Mind the Gap: Platelet Inhibition in Low-Risk Acute Coronary Syndrome Undergoing Percutaneous Revascularization

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Delayed inhibition of platelets during percutaneous coronary intervention (PCI) is associated with adverse rates of ischemic cardiovascular events in patients presenting with acute coronary syndrome. High on-treatment platelet reactivity and platelet aggregation levels as measures of quantitative platelet inhibition are associated with increased risk of periprocedural myocardial infarction and thrombotic events.[1] Clinicians aim for early and potent inhibition of platelet activity utilizing various oral $P2Y_{12}$ receptor inhibitors,[2,3] different formulations,[4] and timing of the loading dose.[5] Nevertheless, periprocedural anticoagulation and antiplatelet management for PCI remains a complex decision-making process often limited by the time window for pretreatment and clinician and/or institutional preferences. With numerous permutations and combinations of anticoagulants and intravenous and oral platelet inhibitors, the decision to choose an appropriate regimen balancing bleeding and therapeutic benefits becomes perplexing.

$P2Y_{12}$ receptor inhibitors administered orally remain the most commonly used strategy among patients undergoing PCI for low-risk acute coronary syndrome. Clopidogrel, a thienopyridine, requires in vivo oxidation by cytochrome CYP3A4 and 2C19 isoenzymes and binds irreversibly to $P2Y_{12}$. Prasugrel is more potent with more rapid onset of action. Ticagrelor is a reversible $P2Y_{12}$ receptor inhibitor that does not require in vivo activation and offers early and effective platelet inhibition. Chewed or crushed formulations of oral agents demonstrate faster peak plasma concentration and more rapid platelet inhibition. Delayed absorption in the setting of impaired perfusion or opioid use and issues such as vomiting, intubation, and hemodynamic instability may reduce the challenges of gastrointestinal absorption with oral administration. Often there is a short duration of time for pretreatment, and even the fast-acting oral agents require a significant period of time to reach therapeutic levels, with variability in effect.

Intravenous agents have been proposed as a means to bridge the therapeutic window from administration of oral $P2Y_{12}$ inhibitors to peak plasma concentration and onset of action. Intravenous $P2Y_{12}$ inhibition with cangrelor or glycoprotein receptor inhibitors (GPI) have been proposed to bridge the gap between the administration of oral agents and the onset of effective platelet inhibition. Cangrelor has been shown to inhibit platelet activity more effectively than clopidogrel alone,[6] and the drug was associated with a reduction in ischemic events in the CHAMPION-PHOENIX (Cangrelor versus Standard Therapy to Achieve Optimal Management of Platelet Inhibition) trial among those not pretreated with clopidogrel.[7] In a group of patients with ST-segment–elevation myocardial infarction, prasugrel administration alone led to suboptimal inhibition of platelet activity for at least 2 hours, but when GPI was added to prasugrel, more potent and sustained platelet inhibition was achieved and maintained, even if GPI infusion was not continued.[8]

Moving beyond high-risk patients, Marian et al report in this issue of the *Journal of the American Heart Association (JAHA)* that among lower risk, troponin-negative patients undergoing PCI, the combination of clopidogrel 600 mg and intravenous eptifibatide bolus was associated with a lower rate of high on-treatment platelet reactivity and faster inhibition of platelet aggregation compared with crushed ticagrelor.[9] This effect was also associated with a lower rate of periprocedural myocardial injury (28% versus 48%, respectively). Bleeding events did not differ between groups, even though the majority of PCIs in the study were performed using a transfemoral approach. Administering a bolus of GPI to bridge the gap in adequate platelet inhibition created by oral agents but eliminating the infusion may have reduced bleeding complications by limiting overall time of exposure to GPI.

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These findings are consistent with a meta-analysis that showed early platelet inhibition significantly reduced ischemic events without an increase in major bleeding events.[10] They add to accumulating evidence that a therapeutic gap between administration of oral $P2Y_{12}$ inhibitors and their maximal effect may be a target for therapy in patients undergoing PCI.[11] This interesting study suggests that rapid and sustained platelet inhibition in low-acuity patients with acute coronary syndromes undergoing percutaneous revascularization can be achieved. Whether "minding the gap" using the regimen proposed to achieve early inhibition of platelets will translate into meaningful clinical outcomes should be investigated rigorously to help change currently established treatment algorithms that do not focus on periods of inadequate antiplatelet therapy during PCI.

Disclosures

None.

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