A Comparison of Lipid and Glycemic Effects of Pioglitazone and Rosiglitazone in Patients With Type 2 Diabetes and Dyslipidemia

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OBJECTIVE — Published reports suggest that pioglitazone and rosiglitazone have different effects on lipids in patients with type 2 diabetes. However, these previous studies were either retrospective chart reviews or clinical trials not rigorously controlled for concomitant glucose- and lipid-lowering therapies. This study examines the lipid and glycemic effects of pioglitazone and rosiglitazone.

RESEARCH DESIGN AND METHODS — We enrolled subjects with a diagnosis of type 2 diabetes (treated with diet alone or oral monotherapy) and dyslipidemia (not treated with any lipid-lowering agents). After a 4-week placebo washout period, subjects randomly assigned to the pioglitazone arm ($n = 400$) were treated with 30 mg once daily for 12 weeks followed by 45 mg once daily for an additional 12 weeks, whereas subjects randomly assigned to rosiglitazone ($n = 402$) were treated with 4 mg once daily followed by 4 mg twice daily for the same intervals.

RESULTS — Triglyceride levels were reduced by 51.9 ± 7.8 mg/dl with pioglitazone, but were increased by 13.1 ± 7.8 mg/dl with rosiglitazone ($P < 0.001$ between treatments). Additionally, the increase in HDL cholesterol was greater (5.2 ± 0.5 vs. 2.4 ± 0.5 mg/dl; $P < 0.001$) and the increase in LDL cholesterol was less (12.3 ± 1.6 vs. 21.3 ± 1.6 mg/dl; $P < 0.001$) for pioglitazone compared with rosiglitazone, respectively. LDL particle concentration was reduced with pioglitazone and increased with rosiglitazone ($P < 0.001$). LDL particle size increased more with pioglitazone ($P = 0.005$).

CONCLUSIONS — Pioglitazone and rosiglitazone have significantly different effects on plasma lipids independent of glycemic control or concomitant lipid-lowering or other antihyperglycemic therapy. Pioglitazone compared with rosiglitazone is associated with significant improvements in triglycerides, HDL cholesterol, LDL particle concentration, and LDL particle size.

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Abbreviations: CHD, coronary heart disease; CVD, cardiovascular disease; LOCF, last observation carried forward; PAI-1, plasminogen activator inhibitor-1.

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

Two core metabolic defects contribute to the development of type 2 diabetes: relative insulin insufficiency and insulin resistance. Approximately 92% of patients with type 2 diabetes demonstrate insulin resistance (1). Even in the absence of overt hyperglycemia, insulin resistance is associated with a cluster of abnormalities that increase the risk for cardiovascular disease (CVD), including dyslipidemia, increased expression of inflammatory markers, activation of procoagulants, hemodynamic changes, and endothelial dysfunction (2,3).

The dyslipidemia associated with insulin resistance and type 2 diabetes is characterized by elevated triglycerides and decreased HDL cholesterol (4–6). Although LDL cholesterol may not be elevated in type 2 diabetes, an increase in the proportion of small, dense, and potentially more atherogenic LDL cholesterol particles is observed (7). In addition to LDL cholesterol, elevated triglyceride levels and reduced HDL cholesterol levels are both risk factors for coronary heart disease (CHD) (8–11). Compared with nondiabetic individuals, patients with type 2 diabetes have a two- to fourfold higher risk of CVD, and dyslipidemia is an important contributor to the increased risk in this population (12).

By targeting insulin resistance, the members of the thiazolidinedione class of oral antihyperglycemic medications possess both a glucose-lowering effect and the potential to alter lipid/lipoprotein metabolism. Two members of the thiazolidinedione class are currently available for the treatment of type 2 diabetes: pioglitazone hydrochloride (Actos; Takeda Pharmaceuticals North America, Lincolnshire, IL) and rosiglitazone maleate (Avandia; GlaxoSmithKline, Research Triangle Park, NC).

This study was conceived following the report of a nonrandomized clinical comparison of potential differences in lipid effects among thiazolidinediones

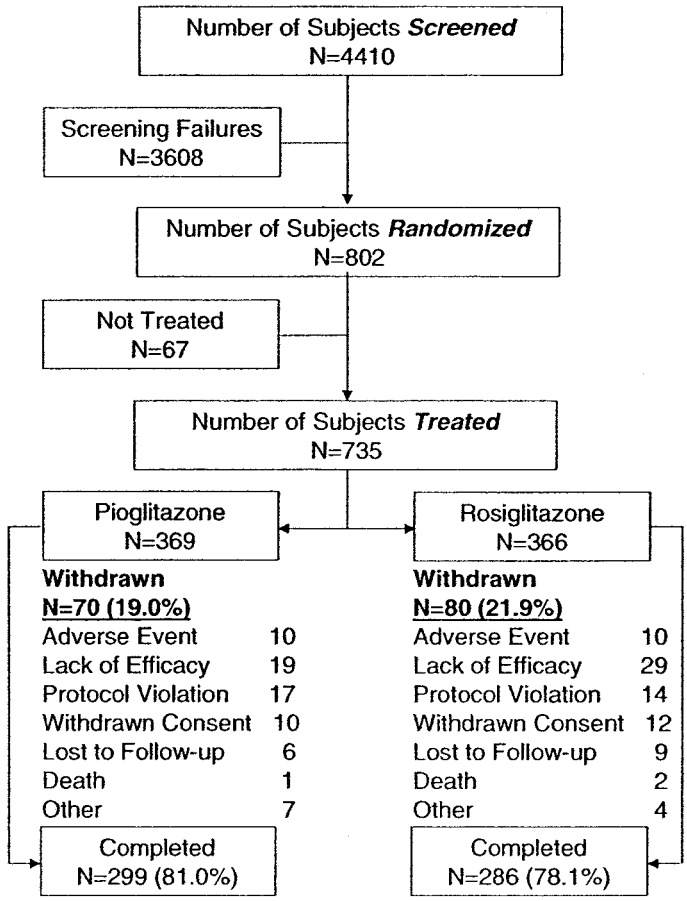

Figure 1—*Patient flow through the study.*

(13). Since that time, multiple reports (14–22) have been published suggesting that pioglitazone has differential effects on lipid parameters in patients with type 2 diabetes when compared with rosiglitazone. However, these previous studies were either retrospective chart review studies, clinical trials not rigorously controlled for concomitant glucose-lowering and lipid-lowering therapies, or systematic reviews. With the primary objective to test the hypothesis that pioglitazone has greater triglyceride-lowering effects than rosiglitazone, this study reports results from the first multicenter, prospective, randomized, double-blind, parallel-group comparison of maximally effective monotherapy doses of pioglitazone and rosiglitazone in patients with type 2 diabetes and dyslipidemia receiving no concomitant glucose-lowering or lipid-lowering therapies.

RESEARCH DESIGN AND METHODS

— Subjects eligible for participation in this clinical trial were men or women ≥35 years of age with a diagnosis of type 2 diabetes (based on World Health Organization criteria) with fasting triglyceride levels ≥150 mg/dl and <600 mg/dl and fasting LDL cholesterol levels <130 mg/dl. Other inclusion criteria included fasting serum C-peptide levels ≥1 ng/ml and HbA_{1c} (A1C) values ≥7 and ≤11% if naïve to previous oral antihyperglycemic therapy or A1C values ≥7 and ≤9.5% if previously treated with oral antihyperglycemic monotherapy.

Subjects were excluded from participation in this study for any of the following: treatment within 60 days of screening with insulin, systemic glucocorticoid therapy, combination oral antihyperglycemic therapy, any lipid-lowering agent, or any weight loss agent; known allergy to any thiazolidinedione; serum creatinine ≥176.8 μmol/dl (≥2.0 mg/dl) or 2+ dipstick proteinuria at screening; alanine aminotransferase or aspartate aminotransferase ≥1.5 times the upper limit of normal or significant clinical liver disease; hemoglobin <10.5 g/dl (females) or <11.5 g/dl (males) at screening; abnormal thyrotropin; functional New York Heart Association Cardiac Disease Class III or IV, history of CVD, or heart surgery within 6 months of screening; receiving renal dialysis or having renal transplant; current therapy for malignancy other than basal cell or squamous cell skin cancer; known history of HIV infection; signs or symptoms of drug or alcohol abuse; and any condition or situation precluding adherence to and completion of the protocol. For female subjects, appropriate birth control was required, and pregnancy, breast-feeding, or the intent to become pregnant during the study period prohibited participation.

Subjects were enrolled from the U.S. (78 sites), Puerto Rico (11 sites), Mexico (4 sites), and Colombia (7 sites). Conducted in accordance with the Declaration of Helsinki guidelines on good clinical practice, this study was approved by each investigator's institutional ethical review board.

Screening for eligibility occurred at visit 1 after written informed consent was obtained. At visit 2, subjects were randomly assigned to one of the two treatment groups, although active study drug administration was not initiated until 4 weeks later (visit 3). Randomization occurred in a stratified fashion with four strata corresponding to previous oral antihyperglycemic treatment (previously treated or naïve) and sex (male or female). Subjects discontinued any current oral antihyperglycemic therapy and received oral placebo therapy throughout the 4-week, single-blind, lead-in period. At visit 3, subjects received either 30 mg pioglitazone once daily or 4 mg rosiglitazone once daily for 12 weeks according to the randomization assigned at visit 2. Qualified personnel provided dietary counseling on the American Heart Association weight-maintaining Step I diet, and all subjects were instructed to follow this diet throughout the entire study. Clinic visits occurred every 4 weeks following visit 3 through visit 6. At visit 6 and for the final 12 weeks, the doses of pioglitazone and rosiglitazone were increased to the maximally effective doses (for monotherapy) of 45 mg once daily (23) or 4 mg twice daily (24), respectively. Clinic visits occurred every 6 weeks (visits 7 and 8) for the remainder of the 24-week total study.

Table 1—*Characteristics and demographics at visit 3 of all randomly assigned subjects beginning active therapy*

	Pioglitazone	Rosiglitazone	*P* value
n	369	366	
Sex			0.824
Male	199 (53.9)	201 (54.9)	
Female	170 (46.1)	165 (45.1)	
Age (years)	55.9 ± 10.5	56.3 ± 11.3	0.572
Race			0.842
White	239 (64.8)	219 (59.8)	
Hispanic	105 (28.5)	118 (32.2)	
Asian	10 (2.7)	12 (3.3)	
African	9 (2.4)	10 (2.7)	
Other	6 (1.6)	7 (1.9)	
Duration of diabetes (years)	3.9 ± 4.4	4.0 ± 4.6	0.847
Body weight (kg)	93.7 ± 20.6	92.5 ± 21.0	0.450
BMI (kg/m^2)	33.7 ± 12.9	32.6 ± 6.6	0.122
A1C (%)	7.6 ± 1.2	7.5 ± 1.2	0.230
Fasting plasma glucose (mg/dl)	180.5 ± 59.7	177.3 ± 57.4	0.459
Previous treatment*	280 (75.9)	274 (74.9)	0.797
Metformin	97/212 (45.8)	92/206 (44.7)	
Insulin secretagogues†	97/212 (45.8)	95/206 (46.1)	
Thiazolidinediones	18/212 (8.5)	19/206 (9.2)	
Fasting lipid profile			
Total triglycerides (mg/dl)	258.5 ± 159.4	239.5 ± 132.6	0.079
Total cholesterol (mg/dl)	193.4 ± 31.3	193.7 ± 33.7	0.882
LDL cholesterol (mg/dl)	106.9 ± 25.4	109.0 ± 25.9	0.260
HDL cholesterol (mg/dl)	38.8 ± 10.0	39.7 ± 10.3	0.211
Apolipoprotein B (g/l)	1.05 ± 0.20	1.04 ± 0.20	0.781
Fasting free fatty acid (mEq/l)	0.64 ± 0.28	0.62 ± 0.29	0.579
Fasting insulin (μU/ml)	19.7 ± 19.4	17.8 ± 14.3	0.132
Fasting C-peptide (ng/ml)	3.9 ± 1.7	3.6 ± 1.6	0.043
HOMA			
Insulin resistance	8.2 ± 6.4	7.7 ± 7.2	0.386
β-Cell function	83.6 ± 125.2	71.1 ± 69.7	0.095
Systolic blood pressure (mmHg)	128.4 ± 15.9	129.1 ± 16.4	0.584
Diastolic blood pressure (mmHg)	78.7 ± 9.3	78.5 ± 8.9	0.765
Preexisting CVD or previous MI	31 (8.4)	24 (6.6)	0.401
Aspartate aminotransferase (units/l)	22.0 ± 7.1	21.7 ± 7.5	0.547
Alanine aminotransferase (units/l)	27.0 ± 10.7	25.6 ± 10.9	0.063
Creatine phosphokinase (units/l)	108.0 ± 85.1	109.6 ± 77.7	0.790
Plasminogen activator inhibitor 1 (ng/ml)	64.2 ± 43.4	59.6 ± 40.4	0.143
C-reactive protein (mg/l)	7.0 ± 10.1	6.6 ± 7.7	0.580

Data are *n* (%) or means ± SD. *Totals of 280 (pioglitazone) and 274 (rosiglitazone) patients reported previous antidiabetes therapy, but only 212 (pioglitazone) and 206 (rosiglitazone) patients reported the class of previous antidiabetes therapy. †Includes short-acting secretagogues repaglinide and nateglinide. HOMA, homeostasis model assessment; MI, myocardial infarction.

Analytical methods

The following analyses were performed by Covance Central Laboratory Services (Indianapolis, IN): triglycerides, total cholesterol, and plasma glucose in blood samples (following at least 10 h of fasting) using standard enzymatic methods; HDL and LDL cholesterol (Roche Diagnostics, Indianapolis, IN) by direct methods; free fatty acid by the Wako enzymatic method (Wako Chemicals, Richmond, VA); apolipoprotein B by immunoassay (Beckman IMMAGE Immunochemistry System, Beckman Instruments, Brea, CA); A1C by chromatography (Bio-Rad, Hercules, CA); total insulin by immunoassay (Abbott IMX Microparticle EIA, Abbott Laboratories, Abbott Park, IL); C-peptide by radioimmunoassay (Adaltis Italia, Rome, Italy); highly sensitive C-reactive protein by immunonephelometry (Dade Behring, Newark, DE); and plasminogen activator inhibitor-1 (PAI-1) by immunoassay (Asserachrom PAI-1 Antigen EIA, Diagnostica Stago, France). LDL particle size and concentration were measured using proton nuclear magnetic resonance spectroscopy at LipoScience (Raleigh, NC). Surrogates of insulin resistance and β-cell function were estimated by homeostasis model assessments (25). Safety assessments included adverse events, blood pressure and heart rate, hemoglobin and hematocrit, liver function, pedal edema, body weight, and hypoglycemic episodes.

Statistical methods

Data are presented as means ± SE (or SD where indicated). Differences between treatments in demographics and baseline levels (visit 3) for patients entering active drug therapy were evaluated using a χ^2 test for categorical variables or an independent-groups *t* test for continuous variables. Efficacy analyses were conducted on subjects providing a baseline measurement and at least one postbaseline measurement. The last-observation-carried-forward (LOCF) change from baseline level and LOCF actual value were analyzed using a fixed-effects ANCOVA. The ANCOVA model was composed of terms for strata, geographic region in which the investigative site was located (five regions: Mexico/Puerto-Rico/Colombia, Mid-Atlantic/Eastern, West/Midwest/Texas, South/Southeast, and West Coast/Hawaii), treatment, and baseline value. The change from baseline to the last observed value was of primary interest, and the triglycerides change was the primary efficacy variable. The visit-wise changes from baseline were also analyzed using LOCF. LOCF percent change from baseline was also analyzed for the lipid variables. Treatments were compared using least-square means (26–27).

A mixed-model repeated-measures analysis was used to confirm the LOCF triglyceride results. The model used was comprised of terms for strata, geographic region, treatment, visit, treatment × visit interaction, baseline value, and visit × baseline level interaction. The covariance structure was modeled using an unstructured covariance matrix within each treatment. The Kenward-Roger degrees of freedom were used for the tests. Addition-

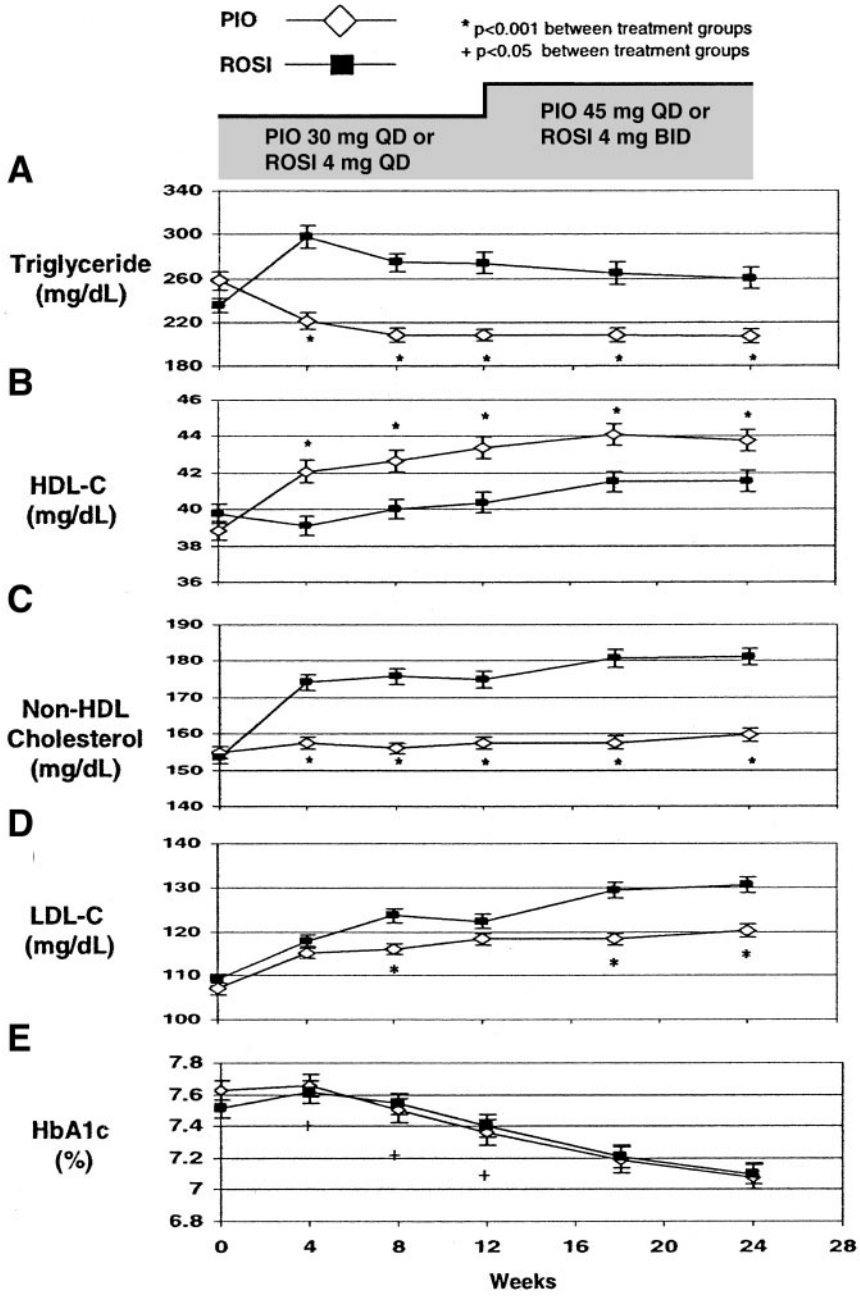

Figure 2—*Comparison of fasting triglyceride* (A)*, HDL cholesterol* (B)*, non-HDL cholesterol* (C)*, LDL cholesterol* (D)*, and mean A1C* (E) *levels observed during 24 weeks of therapy with pioglitazone (PIO) and rosiglitazone (ROSI). LDL cholesterol levels were directly measured (not calculated). Patients were randomly assigned to either 12 weeks of 30 mg/day pioglitazone followed by 12 weeks of 45 mg/day pioglitazone (◇) or 12 weeks of 4 mg/day rosiglitazone once daily followed by 12 weeks of 4 mg rosiglitazone twice daily (■). Vertical bars represent SE.* *P < *0.001 between treatment groups;* +P < *0.05 between treatment groups.*

ally, the change from baseline triglycerides was analyzed for the subset of patients who completed the study. SAS version 8.2 (SAS Institute, Cary, NC) was used for all analyses. All tests were two sided, and results were considered statistically significant at $P \leq 0.05$.

RESULTS — Figure 1 summarizes patient flow through the study. Similar numbers of subjects completed therapy for the pioglitazone and rosiglitazone groups. The distribution of subjects among the various withdrawal categories was also similar between treatment groups.

There were no statistically significant differences between the treatment groups in respect to demographics, baseline characteristics, and laboratory measurements with the exception of fasting C-peptide levels, which were lower in subjects randomly assigned to rosiglitazone (Table 1).

Figure 2 shows the 24-week time course for fasting triglycerides, HDL cholesterol, non-HDL cholesterol, LDL cholesterol, and A1C. Baseline and end point values for each are found in Table 2.

By the first posttherapy visit, triglyceride levels were significantly decreased with pioglitazone and significantly increased with rosiglitazone compared with baseline. Differences in triglyceride levels between treatment groups were significant at every time point ($P < 0.001$) (Fig. 2*A*). By week 24, triglyceride levels in pioglitazone-treated subjects were significantly reduced by 51.9 ± 7.8 mg/dl (12.0 ± 3.0%, median of 19.8%) below baseline (Table 2), whereas triglyceride levels in rosiglitazone-treated subjects were elevated by 13.1 ± 7.8 mg/dl (14.9 ± 3.1%, median of 3.5%) above baseline (the percent change represents the mean of the individual percent changes from baseline). The 95% CI (based on the ANCOVA model) for the mean change from baseline to the last observed value was −67.2 to −36.6 mg/dl in the pioglitazone group and −2.2 to +28.5 mg/dl in the rosiglitazone group. The mixed-model repeated-measures results for change from baseline triglyceride level (data not shown) as well as the results from an analysis of study completers (data not shown) were similar to the LOCF results.

Both pioglitazone and rosiglitazone increased HDL cholesterol over time, but mean changes from baseline to end point were significantly greater with pioglitazone compared with rosiglitazone, respectively: 5.2 ± 0.5 mg/dl (14.9 ± 1.2%) versus 2.4 ± 0.5 mg/dl (7.8 ± 1.2%) ($P < 0.001$) (Table 2). The differences in HDL cholesterol levels between treatment groups were significant at every time point ($P < 0.001$) (Fig. 2*B*).

Non-HDL cholesterol levels remained relatively constant in pioglitazone-treated subjects but were markedly increased with rosiglitazone therapy over the treatment period, such that the differences between treatment groups were significant at every time point ($P < 0.001$)

Table 2—*Effects of pioglitazone and rosiglitazone on outcome measures for subjects with at least one postbaseline measurement*

	Pioglitazone	Rosiglitazone	*P* value
n	363	356	
Triglyceride (mg/dl)			
Baseline	257.8 ± 8.2	235.3 ± 6.6	
Change from baseline	−51.9 ± 7.8*	13.1 ± 7.8	<0.001
Percent change from baseline	−12.0 ± 3.0*	14.9 ± 3.1*	<0.001
HDL cholesterol (mg/dl)			
Baseline	38.8 ± 0.5	39.8 ± 0.6	
Change from baseline	5.2 ± 0.5*	2.4 ± 0.5*	<0.001
Percent change from Baseline	14.9 ± 1.2*	7.8 ± 1.2*	<0.001
Non-HDL cholesterol (mg/dl)			
Baseline	154.8 ± 1.6	153.6 ± 1.6	
Change from baseline	3.6 ± 1.9	25.7 ± 2.0*	<0.001
Percent change from baseline	3.8 ± 1.3*	18.6 ± 1.3*	<0.001
LDL cholesterol† (mg/dl)			
Baseline	107.1 ± 1.3	109.1 ± 1.4	
Change from baseline	12.3 ± 1.6*	21.3 ± 1.6*	<0.001
Percent change from baseline	15.7 ± 1.9*	23.3 ± 1.9*	0.002
Total cholesterol (mg/dl)			
Baseline	193.6 ± 1.6	193.4 ± 1.8	
Change from baseline	8.8 ± 1.9*	28.2 ± 1.9*	<0.001
Percent change from baseline	5.7 ± 1.0*	15.9 ± 1.0*	<0.001
Total-to-HDL cholesterol ratio			
Baseline	5.3 ± 0.1	5.1 ± 0.1	
Change from baseline	−0.3 ± 0.1*	0.7 ± 0.1*	<0.001
Apolipoprotein B (g/l)			
Baseline	1.05 ± 0.01	1.04 ± 0.01	
Change from baseline	0.00 ± 0.01	0.11 ± 0.01*	<0.001
Free fatty acid (mEq/l)			
Baseline	0.64 ± 0.01	0.62 ± 0.02	
Change from baseline	−0.11 ± 0.02*	−0.12 ± 0.02*	0.681
A1C (%)			
Baseline	7.6 ± 0.1	7.5 ± 0.1	
Change from baseline	−0.7 ± 0.1*	−0.6 ± 0.1*	0.129
Fasting plasma glucose (mg/dl)			
Baseline	180.6 ± 3.1	176.5 ± 3.0	
Change from baseline	−33.2 ± 2.2*	−36.6 ± 2.2*	0.233
Fasting insulin (μU/ml)			
Baseline	19.7 ± 1.0	17.9 ± 0.8	
Change from baseline	−4.5 ± 0.5*	−4.6 ± 0.5*	0.918
Fasting C-peptide (ng/ml)			
Baseline	3.9 ± 0.1	3.7 ± 0.1	
Change from baseline	−0.7 ± 0.1*	−0.7 ± 0.1*	0.652
HOMA of insulin resistance			
Baseline	8.2 ± 0.3	7.8 ± 0.4	
Change from baseline	−2.8 ± 0.2*	−3.0 ± 0.2*	0.449
HOMA β-cells			
Baseline	83.8 ± 6.6	71.8 ± 3.7	
Change from baseline	8.0 ± 3.5*	6.7 ± 3.6	0.780
PAI-1 (ng/ml)			
Baseline	62.8 ± 2.3	60.0 ± 2.3	
Change from baseline	−10.4 ± 2.0*	−11.7 ± 2.0*	0.623
C-reactive protein (mg/l)			
Baseline	7.0 ± 0.6	6.6 ± 0.4	
Change from baseline	−2.0 ± 0.3*	−2.5 ± 0.3*	0.288

Data are means ± SE. *$P \leq 0.05$ vs. baseline; change from baseline and percent change from baseline are least-square means adjusted for baseline level. †LDL cholesterol levels were directly measured (not calculated). HOMA, homeostasis model assessment.

(Fig. 2*C*). By week 24, non-HDL cholesterol levels in pioglitazone-treated subjects were 3.6 ± 1.9 mg/dl (3.8 ± 1.3%) above baseline, whereas levels in rosiglitazone-treated subjects increased 25.7 ± 2.0 mg/dl (18.6 ± 1.3%) above baseline ($P < 0.001$ between treatments) (Table 2).

Both pioglitazone and rosiglitazone also increased LDL cholesterol over time, but mean changes from baseline to end point were significantly less with pioglitazone compared with rosiglitazone, respectively: 12.3 ± 1.6 mg/dl (15.7 ± 1.9%) versus 21.3 ± 1.6 mg/dl (23.3 ± 1.9%) ($P < 0.001$) (Table 2). The differences in LDL cholesterol levels between treatment groups were significant at every time point ($P < 0.001$) except at weeks 4 and 12 (Fig. 2*D*). Lastly, apolipoprotein B was unchanged in the pioglitazone group but significantly increased in the rosiglitazone group (Table 2).

Figure 3 compares the effects of pioglitazone and rosiglitazone on LDL particle concentration and particle size at end point. These agents had opposing effects on particle concentration: a significant reduction was observed with pioglitazone, whereas rosiglitazone therapy resulted in a significant increase. Both agents increased particle size, but the increase observed with pioglitazone was significantly greater than that observed with rosiglitazone.

Both agents significantly improved glycemic control. Although statistical differences between treatment groups were observed for A1C values between weeks 4 and 12, these differences are not clinically significant (Fig. 2*E*). Furthermore, there was no difference between agents with respect to A1C or fasting plasma glucose changes at end point (Table 2). No significant differences were observed between agents for changes in free fatty acid levels, PAI-1, C-reactive protein, and indices of insulin secretion and sensitivity (Table 2).

Mean body weight changes from baseline were similar for both pioglitazone (2.0 ± 0.2 kg) and rosiglitazone (1.6 ± 0.2 kg) ($P = 0.164$). Additionally, no differences between agents were observed with regard to liver function tests (alanine aminotransferase and aspartate aminotransferase), creatine phosphokinase, blood pressure and heart rate, hemoglobin and hematocrit, hypoglycemic episodes, or adverse events including edema and congestive heart failure.

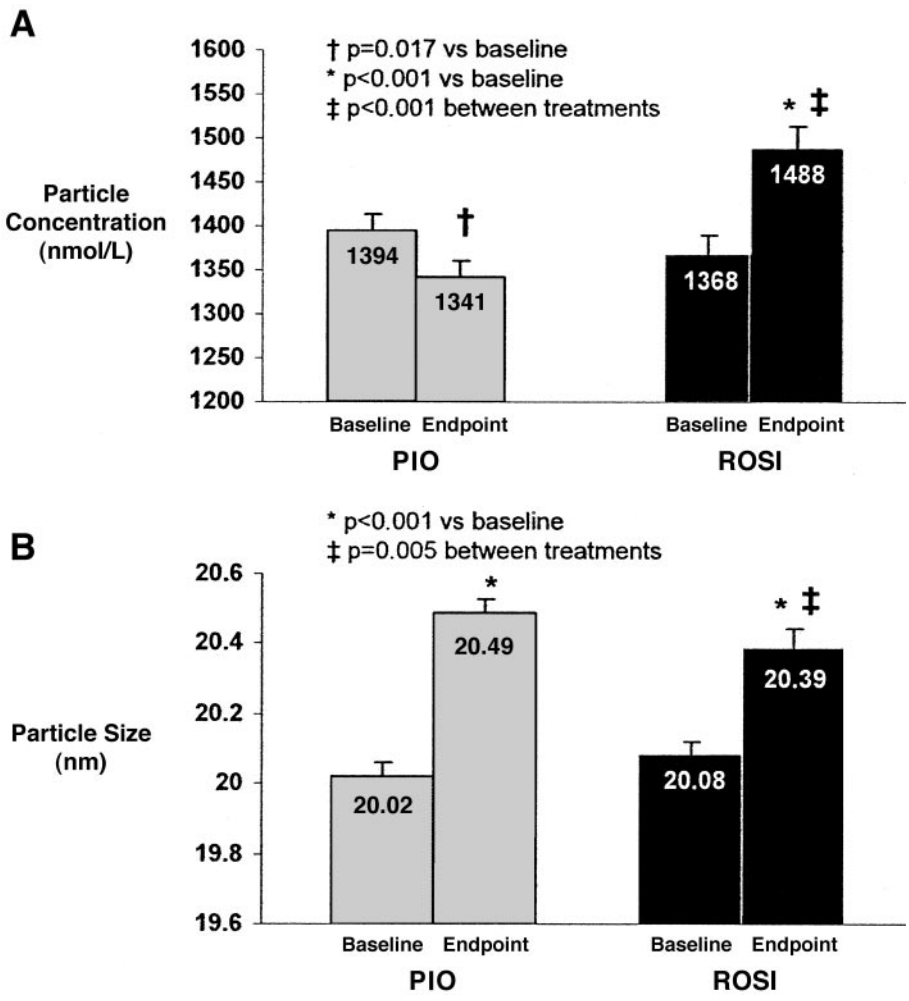

Figure 3—*Comparison of mean LDL particle concentration* (A) *and particle size* (B) *at baseline and end point (24 weeks) for patients treated with pioglitazone (PIO) and rosiglitazone (ROSI). Vertical bars represent SE.*

CONCLUSIONS — This prospective, randomized, multicenter, double-blind clinical trial demonstrates that pioglitazone and rosiglitazone exert different effects on plasma lipids. Pioglitazone is associated with significant improvements versus rosiglitazone in triglyceride, HDL cholesterol, non-HDL cholesterol, and LDL particle concentrations and LDL particle size, despite similar effects on glycemic control and surrogate measures of insulin resistance.

The different lipid responses to maximal monotherapy doses of pioglitazone and rosiglitazone observed in this study are consistent with results from prior, less well-controlled comparison studies and the large, randomized, multicenter placebo-controlled trials for pioglitazone (23,28,29). Additionally, a meta-analysis of these studies (18) demonstrates results very similar to those of our study. The mechanism(s) by which these agents exert differential effects on the lipid profile are not clearly understood, and studies are underway to elucidate these mechanisms.

The effects of lipids on cardiovascular disease are well known. At increased concentrations, LDL cholesterol, total cholesterol, and triglycerides, and HDL cholesterol at decreased concentrations, are known to be risk factors for CVD in the general population (8–11) and in subjects with type 2 diabetes (34). Although lowering LDL cholesterol is the primary target according to both the National Cholesterol Education Program Adult Treatment Panel III (35,36) and American Diabetes Association guidelines (12), raising HDL cholesterol is a secondary target, the benefit of which was demonstrated by the Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT) study (37), in which increasing HDL cholesterol and lowering triglycerides with the fibrate gemfibrozil decreased cardiovascular events by 24%. In subjects with hypertriglyceridemia (>200 mg/dl), lowering non-HDL cholesterol to levels <130 mg/dl is recommended for high-risk subjects by the National Cholesterol Education Program Adult Treatment Panel III (36). In our study, rosiglitazone raised non-HDL cholesterol levels and pioglitazone did not.

The dyslipidemia of diabetes is usually characterized by a combination of increased triglyceride and decreased HDL cholesterol levels and, most often, near-normal LDL cholesterol concentrations (38). However, insulin resistance with or without hyperglycemia is associated with qualitative changes in the composition of LDL particles shown to be associated with greater risk for atherosclerosis and cardiovascular disease (39). These changes in the LDL particles include a decrease in particle size and a greater density of each particle concomitant with a relative decrease in the cholesterol content of each particle (40). It is generally accepted that the increase in triglyceride levels in type 2 diabetes is in part responsible for these atherogenic changes in the LDL profile (5,7,11,41,42).

In the current study, pioglitazone and rosiglitazone differed significantly with opposing effects on triglycerides. Although both agents increased HDL cholesterol, pioglitazone increased HDL cholesterol more. Furthermore, pioglitazone caused a shift from small, dense LDL particles to larger, more buoyant LDL particles. This change in the size of the particles was accompanied by a decrease in particle concentration (particle number), an effect not observed with rosiglitazone. Rosiglitazone was associated with an increase in LDL particle size as well as an increase in triglyceride levels and LDL particle numbers. These observed differences in the lipid effects between pioglitazone and rosiglitazone raise several mechanistic questions. First, the shift toward larger LDL particles observed with rosiglitazone therapy cannot be due to effects on triglyceride levels. Secondly, the increase in LDL by pioglitazone can only be explained by increases in particle size, as the measured number of LDL particles

was slightly reduced. The greater increase in LDL observed with rosiglitazone is the result of both increases in particle size and particle number. These observations suggest that previous speculation (43,44) that differences in lipid effects between pioglitazone and rosiglitazone might be due to differential effects on particle size are no longer tenable.

Finally, in light of the recent guidelines, subjects with diabetes often are prescribed lipid-lowering medication, most frequently a statin. However, subjects in this study were not treated with such therapy. This study was purposely designed to eliminate the confounding influence of concomitant glucose-lowering and lipid-lowering medications to allow for a clear assessment of the glycemic and lipid effects of the two thiazolidinediones. Simvastatin, when added to either pioglitazone or rosiglitazone, produced similar mean lipid changes from baseline with both these thiazolidinediones, suggesting that differences between these agents would be preserved with concomitant statin therapy (45). A current, ongoing study named COMPLEMENT has been designed to assess these parameters in subjects with diabetes who are simultaneously taking a statin (46).

In summary, the current study demonstrates that pioglitazone and rosiglitazone differ in their effects on triglyceride, HDL cholesterol, non-HDL cholesterol, and LDL cholesterol particle concentrations and particle size. These differences were observed despite the finding that these agents produced similar improvements in many of the nonlipid CHD/CVD risk factors associated with insulin resistance and type 2 diabetes (A1C, fasting plasma glucose, fasting insulin levels, homeostasis model assessment of insulin resistance, PAI-1, and C-reactive protein). Whether these differences in lipid effects translate into differences for the risk of CVD is not clear. Although no trials directly comparing the effects of pioglitazone and rosiglitazone on CVD outcomes are underway, multiple ongoing trials are evaluating CVD event reduction with either pioglitazone or rosiglitazone (Prospective Pioglitazone Clinical Trial in Macrovascular Events [PROactive] [47], Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of glycemia in Diabetes [RECORD] [48], and the Rationale for the Bypass Angioplasty Revascularization Investigation 2 Diabetes [BARI 2D] trial [49]). These studies should provide insight into the cardiovascular benefits of the two drugs.

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