Update on Antiplatelet Therapy for Peripheral Arterial Disease

Current data and guidelines for choosing the best pharmacological option for each PAD patient.

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Despite remarkable advances in the endovascular treatment of atherosclerotic peripheral arterial disease (PAD), significant challenges remain. By design, angioplasty and indwelling stents cause traumatic plaque fracture. Consequences of this include both an acute injury to the vessel wall, predisposing to thrombosis, and the delayed development of myointimal hyperplasia. Advances in drug-eluting technology promise attenuation of the latter problem. The other desirable therapeutic target is the modification of the prothrombotic milieu. With vitamin K antagonists showing a lack of efficacy in patients with PAD, attention has shifted to antiplatelet therapy. Because vessel injury results in increased platelet activation, antiplatelet agents have become the primary remedy to minimize the effects of atherothrombosis. The benefit of platelet inhibition after percutaneous coronary intervention (PCI) is well documented, and it is tempting to generalize these indications to peripheral intervention.

GUIDELINES AND RECOMMENDATIONS

For decades, the mainstay of antiplatelet therapy has been aspirin therapy of differing doses (Table 1). Even though the combination of aspirin and sustained-release dipyridamole is beneficial for cerebrovascular disease, the addition of dipyridamole to aspirin is of no additional benefit for patients with PAD, as was emphasized by the 2012 CHEST guidelines on antithrombotic therapy.[1] Although warfarin has not been beneficial, restenosis does appear to be reduced by low-molecular-weight heparin, and even dextran may have some benefit, both probably due to platelet inhibition.[2] Contemporary management usually involves the choice between single-antiplatelet therapy versus dual-antiplatelet therapy consisting of aspirin with an adenosine diphosphate receptor inhibitor.

The 2011 American College of Cardiology Foundation/American Heart Association PAD Guideline–focused update included a recommendation for monotherapy, with either aspirin or clopidogrel, for the reduction of myocardial infarction, stroke, or vascular death in both symptomatic and asymptomatic patients with PAD.[3] In addition, a new class IIb recommendation was added for dual-antiplatelet therapy, utilizing aspirin and clopidogrel for cardiovascular (CV) risk reduction in patients with symptomatic PAD. The recommendation was based on a subgroup analysis of more than 3,000 patients with PAD in the CHARISMA trial, comparing aspirin versus dual-antiplatelet therapy with aspirin and clopidogrel.[4] Thus, it may be common for patients to present for peripheral intervention while already on maintenance dual-antiplatelet therapy, especially when it is associated with existing coronary disease.

Baseline monotherapy with aspirin is also part of the standard treatment in patients with symptomatic atherosclerosis in other vascular beds, so again, the usual clinical question relates to the utility of dual-antiplatelet therapy. Dual therapies with clopidogrel, prasugrel, or ticagrelor in addition to aspirin are indicated after PCI. Of note, all three agents have "black box" warnings in their prescribing information. In 2010, the US Food and Drug Administration issued a warning regarding clopidogrel, stating that 2% to 14% of the population has reduced

TABLE 1. ANTIPLATELET AGENTS[a,b]

Class	Half-Life (Hours)	Dosing	Cost	Indications	Concerns
COX inhibitors					
Aspirin	2–6 (dose dependent)	75–325 mg OD	$	Multiple	Aspirin resistance, allergy, gastrointestinal intolerance
Glycoprotein IIb/IIIa inhibitors (intravenous only)					
Abciximab (ReoPro)	0.5	0.125 mcg/kg/min	$$$	ACS, PCI	Thrombocytopenia
Eptifibatide (Integrilin)	2.5	2 mcg/kg/min	$$$	ACS, PCI	Thrombocytopenia
Tirofiban (Aggrastat)	2	0.1 mcg/kg/min	$$$	ACS, PCI	Thrombocytopenia
Adenosine diphosphate receptor (P2Y12) inhibitors					
Clopidogrel (Plavix)	8	75 mg OD	$$	CVRR, ACS	Decreased effect in poor metabolizers; hold > 7 days before surgery
Prasugrel (Effient)	7	10 mg OD	$$$	PCI	Hold > 7 days before surgery; avoid with history of stroke or transient ischemic attack; reconsider if older than 75 y
Ticagrelor (Brilinta)	9	90 mg BID	$$$	ACS	Stop > 5 days before surgery; limit aspirin to 75–100 mg
Ticlopidine (Ticlid)	12	250 mg BID	$$	Stroke prevention	Neutropenia, aplastic anemia
Thromboxane inhibitors					
Dipyridamole (Persantine)	10	50–100 mg TID	$ $	Transient ischemic attack (Aggrenox)	Hypotension, dizziness, nausea
Phoshodiesterace inhibitors					
Cilostazol	12	100 mg BID	$$	Claudication	Headache, diarrhea, pancytopenia (avoid in congestive heart failure)

[a]Adapted from Epocrates prescribing information.
[b]Cost per 30 days: $, < $100; $$, $100–200; $$$ > $200.
Abbreviations: BID, twice daily; CVRR, cardiovascular risk reduction; OD, once daily; TID, three times a day.

CYP2C19 activity, which results in ineffective conversion of the prodrug to its active metabolite. Although not in the warning, an additional concern for suboptimal results with clopidogrel stems from the variability noted with regard to smoking status. Scrutiny of randomized trials has shown a consistent lack of clinical efficacy among patients who do not smoke, yet the agent is routinely used in nonsmokers.[5]

Prasugrel is similarly indicated for reducing CV events in patients with acute coronary syndrome (ACS) who are managed with PCI. Although more efficacious compared to clopidogrel for reduction of CV events (number needed to treat = 46 during a 15-month period), this benefit was offset by an increased risk of intracranial hemorrhage (number needed to harm = 167). As a result, prasugrel is contraindicated in patients with a history of stroke or transient ischemic attack, and caution is advised in patients who are older than 75 years.[6] Ticagrelor also has a warning regarding bleeding risk but is not contraindicated with a history of stroke. This dilemma of balancing bleeding risk versus thrombosis risk represents the key challenge in using these agents.[7] To highlight the other end of the spectrum, the promising intravenous P2Y12 inhibitors, cangrelor and elinogrel, have been dropped from development for percutaneous interventions after failing to show increased benefit compared to clopidogrel.

RECENT TRIAL DATA

Safety concerns related to major bleeding risk have also been evident in the recent clinical trial experience, as seen with vorapaxar—a novel antiplatelet agent that selectively inhibits the cellular actions of thrombin through antagonism of PAR-1. More than 26,000 patients with symptomatic atherosclerosis, including patients with PAD, were randomized to active drug versus placebo in addition to usual care. After 3 years, a significant reduction in ischemic events and CV death was noted, with the increased risk of intracranial hemorrhage, particularly in patients with a history of stroke.[8] Whether increased bleeding risk will prevent the launch of vorapaxar remains to be seen. Increased bleeding risk did not prevent prasugrel from coming to market, but prasugrel did achieve a primary endpoint of efficacy in ACS, whereas vorapaxar did not.[9]

Specific trials comparing aspirin to dual-antiplatelet therapy in percutaneous peripheral arterial interventions are sparse. Two recent Cochran reviews on antiplatelet agents in patients with PAD are notably silent in this regard.[10,11] The CAMPER trial proposed comparing aspirin to dual-antiplatelet therapy in PAD patients but had to be terminated due to poor enrollment. The 2012 CHEST guidelines recommend dual-antiplatelet therapy for patients with ACS who have undergone PCI with stent placement, but single—rather than dual-antiplatelet therapy—is recommended for patients undergoing peripheral artery angioplasty with or without stenting.[1]

> Given the evidence, the use of antiplatelet pharmacogenetics appears to be ready for routine implemenation.

Comparison between coronary and peripheral interventions may also be difficult because the rate of platelet nonresponsiveness to clopidogrel has been reported as significantly higher in those undergoing percutaneous peripheral intervention compared to patients undergoing PCI.[12] In a recent German study, 80 patients with PAD being treated with endovascular therapy were randomized to aspirin versus aspirin plus clopidogrel for 6 months. Thirty percent of patients who received clopidogrel were found to be resistant based on platelet activation markers. Nonetheless, in the clopidogrel-responsive patients, dual-antiplatelet therapy was associated with reduced peri-interventional platelet activation and a reduced need for target lesion revascularization without higher bleeding complications.[13]

Of note, the two clopidogrel patients who required rescue revascularization were both resistant to clopidogrel, highlighting the need for dual-antiplatelet therapy that is tailored to the individual patient. This need for personalized antiplatelet therapy has already been demonstrated in relation to stent thrombosis in the coronary arteries.[14] It makes sense that patients with peripheral stent thrombosis would benefit from the same approach, particularly in patients who are nonresponsive to aspirin.

Ticagrelor appears to be a viable alternative, albeit with the caveat of a requirement to adjust the aspirin dose. There is reduced efficacy of ticagrelor when combined with daily aspirin doses > 100 mg. Ticagrelor has been directly compared to clopidogrel in patients with ACS in the large-scale PLATO trial, with favorable results.[15] Successful platelet inhibition with ticagrelor has also been demonstrated in clopidogrel nonresponders.[16] Given the evidence, the use of antiplatelet pharmacogenetics appears to be ready for routine implementation.

CONCLUSION

The risks and rewards of limb salvage are enormous, and the attraction of a durable percutaneous intervention is obvious. Adjunctive medical therapy, including antiplatelet therapy, is essential for maintaining the initial technical success. Although atherothrombosis is a systemic disease,

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various arterial beds behave differently. Extrapolating the data on dual-antiplatelet therapy in coronary interventions to peripheral interventions commonly occurs, but there are very few high-quality, randomized data to justify this practice. Therefore, there is potential for decreased vessel patency and possible safety concerns. Personalizing antiplatelet therapy based on pharmacogenetics is intriguing, and studies demonstrating its cost effectiveness are needed. Although surrogate markers for the prothrombotic state can be measured, clinical endpoints of primary vessel patency and amputation-free survival should be the primary focus. In the meantime, extrapolation of data from coronary interventions will continue. Even without pharmacogenetic testing, individualizing the choice of antiplatelet therapy based on patient age, smoking history, traditional bleeding risks, and previous stroke should be the current standard of care. ■

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