

Low-Dose Rosiglitazone in Patients With Insulin-Requiring Type 2 Diabetes

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Background: The objective was to compare the efficacy and safety of adding low-dose rosiglitazone (2 or 4 mg/d) to insulin therapy vs continued insulin monotherapy in patients with type 2 diabetes mellitus who were unable to achieve glycemic control with insulin therapy alone.

Methods: In this 24-week, double-blind study, 630 individuals with type 2 diabetes mellitus that was inadequately controlled with insulin therapy alone were randomized to treatment with rosiglitazone (2 or 4 mg/d) or placebo in combination with ongoing insulin therapy. The dosage of insulin therapy could be adjusted at the investigator's discretion if required for hypoglycemia or additional glycemic control.

Results: The addition of rosiglitazone (2 or 4 mg/d) to insulin therapy significantly decreased mean glycated hemoglobin concentrations compared with placebo plus insulin (-0.3% [$P=.02$] and -0.4% [$P<.001$]) and compared with baseline (-0.6% and -0.8% [both $P<.001$]) after 24 weeks. The addition of 2 or 4 mg/d of rosiglitazone sig-

nificantly decreased the C-reactive protein level (vs baseline: -22.0% [$P<.001$] and -34.2% [$P<.001$]; vs placebo: -22.2% [$P=.003$] and -32.0% [$P<.001$]) and fibrinogen (vs baseline: -10.5% and -12.0% [both $P<.001$]; vs placebo: -7.9% [$P=.002$] and -7.6% [$P=.004$]), while 4 mg/d of rosiglitazone significantly reduced matrix metalloproteinase 9 levels (vs baseline: -17.1% [$P=.007$]; vs placebo: -23.3% [$P<.001$]). The adverse event profile, including incidence of hypoglycemia and edema, was similar between treatment groups, and most adverse events were mild to moderate in intensity.

Conclusions: The addition of low-dose rosiglitazone to insulin therapy is an effective and well-tolerated treatment option for patients with type 2 diabetes mellitus who continue to have poor glycemic control despite administration of exogenous insulin as monotherapy.

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PHYSICIANS FACE SIGNIFICANT challenges in trying to optimize treatment of individuals with advanced type 2 diabetes mellitus (T2DM), many of whom already have microvascular or macrovascular complications and for whom treatment options for tight or adequate glycemic control are limited. While both the Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS) have demonstrated that tight glycemic control can delay the onset and slow the progression of diabetes-related complications,^{1,2} optimal glycemic control did not improve in the diabetic population between the National Health and Nutrition Examination Survey (NHANES) III (1988-1994) and NHANES (1999-2002).³ Ultimately, more than 40% of individuals with diabetes who cannot maintain control with traditional oral therapy

require intensive insulin therapy to improve glycemic control.^{4,5}

During insulin therapy, individuals with T2DM often continue to lose glycemic control and require a high daily dose of insulin owing to severe insulin resistance and continuing loss of β -cell function over time.⁶ However, increasing the insulin dose is often associated with increased frequency and severity of hypoglycemia⁷ and weight gain, making the risks of tight glycemic control outweigh the benefits. Consequently, some insulin-treated patients still have elevated glycated hemoglobin (HbA_{1c}) concentrations, even at high insulin doses.

The use of oral antidiabetic agents (OADs) in combination with insulin is generally as effective as insulin monotherapy in achieving glycemic control,⁷ but often with a better tolerability. Compared with other OADs,^{2,8} insulin sensitizers such as the thiazolidinediones

(TZDs) may be a more rational choice to combine with insulin therapy. These agents modify underlying disease processes, with demonstrated effects in improving insulin sensitivity and potentially beneficial effects on β -cell function.⁹⁻¹⁴ Also, the use of TZDs may lead to reduced exogenous insulin requirements and decrease hyperinsulinemia.^{10,11} Furthermore, studies have suggested that TZDs have nonglycemic benefits on nontraditional markers of cardiovascular (CV) risk, including C-reactive protein, plasminogen activator inhibitor 1 (PAI-1), and matrix metalloproteinase 9.^{15,16} Such potential CV effects may also be observed in patients taking a TZD in combination with insulin.

Several clinical trials have investigated the efficacy and tolerability of combination therapy with TZDs and insulin. However, despite significant improvements in glycemic control, use of higher TZD doses combined with insulin has been associated with hypoglycemia, weight gain, and fluid-related adverse events.^{5,17-21} It is possible that lower TZD doses combined with insulin may achieve glycemic goals and lead to improvements in inflammation and hypercoagulation, while retaining an acceptable adverse event profile. Our goal was to compare the efficacy and safety of the addition of low-dose rosiglitazone therapy (2 or 4 mg/d) for patients with T2DM who were not achieving glycemic goals with insulin therapy alone.

METHODS

STUDY POPULATION

The study was a randomized, double-blind, parallel-group, placebo-controlled investigation that was carried out in 128 centers in the United States. Subjects with T2DM (as defined by the American Diabetes Association)²² who were aged 18 to 70 years and had clearly failed insulin therapy (ie, with $HbA_{1c} > 7.5\%$, which was the level chosen to minimize the risk of hypoglycemia during the study) were recruited. Before screening, all participants must have been taking insulin monotherapy for at least 8 weeks at a minimum dosage of 30 U/d. Participants taking insulin in combination with a single OAD were eligible if they discontinued taking the oral agent 8 weeks before screening. Subjects were excluded if they met any of the following criteria: TZD use (within 6 months before screening); use of more than 1 OAD in combination with insulin (within 3 months before screening); fasting plasma glucose (FPG) level higher than 270 mg/dL (>15.0 mmol/L); edema or history of peripheral edema requiring pharmacologic treatment (within 12 months before screening); unstable or severe angina or coronary insufficiency (New York Heart Association class 3 or 4); or history of, or ongoing, congestive heart failure.

STUDY DESIGN

Subjects meeting entry criteria entered a 2-week run-in period with placebo concurrent with their ongoing insulin regimen (Figure 1A). Study participants were then randomized to 24 weeks of treatment with 2 mg/d of rosiglitazone, 2 mg/d of rosiglitazone titrated to 2 mg twice daily at week 8, or placebo in combination with their prior insulin regimen. The dosage of insulin therapy could be adjusted at the investigator's discretion for optimal glycemic control, without causing frequent or

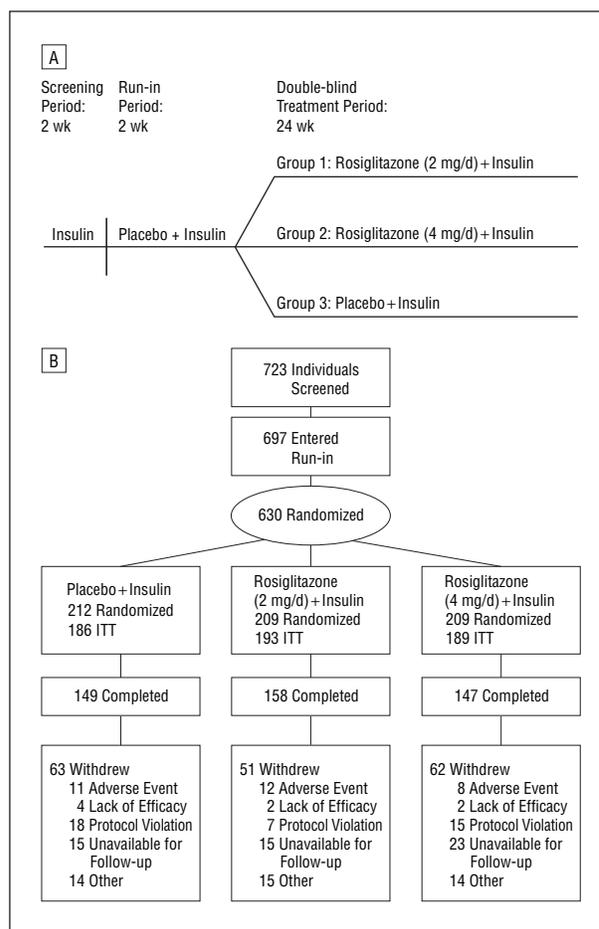


Figure 1. Study design (A) and study population (B): patient disposition. Group 2 subjects were initially randomized to 2 mg/d of rosiglitazone, titrated to 2 mg twice daily at week 8. ITT indicates intent to treat.

severe hypoglycemia. There were no protocol guidelines regarding the timing of insulin doses during the day or with respect to laboratory assessments at study visits.

EFFICACY AND SAFETY EVALUATIONS

The primary efficacy end point was change in HbA_{1c} concentrations from baseline to week 24. Secondary efficacy end points included proportion of subjects achieving an HbA_{1c} concentration of less than 7.0%, proportion of participants responding to treatment (defined as achieving a decrease in $HbA_{1c} \geq 0.7\%$ from baseline), and change from baseline in FPG and C-peptide levels and total daily insulin dose. Other end points included changes in levels of C-reactive protein, fibrinogen, PAI-1, and metalloproteinase 9. Safety evaluations included laboratory values, vital signs, and adverse events. All CV adverse events with potential relationship to fluid retention or ischemia, including congestive heart failure, cardiac failure, pulmonary edema, cardiac arrest, myocardial infarction, myocardial ischemia, and sudden death, were reviewed by an independent adjudication committee.

Also, a substudy was performed to assess the extent of asymptomatic ischemic heart disease and the possible effects of study treatment on cardiac safety parameters. Patients recruited to this substudy underwent Doppler echocardiography at rest, after dobutamine-induced heart rate elevation, at baseline, and at final study visit. All assays were performed by a central laboratory (Quest Diagnostics, Van Nuys, Calif).

Table. Demographic and Baseline Characteristics

Characteristic	Placebo + Insulin (n = 186)	Rosiglitazone (2 mg/d) + Insulin (n = 193)	Rosiglitazone (4 mg/d) + Insulin (n = 189)
Age, mean ± SD, y	53.8 ± 10.2	52.7 ± 9.6	52.6 ± 10.1
Male, No. (%)	86 (46.2)	110 (57.0)	91 (48.1)
Race/ethnicity, No. (%)			
White	105 (56.5)	110 (57.0)	108 (57.1)
Black	47 (25.3)	39 (20.2)	47 (24.9)
Asian	3 (1.6)	6 (3.1)	5 (2.6)
Other	31 (16.7)	38 (19.7)	29 (15.3)
Nonsmokers, No. (%)	143 (76.9)	149 (77.2)	147 (77.8)
BMI, mean ± SD	33.0 ± 6.5	32.8 ± 7.4	33.7 ± 7.1
Weight, mean ± SD, kg	95.1 ± 20.9	97.2 ± 22.3	96.8 ± 20.8
Systolic blood pressure, mean ± SD, mm Hg	128 ± 15	127 ± 16	128 ± 15
Diastolic blood pressure, mean ± SD, mm Hg	78 ± 9	78 ± 9	78 ± 9
Years since diagnosis of diabetes, mean ± SD	12.6 ± 8.6	12.5 ± 8.3	13.0 ± 7.3
Pretherapy insulin use, mean ± SD, y	5.0 ± 7.0	5.1 ± 6.3	5.2 ± 6.4
HbA _{1c} , mean ± SD, %	9.1 ± 1.3*	8.9 ± 1.1	9.0 ± 1.2
FPG, mean ± SD, mg/dL	181.0 ± 67.0*	176.7 ± 58.5†	180.7 ± 74.3
LDL cholesterol, geometric mean ± SE, mg/dL	105.1 ± 2.6	109.4 ± 2.5	110.4 ± 2.6
HDL cholesterol, geometric mean ± SE, mg/dL	43.5 ± 0.8	42.1 ± 0.8	41.6 ± 0.8
Triglycerides, geometric mean ± SE, mg/dL	121.9 ± 5.8	121.4 ± 5.7	126.2 ± 5.7
Total daily insulin dose, mean ± SD, U	80.3 ± 46.9	77.9 ± 44.1	73.5 ± 41.3
Total daily insulin injections, mean ± SD	2.5 ± 1.1*	2.4 ± 1.0	2.3 ± 0.9
NSAIDs, No. (%)‡	84 (39.6)	90 (43.1)	73 (34.9)
ACE inhibitors and ARBs, No. (%)‡	110 (51.9)	114 (54.5)	110 (52.6)
Lipid-lowering agents, No. (%)‡	79 (37.3)	75 (35.9)	70 (33.5)

Abbreviations: ACE, angiotensin-converting enzyme; ARBs, angiotensin II receptor blockers; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); FPG, fasting plasma glucose; HbA_{1c}, glycated hemoglobin; NSAIDs, nonsteroidal anti-inflammatory drugs, including aspirin.

SI conversion factors: To convert FPG, LDL and HDL cholesterol, and triglyceride values to millimoles per liter, multiply by 0.0555, 0.0259, and 0.0113, respectively.

*Number of subjects, 185.

†Number of subjects, 192.

‡Concomitant medications.

STATISTICAL ANALYSES

Statistical analyses of primary efficacy parameters were based on the intent-to-treat population, with last observation carried forward. The intent-to-treat population consisted of all randomized participants who received at least 1 dose of study medication and had at least 1 valid on-therapy observation for an efficacy variable. The last observation was carried forward for subjects who had missing values or who withdrew from the study. The all-randomized-subjects population, which consisted of participants who received at least 1 dose of study medication, was used for analysis of CV biomarkers and safety.

For the primary efficacy end point, a 2-sided test was used to test the null hypothesis of no difference in mean change in HbA_{1c} concentration between either of the rosiglitazone groups and the placebo group from baseline to week 24. The Dunnett multiple comparison procedure was used to adjust for multiple comparisons and to calculate the adjusted 95% confidence intervals (CIs). Between-group differences were estimated using analysis of covariance (PROC MIXED in SAS; SAS Institute Inc, Cary, NC), with terms for treatment and baseline measurement. The same method of analysis was used for assessment of treatment difference in FPG and C-peptide levels, total daily insulin dose, and biomarkers. For biomarkers, analysis of covariance was performed based on log-transformed data. Responder analyses for HbA_{1c} and FPG were assessed using a logistic regression (PROC LOGISTIC in SAS), with terms for baseline measurement and treatment. Summary statistics for percentage of change from baseline in biomarkers at week 24 were tested using paired *t* tests based on log-transformed data.

Written informed consent was obtained from all subjects prior to participation in the study. The study was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki (1996).

RESULTS

STUDY POPULATION

A total of 723 subjects were screened, with 630 subjects randomized to double-blind treatment; 568 had at least 1 on-therapy efficacy measurement and formed the intent-to-treat population (Figure 1B). Of those randomized, 63 (29.7%) of 212 subjects in the placebo group, 51 (24.4%) of 209 subjects in the 2-mg/d rosiglitazone group, and 62 (29.7%) of 209 subjects in the 4-mg/d rosiglitazone group withdrew from the study. A total of 11 (5%) of 212 subjects receiving placebo and 20 (5%) of 418 subjects receiving rosiglitazone (2 or 4 mg/d) withdrew because of adverse events. The most common reason for premature discontinuation of study treatment was unavailability of subjects for follow-up, and there were no clear treatment-related differences in withdrawal rates.

Baseline demographics were similar between the treatment groups, which were well matched for mean concentrations of HbA_{1c} and FPG, total daily insulin dose, and frequency of insulin injections (Table). Concomitant medical conditions, including hypertension (54%), hypercholesterolemia (21%), hyperlipidemia (20%), and depression (17%), were similar among treatment groups. The most commonly used concomitant medications included agents acting on the renin-angiotensin system (53%), anti-inflammatory and antirheumatic agents (39%), and lipid-lowering agents (36%).

GLYCEMIC CONTROL

The addition of rosiglitazone significantly decreased mean HbA_{1c} concentrations compared with both baseline and placebo, with similar reductions observed in the rosiglitazone groups at 24 weeks (Figure 2A). The addition of 2 or 4 mg/d of rosiglitazone reduced HbA_{1c} concentrations by -0.6% or -0.8%, respectively, vs baseline (both *P* < .001) and by -0.3% (*P* = .02) and -0.4% (*P* < .001) vs placebo.

There was a small, although statistically significant, reduction in HbA_{1c} concentrations compared with baseline in the placebo group (−0.4% [*P*<.001]).

Even in insulin-treated subjects with poor glycemic control, significantly more subjects achieved HbA_{1c} concentrations of less than 7% in both of the rosiglitazone treatment groups compared with the placebo group (Figure 2B). Also, there was a significantly greater proportion of patients achieving a reduction of 0.7% or more in HbA_{1c} concentrations with 4 mg/d of rosiglitazone compared with placebo (55% vs 42%; odds ratio, 2.09 [95% CI, 1.35–3.23; *P*=.001]), although the difference between the 2-mg/d rosiglitazone and placebo groups was not significant (odds ratio, 1.21 [95% CI, 0.78–1.86; *P*=.40]).

The addition of 4 mg/d of rosiglitazone to the regimen significantly decreased FPG levels compared with baseline (−18 mg/dL [−1.0 mmol/L], *P*=.005), but no significant difference was observed in the 2-mg/d rosiglitazone (*P*=.76) and placebo (*P*=.39) groups. There was no significant treatment effect compared with placebo (*P*=.95 and *P*=.09 for the 2-mg/d and 4-mg/d rosiglitazone groups, respectively). At week 24, the mean ± SD total daily dose of insulin was 81.8 ± 49.4 U, 79.2 ± 45.2 U, and 73.4 ± 41.7 U in the placebo, 2-mg/d rosiglitazone, and 4-mg/d rosiglitazone groups, respectively. No significant change in total daily insulin dose was observed in any of the treatment groups compared with baseline or between groups.

C-PEPTIDE LEVELS

Fasting C-peptide levels decreased in all groups compared with baseline, with significant reductions observed in the 2-mg/d rosiglitazone (−0.2 ng/mL [−0.05 nmol/L], *P*=.04) and placebo (−0.1 ng/mL [−0.04 nmol/L], *P*=.03) groups. The decrease in the 4-mg/d rosiglitazone group was not significant (−0.1 ng/mL [−0.04 nmol/L], *P*=.21). No significant differences were observed in either the 2-mg/d (*P*=.77) or the 4-mg/d (*P*=.76) rosiglitazone treatment group compared with the placebo group.

CV RISK FACTORS

The effects of study treatments on CV biomarkers are detailed in **Figure 3**. The addition of 2 and 4 mg/d of rosiglitazone to insulin therapy significantly decreased C-reactive protein levels at week 24 compared with both baseline (−22.0% [*P*<.001] and −34.2% [*P*<.001], respectively) and placebo (−22.2% [*P*=.003] and −32.0% [*P*<.001], respectively). Similarly, significant reductions in fibrinogen were observed with 2 and 4 mg/d of rosiglitazone vs baseline (−10.5% and −12.0% [both *P*<.001], respectively) and placebo (−7.9% [*P*=.002] and −7.6% [*P*=.004], respectively). There was a statistically significant 20% increase in PAI-1 activity in the 2-mg/d rosiglitazone group (*P*<.001), but there was no statistically significant change in PAI-1 activity in either rosiglitazone group (2-mg/d, *P*=.09; 4-mg/d, *P*=.17) or the placebo group (*P*=.80), nor was there any significant change in the PAI-1 levels in any of the 3 groups (*P*=.10, *P*=.53, and *P*=.12, respectively).

The addition of 4 mg/d of rosiglitazone significantly decreased metalloproteinase 9 levels from baseline (−17.1%

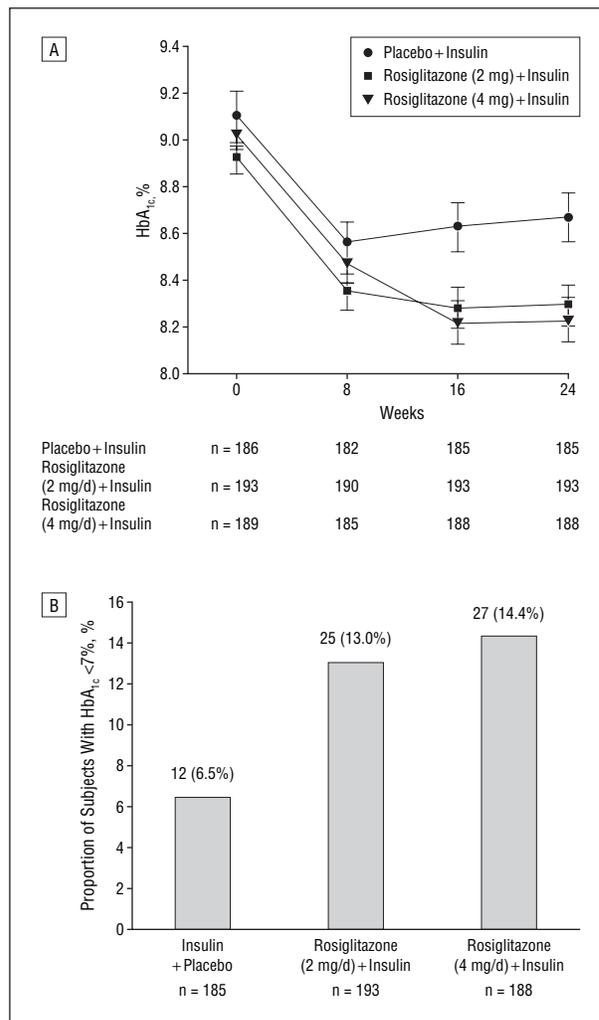


Figure 2. Mean glycosylated hemoglobin (HbA_{1c}) concentrations over time (A) and proportion of subjects achieving an HbA_{1c} concentration less than 7% at week 24 (B) (intent-to-treat population with last observation carried forward). Error bars indicate SE; asterisks, *P*<.001 vs baseline.

[*P*=.007]) compared with placebo (−23.3% [*P*<.001]) at week 24, while significant reductions in metalloproteinase 9 were also observed with the addition of 2 mg/d of rosiglitazone compared with placebo (−15.3% [*P*=.03]). No significant changes in CV biomarkers were observed in the placebo group at week 24 compared with baseline. No conclusive results were available from the dobutamine stress echocardiography substudy owing to inadequate patient enrollment.

SAFETY AND TOLERABILITY

The proportion of subjects reporting adverse events during therapy was similar between treatment groups, with the majority of adverse events considered to be mild or moderate in severity. The incidence of reported severe adverse events on therapy was 9.4% in the placebo group and 7.2% in both the 2-mg/d rosiglitazone and the 4-mg/d rosiglitazone groups. The most frequently reported severe adverse event in all treatment groups was hypoglycemia. The incidence of hypoglycemia (both symptomatic and confirmed [blood glucose, <50 mg/dL (2.8 mmol/L)]) was similar between treatment groups and

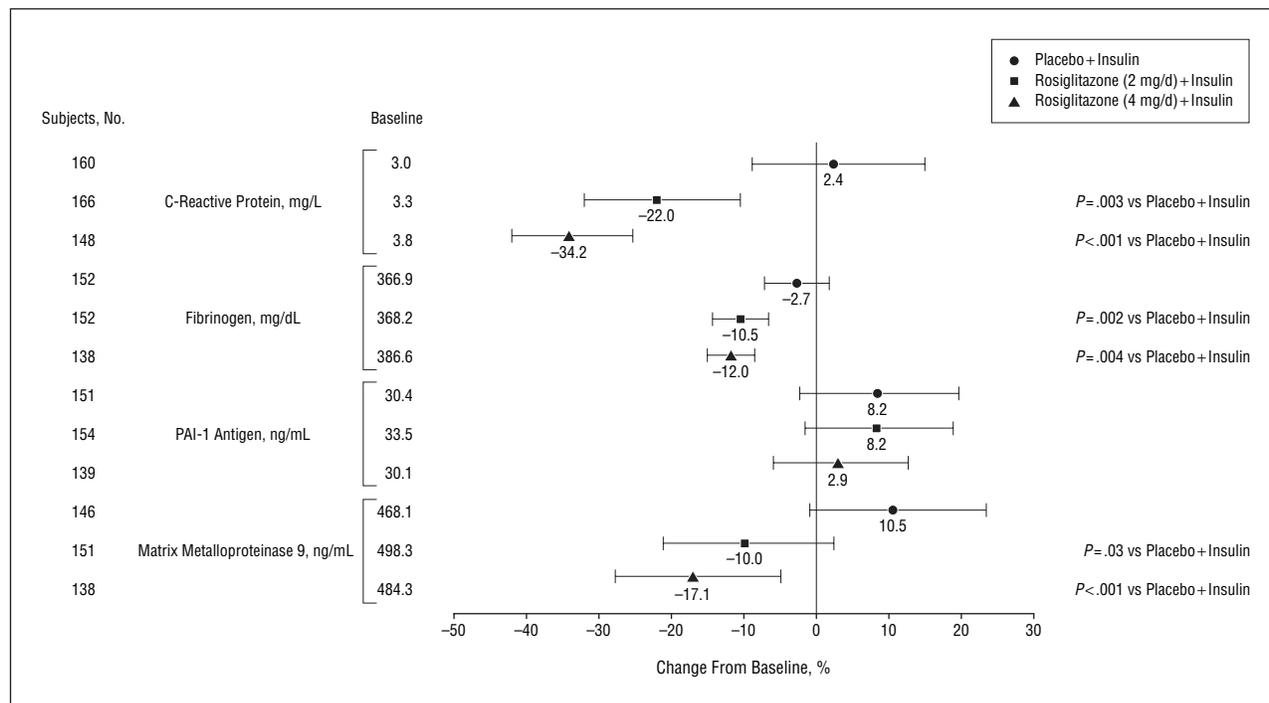


Figure 3. Mean changes in cardiovascular biomarkers from baseline to week 24 (all randomized subjects). To convert fibrinogen values to micromoles per liter, multiply by 0.0294. Change from baseline indicates geometric means; error bars, 95% confidence intervals.

mostly mild to moderate in intensity. Severe hypoglycemia was reported in 5 subjects in the placebo group, 6 subjects in the 2-mg/d rosiglitazone group, and 4 subjects in the 4-mg/d rosiglitazone group.

Individuals with T2DM who are receiving insulin therapy have shown a higher incidence of CV events. Overall, the independently adjudicated incidence of cardiac events was low and similar between treatment groups. A slightly greater proportion of subjects randomized to rosiglitazone plus insulin reported and were adjudicated as having CV adverse events (2.4% in the 2-mg/d rosiglitazone group and 1.4% in the 4-mg/d rosiglitazone group) than were subjects in the placebo plus insulin group (0.9%). In subjects reporting CV adverse events, more individuals had multiple CV risk factors (including hypertension, dyslipidemia, current cigarette smoking, and ischemic heart disease) in the rosiglitazone groups at study entry (75%, 80%, and 86% in the placebo plus insulin group and the 2- and 4-mg/d rosiglitazone groups, respectively). Edema was observed in all groups: placebo (10.8%), 2-mg/d rosiglitazone (5.7%), and 4-mg/d rosiglitazone (11.0%). Most edema was mild to moderate in intensity, and there were few withdrawals from the study as a result of edema (1.4%). A small number of subjects treated with rosiglitazone plus insulin reported on-therapy adverse events of congestive heart failure (2 subjects in the 2-mg/d rosiglitazone group [1%] and 2 subjects in the 4-mg/d rosiglitazone group [1%]).

Significant weight gain occurred in all 3 treatment groups at week 24 compared with baseline. The 2- and 4-mg/d rosiglitazone groups showed a dose-ordered mean increase in weight from baseline to week 24 (+1.94 kg and +3.16 kg, respectively). Weight gain was lowest in the placebo group (+0.84 kg).

COMMENT

In this study, individuals with T2DM and poor glycemic control despite insulin therapy were evaluated for their response to the addition of low-dose rosiglitazone. These subjects were at an advanced stage of the condition, with a long duration of diabetes of approximately 13 years and a high insulin dose averaging more than 70 U/d, with a mean HbA_{1c} concentration of approximately 9%. Such individuals are most likely to have pronounced insulin resistance and poor β -cell function as well as difficulties achieving adequate glycemic control. Furthermore, many subjects had comorbid conditions, including obesity with a mean body mass index of 33 (calculated as weight in kilograms divided by height in meters squared), hypertension (>50% by medical history), and hypercholesterolemia and hyperlipidemia (>20% by medical history). Also, many were taking concomitant medications, including agents acting on the renin-angiotensin system (53%), anti-inflammatory and antirheumatic agents (39%), and lipid-lowering agents (36%).

Results from this study confirm the benefits of adding low-dose rosiglitazone to the therapeutic regimen of insulin-treated individuals with poorly controlled T2DM. Superior reductions in HbA_{1c} concentrations were observed in subjects taking rosiglitazone plus insulin compared with those taking placebo plus insulin. Despite poor glycemic control at baseline, more individuals receiving rosiglitazone were able to achieve the American Diabetes Association target of an HbA_{1c} concentration of less than 7% compared with placebo (13% in the 2-mg/d rosiglitazone group and 14.4% in the 4-mg/d rosiglitazone

group vs 6.5% in the placebo group). In contrast with previous TZD plus insulin combination studies,^{5,17-21} no significant changes in FPG levels were observed in the rosiglitazone plus insulin groups compared with the placebo plus insulin group. It is possible that morning insulin dosing before the laboratory test may have confounded FPG assessment, as the study protocol did not specify timing of insulin doses with respect to laboratory assessments at study visits.

In the current study, the total daily insulin dose did not differ significantly between treatment groups. This observation in insulin dose varies from the reductions in daily insulin dose previously observed in subjects taking TZDs in addition to insulin.^{5,17,18,20} Possible reasons for the observed difference in our study include the low dose of rosiglitazone added to insulin therapy in this advanced diabetic cohort, the high HbA_{1c} concentrations at baseline, and the discretionary change of insulin dose by the investigator. Although insulin sensitivity and β -cell function were not directly evaluated owing to the presence of exogenous insulin therapy, significant reductions in the HbA_{1c} concentrations with the unchanged insulin daily dose observed in the rosiglitazone groups suggests improvement of insulin sensitivity and insulin use, consistent with previous observations.^{9,12-14,16} It is important to note that the A Diabetes Outcome Progression Trial (ADOPT) reported that rosiglitazone monotherapy provided more effective and durable glycemic control than sulfonylurea and metformin monotherapy over 5 years; however, the benefits and risks of each medication should be evaluated when considering a choice of an OAD combination with insulin therapy.^{23,24}

Increased hypoglycemia, weight gain, edema, new or worsened cardiac failure, and other CV adverse events have been observed with higher TZD doses in combination with insulin therapy in previous studies.^{17,21,25} In our study, a similar incidence of hypoglycemia (confirmed and symptomatic) was observed in each group. The incidence of edema was low and similar between treatment groups, while weight gain was observed in all 3 groups, although it was higher in the rosiglitazone plus insulin groups, as previously described. The overall adjudicated CV events, including edema- and ischemia-related CV events, were low and only slightly higher in the rosiglitazone plus insulin groups. It is worth noting that the 4-mg/d rosiglitazone group in particular had multiple CV risk factors on entry into the study.

Taken together, these findings suggest that there is a favorable risk-benefit profile with low-dose rosiglitazone added to insulin therapy and that the addition of low-dose rosiglitazone to insulin therapy reduces non-traditional biomarkers of CV risk. In particular, the significant reduction in C-reactive protein levels is consistent with prior rosiglitazone monotherapy and combination therapy with either sulfonylurea or metformin and with rosiglitazone or pioglitazone treatment in combination with insulin therapy.^{18,26} An unexpected result was the inconclusive effect on PAI-1, in contrast with previous studies in which PAI-1 levels were significantly reduced with rosiglitazone or pioglitazone therapy.^{27,28} There were no imbalances in the use of relevant concomitant medications between treatment groups.

In summary, although the clinical relevance of these observations has yet to be fully established, the results presented herein may be indicative of the potential beneficial effects of rosiglitazone therapy for vascular inflammation and fibrinolytic activity.^{15,29} The PROspective pioglitazone Clinical Trial In macroVascular Events (PROactive) study reported a 10% relative risk reduction in primary end points based on composite CV events, although this was not statistically significant ($P=.10$).³⁰ Further confirmation of such potentially beneficial effects will come from investigations of TZDs on CV risk, which are currently under way in long-term outcomes studies such as the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes (RECORD) and the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trials.^{31,32} Low doses of rosiglitazone in combination with insulin therapy were shown to be effective and well tolerated in the treatment of T2DM and have potentially beneficial effects on CV risk factors. Type 2 diabetes is a progressive disease, and insulin treatment alone is often not sufficient for insulin-requiring patients. The addition of rosiglitazone to insulin therapy offers a potential option for reaching diabetes treatment goals.

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