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Pioglitazone and Heart Failure: Results From a Controlled Study in Patients With Type 2 Diabetes Mellitus and Systolic Dysfunction

Scott Harris, DO;[1] David Tepper, MD;[2] Randy Ip, BS[1]
From Thoracic and Cardiovascular Institute, PC, Lansing, MI;[1] and South Broward Cardiology Consultants, Hollywood, FL[2]

Abstract. *Background.* Thiazolidinediones are associated with fluid retention, often interpreted as worsening cardiac function, limiting their use in patients with heart failure (HF). We compared the effects of pioglitazone and glyburide on cardiac function in patients with type 2 diabetes, systolic dysfunction, and New York Heart Association functional class II or III HF.

Methods and Results. Participants received pioglitazone or glyburide (±insulin) for 6 months in this double-blind, randomized, multicenter study. The primary end point was time to HF, a composite of cardiovascular mortality, and hospitalization or emergency department visit for HF. Secondary end points included echocardiographic and functional classification assessments. An earlier time to onset and higher incidence of the primary end point was noted with pioglitazone (13%) vs glyburide (8%) (*P*=.024). Hospitalization or emergency department visit occurred in 30 pioglitazone and 15 glyburide participants, 19 and 12 of whom, respectively, continued treatment. Cardiac mortality (5 vs 6 participants, respectively) and cardiac function, as measured by change in ventricular mass index (*P*=.959), ejection fraction (*P*=.413), or fractional shortening (*P*=.280), were similar between treatments.

Conclusions. Pioglitazone was associated with a higher incidence of hospitalization for HF without an increase in cardiovascular mortality or worsening cardiac function (by echocardiography).—*Giles TD, Miller AB, Elkayam U, et al. Pioglitazone and heart failure: results from a controlled study in patients with type 2 diabetes mellitus and systolic dysfunction.* J Card Fail. *2008;14(6): 445–452.*

Comment. This well-designed trial demonstrated a higher incidence of HF exacerbation in the pioglitazone patients compared with the glyburide cohort. Notable within the pioglitazone group is the HF incidence discrepancy between those who received concomitant insulin and those who did not (14.1% vs 5.0%, respectively). The results are consistent with the sodium-retaining effects of insulin and a putative synergistic effect with increased sodium reabsorption in the renal collecting duct seen in the thiazolidinedione drug class. In addition, when insulin was added to the glyburide cohort for glycemic control, HF admissions were more frequent than in patients who received no insulin (6.4% and 3.4%, respectively). Increases in HF admissions notwithstanding with pioglitazone, cardiac index increased with pioglitazone compared with glyburide (0.14±0.79 L/min/m^2 vs −0.03±0.55 L/min/m^2). Mortality was not significantly different between the 2 groups.

Conclusion. The authors confide that rapid increases of pioglitazone (every 2 weeks) also contributed to the increase in HF in this group. The addition of metformin and/or a renal collecting duct–acting diuretic to reduce insulin requirements and renal sodium reabsorption, respectively, may be useful. While pioglitazone increased HF admissions, especially with adjunctive insulin use, mortality and cardiac function were unchanged. Further, all patients recovered with standard HF therapy. Pioglitazone has been associated with decreased cardiac mortality in patients with diabetes, thus its use in these patients is desirable, provided exacerbations of HF can be ameliorated.