ADVANCES IN HEMATOLOGY

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New Antiplatelet Agents: Are We Better Off Now Than We Were With Aspirin?

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H&O What is the role of antiplatelet agents, and how has it changed in recent years?

SC Antiplatelet drugs belong to the wider class of antithrombotic agents. Because platelets exert their major role in arterial rather than venous thrombogenesis, the use of antiplatelet drugs has been focused on preventing arterial thrombosis. More recently, some evidence has become available that antiplatelet drugs also are useful in certain types of venous thrombotic disease.

Antiplatelet agents are used successfully in both acute and chronic clinical settings. The goal is to counteract platelet aggregation at sites of arterial endothelial injury or unstable atherosclerotic plaques, thereby preventing arterial obstruction or occlusion and downstream microembolism into the systemic circulation. Thus, platelet function inhibition is an important weapon in life-threatening clinical conditions, such as strokes, peripheral arterial disease, and acute coronary syndromes (ACS)—especially acute myocardial infarction (AMI).

H&O What are the newest strategies for platelet inhibition?

SC The main strategies for inhibition of platelet function are blockade of the arachidonic acid cascade in the platelet membrane and inhibition of the adenosine diphosphate (ADP) aggregation pathway. Aspirin irreversibly inhibits cyclooxygenase 1 (COX-1), an enzyme responsible for the formation of thromboxane A_2—a potent inducer and amplifier of platelet activation and aggregation. Aspirin has become the reference and baseline antiplatelet drug. Other agents acting through the arachidonate pathway, such as direct inhibitors of thromboxane A_2 or inhibitors of the thromboxane receptors, have not achieved widespread clinical use. The other important pharmacologic strategy is blockade of the ADP pathway. Blockage of the ADP pathway can be accomplished by inhibition of phosphodiesterase 5 (eg, with dipyridamole). An even more efficient way to block the ADP pathway is direct inhibition of the P2Y12 platelet receptor (the ADP receptor), such as with thienopyridinic or cyclopentyl-triazolo-pyrimidinic compounds. (Thienopyridinic compounds include ticlopidine, clopidogrel [Plavix, Bristol-Myers Squibb and Sanofi], and prasugrel [Effient, Daiichi Sankyo and Lilly]); cyclopentyl-triazolo-pyrimidinic compounds include ticagrelor [Brilinta, AstraZeneca] and cangrelor.) Other mechanisms of novel or experimental antiplatelet drugs are also being studied.

H&O How do the safety and efficacy of ticagrelor compare with those of clopidogrel and aspirin?

SC Ticagrelor is a fast, potent, and reversible inhibitor of platelet function that induces blockade of the P2Y12 platelet ADP receptor. Although ticagrelor is not a prodrug, it undergoes transformation in the liver into an equally effective metabolite. A complementary action of ticagrelor

is the release of adenosine, which may contribute to its antiplatelet effect but also may cause side effects ,such as transient dyspnea, bradyarrhythmia, and gastrointestinal ailments. Unlike with clopidogrel, but similarly to prasugrel, the catabolism of ticagrelor is not influenced by the CYP2C19 cytochrome system. As a result, ticagrelor is virtually exempt from the genetically induced variability of response with clopidogrel.

The efficacy and safety of ticagrelor vs clopidogrel in ACS were evaluated in the PLATO (Platelet Inhibition and Patient Outcomes) trial, which was published in the *New England Journal of Medicine* in 2009. PLATO was a large, multicenter, randomized, double-blind study of more than 18,000 patients with ACS who presented with ST-segment elevation myocardial infarction (STEMI) or non-STEMI. Ticagrelor treatment was associated with significantly fewer recurrent ischemic events at 12 months compared with clopidogrel (hazard ratio, 0.84), with reductions in AMI, vascular mortality, and total mortality, but not in stroke.

Ticagrelor was, however, associated with a higher rate of major bleeding unrelated to coronary artery bypass procedures, including more episodes of intracranial bleeding. However, an overall net clinical benefit of ticagrelor vs clopidogrel was confirmed with the support of substudies in different groups of patients. The moderately higher bleeding risk with ticagrelor vs clopidogrel (and also the higher efficacy) could be related to the more uniform response of platelets to ticagrelor than to clopidogrel. Despite other concerns raised by some authors, I believe that the moderate increase in bleeding risk will not necessarily affect the clinical use of ticagrelor in ACS, provided that a careful evaluation of the individual bleeding risk is performed.

So far, no trial has directly compared the efficacy and safety of ticagrelor and prasugrel. As for aspirin, this drug is universally accepted as a baseline treatment in ACS, and a comparison trial in this clinical setting is unlikely.

H&O What do physicians need to know about combining aspirin with other antiplatelet agents or with warfarin?

SC Physicians should know that aspirin can also be used in combination with other antiplatelet agents. These combinations can be more effective than a single agent because each agent acts on a different pathway of platelet function. The combination of aspirin and dipyridamole was tested in clinical trials of patients with cerebrovascular disease, and was shown to be superior to aspirin alone in preventing a new stroke and other cardiovascular events, without an increase in episodes of major bleeding. More recently, the combination of aspirin and clopidogrel emerged as a potent antiplatelet strategy (superior to aspirin alone) in the treatment of ACS with or without angioplasty and stenting, and immediately after an AMI (this study was published in *Circulation* in 2003). The increase in major bleeding observed with aspirin/clopidogrel compared with aspirin alone was largely compensated for by a more effective prevention of thrombotic complications and cardiovascular events. Conversely, when aspirin/clopidogrel was compared with aspirin alone in the setting of chronic cerebrovascular or cardiovascular disease, the benefit of clopidogrel was smaller or even absent, and outweighed by the increase in major bleeding. Thus, a net clinical benefit is apparent only in acute settings in patients at high risk for cardiovascular events, and not in chronic conditions.

Because of the high occurrence (approximately 30%) of low response to clopidogrel due to genetic or acquired factors, drugs such as prasugrel and ticagrelor—which have a similar mechanism of action but less variability of response—are presently major candidates to substitute for clopidogrel in combination with aspirin. Combination therapy with warfarin (or its analogues) and low-dose aspirin is used in cases of mandatory medication with oral anticoagulants, such as in high-risk atrial fibrillation with concomitant coronary disease requiring antiplatelet therapy. In certain cases of ACS with coexisting high-risk atrial fibrillation, triple antithrombotic therapy with aspirin/clopidogrel/warfarin has also been attempted. This combination is highly hemorrhagenic; it can be used only in highly specialized centers, and individual thrombotic and hemorrhagic risks must be carefully controlled.

H&O What are the causes of variation in response to antiplatelet agents?

SC Interindividual variability in response to antiplatelet agents—especially aspirin and clopidogrel—has emerged as a relevant clinical problem, particularly in the high-risk clinical setting of ACS. Such variability is improperly referred to as "resistance" despite the fact that biologic resistance to aspirin and/or clopidogrel is only one of the possible mechanisms behind variability in response.

A number of studies have suggested that patients with biologically defined poor response to aspirin and/or clopidogrel have an increased risk of recurrent atherothrombotic events compared with patients who have a normal biologic platelet response. This correlation has little bearing on individual cases, however, given the variety of methods used to evaluate antiplatelet response and their still unsatisfactory standardization.

Variability of response depends first upon generic factors, such as poor adherence, inadequate absorption, drug interactions (eg, between aspirin and ibuprofen or between clopidogrel and some proton pump inhibitors and calcium channel blockers), inflammatory conditions

stimulating the inducible cyclooxygenase 2 (COX-2, which is relatively insensitive to aspirin), monocyte activation, and oxidative stress. Another factor that can induce apparent aspirin resistance is increased platelet turnover. In this condition, active thrombogenesis induces platelet consumption and consequent hyperproduction, with fast reappearance of young, nonaspirinated platelets.

In recent years, the pharmacogenetic mechanisms of antiplatelet resistance have attracted great interest. Regarding aspirin, the C50T polymorphism of the gene coding for COX-1 seems to be associated with reduced platelet response, but its clinical relevance has not been established. In contrast, gene-related factors are of utmost importance in regulating response to clopidogrel. The main mechanisms are related to polymorphisms of the gene for cytochrome P450, which regulates the rate of formation in the liver of the active metabolite of clopidogrel. Gene-induced low response to clopidogrel is clinically relevant for poor clinical outcomes, as shown by a number of clinical studies.

Moreover, the response to antiplatelet drugs can be lowered by multiple mechanisms in several morbid conditions, such as ACS, diabetes, AMI, stroke, obesity, high cholesterol, and hypertension. However, the importance of antiplatelet resistance in chronic settings (long-term antiplatelet prevention) in still unclear.

Poor biologic response to aspirin does not exceed 5% to 10% in healthy individuals, but reaches 25% in patients with diabetes. Clopidogrel resistance is particularly frequent in patients with ACS, reaching a prevalence of 25% to 30%, and is even more likely in ACS patients with type 2 diabetes.

Strategies intended to overcome low response to antiplatelet agents (especially clopidogrel) in ACS include treating any involved morbid conditions or risk factors, increasing the loading does of clopidogrel, and personalizing antiplatelet therapy by measuring platelet function or genetic testing. The most important strategy, however, is investigating and introducing new drugs that are less affected (or minimally affected) by the problem of antiplatelet drug resistance, such as prasugrel and ticagrelor.

H&O What is the best way to test the degree of platelet inhibition to assure safety and efficacy?

SC The main biologic assays that are available to test platelet function are classic light transmission aggregation, impedance whole blood aggregometry, determination of dehydrothromboxane B_2 in urine, the platelet function analyzer (PFA-100, Dade-Behring) system, a rapid platelet function assay (VerifyNow, Accumetrics), and the vasodilator-stimulated phosphoprotein (VASP) phosphorylation assay. The platelet function analyzer system and the dehydrothromboxane test are specific for aspirin only, the VASP assay is specific for clopidogrel and similar compounds, and aggregometry tests and the rapid platelet function assay can be used with any antiplatelet drug. The results of these different tests are not homogeneous, and therefore have a poor correlation with clinical outcomes.

The concept of residual platelet reactivity (RPR) during antiplatelet treatment is a helpful one. RPR results from several factors, such as the baseline degree of activation of platelets, the contribution of cellular types other than platelets (especially in inflammatory conditions with stimulation of COX-2), the production of proaggregating isoprostanes, and of course, the presence of genetic resistance. High RPR—preferably measured with aggregometry tests—has been found to be correlated with recurrent thrombotic events in ACS.

Two options have been proposed in order to personalize antiplatelet therapy: genotyping and phenotyping. It must be noted that measuring RPR (ie, phenotyping) gives a broader picture of the degree of platelet response. Genetic causes of poor platelet response explain only 12% of the response variability for clopidogrel, however, and whether they place a role in aspirin response is controversial. Genotyping for low platelet response, although important for clinical research in specialized centers, lost much of its practical value with the introduction of new inhibitors of P2Y12 platelet receptors (eg, prasugrel and ticagrelor), which are little affected by gene polymorphism-induced low response.

H&O How does the disease state affect what agents are selected?

SC Antiplatelet therapy is routinely used in patients who have suffered a noncardioembolic, ischemic stroke, although its efficacy is less pronounced than in patients with ACS. This reduction in response is probably due to the multiple mechanisms involved in ischemic stroke. Low-dose aspirin, the baseline and reference drug, reduces the risk of recurrent stroke by 15% to 20%. No further benefits have been obtained by using higher doses of aspirin. Clopidogrel has been shown be marginally more effective than aspirin. Combination therapy with aspirin and dipyridamole has been shown to be more effective than aspirin alone, whereas the combination of aspirin and clopidogrel is not recommended because of excess bleeding. Substantial equivalence has been demonstrated for aspirin/dipyridamole and clopidogrel alone. Prasugrel and ticagrelor have not been studied in this specific setting, and may be associated with an increased risk of intracranial bleeding. In cardioembolic stroke, the use of aspirin is confined to low-risk patients; however, one of the new oral anticoagulants, apixaban (Eliquis, Bristol-Myers Squibb), was superior to aspirin in a trial of patients who were potential candidates for aspirin therapy.

A large number of healthy people take aspirin every day in an effort to prevent cardiovascular events, even though they have no history of such events. Although people who take daily aspirin are less likely to have a nonfatal myocardial infarction, this benefit should be evaluated in context. People who take daily aspirin for primary prevention are no less likely to have a fatal or nonfatal cardiovascular event, and are more likely to have a stroke mainly caused by intracranial bleeding.

A number of major trials and related meta-analyses have in fact shown that the benefit of low-dose aspirin in primary prevention is modest. Indeed, even in subjects with diabetes, hypertension, or asymptomatic peripheral arterial disease, low-dose aspirin confers little benefit in patients without a history of major cardiovascular events.

Although daily aspirin saves 10 to 20 lives per 1000 patients per year for secondary prevention of cardiovascular events, it saves just 0.6 to 0.8 lives per 1000 patients per year for primary prevention. Aspirin causes 0.3 to 0.5 major bleeds per 1000 patients per year. As a result, low-dose aspirin should not be recommended for generalized primary prevention of cardiovascular events.

However, the story of aspirin in primary prevention is not over. Aspirin does have a small effect on total mortality—an approximate 6% reduction in relative risk—that has repeatedly been observed in various primary prevention trials. Most of this effect is from reductions in nonvascular deaths, especially cancer deaths. I will not get into the possible mechanisms of this effect here, but I would like to emphasize that this reduction in cancer mortality appears only after 3 years of treatment, peaks at 5 years of treatment, and may persist for 20 years after treatment ends. Conversely, the cardiovascular effects and the bleeding risk decline after 3 to 5 years.

The absolute size of the reduction in cancer mortality is small: just 0.3 to 0.4 deaths avoided for every 1000 patients per year who take the drug. It is statistically significant, however, which has renewed researchers' and clinicians' interest in the use of aspirin for primary prevention. Until more is known, a reasonable suggestion is to recommend low-dose primary aspirin prophylaxis for people whose risk of a cardiovascular event is at least 20 events per 1000 patients per year and who have a low hemorrhagic risk. Furthermore, aspirin administration should be protracted to at least 5 years to realize the benefit in cancer mortality, especially if the patient is at increased risk for colorectal cancer.

H&O What are the most promising drugs that are being investigated for platelet inhibition?

SC The new agents that are being investigated are: triflusal or other COX-1 pathway inhibitors; cangrelor and elinogrel, both $P2Y_{12}$ inhibitors; cilostazol (Pletal, Otsuka), a phosphodiesterase 3 inhibitor; vorapaxar and atopaxar, both inhibitors of thrombin-induced platelet aggregation; sarpogrelate, which blocks serotonin-induced platelet aggregation; and some new agents inhibiting the von Willebrand factor prothrombotic effect. Cilostazol is the only one of these agents to have been introduced in clinical use.

Suggested Readings

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