Clopidogrel Response Variability and Future Therapies

Clopidogrel: Does One Size Fit All?
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Case Presentation: A 75-year-old woman presents to the hospital with a non–ST-elevation myocardial infarction (MI) and is found to have a subtotal occlusion of the proximal left anterior descending coronary artery. A drug-eluting stent is successfully deployed without complication, and the patient is given a 300-mg loading dose of clopidogrel. She is started on a treatment regimen that includes aspirin 325 mg daily and clopidogrel 75 mg daily. On hospital day 4, she develops recurrent chest pain and is found to have ST-segment elevation on ECG. She is taken to coronary angiography, where she is found to have an occlusive thrombus within a well-deployed stent. After percutaneous coronary intervention (PCI), how should this patient be managed?

Background
Platelets play a central role in initiating and propagating pathological thrombosis after spontaneous or mechanical plaque rupture. Antiplatelet therapies, including aspirin and thienopyridines, are key components of pharmacotherapy in acute coronary syndromes (ACS) and PCI.1,2 As monotherapy, treatment with clopidogrel modestly reduces cardiovascular (CV) events in patients with established atherosclerotic disease compared with aspirin treatment.3 When combined with aspirin, clopidogrel provides additive reduction in the risk of ischemic events in patients with non–ST-elevation ACS and in patients undergoing PCI.4,5 In addition, clopidogrel helps to maintain infarct-related artery patency and clinical outcomes in patients with ST-elevation MI receiving fibrinolytic therapy.6,7

Clopidogrel, a prodrug, relies on cytochrome P450–dependent pathways to form its active metabolite and inhibits platelet aggregation through irreversible blockade of the platelet P2Y₁₂ receptor (Figure 1). When a 300-mg loading dose is used, clopidogrel requires at least 4 to 6 hours to achieve its maximal effect.8 Analyses from the Clopidogrel for the Reduction of Events During Observation (CREDO) trial suggest that clopidogrel pretreatment 6 to 15 hours before PCI is necessary to significantly reduce CV events.5,9 Clinicians often are reluctant, however, to administer clopidogrel before angiography because of concerns about bleeding in patients who require coronary artery bypass graft surgery within 5 days of receiving the drug.10

Response Variability
Despite improved outcomes with modern-day therapies,≈8% to 10% of patients experience a recurrent CV event during the first year after ACS.4,5 In addition,≈1% to 3% have a subacute stent thrombosis after PCI with potentially catastrophic consequences, including a high risk of early mortality.11

Several studies have demonstrated substantial interpatient variability in measures of platelet inhibition after treatment with clopidogrel (Figure 2).12–18 The prevalence of individuals who are deemed to have an inadequate response to clopidogrel varies between 4% and 34%, depending on the method of testing and the definition of “resistance” or “hyporesponsiveness” used in the individual analyses.2 Differences in assays, agonist concentrations, and cut points have contributed to the confusion about the true prevalence of these conditions. As such, there remains no clear consensus on the definition of clopidogrel resistance. Moreover, the question remains whether this phenomenon can in fact be blamed for clinical failures. For this reason, we believe that the term clopidogrel resistance should be limited to those who...
fail to achieve a desired pharmacological response to drug therapy, rather than patients who experience recurrent ischemic events while on clopidogrel (Figure 3).

Mechanisms of Resistance

Multiple mechanisms for response variability have been proposed (Figure 4). Although not an inherent failure of drug therapy, poor patient compliance is an important consideration if an inadequate response to clopidogrel is noted. In addition, interpatient variability in intestinal drug absorption may contribute to the observed differences in individual response. Growing evidence suggests that variability in cytochrome P450–dependent enzyme activity, in part due to genetic polymorphisms, is responsible for a significant component of the interpatient differences in response to clopidogrel. The cytochrome P450–dependent pathways are known to be influenced by many drugs, thereby raising concern for drug-drug interactions. In particular, high-dose atorvastatin has been shown to attenuate platelet inhibition by clopidogrel in a dose-dependent manner; however, the clinical importance of these findings has been disputed.

Measuring Platelet Reactivity

To evaluate the clinical importance of platelet reactivity, reliable measures of platelet function are required. Light transmission aggregometry has become the de facto “gold standard” for measuring platelet inhibition in response to clopidogrel. With this method, inhibition of platelet aggregation (IPA) is determined by measuring the change in light transmittance through platelet-rich plasma in response to an agonist (eg, ADP) before and after drug therapy. Disadvantages of this technique include its complex methodology, resulting in difficulty with standardization among laboratories. In addition, the method requires assessment of IPA both before and after drug administration, thereby limiting its utility for patients on long-term therapy. Assays that quantify intermediaries that are downstream to the P2Y12 receptor such as vasodilator-stimulated phosphoprotein might be more specific for thienopyridine activity. More recently, point-of-care assays have become available that offer the advantages of rapid results, ease of use, and no need for predrug measurements in certain cases.

Clinical Relevance of Response Variability

Although pharmacodynamic variability in response to clopidogrel has been clearly demonstrated, limited data to date suggest that this in vitro laboratory finding may have important clinical consequences. Several case-control studies have demonstrated higher posttreatment platelet reactivity or incomplete inhibition of ADP-induced platelet aggregation among patients with subacute stent thrombosis after PCI. Mean platelet reactivity after elective stenting correlates with the subsequent release of cardiac biomarkers of necrosis. Moreover, in a prospective analysis of patients with ST-elevation MI, patients with a reduced pharmacological response to clopidogrel had a significantly higher CV event rate over 6 months of follow-up. Taken together, these studies support the hypothesis that platelet responsiveness carries direct clinical relevance. Prospective evaluations in larger patient populations are required to confirm these findings and to assess what levels of platelet inhibition are optimal for reducing CV
Clinical Importance of Response Variability?

Managing an Inadequate Response

Because growing evidence suggests that an inadequate response to clopidogrel therapy is associated with worse outcomes, treatment strategies must be developed to help manage this finding. The first step in assessing an inadequate response should be to identify readily reversible causes, including inappropriate drug administration and medication noncompliance.

Raising the Dose of Clopidogrel: Does One Size Fit All?

One approach is to increase the initial loading dose of clopidogrel to 600 or 900 mg to achieve higher, more consistent, and more rapid levels of platelet inhibition. Early data suggest that a 600-mg loading dose may improve CV outcomes in patients undergoing PCI, reduce the incidence of periprocedural MI, and carry an acceptable safety profile. The overall clinical benefit of this approach is currently being evaluated in the Clopidogrel Optimal Loading Dose Usage to Reduce Recurrent Events/Optimal Antiplatelet Strategy for Interventions (CURRENT/OASIS-7) trial (ClinicalTrials.gov identifier: NCT00335452).

There may be a limit or “ceiling effect” to the IPA that can be achieved with clopidogrel dose escalation. Although investigators have reported higher platelet inhibition with the 900-mg compared with the 300-mg loading dose, some investigators have found no significant difference in platelet inhibition between the 900- and 600-mg doses of clopidogrel in patients undergoing angiography when measured 4 hours after a loading dose. Of interest, the serum concentration of inactive prodrug and active metabolite did not differ significantly between the 600- and 900-mg doses, suggesting that intestinal absorption rather than metabolism may limit additional platelet inhibition at higher doses.

In addition to higher loading doses, a daily clopidogrel maintenance dose of 150 mg (or 75 mg twice daily) may achieve higher platelet inhibition compared with the standard 75-mg daily dose and, thus far in limited reports, has not been shown to increase the risk of bleeding during short-term follow-up. Longer-term studies are necessary to evaluate the safety and efficacy of a higher maintenance dose.

Interpatient variability in response to drug therapy is not unique to clopidogrel. Genetic and environmental factors may contribute variably to differences in baseline platelet reactivity and patient response to clopidogrel and other medications. For patients who require oral anticoagulation, for example, it is accepted that the dose of warfarin necessary to achieve therapeutic anticoagulation may vary widely among individuals, and prothrombin times are routinely measured. Similarly, as reliable assays become available to measure the pharmacological effects of clopidogrel, it will become increasingly feasible to evaluate whether dose escalation will prove to be a useful strategy.

Potential Sites for Response Variability

Intestinal Absorption

Hepatic Metabolism

Active Metabolite

P2Y12 Receptor (irreversible inhibition)

GP IIb/IIIa receptor expression

Figure 3. Conceptualized distinction between pharmacological response to therapy and treatment failures.

Figure 4. Proposed mechanisms for interindividual variability in platelet inhibition in response to clopidogrel. GP indicates glycoprotein.
for individual patients with an inadequate pharmacological response to therapy and to determine whether routine platelet function testing during follow-up or at PCI should be implemented.

**Current Guidelines**

Current recommendations from the American College of Cardiology/American Heart Association/Society for Cardiovascular Angiography and Interventions list a class IIa indication for a loading dose of clopidogrel >300 mg for patients undergoing PCI who need to achieve higher platelet inhibition more rapidly but emphasize that the relative efficacy and safety of this approach remain incompletely defined. In addition, a class IIa indication is listed for a 150-mg daily maintenance dose in subjects in whom subacute stent thrombosis may be catastrophic (eg, unprotected left main, bifurcating left main, or last patent coronary vessel) and in whom an IPA <50% is demonstrated, although no particular assay technique is specified. The European Society of Cardiology endorsed a 600-mg loading dose of clopidogrel if PCI is performed <6 hours after initial drug administration.

**Novel Antiplatelet Therapies**

Several antiplatelet agents are now in development (Figure 5) and aim to address potential limitations of clopidogrel, including delayed onset of action, moderate levels of platelet inhibition, and interindividual variability.

**Prasugrel**

Prasugrel (CS-747, LY640315) is a rapid-acting thienopyridine that achieves higher and more consistent levels of platelet inhibition compared with clopidogrel. Prasugrel, like clopidogrel, requires hepatic metabolism to form its active metabolite and irreversibly inhibits the P2Y<sub>12</sub> receptor. In a crossover study of healthy volunteers, the IPA was higher and more consistent with a 60-mg loading dose of prasugrel than with 300 mg of clopidogrel. The enhanced potency of prasugrel may be explained by differences in drug absorption or metabolism to the active metabolite, because both clopidogrel and prasugrel have similar potency when equivalent molar concentrations of active metabolite are compared ex vivo; prasugrel achieves 10- to 100-fold higher levels of active metabolite in vivo.

In the Joint Utilization of Medications to Block Platelets Optimally–Thrombolysis in Myocardial Infarction (JUMBO-TIMI 26) trial, prasugrel was found to be well tolerated and to have a safety profile similar to that of clopidogrel when subjects undergoing elective or urgent PCI were treated for up to 30 days. Although the study was not powered to examine efficacy, subjects receiving prasugrel tended to have lower rates of adverse CV events, including a lower risk of periprocedural MI or need for revascularization.

Enrollment is underway in the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel (TRITON-TIMI 38), a phase III trial studying subjects with ACS undergoing PCI (ClinicalTrials.gov identifier: NCT0097591). TRITON-TIMI 38 is the first large trial to help determine whether achieving higher levels of IPA will lead to improved clinical outcomes. In an additional study, the relative potency of prasugrel is being compared with a higher loading dose (600 mg) and maintenance dose (150 mg daily) of clopidogrel by examining measures of platelet function, inflammation, and myocyte necrosis in patients undergoing elective PCI in the Prasugrel in Comparison to Clopidogrel for Inhibition of Platelet Activation and Aggregation (PRINCIPLE)–TIMI 44 study (ClinicalTrials.gov identifier: NCT00357968).

**AZD6140**

Because genetic and acquired variability in the cytochrome P450–dependent pathways may contribute to clopidogrel response variability, drugs that directly target the P2Y<sub>12</sub> receptor without the need for metabolism may have promise. AZD6140 is an orally active, reversible, competitive inhibitor of the P2Y<sub>12</sub> receptor. The drug is the first in a new class of oral antiplatelet agents known as cyclopentyl triazolopyrimidines. AZD6140 has onset of action within 2 hours in the absence of a loading dose, a short half-life (~12 hours) that requires twice-daily dosing, and a shorter time for drug offset after discontinuation. Preclinical and phase II studies have demonstrated higher and more consistent levels of platelet inhibition with AZD6140 compared with clopidogrel.

The largest clinical experience with AZD6140 to date is the Double-Blind, Double-Dummy, Parallel Group Randomised Dose Confirmation and Feasibility Study of AZD6140+Acetylsalicylic Acid (ASA) Compared With Clopidogrel+ASA in Patients...
With Non-ST Segment Elevation Acute Coronary Syndromes (DISPERSE-2) trial, which evaluated the safety, tolerability, and antiplatelet effects of AZD6140 in 990 patients with non–ST-elevation ACS. Subjects treated with AZD6140 had higher levels of platelet inhibition and showed a trend toward lower rates of recurrent MI compared with subjects treated with clopidogrel and with a similar risk of bleeding.55 There were higher rates of dyspnea, hypotension, and nausea in patients randomized to treatment with AZD6140, although rates of drug discontinuation were similar across treatment arms.55 The Platelet Inhibition and Patient Outcomes (PLATO) trial (ClinicalTrials.gov identifier: NCT00391872) will compare the clinical efficacy of AZD6140 to clopidogrel in patients with ACS.

Cangrelor
Cangrelor (AR-C69931MX) is a potent, nonthienopyridine P2Y12 receptor antagonist that offers several distinct features, including an intravenous formulation, reversibility, and a short half-life (3 to 5 minutes). Because it does not require metabolism to become active, cangrelor can achieve nearly complete inhibition of ADP-induced platelet aggregation with very rapid onset.56 Because the antiplatelet effects of cangrelor can be completely reversed in 20 to 50 minutes, the compound may offer an advantage for patients who need to achieve rapid platelet inhibition for PCI with the ability for swift reversal (eg, those who may require urgent coronary artery bypass graft). Early-phase testing has demonstrated that cangrelor achieves very high degrees of platelet inhibition with an acceptable safety profile in patients with non–ST-elevation ACS not undergoing PCI.56,57 A pharmacodynamic study of cangrelor in patients undergoing PCI demonstrated a trend toward shorter bleeding times compared with treatment with abciximab. Additional evaluation of this agent is being pursued in phase III studies, including the Clinical Trial Comparing Cangrelor to Clopidogrel in Subjects Who Require Percutaneous Coronary Intervention (CHAMPION-PCI: Clinical Trials.gov identifier: NCT00305162) and the Clinical Trial Comparing Treatment With Cangrelor (inCombination With Usual Care) to Usual Care, in Subjects Who Require Percutaneous Coronary Intervention (CHAMPION-PLATFORM; ClinicalTrials.gov identifier: NCT00385138).

Conclusions
Despite a robust and consistent benefit across large clinical trials, a significant interindividual variability in pharmacological response to clopidogrel has been demonstrated; one size does not fit all. Patients with a diminished response to clopidogrel may be at increased risk of adverse events. Current guidelines do not clearly define what actions should be taken for the pharmacological management of patients with stent thrombosis such as the patient described in the opening clinical vignette. A reasoned approach would be to identify potential causes, including mechanical difficulties (incompletely deployed stent or edge dissection) or noncompliance with prescribed antiplatelet therapy. In the absence of these findings, the clinician may consider empirically increasing the dose of clopidogrel to 150 mg daily after PCI; however, the net clinical benefit of such a strategy remains untested. Additional measures include reducing the dose or eliminating medications that may interfere with clopidogrel metabolism. These strategies were adopted in the management of the patient in the opening case of the article, including an increase in the maintenance dose of clopidogrel to 150 mg daily. The patient was subsequently discharged home and at this time has not had any recurrent ischemic events during follow-up. Platelet function testing may prove to be useful to clinicians to guide therapy, but the ideal assay method and values required to reduce clinical events remain undetermined. Several novel antiplatelet therapies may help to address some of the limitations of current therapies and, if approved, may serve as options to help reduce adverse outcomes or as treatment alternatives for patients with an inadequate response to therapy or subacute stent thrombosis.

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