ORIGINAL ARTICLE

# Pioglitazone for Diabetes Prevention in Impaired Glucose Tolerance

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## ABSTRACT

### BACKGROUND

Impaired glucose tolerance is associated with increased rates of cardiovascular disease and conversion to type 2 diabetes mellitus. Interventions that may prevent or delay such occurrences are of great clinical importance.

### METHODS

We conducted a randomized, double-blind, placebo-controlled study to examine whether pioglitazone can reduce the risk of type 2 diabetes mellitus in adults with impaired glucose tolerance. A total of 602 patients were randomly assigned to receive pioglitazone or placebo. The median follow-up period was 2.4 years. Fasting glucose was measured quarterly, and oral glucose tolerance tests were performed annually. Conversion to diabetes was confirmed on the basis of the results of repeat testing.

### RESULTS

Annual incidence rates for type 2 diabetes mellitus were 2.1% in the pioglitazone group and 7.6% in the placebo group, and the hazard ratio for conversion to diabetes in the pioglitazone group was 0.28 (95% confidence interval, 0.16 to 0.49; P<0.001). Conversion to normal glucose tolerance occurred in 48% of the patients in the pioglitazone group and 28% of those in the placebo group (P<0.001). Treatment with pioglitazone as compared with placebo was associated with significantly reduced levels of fasting glucose (a decrease of 11.7 mg per deciliter vs. 8.1 mg per deciliter [0.7 mmol per liter vs. 0.5 mmol per liter], P<0.001), 2-hour glucose (a decrease of 30.5 mg per deciliter vs. 15.6 mg per deciliter [1.6 mmol per liter vs. 0.9 mmol per liter], P<0.001), and $HbA_{1c}$ (a decrease of 0.04 percentage points vs. an increase of 0.20 percentage points, P<0.001). Pioglitazone therapy was also associated with a decrease in diastolic blood pressure (by 2.0 mm Hg vs. 0.0 mm Hg, P=0.03), a reduced rate of carotid intima–media thickening (31.5%, P=0.047), and a greater increase in the level of high-density lipoprotein cholesterol (by 7.35 mg per deciliter vs. 4.5 mg per deciliter [0.4 mmol per liter vs. 0.3 mmol per liter], P=0.008). Weight gain was greater with pioglitazone than with placebo (3.9 kg vs. 0.77 kg, P<0.001), and edema was more frequent (12.9% vs. 6.4%, P=0.007).

### CONCLUSIONS

As compared with placebo, pioglitazone reduced the risk of conversion of impaired glucose tolerance to type 2 diabetes mellitus by 72% but was associated with significant weight gain and edema. (Funded by Takeda Pharmaceuticals and others; ClinicalTrials.gov number, NCT00220961.)

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Type 2 diabetes mellitus affects 21 million Americans,[1] and its prevalence is increasing.[2] Microvascular and macrovascular complications are common in type 2 diabetes mellitus and are related to both the severity and the duration of hyperglycemia.[3] The natural history of type 2 diabetes mellitus has been well defined,[4] starting with a genetic predisposition and progression from normal glucose tolerance with insulin resistance to impaired glucose tolerance and eventually type 2 diabetes mellitus with the superimposition of beta-cell failure.

Because hyperglycemia plays a central role in the microvascular and macrovascular complications of diabetes,[3,5,6] it is possible that interventions that prevent or delay hyperglycemia may effectively prevent or delay these long-term complications. Studies have shown that the rate of conversion of impaired glucose tolerance to type 2 diabetes mellitus is reduced with lifestyle modification[7]; the use of metformin,[7] thiazolidinediones,[8-11] or acarbose[12]; and bariatric surgery.[13] The greatest reductions in conversion rates have been observed with weight loss, the use of thiazolidinediones, and surgery. Troglitazone was reported to be associated with a 55% decrease in the rate of conversion to diabetes among women with prior gestational diabetes,[11] but this agent is no longer available. In one study,[9] the use of rosiglitazone decreased the risk of diabetes in adults with impaired glucose tolerance by 62%; given concerns about cardiovascular safety,[14] however, the Food and Drug Administration has restricted the use of rosiglitazone therapy to patients in whom glycemic control cannot be achieved with other medications and who cannot take pioglitazone. We undertook the present study to examine the effect of pioglitazone on diabetes risk and cardiovascular risk factors in adults with impaired glucose tolerance.

## METHODS

### PATIENTS

We recruited male and female patients who were 18 years of age or older and had impaired glucose tolerance (defined as a 2-hour glucose level of 140 to 199 mg per deciliter [7.8 to 11.0 mmol per liter] during a single oral glucose-tolerance test)[15] and a body-mass index (BMI, the weight in kilograms divided by the square of the height in meters) of 25 or more. Patients were eligible for enrollment if they had a fasting plasma glucose level between 95 and 125 mg per deciliter (5.3 and 6.9 mmol per liter) and at least one other risk factor for diabetes.[16] The complete list of inclusion and exclusion criteria is provided in Table 1 in the Supplementary Appendix, available with the full text of this article at NEJM.org. The criteria have also been published previously.[16] During the course of recruitment, the glycemic inclusion criteria were modified to include patients with a fasting plasma glucose level between 90 and 125 mg per deciliter (5.0 and 6.9 mmol per liter) if their 2-hour plasma glucose level during the oral glucose-tolerance test was between 170 and 199 mg per deciliter (9.4 and 11.1 mmol per liter)[17]; the change was made in recognition of the high risk of diabetes in such persons.

The first participant was recruited in January 2004, with the screening ultimately including 1827 potentially eligible patients with impaired glucose tolerance (Fig. 1). The enrollment of 602 participants was completed in March 2006. Participants were followed until they reached the primary end point of diabetes, withdrew from the study, were lost to follow-up, or completed the end of the study.

### STUDY DESIGN

The study design and protocol, which have been described previously,[16] are available at NEJM.org. Eight centers participated in the study, which was approved by the institutional review board at each site. Written informed consent was obtained from all participants. The first author designed the study and, along with the coauthors, wrote the first draft and revisions and approved the final version; he also holds the data at the University of Texas Health Science Center in San Antonio. The study was conducted in accordance with the protocol. All authors made the decision to submit the manuscript for publication. All results were transmitted to the Data Coordinating Center in Phoenix, Arizona, where they were recorded and audited and then sent to the Data Analysis Center in San Antonio. Takeda Pharmaceuticals provided financial support for the study but had no access to the data.

After eligibility for the study was ascertained, participants underwent randomization according to center and sex and received 30 minutes of dietary instruction consistent with the goals of the Diabetes Prevention Program,[7] which was re-

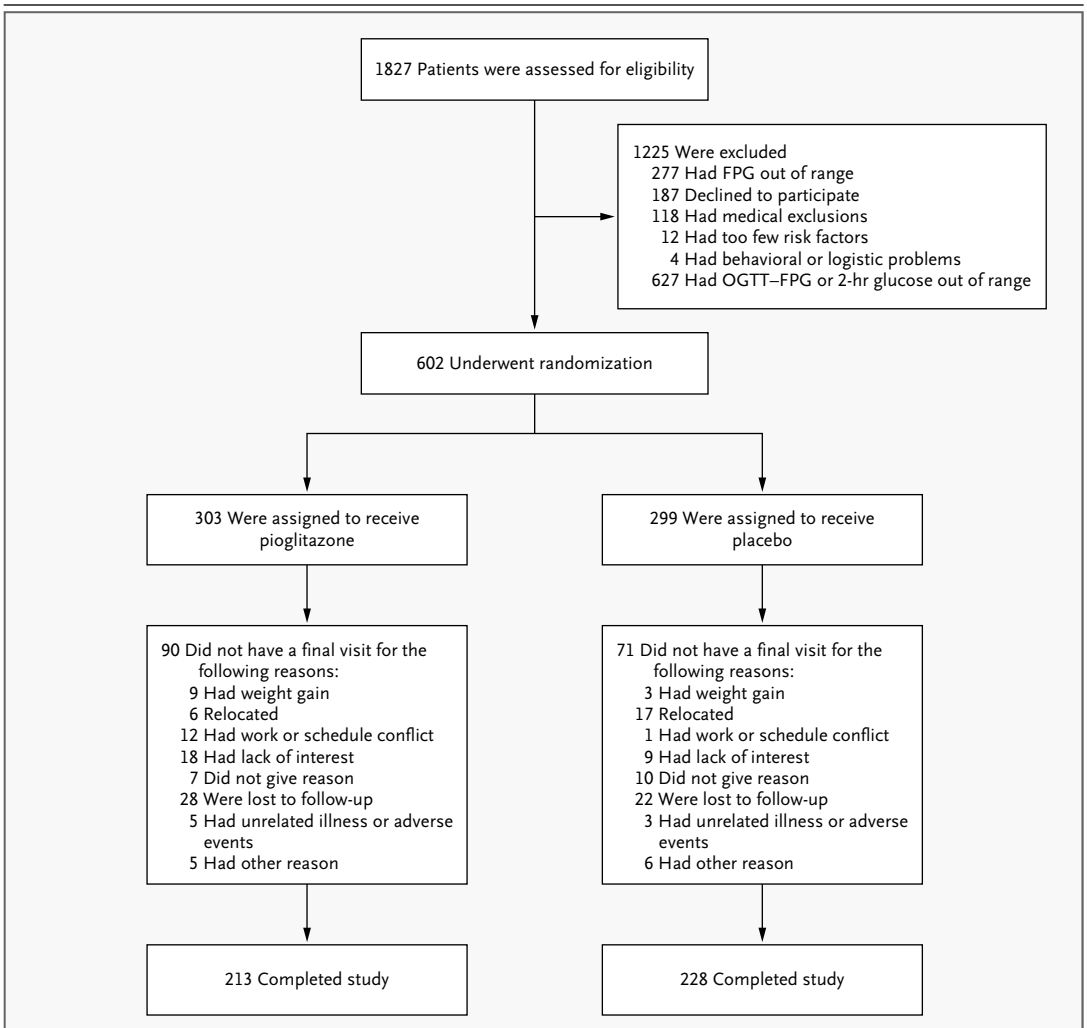


**Figure 1. Enrollment, Randomization, and Follow-up of Study Patients.**
FPG denotes fasting plasma glucose, and OGTT oral glucose-tolerance test.

inforced on follow-up visits. Once enrolled, participants were asked to fast overnight before undergoing an oral glucose-tolerance test at 8 a.m. the next day. Samples were collected every 15 minutes for 2 hours for measurements of glucose, insulin, and C-peptide.[16] Additional baseline assessments included measurements of blood pressure, height, weight, waist circumference, and level of $HbA_{1c}$; a lipid profile; screening blood tests; urinalysis, with calculation of the ratio of microalbumin to creatinine; and electrocardiography. At seven centers, high-resolution B-mode ultrasonography was performed at baseline, 15 to 18 months after baseline, and at the end of the study, to assess the far wall of the right distal common carotid artery (for details, see the Methods section in the Supplementary Appendix).[18,19] Body-fat content was measured with the use of a dual-energy x-ray absorptiometer (DXA) (Hologic).

Participants initially received 30 mg of pioglitazone per day or placebo. One month after randomization, the dose of pioglitazone was increased to 45 mg per day. Participants returned at 2, 4, 6, 8, 10, and 12 months during the first year of the study and once every 3 months thereafter. At each visit, weight, blood pressure, and pulse were measured and the extent of edema was graded (with an increase in edema defined as an increase of two grades or more from baseline) (for details, see Table 2 in the Supplementary

Appendix). Fasting plasma glucose was also measured at each follow-up visit. The levels of $HbA_{1c}$, alanine aminotranferase, and aspartate aminotransferase were measured every 6 months, and the oral glucose-tolerance test was repeated annually. All measurements obtained at baseline were repeated at the end of the study.

### CONVERSION OF IMPAIRED GLUCOSE TOLERANCE TO DIABETES

The primary outcome was the development of diabetes[15] (defined as a fasting plasma glucose level ≥126 mg per deciliter [≥7.9 mmol per liter] or a 2-hour glucose level ≥200 mg per deciliter [11.1 mmol per liter]); an oral glucose-tolerance test was performed to confirm the diagnosis. If the diagnosis was not confirmed, patients continued with their assigned therapy. Diabetes was not confirmed but was considered to have developed in five patients receiving pioglitazone and five patients receiving placebo. At the final visit, six patients had a single oral glucose-tolerance test with results that met the diagnostic criteria for diabetes; four of the six were started on antidiabetic medication by their physician.

### MEASUREMENTS AND CALCULATIONS

Insulin sensitivity was derived from plasma glucose and insulin measurements obtained during the oral glucose-tolerance test (Matsuda index)[20] and from the results of an intravenous glucose-tolerance test with frequent sampling.[21] Beta-cell function was calculated as the index of insulin secretion factored by insulin resistance ($\Delta I_{0-120}/\Delta G_{0-120} \times$ Matsuda index) during the oral glucose-tolerance test, where $\Delta I_{0-120}/\Delta G_{0-120}$ represents the mean incremental concentrations of plasma insulin and glucose during the 120-minute oral glucose-tolerance test.[22] Beta-cell function was also calculated as the product of insulin secretion and insulin sensitivity ($\Delta I_{0-10} \times S_I$) during the intravenous glucose-tolerance test with frequent sampling. Laboratory methods are described in detail in the Methods section in the Supplementary Appendix.

### STATISTICAL ANALYSIS

The development of diabetes,[15] the primary outcome, was assessed by means of life-table analysis of the time from randomization to incident diabetes. Separate life-table estimated cumulative incidence curves were calculated for the pioglitazone and placebo groups and compared with the use of the log-rank test.[23] The Cox proportional-hazards model was used to estimate the effect of pioglitazone on the primary outcome.[24] Data for patients who were lost to follow-up or who withdrew were censored at the time of the last visit. Statistical tests were two-sided, with an alpha level of 0.05. Data are reported as means ±SE. We calculated that enrollment of approximately 600 patients was required to achieve 90% power, if treatment with pioglitazone decreased the rate of conversion from impaired glucose tolerance to type 2 diabetes mellitus by 50%.[16]

For analyses of secondary outcomes, which included changes in levels of fasting plasma glucose, 2-hour glucose, and $HbA_{1c}$, between-group comparisons of changes in repeated or continuous measures were performed with the use of general linear mixed models, with data transformed to logarithms when appropriate. The statistical heterogeneity of treatment effects within subgroups was assessed. No adjustment was made for multiple comparisons, and subgroup analyses were not prespecified.

Two approaches were used to assess whether patients who completed the study differed from those who withdrew. The first approach involved a withdrawal-free survival analysis of time to withdrawal, with the final study visit used as the censoring variable. Data for patients who underwent an oral glucose-tolerance test at the end-of-study visit were censored at 3 years. All other patients were counted as having withdrawn as of the last study visit. On the basis of this analysis, the hazard ratio for withdrawal in the pioglitazone group as compared with the placebo group was 1.125 ($P=0.42$). In the second approach, missing data (for the two study groups combined) were assessed for each continuous measure with analysis of variance, stratified according to whether the measure was missing at each subsequent visit. Since neither approach produced statistically significant evidence of bias due to missing data, the primary and secondary analyses were performed without data imputation.

## RESULTS

### PARTICIPANTS

The mean age of the 602 study participants was 52.3±0.5 years, and 58% were women (Table 1). The mean BMI was 34.5±0.4. A total of 407 pa-

**Table 1. Baseline Characteristics of the Patients.***

| Characteristic | Pioglitazone (N=303) | Placebo (N=299) | P Value |
|---|---|---|---|
| Isolated impaired glucose tolerance — no. | 98 | 97 | 0.98 |
| Both impaired glucose tolerance and impaired fasting glucose tolerance — no. | 205 | 202 | 0.98 |
| Ratio of women to men — % | 58/42 | 58/42 | 0.96 |
| Race or ethnic group — no.† | | | 0.45 |
| Hispanic | 79 | 75 | |
| White | 156 | 171 | |
| Black | 57 | 44 | |
| Other | 11 | 9 | |
| Family history of diabetes — no. (%) | 177 (58.4) | 186 (62.2) | 0.34 |
| History of gestational diabetes mellitus — no. (% of women) | 24 (14) | 37 (21) | 0.07 |
| Mean age — yr | 53.0±0.4 | 51.5±0.7 | 0.12 |
| Age group — % | | | |
| 18–39 yr | 36 | 42 | 0.155 |
| 40–59 yr | 32 | 28 | 0.33 |
| ≥60 yr | 32 | 30 | 0.66 |
| Height — cm | 166±0.5 | 167±0.6 | 0.47 |
| Mean BMI | 33.0±0.4 | 34.5±0.4 | 0.44 |
| BMI group — no. (%) | | | |
| <30 | 79 (26.0) | 76 (25.4) | 0.95 |
| 30–35 | 109 (36.0) | 100 (33.4) | 0.71 |
| >35 | 114 (37.6) | 122 (40.8) | 0.65 |
| Waist circumference — cm | | | |
| Men | 110.5±1.1 | 112.2±1.3 | 0.70 |
| Women | 103.1±0.9 | 103.7±1.0 | 0.31 |
| $HbA_{1c}$ — % | 5.5±0.4 | 5.5±0.4 | 0.23 |
| Fasting plasma glucose — mg/dl | 105±0.4 | 105±0.4 | 0.72 |
| 2-Hr plasma glucose — mg/dl | 168±1 | 168±1 | 0.80 |
| Fasting plasma insulin — mU/liter | 10.5±0.5 | 10.7±0.6 | 0.84 |
| Lipid levels — mg/dl | | | |
| Total cholesterol | 169±2 | 173±2 | 0.22 |
| LDL cholesterol | 104±2 | 108±2 | 0.20 |
| HDL cholesterol | 40±1 | 41±1 | 0.57 |
| Triglycerides | 122±3 | 121±3 | 0.84 |
| Fasting free fatty acids (μmol/liter) | 551±13 | 528±13 | 0.17 |
| Blood pressure — mm Hg | | | |
| Systolic | 127±0.9 | 128±0.9 | 0.57 |
| Diastolic | 74±0.6 | 74±0.6 | 0.99 |

* Plus–minus values are means ±SE. No intergroup differences were significant. To convert the values for glucose to millimoles per liter, multiply by 0.05551. To convert the values for insulin to picomoles per liter, multiply by 6.945. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129. BMI denotes body-mass index (the weight in kilograms divided by the square of the height in meters), HDL high-density lipoprotein, and LDL low-density lipoprotein.

† Race or ethnic group was self-reported.

tients had both impaired fasting glucose and impaired glucose tolerance, and 195 had isolated impaired glucose tolerance. Baseline levels of $HbA_{1c}$, fasting plasma glucose, and 2-hour glucose were 5.50±0.04%, 105±0.3 mg per deciliter (5.8±0.02 mmol per liter), and 168±1 mg per deciliter (9.32±0.06 mmol per liter), respectively. None of the baseline clinical, anthropometric, or laboratory variables differed significantly between the placebo group and the pioglitazone group (Table 1).

### FOLLOW-UP

During a median follow-up period of 2.4 years (mean, 2.2), diabetes developed in 50 of the 299 patients in the placebo group (16.7%) and in 15 of the 303 patients in the pioglitazone group (5.0%). The annual average incidence of diabetes, calculated on the basis of person-years, was 7.6% in the placebo group and 2.1% in the pioglitazone group (P<0.001) (Fig. 2). The hazard ratio for development of diabetes in the pioglitazone group was 0.28 (95% confidence interval, 0.16 to 0.49; P<0.001). Adjustment for baseline characteristics did not alter the hazard ratio. The number of people who would need to be treated to prevent one case of diabetes was 8 for 2.2 years of the trial and 18 for 1 year. Among the patients who completed the study, 103 of those in the pioglitazone group (48%) and 65 of those in the placebo group (28%) had normal glucose tolerance (P<0.001).

A total of 161 patients did not complete the study (71 in the placebo group and 90 in the pioglitazone group). The median follow-up time for these patients was 7.6 months. Baseline characteristics of the patients who did not complete the study were similar to those of the 441 patients who completed the study (i.e., those who had conversion to type 2 diabetes mellitus during the study or who completed the oral glucose-tolerance test at the end of the trial). Reasons for not completing the study included weight gain (in 9 patients in the pioglitazone group and 3 in the placebo group); patients also left for reasons unrelated to the study medication (Fig. 1). The rate of adherence to the study regimen, assessed by means of pill counts, was greater than 80% in both groups. At the end of the study, 64% of the patients in the treatment group were taking pioglitazone at a daily dose of 45 mg and 81% of those in the placebo group were taking the corresponding placebo dose. The major reasons for not increasing the dose of pioglitazone from 30 to 45 mg per day or for not maintaining the 45-mg dose were weight gain and edema.

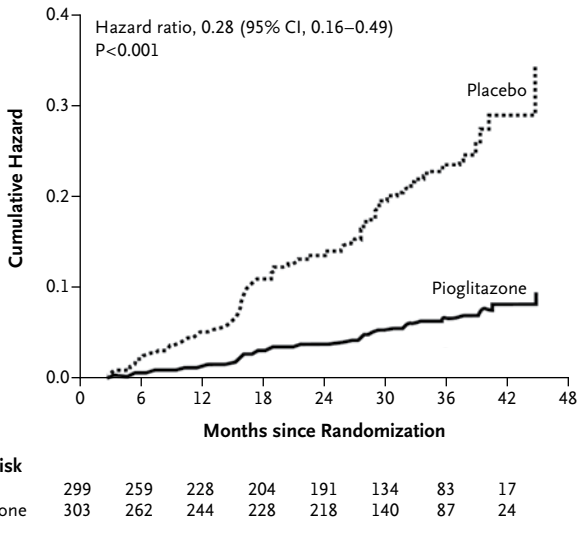


**Figure 2. Kaplan–Meier Plot of Hazard Ratios for Time to Development of Diabetes.**

### EFFECTS OF PIOGLITAZONE

Protection from diabetes with pioglitazone was of similar magnitude (with no significant heterogeneity) in subgroups defined by sex, age, weight, race or ethnic group, and fasting glucose level, as well as in patients with both impaired glucose tolerance and impaired fasting glucose and those with isolated impaired glucose tolerance (Fig. 3). There was no evidence of heterogeneity of the response according to the baseline level of $HbA_{1c}$.

Greater reductions in fasting and 2-hour glucose levels were achieved in the pioglitazone group than in the placebo group (P<0.001 for both comparisons), with a between-group difference of 3.5±1.1 mg per deciliter (0.2±0.06 mmol per liter) and 14±3 mg per deciliter (0.8±0.17 mmol per liter), respectively, at the end of the study (Fig. 4A and 4B). Levels of $HbA_{1c}$ differed between the groups throughout the study (P<0.001), increasing by 0.20±0.02% in the placebo group, with no change in the pioglitazone group. Body weight, BMI, and body fat increased in the placebo group (96.7±1.2 to 97.3±1.3 kg, 34.5±0.4 to 34.7±0.4, and 39.0±0.7 to 39.3±0.7%, respectively) and in the pioglitazone group (94.9±1.2 to 98.7±1.3 kg,

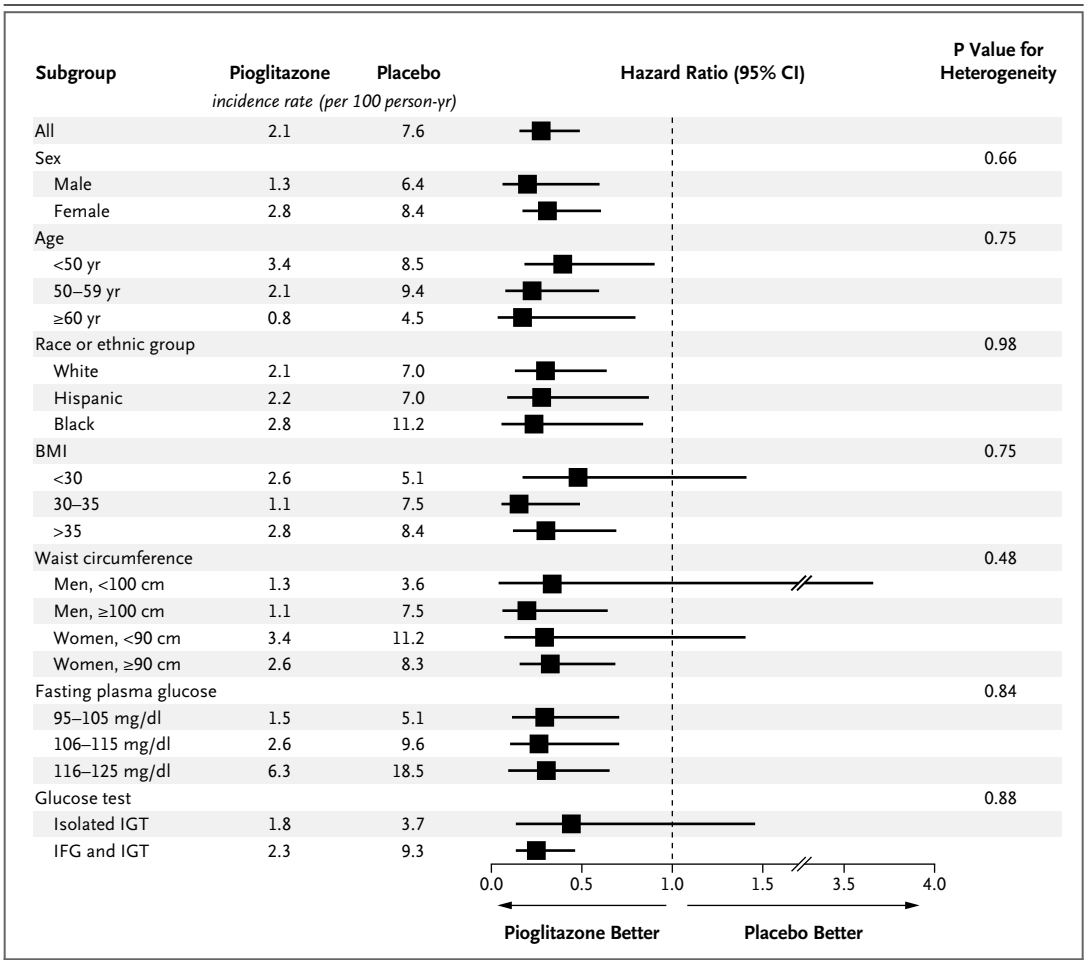


**Figure 3. Incidence Rates, Hazard Ratios, and Tests for Heterogeneity for All Patients and Selected Subgroups.**

The figure shows incidence rates per 100 person-years and corresponding hazard ratios and confidence intervals for the effects of pioglitazone as compared with placebo on the conversion of impaired glucose tolerance to diabetes. The x axis is interrupted to allow for better visual presentation. BMI denotes body-mass index (the weight in kilograms divided by the square of the height in meters), IFG impaired fasting glucose, and IGT impaired glucose tolerance. To convert the values for glucose to millimoles per liter, multiply by 0.05551.

34.1±0.4 to 35.5±0.4, and 40.0±0.8 to 41.9±0.7%, respectively), but the increments were greater with pioglitazone (P<0.001 for all comparisons).

Systolic blood pressure declined slightly in both groups, but the difference in decline between the groups was not significant. Diastolic blood pressure was consistently lower in the pioglitazone group (P=0.01). As compared with placebo, pioglitazone reduced levels of both alanine aminotranferase and aspartate aminotransferase (P<0.001). The change in high-density lipoprotein (HDL) cholesterol was greater with pioglitazone (40±1 to 48±1 mg per deciliter [2.2±0.06 to 2.7±0.06 mmol per liter]) than with placebo (41±1 to 45.1±0.7 mg per deciliter [2.3±0.06 to 2.5±0.04 mmol per liter]) (P=0.008 for the difference between groups). Triglyceride levels declined significantly with pioglitazone (129±7.5 to 110±4.0 mg per deciliter [7.2±0.42 to 6.1±0.22 mmol per liter], P=0.007) but not with placebo (124±4.6 to 113±4.0 mg per deciliter [6.9±0.25 to 6.30±0.22 mmol per liter], P=0.90); the difference between groups was not significant. Neither pioglitazone nor placebo altered levels of low-density lipoprotein cholesterol.

Insulin sensitivity as measured with the Matsuda index increased more with pioglitazone than with placebo (4.31±0.24 to 7.65±0.34 vs.

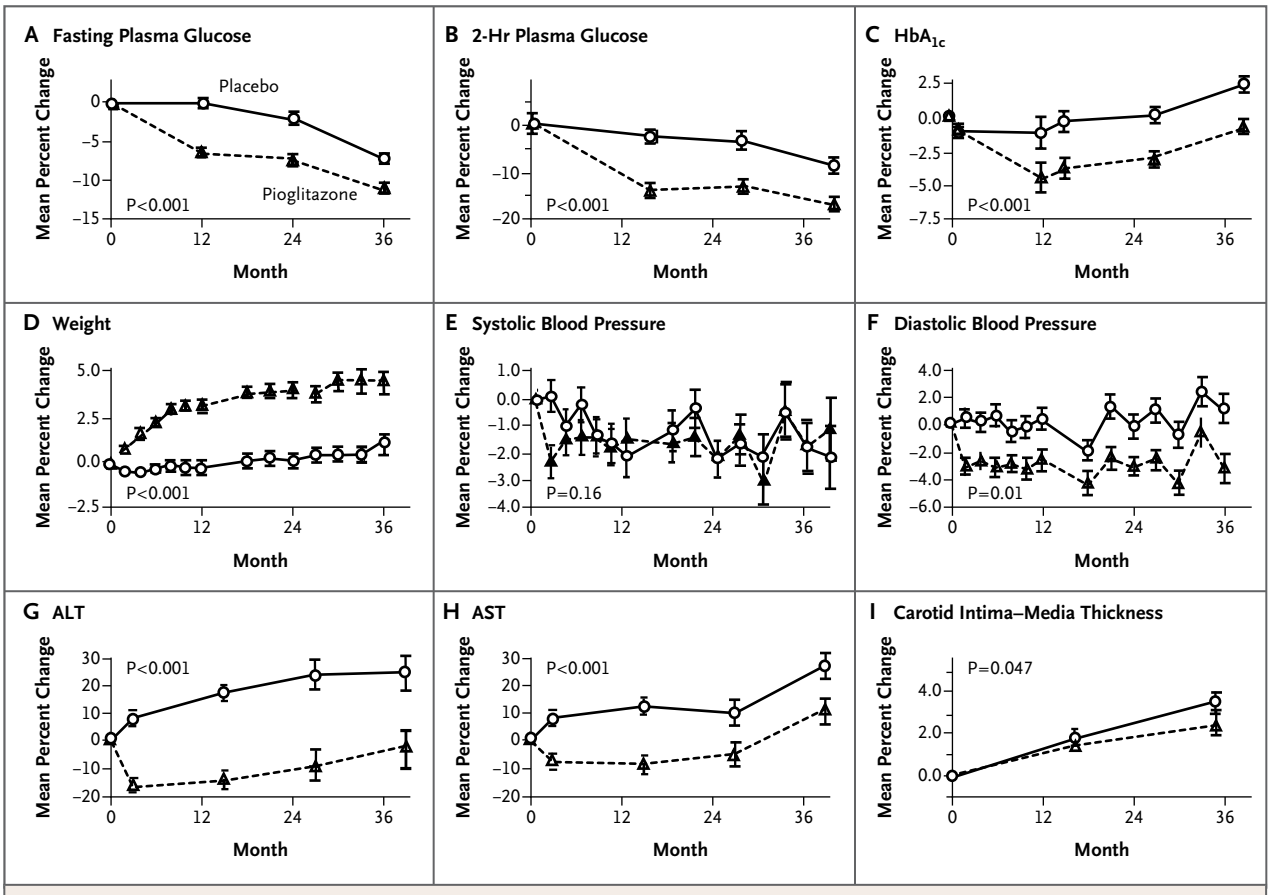


**Figure 4. Effects of Pioglitazone as Compared with Placebo.**

Over the course of the study, mean percentage changes and standard errors in continuous measures were calculated with the use of a linear, mixed-repeated-measures model fit to all available data for each measure. As compared with placebo, treatment with pioglitazone (dashed lines) had beneficial effects on fasting plasma glucose levels (Panel A), 2-hour plasma glucose levels (Panel B), and $HbA_{1c}$ levels (Panel C) and on systolic and diastolic blood pressure (Panels E and F, respectively), alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels (Panels G and H, respectively), and carotid intima–media thickness (Panel I). Weight gain was greater with pioglitazone than with placebo (Panel D). (Body-mass index was calculated at each examination with the use of height measured at baseline; as a result, the percentage change in BMI is identical to the percentage change in weight.) A total of 365 patients (placebo group, 186; pioglitazone group, 179) completed the follow-up examination at 15 to 18 months for measurement of carotid intima–media thickness, and 336 patients (placebo group, 173; pioglitazone group, 163) completed the final examination for measurement of carotid intima–media thickness. P values are shown for the interaction between time and study group, indicating whether the slopes differ significantly over time.

4.31±0.30 to 5.23±0.31, P<0.001). Insulin sensitivity as determined with the use of an intravenous glucose-tolerance test with frequent sampling in a subgroup of 191 patients was not altered in either group. The index of insulin secretion factored by insulin resistance, calculated on the basis of the oral glucose-tolerance test ($I_{0-120}/\Delta G_{0-120} \times$ Matsuda index), increased more with pioglitazone than with placebo (3.43±0.12 to 5.44±0.31 vs. 3.81±0.30 to 4.20±0.20, P<0.005). Similarly, the insulin secretion–insulin resistance index, calculated with data from the frequent-sampling intravenous glucose-tolerance test, increased more with pioglitazone than with placebo (848±65 to 1186±113 vs. 824±47 to 832±57, P<0.01).

Carotid intima–media thickening increased more slowly in the pioglitazone group than in the placebo group throughout the study (Fig. 4I). The differences between groups were 16.4% at the study midpoint and 31.5% at the end of the study (P=0.047 for the overall difference between

groups). The ratio of urinary microalbumin to creatinine was low at baseline; during the study it fell slightly and similarly in the two groups (1.85±0.2 to 1.53±0.2 mg per gram in the pioglitazone group vs. 1.47±0.3 to 1.25±0.3 mg per gram in the placebo group, P=0.20).

### ADVERSE EVENTS

Adverse events occurred in 121 patients in the placebo group and 151 patients in the pioglitazone group (P=0.03) (Table 2). Edema increased at some point during the trial in 19 patients receiving placebo (6.4%) and 39 patients receiving pioglitazone (12.9%) (P=0.007). Events related to the cardiovascular system numbered 23 in the placebo group (7.7%) and 26 in the pioglitazone group (8.6%) (Table 3 in the Supplementary Appendix), with 1 case of congestive heart failure in each group (0.3%). One unexplained sudden death occurred in the placebo group, and three deaths occurred in the pioglitazone group (one unexplained sudden death, one death from biliary carcinoma, and one death from a carcinoid tumor). Nine fractures occurred in 8 of the patients receiving pioglitazone (3%) and eight fractures occurred in 7 of the patients receiving placebo (2.6%) (Table 4 in the Supplementary Appendix). All fractures were associated with trauma.

**Table 2. Number and Type of Adverse Events.***

| Adverse Event | Pioglitazone (N=303) | Placebo (N=299) |
|---|---|---|
| | *no. of events* | |
| Cancer | 3 | 8 |
| Cardiovascular system | 26 | 23 |
| Central nervous system | 6 | 5 |
| Death | 3 | 1 |
| Digestive system | 13 | 12 |
| Edema† | 39 | 19 |
| Elective surgery | 22 | 16 |
| Endocrine system | 1 | 3 |
| Immune system | 2 | 4 |
| Musculoskeletal system | 12 | 13 |
| Ophthalmologic system | 0 | 1 |
| Respiratory system | 9 | 6 |
| Reproductive system | 4 | 4 |
| Skin | 6 | 3 |
| Urogenital system | 5 | 3 |
| Weight gain‡ | 205 | 128 |
| Total | 356 | 249 |

* For the comparison of placebo and pioglitazone regarding frequency of edema, cardiovascular events, and total events, P=0.007, P=0.80, and P=0.03, respectively. The total number of adverse events — excluding edema — did not differ significantly between groups (P=0.52).
† Edema was defined as an increase above baseline by two or more grades on one or more distinct study visits.
‡ Weight gain was defined as a gain of more than 1 kg.

## DISCUSSION

Although they are considered to have prediabetes, patients in the upper third of the range for impaired glucose tolerance are at or close to the maximum level of insulin resistance and have lost approximately 80% of beta-cell function.[25,26] Histologic studies suggest that the beta-cell mass in patients with impaired fasting glucose is significantly reduced as compared with persons who have normal fasting glucose,[27] and two thirds of the patients in our study had impaired fasting glucose. Moreover, at least 10% of patients with impaired glucose tolerance have background diabetic retinopathy,[28,29] and peripheral neuropathy is common in these patients.[30] Because the characteristic pathophysiological defects of type 2 diabetes mellitus and the microvascular complications of diabetes are already evident in patients with impaired glucose tolerance, it is reasonable to consider interventions at this stage to prevent the development of overt diabetes.

Lifestyle interventions effectively reduce the conversion of impaired glucose tolerance to diabetes[31-34] and remain the primary approach to prevention of type 2 diabetes mellitus. However, many people remain at risk for type 2 diabetes mellitus despite attempts at lifestyle changes.[7,31,32,34] Metformin reduces the risk of conversion to type 2 diabetes mellitus by 31%, without weight gain.[7] Thiazolidinediones also effectively reduce the risk of development of type 2 diabetes mellitus in patients with impaired glucose tolerance.[8-11] In our study, pioglitazone decreased the rate of conversion to diabetes by 72%, a change that was slightly larger than that observed with other thiazolidinediones (52 to 62%) and lifestyle modification (58%). Although subgroup analyses were not prespecified in our study design, pioglitazone reduced the risk of conversion to diabetes in patients with isolated impaired glucose tolerance, in those with both

impaired fasting glucose and impaired glucose tolerance, in both men and women, and in all age and weight groups. The proportion of patients who had a return to normal glucose tolerance was greater with pioglitazone than with placebo. The mean weight gain in patients treated with pioglitazone was 3.6 kg. However, the greater the weight gain, the greater the improvements in beta-cell function and insulin sensitivity, and thus the greater the reduction in $HbA_{1c}$.[26,35,36] The effect of weight gain on cardiovascular risk cannot be ascertained, but in the Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROactive) (ClinicalTrials.gov number, NCT00174993),[37] a weight gain of 3.6 kg was not associated with an increase in the composite cardiovascular end point.

It is not feasible to conduct studies of microvascular outcomes in patients with impaired glucose tolerance because of the large sample and long study duration required. However, if development of diabetic hyperglycemia can be delayed or prevented, it is plausible that the onset of microvascular complications might be slowed. During the course of this study, fasting and 2-hour glucose levels and $HbA_{1c}$ levels were significantly lower in the pioglitazone group than in the placebo group. The small difference in levels of $HbA_{1c}$ between the two groups is not surprising, given the low baseline level of $HbA_{1c}$ in patients with impaired glucose tolerance. However, further glycemic separation between groups over time would presumably have a beneficial effect on microvascular disease.

Pioglitazone was associated with lower diastolic blood pressure, higher levels of HDL cholesterol, and reduced rates of carotid intima–media thickening, as compared with placebo. Carotid intima–media thickening is highly correlated with cardiovascular events, and changes in this measure over time have predictive value beyond that of standard markers of risk.[18,38] Such results suggest that pioglitazone may provide some protection against the development of atherosclerotic cardiovascular disease, which is consistent with reports of reductions in the volume of coronary plaque[39] and in mortality, nonfatal myocardial infarction, and stroke, the secondary end points in the PROactive.[37]

Loss to follow-up was relatively high in both study groups (24% in the placebo group and 30% in the pioglitazone group, not a significant difference). Since withdrawal rates and baseline characteristics were similar between groups, biased results seem unlikely. The modest difference in levels of $HbA_{1c}$ between groups suggests that the reduced progression of carotid intima–media thickening with pioglitazone may reflect improvements in other metabolic variables (Fig. 4). Although pioglitazone is a well-documented insulin sensitizer, insulin resistance was reduced according to the Matsuda index of insulin sensitivity measured during the oral glucose-tolerance test but not according to measurement of insulin sensitivity during the frequent-sampling intravenous glucose-tolerance test. These disparate results may partly reflect the greater variation among centers in the results of the intravenous glucose-tolerance test with frequent sampling, which is more difficult to perform.

Edema and weight gain were greater with pioglitazone than with placebo, as reported previously,[8,40] and edema largely accounted for the increase in adverse events associated with pioglitazone. Physician-reported congestive heart failure developed in only one patient in each group. Although an increased incidence of fractures has been reported with the use of thiazolidinediones, in this study, the incidence was similar in both groups, and all fractures were related to trauma.

In summary, treatment with pioglitazone in patients with impaired glucose tolerance reduced the risk of diabetes, although pioglitazone was associated with significant weight gain and edema. Treatment of 18 participants for 1 year prevented one case of diabetes. Use of pioglitazone improved diastolic blood pressure, HDL cholesterol levels, and serum levels of alanine aminotranferase and aspartate aminotransferase, and it slowed progression of carotid intima–media thickening. The influence of these effects on long-term diabetic complications remains to be determined.

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