**EDITORIAL COMMENT**

**Fluid Retention With Thiazolidinediones**

**Does the Mechanism Influence the Outcome?**

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Heart failure (HF) and diabetes mellitus (DM) are common medical problems that are both increasing in prevalence (1,2). Diabetes mellitus is a well-known and important independent risk factor for HF (3,4). Thus it is not surprising that DM is present in nearly 20% of all patients hospitalized for a first episode of acute decompensated HF, in more that 25% of patients enrolled in recent clinical trials of HF, and in 38% of Medicare beneficiaries with HF (5–9). Any hypoglycemic agent that exacerbates HF, therefore, represents an important clinical problem.

Thiazolidinediones (TZDs) effectively improve glycemic control in patients with type 2 diabetes mellitus (T2DM) when used alone or in combination with other hypoglycemic agents (10). The insulin-sensitizing effects of TZDs are mediated by agonism of the peroxisome proliferator-activator receptor gamma, a nuclear receptor expressed in adipose tissue, vascular endothelium, pancreatic beta cells, and macrophages. In addition to improving glycemic control, TZDs have a wide range of other effects of potential benefit in patients with HF, including the lowering of blood pressure, improving endothelial function, improving lipids, decreasing circulating fatty acid levels, decreasing angiotensin II levels, and reducing the progression of atherosclerosis (11–13). Possibly reflecting the positive view practitioners have of these theoretical benefits, the use of TZDs in Medicare beneficiaries hospitalized with DM and the primary diagnosis of HF increased from 7.2% in 1998 to 1999 to 16.2% in 2000 to 2001 (14). Indeed, the PROactive study, in which patients were randomized with known macrovascular disease and T2DM to pioglitazone or placebo, reported a significantly lower risk of the secondary composite end point of death, myocardial infarction, and stroke (absolute risk reduction of 2%, hazard ratio 0.84, 95% confidence interval 0.72 to 0.98, p = 0.027) (15). However, the primary end point, which included both cardiovascular and procedural events, was not significantly reduced by pioglitazone (absolute risk reduction of 2%, hazard ratio = 0.90, 95% confidence interval 0.80 to 1.02, p = 0.095), generating further debate about the impact of TZDs on cardiac risk.

Thiazolidinedione therapy may also cause weight gain, fluid retention, and peripheral edema in patients and may result in elevations in natriuretic peptide levels—side effects that are of particular concern in patients with HF (11,16). These effects, particularly the fluid retention and edema, led to a Consensus Statement from the American Heart Association (AHA) and the American Diabetes Association (ADA) recommending caution in prescribing TZDs for patients with New York Heart Association (NYHA) functional class I and II HF and avoiding TZDs entirely in patients with NYHA functional class III and IV HF (16). Fluid retention and peripheral edema occur in 3% to 5% of patients with T2DM started on TZDs and up to 15% of patients treated with both TZDs and insulin (11,16). In clinical trials that excluded patients with a history of HF, there were small, but sometimes significant, increases in HF episodes with TZDs (≤1%) (11,17). However, in the PROactive study, TZD-treated patients had a 6% incidence of HF hospitalization compared with 4% in the control group (p = 0.007) (15). Although the number of PROactive study participants with prevalent HF at enrollment was not reported, a significant number (47%) had suffered a previous myocardial infarction. Thus, the risk of hospitalization for HF with TZDs appears to increase as the prevalence of significant underlying heart disease increases. This reported increase in the risk of HF raises the question of whether the TZDs cause myocardial depression resulting in HF, especially in patients with preexisting HF and LV dysfunction.

In this issue of the Journal, Dargie et al. (18) present the results of a randomized, placebo-controlled clinical trial designed to determine whether the TZD rosiglitazone (RSG) negatively affects myocardial function as measured by changes in left ventricular ejection fraction (LVEF) in subjects with NYHA functional class I and II HF and an LVEF ≤45% (18). During a 52-week period, the authors noted no significant change in LVEF or left ventricular (LV) end-diastolic or -systolic volumes in the RSG group compared with the control group. There were also no differences in measures of diastolic function, although these measurements were not collected in all patients, nor were they prespecified end points. These results confirm the
findings of previous studies. Ghazzi et al. (19) compared LV mass index, cardiac index, and stroke volume index in 154 subjects with noninsulin-dependent DM randomized to troglitazone or glyburide (19). At 24 and 48 weeks of follow-up, there were no significant changes in left ventricular mass index in the troglitazone group, but there were modest increases in cardiac index and stroke volume index postulated to be due to a decrease in peripheral vascular resistance. St. John Sutton et al. (20) compared the effects of RSG to glyburide in subjects with normal LVEF and no history of HF and found no decrease in LVEF and no increase in LV mass index or LV end-systolic or -diastolic volumes with either agent over the course of 52 weeks. Because these studies did not specifically target subjects with a history of HF, the Dargie et al. (18) study provides additional reassurance that the TZDs do not cause myocardial depression, even in patients with mild HF and systolic dysfunction.

Furthermore, Dargie et al. (18) reported no increase in definite or possible worsening of clinical HF with RSG, but the number of these episodes was small. The close follow-up in this study along with the increase in HF medications also may have limited the number of episodes of worsening HF. There were also considerably more cases of new or worsening edema in the RSG group (25.5% vs. 8.8%, p = 0.005) and 32.7% of RSG-treated patients required an increase in HF medications compared with 17.5% in the control group, most of which were increases in diuretics. Despite the increase in diuretics, there was a small, but significant, increase in brain natriuretic peptide levels in the RSG group, suggesting a modest increase in myocardial transmural pressure.

Does this study help physicians who are confronted with a patient with HF and T2DM with poor glycemic control for whom TZD therapy might improve glycemic control? On the basis of this study, it seems unlikely that there is a clinically significant effect of TZDs on LV systolic function. Other mechanisms of fluid retention and edema, including sympathetic activation, increased vascular permeability, and the response to vasodilatation, have been suggested as mechanisms of this phenomenon (16). However, increasing evidence in animal models suggests that the fluid retention with TZDs is due to sodium retention in the distal nephron (21,22). If this is the case in humans, it is undoubtedly of importance in a patient with or at high risk for HF, although it also raises the possibility that the fluid retention seen with TZD therapy may be treated with diuretics that target the distal nephron (i.e., amiloride or spironolactone) (23).

Whatever the mechanism of fluid retention, patients with a history of HF will require careful monitoring when TZDs are initiated and, even with careful follow-up, many patients will apparently require either a decrease in dose or discontinuation of the TZD or an increase in HF medications, especially diuretics. It is not clear, however, whether the potential benefits of TZDs on glycemia and cardiovascular risk factors would be counterbalanced by the potential detrimental effects of increased diuretic doses for controlling edema. Retrospective studies have suggested that increasing doses of loop diuretics may be associated with worsened outcomes in patients with HF (24,25). These concerns are alleviated somewhat by a retrospective study of Medicare beneficiaries with DM and a principal discharge diagnosis of HF that found lower overall mortality with TZD therapy despite a higher risk of readmission for HF (26).

Thus, Dargie et al. (18) have provided important information about the lack of a significant effect of TZDs on LV systolic function in subjects with HF, a history of NYHA functional class I and II, and LVEF ≤45%, but their data also confirm that worsening edema with the TZDs in such patients remains an important clinical problem. Until better data emerge to guide the management of the fluid retention associated with TZDs, the recommendations of the AHA/ADA consensus committee about the use of TZDs in patients with HF remain relevant to the treatment of the increasing number of patients with DM and HF.

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REFERENCES


17. The DREAM (Diabetes Reduction Assessment with ramipril and rosiglitazone Medication) Trial Investigators. Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomized controlled trial. Lancet 2006;368:1096–104.


