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Letter to the Editor

Review of the accumulated PLATO documentation supports reliable and consistent superiority of ticagrelor over clopidogrel in patients with acute coronary syndrome

Commentary on: DiNicolantonio JJ, Tomek A, Inactivations, deletions, non-adjudications, and downgrades of clinical endpoints on ticagrelor: Serious concerns over the reliability of the PLATO trial, International Journal of Cardiology, 2013

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Four years ago we presented the first results from Platelet Inhibition and Patient Outcomes (PLATO) trial testing the superiority of ticagrelor as compared with clopidogrel in 18,624 patients with ST-elevation myocardial infarction (STE-MI) or non-ST-elevation acute coronary syndromes (NSTE-ACS) from 41 countries [1]. The trial met its primary objective and showed a significant reduction in the primary composite (death from vascular causes, myocardial infarction, or stroke) with ticagrelor compared to clopidogrel (9.8% vs. 11.7%, Hazard Ratio [HR] 0.84, 95% confidence interval [CI]: 0.77–0.92, $p < 0.001$, respectively). There were also significant reductions of the individual endpoints of total death, cardiovascular death, myocardial infarction and stent thrombosis. There were no differences in overall major bleeding but a significant increase in non-procedure related major bleeding. The results were consistent across 32 different predefined subgroups except for geography where there was an interaction and an indication of a different efficacy result in North America [2].

The PLATO study group has since 2009 performed, presented and, in major medical scientific journals, published a long series of predefined and post-hoc analyses to further explore and better understand the effects of ticagrelor. The results have been very consistent with similar results in patients with STEMI or NSTE-ACS [3], intention for invasive or non-invasive treatment [4,5], diabetes mellitus or not [6], renal dysfunction or not [7], elderly or younger [8], non-smokers or smokers [9], pulmonary disease or not [10,11] and previous stroke or not [12]. Stent thrombosis was reduced both with bare-metal and drug eluting stents when compared with both higher and lower clopidogrel loading doses [13]. The reduction of mortality was shown caused by a combination of less cardiovascular, bleeding and infection-related deaths [14]. The reduction of cardiovascular events was consistent both in patients with and without CYP2C19 loss-of-function polymorphisms [15].

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The geographical heterogeneity with lack of superiority of ticagrelor in the U.S. was found likely explained by an interaction with the use of a high dose aspirin in about half of the patients in North-America, which was in accordance with a similar lack of efficacy in the very small proportion with a high aspirin dose in the rest of the world, although chance alone cannot be excluded as an explanation [16]. No interaction has been shown with other medications e.g. proton-pump inhibitors [17]. The reduction in event rate by ticagrelor has also been shown consistent over time with a reduction not only of the first but also of the total number of events over the whole treatment period [18]. Finally the cost-effectiveness analysis shows a very favorable incremental cost per life-year gained [19].

These results have led to regulatory approval of ticagrelor for the treatment of STEMI and NSTE-ACS in 100 countries worldwide. Furthermore the European, AHA/ACC and other guideline committees now are recommending ticagrelor as a first line treatment both in STEMI treated with primary PCI and in NSTE-ACS regardless if an invasive or non-invasive treatment strategy is used [20–22]. Importantly the uptake of ticagrelor as the preferred P_2Y_{12} inhibitor has been rapid in many countries, not least in Europe, where now further improved survival and reduction of recurrent ischaemic events can be expected. Because of the geographical heterogeneity with a lack of benefit of ticagrelor in the U.S. cohort the FDA reviewers very critically and meticulously scrutinized the ticagrelor submission. Therefore there passed around a year before the publication of all FDA internal documents in 2011. After a public and internal discussion of all available information FDA approval was granted based on the 8 out of 9 favorable votes at the advisory committee meeting.

Two individuals have in a number of publications, several of which in IJC, repeated their doubts about the validity of the PLATO results. In a recent paper in International Journal of Cardiology in August 2013, one of these authors is allowed to publish serious accusations that the PLATO trial academic leadership, operational staff, investigators, monitors, event adjudicators and the sponsor have committed illegal and fraudulent actions by secretly breaking the blinding of the study treatment and intentionally deleted, concealed, underreported, downgraded or misadjudicated events in patients that they are claimed to have known were assigned to ticagrelor (by unknown means) [23].

In the paper [23] the authors present analyses, without describing the statistical methodology, based on reported outcomes in 10 out of 41 countries claiming that monitoring of the study by the sponsor should have provided more favorable results of ticagrelor than monitoring by a CRO. This issue has however already previously been addressed by two senior academic statisticians using advanced multivariable statistical technologies based on the whole study population in all the 41 countries [24]. The complete results were recently published in a peer-reviewed journal concluding that: “When examined in the overall population of patients, there was a treatment by monitoring source interaction and monitoring source appears to account for 61% of the treatment by region interaction. While this is an interesting observation, all U.S. sites were monitored by non-Sponsor personnel. Hence, it is likely that treatment by region and treatment by monitor interactions are strongly confounded and lead to an expectation that both are individually explained by the interaction of treatment and ASA maintenance dose. A sequence of Cox regression models was applied to the data in an attempt to better appreciate the interplay between region, monitoring source and ASA maintenance dose. These analyses confirmed the stated expectation. Hence, while it is not possible to draw firm conclusions about whether monitoring source is an independent contributor or explanatory effect, it appears that ASA maintenance dose remains the dominant covariate in explaining the interaction between region and randomized treatment.” Thus, based on appropriate statistical analyses there is no reason to suspect an influence of monitoring organization on the study outcomes in the PLATO trial.

In the IJC manuscript there are completely unfounded accusations that the PLATO study was not adequately blinded [23]. In contrast, the PLATO trial was a carefully blinded study in accordance with the GCP guidelines. According to the protocol, the treatment code should not be broken except in medical emergencies when the appropriate management of the patient necessitates knowledge of the treatment randomization. In order to meet FDA and other regulatory agencies reporting requirements, for expedited SAE reporting, Suspected Unexpected Serious Adverse Reactions (SUSAR), Patient Safety personnel not directly involved with the conduct of the study were unblinded in order to appropriately process SAE reports. This is a common procedure in clinical outcome studies, in order to secure patient safety during study conduct. In the full analysis set 452 out of 18,624 patients were unblinded for any reason prior to database lock (DBL). There was no imbalance between treatment arms. 238 (2.6%) patients randomized to ticagrelor were unblinded by any reason prior to DBL, as compared to 214 (2.3%) of the patients randomized to clopidogrel. In many of these cases unblinding did occur after patients had completed the randomized study period event free or after experiencing an event comprised by the primary endpoint. 155 (1.7%) of the patients randomized to ticagrelor were unblinded while still contributing to the primary analysis, as compared to 118 (1.3%) of those randomized to clopidogrel. The number of patients being unblinded prior to experiencing an event included in the primary endpoint was also similar between treatment arm, 13 on ticagrelor and 15 on clopidogrel. To demonstrate that unblinding of treatment allocation prior to a primary endpoint did not affect the outcome of the study, all 15 patients randomized to clopidogrel, with a treatment allocation known to anyone prior to the occurrence of the event, were censored at the earliest occasion of unblinding. The results of this sensitivity analysis verified that the difference in the primary composite endpoint remained statistically significant. These results were submitted to the FDA in response to questions from the FDA reviewer prior to approval of ticagrelor. The FDA reviewer found one misclassified patient, among 389 who were unblinded for SUSAR reporting, but refers to no other errors despite having access to full data set for the entire 18,624 patients (corresponding to 0.005%). The FDA Division Director has the following comment on this issue: “Although Dr. Marciniak seems suspicious, neither he nor DSI found evidence of sponsor misbehaviour. Considering the effort Dr. Marciniak expended on review of individual cases, he found relatively few problems of any kind. As far as I can tell, data quality issues are not of great concern.”

The IJC paper also accuses the PLATO trial for unfair reporting and analyses of myocardial infarction and present some tables on this issue based on data accumulated from a diversity of documents [23]. These results are not in agreement with our recently presented analyses of myocardial infarction using the raw data sets from all individual PLATO patients (Mahaffey K et al, ACC Scientific Sessions, March 2013). The following is a summary of these results. “In the PLATO trial a central clinical events committee (CEC) prospectively defined and adjudicated all suspected MI events. Treatment comparisons used CEC-adjudicated data and, per protocol, excluded silent MI. Overall, 1300 (611 ticagrelor, 689 clopidogrel) MIs reported by the CEC occurred during the trial. Of these, 1097 (504 ticagrelor, 593 clopidogrel) contributed to the primary composite endpoint. Site investigators reported 1198 (580 ticagrelor, 618 clopidogrel) MIs. Ticagrelor reduced overall 12-month Kaplan–Meier MI rates (5.8% ticagrelor, 6.9% clopidogrel; hazard ratio [HR]: 0.84; 95% confidence interval [CI]: 0.75–0.95). Analyses of overall MI using site investigator reported data showed similar results HR: 0.88; 95% CI: 0.78–1.00.” Thus, in contrast to what is stated in the IJC manuscript, ticagrelor significantly reduced the incidence of MI compared with clopidogrel, with consistent results both based on CEC evaluation and site reporting.

Most other issues raised in the IJC manuscript [23] are copied from the FDA Documents and mainly from the statements of the Medical Reviewer Dr. Marciniak. These questions have already previously been addressed by the FDA Division Director Dr. Norman Stockbridge in his final report on the PLATO trial evaluation, which also is available in the FDA

website. The FDA Division Director expressed the opinion that the data quality issues overall were few and of no great concern in relation to the anecdotal cases that the Medical Reviewer considered problematic. The FDA Division comments on the data quality in his review prior to the approval of ticagrelor: "Dr. Marciniak's review contains anecdotes for (23) cases he considers problematic. These amounts to about one case per 1000 subjects enrolled, but without subject IDs some of the descriptions may refer to the same subject. Importantly, Dr. Marciniak's review gives little insight into how cases came under his scrutiny, so the possibility exists for the inadvertent introduction of bias in case selection. Thus, one has to decide whether the total number of problems identified by Dr. Marciniak is enough to call for re-evaluation or a new study, but I do not believe that one can make reliable inference from the distribution of cases Dr. Marciniak identified by treatment groups."

As experienced scientists, authors of many scientific papers and members of editorial boards of several journals we are amazed that IJC publishes these unfounded accusations of fraudulent behavior in the PLATO trial. We find such allegations unacceptable in a peer-reviewed scientific journal especially when based on erroneous data, improper statistical methodology, and severely biased citations of already refuted data and statements from other publications and a long series of self-citations. Given the severity of the accusations made, we would have expected the IJC editors to provide the PLATO authors an opportunity to review and respond to this manuscript before committing to its publication. As members of the cardiovascular scientific community, we support the notions of open access to analyses of data as one more way to assure validity of clinical trial information. The complete PLATO database is available at two independent academic institutions, which continuously perform and publish new analyses in peer-reviewed major scientific journals based on requests from and collaboration between the PLATO investigators and involving also other investigators. Unfortunately the paper in IJC is an example of the dangers of open access to data when the peer review and editorial processes fail to do due diligence.

The results of the PLATO as other clinical trials with ticagrelor have fully been disclosed in documents from regulatory agencies and extensively published in peer-reviewed journals and are of course open for scientific discussion and debate. Any reader of scientific papers should be able to review the results critically, draw conclusions and translate the results into clinical practice. In doing so, the reader can be confident that the reported DSMB monitored, regulatory agency scrutinized and peer-reviewed published data from the PLATO trial, as well as from other meticulously performed clinical trials, are correct and reported without bias. This extremely well regulated process might seem both overly slow and forbiddingly costly but is still the safest way to bring new innovative treatments to our patients. Based on such a long process with PLATO, now is the time to switch from investigation to implementation of ticagrelor in the majority of patients with acute coronary syndrome in order to improve their survival and reduce the risk of recurrent events.

Conflicts of interest

LW: Research grants from AstraZeneca, Merck & Co, Boehringer-Ingelheim, Bristol-Myers Squibb/Pfizer, GlaxoSmithKline; consultant for Merck & Co, Regado Biosciences, Evolva, Portola, C.S.L. Behring, Athera Biotechnologies, Boehringer-Ingelheim, AstraZeneca, GlaxoSmithKline, and Bristol-Myers Squibb/Pfizer; lecture fees from AstraZeneca, Boehringer-Ingelheim, Bristol-Myers Squibb/Pfizer, GlaxoSmithKline, and Merck & Co.; honoraria from Boehringer Ingelheim, AstraZeneca, Bristol-Myers Squibb/Pfizer, GlaxoSmithKline, and Merck & Co.; travel support from AstraZeneca and Bristol-Myers Squibb/Pfizer. **RCB**: Scientific advisory: Merck, Portola, Boehringer-Ingelheim, Bayer, Daiichi-Sankyo; research grants from AstraZeneca. **CPC**: Research grants/support from Accumetrics, AstraZeneca, C.S.L. Behring, Essentialis, GlaxoSmithKline, Merck & Co, Regeneron, Sanofi, and Takeda; on advisory boards for Alnylam, Bristol-Myers Squibb, Lipimedix, and Pfizer (funds donated to charity); and holds equity in Automedics Medical Systems. **CH**: Institutional research grants from AstraZeneca, Merck & Co, GlaxoSmithKline, Roche and Bristol-Myers Squibb; honoraria from AstraZeneca; advisory board member for AstraZeneca. **AH**: Employee of AstraZeneca. **SH**: Advisory board member for AstraZeneca, Bristol-Myers Squibb, Pfizer, and Bayer; research support from GlaxoSmithKline and Pfizer. **SKJ**: Institutional research grant from AstraZeneca, Eli Lilly, Bristol-Myers Squibb, Terumo Inc, Medtronic, and Vascular Solutions; honoraria from The Medicines Company, AstraZeneca, Eli Lilly, Bristol-Myers Squibb, and IROKO; consultant/advisory board fees from AstraZeneca, Eli Lilly, Merck, Medtronic, and Sanofi. **HSK**: Honoraria from AstraZeneca, Eli Lilly, GlaxoSmithKline, Roche, and Bayer; holds a Troponin *T* Test Invention patent jointly with Roche and receives royalties for this patent. **KWM**: Consulting fees from AstraZeneca, Bayer, Boehringer-Ingelheim, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Johnson and Johnson, Merck, Ortho/McNeill, Sanofi-Aventis, and Schering-Plough (now Merck); grant support from Bayer, Boehringer-Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Eli Lilly, GlaxoSmithKline, Johnson and Johnson, Merck, Novartis, Portola Pharmaceutical, Pozen, Regado, Sanofi-Aventis, Schering-Plough (now Merck), and The Medicines Company. **KSP**: Consultancy fees from GlaxoSmith Kline. **RFS**: Research grants from AstraZeneca, Eli Lilly/Daiichi Sankyo, and Merck; research support from Accumetrics; honoraria from AstraZeneca, Eli Lilly/Daiichi Sankyo, Merck, Iroko, Accumetrics, and Medscape; consultancy fees from AstraZeneca, Merck, Novartis, Accumetrics, Sanofi-Aventis/Regeneron, Bristol-Myers Squibb, Eisai, Roche and Daiichi Sankyo. **PGS**: Research grants from NYU School of Medicine, Sanofi, Servier; consultancy fees/honoraria from Amarin, Astellas, AstraZeneca, Bayer, Boehringer-Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, GlaxoSmithKline, Lilly, Medtronic, MerckSharpeDohme, Novartis, Otsuka, Pfizer, Roche, Sanofi, Servier, The Medicines Company, and Vivus. **RAH**: Consulting/advisory board fees from Bristol-Myers Squibb, Sanofi, Portola Pharmaceuticals, Johnson & Johnson and Merck; grant support from Eli Lilly/Daiichi Sankyo, Merck, Portola Pharmaceuticals, Sanofi, Johnson & Johnson, Bristol-Myers Squibb, The Medicines Company and AstraZeneca.

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