Pioglitazone Hydrochloride Monotherapy Improves Glycemic Control in the Treatment of Patients With Type 2 Diabetes

A 6-month randomized placebo-controlled dose-response study

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OBJECTIVE — To evaluate the efficacy and safety of four doses of pioglitazone monotherapy in the treatment of patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS — There were 408 patients randomized in this multicenter double-blind placebo-controlled clinical trial. Patients who had HbA_{1c} ≥7.0%, fasting plasma glucose (FPG) ≥140 mg/dl, and C-peptide >1 ng/ml were randomized to receive placebo or 7.5, 15, 30, or 45 mg pioglitazone administered once a day for 26 weeks.

RESULTS — Patients treated with 15, 30, or 45 mg pioglitazone had significant mean decreases in HbA_{1c} (range −1.00 to −1.60% difference from placebo) and FPG (−39.1 to −65.3 mg/dl difference from placebo). The decreases in FPG were observed as early as the second week of therapy; maximal decreases occurred after 10–14 weeks and were maintained until the end of therapy (week 26). In the 15-, 30-, or 45-mg pioglitazone groups, there were significant mean percent decreases in triglycerides, significant mean percent increases in HDL cholesterol, and only small percent changes in total cholesterol and LDL. The subset of patients naive to therapy had greater improvements in HbA_{1c} and FPG (difference from placebo of −2.55% and −79.9 mg/dl for the 45-mg group) compared with previously treated patients. The overall adverse event profile of pioglitazone was similar to that of placebo. There was no evidence of drug-induced hepatotoxicity or drug-induced elevations of alanine aminotransferase levels in this study.

CONCLUSIONS — Pioglitazone monotherapy significantly improves HbA_{1c} and FPG while producing beneficial effects on serum lipids in patients with type 2 diabetes with no evidence of drug-induced hepatotoxicity.

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Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; FPG, fasting plasma glucose; LOCF, last-observation-carried-forward; ULN, upper limitof normal.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Pioglitazone hydrochloride, a thiazolidinedione compound, is a new therapeutic agent for the treatment of type 2 diabetes that reduces insulin resistance by enhancing insulin action in skeletal muscle, liver, and adipose tissue (1).

The mechanism of action of the thiazolidinedione class has yet to be fully elucidated, although mechanistic studies indicate that thiazolidinediones influence several processes to increase cell sensitivity to insulin (2,3), including activation of peroxisome proliferator–activated receptor-γ and alteration of hepatic glucose metabolism (4,5). Currently, two thiazolidinediones are available for clinical use in the U.S.: rosiglitazone and the recently approved pioglitazone.

In animal models of diabetes, pioglitazone reduced the hyperglycemia, hyperinsulinemia, and hypertriglyceridemia characteristic of insulin-resistant states (6,7). The metabolic changes induced by pioglitazone result in increased responsiveness of insulin-dependent tissues and are observed in numerous models of insulin resistance (6,7).

In a small study of 20 patients with type 2 diabetes conducted in Japan, pioglitazone administered as monotherapy showed significant decreases in HbA_{1c} and fasting plasma glucose (FPG) after 12 weeks of therapy (8). The present study is the first large-scale multicenter trial to assess the metabolic effects of four doses of pioglitazone administered as monotherapy in the treatment of patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS

Study design

There were 408 patients with type 2 diabetes randomized in a multicenter double-blind placebo-controlled clinical trial conducted at 35 centers across all regions of the U.S. Investigators consisted of board-certified endocrinologists and primary care physicians in academic and

nonacademic sites. Each patient gave informed consent, and each participating center's investigational review board approved the study protocol before any patients entered the trial.

Patients had to have an HbA_{1c} ≥7.0%, FPG ≥140 mg/dl, and fasting C-peptide >1 ng/ml to be enrolled in the study. Patients who used insulin chronically, had a history of ketoacidosis, or had unstable or rapidly progressive diabetic retinopathy, nephropathy, or neuropathy were excluded, as were patients with impaired liver function (aspartate aminotransferase [AST], alanine aminotransferase [ALT], total bilirubin, or alkaline phosphatase >2.5 × upper limit of normal [ULN]), impaired kidney function (serum creatinine >1.8 mg/dl), or anemia. Patients with a myocardial infarction, a coronary angioplasty or bypass graft, unstable angina, transient ischemic attacks, or a documented cerebrovascular accident within 6 months of the study were also excluded.

The double-blind treatment period of 26 weeks was preceded by a 6- to 8-week single-blind washout period, including 2 weeks for baseline measurements. At the end of the washout period, patients were to have an HbA_{1c} ≥7.0%. Patients were then randomized to one of five parallel treatment groups: pioglitazone 7.5, 15, 30, or 45 mg or placebo. During the double-blind period, patients were seen every 2 weeks for the first 6 weeks and every 4 weeks for the remaining 20 weeks.

To eliminate the effect of weight loss and isolate the observation of any effect of pioglitazone, there were no required modifications of current dietary regimens during the study. In this study, the duration of disease (time since diagnosis) was not recorded because of its limitation in providing accurate information about onset of disease.

Patients who were receiving prior antidiabetic medication were required to discontinue their antidiabetic medication(s) at the beginning of the washout period (i.e., 8 weeks before receiving double-blind treatment). Patients who had never received pharmacological antidiabetic therapy were enrolled in the study and entered a 6-week single-blind run-in period.

Efficacy parameters evaluated in this study included glycemic and lipid measurements. A safety profile included a complete laboratory panel (chemistry, hematology, and urinalysis) and assessment of adverse events.

Efficacy measurements

All laboratory specimens were collected at the participating sites and shipped to a central laboratory (Covance Central Laboratory Services, Indianapolis, IN). Single samples were used for the fasting glucose measurements and fasting plasma lipid concentrations.

HbA_{1c} and FPG constituted the glycemic assessments. HbA_{1c} was measured by automated ion-exchange high-performance liquid chromatography (Bio-Rad Variant Analyzer). Blood glucose was measured by the hexokinase enzymatic method (Hitachi 747-200 analyzer).

Serum lipid measurements taken were triglycerides and cholesterol (total, HDL, and LDL). LDL cholesterol was calculated based on the method by Friedewald et al. (9), which limits the calculation to triglyceride levels <400 mg/dl.

Statistical analysis

Descriptive statistics were used to summarize demographic and baseline characteristics. Comparability of the treatment groups was assessed using a two-way analysis of variance, with treatment and pooled study center as factors for continuous variables (e.g., age), or the Cochran-Mantel-Haenszel test (general association version), stratified by pooled study center, for discrete variables (e.g., sex).

An intent-to-treat approach was used for the primary analysis. Additionally, a completers analysis (i.e., those patients who received double-blind study medication and the investigator indicated had completed the study) was also performed.

The primary time point for the efficacy analyses was week 26 (last postbaseline measurement obtained during the study, excluding follow-up). A last-observation-carried-forward (LOCF) analysis was performed for the efficacy measurements. All efficacy variables were evaluated for the change from baseline. Within each treatment group, paired *t* tests were used to make comparisons to baseline at each time point for each of the efficacy parameters.

Comparisons between placebo and each pioglitazone treatment group, with respect to change from baseline, were carried out using Dunnett's test with estimates of least-square means and variances obtained from a two-way analysis of covariance. The model included terms for treatment, pooled center, and treatment-by-pooled-study-center interaction and the baseline value as a covariate. *P* values ≤0.05 were considered statistically significant.

All patients who were randomized and who received double-blind study medication were evaluated for safety. The proportions of patients who reported adverse events (based on a modified WHOART dictionary) were summarized with frequency counts and percentages. For the standard panel of laboratory tests, mean changes from baseline and the number of patients who had laboratory values outside of the normal range or who had markedly abnormal values were summarized. Descriptive statistics were used to summarize changes in body weight.

RESULTS — There were 408 patients randomized to receive placebo (*n* = 79) or pioglitazone 7.5 mg (*n* = 81), 15 mg (*n* = 81), 30 mg (*n* = 87), or 45 mg (*n* = 80). Overall, the mean age was 53.7 years (range 29–75). Most (78%) patients were Caucasian; 12% were Hispanic, 8% were African-American, 2% were Asian, and 1% were other races. More than half (58%) of the patients were male. There were no significant differences in the baseline demographics or glycemic or lipid characteristics among the five treatment groups.

Of the 408 patients, 31% (127 of 408) were naive to prior antidiabetic therapy. The most common antidiabetic medications taken before the study were sulfonylureas (glyburide and glipizide). A small percentage (13%) of patients had received two or more antidiabetic medications.

The percentage of patients who completed the study was 33% in the placebo group and ranged from 44 to 58% in the pioglitazone groups. The most common reason for study withdrawal was because of lack of glycemic control, defined as insufficient therapeutic effect (an investigator opinion of an increase or no significant improvement in HbA_{1c} values that indicated insufficient diabetic management and posed a risk to the patient), adverse event of symptomatic or asymptomatic hyperglycemia, and patient's withdrawal of consent because of perceived lack of glucose control. More patients in the placebo group were withdrawn from the study because of poor glycemic control compared with patients in any of the pioglitazone groups (49% for the placebo group vs. 35% for the 7.5-mg group, 33% for the 15-mg group, 33% for the 30-mg group, and 29% for the 45-mg group). These withdrawals generally occurred within the first 12 weeks of the double-blind treatment period. A similar number of patients in all five treatment groups withdrew from the study because of adverse events (3% for the

Table 1—*Glycemic parameters*

Parameter	Placebo	Pioglitazone (mg) 7.5	15	30	45
Total population					
HbA_{1c} (%)					
n	79	80	79	85	76
Baseline (mean)	10.4 ± 0.22	10.0 ± 0.22	10.2 ± 0.22	10.2 ± 0.21	10.3 ± 0.22
End of therapy (mean)	11.1 ± 0.26	10.2 ± 0.25	9.9 ± 0.27	9.9 ± 0.29	9.4 ± 0.29
Mean change from baseline	0.7 ± 0.17*	0.2 ± 0.17	−0.3 ± 0.17*	−0.3 ± 0.17*	−0.9 ± 0.18*
Mean difference from placebo		−0.5	−1.0*	−1.0*	−1.6*
FPG (mg/dl)					
n	79	80	79	84	77
Baseline (mean)	268.1 ± 7.93	263.2 ± 7.9	267.0 ± 7.94	269.4 ± 7.72	275.5 ± 8.05
End of therapy (mean)	276.0 ± 7.97	244.0 ± 8.27	233.2 ± 7.82	239.5 ± 11.35	217.1 ± 8.91
Mean change from baseline	9.4 ± 6.72	−18.1 ± 6.77*	−29.6 ± 31.8*	−31.8 ± 6.66*	−55.9 ± 6.90*
Mean difference from placebo		−27.5*	−39.1*	−41.2*	−65.3*
Weight (kg)					
n	79	81	79	87	79
Baseline (mean)	90.4 ± 1.47	93.5 ± 1.59	91.2 ± 1.80	90.3 ± 1.58	90.8 ± 1.56
Mean change from baseline	−1.3 ± 0.36	−0.6 ± 0.29	1.3 ± 0.33	1.3 ± 0.38	2.8 ± 0.39
Mean difference from placebo		0.7	2.6	2.6	4.1
Naive to therapy					
HbA_{1c} (%)					
n	25	27	26	26	21
Baseline (mean)	9.0 ± 0.38	9.3 ± 0.37	9.9 ± 0.37	9.3 ± 0.38	10.0 ± 0.43
End of therapy (mean)	9.8 ± 0.44	9.3 ± 0.38	9.2 ± 0.53	8.8 ± 0.44	8.2 ± 0.43
Mean change from baseline	0.6 ± 0.29*	0.0 ± 0.28	−0.8 ± 0.28*	−0.6 ± 0.29*	−1.9 ± 0.33*
Mean difference from placebo		−0.6	−1.4*	−1.3*	−2.6*
Previously treated					
HbA_{1c} (%)					
n	54	53	53	58	55
Baseline (mean)	10.9 ± 0.26	10.3 ± 0.26	10.4 ± 0.260	10.4 ± 0.25	10.6 ± 0.26
End of therapy (mean)	11.7 ± 0.29	10.6 ± 0.30	10.2 ± 0.309	10.3 ± 0.35	9.9 ± 0.35
Mean change from baseline	0.8 ± 0.20*	0.3 ± 0.20	−0.1 ± 0.203	−0.0 ± 0.19	−0.6 ± 0.20*
Mean difference from placebo		−0.5	−1.0*	−0.9*	−1.4*

Data are means ± SEM unless indicated otherwise. *$P \leq 0.05$.

placebo group vs. 2% for the 7.5-mg group, 4% for the 15-mg group, 5% for the 30-mg group, and 5% for the 45-mg group) and for administrative reasons such as noncompliance and lost to follow-up (9% for the placebo group vs. 10% for the 7.5-mg group, 19% for the 15-mg group, 9% for the 30-mg group, and 9% for the 45-mg group).

Glycemic control: all patients

During all weeks when HbA_{1c} was measured, the placebo group showed mean increases from baseline in HbA_{1c} (Table 1). The differences between the placebo group and the 15-, 30-, and 45-mg groups were statistically significant ($P \leq 0.05$) in favor of the pioglitazone groups beginning at week 14 (week 10 for the 15- and 45-mg groups) until the end of therapy (Fig. 1*A*).

During all weeks when FPG was measured, the placebo group showed significant ($P < 0.05$) mean increases in FPG from baseline (Table 1). All pioglitazone groups had statistically significant mean decreases from baseline at each visit through the end of the study (Fig. 1*B*). For the 15-, 30-, and 45-mg groups, there was a statistically significant difference from placebo at all weeks of therapy. For the 7.5-mg group, there was a statistically significant difference from placebo at week 2 and at weeks 14 through the end of the study.

The baseline HbA_{1c} and FPG in this trial were relatively high at initiation of double-blind therapy. However, in a subset analysis of randomized patients who had a baseline FPG ≤280 mg/dl (n = 217), with mean baseline HbA_{1c} of 9.02% and a mean FPG level of 211.1 mg/dl, pioglitazone showed similar efficacy to the data from all patients. Specifically, differences in HbA_{1c} when compared with placebo were −2.00% with 45 mg, −1.09% with 30 mg, −1.20% with 15 mg, and −0.77% with 7.5 mg.

In addition to the intent-to-treat analysis, the change from baseline in HbA_{1c} and FPG was also analyzed for those patients who completed the study. There were no differences between the completers and intent-to-treat populations with respect to the demographic and baseline characteristics. At the end of the study, differences in HbA_{1c} when compared with placebo were −2.35% with 45 mg, −1.29% with 30 mg, −1.69% with 15 mg, and −0.94% with 7.5 mg and were statistically significant ($P \leq 0.05$) in favor of all pioglitazone groups. The differences in FPG when compared with placebo were −74.5 mg/dl with 45 mg, −42.0 mg/dl with 30 mg, −43.7 mg/dl with 15 mg, and −23.9 mg/dl with 7.5 mg and were statistically significant ($P \leq 0.05$) in favor of the 15-, 30-, and 45-mg groups.

Glycemic control: subset of patients naive to therapy

The placebo group showed mean increases from baseline in HbA_{1c} throughout the study (Table 1). The 15-, 30-, and 45-mg groups

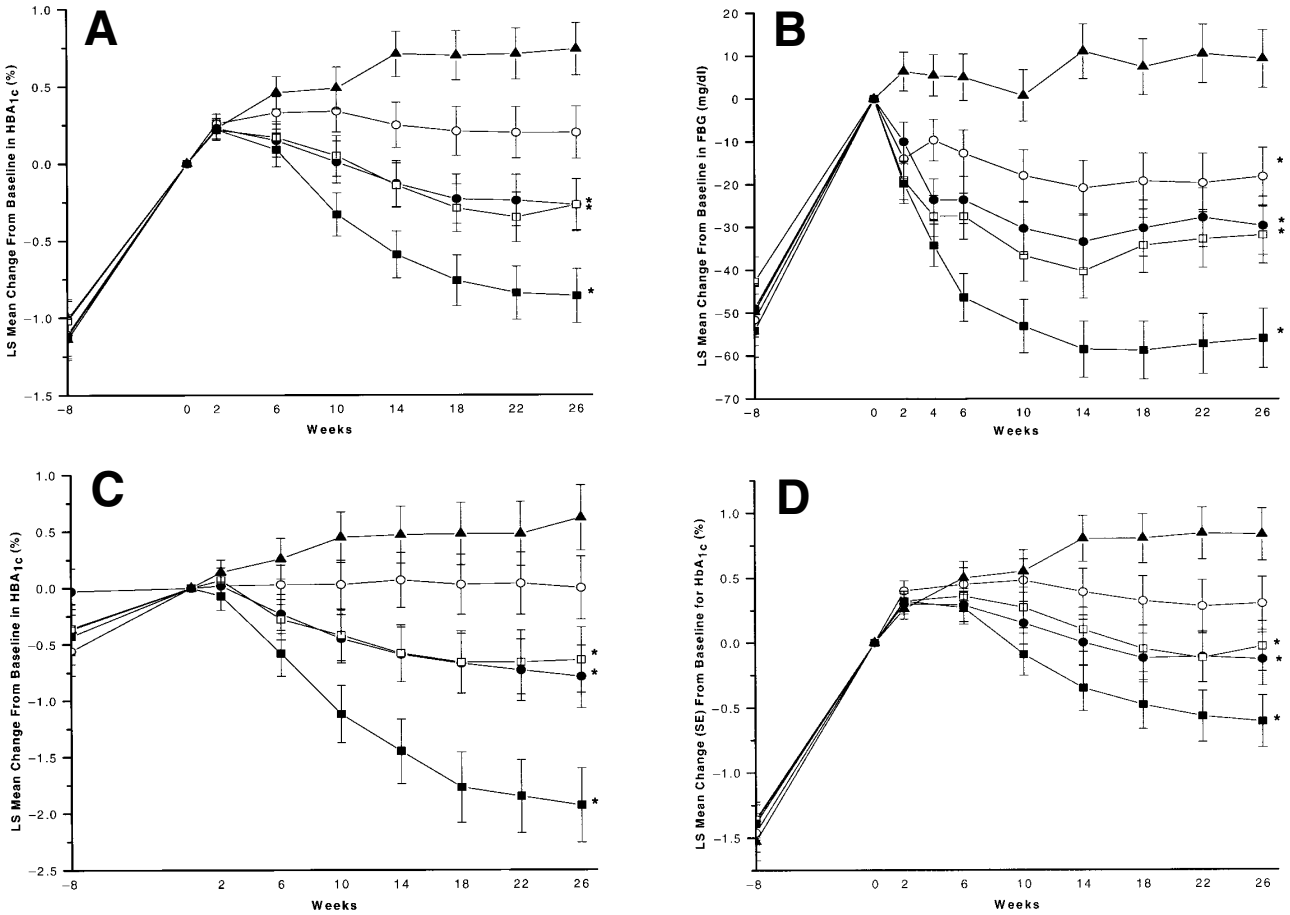

Figure 1—*The least-squares mean change from baseline by visit (LOCF analysis) for all randomized patients in HbA_{1c} (A) and FPG (B), for patients naive to prior antidiabetic therapy in HbA_{1c} (C), and for patients previously treated with antidiabetic therapy in HbA_{1c} (D) during the course of the study. ▲, Placebo; ○, 7.5 mg pioglitazone; ●, 15 mg pioglitazone; □, 30 mg pioglitazone; ■, 45 mg pioglitazone. Data are means ± SEM. *P ≤ 0.05 vs. placebo at the end of the study.*

had mean decreases from baseline at weeks 6–26. The differences between the placebo group and the 15-, 30-, and 45-mg groups were statistically significant ($P \leq 0.05$) at weeks 10–26 (Fig. 1*C*).

Glycemic control: subset of patients previously treated

The placebo group showed mean increases from baseline in HbA_{1c} throughout the study (Table 1). The 15-, 30-, and 45-mg groups had mean decreases from baseline at weeks 18–26. The differences between the placebo group and the 15-, 30-, and 45-mg groups were statistically significant ($P \leq 0.05$) at weeks 14–26 (Fig. 1*D*).

Insulin and C-peptide

All treatment groups had mean decreases from baseline in fasting insulin over the course of the study. However, the small mean decreases from baseline in the placebo group never achieved statistical significance. In contrast, the 30- and 45-mg pioglitazone groups had statistically significant ($P > 0.05$) mean decreases from baseline at weeks 2–26 (except week 26 for the 45-mg group). In addition, the magnitude of the changes from baseline in fasting insulin for the 30- and 45-mg groups were consistently two to three times greater than placebo throughout the study, ranging (i.e., minimum to maximum change) from −2.38 to −4.43 μU/ml for 30 mg, −1.55 to −5.32 μU/ml for 45 mg, and 0.08 to −1.42 μU/ml for placebo. Mean fasting C-peptide was only slightly changed for any treatment by end point (week 26).

Lipids

Patients receiving 15, 30, and 45 mg pioglitazone had decreases in mean percent change from baseline in triglycerides compared with an increase for the placebo-treated patients (Table 2). Conversely, mean percent change from baseline in HDL cholesterol increased to a greater extent in the 15, 30, and 45 mg pioglitazone-treated patients than in the placebo-treated patients at the end of the study (Table 2).

There were no statistically significant differences between any of the pioglitazone treatment groups and placebo group for total cholesterol or LDL cholesterol at any time point during the study. For both total cholesterol and LDL cholesterol, the pioglitazone and placebo groups showed small increases in mean percent change from baseline at all visits during double-blind therapy; the mean percent differences from baseline for LDL cholesterol were significant for the 15- and 45-mg groups and for total cholesterol for the placebo, 15-mg, and 45-mg groups.

Safety evaluations

The overall adverse event rate of pioglitazone was similar to that of placebo (76 vs. 85%, respectively). Relatively few of these

Table 2—*Lipids*

Parameter	Placebo	Pioglitazone (mg) 7.5	15	30	45
Triglycerides					
n	79	80	79	84	77
Baseline (mg/dl)	262.8 ± 34.35	319.0 ± 34.23	283.8 ± 34.40	261.1 ± 33.44	259.7 ± 34.87
End of therapy (mg/dl)	252.7 ± 20.71	264.1 ± 33.08	226.0 ± 20.15	225.2 ± 24.77	218.9 ± 14.24
LS mean % change from baseline	4.8 ± 4.70	8.9 ± 4.73	−9.0 ± 4.74*	−9.6 ± 4.65*	−9.3 ± 4.81*
Mean % difference from placebo		4.1	−13.8	−14.4	−14.1
HDL cholesterol					
n	79	79	79	83	77
Baseline (mg/dl)	41.7 ± 1.24	40.5 ± 1.24	40.4 ± 1.24	40.8 ± 1.21	40.7 ± 1.25
End of therapy (mg/dl)	44.3 ± 1.25	43.4 ± 1.31	45.4 ± 1.19	45.0 ± 1.25	47.8 ± 1.56
LS mean % change from baseline	8.1 ± 2.03*	7.9 ± 2.05*	14.1 ± 2.05*	12.2 ± 2.04*	19.1 ± 2.07*
Mean % difference from placebo		−0.2	6.0	4.1	11.0*
Total cholesterol					
n	79	80	79	84	77
Baseline (mg/dl)	224.6 ± 5.44	214.5 ± 5.42	220.0 ± 5.45	222.7 ± 5.29	213.7 ± 5.52
End of therapy (mg/dl)	231.4 ± 5.23	216.3 ± 5.03	226.3 ± 4.99	227.5 ± 5.39	226.2 ± 5.27
LS mean % change from baseline	4.4 ± 1.55*	2.3 ± 1.56	4.6 ± 1.56*	3.3 ± 1.54	6.4 ± 1.59*
Mean % difference from placebo		−2.1	0.2	−1.1	2.0
LDL cholesterol					
n	66	67	64	74	65
Baseline (mg/dl)	138.8 ± 4.54	122.9 ± 4.52	131.9 ± 4.64	135.6 ± 4.33	126.8 ± 4.60
End of therapy (mg/dl)	141.9 ± 5.10	127.2 ± 3.68	138.2 ± 4.52	139.4 ± 5.10	135.5 ± 4.43
LS mean % change from baseline	4.8 ± 2.62	1.0 ± 2.67	7.2 ± 2.67*	5.2 ± 2.47	6.0 ± 2.69*
Mean % difference from placebo		−3.8	2.4	0.4	1.2

Data are means ± SEM unless indicated otherwise. *$P \leq 0.05$ vs. baseline. LS, least squares.

adverse events were considered associated with treatment (40% of the pioglitazone-treated patients and 38% of the placebo-treated patients). The most commonly reported adverse events that occurred among all patients were upper respiratory tract infection (15.2% for the pioglitazone group, 11.4% for the placebo group; $P > 0.05$) and headache (12.5% for the pioglitazone group, 10.1% for the placebo group).

There was no increase in the frequency of cardiac adverse events in the pioglitazone groups (12 of 329 [3.6%]) compared with the placebo group (5 of 79 [6.3%]). The incidence of edema or peripheral edema was 12 of 329 (3.6%) in the pioglitazone groups, whereas no patients in the placebo group experienced edema or peripheral edema. No patient discontinued as a result of edema or peripheral edema.

Hypoglycemia was reported by 4 of the 329 patients who received pioglitazone, whereas no patients in the placebo group experienced hypoglycemia ($P > 0.05$). All of the events occurred while the patients were at home, so blood glucose levels could not be confirmed. The incidence did not appear to increase with dose. Two of the patients received 7.5 mg pioglitazone, one received 30 mg pioglitazone, and one received 45 mg pioglitazone. For all four patients, the occurrence of hypoglycemia was isolated and transient, resolving within a few hours or less. All of the events were considered mild or moderate in intensity and none resulted in discontinuation.

Mean ALT values at baseline ranged from 24.7 U/l in the 45-mg group to 28.1 U/l in the 7.5-mg group. The incidence of ALT values elevated from baseline to ≥3 × ULN was 1.3% (one patient) for the placebo group, 1.3% (one patient) for the 7.5-mg group, and 2.4% (two patients) for the 30-mg group; no elevations to ≥3 × ULN were noted for the 15- and 45-mg groups. The incidence of ALT values elevated from baseline to ≥1.5 × ULN was 2.6% (two patients) for the placebo group, 2.5% (two patients) for the 7.5-mg group, 2.5% (two patients) for the 15-mg group, and 4.7% (four patients) for the 30-mg group; no elevations to ≥1.5 × ULN were noted for the 45-mg group. The evaluation of AST, alkaline phosphatase, and total bilirubin values elevated from baseline to ≥1.5 × ULN also revealed similar incidences between the pioglitazone group and the placebo group. There were no cases of jaundice.

There appeared to be dose-related decreases in hemoglobin (greatest change of −0.74 g/dl in the 45-mg group), hematocrit (greatest change of −1.3% in the 45-mg group), and erythrocytes (greatest change of -0.26×10^6/μl in the 45-mg group), although values generally remained within normal limits. Changes in mean values for hemoglobin and hematocrit stabilized within 10–14 weeks. No patients discontinued their participation in the study because of anemia.

Beginning at week 10 until the end of the double-blind treatment, the placebo and 7.5-mg groups had mean decreases in body weight compared with mean dose-related increases observed for the 15-, 30-, and 45-mg groups. At the end of the study, the mean change from baseline in body weight was −0.59 kg in the 7.5-mg group, 1.30 kg in the 15-mg group, 1.29 kg in the 30-mg group, 2.82 kg in the 45-mg group, and −1.28 kg in the placebo group. Linear regression analysis demonstrated that weight gain was associated with decreases in HbA_{1c} ($R^2 = 0.1942$).

CONCLUSIONS — The present study demonstrates that in patients with type 2 diabetes, pioglitazone is effective in decreasing HbA_{1c} and FPG. Decreases in FPG began relatively quickly after receiving study med-

ication, and by week 2, statistically significant ($P \leq 0.05$) decreases from baseline as well as statistically significant decreases compared with placebo were observed for all pioglitazone treatment groups. HbA_{1c}, a marker for long-term glycemic control, similarly decreased, achieving statistically significant decreases from baseline as well as statistically significant decreases compared with placebo for most pioglitazone treatment groups by week 14.

For the subset of patients who were naive to antidiabetic therapy, the magnitude of the response was greater than that for the total population. Significant mean decreases in HbA_{1c} generally occurred during earlier weeks (week 6 for the 45-mg group) than that observed for the total population (week 10 for the 45-mg group). At the end of the study, there was a −2.55% mean difference in HbA_{1c} between the 45-mg pioglitazone group and the placebo group.

The greater glycemic effect for those naive to antidiabetic drug therapy is probably related to the study design. Patients who had to discontinue previous antidiabetic medications (e.g., sulfonylureas or metformin) at study enrollment had increases in blood glucose to such an extent during the washout period that the drastic change in glycemic homeostasis may have created a clinical situation previously described as glucose toxicity or glucose desensitization (10,11). It has been previously demonstrated that prolonged hyperglycemia produces deleterious effects on insulin secretion as well as increasing peripheral insulin resistance. In patients whose blood glucose levels are >200 mg/dl, insulin responsiveness was inversely related to the level of blood glucose (11). Although both subgroups (naive and previously treated) had FPG values >200 mg/dl at baseline, the higher values for the previously treated group (284 mg/dl compared with 233 mg/dl for the naive group) may have contributed to the reduced responsiveness for that group.

Although the mean baseline values for HbA_{1c} and FPG were relatively high, in a subset analysis of randomized patients who had a baseline FPG ≤280 mg/dl (baseline mean HbA_{1c} was 9.02% and FPG was 211.1 mg/dl), pioglitazone showed similar efficacy to the data for the total population.

Before week 26, 33% of placebo-treated patients compared with 44–58% of pioglitazone-treated patients discontinued therapy; most withdrawals in all treatment groups were because of poor glycemic control and most occurred before week 12. This result is most likely related to the study design. As mentioned earlier, previously treated patients discontinued their antidiabetic medications and during the washout period, when patients received single-blind placebo, experienced deteriorating glycemic control to such an extent that the ability to quickly respond (i.e., within 12 weeks) to any oral agent could be severely impaired. Previously reported studies have indicated that significant improvements with thiazolidinediones are not observed across the first 8–12 weeks of therapy (12).

The results of the completers analysis showed improved glycemic control (as measured by HbA_{1c} and FPG), as did the LOCF analysis, although the magnitude of the response was greater in the completers analysis.

Although recent data show that modest increases in LDL correlate with increased cardiovascular risk, additional information suggests that the diminution of the rate of cardiovascular disease can be enhanced by increasing HDL cholesterol and, thus, the LDL-to-HDL ratio may be a strong predictor of cardiovascular outcome (13–16). In this study, patients treated with 15, 30, and 45 mg pioglitazone showed significant mean percent decreases from baseline in triglycerides and significant mean percent increases from baseline in HDL. No untoward effects when compared with placebo were observed for LDL cholesterol. The mean percent LDL-to-HDL ratio in this study decreased from baseline, with the largest reductions in the 45-mg group, although the full impact of the serum lipid changes will ultimately need to be assessed by changes, if any, of cardiovascular events.

Pioglitazone was found to be generally well tolerated. The frequency of cardiac adverse events in the pioglitazone group was not greater than that observed in the placebo group. Importantly, there were no cases of jaundice and no evidence of drug-induced hepatotoxicity or drug-induced elevations of ALT levels observed in this study. The results of this study are consistent with all placebo-controlled clinical studies of pioglitazone, in which the incidence of patients with ALT ≥3 × ULN was low and was comparable between patients who received pioglitazone (4 of 1,526 [0.26%]) and patients who received placebo (2 of 793 [0.25%]) (17).

Pioglitazone patients did experience edema and small decreases in hemoglobin, hematocrit, and erythrocyte counts; however, no patients discontinued because of edema or anemia. A dose-related increase in mean weight for patients treated with pioglitazone was observed during the study; however, the increase generally was proportional to improved glycemic control (i.e., decreases in HbA_{1c}). It should be noted that the occurrence of edema, decreases in hemoglobin and hematocrit, and increases in weight have been observed with all of the thiazolidinediones (18–20). A few patients (4 of 329) reported hypoglycemic episodes (blood glucose values not documented); however, none were severe or prompted discontinuation of study medication.

In summary, the results of this study show that pioglitazone is a well-tolerated and efficacious treatment for patients with type 2 diabetes. The ability of pioglitazone to ameliorate some degree of dyslipidemia may provide an additional benefit in this patient population with known cardiovascular complications.

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APPENDIX

The Pioglitazone 001 Study Group

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