

ORIGINAL ARTICLE

Glycemic Durability of Rosiglitazone, Metformin, or Glyburide Monotherapy

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ABSTRACT

BACKGROUND

The efficacy of thiazolidinediones, as compared with other oral glucose-lowering medications, in maintaining long-term glycemic control in type 2 diabetes is not known.

METHODS

We evaluated rosiglitazone, metformin, and glyburide as initial treatment for recently diagnosed type 2 diabetes in a double-blind, randomized, controlled clinical trial involving 4360 patients. The patients were treated for a median of 4.0 years. The primary outcome was the time to monotherapy failure, which was defined as a confirmed level of fasting plasma glucose of more than 180 mg per deciliter (10.0 mmol per liter), for rosiglitazone, as compared with metformin or glyburide. Pre-specified secondary outcomes were levels of fasting plasma glucose and glycated hemoglobin, insulin sensitivity, and β -cell function.

RESULTS

Kaplan–Meier analysis showed a cumulative incidence of monotherapy failure at 5 years of 15% with rosiglitazone, 21% with metformin, and 34% with glyburide. This represents a risk reduction of 32% for rosiglitazone, as compared with metformin, and 63%, as compared with glyburide ($P < 0.001$ for both comparisons). The difference in the durability of the treatment effect was greater between rosiglitazone and glyburide than between rosiglitazone and metformin. Glyburide was associated with a lower risk of cardiovascular events (including congestive heart failure) than was rosiglitazone ($P < 0.05$), and the risk associated with metformin was similar to that with rosiglitazone. Rosiglitazone was associated with more weight gain and edema than either metformin or glyburide but with fewer gastrointestinal events than metformin and with less hypoglycemia than glyburide ($P < 0.001$ for all comparisons).

CONCLUSIONS

The potential risks and benefits, the profile of adverse events, and the costs of these three drugs should all be considered to help inform the choice of pharmacotherapy for patients with type 2 diabetes. (ClinicalTrials.gov number, NCT00279045.)

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This article was published at www.nejm.org on December 4, 2006.

N Engl J Med 2006;355:2427-43.
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THE ATTAINMENT AND MAINTENANCE of near-normal glycemia reduces the risk of long-term complications of diabetes.¹⁻³ Despite lifestyle and pharmacologic interventions, glucose levels increase over time in type 2 diabetes, probably as a consequence of declining β -cell function.⁴ The progressive nature of type 2 diabetes makes it difficult to maintain target levels of glycated hemoglobin with traditional glucose-lowering agents^{5,6} and generally necessitates the escalation of drug doses and the use of combination therapies or insulin.⁷

Thiazolidinediones reduce insulin resistance by sensitizing muscle, liver, and adipose tissue to insulin⁸ and delay progression to type 2 diabetes in patients with glucose intolerance.⁹⁻¹¹ Small clinical studies have suggested that thiazolidinediones preserve β -cell function.^{9,12} Thus, they may be of benefit as initial treatment of type 2 diabetes.

Our study, called A Diabetes Outcome Progression Trial (ADOPT), was a multicenter, randomized, double-blind, controlled clinical trial designed to evaluate the durability of glycemic control in patients receiving monotherapy with a thiazolidinedione, rosiglitazone (Avandia, GlaxoSmithKline); a biguanide, metformin (Glucophage, Bristol-Myers Squibb); or a sulfonylurea, glyburide (Micronase, Pfizer). All the patients in the study had not received previous pharmacologic treatment for type 2 diabetes that had been recently diagnosed (i.e., within 3 years). The primary outcome was the time to monotherapy failure on the basis of plasma glucose levels of more than 180 mg per deciliter (>10.0 mmol per liter) after an overnight fast. The trial permitted the direct comparison of the metabolic effects of these three commonly used glucose-lowering agents over an extended period.

METHODS

STUDY DESIGN

The ADOPT protocol, methods, and baseline characteristics of the cohort have been described previously.^{13,14} Between April 2000 and June 2002, 4360 patients who had not received previous pharmacologic treatment for recently diagnosed type 2 diabetes were randomly assigned to receive double-blind monotherapy with one of the three study drugs (Fig. 1). Investigators at 488 centers in the United States, Canada, and 15 European countries

participated in the study. Randomization was performed centrally and was concealed and stratified according to the sex of the patients in blocks of six. After the exclusion of 9 patients who did not receive a study drug, we evaluated 4351 patients in the safety analyses: 1456 in the rosiglitazone group, 1454 in the metformin group, and 1441 in the glyburide group. Of these patients, 224 (63 in the rosiglitazone group, 57 in the metformin group, and 104 in the glyburide group) withdrew before the first scheduled efficacy evaluation, which yielded a total of 4127 patients (95%) — including 1393 in the rosiglitazone group, 1397 in the metformin group, and 1337 in the glyburide group — for the intention-to-treat efficacy analyses.

The therapeutic goal was a fasting plasma glucose level below 140 mg per deciliter (7.8 mmol per liter). Patients were followed until the termination of the study in June 2006, with a median treatment duration of 4.0 years (maximum, 6.1).

PATIENTS

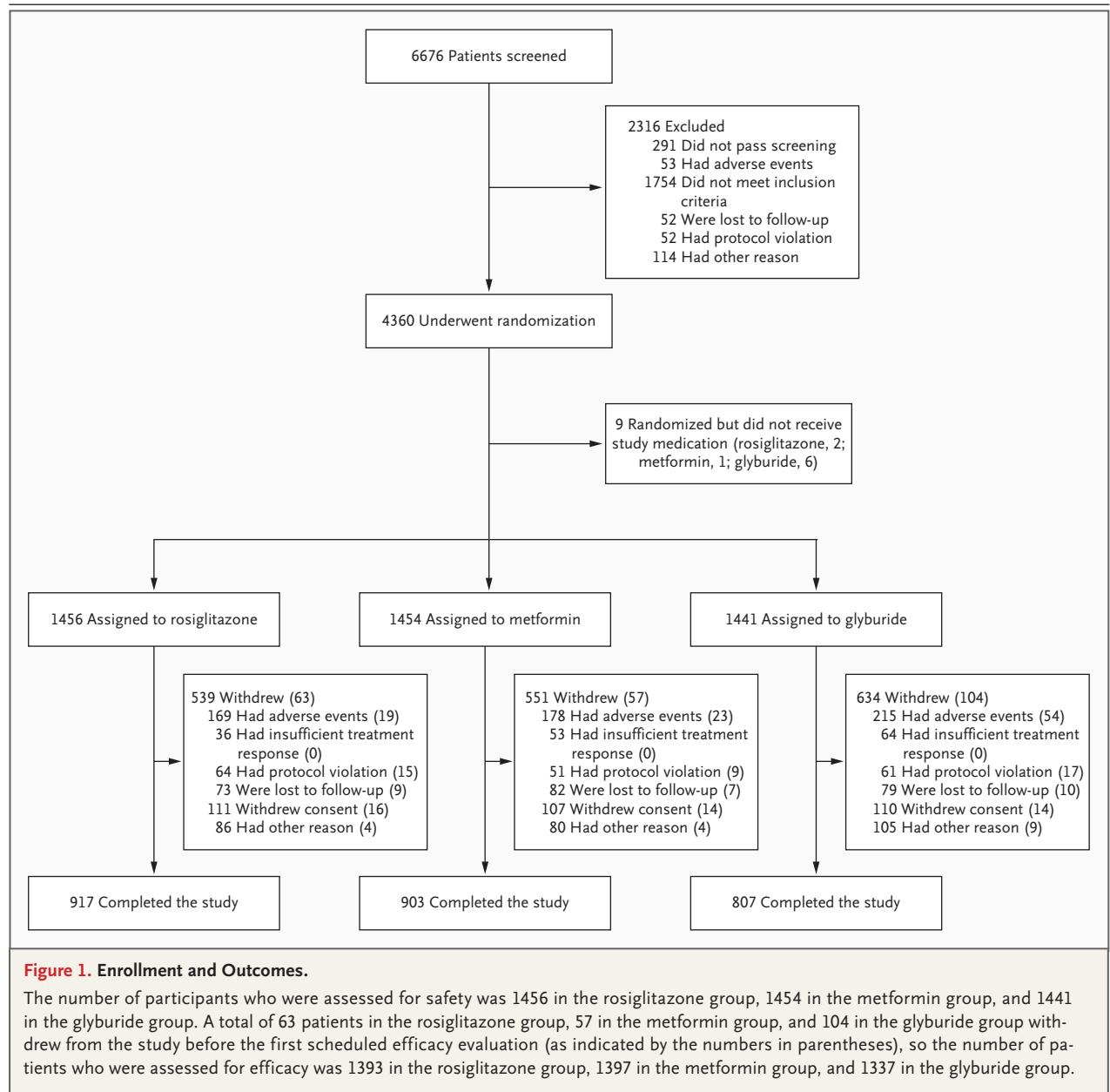
Eligible patients were between the ages of 30 and 75 years, with fasting plasma glucose levels ranging from 126 to 180 mg per deciliter (7.0 to 10.0 mmol per liter) while their only treatment was lifestyle management.¹³ Exclusion criteria included clinically significant hepatic disease, renal impairment, a history of lactic acidosis, unstable or severe angina, known congestive heart failure (CHF, New York Heart Association class I, II, III, or IV), or uncontrolled hypertension.¹³

MONOTHERAPY ADMINISTRATION

In a double-blind regimen, patients received initial daily doses of 4 mg of rosiglitazone, 500 mg of metformin, or 2.5 mg of glyburide. All drugs were prepared in identical capsules to make them indistinguishable. For each drug, the dose was increased according to the protocol to the maximum daily effective dose (4 mg of rosiglitazone twice daily, 1 g of metformin twice daily, and 7.5 mg of glyburide twice daily). A dose increase was required at each visit if the fasting plasma glucose level was 140 mg per deciliter or more; a dose reduction was permitted if adverse events occurred.

BIOCHEMICAL AND CLINICAL MEASUREMENTS

Fasting plasma glucose levels were measured by hexokinase assay (Olympus America), and glycated



hemoglobin by high-performance liquid chromatography (Biorad) every 2 months in the first year and every 3 months thereafter. Liver function tests, complete blood count, and measurements of immunoreactive insulin, C peptide, and lipids were performed at least annually. Blood samples were assayed in a central laboratory.¹³ All study drugs were withheld on the morning of testing. Physical examination and electrocardiography were performed at baseline and annually.

OUTCOME MEASURES

The primary outcome was the time from randomization to treatment failure, which was defined as confirmed hyperglycemia (fasting plasma glucose level, >180 mg per deciliter) on consecutive testing after at least 6 weeks of treatment at the maximum-dictated or maximum-tolerated dose of the study drug. An independent adjudication committee, whose members were unaware of assignments to treatment groups, used prespecified

Table 1. Baseline Characteristics of the Patients.*			
Variable	Rosiglitazone (N=1456)	Metformin (N=1454)	Glyburide (N=1441)
Demographic characteristics			
Age — yr	56.3±10.0	57.9±9.9	56.4±10.2
Male sex — no. (%)	811 (55.7)	864 (59.4)	836 (58.0)
Race or ethnic background — no. (%)†			
White	1270 (87.2)	1295 (89.1)	1282 (89.0)
Black	61 (4.2)	54 (3.7)	61 (4.2)
Asian	39 (2.7)	35 (2.4)	32 (2.2)
Hispanic	76 (5.2)	55 (3.8)	61 (4.2)
Other	10 (0.7)	15 (1.0)	5 (0.3)
Region — no. (%)			
North America	758 (52.1)	758 (52.1)	758 (52.6)
Europe	698 (47.9)	696 (47.9)	683 (47.4)
Time since diagnosis of diabetes — no. (%)			
<1 yr	651 (44.6)	673 (46.3)	637 (44.2)
1–2 yr	758 (52.1)	724 (49.8)	751 (52.1)
>2 yr	47 (3.2)	57 (3.9)	53 (3.7)
Anthropometric characteristics			
Weight — kg	91.5±19.7	91.6±18.7	92.0±20.0
Body-mass index‡	32.2±6.7	32.1±6.1	32.2±6.3
Waist circumference — cm	105.3±14.6	105.6±14.3	105.6±15.1
Hip circumference — cm	111.4±14.1	111.2±13.4	111.8±14.2
Waist-to-hip ratio	0.95±0.09	0.95±0.10	0.94±0.09
Blood pressure			
Systolic — mm Hg	133±16	133±15	133±15
Diastolic — mm Hg	80±9	80±9	79±9
Antihypertensive therapy — no. (%)	744 (51.1)	737 (50.7)	753 (52.3)

criteria (see the Supplementary Appendix, available with the full text of this article at www.nejm.org) to determine whether the primary outcome was reached in cases in which a confirmatory fasting plasma glucose level had not been obtained, a patient had withdrawn because of an insufficient therapeutic effect, or an additional glucose-lowering drug had been administered before the confirmation of hyperglycemia (according to a protocol amendment adopted in February 2004). On the basis of the independent adjudication, treatment was deemed to have failed in 170 patients: 41 of the 143 patients who reached the primary end point (29%) in the rosiglitazone group, 61 of 207 (29%) in the metformin group, and 68 of 311 (22%) in the glyburide group.

The threshold of more than 180 mg per decili-

ter for confirmed hyperglycemia was selected to represent unequivocal failure in the maintenance of adequate glycemic control without incurring undue hyperglycemic symptoms; the threshold of a fasting plasma glucose level of more than 140 mg per deciliter for increasing the dose of a study drug reflected clinical guidelines at the time of study design.¹⁵ The glycated hemoglobin level was not chosen as the primary outcome because guidelines at the initiation of the study focused largely on fasting plasma glucose levels.¹⁵

Prespecified secondary outcomes included the time from randomization to a confirmed fasting plasma glucose level of more than 140 mg per deciliter after at least 6 weeks of treatment at the maximum-tolerated dose of a study drug (for patients who entered the study with a fasting plasma

Table 1. (Continued.)

Variable	Rosiglitazone (N=1456)	Metformin (N=1454)	Glyburide (N=1441)
Metabolic characteristics			
Fasting plasma glucose — mg/dl	151.5±25.8	151.3±25.6	152.4±27.3
Glycated hemoglobin — %	7.36±0.93	7.36±0.93	7.35±0.92
Fasting insulin — pmol/liter	149.9±108.2	151.8±111.6	150.4±113.1
Insulin sensitivity — % [§]			
Median	33.8	33.3	33.1
Interquartile range	22.7–48.6	22.6–47.4	22.5–49.2
β -cell function — % [§]			
Median	68.0	69.5	67.9
Interquartile range	51.4–87.8	52.0–90.2	52.8–87.7
GAD positive — no. (%) [¶]	55 (4.0)	70 (5.1)	50 (3.6)
Lipids			
Total cholesterol — mg/dl			
Median	205	204	202
Interquartile range	177–231	177–231	177–230
LDL cholesterol — mg/dl			
Median	121	120	119
Interquartile range	98–144	96–143	98–144
HDL cholesterol — mg/dl			
Median	46.9	46.5	47.3
Interquartile range	39.0–54.6	39.6–55.0	39.0–55.4
Triglycerides — mg/dl			
Median	163	165	156
Interquartile range	116–230	112–233	112–222
Lipid-lowering therapy — no. (%)	378 (26.0)	377 (25.9)	370 (25.7)

* Plus-minus values are means \pm SD. $P > 0.05$ for all comparisons between treatment groups. LDL denotes low-density lipoprotein, HDL high-density lipoprotein, and GAD glutamic acid decarboxylase. To convert the values for glucose to millimoles per liter, multiply by 0.05551. 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.

[†] Race or ethnic background was reported by the patients.

[‡] The body-mass index is the weight in kilograms divided by the square of the height in meters.

[§] Insulin sensitivity and β -cell function were determined by homeostasis model assessment (HOMA 2) as a percentage of the values in a normal reference population, with the use of the HOMA Calculator (www.dtu.ox.ac.uk).

[¶] GAD status was determined for 1388 patients in the rosiglitazone group, 1379 patients in the metformin group, and 1372 patients in the glyburide group.

^{||} LDL cholesterol levels were calculated for patients with triglyceride levels of less than 400 mg per deciliter, including 1333 patients in the rosiglitazone group, 1340 patients in the metformin group, and 1342 patients in the glyburide group.

glucose level of 140 mg per deciliter or less). Other prespecified outcomes were levels of fasting plasma glucose and glycated hemoglobin, weight, and measures of insulin sensitivity and β -cell function,¹⁶ as determined by homeostasis model assessment (HOMA 2) with the use of the HOMA Calculator (www.dtu.ox.ac.uk).

Site investigators reported all adverse events and collected data during the treatment period.

At the end of the study, a cardiologist who was not connected with the study reviewed a listing of all serious adverse events. Cases suggestive of CHF were then evaluated by this practitioner and another independent cardiologist, both of whom were unaware of treatment assignments, to determine whether CHF was present. A third cardiologist arbitrated in case of disagreement. Site investigators were also asked to report deaths con-

sidered to be related to a study drug that occurred after the treatment period.

STUDY OVERSIGHT

The study protocol was approved by the institutional review board at each center, and all patients provided written informed consent. An independent data safety and monitoring board met twice a year to review unblinded safety data prepared by an independent statistical analysis group at the University of Wisconsin–Madison.

Study design, implementation, and analysis were performed under the supervision of the steering committee, which was composed of seven members from academic institutions and two from the sponsor, GlaxoSmithKline. The sponsor housed all blinded data during the treatment phase of the study and performed data analyses according to a prespecified plan developed with the academic biostatistician and approved by the steering committee. Independent academic statisticians confirmed key efficacy and safety results (see the Supplementary Appendix). Steering committee members, who had access to all data analyses and wrote the manuscript, attest to the veracity and completeness of the data. The decision to publish was made by the committee's academic members, with no restrictions imposed by the sponsor.

STATISTICAL ANALYSIS

We originally calculated that we would need to enroll 3600 patients to provide the study with a power of 90% to detect a 30% reduction in the risk of treatment failure for rosiglitazone, as compared with metformin and glyburide, at a significance level of $P=0.05$ (two-sided, adjusted for two comparisons), assuming an event rate of 0.072 per year for metformin or glyburide and a rate of loss to follow-up of 0.064 per year in each group. The protocol was amended in March 2002 to increase the number of patients to 4182 and in February 2004, to extend the follow-up period beyond 4 years, in order to compensate for an overall rate of withdrawal that was greater than anticipated and an overall rate of primary outcome events that was lower than anticipated. The revised power estimate was 83%, assuming a rate of loss to follow-up of 0.128 per year and a hazard rate for treatment failure of 0.035 per year.

The primary comparisons were rosiglitazone versus metformin and rosiglitazone versus glybu-

ride. A secondary analysis compared metformin and glyburide. The percent reduction in risk was computed as $100 \times (1 - \text{the hazard ratio})$, with the hazard ratio estimated from the Cox proportional-hazards model. The cumulative incidence was estimated with the Kaplan–Meier method and with Gray's method, which adjusts for deaths.¹⁷ Two-sided nominal P values are reported for all comparisons. The Hochberg method was used to determine statistical significance at the 0.05 level, adjusted for two comparisons.¹⁷ Other details about the statistical methods used in the study are available in the Supplementary Appendix.

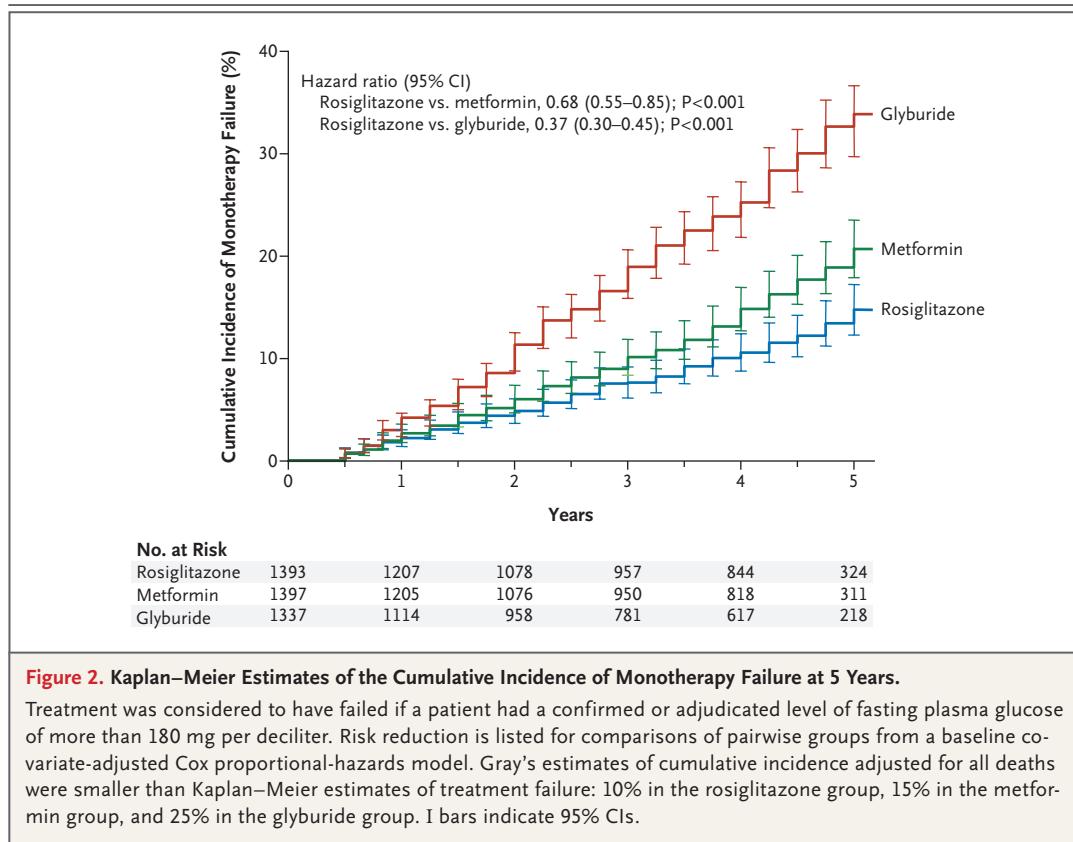
RESULTS

BASELINE CHARACTERISTICS AND FOLLOW-UP

Of the 6676 subjects who were initially screened, 4360 were randomly assigned to the three treatment groups (Fig. 1). Patients were middle-aged, predominantly white, and obese (body-mass index [the weight in kilograms divided by the square of the height in meters], >30), with no significant differences in baseline variables among the groups (Table 1). The median duration of treatment was 4.0 years for rosiglitazone and metformin and 3.3 years for glyburide. The proportion of patients who either reached the primary outcome or completed the study was 63% in the rosiglitazone group, 62% in the metformin group, and 56% in the glyburide group. The primary reasons that patients did not complete the study were adverse events (12% of patients in the rosiglitazone group, 12% in the metformin group, and 15% in the glyburide group; $P<0.001$ for the comparison between the rosiglitazone group and the glyburide group) and withdrawal of consent (7 to 8% of patients in all three groups). The demographic, anthropometric, and metabolic characteristics of patients who withdrew from the study did not differ significantly among treatment groups.

PRIMARY OUTCOME

Monotherapy failed in 143 patients who received rosiglitazone (2.9 per 100 patient-years), 207 who received metformin (4.3 per 100 patient-years), and 311 who received glyburide (7.5 per 100 patient-years). The Kaplan–Meier cumulative incidence at 5 years was 15% with rosiglitazone, 21% with metformin, and 34% with glyburide (Fig. 2). The risk (incidence) was reduced by 32% (95% con-



confidence interval [CI], 15 to 45) with rosiglitazone as compared with metformin and by 63% (95% CI, 55 to 70) with rosiglitazone as compared with glyburide ($P<0.001$ for both comparisons).

At the time of treatment failure, 99.3% of patients in the rosiglitazone group, 98.6% in the metformin group, and 99.0% in the glyburide group were receiving the maximum dose of the study drug. A sensitivity analysis indicated that the benefit of rosiglitazone, as compared with glyburide, was probably not attributable to bias caused by early withdrawal from the study, but this factor could not be excluded for the comparison of rosiglitazone and metformin (see the Supplementary Appendix). Subgroup analyses suggested that the treatment effect was greater with rosiglitazone than with metformin among older patients (≥ 50 years of age) and among those with a larger waist circumference (>110 cm) (Fig. 3). Rosiglitazone was more effective than glyburide in all subgroups.

For treatment failure not requiring adjudication, the findings were similar to those for the

primary outcome: treatment failed in 102 patients in the rosiglitazone group, as compared with 146 patients in the metformin group (risk reduction, 31%; 95% CI, 11 to 46; $P=0.004$) and 243 patients in the glyburide group (risk reduction, 66%; 95% CI, 57 to 73; $P<0.001$).

SECONDARY OUTCOMES

The rate of progression to a confirmed fasting plasma glucose level of more than 140 mg per deciliter also differed significantly among the groups: 79 of 511 patients in the rosiglitazone group, as compared with 127 of 520 patients in the metformin group (risk reduction, 36%; 95% CI, 15 to 52; $P=0.002$) and 160 of 480 patients in the glyburide group (risk reduction, 62%; 95% CI, 51 to 72; $P<0.001$) (Fig. 1 of the Supplementary Appendix).

Within the first 6 months, levels of fasting plasma glucose and glycated hemoglobin decreased in all treatment groups, with glyburide showing the greatest effect (Fig. 4A and 4B). After 6 months, the rates of increase in these glycemic measures

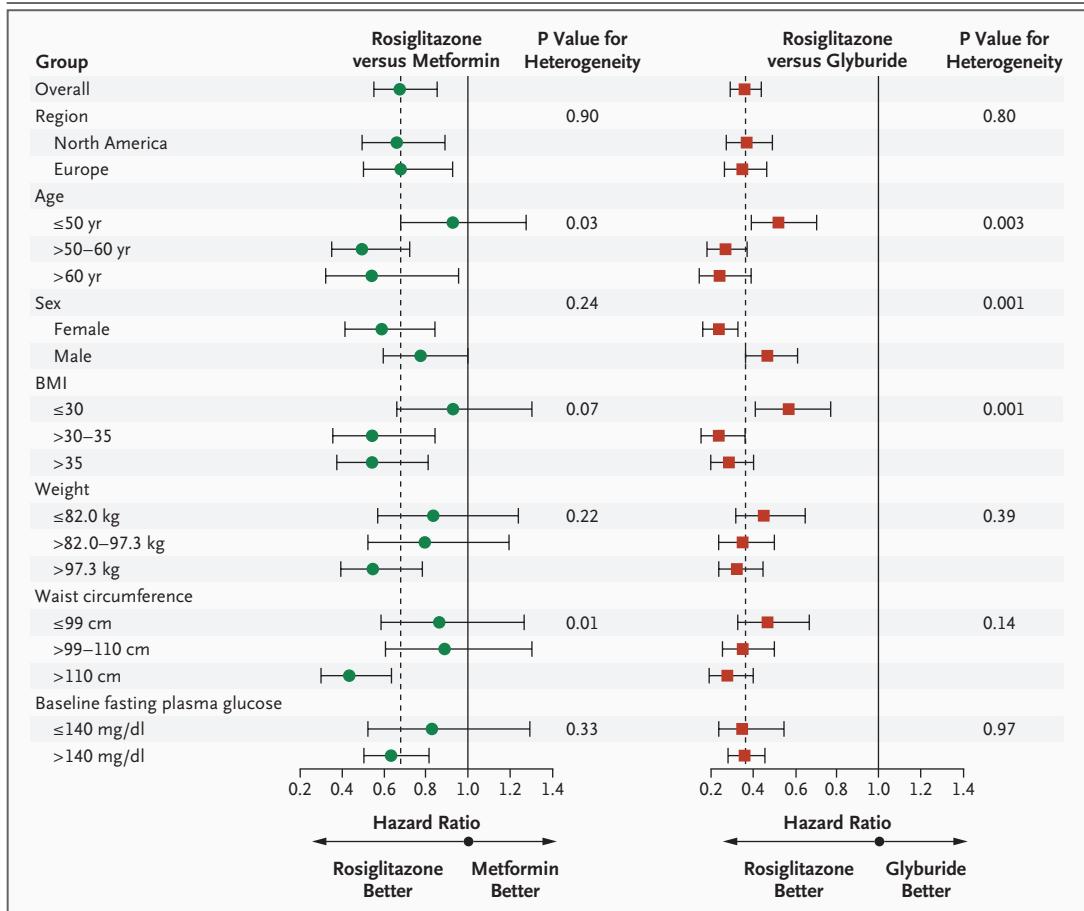


Figure 3. Hazard Ratio for Monotherapy Failure in the Rosiglitazone Group, as Compared with the Metformin and Glyburide Groups in Key Subgroups.

The test for heterogeneity (interaction) indicates whether the treatment effect varied significantly among the subgroups. The Hochberg method was applied to each of the two comparisons of the treatment groups. BMI denotes body-mass index (the weight in kilograms divided by the square of the height in meters).

were greatest in the glyburide group, which had annual increases of 5.6 mg per deciliter (0.31 mmol per liter) in the fasting plasma glucose level and 0.24% in the glycated hemoglobin level ($P < 0.001$ for the comparisons of both values with those in the rosiglitazone group); intermediate in the metformin group, which had annual increases of 2.7 mg per deciliter (0.15 mmol per liter) in the fasting plasma glucose level and 0.14% in the glycated hemoglobin level ($P < 0.001$ for the comparisons of both values with those in the rosiglitazone group); and least in the rosiglitazone group, which had increases of 0.7 mg per deciliter (0.04 mmol per liter) in the fasting plasma glucose level and 0.07% in the glycated hemoglobin level. A worst-rank sensitivity analysis, performed to evaluate

the effect of early withdrawal of patients because of either treatment failure or insufficient therapeutic effect, showed that withdrawals did not significantly influence the results (Fig. 2 of the Supplementary Appendix).

At the 4-year evaluation, 40% of the 1456 patients in the rosiglitazone group had a glycated hemoglobin level of less than 7%, as compared with 36% of the 1454 patients in the metformin group ($P = 0.03$) and 26% of the 1441 patients in the glyburide group ($P < 0.001$). The maximal treatment effect on glycated hemoglobin was achieved at 12 months for patients in the rosiglitazone and metformin groups and at 4 months for those in the glyburide group. From the longitudinal linear model, a mean glycated hemoglobin level of less

than 7% was maintained until the visit at 57 months in the rosiglitazone group, at 45 months in the metformin group, and at 33 months in the glyburide group (Fig. 4B).

As compared with glyburide, metformin was associated with a reduction in the risk of monotherapy failure of 46% (95% CI, 36 to 55; $P < 0.001$) and a reduction in the risk of exceeding a fasting plasma glucose level of 140 mg per deciliter of 41% (95% CI, 25 to 54; $P < 0.001$). At 4 years, metformin, as compared with glyburide, was associated with a reduction in the mean fasting plasma glucose level of 7.6 mg per deciliter (95% CI, 4.6 to 10.6) (0.42 mmol per liter [95% CI, 0.26 to 0.59]; $P < 0.001$) and a reduction in the glycated hemoglobin level of 0.28% (95% CI, 0.20 to 0.37; $P < 0.001$).

During the first 6 months, insulin sensitivity (as determined by HOMA) increased more in the rosiglitazone group (mean ratio of the 6-month value to the baseline value, 1.30; 95% CI, 1.28 to 1.34) than in the metformin group (mean ratio, 1.17; 95% CI, 1.15 to 1.20). Thereafter, insulin sensitivity improved at similar rates in the two groups, with a significant difference between the two groups at 4 years ($P < 0.001$) (Fig. 4C). Insulin sensitivity did not change significantly in the glyburide group.

During the first 6 months, levels of β -cell function (as determined by HOMA) increased more in the glyburide group (mean ratio of 6-month value to baseline value, 1.45; 95% CI, 1.42 to 1.48) than in either the rosiglitazone group (1.17; 95% CI, 1.15 to 1.19) or the metformin group (1.16; 95% CI, 1.14 to 1.19) (Fig. 4D). Thereafter, levels of β -cell function declined in all three groups. The annual rate of decline after 6 months was greatest in the glyburide group (a decrease of 6.1%), intermediate in the metformin group (a decrease of 3.1%), and least in the rosiglitazone group (a decrease of 2.0%) ($P < 0.001$ for the comparison of the rosiglitazone group and the glyburide group and $P = 0.02$ for the comparison of the rosiglitazone group and the metformin group).

Over a period of 5 years, the mean weight increased in the rosiglitazone group (change from baseline, 4.8 kg; 95% CI, 4.3 to 5.3) but decreased in the metformin group (-2.9 kg; 95% CI, -3.4 to -2.3) (Fig. 4E). In the glyburide group, weight gain occurred in the first year (1.6 kg; 95% CI, 1.0 to 2.2), then remained stable. Changes in waist and hip circumferences and waist-to-hip ratio over time are shown in Figures 4F, 4G, and 4H.

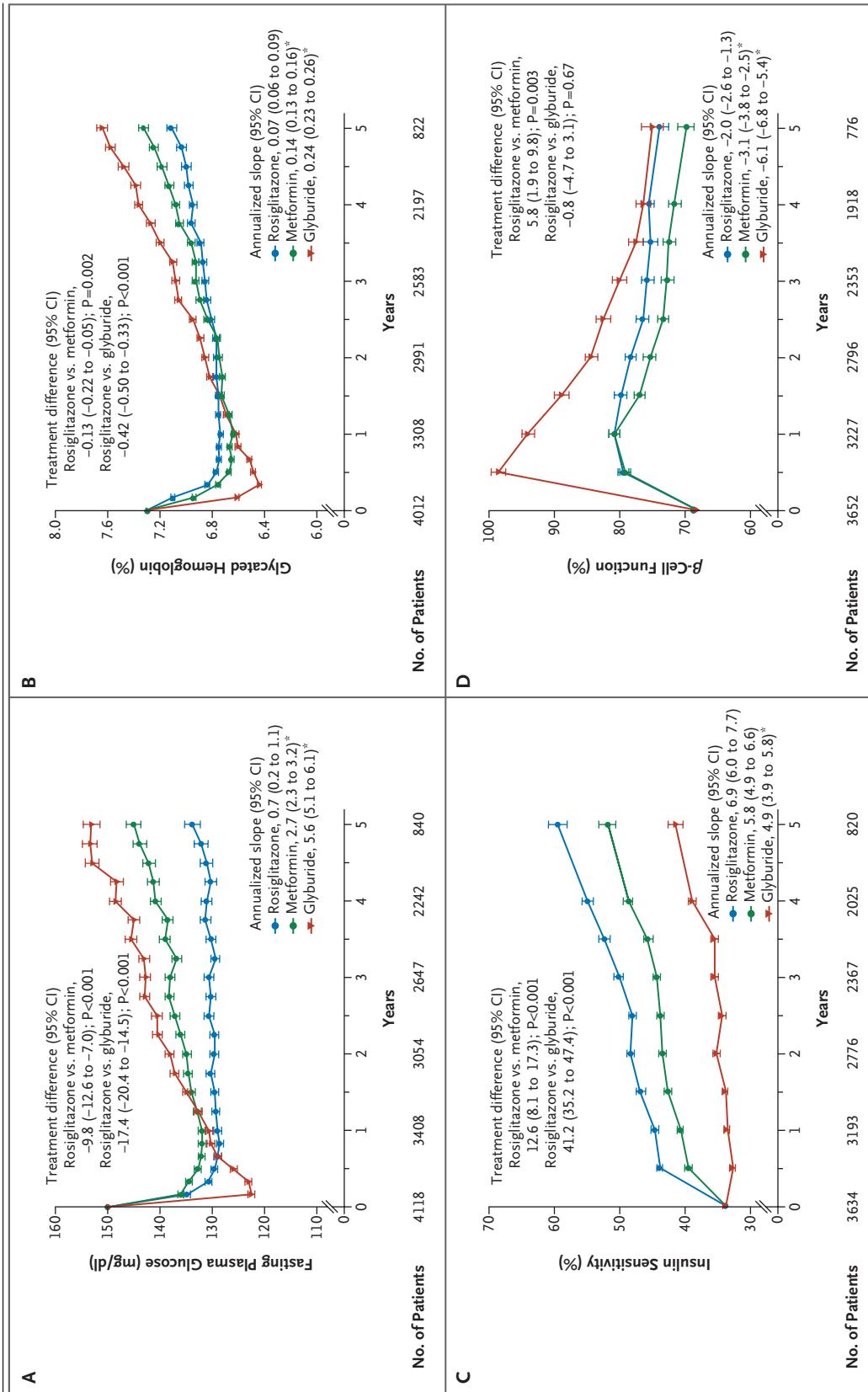
ADVERSE EVENTS, LABORATORY MEASURES, AND CONCOMITANT MEDICATIONS

The number of deaths from all causes was similar in the three groups. However, adverse events differed among the groups (Table 2). Cardiovascular events were reported in 62 patients in the rosiglitazone group, 58 in the metformin group, and 41 in the glyburide group. For all investigator-reported CHF events, 22 occurred in the rosiglitazone group (1.5%), 19 in the metformin group (1.3%), and 9 in the glyburide group (0.6%). The hazard ratio for CHF in the rosiglitazone group, as compared with the metformin group, was 1.22 (95% CI, 0.66 to 2.26; $P = 0.52$); the hazard ratio for the rosiglitazone group, as compared with the glyburide group, was 2.20 (95% CI, 1.01 to 4.79; $P = 0.05$). Episodes of CHF classified as serious adverse events occurred in 12 patients in the rosiglitazone group, 12 in the metformin group, and 3 in the glyburide group.

The independent cardiology review of all serious adverse events identified 51 possible CHF events. Of these, 21 were judged to be true CHF, involving 9 patients in the rosiglitazone group, 8 in the metformin group (with 1 death), and 4 in the glyburide group (with 1 death) ($P = 0.26$ for the comparison between the rosiglitazone group and the glyburide group). No patient was determined to have had more than one CHF event.

Rosiglitazone was more frequently associated with edema and the use of loop diuretics than was either metformin or glyburide ($P < 0.001$ for both comparisons). Rosiglitazone was less frequently associated with gastrointestinal side effects than was metformin ($P < 0.001$), and fewer patients in the rosiglitazone group than in the glyburide group had hypoglycemia ($P < 0.001$).

Levels of alanine aminotransferase decreased significantly from baseline in the rosiglitazone group, remained stable in the metformin group ($P < 0.001$ for the comparison with the rosiglitazone group), and increased significantly from baseline in the glyburide group ($P < 0.001$ for the comparison with the rosiglitazone group) (Table 2). Treatment with rosiglitazone was associated with a significantly decreased hematocrit, as compared with both metformin and glyburide ($P < 0.001$ for both comparisons). Rosiglitazone was associated with significantly higher levels of low-density lipoprotein (LDL) cholesterol than were the other two drugs ($P < 0.001$ for the comparison with metformin and $P = 0.008$ for the comparison with



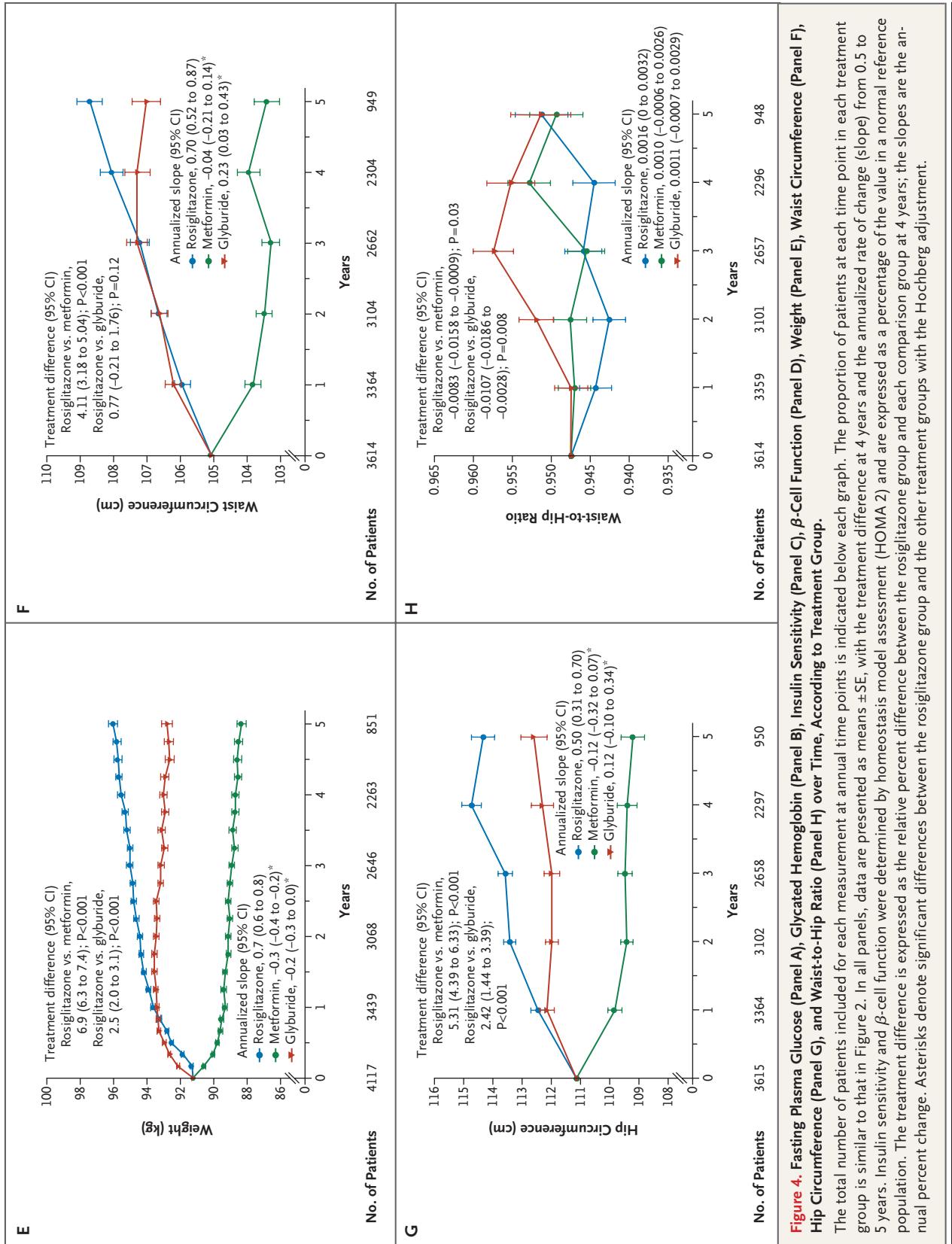


Figure 4. Fasting Plasma Glucose (Panel A), Glycated Hemoglobin (Panel B), Insulin Sensitivity (Panel C), β -Cell Function (Panel D), Weight (Panel E), Waist Circumference (Panel F), Hip Circumference (Panel G), and Waist-to-Hip Ratio (Panel H) over Time, According to Treatment Group.

The total number of patients included for each measurement at annual time points is indicated below each graph. The proportion of patients at each time point in each treatment group is similar to that in Figure 2. In all panels, data are presented as means \pm SE, with the treatment difference at 4 years and the annualized rate of change (slope) from 0.5 to 5 years. Insulin sensitivity and β -cell function were determined by homeostasis model assessment (HOMA 2) and are expressed as a percentage of the value in a normal reference population. The treatment difference is expressed as the relative percent difference between the rosiglitazone group and each comparison group at 4 years; the slopes are the annual percent change. Asterisks denote significant differences between the rosiglitazone group and the other treatment groups with the Hochberg adjustment.

Table 2. Adverse Events, Laboratory Assessment, Concomitant Use of Cardiovascular Drugs, Hospitalization, and Death.*

Variable	Rosiglitazone (N=1456)		Metformin (N=1454)		Glyburide (N=1441)	
	Serious Events	Total Events	Serious Events	Total Events	Serious Events	Total Events
Adverse events — no. of patients (%)						
Total events	346 (23.8)	1338 (91.9)	331 (22.8)	1341 (92.2)	308 (21.4)	1321 (91.7)
Cardiovascular disease	49 (3.4)	62 (4.3)	46 (3.2)	58 (4.0)	26 (1.8)†	41 (2.8)
Myocardial infarction						
Fatal	2 (0.1)	2 (0.1)	2 (0.1)	2 (0.1)	3 (0.2)	3 (0.2)
Nonfatal	22 (1.5)	25 (1.7)	18 (1.2)	21 (1.4)	11 (0.8)	15 (1.0)
Congestive heart failure (investigator-reported)	12 (0.8)	22 (1.5)	12 (0.8)	19 (1.3)	3 (0.2)†	9 (0.6)†
Stroke	13 (0.9)	16 (1.1)	17 (1.2)	19 (1.3)	12 (0.8)	17 (1.2)
Peripheral vascular disease	7 (0.5)	36 (2.5)	6 (0.4)	27 (1.9)	4 (0.3)	31 (2.2)
Gastrointestinal events	8 (0.5)	335 (23.0)	7 (0.5)	557 (38.3)‡	3 (0.2)	316 (21.9)
Nausea	2 (0.1)	112 (7.7)	0	170 (11.7)‡	0	99 (6.9)
Vomiting	0	58 (4.0)	1 (0.1)	84 (5.8)†	0	45 (3.1)
Diarrhea	1 (0.1)	129 (8.9)	1 (0.1)	345 (23.7)‡	0	142 (9.9)
Abdominal discomfort	5 (0.3)	161 (11.1)	6 (0.4)	224 (15.4)‡	3 (0.2)	163 (11.3)
Hypoglycemia§	1 (0.1)	142 (9.8)	1 (0.1)	168 (11.6)	8 (0.6)†	557 (38.7)‡
Weight gain	3 (0.2)	100 (6.9)	0	18 (1.2)‡	0	47 (3.3)‡
Edema	2 (0.1)	205 (14.1)	0	104 (7.2)‡	2 (0.1)	123 (8.5)‡
Laboratory assessment¶						
ALT — IU/liter						
Mean		21.4		24.9‡		27.2‡
95% CI		20.6–22.2		24.1–25.8		26.3–28.1
ALT >3 times upper limit of normal — no. of patients (%)		14 (1.0)		16 (1.1)		11 (0.8)
Hematocrit — %						
Mean		40.6		41.6‡		42.7‡
95% CI		40.4–40.8		41.4–41.8		42.5–42.9
Hematocrit ≥5 percentage points below the reference range — no. of patients (%)		41 (2.8)		22 (1.5)†		14 (1.0)‡
LDL cholesterol — mg/dl						
Mean		104.0		96.5‡		99.3‡
95% CI		101.7–106.4		94.4–98.8		96.9–101.9

glyburide) and with greater use of lipid-lowering therapy.

DISCUSSION

Our international clinical trial suggests that initial treatment of type 2 diabetes with rosiglitazone during a median period of 4 years slowed progression to monotherapy failure (defined as a fasting plasma glucose level >180 mg per deciliter) more effectively than did either metformin or gly-

buride. This was also the case with a lower threshold for monotherapy failure (fasting plasma glucose level, >140 mg per deciliter), a level more consistent with that used in current therapeutic approaches to glucose management.^{18,19} Although rosiglitazone was more effective overall than metformin, heterogeneity analyses showed no subgroup differences apart from a greater effect in older patients and those with a larger waist circumference.

When we designed our study, measurement of

Table 2. (Continued.)						
Variable	Rosiglitazone (N = 1456)		Metformin (N = 1454)		Glyburide (N = 1441)	
	Serious Events	Total Events	Serious Events	Total Events	Serious Events	Total Events
HDL cholesterol — mg/dl						
Mean	51.8		50.5‡		48.9‡	
95% CI	51.3–52.4		50.0–51.0		48.3–49.5	
Triglycerides — mg/dl						
Mean	163.5		166.5		171.7†	
95% CI	159.2–167.9		162.1–171.0		166.8–176.9	
Drugs used concomitantly — no. of patients (%)						
Lipid-lowering agents						
Statins	803 (55.2)		708 (48.7)‡		651 (45.2)‡	
Antihypertensive agents	750 (51.5)		632 (43.5)‡		579 (40.2)‡	
ACE inhibitors	970 (66.6)		969 (66.6)		944 (65.5)	
Angiotensin receptor blockers	559 (38.4)		607 (41.7)		538 (37.3)	
Beta-blockers	259 (17.8)		293 (20.2)		280 (19.4)	
Calcium channel blockers	406 (27.9)		398 (27.4)		379 (26.3)	
Diuretics	271 (18.6)		276 (19.0)		286 (19.8)	
Loop	214 (14.7)		162 (11.1)‡		160 (11.1)‡	
Potassium sparing	90 (6.2)		91 (6.3)		93 (6.5)	
Thiazide	394 (27.1)		369 (25.4)		349 (24.2)	
Death and hospitalization						
Hospitalization for any cause						
Patients — no. (%)	169 (11.6)		172 (11.8)		150 (10.4)	
Events — no.	251		267		203	
Deaths from any cause — no.	34		31		31	

* The total number of patients with adverse events includes all patients with serious events reported by investigators. All deaths were reported, regardless of whether the patient died during or after treatment. A serious adverse event was defined as any event that was fatal, life-threatening, or disabling; resulted in hospitalization or prolonged a hospital stay; was associated with a congenital abnormality, cancer, or a drug overdose (either accidental or intentional); or was regarded by the investigator as serious or suggested any substantial hazard, contraindication, side effect, or precaution. Tests of differences between means of laboratory assessments were conducted by linear model analysis after 4 years of follow-up. Comparisons for cardiovascular disease events in aggregate and by type, as well as for peripheral vascular disease, were calculated by the Cox proportional-hazards model to allow for differential time of follow-up among treatments. Comparisons for other events were based on the test for proportions. ALT denotes alanine aminotransferase, LDL low-density lipoprotein, HDL high-density lipoprotein, and ACE angiotensin-converting enzyme. 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.

† P ≤ 0.05 for the comparison between this treatment group and the rosiglitazone group.

‡ P ≤ 0.01 for the comparison between this treatment group and the rosiglitazone group.

§ Patients self-reported hypoglycemia at the time of a follow-up visit, although levels were not necessarily confirmed by glucose testing.

¶ All laboratory values are mean values at 4 years.

glycated hemoglobin was not in general use for the adjustment of glucose-lowering therapy.¹⁵ Nevertheless, systematic and prespecified collection of data regarding glycated hemoglobin levels provided results applicable to current clinical practice. By comparing three drugs head to head, our study provides long-term evidence that progressive loss of glycemic control can be delayed and a mean level of glycated hemoglobin maintained

at less than 7% for a longer period with rosiglitazone (57 months) than with either metformin (45 months) or glyburide (33 months). Our findings confirm the value of metformin as an initial treatment for type 2 diabetes²⁰ and the greater efficacy of metformin than of glyburide.

Declining β -cell function is the predominant reason for deterioration in glucose tolerance across the spectrum from normal glucose tolerance to

type 2 diabetes in numerous populations.²¹⁻²³ In the United Kingdom Prospective Diabetes Study (UKPDS), neither metformin nor a sulfonylurea altered the rate of loss of β -cell function, although metformin improved insulin sensitivity.⁴ In our study, rosiglitazone slowed the rate of loss of β -cell function and improved insulin sensitivity to a greater extent than did either metformin or glyburide. These complementary findings are consistent with a greater durability of glycemic control with rosiglitazone.²⁴

There were no unexpected adverse events in any of the treatment groups. Rosiglitazone was associated with weight gain, increased levels of LDL cholesterol (and more use of statins), more frequent edema, and a reduction in the hematocrit. Metformin was associated with more frequent gastrointestinal side effects, and glyburide with weight gain and hypoglycemia. An increase from baseline in waist circumference was observed with rosiglitazone and glyburide, but the concomitant increase in hip circumference with rosiglitazone resulted in no net change in the waist-to-hip ratio.¹¹ Redistribution of body fat^{25,26} and varying patterns of adipokine release^{27,28} may explain the improved insulin sensitivity observed with rosiglitazone, despite the increase in weight. The long-term health effect of increases in weight and changes in body composition with thiazolidinediones should be further explored.

Our study was not designed to evaluate cardiovascular disease outcomes. The protocol specified that all patients be free of known CHF on entry into the study. However, a retrospective review of source documents revealed that 17 patients (5 in the rosiglitazone group, 6 in the metformin group, and 6 in the glyburide group) entered the study with a current diagnosis of CHF. Only one of these patients (randomized to metformin) contributed to the events of CHF that are detailed in Table 2. Overall, the proportions of patients with cardiovascular events were similar in the rosiglitazone and metformin groups but were lower in the glyburide group. This observation differs from the UKPDS findings, which suggested that metformin reduces overall mortality and may reduce coronary events.²⁰ This difference may be related to the facts that our study had a shorter follow-up period than did the

British study and that our patients were younger and had better glycemic control at study entry. Furthermore, our definition of treatment failure (a fasting plasma glucose level of more than 180 mg per deciliter) was lower than that in the British study (270 mg per deciliter [15 mmol per liter]).³ The lower rate of cardiovascular events associated with glyburide also differs from epidemiologic studies suggesting an increase in the rates of death and myocardial infarction with sulfonylureas.^{29,30}

Since thiazolidinediones have been associated with an increased risk of CHF,^{11,31,32} we specifically examined serious adverse events that were potentially related to this risk. The rate of CHF associated with rosiglitazone was similar to that in studies involving low-risk populations^{11,31} and to that associated with metformin but higher than that associated with glyburide.

The rate of withdrawal of patients from our study was high, which was a limitation of the study. However, the characteristics of patients who withdrew did not differ among the treatment groups. Many withdrawals resulted from well-characterized side effects of each drug. Although the groups differed with respect to the number of withdrawals prompted by an insufficient therapeutic effect, these differences were small, as compared with the number of patients reaching the primary outcome. The groups did not differ significantly in the number of patients who withdrew because of protocol violations, were lost to follow-up, or withdrew consent. Furthermore, analyses that accounted for the potential bias introduced by early withdrawal provided consistent results, indicating that the findings were robust.

Whether the statistically significant differences between rosiglitazone and metformin would translate into longer-term effects on disease progression or on microvascular or macrovascular outcomes needs to be determined. Taken together, the data from our study document the glycemic durability and risks associated with three commonly used drugs in the initial management of type 2 diabetes. The relative costs of these medications, their profiles of adverse events, and their potential risks and benefits should all be considered to help inform the choice of pharmacotherapy for patients with type 2 diabetes.

Note added in proof: While this article was in production, further examination of data on adverse events identified a higher rate of fractures in the group receiving rosiglitazone. This was an unexpected event that was not part of the prespecified analysis plan.

	Rosiglitazone	Metformin	Glyburide
	number of patients (percent)		
Men	32 (3.95)	29 (3.36)	28 (3.35)
Women	60 (9.30)	30 (5.08)*	21 (3.47)*
Lower limb	36 (5.58)	18 (3.05)†	8 (1.32)*
Upper limb	22 (3.41)	10 (1.69)	9 (1.49)†
Spinal	1 (0.16)	1 (0.17)	1 (0.17)

* P<0.01 for the comparison with rosiglitazone (unadjusted, contingency chi-square test).

† P<0.05 for the comparison with rosiglitazone (unadjusted, contingency chi-square test).

The number of men with fractures did not differ according to the treatment group. More women in the rosiglitazone group had upper limb fractures involving the humerus and hand. Lower limb fractures were primarily increased in the foot. Specifically, the number of women with hip fractures did not differ (two patients receiving rosiglitazone, two receiving metformin, and none receiving glyburide).

Supported by grants from GlaxoSmithKline.

Dr. Kahn reports receiving consulting fees from Bristol-Myers Squibb; consulting fees, grant support, and lecture fees from GlaxoSmithKline and Novartis; and consulting and lecture fees from Merck. Dr. Haffner reports receiving consulting fees from AstraZeneca and Takeda; consulting fees and grant support from Novartis and Pfizer; grant support and consulting and lecture fees from GlaxoSmithKline; consulting and lecture fees from Merck; and lecture fees from Sanofi-Aventis. Dr. Heise, Mr. Jones, Ms. Kravitz, and Ms. O'Neill are employees of GlaxoSmithKline and hold equity interest in the company. Dr. Herman reports receiving consulting fees from Amylin, Eli Lilly, GlaxoSmithKline, Merck, and Wyeth and consulting fees and grant support from Sanofi-Aventis. Dr. Holman reports receiving consulting fees from Amylin and Bayer; consulting fees and grant support from Novartis; consulting and lecture fees from Eli Lilly, Merck; grant support from Bristol-Myers Squibb, Merck, Santec, Novo Nordisk, and Pfizer; lecture fees from Ajinomoto, Astella, and Servier; and lecture fees and grant support from GlaxoSmithKline. Dr. Lachin reports receiving consulting fees from GlaxoSmithKline, MedImmune, and Novartis; lecture fees from Takeda; and having an equity interest in Alba Therapeutics. Dr. Zinman reports receiving consulting fees from Amylin, Novo Nordisk, and Pfizer; consulting fees and grant support from Sanofi-Aventis; consulting fees, grant support, and lecture fees from GlaxoSmithKline and Novartis; consulting and lecture fees from Eli Lilly and Merck; and grant support from King Pharmaceuticals. Dr. Viberti reports receiving consulting fees, grant support, and lecture fees from and having an equity interest in GlaxoSmithKline; consulting fees, grant support, and lecture fees from Novartis; consulting and lecture fees from Daiichi Sankyo and Speedel; and grant support from Pfizer. No other potential conflict of interest relevant to this article was reported.

We thank the patients, without whom this study and these analyses would not have been possible; the independent statisticians, Drs. Todd MacKenzie and Ellen Roecker, who reviewed key efficacy and safety data, respectively; and Drs. John McMurray, Mark Petrie, and Scott Solomon, who reviewed the CHF cases.

APPENDIX

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