The PLATO trial reveals further opportunities to improve outcomes in patients with acute coronary syndrome

Editorial on Serebruany. “Viewpoint: Paradoxical excess mortality in the PLATO trial should be independently verified” (Thromb Haemost 2011; 105.5)

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Acute coronary syndrome (ACS) and its complications are caused by ruptures of atherosclerotic plaques leading to aggregation of platelets and the formation of thrombi at the lesion or an implanted coronary stent. Before the era of early routine coronary stenting, platelet inhibition with aspirin was shown to reduce the risk of myocardial infarction (MI) and improve survival in this setting. In the current era of routine early percutaneous coronary intervention (PCI) further attenuation of platelet aggregation by either P2Y12-receptor inhibition with thienopyridines or glycoprotein 2b/3a inhibitors has provided further reduction of the risk of MI but without any accompanying decrease in mortality (1–4). This disconnect might be explained by a reduction mainly of procedure-related MIs with no consequences for long-term mortality (5) and by an increase in major bleeding associated with raised long-term mortality (6). The PLATElet Inhibition and Clinical Outcomes (PLATO) trial compared the new directly and reversibly acting P2Y12 inhibitor ticagrelor with clopidogrel in 18,624 patients with ST-elevation or moderate-high risk non-ST-elevation ACS recruited in 862 sites and 43 countries (7). In patients assigned to ticagrelor there was a reduction in the primary outcome composite of cardiovascular death, MI, and stroke from 11.7% to 9.8% per year compared to clopidogrel (p<0.001). Ticagrelor also reduced spontaneous and procedure related MI and stent thrombosis as well as cardiovascular and total mortality (7). These benefits were consistent across a spectrum of patients with ACS as evidenced in a series of predefined additional subanalyses from the PLATO trial (8–14). The PLATO trial has therefore shown ticagrelor’s ability to further improve survival beyond the currently recommended treatment strategies in a broad spectrum of patients with ACS most likely because of its capacity to further reduce spontaneous as well as procedure related MI and stent thrombosis without increasing the overall risk of bleeding or other potentially fatal adverse events (7).

In a viewpoint article in this journal (15) there is extensive speculation on various aspects of the PLATO trial conduct and post-hoc dissection of results and inappropriate cross-trial comparisons far outside sound scientific methodology. As the responsible academic investigators we can confidently state that PLATO successfully tested its main hypothesis by incorporating all features of large outcome clinical trials that provide minimal bias and the highest scientific validity, integrity and ethical standards: it was randomised, double-blind, and multicentre; it followed Good Clinical Practice (GCP) and the ethical principles of the Declaration of Helsinki; it was coordinated by highly respected academic research organisations with decades of experience with conducting phase III clinical trials; an academic executive committee comprising international experts in acute coronary syndromes were responsible for the design and the medical, scientific, and operational conduct of PLATO; sites experienced in conducting clinical trials with clinicians expert in treating ACS participated; an independent data and safety monitoring board followed the trial closely during its conduct; an independent committee of expert cardiologists and neurologists blinded to assigned treatment adjudicated the primary and secondary efficacy and bleeding endpoint events (16). For every patient and every site participating in PLATO, reports of vital status, i.e. alive or dead, were correct. Hundreds of automated checks generated thousands of data queries to sites to verify information submitted prior to locking the database comprised of over 22 million entries. Additional manual checks after database lock of the several hundred cases of mortality confirmed correct entries with a single exception: an adjudicator mistranscribed a major bleeding event as a fatal bleed. Having detected this single discrepancy following database lock, the executive committee directed the sponsor to maintain the integrity of the results by not re-analysing those data, but rather by footnoting the instance, especially because this conservative action did not increase the numerical advantage of ticagrelor over clopidogrel in fatal bleeds (20 instead of 19 compared to 23) (7). No patient was reported by a site as dead and later found alive. Investigators submitted death and autopsy reports, hospital death records, and local death registries to substantiate mortality events. The executive committee designed and agreed prospectively on the statistical analysis plans both for the main study and ancillary studies and also had full access to the PLATO database and independently performed or verified all endpoint analyses. As a matter of fact there was and still is a unique transparency of data in the trial between the academic investigators and the sponsor. Both the academic coordinating centres (DCRI and UCR) as well as AstraZeneca have independent access to the complete database. The investigators and sponsor have formed a Statistical Working Group with a...
sharing of ideas and obtaining agreements on using similar or alternative analytic methods allowing the ability to validate analyses by multiple groups and approaches. This type of collegial interaction has now become a great model, which also is implemented in other academic-industry collaborations in our global VIGOUR network clinical trials organisation.

A treatment by region interaction emerged from a large number of tested subgroups, comprising a failure to show the advantages of ticagrelor over clopidogrel in North America, and in particular the United States. Large multinational clinical trials should not undergo a country-by-country evaluation: statistically significant differences between treatments are not expected for each of many dozens of countries. Rather, results should vary from country to country, and distribute across the spectrum, with many clustered near the overall result and others showing more extreme effects in both directions. In PLATO, hazard ratio point estimates varied by country from 0.77 to 1.27, with 31 of 43 (72%) <1.00, as expected for the overall 0.84, showing a clear benefit of ticagrelor over clopidogrel. [Ticagrelor NDA 22–443 Briefing Document for Cardiovascular and Renal Drugs Advisory Committee Meeting. June 2010] The results were not related to the size of countries or enrolment as the top 10 enrolling countries distributed exactly as the countries as a whole: seven countries had hazard ratio point estimates favouring ticagrelor. Country results did not show any relation with the source of site monitors as both sponsor-monitored and non-sponsor monitored countries had results across the expected spectrum of outcomes. Even when excluding the largest enrolling countries with results favouring ticagrelor (Poland and Hungary) the overall result still favours ticagrelor. [Ticagrelor NDA 22–443 Briefing Document for Cardiovascular and Renal Drugs Advisory Committee Meeting. June 2010, http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/UCM220197.pdf]

Initially the treatment by region interaction was by most evaluators considered a chance finding; however, an extensive analysis of the PLATO database independently performed by both the sponsor and the executive committee, finally implicated a higher maintenance dose of concomitant acetylsalicylic acid (ASA), used by half the patients in the USA but rarely outside the USA, as the origin of the apparent treatment by region interaction. In December 2010 the Food and Drug Administration (FDA) requested additional ASA dose analyses from PLATO which were provided in January 2011. A forthcoming publication from the executive committee, currently under review, will shortly publish the detailed ASA-related findings. Considering this interaction, the PLATO results indicate that ticagrelor is even more effective than in the overall trial population, if used with lower dose maintenance ASA both within and outside North America.

As the PLATO results differ from some recent ACS trials regarding the continuous long-term gain in ischaemic events and survival, it is important to understand the potential reasons for the differences in outcome. Previous trials showing benefits of more intense and rapid onset P2Y12-inhibitors versus clopidogrel, on top of aspirin, have shown their main effect early related to the slow onset of a 300 mg loading dose of clopidogrel and mainly reduced early events in association with coronary procedures (17). In contrast to most other trials, PLATO included a broad ACS population with both ST-elevation and non-ST-elevation ACS, regardless of pre-treatment with, or loading dose of, clopidogrel; regardless of planned early procedures; and regardless of timing of ongoing MI and thereby limited opportunities for diagnosing early recurrent MI. Therefore the PLATO trial contains many different subpopulations some of which might be used to illustrate similarities in outcomes with other trials. Thus, the outcome in patients with a genetic predisposition to poor response to clopidogrel (Fig. 1A) seems to reflect the outcomes in the TRITON trial (17) which focused on clopidogrel-naive patients starting with a low 300 mg loading.
dose and its attendant slow onset of the platelet inhibitory effect. The PLATO results in the patient population with a genetic predisposition to good response to clopidogrel (Fig. 1B) seem then to reflect the continuing superiority of ticagrelor versus clopidogrel during long-term treatment regardless of genetic polymorphisms. Thus with ticagrelor there is superiority over clopidogrel regardless of patient genotype (interaction p=0.46) although the timing of benefit might vary between different subpopulations (13). These results also illustrate the hazards of performing cross-trial comparisons. Trials like PLATO (7), designed specifically to enrol a broad patient population including both ST-elevation MI patients planned for invasive procedures and medium-high risk patients with non-ST-elevation ACS planned for either an invasive or non-invasive treatment strategy, would not be expected to have the same event rates or time course of events as studies with more restrictive inclusion criteria and a required intervention strategy such as TRITON (17). However, compared to trials with corresponding patient populations, the magnitude and time course of cardiovascular mortality for the clopidogrel arm in PLATO is similar with that seen in CURE-trial (18), and also similar to the outcomes in the more recent ACS trials OASIS-5 (6), OASIS-6 (19) and ACUTY (20). 

Currently the PLATO Executive Committee is continuing to explore eventual additional reasons for the long-term mortality benefits with ticagrelor or beyond its recognised platelet inhibitory effects. Potential explanations include modulation of endogenous adenosine concentrations particularly over long periods of time, as well as attenuated vascular and inflammatory responses. Further clinical outcome studies with ticagrelor, including the now active PEGASUS-TIMI 54 trial [see http://www.clinicaltrials.gov] will also provide additional insights into the benefits of ticagrelor. Based on the PLATO results ticagrelor has now achieved marketing approval in 30 countries and is under regulatory review in 21 additional countries, including the USA. The FDA Advisory Committee in July, 2010 voted 7 to 1 to approve ticagrelor for the reduction of thrombotic events in patients with non-ST-elevation and ST-elevation ACS intended to be managed by PCI or medically. Therefore, based on observations provided by the PLATO trial, patients with ACS worldwide now can expect a better treatment with less risk of recurrent MI, stent thrombosis and a better survival.

Conflict of interest
Dr. Wallentin reports having received grant support from Astra Zeneca, Boehringer Ingelheim, Eli Lilly, Pfizer-Bristol- Myers Squibb, GlaxoSmithKline, Merck-Schering-Plough and consulting fees from the biotechnology companies Regado, Athera, Evolva and Portola.

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References