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
Table 1. Baseline Characteristics of the 2 Treatment Groups*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Glimperide 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>

IQR indicates interquartile range.

*Data are given as percentage of each group unless otherwise indicated.
†Defined as a systolic blood pressure of more 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.

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.
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 intra-vascular 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. 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 size of our cohort or the duration of our trial may have precluded detection of other important predictors of CAC progression in those with T2DM. However, our identification of ApoB as an important predictor of progression is consistent with cross-sectional analyses from this and another cohort,\textsuperscript{7,13} indicating that ApoB level is an important predictor of prevalent CAC in T2DM.

The major points of our analysis can be summarized as follows. In a racially diverse cohort of patients with T2DM

### Table 3. CIMT as Predictor of CAC Score in 267 Subjects

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline CAC Score</th>
<th>Changed CAC Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline CIMT</td>
<td>−0.04 (0.41)</td>
<td>0.07 (0.23)</td>
</tr>
<tr>
<td>Changed CIMT</td>
<td>0.03 (0.56)</td>
<td>0.01 (0.93)</td>
</tr>
</tbody>
</table>

*Adjusted for age, sex, and race.
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

Acknowledgments
We thank Stephanie Thompson and Mary Lou Briglio for assistance with manuscript preparation.

Sources of Funding
The CHICAGO study was sponsored and funded by Takeda Global Research and Development. Analysis for the current study was supported by an unrestricted grant from Takeda Global Research and Development, an institutional award from the University of Illinois at Chicago, and grant UL1RR029879 from the National Center for Research Resources.

Disclosures
Dr Davidson is a consultant for Abbott, AstraZeneca, Daiichi-Sankyo, Inc, GlaxoSmithKline, Merck, Roche, Sanofi-Aventis, Synarco, and Takeda Pharmaceuticals; is on the Speakers’ Bureau of Abbott, AstraZeneca, Daiichi-Sankyo, Inc, Merck, Roche, and Takeda; and has received grant/research support from Abbott, AstraZeneca, Daiichi-Sankyo, Inc, Merck, Roche, and Takeda; is on the Advisory Board of Abbott, AstraZeneca, Daiichi-Sankyo, Inc, Kinemed, Merck, Roche, and Takeda Pharmaceuticals; and has Equity/Board of Directors for Sonogene, Professional Evaluation, Inc, and Omthera. Dr Haffner is a consultant for AstraZeneca, Merck, and Novartis. Dr Perez is employed by Takeda Global Research and Development. Dr Mazzone is a consultant for Abbott, Merck, and Takeda; and has received grant/research support from Takeda.

References