Platelet Inhibitors: Balancing Art and Science

A case-based look at platelet inhibitors and peripheral arterial intervention.

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The article by Chastain and Stanbro summarizes the "state of the art" regarding the use of antiplatelet agents in postintervention patients with peripheral arterial disease (PAD).[1] However, the data are scant, leaving the clinician to extrapolate information generated from coronary artery disease patients and trials. Likewise, there are no comparative data to differentiate between dual-antiplatelet therapies after percutaneous transluminal angioplasty. The heterogeneity of PAD (focal vs diffuse, iliac vs infrainguinal, calcific vs noncalcific, stenting vs stent grafting) makes recommendations for therapy less specific and therefore clinically challenging. However, there is consensus regarding the absolute need for antiplatelet therapy in postintervention PAD patients because cardiovascular and cerebrovascular morbidity and mortality are common.

Dual-antiplatelet therapy has become the reflex prescription for any peripheral intervention; however, the addition of an adenosine diphosphate (ADP) receptor inhibitor agent increases the risk of bleeding. The critical clinical issue is determining the best balance between bleeding risk and the minimization of thrombotic complications. Because up to one-third of patients may be considered "nonresponders" to clopidogrel therapy, the use of platelet reactivity testing could provide some direction. Antiplatelet testing should be easy to perform, readily available with quick turnaround times, accurate, able to guide therapy, and predict outcomes. Rapid, point-of-care testing is available using platelet function assays (ie, Plateletworks, PFA-100, VerifyNow), measurements of mediators of platelet reactivity (ie, vasodilator-stimulated phosphoprotein phosphorylation using flow cytometry), and functional assays (ie, conductance, turbidimetric, and impedance aggregometry agonist testing). These assays evaluate platelet reactivity and form the basis of phenotypic testing. Currently, there is no universal standardization, and the results are not standardized. Genotypic testing using either buccal skin scraping or blood are under development and suffer from the same lack of universal standardization and outcomes measurement. Being able to identify nonresponders to clopidogrel or those with high posttreatment platelet reactivity does not mean that altering therapy will improve the outcome.

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The guideline statements from the American College of Cardiology Foundation and the American College of Chest Physicians regarding antiplatelet therapy after peripheral intervention recommend single-agent therapy.[2,3] However, this recommendation falls woefully short of addressing the diverse complexity of our patient population. There can always be a "call" for further research,

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but what does the clinician do in the meantime? Let me list several clinical scenarios and our decision-making processes for consideration:

CASE 1

A 65-year-old man with a history of coronary artery disease (CAD) (treated with coronary artery bypass grafting), cigarette smoking, and claudication presented for revascularization of his superficial femoral artery (SFA). He had a 15-cm-long occlusion that was treated with balloon angioplasty (5 mm) followed by nitinol stenting (6 mm). He was on aspirin before the procedure, without an ADP receptor inhibitor. Clopidogrel was added (bolus of 300 mg followed by 75 mg/day) and was prescribed for 3 months after stenting.

If he couldn't afford the medication (the generic version is available), we would beg for at least 1 month's use. If the artery is smaller (4-mm balloon, 5-mm stent) dual therapy would be extended through the first year or indefinitely in patients with compromised runoff (significant tibial artery disease). If a long polytetrafluoroethylene-covered stent is used, our practice is to use dual therapy indefinitely because the thrombosis rate escalates compared with the use of bare nitinol stents. Once drug-eluting stents (Zilver PTX, Cook Medical, Bloomington, IN) are available for the SFA, the strategy would probably be to use dual therapy for at least 1 year after stenting.

Rationale

The most common cause of stent failure for long-segment SFA disease is diffuse in-stent restenosis and reocclusion. This is affected by multiple factors, not the least of which include vessel size, dilated diameter, residual stenosis, quality of run-off, and continued smoking status. The risk is greatest within the first year after intervention. In clinical practice, the balance of cost and benefit differs for all patients, and treatment needs to be individualized. In general, with nitinol stenting, the desire is to use shorter courses (1–3 months) of an ADP receptor inhibitor in addition to aspirin. The presence of multiple negative risk factors (ie, small artery) prompts a longer course to minimize the risk of thrombosis. Covered stents pose an additional risk of acute thrombosis (without underlying stenosis or intimal hyperplasia), and dual-antiplatelet therapy is extended indefinitely, if possible. As drug-eluting stents enter the US market, dual therapy will probably be extended to 1 year based on device experience in the coronary literature.

CASE 2

A 46-year-old woman with bilateral common iliac stenoses causing short-distance claudication was treated with balloon-expandable cobalt chromium stents (8 X 26 mm). She was placed on aspirin therapy at the time of presentation. Within 6 months, she had recurrence (unusually quick) of symptoms, and severe in-stent restenosis was noted. Restenting with covered stents was performed. No platelet reactivity testing was done, but anticardiolipin antibodies (IgG and IgM) were found to be elevated. The patient was then switched to enoxaparin for long-term use, because anecdotally, dual-antiplatelet therapy or warfarin with aspirin is ineffective.

Rationale

High-flow arteries, such as the aorta or common iliac arteries, should have a low restenosis rate after stenting and single-agent antiplatelet therapy. Young patients with precocious atherosclerosis are especially prone to recurrence. Smoking is the most common risk factor, but some also have underlying thrombophilia that may be contributory to the initial disease and to thrombosis. Anecdotally, we have found that these young patients can have anticardiolipin antibodies or beta-2-glycoprotein 1 antibodies, which are atherogenic as well as thrombogenic. The presence of these antibodies prompts extended anticoagulant therapy with low-molecular-weight heparin. Prolonged dual-antiplatelet therapy or therapeutic warfarin with aspirin is insufficient to prevent recurrence, even in the short-term.

CASE 3

A 70-year-old woman with severe, unilateral renal artery stenosis underwent percutaneous transluminal renal angioplasty with stenting (5 X 12 mm). She had no history of symptomatic CAD or cerebrovascular disease. She was given clopidogrel for 3 months to take in addition to aspirin. Due to recurrence, a covered stent (my preference) was used for the secondary procedure. No additional platelet reactivity testing was performed, but it might be useful in this setting. If resistance is noted, ticagrelor (quick onset of a small bolus dose) would be used and continued for at least 12 months.

Rationale

Renal artery disease is caused by aortic atherosclerosis that "grows" into the renal ostium. Stents have to extend

slightly into the aorta to prevent elastic recoil of the aortic plaque. Smaller renal arteries with currently available stents (0.014-inch platforms) have a restenosis risk at 1 year that approaches 25%, even when properly placed. Reintervention with covered stents is more successful than balloon angioplasty or repeat bare-metal stenting. In this situation, dual therapy for an indefinite time frame would be preferred. Patient compliance and objective platelet reactivity testing may help guide therapy duration.

CASE 4

A 63-year-old diabetic man with ischemic ulceration underwent SFA and tibial intervention with balloon angioplasty and stenting (a nitinol stent in the SFA and a drug-eluting stent in the tibial artery). Dual-antiplatelet therapy with aspirin and clopidogrel was used indefinitely. If the patient presents with recurrence, repeat intervention would be performed without altering the antiplatelet regimen. Testing for platelet reactivity could be used in this setting, although there are limited, effective alternatives.

Rationale

The cause of recurrence in patients with multilevel PAD may be a manifestation of overwhelming disease rather than failure of antiplatelet therapy. The flow characteristics of the lower leg, concomitant presence of swelling, infection, presence of peripheral neuropathy, and inactivity of the patient all contribute to the clinical success or failure of therapy. There are just some situations that cannot be adequately sustained with current therapies.

CONCLUSION

Antiplatelet therapeutic options continue to expand and make clinical decision making more challenging. This moving target is hard to resolve based on "evidence" in a homogeneous population (ie, CAD) and near impossible in the heterogeneous PAD population. Studies are needed but will only serve to guide the physician leaving medicine still as an art that needs to be practiced. ■

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