No free lunches: balancing bleeding and efficacy with ticagrelor

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This editorial refers to ‘Bleeding complications with the P₂Y₁₂ receptor antagonists clopidogrel and ticagrelor in the PLATElet inhibition and patient Outcomes (PLATO) trial’¹, by R.C. Becker et al., on page 2933

The development of new oral antagonists of the platelet P₂Y₁₂ receptor has generated both interest and anxiety among practicing physicians. In a field in which clopidogrel was the only choice available for the better part of a decade, prasugrel and ticagrelor represent new treatment options in many parts of the world. Weighing efficacy, safety, and cost to determine appropriate use of these three agents will represent a key challenge over the next few years for physicians, as well as individuals and organizations involved in formulary decisions. To make appropriate decisions, both for the individual patient and for the larger healthcare system, in-depth understanding of safety data is absolutely critical. Thus, the comprehensive report from Becker et al.¹ describing bleeding complications in the PLATO trial is particularly timely and important.

The primary bleeding definition in PLATO combined non-coronary artery bypass graft (CABG) and CABG-related events, which differs notably from other contemporary antplatelet trials that have used non-CABG bleeding as the primary safety endpoint.²,³ While we do not dispute the importance of CABG bleeding, we believe a focus on total bleeding in the PLATO trial may provide a more accurate assessment of the safety of ticagrelor relative to clopidogrel. A strong argument can be made that the CABG bleeding definition in PLATO was too soft: any transfusion of ≥ 4 units of red blood cells was defined as a major bleed, regardless of clinical consequences.⁴ In essence, usual operating room procedures related to transfusion of blood products met the definition of a major bleed. The result was that a large proportion of patients who underwent CABG met the study definition of a major bleed, with rates > 80% in each treatment arm.⁵ By combining soft CABG ‘bleeds’ with more rigorously characterized non-CABG bleeding events, important differences in bleeding were diluted by the high number of CABG-related transfusions. Indeed, although only 10% of the study population underwent CABG, more than two-thirds of the major bleeding events in the PLATO trial were CABG-related. Therefore, non-CABG bleeds, which would be less influenced by transfusion practice and more likely to represent events of clinical importance to the patient, should remain the primary focus for safety comparisons between the two agents.

Multiple key points emerge from this comprehensive analysis of the bleeding profile of ticagrelor. (i) Study drug discontinuation due to non-procedural bleeding occurred >2-fold more frequently with ticagrelor than with clopidogrel. (ii) Although no differences were evident regarding fatal bleeding, rates of non-CABG major bleeding were higher with ticagrelor than clopidogrel using both the PLATO definition [hazard ratio (HR) 1.19, 95% confidence interval (CI) 1.02–1.38] and the TIMI definition (HR 1.25, 95% CI 1.03–1.53). (iii) The composite of major + minor non-CABG bleeding, which is a highly relevant outcome since ‘minor’ bleeds often cause considerable suffering for patients and increase length of stay and costs for the healthcare system, occurred in 8.7% and 7.0% in the two groups (HR 1.27, 95% CI 1.14–1.42). (iv) The excess bleeding appeared to be restricted to spontaneous bleeding events (HR 1.31, 95% CI 1.08–1.60), with no differences reported previously in multiple parameters of procedural bleeding related to CABG and percutaneous coronary intervention (PCI).⁶ With prasugrel, although PCI-related bleeding rates were also similar to those with clopidogrel, CABG-related bleeding was increased; moreover, rates of fatal bleeding were slightly increased with prasugrel, which was not seen in these analyses of ticagrelor.¹,³ (v) The excess spontaneous bleeding events were largely due to gastrointestinal (GI) bleeding and epistaxis, with a small excess of intracranial bleeds also noted (0.34% vs. 0.19%) (Figure 1). (vi) Although the non-CABG bleeding curves appeared to diverge slightly after 30 days of treatment, an excess of major and minor bleeding was still evident within 30 days for patients receiving ticagrelor. (vii) Excess bleeding with ticagrelor was not restricted to individuals predicted to be at high bleeding risk—no treatment interactions were observed in subgroups defined by clinical characteristic or using the CRUSADE bleeding model.¹

These findings have interesting implications for interpretation of the mortality reduction seen with ticagrelor in PLATO. In the primary manuscript, the authors speculated that ‘the improved survival rate...
with ticagrelor might be due to the decrease in the risk of thrombotic events without a concomitant increase in the risk of major bleeding. Clearly, based on the data provided by Becker et al., ticagrelor does increase bleeding complications. Moreover, the reduction in all-cause and cardiovascular mortality with ticagrelor compared with clopidogrel was far larger than would be predicted based on the relatively modest reduction in myocardial infarction (MI). Studies comparing clopidogrel with placebo, and prasugrel with clopidogrel, did not show favourable effects on mortality despite similar relative reductions in MI. These observations suggest that a mechanism distinct from the antiplatelet effect (i.e. an ‘off-target’ effect) is responsible for the reduction in mortality seen with ticagrelor.

To date, the most plausible off-target mechanism proposed to explain the mortality benefit associated with ticagrelor is the prevention of adenosine reuptake into red blood cells, resulting in higher circulating levels of adenosine. Higher adenosine levels almost certainly explain some of the side effects of ticagrelor, including dyspnoea and ventricular pauses, and may also improve myocardial blood flow and contribute to a preconditioning-like effect of the drug, both of which could conceivably influence mortality in at-risk patients following an acute coronary syndrome (ACS). Major research priorities include confirming the favourable mortality signal seen with ticagrelor in additional large clinical trials, and also performing carefully controlled animal and human studies to identify potential mechanisms for this benefit.

Although procedure-related bleeding was similar in both treatment groups in PLATO, non-procedural bleeding was more common among ticagrelor-treated patients, as described in the

**Figure 1** Relative frequency of various locations of non-procedural-related major bleeding in patients receiving ticagrelor in the PLATO trial.
primary study results and in more detail in the study of Becker et al. This is consistent with the fundamental principles of coagulation that all more potent antiplatelet or antithrombotic agents increase bleeding. In other words ‘there is no free lunch!’ Thus, patients receiving ticagrelor will need to be educated about risks and monitored closely for bleeding during outpatient therapy. Although ticagrelor is a reversible agent with a relatively short pharmacological half-life, the offset of its antiplatelet effects is still 3–5 days because of the high levels of platelet inhibition achieved. 10 Thus, platelet transfusion may be necessary for patients with severe bleeding not responsive to local measures. More importantly, prevention of bleeding should be a primary objective. Low dose aspirin (75–100 mg daily) should be used in all patients receiving either clopidogrel (based on the CURRENT-OASIS 7 study11) or ticagrelor (given the lower efficacy with higher aspirin doses1). Moreover, since approximately one-third of non-procedural bleeding was GI bleeding (Figure 1), prospective studies are needed to determine if routine GI prophylaxis with proton pump inhibitors or H₂ blockers can mitigate the GI bleeding risk. Finally, careful balancing of the risks and benefits of more potent antiplatelet therapy remains very important in patients at high bleeding risk, such as the elderly and patients with prior bleeding history or low baseline haemoglobin levels.

Although the investigators present data on ‘net clinical benefit’, using a composite of cardiovascular death, MI, stroke, and major bleeding, this analysis is limited by the inclusion of total CABG + non-CABG bleeding in the bleeding calculation and asymptomatic peri-procedural enzyme elevation in the MI definition. A 4 unit blood transfusion during an uncomplicated CABG, or a three-fold elevation in biomarkers during an uncomplicated PCI, simply does not have the same impact as a spontaneous MI, major bleed, stroke, or cardiovascular death. Yet, these soft events contribute substantially to the net benefit calculation. Fortunately, the marked reduction in all-cause mortality (4.5 vs. 5.9%, HR 0.78, 95% CI 0.69–0.89) and cardiovascular mortality (4.0 vs. 5.1%, HR 0.79, 95% CI 0.69–0.91) in PLATO4 allows a more straightforward balancing of risk and benefit, free from the biases created by endpoint definitions. In the final analysis, the increased bleeding reported by Becker et al. does not negate the robust reduction in mortality seen, and ticagrelor thus represents a potential breakthrough drug for the treatment of ACS. Our hope is that the manufacturer of ticagrelor will price this agent such that patients who stand to benefit will be able to receive the drug. This issue will be particularly important in the current era of constrained resources, with broad availability of low-cost generic clopidogrel on the horizon.

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References