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

Marie Lordkipanidze, BPharm, MSc PhD,a,b Guillaume Marquis-Gravel, MD, MSc,a,c Jean-François Tanguay, MD FRCP,a,c Shamir R. Mehta, MD MSc, FRCPC,d,e and Derek Y.F. So, MD MSc FRCPCf

a Montreal Heart Institute, Montreal, Quebec, Canada
b Faculty of pharmacy, Université de Montréal, Montreal, Quebec, Canada
c Faculty of medicine, Université de Montréal, Montreal, Quebec, Canada
d McMaster University, Hamilton, Ontario, Canada
e Hamilton Health Sciences, Hamilton, Ontario, Canada
f University of Ottawa Heart Institute, Ottawa, Ontario, Canada

ABSTRACT

Background: The current Canadian Cardiovascular Society antiplatelet therapy guidelines recommend the use of ticagrelor or prasugrel over clopidogrel as first-line platelet P2Y12 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 P2Y12 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 non-
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.\(^1\)\(^2\) 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.\(^3\)\(^4\) 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%.\(^5\)\(^6\) The underutilization might be attributed to several possible factors.\(^1\)\(^2\) First, unlike ticagrelor, prasugrel has not shown benefit over clopidogrel in those not undergoing PCI.\(^1\)\(^0\) 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.\(^7\)\(^8\) 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.\(^2\) In contrast, ticagrelor was given up front in the Platelet Inhibition and Patient Outcomes (PLATO) trial\(^9\); 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.\(^4\)\(^1\)\(^1\) 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.\(^3\)\(^1\)\(^2\) Ticagrelor and prasugrel have different chemical structures and mechanisms of action; therefore patients with allergy or intolerance can be switched safely between agents.\(^3\)\(^1\)\(^2\)

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

### Results

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

### Conclusions

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

### 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.\(^1\)\(^4\) 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.\(^7\)

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

The most frequent side effect of ticagrelor is dyspnea, which does not affect pulmonary function.\(^1\)\(^3\) 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.\(^1\)\(^0\) 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).\(^1\)\(^7\)\(^-\)\(^2\) Premature discontinuation of ticagrelor has been reported in up to 25% of patients in real-life observational settings,\(^2\)\(^1\)\(^-\)\(^2\) most frequently related to dyspnea.\(^2\)\(^4\) 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.\(^1\)\(^7\)\(^-\)\(^8\) 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.\(^1\)\(^7\)\(^-\)\(^8\)

### III. Drug interactions with ticagrelor

Although ticagrelor is a direct-acting P2Y12 receptor inhibitor, it is metabolized by cytochrome P450, family 3,
subfamily A (CYP3A) enzymes to AR-C124910XX, an active metabolite, before excretion. 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. The most commonly clinically relevant interactions were with warfarin (3.8%) and nonsteroidal anti-inflammatory drugs (0.4%-4.1%), both associated with increased bleeding risk. Interactions with serotoninergic drugs, including antidepressants, were also commonly reported (0.4%-1.7%). 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. A potential increase in the incidence of bleeding has been postulated on the basis of observational data with other antiplatelets. 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 CYP3A4 inducers, including phenytoin, carbamazepine, and phenobarbital, have been shown to potentiate ticagrelor metabolism and significantly reduce platelet inhibition. In contrast, strong CYP3A inhibitors, such as protease inhibitors, induce accumulation of ticagrelor, leading to enhanced platelet inhibition and increased bleeding risk. 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.

### 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. Prasugrel and ticagrelor mitigate ischemic risks among patients with these genetic variants. Pharmacogenomics 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. 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. 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.37 The reasons for nonadherence are multisystemic,38 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.

Table 3. Guidance for P2Y12 Inhibitor therapy without prasugrel

| < 7 Days from ACS/PCI | Dyspnea/intolerance to ticagrelor | Drug interactions with ticagrelor | Major bleeding or high bleeding risk |
|-----------------------|-----------------------------------|----------------------------------|-------------------------------------|
| Options:             | Options:                          | Options:                         | Options:                           |
| (1) Persist with ticagrelor and reassess based on symptoms; | (1) High-dose clopidogrel 150 mg daily for 7 days (preceded by 600 mg bolus dose) then 75 mg daily*; | (1) De-escalate to clopidogrel (see Fig. 1); | (1) De-escalate to clopidogrel (see Fig. 1). Consider resuming ticagrelor if cause of bleeding resolved; |
| (2) 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; | (2) Consider aspirin interruption or cessation if bleeding or high bleed risk | |
| (3) Consider compassionate release of prasugrel in high-risk patients in whom clopidogrel is not a good option; | (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 | | | |

7-30 Days

| Options: | Options: | Options: |
|---------|---------|---------|
| (1) Persist with ticagrelor and reassess based on symptoms; | (1) De-escalate to clopidogrel (see Fig. 1); | (1) De-escalate to clopidogrel (see Fig. 1). Consider resuming ticagrelor if cause of bleeding resolved; |
| (2) De-escalate to clopidogrel (see Fig. 1); | (2) Consider reassessing the indication for the other drug; | (2) Consider aspirin interruption or cessation if bleeding or high bleed risk |
| (3) Consider compassionate release of prasugrel in high-risk patients in whom clopidogrel is not a good option; | (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 | | |

> 30 Days

| Options: | Options: | Options: |
|---------|---------|---------|
| (1) Persist with ticagrelor and reassess; | (1) De-escalate to clopidogrel (see Fig. 1); | (1) De-escalate to clopidogrel (see Fig. 1); |
| (2) De-escalate to clopidogrel (see Fig. 1); | (2) Consider reassessing the indication for the other drug; | (2) Aspirin cessation with ticagrelor monotherapy if bleed risk high, but no active bleeding |
| (3) Consider compassionate release of prasugrel in high-risk patients in whom clopidogrel is not a good option; | (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 | | |

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

**SAPT with ticagrelor**

Bleeding has been reported as the reason for stopping ticagrelor in up to 30% with premature discontinuation. 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. 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 P2Y12 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 P2Y12 therapies long-term. 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. 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, 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 distributing. 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. 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, coupled with the newly revised European guidelines’ preference of prasugrel over ticagrelor, would support its role in our arsenal of P2Y12 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.

**Funding Sources**

M.L. is a Canada Research Chair in Platelets as vectors and biomarkers, J.-F.T. is supported by the Desgroseilliers-Bérard Research Chair in Interventional Cardiology at the Université de Montréal. D.Y.F.S. is supported by a Mid-Career Investigator Award of the Heart and Stroke Foundation of Ontario.

**Disclosures**

M.L. has received speaker honoraria from Bayer; has received research grants to the institution from Idorsia; has served on a national advisory board for Servier; and has received in-kind and financial support for investigator-initiated grants from Leo Pharma, Roche Diagnostics, Aggredyne, and Fujimori Kogyo. G.M.-G. has received honoraria from Servier and Novartis (unrelated to this work). J.-F.T. has received research grants to the institution from Abbott Vascular, Biosensors, Idorsia, and Novartis; is a member of advisory boards for Bayer Canada, Daichii-Sankyo, Novartis, and Servier; has received speaker honoraria from Astra-Zeneca, Bayer Canada, BMS-Pfizer Alliance, and Servier. S.R.M. has received research grants from Astra Zeneca Canada. D.Y.F.S. has received unrestricted grant support (physician-initiated grant) from Eli Lilly Canada; is a member of the advisory board and has received honoraria from AstraZeneca Canada; is a member of the advisory board for Bayer Canada; has received unrestricted grant support (physician-initiated grant) from Spartan Biosciences; has received unrestricted grant support (physician-initiated grant) from Aggredyne; has received unrestricted grant support (physician-initiated grant) from Diapharma/Roche Diagnostics; and has received honoraria from Abbott Vascular, Canada.

**References**

1. Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2009;361:1045-57.
2. Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2007;357:2001-15.
3. Mehta SR, Bainer KR, Cantor WJ, et al. 2018 Canadian Cardiovascular Society/Canadian Association of Interventional Cardiology focused update of the guidelines for the use of antiplatelet therapy. Can J Cardiol 2018;34:214-33.
4. Levine GN, Bates ER, Bitl JA, et al. 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2016;68:1082-115.
5. Valgimigli M, Bueno H, Byrne RA, et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: The Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J 2018;39:213-60.
6. Collet JP, Thiele H, Barbato E, et al. 2020 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J 2021;42:1289-367.
7. Welsh RC, Sidhu RS, Cairns JA, et al. Outcomes among clopidogrel, prasugrel, and ticagrelor in ST-elevation myocardial infarction patients who underwent primary percutaneous coronary intervention from the TOTAL trial. Can J Cardiol 2019;35:1377-85.

8. Dery JP, Mehta SR, Fisher HN, et al. Baseline characteristics, adenosine diphosphate receptor inhibitor treatment patterns, and in-hospital outcomes of myocardial infarction patients undergoing percutaneous coronary intervention in the prospective Canadian Observational AntiPlatelet Study (COAPT). Am Heart J 2016;181:26-34.

9. Turgon RD, Koshman SL, Youngson E, et al. Association of ticagrelor vs clopidogrel with major adverse coronary events in patients with acute coronary syndrome undergoing percutaneous coronary intervention. JAMA Intern Med 2020;180:420-8.

10. Roe MT, Armstrong PW, Fox KA, et al. Prasugrel versus clopidogrel for acute coronary syndromes without revascularization. N Engl J Med 2012;367:1297-309.

11. Pourdjabbar A, Hibbert B, Chong AY, et al. A pharmacodynamic analysis for the co-administration of inducers of CYP3A with ticagrelor: a cautionary tale in managing patients with acute coronary syndromes. Int J Cardiol 2016;214:423-5.

12. Angiolillo DJ, Rollini F, Storey RF, et al. International expert consensus review topic of the week. J Am Coll Cardiol 2019;73:2454-64.

13. Schupke S, Neumann FJ, Menichelli M, et al. Ticagrelor or prasugrel in patients with acute coronary syndromes. N Engl J Med 2019;381:1524-34.

14. Dangas G, Baber U, Sharma S, et al. Ticagrelor with or without aspirin after complex PCI. J Am Coll Cardiol 2020;75:2414-24.

15. Storey RF, Bleden KP, Patil SB, et al. Incidence of dyspnea and assessment of cardiac and pulmonary function in patients with stable coronary artery disease receiving ticagrelor, clopidogrel, or placebo in the ONSET/ OFFSET study. J Am Coll Cardiol 2010;56:185-93.

16. Zhang N, Xu W, Li O, Zhang B. The risk of dyspnea in patients treated with third-generation P2Y12 inhibitors compared with clopidogrel: a meta-analysis of randomized controlled trials. BMC Cardiovasc Disord 2020;20:140.

17. Bonaca MP, Bhatt DL, Cohen M, et al. Long-term use of ticagrelor in patients with prior myocardial infarction. N Engl J Med 2015;372:1791-800.

18. Bonaca MP, Bhatt DL, Oude Ophuis T, et al. Long-term tolerability of ticagrelor for the secondary prevention of major adverse cardiovascular events: a secondary analysis of the PEGASUS-TIMI 54 trial. JAMA Cardiol 2016;1:425-32.

19. Steg PG, Bhatt DL, Simon T, et al. Ticagrelor in patients with stable coronary disease and diabetes. N Engl J Med 2019;381:1309-20.

20. Jones WS, Baumgartner I, Hiatt WR, et al. Ticagrelor compared with clopidogrel in patients with prior lower extremity revascularization for peripheral artery disease. Circulation 2017;135:241-50.

21. Arora S, Shemisa K, Vadugananathan M, et al. Premature ticagrelor discontinuation in secondary prevention of atherosclerotic CVD: JACC review topic of the week. J Am Coll Cardiol 2019;73:2454-64.

22. Zeymer U, Cully M, Hochadel M. Adherence to dual antiplatelet therapy with ticagrelor in patients with acute coronary syndrome treated with percutaneous coronary intervention in real life. Results of the REAL-TICA registry. Eur Heart J Cardiovasc Pharmacother 2018;4:205-10.

23. Zanchin T, Temperli F, Karagiannis A, et al. Frequency, reasons, and impact of premature ticagrelor discontinuation in patients undergoing coronary revascularization in routine clinical practice: results from the Bern Percutaneous Coronary Intervention Registry. Circ Cardiovasc Interv 2018;11:e006132.

24. Bergmeijer TO, Janssen PWA, van Oevelen M, et al. Incidence and causes for early ticagrelor discontinuation: a “real-world” Dutch registry experience. Cardiology 2017;138:164-8.

25. Biscaglia S, Tonet E, Pavisini R, et al. A counseling program on nuisance bleeding improves quality of life in patients on dual antiplatelet therapy: a randomized controlled trial. PLoS One 2017;12:e0182124.

26. Prami T, Khanfir H, Hasvold P, et al. Concomitant use of drugs known to cause interactions with oral antiplatelets-polypharmacy in acute coronary syndrome outpatients in Finland. Eur J Clin Pharmacol 2020;76:257-65.

27. Teng R, Kujacic M, Hsia J. Evaluation of the pharmacokinetic interaction between ticagrelor and venlafaxine, a cytochrome P-450 2D6 substrate, in healthy subjects. Clin Ther 2014;36:1217-25.

28. Andrade C, Sharma E. Serotonin reuptake inhibitors and risk of abnormal bleeding. Psychiatr Clin North Am 2016;39:413-26.

29. Teng R, Butler K. Effect of the CYP3A inhibitors, diltiazem and ketoconazole, on ticagrelor pharmacokinetics in healthy volunteers. J Drug Assess 2013;2:30-9.

30. Marsouci N, Samer CF, Fontana P, et al. Co-administration of ticagrelor and ritonavir: toward prospective dose adjustment to maintain an optimal platelet inhibition using the PBPK approach. Clin Pharmacol Ther 2016;100:295-304.

31. Grinspoon SK, Douglas PS, Hoffmann U, Ribaudo HJ. Leveraging a landmark trial of primary cardiovascular disease prevention in human immunodeficiency virus: introduction from the REPREVE Coprincipal Investigators. J Infect Dis 2020;222:S1-7.

32. Mega JL, Close SL, Wiviott SD, et al. Cytochrome P450 genetic polymorphisms and the response to prasugrel: relationship to pharmacokinetic, pharmacodynamic, and clinical outcomes. Circulation 2009;119:2553-60.

33. Wallentin L, James S, Storey RF, et al. Effect of CYP2C19 and ABCB1 single nucleotide polymorphisms on outcomes of treatment with ticagrelor versus clopidogrel for acute coronary syndromes: a genetic subsidy of the PLATO trial. Lancet 2010;376:1320-8.

34. Claassens DMF, Vos GJA, Bergmeijer TO, et al. A genotype-guided strategy for oral P2Y12 inhibitors in primary PCI. N Engl J Med 2019;381:1621-31.

35. Notarangelo FM, Maglietta G, Bevilacqua P, et al. Pharmacogenomic approach to selecting antiplatelet therapy in patients with acute coronary syndromes: the PHARMcLO trial. J Am Coll Cardiol 2018;71:1869-77.

36. Pereira NL, Farkouh ME, So D, et al. Effect of genotype-guided oral P2Y12 inhibitor selection vs conventional clopidogrel therapy on ischemic outcomes after percutaneous coronary intervention: the TAILOR-PCI randomized clinical trial. JAMA 2020;324:761-71.

37. Dayoub EJ, Seigerman M, Tuteja S, et al. Trends in platelet adenosine diphosphate P2Y12 receptor inhibitor use and adherence among antiplatelet-naive patients after percutaneous coronary intervention, 2008-2016. JAMA Intern Med 2018;178:943-50.

38. Lauffenburger JC, Choudhry NK. A call for a systems-thinking approach to medication adherence: stop blaming the patient. JAMA Intern Med 2018;178:950-1.
39. Mehta SR, Tanguay JF, Eikelboom JW, et al. Double-dose versus standard-dose clopidogrel and high-dose versus low-dose aspirin in individuals undergoing percutaneous coronary intervention for acute coronary syndromes (CURRENT-OASIS 7): a randomised factorial trial. Lancet 2010;376:1233-43.

40. Mega JL, Hochholzer W, Fredinger AL 3rd, et al. Dosing clopidogrel based on CYP2C19 genotype and the effect on platelet reactivity in patients with stable cardiovascular disease. JAMA 2011;306:2221-8.

41. Storey RF, Angiolillo DJ, Bonaca MP, et al. Platelet inhibition with ticagrelor 60 mg versus 90 mg twice daily in the PEGASUS-TIMI 54 trial. J Am Coll Cardiol 2016;67:1145-54.

42. Kim BK, Hong SJ, Cho YH, et al. Effect of ticagrelor monotherapy vs ticagrelor with aspirin on major bleeding and cardiovascular events in patients with acute coronary syndrome: the TICO randomized clinical trial. JAMA 2020;323:2407-16.

43. Sibbing D, Aradi D, Jacobshagen C, et al. Guided de-escalation of antiplatelet treatment in patients with acute coronary syndrome undergoing percutaneous coronary intervention (TROPICAL-ACS): a randomised, open-label, multicentre trial. Lancet 2017;390:1747-57.

44. Cuisset T, Deharo P, Quilici J, et al. Benefit of switching dual antiplatelet therapy after acute coronary syndrome: the TOPIC (timing of platelet inhibition after acute coronary syndrome) randomized study. Eur Heart J 2017;38:3070-8.

45. Gimbel M, Qaderdan K, Willemsen L, et al. Clopidogrel versus ticagrelor or prasugrel in patients aged 70 years or older with non-ST-elevation acute coronary syndrome (POPular AGE): the randomised, open-label, non-inferiority trial. Lancet 2020;395:1374-81.

46. Federal Court. Federal Court Decisions - Eli Lilly. Canada Inc. v. Apotex Inc, 2018.

47. Teng R, Mitchell P, Butler K. Effect of rifampicin on the pharmacokinetics and pharmacodynamics of ticagrelor in healthy subjects. Eur J Clin Pharmacol 2013;69:877-83.

48. Holmberg MT, Tornio A, Joutsi-Korhonen L, et al. Grapefruit juice markedly increases the plasma concentrations and antiplatelet effects of ticagrelor in healthy subjects. Br J Clin Pharmacol 2013;75:1488-96.

49. Teng R, Butler K. A pharmacokinetic interaction study of ticagrelor and digoxin in healthy volunteers. Eur J Clin Pharmacol 2013;69:1801-8.