Response to Letter Regarding Article, “Ticagrelor in Patients With Acute Coronary Syndromes and Stroke: Interpretation of Subgroups in Clinical Trials”

Drs Serebruany and DiNicolantonio are repeatedly accusing the platelet inhibition and patient outcomes (PLATO) investigators, executive committee, and sponsor for trial misconduct and deliberate misinterpretations. These are extremely serious accusations that we find completely unacceptable in any peer-reviewed journal. The authors continue to present selected data from various sources according to their own preferences to provide support for predefined conclusions with a severely biased intention. First, they accuse the PLATO investigators of slicing and dicing in the analyses of the PLATO database. This is a slur on the greater scientific community because all the PLATO publications have been extensively peer reviewed by independent experts and considered to be scientifically valid and worthy of publication in high-impact journals. However, they focus on selected analyses in the initial Food and Drug Administration (FDA) review documents that were intended to probe the data in a way that would not be considered appropriate in a scientific publication and have not been subjected to peer review by external experts. The internal FDA review process deemed that these analyses and associated criticisms were not robust enough to undermine the case for ticagrelor’s approval as a superior alternative to clopidogrel. We, therefore, consider the selective use by Serebruany and DiNicolantonio of excerpts from the FDA documents to be biased and disingenuous and refer readers to the entire archive of FDA documents for a more balanced assessment of the FDA review. These documents have been in the public domain on the FDA Web site since the approval of ticagrelor in 2011.

Second, we refute Serebruany’s accusation that we misrepresented his patent application since the date of 2011 that we cited appropriately is the date of publication of the application rather than the patent submission date. Again, Serebruany and DiNicolantonio are themselves guilty of misrepresentation by making this further accusation. The name ticagrelor is included in Serebruany’s patent, despite the fact that he played no role in the development of ticagrelor or, to our knowledge, of any other cyclopentyl-triazolopyrimidine that has been developed for human use, and so his patent lies outside of the honorable process of scientists protecting the intellectual property achieved through their own endeavors. We fail to see how success of this application will help to develop better and safer drugs in this class but realize that the applicants have serious conflicts of interest in their anti-ticagrelor campaign.

Finally, we consider the attempts by Serebruany and DiNicolantonio to undermine confidence in the mortality data in PLATO to be an unscientific and nonsensical conspiracy theory that potentially places the lives of patients with acute coronary syndromes at risk if taken seriously by physicians treating these patients. This is perhaps the worst misrepresentation of the evidence base. In fact, the cardiovascular morality rate in the PLATO study in the clopidogrel arm was 5.1%, compared with a cardiovascular mortality rate in the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) study in the clopidogrel arm of 5.1%, despite the fact that PLATO, unlike CURE, included patients with ST-elevation myocardial infarction and had greater requirement for risk factors in the non-ST-elevation patients. The repeated accusations by Serebruany and DiNicolantonio are directed not only to the PLATO executive committee and the trial sponsor, but also to the authorities who thoroughly reviewed the PLATO study results and approved ticagrelor and the journals that published PLATO study results.

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Disclosures

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Letters to the Editor

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