



Comparison of Pioglitazone vs Glyburide in Early Heart Failure: Insights From a Randomized Controlled Study of Patients With Type 2 Diabetes and Mild Cardiac Disease

The use of thiazolidinediones (TZDs) in patients with type 2 diabetes and underlying symptomatic cardiac disease has been limited because of dose-dependent fluid retention observed in some patients with these agents.^{1,2} In susceptible patients, TZD therapy may precipitate or exacerbate signs and symptoms of heart failure (HF),³ although data from animal and clinical studies suggest that TZDs may improve rather than diminish cardiac function.^{4,5} Additional evidence suggests that TZDs, insulin-sensitizing agents that lower blood glucose levels, may mediate improvements in blood pressure, endothelial function, inflammation, and thrombosis, thereby reducing the risk of atherosclerosis in patients with type 2 diabetes.⁶⁻⁸

Nonetheless, there have been recent concerns regarding a potential cardiovascular (CV) risk signal with TZD treatment and increased risk of ischemic events⁹ or HF¹⁰ among diabetic patients. In a recent study, we demonstrated that CV mortality was similar among patients with type 2 diabetes and New York Heart Association (NYHA) class II/III HF treated for 6 months with either pioglitazone or glyburide, despite a significantly higher rate of serious HF among pioglitazone-treated patients.¹¹ Moreover, echocardiographic evaluations showed no deterioration in cardiac function with either treatment. Here we report the findings from a 1-year clinical study in which the effects of pioglitazone or glyburide were evaluated for changes in HF status in patients with type 2 diabetes and asymptomatic NYHA class I HF, a patient population consistent with the US Food and Drug Administration-approved indicated use of pioglitazone.¹²

Pioglitazone may cause fluid retention, a well-known side effect of thiazolidinediones, and may exacerbate heart failure. Patients with type 2 diabetes and mild cardiac disease (New York Heart Association functional class I) received pioglitazone (n=151) or glyburide (n=149) for 1 year. The primary endpoint was change in distance covered in the 6-minute walk test. Main secondary endpoints included comparison of cardiovascular mortality and morbidity, analysis of changes from baseline in cardiac structure and function by echocardiogram, and lipid panel. There was no significant treatment difference in the mean change from baseline in the 6-minute walk test (-11.7 m [95% confidence interval, -29.79 to 6.42]). Cardiovascular mortality and morbidity were not significantly different between the treatment groups. Echocardiographic data suggested no significant deterioration in cardiac function with pioglitazone, although more heart failure (10 vs 7 patients), edema (21.2% vs 12.8%), and weight gain (2.56±4.62 kg vs 0.86±3.85 kg) were observed than with glyburide. Congest Heart Fail. 2010;16:111-117. ©2010 Wiley Periodicals, Inc.

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Methods

Study Design and Population. This multicenter, randomized, double-blind, comparator-controlled study conducted in the United States evaluated exercise tolerance in patients 18 to 80 years of age with type 2 diabetes and mild cardiac disease (ie, NYHA functional class I) who received pioglitazone or glyburide for 1 year during which the study drug was initiated and optimized for glucose control. Mild cardiac disease was

defined as at least one of the following: hypertension with corresponding left ventricular hypertrophy (diagnosed by electrocardiographic criteria, echocardiography, multigated acquisition scanning, or other nuclear procedures); coronary artery disease; previous NYHA functional class II; history of myocardial infarction (MI); previous echocardiogram with left ventricular ejection fraction (LVEF) <50%; previous echocardiogram or angiogram showing ventricular hypokinetic and/or akinetic

segments; or previous echocardiogram with demonstrated diastolic dysfunction in asymptomatic patients. Patients with a CV event (eg, MI, coronary angioplasty or bypass graft, unstable angina pectoris, transient ischemic attack, or documented cerebrovascular accident) within 3 months prior to screening were excluded, as were those with NYHA functional class II or history of class III or IV disease.

Study patients were either naïve to oral antidiabetes medication or on a stable dose of a sulfonylurea, a sulfonylurea/metformin combination, or metformin alone for ≥ 30 days before screening. Patients with previous TZD therapy, who were unresponsive to or intolerant of sulfonylurea treatment, or who had current or past insulin use were excluded.

The study was approved by local institutional review boards and complied with International Conference on Harmonization Good Clinical Practices guidance, World Medical Association Declaration of Helsinki, and local regulations. All patients provided informed consent.

Eligibility screening occurred within 2 weeks of the randomization visit (week 0), at which patients received the first dose of study drug. Study visits were scheduled at weeks 2, 4, 6, 8, 12, 16, 24, 32, 36, 40, 48, and 52 for patients to return to the clinics.

At screening, demographic information, medical history, prior medication use, vital signs, and weight were recorded, and body mass index and NYHA functional class status were determined. A physical examination, 12-lead electrocardiography, and 6-minute walk test were completed. Samples were collected for determination of hemoglobin A_{1c} (HbA_{1c}) and clinical laboratory tests.

Two practice tests were given to patients prior to screening on the 6-minute walk test, and the test was done by the same person from the investigator site to reduce variability. At the randomization visit, a 6-minute walk test and quality-of-life assessments were completed, blood samples were drawn for serum analysis, and vital signs and weight were recorded. Prior sulfonylurea

or sulfonylurea/metformin combination therapies were discontinued at this time.

Concomitant medication use, study medication compliance, and adverse events were assessed throughout the study. Investigators were encouraged to manage blood pressure according to the current guidelines. Blood glucose values were self-monitored and reported at each visit; fasting plasma glucose levels were assessed in the clinic, if necessary. All final assessments were completed at the final visit (week 52 or time of study withdrawal).

Patients were randomly assigned to double-blind treatment with pioglitazone or glyburide. Those naïve to oral antidiabetes therapy initiated treatment with 15 mg pioglitazone or 2.5 mg glyburide. Patients with previous antidiabetes therapy were started on 15 or 30 mg pioglitazone QD or 5 or 10 mg glyburide QD, depending on the sulfonylurea dose taken prior to study entry. In addition to randomized treatment, metformin therapy was continued for patients receiving metformin at screening.

The study drug was up-titrated to 45 mg of pioglitazone or 15 mg of glyburide, as tolerated, to achieve and maintain glucose levels between 100 mg/dL and 180 mg/dL (finger stick) or 70 mg/dL and 140 mg/dL (fasting plasma glucose). Insulin and metformin were allowed as necessary to maintain glyce-mic control.

Endpoints. The primary endpoint was change in the distance covered in the 6-minute walk test from baseline to the final visit. Secondary endpoints included CV mortality and morbidity and changes in CV treatment regimen, heart rate, and echocardiographic parameters (ie, left ventricular mass index [LVMI], LVEF, cardiac index [CI], and fractional shortening [FS]). The safety variables were identified and reviewed by a data safety monitoring board (DSMB). CV morbidity was defined as hospitalization for a CV event. CV mortality was characterized by the DSMB in a blinded fashion. Other variables included changes in Minnesota Living with Heart Failure Questionnaire

scores, NYHA functional classification, blood pressure, and HbA_{1c} and lipid levels; adverse events were recorded as a safety measure. In addition, left ventricular end diastolic volume (LVEDV), left ventricular end systolic volume (LVESV), stroke volume, and cardiac output were determined post hoc for a subset of patients who had both a baseline and final visit technically sufficient echocardiogram recorded.

Statistical Analysis. Data analysis and tabulations of descriptive and inferential statistics were performed using SAS version 6.12 (SAS Institute Inc, Cary, NC). A total of 300 patients (150 per treatment group) was estimated sufficient to achieve at least 90% power to detect the difference of 30 m between the 2 treatment groups by a 2-sample *t*-test of the mean change from baseline in the walk test distance with a .05, two-sided significance level, assuming an 80-m standard deviation.

The intent-to-treat population included any participant who received at least 1 dose of randomized study drug and was used for all clinical endpoint analyses. Baseline values were compared using a 2-way analysis of variance with terms for treatment and pooled center; treatment comparisons for post-baseline values were completed by using a 2-way analysis of covariance with terms for treatment, pooled center, and baseline value (as a covariate) for continuous variables. Categorical variables were analyzed using Cochran-Mantel-Haenszel test. Kaplan-Meier estimates were calculated for time to CV mortality and morbidity; the log-rank test was used for treatment-group comparisons. Analyses of change from baseline to final visit were calculated using the last-observation-carried-forward method.

Clinical Reference Laboratory (Lenexa, KS) performed all laboratory tests. Echocardiograms were recorded at study sites using a standardized protocol and read centrally (BioMedical Systems, St. Louis, MO). A DSMB conducted periodic partially unblinded reviews of all safety data and blinded reviews of all deaths.

Results

Participant Disposition. Three hundred patients (151 in the pioglitazone group and 149 in the glyburide group) were assigned to and received randomized treatment; 234 patients (78.0%) completed the study (Figure 1).

Baseline Characteristics. Treatment groups were balanced for demographic characteristics. The study population had a mean age of 64 years and was mostly male (56%) and Caucasian (61%). Mean (standard deviation [SD]) baseline HbA_{1c} values were 8.6% (1.5%) in the pioglitazone group and 8.3% (1.4%) in the glyburide group; low-density lipoprotein cholesterol values were similar between groups (104.3 [33.6] and 107.2 [34.3] mg/dL; *P*=not significant), whereas high-density lipoprotein cholesterol was lower (42.1 [11.1] mg/dL vs 45.2 [13.1] mg/dL; *P*=.028) and triglycerides were higher (242.4 [133.8] vs 202.4 [115.2] mg/dL; *P*=.002), respectively, in the pioglitazone vs glyburide group. The use of concomitant antidiabetes medications was similar for both treatment groups, with the exception of greater insulin (24 vs 12 patients, respectively) and metformin (76 vs 69 patients, respectively) use in the pioglitazone vs glyburide group. Treatment groups were balanced for proportion of patients with hypertension (59.6% vs 60.4%) and history of coronary artery disease (60.3% vs 55.0%, respectively) in the pioglitazone vs glyburide group. Approximately 14% of patients had previous echocardiographic evidence of diastolic dysfunction and 28% had a previous MI; however, at baseline, all patients had NYHA functional class I HF rating. Use of lipid-altering agents and diuretics was greater in the pioglitazone than in the glyburide group at baseline. The most commonly used diuretics were furosemide (19.9% and 13.4%, respectively) and hydrochlorothiazide (11.9% and 8.1%, respectively).

Exercise Function. At the final visit, the mean treatment-group difference in change from baseline was -11.7 m (95% confidence interval, -29.79 to 6.42). Between weeks 2 and 52, slight

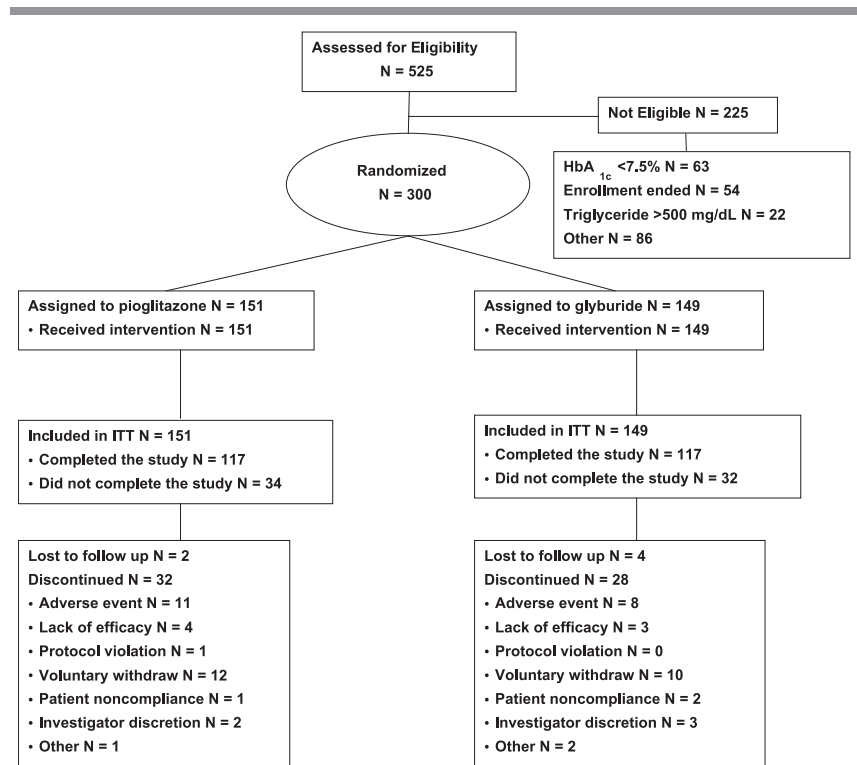


Figure 1. Participant disposition. ITT indicates intent to treat; HbA_{1c}, hemoglobin A_{1c}.

increases in the mean distance covered were observed in both treatment groups, with no statistically significant treatment-group difference noted at any study visit (Figure 2).

CV Mortality and Morbidity. There were no statistically significant differences between the treatment groups in mortality or morbidity due to CV events. There were no deaths and 13 of 151 (8.6%) hospitalizations were due to CV events in the pioglitazone group. There were 2 (1.3%) deaths and 13 of 149 (8.7%) hospitalizations were due to CV events in the glyburide group.

Echocardiographic Parameters. After 1 year of treatment, there were no statistically significant treatment differences in change from baseline in LVMI, LVEF, CI, or FS. In both treatment groups, there was a slight decrease in LVMI and a slight increase in LVEF, indicating a trend of overall improvement (Figure 3).

Additional parameters of cardiac function were derived from echocardiograms for patients who had technically satisfactory recordings at both baseline

and the final visit. This post hoc analysis revealed no treatment-group difference at baseline or percentage change from baseline to the final visit for the derived measures of LVEDV, LVESV, stroke volume, and cardiac output (Table).

Vital Signs. Greater decreases in systolic blood pressure at weeks 6, 12, 16, 24, and 32 (mean differences of 4.5, 3.2, 2.7, 3.7, and 5.3 mm Hg, respectively; *P*<.05) and diastolic blood pressure at weeks 6, 12, 16, and 32 (mean differences of 3.0, 1.8, 2.1, and 3.0 mm Hg, respectively; *P*<.05) were observed with pioglitazone compared with glyburide. At the final visit, the mean (SD) changes in systolic blood pressure were 1.4 (17.06) mm Hg with pioglitazone and 0.2 (16.42) mm Hg with glyburide (*P*=not significant). Mean changes (SD) in diastolic blood pressure with pioglitazone and glyburide at the final visit were -0.7 (10.65) and -0.1 (9.86), respectively (*P*=not significant).

Pioglitazone was associated with minor decreases in mean ventricular heart rate (-0.7 to -0.8 beats per minute [bpm] from a baseline value of

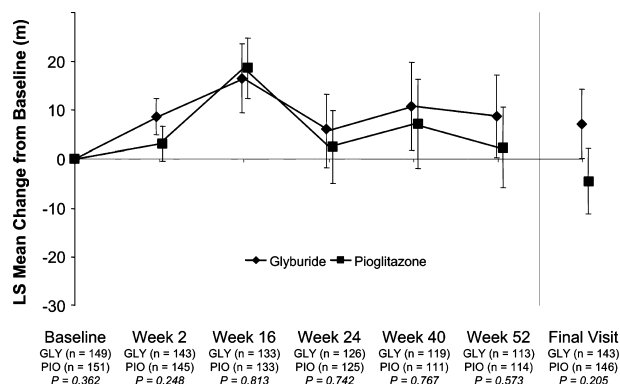


Figure 2. Least squares (LS) mean change in walking distance. Change from baseline in 6-minute walking test distance by study visit. At each visit, “n” included patients who had both a baseline value and a value at that visit. Final visit values were based on a last-observation-carried-forward method; all others were based on observed values. LS mean difference was equal to the LS mean (pioglitazone [PIO]) minus LS mean (glyburide [GLY]); positive value indicates better treatment effect with PIO.

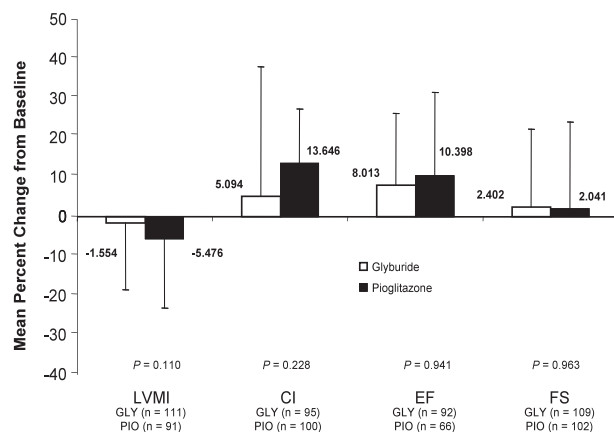


Figure 3. Changes in echocardiographic parameters. Mean percentage change from baseline in echocardiographic parameters at the final visit. Analysis was based on an intent-to-treat population. Final visit values were based on a last-observation-carried-forward method. The treatment comparison was carried out using a 2-way analysis of covariance on the change from baseline to the final visit. LVMI indicates left ventricular mass index; GLY, glyburide; PIO, pioglitazone; CI, cardiac index; EF, ejection fraction; FS, fractional shortening.

70.9±12.93 bpm), whereas glyburide was associated with minor increases (0.4 to 1.6 bpm from a baseline value of 69.0±11.66 bpm); the treatment-group differences between pioglitazone and glyburide were not statistically significant, but they indicate no compensatory response to the observed decrease in blood pressure. No clinically relevant changes were noted for other vital signs or physical examination findings in either treatment group.

Lipid Parameters. Despite significantly lower high-density lipoprotein cholesterol levels and higher triglyceride levels

at baseline, significant improvement occurred in both parameters with pioglitazone. At the final visit, there was a statistically significant treatment difference in high-density lipoprotein cholesterol levels favoring pioglitazone (4.5 mg/dL vs -1.7 mg/dL, respectively, $P<.001$; Figure 4). Although there were larger reductions in triglyceride levels at all visits with pioglitazone, the treatment-group differences were not statistically significant at the final visit (-35.2 mg/dL for pioglitazone vs -11.5 mg/dL for glyburide, $P=.066$). At the final visit, small decreases in mean low-density lipoprotein cholesterol lev-

els were noted with glyburide compared with small increases with pioglitazone, resulting in a significant treatment difference (5.4 mg/dL vs -2.5 mg/dL, respectively, $P=.040$).

Additional Endpoints. There was no statistically significant overall treatment difference to the final visit in HbA_{1c} ($P=.775$). Change from baseline in HbA_{1c} was similar for both the pioglitazone and glyburide groups (least squares means [SD]: -0.80% [0.096%] vs -0.76% [0.100%], respectively, 95% confidence interval for treatment difference, -0.294 to 0.219).

No consistent variations were observed for changes in cardiac medications in either treatment group. The Minnesota Living with Heart Failure Questionnaire scores were almost unchanged from baseline to the final visit in both treatment groups. In the pioglitazone group, 10 patients reported a change in NYHA classification vs 6 patients in the glyburide group. Change from NYHA class II to III was seen in 2 pioglitazone patients vs 1 glyburide participant. Total CV mortality and morbidity was 8.6% in the pioglitazone group (no deaths and 13 of 151 [8.6%] hospitalizations) and 10.0% in the glyburide group (2 of 149 [1.3%] deaths and 13 of 149 [8.7%] hospitalizations).

General Safety. The overall treatment-emergent adverse events were similar in the pioglitazone (133 of 151, 88.1%) vs the glyburide (129 of 149, 86.6%) treatment group. Adverse events resulting in study withdrawal were similar between treatment groups. A total of 87 serious adverse events were reported in 58 patients (23.2% [35 of 151] with pioglitazone and 15.4% [23 of 149] with glyburide). No pioglitazone-treated participant died of a CV event; one died of complications from a diabetic foot ulcer and one after a road traffic accident. Two glyburide-treated patients died, one of cardiac arrest and the other of a subarachnoid hemorrhage.

More pioglitazone users (32 of 151 [21.2%]) than glyburide users (19 of 149 [12.8%]) reported edema; none of these events were considered clinically

Table. Analysis of Cardiac Function Indices

VARIABLE	PIO (15–45 MG QD)		GLY (2.5–15 MG QD)		P VALUE
	No.	MEAN (SD)	No.	MEAN (SD)	
LVEDV					
Baseline	108	90.6 (32.98)	120	88.8 (39.26)	.6372
% Change from baseline to final visit	66	6.3 (24.21)	92	4.3 (32.01)	.8756
LVESV					
Baseline	107	42.5 (25.80)	120	40.9 (28.52)	.5502
% Change from baseline to final visit	66	0.4 (34.20)	92	-2.3 (51.93)	.5526
Stroke volume					
Baseline	130	69.1 (34.62)	126	67.1 (16.92)	.5277
% Change from baseline to final visit	101	15.4 (58.73)	95	5.6 (31.36)	.0877
Cardiac output					
Baseline	130	4374.4 (870.15)	126	4604.0 (1369.24)	.1189
% Change from baseline to final visit	101	15.4 (59.22)	95	5.4 (32.60)	.1393

Abbreviations: GLY, glyburide; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; PIO, pioglitazone; SD, standard deviation. Baseline *P* value was from a 2-way analysis of variance with terms for treatment and pooled center. Post-baseline *P* value was from analysis of covariance with terms for treatment, pooled center, and baseline value (as a covariate).

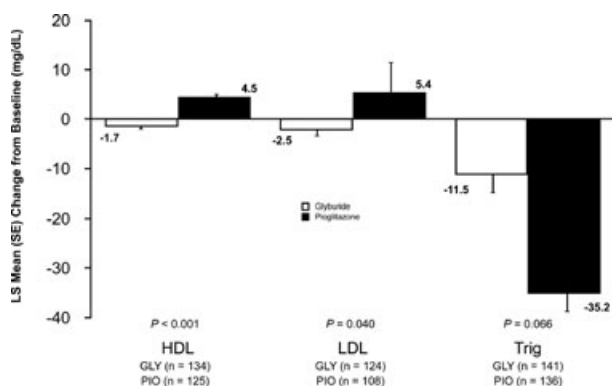


Figure 4. Changes in lipid parameters. Least squares (LS) mean percentage change from baseline in lipid parameters at the final visit. HDL indicates high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; Trig, triglycerides; SE, standard error; GLY, glyburide; PIO, pioglitazone.

significant. Two patients (in the pioglitazone group) discontinued the study because of edema. Weight gain, a known side effect of TZDs, was seen more with pioglitazone than with glyburide: mean weight gain was 2.56 ± 4.62 kg vs 0.86 ± 3.85 kg (pioglitazone vs glyburide, respectively; $P < .001$) at the final visit. The weight increase observed in this 1-year study was similar to that reported over a 6-month period in previous studies.¹¹ One participant (in the pioglitazone group) discontinued the study because of weight gain.

The overall rate of cardiac-related adverse events was 22.5% in the pioglitazone group and 18.1% in the glyburide group. HF was reported for 10 pioglitazone-treated patients and 7 glyburide-treated patients. Of these, hos-

pitalization for HF occurred in 4 pioglitazone-treated patients, 2 of whom had previously existing HF. No participant in the glyburide group required hospitalization for HF.

Laboratory Evaluations. Consistent with previous reports, pioglitazone was associated with improvements in liver enzyme levels (ie, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, total bilirubin, and γ -glutamyl transpeptidase) and minor decreases in hematocrit and hemoglobin compared with the glyburide group.¹²

Discussion

The current study was designed to evaluate the effects of pioglitazone treatment

on HF symptoms in patients with type 2 diabetes and NYHA class I HF, as measured by changes in exercise tolerance. Exercise tolerance, measured at weeks 2, 16, 24, 40, and 52, using a 6-minute walk test, showed that the mean distance covered remained relatively stable in both treatment groups throughout the study and there were no statistically significant differences between the 2 treatment groups. No significant differences were observed in CV mortality and morbidity between the treatment groups either. Similarly, echocardiographic evaluations showed no change in LVEF, LVMI, CI, cardiac output, stroke volume, or FS or in the derived parameters of LVEDV and LVESV. This lack of treatment differentiation on echocardiographic parameters was noted despite more weight gain and a higher incidence of edema with pioglitazone compared with glyburide. Moreover, during the period of improvements in blood pressure, there was no compensatory increase in heart rate to suggest a change in cardiac output or function.

Serious HF was reported in 4 patients in the pioglitazone group: 2 patients had a history of HF; only one had the event considered possibly related to study drug, and the study medication was discontinued. The study medication dosage was not changed or was only temporarily interrupted, for the rest of the cases. All 4 events were resolved after treatment. Neither HF nor any other CV-related cause contributed to the mortality rate

observed in the pioglitazone group,^{10,13} which is particularly important given the estimated 20% to 30% annual mortality incidence associated with HF in the diabetic population¹⁴⁻¹⁷ and the expectation that any treatment that increased the risk of nonreversible HF would be expected to contribute to the overall mortality.

Although 10 patients in the pioglitazone group and 7 patients in the glyburide group experienced treatment-emergent HF reported as an adverse event during the study, no changes were observed as to the ratio of disease progression to more severe HF vs the ratio of pioglitazone-treated patients to glyburide-treated patients who (1) received diuretics as prior medication (63:48 patients), (2) had a previous history of NYHA functional class II at baseline (24:18 patients), or (3) had a maximum change during the study to NYHA functional class II or III (10:6 patients). All 3 measures revealed a similar ratio, between 60% and 76%, of the number of glyburide-treated patients vs the number of pioglitazone-treated patients, suggesting that during the study period there was no greater CV risk for patients receiving pioglitazone therapy compared with those receiving glyburide therapy.

The use of concomitant diabetes medication was similar between the 2 treatment groups of pioglitazone vs glyburide, with the exception of insulin preparations (15.9% vs 8.1%) and metformin (50.3% vs 46.3%). Concomitant

insulin and metformin use were higher in pioglitazone-treated patients due to the slower onset of glycemic-lowering effects of pioglitazone relative to glyburide, and additional oral antidiabetic agents are needed to achieve glycemic control. Nevertheless, our study demonstrated the same trend in CV medication changes in both treatment groups during the trial.

Study Limitations. The sample size was estimated based on a previous study by the Cilazapril-Captopril Multicenter Group that compared the effects of cilazapril and captopril vs placebo on exercise testing in patients with congestive HF (cilazapril and captopril).¹⁸ However, the majority of the patients in the referred study had NYHA class II HF, rather than NYHA class I, and had demonstrated a larger difference of >30 m between comparison groups rather than a maximum difference of 11.7 m between the 2 treatment groups in our study. It has recently been suggested that this test may be of greatest value in patients with more advanced heart disease than in those enrolled in our study.¹⁹

Conclusions

In summary, pioglitazone treatment did not adversely affect exercise tolerance or cardiac function significantly in patients with NYHA functional class I HF, although patients in the pioglitazone treatment group had a more serious dis-

ease state at baseline, and more edema and weight gain developed among pioglitazone users. In fact, measures of cardiac function were modestly improved from baseline for both treatments. Pioglitazone was well tolerated and the overall safety profile was comparable to glyburide.

Our data suggest that any involvement pioglitazone may have in the development of HF is treatable and reversible. Furthermore, these findings are consistent with the American Diabetes Association/American Heart Association prescribing recommendations for TZD use in patients with NYHA functional class I or II HF or at increased risk for congestive HF, namely that TZD treatment should be initiated at the lowest available dose and titrated gradually to therapeutic effect, while monitoring for evidence of weight gain or edema.¹

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