

Effects of Pioglitazone and Rosiglitazone on Blood Lipid Levels and Glycemic Control in Patients with Type 2 Diabetes Mellitus: A Retrospective Review of Randomly Selected Medical Records

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ABSTRACT

Background: The antihyperglycemic effects of pioglitazone hydrochloride and rosiglitazone maleate are well documented. The results of clinical trials and observational studies have suggested, however, that there are individual differences in the effects of these drugs on blood lipid levels.

Objective: The present study evaluated the effects of pioglitazone and rosiglitazone on blood lipid levels and glycemic control in patients with type 2 diabetes mellitus.

Methods: This was a retrospective review of randomly selected medical records from 605 primary care practices in the United States in which adults with type 2 diabetes received pioglitazone or rosiglitazone between August 1, 1999, and August 31, 2000. The outcome measures were mean changes in serum concentrations of triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and glycosylated hemoglobin (HbA_{1c}) values.

Results: Treatment with pioglitazone was associated with a reduction in mean TG of 55.17 mg/dL, a reduction in TC of 8.45 mg/dL, an increase in HDL-C of 2.65 mg/dL, and a reduction in LDL-C of 5.05 mg/dL. Treatment with rosiglitazone was associated with a reduction in mean TG of 13.34 mg/dL, an increase in TC of 4.81 mg/dL, a reduction in HDL-C of 0.12 mg/dL, and an increase in LDL-C of 3.56 mg/dL. With the exception of HDL-C, the differences in mean changes in lipid parameters between treatment groups were statistically significant ($P < 0.001$, pioglitazone vs rosiglitazone). Reductions in HbA_{1c} were statistically equivalent between treatments (1.04% pioglitazone, 1.18% rosiglitazone).

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Conclusions: Treatment with pioglitazone was associated with greater beneficial effects on blood lipid levels than treatment with rosiglitazone, whereas glycemic control was equivalent between the 2 treatments.

Key words: type 2 diabetes, thiazolidinediones, blood lipids, glycemic control, hyperglycemia, hyperlipidemia. (*Clin Ther.* 2002;24:378–396)

INTRODUCTION

The thiazolidinediones (TZDs), a newer class of antihyperglycemic agents, entered the US market with the approval of troglitazone in 1997. The glucose-lowering effect of these drugs appears to be related to their ability to reduce insulin resistance in liver, skeletal muscle, and adipose tissue, thereby increasing the effectiveness of insulin.^{1,2} As a result, fasting and postprandial blood glucose concentrations and circulating insulin levels decrease, and hepatic glucose production may decline.² These pharmacologic actions are mediated through peroxisome proliferator-activated receptors that control genes involved in adipocyte differentiation, fatty acid metabolism, and insulin regulation.^{3,4} Two TZDs, pioglitazone hydrochloride and rosiglitazone maleate, are currently available in the United States for the treatment of type 2 diabetes mellitus. Troglitazone was withdrawn from clinical use on March 21, 2000, as a result of drug-related idiosyncratic liver toxicity and hepatic failure^{5–7} that had led to 63 reported deaths by that time.

The withdrawal of troglitazone has prompted further investigation of this drug class, providing an opportunity to compare and contrast the treatment effects of the newer TZDs in routine clinical set-

tings, both in TZD-naïve patients and those who required a switch from troglitazone. Of particular interest were the similarities and differences between the newer drugs (ie, their relative tolerability and effectiveness compared with troglitazone and each other). Based on an August 2001 search of the Internet and the contemporary medical literature indexed in PubMed, Ovid, and Ingenta, data from clinical trials and other studies have demonstrated no signs or symptoms of liver toxicity related to pioglitazone,^{8,9} whereas 1 letter cited the only known case of elevation in liver enzymes.¹⁰ Liver abnormalities in conjunction with rosiglitazone use have been reported in only 3 patients.^{11–16} Although close monitoring of liver function in patients receiving either pioglitazone or rosiglitazone is still advised,^{8,11} concerns that these agents may be associated with the liver damage and dysfunction seen with troglitazone are diminishing in light of their safety record to date.^{8–16}

Evidence supporting the antihyperglycemic effects of these newer compounds continues to be reported.^{8,11,17–29} In addition, an expanding pool of recently collected data reflects other metabolic and biochemical changes effected by the TZDs.^{8,11,17–33} In particular, a recent retrospective assessment in TZD-naïve patients who had received pioglitazone, rosiglitazone, or troglitazone for type 2 diabetes demonstrated improvements in glycosylated hemoglobin (HbA_{1c}) values as well as changes in serum concentrations of triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C).³¹ Similarly, clinical observations in patients switched from troglitazone to either pioglitazone or rosiglitazone demonstrated

treatment effects on blood lipid levels and HbA_{1c}.^{30,32,33} These observations are of particular interest because patients with type 2 diabetes are at risk for a myriad of vascular complications related to both hyperglycemia and hyperlipidemia. Choosing interventions that modify several risk factors simultaneously is particularly appropriate in the current health care environment.

Whether the 2 remaining TZDs have equivalent potential to improve lipid parameters will be answered best by prospective head-to-head clinical trials. Pending the availability of such prospective research, the present article provides comparative information based on a large, nationwide retrospective evaluation of patients with type 2 diabetes. The purpose of this evaluation was to examine whether there were significant differences between pioglitazone and rosiglitazone with respect to their effects on blood lipid levels and glycemic control in patients with type 2 diabetes treated in a primary care setting.

MATERIALS AND METHODS

A retrospective chart review of data from 605 primary care practices nationwide was conducted between November 2000 and March 2001. Potential contributing investigators were chosen based on their having a patient population that would be likely to meet the study criteria. The intention was to identify physicians who had equal numbers of patients receiving pioglitazone and rosiglitazone sufficient to contribute potentially qualified data to the study and to ensure final sample sizes large enough for meaningful intragroup and intergroup comparisons. To this end, >1000 primary care physicians identified

from prescription and practice-volume data were invited to attend 1 of 9 orientation sessions held across the United States between November and December 2000. Physicians assessed their capacity to participate, the quality of their medical records, and the likelihood of having an equal distribution of patients taking the study drugs. Each investigator received a nominal honorarium.

Participating physicians identified patients with type 2 diabetes who had started treatment with either pioglitazone or rosiglitazone between August 1, 1999, and August 31, 2000. Once patients were identified, their charts were collected, assigned a confidential patient-specific identifier, ordered by a random-number assignment to reduce potential selection bias, and examined sequentially for inclusion criteria (Table I). Chart selection was completed when 5 qualified patients receiving pioglitazone and 5 qualified patients receiving rosiglitazone were found or the practice population of patients with type 2 diabetes was exhausted. In almost all instances, the practice population was exhausted in the process of identifying qualified patients (ie, those who met inclusion criteria), which further reduced the likelihood of patient-selection bias.

For qualifying patients, pretreatment and posttreatment (ie, baseline and follow-up) laboratory TG, TC, HDL-C, LDL-C, and HbA_{1c} values were collected, as well as information on demographic characteristics and concomitant drug use. Primary outcome measures were mean changes in serum TG levels within each study-drug group (baseline vs follow-up) and between study-drug groups (pioglitazone vs rosiglitazone). Secondary outcome measures were mean changes in TC, HDL-C, LDL-C, and HbA_{1c} within each

Table I. Study inclusion and exclusion criteria.

Inclusion criteria

1. Age ≥ 18 years
2. Documented diagnosis of type 2 diabetes
3. Patient began therapy for type 2 diabetes with either pioglitazone or rosiglitazone between August 1, 1999, and August 31, 2000
4. Patient received a total daily dose of pioglitazone 30 or 45 mg or a total daily dose of rosiglitazone 4 or 8 mg as primary or secondary therapy
5. Patient received uninterrupted treatment for ≥ 12 weeks
6. Patient had ≥ 2 office visits (representing baseline and follow-up visits) separated by 12 to 26 weeks
7. Patient had no change in antihyperlipidemic regimens at or between the baseline and follow-up visits
8. Patient underwent ≥ 2 rounds of clinical laboratory testing for study end points
9. Dates of laboratory testing coincided approximately with the baseline and follow-up visits, with baseline testing occurring no earlier than 30 days before the baseline office visit and follow-up testing occurring no sooner than 12 weeks after the baseline office visit and no later than 30 days after the follow-up visit

Exclusion criteria

1. Patient failed previous non-TZD antihyperglycemic combination therapy (failure defined as glycosylated hemoglobin $\geq 8\%$ during therapy) and was switched to either pioglitazone or rosiglitazone monotherapy during the study period
2. Patient received another TZD for type 2 diabetes within 90 days before starting the study drug
3. Patient started a medication (including beta-blockers or thiazide diuretics) at or between the baseline and follow-up visits that could influence the lipid profile
4. Patient had a change in medication regimen (including beta-blockers or thiazide diuretics) at or between the baseline and follow-up visits that could influence the lipid profile
5. Patient received a systemic glucocorticosteroid during the study period

TZD = thiazolidinedione.

group and between groups. Incomplete lipid panels or lack of HbA_{1c} values did not constitute exclusion criteria for the purposes of this investigation. However, as noted in the "Statistical Analyses" section, statistical comparisons of individual study end points were made only if paired data were available. Based on the geographic distribution of investigators, it was assumed that biochemical results came from different laboratories and were based on appropriately collected and analyzed samples.

Data for all patients were abstracted from medical records onto paper case-report forms and submitted to Health Economics Research, Secaucus, New Jersey, for review and analysis. Because information was collected retrospectively from medical records (no patients were treated prospectively) and because patients' identities were not linked to data sets or study results, informed consent was not required (US21CFR Part 50). On receipt, data were double-keyed into a relational database; the fidelity of the entry pro-

cess was validated in a random 10% sample comparison of raw (ie, paper case-report forms) versus entered (ie, database) data (error rate <0.001); discrepant entries were corrected, and individual patient data sets were reviewed according to the study inclusion/exclusion criteria. Data that failed to comply with these criteria were excluded from the final analysis.

Statistical Analyses

SPSS version 10.1 (SPSS Inc, Chicago, Ill) was used for all statistical analyses. Descriptive statistics of patient demographic characteristics within treatment groups were generated to provide a complete overview of the qualified study population. When appropriate, Pearson chi-square tests and Student *t* tests for paired-sample and independent-sample data were used for all primary comparisons of categorical and continuous variables. Analysis-of-variance tests were conducted to identify any statistically significant differences between mean changes in blood lipid levels and HbA_{1c} values. All statistical comparisons were 2-sided tests, conducted at the 0.05 level of significance.³⁴

Clinical outcome measures for TG, TC, HDL-C, LDL-C, and HbA_{1c} were evaluated independently based on patients with paired baseline and follow-up values. Patient demographic profiles (sex, age, race, height, body weight, body mass index [BMI], duration of TZD use, nicotine use, comorbidities, concomitant drug use) were examined based on data collected from all qualified patient records.

Sample Size

Based on reported least-square mean percentage changes from baseline,^{8,19} the

change in TG levels in patients receiving pioglitazone were estimated to be -24.63 mg/dL. Reported changes in TG levels for patients receiving rosiglitazone have been variable and not statistically significant^{11,21,23,24,26}; therefore, the change from baseline in TG levels for patients receiving rosiglitazone was estimated at 0 mg/dL (ie, no change). It was determined that a sample size of 317 in each group would have 80% power to detect a difference in means of 24.63 mg/dL, assuming a common SD of 110.48 mg/dL,¹⁹ using a 2-group Student *t* test with a 2-sided significance level of 0.05.

RESULTS

Of >1000 physicians invited to participate in the study orientation, 768 were enrolled as investigators, and 605 submitted data. They represented primary care practices in 44 states and 442 cities. The investigators completed and submitted 3175 case-report forms. Based on the study protocol, 1115 of all patients considered for inclusion were qualified (525 receiving pioglitazone, 590 receiving rosiglitazone) and 2060 were disqualified (983 receiving pioglitazone, 1067 receiving rosiglitazone, 10 without drug identification) (Figure 1). The most common reasons for disqualification were timing of clinical laboratory testing (*n* = 1765) and medication changes that could influence lipid profiles (*n* = 200).

Demographic and Baseline Characteristics

Patients in the 2 treatment groups had similar baseline characteristics. No statistically significant intergroup differences were noted in sex, age, race, height, body weight, BMI, or nicotine use (Table II). Similarly, no statistically significant dif-

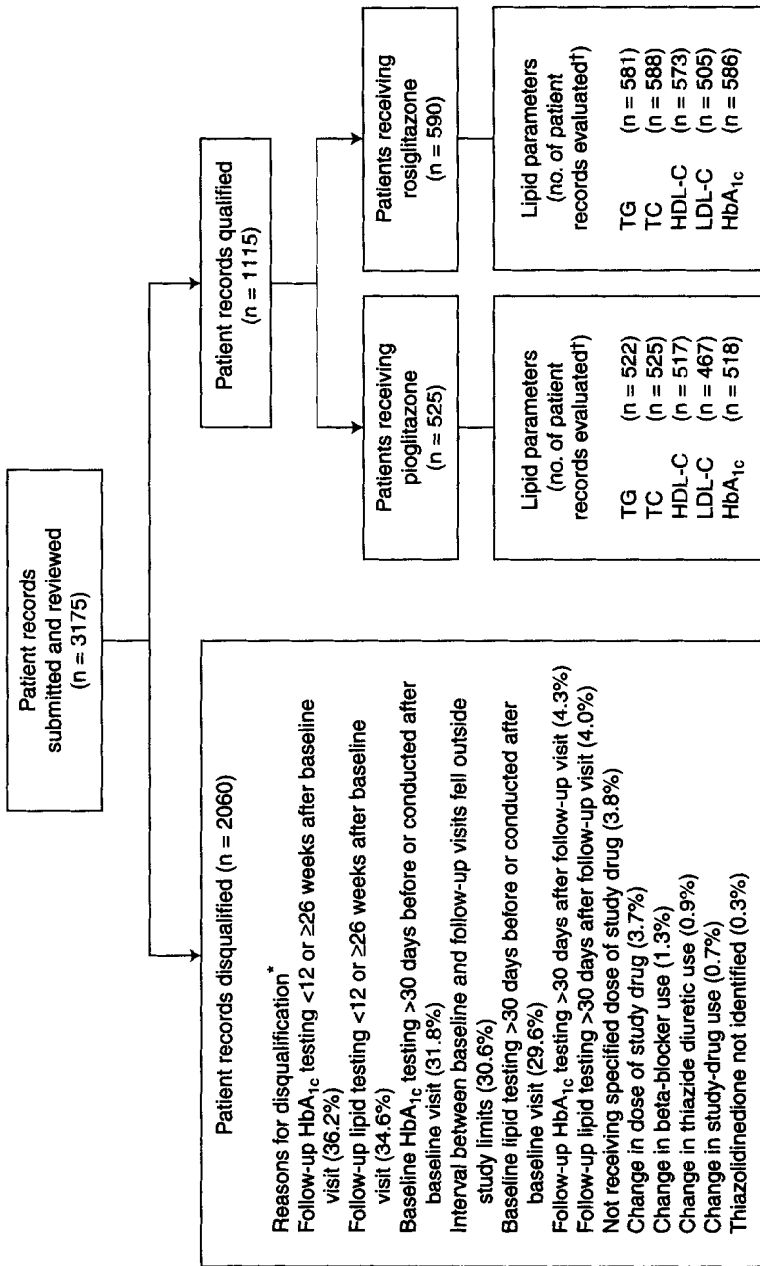


Figure 1. Profile of study population. HbA_{1c} = glycosylated hemoglobin; TG = triglycerides; TC = total cholesterol; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol. *Patients may have been disqualified for >1 reason. Calculated percentages are based on total number of patient records submitted. †Assessment of each end point included only qualified patients with complete baseline and follow-up laboratory values.

ferences were observed in terms of comorbidities (ie, hypertension, coronary artery disease, peripheral vascular disease, symptomatic neuropathy, renal insufficiency, diabetic retinopathy, or cerebrovascular disease) (Table II), concomitant drug use (Table III), or doses of concomitant antihyperglycemic or antihyperlipidemic drugs (Table IV). Moreover, as shown in Table I, the mean (\pm SD) duration of TZD ther-

apy in patients receiving pioglitazone was 17.73 ± 3.83 weeks, compared with 17.41 ± 3.91 weeks in patients receiving rosiglitazone ($P = \text{NS}$).

Baseline values for the study end points were also similar between groups, with the exception of HDL-C levels. The mean (\pm SE) baseline HDL-C level in patients who received pioglitazone was 43.18 ± 0.54 mg/dL, slightly lower than the base-

Table II. Baseline demographic and clinical characteristics.*

	Pioglitazone	Rosiglitazone
Sex, % [†]		
Male	57.66	52.73
Female	42.34	47.27
Age, y (mean \pm SD) [‡]	60.03 \pm 11.28	60.59 \pm 11.25
Race, % [†]		
White	71.79	72.79
Black	13.63	15.65
Hispanic	10.75	8.16
Asian	2.88	2.72
Other	0.96	0.68
Height, in (mean \pm SD) [‡]	66.70 \pm 4.36	66.80 \pm 4.45
Body weight, lb (mean \pm SD) [‡]	209.25 \pm 48.34	209.60 \pm 48.05
Body mass index, kg/m ² (mean \pm SD) [‡]	33.05 \pm 7.35	33.12 \pm 7.70
Duration of TZD therapy, wk (mean \pm SD) [‡]	17.73 \pm 3.83	17.41 \pm 3.91
Nicotine use, % [†]	16.79	13.63
Comorbidities, % [†]		
Hypertension	70.13	73.24
Coronary artery disease	29.23	25.31
Peripheral vascular disease	12.11	10.87
Symptomatic neuropathy	10.49	14.13
Renal insufficiency	7.99	8.36
Diabetic retinopathy	7.68	8.19
Cerebrovascular disease	5.20	5.73

TZD = thiazolidinedione.

*Percentages are based on the numbers of patients for whom the relevant data were reported.

[†]There were no statistically significant differences between study groups, based on Pearson chi-square tests.

[‡]There were no statistically significant differences between study groups, based on Student *t* tests.

Table III. Concomitant medications.*

Drug Class	Pioglitazone	Rosiglitazone
Antihyperglycemic agents, %		
Any	82.86	81.36
Sulfonylureas [†]	51.81	48.98
Metformin	44.76	44.41
Insulin	14.86	16.10
Other [‡]	6.10	5.08
Antihyperlipidemic agents, %		
Any	58.67	60.17
Any statin	53.33	53.73
Atorvastatin	25.52	28.31
Simvastatin	16.19	13.56
Pravastatin	7.24	7.97
Gemfibrozil	3.81	4.58
Fenofibrate	3.05	2.37
Other [§]	5.52	5.42
Other drugs, %		
Antihypertensive agents	62.86	63.73
Diuretics, nonthiazide	17.71	19.15
Beta-blockers	16.76	16.27
Diuretics, thiazide	11.43	13.05
Estrogen replacement therapy	7.05	10.17
Weight-loss product	0.57	0.51

*There were no statistically significant differences between study groups, based on Pearson chi-square tests.

[†]Sulfonylureas identified were chlorpropamide, glimepiride, glipizide, glyburide, tolazamide, and tolbutamide.

[‡]Other antihyperglycemic drugs identified were acarbose, miglitol, and repaglinide.

[§]Other antihyperlipidemic drugs identified were cerivastatin, fluvastatin, lovastatin, and nicotinic acid.

line level of 46.11 ± 1.13 mg/dL in patients who received rosiglitazone ($P = 0.024$). Of 525 patients who were prescribed pioglitazone, 369 (70%) received 30 mg/d and 156 (30%) received 45 mg/d. Of 590 patients who were prescribed rosiglitazone, 271 (46%) received 4 mg/d and 319 (54%) received 8 mg/d.

Lipid Effects

Pretreatment baseline TG levels were similar in the 2 treatment groups. Treat-

ment with pioglitazone therapy resulted in a significantly greater reduction in TG levels than did treatment with rosiglitazone ($P < 0.001$). Patients receiving pioglitazone had a mean (\pm SE) reduction in TG from baseline of 55.17 ± 8.50 mg/dL ($P < 0.001$), whereas patients receiving rosiglitazone had a reduction from baseline of 13.34 ± 6.50 mg/dL ($P = 0.041$), representing respective decreases of 22.51% and 5.57% (Figure 2).

Mean baseline TC levels were similar in the 2 treatment groups. Pioglitazone

Table IV. Doses of concomitant antihyperglycemic and antihyperlipidemic medications.*

	Mean Total Daily Dose, mg/d	
	Pioglitazone	Rosiglitazone
Antihyperglycemic agents		
Glimepiride	5	5
Glipizide	13	14
Glyburide	13	12
Metformin	1636	1695
Antihyperlipidemic agents		
Fibrates		
Fenofibrate	183	167
Gemfibrozil	1080	1156
Statins		
Atorvastatin	22	19
Pravastatin	34	33
Simvastatin	29	30

*There were no statistically significant differences between study groups, based on Student *t* tests.

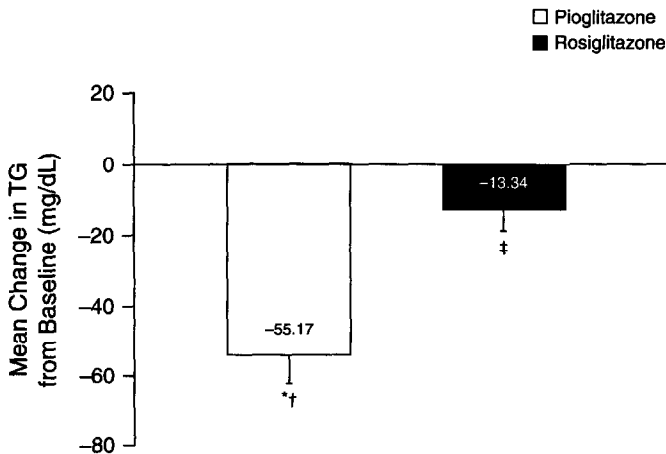


Figure 2. Mean (\pm SE) change in serum triglyceride (TG) levels in patients receiving pioglitazone or rosiglitazone. * $P < 0.001$ versus baseline; † $P < 0.001$ versus rosiglitazone; ‡ $P = 0.041$ versus baseline.

significantly lowered mean (\pm SE) TC levels by 8.45 ± 1.75 mg/dL, or 4.17%, from baseline ($P < 0.001$), whereas rosiglitazone significantly increased TC by 4.81 ± 1.90 mg/dL, or 2.39%, from baseline ($P = 0.011$). The difference between the reduction in TC observed with pioglitazone and the increase observed with rosiglitazone was also statistically significant ($P < 0.001$) (Figure 3).

As noted previously, mean baseline HDL-C levels of patients in the pioglitazone group were significantly lower than those in patients in the rosiglitazone group ($P = 0.024$). After treatment, patients who received pioglitazone had a significant mean (\pm SE) increase in HDL-C of 2.65 ± 0.62 mg/dL, or 6.14% ($P < 0.001$), whereas those receiving rosiglitazone had a mean decrease of 0.12 ± 1.31 mg/dL, or 0.26% ($P = \text{NS}$) (Figure 4). The difference between groups was not statistically significant.

Mean LDL-C levels were similar at baseline in the 2 treatment groups. At follow-up, patients receiving pioglitazone had a significant mean (\pm SE) reduction in LDL-C of 5.05 ± 1.60 mg/dL, or 4.31% ($P = 0.002$), whereas those receiving rosiglitazone had a significant mean increase of 3.56 ± 1.63 mg/dL, or 3.12% ($P = 0.030$) (Figure 5). The difference between the reduction observed in the pioglitazone group and the increase observed in the rosiglitazone group was statistically significant ($P < 0.001$).

Glycemic Control

At baseline, HbA_{1c} averaged 8.7% in each treatment group. At follow-up, the pioglitazone group had an absolute mean (\pm SE) reduction of 1.04 ± 0.18 percentage points, and the rosiglitazone group had an absolute reduction of 1.18 ± 0.18

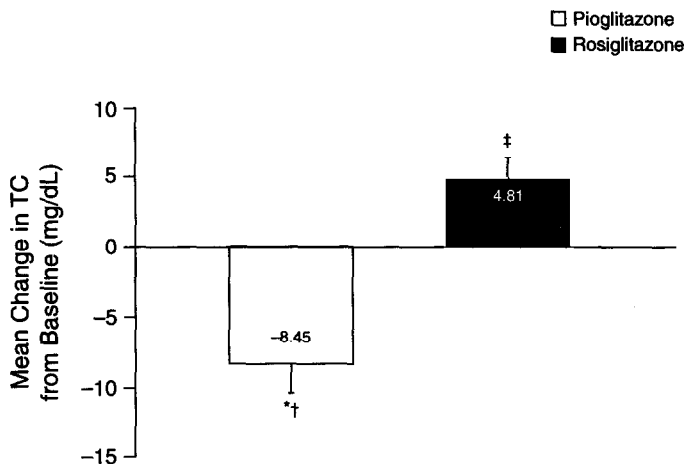


Figure 3. Mean (\pm SE) change in serum total cholesterol (TC) levels in patients receiving pioglitazone or rosiglitazone. * $P < 0.001$ versus baseline; † $P < 0.001$ versus rosiglitazone; ‡ $P = 0.011$ versus baseline.

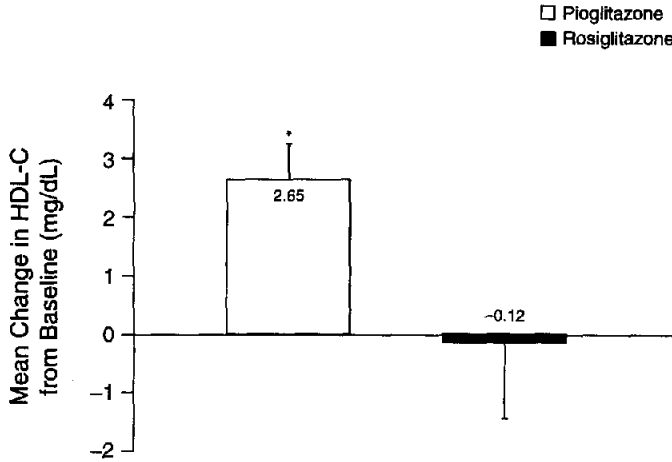


Figure 4. Mean (\pm SE) change in serum high-density lipoprotein cholesterol (HDL-C) levels in patients receiving pioglitazone or rosiglitazone. * $P < 0.001$ versus baseline.

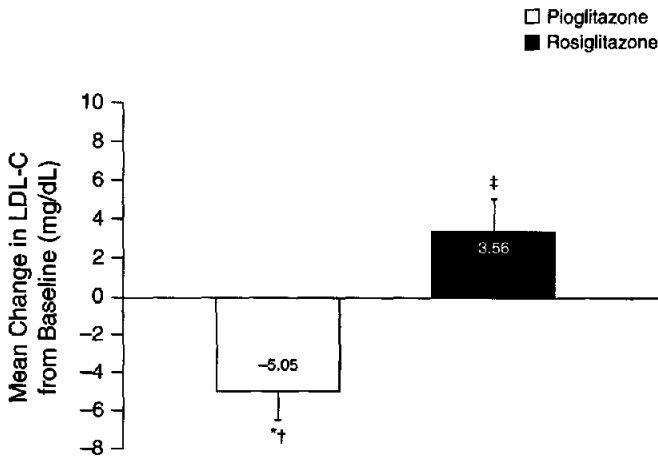


Figure 5. Mean (\pm SE) change in serum low-density lipoprotein cholesterol (LDL-C) levels in patients receiving pioglitazone or rosiglitazone. * $P = 0.002$ versus baseline; † $P < 0.001$ versus rosiglitazone; ‡ $P = 0.030$ versus baseline.

percentage points. The changes from baseline to follow-up were significant in both treatment groups ($P < 0.001$, pioglitazone; $P = 0.011$, rosiglitazone), whereas the difference between treatment groups was not (Figure 6).

Other Effects

Patients in both treatment groups had significant gains in body weight between the baseline and follow-up evaluations ($P < 0.001$). The mean weight gain in the pioglitazone group was 1.97 lbs, compared with 1.64 lbs in the rosiglitazone group. The 0.33-lb difference between groups was not statistically significant.

DISCUSSION

This study found important differences between pioglitazone and rosiglitazone in the treatment of type 2 diabetes in pri-

mary care practice. First, patients who were prescribed pioglitazone had significantly greater improvements in blood lipid levels than did patients who were prescribed rosiglitazone. Second, improvements in HbA_{1c} were statistically equivalent in the 2 treatment groups; however, >50% of the rosiglitazone group were receiving 8 mg/d, the maximum recommended dose, whereas 70% of the pioglitazone group were receiving 30 mg/d, a submaximal dose. The clinical implications of these distinctions relate to potential reductions in risk for the sequelae of diabetes.

For example, patients with diabetes experience macrovascular complications at roughly 2 to 4 times the rate observed in those without diabetes.³⁵⁻³⁷ In the United Kingdom Prospective Diabetes Study³⁸—an investigation in 5102 patients with newly diagnosed diabetes who were followed prospectively for an average of 10 years—the leading prognostic risk factors

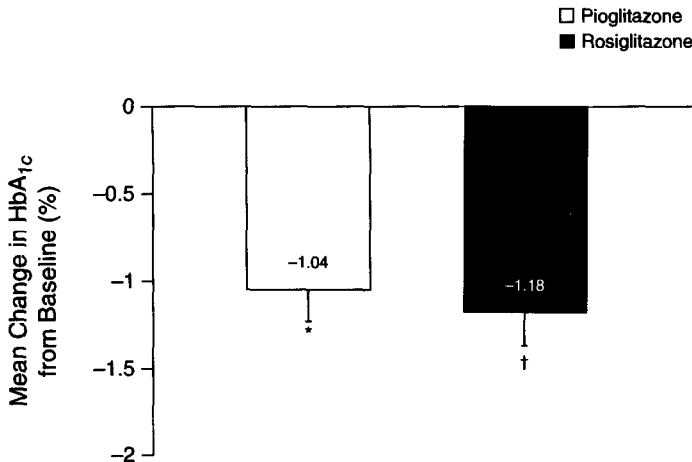


Figure 6. Mean (\pm SE) change in glycosylated hemoglobin (HbA_{1c}) values in patients receiving pioglitazone or rosiglitazone. * $P < 0.001$ versus baseline; † $P = 0.011$ versus baseline.

for development of a coronary event were elevated LDL-C levels, low HDL-C levels, and high HbA_{1c} values. In response to such information, the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults set target LDL-C levels for patients with type 2 diabetes at 100 mg/dL.³⁹

In the present study, pioglitazone treatment was associated with a 5.05-mg/dL decrease in LDL-C levels, whereas rosiglitazone treatment was associated with a 3.56-mg/dL increase. The difference in net posttreatment change between the 2 study groups was ~9 mg/dL in favor of pioglitazone. Whether this magnitude of change and intergroup difference is sufficient to produce clinical benefits that distinguish one drug from the other is an open question. However, it could be speculated that cardiac risk reduction would be more likely with pioglitazone than rosiglitazone treatment, because only pioglitazone combined a significant decrease in LDL-C levels with a significant increase in HDL-C levels. A reduction in coronary morbidity might also be anticipated with rosiglitazone, although this would be derived from improved glucose control alone and might be partially offset by detrimental changes in some lipid levels.⁴⁰

Furthermore, several investigations have focused on the potential pathophysiologic consequences of hypertriglyceridemia,^{41–44} which may result from the effect of very-low-density lipoprotein TG on plasminogen activator inhibitor factor-1 (PAI-1) production. Indeed, hyperinsulinemia, hyperglycemia, and hypertriglyceridemia are known to be key activators of the promoter sequence for the *PAI-1* gene.^{45–48} Thus, patients with poorly controlled type 2 diabetes who have hypertriglyceridemia

are known to have increased levels of PAI-1 and are consequently procoagulable and therefore predisposed to coronary thrombosis.^{46,49} Interestingly, reductions in PAI-1 have been noted in patients taking troglitazone or pioglitazone.⁵⁰ Because TZDs enhance peripheral glucose uptake, endogenous insulin concentrations decrease with their use. Thus, concentrations of insulin and glucose, 2 important activators of the *PAI-1* gene, are likely to be reduced by TZDs.

The Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT) demonstrated that use of gemfibrozil, a TG-lowering and HDL-C-raising fibric acid derivative, was associated with a 22% reduction in coronary heart disease deaths and nonfatal myocardial infarctions.⁴³ In VA-HIT, the mean reduction in TG levels was 31%; HDL-C concentration rose by a mean of 6%. In the present study, TG levels decreased by 23% with pioglitazone and by 6% with rosiglitazone. HDL-C levels increased by 6% with pioglitazone and decreased by 0.26% with rosiglitazone. Although the relative importance of reducing TG levels and increasing HDL-C levels requires clarification, the results of VA-HIT strengthen the view that TG levels play an important role in cardiovascular health and illness and that an elevated TG level is an independent risk factor for cardiovascular events. The importance of controlling TG levels is further underscored by the new NCEP guidelines, which now define a normal TG level as <150 mg/dL³⁹ rather than the previous limit of <200 mg/dL.⁵¹

The role of retrospective research such as the present observational study in the evaluation of therapeutic interventions has been a topic of long-standing debate. Although critical assessments of retrospec-

tive versus prospective research have documented remarkably similar results between rigorously conducted observational studies and randomized, controlled trials,^{52,53} there are some lingering concerns over the validity of retrospective work. A major criticism is that various types of bias may be introduced at multiple levels. Several steps were taken during the planning of this study to reduce or avoid this problem. The nationwide distribution of investigators, the randomization carried out before chart selection, and the large sample size made possible by a national endeavor should all add strength to the validity of the results. Although it is not possible to state this with certainty, the fact that the pool of potentially qualified patients was in most cases exhausted at each investigational site may also have limited the possibility of patients with specific characteristics or responses being selected for inclusion. Moreover, the practically identical baseline demographic characteristics of the 2 treatment groups further indicate that selection bias at the patient level was minimal or nonexistent and that differences in outcomes between the 2 study cohorts were due to the treatments themselves.

The validity of the present observations is supported by the results of independent studies completed in an academic institution³² and in primary care practices.^{30,31,33} In the study by Khan et al,³² 97 patients were prospectively randomized to be switched to either pioglitazone or rosiglitazone when troglitazone was withdrawn from the market. Different effects on lipid profiles were seen after the conversion, despite similar weight gains and glycemic control with the 2 treatments. Statistically significant improvements in all lipid components were de-

tected after conversion to pioglitazone (each, $P < 0.008$), whereas after the switch to rosiglitazone, positive changes were seen in HDL-C levels only ($P < 0.03$). In a study by Gegick and Altheimer,³³ patients experienced similar glycemic control after a switch from troglitazone to pioglitazone or rosiglitazone ($N = 125$). However, conversion to pioglitazone was associated with statistically significant reductions in TC ($P < 0.05$), whereas switching to rosiglitazone led to significant increases in TC, TG, and LDL-C levels ($P < 0.05$). In another study involving conversion from troglitazone to pioglitazone or rosiglitazone, King and Armstrong³⁰ described substantial differences in lipid responses between patients in the 2 treatment groups ($N = 61$), reporting the greatest benefit with pioglitazone and the least benefit with rosiglitazone. King³¹ reported that beneficial effects on blood lipid levels were more often observed with pioglitazone than rosiglitazone in TZD-naïve patients. The changes in blood lipid levels in each of these studies were comparable to those observed in the present larger investigation, demonstrating relative reproducibility of study results and providing external validity.

Two concerns associated with the present study were the similarities and dissimilarities between the qualified- and disqualified-patient data sets, and the potential impact of data from disqualified patients on the study results. A comparison of the qualified and disqualified data was performed to address these concerns. Evaluation of the disqualified-patient data produced results similar to those obtained in the analysis of qualified-patient data in terms of mean changes in study end points, with the exception of TC ($P = 0.047$) (Table V). In the case of TC, disqualified

Table V. Mean (\pm SE) lipid values of disqualified and qualified cases.

Lipid Parameter	Pioglitazone		Rosiglitazone	
	Disqualified	Qualified	Disqualified	Qualified
Triglycerides, mg/dL				
Baseline	232.99 \pm 5.51	245.13 \pm 9.89	236.24 \pm 5.41	239.32 \pm 7.16
Follow-up	184.80 \pm 3.70	189.96 \pm 4.72	217.68 \pm 4.73	225.98 \pm 7.08
Change	-48.19 \pm 4.53	-55.17 \pm 8.50	-18.57 \pm 4.56	-13.34 \pm 6.50
Total cholesterol, mg/dL				
Baseline	205.60 \pm 1.59	202.61 \pm 2.06	206.12 \pm 1.48	201.37 \pm 1.80
Follow-up	194.90 \pm 1.39	194.16 \pm 1.61	206.37 \pm 1.60	206.18 \pm 2.02
Change	-10.70 \pm 1.40	-8.45 \pm 1.75	0.36 \pm 1.51	4.81 \pm 1.90
High-density lipoprotein cholesterol, mg/dL				
Baseline	45.89 \pm 0.86	43.18 \pm 0.54	44.78 \pm 0.54	46.11 \pm 1.13
Follow-up	47.29 \pm 0.69	45.84 \pm 0.76	46.35 \pm 0.74	45.99 \pm 0.92
Change	1.40 \pm 0.98	2.65 \pm 0.62	1.58 \pm 0.76	-0.12 \pm 1.31
Low-density lipoprotein cholesterol, mg/dL				
Baseline	121.38 \pm 2.13	117.25 \pm 1.78	119.96 \pm 1.31	114.03 \pm 1.71
Follow-up	113.76 \pm 1.64	112.20 \pm 1.42	120.09 \pm 1.61	117.59 \pm 1.68
Change	-7.62 \pm 1.75	-5.05 \pm 1.60	0.14 \pm 1.59	3.56 \pm 1.63
Glycosylated hemoglobin, %				
Baseline	8.87 \pm 0.12	8.72 \pm 0.09	8.98 \pm 0.16	8.71 \pm 0.19
Follow-up	7.94 \pm 0.18	7.68 \pm 0.18	7.84 \pm 0.12	7.52 \pm 0.06
Change	-0.93 \pm 0.18	-1.04 \pm 0.18	-1.13 \pm 0.18	-1.18 \pm 0.18

patients who were receiving pioglitazone demonstrated a mean (\pm SE) reduction of 10.70 ± 1.40 mg/dL compared with qualified patients, who demonstrated a mean reduction of 8.45 ± 1.75 mg/dL. In the rosiglitazone group, disqualified patients had a mean increase in TC of 0.36 ± 1.51 mg/dL, compared with a mean increase of 4.81 ± 1.90 mg/dL in qualified patients. There were no other statistically significant differences in mean changes in study end points between the qualified- and disqualified-patient data sets in either treatment group.

CONCLUSIONS

Patients receiving pioglitazone in this study demonstrated significantly greater benefit in terms of changes in blood lipid levels compared with those receiving rosiglitazone, although glycemic control, as measured by HbA_{1c}, was similar in the 2 groups. These results highlight critical distinctions in the therapeutic effects of the 2 study drugs and have important clinical implications for cardiovascular risk reduction in patients with type 2 diabetes. Based on these distinctions, as well as the

biochemistry and pharmacology of pioglitazone and rosiglitazone, any new additions to the TZD class of compounds should be assessed individually and not assumed to produce similar or equal metabolic changes. The differences in the therapeutic response to pioglitazone and rosiglitazone in this study were observed over a 4-month period that began with the initiation of TZD therapy. Longer-term studies are needed to determine whether treatment effects on lipids, glycemic control, and body weight persist over time and whether cardiovascular benefit is realized.

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