

Another view on prasugrel

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The combination of aspirin with clopidogrel is currently the mainstay of antiplatelet therapy for patients with acute coronary syndromes (ACS) (1). While aspirin inhibits platelet thromboxane A₂ production and platelet activation, clopidogrel inhibits adenosine diphosphate (ADP)-induced platelet activation by blocking the P₂Y₁₂ platelet receptor. When added to aspirin therapy in patients with ACS, clopidogrel significantly reduces the risk of recurrent ischaemic events (1).

Clopidogrel's onset of action is delayed and variable between individuals. A therapeutic level of inhibition is reached 4–6 hours (h) after a 300 mg loading dose, and 2 h after a 600 mg loading dose. Laboratory analysis reveals that a substantial proportion of patients do not show adequate inhibition of ADP-induced aggregation. Low responsiveness to clopidogrel has been shown to be significantly associated with adverse outcomes after percutaneous coronary intervention (PCI) (2).

Prasugrel is a novel thienopyridine pro-drug with a greater rate, magnitude, and consistency of platelet ADP inhibition, as compared to clopidogrel. The therapeutic level of the inhibition of platelet aggregation is reached within 1 h after a 60 mg loading dose (3). TRITON-TIMI 38 (4) validated the hypothesis that more intensive antiplatelet blockade via the ADP receptor decreases the incidence of ischaemic events. Patients (13,608) with acute coronary syndromes scheduled for PCI and receiving aspirin were randomly assigned to receive either prasugrel or clopidogrel. After a median duration of 14.5 months, the primary efficacy outcome of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke occurred in 12.1% of patients taking clopidogrel and in 9.9% of those taking prasugrel. Stent thrombosis was also reduced in the prasugrel group (2.4% clopidogrel vs. 1.1% prasugrel). However, major bleeding was increased (1.7% vs. 2.5%), as was fatal bleeding (0.1% vs. 0.4%) in the prasugrel group. Overall mortality did not differ significantly between treatment groups.

In their viewpoint article, Serebruany et al. (5) discuss different aspects of the clinical development of prasugrel and, in particular, the pivotal trial TRITON-TIMI-38. Although their interpretations and evaluations are definitely debatable, this article highlights several points which are of outstanding interest for clinical and research approaches to platelet function inhibition:

- **Standardization:** Serebruany et al. (5) highlight two aspects of standardization. First, the standardization of definitions of endpoints for clinical trials; in order to be able to compare event rates in different studies, a standardized definition of endpoints is desirable. Second, standardization of monitoring techniques for the assessment of anti-platelet therapy is crucial. The authors comment on discrepancies that occurred in the early phase of clinical development of prasugrel, which may be attributed to the use of different equipment for aggregation analysis in participating centers. Today, there is still a wide variation in the literature and clinical practice with respect to instruments, reagents, sample preparation, sample anticoagulants, as well as the analysis algorithms and clinical cut-offs applied for anti-platelet drug monitoring.
- **Patient compliance:** An intensified anti-platelet treatment is usually equalized with a decreased rate of low patient responsiveness to anti-platelet treatment. Serebruany et al. (5) remind us that in a real-life scenario, patient compliance is crucial. Intensifying anti-platelet therapy might generate an increased rate of annoying minor bleeding complications during everyday activities, such as shaving or brushing teeth, which may again lead to patient non-compliance. For the physician, this includes the comforting fact that even with more modern and intensified anti-platelet regimens, the role of personal communication with the patient is still important for the appropriate adherence of the patient to his life-saving treatment.
- **Focus on safety:** With the growing efficacy of antithrombotic treatments in ACS and in other areas such as prophylaxis of deep venous thrombosis, there is an increased focus on drug safety. Melagatran and ticlopidine are examples of antithrombotic drugs that were either withdrawn from the market, or experienced a sharp drop in use due to safety concerns. Referring to prasugrel, Bhatt (6) states that in a “real-world” setting, such as an elderly patient with multiple co-existing conditions, the risk of major bleeding and even fatal bleeding may increase to an even greater degree than was seen in TRITON-TIMI 38. This expectation is also expressed by Serebruany et al. in their viewpoint article (5).
- **Transformation of clinical trials into routine patient management:** Clinical trials have inclusion and exclusion

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criteria. In contrast, physicians must treat all patients, and patient outcome is not limited to observation periods. Correct extrapolation of the results obtained in clinical trials to the multi-morbid patient in real-life is a complex and challenging question.

- **Individualization:** Current anti-platelet therapy in patients with ACS is relatively uniform, with a combination of aspirin and clopidogrel being mostly used. It is expected that once prasugrel is approved, the decision to continue with clopidogrel or switch to prasugrel will have to be evaluated for each case. Patient collectives with known increased risk for stent thrombosis and myocardial infarction seem to have a disproportionately high benefit from the application of prasugrel. Other groups, such as the elderly, underweight, or patients with prior known cerebrovascular disease, will most likely be safer on clopidogrel. The situation will become even more complex when new anti-platelet strategies will receive regulatory approval (thrombin receptor antagonists, thromboxane receptor antagonists, orally available non-prodrug ADP receptor antagonists).

Some of the criticisms summarized in this viewpoint article have been previously raised by Serebruany et al. (7–12) and others (13, 14). In addition, rebuttals by the authors of TRITON TIMI-38 (15–17) and other related publications (18) are available, which, for a balanced view, should be carefully observed.

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At the dose evaluated in TRITON TIMI-38, prasugrel, once approved, will provide a significantly more potent anti-platelet regimen as compared to 75 mg/day clopidogrel. The clinical application of prasugrel has the potential to decrease the rate of stent thrombosis after PCI, especially in high-risk populations such as diabetics as well as in patients lacking sufficient response to clopidogrel treatment according to platelet function analysis (6). From the individualization point of view, the availability of an ADP receptor antagonist with a significantly higher potency compared to clopidogrel is highly desirable.

The higher potency and faster onset of inhibition with prasugrel is associated with an increased risk of bleeding. This could be minimized by appropriate selection of patients, i.e. excluding patients with high bleeding risk or patients who are less likely to benefit from the increased inhibition potential of prasugrel. Again, monitoring of prasugrel or clopidogrel responsiveness *ex vivo* may facilitate the decision for or against either compound (6).

ACS therapy can benefit significantly from an enlargement of the therapeutic options available for anti-platelet treatment.

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