Thiazolidinediones and heart failure

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TO THE EDITOR: Dr. Wilson Tang, in his critical review of the available evidence about thiazolidinediones (TZDs) and heart failure,[1] should surely have discussed the adverse effects outcomes in the largest TZD trial to date, PROactive.[2] This study, which included 5,238 patients with type 2 diabetes with evidence of macrovascular disease, randomized patients to pioglitazone or placebo to be taken in addition to their other glucose-lowering drugs and other medications. This study found a 39% increase in the relative risk of hospitalization for congestive heart failure, as well as a statistically significant increase in any report of heart failure in the pioglitazone group. The number needed to harm for pioglitazone was 33 (treat 33 patients for 34 months to cause one heart failure event). In Dr. Tang's article, this was listed as "not statistically significant," but clearly from the PROactive study this was statistically significant (with a *P* value of less than .001 for any report of heart failure, .003 for heart failure not needing hospital admission, and .007 for heart failure needing hospital admission). Either this was a misprint in Dr. Tang's article, or being on the speaker bureau for Takeda Pharmaceuticals (the maker of pioglitazone) has caused massive myopia.

In the PROactive study, both the primary and preplanned secondary end points were negative in the study. Main secondary outcomes, which were statistically significant, were compiled after the end of the study, but apparently before the data sets were opened. This is highly unusual.

Credible sources have both discounted the conclusions of the PROactive study and questioned its methodology.[3–8] In fact, one commentary in *The Lancet* discussed using data from the United Kingdom Prospective Diabetes Study to simulate the same reductions in hemoglobin A_{1c} and blood pressure as in the pioglitazone group, and found the same outcomes in cardiovascular events but a risk reduction in heart failures.[4]

It is time to stop talking in *may*'s and *might*'s and to look at the data from an unbiased, non-pharmaceutical-sponsored perspective. The role of TZDs in type 2 diabetes remains unclear.

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IN REPLY: I thank Dr. Jaderholm for correctly pointing out the errors in my article regarding the risk of heart failure in the PROactive study.[1]

In the PROactive study, after 3 years of follow-up, nonadjudicated heart failure events had occurred in 10.8% of patients in the pioglitazone group vs 7.5% in the placebo group; the difference was statistically significant ($P < .0001$). Patients taking pioglitazone had a 5.7% rate of hospitalization for heart failure vs 4.1% in the placebo group, which was also statistically significant ($P = .003$). Edema without heart failure occurred in 21.6% of patients in the pioglitazone group vs 13% in the placebo group. These data were emphasized in one of the summary key points at the beginning of my paper (page 390): "The Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROactive; Lancet 2005; 366:1279–1289) found that the use of a TZD was associated with a 16% reduction in the combined end point of heart attack, stroke, and death, despite increased rates of edema and hospi-

talization for heart failure."

The intent of my article was to provide a critical review of the literature in order to address the question, "Do TZDs cause heart failure?" This is an important scientific question, since the development of heart failure in patients with diabetes has been associated with poorer long-term survival.[2] It was my intention to point out that people who take TZDs clearly have a risk of developing fluid retention, but the risk of developing heart failure is less clear.

In fact, all glucose-lowering drugs have been implicated to some degree with regard to their heart failure risks, with insulin being the most prominent.[3] However, the clinical diagnosis of heart failure is often subjective and nonadjudicated, and therefore definitive clinical evidence is limited.

Nevertheless, placebo-controlled echocardiographic studies have not directly linked fluid retention caused by TZDs with worsening cardiac performance.[4] Careful analysis from the Kaiser Permanante Northern California Diabetes Registry of 23,440 patients with type 2 diabetes also did not find evidence that short-term TZD use was associated with an elevated risk of hospitalization from heart failure compared with other standard, first-line diabetes therapies.[5] It is also reassuring that rates of death from heart failure in the PROactive study were similar between the TZD and the placebo groups (25/2605 vs 22/2633, $P = .634$), despite the aforementioned increase in reported rates of edema and hospitalizations for heart failure.[6]

In a recent analysis of 16,417 elderly diabetic patients discharged after hospitalization for heart failure, the use of insulin sensitizers (TZDs and metformin, both contraindicated in heart failure) was associated with a lower death rate compared with drugs other than insulin sensitizers.[7] The discrepancy between the development of heart failure reported in patients with diabetes treated with TZDs and the potential benefit of fewer deaths is interesting and will require further insights from upcoming large clinical trials.

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