

ADVANCES IN HEMATOLOGY

Current Developments in the Management of Hematologic Disorders

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New Antiplatelet Agents

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H&O What are the currently available antiplatelet agents? What are the unmet needs?

DA Antiplatelet agents are commonly used for the prevention of atherothrombotic events. There are numerous antiplatelet agents currently available, but there are 3 main categories that are approved for secondary prevention of ischemic events: aspirin (COX-1 inhibitor); the adenosine diphosphate (ADP) P2Y₁₂ receptor antagonists, which includes ticlopidine (Ticlid, Roche), clopidogrel (Plavix, Sanofi-Aventis/Bristol-Myers Squibb), and most recently, prasugrel (Effient, Eli-Lilly/Daiichi-Sankyo); and the IV glycoprotein 2b/3a receptor antagonists.

In clinical practice, the current standard of care for high risk patients—patients with acute coronary syndromes (ACS) and/or those undergoing percutaneous coronary interventions (PCI)—is represented by the long-term combined use of aspirin and clopidogrel. The IV glycoprotein 2b/3a receptor antagonists are reserved in the acute setting for high risk patients (eg, with positive cardiac markers) undergoing PCI.

It is important to note that clopidogrel, a second generation thienopyridine, has substantially replaced ticlopidine, a first generation thienopyridine, in clinical practice due to its better safety profile. In 2008, Dr. Bertrand and colleagues published the results of the CLASSICS (CLOpidogrel ASpirin Stent International Cooperative Study) trial, which showed the superiority of clopidogrel plus aspirin in safety and tolerability to that of ticlopidine plus aspirin ($P=.005$).¹ The side effects for ticlopidine

mainly include rash, gastrointestinal disturbances, but most importantly bone marrow suppression.

There are several trials that have clearly shown the benefit of dual antiplatelet therapy with the combination of aspirin and clopidogrel. In the CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Events) trial, 12,562 patients with non-ST-segment elevation myocardial infarction ACS were given either clopidogrel and aspirin or placebo; results showed that the relative risk reduction was 20%, in favor of the combination therapy.² Many other trials performed in high risk settings including patients undergoing PCI, such as the CREDO (Clopidogrel for the Reduction of Events During Observation) trial, and those with ST-segment elevation myocardial infarction, such as the CLARITY (Clopidogrel as Adjunctive Reperfusion Therapy) and COMMIT (Clopidogrel and Metoprolol in Myocardial Infarction Trial) trials, confirmed the clinical benefit associated with the adjunctive use of clopidogrel in addition to aspirin.³⁻⁵ However, despite this more aggressive antiplatelet treatment strategy, there is still a considerable number of patients that continue to have recurrent ischemic events.

One of the reasons why recurrence of ischemic events is believed to continue, despite dual antiplatelet therapy, is the fact that there is variability in the effects of this treatment regimen.⁶ This underscores that there are some patients who have suboptimal outcomes while being on aspirin and clopidogrel therapy, warranting the need for newer antiplatelet agents.

H&O What are the possible reasons for variability in patient outcomes?

DA There are multiple mechanisms leading to the variability in antiplatelet drug response, including clinical, cellular, and genetic factors. Clinical factors include poor compliance and comorbidities such as diabetes, ACS, and obesity. Cellular factors include accelerated platelet turnover, increased platelet exposure to ADP, decreased CYP activity, and upregulation of purinergic and/or non-purinergic signaling.

There are several identified genetic factors, but the most important of these is represented by genetic polymorphisms of the CYP enzymes, notably the 2C19 isotype of the cytochrome P450 gene.

H&O What are some of the newer agents that are being investigated today, and how are they different from the older or current agents?

P2Y₁₂ Receptor Antagonists

Prasugrel

Prasugrel (Effient, Eli Lilly/Daiichi Sankyo) is a third generation thienopyridine. Like clopidogrel, it is an irreversible ADP P2Y₁₂ receptor antagonist. It has the property of being more potent than clopidogrel and is also associated with less response variability. Whereas a significant portion of clopidogrel is deactivated by esterases in the early stages of its metabolism, prasugrel is rapidly converted to its active metabolite in a 2-step process, producing higher concentrations of active metabolite than clopidogrel.

Prasugrel has been studied in a large phase III clinical trial called TRITON-TIMI 38 (TRial to assess Improvement in Therapeutic Outcomes by optimizing platelet Inhibition with Prasugrel Thrombolysis in Myocardial Infarction), which showed better clinical outcomes compared to clopidogrel.⁷ In the study, 13,608 patients who were moderate- to high-risk patients with ACS undergoing PCI were randomized to receive either prasugrel (60 mg loading dose followed by a 10 mg/day maintenance dose) or standard-dose clopidogrel (300 mg loading dose followed by a 75 mg/day maintenance dose). The primary efficacy endpoint (composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke) was reached by 9.9% in the prasugrel group compared to 12.1% in the clopidogrel group, showing a 19% relative risk reduction in favor of prasugrel ($P=.0004$). This was mainly driven by a reduction in myocardial infarction.

However, there was also increased risk of bleeding; 2.4% of the prasugrel group experienced major bleeding compared with 1.8% of the clopidogrel group ($P=.03$). Despite the increased bleeding risk, the pre-specified net clinical benefit analysis, defined as the composite of

efficacy and bleeding endpoints, still favored prasugrel (13.9% of patients in the clopidogrel group vs 12.2% in the prasugrel group; $P=.004$). Patients with diabetes mellitus or those with ST elevation myocardial infarction showed the best clinical benefit in the TRITON-TIMI 38 trial, without any increased risk of bleeding. In contrast, there was increased harm in patients with a history of stroke or transient ischemic attack. Less clinical efficacy was demonstrated in patients who were older than 75 years and those who weighed less than 60 kg. For the latter, a dose-reduction has been suggested.

Primarily based on the data of this trial, the U.S. Food and Drug Administration (FDA) recently approved prasugrel for high risk ACS patients managed with PCI.

Ticagrelor

Formerly known as AZD6140, ticagrelor (Brilinta, Astra-Zeneca) is the first oral, direct, and reversible P2Y₁₂ inhibitor, and it has more potent effects and less variability than clopidogrel. Unlike thienopyridines, which are irreversible agents that are prodrugs, meaning they are metabolized in the liver and give origin to an active metabolite which blocks the P2Y₁₂ receptor, ticagrelor acts directly on the P2Y₁₂ receptor. Metabolism is not required to exert the antiplatelet effects of ticagrelor, and its effects are reversible. Ticagrelor yields a level of platelet inhibition significantly greater than that achieved by clopidogrel.

Ticagrelor was investigated in a large-scale phase III clinical trial called PLATO (Platelet Inhibition and Patient Outcomes). In this trial, ticagrelor (180 mg loading dose, 90 mg twice daily thereafter) was compared with clopidogrel (300–600 mg loading dose, 75 mg daily thereafter) for the prevention of cardiovascular events in 18,624 patients admitted with an ACS, irrespective of treatment modality (PCI, coronary artery bypass grafting surgery [CABG], or medical management).⁸ At 12 months, there was a 16% relative risk reduction in the primary endpoint (composite of cardiovascular death, myocardial infarction, or stroke), which occurred in 9.8% of patients receiving ticagrelor compared with 11.7% of those receiving clopidogrel ($P<.001$). This was driven by a reduction in myocardial infarction and death. No significant difference in the rates of study-defined major bleeding was found between the ticagrelor and clopidogrel groups (11.6% and 11.2%, respectively; $P=.43$), but ticagrelor was associated with a higher rate of nonprocedure-related major bleeding.

Cangrelor

Cangrelor is the first IV P2Y₁₂ receptor antagonist and also has a reversible effect. Unlike oral P2Y₁₂ inhibitors, cangrelor has a rapid onset and offset of action and a half-life of a few minutes. Normal platelet recovery is said to occur within 60 minutes. Depending on the dose, cangrelor is

said to be able to potentially achieve 100% platelet inhibition. It does not require the renal or hepatic mechanisms of action or clearance. Cangrelor, which was being developed by the Medicines Company, was studied in 2 large phase III trials—CHAMPION (Cangrelor vs. Standard Therapy to Achieve Optimal Management of Platelet Inhibition—Percutaneous Coronary Intervention)-PCI and CHAMPION-PLATFORM. However, both trials were halted before their conclusion due to demonstrational lack of efficacy; details of the trial will be known by the end of 2009. Cangrelor is currently being evaluated as a bridging strategy in patients undergoing CABG.

Elinogrel

Elinogrel is the first P2Y₁₂ receptor antagonist that is available in both an oral and IV formulation. It is a reversible agent and appears to have more potent effects than clopidogrel. Elinogrel, developed by Portola Pharmaceuticals, is currently in a phase II safety and efficacy study in non-urgent PCI (INNOVATE-PCI). Initiated in December 2008, the 800-patient trial is investigating the drug's clinical efficacy, biologic activity, tolerability, and safety, and involves a head-to-head assessment of elinogrel against clopidogrel.

Protease-activated Receptors-1 Receptor Antagonists

There is also another category, which is the Protease-activated receptors-1 (PAR-1) receptor antagonists, or thrombin receptor antagonists. PAR-1 is apparently a high-affinity receptor for platelet activation at low thrombin concentrations.

SCH 530348

SCH 530348 is a PAR-1 antagonist that is being studied in the most advanced clinical investigation. Manufactured by Schering-Plough, this agent is being evaluated in addition to aspirin and clopidogrel—basically, in addition to the standard of care.

The TRA-PCI (Thrombin Receptor Antagonist—Percutaneous Coronary Intervention) trial, a multinational, randomized, double-blind, placebo-controlled, dose-ranging phase II study that enrolled 1,030 patients who were 45 years or older with coronary artery disease scheduled for PCI, met its primary endpoints of safety and tolerability and showed no increase in major and/or minor bleeding.⁹ The study reported a nonstatistically significant 46% reduction in cardiovascular events compared to standard of care at the highest drug dose tested in the study.

Based on the results of TRA-PCI, 2 large-scale, randomized, placebo-controlled, phase III trials are now under way in approximately 30 countries to test the efficacy of SCH 530348. In the first, Thrombin Recep-

tor Antagonist Clinical Event Reduction (TRA-CER), SCH 530348 will be evaluated in approximately 10,000 patients with ACS with 1 year or more of follow-up. The other trial, Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events (TRA 2P-TIMI 50), will include approximately 19,500 patients with a history of myocardial infarction, ischemic stroke, or peripheral arterial disease. All patients in both studies will receive standard medical care, including aspirin plus clopidogrel.

E5555

Manufactured by Eisai, E5555 is the other thrombin receptor antagonist of interest. This agent is currently under investigation in phase II clinical trials that are part of the LANCELOT (Lessons from Antagonizing the Cellular Effects of Thrombin) clinical trials.

H&O Do these newer agents have different activity for different vascular events?

DA P2Y₁₂ receptor antagonists are being evaluated for their use in patients with coronary disease. Phase III investigations with prasugrel, cangrelor, and ticagrelor were tested in high-risk ACS patients. Elinogrel is still in its preliminary stages of investigation and is currently being studied in elective PCI. These agents are all evaluated in combination with aspirin because it is the combination of aspirin with a P2Y₁₂ inhibitor that represents the standard of care in ACS/PCI patients.

PAR-1 antagonists are being evaluated not only in patients with coronary artery disease but also in patients with peripheral arterial disease and cerebral vascular disease. These agents are studied in addition to standard of care, which include aspirin and clopidogrel.

H&O Does age or ethnicity cause variability with the effects of these newer agents?

DA With prasugrel, we know that patients who did not achieve a clinical benefit from the drug were those who were older than 75 years and those who weighed below 60 kilograms, suggesting the use of a lower dose, which is currently under clinical investigation. Patients with a known cerebrovascular disease had increased harm. Different from clopidogrel, prasugrel is not subject to genetic modulation from genotypes of the cytochrome P450 system in the liver. For the other newer agents, we will learn once trial data will be available.

We do know that historically, older patients have a lower response to antiplatelet agents. However, we do not yet know a single reason why this is, and it is speculated that multiple mechanisms are involved.

With regard to ethnicity, the one thing we do know is that Asian populations have shown to have different responses to antiplatelet therapy. Although Asian populations have a greater tendency to bleed with antiplatelet agents, most recent data show that they have a higher prevalence of the variant alleles for the 2C19 polymorphism associated with the reduced clopidogrel response. African-American patients have shown to have higher thrombogenicity. As mentioned above, there is still limited experience with the newer agents to make any definitive statements on the impact of age or ethnicity.

H&O When prescribing these medications, are there any cautions that clinicians need to keep in mind?

DA Definitely. Especially with the introduction of these newer agents that are more potent, clinicians need to be reminded to prescribe only in scenarios that were tested in clinical trials and according to labeling approved by the FDA for their clinical use. It is important to underscore that these new agents are very potent, and while they can be of important clinical benefit in some patients (such as the high risk patients), they can be harmful (eg, increased bleeding) in others.

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