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Platelet-Function Testing in Patients Undergoing Neurovascular Procedures: Caught between a Rock and a Hard Place

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ABSTRACT

SUMMARY: In the context of neurointerventional procedures, clopidogrel hyper-responsiveness has been associated with hemorrhage; on the other hand, clopidogrel resistance has been associated with thromboembolism. This might seem to make a compelling argument in favor of routine platelet testing. Our reading of the literature leads us to conclude that routine platelet testing in neurointerventional procedures is not, unfortunately, ready for prime time.

ABBREVIATIONS: CREST = Clopidogrel Effect on Platelet Reactivity in Patients with Stent Thrombosis; GRAVITAS = Gauging Responsiveness with a VerifyNow Assay; OASIS-7 = Optimal Antiplatelet Strategy for Interventions; PCI = percutaneous coronary intervention; POPULAR = Point-of-Care Platelet Function Assays Predict Clinical Outcomes in Clopidogrel pre-treated patients undergoing elective PCI; TRIGGER-PCI = Testing Platelet Reactivity in Patients Undergoing Elective Stent Placement on Clopidogrel to Guide Alternate Therapy with Prasugrel.

The articles by Goh et al[1] and Fifi et al[2] in this month's journal highlight the intense scrutiny now focused on platelet-function testing in interventional neuroradiology. The storyline of these 2 bookend articles—on the one hand that clopidogrel hyper-responsiveness was associated with hemorrhage and, on the other hand, that clopidogrel resistance was associated with thromboembolism—seems like compelling evidence in favor of routine platelet testing. However, these articles represent only the tip of a veritable iceberg of literature on the subject of platelet testing in endovascular procedures. If we look below the surface at this iceberg, it becomes clear that similar enthusiasm for platelet testing previously gripped the interventional cardiology community. Both Goh et al[1] and Fifi et al[2] concluded that further study is needed. It is not clear, however, that such urgent study will result in a consensus regarding platelet testing, as evidenced by the iceberg of literature discussed below. Indeed, our reading of the cardiology literature leads us to the opposite conclusion, specifically that routine platelet testing in neurointerventional procedures is not, unfortunately, ready for prime time.

Both sides of this debate can agree on 3 points regarding platelet function testing for neurovascular intervention:

1) A certain number of patients will experience thrombotic complications from neurovascular interventions, despite being compliant with a standard antiplatelet medication regimen.

2) High in vitro platelet reactivity predicts an increased incidence of adverse ischemic outcomes in cardiology patients undergoing PCI.

3) Increasing antiplatelet pharmacotherapy reduces this high on-treatment platelet reactivity in vitro.

These points are well-established in the literature, are beyond dispute, and will not be discussed further. However, to justify the use of routine platelet function testing for neurovascular intervention, proponents must make the following assumptions:

1) The increased incidence of adverse ischemic outcomes includes a proportional increase in the incidence of target-vessel thrombosis.

2) The relationship between high in vitro platelet reactivity and adverse outcomes in cardiology patients undergoing PCI can be extrapolated to neurovascular patients.

3) Increasing antiplatelet pharmacotherapy reduces the incidence of adverse thrombotic events in patients with high in vitro platelet reactivity.

4) A reduction in the incidence of adverse thrombotic events could not be achieved more simply, more cheaply, or more effectively in some other way that does not involve platelet function testing.

Unfortunately, there is little evidence to support any of these latter assumptions, and there is some evidence to suggest that they may, in fact, be wrong.

Assumption 1

The increased incidence of adverse ischemic outcomes includes a proportional increase in the incidence of target-vessel thrombosis. That there is an increased risk of adverse ischemic outcomes in

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patients who exhibit high platelet reactivity despite compliance with an antiplatelet regimen has been established by rigorous and large meta-analysis of the cardiology literature.[3]

More recently, the POPULAR trial[4] demonstrated that the results of certain platelet function tests, but not others, were correlated with an increased risk of adverse ischemic events, though this relationship was not as strong as previously thought. However, this increased risk applies to a broad set of outcomes, including pathology related to untreated coronary and cerebral vessels, of which target-vessel thrombosis is only a small proportion.

The largest studies come from the cardiology literature, and the largest of these was the CREST trial,[5] which was methodologically flawed. Not to be confused with the carotid stent-placement trial with the same acronym, the CREST trial retrospectively identified patients who developed this complication while undergoing coronary intervention (30 cases among 5355). Ten of these 30 patients were then excluded for various reasons. The remaining 20 patients had platelet reactivity assessed anywhere between 4 and 422 days after the episode of thrombosis. No assessment of compliance with medication was performed. Compared with the nonthrombosis group, the thrombosis group had significantly longer lesions treated and lower ejection fractions and were more likely to receive a bare metal rather than drug-eluting stent; these have all been shown by a separate meta-analysis to be independent predictors of stent thrombosis themselves.[6]

Various other trials that also showed a relationship between platelet-function test results and the incidence of target-vessel thrombosis are not particularly compelling due to similarly flawed methodology,[7] small sample size,[8] or limited applicability, due to sample populations being confined to either extremely high-risk patients[9] or to those with drug-eluting stents.[10-12] A more recent well-designed prospective trial by Marcucci et al[13] found no significant relationship between high platelet reactivity and stent thrombosis in patients with coronary stents. The most recent GRAVITAS trial (discussed in more detail below) also failed to show a significant relationship.[14] The afore mentioned POPULAR trial[4] showed that among all the methods of platelet-function testing assessed, only light transmittance aggregometry testing, which is highly impractical for routine clinical situations, was correlated with an increased incidence of stent thrombosis and that this relationship was weaker than that demonstrated for other ischemic outcomes.

Before the publication of the articles by Goh et al[1] and Fifi et al[2] in this month's journal, there was only 1 study in the literature describing a relationship between elevated residual platelet reactivity and an increased incidence of target-vessel thrombosis in neurovascular patients,[15] but it included only 50 patients, and all were being treated for supra-aortic arteriosclerotic lesions. The data from Fifi et al[2] are potentially more convincing, but again, most patients were being treated for atherosclerotic disease and most of the thrombotic episodes were in these patients. As such, the results may not be generalizable to patients with aneurysms. Therefore, the use of platelet-function testing may be justifiable in atheropathic cardiology patients (and patients undergoing carotid stent placement), who stand to have an overall mortality and morbidity benefit separate from that associated with reduced stent thrombosis. However, in the (generally) younger patient with (generally) fewer risk factors for ischemia undergoing aneurysm treatment, the overall mortality benefit is likely to be reduced. This benefit may, in turn, be outweighed by the increased risk of bleeding that inevitably comes with increased platelet inhibition,[16] as demonstrated by Goh et al.[1]

Assumption 2

The relationship between high in vitro platelet reactivity and adverse outcomes in cardiology patients can be extrapolated to neurovascular patients. Aside from the questionable assumption of a correlation between reactivity and the specific outcome of target-vessel thrombosis, the automatic extrapolation of results from cardiology patients to neurovascular patients should be scrutinized.

Cardiology patients are far more likely to have presented with acute ischemia and are more likely to be older, to have diabetes, and to smoke cigarettes. All of these may confound both in vitro platelet reactivity and in vivo sensitivity to that reactivity.[17-19] The discrepant results of studies comparing platelet-function test results with the incidence of stent thrombosis mentioned above may be explained by the fact that the predictive values of these tests are greatest in high-risk patients; this category generally does not include neurovascular patients. It also seems reasonable that cardiology patients will be more likely to be coadministered drugs (statins or proton pump inhibitors) that inhibit the hepatic production of the active metabolite of clopidogrel; a poor response to clopidogrel may, therefore, be less prevalent and less severe among neurovascular patients, reducing the need for testing. Although the important results of Fifi et al[2] suggest that high on-treatment platelet reactivity predicts an increased incidence of complications in our patient population, further trials with subgroup analysis of patients undergoing stent placement for aneurysm treatment are required.

Assumption 3

Increasing antiplatelet pharmacotherapy reduces the incidence of adverse thrombotic events. Numerous studies have shown that various laboratory measurements of high on-treatment platelet reactivity can be reduced, either by increasing the clopidogrel dose[20-22] or switching treatment to prasugrel,[23] cilostazol,[24,25] ticlopidine,[26] or ticagrelor.[27] The natural assumption was that similar alterations of pharmacotherapy in patients with high residual platelet reactivity would result in a reduction in the incidence of thrombotic events.

Initial small cardiology trials setting out to test this hypothesis[28-30] suggested promising results, so several large prospective randomized trials were planned to prove that platelet-function testing could guide pharmacotherapy. The results of the first of these trials were recently published by the GRAVITAS investigators.[14] The results they obtained, in >2000 randomized patients, were uniformly dismal, with no significant improvement in any clinical outcome, despite a significant reduction in platelet reactivity. A second trial, TRIGGER-PCI, was halted by its pharmaceutical sponsor for futility, after a preliminary analysis showed an unexpectedly low event rate.[31] A recent smaller study of 800 patients demonstrated a reduction in the rates of in-stent thrombosis when patients with high on-treatment platelet reactivity re-

ceived repeated loading doses of antiplatelet drugs.[32] Further small studies of approximately 200–300 subjects have subsequently been performed, by using various different tests of platelet function and various alterations to treatment in poor responders, and have shown some success.[33-36] A recent meta-analysis[37] of some of these trials demonstrated an overall reduction in mortality and stent thrombosis with modification of antiplatelet therapy on the basis of platelet function testing, though the tests and modifications used were disparate and the overall benefit was highly dependent on the background risk of stent thrombosis (which may be lower in neurovascular patients).

With Fifi et al,[2] reporting only a nonsignificant trend to a reduced thromboembolic complication rate with platelet function testing-guided manipulation of pharmacotherapy, the evidence for this practice remains inconclusive. Intrinsically high platelet reactivity may cause, or be associated with, an increased risk of thrombotic complications that cannot be completely or safely nullified, regardless of manipulation of pharmacotherapy or improvement of in vitro test results.

In any case, these trials are fundamentally flawed in that they only assessed the effects of increasing platelet inhibition in clopidogrel-resistant patients, without a control group of normal responders. This omission ignores the previously tested[38,39] possibility that all patients may have benefited from increased inhibition, regardless of the results of platelet-function testing. Indeed, the OASIS-7 trial[40] demonstrated that double-dose clopidogrel reduces the incidence of stent thrombosis and other ischemic events in unselected patients, further highlighting this design weakness. Of course, as Goh et al[1] have demonstrated, increasing platelet inhibition comes with increased bleeding risks, which may not be acceptable in neurovascular patients with comparatively lower thrombotic risk.

Assumption 4

A reduction in the incidence of adverse thrombotic events could not be achieved more simply, more cheaply, or more effectively in some other way that does not involve platelet-function testing. Even if, at some point in the future, a randomized prospective trial demonstrates a benefit to altering antiplatelet pharmacotherapy according to the result of platelet-function tests, this would not automatically make it best practice. The cost, inconvenience, and any possible delay of endovascular treatment associated with testing must be compared with other methods of reliable platelet inhibition, as must the relative efficacy of the various methods.

Already, there is substantial evidence to support the routine use of prasugrel (which has the same mechanism of action as clopidogrel but with greater and more predictable inhibition due to improved pharmacokinetics) instead of clopidogrel in all patients undergoing stent placement.[41-43] The cost of prasugrel may be comparable with the combined cost of clopidogrel and platelet-function testing; and the increased risk of bleeding seen with prasugrel may be mainly or wholly due to reduced platelet inhibition in clopidogrel poor responders (which is the very phenomenon that needs to be overcome).[44] An identical case could be made for the routine use of ticagrelor or cangrelor in place of clopidogrel, with the addition of adenosine-mediated benefits that neither clopidogrel nor prasugrel can provide.[45,46]

A case can also be made for triple antiplatelet therapy: cilostazol has been shown to enhance the platelet inhibition of clopidogrel in unselected patients.[25,47] Furthermore, patients with anemia have been shown to have significantly higher on-treatment platelet reactivity than those with normal hemoglobin levels; testing for and treatment of anemia may be a safe and effective way to enhance antiplatelet therapy, with additional health benefits.[48]

Finally and perhaps most simply, much of the problem of elevated residual on-treatment platelet reactivity could be overcome by increasing the maintenance dose of clopidogrel in all patients undergoing endovascular procedures, irrespective of test results, as demonstrated in OASIS-7.[40]

Which Test to Choose: What to Do with the Results

The ideal test for platelet function should be the test that best predicts which patients will have an improved clinical outcome from tailored pharmacotherapy. As discussed above, the only large well-controlled trial to assess this (GRAVITAS) found no improvement in outcomes when the pharmacotherapy was altered on the basis of the results of the VerifyNow P2Y12 test (Accumetrics, San Diego, California).[14] VerifyNow is, however, the point-of-care test that appears to best correlate with poor outcome,[4] despite the fact that its correlation with the labor-intensive platelet function tests that are not currently practical in clinical practice (such as lymphotoxin-α [LTA]) and vasodilator-stimulated phosphoprotein phosphorylation [VASP]) is modest.[49] The smaller trials showing success from tailored pharmacotherapy have used various different tests, including VerifyNow, LTA/VASP, and Multiplate Analyzer (Roche, Indianapolis, Indiana). One of these may be proved superior to the others, but the point is currently moot: OASIS-7[40] demonstrates that evaluating the results of the platelet-function tests that one administers may be a redundant step because it is possible that all patients could benefit from an increased clopidogrel dose or the use of a different antiplatelet agent, regardless of test results. Furthermore, the optimal level of platelet inhibition is yet to be clearly established. Goh et al[1] have shown that as platelet inhibition is increased, bleeding risk is increased, and the risk-benefit relationship is likely to be heterogeneous between patient groups.

Summary

Although the concept of individually tailored antiplatelet pharmacotherapy was conceptually appealing, the evidence for its use is, to say the least, unconvincing. This evidentiary weakness is especially dire for neurovascular procedures because the vascular pathology, the devices used, and the type of patients treated are so different from those assessed in the cardiology-dominated literature. Aside from the lack of sufficient evidence to support the notion that altering pharmacotherapy regimens based on the results of platelet function assays improves clinical outcomes, pharmacology (and pharmaceutical company trial money) has moved beyond clopidogrel to the next generation of more reliable antiplatelet agents; the results of any further trials are likely to be "too little, too late."

Key Points

1) Evidence for a relationship between platelet-function-testing results and the incidence of target vessel thrombosis is weak.

2) Almost all of the evidence in favor of such a relationship is found in the cardiology literature, which cannot be automatically extrapolated to neurovascular patients, pathology, and procedures, for a number of reasons.

3) Prospective, randomized, double-blind trials have failed to show any clinical benefit from altering pharmacotherapy based on the results of platelet function tests.

4) There are cheaper, faster, and more effective methods to improve inhibition of platelet aggregation and reduce adverse thrombotic events already available.

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