Thiazolidinediones and Blood Lipids in Type 2 Diabetes


Abstract—We evaluated study population characteristics and treatment effects on blood lipids between studies in which either rosiglitazone (RSG) or pioglitazone (PIO) was investigated in patients with type 2 diabetes. We performed a summary analysis of all published double-blind, placebo-controlled studies with RSG (4 and 8 mg/d) and PIO (15, 30, and 45 mg/d). Data were analyzed by the random-effects model. Nineteen trials met our inclusion criteria, yielding 5304 patients, 3236 in studies with RSG and 2068 in studies with PIO. Subjects treated with PIO were more obese and showed more pronounced hyperglycemia and dyslipidemia (increased triglycerides and decreased HDL cholesterol) at baseline than did subjects treated with RSG. By weighted linear-regression analysis, studies with PIO showed greater beneficial effects on triglycerides, total cholesterol, and LDL cholesterol, after adjustment for the respective lipid levels at baseline. RSG 8 mg/d showed greater increases in total cholesterol and LDL cholesterol than did RSG 4 mg/d. PIO 30 mg/d showed greater reductions in triglycerides than did PIO 15 mg/d. Studies conducted with PIO showed more beneficial effects on blood lipids, but also different study population characteristics in comparison with studies conducted with RSG. Differences in both pharmacologic properties between agents and study population characteristics are likely to have influenced the results. (Arterioscler Thromb Vasc Biol. 2003;23:1744-1749.)

Key Words: thiazolidinediones • rosiglitazone • pioglitazone • lipids • cardiovascular disease

Thiazolidinediones (TZDs) are oral antihyperglycemic agents that reduce insulin resistance in peripheral tissues and decrease hepatic glucose production.1 TZDs are potent, synthetic ligands for peroxisome proliferator-activated receptor gamma-γ (PPAR-γ) activation, which mediates the physiologic response by altering transcription of genes that regulate glucose and lipid metabolism.2–4 Currently, there are 2 TZDs available: rosiglitazone (RSG) and pioglitazone (PIO). Troglitazone has been retracted from the market because of substantially increased risk of severe hepatotoxicity.5–7 The clinical potency of TZDs is correlated closely with their PPAR-γ binding affinity. RSG has a greater PPAR-γ binding affinity than does PIO, which translates to a clinical dose that is ≈1/6th that of PIO.4,8 Accordingly, the maximum recommended dose of 8 mg/d RSG corresponds to the maximum recommended dose of 45 mg/d PIO, whereas the submaximum dose of 4 mg/d RSG corresponds to the 30 mg/d submaximum dose of PIO.

The antihyperglycemic effects of RSG and PIO are well documented. RSG and PIO both demonstrate effective glycemic control when used as monotherapy or in combination with other antihyperglycemic agents.9–12 TZDs also have important nonglycemic effects, such as modulation of lipid metabolism. It has been suggested that RSG and PIO differ in their effects on blood lipids and lipoproteins. Several studies have shown that treatment with PIO is associated with a greater beneficial effect on blood lipid levels than treatment with RSG.13–16 Because dyslipidemia is an important risk factor for atherosclerosis, differential therapeutic modulation of lipid levels might confer a different level of protection from cardiovascular disease in patients with type 2 diabetes.

Several factors need to be considered when interpreting the effects of different TZDs on blood lipids. First, the differences between RSG and PIO might be related to specific pharmacologic properties of these agents. It has been shown that at the same clinical dose, PIO is associated with greater PPAR-α activation than is RSG.17 PPAR-α is the main target for fibrates, a class of lipid-lowering drugs, which mainly reduce triglycerides (TGs) and increase HDL cholesterol (HDL-C).18,19 Second, it is well recognized that the lipid-lowering responses of fibrates and statins are enhanced in patients with more pronounced dyslipidemia at baseline.20,21 Baseline lipid levels might therefore influence the magnitude of treatment effects by TZDs.

We performed a summary analysis of all published double-blind, placebo-controlled studies to evaluate the effects of RSG and PIO on blood lipids in patients with type 2 diabetes. In addition, we critically evaluated study population characteristics between studies conducted with RSG and PIO.

Methods

Selection Criteria
We used PUBMED (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi) to search the MEDLINE database up to December 2002 to identify all.
TABLE 1. General Characteristics of Studies With Rosiglitazone

<table>
<thead>
<tr>
<th>Study</th>
<th>Journal, Year</th>
<th>Total Sample Size, No. (%) females</th>
<th>Monotherapy</th>
<th>Weight-Maintenance Diet</th>
<th>Mean Age, y</th>
<th>Treatment Dose, mg/d</th>
<th>Duration of Treatment, wk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miyazaki et al 23</td>
<td>Diabetologia, 2001</td>
<td>29 (45)</td>
<td>Yes</td>
<td>Yes</td>
<td>55.1</td>
<td>8</td>
<td>12</td>
</tr>
<tr>
<td>Raskin et al 25</td>
<td>Diabetes Care, 2001</td>
<td>313 (44)</td>
<td>No</td>
<td>No</td>
<td>56.8</td>
<td>4 and 8</td>
<td>26</td>
</tr>
<tr>
<td>Lebovitz et al 11</td>
<td>J Clin Endocrinol Metab, 2001</td>
<td>493 (34)</td>
<td>Yes</td>
<td>Yes</td>
<td>60.0</td>
<td>4 and 8</td>
<td>26</td>
</tr>
<tr>
<td>Phillips et al 26</td>
<td>Diabetes Care, 2001</td>
<td>908 (37)</td>
<td>No</td>
<td>No</td>
<td>57.5</td>
<td>4 and 8</td>
<td>26</td>
</tr>
<tr>
<td>Raskin et al 24</td>
<td>Diabetologia, 2000</td>
<td>208 (39)</td>
<td>Yes</td>
<td>No</td>
<td>58.5</td>
<td>4 and 8</td>
<td>8</td>
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<tr>
<td>Nolan et al 27</td>
<td>Diabet Med, 2000</td>
<td>278 (38)</td>
<td>No</td>
<td>No</td>
<td>62.6</td>
<td>4 and 8</td>
<td>8</td>
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<tr>
<td>Wolffenbuttel et al 2</td>
<td>Diabet Med, 2000</td>
<td>375 (44)</td>
<td>No</td>
<td>No</td>
<td>61.3</td>
<td>4</td>
<td>26</td>
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<tr>
<td>Gómez-Perez et al 29</td>
<td>Diab Met Res Rev, 2002</td>
<td>105 (74)</td>
<td>No</td>
<td>No</td>
<td>53.1</td>
<td>4 and 8</td>
<td>26</td>
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<tr>
<td>Fonseca et al 28</td>
<td>JAMA, 2000</td>
<td>339 (32)</td>
<td>No</td>
<td>Yes</td>
<td>58.2</td>
<td>4 and 8</td>
<td>26</td>
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<tr>
<td>Patel et al 30</td>
<td>Diabetes Obes Metab, 1999</td>
<td>155 (31)</td>
<td>Yes</td>
<td>Yes</td>
<td>58.3</td>
<td>4</td>
<td>12</td>
</tr>
<tr>
<td>Carey et al 31</td>
<td>Obes Res, 2002</td>
<td>33 (18)</td>
<td>Yes</td>
<td>Yes</td>
<td>56.1</td>
<td>8</td>
<td>16</td>
</tr>
<tr>
<td>Pooled characteristics</td>
<td></td>
<td>3236 (39)</td>
<td>66%</td>
<td>34%</td>
<td>58.6</td>
<td>56% maximum dose</td>
<td>22</td>
</tr>
</tbody>
</table>

Results

Study Characteristics

Nineteen trials met our inclusion criteria, yielding 5304 patients: 3236 patients in studies with RSG (Table 1)11,12,23–31 and 2068 patients in studies with PIO (Table 2)9,10,32–37 RSG trials and PIO trials were comparable in sex distribution. Subjects in RSG trials were older than those in PIO trials. Sixty-six percent of the subjects in RSG trials received the study medication as monotherapy, whereas only 27% of the subjects did so in the PIO trials. A concurrent weight maintenance diet was more prevalent in PIO trials than in RSG trials (52% vs 34%, respectively). Fifty-six percent of the RSG group and 8% of the PIO group received the maximum recommended dose (8 mg/d for RSG and 45 mg/d for PIO, respectively). Fifty-seven percent received 30 mg/d PIO and 35%, 15 mg/d PIO. Mean duration of treatment was 22 weeks in the RSG trials and 18 weeks in the PIO trials.

Baseline Characteristics

The baseline characteristics of the RSG group, PIO group, and accompanying placebo groups (RSG placebo and PIO placebo) are shown in Table 3. Subjects in the PIO group were significantly younger and more obese than were those in the RSG group. In addition, subjects in the PIO group were characterized by a more pronounced hyperglycemia (increased fasting glucose and glycosylated hemoglobin) and dyslipidemia (increased TGs and decreased HDL-C) than in the RSG group. There were no differences in baseline characteristics between the TZDs and their accompanying placebo groups (RSG vs RSG placebo and PIO vs PIO placebo, respectively).

Treatment Effects of RSG and PIO

χ² tests revealed no statistical evidence of heterogeneity of study results (data not shown). The treatment effects of RSG...
and PIO on blood lipids are shown in Figure 1. The treatment effects are shown as mean changes from baseline of TZD minus placebo for each lipid parameter (ΔRSG placebo and ΔPIO placebo, respectively). PIO was associated with significantly greater beneficial effects on all blood lipid levels.

**Influence of Baseline Lipid Levels on Treatment Effects**

Because subjects in studies with PIO were more dyslipidemic at baseline than were those in studies with RSG, we performed a weighted linear-regression analysis for each lipid parameter. From this analysis, posttreatment TGs (Δ0.45, P < 0.01), TC (Δ0.56, P < 0.001) and LDL-C (Δ0.31, P < 0.05) were higher in studies with RSG than in studies with PIO. However, posttreatment HDL-C was not significantly different between RSG and PIO (Δ0.02, P = NS).

**Treatment Effects of RSG and PIO per Treatment Dose**

Treatment with the respective maximum recommended dose of each TZD was more prevalent in the RSG group than in the PIO group. Therefore, we performed a subgroup analysis in which we evaluated the effects of RSG and PIO on blood lipids per treatment dose (Table 4). The maximum and submaximum recommended doses of RSG (8 and 4 mg/d, respectively) had similar effects on TG and HDL-C. However, RSG at 8 mg/d was associated with significantly greater increases in TC and LDL-C compared with 4 mg/d RSG. PIO 30 mg/d was associated with significantly greater reductions in TG than was PIO 15 mg/d. The different doses of PIO had comparable effects on TC, HDL-C, and LDL-C.

**Subgroup Analysis of Monotherapy Trials and Combination Therapy Trials**

Because monotherapy was more prevalent in studies with RSG, we evaluated the treatment effects of RSG and PIO on blood lipids for monotherapy trials and combination therapy trials separately (Table 5). RSG combination therapy trials showed greater beneficial effects on all lipid levels than did RSG monotherapy trials. PIO combination therapy trials showed similar effects on blood lipids compared with PIO monotherapy trials. PIO monotherapy trials showed greater beneficial effects on all lipid levels compared with RSG monotherapy trials, whereas PIO combination therapy trials showed greater beneficial effects on TGs, TC, and LDL-C than did RSG combination therapy trials.

### Table 2. General Characteristics of Studies With Pioglitazone

<table>
<thead>
<tr>
<th>Study</th>
<th>Journal, Year</th>
<th>Total Sample Size, No. (% females)</th>
<th>Monotherapy Weight-Maintenance Diet</th>
<th>Mean Age, y</th>
<th>Treatment Dose, mg/d</th>
<th>Duration of Treatment, wk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miyazaki et al 32</td>
<td>Diabetes Care, 2001</td>
<td>23 (26)</td>
<td>No</td>
<td>Yes</td>
<td>54.5</td>
<td>45</td>
</tr>
<tr>
<td>Kawamori et al 33</td>
<td>Diab Res Clin Pract, 1998</td>
<td>30 (37)</td>
<td>No</td>
<td>No</td>
<td>54.8</td>
<td>30</td>
</tr>
<tr>
<td>Einhorn et al 34</td>
<td>Clin Ther, 2000</td>
<td>328 (43)</td>
<td>No</td>
<td>Yes</td>
<td>55.6</td>
<td>30</td>
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<tr>
<td>Aronoff et al 9</td>
<td>Diabetes Care, 2000</td>
<td>319 (42)</td>
<td>Yes</td>
<td>No</td>
<td>53.7</td>
<td>15, 30, and 45</td>
</tr>
<tr>
<td>Miyazaki et al 35</td>
<td>Diabetes Care, 2002</td>
<td>45 (47)</td>
<td>Yes</td>
<td>No</td>
<td>54.7</td>
<td>15, 30, and 45</td>
</tr>
<tr>
<td>Rosenblatt et al 36</td>
<td>Coron Artery Dis, 2001</td>
<td>197 (47)</td>
<td>Yes</td>
<td>Yes</td>
<td>54.5</td>
<td>30</td>
</tr>
<tr>
<td>Kipnes et al 10</td>
<td>Am J Med, 2001</td>
<td>560 (41)</td>
<td>No</td>
<td>Yes</td>
<td>56.7</td>
<td>15, 30</td>
</tr>
<tr>
<td>Rosenstock et al 37</td>
<td>Int J Clin Pract, 2002</td>
<td>566 (53)</td>
<td>No</td>
<td>No</td>
<td>57.1</td>
<td>15, 30</td>
</tr>
<tr>
<td>Pool characteristics</td>
<td></td>
<td>2068 (45)</td>
<td>27%</td>
<td>52%</td>
<td>55.8</td>
<td>8% maximum dose</td>
</tr>
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</table>

### Table 3. Baseline Characteristics

<table>
<thead>
<tr>
<th>Study</th>
<th>RSG Studies</th>
<th>PIO Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RSG-Group</td>
<td>RSG-Placebo</td>
</tr>
<tr>
<td>No. of patients</td>
<td>2194</td>
<td>1042</td>
</tr>
<tr>
<td>Age, y</td>
<td>58.6 (0.2) *</td>
<td>58.9 (0.3) †</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>29.7 (0.09) *</td>
<td>29.6 (0.13) †</td>
</tr>
<tr>
<td>Glucose, mmol/L</td>
<td>12.01 (0.07) *</td>
<td>11.63 (0.09) †</td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>9.0 (0.03) *</td>
<td>8.9 (0.05) †</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>2.25 (0.04) *</td>
<td>2.09 (0.05) †</td>
</tr>
<tr>
<td>Cholesterol, mmol/L</td>
<td>5.48 (0.02)</td>
<td>5.46 (0.03)</td>
</tr>
<tr>
<td>HDL-C, mmol/L</td>
<td>1.15 (0.01) *</td>
<td>1.15 (0.01) †</td>
</tr>
<tr>
<td>LDL-C, mmol/L</td>
<td>3.30 (0.02)</td>
<td>3.31 (0.03)</td>
</tr>
</tbody>
</table>

Data are mean (SE). All data were analyzed by using the random-effects model. In this analysis, comparisons between different TZD (RSG vs PIO) and between TZD and placebo (RSG vs placebo and PIO vs placebo) were performed. *P < 0.001 vs RSG-group; †P < 0.001 vs PIO-placebo.
Discussion

In clinical practice, there is much debate concerning the potential different effects of RSG and PIO on blood lipids. This might have important implications, because dyslipidemia is a major risk factor for atherosclerosis in patients with type 2 diabetes. Because no data on prospective, randomized, double-blind PIO versus RSG studies were available, we performed a summary analysis of all published double-blind, placebo-controlled studies with either RSG or PIO. The main outcome of our summary analysis is that studies with PIO showed more beneficial treatment effects on blood lipids in comparison with studies with RSG, but important differences in baseline characteristics existed between the study populations.

During the past several years, TZDs have received increasing attention for treatment of patients with type 2 diabetes. The antihyperglycemic effects of RSG and PIO are well documented and appear to be equivalent between comparable doses of the 2 agents. In addition to glucose lowering, TZDs influence lipid metabolism, most likely by directing a PPAR-γ-mediated change in adipocyte metabolism and insulin sensitivity. Hence, TZDs could potentially modulate the characteristic diabetic dyslipidemia, which is characterized by increased TGs, reduced HDL-C and the predominance of atherogenic, small, dense LDL particles.

### TABLE 4. Treatment Effects of RSG and PIO Per Treatment Dose

<table>
<thead>
<tr>
<th>Treatment</th>
<th>RSG 4 mg/d</th>
<th>RSG 8 mg/d</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔTriglycerides, mmol/L</td>
<td>+0.13 (0.06)</td>
<td>+0.05 (0.07)</td>
</tr>
<tr>
<td>ΔCholesterol, mmol/L</td>
<td>+0.52 (0.04)*</td>
<td>+0.70 (0.04)</td>
</tr>
<tr>
<td>ΔHDL-C, mmol/L</td>
<td>+0.05 (0.01)</td>
<td>+0.06 (0.01)</td>
</tr>
<tr>
<td>ΔLDL-C, mmol/L</td>
<td>+0.34 (0.03)*</td>
<td>+0.48 (0.04)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment</th>
<th>PIO 15 mg/d</th>
<th>PIO 30 mg/d</th>
<th>PIO 45 mg/d</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔTriglycerides, mmol/L</td>
<td>-0.44 (0.08)†</td>
<td>-0.66 (0.07)</td>
<td>-0.38 (0.18)</td>
</tr>
<tr>
<td>ΔCholesterol, mmol/L</td>
<td>-0.01 (0.06)</td>
<td>+0.01 (0.05)</td>
<td>+0.10 (0.15)</td>
</tr>
<tr>
<td>ΔHDL-C, mmol/L</td>
<td>+0.10 (0.02)</td>
<td>+0.09 (0.02)</td>
<td>+0.11 (0.04)</td>
</tr>
<tr>
<td>ΔLDL-C, mmol/L</td>
<td>+0.08 (0.06)</td>
<td>-0.01 (0.04)</td>
<td>+0.15 (0.12)</td>
</tr>
</tbody>
</table>

ΔTriglycerides, ΔCholesterol, ΔHDL-C, and ΔLDL-C is the difference in concentration for triglyceride, total cholesterol, HDL-C and LDL-C, respectively, between the active treatment group and placebo group for each specific TZD dose. Data are mean (SE).

*P<0.05 vs RSG 8 mg/d. †P<0.05 vs PIO 30 mg/d.

### TABLE 5. Treatment Effects of RSG and PIO for Monotherapy Trials and Combination Therapy Trials

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Monotherapy</th>
<th>Combination Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔTriglycerides, mmol/L</td>
<td>+0.21 (0.06)*</td>
<td>-0.06 (0.07)</td>
</tr>
<tr>
<td>ΔCholesterol, mmol/L</td>
<td>+0.68 (0.03)*</td>
<td>+0.46 (0.05)</td>
</tr>
<tr>
<td>ΔHDL-C, mmol/L</td>
<td>+0.03 (0.01)*</td>
<td>+0.11 (0.01)</td>
</tr>
<tr>
<td>ΔLDL-C, mmol/L</td>
<td>+0.43 (0.03)*</td>
<td>+0.33 (0.04)</td>
</tr>
</tbody>
</table>

Pioglitazone trials

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Monotherapy</th>
<th>Combination Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔTriglycerides, mmol/L</td>
<td>-0.51 (0.09)†</td>
<td>-0.57 (0.06)†</td>
</tr>
<tr>
<td>ΔCholesterol, mmol/L</td>
<td>+0.05 (0.07)†</td>
<td>-0.01 (0.05)†</td>
</tr>
<tr>
<td>ΔHDL-C, mmol/L</td>
<td>+0.09 (0.02)†</td>
<td>+0.10 (0.01)</td>
</tr>
<tr>
<td>ΔLDL-C, mmol/L</td>
<td>+0.07 (0.08)†</td>
<td>+0.02 (0.04)†</td>
</tr>
</tbody>
</table>

Data are mean (SE).

*P<0.05 vs combination therapy. †P<0.05 vs RSG trials.
We found that studies with PIO show greater beneficial effects on TGs, TC, and LDL-C than did studies with RSG. Whether the magnitude of these differences is sufficient to produce clinically relevant cardiovascular benefits is an open question. The currently available data support a dose-dependent effect of RSG on TC and LDL-C, whereas PIO might exert dose-related effects on TGs. However, only a small number of subjects were receiving the maximum recommended dose of PIO.

Studies with PIO showed greater beneficial effects on TGs than did studies with RSG. Several factors might explain the differential effects of RSG and PIO on TG levels. First, it has been shown that at the same clinical dose, PIO is associated with greater PPAR-α activation than is RSG.17 PPAR-α is the main target for fibrates, a class of lipid-lowering drugs, which mainly reduce TGs and increase HDL-C.18,19 Increased PPAR-α activation by PIO might explain the observed beneficial effects of PIO on TGs. Second, it is well recognized that the lipid-lowering responses are partly dependent on the baseline characteristics of the study group. The lipid-lowering responses of fibrates and statins are enhanced in patients with more pronounced dyslipidemia at baseline.20,21 In our summary analysis, we have shown that subjects treated with PIO were characterized by a more pronounced dyslipidemia (increased TGs and decreased HDL-C) at baseline than were those treated with RSG. These differences in patient baseline characteristics between studies with RSG and PIO are likely to have influenced the magnitude of the effects on TGs and HDL-C. The observation that after adjustment for baseline HDL-C, there was no longer a statistically significant difference in posttreatment HDL-C between RSG and PIO supports this hypothesis. Moreover, in a recent study with PIO, it was shown that patients with the lowest baseline HDL-C levels responded with HDL-C increases of greater magnitude than did those who had higher HDL-C levels at baseline.36 Studies with RSG showed greater increases in TC and LDL-C compared with studies with PIO, despite similar baseline levels. Why RSG and PIO exert different effects on TC and LDL-C is an open issue. Interestingly, TZDs improve LDL particle density, causing a shift from small, dense LDL particles to larger, buoyant LDL particles, which are less prone to oxidative modification and are therefore, thought to be less atherogenic.39–42 These changes in LDL-C density elicited by TZDs might be more meaningful than the small changes in overall LDL-C levels.

Besides differences in baseline lipids, subjects treated with PIO were more obese and had worse glycemic control at baseline than did subjects treated with RSG. In addition, a concurrent weight maintenance diet was more prevalent in PIO trials than in RSG trials, whereas more subjects in RSG trials were on monotherapy. These factors might also have influenced the results. Interestingly, RSG combination therapy trials showed greater beneficial effects on all blood lipids compared with RSG monotherapy trials. These differences were not observed in studies with PIO. Because monotherapy was more prevalent in RSG trials, this could have contributed to the results. Regrettably, the number of studies was limited, and we could not adjust for other relevant parameters (eg, body mass index, glycemic control) to more reliably estimate the differences in treatment effects between studies with RSG and those with PIO. Although differences in study population characteristics were a confounding factor for our analysis, it should be noted that this is also one of the most interesting findings that is often not accounted for when discussing differential effects of TZDs in clinical practice. Apparently, studies with RSG are performed in a “different patient population” than are studies with PIO. Our results emphasize the importance of study population characteristics when examining clinical data from studies performed with different TZDs. Clearly, there is a need for direct, double-blind comparisons of the 2 agents in the same population.

Our data are in line with several open-label, prospective or retrospective studies on the effects of RSG and PIO on blood lipids.14,15 Khan et al14 performed an open-label, randomized comparison of RSG and PIO in patients previously treated with troglitazone. In that study, conversion to pioglitazone was associated with significant improvements in all lipid levels, whereas conversion to RSG led to significant increases in all lipid levels, despite similar weight increases and glycemic control in the RSG group and PIO group. In a recent retrospective review of randomly selected medical records, it was shown that treatment with PIO was associated with greater beneficial effects on blood lipid levels than was treatment with RSG, despite similar glycemic control.13 However, that article failed to take into account a large body of evidence from double-blind, randomized, placebo-controlled studies, which represent the “gold standard” for clinical analysis.

In conclusion, studies conducted with PIO showed more beneficial effects on blood lipids, but also different study population characteristics, in comparison with studies conducted with RSG. Differences in both pharmacologic properties and study population characteristics between the 2 agents are likely to have influenced the results. When examining the available clinical data from studies performed with different TZDs, it is important to interpret the results in light of the prevailing study population characteristics.

References
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Sala RA, Waris G, Gotto EM. Efficacy and safety of rosiglitazone plus
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Arterioscler Thromb Vasc Biol. 2003;23:1744-1749; originally published online August 7, 2003;
doi: 10.1161/01.ATV.000009521.25968.4D

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