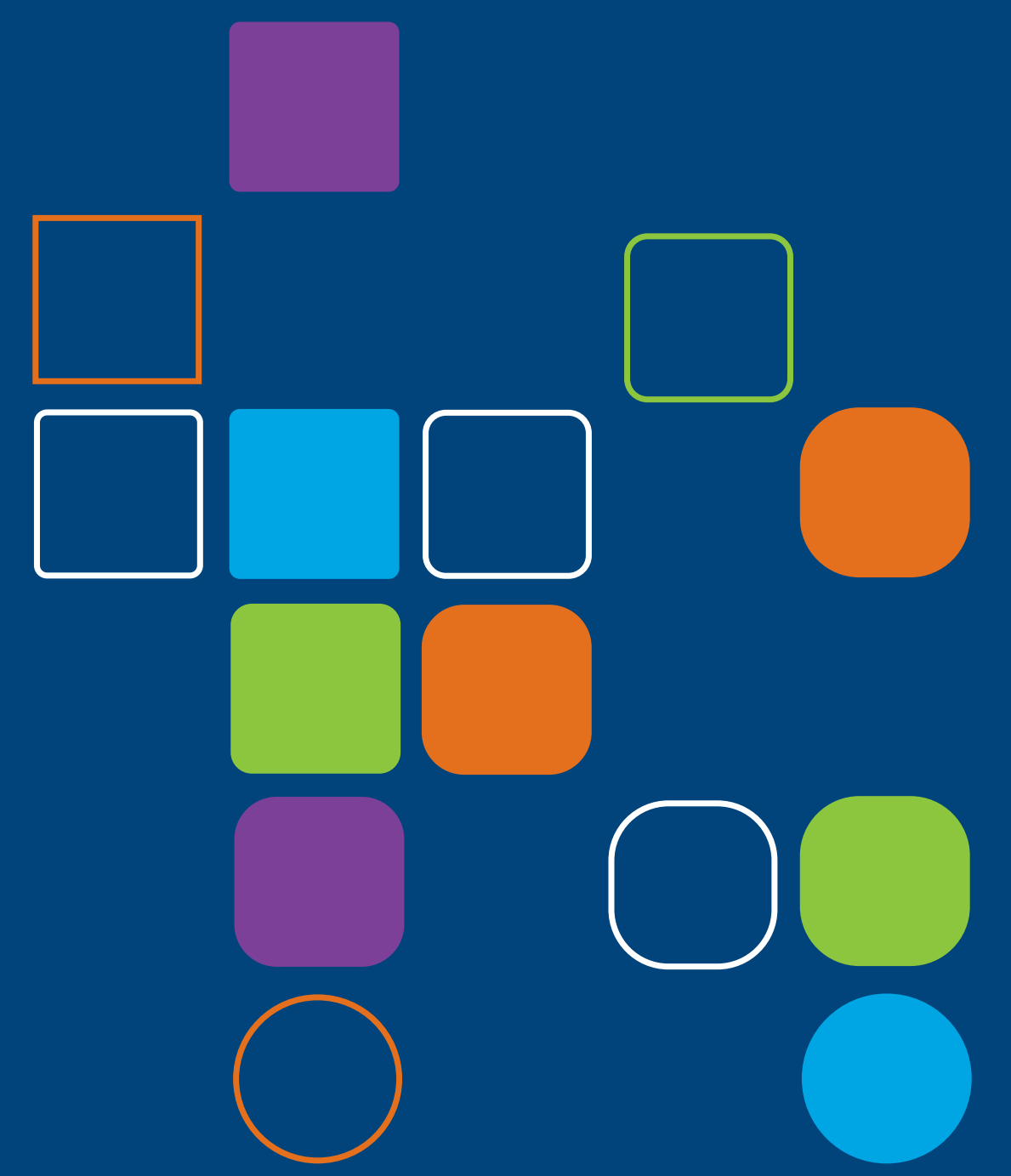


Pioglitazone Add-on to Either Metformin or Sulphonylurea: Glycaemic Results from PROactive



Bernard Charbonnel¹, Kare Birkeland², André Scheen³ on behalf of the PROactive investigators.
¹Nantes, France; ²Oslo, Norway; ³Liege, Belgium

ABSTRACT

Aims: Although glucose-lowering monotherapy initially improves glycaemic control, many patients with type 2 diabetes experience a progressive deterioration in control and need multiple agents. We assessed glycaemic effects of pioglitazone when added to metformin or sulphonylurea (SU) monotherapy in patients from PROactive (mean follow-up=34.5 months).

Methods: Patients were randomised to pioglitazone (force-titrated up to 45mg) or placebo, in addition to other glucose-lowering medication. Baseline HbA_{1c} values were similar between the metformin (n=514) and SU (n=1001) groups.

Results: Significantly greater reductions in HbA_{1c} were noted with pioglitazone compared with placebo (mean differences of 0.57%, 0.53%, 0.51% and 0.56% at 6, 12, 24 months and final visit, respectively [add-on to metformin] and 0.65%, 0.68%, 0.50% and 0.55% at 6, 12, 24 months and final visit, respectively [add-on to SU]; P<0.0001 at all timepoints). In the metformin group, fewer pioglitazone patients switched to or added SU (16%) or insulin (3%) to their monotherapy regimen than placebo-treated patients (29% and 6%, respectively). The mean daily dose of metformin increased to a lesser extent in the pioglitazone group (168mg vs 242mg with placebo, P=0.221). In the SU cohort, fewer pioglitazone-treated patients switched to or added metformin (15%) or insulin (6%) than placebo-treated patients (30% and 15%, respectively). Mean daily doses of the main SUs (glibenclamide, gliclazide and glimepiride) had decreased in the pioglitazone group relative to the placebo group at final visit.

Hypoglycaemia occurred in 8% of the pioglitazone+metformin and 21% of the pioglitazone+SU groups vs 13% of the placebo+metformin and 13% of the placebo+SU groups. In the pioglitazone groups, there were weight increases of 3.9kg (metformin) and 2.6kg (SU) vs decreases of 1.3kg in both of the placebo groups.

Conclusions: Intensifying a monotherapy to a dual therapy regimen by adding pioglitazone resulted in sustained glycaemic control and a reduced need for insulin.

INTRODUCTION

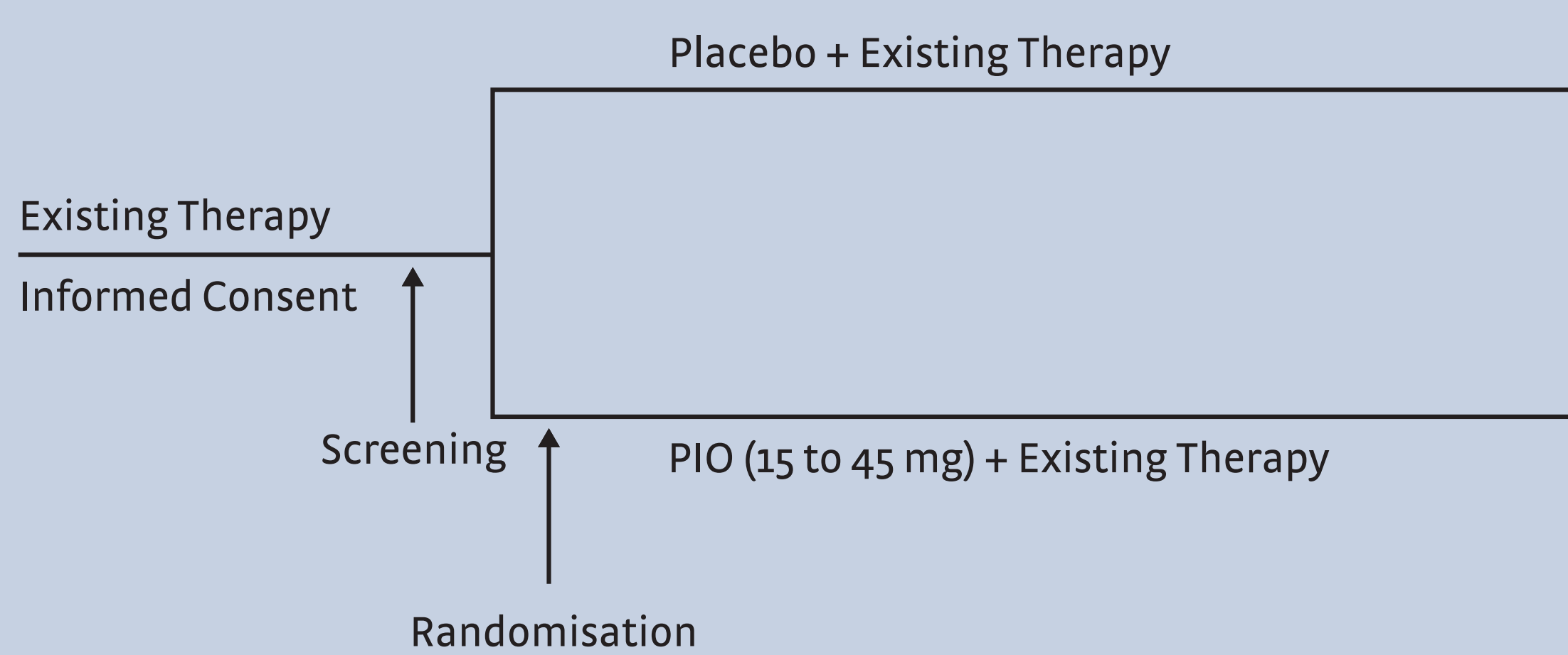
Although glucose-lowering therapies are initially effective in improving glycaemic control, monotherapy with metformin or a sulphonylurea eventually fails over the long-term due to a continuous decline in beta-cell function, resulting in a progressive deterioration in glycaemic control over time [1-3]. Therefore, patients will have an increased need for dual therapies to overcome such monotherapy failure. In fact, it has been estimated that within 3 years of initiation of glucose-lowering monotherapy, 50% of patients will be on a second agent [2]. The combination of glucose-lowering agents that simultaneously target the three main metabolic abnormalities of type 2 diabetes mellitus, such as sulphonylureas that promote insulin secretion, metformin that inhibits hepatic glucose overproduction, and thiazolidinediones that increase insulin sensitisation, is increasingly used to manage more advanced type 2 diabetes mellitus.

The PROspective pioglitazone Clinical Trial In macroVascular Events (PROactive) examined the effect of a thiazolidinedione, pioglitazone, in addition to existing glucose-lowering and cardiovascular medication, on the incidence of macrovascular comorbidity and total mortality in over 5,000 high-risk patients with type 2 diabetes mellitus [4]. In the total population of patients in PROactive, there were statistically significant differences in favour of pioglitazone vs placebo add-on therapy on HbA_{1c} levels (-0.8% vs -0.3%, respectively; P<0.0001) and diabetic dyslipidaemia (triglycerides: -11.4% vs 1.8%, respectively, and HDL cholesterol: 19.0% vs 10.1%; both P<0.0001) [4]. Here we evaluate in a post hoc analysis the effects of pioglitazone compared to placebo on HbA_{1c} and lipids in patients receiving metformin only at baseline and patients receiving a sulphonylurea only at baseline (metformin monotherapy or sulphonylurea monotherapy).

STUDY DESIGN AND METHODS

Design: Multicentre, randomised, double-blind, placebo-controlled, parallel-group study conducted in 321 centres in 19 European countries. Dosing started at 15 mg pioglitazone (or matching placebo) taken once daily with current glucose-lowering and cardiovascular (CV) medications and was titrated to 45 mg within 2 months, as tolerated, and maintained for the remainder of the study. Mean duration of exposure to study drug was 30.3 months and mean follow up was 34.5 months.

Study Design



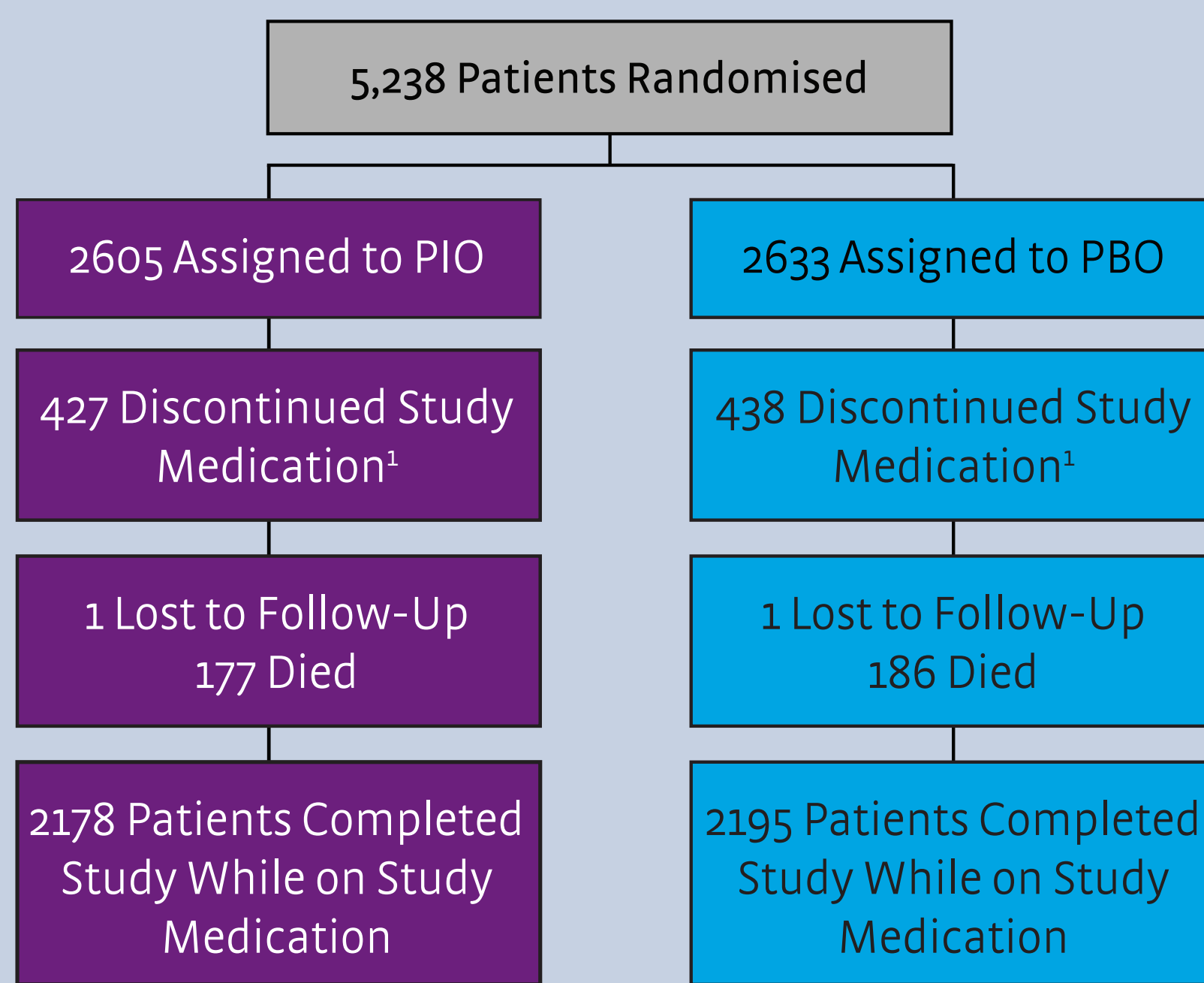
Inclusion criteria:

- Male or female, 35 to 75 years of age, inclusive
- HbA_{1c} above the upper limit of normal (local equivalent of 6.5%)
- Established history of macrovascular disease

Exclusion criteria:

- Type 1 diabetes
- Established insulin monotherapy
- MI, stroke, CABG, or PCI in the 6 months prior to enrollment
- Heart failure defined as NYHA class II or above
- Significantly impaired hepatic function
- Hypersensitivity to or current use of a thiazolidinedione

Patient Disposition



¹The most common reasons for discontinuation were adverse events (PIO, N=235; PBO, N=202) and withdrawal of consent (PIO, N=171; PBO, N=179).

RESULTS

Table 1. Baseline Patient Characteristics and Laboratory Data in Metformin Monotherapy and Sulphonylurea Monotherapy Cohorts

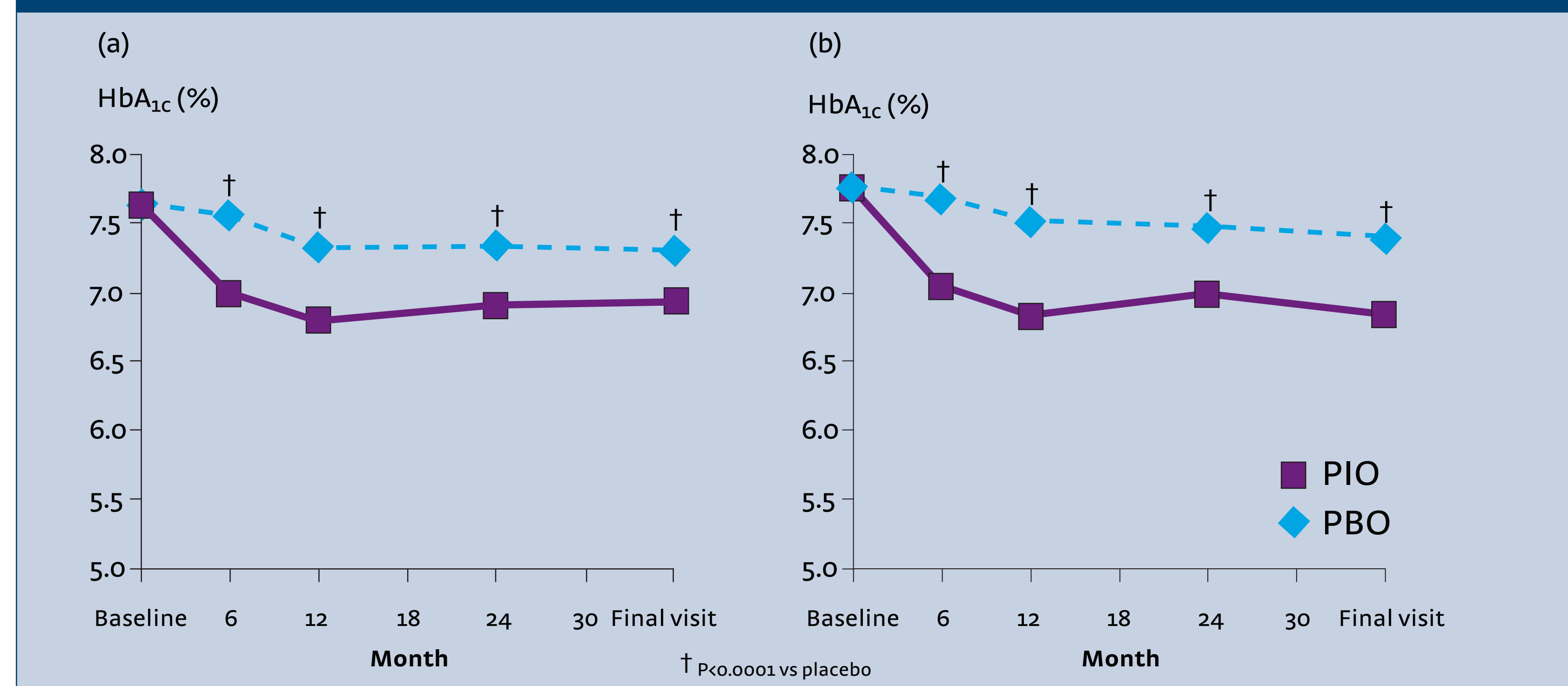
	Metformin only		Sulphonylurea only	
	Pioglitazone n=253	Placebo n=261	Pioglitazone n=508	Placebo n=493
Male, n (%)	176 (69.6)	174 (66.7)	345 (67.9)	348 (70.6)
Caucasian, n (%)	247 (97.6)	256 (98.1)	503 (99.0)	486 (98.6)
Age (yrs)	60.8±7.6	60.3±7.9	63.2±7.7	62.9±7.8
Duration of diabetes (yrs)	5.1±5.1	5.6±5.4	7.3±6.0	6.9±6.1
Body Mass Index (kg/m ²)	31.9±4.7	32.0±5.3	29.7±4.6	29.9±4.3
Microvascular Disease*, n (%)	64 (25.3)	60 (23.0)	173 (34.1)	146 (29.6)
HbA _{1c} (%)	7.6±1.3	7.6±1.2	7.8±1.3	7.7±1.4
Triglycerides (mmol/L)	2.1±1.1	2.2±1.3	2.1±1.3	2.1±1.4
HDL cholesterol (mmol/L)	1.2±0.3	1.2±0.3	1.2±0.3	1.2±0.3
LDL cholesterol (mmol/L)	2.9±0.8	2.9±1.0	3.1±0.9	3.1±1.0
LDL cholesterol/HDL cholesterol ratio	2.6±0.9	2.6±1.0	2.8±1.0	2.8±0.9

Values are presented as mean ± SD, unless otherwise noted.

*Retinopathy, nephropathy, neuropathy.

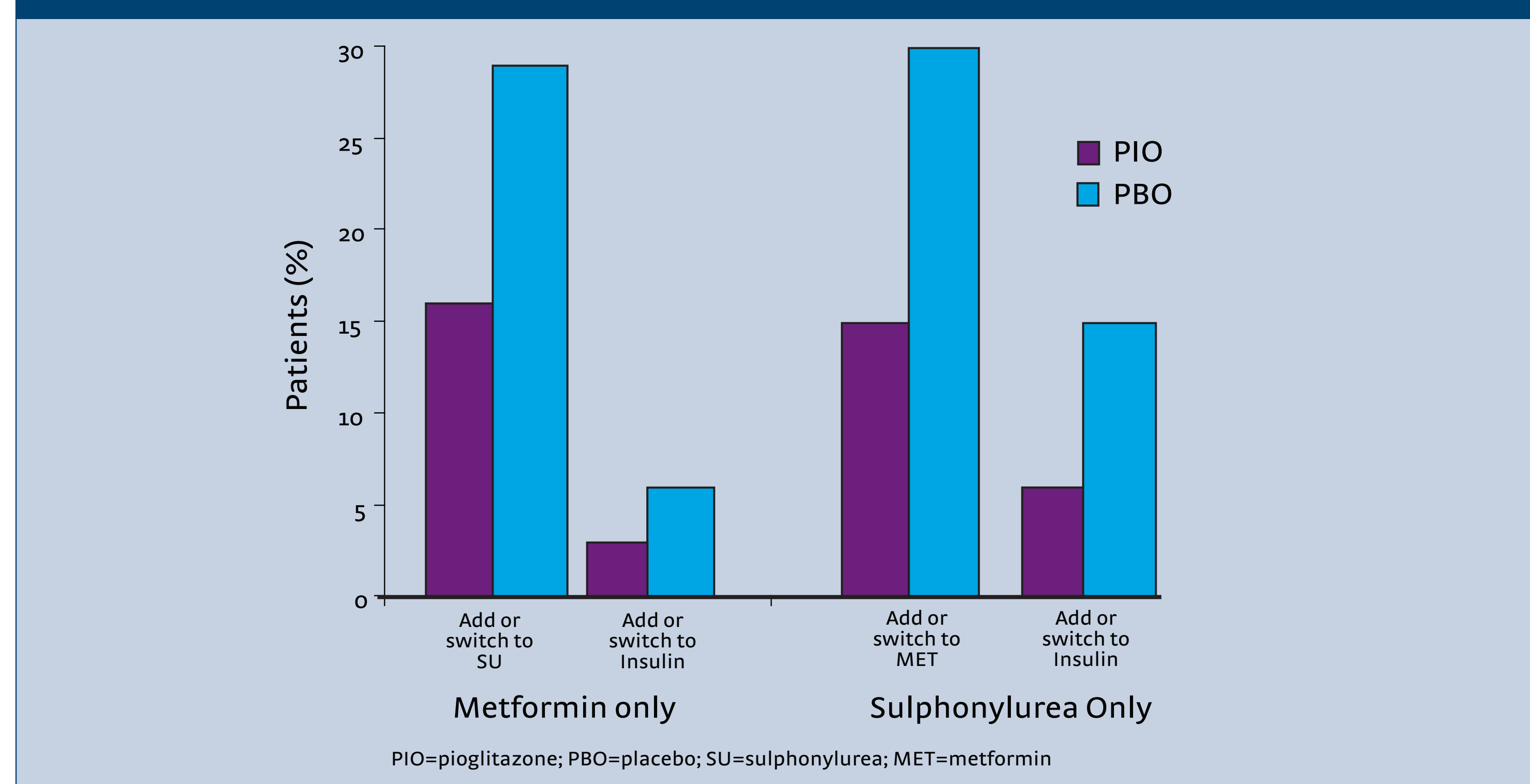
- The overall patient population was approximately two-thirds male and predominantly Caucasian (>97%), with an average age of approximately 62 years.
- There were no differences in any of the baseline characteristics between the pioglitazone and placebo groups within cohorts.
- At baseline, lipid levels were similar between cohorts (metformin monotherapy and SU monotherapy) and between treatment groups within each cohort.
- Approximately half of all patients in the two cohorts (46–52%) had an MI and one-fifth (16–20%) had a stroke at least 6 months before entry into the study.
- Cardiovascular medication use was similar between treatment groups at baseline: more than half of patients were on ACE inhibitors (58–64%) and/or beta-blockers (54–60%).
- Statin use was greater in the metformin monotherapy cohort compared to the SU monotherapy cohort (51% vs 38%, respectively).

Figure 1: Changes in glycaemic control (as measured by HbA_{1c}) over time with pioglitazone (solid lines) or placebo (dashed lines) in (a) the metformin cohort, (b) the sulphonylurea cohort



- Pioglitazone add-on therapy to metformin or sulphonylurea monotherapy resulted in statistically significantly lower HbA_{1c} values compared to placebo add-on therapy at all timepoints throughout the study. The improved glycaemic control was first noted at month 6, the first HbA_{1c} measurement, and was sustained throughout the duration of the study in both cohorts (P<0.0001).

Figure 2. Change in Baseline Medication



- The improved glycaemic control with pioglitazone was accompanied by approximately half as many patients switching to or adding another oral agent or insulin to their treatment regimen than in the placebo group.
- In the metformin cohort, the mean daily dose of metformin had increased in both groups at final visit, but to a lesser extent in the pioglitazone group (168 mg vs 241 mg with placebo; P=0.221). In the sulphonylurea cohort, the mean daily doses of the most often used sulphonylureas (ie, glibenclamide, gliclazide, and glimepiride) had decreased in the pioglitazone group relative to the placebo group at final visit (glibenclamide: -0.7 mg vs -0.1 mg for placebo, P=0.4223; gliclazide: -41 mg vs -14 mg for placebo, P=0.002; glimepiride: -0.3 mg vs +0.5 mg for placebo, P=0.0005).

Table 2. Change in Lipids from Baseline to Final Visit in Patients Receiving Metformin or Sulphonylurea

	Metformin only		P-value	Sulphonylurea only		P-value
	Pioglitazone n=253	Placebo n=261		Pioglitazone n=508	Placebo n=493	
Mean % change from baseline ± SD						
Triglycerides (mmol/L)	n=215 -2.6±47.0	n=222 14.9±84.9	<0.0001	n=434 -1.1±58.9	n=409 11.7±58.0	<0.0001
HDL cholesterol (mmol/L)	n=214 20.6±23.7	n=222 10.4±23.2	<0.0001	n=435 21.8±25.1	n=410 12.7±26.7	<0.0001
LDL cholesterol (mmol/L)	n=214 12.6±36.8	n=222 10.0±49.3	0.212	n=435 9.8±33.9	n=410 4.8±36.8	0.014
LDL/HDL ratio	n=214 -2.7±40.3	n=222 1.3±35.2	0.073	n=435 -6.9±32.6	n=410 -5.3±30.7	0.264

- Patients in the pioglitazone groups had significant improvements in markers of diabetic dyslipidaemia compared with placebo: both groups showed statistically significantly greater mean decreases in triglyceride levels and mean increases in HDL cholesterol levels compared with the placebo group.
- There were mean increases in LDL cholesterol in both treatment groups, irrespective of underlying baseline glucose-lowering treatment, with similar increases noted in both treatment groups in the metformin only cohort, but significantly greater increases noted in the pioglitazone compared to placebo group in the sulphonylurea only cohort.
- The LDL cholesterol/HDL cholesterol ratio was improved with pioglitazone compared with placebo in both cohorts, but improvement with placebo was only seen in the sulphonylurea cohort.

Safety

- Among pioglitazone-treated patients, 27% of patients in the metformin group and 22% in the sulphonylurea group had oedema vs 15% and 11%, respectively, of placebo-treated patients. Hypoglycaemia occurred more in the pioglitazone plus sulphonylurea group than the pioglitazone plus metformin group (21% vs 8%, respectively) and 13% in both of the placebo groups.
- There were weight increases of 3.9 kg in the pioglitazone groups when added to metformin monotherapy and 2.6 kg when added to sulphonylurea monotherapy vs a decrease of 1.3 kg in both of the placebo groups.

CONCLUSION

Adding pioglitazone to an existing monotherapy treatment regimen of either metformin or a sulphonylurea resulted in sustained improvements in glycaemic control, significant reductions in triglyceride levels, significant increases in HDL-C, and a reduced need for insulin.

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