Ticagrelor in Patients With Acute Coronary Syndromes and Stroke

Interpretation of Subgroups in Clinical Trials

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Phase 3 prospective randomized trials are designed and have statistical power for the investigation of 1 major hypothesis in a predefined population using predefined clinical end points. These large outcome trials are conducted following rules and regulations specified by Good Clinical Practice and the ethical principles of the Declaration of Helsinki to maintain the highest scientific validity and ethical standards and minimize bias. Predefined, subgroup analyses are by definition underpowered for evaluation of the primary and secondary events but often performed to generate hypotheses for further understanding of the effects and side effects in important subgroups.

The Platelet Inhibition and Patient Outcome (PLATO) trial successfully tested its main hypothesis: that ticagrelor compared with clopidogrel would result in a lower risk of recurrent thrombotic events in a broad patient population with acute coronary syndromes. An academic executive committee was responsible for the design and the medical, scientific, and operational conduct of PLATO; expert sites and investigators conducted the trial, which was monitored closely by an independent data and safety monitoring board; and all primary and secondary efficacy and safety events were adjudicated by an independent committee of expert cardiologists and neurologists blinded to assigned treatment. Two independent academic groups have full access to the PLATO database and have performed all analyses for publication.

Patients with acute coronary syndromes and with a history of stroke or transient ischemic attacks (TIA) are at particularly high risk for recurrent cardiovascular events, including death and myocardial infarction, as well as bleeding complications, including an increased risk of intracranial bleeding. In this high-risk population, the balance between safety and efficacy of antithrombotic treatment is therefore particularly important. Establishing the clinical efficacy and safety of ticagrelor versus clopidogrel in patients with previous stroke or TIA was a prespecified subgroup analysis of PLATO included in the appendix of the primary trial publication. Among the 18,624 patients randomized in PLATO, 1152 (6.2%) were reported as having a history of stroke or TIA by the investigators. These patients presented higher rates of the primary composite end point, myocardial infarction, death, stroke, major bleeding and intracranial bleeding as compared with those patients without previous stroke or TIA. The reductions of the primary and secondary end points of ticagrelor versus clopidogrel were consistent with the overall PLATO trial results. Thus, the relative reduction of the primary end point with ticagrelor compared with clopidogrel was 13% in patients with and 16% in patients without a history of previous stroke or TIA, with no significant treatment-by-stroke history interaction test (P=0.39) after multivariable adjustment. The relative reduction of all-cause death, with ticagrelor versus clopidogrel, was 38% and 19% in patients with or without a previous history of stroke, respectively, with no significant treatment-by-stroke history interaction (P=0.98).

In the subgroup of patients with a previous history of stroke, there were similar rates of stroke (3.7% versus 3.0%), hemorrhagic stroke (0.4% versus 0.4%), and fatal stroke (0.6% versus 1.2%) in the ticagrelor and clopidogrel groups. The rates of PLATO-defined major bleeding and noncoronary artery bypass graft–related major bleeding were not significantly different between patients assigned ticagrelor and clopidogrel (14.6% versus 14.9% and 5.9% versus 6.8%, respectively). Intracranial bleeding occurred infrequently and with no difference between the ticagrelor and clopidogrel groups (0.9 versus 0.7%).

Consistent with the overall PLATO trial results, the subgroup analysis of the high-risk subset of patients with a history of stroke or TIA shows that more potent inhibition of platelet aggregation with the reversibly binding P2Y₁₂ receptor inhibitor ticagrelor reduces ischemic events with no

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PLATO Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique Identifier: NCT00391872.

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significant increase in prespecified bleeding events. In fact, despite the more potent antithrombotic effect, the risk of intracranial hemorrhage or fatal stroke was low, and the total mortality was significantly reduced by ticagrelor.

DiNicolantonio and Serebruany recently published a commentary concerning outcomes with ticagrelor as compared with clopidogrel in patients with a history of stroke in the PLATO trial—one of several letters and editorials critical of the PLATO trial. In the current letter, the authors derived data, retrieved from the online publically available Food and Drug Administration (FDA) briefing documents because they did not have access to individual patient data. Based on this approach, they question the results of the prespecified analysis published by the PLATO study group in a peer-reviewed publication in Circulation (to which they mistakenly refer to as an editorial). In their commentary, the authors seem to add and delete data according to their own preferences to provide support for predefined conclusions. Consistently, they calculate numbers needed to harm and draw conclusions from nonsignificant differences between subgroups. The authors seem to mix figures from the overall PLATO trial with the previous stroke/TIA subgroup and the geographic subgroup analyses to select the results that best fit their conclusions, whereas excluding results that invalidate it. Specifically in the Table, which is labeled ticagrelor versus clopidogrel in patients with a history of cerebrovascular disease in PLATO, they have included outcome variables from selected subgroups and subsubgroups from the overall PLATO trial on lines 2 to 4, whereas they seem to have included data from the subpopulation with previous stroke/TIA on lines 1 and 5. The data on line 1 are retrieved from post hoc analyses in the FDA briefing document, and data on line 5 is retrieved from an editorial.

The FDA performed what was referred to as Additional Safety Analysis, including events designated as cerebrovascular accident adverse events by the site investigators. These data appear in the authors’ commentary as indicating that there exists an even greater risk of stroke in the ticagrelor arm. However, they chose not to refer to the conclusions in this same FDA document stating that the cases that were reported as strokes by the site investigators and subsequently downgraded by the clinical events committee to TIA or No Event were appropriately and reasonably adjudicated, and that no systematic adjudication problem or misclassification was found. Furthermore, the authors did not refer to the final sentence in another part of the document in which a reviewer states: “While the stroke rate is slightly higher with ticagrelor, the lower MACE rate (including the strokes) mitigates any concerns that I have about strokes.”

Additionally, using self-citation, the authors suggest that the mortality results from the overall trial may have been tampered with by the sponsor, and by inference, by the many academic investigators participating in oversight of the trial. This is an extremely serious accusation, completely unacceptable in a peer-reviewed academic journal when unsubstantiated and without evidence. This accusation is based on the heterogeneity of trial results among countries, a finding which is common in large-scale clinical trials and which, in the context of PLATO, has been extensively discussed and analyzed by the FDA and by the PLATO group. Finally, the authors disregard conventional statistical probability concepts and instead draw conclusions and calculate numbers needed to harm based on nonsignificant results from severely underpowered subgroups. This is bad science.

In fact, the authors’ strong negative description of the results of ticagrelor is a direct contradiction to their actions. After the publication of the PLATO results, Dr Serebruany filed a patent on the use of ticagrelor, US Patent Application 20110144049—Treating Cardiac Arrhythmias, Heart Failure, Peripheral Artery Disease and Stroke with...
Cyclopentyl-Triazolo-Pyrimidine or Derivative Thereof, in which he specifically makes a claim to treat patients with stroke. In the patent file it is further stated: “In summary, the study [PLATO] revealed a remarkable advantage of ticagrelor. Unless the regulatory authorities discover serious flaws with the study, which is unlikely, the drug can substantially change the present landscape of oral antiplatelet therapy, especially in high-risk patients. Despite a somewhat unfavorable 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 myocardial infarction, and convincing pattern of growing over time benefit.”

Results of clinical trials are reported in peer-reviewed journals and are open for scientific discussion and debate. As active members of the academic community, we support open science, debate, and discussion. We do not and cannot support bad science propagated for reasons unclear to us except perhaps to engender publicity and media attention. Any reader of scientific articles should be able to review the results critically, draw conclusions, and translate the results for clinical practice. In doing so, the reader should be confident that the reported data derived from meticulously performed clinical trials are correct and reported with minimal bias. Unfortunately, DiNicolantonio and Serebruany report selected data derived from various sources using improper statistics. The data provided in the commentary are a biased selection of an extensively peer-reviewed and published series of articles.

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