Pioglitazone Decreases Carotid Intima-Media Thickness Independently of Glycemic Control in Patients With Type 2 Diabetes Mellitus

Results From a Controlled Randomized Study

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Background—Patients with type 2 diabetes mellitus are at high risk of cardiovascular disease. Carotid intima-media thickness (IMT) is a strong predictor of myocardial infarction and stroke.

Methods and Results—We compared the effects of pioglitazone-based therapy (45 mg/d) and glimepiride-based treatment (2.7±1.6 mg/d) for 12 and 24 weeks on metabolic control (HbA1c), insulin resistance (homeostasis model assessment), and carotid IMT (B-mode ultrasonography) in a randomized controlled study in 173 orally treated patients with type 2 diabetes (66 women, 107 men; mean±SD age, 62.6±7.9 years; body mass index, 31.8±4.6 kg/m²; HbA1c, 7.5±0.9%). Treatment was generally well tolerated in both groups. Despite similar improvements in metabolic control (HbA1c) after 24 weeks (−0.8±0.9% [pioglitazone] versus −0.6±0.8% [glimepiride]; P=NS), carotid IMT was reduced only in the pioglitazone group after 12 weeks (−0.03±0.052 versus −0.002±0.047 mm [glimepiride]; P<0.01 between groups) and 24 weeks (−0.054±0.059 versus −0.011±0.058 mm [glimepiride]; P<0.005 between groups). Insulin resistance was also improved only in the pioglitazone group (homeostasis model assessment, −2.2±3.4 versus −0.3±3.3; P<0.0001 between groups). Reduction of IMT correlated with improvement in insulin resistance (r=0.29, P<0.0005) and was independent of improvement in glycemic control (r=0.03, P=0.68).

Conclusions—We found a substantial regression of carotid IMT, independent of improved glycemic control, after 12 and 24 weeks of pioglitazone treatment. This finding may have important prognostic implications for patients with type 2 diabetes mellitus. (Circulation. 2005;111:2525-2531.)

Key Words: atherosclerosis ■ carotid arteries ■ diabetes mellitus ■ insulin resistance

Patients with type 2 diabetes mellitus are at high risk for cardiovascular disease; their risk is 2- to 6-fold higher than that in persons without diabetes. The clustering of traditional risk factors such as arterial hypertension and hypercholesterolemia cannot explain the excessive cardiovascular burden of patients with type 2 diabetes. Studies such as the UKPDS targeting blood glucose with oral antidiabetic agents have not shown improvement in cardiovascular risk. Multifactorial intervention is effective in reducing cardiovascular morbidity and mortality in patients with type 2 diabetes, but studies on cardiovascular end points are scarce.

Peroxisome proliferators activator receptor (PPAR)-γ activation by thiazolidinediones is a promising treatment for diabetes mellitus; it reduces insulin resistance and leads to improved glycemic control in patients with type 2 diabetes mellitus. PPAR-γ agonists have displayed unique characteristics in both animal and clinical studies, indicating that they have antiatherogenic effects. They inhibit the production of inflammatory cytokines in monocytes, induce apoptosis in macrophages, and reduce the expression of adhesion molecules in endothelial cells. These effects have been seen in both diabetic and nondiabetic atherosclerosis-prone animal models. An antiatherogenic effect also exists in humans. Two pilot studies with troglitazone and pioglitazone have shown reduced carotid intima-media thickness (IMT) in patients with type 2 diabetes mellitus.

Carotid IMT is a well-described surrogate marker for cardiovascular risk. A thickened carotid intima-media layer correlates not only with the presence of cardiovascular risk factors but also with the risk of future macrovascular events such as myocardial infarction and stroke. The interventional approach to reduce cardiovascular risk factors with ACE system blockers, calcium antagonists, or β-blockers can result in a reduction in progression or even net regression of...
carotid IMT. The most potent agents to date are the statins, which have consistently shown effects on carotid IMT in nondiabetic patients with hypercholesterolemia and/or atherosclerotic disease. However, carotid IMT is bigger in patients with type 2 diabetes compared with control subjects, reflecting the excessive cardiovascular risk of this particular patient population. Only limited evidence exists with respect to the effect of intervention in type 2 diabetes on carotid IMT; antiplatelet therapy and ACE inhibition slow the progression of thickening, and amlodipine has been shown to reduce carotid IMT in a small patient group. Thiazolidinediones also reduced carotid IMT in some studies, but at the same time, glycemic control was substantially improved in these trials. Therefore, the question remains whether thiazolidinediones may inhibit atherosclerosis independently of glycemic control in patients with type 2 diabetes.

We conducted the present study to investigate whether pioglitazone therapy decreases carotid IMT in patients with type 2 diabetes for a period of 24 weeks. To neutralize possible concomitant effects of improved metabolic control in the pioglitazone-treated group, a glimepiride-based comparator control group was treated to achieve a similar metabolic status.

**Methods**

**Study Subjects**

In a monocentric study, 192 orally treated patients with type 2 diabetes mellitus who had never received thiazolidinediones were consecutively randomized to receive either a fixed dose of pioglitazone 45 mg in the morning or glimepiride 1 to 6 mg/d titrated for optimal glycemic control for 24±4 weeks. Inclusion criteria were previously known type 2 diabetes treated with oral antidiabetic agents, age of 40 to 75 years, HbA1c 6.6% and <7.0%, individual medical advice was given to every patient at the beginning and offered throughout the duration of the study. Other additional oral antidiabetic therapy, including sulfonylurea but not metformin, was permitted in the pioglitazone group. In the glimepiride group, all kinds of other oral treatment except thiazolidinediones were permitted. Average compliance assessed by table count (amount taken divided by amount prescribed) was comparable in both groups (pioglitazone, 98.5%; glimepiride, 106.1%; overall, 101.1%). All measurements were obtained in the morning with the patient fasting from midnight on. Patients were asked to refrain from coffee and tea for 8 hours before study visits. Blood pressure was measured with the patient in a sitting position for ≥5 minutes with the cuff selected for appropriate width (cuff bladder encircling ≥80% of the arm) on the left arm. Patient height was measured at the first visit, and patient weight without clothing other than underwear was measured at the first and every subsequent visit.

**Biochemical Parameters**

Blood samples were immediately centrifuged, and plasma and serum samples were kept at −20°C until laboratory testing. HbA1c was determined by means of high-performance liquid chromatography (Adams TMA1C HA-8160, Menarini Diagnostics). Glucose was measured with a standard glucose oxidase reference method (Super GL, RTL). Fasting serum insulin was determined by means of chemiluminescence (MLT Insulin Assay, Sckema). Insulin resistance was calculated from the fasting insulin and glucose values by means of the homeostasis model assessment (HOMA-IR) analysis (HOMA-IR score equals insulin [mU/L] times glucose [mmol/L] divided by 22.5), with values >2 classified as insulin resistant.

Total cholesterol was measured with an enzymatic color test (OSR 6116 and 6216, Olympus Diagnostica); LDL, by a selective protection method (OSR 6183 and 6283, Olympus Diagnostica); HDL, by an immunoinhibition method (OSR 6187 and 6287, Olympus Diagnostica); and triglycerides, by enzymatic color testing (OSR 6153, Olympus Diagnostica; all on Olympus AU 640, Olympus Diagnostic). Free fatty acids were measured with an enzymatic test (Nefac, Wako Chemicals GmbH, on Hitachi 717, Roche Diagnostics), and turbidimetric methods were used to determine the following parameters: high-sensitivity C-reactive protein (hsCRP: Olympus) and von Willebrand factor (Instrumentation Laboratory GmbH).

**Carotid IMT**

Carotid IMT was evaluated 3 times by a single operator at intervals of 12±2 weeks with high-resolution B-mode ultrasonography on a single machine (Caris Plus, Esatoe SpA) with a 10-MHz linear-array transducer (LA 523). All recordings were obtained with the patient resting in a supine position, with the head turned slightly to the contralateral side and simultaneous ECG recording. The common coronary artery, including the carotid bulb, was visualized, and 2 longitudinal B-mode images of the left and the right common carotid arteries at end diastole (onset of the R wave in the ECG) were recorded and electronically stored.

In a separate reading center, the technically best image of either side was measured by 1 physician blinded to patient profile and treatment assignment. Having the same sonographer and reader at both patient visits provided the highest intraclass correlation coefficient. Measurements of carotid IMT were conducted in the 10-mm linear segment proximal to the carotid bulb at 2 plaque-free sites twice in the near wall and twice in the far wall on both sides and combined as mean carotid IMT. The combination of readings from the near and far walls yields the strongest association with cardiovascular disease. Because a separate analysis of the right or the common carotid artery had no influence on study results, the average IMT of both sides was used for all analyses. Plaques, defined as a local thickness of ≥2 mm, were documented.

The reproducibility of the ultrasonographic method was tested in a subset of 19 chosen randomly patients who underwent the measurement protocol twice within 1 to 5 days. The average difference in carotid IMT between these paired measurements was 0.012±0.008 mm, or 1.18% of the mean carotid IMT. The intraclass correlation coefficient was 0.99 (P<0.001).

**Statistical Analysis**

Statistical analysis was performed by means of appropriate parametric and nonparametric methods. Treatment groups were compared at baseline by using a Wilcoxon rank-sum test for continuous variables and χ² for categorical variables. Statistical evaluation of changes from baseline was performed by means of ANCOVA models, with treatment group as a factor and baseline value as a covariate. The difference between treatment groups was assessed by using t statistics for the hypothesis that treatment group is a relevant factor in the model. The change from baseline within each treatment group was assessed by using t test statistics for the hypothesis of least-square mean equal to 0 within the ANCOVA model. The correlation was assessed with Spearman’s correlation coefficient. Summary statistics are presented as mean±SD. Because treatment with renin-angiotensin system–inhibiting substances and statins might lead to
The average dose of glimepiride per day was 2.7 mg, and the daily dose range was 1 to 6 mg/d. Because the dose of glimepiride could be decreased significantly (\(P = 0.0001\)), peripheral edema (21 versus 2; \(P = 0.0001\)), dyspnea on exertion (3 versus 0; \(P = 0.2464\)), and cardiac failure (2 versus 0; \(P = 0.4976\)); the 2 patients with cardiac failure required hospitalization. The first patient, a 68-year-old white male, had a medical history of arterial hypertension and coronary heart disease. He was admitted to the hospital for dyspnea and angina pectoris after taking pioglitazone for 3 months. At admission, mild congestive heart failure secondary to a hypertensive crisis was diagnosed, and acute coronary syndrome was ruled out. He was treated with intensified antihypertensive treatment and diuretic, recovered well, and was discharged after 1 week. This patient continued the study and finished the full study duration of 6 months without further complications. The second patient was a 58-year-old white male who had a history of type 2 diabetes mellitus, arterial hypertension, hypercholesterolemia, and peripheral artery disease before the study. Three weeks after starting pioglitazone, he became increasingly dyspneic and was admitted to the hospital. He had left ventricular failure secondary to coronary heart disease and atrial fibrillation. The patient recovered after angioplasty of 2 stenoses in his left anterior descending coronary artery and spontaneous conversion to sinus rhythm. Because of continued severely impaired left ventricular function at echocardiography, he was withdrawn from the trial.

### Results

#### General Results

Both treatment groups were similar with respect to age, gender distribution, glycemic status, presence of cardiovascular risk factors, and baseline carotid IMT. Concomitant treatment with renin-angiotensin system inhibition (defined as ACE inhibition or angiotensin receptor type 1 antagonist) and statin treatment, both of which might affect carotid IMT, were equally distributed in both groups at the start and end of the study (Table 1).

Of 192 enrolled patients, 179 were treated (92 in the pioglitazone group, 87 in the glimepiride group), and 173 were included in the per-protocol analysis population (89 in the pioglitazone group, 87 in the glimepiride group). The study was fully completed by 162 patients (81 in each group). The most frequent reason for early termination was patient decision (7 in the pioglitazone group, 3 in the glimepiride group; \(P = 0.2258\)). All patients in the pioglitazone group received 45 mg/d. Because the dose of glimepiride could be adjusted during the study, the daily dose range was 1 to 6 mg/d. The average dose of glimepiride per day was 2.7 ± 1.6 mg.

### Safety and Tolerability

Both treatments were generally well tolerated; in particular, symptomatic hypoglycemia was distributed equally in both groups (21 episodes in 17 patients in the pioglitazone group, 26 episodes in 17 patients in the glimepiride group; \(P = 0.8563\)). No episodes of severe hypoglycemia (defined as need for external help because of hypoglycemia) were recorded. Study termination as a result of drug-related side effects was reported in 1 patient in the pioglitazone group. Treatment with pioglitazone was associated with a higher number of cases of increased body weight (20 versus 2; \(P < 0.0001\)), peripheral edema (21 versus 2; \(P < 0.0001\)), dyspnea on exertion (3 versus 0; \(P = 0.2464\)), and cardiac failure (2 versus 0; \(P = 0.4976\)); the 2 patients with cardiac failure required hospitalization. The first patient, a 68-year-old white male, had a medical history of arterial hypertension and coronary heart disease. He was admitted to the hospital for dyspnea and angina pectoris after taking pioglitazone for 3 months. At admission, mild congestive heart failure secondary to a hypertensive crisis was diagnosed, and acute coronary syndrome was ruled out. He was treated with intensified antihypertensive treatment and diuretic, recovered well, and was discharged after 1 week. This patient continued the study and finished the full study duration of 6 months without further complications. The second patient was a 58-year-old white male who had a history of type 2 diabetes mellitus, arterial hypertension, hypercholesterolemia, and peripheral artery disease before the study. Three weeks after starting pioglitazone, he became increasingly dyspneic and was admitted to the hospital. He had left ventricular failure secondary to coronary heart disease and atrial fibrillation. The patient recovered after angioplasty of 2 stenoses in his left anterior descending coronary artery and spontaneous conversion to sinus rhythm. Because of continued severely impaired left ventricular function at echocardiography, he was withdrawn from the trial.

### Effects of Pioglitazone and Glimepiride After 12±2 Weeks

After adjustment for statin and RAS inhibitor therapy, IMT decreased significantly (\(P < 0.0001\)) by \(-0.033 ±0.052\) mm in the pioglitazone group, whereas no significant change was...
noted in the glimepiride group (−0.002 ± 0.047 mm; Figure 1). Glycemic control as determined by HbA1c was not different between groups (pioglitazone, −0.44 ± 0.76%; glimepiride, −0.51 ± 0.69%; P = 0.3366).

Effects of Pioglitazone and Glimepiride After 24±4 Weeks

After adjustment for statin and RAS inhibitor therapy, a further continuous decrease (−0.054 ± 0.059 mm) was found in carotid IMT in the pioglitazone group that was more pronounced than the changes in the glimepiride group (−0.011 ± 0.058 mm; P < 0.0001) (Figure 1). HbA1c decreased by a substantial and similar magnitude in the pioglitazone (−0.8 ± 0.9%) and glimepiride (−0.6 ± 0.8%, P = 0.1291) groups. The values for hsCRP decreased only in the pioglitazone group (pioglitazone, −0.80 ± 0.29 mg/L; glimepiride, −0.14 ± 0.23; P < 0.0005).

In both treatment groups, a decrease was observed in the glucose values that was again more pronounced in the pioglitazone group (pioglitazone, −18 ± 34 mg/dL; glimepiride, −5 ± 31 mg/dL; P < 0.01). Fasting serum insulin concentrations decreased significantly (P < 0.001) in only the pioglitazone group (−4.69 ± 6.20 mU/L), whereas they remained constant in the glimepiride group (0.37 ± 5.67 mU/L). HOMA-IR score was reduced by −2.21 ± 3.40 in the pioglitazone group, whereas no change occurred in the glimepiride group (0.27 ± 3.30; P < 0.0001 between the groups).

In parallel, an improvement was seen in blood pressure in the pioglitazone group only (systolic: −9.4 ± 20.1 mm Hg, P < 0.0001; diastolic: −4.4 ± 11.2 mm Hg, P = 0.001), whereas it was unchanged in the glimepiride group (systolic: −1.4 ± 19.6 mm Hg, P = 0.2788; diastolic: 1.2 ± 11.2 mm Hg, P = 0.6919; P < 0.01 for both parameters between groups at end point). A summary of all observation parameters is given in Table 2.

Factors Determining the Change in IMT

To identify possible mechanisms for the observed decrease in carotid IMT, important risk factors, including HbA1c, fasting serum glucose and insulin, LDL and HDL cholesterol, HOMA-IR score, arterial blood pressure, and hsCRP, were analyzed regarding their relation to the change in IMT (Table 3). HbA1c did not correlate with the change in IMT in either the pooled sample or any treatment group. In the pooled analysis, correlation of the change in IMT and the change in HOMA-IR score, fasting serum glucose, and serum insulin was detected. In the pioglitazone group, a significant corre-
lation was detected for changes in IMT and serum insulin (0.32, \(P < 0.005\)) and HOMA-IR score (0.26, \(P < 0.05\)) but not with fasting serum glucose levels; in the glimepiride group, a significant correlation was detected between changes in IMT fasting serum glucose level (0.28, \(P < 0.05\)) only.

To further analyze the interaction between the parallel reductions in IMT and hsCRP in the pioglitazone group, patient groups were stratified according to low-risk (<1 mg/L), intermediate-risk (1 to 3 mg/L), and high-risk (>3 mg/L) hsCRP levels\(^{30}\) at study entry. All patients in the different risk groups had a comparable reduction in IMT when treated with pioglitazone and no changes with glimepiride (see Figure 2).

### Discussion

Therapy with pioglitazone for 24 weeks decreased carotid IMT in patients with type 2 diabetes, and this effect was independent of glycemic control. Other confounding factors such as renin-angiotensin system inhibition,\(^{24}\) statins,\(^{31}\) and antiplatelet therapy\(^{23}\) were well controlled either by equal distribution among the treatment groups or by adjusted analysis. Pioglitazone therapy was accompanied by a greater incidence of peripheral edema and weight gain in our study.

Patients with type 2 diabetes mellitus are at high risk for cardiovascular events, and so far, only limited data exist on the cardiovascular benefit of agents targeted to treat hyperglycemia. Carotid IMT has proved to be a powerful tool for assessing cardiovascular risk. Results of a number of small studies have shown that reduced progression\(^{23,24}\) or net regression\(^{13,14,32}\) of carotid IMT is attainable in patients with type 2 diabetes mellitus. Large trial results demonstrated that in patients with hypercholesterolemia, statins inhibit the progression of IMT.\(^{19,33}\) Recently, results of the ARBITER trial showed that aggressive lowering of LDL leads to regression of carotid IMT in patients with hypercholesterolemia.\(^{31}\) Relative regression of IMT in this trial was 2% to 3% in 6 months and 5% to 6% in 12 months. In comparison, we observed a relative reduction of 5.5% after 24 weeks of pioglitazone treatment. Thus, the regression of IMT with pioglitazone in patients with type 2 diabetes in our trial seems to be of the same magnitude as the regression achieved with high-dose statin therapy in hypercholesterolemia. Although not controlled for improvement in glucose metabolism, 2 previous small pilot trials with thiazolidinediones in patients with type 2 diabetes showed a similar and rapid reduction in carotid IMT within 3 months.\(^{13,14}\) Taken together, thiazolidinediones seem to lead to carotid IMT regression in patients with type 2 diabetes mellitus within months, and the magnitude of the reduction is comparable to the effect of high-dose statin therapy in patients with hypercholesterolemia. This effect may continue.

The findings of our study imply that improved glycemic control is unlikely to be the cause of IMT decrease; both the pioglitazone and glimepiride groups had comparable HbA\(_1c\) values before and after the study. However, patients in the pioglitazone group had slight but significant improvements in systolic and diastolic blood pressures, HDL, and triglycerides compared with the control group. This improvement might be

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**Table 3. Spearman Coefficient for Correlation With the Relative Change in IMT After 24 Weeks of Treatment**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Pioglitazone Coefficient</th>
<th>Pioglitazone (P)</th>
<th>Glimepiride Coefficient</th>
<th>Glimepiride (P)</th>
<th>All Patients Coefficient</th>
<th>All Patients (P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting serum glucose</td>
<td>0.05</td>
<td>0.6321</td>
<td>0.28</td>
<td>0.0117</td>
<td>0.18</td>
<td>0.0262</td>
</tr>
<tr>
<td>Fasting serum insulin</td>
<td>0.32</td>
<td>0.0044</td>
<td>-0.02</td>
<td>0.8735</td>
<td>0.28</td>
<td>0.0005</td>
</tr>
<tr>
<td>HOMA-IR score</td>
<td>0.26</td>
<td>0.0250</td>
<td>0.12</td>
<td>0.3072</td>
<td>0.29</td>
<td>0.0003</td>
</tr>
<tr>
<td>HbA(_1c)</td>
<td>-0.11</td>
<td>0.3447</td>
<td>0.11</td>
<td>0.3160</td>
<td>0.03</td>
<td>0.6810</td>
</tr>
<tr>
<td>hsCRP</td>
<td>0.05</td>
<td>0.6545</td>
<td>0.13</td>
<td>0.2504</td>
<td>0.10</td>
<td>0.2268</td>
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<tr>
<td>Body mass index</td>
<td>0.02</td>
<td>0.8596</td>
<td>-0.17</td>
<td>0.1218</td>
<td>-0.17</td>
<td>0.0322</td>
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<tr>
<td>Systolic blood pressure</td>
<td>-0.01</td>
<td>0.9575</td>
<td>-0.10</td>
<td>0.3581</td>
<td>0.01</td>
<td>0.9022</td>
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<tr>
<td>Diastolic blood pressure</td>
<td>-0.03</td>
<td>0.7874</td>
<td>-0.15</td>
<td>0.1780</td>
<td>-0.03</td>
<td>0.7308</td>
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<tr>
<td>Total cholesterol</td>
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<td>0.5093</td>
<td>0.08</td>
<td>0.4606</td>
<td>-0.03</td>
<td>0.6912</td>
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<tr>
<td>LDL cholesterol</td>
<td>0.06</td>
<td>0.5910</td>
<td>0.01</td>
<td>0.9204</td>
<td>-0.02</td>
<td>0.7845</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>-0.01</td>
<td>0.9506</td>
<td>-0.09</td>
<td>0.4276</td>
<td>-0.07</td>
<td>0.3916</td>
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<tr>
<td>LDL/HDL ratio</td>
<td>0.01</td>
<td>0.9137</td>
<td>-0.09</td>
<td>0.4436</td>
<td>0.05</td>
<td>0.5521</td>
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<tr>
<td>Triglycerides</td>
<td>0.20</td>
<td>0.0698</td>
<td>0.11</td>
<td>0.3466</td>
<td>0.17</td>
<td>0.0293</td>
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<tr>
<td>Free fatty acids</td>
<td>0.05</td>
<td>0.6645</td>
<td>-0.15</td>
<td>0.1755</td>
<td>0.01</td>
<td>0.9328</td>
</tr>
<tr>
<td>Von Willebrand factor</td>
<td>0.14</td>
<td>0.2410</td>
<td>-0.04</td>
<td>0.7041</td>
<td>0.04</td>
<td>0.5933</td>
</tr>
</tbody>
</table>

**Figure 2.** Mean decrease in carotid IMT in patients in 3 different hsCRP risk groups.\(^{30}\)
closely linked to the improvement of insulin resistance also seen in the pioglitazone group. In other trials, treatment with PPAR-γ activators has resulted in a reduction in cardiovascular risk factors such as dyslipidemia and hypertension in type 2 diabetic and nondiabetic patients. Insulin resistance is associated with a clustering of cardiovascular risk factors, including suppression of insulin-mediated nitric oxide production in the endothelium, increased carotid IMT, and suppression of vasoprotective adipocytokines such as adiponectin; it has been proposed as the common link between type 2 diabetes and cardiovascular disease. Overall protective metabolic effects of thiazolidinediones in prediabetic women with previous gestational diabetes and insulin resistance have been shown by Buchanan et al in the TRIPOD study. Thus, we can conclude that thiazolidinediones reduce insulin resistance, which leads to an increase in adiponectin, followed by a decrease in endothelial adhesion molecule secretion. Thus, the improvement in several components of the metabolic syndrome jointly may be the reason for reduced IMT in the pioglitazone group.

However, a growing body of evidence clearly supports thiazolidinedione vasculoprotective effects that are independent of metabolic control. In patients with type 2 diabetes mellitus, neointimal tissue proliferation after coronary stent placement was inhibited independently of glycemic control. Rosiglitazone inhibited progression of carotid IMT in nondiabetic patients with coronary heart disease. We and prior investigators found that PPAR-γ activation lowers hsCRP. In our study, a similar degree of IMT reduction was found at low, intermediate, and high baseline concentrations of hsCRP. Anti-inflammatory effects may contribute to the link between IMT reduction and pioglitazone therapy as suggested by other investigators; however, a causal relationship cannot be deducted from our findings because no correlation could be found between the degree of changes in hsCRP and IMT. Moreover, PPAR-γ activation leads to a reduction in blood concentrations of matrix metalloproteinase-9 and soluble CD40 ligand, both new markers of cardiovascular risk. In conclusion, thiazolidinediones seem to exert antiatherogenic effects through a multitude of mechanisms, including a decrease in insulin resistance, inhibition of atherogenic processes in the vascular wall, and a reduction in established and new cardiovascular risk factors. The results of our study cannot distinguish between the possible mechanisms or explain the pathogenetic principle underlying the reduction of carotid IMT; more studies are necessary to elucidate the interactions.

In the SECURE study, a substudy of the large HOPE trial, the slowing of carotid IMT progression was linked to a parallel reduction in stroke incidence of the same magnitude. It seems possible that the decrease in carotid IMT observed in our study would lead to at least the same, if not even a greater, reduction in cardiovascular morbidity and mortality, but this subject needs to be addressed in end-point trials.

**Study Limitations**

Carotid IMT is the only noninvasive imaging test recommended by the American Heart Association for evaluating the risk of coronary artery disease. However, there is no generally accepted standardized method to measure carotid IMT. The distal portion of the common carotid artery is validated for its reproducibility and is relatively free of plaques, which commonly occur at the origin of the internal carotid artery. Carotid IMT is a parameter for early measurement of atherosclerosis, and including plaques in the analysis may potentially lead to overestimation of the atherosclerotic burden.

The study was not performed in a double-blind fashion, which may be regarded as a disadvantage. The reason for the open design is the dissimilar pharmacodynamic effects of both agents used. Glimepiride needs to be uptitrated to prevent hypoglycemic episodes, whereas upitation is not required for pioglitazone. In an effort to overcome possible bias, we blinded the sonographer and image analyzer to patient profile and treatment arm.

In conclusion, we have shown that treatment with pioglitazone for 24 weeks leads to a significant decrease in carotid IMT in patients with type 2 diabetes that is independent of glycemic control. Our study results support the growing body of evidence for an anti-atherogenic effect of PPAR-γ activators that reach beyond glycemic control and might imply prognostic benefits for patients treated with this class of drugs and especially for patients with type 2 diabetes.

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