Role of Ticagrelor in Clopidogrel Nonresponders: Resistance Is Futile?

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Dual antiplatelet therapy with aspirin and a thienopyridine drug that blocks the platelet adenosine diphosphate receptor P2Y12 is the cornerstone of management in patients presenting with acute coronary syndrome (ACS). Clopidogrel is the most widely used thienopyridine, with evidence of benefit in non-ST-elevation myocardial infarction (MI),1 percutaneous coronary intervention (PCI),2 and ST-elevation MI treated with thrombolysis or primary PCI.3-4

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However, clopidogrel has several suboptimal characteristics. First, despite administration of a 600 mg loading dose, clopidogrel requires at least 2 hours to achieve effective platelet inhibition, which is clearly disadvantageous during urgent PCI. Second, the irreversible P2Y12 receptor inhibition may be associated with an increased risk of hemorrhagic complications, particularly in patients requiring urgent coronary artery bypass grafting or other surgery. Furthermore, clopidogrel is a prodrug that requires 2-stage hepatic activation by cytochrome P450 (CYP) enzymes. This is susceptible to genetic polymorphisms, resulting in a variable response and an attenuated antiplatelet effect. Indeed, reduced function alleles (especially CYP2C19*2), which are present in ~30% of the population, lead to diminished production of the active metabolite.5 This phenomenon, often called clopidogrel resistance, is associated with increased risk of atherothrombotic complications, including stent thrombosis.5,6 Clopidogrel’s limitations have stimulated the search for alternative antiplatelet agents.

The development of prasugrel was a major step forward. Prasugrel is a thienopyridine with 10-fold more potent anti-P2Y12 receptor inhibitory activity than clopidogrel and a more rapid onset of action. Like clopidogrel, prasugrel also requires biotransformation to active metabolites via CYP enzymes. In contrast, CYP polymorphisms do not affect P2Y12 receptor inhibitory activity than clopidogrel and a more rapid onset of action. Like clopidogrel, prasugrel also requires biotransformation to active metabolites via CYP enzymes. In contrast, CYP polymorphisms do not affect active metabolite levels, platelet inhibition, or clinical cardio-vascular event rates in patients treated with prasugrel.7 In the study by Mega et al,7 the common CYP functional variants associated with clopidogrel resistance were assessed in healthy volunteers and a cohort of the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel-Thrombolysis In Myocardial Infarction 38 (TRITON-TIMI 38) patients allocated to prasugrel. CYP polymorphisms did not attenuate the pharmacological response to prasugrel and were not associated with adverse cardiovascular outcomes. These important observations may contribute to the differences in clinical response to these drugs.

The TRITON-TIMI 38 trial8 demonstrated a relative risk reduction of 19% in the primary efficacy endpoint (death from cardiovascular causes, nonfatal MI, and nonfatal stroke) with prasugrel compared with clopidogrel in ACS patients scheduled for PCI. This benefit was amplified in high-risk groups, such as patients with diabetes mellitus or ST-elevation MI, and it was apparent as early as day 3. Additionally, the frequency of both early and late stent thrombosis was reduced by approximately 50%.8 These important findings validate the hypothesis that a more potent antiplatelet regimen can reduce ischemic events. However, the sacrifice is an increased risk of bleeding. Prasugrel was associated with a statistically significant increase in non-coronary artery bypass grafting-related TIMI major bleeding (the key safety endpoint), coronary artery bypass grafting-related TIMI major bleeding, and a small increase in fatal bleeding. More important, a prespecified analysis of net clinical benefit showed statistical significance in favor of prasugrel.8 Avoiding prasugrel (or reducing its dose) in groups with a higher risk of bleeding and less evidence of clinical efficacy (age ≥75 years, weight <60 kg, and previous stroke or transient ischemic attack) may attenuate the increased bleeding risk.

What are the alternatives? Ticagrelor is an oral, direct, reversible, nonthienopyridine P2Y12 receptor antagonist that has a rapid, powerful, and consistent antiplatelet effect. Because ticagrelor is not a prodrug, a loading dose of 180 mg achieves effective inhibition of platelet aggregation within 30 minutes. Platelet function returns to normal 2 to 3 days after discontinuation.8 The Study of Platelet Inhibition and Patient Outcomes (PLATO) trial compared ticagrelor to clopidogrel in ACS patients managed invasively or noninvasively.9 Ticagrelor was associated with a 16% relative risk reduction in the primary endpoint (composite of death from vascular causes, MI, and stroke) and a 22% relative risk reduction in all-cause mortality. There was no significant difference in the primary safety endpoint (overall rate of major bleeding) between the ticagrelor and clopidogrel groups (11.6% and 11.2%, respectively; P = 0.43), but ticagrelor was associated with a higher rate of major bleeding not related to coronary artery bypass grafting (4.5% versus 3.8%; P = 0.03), including more instances of fatal intracranial bleeding and less fatal bleeding of other types.10 Additionally, ticagrelor reduced
all-cause mortality and stent thrombosis in the PLATO cohort managed with an early invasive strategy. As with prasugrel, enhanced platelet inhibition had an early positive effect independent of the clopidogrel loading dose. Ticagrelor was not assessed against a maintenance dose of 150 mg clopidogrel for 1 week as was used in the Clopidogrel Optimal Loading Dose Usage to Reduce Recurrent Events/Optimal Antiplatelet Strategy for InterventionS (CURRENT-OASIS) 7 trial.

Perhaps prasugrel or ticagrelor may have a major role in patients with so-called clopidogrel resistance. One issue that still remains is the (un)certainty of defining the latter phenomenon.

In this issue of Circulation, Gurbel et al investigated the antiplatelet effect of ticagrelor dosed according to the PLATO trial in patients deemed nonresponsive to clopidogrel and the effects of switching from clopidogrel to ticagrelor in the neatly executed REsponse to Ticagrelor in Clopidogrel Non-responders and ReSPONDers (RESPOND) study. Clopidogrel responsiveness to a single 300 mg dose was assessed by light transmittance aggregometry based on 20 µmol/L adenosine diphosphate-induced platelet aggregation determined before a dose and 6 to 8 hours after a dose. Both responders and nonresponders received either clopidogrel (600 mg loading, followed by 75 mg daily) or ticagrelor (180 mg loading, followed by 90 mg twice daily) for 14 ± 2 days. Subsequently, all nonresponders and half of the responders switched therapy for a further 14 ± 2 days. Ticagrelor rapidly achieved greater platelet inhibition than clopidogrel. In clopidogrel nonresponders, switching to ticagrelor produced a significant decrease in platelet aggregation. Platelet reactivity was below that previously associated with a risk of ischemic events as measured by light transmittance aggregometry, VerifyNow (Acumetrics, San Diego, Calif), and vasodilator stimulated phosphoprotein phosphorylation in 98% to 100% of patients on ticagrelor (irrespective of clopidogrel responsiveness) versus 44% to 70% of patients on clopidogrel.

Given that both prasugrel and ticagrelor appear superior to clopidogrel, how would they compare against each other, especially in clopidogrel nonresponders? No studies have specifically examined this idea, in either the lab or clinical setting, which makes direct comparisons difficult. However, both prasugrel and ticagrelor inhibit ≥80% of 20 µmol/L adenosine diphosphate-induced platelet aggregation, compared with 40% to 50% with clopidogrel. In the Prusagrel in Comparison to Clopidogrel for Inhibition of Platelet Activation and Aggregation-Thrombolysis in Myocardial Infarction 44 (PRINCIPLE-TIMI 44) study, the prasugrel regimen as used in the TRITON-TIMI 38 trial produced faster and greater inhibition of platelet activation than 600 mg clopidogrel, followed by 150 mg of a maintenance dose. Switching from clopidogrel to prasugrel maintenance therapy yielded an increase in platelet inhibition. However, clopidogrel responsiveness per se was not assessed, and therefore the antiplatelet effects of prasugrel versus ticagrelor in clopidogrel nonresponders cannot be compared.

Resistance to antiplatelet drugs

The definition of aspirin and clopidogrel resistance is controversial. Lab response to antiplatelet agents appears to be normally distributed, and it therefore depends on where the cutoff of sufficient platelet inhibition lies. Moreover, there may not be a linear relationship between enhanced antiplatelet effect and a relevant reduction in ischemic events. Clinically, so-called resistance broadly encompasses individuals with recurrent atherothrombotic events despite appropriate medication and lab-assessed failure to sufficiently inhibit platelet aggregation. This incorporates both intrinsic (eg, P2Y12 receptor density and affinity, internal cell signaling variability) and extrinsic factors (eg, absorption, biotransformation, drug interactions, underdosing, increased platelet turnover, and, ultimately, noncompliance). However, atherosclerosis is a multifactorial disease, and therefore some patients will inevitably experience recurrent atherothrombotic events despite optimal platelet inhibition. Accordingly, a clinical definition of platelet resistance is also problematic.

Noncompliance with antiplatelet therapy may be as high as 22%. Thus, resistance may be overestimated if noncompliance is not eliminated. Clopidogrel resistance may become increasingly relevant as it moves to the generic market given that it may become increasingly widely prescribed.

Identification of clinically meaningful in vivo pharmacological resistance in a reproducible, cost-effective, and timely manner, using an in vitro test, is challenging. Several tests of antiplatelet resistance lack acceptable sensitivity, specificity, and reproducibility. Platelet reactivity is only measured via a single pathway, whereas a synergistic blockade of multiple pathways is likely to be important in vivo. A more complex approach to the assessment of platelet function may improve the accuracy of predicting thrombotic events.

Quo vadis?

Rapid decision making about the optimal antiplatelet regimen is essential in ACS management, especially in patients requiring primary PCI. Identification and management of clinically relevant clopidogrel nonresponsiveness is therefore a priority. Ideally, antiplatelet therapy could be individualized, incorporating a validated assessment of ischemic and bleeding risks and perhaps CYP2C19 genotyping. A point-of-care test determining responsiveness could facilitate appropriate drug selection. Subsequently, the dose may be adjusted to optimize therapeutic effect while minimizing bleeding risk. In the RESPOND study, nonresponders had consistently lower clopidogrel-induced platelet inhibition with all assays studied. This result suggests that screening with a single 300 mg dose can perhaps identify clopidogrel nonresponders. An alternative agent may be an effective strategy in this scenario. Evaluation of whether this strategy translates into long-term benefit in a prospective clinical trial will be necessary to move beyond mere speculation.

However, if ticagrelor is to become a mainstream antiplatelet drug, certain caveats should be heeded. Ticagrelor requires twice-daily dosing because of its rapid reversibility. This requirement necessitates scrupulous compliance to minimize the risk of recurrent ischemic events and stent thrombosis. Additionally, ticagrelor is associated with dyspnea and bradycardia, which may lead to discontinuation. For example, dyspnea was more common with ticagrelor in the PLATO study (13.8% versus 7.8% with clopidogrel).
patients discontinued ticagrelor because of dyspnea (0.9% versus 0.1% with clopidogrel). Discontinuation of the study drug because of adverse events occurred slightly more frequently with ticagrelor (7.4% versus 6.0% with clopidogrel; \(P<0.001\)) in the PLATO study.\(^\text{10}\) The dyspnea and bradycardia could be related to the inhibition of adenosine uptake by erythrocytes, but paradoxically this has been hypothesized to contribute to the therapeutic effect of ticagrelor by reducing blood pressure, improving microcirculatory function, and protecting against reperfusion injury.

**Conclusions**

Strong evidence supports the hypothesis that drugs which enhance platelet inhibition reduce the risk of recurrent ischemic events.\(^\text{8,10}\) If this is combined with an absence of overall increased bleeding\(^\text{8}\) or is directed toward subgroups likely to benefit most,\(^\text{10}\) then the benefits may be even greater. Moreover, strategies that directly reduce the incidence of bleeding complications, such as radial artery access, are intrinsically linked with enhanced outcomes of more potent antiplatelet drugs. The antiplatelet armamentarium continues to evolve rapidly, affording clinicians an increasing choice in drug therapy in patients with ACS. Long-term results and comparisons between prasugrel and ticagrelor in prospective randomized clinical trials are awaited with great interest.\(^\text{19}\) With the availability of novel antiplatelet agents with more potent platelet inhibition, aspirin and clopidogrel resistance may soon be irrelevant.

**Disclosures**

Dr Lip was an investigator in the PLATO study and has received funding for research, educational symposia, consultancy, and lecturing from different manufacturers of drugs used to treat thrombosis.

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