Effect of Pioglitazone Compared With Glimepiride on Carotid Intima-Media Thickness in Type 2 Diabetes
A Randomized Trial

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PATIENTS WITH TYPE 2 DIABETES mellitus (DM) have a marked increase in the risk of myocardial infarction (MI), and a substantially worse prognosis after MI compared with patients without diabetes.1-3 In recent years, it has become apparent that optimal control of blood pressure and low-density lipoprotein cholesterol (LDL-C) level can substantially reduce excess cardiovascular risk in patients with diabetes.4-6 However, even with optimal control of these potent cardiovascular risk factors, incremental risk for cardiovascular events remains high compared with individuals without diabetes.2,3,6 New approaches are, therefore, needed to further reduce cardiovascular risk in patients with diabetes.

Emerging evidence suggests that thiazolidinediones could be useful for reducing cardiovascular risk. In isolated vessel-wall cells, troglitazone, pioglitazone, and rosiglitazone have been shown to modulate gene expression in a manner that would be predicted to be atheroprotective in vivo.7,8 In humans, these agents have been shown to have beneficial effects on systemic inflammatory and coagulation markers, lipoprotein profile, and endothelial cell function.9-12 Some of these beneficial ef-
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-effects may be independent of effects on glycemia. In animal models of atherosclerosis, thiazolidinediones have been shown to reduce atherosclerotic plaque area independent of changes in glycemia or lipid profile.

When investigating the usefulness of therapies for preventing cardiovascular events, several surrogate endpoints for estimating future risk of such events have been evaluated. The measurement of carotid intima-media thickness (CIMT) is among the best validated of these surrogate end points. CIMT has been shown to highly correlate with risk of future cardiovascular events, and changes in CIMT over time have additional predictive value. Statins, established agents for reducing risk of cardiovascular disease events, have been shown to reduce progression of CIMT.

There have been recent reports examining the effect of thiazolidinediones on CIMT in patients with diabetes. Minamikawa et al reported that troglitazone compared with no added treatment reduced CIMT at 3 and 6 months in 135 Japanese patients. Langenfeld et al compared pioglitazone with glimepiride in 173 white German participants and reported a reduction in CIMT at 24 weeks. The participants had a baseline systolic blood pressure of approximately 148 mm Hg and an LDL-C level of approximately 136 mg/dL (3.5 mmol/L). In spite of this elevated LDL-C level, statin use was less than 20% at the start of the study. Hodis et al recently reported results from 299 patients with type 2 DM. This cohort was more than 66% female and more than 86% Hispanic American and was randomized to receive troglitazone or placebo for 2 years. Overall, the change in CIMT was not different between the 2 treatment groups, although a beneficial effect of troglitazone was observed in the subgroup with a baseline CIMT of 0.8 mm or greater. Because of important issues related to small cohort size, short duration of treatment, homogeneity of study population with respect to race/ethnicity, the presence of uncontrolled cardiovascular risk factors, and inconsistent results, there remains an important question regarding the effect of thiazolidinediones on CIMT in type 2 DM.

In this article, we report the findings of a long-term randomized and comparator-controlled clinical trial conducted in patients with type 2 DM recruited from an ethnically/racially diverse population of a large US metropolitan area. We compared the effect of pioglitazone with that of glimepiride on progression of CIMT. Glimepiride was chosen as a comparator because a placebo control could not be ethically justified in terms of maintaining adequate glycemic control. In addition, glimepiride represents a class of drugs that is commonly used to treat diabetes in the United States, and its mechanism of action is distinct from that of pioglitazone.

METHODS

Study Design and Participants

The CHICAGO (Carotid Intima-Media Thickness in Atherosclerosis Using Pioglitazone) trial 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. Individuals eligible for participation were men and women between the ages of 45 and 85 years with type 2 DM that was diet-controlled or treated with sulfonylurea or thiazolidinedione within 12 weeks of treatment randomization; did not respond to or were intolerant of sulfonylurea or thiazolidinedione treatment; required more than 2 oral agents for glycemic control; had unexplained microscopic hematuria, a triglycerides level greater than 500 mg/dL (5.7 mmol/L), elevated serum creatinine level, decreased hemoglobin level, an alanine transaminase level of 2.5 or more times the upper limit of normal; had active liver disease or jaundice; or weighed more than 135 kg or had a body mass index (calculated as weight in kilograms divided by height in meters squared) greater than 45.

Race/ethnicity was initially divided by self-identification as white, black, Hispanic, Oriental, Native American, or other. All of the participants in the “other” category were Asian and so were pooled into an Oriental/Asian group. Race/ethnicity was monitored to allow estimation at the end of the study if the cohort generally reflected the racial/ethnic makeup of patients with type 2 DM in the United States. The study complied with the International Conference for Harmonisation—Good Clinical Practice guidelines, the World Medical Association Declaration of Helsinki, and local regulations. The study protocol was approved by central or local institutional review board committees, and all participants provided written informed consent.

Eligible participants received randomized treatment with pioglitazone hydrochloride (15-45 mg/d) or glimepiride (1-4 mg/d). The initial study drug dose was based on sulfonylurea use and dose at study entry. Patients not taking sulfonylurea or taking a low dose of sulfonylurea started taking daily pi-
oglitazone (15 mg) or glimepiride (1 mg). All other patients were given daily pioglitazone (30 mg) or glimepiride (2 mg). Study drug doses were titrated to reach and maintain target glycemic goals defined as a fasting plasma glucose level of 140 mg/dL (7.8 mmol/L) or lower. The use of metformin or insulin was allowed in either group to reach glycemic goals.

The study protocol specified following American Diabetes Association guidelines for lipid and blood pressure control that were current at the start of the study.26,27 Participants received randomized study drug (pioglitazone or glimepiride) within 3 weeks of screening. For participants requiring the addition or adjustment of statin dose to meet American Diabetes Association targets, an additional time for statin dose stabilization prior to randomization (up to 7 weeks) was permitted. Study visits were scheduled at 4, 8, 16, 24, 32, 40, 48, 60, and 72 weeks after the randomization visit. CIMT was evaluated at baseline and at 24, 48, and 72 weeks (or at the time of early termination). Fasting plasma glucose levels were determined at all visits, HbA1c values at all visits after week 8, and lipid levels (triglycerides, total cholesterol, and plasma glucose in blood samples using standard enzymatic methods (Roche Diagnostics, Indianapolis, Ind); levels of HDL-C and LDL-C by direct methods (Roche); and HbA1c values by high-performance liquid chromatography (Bio-Rad, Hercules, Calif).

**Measurement of Carotid Intima-Media Thickness**

Carotid arteries were imaged by high-resolution B-mode carotid artery ultrasound using an HDI 5000 ultrasound system with a linear-array 7.5-MHz transducer (Phillips Medical Systems NA, Bothell, Wash). All scanning throughout the study was performed by a single ultrasonographer at the same location using the same equipment. Sonographer performance was evaluated by determining the difference between 2 complete examinations of 30 participants performed at least 1 week apart. The mean difference between the 2 readings was 0.002 (SD, 0.058) mm. The CIMT was averaged over 70 to 100 individual measurements taken along a 1-cm segment of the common carotid artery proximal to the bifurcation.

**Statistical Analysis**

Sample size was calculated based on the assumption of a 0.08-mm group difference in the primary end point at the end of the study, with an SD of 0.224 for individual differences and 90% power for a 2-sided, 2-sample t test at a .05 significance level. Sample size was set to 200 per group in anticipation of a 20% dropout rate. Early in the recruitment the steering committee decided to include all patients who were already in the screening process when the 400 total was reached, to adjust for a somewhat higher than expected early dropout rate.
Unless otherwise noted, analyses were based on intention-to-treat and last-observation-carried-forward principles. Three sites had fewer than 6 participants, and each was pooled with a neighboring site when adjusting for site differences. All treated participants were included who had baseline observations and follow-up observations within 14 days after the last dose of study drug for CIMT measures and 7 days after last dose for other measures. Serious adverse events were included if they occurred within 30 days of the last dose of study medication.

Descriptive statistics were used to characterize participants at baseline by treatment group. Medications used within 8 weeks prior to screening are also reported, with combination antihypertensive medications (combinations of angiotensin-converting enzyme inhibitors, β-blockers, angiotensin II receptor blockers, or diuretics) counted in both categories. Baseline group comparisons were adjusted for site, using 2-way analysis of variance for continuous measures and Cochran-Mantel-Haenszel tests for categorical measures.

For primary and secondary end points, analysis of covariance analyses were used and included adjustment for fixed effects of site and CIMT baseline values. The same structure was used for models for relative changes in HbA1c values and levels of HDL-C. Significance of treatment effects was assessed using F tests. Time course was plotted using the LSMEANS function in SAS to show adjusted mean estimates with standard error bars. All analyses were prespecified in the statistical analysis plan, with significance set at .05 (2-sided). A sensitivity analysis of the primary end point analysis used 10-fold multiple imputation, modeling missing final observations using age, sex, treatment group, pooled site, and baseline CIMT. Analyses were performed in R version 2.3.0 (R Foundation for Statistical Computing; available at http://www.R-project.org) and SAS version 8.2 (SAS Institute Inc, Cary, NC).

RESULTS

Of the 1346 patients screened for eligibility, 462 (34%) were randomly assigned to treatment (FIGURE 1). The study was completed by 68% of the pioglitazone-treated and 72% of the glimepiride-treated patients. The reasons for study discontinuation were generally similar between treatment groups. Within the intention-to-treat population, those patients who had both a baseline and one qualifying postbaseline CIMT image were included in the CIMT analysis (CIMT population). This included 76% and 81% of patients from the pioglitazone and glimepiride groups, respectively. One hundred seventy-five pioglitazone-treated and 186 glimepiride-treated patients met the criteria for inclusion for the CIMT analysis.

The treatment groups were well balanced for baseline demographic and clinical characteristics (TABLE 1). More participants in the glimepiride group had a history of MI (31 vs 18) and used aspirin or diuretics. The majority of patients entering the study were taking an oral diabetes treatment regimen, and most were receiving treatment for hypertension and lipid abnormalities. Glycemic control was good, with a mean HbA1c value of 7.4%. Blood pressure was well controlled, and a majority of patients were using renin-angiotensin system modulators. The majority of patients were taking statin therapy at baseline, and over the course of the study statin use increased to 57.4% and 60.5% in the pioglitazone and glimepiride groups, respectively. The CIMT population was similar to the intention-to-treat population with respect to baseline demographics and clinical characteristics.

FIGURE 2A shows the mean change from baseline to week 72 in posterior-wall mean CIMT of the right and left common carotid arteries over time. The baseline mean CIMT was 0.771 (SD, 0.008) mm and 0.779 (SD, 0.008) mm in the pioglitazone and glimepiride.
from baseline in the pioglitazone compared with the glimepiride group was −0.013 mm (95% confidence interval [CI], −0.024 to −0.002; \( P = .02 \)). As an alternative to last observation carried forward, 10-fold multiple imputations were performed for missing values and confirmed a treatment effect of 0.013 mm (95% CI, −0.024 to −0.001; \( P = .03 \)).

Change from baseline to week 72 in posterior wall maximum CIMT was a secondary end point (Figure 2B). Baseline maximum CIMTs were 1.038 (SD, 0.0101) mm and 1.042 (SD, 0.0101) mm in the pioglitazone and glimepiride groups, respectively. The final maximum CIMT increased by 0.002 mm in the pioglitazone group and by 0.026 mm in the glimepiride group. The treatment-group difference was −0.024 mm (95% CI, −0.042 to −0.006; \( P = .008 \)). Changes in maximal CIMT over time were similar to those observed for mean CIMT. The small excess of participants with a history of MI in the glimepiride group, when included in a model for the primary end point, was not a significant predictor. The favorable treatment effect for pioglitazone was uniform across all pre-specified subgroups for mean CIMT analysis (Figure 3), including statin users and nonusers.

Absolute changes in 2 important metabolic parameters over the course of the study are shown in Figure 4. In the pioglitazone group, HbA\(_1c\) values decreased by week 16 and remained relatively stable throughout the study. There was a rapid decrease in HbA\(_1c\) values in the glimepiride group, followed by a gradual increase by week 72. There was no significant difference in the HbA\(_1c\) values between the 2 treatment groups until week 48. For HDL-C levels, there was a significant increase with pioglitazone compared with glimepiride treatment at week 24; this increase was maintained throughout follow-up.

Mean baseline triglyceride levels were 178.6 (SD, 8.1) mg/dL (2.02 [SD, 0.092] mmol/L) and 170.4 (SD, 8.1) mg/dL (1.93 [SD, 0.092] mmol/L) in the pioglitazone and glimepiride groups, respec-
Relatively. At the end of the study, triglyceride levels decreased 13.5% in the pioglitazone group and increased 2.1% in the glimepiride group (treatment difference, 15.6%; 95% CI, 24.0% to 7.3%; \( P < .001 \)). Mean baseline LDL-C levels were 113.8 (SD, 2.4) mg/dL (2.95 [SD, 0.062] mmol/L) in the pioglitazone group and 111.3 (SD, 2.4) mg/dL (2.88 [SD, 0.062] mmol/L) in the glimepiride group. At the end of the study, LDL-C levels increased 5.8% and 1% in the pioglitazone and glimepiride groups, respectively (\( P = .12 \)). At the end of the study, there was a decrease of 2.0 (SD, 13.8) mm Hg and 0.3 (SD, 16.1) mm Hg in systolic blood pressure in the pioglitazone and glimepiride treatment groups, respectively (\( P = .27 \)).

Table 2 presents the number of patients with an adjudicated first event in prespecified clinical end points. Overall, few patients had a clinical event. No cardiovascular deaths were reported, and there was 1 noncardiovascular death from pancreatic carcinoma in an 80-year-old woman. A numerically higher incidence for clinical end points was observed in the glimepiride compared with the pioglitazone group, and coronary revascularization contributed most to this. Only 1 adjudicated event (a coronary revascularization in the pioglitazone group) occurred in patients with a history of MI at baseline. Congestive heart failure occurred in 1 pioglitazone-treated patient. A single second event (a coronary revascularization performed 1 year af-

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the initial event) occurred in a patient randomized to receive glimepiride.

Table 3 shows the reporting rates for all adverse events. The frequency and type of adverse events seen in the CHICAGO trial are consistent with those seen in previous studies.31 As expected, hypoglycemia was slightly more common with glimepiride than with pioglitazone and resulted in termination of 2 participants in the glimepiride group and 1 in the pioglitazone group. Peripheral edema was more common with pioglitazone than with glimepiride. Treatment-limiting edema occurred in 4 pioglitazone-treated participants. On average, weight gain was more frequent with pioglitazone than with glimepiride throughout the study but was rarely treatment-limiting. One participant in each group discontinued treatment due to weight gain. At the final visit, mean weight gain was 3.2 (SD, 3.4) kg for pioglitazone and 1.0 (SD, 3.7) kg for glimepiride (P < .001).

COMMENT

In this randomized trial of 462 patients with type 2 DM, we found that, compared with glimepiride, pioglitazone reduced CIMT progression, a validated surrogate end point for coronary artery disease and cardiovascular risk.18,19 The CHICAGO trial was conducted in a single geographic region, allowing measurement of CIMT to be performed at a single location by a single sonographer. The analysis used automated digital edgetechnology and included multiple measurements in each carotid artery segment. Our study population was recruited from a racially and ethnically diverse population of a large US city and...
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Table 3. Summary of Adverse Events (Intention-to-Treat Population)

<table>
<thead>
<tr>
<th>Event</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pioglitazone (n = 230)</td>
</tr>
<tr>
<td>Deaths</td>
<td>1</td>
</tr>
<tr>
<td>Any adverse event</td>
<td>206 (90.6)</td>
</tr>
<tr>
<td>Any serious adverse event</td>
<td>25 (10.9)</td>
</tr>
<tr>
<td>Any adverse event causing discontinuation</td>
<td>26 (11.3)</td>
</tr>
<tr>
<td>Adverse events ≥5% incidence rate in either group</td>
<td></td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>45 (19.6)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>30 (13.0)</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>30 (13.0)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>26 (11.3)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>26 (11.3)</td>
</tr>
<tr>
<td>Headache</td>
<td>20 (8.7)</td>
</tr>
<tr>
<td>Influenza</td>
<td>20 (8.7)</td>
</tr>
<tr>
<td>Cough</td>
<td>16 (7.0)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>16 (7.0)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>16 (7.0)</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>16 (7.0)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>15 (6.5)</td>
</tr>
<tr>
<td>Weight gain</td>
<td>15 (6.5)</td>
</tr>
<tr>
<td>Nausea</td>
<td>14 (6.1)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>12 (5.2)</td>
</tr>
<tr>
<td>Pain in back</td>
<td>11 (4.8)</td>
</tr>
</tbody>
</table>

*Twenty-six pioglitazone-treated participants discontinued study-drug dosing because of an adverse event; however, adverse-event documentation was available for only 25 of these participants. Adverse events are listed in order of decreasing frequency in the pioglitazone group.

generally reflects the diversity of the type 2 DM population in the United States. Our results demonstrate reduction of CIMT progression with pioglitazone treatment in a cohort with a better level of management of cardiovascular risk factors (ie, a higher rate of statin use, LDL-C levels near 100 mg/dL [2.6 mmol/L], and near-optimal blood pressure control) compared with previously reported cohorts.22 Our study also included repeated measurements up to 72 weeks, beyond the 3- to 6-month treatment period in previous trials using pioglitazone:13,21,22 A prespecified subgroup analysis based on age, sex, systolic blood pressure, duration of type 2 DM, body mass index, HbA1c value, and statin use showed a uniform beneficial effect of pioglitazone treatment.

Systolic blood pressure was reduced by a small amount in both treatment groups. This effect was slightly larger in the pioglitazone group, but treatment differences did not reach statistical significance. Prespecified cardiovascular end points were adjudicated in a double-blinded fashion by an independent panel and more of these events, mostly related to coronary revascularization, occurred in the glimepiride group (Table 2). There was 1 case of new congestive heart failure with pioglitazone therapy, while hypoglycemia was slightly more common with glimepiride. As expected, edema and weight gain were more common in the pioglitazone group. CIMT has been extensively evaluated as a surrogate marker of atherosclerosis and cardiovascular risk.18,19 It has recently been suggested that changes in maximum CIMT progression rates vary widely in patients with diabetes, from 0.083 mm over 6 months to 0.007 mm over 1 year.34,35 In a recent review of 11 CIMT intervention trials in diabetes,36 the mean CIMT progression rate in the control groups was 0.034 mm per year but varied considerably between trials based on level of control of cardiovascular risk factors. The low rate of progression in the control group of the current study likely reflects the control of systolic blood pressure and LDL-C level.

The beneficial effect of pioglitazone on CIMT in patients with type 2 DM is consistent with results of the recently reported PROActive (Prospective Pioglitazone Clinical Trial in Macrovascular Events) study.37 This trial randomized more than 5000 patients with type 2 DM who had evidence of macrovascular disease to receive pioglitazone or placebo in addition to existing therapy. While treatment with pioglitazone did not significantly reduce the risk of the composite primary end point (which included death from any cause, nonfatal MI, stroke, acute coronary syndrome, leg amputation, coronary revascularization, or leg revascularization), it did significantly reduce by 16% the risk of the main secondary end point (a composite of all-cause mortality, MI, or stroke).

Several potential mechanisms can be considered for a beneficial effect of pioglitazone on atherosclerosis. Treatment with thiazolidinediones has been shown to modify nontraditional markers of cardiac risk such as circulating inflammatory and coagulation markers and to improve endothelial-cell function.9-12,38,39 Thiazolidinedione treatment can also positively modify blood pressure, glycemia, and lipid levels.9-12 In the current study, blood pressure changes were not significantly different between the pioglitazone and...
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Glimepiride groups. HbA1c values were reduced more in the pioglitazone group compared with the glimepiride group (by 0.32% at 72 weeks). However, it is noteworthy that the treatment advantage for pioglitazone on HbA1c values in this study did not become significant until week 48. In prior studies, treatment with pioglitazone has been shown to have a substantial benefit on diabetic dyslipidemia, including increasing HDL-C levels and reducing triglycerides levels. Both of these effects were observed in our study and could have contributed to improvement in CIMT. Finally, it also remains possible that thiazolidinediones can have a direct beneficial effect on the vessel wall.

Our study has several limitations. First, it was not powered to detect a difference in cardiovascular end points and, therefore, does not establish that treatment with pioglitazone compared with glimepiride will reduce these end points in patients with type 2 DM. Because we used glimepiride as an active comparator, we also cannot definitively rule out that the treatment difference was due to a proatherogenic effect of glimepiride. We believe, however, that this explanation is somewhat unlikely in view of the fact that the treatment difference was largely the result of an effect of pioglitazone to suppress or delay the progression of CIMT. Our study also had a dropout rate that approximated 30%. However, dropout rates were balanced in the 2 treatment groups, and the participants who remained in the study (ie, the CIMT population) were similar to those in the intention-to-treat population (Table 1). In addition, an analysis of baseline characteristics of participants who dropped out showed no difference compared with those who remained in the study. Finally, thiazolidinediones may cause acute changes in intravascular volume and affect vascular tone. Such changes also result from antihypertensive therapy, and an issue has been discussed in the literature regarding a potential role for changes in intravascular volume, vascular tone, or both in producing rapid changes in CIMT. In the current study, the observation that treatment difference appeared to increase over time argues against an important role for changes in intravascular volume or vascular tone. In a recent evaluation of the effect of antihypertensive therapy on CIMT, Zanchetti et al10 concluded that only 1% of CIMT change could be attributed to overall change in carotid artery diameter.

Notwithstanding these limitations, our results demonstrate, in a relatively large and long-term randomized trial, that pioglitazone slowed progression of CIMT compared with glimepiride. This benefit was measured in participants with excellent blood pressure control, statin use greater than 50%, and mean LDL-C levels of 113.8 (SD, 2.4) mg/dL (2.95 [SD, 0.062] mmol/L). Additional data will be needed to determine the clinical significance of these findings; specifically, whether a strategy of routine use of pioglitazone instead of glimepiride substantially reduces major cardiovascular events.

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Author Contributions: Dr Meyer had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Dr Meyer performed an independent statistical analysis, and all of the results shown in this article reflect his work.

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