Rapid P2Y<sub>12</sub> Inhibition
Still an Unmet Medical Need

Johanne Silvain, MD, PhD; Gilles Montalescot, MD, PhD

Acute coronary syndrome (ACS) is still a serious condition associated with decreased quality of life, increased healthcare expenditures, and premature death. The prevalence of ACS is expected to increase with aging of the population and with the epidemics of obesity and diabetes. The short- and long-term mortality after an ACS has been dramatically reduced by the development of revascularization techniques and new antithrombotic agents. The past decade has seen many trials evaluating new oral and parenteral antiplatelet agents with greater potency than aspirin and clopidogrel. Several antiplatelet agents have been developed, with the ultimate goal to obtain optimal antiplatelet therapy for both the acute and the chronic phases of disease.

Articles see p 336, 347

Ideally, efficiency requires several pharmacodynamic properties, such as a fast onset of action (immediate onset for emergency situations), a strong degree of platelet inhibition (at least stronger than the standard of care [aspirin and clopidogrel]), a narrow interindividual variability with no impact of genetic variants and no drug-to-drug interaction, and an easy administration (an oral drug for maintenance therapy and an intravenous formulation for rapid loading). Of course, this drug should also lead to a convincing reduction of recurrent ischemic events in an adequately powered phase 3 trial.

With regard to safety, the illusion of having the same dose of a single antiplatelet drug to treat all clinical situations has passed. The degree of platelet activation and aggregation is different across clinical situations (eg, acute ST-segment-elevation myocardial infarction [STEMI] versus secondary prevention) and varies over time in the same patient. Recent large phase 3 trials have confirmed the importance of dosing variability in PCI results and patient prognosis. Indeed, we know from mechanistic studies that platelets play a crucial role predominantly in the early stage of thrombus formation, findings that could explain why GP IIb/IIIa inhibitors do not demonstrate efficacy in trials in mostly patients presenting with late STEMI, whereas it was beneficial when administered more rapidly after the onset of symptoms, such as in the European prehospital studies. With the advent of prasugrel and ticagrelor (2 orally administered P2Y<sub>12</sub> inhibitors that are faster and more potent than clopidogrel), the question of the usefulness of GP IIb/IIIa inhibitors logically arose. In both the TRITON (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel) and the PLATO (Platelet Inhibition and Patient Outcomes) trials, these intravenous inhibitors were authorized and apparently did not blunt the additional benefit of the 2 new P2Y<sub>12</sub> inhibitors over clopidogrel. Because no randomized trial evaluated the benefit of the GP IIb/IIIa blockade versus placebo on top of these new P2Y<sub>12</sub> antagonists, there is uncertainty about the risk and benefit of simultaneously using...
both types of antiplatelet agents. Subsequently, we need to know more about the pharmacodynamics and clinical benefits of these new intravenous P2Y12 antagonists.

**New Oral P2Y12 Inhibitors**

The 2 new oral P2Y12 inhibitors prasugrel and ticagrelor seem to have overcome most of the pharmacological issues that were encountered with clopidogrel. Both are more potent; have a faster onset of action; and are not affected by genetic variants or drug-to-drug interaction, especially with the concomitant use of proton pump inhibitors. More importantly, prasugrel and ticagrelor have shown that stronger P2Y12 inhibition leads to a respective, significant 19% and 16% relative risk reduction of a similar primary end point combining cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke. Ticagrelor also showed a 1.1% absolute reduction of cardiovascular death. However, both agents had a significant 0.6% absolute excess of TIMI (Thrombolysis in Myocardial Infarction) major bleeding event not related to coronary artery bypass graft surgery (25% relative excess with prasugrel and 27% with ticagrelor). Logically, international guidelines were updated with class I recommendations for these drugs that should replace clopidogrel in patients with ACS in whom the bleeding risk is low or intermediate.

However, both prasugrel and ticagrelor are oral antiplatelet agents and lack an intravenous formulation. Their onset of action is supposed to be fast, ≈30 minutes in healthy volunteers or in stable coronary patients. However, it seems from a recent work from Bonello and colleagues that in patients with ACS (including >40% of those with STEMI), the observation of an optimal platelet inhibition might be closer to several hours, at least for the prasugrel 60-mg loading dose. These data were confirmed by Valgimigli and colleagues in a nicely designed randomized biological study where an optimal platelet inhibition was obtained with prasugrel between 2 and 6 hours in patients with STEMI, supporting the need for a more rapidly effective intravenous agent. In this case, the addition of the GP IIb/IIIa inhibitor tirofiban was suggested by the cangrelor data when clopidogrel is orally administered may be easier to manage with 2 formulations of the same drug developed by the same pharmaceutical company.

**Cangrelor**

Cangrelor is an intravenous ATP analog that reversibly binds to and inhibits the P2Y12 ADP receptor. Cangrelor showed in phase 1 to 2 trials that its administration could provide substantially greater P2Y12 receptor blockade (>95%) than any oral P2Y12 antagonist. Moreover, the initial experience with intravenous cangrelor during PCI suggested an acceptable risk of bleeding or adverse cardiac events while achieving rapid and reversible inhibition of platelet aggregation through competitive binding to the ADP P2Y12 platelet receptor with less prolongation of bleeding time than the GP IIb/IIIa receptor antagonist abciximab.

In terms of clinical outcomes, in the 2 CHAMPION (Cangrelor versus Standard Therapy to Achieve Optimal Management of Platelet Inhibition) trials regrouping of 14 172 patients, cangrelor failed to show superiority over a 600-mg loading dose of clopidogrel in reducing the composite end point of death, myocardial infarction, or ischemia-driven revascularization at 48 hours after PCI. However, the rates of stent thrombosis and death from any cause were significantly reduced in the cangrelor group at 48 hours, just like with the other oral P2Y12 agents, suggesting efficacy of cangrelor and a class effect on these end points. Several hypotheses were raised to explain the negative findings in these 2 studies, such as timing of administration, competition at the P2Y12 receptor level with clopidogrel, trial design, and end points definition. Since, cangrelor has been tested successfully in the small BRIDGE (Maintenance of Platelet Inhibition With Cangrelor After Discontinuation of Thienopyridines in Patients Undergoing Surgery) trial, confirming the biological efficacy of the drug in patients scheduled for heart surgery. The clinical efficacy is now being retested in the CHAMPION-PHOENIX (A Clinical Trial Comparing Cangrelor to Clopidogrel Standard of Care Therapy in Subjects Who Require Percutaneous Coronary Intervention) trial, which should include 10 900 patients undergoing PCI (http://www.clinicaltrials.gov; Unique identifier: NCT0115657).

**Elinogrel**

Elinogrel is a novel selective, competitive, and reversible P2Y12 inhibitor that has both an intravenous and an oral formulation. Like ticagrelor and unlike thienopyridines, it does not require metabolic activation, and it directly inhibits the P2Y12 receptor. Elinogrel also has a terminal half-life of 9 to 12 hours, justifying a twice-daily regimen for the maintenance dose and a balanced clearance through kidney and liver.

In this issue of *Circulation: Cardiovascular Interventions*, Angiolillo and colleagues present the pharmacokinetic and the pharmacodynamic results of elinogrel compared with clopidogrel in the dose-ranging trial INNOVATE-PCI (Intravenous and Oral Administration of Elinogrel to Evaluate Tolerability and Efficacy in Non-Urgent PCI Patients I). This study shows that in the acute phase of treatment, the 120-mg IV bolus of elinogrel achieved more rapid and more potent platelet inhibition than a clopidogrel loading dose of 300 to 600 mg (60% of patients received a 600-mg loading dose). Not surprisingly, although the effect of the clopidogrel loading dose was maximal after 6 hours, elinogrel achieved a higher level of platelet inhibition (>85%) 15 to 30 minutes after administration. Elinogrel concentration was maximal 15 to 30 minutes after administration and decreased rapidly after the bolus dose, whereas the level of platelet inhibition reached a steady state of 90% at 8 hours after the initial bolus. The effect was sustained through the transition to the oral
form of elinogrel in the post-PCI phase. A similar level of platelet inhibition was obtained with the 100- and 150-mg maintenance dose of oral elinogrel, with a trend toward a more profound platelet inhibition compared with clopidogrel 75 mg. Finally, in terms of pharmacodynamics, elinogrel fulfilled its goal by providing faster and more complete platelet inhibition with the intravenous formulation than clopidogrel, whereas the oral formulation was also effective in terms of platelet inhibition compared with clopidogrel. Of course, we do not know what would have resulted if patients had been loaded with clopidogrel 6 hours instead of an average of 9 minutes before PCI, if higher doses had been used, or if prasugrel or ticagrelor had been used.

In this same issue of *Circulation: Cardiovascular Interventions*, Welsh and colleagues present the clinical results of the INNOVATE-PCI trial, which was designed to include 800 patients in 4 different arms. The control arm comprised patients who received a clopidogrel loading dose of 300 mg (33.5%) or a clopidogrel loading dose of 600 mg (66.5%) >12 hours before PCI. This arm was compared with 3 different arms with different doses of elinogrel. Because the loading dose of elinogrel was changed by the data and safety monitoring board to 120 mg after 80 patients were enrolled, the 3 arms differed only by the maintenance dose of elinogrel administered orally (50 mg, 100 mg, and 150 mg BID). Rapidly in the trial, the data and safety monitoring board also recommended interruption of the 50-mg arm. Finally, 652 patients were included in this dose-ranging study, which was entirely exploratory because primary or secondary end points were not clearly listed or precisely defined, and no sample size calculation was performed, limiting the conclusions that can be drawn from the study.

If we examine the signals provided by this exploratory PCI study, we have on one side a nonsignificant higher rate of periprocedural myocardial infarction in the elinogrel arms (7.4%) than in the clopidogrel arm (4.8%) (odds ratio, 1.59; 95% CI, 0.79–3.48) during the first 24 hours or at discharge and a similar finding for the composite end point of death, myocardial infarction, stroke, urgent target vessel revascularization, and stent thrombosis at 120 days follow-up (10.4% with elinogrel and 5.8% with clopidogrel). This signal toward a higher rate of ischemic events was also present for each individual end point and may raise concern. This is also an apparent disconnection with the findings of the platelet substudy, a result somewhat similar to what was observed with cangrelor. On the safety side, no difference was observed with clopidogrel in terms of major bleeding; however, there was a higher rate of combined TIMI bleeding (odds ratio, 2.42; 95% CI, 1.16–5.69) mainly because of a higher rate of TIMI bleeding requiring medical attention during the 24 hours after intravenous elinogrel therapy. At 120 days, an increased rate of combined TIMI bleeding was observed, with a pattern toward a dose response for oral elinogrel with 6.7% of bleeding with clopidogrel, 10.9% with elinogrel 100 mg (hazard ratio, 1.66; 95% CI, 0.85–3.25), and 15.0% with elinogrel 150 mg (hazard ratio, 2.30; 95% CI, 1.22–4.31). These results and our comments should be taken with much caution considering the phase 2 nature of the study, the changes in design made by the data and safety monitoring board, the lack of power for all clinical outcomes, and the nonsignificant differences on clinical efficacy.

No plausible explanation has been proposed for the discrepancy between the somewhat disappointing clinical results and the favorable pharmacodynamic profile of elinogrel. The play of chance is still plausible, and we need to see a large clinical outcome trial, preferably adequately powered, in a high-risk population presenting for emergent catheterization (eg, primary PCI). There is a need for immediate and strong platelet inhibition using an intravenous formulation of P2Y12 inhibitors in this population. Success in this setting would then open new avenues for these reversible agents.

**Disclosures**

Dr Silvain reports receiving research grants from Sanofi-Aventis, Daiichi Sankyo, Eli Lilly, Brahms, INSERM, Fédération Française de Cardiologie, and Société Française de Cardiologie; consulting fees from Daiichi Sankyo and Eli Lilly; and speaker honoraria from AstraZeneca, Daiichi Sankyo, Eli Lilly, Iroko Cardio, and Servier. Dr Montalescot reports receiving grant support from Abbott Vascular, Boston Scientific, Cordis, Eli Lilly, Fédération Française de Cardiologie, Fondation de France, Guerbet Medical, INSERM, ITC Edison, Medtronic, Pfizer, Sanofi-Aventis, Société Française de Cardiologie, and Stago and consulting or board fees and lecture fees from AstraZeneca, Bayer, Boehringer Ingelheim, Cardiovascular Research Foundation, Cleveland Clinic Research Foundation, Daiichi Sankyo, Duke Institute, Eli Lilly, Europa, Lead-up, GlaxoSmithKline, Institut de Cardiologie de Montreal, Menarini, Nanospheres, Novartis, Pfizer, Portola, Sanofi-Aventis, The Medicines Company, and the TIMI study group.

**References**


Rapid P2Y_12 Inhibition: Still an Unmet Medical Need
Johanne Silvain and Gilles Montalescot

_Circ Cardiovasc Interv._ 2012;5:328-331
doi: 10.1161/CIRCINTERVENTIONS.112.970319

_Circulation: Cardiovascular Interventions_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2012 American Heart Association, Inc. All rights reserved.
Print ISSN: 1941-7640. Online ISSN: 1941-7632

The online version of this article, along with updated information and services, is located on the World Wide Web at:

http://circinterventions.ahajournals.org/content/5/3/328

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation: Cardiovascular Interventions_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation: Cardiovascular Interventions_ is online at:
http://circinterventions.ahajournals.org//subscriptions/