Canadian Journal of Cardiology 31 (2015) 1481–1484

Training/Practice
Contemporary Issues in Cardiology Practice

Current Evidence on Platelet $P2Y_{12}$ Receptor Inhibitors: Is There Still a Role for Clopidogrel in 2015?

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ABSTRACT

Antiplatelets play a significant role in the management of patients with coronary disease. Novel inhibitors of the platelet $P2Y_{12}$ receptor have more rapid, potent, and consistent inhibitory effect on platelets compared with clopidogrel. Evidence from large clinical studies have defined populations in which novel agents are superior to clopidogrel. Ticagrelor or prasugrel in addition to aspirin should be used preferentially for patients with ST-elevation myocardial infarction because of significant anti-ischemic benefits. In patients with non-ST segment elevation acute coronary syndromes, ticagrelor has proven superiority over clopidogrel whether or not an invasive strategy is adopted, and prasugrel has been shown to be beneficial when started at the time of percutaneous coronary intervention. Of note, neither prasugrel nor ticagrelor have been studied in patients who underwent percutaneous coronary intervention for stable coronary disease or those who required 'triple therapy.' In these situations, clopidogrel should remain the default until further data are available. Prolonged use of clopidogrel in patients with drug-eluting stents beyond 12 months is emerging as a novel indication for the agent.

RÉSUMÉ

Les antiplaquettaires jouent un rôle important dans la prise en charge des patients souffrant d'une maladie coronarienne. Les nouveaux inhibiteurs du récepteur plaquettaire $P2Y_{12}$ ont un effet inhibiteur plus rapide, plus puissant et plus constant sur les plaquettes comparativement au clopidogrel. Les données probantes provenant de grandes études cliniques ont défini les populations chez lesquelles les nouveaux agents sont supérieurs au clopidogrel. Le ticagrelor ou le prasugrel en association avec l'aspirine devrait être utilisé de préférence chez les patients ayant subi un infarctus du myocarde avec sus-décalage du segment ST en raison de leurs avantages anti-ischémiques significatifs. Chez les patients souffrant d'un syndrome coronarien aigu sans sus-décalage du segment ST, le ticagrelor a prouvé sa supériorité par rapport au clopidogrel, qu'une stratégie effractive soit adoptée ou non, et le prasugrel s'est avéré bénéfique lorsqu'il est commencé au moment de l'intervention coronarienne percutanée. Notamment, ni le prasugrel ni le ticagrelor n'ont été étudiés chez les patients qui subissaient une intervention coronarienne percutanée pour une maladie coronarienne stable ou chez ceux qui avaient besoin d'une trithérapie. Dans ces situations, le clopidogrel devrait être utilisé par défaut jusqu'à ce que d'autres données soient disponibles. L'utilisation prolongée du clopidogrel chez les patients porteurs d'une endoprothèse médicamentée au-delà de 12 mois s'impose comme une nouvelle indication du médicament.

Antiplatelets play a major role in the management of patients with coronary artery disease (CAD), particularly among those with acute coronary syndromes (ACS) and/or undergoing percutaneous coronary intervention (PCI). Dual antiplatelet therapy with aspirin and clopidogrel has been shown to reduce mortality, nonfatal myocardial infarction (MI), and stroke, and therefore, until recently, has been standard therapy. The arrival of novel inhibitors of the platelet $P2Y_{12}$ receptor offers increased potency and faster onset of action. However, appropriate evidence-based use of these agents is imperative.

Prasugrel, a newer thienopyridine, is a prodrug that requires a single step activation to its active metabolite and binds to the platelet $P2Y_{12}$ receptor. Compared with clopidogrel, prasugrel provides more rapid, consistent, and potent effects.[1] Ticagrelor, a cyclo-pentyl-triazolo-pyrimidine, does not require biotransformation because it is a direct reversible antagonist of the $P2Y_{12}$ receptor. Therefore, its onset is rapid, as is its reversibility.[2]

Received for publication March 13, 2015. Accepted April 17, 2015.

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See page 1484 for disclosure information.

http://dx.doi.org/10.1016/j.cjca.2015.04.019

Novel Antiplatelets in ACS

Prasugrel was compared with clopidogrel in the **Tri**al to Assess **I**mprovement in **T**herapeutic **O**utcomes by Optimizing Platelet Inhibitio**n** With Prasugrel (TRITON) trial, which included patients with non-ST segment elevation ACS (NSTEACS; 74%) and ST-elevation myocardial infarction (STEMI) (26%). Of note, patients with NSTEACS had their coronary anatomy delineated and deemed eligible for PCI before randomization. Prasugrel reduced the composite of cardiovascular death, nonfatal MI, or stroke by 19% (9.9% vs 12.1%, respectively, $P < 0.001$). However, this was achieved at the expense of increased **T**hrombolysis **i**n **M**yocardial **I**nfarction (TIMI) major and fatal bleeding.[1] Results from TRITON suggest that prasugrel should be avoided in patients with previous transient ischemic attack (TIA) or stroke. Caution should also be exercised in patients aged ≥ 75 years or those < 60 kg in weight. A reduced dose (5 mg), currently unavailable in Canada, might be considered in these patients because its use has been demonstrated to be safe in subgroups in the **Tar**geted Platelet **I**nhibition to C**l**arify the **O**ptimal Strate**g**y to Medicall**y** Manage **A**cute **C**oronary **S**yndromes (TRILOGY-ACS)trial.

In the **Plat**elet Inhibition and Patient **O**utcomes (PLATO) trial, ticagrelor was compared with clopidogrel in patients with STEMI or NSTEACS, who were managed invasively or noninvasively.[2] Ticagrelor significantly reduced the composite of cardiovascular death, MI, and stroke by 16% (9.8% vs 11.7%, respectively; $P < 0.001$). Although the overall rate of TIMI major or fatal bleeding was similar in both groups, ticagrelor use resulted in a significant increase in bleeding not related to coronary artery bypass graft compared with clopidogrel. Intriguingly, a mortality benefit was observed in the ticagrelor group. More recent investigations suggest a link to reduced infarct size and hypotheses on the pleotropic effects of ticagrelor attributed to plasma adenosine continue to attract interest.

Patients with STEMI were evaluated in a substudy of TRITON.[1] Patients treated with prasugrel had a significant reduction in the composite of cardiovascular death, nonfatal MI, or stroke compared with clopidogrel at 30 days and 15 months (relative risk reduction 32%; $P = 0.0017$ and 21%; $P = 0.02$, respectively). Overall, there was reduced mortality with prasugrel with no excess bleeding except among those who required coronary artery bypass grafting. Ticagrelor was studied in the STEMI subgroup of PLATO[2] and showed results consistent with those observed in the overall cohort, with the primary end point of major adverse cardiac events trending statistical significance. The rates of TIMI major and fatal bleeding were similar between ticagrelor and clopidogrel. Of note, neither ticagrelor nor prasugrel was studied a priori in patients who underwent a pharmacoinvasive approach, even though TRITON included patients who received PCI more than 24 hours after fibrinolysis.

With Novel Antiplatelets, Is There Still a Role for Clopidogrel in 2015?

Patients who receive anticoagulation therapy

Excess major bleeding has been documented in patients who receive prasugrel or ticagrelor, treated with PCI or medically. Accordingly, their use should be carefully weighed in patients with increased bleeding risk. Neither agent has been studied in combination with oral anticoagulants. 'Triple therapy' with the combination of novel antiplatelets and vitamin K antagonist (VKA) or the novel oral anticoagulants remains an important unanswered question. Studies on different dosages or combinations of these antithrombotics are required, especially in the era of third-generation drug-eluting stents with lower stent thrombosis rates. Hence, triple therapy, with the novel $P2Y_{12}$ agents, should be avoided until further data are available. An ongoing study on patients with atrial fibrillation who received stents, An O**p**en-label, Randomized, Controlled, Multicenter Study Explor**i**ng Tw**o** Treatmen**t** Strat**e**g**i**es of **R**ivaroxaban and One of Oral Vitamin K Antagonist in Patients With **A**trial **F**ibrillation Who Undergo **P**ercutaneous **C**oronary **I**ntervention (PIONEER AF-PCI), include a small (15%) subgroup who are either receiving prasugrel or ticagrelor but variable duration of triple therapy with either rivaroxaban or VKA. This may allow detection of a signal for caution; however, the investigatory nature of the trial might not be large enough to provide definitive answers. Until safety and efficacy data become available, clopidogrel should remain standard whether as part of 'triple therapy' or solely in combination with a VKA as per the recent **W**hat Is the **O**ptimal Antiplat**e**let and Anticoagulation Therapy in Patients With Oral Anticoagulation and Coronary **S**ten**t**ing (WOEST) trial.[3]

Patients with stable CAD who have received PCI and have had prolonged use of $P2Y_{12}$ inhibitors

Prasugrel and ticagrelor were only shown to be beneficial in patients with ACS and have not been studied in PCI for stable CAD. Therefore, clopidogrel remains the default in this population (Fig. 1). The **D**ual **A**nti**p**latelet **T**herapy (DAPT) study[4] further investigated the prolonged use of dual antiplatelet therapy to 30 months among patients who received drug-eluting stents. The study, consisting of $> 65\%$ patients receiving clopidogrel and the remainder on prasugrel, demonstrated a reduction in ischemic complications, but this came at a cost of increased bleeding. Accordingly, the prolonged use of clopidogrel in the cohort should be weighed against the bleeding risk in individual patients. The more recently presented Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin (PEGASUS) trial investigated prolonged use of ticagrelor beyond 30 months after ACS and showed a reduction in ischemic complications at the expense of excess major bleeding.

Patients with a history of cerebrovascular accidents

Patients with a history of cerebrovascular diseases (TIA, stroke, carotid or vertebrobasilar artery disease) who were treated with ticagrelor in the PLATO trial, compared with patients treated with clopidogrel, had a 2-fold increase in the risk of recurrent TIA or stroke (8.1 vs 4.0; $P = 0.24$). Although the difference was not significant, this was extensively reviewed in a FDA report. Of concern was that patients with a history of TIA/stroke who had received ticagrelor had a 5-fold increase in the risk for recurrent events compared with