

Debate Continues on Ticagrelor in PLATO

Lisa Nainggolan | March 14, 2011

March 11, 2011 (Durham, North Carolina) — AstraZeneca should conduct a second trial with its investigational antiplatelet agent **ticagrelor** (Brilinta) in the post–acute coronary syndrome (ACS) setting in order to explore why the North American sites in its pivotal trial, **PLATO**, showed a statistically insignificant trend toward worse outcomes with ticagrelor vs **clopidogrel** (Plavix, Bristol-Myers Squibb/Sanofi-Aventis), say two US doctors [1].

In fact, AstraZeneca has confirmed to **heartwire** that it is conducting the type of trial Ohman and Roe suggest, **PEGASUS-TIMI 54**, which began patient enrollment in the last quarter of 2010.

Drs E Magnus Ohman (Duke Clinical Research Institute, Durham, NC) and **Matthew T Roe** (Duke University Medical Center, Durham, NC) express their opinion in an editorial published online March 11, 2011 in *Thrombosis and Haemostasis*, accompanying a viewpoint [2] by **Dr Victor Serebruany** (HeartDrug Research Laboratories, Johns Hopkins University, Towson, MD) published online March 8.

This "North American" anomaly is widely believed to be one of the main reasons that the US **FDA** has not yet approved ticagrelor; in December it delayed a decision on ticagrelor for a second time, although AstraZeneca has since announced that the agency will now rule on the antiplatelet agent by July 20 this year.

In his viewpoint, Serebruany expands upon what he calls the "paradoxical excess mortality in PLATO," listing a number of reasons he is concerned about much of the data from this trial. This was provided as an analytical report to the FDA on October 26, 2010, he says, and much of it has been included in **heartwire**'s prior coverage **heart wire**'s prior coverage of this topic, but this is the first formal publication of the information.

Also accompanying this viewpoint is another editorial, this one from the PLATO investigators [3], led by **Dr Lars Wallentin** (Uppsala Clinical Research Centre, Sweden), in which they champion the PLATO findings and refute many of Serebruany's assertions, which they call "extensive speculation . . . and inappropriate cross-trial comparisons far outside sound scientific methodology." They point out that ticagrelor is now approved in 30 countries and is under review in a further 21.

Outcomes for Ticagrelor Worse in North America

The overall results of the 18 000-patient PLATO trial, conducted in 43 countries around the world, showed that ticagrelor plus aspirin reduced the primary end point—a composite of death from vascular causes, MI, or stroke—by 16% compared with clopidogrel plus aspirin over 12 months (9.8% of patients receiving ticagrelor suffered a primary end point event compared with 11.7% of those taking clopidogrel [$p<0.001$]).

But the outcome in 1814 patients in the US and Canada was worse in those taking ticagrelor than in those on clopidogrel, with a primary end point occurring in 11.9% of ticagrelor-treated patients compared with 9.6% of those on clopidogrel, although the difference was not significant.

In his viewpoint, Serebruany reiterates previously raised issues, including this North American anomaly. He says that ticagrelor fared worse than clopidogrel in other countries, too, including Russia and Georgia, and he provides a diagram depicting the distribution of outcomes in PLATO by participating country.

In North America, Russia, and Georgia, sites were monitored by third parties, independent clinical research organizations (CROs), Serebruany points out. This is in contrast to countries such as Poland and Hungary--which together accounted for 21% of enrolled patients but yielded "an astronomical 46% (n=69)" of all end points favoring ticagrelor--where AstraZeneca hired site monitors. He calls for the "reexamination of PLATO" records in countries such as Poland and Hungary.

But in their editorial, Ohman and Roe take issue with what they say are Serebruany's assertions that the sponsor may have influenced the mortality rate, stating that standard protocol would make this "impossible."

Wallentin et al agree with the Duke doctors wholeheartedly, listing at great length all of the checks they say were in place. "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."

And they note: "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 spectrum of outcomes." Also, "even when excluding the largest enrolling countries with results favoring ticagrelor (Poland and Hungary), the overall result still favors ticagrelor," they assert.

AstraZeneca spokesperson **Sarah Lindgreen** told **heartwire** : "AstraZeneca disagrees with the statements made regarding data integrity and the conduct of the PLATO study by Serebruany in his viewpoint. In order to meet internationally recognized standards of clinical trial conduct, AstraZeneca adheres to good clinical practice (GCP) guidelines and conducts rigorous quality audits. The PLATO study was conducted in compliance with GCP guidelines."

Is Aspirin a Smokescreen, or Not? More Patients Needed in Major Regions

Serebruany also says that attempts to lay the blame for the anomalous findings in North America at the door of high-dose aspirin are a smokescreen and "represent an attempt to shift the attention from real problems." He also refutes another explanation, that these results are due to the play of chance, pointing out that in **TRITON-TIMI 38**--a trial similar to PLATO with the same primary end point (CV death, MI, or stroke), but a different antiplatelet agent, **prasugrel** (Effient, Lilly/Daiichi Sankyo), vs clopidogrel--no differences in outcome were seen between geographical regions.

But Wallentin et al say the "treatment by region interaction" observed in North America "and in particular in the United States" does originate from a higher maintenance dose of aspirin used by half the patients in the US, "but rarely outside," as pinpointed by "an extensive analysis of the PLATO database independently performed by both the sponsor and the executive committee." And, in fact, these additional aspirin analyses were provided to the FDA in January, they note, and "a forthcoming [paper] from the executive committee,

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currently under review, will shortly publish the detailed aspirin-related findings."

drug development program.

Ohman and Roe say the problem with trying to verify whether high-dose aspirin or indeed chance is an explanation for the "rather striking" North American findings is that the sample size from there is so small, representing only 9.7% of the overall PLATO patient population.

"We believe that we can no longer perform large-scale clinical trials in ACS with very small regional contributions (<10% of total trial enrollment) from the major regions of the world. The PLATO results should serve as a warning to all stakeholders in global CV research that balanced enrollment around the world in pivotal trials should be the goal for any future drug development program," the Duke doctors state.

Cross-Trial Comparisons Are Inappropriate, With Little Relevance

Serebruany's viewpoint includes another of his bugbears: that in PLATO overall, the all-cause death rate in the clopidogrel arm was 5.9%, which is even greater than mortality in the **CURE** trial (5.7%) conducted 10 years ago and ridiculously high when compared with contemporary trials such as TRITON-TIMI 38.

"Importantly, the USA mortality differs tremendously from overall PLATO mortality," he says. It was 3.22% with clopidogrel in PLATO in the US, which is identical to that seen with clopidogrel in TRITON-TIMI 38. The mortality rate with ticagrelor in the US was 3.84% in PLATO, similar to that seen in all three arms of the ACUITY trial at one year (range 3.6%–3.9%).

But Ohman and Roe contend that "there are several flaws with his arguments," including the fact that it is unfair to compare the PLATO findings with those of CURE and ACUITY, because these did not include any ST-segment-elevation MI (STEMI) patients, whereas 40% of PLATO enrollees had suffered STEMI, and these patients are known to have high early mortality. "It is therefore expected that the overall mortality rates should be substantially different in these trials," they observe.

Wallentin et al say PLATO "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-TIMI 38." And in any case, Wallentin added to **heartwire** : "These cross-trial comparisons should not be done; they are inappropriate and have very little relevance."

On the subject of another unexpected finding--the divergence of mortality curves over time, whereby there was a lack of early mortality benefit with ticagrelor but a delayed "bubble" between three and six months in PLATO--Ohman and Roe say there are a couple of possible explanations.

Some suggest the adenosine effect of ticagrelor reduces mortality in the absence of MI reduction, "a very intriguing finding that, if true, could have some very important implications for the duration of ticagrelor therapy after an ACS," they note. Or the divergence in all-cause mortality could be a "lower or neutral effect on major bleeding events," say the Duke doctors.

According to Wallentin et al, the PLATO executive committee is continuing to explore this issue. "Potential explanations include modulation of endogenous adenosine concentrations," they write.

But Serebruany, for his part, says the pattern of mortality with ticagrelor in PLATO "is totally different from TRITON, . . . alarming, and lacks any scientific explanation." If the suggested adenosine-related mechanism of potential ticagrelor mortality benefit in PLATO was true, one would have expected the compound **rolofylline** (Merck) to be efficacious in heart failure--since both agents similarly exert their effects via modulation of adenosine receptors--but it was not in the recent **PROTECT** trial, he points out.

TIMI Group to Run PEGASUS With Ticagrelor

Serebruany brings up some other issues in the viewpoint, not mentioned previously, including the fact that ticagrelor's parent compound, **cangrelor** (the Medicines Company), failed to show any benefit in the **CHAMPION** study.

And he points out that the TIMI study group conducted some phase 2 studies with ticagrelor, **DISPERSE** and **DISPERSE-2**, which had "highly unfavorable results, including more deaths for ticagrelor." The TIMI investigators were consequently not involved with the pivotal PLATO trial, he notes, but they are now running the PEGASUS trial with ticagrelor in stable coronary disease.

Serebruany's inference is that the TIMI group would have been the likely choice to conduct PLATO but was overlooked when the phase 2 results with ticagrelor were negative. Following the furor with the North American results of PLATO, the group has now been asked to conduct PEGASUS.

However, until the mortality issue in PLATO is cleared up, "any more ticagrelor studies in the US seem unethical, and PEGASUS should be put on hold," Serebruany asserts.

Wallentin et al, on the other hand, say the PEGASUS-TIMI 54 trial is "now active" and will "provide additional insights into the benefits of ticagrelor."

I find both editorials entertaining but not substantial. They do not explain numerous gross mismatches in the trial.

Company spokesperson **Donna Huang** told **heartwire** that PEGASUS will enroll 21 000 patients from 30 countries, with 25% of those recruited expected to be from the US. However, she stressed that the FDA "has not requested the PEGASUS-TIMI 54 study."

Asked for his opinion on the editorials accompanying his viewpoint, Serebruany told **heartwire** : "I find both entertaining but not substantial. They do not explain numerous gross mismatches in the trial. Words are no longer relevant here, only facts are."

Serebruany is listed as an inventor for the US patent application "Treating cardiac arrhythmias, heart failure, peripheral artery disease and stroke with cyclopentyl-triazolopyrimidine or derivative thereof" (USN 61/253,829) assigned to HeartDrug Research. He received funding for research studies with clopidogrel and consultant fees from both clopidogrel and ticagrelor manufacturers. He is also the owner of HeartDrug Research. Disclosures for Ohman and Roe and for Wallentin et al are not provided in the papers.

References

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