ORIGINAL ARTICLE

Pioglitazone after Ischemic Stroke or Transient Ischemic Attack

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ABSTRACT

BACKGROUND

Patients with ischemic stroke or transient ischemic attack (TIA) are at increased risk for future cardiovascular events despite current preventive therapies. The identification of insulin resistance as a risk factor for stroke and myocardial infarction raised the possibility that pioglitazone, which improves insulin sensitivity, might benefit patients with cerebrovascular disease.

METHODS

In this multicenter, double-blind trial, we randomly assigned 3876 patients who had had a recent ischemic stroke or TIA to receive either pioglitazone (target dose, 45 mg daily) or placebo. Eligible patients did not have diabetes but were found to have insulin resistance on the basis of a score of more than 3.0 on the homeostasis model assessment of insulin resistance (HOMA-IR) index. The primary outcome was fatal or nonfatal stroke or myocardial infarction.

RESULTS

By 4.8 years, a primary outcome had occurred in 175 of 1939 patients (9.0%) in the pioglitazone group and in 228 of 1937 (11.8%) in the placebo group (hazard ratio in the pioglitazone group, 0.76; 95% confidence interval [CI], 0.62 to 0.93; P=0.007). Diabetes developed in 73 patients (3.8%) and 149 patients (7.7%), respectively (hazard ratio, 0.48; 95% CI, 0.33 to 0.69; P<0.001). There was no significant between-group difference in all-cause mortality (hazard ratio, 0.93; 95% CI, 0.73 to 1.17; P=0.52). Pioglitazone was associated with a greater frequency of weight gain exceeding 4.5 kg than was placebo (52.2% vs. 33.7%, P<0.001), edema (35.6% vs. 24.9%, P<0.001), and bone fracture requiring surgery or hospitalization (5.1% vs. 3.2%, P=0.003).

CONCLUSIONS

In this trial involving patients without diabetes who had insulin resistance along with a recent history of ischemic stroke or TIA, the risk of stroke or myocardial infarction was lower among patients who received pioglitazone than among those who received placebo. Pioglitazone was also associated with a lower risk of diabetes but with higher risks of weight gain, edema, and fracture. (Funded by the National Institute of Neurological Disorders and Stroke; ClinicalTrials.gov number, NCT00091949.)

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Ischemic stroke and transient ischemic attack (TIA) affect more than 14 million persons worldwide annually.[1,2] Affected patients are at increased risk for future cardiovascular events,[3,4] and prevention of these adverse outcomes is a major goal in their care.

Treatment of insulin resistance represents a potential new preventive strategy that could be added to standard care after ischemic stroke or TIA.[5] Insulin resistance is nearly universal in patients with type 2 diabetes but is also present in more than 50% of patients without diabetes who have had an ischemic stroke or a TIA.[6] The presence of insulin resistance increases the risk of vascular disease, possibly because of associated hypertension, hyperglycemia, hyperinsulinemia, dyslipidemia, endothelial dysfunction, hypercoagulability, inflammation, and increased platelet reactivity.[7-9]

Clinical strategies to improve insulin sensitivity include exercise,[9,10] diet,[11] weight reduction,[12] and medications.[9,13] The thiazolidinedione class of peroxisome proliferator–activated receptor γ (PPAR-γ) agonists are among the most potent insulin-sensitizing drugs available.[14] One medication in this class, pioglitazone, may reduce the risk of cardiovascular events, including stroke, in patients with type 2 diabetes, for whom the drug is currently approved as a glucose-lowering agent.[15,16] We designed the Insulin Resistance Intervention after Stroke (IRIS) trial to test the hypothesis that pioglitazone would reduce the rates of stroke and myocardial infarction after ischemic stroke or TIA in patients without diabetes who have insulin resistance.

Methods

Trial Design and Oversight

The design of this international, double-blind, placebo-controlled clinical trial has been reported previously.[17] Trial leadership, committee structure, and sites are described in the Supplementary Appendix, available with the full text of this article at NEJM.org. Members of the operations committee and the statisticians designed the study. From 2005 through 2013, investigators at 179 hospitals and clinics enrolled patients and collected data. The statistical analysis was performed at the Department of Veterans Affairs Connecticut Health Care System. The first author wrote the first draft of the manuscript. All the other authors contributed revisions and vouch for the reported data. Pioglitazone and placebo tablets were donated by Takeda Pharmaceuticals International. Representatives of Takeda were provided with a copy of the protocol (available at NEJM.org) and manuscript but had no role in the development of the protocol, the conduct of the trial, the interpretation of the data, or the preparation of the manuscript. The trial was monitored by an independent data and safety monitoring board appointed by the National Institute of Neurological Disorders and Stroke, which funded the study. Trial operations were approved by the local ethics committee at each site. The study was conducted and reported with fidelity to the protocol.

Trial Patients

Eligible patients were at least 40 years of age and had had a qualifying ischemic stroke or TIA[17] during the 6 months before randomization. All the patients provided written informed consent. Patients were required to have insulin resistance, which was defined as a value of more than 3.0 on the homeostasis model assessment of insulin resistance (HOMA-IR) index. The HOMA-IR value was calculated as the level of fasting glucose (measured in millimoles per liter) times the level of fasting insulin (measured in microunits per milliliter) divided by 22.5.[18] The index threshold of 3.0 was chosen because it identifies the highest quartile among populations without diabetes.[19,20] Because insulin sensitivity may be transiently impaired after a stroke,[21] the screening blood test was conducted at least 14 days after the index event.

Patients with diabetes were excluded from the trial. Diabetes was diagnosed if a potential participant was taking medication for diabetes or met the 2005 criteria of the American Diabetes Association (ADA) for fasting plasma glucose (i.e., ≥126 mg per deciliter [7 mmol per liter]), as confirmed by repeated testing.[22] We did not perform an oral glucose-tolerance test but excluded patients with a glycated hemoglobin level of 7.0% or more. We also excluded patients with New York Heart Association class 3 or 4 heart failure or class 2 heart failure with a reduced ejection fraction.[17] Other criteria for exclusion included active liver disease, an alanine aminotransferase level of more than 2.5 times the upper limit of the normal range, a hemoglobin level of less than 8.5 g per deciliter, moderate or severe dependent pitting edema, carotid revascularization within 14 days before randomization,

and use of an estrogen-containing contraceptive or oral glucocorticoid. In response to regulatory changes that were adopted during the trial, the data and safety monitoring board approved additional exclusions for a history of heart failure, bladder cancer, or certain conditions that increased the risk of bladder cancer.[17]

TRIAL PROCEDURES

Eligible patients were randomly assigned in a 1:1 ratio to receive either pioglitazone or matching placebo. The initial dose was 15 mg of pioglitazone daily or placebo. Patients who reported no new or worsening edema, shortness of breath, myalgia, or excessive weight gain were instructed to increase the dose to two pills daily (30 mg of pioglitazone or placebo) at 4 weeks and to three pills daily (45 mg of pioglitazone or placebo) at 8 weeks. At 12 weeks, patients were started on one 45-mg pioglitazone tablet or placebo tablet daily.

If patients reported any of the aforementioned signs or symptoms, study investigators treated them according to algorithms. A reduction in study-drug dose was included in the algorithms and was also permitted by the internal safety committee if such a reduction allowed the patient to continue taking the drug. Pioglitazone and placebo were permanently discontinued if heart failure or bladder cancer developed or if a patient had two distinct low-energy bone fractures (i.e., resulting from a fall from a sitting or standing position or from a low platform, such as a bed).

Patients were contacted every 4 months, and participation ended at 5 years or at the last scheduled contact before July 2015. Investigators monitored patients' adherence to the assigned regimen by asking about drug use and performing pill counts. If a patient briefly stopped taking a study drug, investigators included such intervals as zero use in calculations of adherence. Adherence calculations were stopped at the date a patient withdrew consent.

TRIAL OUTCOMES

The primary outcome was a first fatal or nonfatal stroke or fatal or nonfatal myocardial infarction.[17] Prespecified secondary outcomes were stroke; acute coronary syndrome; the composite of stroke, myocardial infarction, or heart failure resulting in hospitalization or death; death from any cause; diabetes; and cognitive decline from baseline, as assessed by means of the Modified Mini–Mental State Examination (on which scores range from 0 to 100, with higher scores indicating better function[23]).[17] No other outcomes were prespecified. All outcomes and selected safety events (i.e., bone fracture, macular edema, and cancer) were adjudicated by the members of independent committees in a blinded fashion.

STATISTICAL ANALYSIS

We determined that enrollment of 3136 patients would provide a power of 90% to detect a 4-year cumulative rate of stroke or myocardial infarction that was 20% lower in the pioglitazone group than in the placebo group, assuming a two-sided type I error of 0.05 and a 27% outcome rate in the placebo group. Four interim analyses of the primary outcome were conducted for efficacy and futility with the use of the O'Brien–Fleming method.[19] At the second and third interim analyses, the data and safety monitoring board recommended an extension of recruitment and follow-up owing to slower recruitment and a lower overall event rate than anticipated in order to maintain the statistical power. Decisions were made in closed sessions, and investigators were not aware of event rates during the trial.

All analyses were performed on an intention-to-treat basis. The primary outcome and all prespecified secondary outcomes except cognitive function were analyzed by means of the time-to-first-event method. Cumulative event-free probabilities were calculated with the use of Kaplan–Meier analysis[24] and tested with the use of the log-rank statistic on the basis of a two-sided type I error rate of 0.05. The P value for the primary outcome was adjusted for interim monitoring with the use of East software, version 6.3 (Cytel), and the P values for the five prespecified time-to-event secondary outcomes were adjusted for multiple testing with the Hochberg procedure and a family-wise error rate of 0.05. We used the Cox model[25] to estimate the effect of pioglitazone, as compared with placebo, as a hazard ratio with 95% confidence intervals. The confidence interval for the primary outcome was adjusted for interim analyses with the use of East software, version 6.3, and confidence intervals for the secondary outcomes were adjusted for multiple comparisons with the method of Efird and Nielsen.[26] In planned supplementary analyses, the Cox model was used to estimate the hazard

ratio for the primary outcome after adjustment for prespecified baseline covariates and to test for interactions between treatment and covariates in 13 prespecified subgroups, with P values adjusted for multiple testing.[27] Missing time-to-event data were treated as noninformative censoring. We used a repeated-measures covariance-pattern model on the assumption that data were missing at random to analyze the effect of treatment on cognitive function; in this analysis, the change from baseline in the annual score on the Modified Mini–Mental State Examination was the outcome.

We also conducted two types of ancillary analysis. During the trial, new definitions for stroke,[28] myocardial infarction,[29] and diabetes[30] were published. The data and safety monitoring board approved ancillary analyses that used these updated outcome definitions. In addition, we examined changes in measures reported to be affected by pioglitazone, including the HOMA-IR index; insulin, glucose, lipid, and C-reactive protein levels; and blood pressure. All these measures were listed in the protocol but were not considered to be outcome events. P values for safety and ancillary analyses were not adjusted for multiple comparisons. We used SAS software, version 9.3, for all analyses, except as noted.

RESULTS

TRIAL POPULATION

A total of 3895 patients were enrolled, with 67% from sites in the United States (Fig. S1 in the Supplementary Appendix). Alleged irregularity in the informed-consent process at one institution resulted in halting of local research activities while the data were still blinded. The 19 patients at this site were removed from the study, resulting in a final cohort of 3876 patients (1939 in the pioglitazone group and 1937 in the placebo group).

The two study groups had similar characteristics at baseline (Table 1, and Table S1 in the Supplementary Appendix). In the two study groups, the mean age was 63.5 years. The index event was stroke in 88% of the patients in the pioglitazone group and 87% in the placebo group; the median times from the index event to randomization were 81 days and 79 days, respectively, and the median HOMA-IR index values were 4.7 and 4.6, respectively. In the two study groups, the mean baseline glycated hemoglobin level was 5.8%. According to the 2010 criteria of the ADA (which include a glycated hemoglobin level of ≥6.5% as diagnostic of diabetes), diabetes was present in 116 of 1939 patients (6.0%) in the pioglitazone group and in 129 of 1937 (6.7%) in the placebo group (Table S2 in the Supplementary Appendix).

During a median follow-up of 4.8 years, a total of 227 patients (5.9%) withdrew consent and 99 (2.6%) were lost-to-follow-up (Fig. S1 in the Supplementary Appendix). Baseline features were similar for patients who were lost to follow-up in the two groups. Patients in the two groups had similar rates of adherence to recommended practices for secondary prevention (Table S3 in the Supplementary Appendix).

Patients in the pioglitazone group had lower adherence to the drug regimen than did those in the placebo group (Table S4 in the Supplementary Appendix); at the exit visit, 60% of the patients in the pioglitazone group were still taking pioglitazone and 67% in the placebo group were still taking placebo. The reasons for drug discontinuation were similar in the two groups, except that more patients in the pioglitazone group than in the placebo group stopped because of edema or weight gain (172 patients vs. 51 patients) or were removed for safety reasons (primarily heart failure, repeated fracture, and incidence of or risk factors for bladder cancer) (146 patients vs. 117 patients). In the pioglitazone group, the median daily dose each year ranged from 29 mg to 40 mg.

CLINICAL OUTCOMES

The primary outcome of stroke or myocardial infarction occurred in 175 of 1939 patients (9.0%) in the pioglitazone group and in 228 of 1937 (11.8%) in the placebo group (hazard ratio in the pioglitazone group, 0.76; 95% confidence interval [CI], 0.62 to 0.93; P=0.007) (Table 2 and Fig. 1, and Table S5 in the Supplementary Appendix). This finding did not change after adjustment for covariates.

Among the secondary outcomes, the rate of progression to diabetes was significantly lower in the pioglitazone group than in the placebo group (hazard ratio, 0.48; 95% CI, 0.33 to 0.69; P<0.001) (Table 2). Pioglitazone had no significant effect on cognition, as compared with placebo. The overall between-group difference in the change from baseline in the least-squares mean score on the Modified Mini–Mental State Examination was −0.02 (95% CI, −0.33 to 0.28;

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Pioglitazone (N = 1939)	Placebo (N = 1937)
Demographic feature		
Age — yr	63.5±10.6	63.5±10.7
Male sex — no. (%)	1293 (66.7)	1245 (64.3)
Black race — no./total no. (%)†	218/1906 (11.4)	225/1904 (11.8)
Hispanic ethnic group — no./total no. (%)†	75/1927 (3.9)	72/1929 (3.7)
Clinical history		
Stroke — no./total no. (%)		
At entry	1693/1928 (87.8)	1682/1930 (87.2)
Previous	246/1938 (12.7)	242/1935 (12.5)
Hypertension — no./total no. (%)	1380/1938 (71.2)	1390/1936 (71.8)
Coronary artery disease — no./total no. (%)	241/1938 (12.4)	221/1936 (11.4)
Atrial fibrillation — no./total no. (%)	134/1914 (7.0)	130/1912 (6.8)
Physical and cognitive examination‡		
Body-mass index	29.9±5.6	30.0±5.3
Blood pressure — mm Hg		
Systolic	133.2±17.7	133.0±17.3
Diastolic	79.4±10.7	79.0±10.5
Score on Modified Mini–Mental State Examination — median (IQR)	96 (92–99)	97 (92–99)
Score on NIH Stroke Scale — median (IQR)	0 (0–2)	0 (0–1)
Score on Modified Rankin Scale — median (IQR)	1 (0–2)	1 (0–1)
Laboratory data		
Fasting glucose — mg/dl	98.3±10.0	98.2±9.9
Median fasting insulin (IQR) — μU per milliliter	19 (16–26)	19 (16–25)
HOMA-IR index — median (IQR)	4.7 (3.8–6.2)	4.6 (3.7–6.2)
Glycated hemoglobin — %	5.8±0.4	5.8±0.4
Fasting cholesterol — mg/dl		
LDL	87.6±31.5	87.9±31.5
HDL	47.0±12.8	47.1±12.6
Fasting triglycerides — mg/dl	142.5±73.8	139.4±71.8
Concomitant medication		
Statin — no./total no. (%)	1594/1932 (82.5)	1592/1932 (82.4)
Antiplatelet — no./total no. (%)	1781/1936 (92.0)	1786/1934 (92.3)
Oral anticoagulant — no./total no. (%)	232/1932 (12.0)	209/1932 (10.8)
ACE inhibitor or angiotensin-receptor blocker — no./total no. (%)	1090/1932 (56.4)	1054/1932 (54.6)
Diuretic — no./total no. (%)	581/1932 (30.1)	534/1932 (27.6)
Beta-blocker — no./total no. (%)	615/1932 (31.8)	613/1932 (31.7)
Interval after index event		
No. of days to HOMA-IR testing — median (IQR)	56 (30–98)	56 (31–97)
No. of days to randomization — median (IQR)	81 (51–121)	79 (52–121)

* Plus–minus values are means ±SD. There were no significant differences between the groups at baseline. Features are presented as median values when distributions are highly skewed. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. To convert the values for glucose to millimoles per liter, multiply by 0.05551. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129. ACE denotes angiotensin-converting enzyme, HDL high-density lipoprotein, HOMA-IR homeostasis model assessment of insulin resistance, IQR interquartile range, and LDL low-density lipoprotein.

† Race or ethnic group was self-reported.

‡ The body-mass index is the weight in kilograms divided by the square of the height in meters. Scores on the Modified Mini–Mental State Examination range from 0 to 100, with higher scores indicating better function. Scores on the National Institutes of Health (NIH) Stroke Scale range from 0 to 42, with higher scores indicating worse function. Scores on the Modified Rankin Scale range from 0 to 5, with higher scores indicating worse function.

Table 2. Primary and Secondary Outcomes.

Outcome	Pioglitazone (N=1939)	Placebo (N=1937)	Hazard Ratio (95% CI)*	Adjusted P Value†
	no. of patients (%)			
Primary outcome				
Stroke or myocardial infarction‡	175 (9.0)	228 (11.8)	0.76 (0.62–0.93)	0.007
Stroke	123 (6.3)	150 (7.7)		
Fatal	9 (0.5)	13 (0.7)		
Nonfatal	114 (5.9)	137 (7.1)		
Myocardial infarction	52 (2.7)	78 (4.0)		
Fatal	7 (0.4)	14 (0.7)		
Nonfatal	45 (2.3)	64 (3.3)		
Secondary outcome§				
Stroke	127 (6.5)	154 (8.0)	0.82 (0.61–1.10)	0.19
Acute coronary syndrome: myocardial infarction or unstable angina	96 (5.0)	128 (6.6)	0.75 (0.52–1.07)	0.11
Stroke, myocardial infarction, or serious heart failure¶	206 (10.6)	249 (12.9)	0.82 (0.65–1.05)	0.11
Diabetes mellitus	73 (3.8)	149 (7.7)	0.48 (0.33–0.69)	<0.001
Death from any cause	136 (7.0)	146 (7.5)	0.93 (0.73–1.17)	0.52

* Hazard ratios were calculated by means of a Cox regression model with corresponding 95% confidence intervals. The confidence interval for the primary outcome was adjusted for interim monitoring; confidence intervals for the secondary outcomes were adjusted for multiple comparisons.
† The P value for the primary outcome was adjusted for interim monitoring. P values for the five secondary outcomes were adjusted for multiple comparisons by the Hochberg procedure using an overall familywise type I error of 5%.
‡ Only the first event, stroke or myocardial infarction, was counted for each patient.
§ In the composite categories, only the first event was counted for each patient (e.g., a patient with myocardial infarction followed by unstable angina would be counted only as having a myocardial infarction in the category for acute coronary syndrome). More strokes are listed as occurring as a secondary outcome than a primary outcome because the secondary outcome included strokes occurring after myocardial infarction.
¶ Serious heart failure was defined as an episode resulting in hospitalization or death.

P=0.88). There were no significant differences in any of the prespecified subgroups (Fig. 2).

In ancillary analyses, the effect of pioglitazone on the primary outcome was similar when stroke and myocardial infarction were defined according to updated criteria[28,29] (hazard ratio, 0.73; 95% CI, 0.60 to 0.88). The finding for diabetes was also unchanged when a cutoff for glycated hemoglobin of 6.5% or more was used in local analysis, consistent with the 2010 ADA recommendation[30] (hazard ratio, 0.49; 95% CI, 0.38 to 0.64).

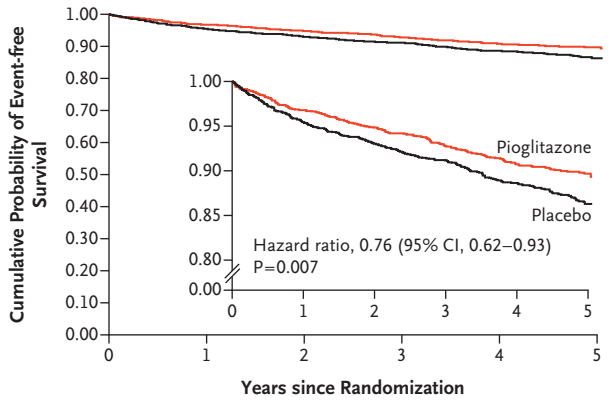
After 1 year, the HOMA-IR index and C-reactive protein level were lower in the pioglitazone group than in the placebo group (Table S6 in the Supplementary Appendix). During the trial, levels of fasting glucose, fasting triglycerides, and systolic blood pressure were also lower in the pioglitazone group, as was diastolic blood pressure in years 1 to 4. Levels of both high-density lipoprotein (HDL) cholesterol and low-density lipoprotein (LDL) cholesterol were higher in the pioglitazone group than in the placebo group (Fig. S2 in the Supplementary Appendix).

SAFETY OUTCOMES

Patients in the pioglitazone group had more weight gain, edema, shortness of breath, and bone fractures than did patients in the placebo group (Table 3, and Table S7 in the Supplementary Appendix). The maximum between-group difference in weight change was observed at year 4 (mean weight gain of 2.6 kg in the pioglitazone group vs. mean weight loss of 0.5 kg in the placebo group, P<0.001). Among the patients in the pioglitazone group, 52.2% gained more than 4.5 kg and 11.4% gained more than 13.6 kg; the corresponding percentages in the placebo group were 33.7% and 4.5%. The rates of edema were higher in the pioglitazone group than in the

placebo group (35.6% vs. 24.9%, P<0.001), as were rates of serious bone fracture (i.e., requiring hospitalization or surgery), which were reported in 99 patients and 62 patients, respectively (5.1% vs. 3.2%, P=0.003).

Although shortness of breath was reported more frequently in the pioglitazone group than in the placebo group, there was no significant between-group difference in the number of patients with heart failure (74 in the pioglitazone group and 71 in the placebo group, P=0.80) or in the number of patients hospitalized for heart failure (51 and 42, respectively; P=0.35) (Table S7 in the Supplementary Appendix). Incident bladder cancer occurred in 12 patients in the pioglitazone group and in 8 in the placebo group (P=0.37). The total incidence of cancer did not differ significantly between the two groups (133 patients and 150 patients, respectively; P=0.29). There was no significant between-group difference in the incidence of other monitored adverse events, with the exception of a change in the alanine aminotransferase level, which was more favorable with pioglitazone.



No. at Risk						
Pioglitazone	1939	1793	1701	1491	1196	481
Placebo	1937	1778	1690	1476	1182	459

Figure 1. Primary Outcome.

By 5 years, the primary outcome (fatal or nonfatal stroke or fatal or nonfatal myocardial infarction) had occurred in 175 of 1939 patients (9.0%) in the pioglitazone group and in 228 of 1937 (11.8%) in the placebo group. The inset shows the same data on an enlarged y axis. The numbers at risk were the numbers of patients who were alive without an event and still being followed at the beginning of each time point.

DISCUSSION

In this trial involving patients without diabetes who had a recent history of ischemic stroke or TIA and who had insulin resistance, the rate of the primary outcome was lower among patients who received pioglitazone than among those who received placebo. The incidence of a new diagnosis of diabetes was also lower with pioglitazone.

The results of the IRIS trial are in contrast to the findings of two trials involving patients with type 2 diabetes. In the Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROactive) trial,[15,16] the rate of primary outcome of death, myocardial infarction, stroke, acute coronary syndrome, vascular surgery, or amputation was not significantly lower among patients in the pioglitazone group than among those in the placebo group. In the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI-2D) trial,[31] the rate of primary outcome of death, stroke, or myocardial infarction was not significantly lower among patients receiving rosiglitazone and metformin (insulin-sparing strategy) than among those receiving insulin and sulfonylurea therapy (insulin-providing strategy). However, the IRIS results are consistent with findings regarding a secondary outcome in the PROactive trial (i.e., that the rates of death, myocardial infarction, or stroke were significantly lower with pioglitazone than with placebo) and with findings of trials showing a favorable effect of pioglitazone on the progression of subclinical atherosclerosis among patients with and those without diabetes.[32-34]

In our trial, the mechanism that is responsible for the lower rates of stroke and myocardial infarction in the pioglitazone group than in the placebo group is uncertain. Pioglitazone activates PPAR-γ and also causes partial activation of PPAR-α.[35] These actions modulate the transcription of genes with favorable effects on insulin sensitivity,[13,36] fat distribution,[37] plasma glucose,[35,38] lipid and protein metabolism,[36,38] vascular endothelial function,[39] and inflammation.[35,40] In the IRIS trial, pioglitazone improved insulin sensitivity, blood pressure, and circulating levels of glucose, triglycerides, HDL cholesterol, and C-reactive protein. The enhancement of insulin sensitivity may be central to the benefit of pioglitazone. However, other measured and unmeasured effects may have contributed to the benefit of the drug with respect to our primary outcome.

We observed previously recognized adverse effects of pioglitazone on weight gain, edema, and bone fracture. Weight gain with PPAR-γ agonists, such as pioglitazone, reflects an increase in adi-

Subgroup	Pioglitazone	Placebo	Hazard Ratio (95% CI)	P Value for Interaction
	no. of events/total no. (%)			
Age				0.72
<65 yr	81/1077 (7.5)	111/1091 (10.2)	0.73 (0.55–0.97)	
≥65 yr	94/862 (10.9)	117/846 (13.8)	0.79 (0.60–1.03)	
Sex				0.30
Male	126/1293 (9.7)	147/1245 (11.8)	0.81 (0.64–1.03)	
Female	49/646 (7.6)	81/692 (11.7)	0.65 (0.46–0.93)	
Race				0.75
White	144/1600 (9.0)	189/1619 (11.7)	0.77 (0.62–0.95)	
Black	22/218 (10.1)	32/225 (14.2)	0.67 (0.39–1.16)	
Other	8/88 (9.1)	5/60 (8.3)	1.08 (0.35–3.29)	
Ethnic group				0.51
Hispanic	7/75 (9.3)	12/72 (16.7)	0.58 (0.23–1.46)	
Non-Hispanic	168/1852 (9.1)	215/1857 (11.6)	0.78 (0.63–0.95)	
Body-mass index				0.14
<30	99/1123 (8.8)	142/1096 (13.0)	0.67 (0.52–0.87)	
≥30	75/810 (9.3)	85/835 (10.2)	0.91 (0.67–1.24)	
Coronary artery disease				0.72
Yes	36/241 (14.9)	47/221 (21.3)	0.70 (0.45–1.08)	
No	139/1697 (8.2)	181/1715 (10.6)	0.77 (0.62–0.96)	
Hypertension				0.94
Yes	141/1380 (10.2)	186/1390 (13.4)	0.76 (0.61–0.95)	
No	34/558 (6.1)	42/546 (7.7)	0.77 (0.49–1.21)	
HOMA-IR index				0.25
<4.6	76/933 (8.1)	114/948 (12.0)	0.67 (0.50–0.90)	
≥4.6	99/1006 (9.8)	114/989 (11.5)	0.85 (0.65–1.11)	
Glycated hemoglobin				0.38
<5.7%	52/672 (7.7)	78/690 (11.3)	0.67 (0.47–0.95)	
≥5.7%	123/1266 (9.7)	150/1247 (12.0)	0.81 (0.64–1.02)	
HDL cholesterol				0.17
<40 mg/dl	77/787 (9.8)	84/785 (10.7)	0.90 (0.66–1.23)	
≥40 mg/dl	98/1147 (8.5)	144/1149 (12.5)	0.68 (0.53–0.88)	
Fasting glucose				0.48
<100 mg/dl	106/1126 (9.4)	132/1137 (11.6)	0.81 (0.62–1.04)	
≥100 mg/dl	69/813 (8.5)	96/800 (12.0)	0.70 (0.51–0.95)	
Triglycerides				0.22
<150 mg/dl	111/1260 (8.8)	137/1293 (10.6)	0.83 (0.65–1.07)	
≥150 mg/dl	64/675 (9.5)	91/641 (14.2)	0.65 (0.47–0.89)	
Medication adherence				0.79
<80%	111/1071 (10.4)	123/834 (14.7)	0.69 (0.53–0.89)	
≥80%	61/861 (7.1)	103/1090 (9.4)	0.73 (0.53–1.00)	

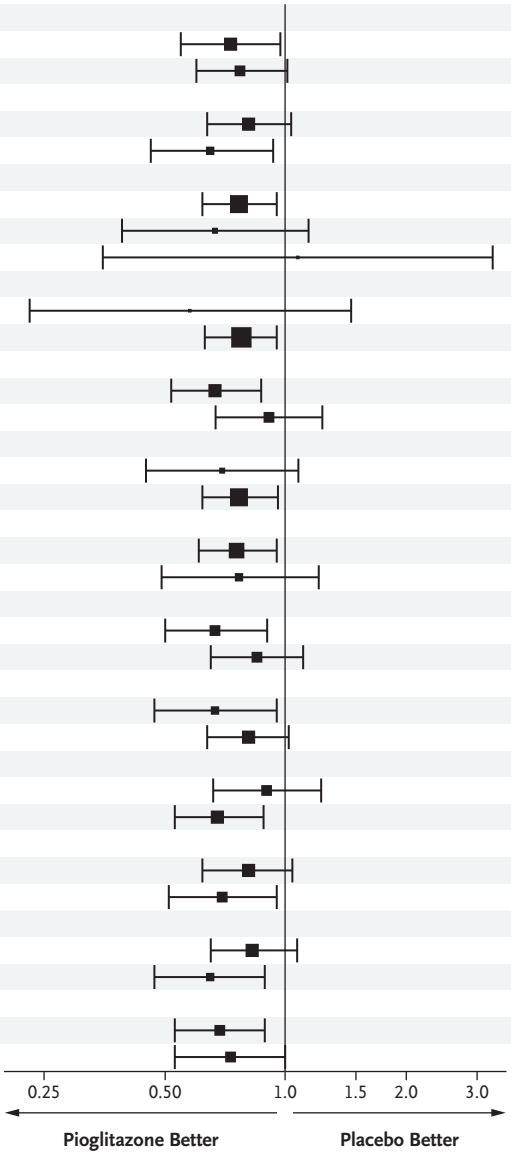


Figure 2. Subgroup Analyses of the Primary Outcome.

Shown is the relative benefit of pioglitazone as compared with placebo in 13 subgroups that were examined for their interaction with the treatment. P values have not been adjusted for multiple comparisons. (P=0.94 after adjustment for multiple comparisons in each subgroup.) The size of the squares corresponds to the number of patients in each subgroup. The body-mass index is the weight in kilograms divided by the square of the height in meters. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. To convert the values for glucose to millimoles per liter, multiply by 0.05551. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129. HDL denotes high-density lipoprotein, and HOMA-IR homeostasis model assessment of insulin resistance.

pose tissue mass and a tendency for fluid accumulation owing to renal sodium retention.[41] Sodium retention, if unchecked, can also increase the risk of heart failure.[42] However, in the IRIS trial, we did not observe a greater incidence of heart failure in the pioglitazone group than in the placebo group, which was probably because we excluded patients with a history of heart failure and used safety algorithms that triggered dose reduction for excessive weight gain or edema.

Table 3. Adverse Events, According to Severity.*

Event	Pioglitazone (N=1939)	Placebo (N=1937)	P Value
	no. of patients (%)		
Serious adverse event			
Hospitalization	908 (46.8)	946 (48.8)	0.21
Death	136 (7.0)	146 (7.5)	0.53
Incident cancer			
Any	133 (6.9)	150 (7.7)	0.29
Prostate	28 (1.4)	25 (1.3)	0.68
Breast	10 (0.5)	16 (0.8)	0.24
Lung	13 (0.7)	11 (0.6)	0.68
Bladder	12 (0.6)	8 (0.4)	0.37
Other	75 (3.9)	93 (4.8)	0.15
Bone fracture†	99 (5.1)	62 (3.2)	0.003
Heart failure‡	51 (2.6)	42 (2.2)	0.35
Other§	2 (0.1)	1 (0.1)	0.50
Other adverse event			
Bone fracture¶	133 (6.9)	94 (4.9)	0.008
Heart failure¶	29 (1.5)	32 (1.7)	0.70
Weight gain			
>4.5 kg	1013 (52.2)	653 (33.7)	<0.001
>13.6 kg	221 (11.4)	88 (4.5)	<0.001
Edema‖	691 (35.6)	483 (24.9)	<0.001
Shortness of breath	342 (17.6)	292 (15.1)	0.03
Alanine aminotransferase >ULN	26 (1.3)	59 (3.0)	<0.001
Macular edema	3 (0.2)	2 (0.1)	0.66

* ULN denotes the upper limit of the normal range.
† This category of adjudicated bone fracture refers to bone fracture that resulted in hospitalization, surgery, or a procedure.
‡ This category of adjudicated heart failure refers to heart failure that resulted in hospitalization or death.
§ Other serious events included sigmoid lipoma resulting in obstruction and sigmoid colectomy and hypoglycemia with unresponsiveness in the pioglitazone group and severe headache in the placebo group.
¶ Included in this category are adjudicated events that did not meet the criteria for serious events, as defined above.
‖ Edema was defined as self-reported new or worse swelling of the feet or lower legs.

Pioglitazone has been associated with an increased risk of bone fracture.[43] The mechanism is uncertain, and studies have not shown a consistent effect of the drug on bone density.[44,45]

Observational research conducted in 2011 and 2012 suggested that pioglitazone may increase the risk of bladder cancer.[46,47] However, more recent studies[48,49] showed no significant association for any dose or duration of therapy.[49] Other research suggests that PPAR-γ agonists might prevent certain cancers.[50,51] Although we did not observe a significant effect of treatment on the incidence of total or any specific cancer, our study was not powered to address these questions.

The patients in our study were classified as having insulin resistance on the basis of the HOMA-IR index. We selected this measurement because it is easy to perform and is closely correlated with more definitive but complex tests.[20,52] However, a component of the HOMA-IR index is the plasma insulin level, which is not globally standardized. To account for this, all HOMA-IR testing in the IRIS trial was performed in central laboratories. To replicate IRIS eligibility criteria, laboratories would need either to adopt the IRIS assays or to calibrate their own results to the IRIS assays.

In conclusion, we found that pioglitazone, a therapy directed at improving insulin sensitivity, can prevent cardiovascular events among patients who have insulin resistance along with cerebrovascular disease. The findings suggest that the

administration of pioglitazone in 100 patients similar to those in our trial for about 5 years could prevent 3 patients from having a stroke or myocardial infarction. However, during the same period, the treatment would be expected to result in bone fractures requiring surgery or hospitalization in 2 patients. It seems reasonable to consider individual treatment preference and risk of drug-related adverse events in addition to potential benefits when making patient-specific decisions regarding therapy.

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APPENDIX

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