Coronary Heart Disease

Effect of Rosiglitazone on Progression of Coronary Atherosclerosis in Patients With Type 2 Diabetes Mellitus and Coronary Artery Disease

The Assessment on the Prevention of Progression by Rosiglitazone on Atherosclerosis in Diabetes Patients With Cardiovascular History Trial

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Background—Rosiglitazone has several properties that may affect progression of atherosclerosis. The Assessment on the Prevention of Progression by Rosiglitazone on Atherosclerosis in Diabetes Patients With Cardiovascular History (APPROACH) study was undertaken to determine the effect of the thiazolidinedione rosiglitazone on coronary atherosclerosis as assessed by intravascular ultrasound compared with the sulfonylurea glipizide.

Methods and Results—This was a randomized, double-blind, controlled 18-month study in 672 patients aged 30 to 80 years with established type 2 diabetes mellitus treated by lifestyle, 1 oral agent, or submaximal doses of 2 oral agents who had at least 1 atherosclerotic plaque with 10% to 50% luminal narrowing in a coronary artery that had not undergone intervention during a clinically indicated coronary angiography or percutaneous coronary intervention. The primary outcome was change in percent atheroma volume in the longest and least angulated epicardial coronary artery that had not undergone intervention. Secondary outcomes included change in normalized total atheroma volume and change in total atheroma volume in the most diseased baseline 10-mm segment. Rosiglitazone did not significantly reduce the primary outcome of percent atheroma volume compared with glipizide (-0.64%; 95% confidence interval, -1.46 to 0.17; P=0.12). The secondary outcome of normalized total atheroma volume was significantly reduced by rosiglitazone compared with glipizide (-5.1 mm³; 95% confidence interval, -10.0 to -0.3; P=0.04); however, no significant difference between groups was observed for the change in total atheroma volume within the most diseased baseline 10-mm segment (-1.7 mm³; 95% confidence interval, -3.9 to 0.5; P=0.13).

Conclusions—Rosiglitazone did not significantly decrease the primary end point of progression of coronary atherosclerosis more than glipizide in patients with type 2 diabetes mellitus and coronary atherosclerosis.


Type 2 diabetes mellitus is a strong independent risk factor for cardiovascular diseases, and epidemiological studies have shown that this risk is progressively related to the degree of hyperglycemia as measured by the hemoglobin A1c. Whereas recent trials of more intensive versus less intensive glucose lowering with a menu of drugs did not detect a clear cardiovascular benefit, the observation of reduced myocardial infarction and all-cause mortality in metformin-treated obese subjects during active therapy in the United Kingdom Prospective Diabetes study and in all participants after an additional 8.5 years of passive follow-up suggests that specific glucose-lowering drugs may have cardiovascular benefits. Coronary atherosclerosis forms the substrate for vulnerable plaque, which is hypothesized to precede clinical coronary events. Coronary atherosclerosis can be directly assessed with the use of intravascular ultrasonography.
Thiazolidinediones have effects on cardiovascular risk factors, including insulin sensitivity, inflammatory biomarkers, endothelial function, coagulability, plaque instability, and blood pressure, that may slow the progression of coronary atherosclerosis. Some controlled trials of both thiazolidinediones (rosiglitazone and pioglitazone) in patients with type 2 diabetes mellitus have suggested a favorable effect of these agents on carotid atherosclerosis and in-stent restenosis; however, the applicability of these data to native vessel coronary disease is uncertain. Moreover, a recent large randomized trial of 1 thiazolidinedione (pioglitazone) demonstrated that it reduced progression of coronary atherosclerosis in arteries that had not undergone intervention more than glimepiride. To date, comparable data with the use of rosiglitazone have not been available.

The Assessment on the Prevention of Progression by Rosiglitazone on Atherosclerosis in Diabetes Patients With Cardiovascular History (APPROACH) trial was designed to compare the effect of rosiglitazone and glipizide, agents that reduce glucose through different mechanisms, on progression of coronary atherosclerosis. Importantly, the trial was designed to provide comparable glycemic control between treatment arms and to evaluate the treatment effect on a background of optimized contemporary therapy for secondary prevention of coronary disease including statins, antiplatelet agents, and antihypertensive medications.

### Methods

**Study Design and Eligibility Criteria**

A detailed description of the APPROACH trial has been published previously. APPROACH was a prospective, multicenter, double-blind, randomized, active-controlled trial (Figure 1) of 672 patients from 92 centers in 19 countries, who were aged 30 to 80 years with established type 2 diabetes mellitus and who had clinically indicated coronary angiography or percutaneous coronary intervention (PCI) between February 2005 and January 2007. Patients were included if they had at least 1 atherosclerotic plaque with 10% to 50% luminal narrowing in a coronary artery that had not undergone intervention and if their diabetes mellitus was treated with either lifestyle approaches alone (with a hemoglobin A1C ≤7% and ≤10%) or with oral agents comprising 1 oral agent at any dose or 2 oral agents, in which case each was prescribed at ≤50% of its maximal dose (with a hemoglobin A1C ≤6.5% and ≤8.5%). Exclusion criteria were as follows: ST-segment elevation myocardial infarction in the prior 30 days; coronary artery bypass graft surgery; severe valvular heart disease; left ventricular ejection fraction <40%; any heart failure (New York Heart Association class I to IV); uncontrolled hypertension (systolic blood pressure >170 mm Hg or diastolic blood pressure >100 mm Hg); renal insufficiency (serum creatinine ≥1.5 mg/dL for men or ≥1.4 mg/dL for women); and active liver disease.

Participant safety was monitored by an Independent Data Monitoring Committee who periodically reviewed rates of clinical outcomes according to unmasked therapy. The study protocol and consent forms were reviewed by the institutional review board at each site, and all patients provided written informed consent. Study design, implementation, and analysis were performed under the supervision of the Steering Committee, which was composed of 7 members from cardiovascular and diabetes centers around the world.
Management of Glycemia and Follow-Up

Patients were randomized in a 1:1 ratio to receive masked rosiglitazone (4 mg/d) or glipizide (5 mg/d) in 1 pill. At the time of randomization, the doses of other oral antidiabetic drugs were reduced by 50% and were discontinued during a visit 1 month later. At that time and after 2 and 3 months, the dose of masked study drug was increased if tolerated and if the mean daily glucose level calculated from the patient’s logbook of capillary tests in the 3 days before the visit was ≥126 mg/dL (7.0 mmol/L). If >1 titration was required, 2 pills per day were given. Titration doses of rosiglitazone at the first, second, and third titration were 4 mg/d (1 pill; unchanged dose), 8 mg/d (as 2 pills with active drug in the morning and placebo in the evening), and 4 mg BID, respectively; glipizide dosing at these visits was 10 mg/d (1 pill), 10 mg in the morning and 5 mg in the evening (as 2 pills), and this same dose as the third titration, respectively. Open-label metformin (maximal total daily dose 2550 mg) and then once-daily basal insulin or both were added after the first 3 months if needed to maintain a hemoglobin A1C ≤7% with the use of a glycemic titration algorithm designed to provide comparable glycemic control between treatment groups. Nonstudy drugs were reduced before study drugs in the event of hypoglycemia requiring dose reductions. Unless informed consent was formally withdrawn, all patients were followed until 18 months from randomization, and clinical status was ascertained regardless of whether they continued to take study medication.

IVUS Examination and Image Analysis

The longest and least angulated epicardial coronary artery that had not undergone intervention was selected for IVUS examination. Angiographers were instructed to choose a plaque within which there was at least 20% stenosis by visual assessment. They were also instructed to ensure that the region of interest was flanked by 2 anatomic landmarks that could be easily identified at follow-up (ie, side branches). After intracoronary administration of nitroglycerin, an ultrasonic catheter (2.5F Atlantis SR Pro Imaging 40 MHz) connected to a Galaxy G2 digital imaging console (Boston Scientific, Natick, Mass) was advanced into the target vessel. The imaging transducer was positioned just distal to an identifiable side branch, and then motorized pullback of the transducer was performed at 0.5 mm/s. Follow-up IVUS examination was performed at study completion in all patients providing informed consent (irrespective of whether they continued to take study medication) with imaging of the same coronary artery segment identified at the baseline examination. If a participant required cardiac catheterization for a clinical indication between 9 and 18 months, follow-up IVUS examination could be performed at that time instead of at study completion.

IVUS Outcomes

Core laboratory personnel (Cardialysis, Rotterdam, the Netherlands) who were blinded to treatment assignment analyzed all IVUS images using validated software (Curad, version 3.1, Wijk bij Duurstede, the Netherlands), which facilitates detection of luminal and external elastic membrane (EEM) boundaries in reconstructed longitudinal views, the Intelligate image-based gating method to take study medication.

Clinical Cardiovascular Outcomes

Investigators submitted end point forms for any event that could potentially represent a myocardial ischemic event or heart failure. An independent end point committee blinded to treatment assignment prospectively adjudicated these cardiovascular events, which included cardiovascular and noncardiovascular death, nonfatal myocardial infarction and stroke, coronary revascularization, hospitalization for recurrent myocardial ischemia, and heart failure.

Statistical Methods

Continuous variables are expressed as mean and SD or median and interquartile range if nonnormally distributed, with categorical variables reported as percentage. IVUS outcomes were analyzed with the use of ANCOVA with terms for treatment group, baseline value, geographic region, gender, entry cardiac procedure (angiography or PCI), and prior oral antidiabetic medication. The change in PAV for each allocated group was calculated by estimating the model-adjusted mean change in PAV across the cohort. All P values are 2-sided and not adjusted for multiple testing, with P values ≤0.05 considered significant. A worst-rank sensitivity analysis was performed as described previously to assess the potential influence on the primary end point of randomized patients who did not complete the follow-up IVUS examination because of a cardiovascular event. Finally, to assess variability between core laboratories, the same patients were analyzed twice longitudinally and twice cross sectionally. The mean (SD) differences (in mm²) were 0.10 (0.36) mm² for vessel area and 0.001 (0.46) mm² for lumen area. Finally, to assess variability between core laboratories, the same patients were analyzed twice longitudinally and twice cross sectionally, respectively. Open-label metformin (maximal total daily dose, 2550 mg) and then once-daily basal insulin or both were added after the first 3 months if needed to maintain a hemoglobin A1C ≤7% with the use of a glycemic titration algorithm designed to provide comparable glycemic control between treatment groups. Nonstudy drugs were reduced before study drugs in the event of hypoglycemia requiring dose reductions. Unless informed consent was formally withdrawn, all patients were followed until 18 months from randomization, and clinical status was ascertained regardless of whether they continued to take study medication.

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\[ TAV = \left[ \frac{\Sigma (EEM_{CSA} - LUMEN_{CSA})}{N} \right] \times \text{overall median segment length}. \]
lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides, and PAV (less than or equal to the median versus more than the median value), was performed with the use of ANCOVA with a test for treatment-by-subgroup interaction. The effect of treatment allocation on time to first occurrence of the various cardiovascular outcomes was estimated with a Cox proportional hazards model that included terms for treatment group, region, angiography versus PCI, and prior oral agent use.

Sample size calculations determined that 206 patients per group with evaluable baseline and follow-up IVUS examinations were required to provide 90% power with a 2-sided $\alpha$ of 0.05 to detect a treatment difference between the groups of 1.6%, with the assumption of a 5.0% SD for the primary IVUS outcome. These assumptions were based on prior IVUS studies of lipid-lowering therapies in patients with diabetes mellitus.10 Given prior noncompletion rates among patients with type 2 diabetes mellitus in contemporary IVUS studies ranging from 25% to 35%,9,10,23,27 a total sample size of 634 randomized patients was required under the worst-case assumption of a 35% noncompletion rate. All analyses were performed with the use of SAS version 9.1 (SAS Institute, Cary, NC). Finally, to ensure the accuracy of the analyses, data for the primary and secondary end points were provided to an external biostatistician (Dr Todd A.

### Table 1. Baseline Characteristics of Randomized Patients

<table>
<thead>
<tr>
<th></th>
<th>Glipizide (n=339)</th>
<th>Rosiglitazone (n=333)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>60.2 (9.0)</td>
<td>61.8 (8.4)</td>
<td>0.03</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>223 (65.8)</td>
<td>233 (70.0)</td>
<td>0.25</td>
</tr>
<tr>
<td>Current smoker, n (%)</td>
<td>57 (16.8)</td>
<td>55 (16.5)</td>
<td>1.00</td>
</tr>
<tr>
<td>Duration of diabetes mellitus, median (IQR), y</td>
<td>4.6 (1.7–8.9)</td>
<td>5.0 (2.2–7.9)</td>
<td>0.90</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>272 (80.2)</td>
<td>266 (79.9)</td>
<td>0.92</td>
</tr>
<tr>
<td>Dyslipidemia, n (%)</td>
<td>227 (67.0)</td>
<td>232 (69.7)</td>
<td>0.46</td>
</tr>
<tr>
<td>Prior myocardial infarction, n (%)</td>
<td>82 (24.2)</td>
<td>81 (24.3)</td>
<td>1.00</td>
</tr>
<tr>
<td>Presenting condition, n (%)</td>
<td>130 (38.3)</td>
<td>128 (38.4)</td>
<td>1.00</td>
</tr>
<tr>
<td>Acute coronary syndrome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elective procedure</td>
<td>209 (61.7)</td>
<td>205 (61.6)</td>
<td></td>
</tr>
<tr>
<td>Baseline procedure, n (%)</td>
<td>171 (50.4)</td>
<td>166 (49.8)</td>
<td>0.94</td>
</tr>
<tr>
<td>Coronary angiography</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>PCI</td>
<td>168 (49.6)</td>
<td>167 (50.2)</td>
<td></td>
</tr>
<tr>
<td>Medication use, n (%)</td>
<td>279 (82.3)</td>
<td>280 (84.1)</td>
<td>0.61</td>
</tr>
<tr>
<td>Aspirin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other antplatelet</td>
<td>195 (57.5)</td>
<td>196 (58.9)</td>
<td>0.75</td>
</tr>
<tr>
<td>β-blocker</td>
<td>223 (65.8)</td>
<td>241 (72.4)</td>
<td>0.07</td>
</tr>
<tr>
<td>ACE inhibitor or ARB</td>
<td>238 (70.2)</td>
<td>237 (71.2)</td>
<td>0.80</td>
</tr>
<tr>
<td>Nitrates</td>
<td>137 (40.4)</td>
<td>125 (37.5)</td>
<td>0.48</td>
</tr>
<tr>
<td>Statin</td>
<td>262 (77.3)</td>
<td>248 (74.5)</td>
<td>0.42</td>
</tr>
<tr>
<td>Fibrate or other lipid-lowering agent</td>
<td>24 (7.1%)</td>
<td>34 (10.2%)</td>
<td>0.17</td>
</tr>
<tr>
<td>Weight, mean (SD), kg</td>
<td>83.8 (18.5)</td>
<td>82.0 (19.1)</td>
<td>0.22</td>
</tr>
<tr>
<td>Body mass index, mean (SD), kg/m²</td>
<td>29.8 (5.3)</td>
<td>29.3 (5.5)</td>
<td>0.14</td>
</tr>
<tr>
<td>Blood pressure, mean (SD), mm Hg</td>
<td>131.0 (15.1)</td>
<td>127.9 (16.1)</td>
<td>0.004</td>
</tr>
<tr>
<td>Systolic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diastolic</td>
<td>76.3 (10.0)</td>
<td>75.2 (10.2)</td>
<td>0.16</td>
</tr>
<tr>
<td>Serum creatinine, mean (SD), mg/dL</td>
<td>0.98 (0.22)</td>
<td>1.02 (0.25)</td>
<td>0.02</td>
</tr>
<tr>
<td>Hemoglobin A₁c, mean (SD), %</td>
<td>7.2 (0.9)</td>
<td>7.1 (0.8)</td>
<td>0.08</td>
</tr>
<tr>
<td>BNP,* median (IQR), pg/mL</td>
<td>25 (12–53)</td>
<td>25 (11–58)</td>
<td>0.98</td>
</tr>
<tr>
<td>Fasting insulin,* median (IQR), μU/mL</td>
<td>13.0 (8.6–18.1)</td>
<td>13.0 (8.6–20.7)</td>
<td>0.49</td>
</tr>
<tr>
<td>LDL cholesterol, mean (SD), mg/dL</td>
<td>91.2 (35.5)</td>
<td>89.6 (35.9)</td>
<td>0.63</td>
</tr>
<tr>
<td>HDL cholesterol, mean (SD), mg/dL</td>
<td>42.7 (10.7)</td>
<td>42.4 (11.1)</td>
<td>0.77</td>
</tr>
<tr>
<td>Triglycerides, median (IQR), mg/dL</td>
<td>159.3 (122.1–204.9)</td>
<td>162.0 (122.1–211.5)</td>
<td>0.93</td>
</tr>
<tr>
<td>hsCRP, median (IQR), mg/L</td>
<td>5.4 (2.5–11.0)</td>
<td>4.9 (2.2–11.3)</td>
<td>0.54</td>
</tr>
<tr>
<td>MMP-9, median (IQR), μg/L</td>
<td>86.9 (43.8–195.1)</td>
<td>88.6 (44.1–221.6)</td>
<td>0.44</td>
</tr>
</tbody>
</table>

IQR indicates interquartile range; ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; hsCRP, high-sensitivity C-reactive protein; and MMP-9, matrix metalloproteinase-9. SI conversion factors: to convert fasting plasma glucose to mmol/L, multiply by 0.0555; LDL and HDL cholesterol values to mmol/L, by 0.0259; triglyceride values to mmol/L, by 0.0113; serum creatinine to μmol/L, by 88.4; fasting insulin to pmol/L, by 6.945; and c-reactive protein to nmol/L, by 9.524.

*Performed in a subset of patients (B-natriuretic peptide [BNP], n=464; fasting insulin, n=435.)
MacKenzie, Dartmouth Medical School), who independently repeated and confirmed all of the findings reported herein. All authors had access to study data and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors have read and agree to the manuscript as written.

Results

Participants

Of 1147 people who were screened, 672 (68% men) of mean (SD) age 61 (9) years with median diabetes mellitus duration of 4.8 years and mean hemoglobin A1C of 7.2% (0.9) were randomized to either glipizide (n=339) or rosiglitazone (n=333) from 92 sites in 19 countries (Figure 1). Baseline characteristics by treatment group are noted in Table 1; by chance, patients allocated to rosiglitazone versus glipizide were slightly older and had a slightly higher serum creatinine and lower systolic blood pressure. Because randomization was stratified by the cardiac procedure, 50% of enrolled patients had diagnostic coronary angiography, and 50% had a PCI. A total of 38% presented with acute coronary syndrome, and 76% were on statins. A total of 229 of 339 patients (67.5%) allocated to glipizide and 233 of 333 (70%) allocated to rosiglitazone had an evaluable baseline and follow-up IVUS. Compared with participants who did not have 2 evaluable IVUS examinations, those who did had a slightly lower diastolic blood pressure (P=0.04), were more likely to be from South America (P=0.001), were less likely to be on 2 oral antidiabetic agents (P=0.004), and were more likely to have had a stent inserted (P=0.006). An assessment of vital status at the 18-month final visit was available in 317 patients (93.5%) allocated to glipizide and 316 patients (94.9%) allocated to rosiglitazone.

Patients were followed for a median of 18.6 months (interquartile range, 18.2 to 18.9) and a mean (SD) of 16 (6) months; patients allocated to glipizide were adherent (took ≥80% and ≤120% of their study medications) at 90.7% of visits, and those allocated to rosiglitazone were adherent at 92.7% of visits. Adverse effects that were either of interest on the basis of prior studies, that occurred infrequently during the trial (Table 3); 5 of the cardiovascular events in the rosiglitazone group (1 revascularization, 2 nonfatal myocardial infarctions, 1 nonfatal stroke, and 1 cardiovascular death) occurred within 5 days of the baseline cardiac catheterization and were classified as procedure related.

The mean (SD) dose of study drug for patients who had a baseline and follow-up IVUS was 12.3 (4.3) mg for glipizide and 6.8 (1.8) mg for rosiglitazone. Of these patients, 220 (96.1%) allocated to glipizide and 220 (94.4%) allocated to rosiglitazone had their follow-up IVUS done ≥17 months after the baseline IVUS. Figure 2 illustrates the change from baseline in hemoglobin A1C, blood pressure, lipids, and weight for each group, and Table 4 lists the postrandomization mean or median values for these and other variables, as well as the statistical significance of the difference between the two groups.

Table 2. Major Adverse Events in All Randomized Patients

<table>
<thead>
<tr>
<th>Event</th>
<th>Glipizide (n=339)</th>
<th>Rosiglitazone (n=333)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events requiring change or stop in study medication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>1 (&lt;1)</td>
<td>2 (&lt;1)</td>
<td>0.62</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>12 (4)</td>
<td>0 (0)</td>
<td>0.0004</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>24 (7)</td>
<td>29 (9)</td>
<td>0.48</td>
</tr>
<tr>
<td>Severe hypoglycemia (requiring external assistance)</td>
<td>3 (&lt;1)</td>
<td>0 (0)</td>
<td>0.25</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>96 (28)</td>
<td>27 (8)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Bone fracture</td>
<td>2 (&lt;1)</td>
<td>6 (2)</td>
<td>0.17</td>
</tr>
<tr>
<td>Hemoglobin decrease &gt;3 g/dL from baseline</td>
<td>10 (3)</td>
<td>26 (8)</td>
<td>0.006</td>
</tr>
</tbody>
</table>

Values are number of patients with an event (%). Adverse events requiring changes in study drug, reported in ≥5% of patients in either group, significantly differed between groups or were of interest on the basis of other studies are listed.

Effect on IVUS End Points

Table 5 notes the effect of allocated therapy on the primary and secondary IVUS end points. During the course of the study, PAV (the primary outcome) did not significantly change from baseline in patients allocated to glipizide (0.43%; 95% confidence interval [CI], −0.22 to 1.08; P=0.19) or in patients allocated to rosiglitazone (−0.21%; 95% CI, −0.86 to 0.44; P=0.53). Moreover, rosiglitazone did not significantly reduce PAV compared with glipizide (−0.64%; 95% CI, −1.46 to 0.17; P=0.12). Similar findings were noted (1) when the data were analyzed after adjustment for baseline differences in age, creatinine, and systolic blood pressure; (2) when patients in the glipizide group, those allocated to rosiglitazone had less hypoglycemia and more anemia. No between-group difference was noted in the rate of cardiovascular events (all adjudicated) that occurred infrequently during the trial (Table 3); 5 of the cardiovascular events in the rosiglitazone group (1 revascularization, 2 nonfatal myocardial infarctions, 1 nonfatal stroke, and 1 cardiovascular death) occurred within 5 days of the baseline cardiac catheterization and were classified as procedure related.

The mean (SD) dose of study drug for patients who had a baseline and follow-up IVUS was 12.3 (4.3) mg for glipizide and 6.8 (1.8) mg for rosiglitazone. Of these patients, 220 (96.1%) allocated to glipizide and 220 (94.4%) allocated to rosiglitazone had their follow-up IVUS done ≥17 months after the baseline IVUS. Figure 2 illustrates the change from baseline in hemoglobin A1C, blood pressure, lipids, and weight for each group, and Table 4 lists the postrandomization mean or median values for these and other variables, as well as the statistical significance of the difference between the two groups.

Table 2. Major Adverse Events in All Randomized Patients

<table>
<thead>
<tr>
<th>Event</th>
<th>Glipizide (n=339)</th>
<th>Rosiglitazone (n=333)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events requiring change or stop in study medication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>1 (&lt;1)</td>
<td>2 (&lt;1)</td>
<td>0.62</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>12 (4)</td>
<td>0 (0)</td>
<td>0.0004</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>24 (7)</td>
<td>29 (9)</td>
<td>0.48</td>
</tr>
<tr>
<td>Severe hypoglycemia (requiring external assistance)</td>
<td>3 (&lt;1)</td>
<td>0 (0)</td>
<td>0.25</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>96 (28)</td>
<td>27 (8)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Bone fracture</td>
<td>2 (&lt;1)</td>
<td>6 (2)</td>
<td>0.17</td>
</tr>
<tr>
<td>Hemoglobin decrease &gt;3 g/dL from baseline</td>
<td>10 (3)</td>
<td>26 (8)</td>
<td>0.006</td>
</tr>
</tbody>
</table>

Values are number of patients with an event (%). Adverse events requiring changes in study drug, reported in ≥5% of patients in either group, significantly differed between groups or were of interest on the basis of other studies are listed.

Effect on IVUS End Points

Table 5 notes the effect of allocated therapy on the primary and secondary IVUS end points. During the course of the study, PAV (the primary outcome) did not significantly change from baseline in patients allocated to glipizide (0.43%; 95% confidence interval [CI], −0.22 to 1.08; P=0.19) or in patients allocated to rosiglitazone (−0.21%; 95% CI, −0.86 to 0.44; P=0.53). Moreover, rosiglitazone did not significantly reduce PAV compared with glipizide (−0.64%; 95% CI, −1.46 to 0.17; P=0.12). Similar findings were noted (1) when the data were analyzed after adjustment for baseline differences in age, creatinine, and systolic blood pressure; (2) when patients in the glipizide group, those allocated to rosiglitazone had less hypoglycemia and more anemia. No between-group difference was noted in the rate of cardiovascular events (all adjudicated) that occurred infrequently during the trial (Table 3); 5 of the cardiovascular events in the rosiglitazone group (1 revascularization, 2 nonfatal myocardial infarctions, 1 nonfatal stroke, and 1 cardiovascular death) occurred within 5 days of the baseline cardiac catheterization and were classified as procedure related.

The mean (SD) dose of study drug for patients who had a baseline and follow-up IVUS was 12.3 (4.3) mg for glipizide and 6.8 (1.8) mg for rosiglitazone. Of these patients, 220 (96.1%) allocated to glipizide and 220 (94.4%) allocated to rosiglitazone had their follow-up IVUS done ≥17 months after the baseline IVUS. Figure 2 illustrates the change from baseline in hemoglobin A1C, blood pressure, lipids, and weight for each group, and Table 4 lists the postrandomization mean or median values for these and other variables, as well as the statistical significance of the difference between the two groups.
pressure (95% CI, −0.60% to 0.60%; 95% CI, −1.43 to 0.23; \( P = 0.15 \)) and (2) when the data were analyzed with a worst-rank analysis comprising 243 glipizide (72%) and 247 rosiglitazone patients (74%), in which the 28 patients (14 per group) who did not have 2 evaluable IVUS examinations due to a cardiovascular event were assigned a rank on the basis of their event as described above (\( P = 0.20 \)). The main secondary end point of \( TAV_N \) did not significantly change in patients allocated to glipizide (1.2 mm\(^3\); 95% CI, −2.7 to 5.1; \( P = 0.54 \)). However, it significantly decreased by 3.9 mm\(^3\) (95% CI, −7.8 to −0.2; \( P = 0.049 \)) in patients allocated to rosiglitazone, and, compared with glipizide, rosiglitazone significantly reduced \( TAV_N \) by 5.1 mm\(^3\) (95% CI, −10.0 to −0.3; \( P = 0.04 \)). Atheroma volume within the most diseased baseline 10-mm segment was the other main secondary IVUS end point and decreased from baseline by 3.6 mm\(^3\) (95% CI, −5.3 to −1.8; \( P < 0.0001 \)) in patients allocated to glipizide and by 5.3 mm\(^3\) (95% CI, −7.0 to −3.5; \( P < 0.0001 \)) in patients allocated to rosiglitazone; the effect of rosiglitazone did not significantly differ from that of glipizide (−1.7 mm\(^3\); 95% CI, −3.9 to 0.5; \( P = 0.13 \)).

When analyzed according to prespecified subgroups (Figure 3), an interaction between treatment allocation and diabetes mellitus duration was noted (\( P = 0.005 \)) such that rosiglitazone reduced the \( PAV \) more than glipizide in patients with diabetes mellitus duration longer than the median duration of 4.9 years (ie, a 1.8% decrease versus a 0.5% increase in those with a shorter diabetes mellitus duration).

### Table 3. Adjudicated Clinical Cardiovascular Outcomes in All Randomized Patients

<table>
<thead>
<tr>
<th>Event</th>
<th>Glipizide (n=339)</th>
<th>Rosiglitazone (n=333)</th>
<th>( P^* )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite of all-cause death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or hospitalization for myocardial ischemia</td>
<td>38 (11.2)</td>
<td>39 (11.7)</td>
<td>0.58</td>
</tr>
<tr>
<td>Composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke</td>
<td>10 (2.9)</td>
<td>14 (4.2)</td>
<td>0.31</td>
</tr>
<tr>
<td>All-cause death</td>
<td>7 (2.1)</td>
<td>8 (2.4)</td>
<td>0.72</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>3 (0.9)</td>
<td>4 (1.2)</td>
<td>0.50</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonfatal</td>
<td>6 (1.8)</td>
<td>7 (2.1)</td>
<td>0.71</td>
</tr>
<tr>
<td>Fatal</td>
<td>1 (0.3)</td>
<td>1 (0.3)</td>
<td>0.89</td>
</tr>
<tr>
<td>Stroke</td>
<td></td>
<td></td>
<td>0.13</td>
</tr>
<tr>
<td>Nonfatal</td>
<td>1 (0.3)</td>
<td>5 (1.5)</td>
<td></td>
</tr>
<tr>
<td>Fatal</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Coronary revascularization</td>
<td>27 (8.0)</td>
<td>26 (7.8)</td>
<td>0.82</td>
</tr>
<tr>
<td>Hospitalization for myocardial ischemia</td>
<td>7 (2.1)</td>
<td>11 (3.3)</td>
<td>0.25</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>3 (0.9)</td>
<td>8 (2.4)</td>
<td>0.14</td>
</tr>
</tbody>
</table>

Values are number of patients with an event (%). Noncardiovascular causes of death for the glipizide participants include cancer (n=2), septic shock (n=1), and spinal fracture with cord compression (n=1) and for the rosiglitazone participants include cancer (n=3) and chronic obstructive lung disease (n=1).

\(^*\)All \( P \) values calculated with the use of the Cox proportional hazards model with time to first event.

In this 1.5-year trial, rosiglitazone did not reduce progression of coronary artery plaque as measured by the primary IVUS end point of \( TAV_N \) compared with glipizide. The prespecified subgroup analyses suggest an effect of rosiglitazone on \( PAV \) in participants with the longest diabetes mellitus duration longer than the median duration of 4.9 years (ie, a 1.8% decrease versus a 0.5% increase in those with a shorter diabetes mellitus duration).

#### Discussion

In this 1.5-year trial, rosiglitazone did not reduce progression of coronary artery plaque as measured by the primary IVUS end point of \( PAV \) compared with glipizide. The prespecified subgroup analyses suggest an effect of rosiglitazone on \( PAV \) in participants with the longest diabetes mellitus duration longer than the median duration of 4.9 years (ie, a 1.8% decrease versus a 0.5% increase in those with a shorter diabetes mellitus duration).
Atherosclerotic plaque progression more than glipizide in light of the absence of benefit on the primary IVUS outcome. Although not significant, the APPROACH findings are qualitatively similar to those of a similar trial in which another thiazolidinedione (pioglitazone) was compared with glimepiride. In that trial, pioglitazone significantly reduced the primary outcome of PAV by 0.89% compared with glimepiride during 18 months of therapy (\(P=0.0001\)).

Table 4. Postrandomization Values and Medication Use at Final Visit

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Glipizide (n=229)</th>
<th>Rosiglitazone (n=233)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continuous variables</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean hemoglobin A(1c) (95% CI), %</td>
<td>6.9 (6.8–7.0)</td>
<td>7.0 (7.0–7.1)</td>
<td>0.01</td>
</tr>
<tr>
<td>Mean blood pressure (95% CI), mm Hg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>131.1 (129.6–132.6)</td>
<td>130.7 (129.3–132.2)</td>
<td>0.71</td>
</tr>
<tr>
<td>Diastolic</td>
<td>76.7 (75.8–77.7)</td>
<td>75.4 (74.5–76.4)</td>
<td>0.03</td>
</tr>
<tr>
<td>Mean LDL (95% CI), mg/dL</td>
<td>84.9 (80.7–89.1)</td>
<td>95.3 (91.0–99.6)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Mean HDL (95% CI), mg/dL</td>
<td>45.5 (44.3–46.7)</td>
<td>48.7 (47.5–49.9)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Median triglycerides (95% CI), mg/dL</td>
<td>156.2 (150.4–164.6)</td>
<td>146.5 (138.9–151.3)</td>
<td>0.14</td>
</tr>
<tr>
<td>Median hsCRP (95% CI), mg/L</td>
<td>1.9 (1.7–2.1)</td>
<td>0.9 (0.8–1.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Median MMP-9 (95% CI), ug/L</td>
<td>56.8 (54.2–61.0)</td>
<td>47.9 (44.4–50.8)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mean weight (95% CI), kg</td>
<td>83.6 (83.1–84.1)</td>
<td>84.0 (83.5–84.5)</td>
<td>0.22</td>
</tr>
</tbody>
</table>

Final visit medication use, No. (%)

<table>
<thead>
<tr>
<th></th>
<th>Glipizide</th>
<th>Rosiglitazone</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>190 (83.0)</td>
<td>199 (85.4)</td>
<td>0.52</td>
</tr>
<tr>
<td>Other antiplatelet</td>
<td>93 (40.6)</td>
<td>82 (35.2)</td>
<td>0.25</td>
</tr>
<tr>
<td>ß-blocker</td>
<td>152 (66.4)</td>
<td>158 (67.8)</td>
<td>0.77</td>
</tr>
<tr>
<td>ACE inhibitor or ARB</td>
<td>166 (72.5)</td>
<td>176 (75.5)</td>
<td>0.46</td>
</tr>
<tr>
<td>Nitrates</td>
<td>78 (34.1)</td>
<td>76 (32.6)</td>
<td>0.77</td>
</tr>
<tr>
<td>Statin</td>
<td>179 (78.2)</td>
<td>190 (81.5)</td>
<td>0.42</td>
</tr>
<tr>
<td>Fibrate or other lipid-lowering agent</td>
<td>27 (11.8)</td>
<td>35 (15.0)</td>
<td>0.34</td>
</tr>
<tr>
<td>Metformin</td>
<td>153 (66.8)</td>
<td>152 (65.2)</td>
<td>0.77</td>
</tr>
<tr>
<td>Any insulin</td>
<td>21 (9.2)</td>
<td>14 (6.0)</td>
<td>0.22</td>
</tr>
</tbody>
</table>

\(P\) values pertain to between-group differences in variables after randomization and in medication use at the final visit. hsCRP indicates high-sensitivity C-reactive protein; MMP-9, matrix metalloproteinase-9; ACE, angiotensin-converting enzyme; and ARB, angiotensin II receptor blocker.

Table 5. IVUS End Points

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Glipizide</th>
<th>Rosiglitazone</th>
<th>Treatment Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Value of IVUS Measurement (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD) PAV†</td>
<td>40.6 (11.0)</td>
<td>40.2 (11.4)</td>
<td>−0.64 (−1.46, 0.17)‡</td>
</tr>
<tr>
<td>Mean (SD) TAVN, mm^3‡</td>
<td>233.2 (115.2)</td>
<td>221.6 (100.7)</td>
<td>−5.12 (−9.98, −0.26)¶</td>
</tr>
<tr>
<td>Mean (SD) atheroma volume in the most diseased 10-mm segment, mm^3#</td>
<td>75.6 (32.6)</td>
<td>71.0 (30.0)</td>
<td>−1.7 (−3.93, 0.49)</td>
</tr>
<tr>
<td>Mean (SD) total vessel volume, mm^3</td>
<td>609.4 (311.8)</td>
<td>555.1 (298.0)</td>
<td>−3.6 (−12.15, 5.02)</td>
</tr>
<tr>
<td>Mean (SD) total lumen volume, mm^3</td>
<td>359.7 (195.7)</td>
<td>332.7 (192.4)</td>
<td>0.3 (−8.40, 9.05)</td>
</tr>
</tbody>
</table>

*Change from baseline for each allocated group was estimated with the use of ANCOVA with terms for treatment group, baseline value, geographic region, gender, entry cardiac procedure (angiography or PCI), and prior oral antidiabetic medication.
†Primary IVUS outcome.
‡Key IVUS secondary outcomes.
¶P=0.04.
#P<0.0001.
**P=0.02.

Similar \(P\) values were obtained for the primary and key secondary outcomes when reanalyzed with a nonparametric test on rank-transformed data. The treatment difference in PAV between the 21 glipizide and 28 rosiglitazone participants who both had a clinical outcome and a final evaluable IVUS was −0.24% (95% CI, −3.66, 3.18; \(P=0.89\)).
absence of a significant effect of rosiglitazone in this study may be due to the fact that the PAV in the glipizide control group only increased modestly with time. These observations and reports of similar beneficial effects of these 2 drugs on carotid intima-media thickness\textsuperscript{21,29} and the need for revascularization after PCI\textsuperscript{30} suggest that they have similar effects on atherosclerosis. Whether they have similar or different effects on cardiovascular outcomes remains uncertain, especially in light of recent meta-analyses relative to the cardiovascular safety of rosiglitazone.\textsuperscript{31–37} The effect of these drugs on cardiovascular outcomes can only be assessed by directly comparing them with each other and with placebo in a large head-to-head cardiovascular outcome trial. Such a trial (Thiazolidinedione Intervention With Vitamin D Evaluation [TIDE]) is now under way (http://www.clinicaltrials.gov; Unique Identifier NCT00879970).

Strengths of this study are the large sample size, the use of masked therapies, high adherence rates, achievement of similar levels of cardiovascular risk factors in both groups, and careful validated measurements of IVUS indices. These findings are limited by the fact that 32.5% of patients allocated to glipizide and 30% of patients allocated to rosiglitazone did not have 2 evaluable IVUS measurements. Moreover, the observation that patients without 2 evaluable IVUS measurements were less likely to have had a stent inserted at baseline and were on fewer antidiabetic agents than those who had the 2 IVUS measurements suggests that the patients who did have the 2 IVUS measurements were those with more advanced atherosclerosis at baseline. However, the findings of the worst-rank analysis, which includes 490 of the 672 randomized participants (73%) who received at least 1 dose of blinded medication and which was similar to the

<table>
<thead>
<tr>
<th>Subgroups</th>
<th>Treatment Difference</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% (95% CI)</td>
<td></td>
</tr>
<tr>
<td>Region:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AS</td>
<td>-1.61 (-3.02 to 0.151)</td>
<td>0.5380</td>
</tr>
<tr>
<td>EU</td>
<td>-0.73 (-1.07 to 0.038)</td>
<td>0.911</td>
</tr>
<tr>
<td>NA</td>
<td>0.35 (-0.02 to 0.715)</td>
<td>0.087</td>
</tr>
<tr>
<td>SA</td>
<td>-0.02 (-1.33 to 1.59)</td>
<td>0.9676</td>
</tr>
<tr>
<td>Coronary Angiography</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCI</td>
<td>-1.12 (-2.50 to 0.246)</td>
<td>0.098</td>
</tr>
<tr>
<td>Prior Dx:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug Native</td>
<td>1.15 (-0.811 to 3.146)</td>
<td>0.1290</td>
</tr>
<tr>
<td>Low Dose Combination Therapy</td>
<td>-1.35 (-3.929 to 0.331)</td>
<td>0.094</td>
</tr>
<tr>
<td>Metformin Monotherapy</td>
<td>-0.95 (-1.675 to 1.345)</td>
<td>0.173</td>
</tr>
<tr>
<td>SU Monotherapy</td>
<td>-1.91 (-2.998 to 0.368)</td>
<td>0.099</td>
</tr>
<tr>
<td>Age:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 80</td>
<td>0.12 (-0.064 to 1.310)</td>
<td>0.2743</td>
</tr>
<tr>
<td>&gt; 80</td>
<td>-1.19 (-2.537 to 0.252)</td>
<td>0.0743</td>
</tr>
<tr>
<td>Sex:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>-0.07 (-1.527 to 1.389)</td>
<td>0.3421</td>
</tr>
<tr>
<td>Male</td>
<td>-0.91 (-1.855 to 0.001)</td>
<td>0.098</td>
</tr>
<tr>
<td>BMI:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ Median</td>
<td>-0.95 (-1.721 to 0.615)</td>
<td>0.3541</td>
</tr>
<tr>
<td>&gt; Median</td>
<td>-0.92 (-1.698 to 0.039)</td>
<td>0.112</td>
</tr>
<tr>
<td>SYNTAX BP at Baseline:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 130 mmHg</td>
<td>-2.39 (-4.07 to 0.633)</td>
<td>0.0112</td>
</tr>
<tr>
<td>&gt; 130 mmHg</td>
<td>-2.22 (-4.231 to 0.659)</td>
<td>0.099</td>
</tr>
<tr>
<td>Statin Use at Baseline:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>-1.60 (-2.627 to 0.516)</td>
<td>0.0129</td>
</tr>
<tr>
<td>Yes</td>
<td>-0.31 (-1.393 to 0.582)</td>
<td>0.098</td>
</tr>
<tr>
<td>Diabetes Duration:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ Median</td>
<td>0.50 (-0.634 to 1.642)</td>
<td>0.0046</td>
</tr>
<tr>
<td>&gt; Median</td>
<td>-1.03 (-2.975 to -0.092)</td>
<td>0.007</td>
</tr>
<tr>
<td>HbA1c % at Baseline:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ Median</td>
<td>-0.77 (-1.837 to 0.338)</td>
<td>0.0691</td>
</tr>
<tr>
<td>&gt; Median</td>
<td>-0.35 (-1.557 to 0.857)</td>
<td>0.527</td>
</tr>
<tr>
<td>HDL-c at Baseline:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ Median</td>
<td>-1.02 (-2.284 to 0.248)</td>
<td>0.1111</td>
</tr>
<tr>
<td>&gt; Median</td>
<td>-0.02 (-2.113 to 1.077)</td>
<td>0.021</td>
</tr>
<tr>
<td>LDL-c at Baseline:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ Median</td>
<td>0.00 (-1.697 to 1.698)</td>
<td>0.9947</td>
</tr>
<tr>
<td>&gt; Median</td>
<td>-0.95 (-1.861 to 0.142)</td>
<td>0.072</td>
</tr>
<tr>
<td>Triglycerides at Baseline:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ Median</td>
<td>-0.20 (-1.839 to 0.714)</td>
<td>0.7120</td>
</tr>
<tr>
<td>&gt; Median</td>
<td>-0.22 (-1.498 to 0.149)</td>
<td>0.094</td>
</tr>
<tr>
<td>hsCRP at Baseline:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ Median</td>
<td>0.95 (-1.004 to 1.939)</td>
<td>0.303</td>
</tr>
<tr>
<td>&gt; Median</td>
<td>-1.49 (-2.657 to -0.321)</td>
<td>0.001</td>
</tr>
<tr>
<td>Percent Atherosoma Volume at Baseline:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ Median</td>
<td>-0.03 (-1.09 to 0.783)</td>
<td>0.9952</td>
</tr>
<tr>
<td>&gt; Median</td>
<td>-0.07 (-0.263 to 0.129)</td>
<td>0.495</td>
</tr>
</tbody>
</table>

Figure 3. Effect of rosiglitazone vs glipizide on the primary outcome of change in PAV according to predefined subgroups in patients with 2 evaluable IVUS measures. P values reflect the test for an interaction between the subgroups and allocation to rosiglitazone vs glipizide. Median values are as follows: body mass index (BMI), 28.9 kg/m\textsuperscript{2}; diabetes mellitus duration, 4.9 years; hemoglobin A\textsubscript{1c}, 7.1%; HDL, 42.5 mg/dL; LDL, 87.0 mg/dL; triglycerides, 165.0 mg/dL; high-sensitivity C-reactive protein (hsCRP), 5.2 mg/L; PAV, 41.3%. AS indicates Asia; EU, Europe, NA, North America, SA, South America; OAD, oral antidiabetic drug; SU, sulfonylurea; and BP, blood pressure.
analysis of patients with the 2 evaluable IVUS measurements, suggest that it is unlikely that data from these individuals would have substantively altered the findings. These findings are also limited by the observation that rosiglitazone participants had a higher hemoglobin A1C level and that glipizide-treated patients had a lower LDL level after randomization despite blinded adjustment of medications designed to achieve similar levels of hemoglobin A1C and LDL.

In summary, this study did not prove the hypothesis that rosiglitazone has a greater antiatherosclerotic effect than glipizide in patients with type 2 diabetes mellitus. However, reduced plaque progression in the presence of more advanced diabetes mellitus and the reduced secondary IVUS outcome suggest that there may be a benefit in some subgroups. Ongoing analyses will evaluate which factors relate to changes in atherosclerosis as measured by IVUS and will explore the effects of rosiglitazone on atherosclerosis and plaque in more detail.

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Disclosures

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References


**CLINICAL PERSPECTIVE**

The thiazolidinedione class of drugs has many favorable metabolic and vascular anatomic effects in people with type 2 diabetes mellitus. Whereas the Assessment on the Prevention of Progression by Rosiglitazone on Atherosclerosis in Diabetes Patients With Cardiovascular History (APPROACH) trial did not show a clear reduction in coronary atherosclerosis versus glipizide, its results are consistent with other studies of rosiglitazone and pioglitazone that did suggest reduced carotid and coronary atherosclerosis. Moreover, the large randomized outcomes trials of the thiazolidinediones that have been completed to date are consistent with the hypothesis that (1) pioglitazone may reduce cardiovascular outcomes compared with placebo and (2) the effect of rosiglitazone on cardiovascular outcomes is similar to that of metformin and to that of sulfonylureas. With the exception of fluid retention and pulmonary edema, these trial findings support the importance of clearly testing the cardiovascular effects of both of these drugs within 1 trial. The Thiazolidinedione Intervention With Vitamin D Evaluation (TIDE) trial is a large placebo-controlled trial of 16 000 participants that is currently assessing the cardiovascular effects of both thiazolidinediones versus placebo when added to current therapy. It will also clearly evaluate whether either of the 2 thiazolidinediones differ with respect to cardiovascular outcomes and will clearly determine whether either or both of these drugs prevents, promotes, or has a neutral effect on serious cardiovascular outcomes.
Effect of Rosiglitazone on Progression of Coronary Atherosclerosis in Patients With Type 2 Diabetes Mellitus and Coronary Artery Disease: The Assessment on the Prevention of Progression by Rosiglitazone on Atherosclerosis in Diabetes Patients With Cardiovascular History Trial

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