, only the latter 3 are routinely used after ACS and PCI. Clopidogrel is the

tional and international guidelines for de-escalation of P2Y12 receptor antagonists.

**Conclusions:** The discontinuation of prasugrel poses a challenge for clinicians. Clinicians must consider key factors in determining the best alternate therapy.

standard P2Y12 agent after PCI for stable coronary artery disease. For ACS, ticagrelor and prasugrel have been shown in large studies to be superior to clopidogrel in decreasing major adverse cardiovascular events (MACE), at the cost of increased bleeding complications.<sup>1,2</sup> Canadian and international guidelines endorse a preference of these 2 more potent P2Y12 drugs over clopidogrel as first-line in patients with ST-elevation myocardial infarction and non-ST elevation ACS at moderate to high risk of recurrent events; notably, a preference of prasugrel over ticagrelor post-PCI was endorsed in the 2020 European Society of Cardiology non-ST elevation ACS guidelines.<sup>3-6</sup> In Canada, ticagrelor has been more commonly prescribed than prasugrel. In several published Canadian-based studies, the initial choice of prasugrel as the first-line agent ranged from 0.4% to 12.5%; in contrast, ticagrelor use in the same studies ranged from 11.1% to 36.4%.<sup>7-9</sup> The underutilization might be attributed to several possible factors.<sup>1,2</sup> First, unlike ticagrelor, prasugrel has not shown benefit over clopidogrel in those not undergoing PCI.<sup>10</sup> Second, ticagrelor demonstrated reduced cardiovascular mortality compared with clopidogrel in its pivotal trial; whereas prasugrel's benefit was driven by nonfatal events. Third, prasugrel should not be used in patients with previous transient ischemic attack or stroke; and a low 5-mg dose (which was never available in Canada) should be used among those age 75 years or older or with low body weight.<sup>3</sup> Fourth, patients in the **Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel Thrombolysis in Myocardial Infarction (TRITON-TIMI) 38** study, with non-ST-elevation myocardial infarction, only received prasugrel after anatomy was delineated at angiography.<sup>2</sup> In contrast, ticagrelor was given up front in the **Platelet Inhibition and Patient Outcomes (PLATO)** trial<sup>1</sup>; thus, making ticagrelor more applicable for physicians in non-PCI centres, where patients might wait up to several days before angiography.

Ticagrelor has practical challenges in a real-world setting, including side effects, such as dyspnea, which might require cessation or switching of medications. Drug interactions, affecting ticagrelor pharmacodynamics, might also preclude its use among patients with other medical conditions.<sup>11</sup> Apropos to guidelines and evidence from studies are that if a patient cannot take a first-line agent, the default should be a change between first-line agents, as opposed to a de-escalation to clopidogrel.<sup>3,12</sup> Ticagrelor and prasugrel have different chemical structures and mechanisms of action; therefore patients with allergy or intolerance can be switched safely between agents.<sup>3,12</sup>

Notably, in the **Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary**

**Résultats :** Plusieurs scénarios cliniques où le prasugrel devrait être indiqué sont recensés et abordés. Les réflexions sur les solutions de rechange au traitement, notamment une revue des lignes directrices nationales et internationales en matière de désescalade des antagonistes des récepteurs P2Y12, sont présentées.

**Conclusions :** La cessation de la distribution du prasugrel pose problème aux cliniciens. Les cliniciens doivent tenir compte des facteurs clés pour déterminer le meilleur traitement de remplacement.

Treatment 5 (ISAR-REACT 5) study, ticagrelor was evaluated against prasugrel in a head-to-head open-label comparison in patients with ACS and showed prasugrel superior in reducing MACE.<sup>13</sup> Because this study was relatively recent, its findings likely did not influence Canadian physicians' practice patterns at the time of prasugrel's withdrawal in Canada.

## Clinical Scenarios in Which Prasugrel Would Be Clinically Indicated

### I. Stent thrombosis or other thrombotic events during treatment with ticagrelor

Although stent thrombosis among patients compliant with ticagrelor is rare, it is documented in up to 0.8% undergoing complex PCI.<sup>14</sup> Although no clear evidence guides management of patients with stent thrombosis during treatment with ticagrelor, the 2018 Canadian Cardiovascular Society antiplatelet guidelines do suggest consideration for a switch between the agents, if technical considerations are ruled out.<sup>3</sup>

### II. Patients experiencing sustained dyspnea due to ticagrelor

The most frequent side effect of ticagrelor is dyspnea, which does not affect pulmonary function.<sup>15</sup> In a meta-analysis, comprising 63,484 patients, ticagrelor was associated with substantially higher risk of dyspnea (relative risk = 2.65; 95% confidence interval, 1.87-3.76) as compared with clopidogrel.<sup>16</sup> Dyspnea from ticagrelor was reported in 13.8%-21.4% of participants randomized in trials necessitating discontinuation of study drug in 0.9%-6.9% (Table 1).<sup>1,17-20</sup> Premature discontinuation of ticagrelor has been reported in up to 25% of patients in real-life observational settings,<sup>21-23</sup> most frequently related to dyspnea.<sup>24</sup> In the **Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Tablets Compared to Placebo on a Background of Aspirin—Thrombolysis in Myocardial Infarction 54** (PEGASUS-TIMI 54) trial, the 60-mg and the 90-mg twice daily ticagrelor doses were associated with higher rates of dyspnea and of premature discontinuation of the study drug compared with placebo.<sup>17,18</sup> A tendency toward a higher rate of these events was observed with the 90-mg twice daily dose compared with the 60-mg twice daily dose, although no formal statistical comparison was presented.<sup>17,18</sup>

### III. Drug interactions with ticagrelor

Although ticagrelor is a direct-acting P2Y12 receptor inhibitor, it is metabolized by cytochrome P450, family 3,

**Table 1. Comparative discontinuation rates of ticagrelor in major randomized controlled trials**

Patients	PLATO <sup>2</sup>		PEGASUS-TIMI 54 <sup>17</sup>		THEMIS <sup>1,9</sup>		ISAR-REACT 5 <sup>13</sup>	
	18,624 Patients with ACS	21,162 Patients with MI 1 to 3 years earlier	21,162 Patients with MI 1 to 3 years earlier	19,220 Patients with stable CAD and type 2 diabetes	4108 Patients with ACS and planned invasive evaluation	19,220 Patients with stable CAD and type 2 diabetes	4108 Patients with ACS and planned invasive evaluation	
Follow-up time	1 Year	Median: 33 months	Median: 33 months	Median: 39.9 months	1 Year	Median: 39.9 months	1 Year	
Study drugs	Clopidogrel 75 mg QD	Ticagrelor 90 mg BID	Placebo	Ticagrelor 90 mg BID	Placebo	Placebo	Prasugrel 10 mg QD	Ticagrelor 90 mg BID
Premature discontinuation of study drug, %	21.5	23.4 ( $P < 0.002$ )	21	29 ( $P < 0.001$ )	25.4	34.5 ( $P < 0.001$ )	NA	NA
Dyspnea, %	7.8	13.8 ( $P < 0.001$ )	6.4	15.8 ( $P < 0.001$ )	7.3	21.4 ( $P < 0.001$ )	NA	NA
Dyspnea leading to discontinuation, %	0.1	0.9 ( $P < 0.001$ )	0.79	4.55 ( $P < 0.001$ )	0.8	6.9 ( $P < 0.001$ )	0.0	2.5

ACS, acute coronary syndromes; BID, twice daily; CAD, coronary artery disease; ISAR-REACT 5, Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment 5; MI, myocardial infarction; PEGASUS-TIMI 54, Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin; PLATO, Platelet Inhibition and Patient Outcomes; QD, once daily; THEMIS, Effect of Ticagrelor on Health Outcomes in Diabetes Mellitus Patients Intervention Study.

\* In the THEMIS trial, the dose of ticagrelor was 90 mg BID in the intervention arm. This dose was reduced to 60 mg BID with an amendment during the course of the trial.

subfamily A (CYP3A) enzymes to AR-C124910XX, an active metabolite, before excretion.<sup>25</sup> In a large observational patient-level registry, 25% of patients initiating ticagrelor in the context of ACS were taking at least 1 potentially interacting drug.<sup>26</sup> The most common clinically relevant interactions were with warfarin (3.8%) and nonsteroidal anti-inflammatory drugs (0.4%-4.1%), both associated with increased bleeding risk.<sup>26</sup> Interactions with serotonergic drugs, including antidepressants, were also commonly reported (0.4%-1.7%).<sup>26</sup> The clinical importance of the interaction with selective serotonin reuptake inhibitors is uncertain. No significant pharmacokinetic interaction was seen between ticagrelor and venlafaxine, despite potential interaction via the cytochrome P450, family 2, subfamily D, member 6 (CYP2D6) enzyme.<sup>27</sup> A potential increased cumulative risk of bleeding has been postulated, on the basis of observational data with other antiplatelets.<sup>28</sup> As such, closer monitoring of patients taking these drugs is reasonable, but their concurrent use does not preclude ticagrelor initiation. Table 2 includes known clinically meaningful drug interactions that affect ticagrelor. Concomitant use of ticagrelor with potent CYP3A inducers, including phenytoin, carbamazepine, and phenobarbital, have been shown to potentiate ticagrelor metabolism and significantly reduce platelet inhibition.<sup>11</sup> In contrast, strong CYP3A inhibitors, such as protease inhibitors, induce accumulation of ticagrelor, leading to enhanced platelet inhibition and increased bleeding risk.<sup>29,30</sup> These drugs are encountered infrequently in patients with ACS, although increased cardiometabolic risk in HIV-positive patients compounded by adverse cardiometabolic effects of antiretroviral therapy might lead to more patients requiring antiplatelet therapy for ACS.<sup>31</sup>

#### IV. Genetic considerations

Common *CYP2C19* loss-of-function alleles, ranging from 25% to 40% depending on ethnic origins, affect clopidogrel metabolism and put carriers at risk for ischemic complications after PCI.<sup>32</sup> Prasugrel and ticagrelor mitigate ischemic risks among patients with these genetic variants.<sup>32,33</sup> The **Pharmacogenetics of Clopidogrel in Patients With Acute Coronary Syndromes (PHARMCLO)** and **POPular Genetics** studies had both evaluated a pharmacogenomic approach, in which carriers of at-risk alleles were treated with ticagrelor or prasugrel, while noncarriers received clopidogrel.<sup>34,35</sup> Compared with standard of care per physicians' discretion, the former study showed a reduction in the composite primary end point of ischemic and bleeding outcomes; the latter showed pharmacogenomics to be noninferior for ischemic complications, but reduced bleeding. In a post hoc analysis of the recent **Tailored Antiplatelet Initiation to Lessen Outcomes Due to Decreased Clopidogrel Response After Percutaneous Coronary Intervention (TAILOR-PCI)** trial, a genotype-guided approach in the first 3 months post PCI showed a reduction in ischemic outcomes.<sup>36</sup> For patients known to be carriers of loss-of-function variants and intolerant of ticagrelor, prasugrel treatment remains the reasonable first choice.

#### V. Patients with issues of nonadherence

Adherence to taking P2Y12 inhibitors is an important determinant of efficacy, with lower rates of compliance being

**Table 2. Selected drug interactions with ticagrelor**

Drugs	Effect when coadministered with ticagrelor	Precautions	References
CYP3A inducers (eg, rifampicin, antiepileptics [carbamazepine, phenytoin])	Decreased ticagrelor pharmacokinetic parameters, leading to reduced ticagrelor bioavailability and half-life	Reduced platelet inhibition on ticagrelor	11,47
CYP3A inhibitors (eg, HIV protease inhibitors [ritonavir], antifungals [ketoconazole], grapefruit juice)	Increased ticagrelor pharmacokinetic parameters, leading to potential accumulation	Increased platelet inhibition on ticagrelor, requiring significantly lower dosing	29,30,48
Narrow therapeutic window P-glycoprotein transporter-dependent drugs (eg, digoxin)	Increased digoxin plasma concentrations	Closer monitoring of P-glycoprotein transporter substrates with a narrow therapeutic window upon ticagrelor initiation	49

CYP3A, cytochrome P450, family 3, subfamily A.

associated with MACE. In a large cohort of 55,340 commercially insured patients, ticagrelor had significantly lower long-term adherence than clopidogrel.<sup>37</sup> The reasons for nonadherence are multisystemic,<sup>38</sup> but the twice-daily dosing of ticagrelor compared with prasugrel and clopidogrel might play a role; thus, it is a potential consideration in choosing P2Y12 inhibitors for patients, when medication adherence might be a concern.

### Considerations for Selecting Alternative Strategies

Discontinuation of Effient from the Canadian market unveils a gap in clinical management of high-risk patients, early after ACS or complex PCI. Two important factors must be considered concurrently in determining the safest course in patients who might benefit from more intensive P2Y12 inhibition, but for whom ticagrelor is not an option. The first

**Table 3. Guidance for P2Y12 inhibitor therapy without prasugrel**

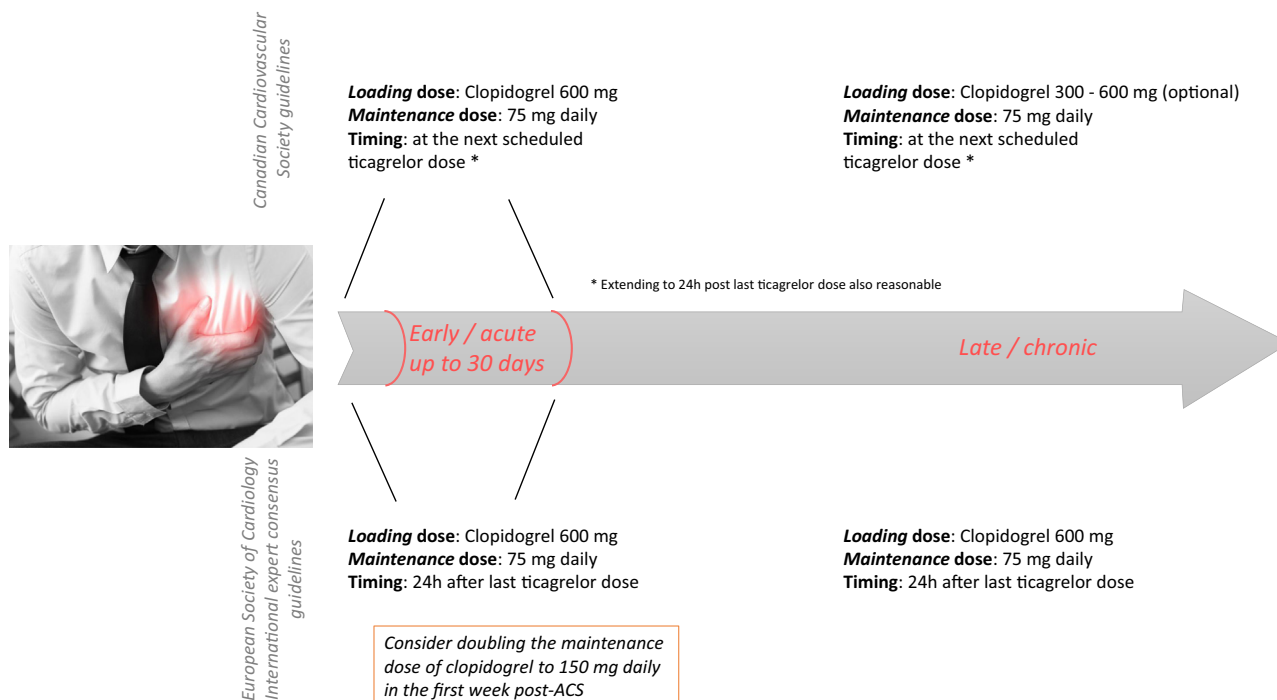
	Dyspnea/intolerance to ticagrelor	Drug interactions with ticagrelor	Major bleeding or high bleeding risk
< 7 Days from ACS/PCI	Options: (1) Persist with ticagrelor and reassess on the basis of symptoms; (2) High-dose clopidogrel 150 mg daily for 7 days (preceded by 600 mg bolus dose) then 75 mg daily*; (3) Consider compassionate release of prasugrel in high-risk patients in whom clopidogrel is not a good option; (4) Consider reducing the dose to 60 mg twice daily	Options: (1) High-dose clopidogrel 150 mg daily for 7 days (preceded by 600 mg bolus dose) then 75 mg daily*; (2) Consider reassessing the indication for the other drug; (3) Consider compassionate release of prasugrel in high-risk patients in whom clopidogrel is not a good option	Options: (1) De-escalate to clopidogrel (see Fig. 1). Consider resuming ticagrelor if cause of bleeding resolved; (2) Consider aspirin interruption or cessation if bleeding or high bleed risk
7-30 Days	Options: (1) Persist with ticagrelor and reassess based on symptoms; (2) De-escalate to clopidogrel (see Fig. 1); (3) Consider compassionate release of prasugrel in high-risk patients in whom clopidogrel is not a good option; (4) Consider reducing the dose to 60 mg twice daily	Options: (1) De-escalate to clopidogrel (see Fig. 1); (2) Consider reassessing the indication for the other drug; (3) Consider compassionate release of prasugrel in high-risk patients in whom clopidogrel is not a good option	Options: (1) De-escalate to clopidogrel (see Fig. 1). Consider resuming ticagrelor if cause of bleeding resolved; (2) Consider aspirin interruption or cessation if bleeding or high bleed risk
> 30 Days	Options: (1) Persist with ticagrelor and reassess; (2) De-escalate to clopidogrel (see Fig. 1); (3) Consider compassionate release of prasugrel in high-risk patients in whom clopidogrel is not a good option; (4) Consider reducing the dose to 60 mg twice daily	Options: (1) De-escalate to clopidogrel (see Fig. 1); (2) Consider reassessing the indication for the other drug; (3) Consider compassionate release of prasugrel in high-risk patients in whom clopidogrel is not a good option	Options: (1) De-escalate to clopidogrel (see Fig. 1); (2) Aspirin cessation with ticagrelor monotherapy if bleed risk high, but no active bleeding†

All suggested therapies are on the basis of expert opinions and extrapolation of best evidence.

ACS, acute coronary syndromes; GLOBAL LEADERS, Ticagrelor Plus Aspirin Followed by Ticagrelor Monotherapy vs a Current-Day Intensive Dual Antiplatelet Therapy in Patients Undergoing Percutaneous Coronary Intervention With Bivalirudin and Biomatrix Family Drug-Eluting Stents; CURRENT-OASIS 7, Clopidogrel and Aspirin Optimal Dose Usage to Reduce Recurrent Events—Organization to Assess Strategies in Ischemic Syndromes 7; PCI, percutaneous coronary intervention, TWILIGHT, Ticagrelor With Aspirin or Alone in High-Risk Patients After Coronary Intervention.

\* Per CURRENT-OASIS 7.

† Per TWILIGHT study if after 3 months, or GLOBAL LEADERS study after 1 month.



**Figure 1.** Overview of de-escalation strategies from ticagrelor to clopidogrel in the Canadian, European, and international guidance documents. The orange box is an additional consideration from this group. The early period covers up to 30 days after the acute coronary event. ACS, acute coronary syndromes.

is timing from index ACS or PCI, because those within the first few days or weeks are at highest risk for ischemic complications. The second is the reason underlying the switch. Strategies for those with bleeding will be inherently different to those with intolerances or other rationale. Because prasugrel is associated with increased major bleeding relative to clopidogrel, a switch to prasugrel when bleeding is a concern would not be considered appropriate. Intuitively, serious bleeding concerns in high-risk patients will favour a de-escalation to clopidogrel or to single antiplatelet therapy (SAPT), whereas intolerance or nonadherence would favour alternative potent P2Y12 regimens. With these 2 factors accounted, possible solutions are presented in Table 3. Figure 1 further summarizes Canadian, European, and international guidelines on safest means to switching from ticagrelor to clopidogrel if it is deemed required.

### Alternative clopidogrel regimen

High-dose clopidogrel during the first week after PCI minimizes ischemic complications in patients early after ACS. This approach, studied in Clopidogrel and Aspirin Optimal Dose Usage to Reduce Recurrent Events-Organization to Assess Strategies in Ischemic Syndromes (CURRENT-OASIS) 7, showed doubling clopidogrel loading (600 mg) and maintenance doses (150 mg daily) for 1 week after ACS treated with PCI was associated with a diminution of MACE.<sup>39</sup> The reduction in the rate of stent thrombosis with double-dose clopidogrel was 31%, which was similar to the effect of ticagrelor in PLATO (25% reduction).<sup>1,2</sup> In the Escalating Clopidogrel by Involving a Genetic Strategy - Thrombolysis in Myocardial Infarction 56 (ELEVATE-TIMI

56) trial, high maintenance clopidogrel doses of 225 mg daily in heterozygous carriers of *CYP2C19* loss-of-function alleles yielded similar levels of platelet inhibition compared with standard 75 mg in noncarriers.<sup>40</sup> However, the effect of a genotype-guided dosing strategy for clopidogrel as replacement for ticagrelor after ACS and PCI on outcomes has not been studied and is not routinely recommended clinically.

### Reduced-dose ticagrelor

Lowering ticagrelor dose from 90 mg to 60 mg to decrease side effects is theoretically attractive, on the basis of pharmacodynamic data showing 60 mg achieving similar platelet inhibition, and a numerical reduction in major bleeding and incidence of dyspnea.<sup>17,41</sup> However, this dose has not been evaluated in the early ACS setting. Additionally, rates of discontinuation for side effects compared with a 90-mg dose were not statistically different in PEGASUS-TIMI 56.<sup>17</sup>

### SAPT with ticagrelor

Bleeding has been reported as the reason for stopping ticagrelor in up to 30% with premature discontinuation.<sup>18,25</sup> In the Ticagrelor With Aspirin or Alone in High-Risk Patients After Coronary Intervention (TWILIGHT) and Ticagrelor Monotherapy After 3 Months in the Patients Treated With New Generation Sirolimus Stent for Acute Coronary Syndrome studies, a strategy of ticagrelor monotherapy vs dual antiplatelet therapy was evaluated in patients 3 months after ACS or complex PCI.<sup>14,42</sup> A reduction of clinically relevant

bleeding and no differences in MACE were reported, suggesting early SAPT with ticagrelor alone may be considered among patients with bleeding risk or those with actionable, but not major bleeding.

### De-escalation to clopidogrel

Clopidogrel had been the standard of care before arrival of more potent P2Y<sub>12</sub> inhibitors. De-escalation to clopidogrel 14-30 days after the index event was investigated in the **Timing of Platelet Inhibition After ACS (TOPIC)** and **Testing Responsiveness to Platelet Inhibition on Chronic Antiplatelet Treatment for Acute Coronary Syndromes (TROPICAL-ACS)** trials, suggesting noninferiority of these approaches vs maintaining more intensive P2Y<sub>12</sub> therapies long-term.<sup>43,44</sup> In the Ticagrelor or prasugrel versus clopidogrel in elderly patients with an acute coronary syndrome: optimization of antiplatelet treatment in patients aged older than 70 years (POPular AGE) study, clopidogrel was shown to be a reasonable alternative to ticagrelor in patients older than the age of 70 years, mainly because of reductions in bleeding risk.<sup>45</sup> Thus, use of clopidogrel is acceptable in patients with higher bleeding risk and lower thrombotic risk.

### Limited access to prasugrel

For patients with stent thrombosis during ticagrelor treatment, when prasugrel might be integral and alternate strategies might put them at risk, there are mechanisms to apply for compassionate release, with prasugrel importation from other countries. Unfortunately, evaluation on a patient-by-patient basis renders the process unpredictable. On a long-term basis, a generic form of prasugrel would be required to bridge the gap in clinical care. Although approval is under way, as yet generic formulations are not available in Canada.

### Conclusion

Despite evidence of superiority in ACS,<sup>2,13</sup> prasugrel was not able to garner a large market share in Canada; this likely being the primary reason for its discontinuation from the Canadian market. We can postulate on potential contributors to the lower uptake in clinical practice, including a higher risk of major and life-threatening bleeding, lack of reduction in mortality compared with clopidogrel, lack of benefit over clopidogrel in ACS patients managed medically, unavailability of the 5-mg dosing, and limitations in the generalizability of the pivotal trial establishing the benefit of prasugrel. Additionally, loss of patent protection might also have provided impetus for the drug's discontinuation by its distributor. Indeed, the decision to stop supplying Effient was announced 1 year after an unsuccessful attempt to protect its Canadian patent on a combination of prasugrel and aspirin in 2018.<sup>46</sup> In retrospect, it is easy to identify areas in which prasugrel was likely underutilized. For example, in high-risk patients with side effects or drug interactions to ticagrelor, prasugrel should have been the evidence-based second choice. Data from ISAR-REACT 5,<sup>13</sup> coupled with the newly revised European guidelines' preference of prasugrel over ticagrelor,<sup>6</sup> would support its role in our arsenal of P2Y<sub>12</sub> inhibitors. If generic prasugrel becomes available, it might be an opportunity for physicians to re-examine the evidence for its use in higher-risk patients.

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