Measured Drug Effect and Cardiovascular Outcomes in Patients Receiving Platelet P2Y₁₂ Receptor Antagonists
Clarifying the Time and Place for Intensive Inhibition

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The clinical efficacy of oral P2Y₁₂ antagonists in reducing recurrent cardiovascular events in patients with acute coronary syndromes (ACS) treated with percutaneous coronary intervention (PCI) or with either a conservative or early invasive strategy is well established. However, the effect of clopidogrel on P2Y₁₂-mediated platelet reactivity varies widely among individuals. Platelet function tests are now clinically available that can measure P2Y₁₂-mediated platelet reactivity, thereby providing a measurement of drug effect in patients treated with a P2Y₁₂-receptor antagonist. Platelet function testing has provided a measure of certainty to the understanding of cardiovascular diseases: agents that provide powerful and consistent inhibition of P2Y₁₂-mediated reactivity reduce postprocedural myocardial infarction and stent thrombosis, confirming the mechanistic hypothesis that P2Y₁₂-receptor signaling is a major component of pathophysiological thrombus formation in patients with ACS treated with PCI.

In turn, however, platelet function testing has added uncertainty because if platelet reactivity among patients while receiving treatment (“on-treatment” reactivity) is a measure of the risk of future events, then the comparative benefit of the newer, more expensive P2Y₁₂ antagonists may uniquely depend on the magnitude of the effect of clopidogrel in a particular individual (however, different drugs may differentially affect the P2Y₁₂ site). This concept of selective intensive antiplatelet therapy based on a measured drug effect, which has not been proven in a definitive, randomized trial, has provoked intense debate in the cardiology community.

Although substantial data indirectly support the validity of the platelet function testing hypothesis, randomized trials to date have been limited by insufficient power, insufficient pharmacodynamic intervention, and potential selection bias for low-risk patients. Platelet function testing was not systematically performed in the trial that demonstrated the superiority of prasugrel over clopidogrel in patients with ACS treated with PCI. It is therefore speculative whether the benefit of prasugrel could be greatest in patients who demonstrate the least drug effect while receiving clopidogrel or could be minimal in patients treated with clopidogrel who display a potent drug effect.

In this issue of JAMA, Gurbel and colleagues report the results of the platelet function substudy of the Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes (TRILOGY ACS) trial, which included 2564 patients, approximately 28% of those enrolled in the overall trial. In the overall trial, prasugrel was not superior to clopidogrel in reducing recurrent cardiovascular events in medically managed patients with ACS who were not intended to undergo revascularization. In the current study, the investigators measured on-treatment reactivity at several time points over the course of follow-up using the VerifyNow P2Y₁₂ test, which has been previously shown to reliably measure the P2Y₁₂ effect of clopidogrel and prasugrel as well as correlate with active metabolite exposure of both drugs.

The goals of the platelet function substudy were 2-fold: to confirm that prasugrel at the doses used provided a greater drug effect (ie, lower on-treatment reactivity) than clopidogrel and to determine whether there was an association between the achieved level of reactivity over time and clinical outcomes, irrespective of study drug assignment. At all time points tested, patients randomly assigned to receive 10 mg of prasugrel (or 5-mg prasugrel if aged ≥75 years or weight <60 kg) displayed significantly lower levels of on-treatment reactivity than those...
randomly assigned to receive 75 mg of clopidogrel, although the absolute difference between the study drugs was attenuated with the low-dose prasugrel regimen. Therefore, prasugrel did what it was designed to do.

The investigators then explored the relationship between platelet function and outcomes using several statistical techniques. First, they treated on-treatment reactivity as a time-dependent covariate to assess the association between reactivity and outcomes over time; second, they performed an analysis 30 days after randomization to determine whether on-treatment reactivity at this point was related to risk of subsequent events; and third, they repeated these models imputing missing platelet function testing data, which totaled nearly 25% of all platelet function measurements performed. Despite the complexity and number of analyses, the findings were generally consistent: on-treatment reactivity was significantly associated with the composite end point of cardiovascular death, myocardial infarction, or stroke as well as all-cause mortality alone, but these associations were no longer significant after adjustment for other known predictors for recurrent events after ACS. The authors justifiably conclude that the lack of an independent relationship between on-treatment reactivity and outcomes may explain the comparable clinical outcomes between prasugrel and clopidogrel in the overall TRILOGY ACS trial.

There are several limitations to these analyses, particularly with regard to detecting any influence of on-treatment reactivity on early outcomes because patients at early time points were not tested at steady state levels of platelet inhibition and the 30-day analysis does not include these early events. In addition, since the TRILOGY ACS trial randomized patients up to 10 days after initial presentation (median duration, 4.5 days), the study cannot address the relationship between on-treatment reactivity and very early outcomes.

Where does this leave the hypothesis that platelet function testing can identify patients at high risk of cardiovascular events and in turn guide the intensification of antiplatelet therapy? The findings provide important insights about the limitations of platelet function testing and intensified P2Y₁₂ inhibition in clinical practice. First, the association between P2Y₁₂-mediated platelet reactivity and outcomes appears to depend critically on the context within which it is measured. In studies involving more than 11,000 patients undergoing PCI,³,⁶,¹² high on-treatment reactivity is associated with a substantial adjusted hazard of major adverse cardiovascular events, particularly stent thrombosis, and appears to improve risk classification above and beyond other risk factors.³ The absolute risk appears to be less pronounced in patients undergoing PCI for stable coronary artery disease. In contradistinction, as demonstrated by Gurbel and colleagues,⁹ P2Y₁₂-mediated platelet reactivity during the subacute and chronic phases of therapy is not strongly associated with outcomes among medically treated patients with ACS. Indeed, the importance of context is consistent with the observation that the hazard associated with CYP2C¹⁹*₂ allele carriage—a major determinant of high on-treatment reactivity while receiving clopidogrel—is greatest among populations with high rates of PCI, in particular for stent thrombosis, while the hazard is attenuated or absent among medically treated patients.¹³⁻¹⁵

Extrapolating the findings of the TRILOGY ACS platelet function substudy⁶ to all patients with ACS managed noninvasively may be problematic. Survival or other types of bias introduced by the delayed randomization design of the TRILOGY ACS trial may have attenuated the pathophysiologic importance of platelet P2Y₁₂ receptor inhibition: in the Platelet Inhibition and Patient Outcomes (PLATO) trial, which randomized patients to the study drug while in the acute phase of ACS presentation, the ischemic benefit of ticagrelor over clopidogrel in the patients initially intended for noninvasive management was consistent with that of the overall trial.¹⁶ This emphasizes the key role of P2Y₁₂ receptor antagonism in that population; however, because a large platelet function substudy was not performed, a benefit from potential off-target effects of ticagrelor cannot be excluded.¹⁷,¹⁸ In addition, the TRILOGY ACS substudy does not address the potential clinical efficacy of platelet function testing to guide therapy in patients with ACS treated with PCI, a population underrepresented in the Gauging Responsiveness with a VerifyNow Assay-Impact on Thrombosis and Safety (GRAVITAS) trial and not addressed in the Testing Platelet Reactivity in Patients Undergoing Elective Stent Placement on Clopidogrel to Guide Alternative Therapy With Prasugrel (TRIGGER-PCI) trial.

The TRILOGY ACS platelet function substudy establishes an important precedent for future trials. Systematic blood sample collection should be considered in randomized clinical trials designed to evaluate novel therapeutics or to expand product labeling. This might permit pharmacodynamic or exploratory pharmacogenomic analyses by independent groups that might be useful in identifying individuals who may safely derive the greatest treatment benefit. Even in trials with neutral results, such analyses may provide insight into unexpected pathophysiologic mechanisms that may in turn lead to the development of new, more effective treatment strategies. In the case of medically managed patients recovering from ACS, such strategies are sorely needed.

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