

EDITORIAL COMMENT

## PROactive in Patients With Type 2 Diabetes and Previous Myocardial Infarction

### Swinging the Sword of Damocles?\*

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Type 2 diabetes increases the risk of coronary heart disease at least by 2- to 3-fold. Patients with type 2 diabetes without a history of myocardial infarction (MI) have the same risk for fatal MI as nondiabetic subjects with a history of MI (1,2). Moreover, type 2 diabetic patients with previous MI are even more susceptible to coronary events and need all available evidence-based tools for cardiovascular risk reduction. Thiazolidinediones or glitazones are selective ligands of peroxisome-proliferator-activated receptor (PPAR)-gamma addressing insulin resistance, a culprit of the metabolic syndrome and type 2 diabetes (3). Currently, 2 widely used compounds of thiazolidinediones, pioglitazone and rosiglitazone, have been approved for the treatment of hyperglycemia in type 2 diabetes. Because of their effect on

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alleviating insulin resistance, hyperglycemia, and metabolic abnormalities related to insulin resistance such as dyslipidemia and inflammation, there has been great interest in whether these drugs could decrease the cardiovascular complications in type 2 diabetic patients. In this issue of the *Journal*, results of 2,445 patients with type 2 diabetes and previous MI patients from a substudy of the PROactive (PROspective pioglitazone Clinical Trial In macroVascular Events) study are reported (4).

The primary end point of the PROactive study was the first occurrence of any of the events defined in a composite end point of both diseases (all-cause mortality, nonfatal MI,

nonfatal stroke, acute coronary syndrome) and procedures (coronary or leg revascularization or leg amputation). Inclusion of both disease and procedure end points has been criticized (5) and may also have influenced the results in this substudy. As in the main study population (6), the primary end point did not differ between the pioglitazone and placebo group in the substudy of patients with previous MI ( $p = 0.135$ ). The study group also defined a main secondary end point including death, nonfatal MI, and stroke. The definition of this end point was released only 12 days before locking the database and has led to a lively debate. Although the effect of pioglitazone on the main secondary end point was significant in the main PROactive study, this was not the case in this substudy ( $p = 0.0585$ ), perhaps owing to the decreased statistical power when compared with the main study and the fact that the study was closed prematurely. However, the study group had another statistical analysis strategy for the substudy finalized before the unblinding of the study, which could be criticized for resembling a fishing approach. These 3 prespecified end points in the present study (4) consisted of different combinations of MI, cardiovascular death, and stroke. From these end points, only one, fatal or nonfatal MI, was significantly different between the groups ( $p = 0.0453$ ). The reason may be that there was more heart failure (HF) in the pioglitazone group (defined earlier), contributing to cardiovascular death, which was included in the other composite end points. In post-hoc analysis, the incidence of acute coronary syndrome was modestly but significantly decreased in the pioglitazone group ( $p = 0.0346$ ), whereas there were no differences in all-cause mortality, cardiac death, nonfatal MI, coronary revascularization, or stroke.

In the substudy, the decrease of glycosylated hemoglobin A<sub>1c</sub> in the pioglitazone group was 0.8% (0.4% decrease in placebo group) and was similar to that observed in the main PROactive study. It is important to notice that in PROactive the pioglitazone/placebo was added to all other medications, including other glucose-lowering medications. Decrease in hyperglycemia can be considered noteworthy and could in part explain the beneficial effects on the MI end points as shown in the UKPDS (United Kingdom Prospective Diabetes) Study (7). Also, the other effects of pioglitazone on cardiovascular risk factors could be involved (3). As also shown in this study, pioglitazone increases serum high-density lipoprotein cholesterol and decreases serum triglycerides and, in that sense, is more beneficial than rosiglitazone (3). As there are data that glitazones may also alleviate inflammation, it is unfortunate that no serum samples were collected for analyzing these effects. In this study, approximately 33% of the patients were receiving insulin therapy at baseline; insulin use increased to 36% in the pioglitazone group and to 46% in the placebo group, demonstrating the insulin-sensitizing effect of pioglitazone. The use of insulin was more common in this subgroup with previous MI when compared to those without history of MI.

\*Editorials appearing in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of *JACC* or the American College of Cardiology.

†The Sword of Damocles is a commonly used expression referring to an ancient legend, symbolizing the imminent threat faced by those in positions of power. More generally, it is used to denote an uncertain situation, especially one in which misfortune is depending only on a delicate trigger or chance.

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An essential observation was that use of insulin was associated with increase in MI (hazard ratio [HR] 1.59,  $p = 0.0053$ ). This merits a re-evaluation of the use of glitazones in combination therapy with insulin in all insulin-treated patients in a routine clinical practice. Indeed, in Europe, use of insulin has been a contraindication for glitazones, although the latest American Diabetes Association/European Association for the Study of Diabetes guidelines also recommend this option (8).

The worrying increase in edema and HF has been relatively consistently reported in glitazone trials. This seems to be a class effect of glitazones. In the DREAM (Diabetes Reduction Assessment With Ramipril and Rosiglitazone Medication) study, including 5,269 subjects, rosiglitazone was used in subjects with either impaired glucose tolerance or fasting glucose but with no evidence of cardiovascular disease. In the DREAM study, the incidence of HF was 0.5% in the rosiglitazone group and 0.1% in the placebo group (HR 7.03 with a confidence interval of 1.60 to 30.9) (9). However, in the ADOPT study, including 4,360 patients with type 2 diabetes and reasonably good metabolic control, the rosiglitazone group had similar incidence of HF to the metformin group (1.5% vs. 1.3%, rosiglitazone vs. metformin) but increased incidence when compared with the sulphonylurea group (0.6%) (10). Patients with previous MI are at increased risk of HF, and this was also true in this PROactive substudy. The numbers of any reported HF and HF leading to hospitalization were significantly higher in the pioglitazone group when compared with the placebo group. Emphasizing the poorer prognosis of those with previous MI, the number of HFs was higher in this substudy when compared with those with no previous MI in the main PROactive study. For clinicians, the increased risk of HF with glitazones means more careful decision-making when optimizing the treatment of type 2 diabetic patients with previous MI. In general, the number-needed-to-treat should be accompanied by the number-needed-to-harm to better estimate the benefits of the treatments.

To summarize, pioglitazone treatment in patients with previous MI may provide modest additional benefit, which could have been more evident in the PROactive substudy if

the number of patients were larger and the duration of the study were longer. However, clinicians should weigh the benefits against the fact that the incidence of HF is increased, which is especially important in patients with a history of MI. After all, the risk of HF is present and is definitely a cardiac end point not to be neglected.

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