A Freeze on Tailored Antiplatelet Therapy?

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It is widely known that there is interindividual variation in the response to aspirin and clopidogrel, drugs that represent two major classes of antiplatelet therapies in use today. Variation in response can be defined clinically, i.e., not all patients who are exposed to the drug are protected from platelet-mediated thrombotic events such as myocardial infarction (MI). Response can also be defined pharmacodynamically in the laboratory employing ex vivo measures of platelet inhibition such as the VerifyNow® platform- a whole blood, point-of-care test. A rich history of epidemiologic and genetic data demonstrates an association between variability in laboratory responses and clinical outcomes among patients receiving antiplatelet therapy. To test the hypothesis that measures of ex vivo platelet function are truly risk factors and not merely risk markers, the ARCTIC study randomly assigned patients undergoing percutaneous coronary intervention (PCI) to a strategy of platelet function testing and subsequent adjustment of antiplatelet therapy vs. usual care. The primary results from ARCTIC failed to demonstrate a benefit from incorporating platelet function test results into management of antiplatelet therapies in this population. In a secondary analysis published in this issue of Circulation, the ARCTIC investigators assessed the extent to which outcomes differed after hospital discharge by performing a landmark analysis. Similar to the previously reported primary findings, a strategy of platelet function test-driven treatment changes did not affect clinical outcomes from the time of discharge through the end of follow up. Although the question asked is sound and of potential clinical relevance, many unanswered questions remain to better determine in whom and under what conditions a strategy of tailored antiplatelet therapy may improve clinical outcomes.

The decision to perform a landmark analysis based on the time of hospital discharge was chosen in an effort to exclude periprocedural events. However, the collective data from prior
clinical trials of platelet P2Y12 receptor antagonists in PCI has shown that the bulk of events and benefit from therapy is concentrated within the first few days to weeks of therapy.\textsuperscript{3-5} In ARCTIC, the vast majority (>75\%) of events occurred prior to hospital discharge. This “clustering” to the early phase following PCI is consistent with a platelet-mediated causal mechanism. Events that occur later or during the convalescence period following PCI are more heterogeneous in nature, and therefore less likely to be directly impacted by tailored antiplatelet therapy. The benefit of antiplatelet therapy may be greatest early during therapy in part because we and others have observed a waning effect of aspirin over time with the greatest inhibition of platelet function in the first 1-2 weeks of treatment initiation.\textsuperscript{6,7} Further, the strategy in response to detecting high, on-treatment platelet reactivity in ARCTIC included administration of a peri-procedural glycoprotein IIb/IIIa inhibitor. After discharge, the most commonly selected strategies were increased clopidogrel or aspirin doses (prasugrel was rarely used)- neither has been shown to provide additional protection from ischemic events compared to standard doses.\textsuperscript{8} Instead, it is conceivable that transition to either prasugrel or ticagrelor after discharge in those with high on-treatment platelet reactivity may have demonstrated a benefit.\textsuperscript{3,4} For each of the above reasons, it may have been particularly difficult to detect a signal of benefit from tailored antiplatelet therapy in the period following hospital discharge.

The findings from the landmark analysis do not resolve the unanswered question of whether a strategy of tailored antiplatelet therapy is beneficial for patients with acute coronary syndrome (ACS) who undergo PCI. Overall, participants in the ARCTIC trial were a low-to-moderate-risk group with only one-third presenting to the hospital with ACS. It may well be, based on the available information, that this latter group is most likely to benefit from a strategy of tailored antiplatelet therapy. Accordingly, one could conclude that the current analysis,
consistent with existing guidelines and prior studies, underscores a lack of evidence for routine platelet function testing and tailored therapy among low-to-moderate risk, non-ACS patients who undergo PCI.\textsuperscript{9,10}

In addition, these analyses do not exclude the possibility that a “response” to antiplatelet therapy is an actionable risk factor for platelet-mediated events. \textit{Ex vivo} platelet function tests designed to gauge platelet aggregation in response to physiologic agonists are often selected as a road map to tailor antiplatelet therapy because of their ease of use and relative familiarity. This is a reasonable approach and, in principle, supports the National Institutes of Health’s initiative for precision medicine as a means to deliver more affordable health care.\textsuperscript{11} One must, however, acknowledge that there are several, well-described, limitations to traditional \textit{ex vivo} platelet function test platforms. The most commonly cited are that the agonist concentrations, additives, and conditions employed poorly mimic \textit{in vivo} platelet and cellular biology. In addition, most \textit{ex vivo} platforms focus primarily on platelet aggregation and essentially ignore secretion, adhesion, tethering, and signaling. They also are incapable of providing even a glimmer of a new world that is rapidly emerging that includes the platelet transcriptome, proteome, metabolome, post-transcriptional and post-translational regulation and microvesicle delivery of biologically active materials to other circulating cells and to the vessel wall. Though measuring such diverse effects in a clinical setting is challenging, these molecules, coupled with the power of informatics, may provide translatable biomarkers\textsuperscript{12-15} for measuring the comprehensive effects of platelet inhibitors in human health and disease.

As the authors correctly point out, these analyses do not exclude a potential role of tailored therapy based on genetic testing for \textit{CYP2C19}. In many ways \textit{CYP2C19} genetic variants are ideal (albeit incomplete) biomarkers for the response to clopidogrel. Variants at this locus
are true “pharmacogenomic” biomarkers. This is to say that in the absence of clopidogrel, individuals who carry these variants have no differences in platelet function\textsuperscript{16} or clinical outcomes\textsuperscript{16, 17}. A similar pattern may be emerging for \textit{PEARI} variants in patients exposed to aspirin\textsuperscript{18}, though this has not been a consistent finding\textsuperscript{19}. In contrast, \textit{ex vivo} platelet function test results are associated with comorbidities such as diabetes even in the absence of antiplatelet therapy\textsuperscript{7} thus may more reflect overall risk than a specific response to a medication. Biomarkers with the same types of attributes as \textit{CYP2C19} and possibly \textit{PEARI} may prove to be more useful in designing strategies to tailor the choice and/or duration of antiplatelet therapy.

In summary this secondary analysis by the ARCTIC investigators adds to an existing body of evidence\textsuperscript{17, 20} that a strategy of tailored antiplatelet therapy around \textit{ex vivo} platelet function is unlikely to benefit low-to-moderate risk PCI patients prescribed clopidogrel. However, it remains an untested hypothesis that tailoring P2Y12 inhibitor therapy may improve clinical outcomes in ACS patients who receive PCI therapy using existing biomarkers of clopidogrel response. Further, there still may be opportunities to tailor antiplatelet therapies beyond the ACS/PCI population with the goal of improving clinical outcomes. To achieve these goals, however, more sensitive and comprehensive tools to quantify those effects of platelet inhibitors that mediate their beneficial effects and precipitate their harms are needed. Until that time, though, the concept of selecting the right antiplatelet therapy for the right patient remains an important and achievable goal.

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