Novel Antiplatelets in Development

A CME-certified monograph in the Coronary Invaders series at www.coronaryinvaders.com

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A CME-certified Monograph

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Learning Objectives
After participating in this activity, learners will be able to:

• Recognize the clinical limitations of available antiplatelet drugs
• Differentiate the pharmacologic properties of novel antiplatelets from currently available agents
• Evaluate recent data advances on the safety and efficacy of antiplatelet agents under development

Program Overview
Because platelets perform a key role in both thrombus and atherosclerotic plaque formation, antiplatelet therapy is critical treatment for managing patients with acute coronary syndromes (ACS). Limitations to current therapeutic options include modest levels of platelet inhibition, variability in response, slow rates of onset, and continued thrombotic and atherosclerotic events despite treatment. Participants will learn and evaluate developments in new therapeutic targets on the platelet, as well as agents under investigation, and be able to apply this knowledge toward improving the care of patients with ACS.

Target Audience
This educational activity has been developed for physicians and other health care providers in primary care, cardiology, and emergency medicine who manage ischemic risk in patients with ACS in the acute, periprocedural, and chronic settings.

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He has received research grant support from Accumetrics, Amgen, AstraZeneca, Bayer Healthcare, Beckman Coulter, Bristol-Myers Squibb, CV Therapeutics, Eli Lilly and Company, GlaxoSmithKline, Inotek Pharmaceuticals, Integrated Therapeutics, Merck and Company, Merck/Schering-Plough Joint Venture, Millennium Pharmaceuticals, Nanosphere, Novartis Pharmaceuticals, Nuvelo, Pfizer, Roche Diagnostics, sanofi-aventis, Sanofi-Synthelabo, Singulex, and Schering-Plough; received honoraria from Bayer Diagnostics, Beckman Coulter, CV Therapeutics, Dade-Behring, sanofi-aventis, and Roche Diagnostics. He has served on advisory boards for Beckman Coulter, Critical Diagnostics, Genentech, and OrthoClinical Diagnostics, and has served as a consultant to GlaxoSmithKline and sanofi-aventis.

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• Is evaluated for its effectiveness in meeting identified educational needs
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MODULE
The Role of Platelet Activation in the Pathogenesis of Atherothrombosis

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Variable Response to Currently Available Antiplatelet Agents and the Potential Impact on Clinical Outcomes

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Novel Antiplatelets in Development

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An Introduction to Antiplatelet Agents: Ideals, Limitations, and Receptor Targets
Platelets play a key role in both thrombus and atherosclerotic plaque formation, so antiplatelet therapy is crucial for managing patients with acute coronary syndromes (ACS) and coronary artery disease (CAD), as well as those undergoing percutaneous coronary intervention (PCI). Standard antiplatelet treatment includes aspirin plus clopidogrel, but there are a number of limitations to current therapeutic options. Some patients continue to experience thrombotic and atherosclerotic events during treatment, underlining the need for improved antiplatelet treatments.

Ideally, an antiplatelet agent would
- have rapid onset,
- be easy to administer,
- prove predictably effective in most patient groups,
- have a short duration of action (so that it could be easily reversed if the patient needed urgent surgery), and
- diminish platelet aggregation effectively without promoting bleeding.

Unfortunately, the antiplatelet agents currently in use—aspirin and clopidogrel—fall short of ideal. These agents provide only modest levels of platelet inhibition and there is a good deal of variability in response.\(^1,2\) In addition, clopidogrel has a slow onset of action, so it may not be active when most needed. Also, because it binds irreversibly and promotes bleeding, clopidogrel presents problems if cardiac surgery is needed.

Platelets undergo a multistep activation process that requires an initiating factor—often adenosine diphosphate (ADP)—and subsequent amplification through binding to 3 main receptor types: the P2Y\(_{12}\) ADP receptor, the thrombin protease-activated receptor (PAR), and the thromboxane A\(_2\)/prostaglandin H\(_2\) (TH) receptor (Figure 1). We will explore each of these receptor types and the novel antiplatelet agents designed to inhibit their action. These novel agents show promise for providing more effective, less variable, and safer antiplatelet action than aspirin and clopidogrel.

P2Y\(_{12}\) Antagonists
P2Y\(_{12}\) receptors amplify and sustain platelet activation in response to initiating ADP; activation of these receptors is necessary for platelet aggregation.\(^3\) The thienopyridines ticlopidine and clopidogrel are P2Y\(_{12}\) receptor antagonists and there are several promising P2Y\(_{12}\) antagonists in development.

Prasugrel
Prasugrel, like clopidogrel, is an oral, irreversible thienopyridine P2Y\(_{12}\) receptor antagonist. Also like clopidogrel, prasugrel is a prodrug that must be metabolized to its pharmacologically active form. However, the 2 prodrugs are metabolized through different pathways, resulting in significant differences in onset of action.\(^4\) In addition to its effects on the P2Y\(_{12}\) receptor, the active metabolite of prasugrel may also delay thrombin generation and clot development in whole blood.\(^5\)
A crossover ex vivo study compared the rate of onset, extent, and variability of platelet inhibition with loading doses of clopidogrel and prasugrel. Platelet aggregation was significantly better inhibited with prasugrel than clopidogrel for the first 24 hours (P < .01) and response was more consistent as well (P < .01) at lower plasma concentrations of active metabolite. A second ex vivo study confirmed these findings: prasugrel was more effective than clopidogrel in changing maximal platelet aggregation and inhibiting platelet aggregation 2–24 hours after a loading dose (P < .001). In addition, although 17–43% of subjects were poor responders to clopidogrel, there were no poor responders to prasugrel.

In the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction 38 (TRITON–TIMI 38) clinical trial, clinicians compared prasugrel to clopidogrel in 13,608 patients with moderate-to-high-risk ACS scheduled for PCI. Prasugrel was used at a 60 mg loading dose and a 10 mg maintenance dose; clopidogrel was used at a 300 mg loading dose and a 75 mg maintenance dose. Investigators followed patients for 6–15 months. They found that prasugrel significantly reduced the risk of ischemic events, the primary efficacy endpoint (P < .001). However, this was at the cost of increased risk of TIMI major bleeding (non–coronary-artery bypass grafting [CABG]), the primary safety endpoint (P < .03). Net clinical benefit (balancing ischemic events and bleeding) was superior with prasugrel, except in those at particularly high risk of bleeding.

Since, in clinical practice, clopidogrel is often used at higher-than-approved doses, the Prasugrel in Comparison to Clopidogrel for Inhibition of Platelet Activation and Aggregation–Thrombolysis in Myocardial Infarction 44 (PRINCIPLE-TIMI 44) trial compared the effects of prasugrel with high-dose clopidogrel in 201 patients undergoing cardiac catheterization before scheduled PCI. Researchers compared a 60 mg loading dose of prasugrel to a 600 mg loading dose of clopidogrel, and those who underwent PCI entered a 28-day crossover comparison of maintenance doses—10 mg/day of prasugrel versus 150 mg/day of clopidogrel, 14 days on each drug. The primary endpoint of the loading phase, inhibition of platelet aggregation (IPA) at 6 hours, was significantly higher with prasugrel (74.8 ± 13.0%) than clopidogrel (31.8 ± 21.1%; P < .0001). Similarly, the primary endpoint of the maintenance phase, IPA after 14 days of treatment, was higher in prasugrel (61.3 ± 17.8%) compared to clopidogrel (46.1 ± 21.3%; P < .0001). Although there was more bleeding in the prasugrel group, the difference did not reach significance in this small study. These results demonstrate more potent antiplatelet effects with prasugrel than with high-dose clopidogrel.

**AZD6140 (ticagrelor)**

Unlike the thienopyridines clopidogrel and prasugrel, AZD6140 is a reversible P2Y12 receptor antagonist that almost completely inhibits ADP-induced platelet aggregation ex vivo. AZD6140 does not need conversion to an active form, and there is less response variability than seen with clopidogrel. A single oral dose was completely effective in inhibiting platelet aggregation 2 hours post-dose in normal subjects, with a plasma half-life of approximately 12 hours.

A double-blind, randomized trial compared different doses of AZD6140 (50, 100, and 200 mg twice daily or 400 mg once daily) with clopidogrel (75 mg daily) in 200 patients with CAD. Initial dose peak IPA of 80–95% was seen 2–4 hours post-dose with AZD6140 at the 3 higher doses but was less than 20% for clopidogrel over the first 12 hours. At steady-state, the 3 higher doses of AZD6140 yielded a peak IPA of 85–95% and clopidogrel yielded a peak IPA of approximately 60%. AZD6140 was generally well-tolerated, with only one major bleeding event at the 400 mg dose.

The Double-Blind, Double-Dummy, Parallel Group Randomized Dose Confirmation and Feasibility Study of AZD6140 + Acetylsalicylic Acid (ASA) Compared with Clopidogrel + ASA in Patients with Non-ST Segment Elevation Acute Coronary Syndromes (DISPERSE-2) trial assessed the safety, tolerability, and initial efficacy of AZD6140 compared with clopidogrel in 990 patients with non-ST elevation ACS (NSTE-ACS). All patients received aspirin and were randomized to receive AZD6140 90 or 180 mg twice daily or clopidogrel 300 mg loading dose plus 75 mg once daily for up to 12 weeks.

There were no significant differences in the primary endpoint, a composite of major and minor bleeding at 4 weeks (9.8% in AZD6140 90 mg, 8.0% in AZD6140 180 mg, and 8.1% in clopidogrel). An increase in minor bleeding over the entire study period emerged in the higher dose AZD6140 group compared with clopidogrel.
bolus of cangrelor plus a 1-hour 4 mcg/kg infusion followed by a 600 mg loading dose of clopidogrel. Although initiating clopidogrel immediately after terminating cangrelor infusion yielded the expected results, platelet inhibition was significantly less efficacious when both P2Y12 receptor antagonists were given simultaneously.  

A Phase III trial of cangrelor compared with clopidogrel in 9000 patients undergoing PCI for ACS is underway.  

Thrombin Receptor Antagonists  
Thrombin is the most potent known activator of platelets. The protease activated receptor 1 (PAR1) appears to be the major human platelet receptor through which thrombin promotes platelet activation. Two oral PAR1 antagonists or thrombin receptor antagonists (TRAs) are currently in Phase II or Phase III investigation as antplatelet agents, SCH 530348 and E5555. By interacting with PAR1, these agents selectively inhibit the cellular effects of thrombin without blocking thrombin-mediated generation of fibrin.  

SCH 530348  
The first drug in the TRA class, SCH 530348, does not appear to affect the collagen pathway—an important pathway for normal hemostasis during tissue injury—and therefore has potential to inhibit thrombosis without a meaningful increase in bleeding. Results of a Phase II trial support this hypothesis.  

The Thrombin Receptor Antagonist-Percutaneous Coronary Intervention (TRA-PCI) trial was a randomized, double-blind, placebo-controlled study designed to assess the safety and tolerability of SCH 530348 in 1030 patients undergoing nonemergent PCI or catheterization with possible PCI.  

Physicians randomized patients to 3 loading doses of SCH 530348 (10, 20, or 40 mg) or placebo prior to catheterization. All patients received aspirin, clopidogrel, and either heparin or bivalirudin. The 573 patients who underwent PCI were further randomized to receive maintenance SCH 530348 (0.5, 1.0, or 2.5 mg daily), if they had received loading SCH 530348 or to placebo for 60 days. The primary outcome was TIMI major plus minor bleeding at 60 days in patients undergoing PCI.  

Although bleeding was less in the groups receiving SCH 530348 than the placebo group (2.8% versus 3.3%) this difference was not significant. The study, not
powered to establish efficacy, showed a nonsignificant trend toward fewer major cardiac events, particularly death or MI, in the group receiving SCH 530348 (4.5%) than the group receiving placebo (7.3%).

Two Phase III trials are now underway to determine efficacy of SCH 530348. The Thrombin Receptor Antagonist for Clinical Events Reduction (TRACER) trial aims to enroll 10,000 patients with non-ST-segment elevation acute coronary syndrome (NSTE-ACS), and the Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events (TRA 2P-TIMI 50) secondary prevention trial looks to examine 19,500 patients with atherosclerosis.

**E5555**

In preclinical studies, E5555 inhibited thrombin-induced platelet aggregation, intimal thickening, and vascular smooth muscle proliferation without changing bleeding time.

Two randomized, controlled, double blind Phase II trials are underway to assess the safety and tolerability of E5555—one with an expected enrollment of 600 patients with coronary artery disease and the other with an expected enrollment of 600 patients with NSTE-ACS.

**Thromboxane A2/Prostaglandin H₂ (TH) Receptor Antagonists**

Aspirin, the most widely-used antiplatelet agent, inhibits production of thromboxane A₂ (TxA₂) to reduce the amount of this potent agonist available to bind to the TH receptor. However, there are other TH receptor agonists not affected by aspirin, so aspirin only partially inhibits platelet activation and thrombus formation. Although researchers have investigated a number of potential TH receptor antagonists, the only one to date that looks promising as a clinical agent is terutroban, formerly known as S18886.

Preclinical studies found that terutroban rapidly inhibits platelet-dependent thrombosis in vivo, as well as platelet aggregation and stent-induced thrombosis ex vivo. Moreover, a Phase II study in patients with peripheral artery disease found that this oral drug acts rapidly, with maximal aggregation inhibition reached by 1 hour of ingestion of 10 or 30 mg a day and no attributable adverse events over 12 weeks.

A Phase III trial of terutroban versus antithrombotic agents, Prevention of Cerebrovascular and Cardiovascular Events Of Ischemic Origin with Terutroban in Patients with a History of Ischemic Stroke or Transient Ischaemic Attack (PERFORM), is underway with a target enrollment of 18,000 patients who have a history of ischemic stroke or transient ischemic attack. The primary efficacy outcome is the number of cerebrovascular and CV events.

**Conclusions**

Antiplatelet therapy is a cornerstone of acute and chronic therapy for the patient with atherothrombosis. Nevertheless, recent observations have confirmed the possibility of improving current options. Achieving an optimal balance between antithrombotic efficacy and bleeding remains an important and incompletely met goal. Advances in our understanding of platelet biology have led researchers to new agents and new therapeutic targets that are presently under investigation. Ongoing research will determine whether such novel approaches will improve the care of patients with atherothrombosis.
References

Post-test

1. Which one(s) of the following characterize(s) an ideal antiplatelet agent?
   a. Rapid onset
   b. Easily administered
   c. Predictably effective in all patients
   d. Diminished platelet aggregation without increased bleeding
   e. All of the above

2. Which one(s) of the following agents inhibit(s) ADP-induced platelet activation by blocking the P2Y12 receptor?
   a. AZD6140
   b. SCH 530348
   c. Prasugrel
   d. Cangrelor
   e. All of the above
   f. a, b, and c
   g. a, c, and d

3. PRINCIPLE-TIMI 44 showed a significant increase in inhibition of platelet aggregation with which of the following?
   a. Prasugrel 60 mg loading dose
   b. Clopidogrel 600 mg loading dose
   c. Prasugrel 10 mg maintenance dose
   d. Clopidogrel 150 mg maintenance dose
   e. None of the above
   f. a and c
   g. b and d

4. By interacting with PAR1, thrombin receptor antagonists inhibit the cellular effects of ________?
   a. Thromboxane A₂
   b. ADP
   c. Thrombin
   d. Prostaglandin H₂
   e. None of the above
   f. All of the above

5. Which of the following agents is a thromboxane A₂/prostaglandin H₂ (TH) receptor antagonist?
   a. AZD6140
   b. Cangrelor
   c. SCH 530348
   d. Terutroban
   e. None of the above
Evaluation

Please circle the number that best reflects your opinion of the following statements:

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<th>Strongly Disagree</th>
<th>Disagree</th>
<th>Neither Agree nor Disagree</th>
<th>Agree</th>
<th>Strongly Agree</th>
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<td>As a result of participating in this activity, are you now better able to:</td>
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<td>Recognize the clinical limitations of available antiplatelet drugs?</td>
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<td>Differentiate between the pharmacologic properties of novel antiplatelet agents and currently available drugs?</td>
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<td>Evaluate recent data regarding advances in the safety and efficacy of antiplatelet agents under development?</td>
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<th>Poor</th>
<th>Fair</th>
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<td>How would you rate the overall quality of this activity?</td>
<td>1</td>
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Program Value

1. Please identify the most important thing you learned that will affect the care of patients in your practice:
   - [ ] The clinical limitations of currently available antiplatelet therapies
   - [ ] The difference between pharmacologic properties of novel and currently available antiplatelet agents
   - [ ] Recent data regarding the development of new antiplatelet agents
   - [ ] Other (please describe): _________________________________________________________

2. As a result of this program, how will you most likely improve care of ACS patients in your practice setting?
   - [ ] I can recognize continued risk of atherosclerotic/thrombotic events despite antiplatelet therapy
   - [ ] I can implement evidence-based treatment strategies
   - [ ] I can evaluate new antiplatelet therapies as they become available
   - [ ] Other (please describe): _________________________________________________________

3. What barriers prevent optimal, evidence-based care for your ACS patients? (Check all that apply.)
   - [ ] Lack of clear guidelines regarding appropriate treatment for patients at continued risk for thrombotic events despite treatment with available antiplatelet agents
   - [ ] Concerns about bleeding risk
   - [ ] Lack of familiarity with how to apply new clinical trial evidence to practice setting
   - [ ] Financial or time constraints in proper patient assessment
   - [ ] Other (please describe): _________________________________________________________
4. Based on the information presented at this program, will you change your approach to managing patients with ACS?

☐ Definitely ☐ Most likely
☐ Not very likely ☐ No

5. This educational program was fair, balanced, and free of commercial bias.

☐ Yes ☐ No

If no, please explain: ________________________________________________________________

6. What additional topics should be covered in future CME activities, to inform and enhance your clinical practice?

____________________________________________________________________________________
____________________________________________________________________________________
____________________________________________________________________________________

7. What kind of future educational activities can best help you improve ACS patient care in your practice setting?

☐ Case-based simulations that permit application of data and guidelines to real-world practice
☐ Didactic presentations by national experts
☐ Workshop-like activities that simulate application of new data to treatment protocols
☐ Presentations on how other practice settings have successfully improved ACS care
☐ E-based learning that permits personal exploration of data and information
☐ Other (please describe): ______________________________________________________________

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