The PLATO trial: do you believe in magic?

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Online publish-ahead-of-print 18 December 2009

The recently published and presented PLATElet Inhibition and Clinical Outcomes (PLATO) trial was a pivotal Phase III, randomized, double-blind, parallel-group, multinational, clinical study.1 The trial compared head-to-head the efficacy of the experimental antiplatelet agent ticagrelor (formerly known as AZD6140, to be marketed as BrilintaTM) vs. standard care with clopidogrel. Patients (n = 18 624) with high risk acute coronary syndromes undergoing coronary intervention were randomized to ticagrelor 180 mg loading dose followed by 90 mg twice daily thereafter, or clopidogrel 300–600 mg loading dose followed by 75 mg once daily for 6–12 months. The primary endpoint was the time of the first event of death from vascular causes, myocardial infarction (MI), or stroke, and occurred in 11.7% of patients treated with clopidogrel vs. 9.8% of patients randomized to ticagrelor, representing a highly significant benefit [hazard ratio (HR) = 0.84; confidence interval (CI) = 0.77–0.92; P < 0.001] of the experimental drug.1 Triaging these three components of the combined endpoint suggests that the difference in favour of ticagrelor was driven by the reduction of vascular death (P < 0.001) and MI (P < 0.005), but not stroke (P = 0.22). There were significantly more fatal intracranial bleedings (11 vs. 1, P = 0.02), but numerically less overall fatal bleeding (20 vs. 23) after ticagrelor. Among side effects associated with ticagrelor, dyspnoea (already recognized in the earlier studies with AZD6140, and probably caused by transitory bronchoconstriction) was the most prominent one (HR = 1.84; CI = 1.68–2.02; P < 0.001), followed by ventricular pauses (P < 0.01), and laboratory findings of increased uric acid as well as elevated creatinine (P < 0.001 for both).

Obviously the PLATO data will undergo detailed scrutiny and verification during the assessment by regulatory authorities; however, some considerations already seem appropriate.

Mortality

There were 107 more lives saved with ticagrelor than after conventional clopidogrel (399 vs. 506), representing a highly significant absolute mortality reduction (HR = 0.78; CI = 0.69–0.89; P < 0.001). These remarkable benefits make ticagrelor a top achiever among any antiplatelet agent in a setting of a large randomized trial against an active comparator. The closest to the PLATO absolute mortality reduction has been observed in the COMMIT trial2 when 119 lives were saved with clopidogrel in patients at presentation with acute MI.3 However, the sample size in COMMIT was three times larger than in PLATO, no pre-treatment with clopidogrel was allowed, and—most importantly—the PLATO mortality benefit was achieved against clopidogrel, while in COMMIT it was achieved against placebo.2 In short, even by a very conservative assessment, the mortality benefit in PLATO is at least three times more profound than in COMMIT. The only other antiplatelet trial exhibiting absolute mortality reduction was the historical ISIS-2 with aspirin,4 however, it is very difficult to compare the death benefits between these trials. Although being comparable with PLATO by sample size, ISIS-2 was done about a quarter of a century ago, it was designed against placebo, when aspirin alone saved 212 lives (804 vs. 1016 deaths in the placebo arm) acutely. Finally, in PLATO, the mortality reduction (107 deaths) numerically exceeds the MI prevention benefit (89 events), making it a hitherto unmatched achievement.1 If confirmed, such impressive mortality benefit will be absolutely critical for the further success of ticagrelor, providing the drug with so much needed room to compensate for the unfavourable safety profile. In fact, the large vascular and all-cause mortality benefit after ticagrelor represents an entirely unexpected advancement, which will serve as a cornerstone argument for the drug approval process and subsequent implementation in clinical practice.

MI reduction

The MI reduction in PLATO is also impressive. It is not only the absolute difference between the treatment arms favouring ticagrelor, but also the fact that MI adjudication was handled utilizing realistic, strict universal acute MI definition,5 rather than inflated assessment of MIs adding enzymatic leaks and almost every ischaemic episode. Indeed, following the recent trend towards lower MI rates,6 a reduction from 6.9% in the clopidogrel arm to 5.8% after ticagrelor—especially late in the trial—unquestionably represents a solid achievement.

Stroke

The PLATO results are in line with other studies where antiplatelet agents failed to demonstrate clear benefit in this high-risk
population. It seems that more delicate platelet inhibition is needed to improve outcomes after ischaemic stroke, and still prevent haemorrhagic intracranial events. The PLATO results also support the hypothesis that cerebrovascular and cardiovascular thrombotic occlusions may be of entirely different nature with regard to their pathogenesis and optimal prevention strategies.

**Timing**

The timing of benefit in PLATO looks ideal for long-term therapy. Unlike some other trials, the benefit after ticagrelor is somewhat delayed, growing slowly, but constantly over the entire time of the trial. The largest outcome benefit is observed at the end of the follow-up, ultimately justifying a chronic treatment regimen with ticagrelor. Importantly, since both pre-treatment and an adequate loading dose of clopidogrel have been permitted in PLATO, the peri-procedural benefit of ticagrelor is quite limited, potentially suggesting an additional advantage of combined acute use with intravenous glycoprotein (GP) IIb/IIIa inhibitors and bivalirudin.

**Heart surgery**

The heart surgery cohort shows a slight advantage of ticagrelor over clopidogrel. This is understandable since the experimental drug is reversible and can be easily discontinued if emergency coronary artery bypass graft (CABG) is required. There was a numerical trend towards fewer CABG-related bleeding events after ticagrelor; however, this benefit was not significant, and much less dominant than anticipated. Since heart surgeons are usually unhappy to operate on a patient on clopidogrel therapy, ticagrelor may offer a slightly better alternative with regard to bleeding risks.

**Cancer**

Cancer rates in PLATO trended lower after ticagrelor ($n = 132; 1.4\%$) than after clopidogrel ($n = 155; 1.7\%$). This is an extremely important finding since this issue is under scrutiny by regulatory agencies due to an unexpected increase of cancer with another antiplatelet agent. Based on the CAPRIE" and CHARISMA" trials, the FDA found no evidence that clopidogrel promotes cancer;" therefore, the lack of a cancer signal in PLATO with ticagrelor is reassuring, and will be an additional argument for future regulatory approval.

**Adverse events**

The adverse events profile with ticagrelor is clearly inferior to that with clopidogrel. In contrast to all thienopyridines, classical examples of adenosine overload such as transitory bronchoconstriction causing dyspnoea, arrhythmogenic hazards resulting in ventricular asystole or pauses, and metabolically induced anxiety manifesting itself as agitation or panic attacks were commonly observed after ticagrelor. Impaired purine catabolism due to increased adenosine levels may cause elevated serum creatinine and uric acid, more frequently observed with ticagrelor in PLATO. Importantly, both creatinine and uric acid return to pretreatment values after ticagrelor discontinuation, suggesting that the metabolic purine dysbalance is a real phenomenon, rather than a play of chance.

**Mechanisms**

Potential mechanisms responsible for such an accomplishment as observed in PLATO, especially with regard to the mortality benefit, are unclear. Claiming that such a remarkable outcome was anticipated is not in agreement with the facts, since the Phase II data yielded from the DISPERSE trials did not hint at such a sizeable advantage. In fact, combining the DISPERSE" and DISPERSE-II" data sets revealed an MI reduction from 4.3\% in clopidogrel to 2.4\% after ticagrelor, but the remainder of the vascular outcomes actually looked better for clopidogrel, including lower rates for severe recurrent ischaemia (2.1\% ticagrelor vs. 0.9\% clopidogrel), recurrent ischaemia (3.3\% vs 2.8\%), and—most importantly—deaths (1.95\% vs. 1.2\%, respectively). The mechanistic cornerstone of the outcome after ticagrelor as observed in PLATO is most probably directly related to the up-regulation of the adenosine receptors. In addition to causing reversible platelet inhibition, adenosine is involved in numerous biological activities including cardioprotection from reperfusion injury, apoptosis, myocyte regeneration, improved myocardial contractility, and electrical stability. Although ticagrelor is not an ATP analogue, and may not cause massive adenosine overload, changes in adenosine metabolism are critical for the comprehension of the PLATO results. Potential mechanisms that target adenosine metabolism through ticagrelor and which may affect vascular outcomes, platelets, and associated side effects are presented in Figure 1.

**Beyond platelets**

Based on the analyses of recent trials, the vascular outcome benefit of ticagrelor cannot be explained by faster and more potent platelet inhibition alone when compared with clopidogrel. The lack of a long-term advantage and of a mortality benefit in the TRITON trial, as well as identical death rates in the CURRENT study, clearly underscore the hypothesis that low platelet responsiveness after clopidogrel, the so-called ‘resistance’, causes worsened vascular outcomes. While the antiplatelet potency of the ticagrelor dose used in PLATO closely matched the prasugrel dosing regimen used in TRITON, the magnitude and timing of outcome patterns are entirely different. Therefore, it is probably not the faster speed of action, nor the higher potency of platelet inhibition with ticagrelor compared with clopidogrel, but clearly something beyond pure P2Y12 receptor inhibition by this novel cyclopentyl-triazolo-pyrimidine now known as ticagrelor. Being a pyrimidine, ticagrelor differs from thienopyridines (ticlopidine, clopidogrel, and prasugrel) by the reversible nature of P2Y12 blockade, exhibiting direct antiplatelet properties with no dependence on complicated hepatic metabolism. Considering that ticagrelor is a ‘first-in-class’ type of drug, and it is not a thienopyridine like ticlopidine, clopidogrel, and prasugrel, it seems that ADP receptor blockade may not be the most important commodity of ticagrelor. Most probably the mechanism responsible for such benefit is complex, related to the alterations of chronic adenosine modulation by purinoreceptors in blood, thereby potentially improving
myocardial contractility and vascular tone, and directly protecting cardiomyocytes. Considering that the adenosine receptors A1, A2A, A2B, and A3 modulate oppositely directed physiological functions, their interplay and differential up-regulation may explain some of the proarrhythmic properties of ticagrelor early during drug administration, with prevention of ventricular tachyarrhythmias and sudden death late in the trial. Since in PLATO ticagrelor prevented more deaths than MIs, it may be worthwhile to focus future investigations on the prevention of fatal ventricular tachycardias and sudden death, as well as other arrhythmias, and heart failure benefit rather than thrombotic occlusions alone.

**Summary**

The PLATO trial revealed a remarkable advantage of ticagrelor over clopidogrel in ACS patients. Unless the regulatory authorities discover serious flaws with the study, which is unlikely, the drug may substantially change the present landscape of oral antiplatelet therapy, especially in high-risk patients. Despite a somewhat unfavourable safety profile, ticagrelor has a lot of room to compensate for these well-defined side effects based on a documented absolute mortality reduction, solid prevention of MI, and convincing pattern of benefit growing over time.

**Conflict of interest:** V.L.S. is listed as an inventor and received compensation for the US Patent Application P-17232 ‘Method for treating vascular diseases with prasugrel’ assigned to Lilly. He received funding for research studies with both clopidogrel and prasugrel, but not with ticagrelor, and received speakers honoraria from Astra-Zeneca. D.A. received speakers and consultancies honoraria from Astra-Zeneca and Sanofi-Aventis.

**References**


4. ISIS-2. Trial Investigators. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial...