

Clinical Trials

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

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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 (NYHA) functional Class II/III HF.

Methods and Results: Participants received pioglitazone or glyburide (\pm 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 room (ER) visit for HF. Secondary endpoints included echocardiographic and functional classification assessments. An earlier time to onset and higher incidence of the primary endpoint was noted with pioglitazone (13%) versus glyburide (8%) ($P = .024$). Hospitalization or ER visit occurred in 30 pioglitazone and 15 glyburide participants, 19 and 12 of whom, respectively, continued treatment. Cardiac mortality (5 versus 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). (*J Cardiac Fail* 2008;14:445–452)

Key Words: Cardiovascular disease, thiazolidinediones, left ventricular dysfunction.

Type 2 diabetes mellitus is associated with a heavy cardiovascular (CV) burden, particularly coronary heart disease.¹ The increased risk for heart failure in this patient population is estimated to be 2 to 11 times greater than that for an age-matched nondiabetic population.²

Thiazolidinediones (TZDs) are insulin-sensitizing agents used to treat type 2 diabetes. Insulin resistance is associated with disturbances in glucose and lipid metabolism, adipose differentiation, and markers of endothelial function, coagulation, and inflammation,³ all of which contribute to

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atherosclerosis. Despite improvements in many surrogate markers of CV risk with TZD treatment, their use is limited by the dose-dependent, generally mild to moderate, fluid retention observed with these agents,^{4,5} the mechanism of which is poorly understood, but may involve enhanced sodium absorption across the collecting duct of the nephron, where PPAR γ receptors, the pharmacologic target of TZDs, are abundant.^{6,7}

Previously, rosiglitazone,⁸ and pioglitazone⁹ showed preserved cardiac function and structure relative to placebo or glyburide, respectively. Here we report the results of a clinical study that evaluated the potential of pioglitazone versus glyburide to alter cardiac function in type 2 diabetic patients with symptomatic HF. Compared with previous reports,⁸ this is the most advanced heart failure (HF) diabetic patient population studied in a controlled clinical trial of TZD therapy to date.

Methods

Study Design

This was a prospective, double-blind, multicenter, controlled study evaluating HF progression in participants with type 2 diabetes mellitus and systolic dysfunction with symptomatic HF after 6 months of treatment with pioglitazone or glyburide (\pm insulin). Study visits occurred weekly for the first 2 weeks and monthly thereafter. Glyburide provided a reasonable estimate of background CV event rates in this patient population.

The International Conference for Harmonisation-Good Clinical Practice guidance, the Declaration of Helsinki (2000), and local regulations were followed. All participants provided written informed consent. The study is registered on clinicaltrials.gov (NCT00521820).

Participants

Participants were ≥ 18 years of age with an hemoglobin A1c (HbA1c) $\geq 7.0\%$, body mass index ≤ 48 kg/m², New York Heart Association (NYHA) functional Class II/III HF (ie, cardiac disease resulting in moderate limitation of physical activity; comfortable at rest, but symptoms of fatigue, palpitations, dyspnea, or anginal pain occurring with less than what would be considered ordinary activity), left ventricular systolic dysfunction (ie, left ventricular ejection fraction [LVEF] $\leq 40\%$) at screening, receiving sulfonylurea therapy (\pm insulin) for ≥ 30 days before screening, or discontinued metformin therapy within 30 days of screening.

Subjects naive to antidiabetic therapy or with type 1 diabetes, serum creatinine > 2.0 mg/dL (males) or > 1.8 mg/dL (females), systolic blood pressure (SBP) > 150 mm Hg or diastolic blood pressure (DBP) > 100 mm Hg, or recent (≤ 3 months) myocardial infarction, coronary angioplasty or bypass graft, unstable angina, transient ischemic attack or stroke, or severe/advanced peripheral vascular disease were excluded.

Study Procedures

Echocardiograms were recorded by standard protocol at screening and final visits, and read by a single treatment-blinded reader (BioMedical Systems, St Louis, MO). Measured indices included

LVEF, left ventricular mass index (LVMI), cardiac index (CI), and fractional shortening (FS).

NYHA functional classification was evaluated using standard assessments and definitions at each visit. Exercise tolerance (standardized 6-minute walk test) and global assessments of HF status were determined at baseline and final visit.

Adverse events (AEs) and clinical laboratory assessments were determined at each visit. Laboratory assessments were performed at Clinical Reference Laboratory (Lenexa, KS) and included standard serum chemistry (including kidney and liver function assessments), hematology, and urinalysis (including pH, protein, glucose, ketones, and specific gravity).

Treatment

Oral diabetes therapies were stopped at the screening visit (ie, within 2 weeks before randomization). Treatment randomization was to pioglitazone (30 mg) or glyburide (10 mg) in a 1:1 ratio, stratified by baseline insulin use. Doses were increased as tolerated to 45 mg pioglitazone or 15 mg glyburide if fasting plasma glucose (FPG) was > 140 mg/dL (determined weekly for the first 2 weeks and monthly thereafter). Insulin was the only allowed rescue medication. For hypoglycemia, study drug dose was decreased for noninsulin users; insulin dose was decreased before study drug for insulin users. Maximum tolerated study drug doses were used for the study duration.

Determination of the Primary End Point

The primary end point, HF progression, was a composite of CV mortality and hospitalization or ER visit for HF. An independent treatment-blinded clinical end point committee adjudicated all endpoint events using information provided by the study center and all available hospital documentation (ie, admission/discharge documents, physician notes, laboratory/radiography study results, death certificates). Documented increasing dyspnea on exertion, worsening orthopnea or nocturnal dyspnea, increasing fatigue/decreasing exercise tolerance, renal hypoperfusion (ie, worsening renal failure) not from adjusted diuretic or after load reduction therapy, pulmonary edema, increased jugular venous pressure (relative to baseline), or radiologic evidence confirmed a HF diagnosis. A data safety monitoring board conducted periodic, unblinded reviews of all safety data and had the sole authority to stop the study for safety reasons.

Statistical Methods

Statistical analyses (SAS, v8.2, Cary, NC) were performed on the intent-to-treat cohort, defined as participants who received at least 1 dose of study drug. The time to first event was estimated using the Kaplan-Meier method. Assuming a 10% dropout rate, a sample size of 300 per group was estimated to allow 90% power to detect a 10-percentage point treatment differential at 24 weeks with a minimum event rate of 10% in 1 group and 20% in the other group. Significance was assessed at 0.05 and reported as 2-sided. Continuous variables were compared using a 2-way analysis of covariance with fixed effects terms of treatment, center, baseline insulin use, and baseline value (as covariate). Descriptive statistics for LVMI, CI, FS, and LVEF were derived using observed values. Analyses of change from baseline to final visit used the last observation carried forward method. Low-density lipoprotein cholesterol (LDL-C) values coincident with triglyceride values greater than 400 mg/dL were excluded from the summary.

Results

The study started in June 2000. In November 2003, the data safety monitoring board observed a treatment-group imbalance for the composite endpoint and withdrawal rate. An independent, unblinded analysis revealed a treatment-group difference in the composite endpoint ($P = .09$) favoring glyburide, prompting the data safety monitoring board recommendation for early study termination.

Disposition and Baseline Characteristics

Of the 518 participants receiving study drug (pioglitazone 262; glyburide 256), 264 were enrolled in US sites and 254 in non-US sites (Fig. 1). Participant enrollment at non-US sites included 249 participant enrolled in Argentina, 1 participant in Colombia, and 4 participants in Mexico. Overall, 60% of the pioglitazone group and 72% of the glyburide group completed the study. During the first 8 weeks of the study, twice as many pioglitazone as glyburide participants discontinued treatment (18% [47/262] versus 9% [22/256], respectively). Thereafter, the discontinuation rates were similar between groups (21% versus 19%, respectively). Reasons for discontinuation were similar with the exception of AEs (24 pioglitazone versus 14 glyburide), lack of efficacy (10 versus 4, respectively), and withdrew consent (18 versus 7, respectively).

Treatment groups were balanced for baseline demographics and clinical characteristics (Table 1). At baseline, approximately one-third of participants in each group were using insulin. During the study, insulin treatment was initiated in twice as many pioglitazone as glyburide users (53 [20%]

Table 1. Demographic and Baseline Characteristics (ITT Population)

	Pioglitazone (n = 262)	Glyburide (n = 256)
Age (y)	64.2 (9.92)	63.4 (9.38)
Men, n (%)	184 (70.2)	197 (77.0)
Caucasian, n (%)	180 (68.7)	170 (66.4)
HbA1c (%)	8.74 (1.558)	8.95 (1.783)
FPG (mg/dL)	186.5 (75.99)	185.9 (76.54)
BMI (kg/m ²)	29.6 (5.20)	29.7 (5.37)
SBP (mm Hg)	125.8 (14.05)	125.5 (14.64)
DBP (mm Hg)	74.9 (10.25)	74.9 (9.95)
HR (beats/min)	73.3 (10.63)	72.2 (10.93)
Time since diagnosis of T2DM (mo)	141.7 (110.51)	140.5 (113.7)
Time since first diagnosis of CHF (mo)	59 (53.3)	55 (58.0)
Etiology of heart failure, n (%)		
Ischemic heart disease	186 (71.0)	167 (65.2)
Hypertension	36 (13.7)	43 (16.8)
Idiopathic dilated cardiomyopathy	34 (13.0)	34 (13.3)
Valvular heart disease	1 (0.4)	3 (1.2)
Other cause	5 (1.9)	9 (3.5)
NYHA, n (%)		
Class I	0 (0)	2 (0.8)
Class II	213 (81.3)	208 (81.3)
Class III	49 (18.7)	46 (18.0)
Insulin	89 (34.0)	83 (32.4)
CHF medications, n (%)		
Renin-angiotensin system antagonist or blocker	240 (92)	233 (91)
Diuretic*	210 (80.0)	219 (86)
Furosemide	186 (71.0)	194 (75)
Hydrochlorothiazide	31 (12)	27 (10)
Metolazone	15 (6)	11 (4)
Spironolactone	80 (30)	90 (35)
β-blockers	170 (65)	172 (67)
Others cardiac therapies (amiodarone, digoxin, glyceryl trinitrate, or isosorbide mononitrate therapies)	173 (66)	179 (70)
LV ejection fraction (%)	n = 203	n = 206
Mean (SD)	29.7 (10.27)	29.4 (10.02)
Range	4.46–72.87	7.11–65.63
Fractional shortening (%)	n = 226	n = 223
Mean (SD)	21.9 (7.0)	21.0 (6.5)
Range	3.41–42.41	4.11–46.32

Values are presented as mean (SD) unless otherwise indicated. ITT, intent-to-treat; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; NYHA, New York Heart Association; HbA1c, hemoglobin A1c; FPG, fasting plasma glucose; CHF, congestive heart failure; LV, left ventricular; SD, standard deviation. *Diuretics used by at least 5% of participants in either treatment group are listed.

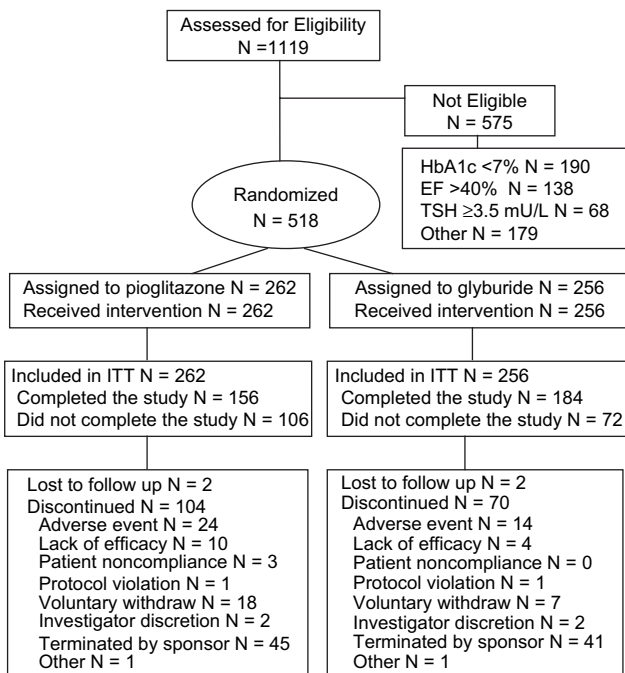


Fig. 1. Participant disposition. ITT, intent to treat; HbA1c, hemoglobin A1c; EF, ejection fraction; TSH, thyroid-stimulating hormone.

versus 29 [10%], respectively); most new insulin use occurred early in the study. By Week 8, 14.9% and 9.8% of participants in the pioglitazone and glyburide groups, respectively, had added insulin. Participants received optimal HF management that included renin-angiotensin system antagonist or blocker, diuretic, antithrombotic, β-blocking, and amiodarone, digoxin, glyceryl trinitrate, or isosorbide mononitrate therapies. During the study, diuretic use increased from 80.2% to 82.4% in the pioglitazone group and from 85.5% to 87.9% in the glyburide group.

Baseline LVEF values were similar between groups (29.7% pioglitazone versus 29.4% glyburide), although the mean value for participants enrolled at non-US sites (27.5% versus 28.65%, respectively) was lower than for

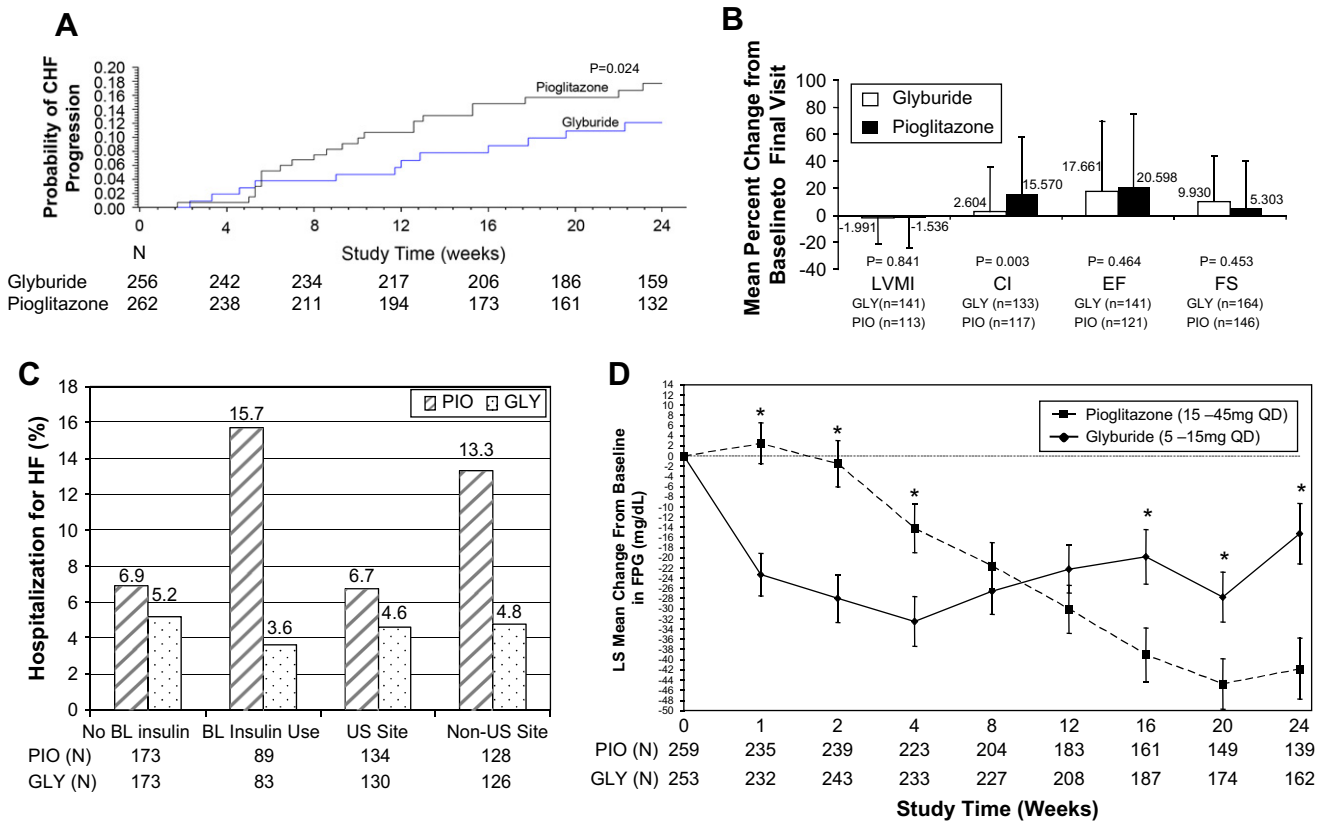


Fig. 2. (A) Kaplan-Meier estimates of probability of first event based on determination by clinical end point committee. *P* value is on the treatment-group difference at final visit. (B) Hospitalization for heart failure by baseline insulin use and by geographic region (ITT analysis). (C) Mean percent change from baseline to final visit in echocardiographic parameters (ITT analysis). Final visit analysis incorporated the last observation for each subject. (D) Mean change from baseline in FPG by study week and treatment group (ITT analysis). PIO, pioglitazone; GLY, glyburide; ITT, intent to treat; LVMI, left ventricular mass index; CI, cardiac index; EF, ejection fraction; FS, fractional shortening; FPG, fasting plasma glucose.

participants enrolled at US sites (32.2% versus 30.1%, respectively). Similarly, FS values were lower among participants at non-US sites (21.2% versus 20.5%) than US sites (22.7% versus 21.7%, respectively). These findings indicate that participants enrolled outside of the US tended to have more advanced heart failure disease.

Progression of HF

Pioglitazone was associated with an earlier time to onset (Fig. 2) (*P* = .024) and a higher incidence rate of the composite end point compared with glyburide (Table 2). Whereas mortality contributed little to the overall rate and was similar between treatments (5 with pioglitazone and 6 with glyburide), overnight hospitalization for HF contributed disproportionately to the composite endpoint and was higher in the pioglitazone group. Thirty pioglitazone and 15 glyburide participants were hospitalized or had an emergency room visit for HF; of these, 19 and 12 participants, respectively, continued in the study, indicating most cases of HF were reversible and not treatment limiting.

Subgroup analyses of the primary composite end point, although limited by smaller sample sizes and fewer events than the overall analysis, revealed higher event rates with pioglitazone versus glyburide among participants using insulin at baseline (19.1% versus 8.4%; respectively, *P* = .032), whereas event rates among participants not using insulin at baseline (10.4% versus 8.1%, respectively; *P* = .285), with concomitant insulin use during the study (16.9% vs 11.0%, respectively; *P* = .172), and without concomitant insulin use (9.2% and 6.1%, respectively; *P* = .185) were similar between group. As with the primary analysis,

Table 2. Incidence of Primary End Point and Contributing Events (ITT Analysis)

	Pioglitazone (n = 262)	Glyburide (n = 256)	<i>P</i> Value
Composite event n (%)	35 (13.4)	21 (8.2)	.024
Death from CV cause	5 (1.9)	6 (2.3)	
Overnight hospitalization for worsening CHF	26 (9.9)	12 (4.7)	
ER visit for CHF	4 (1.5)	3 (1.2)	

CV, cardiovascular; CHF, congestive heart failure; ER, emergency room. *P* value for treatment-group difference, determined by log-rank test.

hospitalization for HF contributed disproportionately to the composite end point among baseline and concomitant insulin users, whereas the rate of hospitalization for HF was low and balanced among participants who did not use insulin (Fig. 2).

Participants enrolled at non-US sites tended to enter the study with more severe disease as measured by mean EF and FS. Subgroup analyses of the composite endpoint by region also revealed a higher incidence of events for the non-US cohort (pioglitazone 17.2% versus glyburide 9.5%, $P = .061$) than for the US cohort (9.7% versus 6.9%, respectively $P = .241$). Within the composite end point, the rate of hospitalization was similar among glyburide users irrespective of region (4.8% non-US versus 4.6% US), but was twice as high at non-US (13.3%) versus US sites (6.7%) among pioglitazone users (Fig. 2).

Higher rates of HF progression were reported for pioglitazone users in the >64-years-of-age cohort (pioglitazone 14.7%; glyburide 7.1%; $P = .037$) and among men (13.0% versus 7.1%, respectively; $P = .030$), whereas the rates were similar between groups in the ≤64-years-of-age cohort and among women (14.1% versus 11.9%; $P = .477$) (12.0% versus 9.0%, respectively; $P = .270$).

Cardiac Function

Despite an increased reporting of HF with pioglitazone, echocardiographic data indicate preserved rather than worsening cardiac function with similar changes in the LVMI (g/m^2) (pioglitazone -4.1 [47.08]; glyburide -6.9 [37.52]; $P = .959$), FS (%) (0.2 [6.79] and 1.2 [6.42], respectively; $P = .280$), and LVEF (%) (3.6 [10.20] and 2.5 [9.86], respectively; $P = .413$) noted between treatment groups. Cardiac index ($\text{L}\cdot\text{min}\cdot\text{m}^2$), however, was significantly increased with pioglitazone compared with glyburide (0.14 ± 0.79 versus -0.03 ± 0.55 , respectively, $P = .012$) (Fig. 2), and significant increases in CI were also observed for pioglitazone users in both the US and non-US cohorts. No treatment-group differences were observed within the US and non-US cohorts for LVMI, FS, or LVEF. Notably, the absolute relative improvements in CI seen with pioglitazone were similar between regions despite the significantly poorer baseline readings at non-US sites.

Significant treatment effects on blood pressure favoring pioglitazone were observed at Weeks 8 and 12 for SBP and at Weeks 4, 8, 12, and final visit for DBP. There were no notable treatment effects on any other measured vital sign, electrocardiogram parameter, physical examination, 6-minute walk test, changes in NYHA functional classification, or laboratory parameter with the exception of heart rate. At all time points, mean decreases in heart rate were noted with pioglitazone; mean decreases up to Week 12 and minor increases thereafter were noted with glyburide.

Metabolic Effects

FPG was significantly decreased with glyburide relative to pioglitazone during the first 4 weeks of treatment (Fig. 2). Nearly half of pioglitazone users compared with one third of glyburide users were at maximal dose by Week 2. By Week 4, a steady and consistent increase in mean FPG was noted with glyburide, whereas decreases were noted with pioglitazone. By Week 16, and thereafter, a significant difference in mean FPG was observed favoring pioglitazone. Consistent with changes in FPG was a reduction in HbA1c with pioglitazone compared with glyburide least squares (LS) (means -0.98% versus -0.73% , respectively), that was first noted at Week 20 and sustained for the remainder of the study (at Week 24, $P = .007$).

At Week 24, significant differences were seen between pioglitazone and glyburide in triglycerides (-36.8 versus 7.6 mg/dL, $P < .001$ [LS mean % change -11.7 versus 7.2]), high-density lipoprotein cholesterol (HDL-C) (4.8 versus -0.8 mg/dL, $P < .001$ [LS mean % change 15.5 versus -0.5]), and LDL-C (6.9 versus -2.4 mg/dL, $P = .016$ [LS mean % change 7.0 versus 2.4], respectively).

General Safety

Overall rates of AEs and serious AEs were similar between treatment groups, though more pioglitazone than glyburide participants discontinued because of an AE (Table 3). Hypoglycemia was more common with glyburide; edema was more common with pioglitazone. The most commonly reported AE leading to study discontinuation was aggravated HF (2.3%, pioglitazone; 1.2%, glyburide).

Weight gain, known to occur with both TZDs and insulin, was more than twice as likely to be reported as an AE (6.1% versus 2.7%) and mean weight gain was greater

Table 3. Treatment-Emergent Adverse Events (ITT Population)

Event Category	Pioglitazone (n = 262)	Glyburide (n = 256)
Total AEs ($\geq 5\%$)*	74.0%	74.6%
CHF/cardiac failure aggravated [†]	15.6%	10.2%
Hypoglycemia	9.5%	16.0%
Edema lower limb	9.5%	5.1%
Dizziness	8.4%	6.6%
Weight increased	6.1%	2.7%
Bronchitis	2.7%	5.5%
Diarrhea	5.3%	3.5%
AEs causing discontinuation ($\geq 1.5\%$) [‡]	11.8%	7.4%
CHF/cardiac failure aggravated [†]	3.8%	2.0%
Hyperglycemia	1.9%	0.4%
Serious AEs ($\geq 1.5\%$) [‡]	19.8%	18.0%
CHF/cardiac failure aggravated [†]	7.6%	3.5%
Myocardial infarction	1.5%	0.8%
Ventricular tachycardia	0	1.6%
Pneumonia	1.9%	1.6%
Sudden death	0.4%	1.6%

CHF, congestive heart failure.

*Events reported for $\geq 5\%$ of participants in either group are shown.

[†]Data are investigator reports, not adjudicated endpoint events.

[‡]Events reported for $\geq 1.5\%$ of participants in either group are shown.

(2.10 kg versus 1.23 kg, respectively, $P = .012$) with pioglitazone than with glyburide. Among insulin users, mean weight gain was 2.20 kg and 1.44 kg, respectively, whereas among noninsulin users it was 0.87 kg and 0.26 kg, respectively. Moreover, insulin use more than tripled the reporting rate of weight gain among pioglitazone users (9.2% with insulin versus 2.5% without insulin).

Discussion

Pioglitazone was associated with an excess of overnight hospitalizations for HF, resulting in a higher rate of the composite end point versus glyburide in this study population of type 2 diabetic patients with preexisting symptomatic HF. The separation between treatment groups for time to first event occurred at approximately 6 weeks, stabilized thereafter, and was driven almost entirely by hospitalization for HF. CV-related deaths contributed little to the overall composite end point in either group and CV mortality was not increased with pioglitazone despite the higher rates of hospitalization for HF. Importantly, once hospitalized for HF, participants in the pioglitazone group did not have worse outcome compared with participants in the glyburide group: HF was generally reversible, not treatment limiting, and not associated with increased CV-related deaths or adverse events (excluding events of HF).

In our study, a greater proportion of pioglitazone than glyburide participants received insulin (54.2% and 43.8%, respectively), and most new insulin use was initiated early in the trial. Additionally, dose titration tended to take place earlier in the pioglitazone group, as most participants were receiving maximal dose by Week 2. The increased use of insulin and more rapid dose titration in the pioglitazone group, both of which were driven by FPG targets stipulated in the protocol, are consistent with known properties of the 2 study medications. Glyburide and other sulfonylureas, which are insulin secretagogues, lower glucose levels effectively in the short term but tend to lose effectiveness over time. TZDs, however, may take longer to reach peak effect but appear to provide equivalent or better long-term control than sulfonylureas, as was observed in the present study.

Rapid dose titration and disproportionate insulin use in the pioglitazone group also likely contributed to the increased reports of HF among pioglitazone users. TZDs are associated in a dose-dependent fluid retention, whereas insulin, a sodium-retaining hormone, is associated with an estimated risk for HF of 14% to 24% when used as monotherapy or in combination therapies in patients with type 2 diabetes.¹⁰ In our study, hospitalization for HF was reported for 14.1% of pioglitazone participants and 6.4% of glyburide participants who used insulin, compared with 5.0% versus 3.4%, respectively, among participants for whom insulin was not added.

Increased left ventricular size and reduced ejection fraction are typical with systolic dysfunction in HF. Despite the earlier time to and higher incidence rate of HF, there was no evidence of worsening cardiac function or structure with

pioglitazone after 24 weeks of treatment relative to glyburide. Changes in echocardiographic parameters were similar between treatment groups, with the exception of CI, which showed significant increases with pioglitazone versus glyburide. The increase in cardiac output is consistent with the clinically relevant decreases in blood pressure noted with pioglitazone, changes that have been observed in other TZD studies.^{11,12} Additionally, positive effects on triglycerides and HDL-C were noted with pioglitazone.

Our data also support previous studies of pioglitazone on other CV outcomes, such as MI and CV death. In PROactive, pioglitazone was associated with a 16% (95% CI 0.72–0.98; $P = .027$) risk reduction for a composite end point of all-cause mortality, non-fatal MI (excluding silent MI), and non-fatal stroke relative to placebo.¹³ Additionally, among patients with a previous MI, the risk of recurrent MI was significantly reduced,¹⁴ as was the risk of recurrent stroke among patients with previous stroke.¹⁵ Among patients who reported serious HF in PROactive, treatment had no effect on mortality.^{16,17} Together, these findings indicate that the potential CV benefits of pioglitazone treatment were not offset by the higher rate of serious HF in the high-risk PROactive patient population.

Although neither pioglitazone nor the TZD rosiglitazone has been shown to have deleterious effects on cardiac structure or function,⁸ there appear to be incompletely understood differences between these agents that impact their overall CV safety profile. In contrast to the trend of CV benefit observed in PROactive and in the recent meta-analysis of pioglitazone studies published by Lincoff et al,¹⁸ reports suggest that rosiglitazone treatment is associated with increased risk of MI and CV death.¹⁹ Such differences in outcome may, in part, be explained by the distinct lipid effects of these two TZDs. In a head-to-head study²⁰ of 802 patients with diabetic dyslipidemia, pioglitazone significantly improved triglyceride and HDL-C levels, and increased LDL-C to a significantly lesser extent relative to rosiglitazone. In a separate study, 305 patients with diabetic dyslipidemia who were on rosiglitazone and stable statin therapy were switched to pioglitazone (statin therapy was maintained).²¹ After 17 weeks of treatment, significant decreases in triglyceride, total cholesterol, and LDL-C levels were noted. These improvements were accompanied by favorable shifts in LDL subfractions from smaller dense particles to the less atherogenic large buoyant particles. Although no study evaluating the correlation between pioglitazone-induced changes in lipids and other markers of atherosclerosis has been conducted, it is reasonable to hypothesize that these unique features of pioglitazone may contribute to the trend for beneficial CV outcomes observed in PROactive and may explain the absence of an apparent cardioprotective effect with rosiglitazone.

Several lessons were learned from this study. First, HF associated with pioglitazone use does not diminish cardiac function or structure. Second, use of metformin during the run-in period may have provided sufficient glycemic control early in the study, thereby eliminating the need to

initiate early insulin therapy. Third, starting patients at the lowest dose of pioglitazone and slowly titrating based on HbA1c rather than FPG would have allowed sufficient time for pioglitazone to exert its glucose-lowering effects without a premature dose increase. Slow-dose titration is particularly important in patients with HF given that TZD treatment is associated dose-dependent fluid retention, which may have exacerbated symptoms of HF in this study.

Metformin was contraindicated for use in diabetic patients with heart failure at the time the study was designed. Consequently, glycemic control was maintained via dose titration and addition of insulin, circumstances that increased the risk for HF among pioglitazone users. The lack of an oral alternative to insulin likely had a second important impact on the study—it contributed to the relatively high dropout rate noted with pioglitazone, most of which was attributed to treatment failure and withdrawal of consent. The differential dropout rate was greatest during the first 8 weeks of the study (18% versus 8.6%, respectively), when there was a significant treatment-group difference in HbA1c favoring glyburide; thereafter, the dropout rates were similar (21% vs 19.1%, respectively). Since the study completed, the restrictions for use of metformin in patients with HF have been relaxed and recent studies suggest metformin may have beneficial effects in this patient population.²²

Limitations of the Study

This study, the first to evaluate a TZD in a patient population with symptomatic systolic dysfunction, had several limitations, including a 2-week screening period in which oral antidiabetic medications were withheld, a rapid dose titration schedule contrary to dosing recommendations for clinical use of pioglitazone, and dose escalation based on FPG rather than HbA1c. These limitations likely contributed to the differential completion rate in each arm of the study, which, in turn, may have affected the comparability of the treatment groups.

Our study confirms the need for slow dose titration, monitoring for weight gain and edema, and careful use of insulin in this patient population, recommendations consistent with the current ACTOS package insert⁴ and the American Diabetes Association/American Heart Association guidelines for TZD use in type 2 diabetics with systolic or diastolic dysfunction.²³

Conclusion

In this study in patients with type 2 diabetes and systolic dysfunction with NYHA functional Class II/III HF, there was an excess of overnight hospitalization for HF with pioglitazone without an excess of CV mortality or worsening cardiac function. HF that occurred with pioglitazone was reversible and not treatment limiting. These results support current guidelines that recommend initiating thiazolidinedione therapy at the lowest dose and titrating gradually in

patients with type 2 diabetes and HF (NYHA Class I and II), whereas monitoring for edema or weight gain.

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