Inhibitors of the Platelet Thrombin Receptor
Will They Live up to Their Promises?

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Not that long ago, aspirin, heparin, and warfarin were the only available antithrombotic agents for treating cardiovascular disease patients at risk of thrombotic events. These agents are still used in several places around the world, and it is remarkable how difficult it was to discover other agents that are more effective and/or safer. Since the mid-1980s we have been witnessing an explosion of research on new antithrombotic therapies, resulting in the availability of ticlopidine and clopidogrel (thienopyridine P2Y<sub>12</sub>-receptor inhibitors), low–molecular-weight heparins (eg, enoxaparin), and intravenous GPIIb/IIIa-receptor inhibitors (abciximab, eptifibatide, and tirofiban), later followed by fondaparinux (a synthetic indirect intravenous anti-Xa agent), bivalirudin (an intravenous direct anti-Xa agent), and more recently, prasugrel (a more potent thienopyridine) (Figure).

In the near future, several new oral antithrombotic agents may become available for treating patients with cardiovascular diseases: ticagrelor (the first direct reversible P2Y<sub>12</sub> antagonist), dabigatran (an oral direct anti-Xa agent), rivaroxaban (an oral direct anti-Xa agent), and apixaban (also an oral direct anti-Xa agent). Other P2Y<sub>12</sub> antagonists (eg, elinogrel) and oral anti-Xa agents (edoxaban, betrixaban, YM150, and TAK-442) are being studied or will be studied in phase-III programs (Figure).

New antiplatelet therapies that target pathways not affected by aspirin or P2Y<sub>12</sub>-receptor antagonists could provide more comprehensive inhibition of platelet activation, and contribute to a greater inhibition of platelet-mediated thrombosis. Inhibition of protease-activated receptor-1 (PAR-1), a receptor for thrombin, is a new attractive approach in the development of better and safer antiplatelet therapy. As shown in the Figure, thrombin is the key effector of the coagulation cascade, but is also the most potent activator of platelets. Preclinical and early clinical work has indicated that inhibition of the PAR-1 receptor does not interfere with the formation of the first monolayer of platelets (primary hemothasia) near the damaged vessel wall and does not inhibit fibrin generation or prolong bleeding times. These agents are currently being studied in patients with acute and chronic atherosclerotic vascular disease. The results of 2 large phase-II studies with one of these agents, atopaxar, are reported in this issue of Circulation. In the first study, 603 patients with a non-ST-elevation acute coronary syndrome (ACS) treated within 72 hours after onset of symptoms, were given 400 mg atopaxar per os followed by 50, 100, or 200 mg daily or matching placebo for 12 weeks. The primary end point, the incidence of major or minor bleeding according to the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial<sup>1</sup> definitions was similar between the combined atopaxar and placebo groups (3.1% versus 2.2%; P=0.63) although the incidence of major bleeding was numerically higher in the atopaxar groups (1.8% versus 0%; P=0.12), including 1 hemorrhagic stroke. Remarkably, no dose-related trend was found. The trial was not sized to find significant differences in clinical ischemic end points, but a statistically significant 34% reduction in signs of ischemia was found on Holter monitoring during the first 48 hours after the start of study treatment in the combined atopaxar groups when compared with placebo. Platelet function tests showed a predosing inhibition of platelet aggregation to 15 μmol/L thrombin receptor activating peptide at 12 weeks of 66.5%, 71.5%, and 88.9% in the 50-mg, 100-mg, and 200-mg groups, respectively (P for trend=0.07). Transient liver function abnormalities and a relative QTc prolongation were observed with the 100- and 200-mg doses apparently without clinical consequences. In the second study, 720 high-risk stable coronary artery patients were randomized to the same maintenance doses of atopaxar or placebo for 24 weeks. The overall incidence of bleeding complications was low, but more CURE major bleeding complications were seen in the atopaxar groups: 0.9% versus 0% (difference not significant). In this study, there was a statistically significant dose-related trend in bleeding complications when minor bleedings were also taken into account: 3.9%, 1.7%, and 5.9% versus 0.6% for placebo (P trend=0.01). With regard to ischemic end points, a numerically lower incidence of major adverse cardiac events was found with each dose of atopaxar when compared with placebo. No dose-related trend for efficacy end points, however, was found, given that the lowest incidence of major adverse cardiac events occurred in the 50-mg arm: 1.7% versus 2.9% for the 100-mg and 3.2% for the 200-mg dose and 4.6% for placebo. As in the ACS trial, transient elevations of liver transaminases and a dose-dependent QTc prolongation without apparent clinical correlates were noticed.

The overall results of these 2 phase-II studies could be considered sufficiently positive to embark on a phase-III program. However, the numerically higher incidence of major bleeding complications, the above-mentioned liver elevation of liver transaminases, and dose-related QTc prolongation led us to conclude that atopaxar is not sufficiently promising to warrant further development in acute coronary syndromes.
dysfunction and relative QTc prolongation, and the lack of a convincing dose-related trend for bleeding risk and efficacy are somewhat troublesome. Of additional concern are the recent decisions by the Data and Safety Monitoring Committee (DSMC) relating to 2 large phase-III trials with another PAR-1 inhibitor, vorapaxar. The DSMC recommended to stop 1 of the 3 arms of a secondary prevention trial, Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events (TRA2P) and to close out the Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome (TRACER) study. In TRA2P, a total of 25 714 patients with a history of ischemic stroke or transient ischemic attack (TIA), coronary artery disease, or peripheral arterial disease were randomized to 2.5 mg vorapaxar or placebo for at least 1 year on top of standard antiplatelet therapy. The DSMC recommended suspending further treatment with study medication in those subjects with a history of ischemic stroke because of an excess in intracranial bleedings in patients randomized to vorapaxar. The study was allowed to continue in the 2 other arms (patients with a history of coronary heart disease and peripheral arterial disease). The other study, TRACER, has recruited 12 977 patients with a recent non-ST-elevation ACS. All patients were supposed to be on study treatment (2.5 mg vorapaxar after a loading dose of 40 mg or matching placebo) for at least 1 year on top of standard antiplatelet therapy. The DSMC recommended suspending further treatment with study medication in those subjects with a history of ischemic stroke because of an excess in intracranial bleedings in patients randomized to vorapaxar. The study was allowed to continue in the 2 other arms (patients with a history of coronary heart disease and peripheral arterial disease). The other study, TRACER, has recruited 12 977 patients with a recent non-ST-elevation ACS. All patients were supposed to be on study treatment (2.5 mg vorapaxar after a loading dose of 40 mg or matching placebo) for at least 1 year on top of standard antiplatelet therapy with aspirin and clopidogrel (and recently, prasugrel). The DSMC communicated to the investigators that a sufficient number of events were collected to test the primary hypothesis of the study. No further reasons for the premature closeout were communicated. Obviously, the future of the PAR-1 receptor antagonists will depend on the final results of the 2 phase-III studies with vorapaxar. Already, it seems likely that a more aggressive antiplatelet therapy with vorapaxar on top of standard antiplatelet therapy causes more intracranial bleedings in patients with a history of stroke or TIA. Of note, in the phase-II program with atopaxar, 1 intracranial hemorrhage was found in a total population 997 patients randomized to atopaxar. The increased risk of intracranial bleeding observed in the stroke arm of TRA2P is not a total surprise if one considers the higher bleeding risk of the combination of aspirin and clopidogrel in the Management of Atherothrombosis with Clopidogrel in High-Risk Patients with Recent TIA or Ischemic Stroke (MATCH) trial, as compared with clopidogrel alone in patients with a recent ischemic stroke or TIA. The higher rate of bleeding complications (and lower clinical efficacy) with prasugrel in the subgroup of ACS patients with a history of stroke or TIA in the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction (TRITON), and the higher incidence of intracranial bleedings in patients with a recent stroke, treated with aspirin and dipyridamole versus clopidogrel alone, in the Prevention Regimen for Effectively Avoiding Second Strokes (PROFESS) trial, also suggest that a more potent antiplatelet regimen is not beneficial, and perhaps harmful, in these patients. However, in patients with coronary artery disease, especially those who survived an ACS, there is clear evidence of a high rate of recurrent ischemic events, including death after discharge from the hospital in spite of dual antiplatelet therapy (even with the more potent new agents prasugrel and ticagrelor) and revascularization. Insufficient antithrombotic protection, however, is only one of the possible reasons for this high event rate. Besides the occurrence of heart failure, poor control of blood pressure, cholesterol and glucose levels, overweight, lack of exercise, and, indeed, bleeding complications leading to interruption of antiplatelet treatment and resulting in recurrent ischemic events are other likely explanations.

Even if suboptimal antithrombotic protection would be the main cause of recurrent ischemic events and if the extra bleeding risk with the PAR-1 inhibitors would be acceptable in comparison with the reduction in ischemic events, for reasons of compliance and cost it is doubtful that many patients would be willing to take 2 or 3 antiplatelet agents or 2 antiplatelet agents and an anticoagulant (on top of other medication like statins and antihypertensive agents) for a long period of time. We have learned from other fields in medicine...
that too much lowering of blood pressure or glucose levels may be harmful. We must avoid similar outcomes with our new antithrombotic strategies. More simple regimes have to be tested with the new PAR-1 antagonists but also with other promising agents such as dabigatran and the anti-Xa agents.

**Disclosures**

Dr Van de Werf is a member of the executive committee of TRACER and a member of the steering committee of TRA2P.

**References**


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