CARDIOLOGY Rounds®

As presented in the rounds of the Division of Cardiology, St. Michael's Hospital, University of Toronto

Clopidogrel Resistance

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Antiplatelet therapy is a cornerstone of cardiovascular (CV) medicine, and acetylsalicylic acid (ASA) and clopidogrel have emerged as critical therapies in the treatment of CV disease. Despite their efficacy, patients on these medications continue to experience adverse clinical events. In fact, millions of patients are currently on low-dose antiplatelet therapy, but it is unknown how many of these patients are undertreated or on the wrong medication. Further, resistance to both clopidogrel and ASA is an emerging clinical entity with potentially severe consequences, such as recurrent myocardial infarction (MI), stroke, or death. The mechanism of this resistance remains incompletely defined, but there are specific clinical, cellular, and genetic factors that influence therapeutic failure. These factors range from physicians who fail to prescribe these medications despite appropriate indications, to polymorphisms of platelet membrane glycoproteins. As new bedside tests are developed, a rapid and accurate diagnosis of antiplatelet resistance remains an issue. Nevertheless, by understanding the mechanism of therapeutic failure and by improving the diagnosis of this clinical entity, a new era of individualized antiplatelet therapy may arise to improve patient care with routine measurements of platelet activity similar to the monitoring of cholesterol, blood pressure, and blood sugar. The focus of this issue of *Cardiology Rounds* is on the mechanism of clopidogrel action, the available tools and means of assessing and explaining its responsiveness, as well as the management options for the future.

Introduction

Platelets normally circulate in a resting form, but with a vascular injury (eg, rupture of an atherosclerotic plaque in a coronary artery), platelets respond by activating and aggregating. These 2 responses play an important role in the pathogenesis of arterial thrombosis leading to acute coronary syndromes (ACS) and in thrombotic complications during and after percutaneous coronary interventions (PCIs).[1,2] The goal of antiplatelet therapy is to prevent or treat this platelet-dependent thrombus.

ADP receptors and mechanism of action of clopidogrel

Clopidogrel, the primary subject for this review, is a member of a clinically important category of antiplatelet drugs, the $P2Y_{12}$ antagonists. Adenosine diphosphate (ADP), an important platelet agonist *in vivo*, has 2 types of receptors in the platelet plasma membrane: $P2Y_1$ and $P2Y_{12}$.[1] $P2Y_1$ is a 7-transmembrane receptor linked to a Gq protein (Figure 1). The end result of ADP signalling through its $P2Y_1$ receptor is calcium mobilization, platelet shape change, and rapidly reversible platelet aggregation. $P2Y_{12}$ is also a 7-transmembrane domain receptor, but it is linked to a G inhibitory protein (Figure 1). The outcome of ADP signalling through its $P2Y_{12}$ receptor is amplification of stable platelet aggregation and secretion.

Currently-approved $P2Y_{12}$ antagonists

Currently, the Food and Drug Administration (FDA) has approved 2 $P2Y_{12}$ antagonists, ticlopidine and clopidogrel; both antagonists are thienopyridines that are metabolized through cytochrome P450 (CYP) in the liver. The thienopyridine metabolites, and not the parent ticlopidine or clopidogrel molecules, irreversibly antagonize the $P2Y_{12}$ receptor (Figure 1). Ticlopidine, the first FDA-approved $P2Y_{12}$ antagonist, is given orally twice a day. However, in Canada and most other countries, ticlopidine has been largely replaced in clinical practice by clopidogrel, which is given orally in a more convenient daily dose. Clopidogrel is also preferred due to a better side-effect profile, in particular, less neutropenia and a lower incidence of the rare, but dangerous thrombotic thrombocytopenic purpura.[3]

As noted, clopidogrel selectively and irreversibly inhibits the $P2Y_{12}$ receptor,[4] but it is an inactive prodrug that requires oxidation by the hepatic CYP system to generate an active metabolite. However, only ~15% of the prodrug is CYP-metabolized in the liver to an active metabolite, ~85% of the prodrug is hydrolyzed by esterases in the blood to an inactive carboxylic acid derivative. This process involves

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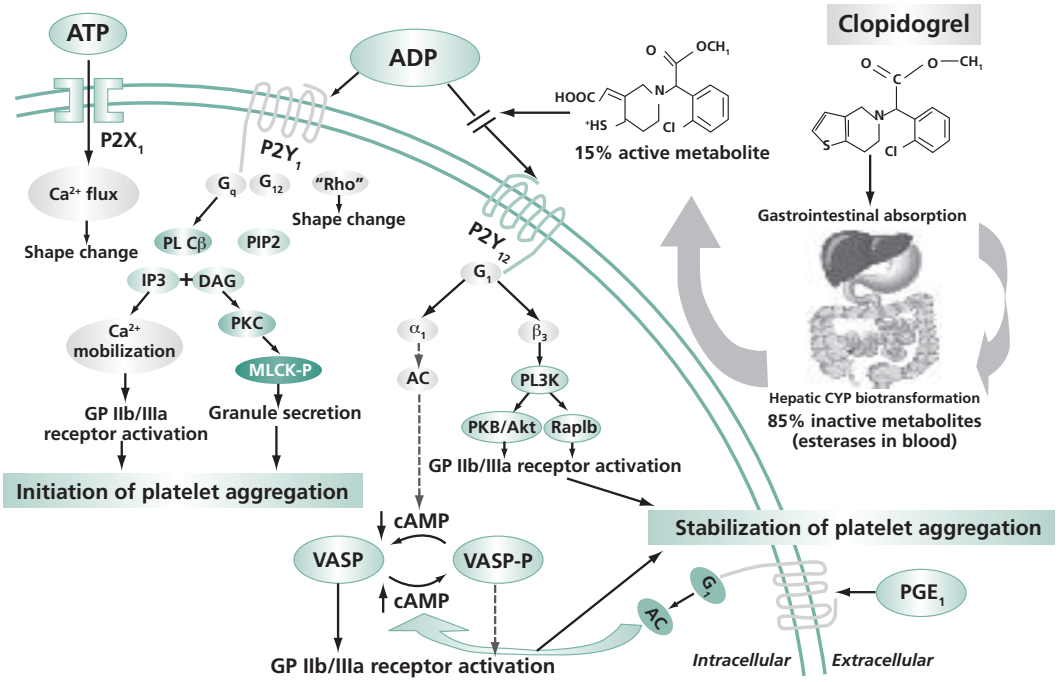
Figure 1: P2 receptors and mechanisms of action of clopidogrel



ADP = adenosine diphosphate; PL = phospholipase; PIP2 = phosphatidylinositol bisphosphate; IP3 = inositol triphosphate; DAG = diacylglycerol; PKC = protein kinase C; MLCK-P = phosphorylation of myosin light chain kinase; GP = glycoprotein; cAMP = cyclical adenosine monophosphate; VASP = vasodilator-stimulated phosphoprotein; PGE1 = prostaglandin E1

oxidation of the thiophene ring of clopidogrel to form an intermediate metabolite (2-oxo-clopidogrel), which is further oxidized, resulting in the opening of the thiophene ring and the formation of a carboxyl and thiol group. In the active metabolite of clopidogrel, the reactive thiol group forms a disulfide bridge between ≥1 cysteine residues of the $P2Y_{12}$ receptor, resulting in its irreversible blockade for the life span of the platelet. Thus, $P2Y_{12}$ receptor blockade acts early in the cascade of events leading to the formation of the platelet thrombus and effectively inhibits platelet aggregation. In fact, platelet $P2Y_{12}$ blockade prevents platelet degranulation and the release reaction, which elaborates prothrombotic and inflammatory mediators from the platelet, and also inhibits the transformation of the glycoprotein (GP) IIb/IIIa receptor to a form that binds fibrinogen and links platelets (Figure 1).

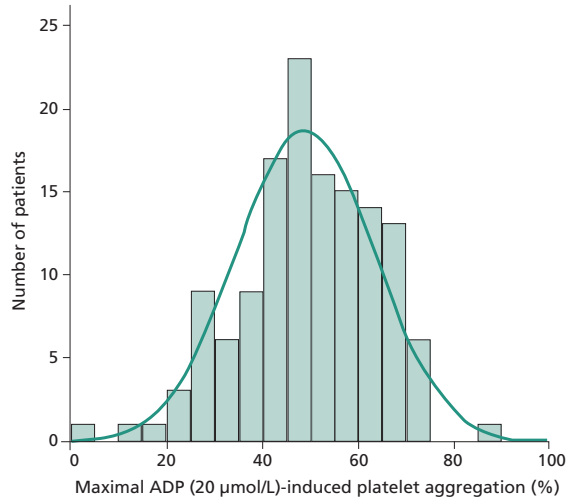
Several large, multicentre, randomized controlled trials (RCTs) have demonstrated the benefits of clopidogrel. The Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) trial was performed in 12 562 patients with acute coronary syndrome, unstable angina, or non-ST-elevation MI.[3] Patients were randomized to either a clopidogrel loading dose of 300 mg or placebo, followed by clopidogrel 75 mg daily plus ASA 75 to 325 mg daily, or placebo plus ASA 75 to 325 mg daily. Patients were followed for 12 months, with a primary endpoint of MI, stroke, and CV death; a relative risk reduction (RRR) of 20% was demonstrated in the clopidogrel-treated group (P=0.001).

The Percutaneous Coronary Intervention CURE (PCI-CURE) study[5] was a continuation of the CURE study in the 2658 patients who went on to PCI. These patients received open-label thienopyridine and, at 30-days post-PCI, they were randomized to clopidogrel plus ASA or placebo plus ASA and followed for 12 months. Based on a composite endpoint of CV death or MI from randomization to the end of follow-up in PCI-CURE, patients treated with clopidogrel had a 31% RRR compared with patients treated with placebo (P=0.002). The Clopidogrel for the Reduction of Events During Observation (CREDO) trial confirmed the beneficial effect of clopidogrel in post-PCI patients.[6] Subsequently, the Clopidogrel and Metoprolol in Myocardial Infarction Trial (COMMIT)[7] and CLopidogrel as Adjunctive Reperfusion Therapy-Thrombolysis In Myocardial Infarction 28 (CLARITY-TIMI 28)[8] trials demonstrated the benefit of clopidogrel and ASA in patients with ST-elevation MI. However, the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA)[9] trial in 15 603 patients with stable CV disease or asymptomatic patients with multiple CV risk factors, revealed that the combination of clopidogrel plus ASA was not significantly more effective than ASA alone in reducing the rate of MI, stroke, or death from CV causes. Furthermore, the risk of moderate-to severe bleeding was increased.[9] In a retrospective analysis of the CHARISMA trial, dual antiplatelet therapy with clopidogrel and ASA in the primary prevention subgroup of patients was associated with an increase in CV death.[10] The cause of this apparent harm has not been elucidated.

Definition of clopidogrel responsiveness

Standardized definitions for individual responsiveness to clopidogrel are still lacking. This is due not only to the numerous assays currently available to assess clopidogrel-induced antiplatelet effects, but also to the methodological variability within each technique. Light transmittance aggregometry (LTA) has been the most extensively evaluated

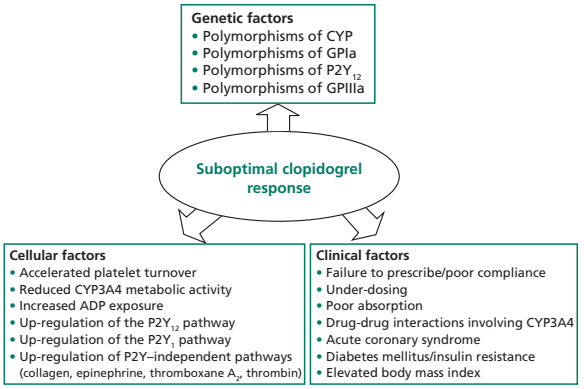
Figure 2: Interindividual variability in platelet aggregation



ADP = adenosine diphosphate

method to assess clopidogrel responsiveness, and has used several definitions for clopidogrel responsiveness. Earlier studies defined clopidogrel responsiveness according to the absolute differences between pre- and post-treatment platelet reactivity;[11] other studies defined clopidogrel responsiveness according to the degree of inhibition of platelet aggregation (IPA), defined as the percentage decrease in aggregation values obtained at baseline and after treatment.[12] These studies have shown clopidogrel-induced antiplatelet effect to be highly variable and found that a considerable number of patients have poor or no antiplatelet effects. Using an arbitrary cut-off value of <10% with the respective definitions, these *ex vivo* platelet-function studies have led to a definition of patients with poor antiplatelet effects as "clopidogrel resistant" or "nonresponders." However, subsequent investigations have used different doses of agonists, different cut-off values, and different assay methods for defining clopidogrel-induced antiplatelet effects, resulting in a highly variable reported prevalence of poor clopidogrel responders.[13,14] In addition, the use of different nomenclature to define individuals with ineffective clopidogrel platelet inhibition, such as "low-responder," "hyporesponder," "semiresponder," and "suboptimal responder," has further compounded the confusion on this topic. Nevertheless, increasing knowledge about the clinical impact of interindividual variability in clopidogrel-induced antiplatelet effects has allowed current definitions to progress. Previous definitions of clopidogrel response, which imply knowledge of baseline platelet function for its assessment, overestimate ischemic risk compared with post-treatment values of platelet reactivity.[15] Given the improved prognostic implications of post-treatment platelet reactivity, current investigations now aim to establish therapeutic thresholds for defining optimal $P2Y_{12}$ inhibition in clopidogrel-treated patients. Post-treatment platelet reactivity values as a measure of clopidogrel effectiveness is in line with the quantification of other biological variables and the response to treatment. Accordingly, similar to other biological processes, clopidogrel responsiveness should not be considered dichotomous, but rather a continuously variable parameter (Figure 2).[16]

Figure 3: Proposed mechanisms leading to variability in individual responsiveness to clopidogrel



ADP = adenosine diphosphate; CYP = cytochrome P450; GP = glycoprotein

Mechanisms leading to clopidogrel response variability

The possible mechanisms of clopidogrel response variability or "resistance" are shown in Figure 3. Noncompliance is an important issue; if a patient is not taking clopidogrel or only taking it intermittently, with platelet-function testing, the patient will appear to be hyporesponsive or "resistant" to clopidogrel. In addition to clopidogrel, many other drugs are metabolized through cytochrome P450 in the liver and, therefore, may interfere with the effectiveness of clopidogrel. One reported example of this phenomenon is atorvastatin,[17] but large clinical studies have not confirmed this as a clinically relevant interaction.[18,19] Single-nucleotide polymorphisms (SNPs), eg, the IVS10+12G>A SNP of the CYP3A4 gene, may modulate platelet activation in patients treated with clopidogrel and contribute to clopidogrel response variability.[20] Alternatively, the question is raised whether clopidogrel response variability or "resistance" is really:

- treatment failure unrelated to a lack of clopidogrel effectiveness (because arterial thrombosis is multifactorial and not solely dependent on $P2Y_{12}$-dependent signalling)?
- platelet response variability, since there is evidence in both normal subjects and patients that preclopidogrel response to ADP predicts postclopidogrel response to ADP?[20,21]

This variability has been determined by a number of different platelet function assays (turbidometric platelet aggregation, platelet surface P-selectin, platelet surface activated integrin alpha IIb beta-3, monocyte-platelet aggregates, neutrophil-platelet aggregates);[11-15] as a result, these data suggest that variability lies, at least in part, within the platelet response to ADP rather than the platelet response to clopidogrel.

Management of a patient with clopidogrel hyporesponsiveness or "resistance"

Variability in clopidogrel-induced antiplatelet effects has become an emerging clinical entity with potentially severe consequences;[22] therefore, it is imperative to determine effective clinical management of this phenomenon. Unfortunately, not only the assessment of resistance, but also the treatment of these patients remains undefined. An initial approach would be to correct the clinical factors that may lead to poor responsiveness; eg, it is important for physicians to ensure proper

patient compliance.[23] Interference from other drugs metabolized via cytochrome P450 may be a consideration,[24] but the evidence for a clinically important effect is not strong.[25,26] No published studies have addressed the clinical effectiveness of altering therapy based on a laboratory finding of clopidogrel resistance; as a result, the correct treatment, if any, of clopidogrel hyporesponsiveness or "resistance" remains unknown.[27] Nevertheless, the current American College of Cardiology/American Heart Association PCI guidelines[23] have a Class IIb recommendation based on level C evidence that, in patients in whom subacute stent thrombosis may be catastrophic or lethal, platelet aggregation studies may be considered and the maintenance dose of clopidogrel increased from 75 mg to 150-mg/day if <50% inhibition of platelet aggregation is demonstrated. Although currently there are no published clinical outcomes studies to support this approach, a 150 mg daily maintenance dose of clopidogrel has recently been shown to provide more effective platelet inhibition (as determined by ADP-induced turbidometric platelet aggregation, the VerifyNow® $P2Y_{12}$ assay, and vasodilator-stimulated phosphoprotein [VASP] phosphorylation) than the current standard maintenance dose of 75 mg daily.[28,29] Nevertheless, even at the higher maintenance dose of 150 mg daily, there is still great variability in the degree of platelet inhibition,[28,29] and the possibility of increased hemorrhagic risk has not been studied.

In the PCI setting, a loading dose of 600 mg of clopidogrel, rather than the previous standard loading dose of 300 mg, has been widely adopted based on small studies demonstrating more rapid and profound inhibition of ADP-induced turbidometric platelet aggregation, reduced myonecrosis markers, and reduced major adverse cardiac events (MACE) at 30 days.[28,30,31] An increase in the clopidogrel-loading dose from 600 mg to 900 mg may[31] or may not[32] result in an additional significant increase in platelet-function inhibition. However, even at these higher loading doses, there is still large variability in the degree of platelet inhibition.[30-33] The ongoing clopidogrel optimal loading dose Usage to Reduce Recurrent Events/Optimal Antiplatelet Strategy for Interventions 7 (CURRENT/OASIS 7)[34] trial may help clarify the optimal loading and maintenance doses of clopidogrel. This trial will evaluate whether high-dose clopidogrel achieves better clinical outcomes than standard dose in 18-20 000 inpatients with ST- or non-ST-segment-elevation-ACS patients undergoing PCI. Patients randomized to the high dose will receive a 600-mg loading dose and then a 150-mg daily maintenance dose from Day 2 to Day 7; patients randomized to the standard dose will receive a 300-mg loading dose then 75-mg daily maintenance dose from Day 2 to Day 7; from Day 8 to Day 30, all patients will receive clopidogrel 75 mg daily. In addition, all patients will be randomized to receive low-dose ASA (75–100 mg) or high-dose (300–325 mg); regardless of randomized allocation to high- or low-dose ASA, all patients will receive ASA ≥300 mg on Day 1.

It has recently been shown that the administration of a 600-mg loading dose in patients already on chronic clopidogrel therapy results in an additional inhibition of ADP-induced platelet aggregation, suggesting that the current recommended maintenance dose of clopidogrel may be insufficient in producing optimal platelet inhibition.[35] The currently used maintenance dose for chronic clopidogrel therapy (75 mg/day) was chosen because a degree of platelet inhibition is reached similar to that achieved with ticlopidine (250 mg twice daily).[36] Therefore, it has been suggested that increasing the maintenance dose to 150 mg/day may improve individual responsiveness to clopidogrel in selected patient populations. The Intracoronary Stenting and Antithrombotic Regimen: Choose a High Oral maintenance dose for Intensified Clopidogrel Effect (ISAR CHOICE-2)[37] trial revealed that in an unselected cohort of patients, a 150-mg maintenance dose resulted in enhanced platelet inhibition compared with a standard 75-mg maintenance dose regimen 1 month after undergoing low-risk PCI. The Optimizing anti-Platelet Therapy In diabetes Mellitus (OPTIMUS)[29] study selectively studied diabetes mellitus patients with high post-treatment platelet reactivity while in their chronic phase of treatment. Although a 150-mg clopidogrel maintenance dose resulted in marked platelet inhibition of numerous platelet function measures compared with a 75-mg dose, a considerable number of patients still remained above the therapeutic threshold of post-treatment platelet reactivity used in this study, suggesting the need for more potent $P2Y_{12}$ inhibitors or alternative antithombotic regimens in these high-risk patients.

Future directions

The current therapeutic alternatives for treating patients with poor clopidogrel response remain limited. Novel $P2Y_{12}$ receptor antagonists with more potent antiplatelet effects are currently under clinical investigation.[38] These novel molecules are all characterized by more potent antiplatelet effects, reduced interindividual response variability and, therefore, are less likely to lead to resistance. The $P2Y_{12}$ receptor antagonists under clinical investigation include prasugrel, AZD6140, and cangrelor.

Prasugrel is an investigational orally administered thienopyridine prodrug that, like clopidogrel, is metabolized via CYP in the liver.[39,40] The active metabolite of prasugrel irreversibly inhibits the platelet $P2Y_{12}$ receptor to a similar extent as the active metabolite of clopidogrel.[41] However, prasugrel has a more efficient *in vivo* generation of an active metabolite than clopidogrel.[40] As a result, a prasugrel 60-mg loading dose results in a much more rapid, potent, and consistent inhibition of platelet function than the standard clopidogrel loading dose of 300 mg,[42,43] and the more recently adopted clopidogrel-loading dose of 600 mg.[33] Furthermore, a maintenance dose of prasugrel 10-mg daily results in a more potent and consistent inhibition of platelet function than the standard clopidogrel maintenance dose of 75 mg daily.[33] Animal studies have demonstrated that prasugrel has a much more potent antithrombotic effect than clopidogrel,[41] and Phase II studies of prasugrel in humans revealed no significant increase in bleeding compared with clopidogrel.[44] The 13 608-patient Phase III Trial to assess Improvement in Therapeutic Outcomes by optimizing platelet inhibition with prasugrel – Thrombolysis in Myocardial Infarction 38 (TRITON-TIMI 38),[45] was

recently completed. This trial demonstrated that in patients with ACS and scheduled PCI, prasugrel (60-mg loading dose and a 10-mg daily maintenance dose), as compared with approved doses of clopidogrel (300-mg loading dose and a 75-mg daily maintenance dose), was associated with significantly reduced rates of ischemic events, including stent thrombosis, but an increased risk of major bleeding, including fatal bleeding. The primary efficacy endpoint occurred in 12.1% of patients receiving clopidogrel and 9.9% of patients receiving prasugrel (hazard ratio [HR] for prasugrel vs clopidogrel, 0.81; 95% confidence interval [CI], 0.73 to 0.90; $P<0.001$). Significant reductions were found for the prasugrel group in the rates of MI (9.7% clopidogrel vs 7.4% prasugrel; $P<0.001$), urgent target-vessel revascularization (3.7% vs 2.5%; $P<0.001$), and stent thrombosis (2.4% vs 1.1%; $P<0.001$). Major bleeding was found in 2.4% of prasugrel patients vs 1.8% in clopidogrel patients (HR, 1.32; 95% CI, 1.03 to 1.68; $P=0.03$). In the prasugrel group, the rate of life-threatening bleeding was greater (1.4% vs 0.9%; $P=0.01$), including nonfatal (1.1% vs 0.9%; HR, 1.25; $P=0.23$) and fatal bleeding (0.4% vs 0.1%; $P=0.002$). A *post hoc* subgroup exploratory analysis of the data identified 3 subgroups of interest with less clinical efficacy and greater absolute levels of bleeding than the overall cohort, resulting in less net clinical benefit or in clinical harm. These subgroups were: patients with a history of stroke or transient ischemic attack, age ≥75 years, and body weight <60 kg.[45]

The Prasugrel in Comparison to Clopidogrel for Inhibition of Platelet Activation and Aggregation – Thrombolysis in Myocardial Infarction 44 (PRINCIPLE-TIMI 44)[46] trial demonstrated that, among patients undergoing cardiac catheterization with a planned PCI, a 60-mg prasugrel loading-dose resulted in greater platelet inhibition than the now widely used higher clopidogrel loading dose of 600 mg. Maintenance therapy with prasugrel 10 mg daily resulted in a greater antiplatelet effect than the high clopidogrel maintenance dose of 150 mg daily. This trial was not powered for clinical outcomes.[46]

AZD6140 is another investigational $P2Y_{12}$ antagonist. To increase oral bioavailability, the structure of AZD6140 was modified from AR-C109318XX.[47] Unlike ticlopidine, clopidogrel, and prasugrel, AZD6140 is:

- not a thienopyridine, but an adenosine triphosphate (ATP) analog
- a direct $P2Y_{12}$ antagonist (ie, no metabolism of a prodrug is required)
- a reversible $P2Y_{12}$ antagonist[47]

Like prasugrel, AZD6140:

- results in a more rapid onset of action and greater degree of platelet inhibition than clopidogrel
- maintenance therapy results in more potent inhibition of platelet function than the standard clopidogrel maintenance dose of 75 mg daily
- reveals no significant increase in bleeding compared with clopidogrel in Phase II studies.[47-49]

In these Phase II studies, dyspnea was greater, in an apparently dose-dependent manner, in patients on AZD6140 compared with patients on clopidogrel. AZD6140 is given orally twice a day and is currently in a Phase III trial: The Platelet inhibition and patient Outcomes (PLATO) trial.[50]

Cangrelor is an investigational, direct-acting, reversible $P2Y_{12}$ antagonist. Unlike the above-described orally-administered $P2Y_{12}$ antagonists (ticlopidine, clopidogrel, prasugrel, and AZD6140), cangrelor is administered intravenously, which together with the rapid reversal of its effects after the end of the infusion, may be potentially advantageous in the PCI setting. Like prasugrel and AZD6140, cangrelor results in a more rapid onset of action and greater degree of platelet inhibition than clopidogrel, and demonstrated no significant increase in bleeding compared with clopidogrel in Phase II studies.[51,52] Cangrelor is currently in Phase III trials: CHAMPION-PCI and CHAMPION-PLATFORM.

PRT060128 is an investigational, direct-acting, reversible $P2Y_{12}$ antagonist with a novel structure that can potentially be administered orally or intravenously; it has completed Phase I clinical studies.

Conclusions

The $P2Y_{12}$ antagonist, clopidogrel, has a well-established role as an antithrombotic agent in the settings of PCI and ACS. However, several challenges remain, including the relatively slow onset of action of clopidogrel. Current available data indicate that ~4%–30% of patients treated with conventional doses of clopidogrel do not display adequate antiplatelet response. Clopidogrel resistance is a term that is widely used, but not clearly defined; it has been used to reflect a failure of clopidogrel to achieve its platelet inhibition effect. The terms "clopidogrel resistance," "nonresponse," and "low response" to clopidogrel are used synonymously, which may confuse readers. Since the clopidogrel response has been primarily evaluated by platelet function tests, these terms can be considered interchangeable, reflecting the failure of clopidogrel to achieve its expected antiplatelet effect. Novel $P2Y_{12}$ antagonists, including prasugrel, AZD6140, and cangrelor, have a faster onset of action, as well as more potent, and less variable inhibition of platelet function *ex vivo*. Whether this promise will be translated into clinical benefits for patients will be determined by the results of Phase III clinical trials.

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Disclosure Statement: *Dr. Alqahtani and Dr. Moe have stated that they have no disclosures to announce in association with the contents of this issue.*

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This publication is made possible by an educational grant from

Merck Frosst Canada Ltd.