ADVANCES IN HEMATOLOGY

Current Developments in the Management of Hematologic Disorders

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Future Directions for Antiplatelet Drugs

Sergio Coccheri, MD
Professor of Cardiovascular Medicine
University of Bologna
Bologna, Italy

H&O What are some of the current options in antiplatelet therapy?

SC The most common options for antiplatelet therapy are aspirin, a cyclooxygenase-1 inhibitor, and clopidogrel (Plavix, Bristol-Myers Squibb/Sanofi-Aventis), which is an adenosine diphosphate (ADP) receptor blocker. These drugs are used as single agents and in combinations, such as aspirin plus clopidogrel, and (mostly in Europe) aspirin with dipyridamole, a nonselective phosphodiesterase inhibitor. As single agents, aspirin and clopidogrel reduce major cardiovascular events in patients with chronic conditions by approximately 25%, with clopidogrel having marginal superiority over aspirin. In patients with high-risk conditions, such as acute coronary syndromes, the combination of aspirin plus clopidogrel can reduce the risk of major cardiovascular events by 40% or more.

Major adverse events associated with aspirin include intracranial and extracranial bleeding, mainly gastrointestinal. Elderly patients as well as those with diabetes are at greater risk of adverse events. The combination of aspirin with clopidogrel further increases the bleeding risk. Therefore, antiplatelets are mainly recommended as secondary prevention in patients with a medium to high risk of cardiovascular events, rather than as primary prevention in patients at low risk. The combination of aspirin plus clopidogrel is especially indicated in patients who have acute coronary syndromes, regardless of whether the patient is undergoing percutaneous coronary intervention or has received a coronary stent. In a recent study of cerebrovascular patients, single-agent clopidogrel was found to be equivalent to combination therapy with aspirin plus dipyridamole, in terms of both efficacy and safety.

H&O Is there variability in patient response to antiplatelet therapy?

SC Responses to aspirin and clopidogrel are variable. For aspirin, the main causes for varied patient response include noncompliance with treatment, increased platelet turnover, and, to a lesser extent, cyclooxygenase-1 polymorphisms. Clinical conditions, such as diabetes, obesity, and metabolic syndrome, also play a role.

For clopidogrel, the main cause of a decreased response is considered to be the presence of polymorphisms in the genes of the liver cytochrome system (loss-of-function polymorphisms). Another reported cause is pharmacologic interaction with other drugs, including some (not all) proton pump inhibitors and calcium channel blockers. However, the clinical relevance of these interactions is still being debated and has even recently been denied. Physiologic and clinical conditions such as age, diabetes, and coronary artery disease can also influence response to clopidogrel. Ethnic differences have been noted, and some of the previously mentioned polymorphisms are less frequent in Asian populations.

Adjustment of the clopidogrel dose—an increase in the loading dose and/or the maintenance dose—has been successfully applied in patients with acute coronary syndrome. It has become more common to increase the loading dose of clopidogrel.

H&O Is response variability or resistance a concern in patients receiving antiplatelet therapy?

SC Response variability is considered a concern, especially in patients who are at higher risk of developing a thrombosis, such as those with coronary syndrome and/or who have coronary stents, particularly drug-eluting stents. The role of resistance to antiplatelet drugs in chronic conditions has received little investigation.

H&O Why are new antiplatelet agents needed?

SC New antiplatelet agents are needed for several reasons. First, drugs with more potency may be associated with better clinical outcomes. Second, in certain patient subgroups, such as the elderly, the bleeding risk associated with the currently available agents is not negligible. Third, the current drugs are associated with variable responses as mentioned, and some patients may develop resistance. In order to overcome this variability of response to some antiplatelet drugs, we need to either potentiate them with the use of adjuvant drugs or develop more potent agents.

H&O What are the newer antiplatelet agents?

SC Prasugrel (Effient, Daiichi Sankyo, Inc/Eli Lilly) is an ADP receptor blocker that can be used in patients with acute coronary syndrome at a loading dose of 60 mg and a maintenance dose of 10 mg. It is a thienopyridine, analogous to clopidogrel. It was shown to be more active than clopidogrel in patients with coronary syndrome and diabetes, who are more prone to resistance to clopidogrel. Prasugrel is not affected by cytochrome polymorphisms, and it is therefore active in patients who are resistant to clopidogrel. However, prasugrel may be associated with higher bleeding in the elderly—in fact, there is a warning not to use it in patients who are older than 75 years. The general profile of prasugrel is, however, sound.

Another very promising ADP receptor blocker is ticagrelor (Brilinta, AstraZeneca), which has excellent efficacy and safety. Ticagrelor is effective regardless of the presence of diabetes.

Another possible approach to antiplatelet therapy involves the reappraisal of a neglected class of drugs, the direct thromboxane inhibitors. In the DAVID (Drug Evaluation in Atherosclerotic Vascular Disease in Diabetics) study, my colleagues and I examined the use of picotamide (Novartis). In terms of mortality, picotamide was more effective than aspirin in diabetic patients with peripheral arterial disease.

There are a number of new drugs that are not yet available but are being investigated in human pharmacology studies. Vorapaxar (Merck) is the first inhibitor of thrombin-induced platelet aggregation, an important mechanism of action in vivo hitherto neglected in clinical pharmacology. Another drug is DZ-697b (Daiichi Sankyo), an inhibitor of ristocetin-induced platelet aggregation.

New antiplatelet agents are likely to benefit patients with acute or high-risk atherothrombotic conditions, and, of course, patients who are less reactive to current antiplatelet drugs.

H&O Is there a personalized medicine approach in antiplatelet therapy?

SC Personalized antiplatelet therapy has been successfully used in acute coronary syndrome, with favorable effects on major cardiovascular events, including stent thrombosis. This personalized approach is based on measurement of platelet reactivity, both at baseline and during treatment, or on genotyping for the involved polymorphisms. The laboratory methods used for measuring response to antiplatelet agents ex vivo have not yet been fully standardized. I think more experience is still necessary for these approaches to be generalized in clinical practice.

H&O What should hematologists and oncologists keep in mind when prescribing antiplatelet agents?

SC Hematologists and oncologists are confronted with conditions in which thrombotic risk and hemorrhagic risk are often simultaneously increased. I therefore believe that the risk/benefit ratio is an especially important matter for hematologists and oncologists.

Antiplatelet drugs should be used with care in patients with myeloproliferative syndromes, especially those with high platelet counts, including hemorrhagic thrombocythemia. Although these disorders are mostly hemorrhagic, they may have a high associated thrombotic tendency.

H&O What are the future directions in antiplatelet therapy?

SC New studies are necessary to better define the role of antiplatelet agents in patients who are also being treated with other drugs, such as statins, drugs used for diabetes, and—especially—drugs used for hypertension. Little is known about the interaction between antiplatelet therapy and these drugs. Another direction of clinical research should be to better define those patients who would benefit from primary prevention. The validity of personalized antiplatelet therapy should be proven, although first there must be standardization of the methodology used to measure platelet reactivity.

Suggested Readings

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