An Observational Study of the Effect of Two Thiazolidinediones on Blood Lipid Levels: Rosiglitazone and Pioglitazone in Routine Clinical Practice

Deborah Griffis, PharmD,^{1*} Trent McLaughlin, PhD,² Riad Dirani, PhD,³ and Rob Thwaites, MS³

¹AdvancePCS, Phoenix, Arizona, ²NDCHealth, Phoenix, Arizona, and

³GlaxoSmithKline, Philadelphia, Pennsylvania

ABSTRACT

Background: Rosiglitazone maleate and pioglitazone hydrochloride are established antihyperglycemic agents that are effective when used as monotherapy or in combination with other medications. However, the data regarding the effects of these agents on blood lipid levels are contradictory.

Objective: The aim of this study was to determine whether the use of rosiglitazone and pioglitazone in clinical practice is associated with any changes in blood lipid levels.

Methods: A retrospective chart review using electronic medical record data was conducted of patients with type 2 diabetes mellitus who were newly treated with either rosiglitazone or pioglitazone and had 1 lipid measurement within 6 months prior to and 12 months following initial thiazolidinedione (TZD) therapy. Outcome measures were mean changes in low- and high-density lipoprotein cholesterol (LDL-C and HDL-C, respectively). To control for differences in baseline characteristics and/or selection bias, the treatment cohorts were compared using multivariate statistical techniques.

Results: A total of 371 patients were included in the study; the pioglitazone cohort comprised 148 patients (82 women, 66 men; mean [SD] age, 64.9 [10.8] years) and the rosiglitazone cohort comprised 223 patients (113 men, 110 women; mean [SD] age, 66.1 [11.9] years). Pioglitazone-treated patients had a statistically higher mean baseline LDL-C compared with rosiglitazone-treated patients (125.0 mg/dL vs 116.6 mg/dL; $P = 0.04$). On average, LDL-C levels decreased over the study period, with no significant differences between the 2 cohorts (9.9 mg/dL vs 4.3 mg/dL for pioglitazone and rosiglitazone, respectively), although changes in both cohorts were statistically significant ($P < 0.001$).

*At the time the study was conducted, Deborah Griffis, PharmD, was an employee of NDCHealth, Phoenix, Arizona.

Accepted for publication February 10, 2004.

Reproduction in whole or part is not permitted.

0011-393X/04/\$19.00

Conclusions: TZD therapy appears to be associated with a small decrease in LDL-C within the first 6 months after initiation. No differences in changes in LDL-C or HDL-C could be discerned between patients treated with rosiglitazone compared with pioglitazone. (*Curr Ther Res Clin Exp.* 2004;65:149–160) Copyright © 2004 Excerpta Medica, Inc.

Key words: thiazolidinedione, pioglitazone, rosiglitazone.

INTRODUCTION

Approximately 16 million Americans have diabetes mellitus (DM).¹ This number is expected to rise dramatically in the upcoming years as the population ages and Americans grow more obese.¹ Worldwide estimates have stated that ~200 million people have the disease, with >80% of these patients having type 2 DM.² Patients with DM are at increased risk for developing serious long-term complications, including microvascular and cardiovascular disease. It is well established that achieving and maintaining control of blood glucose is necessary to protect against DM-related complications.^{3,4} When diet and exercise regimens fail to maintain glycemic control, treatment with antidiabetic agents is necessary. Patients with type 2 (ie, insulin-resistant) DM are typically treated with oral hypoglycemic agents, including metformin, acarbose, sulfonylureas (SU), and thiazolidinediones (TZDs), either alone or in combination with insulin.^{5,6}

TZDs are the newest class of oral antidiabetic agents, and they directly improve insulin resistance in adipose tissue, skeletal muscle, and the liver. TZDs have been proved to be valuable agents in the antidiabetic armamentarium because they are effective as monotherapy or in combination with other agents, and they are not associated with hypoglycemia.⁷ Troglitazone, the first TZD available on the US market, was withdrawn in 2000 because of concerns about hepatotoxicity.

Today, 2 TZDs—pioglitazone hydrochloride and rosiglitazone maleate—are available for use in the United States. Evidence from clinical trials^{8,9} suggests that the effectiveness of these products as monotherapy is similar to that of single-agent SU or metformin therapy.

Insulin resistance seen in patients with DM is associated with increased low-density lipoprotein cholesterol (LDL-C) and triglyceride (TG) levels and reduced levels of high-density lipoprotein cholesterol (HDL-C).¹⁰ Hypertriglyceridemia and/or hypercholesterolemia are considered risk factors for cardiovascular disease.¹¹ Although both currently marketed TZDs have been shown to be effective in decreasing and controlling blood glucose levels, the effect of these drugs on lipid levels is not as clear. Trials^{12–15} of TZDs in humans have resulted in conflicting reports about the influence of these agents on total cholesterol (TC) levels. There are also conflicting reports^{16–19} about the effects of these agents on HDL-C and LDL-C levels.

A recent analysis²⁰ comparing the changes in cholesterol levels with rosiglitazone versus pioglitazone found decreased TC and LDL-C levels in patients treated with pioglitazone and increased TC and LDL-C levels in patients treated with rosiglitazone. In that nonrandomized, retrospective study, the authors analyzed changes in lipid levels over the course of the study, but they did not control for baseline lipid levels in the 2 treatment groups. A head-to-head, prospective, randomized clinical trial of the 2 agents would be the best way to determine whether they have different effects on lipid levels. In the absence of such a trial, we conducted an observational study controlling for several potential confounding variables to assess changes in lipid levels seen in patients with type 2 DM treated with rosiglitazone or pioglitazone.

PATIENTS AND METHODS

This retrospective database analysis used electronic medical records (EMRs) extracted from the GE Medical Systems Centricity Physician Office (GE Medical Clinical Data Services, Portland, Oregon). This database captures longitudinal clinical information directly from the clinical encounter, including demographic characteristics, diagnoses, medications, cardiac risk factors, tests, test results, procedures, functional status, and other data elements. At the time the analysis was conducted, data were available for ~400,000 patients receiving ambulatory care (mainly primary care) from >500 physicians in practices in Oregon, Arizona, Texas, Iowa, Virginia, New Hampshire, and Maine. Data were entered into the database daily; therefore, current data were available for research as were historical data from patient encounters back to the date the physician's practice initiated use of the EMR system.

All patient identifiers were encrypted and certified 100% HIPAA (Health Insurance Portability and Accountability Act) compliant. Contributing practices reviewed the study plan prior to initiation of the research and were given the opportunity to opt out.

Patients aged ≥ 18 years who had a documented diagnosis of type 2 DM in their problem list (ie, the list of medical conditions/reasons for care), were treated with rosiglitazone* or pioglitazone[†] from January 1, 2000, through June 30, 2001, and who had ≥ 1 lipid measurement within 6 months prior to and 12 months following initiation of therapy were considered eligible for analysis. Patients who had used troglitazone at any time were excluded from the analysis.

Outcomes of interest for this analysis included plasma LDL-C and HDL-C levels. In addition to lipid levels and glycosylated hemoglobin levels, the following variables were collected for each patient meeting the inclusion criteria: age, sex, body weight, comorbid conditions, use of other hypoglycemic and/or

*Trademark: Avandia® (GlaxoSmithKline, Philadelphia, Pennsylvania).

[†]Trademark: Actos® (Takeda Pharmaceuticals North America, Inc., Lincolnshire, Illinois).

lipid-regulating drugs (LRDs), and insurance type. Comorbid conditions were identified from each patient's problem list.

Concomitant use of LRDs could have significantly influenced any observed changes in blood lipid levels. Therefore, patients receiving either rosiglitazone or pioglitazone were classified into groups according to whether or not they were prescribed an LRD at baseline. This variable was used as a covariate in the multivariate analyses.

To accurately assess the effect of the medication on blood lipid levels, patients were stratified into groups based on their initial lipid values. LDL-C was used to classify patients into the following groups, according to the National Cholesterol Education Program (NCEP) III²¹ categories: very high (≥ 190 mg/dL), high (160–<190 mg/dL), borderline high (130–<160 mg/dL), near optimal (100–<130 mg/dL), and optimal (<100 mg/dL). Because patients at or near optimal lipid levels might exhibit smaller decreases in LDL-C, a subanalysis comparing changes in lipid levels between the 2 drugs was performed by removing these patients from the sample. Patients' lipid levels were recorded as part of a regular physician visit using standard collection and analytical techniques.

Statistical Analysis

Descriptive statistics comparing patient demographic characteristics between the 2 treatment groups were generated. Absolute changes in LDL-C and HDL-C were calculated for both groups. Changes in lipid levels for both groups were also generated for the sample in which patients who had reached their optimal LDL-C level before TZD initiation were removed. Mean changes in lipid levels in the rosiglitazone and pioglitazone cohorts were compared using univariate *t* tests. A significance level of 0.05 was used for all analyses. SAS software version 8.1 (SAS Institute Inc., Cary, North Carolina) was used for all statistical analyses.

Multivariate models were used to control for several factors that may be related to change in lipid levels and to test for differences between treatment groups. Mean changes in LDL-C and HDL-C were the dependent variables and were calculated as (starting value) – (ending value). A total of 6 models that tested changes in LDL and HDL were constructed: the initial (overall) models that included all patients and 2 pairs of models for patients pretreated with an LRD and for changes in LDL-C and HDL-C for patients who were not prescribed an LRD prior to TZD initiation.

RESULTS

A total of 371 patients were included in the study; the pioglitazone cohort comprised 148 patients (82 women, 66 men; mean [SD] age, 64.9 [10.8] years) and the rosiglitazone cohort comprised 223 patients (113 men, 110 women; mean [SD] age, 66.1 [11.9] years) (Table I).²¹ No significant differences were identified between the 2 cohorts at baseline in demographic characteristics, body weight, NCEP III category, or use of LRDs.

Table I. Baseline demographic and clinical characteristics of study patients (N = 371).

Characteristic	Pioglitazone (n = 148)	Rosiglitazone (n = 223)
Age		
Mean (SD), y	64.9 (10.8)	66.1 (11.9)
Age category, no. (%)		
18–44 y	8 (5.4)	8 (3.6)
45–54 y	24 (16.2)	28 (12.6)
55–64 y	36 (24.3)	62 (27.8)
65–74 y	46 (31.1)	58 (26.0)
75+ y	34 (23.0)	67 (30.0)
Sex, no. (%)		
Women	82 (55.4)	110 (49.3)
Men	66 (44.6)	113 (50.7)
Body weight, mean (SD), kg		
Women	87.1 (18.5) (n = 78)	87.6 (22.0) (n = 103)
Men	98.2 (16.7) (n = 55)	98.2 (16.5) (n = 108)
LRD use, no. (%)	84 (56.8)	139 (62.3)
Starting TZD dose, no. (%) [*]		
Low	67 (45.3) [†]	16 (7.2)
Medium	48 (32.4)	183 (82.1)
High	33 (22.3)	24 (10.8)
NCEP III ²¹ category, no. (%) [‡]		
Optimal	39 (26.4)	78 (35.0)
Near optimal	52 (35.1)	72 (32.3)
Borderline high	30 (20.3)	44 (19.7)
High	20 (13.5)	21 (9.4)
Very high	7 (4.7)	7 (3.1)
Diagnoses on record, no. (%) [§]		
Dyslipidemia	26 (17.6)	26 (11.7)
Hypertension	21 (14.2)	14 (6.3)
Obesity	9 (6.1)	8 (3.6)
Coronary artery disease	8 (5.4)	13 (5.8)

LRD = lipid-regulating drug; TZD = thiazolidinedione; NCEP = National Cholesterol Education Program.

^{*}Low: pioglitazone = 15 mg, rosiglitazone = 2 mg; medium: pioglitazone = 30 mg, rosiglitazone = 4 mg; high: pioglitazone = 45 mg, rosiglitazone = 8 mg.

[†] $P < 0.05$ versus rosiglitazone group.

[‡]NCEP categories in terms of low-density lipoprotein cholesterol level: optimal = <100 mg/dL; near optimal = 100–<130 mg/dL; borderline high = 130–<160 mg/dL; high = 160–<190 mg/dL; very high = ≥190 mg/dL.

[§]As recorded in patient problem list (ie, the list of medical conditions/reasons for care).

The initial TZD dose was significantly different between the 2 groups: pioglitazone-treated patients were more likely to receive a lower starting dose than rosiglitazone-treated patients ($P < 0.05$) (Table I). Baseline hypoglycemic and LRD use are presented in **Table II**. The 2 cohorts were similar with respect to use of other medications prior to the index date.

As shown in **Table III**, the mean (SD) baseline LDL-C values for pioglitazone-treated patients were significantly higher than that for the rosiglitazone cohort (125.0 [40.2] mg/dL vs 116.6 [35.3] mg/dL; $P = 0.04$), although, as indicated in Table I, this did not translate into significant differences with respect to NCEP III category. Of patients receiving LRD treatment at baseline, a greater proportion of rosiglitazone-treated patients were in the NCEP III optimal category compared with similar pioglitazone-treated patients (46.8% vs 31.0%; $P = 0.02$). No statistically significant differences were observed with respect to baseline HDL-C values.

Following the initiation of TZD treatment, most patients experienced a 4- to 10-mg/dL decrease in LDL-C, although wide variability in this change was found both within and between cohorts, as evidenced by the large SDs. Because of this, no statistically significant differences in mean change could be discerned between the 2 cohorts. The fact that the mean baseline LDL-C was significantly

Table II. Baseline use of concomitant drugs.*

Drug Type	Pioglitazone (n = 148)	Rosiglitazone (n = 223)
Hypoglycemic drugs, no. (%)		
Sulfonylureas	74 (50.0)	117 (52.5)
Metformin	66 (44.6)	111 (49.8)
Insulin	22 (14.9)	25 (11.2)
LRDs, no. (%)		
HMG-CoA reductase inhibitors	72 (48.6)	130 (58.3)
Bile acid sequestrants	0 (0.0)	3 (1.3)
Other LRDs	18 (12.2)	19 (8.5)
Postindex [†] (new starts)		
Hypoglycemic drugs, no. (%)		
Metformin	19 (12.8)	22 (9.9)
Sulfonylureas	15 (10.1)	25 (11.2)
Insulin	8 (5.4)	17 (7.6)
LRDs, no. (%)		
HMG-CoA reductase inhibitors	26 (17.6)	36 (16.1)
Bile acid sequestrants	0 (0.0)	0 (0.0)
Other LRDs	1 (0.7)	3 (1.3)

LRDs = lipid-regulating drugs; HMG-CoA = 3-hydroxy-3-methylglutaryl coenzyme A.

*No significant between-group differences were found.

[†]Postindex = 12-month period after initiation of pioglitazone or rosiglitazone therapy.

Table III. Thiazolidinedione (TZD) dose titration and laboratory findings.*

	Pioglitazone (n = 148)	Rosiglitazone (n = 223)
TZD dose titration, no. (%) [†]		
Decrease	4 (2.7)	13 (5.8)
No change	106 (71.6)	152 (68.2)
Increase	38 (25.7)	58 (26.0)
LDL-C, mean (SD), mg/dL		
Baseline	125.0 (40.2)	116.6 (35.3) [‡]
Study end	115.0 (34.6)	112.3 (34.7)
Change	−9.9 (43.5)	−4.3 (38.0)
Change, excluding patients with optimal LDL-C at baseline	−19.5 (42.3) [§]	−15.7 (33.9) [§]
HDL-C, mean (SD), mg/dL		
Baseline	43.9 (10.8)	45.2 (12.8)
Study end	46.5 (11.1)	46.6 (13.9)
Change	2.5 (7.9)	1.4 (8.8)
Change, excluding patients with optimal LDL-C at baseline	2.2 (3.6)	0.9 (9.4)
HbA _{1c} , mean (SD), %		
Baseline	8.6 (1.8)	8.5 (1.8)
Study end	7.5 (1.6)	7.5 (1.5)
Change	−1.0 (1.7)	−1.0 (1.8)
Change, excluding patients with optimal LDL-C at baseline	−1.2 (1.8)	−1.0 (1.5)

LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol; HbA_{1c} = glycosylated hemoglobin.

*Mean (SD) no. of days between baseline and ending measurements: pioglitazone, 151 (207.5) days; rosiglitazone, 245 (201.4) days.

[†]As measured by daily dosage recorded at index date versus daily dosage recorded at last LDL-C measurement.

[‡] $P = 0.04$ versus pioglitazone group.

[§] $P < 0.001$ versus baseline.

lower for the rosiglitazone cohort ($P = 0.04$) may have impacted the results. To address this, the mean change in LDL-C was compared between the 2 cohorts after excluding patients in the NCEP III optimal category at baseline; again, no statistically significant differences were identified between the 2 cohorts (9.9 mg/dL vs 4.3 mg/dL for pioglitazone and rosiglitazone, respectively), although changes in both cohorts were statistically significant (both $P < 0.001$).

HDL-C did not change significantly in either study cohort after TZD treatment, nor was the difference between the 2 cohorts statistically significant.

After differences in baseline characteristics in the 2 cohorts were accounted for, no statistically significant changes in LDL-C or HDL-C were found between the 2 cohorts. This was true for all patients, regardless of whether they were receiving LRDs at baseline (Table IV).²² Factors that were correlated with

Table IV. Multivariate analyses of change in low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C).^{*,†}

Model	Variable	Referent	Parameter Estimate	SE
Change in LDL-C				
LRD use at baseline ($r = 0.3982$)	Pioglitazone ($n = 84$)	Rosiglitazone ($n = 139$)	-20.89	23.00
No LRD use at baseline ($r = 0.3807$)	Pioglitazone ($n = 64$)	Rosiglitazone ($n = 84$)	12.54	25.62
All patients ($r = 0.3653$)	Pioglitazone ($n = 148$)	Rosiglitazone ($n = 223$)	-2.75	16.62
Change in HDL-C				
LRD use at baseline ($r = 0.1130$)	Pioglitazone ($n = 84$)	Rosiglitazone ($n = 139$)	4.47	5.89
No LRD use at baseline ($r = 0.2001$)	Pioglitazone ($n = 64$)	Rosiglitazone ($n = 84$)	-9.35	7.28
All patients ($r = 0.1061$)	Pioglitazone ($n = 148$)	Rosiglitazone ($n = 223$)	-3.99	4.12

LRD = lipid-regulating drug.

*Covariates: age, sex, interval between measurements, glycosylated hemoglobin >8%, baseline body weight, Charlson Comorbidity Index,²² baseline LDL-C/HDL-C, use of LRD (for overall models), and insurance type.

†No statistically significant between-group differences were found.

change in LDL-C (HDL-C) levels included baseline body weight, baseline LDL-C (HDL-C) level, and adding a new lipid-lowering therapy to the patient's treatment regimen.

DISCUSSION

This study was undertaken to compare rosiglitazone and pioglitazone use and performance in the clinical practice setting. Based on these findings, there is some evidence to suggest that TZD treatment may positively impact LDL-C; however, other factors, such as LRDs, as expected, appear to have greater significance. As hypothesized, changes in LDL-C and HDL-C levels were not significantly different between the 2 groups when the potential effect of other confounding variables was controlled for.

Our findings suggest that rosiglitazone and pioglitazone are similar in terms of their impact on lipid profiles. This appeared to be true among patients who were previously treated with antihyperlipidemic therapy as well as for those who did not receive treatment prior to the initiation of pioglitazone or rosiglitazone therapy. In a retrospective chart review, Boyle et al¹⁹ suggested that treatment with pioglitazone was associated with greater beneficial effects on blood lipid levels than treatment with rosiglitazone. The study suggested that the treatment groups were similar with respect to a variety of baseline patient demographic characteristics; however, the authors reported statistics on mean values and did not report similarities and/or differences among the distribution of starting values. In the present analysis, the most significant predictor of change in LDL-C or HDL-C was baseline level, with the greatest decrease in LDL-C being observed in patients with the highest baseline level. This is consistent with the results of other studies. Results of a literature review²⁰ suggested that the impact of rosiglitazone and pioglitazone on serum lipid levels, particularly TG, depends largely on the baseline lipid levels and that both drugs reduce serum TG levels when baseline levels are elevated. This finding is consistent with the results reported here; overall trends suggested a potential benefit of TZD treatment with respect to LDL-C reduction. When patients with optimal LDL-C at baseline were excluded, a greater reduction in LDL-C was observed compared with the overall results. In both instances, no statistically significant differences were discerned between pioglitazone and rosiglitazone with respect to LDL-C reduction.

In the present study, patients who were receiving drugs that directly impacted lipid profiles were included. Because the study sample size prohibited us from excluding patients who had changes to their LRD regimen, we attempted to control for this influence by including use of new drugs in the models. In a similar analysis,¹⁹ which also allowed patients to receive concurrent antihyperlipidemic therapy, the authors tried to control for this by requiring that patients maintain a consistent lipid-lowering regimen. However, no attempt was made to ascertain the duration of therapy prior to initiating TZD

therapy in that analysis. This is an important distinction because the maximum benefits of antihyperlipidemic therapy may not be seen for 4 to 6 weeks. Because this was an observational study of patients treated under actual practice conditions, the trends presented in this analysis should not be assumed to denote causality. Because the data were retrospectively collected from EMRs, it was not possible to determine or account for differences in LDL-C measurement. In other words, because values were not measured directly but were taken from the patient records, there might have been differences in how LDL-C was determined. Similarly, TG levels were not available for all study patients; therefore, this analysis focused only on LDL-C and HDL-C levels.

One noteworthy bias that could not be addressed in this analysis, due to small sample size, was the difference in mean dosage between the 2 cohorts. Physicians appeared to be more willing to try different dosing regimens with pioglitazone than with rosiglitazone; the vast majority of rosiglitazone-treated patients were given the same dose. Further analysis should focus on comparable doses to confirm the results observed here.

Despite these limitations, the results of the present analysis are consistent with those observed in a number of randomized, controlled trials^{23–25}. TZD treatment appears to have a positive impact on lipid profiles, and there is a class effect with TZDs (ie, there are only negligible differences between the individual agents in the class).

CONCLUSIONS

While there have been some recently published reports suggesting that the 2 currently marketed TZDs differ with respect to impact on glycemic control and/or lipid profiles, this analysis of patients treated in the general practice setting could not identify any such differences. Potential reasons for the disparity in results between this analysis and previous work include differences in study design and/or methodology and the time period(s) used. Future research in this area would benefit from larger samples; however, it is imperative that factors such as use of LRD therapy and differing dosing of the study drugs are taken into account.

REFERENCES

1. Skyler JS, Oddo C. Diabetes trends in the USA. *Diabetes Metab Res Rev*. 2002;18 (Suppl 3):S21–S26.
2. Eschwege E, Simon D, Balkau B. The growing burden of diabetes in the world population. *IDF Bulletin*. 1997;42:14–19.
3. Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med*. 1993;329:977–986.
4. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of com-

- plications in patients with type 2 diabetes (UKPDS 33) [published correction appears in *Lancet*. 1999;354:602]. *Lancet*. 1998;352:837–853.
5. Lebovitz HE. Treating hyperglycemia in type 2 diabetes: New goals and strategies. *Cleve Clin J Med*. 2002;69:809–820.
 6. Gutowski C. Understanding new pharmacologic therapy for type 2 diabetes. *Nurse Pract*. 1999;24:15–18, 21–22, 24–25.
 7. Goldstein BJ. Differentiating members of the thiazolidinedione class: A focus on efficacy. *Diabetes Metab Res Rev*. 2002;18(Suppl 2):S16–S22.
 8. Schneider R, Egan J, Houser V, et al. Pioglitazone is effective in the treatment of patients with type 2 diabetes. *Diabetes*. 1999;48(Suppl 1):A109. Abstract.
 9. Lebovitz HE, Dole JF, Patwardhan R, et al. Rosiglitazone monotherapy is effective in patients with type 2 diabetes [published corrections appear in *J Clin Endocrinol Metab*. 2001;86:1659; *J Clin Endocrinol Metab*. 2002;2:iv]. *J Clin Endocrinol Metab*. 2001;86:280–288.
 10. Parker JC. Troglitazone: The discovery and development of a novel therapy for the treatment of type 2 diabetes mellitus. *Adv Drug Deliv Rev*. 2002;54:1173–1197.
 11. Austin MA. Plasma triglyceride as a risk factor for coronary heart disease: The epidemiological evidence and beyond. *Am J Epidemiol*. 1989;129:249–259.
 12. Mimura K, Umeda F, Hiramatsu S, et al. Effect of a new oral hypoglycemic agent (CS-045) on metabolic abnormalities and insulin resistance in type 2 diabetes. *Diabet Med*. 1994;11:685–691.
 13. Schwartz S, Raskin P, Fonseca V, Graveline JF. Effect of troglitazone in insulin-treated patients with type II diabetes mellitus. *N Engl J Med*. 1998;338:861–866.
 14. Ghazzi MN, Perez JE, Antonucci TK, et al, for the Troglitazone Study Group. Cardiac and glycemic benefits of troglitazone treatment in NIDDM. *Diabetes*. 1997;46:433–439.
 15. Khan MA, St Peter JV, Xue JL. A prospective, randomized comparison of the metabolic effects of pioglitazone or rosiglitazone in patients with type 2 diabetes who were previously treated with troglitazone. *Diabetes Care*. 2002;25:708–711.
 16. Vestergaard H, Lund S, Pedersen O. Rosiglitazone treatment of patients with extreme insulin resistance and diabetes mellitus due to insulin receptor mutations has no effects on glucose and lipid metabolism. *J Intern Med*. 2001;250:406–414.
 17. Freed MI, Ratner R, Marcovina SM, et al, for the Rosiglitazone Study 108 Investigators. Effects of rosiglitazone alone and in combination with atorvastatin on the metabolic abnormalities in type 2 diabetes mellitus. *Am J Cardiol*. 2002;90:947–952.
 18. Gegick CG, Alheimer MD. Comparison of effects of thiazolidinediones on cardiovascular risk factors: Observations from a clinical practice [published correction appears in *Endocr Pract*. 2001;7:330]. *Endocr Pract*. 2001;7:162–169.
 19. Boyle PJ, King AB, Olansky L, et al. 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. *Clin Ther*. 2002;24:378–396.
 20. Lebovitz HE. Differentiating members of the thiazolidinedione class: A focus on safety. *Diabetes Metab Res Rev*. 2002;18(Suppl 2):S23–S29.
 21. National Institutes of Health (NIH) National Cholesterol Education Program. *Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATP III)*. Bethesda, Md: NIH National Heart, Lung, and Blood Institute, 2002. NIH publication 02-5215.
 22. D'Hoore W, Sicotte C, Tilquin C. Risk adjustment in outcome assessment: The Charlson comorbidity index. *Methods Inf Med*. 1993;32:382–387.

23. Lebovitz HE, Dole JF, Patwardhan R, et al, for the Rosiglitazone Clinical Trials Study Group. Rosiglitazone monotherapy is effective in patients with type 2 diabetes. *J Clin Endocrinol Metab.* 2001;86:280–288.
24. Phillips LS, Grunberger G, Miller E, et al, for the Rosiglitazone Clinical Trials Study Group. Once- and twice-daily dosing with rosiglitazone improves glycemic control in patients with type 2 diabetes [published correction appears in *Diabetes Care.* 2001; 24:973]. *Diabetes Care.* 2001;24:308–315.
25. Hirose H, Kawai T, Yamamoto Y, et al. Effects of pioglitazone on metabolic parameters, body fat distribution, and serum adiponectin levels in Japanese male patients with type 2 diabetes. *Metabolism.* 2002;51:314–317.

Address correspondence to: Trent McLaughlin, PhD, NDCHealth, 2394 East Camelback Road, Phoenix, AZ 85016. E-mail: Trent.McLaughlin@ndchealth.com