

The TRITON versus PLATO trials: Differences beyond platelet inhibition

Victor L. Serebruany

HeartDrug™ Research Laboratories, Towson, Maryland, USA

Summary

Clopidogrel monopoly as an exclusive oral antiplatelet agent used in combination with aspirin or as a monotherapy for treatment or/and prevention of occlusive thrombotic vascular events has been recently challenged. Based on the indirect comparison of TRITON and PLATO trial data, ticagrelor is clearly superior to prasugrel in a population of patients with acute coronary syndrome (ACS) because of absolute mortality reduction, realistic second myocardial infarction (MI) prevention, growing over time vascular outcome benefit, fewer haemorrhagic fatalities, potentially less coronary artery bypass graft (CABG)- related bleeding events, and lack of cancer risks. Despite an unfavourable immediate safety profile, ticagrelor has a lot of room to compensate for agitation, dyspnea, and ventricular pauses, if used in appropriate patients. It will be naïve and wrong to assume that ticagrelor will completely substitute clopidogrel, especially considering higher discontinu-

ation rates after ticagrelor, generic competition, and other health economics issues. However, unless the regulatory authorities discover some unexpected serious flaws with PLATO, the ticagrelor will substantially change the present landscape of oral antiplatelet therapy, especially in high-risk patients, diabetics, and those with repeated vascular events including stent thrombosis. In contrast, a too exclusive trial design, a lack of persistent vascular benefit despite issues with event adjudication, growing-over-time bleeding complications, an issue with cancer, and finally an increase in mortality risk among unstable angina and non ST-elevated myocardial infarction will likely prevent a broad prasugrel implementation, unless more reassuring evidence becomes available.

Keywords

Prasugrel, ticagrelor, clopidogrel, clinical trials, outcomes

Correspondence to:

Dr. Serebruany
HeartDrug™ Research Laboratories
Johns Hopkins University, Osler Medical Building
7600 Osler Drive, Suite 307
Towson, Maryland, 21204, USA
Tel.: +1 410 847 9490, Fax: +1 443 583 0205
E-mail: heartdrug@aol.com

Received: October 11, 2009

Accepted after minor revision: November 2, 2009

Prepublished online: December 18, 2009

doi:10.1160/TH09-10-0695

Thromb Haemost 2010; 103: 259–261

The era of clopidogrel monopoly as an exclusive oral antiplatelet agent used in combination with aspirin or as a monotherapy for treatment or/and prevention of occlusive thrombotic vascular events has been recently challenged. Large inter-individual response variability, delayed onset of action, two-step hepatic metabolism, and potential link of inadequate response and worsened vascular outcomes triggered the development of new antiplatelet options. Two studies, namely, Trial to assess Improvement in Therapeutic Outcomes by optimizing platelet Inhibition with prasugrel (TRITON) (1), and Platelet Inhibition and Clinical Outcomes (PLATO) (2) trials were phase 3, randomised, double blind, parallel-group, multinational, clinical studies. Both trials compared head-to-head the efficacy of antiplatelet agents: third generation thienopyridine, prasugrel (formerly known as CS-747, marketed as Effient®), and a pioneer cyclopentyl-triazolo-pyrimidine, ticagrelor (formerly known as AZD6140, to be marketing as Brilinta®) versus standard care with clopidogrel. There are substantial differences between ticagrelor and prasugrel. Being a pyrimidine, ticagrelor differs from tienopyridines (ticlopidine, clopidogrel and prasugrel) by reversible nature of P2Y12 blockade, exhibiting direct antiplatelet properties with no dependence on complicated hepatic metabolism. Ticagrelor plasma levels are maintained for no longer than 12 hours, requiring twice daily oral use.

In contrast, prasugrel undergo one-step CYP3A4 hepatic metabolism, targets the cell for the life span of platelet, irreversibly binding to P2Y12 receptors, and subjected to potentially harmful drug-drug interactions. Although no direct platelet inhibition studies among prasugrel, ticagrelor, and clopidogrel are available, in both trials the antiplatelet potency of ticagrelor was similar to prasugrel (about 65–70% inhibition) compared to approximately 40% platelet inhibition achieved after clopidogrel. Importantly, we should be careful in cross-comparing differently designed studies, some assumptions and considerations seem appropriate. Both trials were relatively large, with the identical primary efficacy endpoints (combination of the first occurrence of cardiovascular death, non-fatal myocardial infarction, and stroke), with a relatively long follow up. Patients demographics, antecedent treatment patterns, inclusion of diabetics were very similar between trials. However, there were some notable differences in the trial designs which are outlined in ► Table 1. In order to match more closely, numbers in the clopidogrel arm were exclusively used in Table 1.

Comparison of baseline characteristics between the two trials revealed that PLATO sample size was about 30% larger, with the higher overall ischemic burden than in TRITON. Allowing pretreatment, and higher than 300 mg loading with clopidogrel, in

Table 1: Baseline differences in TRITON and PLATO trials.

Clinical variable	TRITON	PLATO
Sample size (n)	6,795	9,291
ST-elevated MI (%)	26	38
Inclusion: defined coronary anatomy	Yes	No
CABG (%)	1	4.7
Pretreatment with clopidogrel (%)	0	46.1
Clopidogrel loading dose 600 mg+ (%)	0	>19.6
Loading regimen for experimental agent	Yes, 6 : 1	No, 1 : 1
Glycoprotein IIb/IIIa inhibitor use (%)	55	26.8
Follow-up (months)	6–15	12
Switching to clopidogrel at the end of follow-up	Mandatory	Discretion of physician

combination with the inclusion of high-risk coronary artery bypass graft (CABG) patients makes PLATO much more relevant to the real-life clinical scenarios than TRITON, in which multiple exclusions have been implemented. Importantly, platelet GP IIb/IIIa inhibitors were used twice more common in TRITON, and prasugrel loading dose (60 mg) was six times higher than maintenance (10 mg) than in PLATO where loading and daily maintenance regimens were equal (180 mg). Both trials unfortunately decided not to continue the follow-up of their patients as a registry after unblinding; however, PLATO patients were allowed to remain treated with either ticagrelor or clopidogrel at physician's discretion, when all prasugrel-treated patients in TRITON were mandatory switched to clopidogrel. Both trials failed to continue the follow up in the frame of the open-label registry despite the claims of late stent thrombosis prevention. This fact is understandable for the exit strategy in TRITON, where the bleeding risks, and cancer rates after prasugrel grow over time (3), so as very recently reported consistent extra deaths among unstable angina and non-ST-elevated myocardial infarction (MI) patients (4). However, it was unfortunate and surprising for the PLATO investigators not to continue the follow up, when the benefit of ticagrelor over clopidogrel was so obvious, and most importantly, was growing over time (2).

Table 2: Clinical outcomes in TRITON versus PLATO trials.

Outcome measure	TRITON	PLATO
All-cause mortality reduction (%)	4.57 or less	21.15
Cardiovascular mortality reduction (%)	11.33	21.14
Non fatal MI reduction (%)	9.5 to 7.3*	6.9 to 5.8*
Fatal bleeding events versus clopidogrel (n)	21/5	20/23
Timing of benefit	Early	Growing over time
Any malignancy during treatment in active arm (%)	1.59	1.25

* – first number represents the outcome in the clopidogrel arm, second number is for the experimental agent.

The largest differences, however, were observed in the outcomes for both studies, which are outlined in ► Table 2.

Mortality. This hardest to get, and the unquestionably most important outcome measure represents the largest difference between trials. There were 107 more lives saved with ticagrelor than after conventional clopidogrel (399 vs. 506), representing a highly significant absolute mortality reduction (hazard ratio [HR]=0.78; confidence interval [CI]=0.69–0.89; $p<0.001$) (2). This mortality advantage make ticagrelor a top achiever among any antiplatelet agent in a setting of a large randomised trial against an active comparator. In contrast, prasugrel failed to show any mortality benefit over clopidogrel in the TRITON trial (1). While cardiovascular deaths slightly trended in favour of prasugrel (133 vs. 150), however, excess in bleeding fatalities (21 vs. 5), and four extra cancer-related deaths after prasugrel dilute the benefit almost completely. Moreover, final FDA notes from the Prasugrel Action Package revealed more deaths after prasugrel (5 vs. 2) in patients lost in follow-up without primary endpoints (4). In short, while the entire prasugrel benefit in TRITON is exclusively attributed to the reduction of non fatal MIs, in PLATO, the mortality reduction (107 deaths) numerically exceeds the MI prevention benefit (89 events), making it a hitherto unmatched achievement (5), and representing the major clinical outcome difference between the two trials.

Myocardial infarction. At a first glance, the overall nonfatal MI reduction looks more impressive in TRITON than in PLATO. Indeed, the benefit of prasugrel in MI reduction in TRITON is 23.2%, when second MI prevention benefit of ticagrelor in PLATO was “only” 16%. However, there is an important difference between trials. The PLATO MI rates are realistic, match well with other similar studies like CURRENT (6) and ACUITY (7), in contrast to TRITON, where MI adjudication is a matter of considerable controversy due to massive inclusion of extra events (8, 9), half of which were enzymatic or “chemical” MIs rather than real clinical events not identified by investigators, but still adjudicated (3, 4). Therefore, MI prevention in PLATO and TRITON should be judged not only by the absolute difference between the treatment arms both favouring novel antiplatelet agents, but also acknowledging that MI adjudication in PLATO was handled utilising realistic, strict universal acute MI definition (10) rather than inflated assessment of MIs adding enzymatic leaks and almost every ischaemic episode to the totality of evidence. Indeed, following the recent worldwide trend towards lower MI rates (11), a reduction from 6.9% in the clopidogrel arm to 5.8% after ticagrelor – especially late in the trial – unquestionably represents a solid achievement over both clopidogrel and prasugrel.

Timing of benefit in PLATO looks ideal for long-term therapy, in contrast to the TRITON outcome curves. The benefit after ticagrelor is somewhat delayed, what is not surprising considering lack of loading; growing slowly, but constantly over the entire time of the trial (2). The largest outcome benefit is observed at the end of the follow-up, ultimately justifying a chronic treatment regimen with ticagrelor. TRITON, however, revealed early periprocedural benefit of prasugrel over clopidogrel, with lack of additional advantage thereafter (3, 4).

Heart surgery cohort shows a slight advantage of ticagrelor, in contrast to prasugrel inferiority over clopidogrel with regard to the

CABG-associated bleeding risks. However, the anticipated benefit of bleeding reduction due to the reversible nature of P2Y₁₂ platelet receptor blockade after ticagrelor was clearly exaggerated, and was not achieved in PLATO. It turns out that theoretical considerations did not yield the desired benefit challenging the reversibility hypothesis, and practicality of twice daily maintenance ticagrelor regimen. Since heart surgeons are usually discontented to operate on patients with clopidogrel on board (12), ticagrelor may offer a slightly better alternative with regard to bleeding risks, in comparison to prasugrel, causing 3.5 times higher CABG-associated bleeding events than clopidogrel in TRITON.

Cancer risks after prasugrel in TRITON are growing over time, especially in women, and results in 27% increase in colorectal, lung, and breast solid malignancies is alarming (3, 4, 13). Although unaudited, the cancer rates in PLATO trended lower after ticagrelor (n=132; 1.4%) than after clopidogrel (n=155; 1.7%) (2). Based on the CAPRIE (14), and CHARISMA (15) trials, the FDA found no evidence that clopidogrel promotes cancer (3), therefore, lack of a cancer signal in PLATO with ticagrelor is reassuring, and will be an additional argument for future chronic use. If confirmed by regulatory agencies, differences in cancer risks will represent an extremely important finding favoring ticagrelor over prasugrel.

Side events profile of ticagrelor is clearly inferior to prasugrel, and clopidogrel. In contrast to all thienopyridines, classical consequences of adenosine overload such as transitory bronchospasm causing dyspnea (16); arrhythmogenic hazards resulting in ventricular asystole or pauses (17); and metabolically-induced anxiety manifesting as agitation or panic attacks (18) are commonly observed after ticagrelor. Impaired purine catabolism due to increased adenosine levels may cause elevated serum creatinine and uric acid (19), which were observed with ticagrelor in PLATO, the phenomenon not attributed to clopidogrel or prasugrel. Importantly, both creatinine and uric acid return to pretreatment values after ticagrelor discontinuation (1), suggesting that the alterations in purine metabolism is a real phenomenon, rather than a play of chance.

In summary, based on the indirect comparison of TRITON and PLATO trial data, ticagrelor is clearly superior to prasugrel for chronic preventive use because of absolute mortality reduction, realistic second MI prevention, growing over time vascular outcome benefit, fewer haemorrhagic fatalities, potentially less CABG-related bleeding events, and lack of cancer risks. Despite an unfavourable immediate safety profile, ticagrelor has a lot of room to compensate for agitation, dyspnea, and ventricular pauses, if used in appropriate patients. It will be naïve and wrong to assume that ticagrelor will completely substitute clopidogrel, especially considering higher discontinuation rates after ticagrelor, generic competition, and other health economics issues. Obviously, favourable safety profile and acceptable bleeding risks after clopidogrel represent a major driving force for broad use of this agent in a wide spectrum of patients with underlying vascular disease. However, unless the regulatory authorities discover some unexpected serious flaws with PLATO, the ticagrelor will substantially change the present landscape of oral antiplatelet therapy, especially in high-risk patients, diabetics, and those with repeated vascular

events including stent thrombosis. Importantly, both PLATO and TRITON trials included exclusively acute coronary syndrome (ACS) patients. Data for both new agents in stable coronary disease, or for elective stenting are very limited. In conclusion, based on the indirect and admittedly intricate comparison of the TRITON and PLATO trial data, ticagrelor appears superior to prasugrel in the populations of ACS studied.

Disclosure

Dr. Serebruany is listed as an inventor and received compensation for the U.S. 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, but received speakers honoraria from Astra Zeneca.

References

1. Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2007; 357: 2001–2015.
2. Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2009; 361: 1045–1057.
3. The FDA Prasugrel Secondary Review. Available for download at <http://www.fda.gov/ohrms/dockets/ac/09/briefing/2009-4412b1-00-FDA.htm>
4. The FDA Prasugrel Action Package. Available for download at <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseact>
5. Serebruany VL, Atar D. The PLATO trial: Do you believe in magic? *Eur Heart J* 2009; in press.
6. CURRENT Investigators: A 2X2 Factorial Randomized Trial of Optimal Clopidogrel and Aspirin Dosing in Patients with ACS Undergoing an Early Invasive Strategy with Intent For PCI (OASIS-7 trial). Presented at European College of Cardiology Meeting, Barcelona, August 30, 2009.
7. Stone GW, McLaurin BT, Cox DA, et al. Bivalirudin for patients with acute coronary syndromes. *N Engl J Med* 2006; 355: 2203–2216.
8. Serebruany V. Excess rates of nonfatal myocardial infarction in the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel: preventing clinical events or chasing enzymatic ghosts? *Am J Cardiol* 2008; 101: 1364–1366.
9. Serebruany V. The FDA Prasugrel Review: Adjudication of myocardial infarction controversy. *Cardiology* 2009; 114: 126–129.
10. Thygesen K, Alpert JS, White HD on behalf of the Joint ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction. Universal definition of myocardial infarction. *Eur Heart J* 2007; 28: 2525–2538.
11. Stolt Steiger V, Goy JJ, et al. Significant decrease in in-hospital mortality and major adverse cardiac events in Swiss STEMI patients between 2000 and December 2007. *Swiss Med Wkly* 2009; 139: 453–457.
12. Kulik A, Chan V, Ruel M. Antiplatelet therapy and coronary artery bypass graft surgery: perioperative safety and efficacy. *Expert Opin Drug Saf* 2009; 8: 169–182.
13. Serebruany VL. Prasugrel and cancer risks: Potential causes and implications. *Am J Med* 2009; 122: 407–408.
14. CAPRIE Steering Committee. A randomized, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events. *Lancet* 1996; 348: 1329–1339.
15. Bhatt DL, Fox KA, Hacke W, et al. Clopidogrel and Aspirin versus Aspirin Alone for the Prevention of Atherothrombotic Events. *N Engl J Med* 2006; 354: 1706–1717.
16. Serebruany VL, Stebbing J, Atar D. Dyspnea after antiplatelet agents: the AZD6140 controversy. *Int J Clin Pract* 2007; 61: 529–533.
17. Stark U, Brodmann M, Lueger A, Stark G. Antiarrhythmic effects of adenosine on ischemia-induced ventricular fibrillation. *J Crit Care* 2001; 16: 8–16.
18. Stutzmann GE, Marek GJ, Aghajanian GK. Adenosine preferentially suppresses serotonin_{2A} receptor-enhanced excitatory postsynaptic currents in layer V neurons of the rat medial prefrontal cortex. *Neuroscience* 2001; 105: 55–69.
19. Amorini AM, Petzold A, Tavazzi B, et al. Increase of uric acid and purine compounds in biological fluids of multiple sclerosis patients. *Clin Biochem* 2009; 42: 1001–1006.