NEW YORK, NY — Lead investigator for the Platelet Inhibition and Patient Outcomes (PLATO) trial of ticagrelor (AstraZeneca) says that negative press surrounding the trial is slowing the uptake of a guideline-recommended antiplatelet drug in the US and depriving patients of the proven clinical benefits.

Dr Lars Wallentin (Uppsala University, Sweden) spoke with heartwire following the publication of a rebuttal in the International Journal of Cardiology (IJC) [1], responding to what Wallentin called "disturbing" and "unscientific" publications attacking the PLATO study [2].

As long reported by heartwire, the 2009 PLATO trial found that treatment of patients with acute coronary syndrome (ACS) treated with the investigational oral-antiplatelet agent ticagrelor significantly reduced the rate of MI/stroke/CV death compared with clopidogrel (Plavix, Bristol-Myers Squibb/Sanofi-Aventis). Ticagrelor was ultimately approved in the US in 2011, as well as in other countries around the world, although it underwent a protracted review process. The drug and trial have long been dogged by concerns over apparent geographic discrepancies, timing of deaths in the study, site monitoring, MI definitions, and other issues.

The bulk of those concerns, notes Wallentin, have been raised by two authors in particular, Drs Victor Serebruany (HeartDrug Research Laboratories, Johns Hopkins University, Towson, MD) and James DiNicolantonio (Wegmans Pharmacy, Ithaca, NY), who in 2013 alone published no less than 15 papers criticizing some aspect of the drug or its pivotal trial.

Then, this fall, the drug-maker announced that the Department of Justice (DoJ) civil division was investigating the PLATO trial.

To heartwire, Wallentin said that he himself has "heard nothing" from the DoJ and hasn't been interviewed as part of their investigation. Nor does he know why it was launched in the first place.

"I don't know anything about who would have come up with the accusations leading to this DoJ investigation, but to us it creates mainly a delay to the use of a very effective treatment the US, which is a pity. Hopefully this issue will rapidly be resolved."

"Serious Concerns" Published in August

In August, DiNicolantonio, with Dr Ales Tomek (Charles University, Prague, Czech Republic) published what may be the most eye-catching title on PLATO in IJC: "Inactivations, deletions, non-adjudications, and downgrades of clinical endpoints on ticagrelor: Serious concerns over the reliability of the PLATO trial."

That paper pulled comments from FDA medical reviewer Dr Thomas Marciniak's analysis of PLATO, suggesting that sites where the study sponsor was the site monitor saw better results for ticagrelor than sites with third-party monitors, and that the bulk of the reduction in the primary end point with ticagrelor was seen at just two non-US sites.
They also questioned how carefully the study was blinded and how MIs and other events were counted.

I will be interested to see what occurs with the investigation of the PLATO trial by the US Department of Justice.

In their rebuttal, also published in IJC, Wallentin and colleagues note that none of the analyses by DiNicolantonio and Tomek include any description of their statistical methodology. Moreover, they counter, all of the allegations they raise have already been addressed by statisticians and scientists with access to the full database, who've published their findings, or by the FDA, who requested additional details and concluded the concerns were not supported.

Speaking with heartwire, Wallentin alleges that PLATO critics have cherry-picked specific, negative comments by reviewers from the FDA documents, but opted not to publish the final conclusions of those reviews. Wallentin and colleagues quote Dr Norman Stockridge, FDA Division Director, who concluded, "as far as I can tell, data quality issues [in PLATO] are not a great concern."

And for all the papers and analyses DiNicolantonio and Serebruany have published, not once, Wallentin added, has either author requested data from one of the three centers (two academic) that have the full PLATO dataset, or posed a formal question to be investigated by the data centers.

Contacted by heartwire and asked whether Wallentin et al's rebuttal had assuaged his concerns, DiNicolantonio said, "All my opinions are contained within my publications," and "I will be interested to see what occurs with the investigation of the PLATO trial by the US Department of Justice."

Also contacted for his views, Serebruany responded: "No comment."

Editorial Judgment?

Meanwhile, Wallentin et al are extremely critical of the journal that has published the bulk of DiNicolantonio and Serebruany's papers and letters.

"We are amazed that IJC publishes these unfounded accusations of fraudulent behavior in the PLATO trial," they write. "We find such allegations unacceptable in a peer-reviewed scientific journal, especially when based on erroneous data, improper statistical methodology, 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."

In fact, Wallentin told heartwire, he and his colleagues sent their rebuttal to IJC within three week's of the "Serious concerns..." paper, which was published August 5, yet the journal did not formally accept it until November 1, and then didn't publish it until the first week of December. In the interim, IJC published yet another DiNicolantonio and Tomek paper that it accepted August 28 and published September 5.

"We did not really dare to add to comments to our [already submitted] paper because we thought it would create further delays, and we found it very strange that, while having received our commentary, they proceeded to publish an additional, critical paper from
these authors," Wallentin observed for heartwire. "They must have known about our criticisms; still, they published another paper that was even more inadequate than this one, it added nothing."

Asked whether he has any concerns about what the DoJ investigation will turn up, Wallentin insisted: "I don't know anything about the reasons for this investigation at all, and from the outside it is a little bit strange. We have complete confidence in the data."

No company would be foolish enough to start studying a major program without complete confidence in the data.

Moreover, he said, the PLATO investigators have published 40 different papers responding to concerns or conducting further analyses to clarify some of the apparent discrepancies in the results. There are also more than 100 investigator-initiated trials underway. In addition, the data have been examined in-depth by the health authorities who reviewed the trial for the market approval of ticagrelor, which is now available in more than 100 countries.

Finally, Wallentin added, "the company must have extreme confidence in the data, as they are now starting trials in 40,000 to 50,000 patients in all different areas to look for new indications" including chronic CAD, peripheral artery disease, diabetes, and stroke. "They have an enormous program, and I'm quite convinced that no company would be foolish enough to start studying a major program without complete confidence in the data."

Happily, some solid new data are anticipated next year, which Wallentin hopes will put to rest concerns in the US about a lack of ticagrelor benefit. The Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin (PEGASUS) trial has completed enrollment of 21,000 patients and is expected to wrap-up analysis in time for the fall congress season.

That trial, notes Wallentin, who is not participating, is being led by Drs Eugene Braunwald and Marc Sabatine (TIMI Study Group, Boston, MA), and was designed to include enough US patients to answer any questions about geographic differences.

"To us, it's quite disturbing that [critics of the PLATO trial] are creating obstacles and also making people feel that the PLATO data should come under suspicion," Wallentin mused. He notes that uptake of the drug is far higher in Europe than the US, despite both countries' guidelines supporting the use of ticagrelor as first-line treatment in ACS. "That leads to patients not getting a treatment that has been internationally recommended, and it might be that these are leading to patients dying unnecessarily because this treatment reduces mortality."

Wallentin disclosed receiving research grants from AstraZeneca, Merck & Co, Boehringer-Ingelheim, Bristol-Myers Squibb/Pfizer, GlaxoSmithKline; consulting 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.
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