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RESEARCH ARTICLE

Long-term therapy with addition of pioglitazone to metformin compared with the addition of gliclazide to metformin in patients with type 2 diabetes: a randomized, comparative study

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Abstract

Background This 52-week, randomized, double-blind study compared the efficacy and safety of metformin plus pioglitazone with the established combination of metformin plus gliclazide in type 2 diabetes mellitus.

Methods Patients with poorly controlled type 2 diabetes ($HbA_{1c} \geq 7.5\%$ to $\leq 11.0\%$) received either pioglitazone 15 mg o.d. (titrated up to 45 mg; $n = 317$) or gliclazide 80 mg o.d. (titrated up to 320 mg; $n = 313$) and metformin at the pre-study dose. HbA_{1c}, fasting plasma glucose (FPG), insulin, lipids and the urinary albumin/creatinine ratio were measured.

Results There were no significant differences in HbA_{1c} (1% decrease in both groups) and FPG between groups. There was a decrease in fasting insulin in the pioglitazone group compared to an increase in the gliclazide group ($p < 0.001$). There were significantly greater improvements in triglycerides and HDL-cholesterol in the metformin plus pioglitazone group compared to the metformin plus gliclazide group ($p < 0.001$). Mean LDL-cholesterol decreased with metformin plus gliclazide and increased with metformin plus pioglitazone ($p < 0.001$); however, this increase was considerably less marked than that in HDL-cholesterol. The mean urinary albumin/creatinine ratio was reduced by 10% in the metformin plus pioglitazone group compared to an increase of 6% in the metformin plus gliclazide group ($p = 0.027$). The incidence of adverse events was comparable between groups and both combinations were well tolerated.

Conclusions Compared to the established combination of metformin plus gliclazide, this study indicates potential benefits of addition of pioglitazone to metformin in terms of improvements in microalbuminuria and specific abnormalities associated with diabetic dyslipidemia.

Keywords combination; efficacy; long-term; metformin; pioglitazone; type 2 diabetes

Introduction

Pioglitazone is a thiazolidinedione (TZD), a class of drugs recently developed for the treatment of type 2 diabetes. TZDs have a different mechanism of

action from other glucose-lowering agents and are believed to exert their effect by binding to and modifying transcriptional activity of nuclear peroxisome proliferator-activated receptors-γ (PPARγ) that are involved in the regulation of carbohydrate and lipid metabolism [1,2]. Insulin resistance is reduced and glucose disposal in peripheral tissue is enhanced, thereby reducing levels of blood glucose [3,4]. Pioglitazone also suppresses gluconeogenesis in the liver and reduces lipolysis in the adipose tissue. In support of the growing evidence in animal models of diabetes, a recent study in patients with type 2 diabetes suggested that TZDs may have a β-cell sparing effect [5]. In placebo-controlled clinical trials, pioglitazone as monotherapy has been shown to improve glycaemic control, significantly reducing both glycosylated haemoglobin (HbA_{1c}) and fasting plasma glucose (FPG) from baseline [6,7].

Type 2 diabetes is a progressive disease, involving increasing progressive loss of β-cell function with time [8]. The widely used insulin secretagogues, for example, sulphonylureas, that stimulate insulin output from pancreatic β-cells, may be effective as initial therapy, but glycaemic control tends to deteriorate during long-term treatment [9]. Sulphonylureas are associated with a long-term failure rate of approximately 5 to 7% per year [9–12] and combination therapy is then needed to maintain treatment efficacy. Metformin, which acts primarily in the liver to reduce endogenous glucose production [13], in combination with sulphonylurea, is often a successful approach in poorly controlled type 2 diabetes [14–17].

Pioglitazone has proven efficacy in combination with either sulphonylureas or metformin. Previous placebo-controlled studies have shown significant decreases in HbA_{1c} and FPG over a 16-week treatment period compared to sulphonylurea or metformin alone [18,19]. The studies also demonstrated significant decreases in triglycerides and increases in HDL-cholesterol. To date, however, a comparison of the combination of metformin plus pioglitazone with the established combination of metformin plus sulphonylurea has not been conducted. The current study assessed the long-term efficacy, safety and tolerability of add-on therapy of pioglitazone, compared with addition of sulphonylurea, to continued metformin in patients with type 2 diabetes inadequately controlled with metformin alone. As one of the most commonly prescribed sulphonylureas, gliclazide was chosen as the comparator.

Methods

Patients

Patients were enrolled into this double-blind, parallel-group, double-dummy study from 75 centres in nine European countries and Australia. Ethics Committee approval was obtained for each study site and the investigators were either general practitioners or specialists in internal medicine/endocrinology. Patients gave written informed consent before enrolment, and the study was conducted according to the Declaration of Helsinki and the requirements of Good Clinical Practice of the European Community.

Male and female patients with type 2 diabetes, inadequately managed with metformin alone (at $\geq$50% of the maximum recommended dose or at the maximum tolerated dose for $\geq$3 months), were screened. Entry criteria included the following: age between 35 and 75 years, inclusive; HbA_{1c} of $\geq$7.5% or $\leq$11.0%; fasting C-peptide of $\geq$1.5 ng/mL (0.50 nmol/L) and stable or worsening glycaemic control for $\geq$3 months prior to screening. Exclusions included patients with type 1 diabetes; ketoacidosis, myocardial infarction, transient ischaemic attacks or stroke in the previous 6 months; symptomatic heart failure; acute malabsorption or chronic pancreatitis; familial polyposis coli; malignant disease in the previous 10 years 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 insulin, gliclazide, pioglitazone or other sulphonylureas or TZDs was not permitted. During the study, thiazides were allowed to treat oedema, and if antihypertensive treatment was indicated, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor antagonists or calcium antagonists were given.

Study design

The 52-week study period was divided into a 16-week forced dose-titration phase and a 36-week maintenance phase. Eligible patients were randomized to either pioglitazone 15 mg o.d. ($n = 317$) or gliclazide 80 mg o.d. ($n = 313$), plus metformin at their pre-study dose. The pioglitazone dose was titrated to 30 mg and 45 mg and the gliclazide dose to 160 mg, 240 mg (160 mg and 80 mg) and 320 mg (160 mg b.d.). Cessation of titration or down-titration was permitted only on the basis of tolerability issues, including actual hypoglycaemia or increased risk of hypoglycaemia. Patients continued to the next dose level, unless the investigator considered that the increase could put them at risk of hypoglycaemia (increase postponed for one visit from Week 4 or Week 8 or Week-8 dose maintained for rest of study), or the patient reported symptomatic hypoglycaemia (1-step reduction) or if the patient experienced adverse events that required dose reduction (1-step reduction at Week 8, 12 or 16 with no further down-titration). The dose achieved at Week 16 was maintained for the remaining 36 weeks. No decrease in metformin dose from pre-study level was permitted.

Dietary advice was given at baseline with the target of body weight normalization. Patients were instructed to adhere to a disease- and body weight–orientated diet for the entire course of the study and were supplied with individually appropriate calories and nutrients. If the body weight increased by more than 5% during treatment or

HbA_{1c} increased to greater than 9% after completed dose titration, patients were given further intensive dietary advice.

The primary efficacy measure was the change in HbA_{1c} from baseline to Week 52. Changes in FPG, insulin, lipids, C-peptide, 32,33 split pro-insulin and urinary albumin and creatinine (to determine the albumin/creatinine ratio) were measured as secondary endpoints. Measurements of HbA_{1c}, FPG and insulin were made at baseline and at Weeks 4, 8, 12, 16, 24, 32, 42 and 52. Lipids (triglycerides, HDL-cholesterol, LDL-cholesterol and total cholesterol) 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: HDL-cholesterol ratio) as an index of LDL particle size [20]. Urinary albumin and creatinine were measured at baseline and at Weeks 24, 32, 42 and 52. At selected centres, C-peptide and 32,33 split pro-insulin were measured at baseline and at Weeks 24, 42 and 52.

Adverse events were recorded throughout the study. Safety and tolerability were also evaluated by regular measurement of body weight, waist circumference, blood pressure, pulse rate and standard haematology and clinical chemistry laboratory safety tests, and a physical examination was performed at baseline and at Week 52.

Statistical methods

Sample size was based on demonstrating a between-group difference of 0.35% in the change in HbA_{1c} from baseline to Week 52 (the primary efficacy variable) using a two-sided t-test. A total of 225 patients/group completing at least 24 weeks of the study was required, on the basis of a level of 95% power at 5% significance.

The change in HbA_{1c} was determined using an ANCOVA model with the factor 'treatment' and baseline value as covariate. The difference between adjusted means was calculated with 95% CIs, and a two-sided t-test ($\alpha = 0.05$) was performed. The analysis was carried out on the intention-to-treat (ITT) population, which included all patients who had taken at least one dose of study medication and had HbA_{1c} recorded at baseline and at least once post-baseline. Other efficacy variables were analysed in a similar way. Lipids and urinary albumin/creatinine ratio results were also log-transformed before analysis, as certain data were not normally distributed. LDL-cholesterol was calculated using Friedewald's formula.

All patients who had taken 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. Haematology and biochemistry results were summarized as mean change from baseline, and patients with critically abnormal values were identified. Descriptive statistics were used to summarize changes in body weight, demographics, laboratory variables, baseline characteristics and adverse events.

Results

A total of 630 patients received study treatment ($n = 317$ with metformin plus pioglitazone; $n = 313$ with metformin plus gliclazide). Ten patients were not eligible for the ITT population due to missing HbA_{1c} data. The treatment groups were well matched at baseline (Table 1).

At the end of the 16-week dose-titration period, 70% of patients receiving metformin plus pioglitazone had been titrated to the maximum pioglitazone dose (45 mg o.d.). In the metformin plus gliclazide group, 33% of patients were receiving the maximum gliclazide dose of 320 mg/day. The mean daily doses of study

Table 1. Demographic and baseline characteristics: safety population

		Metformin + Pioglitazone ($N = 317$)	Metformin + Gliclazide ($N = 313$)
Sex	Male	161 (50.8%)	154 (49.2%)
	Female	156 (49.2%)	159 (50.8%)
Race	Caucasian	315 (99.4%)	313 (100%)
	Oriental	2 (0.6%)	0
Age (years ± SD) [range]		56 ± 9.2 [35–74]	57 ± 9.0 [34–75]
Weight (kg ± SD) [range]		91.8 ± 16.2 [54–156]	92.7 ± 17.4 [45–162]
BMI (kg/m^2 ± SD) [range]		32.6 ± 5.0 [22.7–52.3]	32.6 ± 5.8 [20.0–58.7]
Waist circumference (cm ± SD)		107 ± 12.0	106 ± 12.8
Duration of diabetes (years ± SD) [range]		5.8 ± 5.1 [0.2–30.9]	5.5 ± 5.1 [0.2–34.7]
Metformin dose (mg/day) [range]		1726 [500–3000]	1705 [500–3000]
HbA_{1c} (% ± SD) [range]		8.71 ± 1.00 [6.6–12.1]	8.53 ± 0.89 [6.9–11.3]
FPG (mmol/L ± SD) [range]		11.8 ± 3.1 [5.4–25.0]	11.3 ± 2.6 [5.8–20.9]
Triglycerides (mmol/L)		2.90 ± 1.94	2.78 ± 1.89
HDL-cholesterol (mmol/L)		1.10 ± 0.25	1.09 ± 0.23
LDL-cholesterol (mmol/L)		3.34 ± 0.98	3.28 ± 0.93
Total cholesterol (mmol/L)		5.64 ± 1.14	5.58 ± 1.15
Urinary albumin/creatinine ratio (mg/mmol)		0.06 ± 0.14	0.05 ± 0.16
Fasting insulin (μIU/mL)		15.3 ± 11.70	15.0 ± 10.07
C-peptide (ng/mL)		3.7 ± 1.40	3.7 ± 1.51

All data are given as mean ± SD.

medication at Week 16 were 39-mg pioglitazone and 212-mg gliclazide. In the metformin plus pioglitazone group, 82.3% completed the 52-week study, and in the metformin plus gliclazide group, 86.6% completed the 52-week study. Thirteen patients (4.1%) in the metformin plus pioglitazone group and 14 (4.5%) in the metformin plus gliclazide group discontinued because of adverse events. Mean duration of treatment was 11 months in both groups.

All data are from the ITT population, unless otherwise specified. At the end of 52 weeks, there was a comparable mean reduction in HbA_{1c} (0.99% in the metformin plus pioglitazone group and 1.01% in the metformin plus gliclazide group) and there was no statistically significant between-group difference (95%CI:−0.15%, 0.19%; $p = 0.837$). The maximum decrease in HbA_{1c} was reached at 24 weeks in the metformin plus pioglitazone group and 16 weeks in the metformin plus gliclazide group. With metformin plus pioglitazone, the improvement in HbA_{1c} control was maintained until the end of the study; however, with metformin plus gliclazide, there was a continual deterioration in the control from the maximum at Week 16 over the remaining treatment period (Figure 1).

Mean FPG was also reduced from baseline to Week 52 by a comparable amount in both groups, with decreases of 2.1 mmol/L (adjusted mean change of 1.9 mmol/L; −34.2 mg/dL) in the metformin plus pioglitazone group and 1.6 mmol/L (adjusted mean change of 1.7 mmol/L; −30.6 mg/dL) in the metformin plus gliclazide group (95%CI: −0.6, 0.3; $p = 0.506$). In the metformin plus pioglitazone group, the maximum mean decrease in FPG was achieved at Week 16 and remained relatively unchanged for the remainder of the 52-week period. With metformin plus gliclazide, the maximum decrease was seen at Week 8, but this was followed, from Week 32, by a deterioration of FPG response (Figure 1).

Changes in lipids are shown in Figure 2 as log-transformed data. Treatment with metformin plus pioglitazone resulted in a decrease from baseline triglyceride levels of 0.60 mmol/L (53.1 mg/dL; correlating with an 18% reduction using log-transformed data) and a mean increase in HDL-cholesterol of 0.18 mmol/L (6.9 mg/dL; 16% log-transformed data) at Week 52. Changes following treatment with metformin plus gliclazide were less marked; there was a 0.22 mmol/L (19.5 mg/dL; −7% log-transformed data) decrease in triglycerides and no change in HDL-cholesterol. The differences between groups were statistically significant ($p < 0.001$; log-transformed data). Metformin plus pioglitazone treatment was associated with a mean increase in LDL-cholesterol of 0.27 mmol/L (10.4 mg/dL; 8% log-transformed data) compared to a decrease of 0.11 mmol/L (4.2 mg/dL; −3% log-transformed data) in LDL-cholesterol with metformin plus gliclazide treatment ($p < 0.001$; log-transformed data). The mean total cholesterol/HDL-cholesterol ratio was reduced with both treatments: 10% for metformin plus pioglitazone (ratio reduction of 0.53), and 4% decrease for metformin plus gliclazide (ratio reduction of 0.20; $p < 0.001$; log-transformed data). The AIP showed larger decreases with metformin plus pioglitazone than with metformin plus gliclazide (0.36 and 0.06, respectively; $p = 0.001$).

As an add-on therapy to metformin, pioglitazone caused a mean decrease of 3.5 μIU/mL in fasting insulin from baseline to Week 52 compared to an increase of 1.1 μIU/mL when gliclazide was added to metformin ($p < 0.001$). A similar pattern was seen with C-peptide and 32,33 split pro-insulin. There was a mean decrease in C-peptide from baseline of 0.3 ng/mL in the metformin plus pioglitazone group ($n = 97$) and a mean increase from baseline of 0.3 ng/mL in the metformin plus gliclazide group ($n = 111$; $p < 0.001$). In addition, 32,33 split pro-insulin was reduced from baseline to Week 52 with metformin plus pioglitazone (−8.0 pmol/L; $n = 168$) and was increased slightly with metformin plus gliclazide (0.5 pmol/L; $n = 166$; $p < 0.001$).

At Week 52, the mean urinary albumin/creatinine ratio was reduced from baseline with metformin plus pioglitazone (10%) and increased with metformin plus gliclazide (6%; $p = 0.027$; log-transformed data).

Adverse events occurred in similar proportions of patients in both treatment groups: 55.5% ($n = 176$; with a total of 533 events, of which 140 were study-related) in the metformin plus pioglitazone group and 58.1%

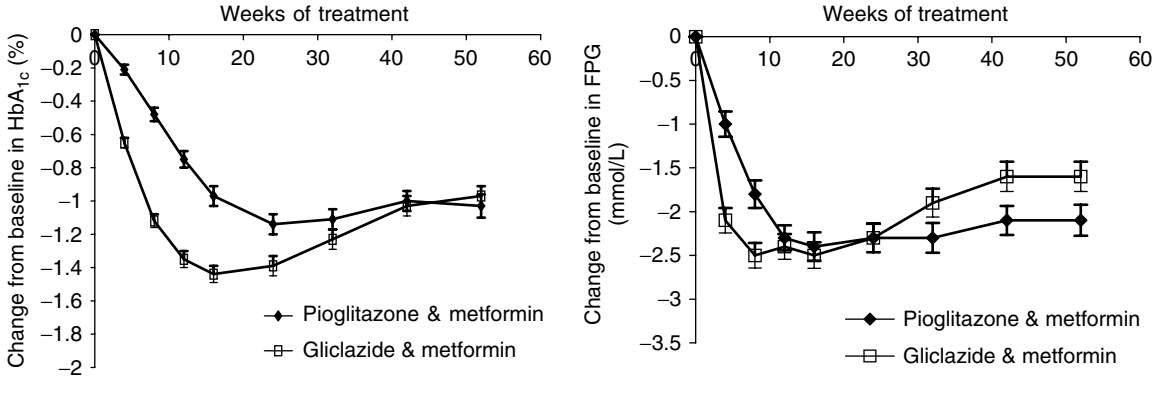

Figure 1. Time course of mean change from baseline to last value (LOCF analysis) for HbA_{1c}(%) and FPG (mmol/L): intention-to-treat population

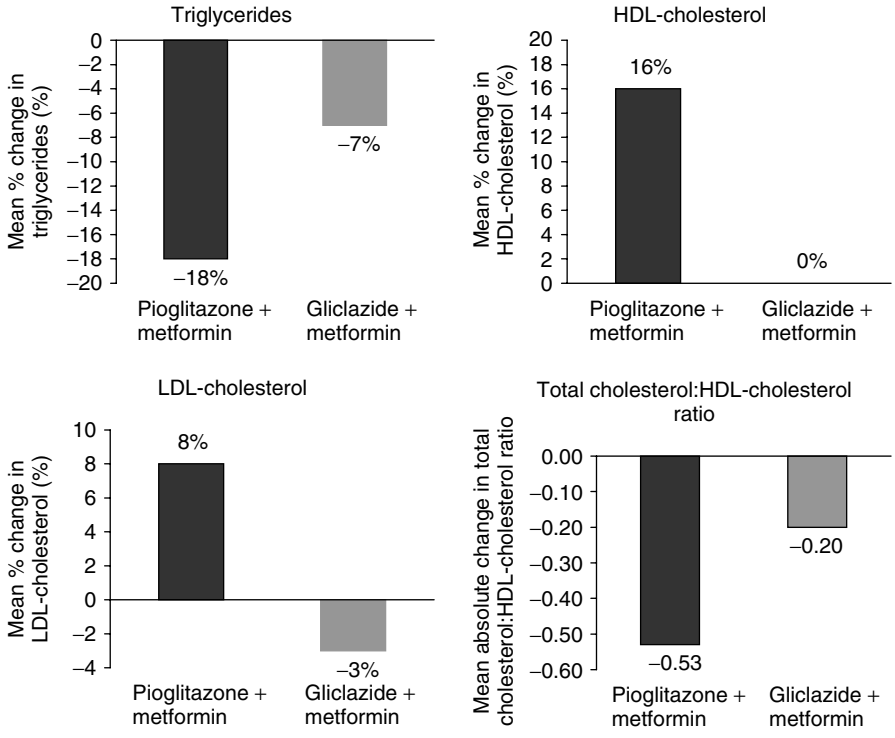

Figure 2. Change from baseline to last value (LOCF analysis) for triglycerides, HDL-cholesterol, LDL-cholesterol and total cholesterol: intention-to-treat population. Treatments compared using adjusted mean ratios from baseline (pioglitazone/gliclazide) with baseline values as covariates and based on log-transformed data: $p < 0.001$

($n = 182$; with a total of 628 events, of which 210 were study-related) in the metformin plus gliclazide group. The majority of adverse events were mild to moderate. The incidence of serious adverse events was higher in the metformin plus gliclazide group (27 events in 20 patients) than in the metformin plus pioglitazone group (17 events in 15 patients). Two patients in the metformin plus gliclazide group died during the study (unrelated to medication).

Hypoglycaemia was the most commonly reported event and occurred more frequently in the metformin plus gliclazide group ($n = 35$; 11.2%) than in the metformin plus pioglitazone group ($n = 4$; 1.3%). None of the events was severe or serious. Two patients receiving metformin plus gliclazide were withdrawn following hypoglycaemic episodes. In the metformin plus pioglitazone group, the most commonly occurring event was oedema, reported for 20 patients (6.3%) versus 7 patients (2.2%) in the metformin plus gliclazide group. In the metformin plus pioglitazone group, oedema led to one patient being withdrawn from the study and two patients had pulmonary, but not peripheral, oedema (one unrelated to the study drug; the other was a serious adverse event associated with myocardial infarction and judged to be related to the study drug by the reporting investigator). The oedema was not associated with an increased incidence of heart failure. In addition, dizziness and vertigo were reported more frequently in the metformin plus pioglitazone group, and hypertension, arthralgia, diarrhoea, paraesthesia and dyspepsia were reported in the metformin plus gliclazide group.

There were mean increases in the body weight of 1.5 kg in the metformin plus pioglitazone group and 1.4 kg in the metformin plus gliclazide group, but no increase in waist measurement in either group. By Week 52, body weight in both groups appeared to have stabilized. There were no clinically relevant changes or between-group differences in blood pressure or pulse rate.

Liver enzymes (aspartate aminotransferase [AST]; gamma glutamyl transpeptidase [GGT]; alanine amino-transferase; alkaline phosphatase) showed consistent mean decreases from baseline, following treatment with metformin plus pioglitazone, with smaller mean changes in the metformin plus gliclazide group. Haemoglobin and haematocrit were reduced in both groups, with mean decreases of 6 g/L and 1.2% respectively in the metformin plus pioglitazone group, and 3 g/L and 0.5% respectively in the metformin plus gliclazide group.

Discussion

Treatment with pioglitazone as an add-on therapy to metformin provided improved glycaemic control over one year in patients whose diabetes had been inadequately controlled with metformin alone before entry into the study. When pioglitazone was added to metformin, the maximum decrease in HbA_{1c} was sustained through to the end of the study (1.0% decrease at Week 52). The decrease in HbA_{1c} at endpoint was clinically equivalent to that seen with metformin plus gliclazide (also ~1.0%); however, it was interesting to note that there was a

progressive, non-significant decline in the metformin plus gliclazide group (change of 0.46% from the nadir to Week 52), suggesting that there may be a deterioration in glycaemic control with the sulphonylurea.

Improvements in glycaemic control were also evident from decreases in FPG and post-load glucose levels. The decrease in FPG was similar in both groups at Week 52, but, as with HbA_{1c}, the improvement in FPG in the gliclazide group gradually deteriorated, whereas the positive effects on FPG of the addition of pioglitazone to existing metformin therapy were maintained more effectively over time. This effect on glycaemic control is possibly due, in part, to the study design, as the maximum dose of gliclazide was not achieved by the majority of patients, and also due to the differing mechanisms of action of the two add-on therapies – gliclazide acts by stimulating insulin output from β-cells, whereas pioglitazone reduces insulin resistance. Pioglitazone may provide sustained glycaemic control via a mechanism that is independent of stimulation of insulin release and that does not place any additional burden on failing β-cells [5].

In addition to the decreases in HbA_{1c} and FPG, metformin plus pioglitazone also reduced levels of fasting insulin, whereas treatment with metformin plus gliclazide caused increased insulin levels – again, probably due to the different mechanism of action of the two agents. Pioglitazone enhances the action of insulin mainly by promoting utilization of glucose in the peripheral tissues; so both fasting and postprandial blood glucose are lowered and insulin secretion is relatively unaffected. Gliclazide, however, acts by stimulating insulin secretion. It is possible that pioglitazone relieves the burden on the β-cells by inducing recovery of β-cell function [5], as reflected in this study by the decreases in levels of C-peptide and insulin precursor molecules. In comparison, these variables were increased from baseline in patients treated with metformin plus gliclazide, resulting in statistically significant between-group differences.

In the diabetic population, dyslipidemia is a significant risk factor for cardiovascular disease [21] and the importance of treating elevated triglycerides and reduced HDL-cholesterol has been identified [22]. Triglyceride levels have been shown to be a marker of heart disease in the presence of low rather than high levels of LDL-cholesterol [23], and hence the effect on triglycerides of adding gliclazide or pioglitazone to metformin is potentially more important in patients with type 2 diabetes. This study demonstrated significant improvements in global lipid profile with metformin plus pioglitazone. Triglyceride levels were decreased and HDL-cholesterol levels increased to a significantly greater extent in the metformin plus pioglitazone group than in the metformin plus gliclazide group. LDL-cholesterol levels were increased in the metformin plus pioglitazone group and decreased in the metformin plus gliclazide group, but to a much lesser magnitude than the changes observed with triglycerides and HDL-cholesterol. This is reflected in the improvements in total cholesterol/HDL-cholesterol ratio, which was statistically significantly better for metformin plus pioglitazone than for metformin plus gliclazide, indicating an overall improved lipid profile when pioglitazone is added to metformin, rather than the addition of gliclazide. The AIP showed a greater decrease with metformin plus pioglitazone compared to the metformin plus gliclazide combination therapy. Since AIP is inversely correlated with LDL particle size [20], the results imply a change in LDL particle size distribution to larger, less atherogenic forms [24,25]. This may be expected as insulin resistance and fasting insulin levels have been demonstrated to be related to the presence of smaller LDL particles and the use of an a insulin sensitizer associated with this qualitative shift in LDL composition [26].

Microalbuminuria is a well-known marker of cardiovascular risk [27]. In this study, the significantly greater decrease in urinary albumin/creatinine ratio with metformin plus pioglitazone treatment compared to an increase with metformin plus gliclazide, despite comparable numbers of patients receiving ACE inhibitors, suggests a further modification of a known cardiovascular risk factor.

Overall, metformin plus pioglitazone was generally well tolerated and the incidence of adverse events was similar to that for metformin plus gliclazide. The majority of adverse events were mild to moderate, with a higher incidence of serious adverse events in the metformin plus gliclazide group than in the metformin plus pioglitazone group. The adverse event profiles differed between the two treatment groups, with respect to hypoglycaemia and oedema. Mean weight gain over 52 weeks was similar in both groups and plateaued by the end of the study.

No negative effects were seen on variables associated with the liver function, and liver tests showed consistently greater improvements with metformin plus pioglitazone than with metformin plus gliclazide during the course of the study. The reductions in liver function tests (AST, ALT, alkaline phosphatase, GGT) observed with metformin plus pioglitazone may be a reflection of reduction of hepatic fat content, which is elevated in many patients with type 2 diabetes [28–30]. There were decreases in haemoglobin and haematocrit, which have been observed in previous studies of pioglitazone [6,18]. Decreases in these variables were also seen in the metformin plus gliclazide group, although the magnitude was smaller.

In summary, the addition of pioglitazone to metformin therapy provided an effective and well-tolerated treatment for patients with inadequately controlled type 2 diabetes. At endpoint, there were similar improvements in glycaemic control when pioglitazone was added to metformin compared to that with gliclazide addition. Although not a specific endpoint, it was noted that the improvements in HbA_{1c} and FPG were maintained over the 52-week period with pioglitazone add-on therapy, whereas when gliclazide was added to metformin, there was a deterioration in both HbA_{1c} and FPG control. There were also beneficial effects on lipids that were specific to pioglitazone addition to metformin, rather than as secondary effects on glycaemic control. Pioglitazone, as an

add-on therapy to metformin in patients with type 2 diabetes inadequately controlled with metformin alone, is an effective and well-tolerated combination for the treatment of type 2 diabetes.

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