Increased High-Density Lipoprotein Cholesterol Predicts the Pioglitazone-Mediated Reduction of Carotid Intima-Media Thickness Progression in Patients With Type 2 Diabetes Mellitus

Michael Davidson, MD; Peter M. Meyer, PhD; Steven Haffner, MD; Steven Feinstein, MD; Ralph D’Agostino, Sr, PhD; George T. Kondos, MD; Alfonso Perez, MD; Zhen Chen, MS; Theodore Mazzone, MD

Background—Measurement of carotid intima-media thickness (CIMT) has been validated as a measure of atherosclerosis and as a predictor of future cardiovascular events. Compared with glimepiride, pioglitazone has been shown to slow the progression of atherosclerosis measured by CIMT in patients with type 2 diabetes mellitus.

Methods and Results—We evaluated individual cardiovascular risk factors as predictors of the change in CIMT produced by pioglitazone treatment by determining whether their addition to a baseline model resulted in loss of significance for the treatment effect on CIMT. Pioglitazone treatment led to improvement in levels of multiple cardiovascular risk markers, including high-sensitivity C-reactive protein, apolipoprotein B, apolipoprotein A1, high-density lipoprotein (HDL) cholesterol, triglyceride, insulin, and free fatty acid. At 24 weeks, there were significant differences in HDL cholesterol, triglyceride, total cholesterol, low-density lipoprotein cholesterol, insulin, body mass index, hip circumference, and high-sensitivity C-reactive protein between the pioglitazone and glimepiride treatment groups. After adjustment for 24-week on-treatment values of cardiovascular risk factors, only inclusion of the changes in HDL cholesterol and insulin significantly impacted the magnitude and significance of the treatment effect on CIMT. Furthermore, irrespective of treatment assignment, increased HDL cholesterol at 24 weeks was a significant predictor of reduced CIMT progression at 72 weeks.

Conclusions—The beneficial effect of pioglitazone on HDL cholesterol at 24 weeks predicted its beneficial effect for reducing CIMT progression at 72 weeks. Changes in HDL cholesterol at 24 weeks, irrespective of treatment, predicted less progression of CIMT at 72 weeks. These results suggest that suppression of atherosclerosis with pioglitazone therapy is linked to its ability to raise HDL cholesterol. (Circulation. 2008;117:2123-2130.)

Key Words: atherosclerosis ■ lipoproteins ■ diabetes mellitus

Measurement of carotid intimal-medial thickness (CIMT) is a validated approach for monitoring atherosclerosis progression, and CIMT has been shown to be highly predictive of future cardiovascular events and cardiovascular death.1-4 Measurement of CIMT has also been shown to be useful for assessing the effect of therapeutic agents on atherosclerosis progression or regression. Statins and niacin, both established agents for reducing cardiovascular events, have also been shown to reduce progression of CIMT.5-7 There is currently a large increase in the prevalence of diabetes, and cardiovascular disease is the most important cause of morbidity and mortality in diabetes.8,9 It is therefore important to assess new approaches for reducing the risk of cardiovascular disease in subjects with diabetes.10,11 In the CHICAGO study (Carotid Intima-Media Thickness in Atherosclerosis Using Pioglitazone),12 the effect of pioglitazone versus glimepiride on CIMT in subjects with type 2 diabetes mellitus was assessed over a 72-week treatment period. The study was designed to test the hypothesis that pioglitazone would have a beneficial effect for reducing CIMT progression compared with glimepiride. This hypothesis was based on the established effects of thiazolidinediones in reducing...
atherosclerosis in animal models and favorably modifying cardiovascular risk factors in humans. For example, in patients with type 2 diabetes mellitus, treatment with pioglitazone has been shown not only to improve indices of glycemia but also to favorably modify levels of inflammatory factors, coagulation factors, lipid and apolipoprotein levels, and blood pressure.

Clinical Perspective p 2130

In the CHICAGO study, pioglitazone significantly reduced progression of mean CIMT in the posterior wall of the common carotid arteries compared with glimepiride. Pioglitazone also reduced progression of maximum CIMT at this site. In addition to measuring treatment-related changes on CIMT in the CHICAGO trial, the investigators also measured the treatment effect on parameters implicated as cardiovascular risk factors in diabetes. The availability of these measures provides an important opportunity for analyzing the relationship of these factors to a validated measure of atherosclerosis progression in diabetes. The importance of this analysis is emphasized by recent reports that large increases in high-density lipoprotein (HDL) cholesterol, a well-validated protective factor against atherosclerosis and cardiovascular disease events in observational studies, did not have a beneficial effect on atherosclerosis progression in subjects treated with torcetrapib, an inhibitor of cholesterol ester transfer protein. Examination of the relationship of treatment-related changes in cardiovascular risk factors to changes in atherosclerosis could also provide insight into a potential mechanism for the beneficial effect of pioglitazone on atherosclerosis.

Here, we present detailed results concerning the effects of pioglitazone and glimepiride on cardiovascular risk factors in diabetes. We further evaluate the relationship of baseline and on-treatment changes in cardiovascular risk factors to treatment-related changes in CIMT over the course of the study.

Methods

Study Design and Participants

CHICAGO was a prospective, randomized, double-blind, comparator-controlled, multicenter study conducted between October 2003 and May 2006 in a multiracial and multiethnic population at 28 clinical sites in the Chicago, Ill, metropolitan area. Eligible subjects were men and women 45 to 85 years of age with type 2 diabetes mellitus (by American Diabetes Association criteria) who were newly diagnosed; had their diabetes controlled by diet or by taking sulfonylurea or metformin monotherapy, sulfonylurea/metformin combination therapy, or insulin; and were asymptomatic for coronary artery disease. The complete trial design has been reported previously.

Randomized treatment consisted of pioglitazone hydrochloride (15 to 45 mg/d) or glimepiride (1 to 4 mg/d). The use of metformin or insulin was allowed in either group to reach glycemic goals. The study protocol specified adherence to American Diabetes Association guidelines for lipid and blood pressure control that were current at the start of the study. The primary end point of the study was absolute change from baseline to final visit in mean posterior-wall CIMT in the right and left common carotid arteries. Absolute change in maximal CIMT from baseline to final visit was included as a secondary end point.

The study protocol was approved by central or local institutional review board committees, and all participants provided written informed consent.

Laboratory Measurements

The following parameters were measured at a central laboratory (Clinical Reference Laboratory; Lenexa, Kan): triglyceride, total cholesterol, and plasma glucose levels from fasting blood samples, measured by standard enzymatic methods (Roche Diagnostics, Indianapolis, Ind); HDL and low-density lipoprotein (LDL) cholesterol, measured by direct methods, and hemoglobin A1C values, measured by high-performance liquid chromatography (Bio-Rad, Hercules, Calif); free fatty acid, measured by the Wako enzymatic method (Wako Chemicals, Richmond, Va); apolipoprotein (apo)-B and apo-A1, measured by immunoturbidimetry (Hitachi/Roche Diagnostics, Basel, Switzerland); human insulin, measured by ELISA (Linco, St. Charles, Mo); and high-sensitivity C-reactive protein (hs-CRP), measured by immunoturbidimetry (Roche Diagnostics). Methods for CIMT measurements have been described in detail previously.

Statistical Analysis

Means, SDs, medians, and quartiles were used to summarize baseline values and changes in values of the various measures at 24 and 72 weeks. The average percent of missing values was small at baseline and at 24 weeks (1.3% at baseline, 4.6% at 24 weeks, and 19.1% at 72 weeks). Consistent with the primary outcome report, we used the last observation carried forward for CIMT at 72 weeks to include data from subjects who participated in the study but did not complete the entire study. Statistical tests were used to compare 24- and 72-week observed values with baseline. Lipids, fasting plasma glucose, and insulin were log-transformed before tests were performed because of skewed distributions. With the exception of hs-CRP, probability values from paired t tests were used as indicators of whether changes over time within treatment groups were significant. We tested for differences in hs-CRP using paired Wilcoxon tests.

We estimated and tested for treatment group differences for each cardiovascular risk predictor in terms of baseline and 24-week changes using observed values. Baseline and 24-week differences were tested with ANCOVA models. Baseline models adjusted for site and treatment group, whereas models for 24-week change also included baseline values as a covariate. Lipids, fasting plasma glucose, and insulin were log-transformed because of skewed distributions. There were 25 models fit for each time category, so we determined significance using a Bonferroni adjusted cutoff of 0.05/25 = 0.002.

Primary interest of the present study focused on identifying predictors and potential mediators of the treatment effect. To identify these, we added change (measured at 24 weeks) to an ANCOVA model for 72-week change in CIMT that already included baseline CIMT (consistent with the International Conference on Harmonisation E9 guidelines), site, and treatment group. The percentage change in the treatment effect estimate relative to a model that did not include the new predictor was calculated, as was the probability value for the treatment effect in the new model. Those predictors that resulted in the treatment effect becoming nonsignificant were identified as predictors, and therefore potential mediators, of the treatment effect. We next added these to ANCOVA models that included only baseline CIMT and site, to evaluate their relationship to CIMT before adjustment for treatment effect (ie, irrespective of treatment).

We examined Cook's distance (to determine whether conclusions rested only on a few influential values) for observations in models that included HDL cholesterol and insulin and repeated fits after the exclusion of observations with the largest values of Cook's distance. Because results were similar to the results utilizing the full sample, results for the reduced sample are not shown. We used a bootstrap analysis to test whether the impact of HDL cholesterol on the treatment effect estimate was sensitive to small changes in sample composition. Using 10,000 ordinary replicates, we constructed bias-corrected and adjusted CIs for the treatment effect and com...
Table 1. Descriptive Statistics by Treatment Group for Baseline Values and 24- and 72-Week Changes

<table>
<thead>
<tr>
<th>Observed Values</th>
<th>Pioglitazone Baseline</th>
<th>24-Week Change</th>
<th>72-Week Change</th>
<th>Glimperide Baseline</th>
<th>24-Week Change</th>
<th>72-Week Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline personal characteristics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>58.9 (7.8)</td>
<td>...</td>
<td>...</td>
<td>59.8 (8.1)</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Men</td>
<td>111 (63.4)</td>
<td>...</td>
<td>...</td>
<td>119 (64.0)</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Smokers</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>69 (39.7)</td>
<td>...</td>
<td>...</td>
<td>69 (37.3)</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>79 (45.4)</td>
<td>...</td>
<td>...</td>
<td>86 (46.5)</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Current</td>
<td>26 (14.9)</td>
<td>...</td>
<td>...</td>
<td>30 (16.2)</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Blood pressure, mm Hg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>130.0 (13.1)</td>
<td>-1.0 (14.0)</td>
<td>-2.8 (15.1)*</td>
<td>128.3 (14.1)</td>
<td>0.7 (13.7)</td>
<td>-1.0 (16.8)</td>
</tr>
<tr>
<td>Diastolic</td>
<td>78.5 (8.5)</td>
<td>-0.9 (8.8)</td>
<td>-2.5 (9.6)*</td>
<td>77.0 (8.3)</td>
<td>0.9 (9.9)</td>
<td>-0.8 (9.3)</td>
</tr>
<tr>
<td>Pulse pressure</td>
<td>51.5 (12.1)</td>
<td>-0.2 (11.9)</td>
<td>-0.3 (13.5)</td>
<td>51.4 (12.2)</td>
<td>-0.2 (11.8)</td>
<td>-0.2 (14.5)</td>
</tr>
<tr>
<td>Lipids, mg/dL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>114.1 (30.9)</td>
<td>7.5 (32.8)*</td>
<td>2.4 (33.7)</td>
<td>108.0 (32.9)</td>
<td>-1.5 (26.3)</td>
<td>-0.7 (31.6)</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>47.5 (12.7)</td>
<td>6.3 (9.9)‡</td>
<td>6.1 (9.2)‡</td>
<td>47.7 (12.2)</td>
<td>-0.4 (6.7)</td>
<td>-0.6 (6.8)</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>176.6 (89.9)</td>
<td>-22.6 (81.8)‡</td>
<td>-33.8 (90.9)‡</td>
<td>173.7 (123.3)</td>
<td>-4.8 (87.5)</td>
<td>-11.7 (102.9)</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>189.2 (37.3)</td>
<td>7.6 (34.4)†</td>
<td>5.3 (37.7)</td>
<td>183.5 (35.6)</td>
<td>-3.5 (28.7)</td>
<td>-3.6 (34.5)</td>
</tr>
<tr>
<td>Free fatty acid</td>
<td>0.60 (0.57)</td>
<td>-0.01 (1.02)*</td>
<td>-0.11 (0.62)‡</td>
<td>0.65 (0.88)</td>
<td>-0.15 (0.91)†</td>
<td>-0.06 (0.67)</td>
</tr>
<tr>
<td>ApoAI</td>
<td>138.5 (29.8)</td>
<td>3.0 (28.8)</td>
<td>9.0 (30.2)‡</td>
<td>134.6 (25.1)</td>
<td>2.6 (22.1)</td>
<td>7.3 (23.7)‡</td>
</tr>
<tr>
<td>ApoB</td>
<td>89.1 (23.2)</td>
<td>-3.2 (20.7)*</td>
<td>-4.6 (23.2)†</td>
<td>84.9 (20.6)</td>
<td>-1.6 (18.9)</td>
<td>-2.1 (19.5)</td>
</tr>
<tr>
<td>Glycemic measures</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin A1c, %</td>
<td>7.4 (1.0)</td>
<td>-0.3 (1.1)†</td>
<td>-0.3 (1.1)†</td>
<td>7.4 (0.9)</td>
<td>-0.2 (1.0)†</td>
<td>-0.1 (1.1)</td>
</tr>
<tr>
<td>Fasting plasma glucose, mg/dL</td>
<td>149.2 (48.3)</td>
<td>-15.3 (45.4)‡</td>
<td>-3.5 (44.1)‡</td>
<td>148.2 (44.7)</td>
<td>-5.9 (47.6)*</td>
<td>9.4 (58.9)</td>
</tr>
<tr>
<td>Insulin, pmol/L</td>
<td>170.3 (169.3)</td>
<td>-48.3 (124.0)‡</td>
<td>-46.0 (131.4)‡</td>
<td>152.1 (91.4)</td>
<td>1.8 (71.3)</td>
<td>4.5 (104.0)</td>
</tr>
<tr>
<td>Anthropomorphic measures</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight, kg</td>
<td>94.8 (18.7)</td>
<td>2.0 (3.7)‡</td>
<td>3.9 (5.7)‡</td>
<td>92.7 (17.9)</td>
<td>0.8 (3.2)‡</td>
<td>1.0 (3.7)‡</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>32.1 (5.1)</td>
<td>0.7 (1.3)‡</td>
<td>1.3 (1.9)‡</td>
<td>32.1 (5.1)</td>
<td>0.3 (1.1)‡</td>
<td>0.4 (1.3)‡</td>
</tr>
<tr>
<td>Waist, cm</td>
<td>107.4 (12.7)</td>
<td>0.8 (6.4)§</td>
<td>1.6 (7.3)*</td>
<td>105.9 (13.4)</td>
<td>0.6 (5.2)</td>
<td>0.8 (6.3)</td>
</tr>
<tr>
<td>Hip, cm</td>
<td>112.0 (12.0)</td>
<td>2.0 (6.8)‡</td>
<td>2.8 (7.2)‡</td>
<td>111.4 (13.5)</td>
<td>0.0 (5.4)</td>
<td>-0.3 (6.4)</td>
</tr>
<tr>
<td>Duration of diabetes, mo</td>
<td>94.2 (85.2)</td>
<td>...</td>
<td>...</td>
<td>90.0 (84.0)</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>hs-CRP, mg/L</td>
<td>2.4 (1.3, 4.6)</td>
<td>-0.6 (-1.9, 0.0)‡</td>
<td>-0.5 (-1.4, 0.1)‡</td>
<td>2.7 (1.2, 6.4)</td>
<td>0.0 (-1.0, 0.8)</td>
<td>-0.2 (-1.0, 0.4)*</td>
</tr>
</tbody>
</table>

Tests of change over time are based on paired t tests for continuous measures (with the exception of hs-CRP, for which paired Wilcoxon tests were used). Values shown are mean ± SD except for men and smokers, which are n (%), and hs-CRP, which is median (25th, 75th percentile). Tests for change and for baseline differences were based on log 10 values of lipids, inflammatory measures, and glycemic measures, with the exception of hemoglobin A1c.

P values for 24 and 72 weeks indicate whether the change within treatment group was significant. Significance levels for change over time are indicated as follows: *P ≤ 0.05; †P ≤ 0.01; ‡P ≤ 0.001.

Results

Table 1 presents descriptive statistics for personal characteristics, blood pressure, lipid, glycemic, anthropometric, and inflammatory measures at baseline and for changes at 24 and 72 weeks by treatment group. Both treatment groups demonstrated significant increases in weight and body mass index, as well as in apoA1. Both treatment groups also demonstrated decreases in free fatty acid level, glycohemoglobin, and fasting plasma glucose levels. In the pioglitazone-treatment group, there were significant increases in LDL cholesterol at 24 weeks and in HDL cholesterol at 24 and 72 weeks. Also in this treatment group, triglyceride levels fell significantly at 24 and 72 weeks, as did apoB and fasting insulin levels. Waist circumference was increased significantly at 72 weeks and hip circumference was increased significantly at 24 and 72 weeks in the pioglitazone-treatment group. hs-CRP levels were unlikely to alter results when the proportion of missing data is less than 2%. We did not pursue multiple imputation or other missing data techniques, consistent with the advice of Harrell et al.26 that missing data techniques are unlikely to alter results when the proportion of missing data is small. Analyses were performed in R version 2.3.027 (including the bootstrap functions of Canty) and confirmed with SAS/STAT software version 9.1.3.

The authors had full access to the data and take full responsibility for its integrity. All authors have read and agree to the manuscript as written.
were decreased in the pioglitazone-treatment group at 24 and 72 weeks and in the glimepiride-treatment group at 72 weeks.

We next wanted to evaluate whether differences in these parameters, which have previously been associated with risk for cardiovascular disease or atherosclerosis, were related to the treatment effect on CIMT. We evaluated differences between the treatment groups in these parameters at baseline and in terms of 24-week change and examined the relationship of baseline and 24-week differences to treatment effects on CIMT. In Table 2, statistics for treatment-group differences at baseline and change at 24 weeks are presented. For most parameters, differences were evaluated on a log scale and are calculated as the value for the pioglitazone-treatment group minus that for the glimepiride-treatment group. Positive numbers, therefore, indicate higher values in the pioglitazone group. Weight and body mass index were almost significantly different between the treatment groups, being higher for pioglitazone.

We next focused on identifying potential mediators of the pioglitazone-treatment effect on CIMT. The parameters shown in Table 2 were added to an ANCOVA model for 72-week change in CIMT that already included baseline CIMT, study site, and treatment group. There was no effect of any of the baseline parameters on treatment-mediated changes in CIMT at 72 weeks (not shown). Although there were numerous measures with a pattern of change that differed between the treatment groups at 24 weeks (Table 2), there were only 2 for which inclusion in a model predicting 72-week change in mean CIMT resulted in a loss of significance for the treatment effect: Δ log HDL cholesterol and Δ log fasting insulin (calculated as log week 24 minus log baseline value; Table 3). None of the other parameters shown in Table 2 impacted the treatment effect of pioglitazone on mean CIMT, and several of these are also included in Table 3. The addition of Δ log HDL cholesterol resulted in a 30.7% decrease in the estimated treatment effect, whereas the addition of Δ log insulin resulted in a 19.8% decrease; the addition of both was almost additive in attenuating the treatment effect by 46.2%, which suggests they were associated with some-
Table 3. Change in Treatment Coefficient and Significance of Treatment Effect on Mean CIMT After Addition of Individual Predictors

<table>
<thead>
<tr>
<th>Predictors Added for Mean CIMT</th>
<th>Treatment Effect Coefficient (SE)</th>
<th>Treatment Coefficient Change, %</th>
<th>P for Treatment Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base model</td>
<td>-0.0134 (0.0056)</td>
<td>...</td>
<td>0.02</td>
</tr>
<tr>
<td>+ Δ Log triglycerides</td>
<td>-0.0139 (0.0057)</td>
<td>3.8</td>
<td>0.02</td>
</tr>
<tr>
<td>+ Δ Hemoglobin A1c</td>
<td>-0.0143 (0.0056)</td>
<td>6.4</td>
<td>0.01</td>
</tr>
<tr>
<td>+ Δ Hip circumference</td>
<td>-0.0143 (0.0058)</td>
<td>6.6</td>
<td>0.02</td>
</tr>
<tr>
<td>+ Δ Log hs-CRP</td>
<td>-0.0129 (0.0057)</td>
<td>-3.5</td>
<td>0.02</td>
</tr>
<tr>
<td>+ Δ Log insulin</td>
<td>-0.0108 (0.0060)</td>
<td>-19.8</td>
<td>0.08</td>
</tr>
<tr>
<td>+ Δ Log HDL</td>
<td>-0.0093 (0.0060)</td>
<td>-30.7</td>
<td>0.12</td>
</tr>
<tr>
<td>+ Δ Log insulin and Δ log HDL</td>
<td>-0.0072 (0.0064)</td>
<td>-46.1</td>
<td>0.26</td>
</tr>
</tbody>
</table>

Δ Log values were calculated as log<sub>10</sub> 24-week minus log<sub>10</sub> baseline values.

Table 4. Change in Treatment Coefficient and Significance of Treatment Effect on Maximal CIMT After Addition of Individual Predictors

<table>
<thead>
<tr>
<th>Predictors Added for Maximal CIMT</th>
<th>Treatment Effect Coefficient (SE)</th>
<th>Treatment Coefficient Change, %</th>
<th>P for Treatment Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base model</td>
<td>-0.0243 (0.0092)</td>
<td>...</td>
<td>0.008</td>
</tr>
<tr>
<td>+ Δ log insulin</td>
<td>-0.0231 (0.0101)</td>
<td>-4.8</td>
<td>0.023</td>
</tr>
<tr>
<td>+ Δ log HDL</td>
<td>-0.0178 (0.0099)</td>
<td>-25.6</td>
<td>0.072</td>
</tr>
<tr>
<td>+ Δ log insulin and Δ log HDL</td>
<td>-0.0162 (0.0107)</td>
<td>-33.3</td>
<td>0.131</td>
</tr>
</tbody>
</table>

Δ Log HDL and Δ log insulin were calculated as described in Table 3.

Discussion

The results of the present report demonstrate that pioglitazone treatment produces a substantial benefit in multiple parameters that have been proposed as putative risk factors for atherosclerosis and/or cardiovascular events in patients with diabetes mellitus. Treatment with pioglitazone produced improvement in hs-CRP, systolic blood pressure, free fatty acid levels, apolipoproteins, and lipid levels, including a 14% increase in HDL cholesterol. Treatment with pioglitazone was also associated with increased LDL cholesterol and borderline increases in weight and body mass index. The increase in the latter measures may have been predominantly related to subcutaneous fat accumulation in the hips, which has been associated with reduced atherosclerosis. Of all on-treatment changes evaluated at 24 weeks, however, only changes in HDL cholesterol and insulin predicted a pioglitazone-related benefit on CIMT at 72 weeks. Changes in other lipid parameters, measures of glycemia, hs-CRP, or anthropometric measures did not predict improvement in CIMT with pioglitazone treatment. The present study included an active comparator to minimize glycemic differences between treatment groups and was not designed to assess the effect of glycemic control on CIMT. The present analysis indicates that pioglitazone produces benefit for CIMT independent of its glycemic effect. This is consistent with conclusions of shorter-term studies that compared the effect of glimepiride and pioglitazone on CIMT. The role of a reduced insulin level as a predictor of benefit suggests improved insulin sensitivity may play a role in atheroprotection. Change in HDL predicted benefit in both mean and maximal CIMT progression, and irrespective of treatment-group assignment, only an increased HDL cholesterol level at 24 weeks was a significant predictor of reduced CIMT progression. The significance of the 24-week change in HDL also significantly related to change in CIMT at 72 weeks. Compared with the first quartile (used as the referent group), subjects in the second quartile had a reduction of CIMT of 0.013±0.008 mm, those in the third quartile had a 0.016±0.008-mm reduction, and those in the fourth quartile had a 0.024±0.008-mm reduction (P=0.02 for trend). An increase in HDL cholesterol of 5% to 16% (which corresponded to the third quartile of log HDL cholesterol change) at 24 weeks predicted a significant benefit for CIMT at 72 weeks.
cholesterol for predicting improvement in CIMT at 72 weeks was not different in subjects using statins compared with those not using statins during the trial. Therefore, even in patients treated with statins, who were already benefiting from the increased HDL cholesterol level associated with this treatment, further increases in HDL cholesterol related to pioglitazone treatment predicted less progression of atherosclerosis on CIMT.

In evaluating the clinical implications of the present study, an important limitation is that we measured atherosclerosis progression using CIMT, which may not relate directly to any beneficial effect of HDL cholesterol elevation by pioglitazone on cardiovascular disease events. In the PROActive trial (PROspective pioglitAzone Clinical Trial In macroVascular Events), treatment with pioglitazone did not significantly reduce the risk of a composite primary end point (which included death due to any cause, nonfatal myocardial infarction, stroke, acute coronary syndrome, leg amputation, coronary revascularization, or leg revascularization). Pioglitazone treatment did, however, significantly reduce (by 16%) the relative risk of the main secondary end point (a composite of all-cause mortality, myocardial infarction, or stroke). A recent meta-analysis of clinical trials of pioglitazone demonstrated an association between pioglitazone treatment and a lower risk of death, myocardial infarction, and stroke. The use of rosiglitazone, the other commercially available thiazolidinedione, was not associated with a reduction in cardiovascular disease events in a similar meta-analysis. The impact of rosiglitazone on CIMT in patients with diabetes has also not been firmly established in large, long-term studies. In a trial that reported results for 447 subjects (165 with type 2 diabetes mellitus), there was no significant effect of rosiglitazone on CIMT progression; however, pioglitazone treatment predicted less progression of atherosclerosis in intravascular ultrasound and CIMT trials.20–22 This emphasizes the need to evaluate not only the level of HDL cholesterol but also its in vivo functionality for suppressing atherosclerosis progression or reducing cardiovascular events.

In the CHICAGO trial, pioglitazone treatment produced multiple benefits on cardiovascular risk factors, including an increase of 14% in HDL cholesterol. HDL cholesterol is an established and potent inverse risk factor for cardiovascular disease in humans, and increasing HDL cholesterol in animals and humans suppresses progression of atherosclerosis. The present analysis, the first to evaluate the relationship between thiazolidinedione-related changes in multiple cardiovascular risk factors and atherosclerosis progression in a large cohort of well-characterized subjects with diabetes, therefore suggests that the beneficial effect of pioglitazone for reducing atherosclerosis progression is derived in part from pioglitazone-related increases in HDL cholesterol. These results contrast with those of the torcetrapib trials in which increases in HDL cholesterol produced by treatment with cholesterol ester transfer protein inhibitors did not reduce atherosclerosis progression. The results in the present report support the importance of addressing low HDL cholesterol levels for suppressing atherosclerosis progression in patients with diabetes.

Sources of Funding
The study was sponsored and funded by Takeda Global Research & Development, Inc, Lincolnshire, Ill. Work on this report also was supported by National Heart, Lung, and Blood Institute grant No. K25 HL68139-01A1 to Dr Meyer.

Disclosures
Dr Mazzone is a consultant for Takeda, Merck, Amylin, and Novartis; received grants/research support from Takeda; and received honoraria from Merck, Pfizer, Takeda, and Novartis. Dr Meyer is a consultant for Takeda. Dr Kondos is a consultant for...


References


As the prevalence of type 2 diabetes mellitus increases in the United States and worldwide, it remains important to evaluate new ways of addressing the accelerated rates of atherosclerosis and cardiovascular disease (CVD) seen in these patients. Even in the statin era, residual incremental CVD risk compared with patients without diabetes remains. One notable accompaniment of type 2 diabetes mellitus is a low level of high-density lipoprotein (HDL) cholesterol. Cross-sectional and observational studies, as well as observations in atherosclerosis-prone animals, indicate that raising HDL cholesterol should be a powerful tool for reducing atherosclerosis and CVD risk in patients with diabetes. We have previously demonstrated that treating type 2 diabetic subjects with pioglitazone reduced progression of carotid intima-media thickness, a measure of carotid atherosclerosis and marker of CVD risk, compared with treatment with glimepiride. In the present analysis, we examined changes in individual cardiovascular risk factors after 24 weeks of treatment for their relationship to carotid intima-media thickness change at 72 weeks. Although treatment with pioglitazone led to improvement in multiple CVD risk parameters, only the increased HDL cholesterol and reduced insulin levels appeared to explain the treatment benefit. Of these, the HDL effect was larger and more consistent. Quartiles of HDL cholesterol change were progressively associated with more carotid intima-media thickness benefit, with an increment of 5% to 16% sufficient to produce a significant benefit for carotid intima-media thickness. These results demonstrate an important relationship between increases in HDL cholesterol produced by pioglitazone treatment and reduced progression of atherosclerosis in subjects with type 2 diabetes mellitus. They also underscore the potential of raising HDL cholesterol as a high-value therapeutic target for reducing atherosclerosis and CVD risk in patients with diabetes.
Increased High-Density Lipoprotein Cholesterol Predicts the Pioglitazone-Mediated Reduction of Carotid Intima-Media Thickness Progression in Patients With Type 2 Diabetes Mellitus

Michael Davidson, Peter M. Meyer, Steven Haffner, Steven Feinstein, Ralph D’Agostino, Sr, George T. Kondos, Alfonso Perez, Zhen Chen and Theodore Mazzone

_Circulation_. 2008;117:2123-2130; originally published online April 14, 2008; doi: 10.1161/CIRCULATIONAHA.107.746610

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2008 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/117/16/2123

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org//subscriptions/