Original Article

Blood Pressure Control and Inflammatory Markers in Type 2 Diabetic Patients Treated with Pioglitazone or Rosiglitazone and Metformin

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The aim of the study was to assess the effects of the combination of metformin plus pioglitazone or rosiglitazone on glucose and blood pressure in type 2 diabetic patients with metabolic syndrome, as well as its tolerability in those patients. In this 12-month, multicentric, double-blind, randomized, controlled, parallel-group trial, all patients began with metformin. Patients were randomized for self-administration of either pioglitazone or rosiglitazone for 12 months. We assessed body mass index (BMI), glycemic control (glycosylated hemoglobin [HbA_{1c}], fasting and postprandial plasma glucose and insulin levels [FPG, PPG, FPI and PPI, respectively] and homeostasis model assessment [HOMA] index) and systolic and diastolic blood pressure (SBP and DBP, respectively), at baseline and at 3, 6, 9 and 12 months of treatment, as well as high-sensitivity C-reactive protein (hs-CRP), nitrites/nitrates and adiponectin (ADN) at baseline and at 12 months of treatment. Significant HbA_{1c} decreases were obtained after 9 ($p<0.05$) and 12 ($p<0.01$) months in both groups. After 9 and 12 months, mean FPG and PPG levels were decreased in both groups ($p<0.05$ and $p<0.01$, respectively). We observed decreases in FPI and PPI at 9 and 12 months ($p<0.05$ and $p<0.01$, respectively) compared to the baseline values in both groups. Furthermore, HOMA index improvement over the baseline value was obtained only at 12 months ($p<0.05$) in both groups. SBP and DBP improved significantly ($p<0.05$, for each) in both groups after 12 months. hs-CRP decreased significantly ($p<0.05$) in both groups after 12 months; nitrites/nitrates and ADN increased significantly ($p<0.05$, for each) in both groups after 12 months. The combination of thiazolinediones and metformin is associated with a slight but significant improvement in the long-term blood pressure control of these patients, and with an improvement in the anti-inflammatory state, both of which are related to a similar reduction in insulin-resistance. (*Hypertens Res* 2007; 30: 387–394)

***Key Words*: thiazolidinediones, pioglitazone, rosiglitazone, metformin, diabetes mellitus**

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Introduction

Coronary artery disease (CAD) is the leading cause of serious morbidity and mortality in patients with diabetes, who have a two- to four-fold increased risk of CAD (*1*). This heightened risk is strongly related not only to the inadequate control of glycemia but also to other cardiovascular risk factors, and in particular to arterial hypertension (*2*). For these reasons, the American Diabetes Association (ADA) has suggested the vigorous treatment of both hyperglycemia and high blood pressure using any available means (*3*). For patients not taking insulin, accumulating evidence suggests that combination therapy using oral antidiabetic agents with different mechanisms of action may be highly effective for achieving and maintaining target blood glucose levels, perhaps reducing the high secondary failure rate of monotherapy (*4*). In the course of the disease, the use of combinations of oral agents may delay the need for insulin while maintaining glycemic control, thus making aggressive oral treatment more acceptable for many patients (*5*).

Metformin is a biguanide antihyperglycemic drug that has been used to treat type 2 diabetes mellitus for over 40 years, and its main mechanism of action is to counteract peripheral insulin-resistance (*6*). Moreover, metformin is the only antihyperglycemic drug demonstrated to have relevant positive effects on hard clinical outcomes: it prevented approximately 40% of vascular events in a large retrospective Canadian study carried out on more than 12,000 patients (*7*), it significantly reduced any diabetes-related endpoint in the United Kingdom Prospective Diabetes Study (*8*) and it decreased the incidence of diabetes by 31% in the large Diabetes Prevention Program (*9*).

Thiazolidinediones are a more recent class of oral hypoglycemic agents. The hypoglycemic effect of thiazolidinediones is related to their ability to increase insulin sensitivity and, consequently, to increase peripheral glucose utilization. Although the exact mechanism of action is not completely understood, the most widely accepted hypothesis is that their effect on insulin sensitivity is related to their well-known ability to bind and activate the nuclear peroxisomal proliferator–activated receptors-γ (PPAR-γ) (*10*).

Some studies have shown that the combination of thiazolidinediones and metformin improved glycemic control in type 2 diabetic patients (*11*, *12*).

Although the metabolic effect of thiazolidinediones has been adequately studied and many data on their effect on blood pressure are available, few data can be found on a head-to-head comparison between pioglitazone and rosiglitazone in combination with metformin. Furthermore, few data exist on inflammation markers related to the use of these treatments.

Thus, the aim of our study was to compare the long-term effects of pioglitazone and rosiglitazone on blood pressure control and on inflammation markers of diabetic patients treated with metformin.

Methods

Study Design

This 12-month, multicentric, double-blind, randomized, controlled, parallel-group trial was conducted at the Department of Internal Medicine and Therapeutics, University of Pavia (Pavia, Italy); and at the G. Descovich Atherosclerosis Study Center of the D. Campanacci Clinical Medicine and Applied Biotechnology Department, University of Bologna (Bologna, Italy).

The study protocol was approved at each site by institutional review boards and was conducted in accordance with the Declaration of Helsinki and its amendments.

Patients

Caucasian patients aged ≥18 years of either sex were eligible for inclusion in the study if they had type 2 diabetes mellitus according to ADA criteria (*13*) (duration, ≥6 months), and if they had poor glycemic control (glycosylated hemoglobin [HbA_{1c}] level, >7.5%) or had experienced adverse effects with diet and oral hypoglycemic agents, such as sulfonylureas or metformin (Table 1), both given up to the maximum tolerated dose (Table 2). All patients also were diagnosed with metabolic syndrome according to the National Cholesterol Education Program (NCEP) Adult Treatment Panel III classification (*14*), and they presented with triglyceridemia (TG, ≥150 mg/dL) (*14*) and hypertension according to the World Health Organization criteria (*15*) (systolic/diastolic blood pressure [SBP/DBP], ≥130/≥85 mmHg). All patients had a fasting C-peptide level >1.0 ng/mL. All were overweight (body mass index [BMI], 25.0–28.1 kg/m^2) (*16*). Suitable patients, identified from a review of case notes and/or computerized clinic registers, were contacted by the investigators in person or by telephone.

Patients were excluded if they had a history of ketoacidosis or had unstable or rapidly progressive diabetic retinopathy, nephropathy or neuropathy; impaired hepatic function (defined as a plasma aminotransferase and/or γ-glutamyltransferase level higher than the upper limit of normal [ULN] for age and sex), impaired renal function (defined as a serum creatinine level higher than the ULN for age and sex) or severe anemia. Patients with serious cardiovascular disease (CVD) (*e.g.*, New York Heart Association class III or IV congestive heart failure or a history of myocardial infarction or stroke) or cerebrovascular conditions within 6 months before study enrollment also were excluded, as were women who were pregnant or breastfeeding or of childbearing potential and not taking adequate contraceptive precautions. No patients were taking hypolipidemic or antihypertensive drugs. All patients provided written informed consent to participate (Fig. 1).

Table 1. Patients Data before Sulfonilureas or Metformin Therapy Allocated Then in Pioglitazone and Rosiglitazone Groups

	Baseline	
	Pioglitazone+ metformin	Rosiglitazone+ metformin
n	48	48
Sex (M/F)	24/24	25/23
Age (years)	55±5	56±4
Duration of diabetes (years)	6±4	5±4
BMI (kg/m^2)	28.2±1.7	28.1±1.6
HbA_{1c} (%)	8.9±1.0	9.0±1.1
FPG (mg/dL)	173±30	171±29
PPG (mg/dL)	209±27	204±26
FPI (μU/mL)	26.6±6.8	26.9±7.0
PPI (μU/mL)	78.1±10.3	77.9±10.9
HOMA index	12.9±5.9	12.1±5.3
SBP (mmHg)	138.3±4.8	137.4±4.6
DBP (mmHg)	86.5±4.3	86.1±4.2
HR (beats/min)	74±6	75±8

Data are means±SD; all group differences are nonsignificant. M, male; F, female; BMI, body mass index; HbA_{1c}, glycosylated hemoglobin; FPG, fasting plasma glucose; PPG, postprandial plasma glucose; FPI, fasting plasma insulin; PPI, postprandial plasma insulin; HOMA index, homeostasis model assessment index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate.

Treatment

All patients self-administered metformin, beginning with a dose of 1,500 mg/day and eventually reaching 3,000 mg/day, for 12 months. The dose depended on the tolerance or glycemic control of the patients (mean dosage: 2,250±750 mg/day).

In addition, patients were randomized (using envelopes containing randomization codes prepared by a statistician) to receive pioglitazone 15 mg once daily or rosiglitazone 4 mg once daily, self-administered daily before lunch for 12 months. A copy of the randomization code was provided only to the person responsible for performing the statistical analysis. The code was only broken after the database was locked, but could have been broken for individual patients in cases of emergency, such as hospitalization or suspicion of a serious adverse event.

Pioglitazone and rosiglitazone were supplied as identical, opaque white capsules in coded bottles to ensure the double-blind status of the study. At baseline, we weighed participants and gave them a bottle containing a 100-day supply of the study medication. Throughout the study, we instructed the patients to take their first dose of medication for a new study period on the day after they received it. A bottle containing the study medication for the next treatment period was given to each participant at every 3-month visit. At the same time, all unused medication was retrieved for inventory. All medications were provided free of charge.

Table 2. Oral Hypoglycemic Agents (Sulfonylureas and Metformin) before the Study Beginning

Name	Pioglitazone+ metformin		Rosiglitazone+ metformin	
	Number	Dose (mg/day)	Number	Dose (mg/day)
Sulfonilureas				
Gliclazide	13	160±80	12	200±40
Glyburide	18	12.5±2.5	17	12.5±2.5
Glimepiride	10	5.0±1.0	11	4.0±2.0
Biguanides				
Metformin	7	2,250±750	8	2,250±750

Data are means±SD; all group differences are nonsignificant.

Diet and Exercise

At baseline, patients began a controlled-energy diet (~600 kcal daily deficit) based on ADA recommendations (*17*); 50% of its calories were from carbohydrates, 30% from fat (6% saturated) and 20% from proteins, with a maximum cholesterol content of 300 mg/day and 35 g/day of fiber. Each center's standard dietary advice was given by a dietitian and/or specialist physician. Dietitians and/or specialists gave each patient 2 weeks of instruction on dietary intake–recording procedures as part of a behavior-modification program, and then, beginning in the first month, used the patients' food diaries for counseling. During the study, behavior-modification sessions on weight-loss strategies were given to individual patients at baseline and each 3 months till the end of the study. All patients reported good compliance with the suggested diet during all study phases.

Individuals were also encouraged to increase their physical activity by walking briskly or riding a stationary bicycle for 20 to 30 min, 3 to 5 times per week. The recommended changes in physical activity throughout the study were not assessed.

Efficacy, Tolerability and Compliance Assessments

Before starting the study, all patients underwent an initial screening including medical history, physical examination, vital signs, a 12-lead electrocardiogram and measurements of height, weight, BMI, HbA_{1c}, fasting plasma glucose (FPG), postprandial plasma glucose (PPG), fasting plasma insulin (FPI), postprandial plasma insulin (PPI), blood pressure, heart rate (HR), high-sensitivity C-reactive protein (hs-CRP), nitrites/nitrates (stable metabolites of NO) and adiponectin (ADN). Changes in BMI, HbA_{1c} and blood pressure were the

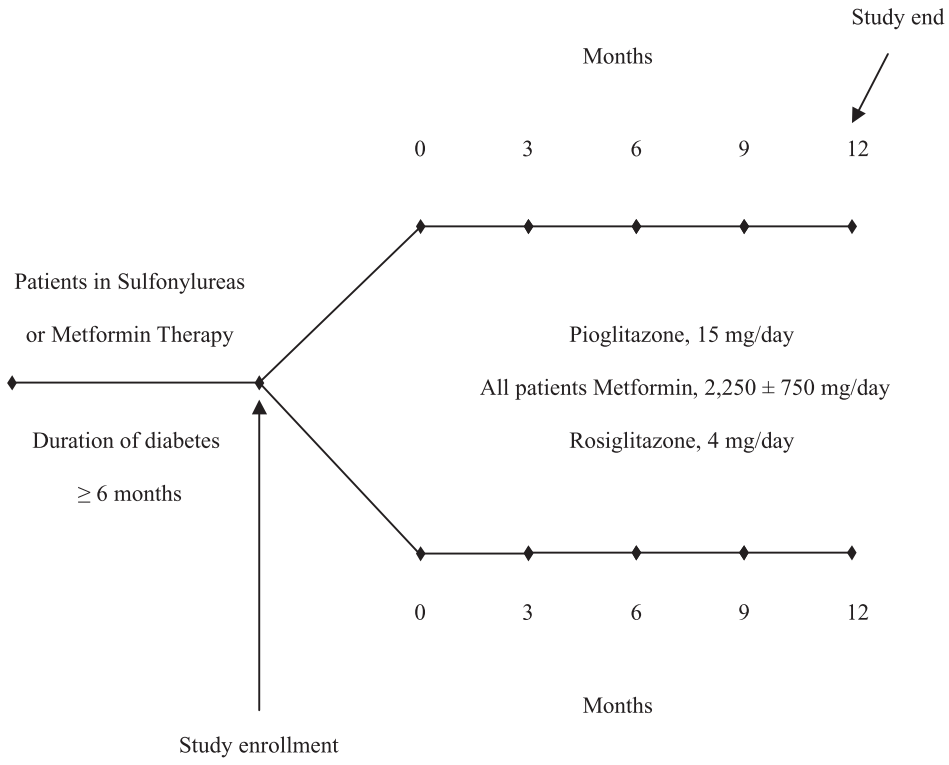

Fig. 1. *Scheme of the study protocol.*

Table 3. Data at Baseline in Pioglitazone and Rosiglitazone Groups

	Baseline	
	Pioglitazone+ metformin	Rosiglitazone+ metformin
n	48	48
Sex (M/F)	24/24	25/23
Age (years)	55±5	56±4
Duration of diabetes (years)	6±4	5±4
BMI (kg/m^2)	26.9±1.2	26.4±1.4
HbA_{1c} (%)	8.2±0.8	8.1±0.9
FPG (mg/dL)	161±24	164±27
PPG (mg/dL)	193±18	191±24
FPI (μU/mL)	25.5±6.1	26.1±5.9
PPI (μU/mL)	72.3±9.3	68.5±9.0
HOMA index	12.4±5.8	11.6±5.1
SBP (mmHg)	135.4±4.5	134.2±4.2
DBP (mmHg)	85.9±3.8	84.8±4.0
HR (beats/min)	70±6	72±8

Data are means±SD; all group differences are nonsignificant. M, male; F, female; BMI, body mass index; HbA_{1c}, glycosylated hemoglobin; FPG, fasting plasma glucose; PPG, postprandial plasma glucose; FPI, fasting plasma insulin; PPI, postprandial plasma insulin; HOMA index, homeostasis model assessment index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate.

primary efficacy variables. Fasting plasma glucose, PPG, homeostasis model assessment (HOMA) index, hs-CRP, nitrites/nitrates and ADN were also used to assess efficacy.

All plasmatic parameters were determined after a 12-h overnight fast, except that PPG and PPI were determined 2 h after lunch. Venous blood samples were taken for all patients between 08.00 and 09.00. We used plasma obtained by the addition of Na_2-EDTA, 1 mg/mL, and centrifuged at 3,000 × *g* for 15 min at 4°C. Immediately after centrifugation, the plasma samples were frozen and stored at −80°C for no more than 3 months. All measurements were performed in a central laboratory.

Body mass index was calculated as weight in kg divided by the square of the height in m. Insulin resistance was estimated using the HOMA index, with the following formula:

$$\text{Insulin resistance} = \text{FPI}\ (\mu\text{U/mL}) \times \text{FPG}\ (\text{mmol/L})/22.5,$$

as described by Matthews *et al*. (*18*) (normal if <2.5, marker of insulin-resistance if ≥2.5).

Glycosylated hemoglobin level was measured by an high performance liquid chromatography (HPLC) method. Plasma glucose was assayed by a glucose-oxidase method. Plasma insulin was assayed with Phadiaseph Insulin RIA (Pharmacia, Uppsala, Sweden). hs-CRP was measured with the use of latex-enhanced immunonephelometric assays on a BN II analyzer (Dade Behring, Deerfield, USA). The intra- and inter-assay coefficients of variation (CsV) were 5.7% and 1.3%,

Table 4. Parameter Changes at 3, 6, 9, and 12 Months of the Study in Pioglitazone Group

	Pioglitazone+metformin			
	3 months	6 months	9 months	12 months
BMI (kg/m^2)	26.8±1.2	26.5±1.1	25.4±1.0	26.6±1.1
HbA_{1c} (%)	7.8±0.7	7.3±0.6	7.0±0.5*	6.8±0.3**
FPG (mg/dL)	153±20	150±19	145±16*	140±15**
PPG (mg/dL)	182±16	178±15	172±14*	162±12**
FPI (μU/mL)	23.6±5.5	22.8±5.2	22.2±5.1	20.2±4.9*
PPI (μU/mL)	70.1±9.0	66.3±8.8	63.2±8.2	60.2±7.9*
HOMA index	11.8±5.6	11.3±4.9	10.8±4.2	9.2±3.9*
SBP (mmHg)	134.9±4.3	134.6±4.2	133.6±4.0	131.3±3.7*
DBP (mmHg)	85.4±3.7	84.5±3.5	84.1±3.4	82.3±3.0*
HR (beats/min)	72±7	73±8	75±7	74±8

Data are means±SD; *$p<0.05$ *vs*. baseline; **$p<0.01$ *vs*. baseline. BMI, body mass index; HbA_{1c}, glycosylated hemoglobin; FPG, fasting plasma glucose; PPG, postprandial plasma glucose; FPI, fasting plasma insulin; PPI, postprandial plasma insulin; HOMA index, homeostasis model assessment index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate.

respectively (*19*).

Nitrite and nitrate plasma levels are used clinically as markers for the activity of NO synthase and NO biosynthesis. The assay is based on the determination of nitrite using the Griess reaction. Nitrate was measured as nitrite after enzymatic conversion by nitrate reductase as described by Green *et al*. (*20*).

Adiponectin level was determined using ELISA kits (B-Bridge International, Sunnyvale, USA). The intra-assay CsV were 3.6% for low and 3.3% for high control samples, while the inter-assay CsV were 3.2% for low and 7.3% for high control samples (*21*).

Blood pressure was measured in each patient (right arm) in the seated position by using a standard mercury sphygmomanometer with a cuff of appropriate size. Measurements were always taken by the same investigator in the morning before daily drug intake (~24 h after dosing) and after the subject had rested for 10 min in a quiet room. Three successive blood pressure readings were obtained at 1-min intervals and averaged. Body mass index, HbA_{1c}, FPG, PPG, FPI, PPI, HOMA index, SBP, DBP and HR were evaluated at baseline and after 3, 6, 9 and 12 months. hs-CRP, nitrites/nitrates and ADN were evaluated at baseline and after 12 months. To evaluate the tolerability of the treatments, all adverse events were recorded.

Blood pressure was measured by physicians not belonging to the study, so as to preserve study blindness by the experimenters.

Statistical Analysis

An intention-to-treat (ITT) analysis was conducted in patients who had received ≥1 dose of study medication and had had a subsequent efficacy observation. Patients were included in the tolerability analysis if they had received ≥1 dose of trial medication after randomization and had undergone a subsequent tolerability observation. Analysis of variance (ANOVA) and analysis of covariance (ANCOVA) models were used to test the null hypothesis that the expected mean SBP and DBP change from baseline to the end of 12 months of double-blind treatment would not differ significantly between pioglitazone and rosiglitazone treatments (*22*). Similar analyses were applied to the other variables. The statistical significance of the independent effects of treatments on the other variables was determined using ANCOVA. A one-sample *t*-test was used to compare values obtained before and after treatment; two-sample *t*-tests were used for between-group comparisons. The Bonferroni correction for multiple comparisons also was carried out. Statistical analysis of data was performed using the Statistical Package for Social Sciences software version 11.0 (SPSS, Chicago, USA). Data are presented as means±SD. For all statistical analyses, $p<0.05$ was considered statistically significant.

Results

Study Sample

A total of 103 patients were enrolled in the trial. Of these, 96 completed the study and 48 (50.0%) were randomized to double-blind treatment with pioglitazone and 48 (50.0%) with rosiglitazone. Seven patients (3 males and 4 females) did not complete the study; the reasons for premature withdrawal included protocol violation, loss to follow-up and other non-compliance. The characteristics of the patient population at study entry, shown in Table 3, were similar between the two treatment groups.

Body Mass Index

No BMI change was observed after 3, 6, 9 or 12 months in both groups. There was no difference in BMI value between the pioglitazone and rosiglitazone groups. Results are

Table 5. Parameter Changes at 3, 6, 9, and 12 Months of the Study in Rosiglitazone Group

	Rosiglitazone+metformin			
	3 months	6 months	9 months	12 months
BMI (kg/m^2)	26.3±1.4	26.2±1.3	25.8±1.2	26.0±1.2
HbA_{1c} (%)	7.9±0.8	7.7±0.8	7.4±0.7*	6.8±0.5**
FPG (mg/dL)	158±26	155±24	152±22*	146±18**
PPG (mg/dL)	185±22	180±21	175±17*	168±15**
FPI (μU/mL)	25.8±5.8	24.9±5.6	23.8±5.4	22.2±5.2*
PPI (μU/mL)	67.2±8.8	62.5±8.5	58.7±8.3	57.5±8.1*
HOMA index	11.0±4.8	10.6±4.7	9.9±4.6	9.2±4.4*
SBP (mmHg)	133.8±4.1	132.7±3.9	131.5±3.8	130.1±3.6*
DBP (mmHg)	84.3±3.9	83.6±3.3	82.9±3.9	81.8±2.9*
HR (beats/min)	72±6	74±8	75±7	73±8

Data are means±SD; *$p<0.05$ *vs*. baseline; **$p<0.01$ *vs*. baseline. BMI, body mass index; HbA_{1c}, glycosylated hemoglobin; FPG, fasting plasma glucose; PPG, postprandial plasma glucose; FPI, fasting plasma insulin; PPI, postprandial plasma insulin; HOMA index, homeostasis model assessment index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate.

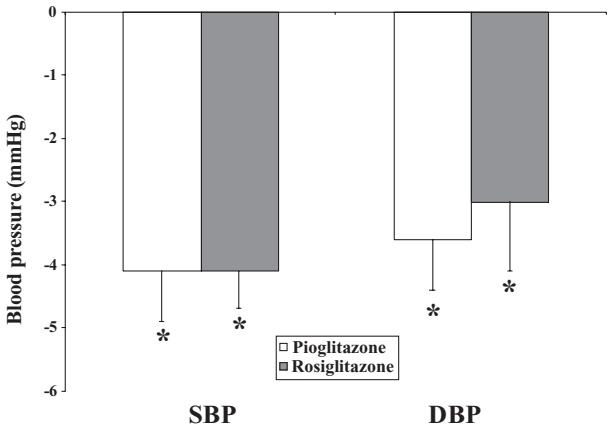

Fig. 2. *Change in SBP and DBP from baseline to 12 months in patients receiving pioglitazone or rosiglitazone. Values are means±SD. *p<0.05, change from baseline. SBP, systolic blood pressure; DBP, diastolic blood pressure.*

reported in detail in Tables 4 and 5.

Glycemic Control

No HbA_{1c} change was observed after 3 or 6 months in both groups, while significant HbA_{1c} decreases were obtained after 9 ($p<0.05$) and 12 ($p<0.01$) months in both groups. No significant FPG or PPG variation was present at 3 or 6 months in both groups. After 9 and 12 months, mean FPG and PPG levels were significantly decreased in both groups ($p<0.05$ and $p<0.01$, respectively) (Tables 4 and 5). Fasting plasma insulin and PPI did not show any significant change after 3 or 6 months, while significant decreases were observed at 9 and 12 months ($p<0.05$ and $p<0.01$, respectively) compared to the baseline values in both groups. Furthermore, the HOMA index was improved only at 12 months ($p<0.05$) compared to the baseline values in both groups.

Blood Pressure Effects

No SBP or DBP change was obtained in either group after 3, 6 or 9 months. Significant SBP and DBP improvement ($p<0.05$, respectively) was present in both groups after 12 months compared to the baseline values (Fig. 2). No significant HR variation was obtained during the study in either group (Tables 4 and 5).

Inflammation Markers

hs-CRP, nitrites/nitrates and ADN changed significantly ($p<0.05$, respectively) in both groups compared to the baseline values after 12 months (Table 6).

Tolerability

Of the 96 patients who completed the study, 8.3% (4/48) of those in the pioglitazone group and 10.4% (5/48) of those in the rosiglitazone group had side effects (not significant). In the pioglitazone group, 2 patients had aspartate aminotransferase (AST) and alanine aminotransferase (ALT) values that increased to 1.5 times the upper limit of normal (<40 U/L), but these values had regressed after 15 days to within normal limits; 2 patients reported transient headache (only for 7 days from the start of therapy). In the rosiglitazone group, 3 patients had AST and ALT values that increased to 2.0 times the upper limit of normal (<40 U/L), but these values had regressed after 15 days to within normal limits; 2 patients reported transient headache (only for 3 days from the start of therapy).

There were no statistically significant changes in transaminases; AST and ALT values were 22±6 and 24±8 U/L at

Table 6. hs-CRP, Nitrites/Nitrates, and ADN Data at Baseline, and after 12 Months in Pioglitazone and Rosiglitazone Groups

	Pioglitazone+metformin		Rosiglitazone+metformin	
	Baseline	12 months	Baseline	12 months
hs-CRP (mg/dL)	0.66±0.25	0.38±0.10*	0.68±0.26	0.41±0.11*
Nitrites/nitrates (μmol/L)	12.21±2.96	28.75±4.53*	11.46±2.73	27.68±4.12*
ADN (μg/mL)	5.7±2.3	6.9±2.9*	5.9±2.4	7.1±3.0*

Data are means±SD; *$p<0.05$ *vs*. baseline. hs-CRP, high sensitivity C-reactive protein; ADN, adiponectin; nitrites/nitrates, stable metabolites of NO.

baseline and 25±8 and 26±9 U/L, respectively, at 12 months in the pioglitazone group, whereas in the rosiglitazone group AST and ALT values were 23±8 and 25±9 U/L at baseline and 25±9 and 27±10 U/L at 12 months, respectively.

Discussion

The third report of the NCEP Adult Treatment Panel III has defined diabetes as a coronary heart disease risk equivalent (*14*). Blood hypertension, hypercholesterolemia and hypo-HDLemia exponentially increase the cardiovascular risk profile of type 2 diabetic patients, among whom these risk factors are highly prevalent. On the other hand, intensive treatment of all modifiable risk factors significantly improves the prognosis of these patients (*3*). In particular, an adequate antihypertensive treatment has recently been suggested to be the best means by which to prevent cardiovascular disease in diabetic subjects (*23*), as it is more effective than tight glycemic control (*1*).

To the best of our knowledge, this is the first study to comparatively evaluate the long-term effects of thiazolidinediones on blood pressure control and on inflammation markers of type 2 diabetic subjects treated with metformin.

The beneficial effect of thiazolidinediones on glycemic control in diabetic subjects was already known (*24*, *25*) and was further confirmed by our actual study: the association of metformin with both pioglitazone and rosiglitazone significantly improved glycemic control in the studied subjects: we observed mean improvements of 16.5% in HbA_{1c} plasma level ($p<0.01$), 13.3% in FPG ($p<0.01$), 14.1% in PPG ($p<0.01$) and 23.2% in PPI ($p<0.05$), with no significant differences between treatment groups. We confirmed the findings of previous studies (*21*, *22*) that pioglitazone appears to have a better effect on plasma lipid levels (total cholesterol [TC]=−9.8%, low-density lipoprotein cholesterol [LDL-C]=−6.9%, high-density lipoprotein cholesterol [HDL-C]=+9.1%, TG=−25.0%) than rosiglitazone (TC=+4.2%, LDL-C=+2.6%, TG=+1.7%).

Regarding the main subject of this report, in a previous report by our research group we observed that pioglitazone and rosigliazone combined with glymepiride caused a significant improvement in both SBP and DBP in subjects affected by metabolic syndrome (*26*). Similar results were found in the present study: slight but statistically significant reductions in both SBP and DBP levels were detected in both the rosiglitazone- and pioglitazone-treated groups, while no significant change in HR was registered. In this study we similarly observed mean reductions of 3% in SBP and 3.8% in DBP, without significant differences between the two treatment groups. The antihypertensive effect of thiazolinediones appears related mainly to the decrease in insulin-resistance and the consequent improvement of endothelial function, as demonstrated by the improvement of the related parameters of inflammation (*27*, *28*). We think that the observed effects are linked solely to the action of the thiazolidinediones, because metformin use is not associated with significant change in blood pressure (*29*).

Based on our results, we can conclude that the combination of a thiazolinedione with metformin for the treatment of type 2 diabetic subjects is associated with a slight but significant improvement in the long-term blood pressure control of these patients, and to an improvement in the anti-inflammatory state, in relation to a similar reduction in insulin-resistance. The choice of the best molecule to prescribe has to be driven by the drug effects on other parameters, such as plasma lipid levels and prothrombotic risk factors.

References

1. Beckman JA, Creager MA, Libby P: Diabetes and atherosclerosis. Epidemiology, Pathophysiology, and Management. *JAMA* 2002; **287**: 2570–2581.
2. Clarke PM, Gray AM, Briggs A, Stevens RJ, Matthews DR, Holman R: Cost-utility analyses of intensive blood glucose and tight blood pressure control in type 2 diabetes (UKPDS 72). *Diabetologia* 2005; **48**: 868–877.
3. Expert Committee on the Diagnosis and Classification of Diabetes Mellitus: American Diabetes Association: Clinical practice recommendations 2002. *Diabetes Care* 2002; **25** (Suppl 1): S1–S147.
4. Charpentier G, Fleury F, Kabir M, Vaur L, Halimi S: Improved glycaemic control by addition of glimepiride to metformin monotherapy in type 2 diabetic patients. *Diabet Med* 2001; **18**: 828–834.
5. Riddle M: Combining sulfonylureas and other oral agents. *Am J Med* 2000; **108** (Suppl 6a): 15S–22S.
6. Vague P: Is metformin more than an oral hypoglycaemic agent? *Diabetes Metab* 2003; **29**: 6S5–6S7.
7. Johnson JA, Simpson SH, Majumdar SR, Toth EL:

Decreased mortality associated with the use of metformin compared with sulphanylurea monotherapy in type 2 diabetes. *Diabetes Care* 2002; **25**: 2244–2248.
8. UK Prospective Diabetes Study (UKPDS) Group: Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes. *Lancet* 1998; **253**: 854–865.
9. The Diabetes Prevention Program Research Group: Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 2002; **346**: 393–403.
10. Ovalle F, Ovalle-Berúmen JF: Thiazolidinediones: a review of their benefits and risks. *South Med J* 2002; **95**: 1188–1194.
11. Charbonnel B, Schernthaner G, Brunetti P, *et al*: Long-term efficacy and tolerability of add-on pioglitazone therapy to failing monotherapy compared with addition of gliclazide or metformin in patients with type 2 diabetes. *Diabetologia* 2005; **48**: 1093–1104.
12. Mooradian AD, Chehade J, Thurman JE: The role of thiazolidinediones in the treatment of patients with type 2 diabetes mellitus. *Treat Endocrinol* 2002; **1**: 13–20.
13. American Diabetes Association: Screening for diabetes (Position Statement). *Diabetes Care* 2001; **24** (Suppl): S21–S24.
14. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults: Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA* 2001; **285**: 2486–2497.
15. 1999 World Health Organization–International Society of Hypertension Guidelines for the Management of Hypertension: Guidelines Subcommittee. *J Hypertens* 1999; **17**: 151–183.
16. World Health Organization: Obesity: Preventing and Managing the Global Epidemic. Report of WHO Consultation on Obesity. Geneva, WHO, 1997.
17. American Diabetes Association: Nutrition recommendations and principles for people with diabetes mellitus (Position Statement). *Diabetes Care* 2001; **24** (Suppl): S44–S47.
18. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC: Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 1985; **28**: 412–419.
19. Rifai N, Tracy RP, Ridker PM: Clinical efficacy of an automated high-sensitivity C-reactive protein assay. *Clin Chem* 1999; **45**: 2136–2141.
20. Green LC, Wagner DA, Glogowski L, *et al*: Analysis of nitrate, nitrite and [^{15}N]nitrate in biological fluids. *Anal Biochem* 1982; **126**: 131–138.
21. Yamauchi T, Kamon J, Waki H, *et al*: The fat-derived hormone adiponectin reverses insulin resistance associated with both lipoatrophy and obesity. *Nat Med* 2001; **7**: 941–946.
22. Winer BJ: Statistical Principles in Experimental Design, 2nd ed. New York, McGraw-Hill, 1971.
23. Mancia G: The association of hypertension and diabetes: prevalence, cardiovascular risk and protection by blood pressure reduction. *Acta Diabetol* 2005; **42** (Suppl 1): S17–S25.
24. Boyle PJ, King AB, Olansky L, *et al*: Effects of pioglitazone and rosiglitazone on blood lipid levels and glycemic control in patients with type 2 diabetes mellitus: a retrospective review of randomly selected medical records. *Clin Ther* 2002; **24**: 378–396.
25. Derosa G, Cicero AF, Gaddi A, *et al*: Metabolic effects of pioglitazone and rosiglitazone in patients with diabetes and metabolic syndrome treated with glimepiride: a twelve-month, multicenter, double-blind, randomized, controlled, parallel-group trial. *Clin Ther* 2004; **26**: 744–754.
26. Derosa G, Cicero AFG, D'Angelo A, *et al*: Thiazolidinedione effects on blood pressure in diabetic patients with metabolic syndrome treated with glimepiride. *Hypertens Res* 2005; **28**: 917–924.
27. Shargorodsky M, Wainstein G, Gavish E, Leibovitz Z, Matas D, Zimlichman R: Treatment with rosiglitazone reduces hyperinsulinemia and improves arterial elasticity in patients with type 2 diabetes mellitus. *Am J Hypertens* 2003; **16**: 617–622.
28. Fullert S, Schneider F, Haak E, *et al*: Effects of pioglitazone in nondiabetic patients with arterial hypertension: a double-blind, placebo-controlled study. *J Clin Endocrinol Metab* 2002; **87**: 5503–5506.
29. Granberry MC, Fonseca VA: Cardiovascular risk factors associated with insulin resistance: effects of oral antidiabetic agents. *Am J Cardiovasc Drugs* 2005; **5**: 201–209.