Competing Perspectives on PROactive

In his commentary on the conduct of the PROactive Study (*Clinical Diabetes* 24:63–65, 2006), Dr. Jay Skyler reiterated his opinion of misconduct by some or all of the study statisticians, the members of the Data Safety and Monitoring Committee (DSMC), or the overall study chairman and his steering committee, and specifically that they colluded in suggesting a new principal secondary end point, having prior knowledge of the study's primary end point likelihood.[1,2] By so doing, he impugns yet again the scientific integrity of all of the above. Despite our earlier unequivocal refutation of his allegations,[3] we feel that his continued onslaught once again calls for an absolute and transparent rebuttal of his allegations.

Throughout the study, blinded patient data from the PROactive participating centers was transmitted directly to an independent data center, Nottingham Clinical Research (U.K.), under the directorship of Dr. Allan Skene. Here, still-blinded data was processed and forwarded to the DSMC statistician, Prof. Gordon Murray in Edinburgh, U.K. Prof. Murray was independent of the sponsor and all other aspects of the study. His unit alone had access to the treatment allocation codes, and, as agreed at study onset, prepared unblinded event tables for discussion by the DSMC at its scheduled meetings under the chairmanship of Prof. Pierre Lefèbvre. At no time during the study did the sponsor have access to the treatment codes.

The DSMC reviewed study progress with its principal role of ensuring patient safety in mind. As such, DSMC members assessed the study's declared primary and secondary end points and any other clinical or biochemical trends that they felt might impinge on patient safety as the trial progressed. They had no concern for the publication or marketing potential of the trial result, and at no time did they suggest any new analyses that might ultimately reflect favorably on the study drug.

Where and when did the previously unpublished new secondary end point cluster of mortality, nonfatal myocardial infarction (MI), or stroke so suspiciously reviled by Skyler appear on the scene? This evolved during discussions with members of the Executive Committee and study sponsors (but not the DSMC) under the auspices of the overall study chairman, Prof. John Dormandy. It was realized that the previously declared end points did not include a comparison of what had now become common in cardiovascular outcome trials, namely a composite of death, nonfatal MI, or stroke. This was debated in complete ignorance of any study events but was incorporated into the final analytical plan that was submitted to the U.S. Food and Drug Administration before database lock and study unblinding, despite uncertainty as to its importance, but in appreciation of its potential clinical relevance. The DSMC had met for the last time before this new addition to the analytical menu and had never seen, let alone discussed, data presented in such a composite, nor made surreptitious hints to that effect.

We believe that adding to a previously declared analytical plan in order to incorporate contemporary ideas in advance of knowledge of study progression is perfectly legitimate provided overall study integrity is preserved. That is what was done in PROactive. We accept that, for undeclared reasons, Skyler has difficulties accepting the findings of the PROactive study, but we unequivocally assure him and your readers that neither conspiracy nor the sacrifice of scientific integrity was involved.

The PROactive Study Executive Committee and Data and Safety Monitoring Committee

The Executive Committee comprises J. Dormandy, B. Charbonnel, E. Erdmann, M. Massi-Benedetti, I. Moules, A. Skene, and M. Tan.

The Data and Safety Monitoring Committee comprises P. Lefèbvre, G. Murray, E. Standl, L. Wilhelmsen, and R. Wilcox.

For the primary sponsor
John Yates, MD, President, Takeda Global Research & Development.

REFERENCES

[1]Skyler JS: PROactive: a sad tale of inappropriate analysis and unjustified interpretation. *Clin Diabetes* 24:63–65, 2006

[2]Skyler JS: PROactive results overstated and misleading. *DOC News* 2:4, 2006

[3]PROactive Study Executive Committee and Data Safety and Monitoring Committee: PROactive study (Letter). *Lancet* 367:982, 2006

Response from Dr. Skyler

I regret that the PROactive Study Group has taken the view that I had "reiterated" an opinion of misconduct on their part after they had clarified the situation. My first commentary appeared in

DOC News in December 2005 and was written at the request of its editor, Dr. Irl Hirsch. My second commentary was adapted from the first at the request of then-editor of *Clinical Diabetes*, Dr. Jennifer Marks. It was submitted on 14 January 2006 and appeared in the February 2006 issue. The PROactive Study Group response to my commentary in *DOC News* was apparently submitted on 24 February 2006 and was forwarded to me by Dr. Hirsch on 13 March 2006. Thus, my *Clinical Diabetes* commentary appeared prior to my seeing the PROactive Study Group explanation of the details surrounding the creation of the "principal secondary end point." I accept their explanation, which is actually more detailed in their current letter. I am sorry that the writers believe that I have impugned their integrity. That was not my intent.

I should note, however, that my commentary emphasized many other aspects of the PROactive study:

1. The lack of consistency across all cardiovascular outcomes
2. The difference in A1C between the two groups, rendering it impossible to attribute the results to pioglitazone per se, as opposed to better glycemic control
3. The fact that benefits were only seen in those subjects not taking statins
4. The increased complications in the pioglitazone group, including congestive heart failure, weight gain, and edema
5. The inappropriate generalization of "benefits" to all patients with diabetes
6. The fact that because the primary end point was negative, the study was a negative study

As for my "undeclared reasons" for having difficulty accepting PROactive, I believe that numbers 1 to 6 above (detailed in my commentary) provide a legitimate basis for challenging the conclusions asserted by the investigators. Moreover, I find the marketing of the PROactive results in a precedent-setting number of talks across North America to lack fair balance in not addressing the issues raised by me and by a number of other commentators referenced in my commentary. It was this marketing onslaught that stimulated the editors (Drs. Hirsch and Marks) to ask for my comments. I appreciate that the PROactive investigators have not been involved in this marketing exercise and may not realize the extent of concern that it has caused many in the U.S. diabetes community.

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