OBJECTIVE — The goal was to assess the 1-year efficacy and safety of the addition of pioglitazone to metformin in end-stage renal disease and the respective groups. Fasting insulin levels were also reduced (pioglitazone arm −1.3 μIU/ml; metformin arm −0.8 μIU/ml). There were no significant between-treatment differences in these three parameters. Pioglitazone addition to SU significantly reduced triglycerides (−16 vs. −9%; P = 0.008) and increased HDL cholesterol (14 vs. 8%; P < 0.001) compared with metformin addition. LDL cholesterol was increased 2% by the addition of pioglitazone and decreased 5% by the addition of metformin to SU (P < 0.001). Urinary albumin-to-creatinine ratio was reduced by 15% in the SU plus pioglitazone group and increased 2% in the SU plus metformin group (P = 0.017). Both combinations were well tolerated with no evidence of hepatic or cardiac toxicity in either group.

CONCLUSIONS — Clinically equivalent improvements in glycemic control were observed for both combinations. Compared with metformin plus SU, addition of pioglitazone to SU resulted in a reduction of the urinary albumin-to-creatinine ratio, a small but significant rise in LDL cholesterol, and significantly greater improvements in triglyceride levels and HDL cholesterol levels. Metformin plus SU was associated with a significant reduction in LDL cholesterol. SU plus pioglitazone is an effective and well-tolerated combination regimen that may provide additional beneficial effects for patients with type 2 diabetes.

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Abbreviations: AIP, atherogenic index of plasma; FPG, fasting plasma glucose; ITT, intent to treat; SU, sulfonylurea; TZD, thiazolidinedione.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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SU plus pioglitazone versus plus metformin

genolysis (12–14). It is an effective and generally well-tolerated agent.

To date, no long-term trials reported have compared the effect of the addition of metformin or pioglitazone to failing SU monotherapy. This study was conducted to compare the efficacy and safety of pioglitazone added to an SU with the commonly used combination of metformin and an SU over 52 weeks in patients with type 2 diabetes inadequately controlled by SU alone.

RESEARCH DESIGN AND METHODS — This was a multicenter, randomized, double-blind, parallel-group study conducted in Europe (Hungary, Finland, U.K., Slovak Republic, Belgium, Estonia, Lithuania, Denmark, Italy, Greece, Sweden, and the Netherlands) and Canada in 639 patients with type 2 diabetes. All patients gave written, informed consent to participate in the study, and local Ethics Committee approval was obtained for each site. The study was conducted in accordance with the Declaration of Helsinki and the requirements of Good Clinical Practice of the European Community.

Male and female patients aged 35–75 years with type 2 diabetes inadequately managed with SU therapy alone (at ≥50% of the maximal recommended dose or at the maximal tolerated dose for ≥3 months) and with stable or worsening glycemic control for ≥3 months were eligible if their Hba1c was between 7.5 and 11.0% and their fasting C-peptide was ≥1.5 ng/ml at screening. Exclusions included patients with: type 1 diabetes or ketoadiagnosis; a history of myocardial infarction, transient ischemic attacks, or stroke in the previous 6 months; symptomatic heart failure; malabsorption or pancreatitis; familial polyposis coli; malignant disease in the previous 10 years; a history of or states associated with lactic acidosis or hypoxemia; or substance abuse. Female patients had to be postmenopausal, sterilized, or using satisfactory contraception, and pregnant or breast-feeding women were excluded. Previous treatment with metformin, pioglitazone, or other TZDs was not permitted. During the study, thiazides were allowed to treat edema, and if antihypertensive treatment was indicated, ACE inhibitors, angiotensin II receptor antagonists, or calcium antagonists were given so as not to affect glucose homeostasis.

Patients were randomized to a 12-month treatment period consisting of a 12-week forced-titration period followed by a 40-week maintenance period. Patients received either pioglitazone up to 45 mg with metformin placebo once daily (o.d.) or metformin 850 mg with pioglitazone placebo up to three times daily (maximal dose of 2,550 mg metformin). Patients started with pioglitazone 15 mg o.d. or metformin 850 mg o.d., and dose levels were increased at weeks 4, 8, and 12. Cessation of titration or down titration was permitted only on the basis of tolerability issues, including actual hyperglycemia or increased risk of hypoglycemia. Patients continued to the next dose level unless the investigator considered that the increase could put them at risk of hypoglycemia (increase postponed for one visit from week 4 to week 8 or the week 8 dose was maintained for the rest of the study), if the patient reported symptomatic hyperglycemia (one-step reduction followed by an increase at the following visit, if possible), or if the patient experienced adverse events that required dose reduction (one-step reduction at week 8 or 12 with no further down titration).

The maximal tolerated doses of pioglitazone or metformin established at week 12 remained unchanged throughout the 40-week maintenance period. Patients also received SU at their prestudy dose, and increases were not permitted. The SU dose could be down titrated only if the patient experienced symptomatic hyperglycemia with an increase to the original dose at the next visit, where possible.

The primary efficacy endpoint was change in Hba1c from baseline to week 52. Changes in FPG, insulin, lipids, C-peptide, 32,33 split proinsulin, and urinary albumin and creatinine (to determine the albumin-to-creatinine ratio) were measured as secondary endpoints. Hba1c, FPG, and insulin levels were measured at baseline and at weeks 4, 8, 12, 16, 24, 32, 42, and 52. Lipids were measured at baseline and at weeks 8, 16, 24, 32, 42, and 52. The atherogenic index of plasma (AIP) was calculated from the log (triglyceride–to-HDL cholesterol ratio) as an index of LDL particle size. Urinary albumin and creatinine were measured at baseline and at weeks 24, 32, 42, and 52. At selected centers, C-peptide and 32,33 split proinsulin (a marker for cardiovascular risk) were measured at baseline and at weeks 8, 16, 24, 32, 42, and 52 to assess any underlying improvement in β-cell function.

Because down titration of study medication was not permitted after week 12, adverse events thought to be drug related after this point were managed by temporary interruption of study medication or permanent discontinuation. Safety and tolerability were also assessed by measuring body weight, waist circumference, blood pressure, and pulse rate at all visits, standard safety laboratory tests at regular intervals, and a physical examination performed at screening and at week 52.

An intent-to-treat (ITT) analysis with last observation carried forward was used to assess efficacy. The ITT population included all patients who had received at least one dose of study medication and had Hba1c recorded at baseline and at least once after baseline. Statistical analysis of the primary efficacy variable (change in Hba1c, from baseline to week 52) was performed using an ANCOVA model with the factor “treatment” and the baseline value as a continuous covariate. Mean differences between groups were calculated with 95% CI, and a two-sided Student’s t test (α = 0.05) was performed. Analyses of the secondary efficacy variables were performed in a similar way. As certain data were not normally distributed, lipids and urinary albumin-to-creatinine ratio analyses were also performed using log-transformed data. LDL cholesterol was calculated using Friedewald’s formula.

All patients who had received at least one dose of study medication were included in the safety analysis. Adverse events were summarized using MedDRA coding at the preferred term level and grouped by system-organ class. Results of the standard laboratory tests were summarized as mean change from baseline, and patients with critically abnormal values were identified.

RESULTS — In total, 639 patients received study treatment (n = 319 with SU plus pioglitazone; n = 320 with SU plus metformin). Eleven patients (n = 4 in the pioglitazone group and n = 7 in the metformin group) were not eligible for the ITT analysis due to missing postbaseline Hba1c data. The treatment groups were well matched with regard to demographic and baseline characteristics (Table 1) and dose distribution of SU. Glibenclamide
Table 1—Demographic and baseline characteristics and week 52 outcome data for safety population

<table>
<thead>
<tr>
<th>Parameters</th>
<th>SU plus pioglitazone</th>
<th>SU plus metformin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Male</strong></td>
<td>171 (53.6)</td>
<td>175 (54.7)</td>
</tr>
<tr>
<td><strong>Female</strong></td>
<td>148 (46.4)</td>
<td>145 (45.3)</td>
</tr>
<tr>
<td><strong>Race (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Caucasian</strong></td>
<td>317 (99.4)</td>
<td>315 (98.4)</td>
</tr>
<tr>
<td><strong>African American</strong></td>
<td>2 (0.6)</td>
<td>3 (0.9)</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td>0</td>
<td>2 (0.6)</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td>60 ± 8.8 (36–75)</td>
<td>60 ± 8.0 (36–75)</td>
</tr>
<tr>
<td><strong>Weight (kg)</strong></td>
<td>85.3 ± 15.1 (50–125)</td>
<td>84.9 ± 14.5 (49–128)</td>
</tr>
<tr>
<td><strong>BMI (kg/m²)</strong></td>
<td>30.2 ± 4.4 (21–45)</td>
<td>30.0 ± 4.6 (19–46)</td>
</tr>
<tr>
<td><strong>Waist circumference (cm)</strong></td>
<td>103 ± 10.9</td>
<td>103 ± 11.0</td>
</tr>
<tr>
<td><strong>Duration of diabetes (years)</strong></td>
<td>7.0 ± 5.6 (0.2–30.7)</td>
<td>7.1 ± 5.6 (0.3–31.7)</td>
</tr>
<tr>
<td><strong>HbA₁c (%)</strong></td>
<td>8.82 ± 0.98 (3.2–15.3)</td>
<td>8.80 ± 0.97 (3.2–15.3)</td>
</tr>
<tr>
<td><strong>FPG (mmol/l)</strong></td>
<td>11.8 ± 2.7</td>
<td>12.0 ± 2.9</td>
</tr>
<tr>
<td><strong>Triglycerides (mmol/l)</strong></td>
<td>2.47 ± 1.69</td>
<td>2.38 ± 1.72</td>
</tr>
<tr>
<td><strong>HDL cholesterol (mmol/l)</strong></td>
<td>1.09 ± 0.24</td>
<td>1.11 ± 0.27</td>
</tr>
<tr>
<td><strong>LDL cholesterol (mmol/l)</strong></td>
<td>3.57 ± 0.86</td>
<td>3.58 ± 0.92</td>
</tr>
<tr>
<td><strong>Total-to-HDL cholesterol ratio</strong></td>
<td>5.45 ± 1.47</td>
<td>5.38 ± 1.53</td>
</tr>
<tr>
<td><strong>AIP (log triglyceride–to–HDL cholesterol ratio)</strong></td>
<td>0.66 ± 0.71</td>
<td>0.62 ± 0.69</td>
</tr>
<tr>
<td><strong>Fasting insulin (μIU/ml)</strong></td>
<td>12.8 ± 8.1</td>
<td>12.4 ± 7.7</td>
</tr>
<tr>
<td><strong>C-peptide (ng/ml)</strong></td>
<td>3.5 ± 1.8</td>
<td>3.5 ± 1.5</td>
</tr>
<tr>
<td><strong>32,33 split proinsulin (pmol/l)</strong></td>
<td>22.7 ± 20.2</td>
<td>22.1 ± 19.5</td>
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<tr>
<td><strong>Aspartate aminotransferase (units/l)</strong></td>
<td>24 ± 11.6</td>
<td>24 ± 10.6</td>
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<tr>
<td><strong>γ-Glutamyl transpeptidase</strong></td>
<td>53 ± 82.4</td>
<td>44 ± 42.2</td>
</tr>
<tr>
<td><strong>Alanine aminotransferase (units/l)</strong></td>
<td>30 ± 15.6</td>
<td>30 ± 15.6</td>
</tr>
<tr>
<td><strong>Alkaline phosphatase (units/l)</strong></td>
<td>81 ± 29.3</td>
<td>82 ± 25.2</td>
</tr>
<tr>
<td><strong>Hemoglobin (g/l)</strong></td>
<td>150 ± 12.0</td>
<td>150 ± 11.8</td>
</tr>
<tr>
<td><strong>Hematocrit (%)</strong></td>
<td>44.1 ± 3.4</td>
<td>44.0 ± 3.2</td>
</tr>
<tr>
<td><strong>Urinary albumin-to-creatinine ratio</strong></td>
<td>0.07 ± 0.25</td>
<td>0.11 ± 0.56</td>
</tr>
</tbody>
</table>

Data are n (%), means ± SD, and means ± SD (range).

(42%), gliclazide (31%), and glimepiride (19%) were the most commonly used SUs in both groups. At the end of the 12-week dose titration period, 62% of patients treated with SU plus pioglitazone and 55% of those treated with SU plus metformin were receiving the maximal dose (45 mg pioglitazone; 2,550 mg metformin). Over 80% of patients completed the study (81.5% in the SU plus pioglitazone group and 87.2% in the SU plus metformin group). The difference in percentage completers was mainly due to withdrawn consent of 5% of patients in the pioglitazone group vs. 1.6% in the metformin group. Withdrawals due to adverse events were comparable in the SU plus pioglitazone and SU plus metformin groups (6.3 and 5.9%, respectively), with the majority due to gastrointestinal disorder events (nine and seven patients, respectively). Mean treatment duration was 11 months in both groups. SU usage from baseline to week 52 remained similar in both treatment groups, and there were very few cases of dose reduction.

All data are from the ITT population unless otherwise specified. In the SU plus pioglitazone group, there was a mean reduction of 1.20% in HbA₁c after 52 weeks of treatment, similar to the reduction of 1.36% observed in the SU plus metformin group. The adjusted mean difference between treatments was not statistically significant (95% CI −0.01 to 0.32; P = 0.065). The maximal response in both groups was observed at 24 weeks (Fig. 1). The percentage of patients achieving an HbA₁c < 7.0% after 52 weeks of treatment was similar in both groups (39% in the pioglitazone group; 40% in the metformin group).

Reduction in FPG from baseline to week 52 was similar in both groups: −2.2 mmol/l with SU plus pioglitazone and −2.3 mmol/l with SU plus metformin with 0.1 mmol/l adjusted mean difference between treatments (95% CI −0.3 to 0.5; P = 0.528). The maximal decrease in FPG was seen at week 16 in the SU plus pioglitazone group and at week 12 in the SU plus metformin group (Fig. 1).

Fasting insulin levels were also reduced at week 52: −1.3 μIU/ml in the SU plus pioglitazone group and −0.8 μIU/ml in the SU plus metformin group (95% CI −1.4 to 0.3; P = 0.199). C-peptide and 32,33 split proinsulin were assessed at selected centers only. Mean C-peptide remained at approximately baseline levels throughout the study in both treatment groups with a small reduction from baseline to week 52 of 0.2 ng/ml in
the SU plus pioglitazone group (n = 78) and no change in the SU plus metformin group (n = 70; 95% CI −0.5 to 0.1; P = 0.160). There was a significantly greater reduction in mean 32.33 split proinsulin in the SU plus metformin group (−8.7 pmol/l; n = 152) than the SU plus pioglitazone group (−6.4 pmol/l; n = 164; 95% CI 0.1−4.6; P = 0.044).

Changes from baseline in triglycerides, HDL cholesterol, LDL cholesterol, and total cholesterol−to−HDL cholesterol ratio at week 52 are shown in Fig. 2 as log-transformed data. With SU plus pioglitazone, triglycerides were reduced by 0.42 mmol/l (correlating with a 16% reduction using log-transformed data) and by 0.28 mmol/l in the SU plus metformin group (−9% log-transformed data), and the difference was statistically significant (95% CI 0.87−0.98; P = 0.008, log-transformed data). In the SU plus pioglitazone group, HDL cholesterol was increased by 0.16 mmol/l (14% log-transformed data) and by 0.09 mmol/l (8% log-transformed data) in the SU plus metformin group; the treatment difference was highly significant (95% CI 1.03−1.08; P < 0.0001; log-transformed data). There was a small increase of 0.08 mmol/l in LDL cholesterol in the SU plus pioglitazone group (2% log-transformed data) compared with a small but significant decrease of 0.16 mmol/l (5% log-transformed data) in the SU plus metformin group (95% CI 1.03−1.10; P = 0.0002; log-transformed data). Total−to−HDL cholesterol ratio was reduced to a similar extent in both groups from baseline to week 52 (ratio of −0.55 in both groups; −11 and −10%, respectively, log-transformed data). In combination with SU, pioglitazone caused significantly larger mean reductions in the triglyceride−to−HDL cholesterol ratio (AIP the logarithmic transformation of the triglyceride−to−HDL cholesterol ratio) than did metformin (−0.30 vs. −0.17; P = 0.001).

Approximately three-quarters (72%) of patients had normal albuminuria at baseline. The urinary albumin−to−creatinine ratio was significantly reduced by 15% from baseline to week 52 in the SU plus pioglitazone group compared with an increase of 2% in the SU plus metformin group (95% CI 0.73−0.97; P = 0.017, log-transformed data). The effect of pioglitazone on urinary albumin−to−creatinine ratio was observed in both normal albuminuric and microalbuminuric subjects, and microalbuminuria resolved at week 52 in 10.2% of the patients in the pioglitazone plus SU group and 7.7% in the metformin plus SU group.

Both treatments showed a similar overall incidence of adverse events: 59.9% (n = 191) in the SU plus pioglitazone group and 61.9% (n = 198) in the SU plus metformin group. The majority of adverse events were mild to moderate. The incidence of serious adverse events was higher in the SU plus metformin group (9.7%) than in the SU plus pioglitazone group (6.6%). Two patients in the SU plus metformin group and one in the SU plus pioglitazone group died during the study (none were thought to be treatment related).

Gastrointestinal disorders occurred more frequently in the metformin than in the pioglitazone arm (23.4 vs. 12.2%) with diarrhea, in particular, occurring more frequently in the metformin group (12.5 vs. 2.5%). There was no difference in the incidence of cardiac disorders between groups (3.1% in the SU plus pioglitazone group and 4.1% in the SU plus metformin group), and no relationship to edema was noted in either treatment groups. Hypoglycemic episodes were the most frequently occurring adverse event in both groups with a slightly higher incidence in the SU plus metformin group (14.1 vs. 10.7%). There were no cases of severe hypoglycemia. Mild-to-moderate edema was the most commonly reported adverse event in the SU plus pioglitazone group (6.9 vs. 1.6%). In addition, pyrexia, increased blood creatine phosphokinase, and weight gain were reported more frequently in the SU plus pioglitazone group, and hypertension, back pain, dizziness, diarrhea, and flatulence were reported in the SU plus metformin group.

A mean weight gain of 2.8 kg was observed in the pioglitazone group compared with a reduction of 1.0 kg in the metformin group over the 52 weeks. The weight changes tended to stabilize in both groups toward the end of the treatment period. There were no clinically significant changes in blood pressure (although it showed a tendency to decrease in both groups) or pulse rate and no clinically significant between-group differences.

Except for aspartate aminotransferase, which remained unchanged, liver function tests were reduced over time in both treatment groups (Table 1). Mean reductions in γ-glutamyl transpeptidase and alanine aminotransferase were greater in the SU plus pioglitazone group (−12 vs. −6 and −5 vs. −2 units/l, respectively), and the reduction in alkaline phosphatase was greater in the SU plus metformin group (−13 vs. −8 units/l). Hemoglobin and hematocrit were reduced to a similar extent (mean
Figure 2—Change (±95% CI) from baseline to last value (last observation carried forward analysis) for triglycerides, HDL cholesterol, LDL cholesterol, total-to-HDL cholesterol ratio, albumin-to-creatinine ratio, and AIP for the ITT population. Treatments compared using adjusted mean ratios from baseline (pioglitazone/metformin) with baseline values as covariates and based on log-transformed data. ■, pioglitazone plus SU; □, metformin plus SU.
Conclusions — Our study results demonstrated that the addition of pioglitazone or metformin in patients insufficiently treated with SU resulted in improved glycemic control throughout the 1-year study period. Hba1c was reduced by 1.2% over the 52-week period and FPG by 2.2 mmol/l. Pioglitazone lowers blood glucose by enhancing insulin sensitivity in skeletal muscle, adipose tissue, and the liver (6,15,16), in part, by reducing intra-abdominal and intrahepatic fat (17). The glycemic control established with an SU plus pioglitazone was comparable with that of an SU plus metformin, and both treatment groups reached a maximal effect by week 24. There was a tendency for control to decline in the SU plus metformin group, however, this was not statistically significant at week 52. An extension trial that is presently being conducted should clarify if this is representative of deterioration in glycemic control in this group.

Levels of fasting insulin at week 52 were reduced by 1.3 μIU/ml in the pioglitazone group, which was similar to the reduction of 0.8 μIU/ml in the metformin group. Because pioglitazone acts predominantly on insulin resistance, improved glycemic control is established in the presence of lower levels of insulin. This reduction in fasting insulin was observed despite using a combination regimen with SUs that are insulin secretagogues. Decreases in insulin precursor molecules were small, although there was a significantly greater decrease when pioglitazone was added to the SU compared with metformin addition (P = 0.04). These differences may represent changes in insulin processing. Additional investigations need to be conducted to determine the significance of these findings.

Reduced HDL cholesterol and elevated triglycerides are well-known independent indicators of cardiovascular risk in patients with type 2 diabetes (18–20). From epidemiological studies, it is known that a 1% increase in HDL cholesterol is associated with a 2–3% reduction in the risk of coronary heart disease (20). Improvements in HDL cholesterol and triglycerides with SU plus pioglitazone (14 and –16%, respectively) were almost twice those observed with SU plus metformin (8 and –9%, respectively). The total cholesterol–to–HDL cholesterol ratio gives an indication of the overall changes in the lipid profile and has been found to be a useful indicator of cardiovascular risk. Although LDL cholesterol increased slightly with SU plus pioglitazone treatment (2%) compared with a reduction with SU plus metformin (–5%), qualitative changes in LDL cholesterol may have occurred during treatment.

These changes were estimated during this study using the AIP, which correlates inversely with the LDL particle size (21). Addition of pioglitazone to the SU caused larger mean reductions in AIP from baseline than did the addition of metformin, implying a possible decrease in cardiovascular risk. As there is an inverse relationship between AIP and LDL particle size, a reduction of AIP implies an increase in LDL particle size and less atherogenicity (21).

Microalbuminuria is another strong risk indicator for cardiovascular events and has been suggested as a marker for patients with endothelial and renal dysfunction, particularly in patients with features of the metabolic syndrome (22–24).

In the results presented here, pioglitazone reduced the urinary albumin-to-creatinine ratio by 15% in combination with an SU. In contrast, metformin as add-on therapy to an SU increased urinary albumin-to-creatinine ratio by 2%. These changes were not related to differences between groups in changes in blood pressure or in the use of agents acting on the renin-angiotensin system (~44% in each group, primarily ACE inhibitors). Although the clinical significance of this is uncertain, improvement in a cardiovascular risk marker with pioglitazone treatment, which is of a similar order to that seen with ACE inhibitors (25), may be of value in this high-risk group. Because pioglitazone significantly improves dyslipidemia and urinary albumin-to-creatinine ratio, any improvements in cardiovascular risk factors may be demonstrated in ongoing pioglitazone outcome studies.

Both SUs and TZDs are known to be associated with weight gain. In this study, there was a mean weight gain of 2.8 kg during the 52 weeks of treatment in the SU plus pioglitazone group. In the SU plus metformin group, however, there was a 1.0-kg decrease. This was expected as metformin is often associated with weight loss (26–30) and may confer some advantage in patients with metabolic syndromes who are often overweight. Weight increases in the SU plus pioglitazone group were still accompanied by improvements in glycemic control, and weight appeared to stabilize by the end of treatment. Further studies are needed to assess if this has any effect on the long-term outcomes of these patients.

The reductions in hemoglobin and hematocrit after treatment with SU plus pioglitazone were identical to those in the SU plus metformin group. There were greater improvements in liver function tests (γ-glutamyl transpeptidase and alanine aminotransferase) in the SU plus pioglitazone group compared with the SU plus metformin group. These reductions observed with SU plus pioglitazone may be a reflection of reduction of hepatic fat content, which is elevated in type 2 diabetes (31).

SU plus pioglitazone combination was generally well tolerated, and the incidence of adverse events was similar in both groups. The majority of adverse events were mild to moderate with a higher incidence of serious adverse events in the SU plus metformin group than in the SU plus pioglitazone group (9.7 vs. 6.6%, respectively). Compared with SU plus metformin, there was an increased incidence of edema in patients treated with SU plus pioglitazone, although this was not associated with heart failure or cardiac events in the study. As expected (32), treatment with metformin was associated with a high incidence of diarrhea (12.5%).

In summary, the addition of pioglitazone to existing SU therapy resulted in improved glycemic control over a 52-week period. The reductions in Hba1c and FPG, together with a reduction in fasting insulin, may reflect the ability of pioglitazone to reduce insulin resistance. Moreover, the decrease in triglycerides and the urinary albumin-to-creatinine ratio and the rise in HDL cholesterol suggest additional benefits in terms of reducing the risk of complications in patients with type 2 diabetes. It should be noted that the addition of metformin to SU resulted in a significant lowering of LDL cholesterol, whereas there was an increase in LDL cholesterol in the pioglitazone plus SU group; however, the magnitude of variation in this parameter was much smaller than with the other lipid values. This study has demonstrated that SU plus pioglitazone is an effective combination.
regimen for patients insufficiently treated with SU monotherapy and may provide possible positive effects on other coronary risk factors associated with the metabolic syndrome.

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References


