Pioglitazone Versus Glimepiride on Coronary Artery Calcium Progression in Patients With Type 2 Diabetes Mellitus

A Secondary End Point of the CHICAGO Study

Michael H. Davidson, Craig A. Beam, Steven Haffner, Alfonso Perez, Ralph D’Agostino, Sr, Theodore Mazzone

Objective—To compare coronary artery calcium (CAC) progression between 2 treatment groups, pioglitazone versus glimepiride.

Methods and Results—The CHICAGO (Carotid Intima-Media Thickness in Atherosclerosis Using Pioglitazone) study demonstrated that pioglitazone significantly decreased carotid intima-media thickness progression compared with glimepiride in patients with type 2 diabetes mellitus. The CAC level was determined at baseline and at the end of 72 weeks of treatment in the pioglitazone (n = 146) and glimepiride (n = 153) treatment groups using electron beam computed tomography. There was no difference in CAC progression between the treatment groups. By using backward and forward selection models, age, race/ethnicity, and baseline apolipoprotein B level predicted CAC progression. There was no relationship between carotid intima-media thickness and CAC progression during the study.

Conclusion—There was no difference in CAC progression in patients with type 2 diabetes mellitus treated with pioglitazone or glimepiride. Age, race/ethnicity, and baseline apolipoprotein B level predicted CAC progression in patients with type 2 diabetes mellitus. (Arterioscler Thromb Vasc Biol. 2010;30:1873-1876.)

Key Words: atherosclerosis ■ diabetes mellitus ■ insulin resistance ■ lipoproteins ■ coronary artery calcium

The increased atherosclerosis in patients with type 2 diabetes mellitus (T2DM) is reflected in an increased coronary artery calcium (CAC) level, measured by electron beam tomography.1,2 CAC is a measure of total coronary atherosclerotic burden that has been validated by histopathology, coronary angiography, and intravascular ultrasonography.3,4 The total CAC score measured represents an anatomical measure of overall cardiac plaque burden, in patients with both types 1 and 2 diabetes.3,5

The CHICAGO (Carotid Intima-Media Thickness in Atherosclerosis Using Pioglitazone) trial assessed the differential effect of pioglitazone versus glimepiride on carotid intima-media thickness progression in patients with T2DM.6 The CHICAGO study demonstrated that pioglitazone, over a 72-week treatment period, slowed the progression of CIMT compared with glimepiride. A secondary end point of the CHICAGO trial was a comparison of the progression of CAC between the 2 treatment groups. It was previously reported that the baseline CAC score in the CHICAGO patients was associated with age, sex, race, systolic blood pressure, triglycerides, apolipoprotein B (ApoB), triglyceride-rich lipoprotein cholesterol (TGRL-C), and the ratio of total cholesterol to high-density lipoprotein cholesterol (HDL-C).7 Low-density lipoprotein cholesterol (LDL-C) or inflammatory markers did not correlate with baseline CAC measures. Herein, we report on the progression of CAC in patients in the CHICAGO trial after 72 weeks of treatment.

Methods

The CHICAGO trial is a randomized 72-week study comparing the effects of glimepiride and pioglitazone on measures of atherosclerotic disease. The primary end point of the trial was treatment-related difference in carotid intima-media thickness from baseline to 72 weeks. Change in CAC score from baseline to 72 weeks was a secondary end point of the trial. Subjects eligible for the trial were between the ages of 45 and 85 years, of either sex, diagnosed as having T2DM (based on American Diabetes Association diagnostic criteria). The complete design of the trial and a description of inclusion and exclusion criteria have previously been published.6 A total of 299 subjects who completed the baseline and 72-week measurements of CAC score were included in the current analysis. Throughout the trial, fasting plasma was obtained to evaluate systemic lipid and lipoprotein levels, intermediary metabolites, indexes of glycemia, and inflammatory factors. The analyses were performed by a clinical reference laboratory (CRL, Lenexa, Kan) using methods previously described in detail.6,7 For measuring CIMT, carotid arteries were imaged by high-resolution B-mode ultrasonography by a single ultra-
### Results

Table 1 presents baseline categorical characteristics for the 2 treatment groups of subjects who had baseline and 72-week measurements of CAC score. The 2 treatment groups were similar for sex, race/ethnicity, smoking history, and presence of hyperlipidemia or hypertension. Baseline CAC score was also not different between the 2 treatment groups. In addition to the factors shown in Table 1, there were no significant differences between the treatment groups for LDL cholesterol, LDL particle number, HDL-C, TGRL-C, ApoB, ApoA1, free fatty acid level, duration of diabetes, VAT, TAT, VAT to TAT ratio, or high-sensitivity C-reactive protein.

The Figure presents box plots for change in coronary calcium for each treatment group. Change over 72 weeks was similar for each treatment in each group, and there was not a significant difference in CAC score progression between the treatment groups. Results of the analysis using the Tobit transformation of the data also showed no difference between the treatment groups (data not shown).

The results of a cross-sectional analysis that identified predictors of CAC score at baseline in this cohort were previously reported. In that analysis, we identified age, systolic blood pressure, sex, and race/ethnicity as significant predictors of prevalent CAC. Among lipid and lipoprotein parameters, only ApoB, triglyceride, TGRL-C, and total cholesterol to HDL-C ratio were significantly associated with the presence of CAC. Waist to hip and VAT to TAT ratios were significantly associated with baseline CAC score but not after the inclusion of ApoB or TGRL-C in the model. For the current analysis, we used forward and backward selection approaches to evaluate age, sex, race/ethnicity, smoking, systolic blood pressure, and baseline anthropometric, metabolic, and lipid/lipoprotein measures (see the “Methods” section) for predicting progression of CAC score over 72 weeks. Of all factors considered, only age, race/ethnicity, and baseline ApoB level were significant predictors of CAC score progression (Table 2). Forward and backward selection approaches gave identical results.

In the CHICAGO cohort, 267 subjects had baseline and 72-week measurements of both CAC score and CIMT. In view of the discordance in results for predicting progression of CIMT and CAC score, we performed an analysis to examine the relationship between these 2 measures. As shown in Table 3, baseline CIMT was not significantly related to baseline CAC score or change in CAC score. Change in CIMT over 72 weeks was not related to either baseline CAC score or 72-week change in CAC score.

### Table 1. Baseline Characteristics of the 2 Treatment Groups*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Glimepiride Group (n=153)</th>
<th>Pioglitazone Group (n=146)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>62</td>
<td>64</td>
<td>0.77</td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>30</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>55</td>
<td>49</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>15</td>
<td>14</td>
<td>0.51</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>13</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Past</td>
<td>46</td>
<td>42</td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>41</td>
<td>41</td>
<td>0.68</td>
</tr>
<tr>
<td>Hypertension†</td>
<td>79</td>
<td>75</td>
<td>0.36</td>
</tr>
<tr>
<td>Hyperlipidemia‡</td>
<td>88</td>
<td>87</td>
<td>0.88</td>
</tr>
<tr>
<td>CAC score, median (IQR)</td>
<td>49 (260)</td>
<td>40 (226)</td>
<td>0.99</td>
</tr>
<tr>
<td>Age, median (IQR), y</td>
<td>59.6 (11.0)</td>
<td>58.4 (11.0)</td>
<td>0.31</td>
</tr>
</tbody>
</table>

*Data are given as percentage of each group unless otherwise indicated.
†Defined as a systolic blood pressure of higher than 130 mm Hg or taking blood pressure medication.
‡Defined as a low-density lipoprotein cholesterol level greater than 100 mg/dL or taking a statin.

IQR indicates interquartile range.

Electron beam tomography was used to measure CAC level, as previously described. Electron beam tomography was used to measure CAC level, as previously described. Abdominal adipose tissue distribution was also measured using electron beam tomography. Visceral adipose tissue (VAT) and total adipose tissue (TAT) were measured at the L4 to L5 vertebrae, as previously described. The potential relationship between treatment and change in Agatston score from baseline, after adjusting for baseline Agatston, was investigated using an analysis of covariance. This analysis was repeated using Tobit transformation of the data (defined as LN[Ayatston+1]) to provide another analysis that considers change as a ratio.

The 2 treatment groups were compared with respect to several baseline variables. Categorical variables were compared using the χ² test (or the Fisher exact test when the expected cell size was ≤5). Continuous variables were compared using the Wilcoxon rank sum test (for treatment group comparisons) or the Kruskal-Wallis test (for progression group comparisons). The relationship between CIMT and CAC score was examined with the Pearson correlation.

To identify predictors of CAC progression in our cohort, both forward and backward elimination were performed. The predicting variables considered included age, sex, race/ethnicity, smoking, systolic blood pressure, and baseline values of lipids/lipoproteins (HDLC, ApoA1, triglycerides, ApoB, TGRL-C, total cholesterol to HDL-C ratio, LDL-C, and LDL particle number); anthropometric measures (VAT to TAT ratio, waist, hip, and body mass index); and metabolic measures (A1C, free fatty acid, duration of diabetes, and C-reactive protein). For both backward and forward selection approaches, entry and exit probabilities were set at the SAS default value of 5%.

All analyses were conducted with commercially available software (SAS v9.1; SAS Institute Inc, Cary, NC).
infarction, and stroke) in the PROactive (PROspective pioglitAzone Clinical Trial In macroVascular Events) Study.\textsuperscript{20} This outcome benefit was sustained with a 28\% relative risk reduction in a subgroup of patients with a previous myocardial infarction.\textsuperscript{21} Therefore, pioglitazone, while demonstrating a clinical benefit using 2 surrogate end points (CIMT and intravascular ultrasound) and reducing major hard cardiac events, did not affect progression of the surrogate end point of CAC. In addition, we could find no correlation between baseline CIMT or change in CIMT and baseline CAC level or progression of CAC in this patient population with T2DM. Furthermore, in a previous analysis\textsuperscript{11} of factors that predicted slowing of CIMT progression, an increase in HDL-C with pioglitazone was the strongest predictor of slowed progression; however, changes in HDL-C did not predict change in CAC.

In the Multi-Ethnic Study of Atherosclerosis trial, CAC was associated more strongly than CIMT with risk of incident cardiovascular disease (2.5-fold versus 1.2-fold).\textsuperscript{22} However, in a recent meta-analysis\textsuperscript{23} of 5 CAC trials that evaluated therapeutic effects, including statins and antihypertensive therapy, the researchers concluded that there were no consistent or reproducible treatment effects of any therapy on progression of CAC measured at 1 year. The CHICAGO data, along with this meta-analysis, call into question the clinical value of serial CAC scanning to evaluate the efficacy of therapeutic interventions for preventing clinical cardiovascular disease. The process of coronary calcification is complex, involving both an increase in plaque burden and the healing of lipid-rich atheroma.\textsuperscript{1} A change in CAC may reflect these potentially competing processes, thereby making this surrogate invalid for assessing a therapeutic response.

There are several limitations that should be considered when interpreting our study. The CHICAGO trial was designed using CIMT as its primary end point, and there was not complete overlap in subjects completing the CIMT and CAC measurements. However, comparison of the 2 CAC treatment groups showed no significant baseline differences (Table 1) in important cardiovascular disease risk factors and no difference in baseline CAC score. The trial was also powered using change in CIMT as its primary end point. However, assuming a progression rate of 50 Agatston units during the trial, and a measurement SD of 30 Agatston units, we estimate 90\% power to detect a 25–Agatston unit difference between the glimepiride and pioglitazone treatment groups. Furthermore, the data in the Figure demonstrate complete overlap of CAC progression in the pioglitazone and glimepiride treatment groups. It seems unlikely that inclusion of additional subjects or observation for a longer time would have changed this result. Finally, the data in Table 2 identify age, race/ethnicity, and ApoB as the only important predictors of CAC progression in this multiracial cohort with T2DM.

The major points of our analysis can be summarized as follows. In a racially diverse cohort of patients with T2DM
treatment with pioglitazone, already demonstrated to produce a beneficial effect on CIMT and coronary atheroma progression compared with treatment with glimepiride, the treatment did not beneficially affect progression of CAC. In addition, there was no relationship between baseline or progression measurements of CAC and CIMT. Exploratory models to identify predictors of CAC progression identified ApoB as the only modifiable risk factor that was related to CAC progression over 72 weeks in subjects with T2DM. This latter finding supports the Joint Consensus Statement from the American Diabetes Association and the American College of Cardiology that recommends incorporating ApoB into caring for patients with cardiometabolic risk once LDL and non–HDL-C goals have been achieved.24

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Disclosures
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References
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