"No Such Thing as a Free Lunch": Personalized $P2Y_{12}$ Inhibition to Optimize Patient Outcomes

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Over the past 2 decades, numerous clinical trials have studied $P2Y_{12}$ inhibition in the setting of an acute coronary syndrome (ACS) with or without percutaneous coronary intervention (PCI). Initially trials were designed to address the question of which $P2Y_{12}$ inhibitor to use. The CURE (Clopidogrel in Unstable Angina to prevent Recurrent Events) study first proved the superiority of clopidogrel over placebo in the overall trial cohort, and in the large subgroup who underwent PCI.[1] Subsequently, the TRITON (Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel—Thrombolysis in Myocardial Infarction 38) study demonstrated a reduction in the combined ischemic end points of death, nonfatal myocardial infarction, or stroke with the use of prasugrel 10 mg once daily compared with clopidogrel in patients undergoing PCI after presenting with an ACS.[2] Finally, the PLATO (Platelet inhibition and patient outcomes) trial showed that ticagrelor 90 mg twice daily reduced combined ischemic end points when compared with clopidogrel.[3]

What these trials also demonstrated, however, is the often-quoted observation of Milton Friedman, ie, that there is "no such thing as a free lunch." The inevitable consequence of increasing ischemia protection is that major bleeding will be increased. PLATO and TRITON both demonstrated a 30% to 40% increase in trial-defined major bleeding in the active arm compared with clopidogrel. Post hoc landmark analyses also demonstrated a time-dependent phenomenon (ie, that the differences in bleeding between agents became greater as treatment duration increased). These observations led investigators to hypothesize that a shorter duration of $P2Y_{12}$ inhibitor (3–6 months) might be sufficient to provide ischemia protection while minimizing bleeding risk. Although trials of shortened $P2Y_{12}$ inhibitor therapy were underpowered to robustly define patient outcomes, meta-analyses demonstrate that a shortened $P2Y_{12}$ inhibitor therapy (6 months) is a reasonable strategy for many patients. However, it is not possible to robustly conclude that a shortened duration of therapy for patients presenting with ACS is safe, because the majority of patients randomized in these studies presented with stable angina.[4] Therefore, the society guidelines have continued to recommend a 12-month $P2Y_{12}$ inhibitor course after an ACS.

Aside from abbreviating $P2Y_{12}$ inhibitor therapy, another strategy to maximize ischemia protection while minimizing bleeding risk is to switch between differing $P2Y_{12}$ inhibitors during the convalescent period. In the TOPIC (Timing of platelet inhibition after acute coronary syndrome) trial, patients who presented with an ACS and who underwent PCI were treated initially with ticagrelor or prasugrel.[5] After 1 month, patients were randomized to continuing on potent $P2Y_{12}$ inhibitor therapy or switching to clopidogrel. Although there did not appear to be an ischemic cost associated with switching, Bleeding Academic Research Consortium (BARC) ≥2 bleeding was less frequent, occurring in 4.0% of patients in the switched dual antiplatelet therapy (DAPT) group and in 14.9% in the unchanged DAPT group (hazard ratio 0.30, 95% CI 0.18–0.50, $P<0.01$).

These studies illustrate that optimizing $P2Y_{12}$ inhibition is challenging even in a lower-risk cohort. However, in the elderly, $P2Y_{12}$ inhibitor decision-making is especially difficult given that age is a strong predictor of ischemic and bleeding events post-ACS. In the original TRITON trial, patients ≥75 years of age did not derive ischemia benefit from treatment with 10 mg of prasugrel versus clopidogrel, and the bleeding excess with prasugrel was especially marked in this group.[6] These findings led to the licence indication for prasugrel to include only those patients younger than 75 years of age. Subsequently the GENERATIONS study—a pharmacodynamic study of prasugrel versus clopidogrel in the elderly—suggested that a more appropriate dose of prasugrel in patients ≥75 years of age might be 5 mg.[7] The Elderly-ACS

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2 trial investigated this dose, randomizing patients ≥75 years of age with an ACS undergoing PCI to a once-daily maintenance dose of prasugrel 5 mg compared with the standard clopidogrel 75 mg.[8] The trial, however, was terminated early for futility with only 1443 of the originally planned 2000 patients being randomized. The trial clinical events were analyzed in the conventional time to first event survival approach, with only 109 ischemic events and 49 bleeding events across both trial arms. Although there were numerical decreases in stent thrombosis and increases in bleeding with prasugrel compared with clopidogrel, these did not reach statistical significance.

In the current study in this issue of the *Journal of the American Heart Association (JAHA)*, Crimi et al performed a post hoc analysis of the Elderly-ACS 2 trial.[9] The investigators adopted a novel approach of calculating the average daily ischemic rate (ADIR) and average daily bleeding rate (ADBR) in an effort to include all clinical events rather than the first event only. They also divided the timing of events during the first year following the index event into different clinical phases (acute, subacute, and late). The investigators found that daily ischemic and bleeding burdens peaked in the first 3 days after the ACS, remained high in the first month, and then gradually decreased throughout later follow-up. This finding is not novel but may help inform clinicians in decision-making in the elderly, particularly if switching is being considered. Although it is interesting to note that recurrent ischemic events were more frequent than bleeding at all time points (and 2.6-fold more frequent overall), it is important to note that the trial—as in the case of most other P2Y$_{12}$ inhibitor trials—excluded patients with anemia, previous bleeding, low platelet count, anticoagulation, and malignancy. Thus, the trial enrolled patients at low risk of bleeding and excluded many conditions seen in the elderly that will significantly increase their risk of bleeding on a P2Y$_{12}$ inhibitor. The investigators also noted significant differences in ADIR versus ADBR between clopidogrel and prasugrel, depending on which clinical phase was studied. In the acute phase (0–3 days), there were no differences in ADIR and ADBR between the study arms, whereas in the subacute phase (4–30 days) patients receiving clopidogrel had a significantly higher absolute difference of ADIR without a difference in ADBR than patients receiving low-dose prasugrel. In the late phase (31–365 days), ADIR remained significantly higher with clopidogrel than with low-dose prasugrel, while ADBR was significantly higher with low-dose prasugrel than with clopidogrel. However, it is important to note that the magnitude of absolute differences in ADIR between the 2 treatments was smaller in the late phase than in the subacute phase.

How do these data and this novel analysis help guide clinicians in their decision making with respect to P2Y$_{12}$ inhibitor therapy? While this analysis is limited by being post hoc and derived from a trial that was terminated early and underpowered, the findings are nevertheless important and of clinical relevance. The use of the average daily rate analysis first increases the power of the original Elderly-ACS 2 trial, and demonstrates that treatment with low-dose prasugrel from the fourth day to the end of follow-up significantly reduced ischemic events as compared with treatment with clopidogrel. Therefore, in patients ≥75 years of age who are at low bleeding risk, treatment with 5 mg of prasugrel may be a reasonable option. Furthermore, the average daily rate analysis also clearly demonstrates not only a significant difference in the ischemic and bleeding event rates during different study phases, but also differences in the absolute and relative magnitude of treatment effects between prasugrel and clopidogrel. Therefore, these data add more support to the concept of personalized P2Y$_{12}$ inhibitor therapy, not only in the choice of agent but also switching in convalescence.

Assimilating the enormous amount of P2Y$_{12}$ inhibitor data is challenging, with physicians needing to make decisions on the choice of P2Y$_{12}$ agent, its duration (short, standard, or long), and also encompasses the concept of switching in convalescence. Given the wealth of data and the differences in ischemic and bleeding risks between patients, consensus and guidelines have moved away from a "one size fits all strategy" to a very much more tailored or bespoke approach. As clinicians we should embrace this approach and consign the concept of "one drug fits all" to history.

Disclosures

None.

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