Effect of Pioglitazone Compared with Glimepiride on Carotid Intima-media Thickness in Type 2 Diabetes

a report by

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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. 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. However, even with optimal control of these potent cardiovascular risk factors, incremental risk for cardiovascular events remains high with individuals without diabetes. 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. In humans, these agents have been shown to have beneficial effects on systemic inflammatory and coagulation markers, lipoprotein profile, and endothelial cell function. Some of these beneficial 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 end-points 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 diabetes. Minamikawa et al. reported that troglitazone compared with no added treatment reduced CIMT at three and six 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 148mmHg and an LDL-C level of approximately 136mg/dl (3.5mmol/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 two years. Overall, the change in CIMT was not different between the two treatment groups, although a beneficial effect of troglitazone was observed in the subgroup with a baseline CIMT of 0.8mm 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.

Below are 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. The study 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 US, and its mechanism of action is distinct from that of pioglitazone.

Study Discussion and 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. The CHICAGO trial was conducted in a single geographical region, allowing measurement of CIMT to be performed at a single location by a single sonographer. The analysis used automated digital edge-detection technology 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 generally reflects the diversity of the type 2 DM population in the US. Our results demonstrate reduction of CIMT progression with pioglitazone treatment in a cohort with a better level of management of cardiovascular risk factors (i.e., a higher rate of statin use, LDL-C levels near 100 mg/dl [2.6mmol/l], and near-optimal blood pressure control) compared with previously reported cohorts. Our study also included repeated measurements up to 72 weeks, beyond the three- to six-month treatment period in previous trials using pioglitazone. A pre-specified subgroup analysis based on age, sex, systolic blood pressure, duration of type 2 DM, body mass index, glycylated hemoglobin (HbA1c) value, and statin use showed a uniform...
Disease Risk Management

**Study—In Brief**

**Objective**
To evaluate the effect of pioglitazone versus glimepiride on changes in CIMT of the common carotid artery in patients with type 2 DM.

**Design, Setting, and Participants**
Randomized, double-blind, comparator-controlled, multicenter trial in patients with type 2 DM conducted at 28 clinical sites in the multiracial/ethnic Chicago metropolitan area between October 2003 and May 2006. The treatment period was 72 weeks (one-week follow-up). CIMT images were captured by a single ultrasonographer at one center and read by a single treatment-blinded reader using automated edge-detection technology. Participants were 462 adults (mean age, 60 years; standard deviation, 8 years; mean body mass index, 32 kg/m²); type 2 DM (mean duration, 7.7 years; mean HbA₁c value, 7.4% [SD, 1.0%]), either newly diagnosed or currently treated with diet and exercise, sulfonylurea, metformin, insulin, or a combination thereof.

**Interventions**
Pioglitazone hydrochloride (15–45mg/d) or glimepiride (1–4mg/d) as an active comparator.

**Main Outcome Measure**
Absolute change from baseline to final visit in mean posterior-wall CIMT of the left and right common carotid arteries.

**Results**
Mean change in CIMT was lower with pioglitazone versus glimepiride at all time-points (weeks 24, 48, 72). At week 72, the primary end-point of progression of mean CIMT was less with pioglitazone versus glimepiride (-0.001mm versus +0.012mm, respectively; difference, -0.013mm; 95% confidence interval, -0.024 to -0.002; p=0.02). Pioglitazone also slowed progression of maximum CIMT compared with glimepiride (0.002mm versus 0.026mm, respectively, at 72 weeks; difference, -0.024mm; 95% confidence interval, -0.042 to -0.006; p=0.008). The beneficial effect of pioglitazone on mean CIMT was similar across pre-specified subgroups based on age, sex, systolic blood pressure, duration of DM, body mass index, HbA₁c value, and statin use.

**Conclusion**
Over an 18-month treatment period in patients with type 2 DM, pioglitazone slowed progression of CIMT compared with glimepiride. For full results and statistical analysis, please view original paper (JAMA, 2006;296) available at: doi:10.1001/jama.296.21.joc60158

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. Pre-specified 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. There was one 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. It has recently been suggested that changes in maximum CIMT may be preferred for measuring treatment-related changes in carotid atherosclerosis. Our results demonstrate beneficial effects of pioglitazone on progression for both mean and maximal CIMT values.

In patients with type 2 DM, measurement of CIMT significantly improves prediction of cardiovascular disease risk compared with the Framingham Risk Score. It has also been shown that changes in CIMT over time correlate with future cardiovascular event rates. Diabetes, which confers increased risk of cardiovascular disease, also accelerates CIMT progression.

However, CIMT progression rates vary widely in patients with diabetes, from 0.083mm over six months to 0.007mm over one year. In a recent review of 11 CIMT intervention trials in diabetes, the mean CIMT progression rate in the control groups was 0.034mm 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. This trial randomized more than 5,000 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. Thiazolidinedione treatment can also positively modify blood pressure, glycemia, and lipid levels. In the current study, blood pressure changes were not significantly different between the pioglitazone and 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 triglyceride 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 directly 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...
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The difference is ACTOS®
pioglitazone HCl

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Please see adjacent Brief Summary of Prescribing Information, including boxed warning regarding lactic acidosis. For more information and Complete Prescribing Information, please visit us at www.actos.com.
**ACTOPLUS MET**

**pioglitazone, metformin hydrochloride**

**Brief Summary of Prescribing Information.** Please see package insert for Complete Prescribing Information.

**INDICATIONS**

**ACTOPLUS MET** is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes, as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes who are already treated with a thiazolidinedione (see PRECAUTIONS, General: Metformin hydrochloride). In the 16-week U.S.-based, double-blind, placebo-controlled clinical trial involving patients with type 2 diabetes, 566 patients (304 patients treated with a combination of pioglitazone and metformin or placebo) were treated with a combination of pioglitazone and metformin or placebo for 15 mg and 30 mg, respectively, in combination with insulin compared to insulin therapy alone. This trial included patients with long-standing diabetes and a history of inadequate glycemic control on other oral agents or injection therapy. The mean change from baseline to week 16 in hemoglobin A1c (HbA1c) was -1.4% in ACTOPLUS MET patients compared to -0.8% in insulin alone. All of these patients had type 2 diabetes. The plasma drug concentrations were assessed for patients treated with pioglitazone at doses of 15 mg and 30 mg (22.6%), coronary heart disease (19.6%), retinopathy (13.1%), myocardial infarction (2.1%), and congestive heart failure (2.1%).

**CONTRAINDICATIONS**

**ACTOPLUS MET** is contraindicated in patients with:

1. Known hypersensitivity to pioglitazone, metformin or any other component of ACTOPLUS MET.

2. Known hypersensitivity to thiazolidinediones, including diabetic ketonuria, or without corona. Diabetic ketonuria be treated with insulin.

**WARNINGS**

**Porphyria**

Lactic Acidosis: Lactic acidosis is a rare, but serious, metabolic complication that may occur in patients receiving metformin. In patients treated with metformin hydrochloride and in clinical trials with pioglitazone hydrochloride and metformin hydrochloride, lactic acidosis may also occur in association with a number of pathological conditions, such as renal dysfunction, including renal failure, and/or congestive heart failure; severe sepsis; hemolytic anemias; and/or other metabolic conditions that may cause disturbances with an increased anion gap, and an increased lactate level. Lactic acidosis is a medical emergency that may cause permanent injury or death.

In type 2 diabetes and CHF (systolic dysfunction) with patients treated with pioglitazone, Metformin should be promptly withheld in the presence of any excess alcohol intake, either acute or chronic, when taking metformin. Metformin should be promptly referred to an ophthalmologist, regardless of the patient’s underlying cardiovascular risk factors, if a patient who develops laboratory abnormalities or clinical illness (especially vague and non-specific symptoms such as nausea, vomiting, hyperventilation, and hypotension) has been reported more frequently in patients treated with than in placebo-treated patients and appears to be dose-related. In postmarketing experience, reports of initiation or worsening of edema have been reported in 2/4700 patients (0.04%) treated with pioglitazone.

**WARNINGS**

**General: Pioglitazone hydrochloride**

Pioglitazone should be used with caution in patients with a history of prediabetes or type 2 diabetes, as it may lead to hyperglycemia. Patients receiving pioglitazone in combination with insulin or with other insulin-sparing antidiabetic drugs have a dose of metformin. ACTOPLUS MET therapy should be discontinued.

**PRECAUTIONS**

**General: Metformin hydrochloride**

In type 2 diabetes and CHF (systolic dysfunction) (22.6%), coronary heart disease (19.6%), retinopathy (13.1%), myocardial infarction (2.1%), and congestive heart failure (2.1%).

**PRECAUTIONS**

**General:** Metformin hydrochloride)

- Metformin hydrochloride is very low (~0.03 cases/1000 patient-years, with ~0.015 cases/1000 patient-years respectively). This possible effect has not been investigated in clinical studies so the frequency is unknown whether there is a causal relationship between pioglitazone and retinopathy, diabetes, and the mechanism of weight gain is unclear but probably involves a combination use of intravenous isovolumetric control materials.

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ment of the health care professional (see PRECAUTIONS, General: Pioglitazone Hydrochloride—METFORMIN HYDROCHLORIDE: SERUM TRANSAMINASE LEVELS). Initial and periodic monitoring of hematologic parameters (e.g., hemoglobin, hematocrit, leukocyte count) should be performed, at least at an annual basis. While metabolic acidosis has not been reported in patients with moribund renal function, therapy if this is suspected, vitamin B12 deficiency should be excluded.

Interruption of Therapy

Patients should be instructed regarding the importance of adhering to dietary measures and the importance of continuing to take the drug during illness and A/C. Periods of stress such as fever, trauma, infection, or surgery, may increase insulin requirements during maintenance therapy and patients should be seeking medical advice promptly.

The following are not contraindications and conditions that are considered to be developmental, as noted in the WARNINGS, Metformin hydrochloride and PRECAUTIONS, General: Pioglitazone hydrochloride—METFORMIN HYDROCHLORIDE: SERUM TRANSAMINASE LEVELS. Metformin hydrochloride should not be used in the presence of advanced renal disease (creatinine clearance <30 mL/min) or if the serum creatinine level is greater than 1.5 mg/dL (133 μmol/L).

The occurrence of any of the following signs or symptoms should prompt patients to consult their physician if they develop unexplained symptoms. Although gastrointestinal symptoms that occur after administration are unlikely to be drug related, such an occurrence of symptoms should be evaluated to determine if it may affect use of the ACTOPLUS MET should immediately report these symptoms to their physician.

Pioglitazone Hydrochloride

In preclinical research studies have suggested that pioglitazone may be a weak inducer of CYP450 3A4, 2C9, and 1A2. The weak induction of CYP450 3A4 may increase the risk of drug interaction compared with ACTOPLUS MET, which is the active pioglitazone component of the ACTOPLUS MET tablet, may result in oxidation in some preclinical animal studies. In a single-dose study, the Cmax of pioglitazone and an inducer of CYP450 (such as rifampin) may significantly be increased in the presence of a CYP450 3A4 inhibitor. The inhibition of CYP450 isotypes by the concomitant use of pioglitazone with CYP450 inhibitors is not known. Consequently, ACTOPLUS MET, the risk of hypoglycemia, its symptoms, and treatment, and problems related to treatment should be evaluated.

Patients should be told to take ACTOPLUS MET as prescribed and instructed that any change in dosing should only be done if directed by their physician.

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Disease Risk Management

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 two treatment groups, and the participants who remained in the study (i.e., the CIMT population) were similar to those in the intention-to-treat population. 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 al. 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 113.8mg/dl (SD, 2.4) (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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7. Hsueh WA, Law RE, PPAR and atherosclerosis: effects in the study (i.e., the CIMT population) were similar to those in the intension-to-treat population. 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 al. concluded that only 1% of CIMT change could be attributed to overall change in carotid artery diameter.

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