A Meta-analysis Comparing the Effect of Thiazolidinediones on Cardiovascular Risk Factors

Elaine Chiquette, PharmD; Gilbert Ramirez, PhD; Ralph DeFronzo, MD

**Background:** In patients with type 2 diabetes mellitus, all therapeutic options should be evaluated for their effect on cardiovascular risk factors, in addition to glycemic control. We conducted a meta-analysis of randomized controlled trials of pioglitazone hydrochloride and rosiglitazone maleate in patients with type 2 diabetes to evaluate their effect on glycemic control, lipids, blood pressure, and weight.

**Methods:** Randomized controlled trials of patients with type 2 diabetes that compared pioglitazone or rosiglitazone with placebo for 12 weeks were included. Primary analysis was to compare thiazolidinediones with placebo. Secondary analysis was to identify whether treatment with pioglitazone differed from rosiglitazone in any outcomes. We calculated weighted mean differences and 95% confidence intervals.

**Results:** Twenty-three randomized controlled trials were identified. Both thiazolidinediones demonstrated similar hemoglobin A1c level decreases of 1.0% to 1.5% and similar increases in body weight of approximately 3.0 kg. Pioglitazone significantly lowered triglyceride level (–40 mg/dL [–0.45 mmol/L]; 95% confidence interval [CI], –53 to –26 mg/dL [–0.60 to –0.29 mmol/L]), increased high-density lipoprotein cholesterol (HDL-C) level (+4.6 mg/dL [+0.12 mmol/L]; 95% CI, 3.6 to 5.5 mg/dL [0.09 to 0.14 mmol/L]), and showed neutral effect on low-density lipoprotein cholesterol (LDL-C) and total cholesterol levels. Rosiglitazone significantly increased HDL-C level (+2.7 mg/dL [+0.07 mmol/L]; 95% CI, 2.0 to 3.4 mg/dL [0.05 to 0.09 mmol/L]), but increased LDL-C level (+15 mg/dL [+0.39 mmol/L]; 95% CI, 13 to 17 mg/dL [0.34 to 0.44 mmol/L]), total cholesterol level (+21 mg/dL [+0.54 mmol/L]; 95% CI, 18 to 25 mg/dL [0.47 to 0.65 mmol/L]), and demonstrated neutral effect on triglyceride level (–1.1 mg/dL [–0.12 mmol/L]; 95% CI, –14 to 12 mg/dL [–0.16 to 0.14 mmol/L]). No data were available on pioglitazone and blood pressure. Rosiglitazone had a neutral effect on systolic (–0.7 mm Hg; 95% CI, –2.6 to 1.1 mm Hg) and diastolic (–0.8 mm Hg; 95% CI, –1.8 to 0.3) blood pressure.

**Conclusions:** Thiazolidinediones have similar effects on glycemic control and body weight. Pioglitazone produced a more favorable lipid profile. Head-to-head comparative trials as well as longer-term cardiovascular outcome studies are needed to determine whether there are differences in efficacy between the 2 thiazolidinediones.

Arch Intern Med. 2004;164:2097-2104
We identified the citations using a comprehensive search strategy developed by the National Institute for Clinical Excellence for identifying randomized controlled trials pertinent to the thiazolidinediones of interest (rosiglitazone and pioglitazone).11,12 We searched all electronic bibliographic databases from inception to January 2004: MEDLINE, Cochrane Controlled Trials Register, Cochrane database of systematic reviews, and National Health Service Centre for Reviews and Dissemination. In addition, we reviewed New Drug Application submissions from rosiglitazone and pioglitazone available on the Food and Drug Administration Web site and abstracts from recent meetings (ie, American Diabetes Association). Reference lists of all relevant articles also were checked. To be included, the citation had to meet the following 6 criteria: (1) was randomized controlled trial (blind or open), (2) enrolled at least 30 adults with type 2 diabetes, (3) evaluated the effect of rosiglitazone maleate (4 or 8 mg) or pioglitazone hydrochloride (30 or 45 mg) in monotherapy or in combination with other antidiabetic medication (eg, sulfonylureas, metformin, or insulin), (4) evaluated the effect of the drug on HbA1c, (5) had a minimum treatment duration of 12 weeks, and (6) was published in English.

Two reviewers independently performed the screening of studies, selection, validation, data extraction, and the assessment of methodological quality. Disagreements were resolved by consensus. No studies were excluded on the basis of methodological quality.

The primary analysis was to compare pioglitazone and rosiglitazone with placebo for all outcomes (HbA1c, fasting blood glucose [FBG], high-density lipoprotein cholesterol [HDL-C], low-density lipoprotein cholesterol [LDL-C], total cholesterol, triglyceride, systolic and diastolic blood pressure, and weight). The secondary analysis was to identify whether treatment effects with pioglitazone differed from that with rosiglitazone in any outcomes.

We calculated the weighted mean difference (WMD) and 95% confidence interval (CI) for all variables. The treatment effects were calculated as mean changes from baseline for thiazolidinedione treatment minus those of placebo for each outcome. A fixed-effects model approach was used, but in case of heterogeneity, a random-effects model was used. Heterogeneity was diagnosed using the χ² test at a P ≤ .10.

To develop parsimonious meta-regression models, we used simple linear regression to identify significant association between clinical outcomes and their baseline values. Analyses were performed with the statistical package Stata (version 6; Stata Corp, College Station, Tex), using the “metan” and “metareg” routines. The routine metareg extends a random effects meta-analysis to estimate the extent to which 1 covariate (in this case pioglitazone or rosiglitazone) explains heterogeneity in the treatment effects.

RESULTS

Twenty-three randomized controlled trials met the inclusion criteria.14-36 The design of each trial included is presented in Table 1. More than 3000 subjects were enrolled in 10 randomized controlled trials evaluating pioglitazone monotherapy and more than 5000 subjects were enrolled in studies evaluating rosiglitazone. The subjects enrolled in the pioglitazone and rosiglitazone trials were of similar age (56.6 vs 57.5 years) and weight (29.3 vs 29.7 kg). At baseline, subjects in the pioglitazone trials had a slightly higher HbA1c level (9.6% vs 9.2%; P < .05), triglyceride level (245 vs 211 mg/dL [2.77 vs 2.38 mmol/L]; P < .05), LDL-C level (127 vs 121 mg/dL [3.29 vs 3.13 mmol/L]; P = .05), and slightly lower HDL-C level (43.9 vs 45.1 mg/dL [1.14 vs 1.17 mmol/L]; P ≥ .05). The median duration of treatment with the study drug was 16 and 26 weeks for pioglitazone and rosiglitazone, respectively. In most trials, subjects who were receiving prior oral antidiabetic medication were required to discontinue their use at the beginning of the run-in/washout phase. The median duration of the run-in/washout phase was 6 weeks for pioglitazone and 4 weeks for rosiglitazone. A minority of trials reported a weight maintenance strategy within their protocol.

The linear regression results were not significant between any clinical outcome and their respective baseline. Therefore, these variables were kept out of the meta-regression model.

GLYCEMIC CONTROL

The effects of thiazolidinediones on glycemic control, as measured by HbA1c and fasting blood glucose, are presented in Table 2 and Table 3. Both doses of pioglitazone hydrochloride (30 mg/d and 45 mg/d) when used as monotherapy significantly reduced HbA1c level by −0.99% (95% CI, −1.32 to −0.66) and −1.21% (95% CI, −1.79 to −0.62) compared with placebo. The addition of pioglitazone hydrochloride (30 mg/d) to other antihyperglycemic agents (metformin or sulfonylurea) led to greater reductions in HbA1c level by −1.16% (95% CI, −1.41 to −0.90) compared with placebo. Only 1 trial used the maximum dose of pioglitazone hydrochloride (45 mg) in combination with sulfonylurea (HbA1c, −1.56%; 95% CI, −1.96 to −1.16). Both doses of rosiglitazone maleate (4 mg/d and 8 mg/d), when used as monotherapy, resulted in significant reductions in HbA1c level by −0.90% (95% CI, −1.42% to −0.38%) and −1.50% (95% CI, −1.75% to −1.24%), respectively, compared with placebo. The combination of rosiglitazone maleate with metformin, with sulfonylureas or with insulin also resulted in greater reductions in HbA1c level compared with placebo at low (4 mg/d) (Δ = −1.05%; 95% CI, −1.19% to −0.90%) and high (8 mg/d) (Δ = −1.26%; 95% CI, −1.48% to −1.04%) doses. In the pioglitazone hydrochloride monotherapy studies (30 mg/d and 45 mg/d combined), fasting plasma glucose (FPG) concentration decreased on average by 51 mg/dL (−2.83 mmol/L) (95% CI, −62 to −39 mg/dL [−3.44 to −2.16 mmol/L]). When pioglitazone was added to another antidiabetic agent, FPG concentration fell approximately 47 mg/dL (−2.61 mmol) (95% CI, −55 to −39 mg/dL [−3.05 to −2.16 mmol/L]). Rosiglitazone, as monotherapy, decreased FPG level by 57 mg/dL (−3.16 mmol/L) (95% CI, −89 to −25 mg/dL [−4.94 to −1.39 mmol/L]) when used as combination therapy, rosiglitazone reduced the FPG by 50 mg/dL (−2.78 mmol/L) (95% CI, −55 to −45 mg/dL [−3.05 to −2.50 mmol/L]).

Overall, the meta-analysis showed a significant reduction in HbA1c and FPG levels for all
### Table 1. Summary of Included Trials

<table>
<thead>
<tr>
<th>Source</th>
<th>Design</th>
<th>Diet</th>
<th>Age, y</th>
<th>HbA1c, %</th>
<th>LDL-C, mg/dL</th>
<th>TG, mg/dL</th>
<th>HDL-C, mg/dL</th>
<th>BMI</th>
<th>Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pioglitazone</td>
<td>RDBP for 12 wk; run-in/washout: 4 wk; previously diet controlled</td>
<td>No change</td>
<td>56</td>
<td>9.3</td>
<td>NR</td>
<td>150</td>
<td>50</td>
<td>NR</td>
<td>Placebo; P 15 mg/d; P 30 mg/d; P 45 mg/d</td>
</tr>
<tr>
<td>Aronoff et al. 2000</td>
<td>RDBP for 26 wk; run-in/washout: 8 wk; 69% stopped OHA prior to entry</td>
<td>None</td>
<td>54</td>
<td>10.3</td>
<td>134</td>
<td>261</td>
<td>41</td>
<td>NR</td>
<td>Placebo; P 7.5 mg/d; P 15 mg/d; P 30 mg/d; P 45 mg/d</td>
</tr>
<tr>
<td>Scherbaum and Goke, 2002</td>
<td>RDBP for 26 wk; run-in/washout: 10 wk; 61% stopped OHA prior to entry</td>
<td>None</td>
<td>58</td>
<td>147</td>
<td>51</td>
<td>24</td>
<td>Placebo</td>
<td>Placebo</td>
<td>P 15 mg/d; P 30 mg/d; P 45 mg/d; P 100 mg/d</td>
</tr>
<tr>
<td>Herz et al., 2003</td>
<td>RDBP for 16 wk; run-in/washout: 3-5 wk; previously diet controlled</td>
<td>No change</td>
<td>58</td>
<td>7.5</td>
<td>NR</td>
<td>168</td>
<td>46</td>
<td>31</td>
<td>Placebo; P 30 mg/d</td>
</tr>
<tr>
<td>Rosenblatt et al., 2001</td>
<td>RDBP for 16 wk; run-in/washout: 6 wk; 60% stopped OHA prior to entry</td>
<td>None</td>
<td>54</td>
<td>10.5</td>
<td>131</td>
<td>318</td>
<td>40</td>
<td>31</td>
<td>Placebo; R 30 mg/d</td>
</tr>
<tr>
<td>Einhorn et al., 2000</td>
<td>RDBP for 16 wk; run-in/washout: 3-6 wk; 30% stopped OHA prior to entry</td>
<td>Weight maintenance</td>
<td>58</td>
<td>9.6</td>
<td>119</td>
<td>299</td>
<td>42</td>
<td>32</td>
<td>Placebo + Met; P 30 mg/d; P 75 mg/d；</td>
</tr>
<tr>
<td>Kaneko et al., 2000</td>
<td>RDBP for 12 wk; run-in/washout: 4 wk; no stopped OHA prior to entry</td>
<td>None</td>
<td>58</td>
<td>9.8</td>
<td>NR</td>
<td>147</td>
<td>51</td>
<td>24</td>
<td>Placebo</td>
</tr>
<tr>
<td>Lebovitz et al., 2001</td>
<td>RDBP for 12 wk; run-in/washout: 4 wk; no stopped OHA prior to entry</td>
<td>None</td>
<td>57</td>
<td>9.9</td>
<td>NR</td>
<td>150</td>
<td>50</td>
<td>24</td>
<td>Placebo + SU; P 15 mg/d; P 30 mg/d; P 60 mg/d</td>
</tr>
<tr>
<td>Phillips et al., 2000</td>
<td>RDBP for 16 wk; run-in/washout: 3-6 wk; 12% stopped OHA prior to entry</td>
<td>Weight maintenance</td>
<td>57</td>
<td>9.9</td>
<td>125</td>
<td>263</td>
<td>42</td>
<td>32</td>
<td>Placebo + Met; P 15 mg/d; P 30 mg/d; P 60 mg/d</td>
</tr>
<tr>
<td>Patel et al., 1999</td>
<td>RDBP for 12 wk; run-in/washout: 4 wk; ? stopped OHA prior to entry (not given)</td>
<td>Weight maintenance</td>
<td>58</td>
<td>9.0</td>
<td>126</td>
<td>209</td>
<td>48</td>
<td>29</td>
<td>Placebo</td>
</tr>
<tr>
<td>Vonghavaravat et al., 2000</td>
<td>RDBP for 26 wk; run-in/washout: 4 wk; ? stopped OHA prior to entry (not given)</td>
<td>Weight maintenance</td>
<td>55</td>
<td>9.0</td>
<td>130</td>
<td>42</td>
<td>27</td>
<td>Placebo</td>
<td>Placebo + SU; R 8 mg/d; R 16 mg/d</td>
</tr>
<tr>
<td>Gomez-Perez et al., 2000</td>
<td>RDBP for 26 wk; run-in/washout: 10 wk; 40% stopped OHA prior to entry (not given)</td>
<td>Weight maintenance</td>
<td>53</td>
<td>9.9</td>
<td>110</td>
<td>210</td>
<td>50</td>
<td>28</td>
<td>Placebo + Met; R 4 mg/d; R 8 mg/d; R 16 mg/d</td>
</tr>
<tr>
<td>Fonseca et al., 2000</td>
<td>RDBP for 26 wk; run-in/washout: 4-7 wk; 40% stopped OHA prior to entry (not given)</td>
<td>Weight maintenance</td>
<td>58</td>
<td>8.8</td>
<td>115</td>
<td>232</td>
<td>45</td>
<td>30</td>
<td>Placebo + Met; R 4 mg/d; R 8 mg/d; R 16 mg/d</td>
</tr>
<tr>
<td>Raskin et al., 2001</td>
<td>RDBP for 26 wk; run-in/washout: 8 wk; all subjects receiving insulin monotherapy prior to entry</td>
<td>Weight maintenance</td>
<td>57</td>
<td>122</td>
<td>226</td>
<td>45</td>
<td>32</td>
<td>Placebo</td>
<td>Placebo + Ins; R 0.4 mg/d; R 0.8 mg/d</td>
</tr>
<tr>
<td>Hutchman et al., 2000</td>
<td>RDBP for 26 wk; run-in/washout: 4 wk; approximately 30% stopped OHA prior to entry</td>
<td>Weight maintenance</td>
<td>60</td>
<td>9.1</td>
<td>122</td>
<td>243</td>
<td>45</td>
<td>30</td>
<td>Placebo + SU; R 2 mg/d; R 4 mg/d; R 8 mg/d</td>
</tr>
<tr>
<td>Moran et al., 2000</td>
<td>RDBP for 26 wk; run-in/washout: 4 wk; approximately 50% stopped OHA prior to entry</td>
<td>Weight maintenance</td>
<td>58</td>
<td>9.2</td>
<td>126</td>
<td>261</td>
<td>44</td>
<td>30</td>
<td>Placebo + SU; R 2 mg/d; R 4 mg/d; R 8 mg/d</td>
</tr>
<tr>
<td>Lowry et al., 2000</td>
<td>RDBP for 26 wk; run-in/washout: 4-10 wk; approximately 50% stopped OHA prior to entry</td>
<td>Weight maintenance</td>
<td>59</td>
<td>9.2</td>
<td>107</td>
<td>227</td>
<td>46</td>
<td>30</td>
<td>Placebo + Met; R 8 mg/d; R 16 mg/d</td>
</tr>
</tbody>
</table>
thiazolidinedione doses whether used as monotherapy or in combination with other antihyperglycemic agents. The mean HbA1c level at baseline was not significantly related to the observed HbA1c level reduction at end of treatment. Mean baseline HbA1c values were similar across studies, with a mean ± SD of 9.3 ± 0.63; the small variability explains why the relationship between baseline and end of treatment values was not significant at the study level, when a stronger relationship has been consistently observed within studies at the individual patient level. The meta-regression found that the drug grouping did not explain the heterogeneity (P = .84).

**LIPIDS EFFECT**

While both thiazolidinediones had similar effects on glycemic control, pioglitazone showed a neutral to beneficial impact on serum lipid levels, whereas rosiglitazone increased LDL-C, total cholesterol, and HDL-C levels and had a neutral effect on triglyceride level. The meta-regression found that the drug grouping was a significant predictor of heterogeneity for all lipid effects (P < .001); therefore, the results were presented and analyzed separately. Rosiglitazone, when used as monotherapy or in combination with other antihyperglycemic agents, was associated with a significant increase in LDL-C level (+15 mg/dL; +0.39 mmol/L), 95% CI, 13 to 18 mg/dL [0.34 to 0.47 mmol/L]), whereas pioglitazone showed a neutral effect on LDL-C level (−0.4 mg/dL [−0.01 mmol/L]; 95% CI, −5 to 4 mg/dL [−0.13 to 0.10 mmol/L]). None of the pioglitazone studies showed a significant difference compared with placebo on LDL-C, whereas every rosiglitazone study showed a statistically significant increase in LDL-C level (Figure 1). Rosiglitazone treatment had no significant effect on the fasting plasma triglyceride concentration, whereas pioglitazone therapy significantly decreased the fasting triglyceride level (−40 mg/dL [−0.45 mmol/L]; 95% CI, −53 to −26 mg/dL [−0.60 to −0.29 mmol/L]). None of the rosiglitazone trials showed a statistically significant change in fasting plasma tri-

---

**Table 2. Mean Change in HbA1c Level**

<table>
<thead>
<tr>
<th>Source</th>
<th>Control, (n) Mean ± SD % Change in HbA1c From Baseline</th>
<th>Treatment, (n) Mean ± SD % Change in HbA1c From Baseline</th>
<th>Placebo Subtracted Effect, % Change in HbA1c, (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Source 1</td>
<td>Treatment Length, wk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Source 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Source 3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Source 4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Source 5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Source 6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Source 7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Source 8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Source 9</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: bid, twice daily; CI, confidence interval; HbA1c, hemoglobin A1c; Ins, insulin; Met, metformin; P, pioglitazone hydrochloride; R, rosiglitazone maleate; SU, sulfonylureas.
glycemic control, whereas 5 of 8 trials with pioglitazone demonstrated a statistically significant reduction in triglyceride level (Figure 2). Both thiazolidinediones significantly increased the HDL-C concentration (pioglitazone: Δ = +4.55 mg/dL [+0.12 mmol/L] with 95% CI, 3.61 to 5.48 [0.09 to 0.14 mmol/L]; rosiglitazone: Δ = +2.71 mg/dL [+0.07 mmol/L] with 95% CI, 2.01 to 3.42 mg/dL [0.05 to 0.09 mmol/L]) (Figure 3). Pioglitazone had no effect on total cholesterol (–0.1 mg/dL [–0.003 mmol/L]; 95% CI, –5 to 5 mg/dL [–0.13 to 0.13 mmol/L]), whereas rosiglitazone significantly increased the total cholesterol (+21.3 mg/dL [0.55 mmol/L]; 95% CI, 17.7 to 24.9 mg/dL [0.46 to 0.64 mmol/L]) (Figure 4). The treatment effects of pioglitazone on fasting plasma triglyceride, LDL-C, and total cholesterol levels were statistically significantly different than those of rosiglitazone (all \( P < .01 \)).

### BLOOD PRESSURE EFFECT

Only 5 trials were included in this outcome analysis. None of the pioglitazone trials reported blood pressure as an outcome. There were no significant differences between rosiglitazone and placebo in changes in systolic (–0.7 mm Hg; 95% CI, –2.6 to 1.1 mm Hg) or diastolic blood pressure (–0.8 mm Hg; 95% CI, –1.8 to 0.3 mm Hg).

### WEIGHT EFFECT

Only 11 of 23 trials were included in this outcome analysis, since most trials did not report variance around the weight change value. Within 6 months of initiating therapy with thiazolidinediones, the average weight gain was +2.7 kg (95% CI, 1.8 to 3.7 kg). The studies were heterogeneous (\( \chi^2 = 111.47; P < .001 \)), but drug grouping was not a predictor of the heterogeneity (\( P > .10 \)). Additional analyses were done to examine the contribution of the Japanese trials to the heterogeneity. The Japanese trials\(^{37} \) included subjects with an average BMI of 25, whereas most studies outside of Japan were conducted in obese individuals (BMI = 30 in average for most studies). For Japanese trials only, the average weight gain was +0.73 kg (95% CI, 0.23 to 1.23 kg) and homogeneous (\( \chi^2 = 0.67; P < .71 \)), whereas the non-Japanese trials resulted in a +3.3 kg weight gain (95% CI, 2.5 to 4.2 kg) and remained heterogeneous (\( \chi^2 = 43.54; P < .001 \)).

### COMMENT

Type 2 diabetes mellitus is more than a disease of glucose metabolism, being associated with a number of metabolic abnormalities, including obesity, insulin resistance, hyperinsulinemia, increased waist circumference and visceral adipose tissue, hypertriglyceridemia, low HDL-C level, small dense LDL-C particles, and high blood pressure.\(^{37,38} \) These abnormalities typically occur in clusters as part of the insulin resistance syndrome (the metabolic syndrome), which precede and predict the development of type 2 diabetes.\(^{39} \) Since all of these abnormalities are recognized risk factors for CVD, it is not surprising that individuals with the insulin resistance syndrome, with or without type 2 diabetes, are at increased risk of CVD.\(^{40-43} \)

Because 80% of patients with type 2 diabetes have the metabolic syndrome,\(^{44} \) its components are appropriate targets to evaluate the ben-

---

**Table 3. Metabolic Effects of Thiazolidinediones**

<table>
<thead>
<tr>
<th>Thiazolidinedione</th>
<th>No. of Studies</th>
<th>Weighted Mean Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pioglitazone, 30 mg (monotherapy)</td>
<td>5</td>
<td>–0.99 (–1.32 to –0.66)</td>
</tr>
<tr>
<td>Pioglitazone, 45 mg (monotherapy)</td>
<td>3</td>
<td>–1.21 (–1.79 to –0.62)</td>
</tr>
<tr>
<td>Pioglitazone, 30 mg (combination therapy)</td>
<td>5</td>
<td>–1.16 (–1.41 to –0.90)</td>
</tr>
<tr>
<td>Pioglitazone, 45 mg (combination therapy)</td>
<td>1</td>
<td>–1.56 (–1.96 to –1.16)</td>
</tr>
<tr>
<td>Rosiglitazone, 4 mg (monotherapy)</td>
<td>3</td>
<td>–0.90 (–1.42 to –0.38)</td>
</tr>
<tr>
<td>Rosiglitazone, 8 mg (monotherapy)</td>
<td>1</td>
<td>–1.50 (–1.75 to –1.24)</td>
</tr>
<tr>
<td>Rosiglitazone, 4 mg (combination therapy)</td>
<td>8</td>
<td>–2.05 (–1.19 to –0.90)</td>
</tr>
<tr>
<td>Rosiglitazone, 8 mg (combination therapy)</td>
<td>6</td>
<td>–1.26 (–1.48 to –1.04)</td>
</tr>
<tr>
<td>Effect on glycemic control, FBG, mg/dL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pioglitazone, 30 mg (monotherapy)</td>
<td>4</td>
<td>–40.98 (–50.6 to –31.3)</td>
</tr>
<tr>
<td>Pioglitazone, 45 mg (monotherapy)</td>
<td>2</td>
<td>–53.8 (–73.5 to –34.4)</td>
</tr>
<tr>
<td>Pioglitazone, 30 mg (combination therapy)</td>
<td>5</td>
<td>–47.2 (–55.1 to –39.2)</td>
</tr>
<tr>
<td>Pioglitazone, 45 mg (combination therapy)</td>
<td>1</td>
<td>–47.2 (–61.7 to –32.7)</td>
</tr>
<tr>
<td>Rosiglitazone, 4 mg (monotherapy)</td>
<td>2</td>
<td>–56.9 (–88.8 to –25.2)</td>
</tr>
<tr>
<td>Rosiglitazone, 4 mg (combination therapy)</td>
<td>7</td>
<td>–45.3 (–50.5 to –40.2)</td>
</tr>
<tr>
<td>Rosiglitazone, 8 mg (combination therapy)</td>
<td>5</td>
<td>–55.1 (–62.4 to –47.9)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; DBP, diastolic blood pressure; FBG, fasting blood glucose; HBA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NA, not applicable; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides.

SI conversions: To convert cholesterol to millimoles per liter, multiply by 0.0259; to convert glucose to millimoles per liter, multiply by 0.0555; to convert triglycerides to millimoles per liter, multiply by 0.0113.

<sup>*More than 1 comparison of the study drugs (pioglitazone hydrochloride and rosiglitazone maleate) may be from the same study.</sup>
The thiazolidinediones represent the newest class of drugs introduced into the United States for the treatment of type 2 diabetes mellitus. In this meta-analysis, we have evaluated the effects of pioglitazone and rosiglitazone on the following components of the insulin resistance syndrome: glycemia, triglycerides, total cholesterol, LDL-C, HDL-C, blood pressure, and body weight. Both thiazolidinediones produced similar decreases in HbA1c level of -1.0% to -1.5% and similar increases in body weight of approximately +3.0 kg. In contrast, pioglitazone had a neutral effect on total cholesterol and LDL-C levels. Despite increased body weight, rosiglitazone therapy had a neutral effect on diastolic and systolic blood pressure, and both thiazolidinediones have been shown to reduce the blood pressure in hypertensive patients with type 2 diabetes. The weight gain associated with thiazolidinediones is therefore unlike the weight gain associated with increased caloric intake. The later is associated with the development of insulin resistance and deterioration in glycemic control, a worsening of the dyslipidemia, and a rise in blood pressure. Moreover, the thiazolidinediones have many in vivo and in vitro beneficial effects on a variety of measures of atherosclerosis and have been shown to slow progression of carotid intimal thickness and coronary stent restenosis. Nevertheless, the impact of this weight gain over many years can only be answered with long-term follow-up trials.

Finally, this meta-analysis should not be used to judge the ability of either neutral effect of rosiglitazone on triglyceride level. Plasma levels of total cholesterol and LDL-C were significantly increased by rosiglitazone, whereas no changes in these lipid fractions were produced by pioglitazone. Plasma HDL-C concentration increased to a similar extent with both agents. The mechanism responsible for these beneficial effects of pioglitazone have yet to be established but may result from its modest agonistic effect on the peroxisome proliferator-activated receptor-α. It also remains to be established whether these beneficial effects of pioglitazone on plasma lipid levels are sufficient to lower the risk of CVD. In addition, whether pioglitazone is superior to rosiglitazone in lipid lowering has not been tested in a head-to-head randomized trial.

Although the effect of both thiazolidinediones to increase body weight has raised some concern, many studies have demonstrated an inverse relationship between body weight and HbA1c. Thus, the greater the increase in body weight, the greater the reduction in HbA1c level. Moreover, despite the weight gain, pioglitazone reduced plasma triglyceride level, raised HDL-C level, and had a neutral effect on total cholesterol and LDL-C levels. Despite increased body weight, rosiglitazone therapy had a neutral effect on diastolic and systolic blood pressure, and both thiazolidinediones have been shown to reduce the blood pressure in hypertensive patients with type 2 diabetes. The weight gain associated with thiazolidinediones is therefore unlike the weight gain associated with increased caloric intake. The later is associated with the development of insulin resistance and deterioration in glycemic control, a worsening of the dyslipidemia, and a rise in blood pressure. Moreover, the thiazolidinediones have many in vivo and in vitro beneficial effects on a variety of measures of atherosclerosis and have been shown to slow progression of carotid intimal thickness and coronary stent restenosis. Nevertheless, the impact of this weight gain over many years can only be answered with long-term follow-up trials.

Finally, this meta-analysis should not be used to judge the ability of either neutral effect of rosiglitazone on triglyceride level. Plasma levels of total cholesterol and LDL-C were significantly increased by rosiglitazone, whereas no changes in these lipid fractions were produced by pioglitazone. Plasma HDL-C concentration increased to a similar extent with both agents. The mechanism responsible for these beneficial effects of pioglitazone have yet to be established but may result from its modest agonistic effect on the peroxisome proliferator-activated receptor-α. It also remains to be established whether these beneficial effects of pioglitazone on plasma lipid levels are sufficient to lower the risk of CVD. In addition, whether pioglitazone is superior to rosiglitazone in lipid lowering has not been tested in a head-to-head randomized trial.

Although the effect of both thiazolidinediones to increase body weight has raised some concern, many studies have demonstrated an inverse relationship between body weight and HbA1c. Thus, the greater the increase in body weight, the greater the reduction in HbA1c level. Moreover, despite the weight gain, pioglitazone reduced plasma triglyceride level, raised HDL-C level, and had a neutral effect on total cholesterol and LDL-C levels. Despite increased body weight, rosiglitazone therapy had a neutral effect on diastolic and systolic blood pressure, and both thiazolidinediones have been shown to reduce the blood pressure in hypertensive patients with type 2 diabetes. The weight gain associated with thiazolidinediones is therefore unlike the weight gain associated with increased caloric intake. The later is associated with the development of insulin resistance and deterioration in glycemic control, a worsening of the dyslipidemia, and a rise in blood pressure. Moreover, the thiazolidinediones have many in vivo and in vitro beneficial effects on a variety of measures of atherosclerosis and have been shown to slow progression of carotid intimal thickness and coronary stent restenosis. Nevertheless, the impact of this weight gain over many years can only be answered with long-term follow-up trials.

Finally, this meta-analysis should not be used to judge the ability of either neutral effect of rosiglitazone on triglyceride level. Plasma levels of total cholesterol and LDL-C were significantly increased by rosiglitazone, whereas no changes in these lipid fractions were produced by pioglitazone. Plasma HDL-C concentration increased to a similar extent with both agents. The mechanism responsible for these beneficial effects of pioglitazone have yet to be established but may result from its modest agonistic effect on the peroxisome proliferator-activated receptor-α. It also remains to be established whether these beneficial effects of pioglitazone on plasma lipid levels are sufficient to lower the risk of CVD. In addition, whether pioglitazone is superior to rosiglitazone in lipid lowering has not been tested in a head-to-head randomized trial.
Effect of pioglitazone hydrochloride (P) or rosiglitazone maleate (R) vs placebo on total cholesterol (HDL-C) in patients with type 2 diabetes. To convert cholesterol to millimoles per liter, multiply by 0.0259. bid Indicates twice daily; CI, confidence interval; Ins, insulin; Met, metformin; SU, sulfonylureas; WMD, weighted mean difference.

Figure 3. Effect of pioglitazone hydrochloride (P) or rosiglitazone maleate (R) vs placebo on total cholesterol (HDL-C) in patients with type 2 diabetes. To convert cholesterol to millimoles per liter, multiply by 0.0259. bid Indicates twice daily; CI, confidence interval; Ins, insulin; Met, metformin; SU, sulfonylureas; WMD, weighted mean difference.

Figure 4. Effect of pioglitazone hydrochloride (P) or rosiglitazone maleate (R) vs placebo on total cholesterol in patients with type 2 diabetes. To convert cholesterol to millimoles per liter, multiply by 0.0259. bid Indicates twice daily; CI, confidence interval; Ins, insulin; Met, metformin; SU, sulfonylureas; WMD, weighted mean difference.

thiazolidinediones to reduce the incidence of cardiovascular events in patients with type 2 diabetes. The long-term effects of pioglitazone and rosiglitazone on cardiovascular morbidity and mortality currently are being evaluated in several large randomized controlled trials: ADOPT (A Diabetes Outcome Progression Trial), RECORD (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes), and PROACTIVE (Prospective Pioglitazone Clinical Trial in Macrovascular Events).

Accepted for Publication: May 22, 2004.

Author Affiliations: University of Texas Health Science Center at San Antonio (Drs Chiquette and DeFronzo); and Des Moines University, Des Moines, Iowa (Dr Ramirez).

Correspondence: Ralph DeFronzo, MD, Diabetes Division, University of Texas Health Science Center at San Antonio, 7703 Floyd Curl Dr, San Antonio, TX 78229 (albarado@uthscsa.edu).

REFERENCES


13. Rosenblatt et al. (P 30 mg/d vs Placebo)

14. Phillips et al. (R 4 mg/d vs Placebo)

15. Kaneko et al. (P 30 mg/d vs Placebo)

16. Einhorn et al. (P 30 mg/d vs Placebo)

17. Herz et al. (P 30 mg/d vs Placebo)

18. Phillips et al. (R 4 mg/d vs Placebo)

19. Hutchman et al. (R 4 mg/d vs Placebo)

20. Hutchman et al. (R 4 mg/d vs Placebo)

21. Vogtckavas et al. (R 2 mg bid vs Placebo)

22. Aronoff et al. (P 45 mg/d vs Placebo)

23. Einhorn et al. (P 30 mg/d vs Placebo)

24. Raskin et al. (R 8 mg/d vs Placebo)

25. Raskin et al. (R 8 mg/d vs Placebo)

26. Phillips et al. (R 4 mg/d vs Placebo)

27. Kaneko et al. (P 30 mg/d vs Placebo)

28. Patel et al. (R 2 mg bid vs Placebo)

29. Lebwoh et al. (R 4 mg/d vs Placebo)

30. Gomez-Perez et al. (R 8 mg/d vs Placebo)

31. Phillips et al. (R 4 mg/d vs Placebo)

32. Vongthavaravat et al. (R 2 mg bid vs Placebo)

33. Fonseca et al. (R 8 mg/d vs Placebo)

34. Moran et al. (R 4 mg/d vs Placebo)

35. Lowry et al. (R 8 mg/d vs Placebo)

36. Hutchman et al. (R 4 mg/d vs Placebo)

37. Kipnes et al. (R 30 mg/d vs Placebo)

38. Herz et al. (R 4 mg/d vs Placebo)

39. Rosenblatt et al. (R 30 mg/d vs Placebo)

40. Rosenblatt et al. (R 30 mg/d vs Placebo)

41. Rosenblatt et al. (R 30 mg/d vs Placebo)

42. Rosenblatt et al. (R 30 mg/d vs Placebo)

43. Kaneko et al. (P 30 mg/d vs Placebo)

44. Kaneko et al. (P 30 mg/d vs Placebo)

45. Kaneko et al. (P 30 mg/d vs Placebo)

46. Kaneko et al. (P 30 mg/d vs Placebo)

47. Kaneko et al. (P 30 mg/d vs Placebo)

48. Kaneko et al. (P 30 mg/d vs Placebo)

49. Kaneko et al. (P 30 mg/d vs Placebo)

50. Kaneko et al. (P 30 mg/d vs Placebo)

51. Kaneko et al. (P 30 mg/d vs Placebo)

52. Kaneko et al. (P 30 mg/d vs Placebo)
15. Kaneko T, Baba S, Toyota T. Dose finding study of AD-4833 in patients with non-insulin dependent dia-
16. Kaneko T, Baba S, Toyota T. Clinical evaluation of an insulin sensitizing agent, AD-4833 in patients with non-insulin dependent diabetes mellitus (NIDDM) on diet therapy alone: a pla-
17. Kaneko T, Baba S, Toyota T. Dose finding study of AD-4833 in patients with non-insulin depen-
18. Einhorn D, Rendell M, Rosenzweig J, Egan JW, Mathisen AL, Schneider RL, The Rosiglitazone 027 Study Group. Pioglitazone hydrochloride in combi-
nation with metformin in the treatment of type 2 diabetes mellitus: a randomized, placebo-
20. Kipnes MS, Kroinick A, Rendell MS, Egan JW, Mathisen AL, Schneider RL, Pioglitazone hydro-
chloride monotherapy in patients with type 2 diabetes: a 24-week, placebo-controlled, double-
22. Rosenblatt S, Miskin B, Glazer NB, Prince MJ, Rob-
etson KE. The impact of pioglitazone on glycemic 
control and atherogenic dyslipidemia in pa-
23. Scherbaum WA, Goke B. Metabolic efficacy and safety of once-daily pioglitazone monotherapy in patients with type 2 diabetes: a double-blind, pla-
24. Raskin P, Rendell M, Riddle MC, Dole JF, Freed MI, Rosenstock J. Addition of low-dose rosiglita-
zon to sulphonylurea therapy improves glycemic control in patients with type 2 diabetes mellitus: a randomized, placebo-
25. Morano E, Salzman A, Yan Y, Pat-
wartham R. Rosiglitazone. BRL 49653: A 26-week randomized, double-blind, double-dummy, multicentered study to evaluate the efficacy, safety and tolerability of rosiglitazone when administered to patients with non-insulin dependent diabetes mellitus (NIDDM) who are inadequately controlled on a maximal dose (20-mg/day) of glyburide: report 079 phase IIIA:
final clinical report. Except in: Lord J, Paisley S, Taylor R. The Clinical Effectiveness and Cost-
Effectiveness of Rosiglitazone for Type 2 Diabetes Mellitus. London, England: National Institute for Clinical 
Excellence; 2000.
26. Lowry FS, Bevivino MV, Salzman A, Yan Y, Pat-
wartham R. Rosiglitazone. BRL 49653: A 26-week randomized, double-blind, double-
dummy, multicentered, placebo-controlled trial to evaluate the efficacy, safety and tolerability of rosiglitazone 4 mg bd when administered to patients with non-insulin depen-
dent diabetes mellitus (NIDDM) who are inadequately controlled on a maintenance dose (2.5g/day) of metformin: report 093 phase IIIA:
final clinical report. Except in: Lord J, Paisley S, Taylor R. The Clinical Effectiveness and Cost-
Effectiveness of Rosiglitazone for Type 2 Diabetes 
27. Hutchman J, Salzman A, Biswas N, Patwardhan R, Rosiglitazone. BRL 49653: A 26-week random-
ized, double-blind, multicenter, placebo-
controlled study to evaluate the efficacy, safety and tolerability of rosiglitazone when administered once daily to patients with non-insulin dependent dia-
betes mellitus (NIDDM) who are inadequately con-
trolled on at least half-maximal dose (10 mg/ 
day) of glyburide: report 096 phase IIIA: final 
clinical report. Except in: Lord J, Paisley S, Tay-
lor R. The Clinical Effectiveness and Cost-
Effectiveness of Rosiglitazone for Type 2 Diabetes 
28. DeFronzo RA, Ferrannini E. Insulin resistance: a multifaced syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia, and arterio-
clinical report. Excerpt in: Lord J, Paisley S, 
Taylors E. The German pioglitazone 
30. Scherbaum WA, Burkhard G. The German piogli-
glitazone on glucose and free fatty acid metabo-
32. Miyazaki Y, Mahankali A, Matsuoka M, et al. Im-
proved glycemic control and enhanced insulin sen-
titivity in liver and muscle in type 2 diabetic sub-
33. Chilcott J, Tappened P, Jones ML, Wight JP. A systematic review of the effectiveness of piogli-
34. Miyazaki Y, Glass L, Triptit C, et al. Effect of resi-
glitazone on glucose and free fatty acid metabo-
35. Noda M, Mandarino LJ, DeFronzo RA. Role of the adipocyte, free fatty acids, and ectopic fat in patho-
37. Chilcott J, Tappened P, Jones ML, Wight JP. A systematic review of the effectiveness of piogli-
38. Scherbaum WA, Burkhard G. The German piogli-
glitazone on glucose and free fatty acid metabo-
40. Miyazaki Y, Mahankali A, Matsuoka M, et al. Im-
proved glycemic control and enhanced insulin sen-
titivity in liver and muscle in type 2 diabetic sub-