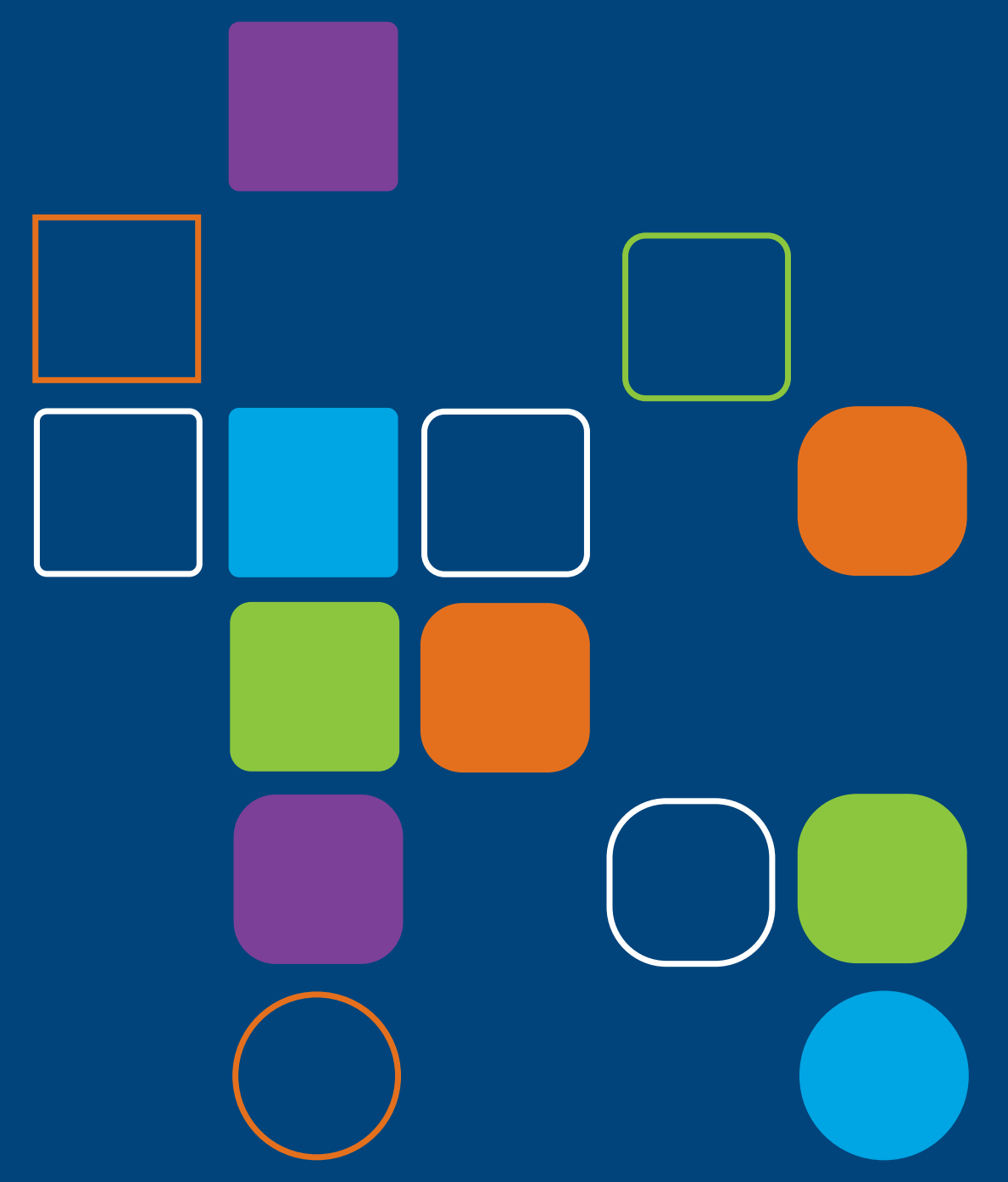


Pioglitazone in Triple Oral Therapy: Long-Term Glycaemic Results from PROactive

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pioglitazone HCl
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ABSTRACT

Aims: Type 2 diabetes is a progressive disease that eventually requires multiple agent therapy, including insulin. We looked at the long-term glycaemic effects of pioglitazone (PIO) add-on therapy in a cohort of patients with type 2 diabetes and macrovascular disease who entered PROactive on metformin plus sulphonylurea (MET+SU).

Methods: PROactive randomised patients to either PIO or PBO, in addition to other glucose-lowering and cardiovascular medication. PIO doses were force-titrated to 45 mg/day. Mean follow-up was 34.5 months. Within the MET+SU cohort (n=1314), mean baseline HbA1c values were similar between groups.

Results: Significantly greater reductions in HbA1c were noted with PIO compared with PBO (mean differences of 0.71% at 6 months, 0.69% at 12 months, 0.64% at 24 months and 0.58% at final visit; P<0.0001 at all timepoints). In addition, more PIO patients had either MET or SU removed from their regimen (16%) and fewer had insulin added to their regimen (16%) than PBO patients (8% and 31%, respectively). The mean daily MET dose increased by 1.9 mg in the PIO group vs 228 mg in the PBO group (P<0.0001). SU doses decreased or were unchanged in the PIO group (glibenclamide = -1.4 mg vs -0.2 mg for PBO, P=0.013; gliclazide = -33 mg vs -23 mg for PBO, P=0.270; glibenclamide = 0 mg vs +0.6 mg for PBO, P=0.009). Oedema occurred in 29% of patients in the PIO group vs 17% in the PBO group (P<0.0001) and hypoglycaemia occurred in 27% in the PIO group vs 20% in the PBO group (P=0.0013). There was a weight increase of 4.1 kg in the PIO group and a decrease of 0.7 kg in the PBO group (P<0.0001).

Conclusions: Adding a dual oral therapy regimen to a triple oral regimen by adding PIO resulted in a sustained improvement in glycaemic control and a reduced need for insulin.

INTRODUCTION

- During their lifetime, patients with type 2 diabetes (T2D) will most likely require multiple pharmacological agents to maintain the recommended glycaemic control [1].
- The progressive nature of the disease, which involves the core defects of insulin resistance and beta-cell dysfunction, makes it increasingly difficult for patients with T2D to maintain glycaemic control, while their own overall insulin production grows increasingly deficient [2].
- As the disease progresses, exogenous insulin therapy along with other pharmacological agents are usually required for adequate glycaemic control.
- Previous studies have shown that further improvement in glycaemic control is achieved when PIO is added to drug therapy regimens (such as metformin [MET] and sulphonylurea [SU]) and that insulin dosage requirements can be reduced with the addition of PIO.
- This *post-hoc* analysis focused on determining if adding PIO to a dual oral regimen is effective and safe as part of triple therapy.
- Secondarily, we also examined if PIO added to a patient's combination MET + SU therapy resulted in any changes in the drug regimen compared to the PBO group.

STUDY DESIGN AND METHODS

This was a multicentre, randomised, double-blind, placebo-controlled, parallel-group study.

The primary PROactive (PROspective pioglitazone Clinical Trial In macroVascular Events) methods have been described previously [3,4].

In the total patient population, patients were treated for 2.5 to 3.5 years, mean drug exposure was 30.4 months, and mean follow-up was 34.5 months. The minimum period of patient observation was 30 months as required by protocol. Final visits occurred between 30 and 42 months after entry into study.

Inclusion criteria:

- Male or female patients, 35 to 75 years of age, inclusive
- HbA1c above the upper limit of normal
- Established history of macrovascular disease

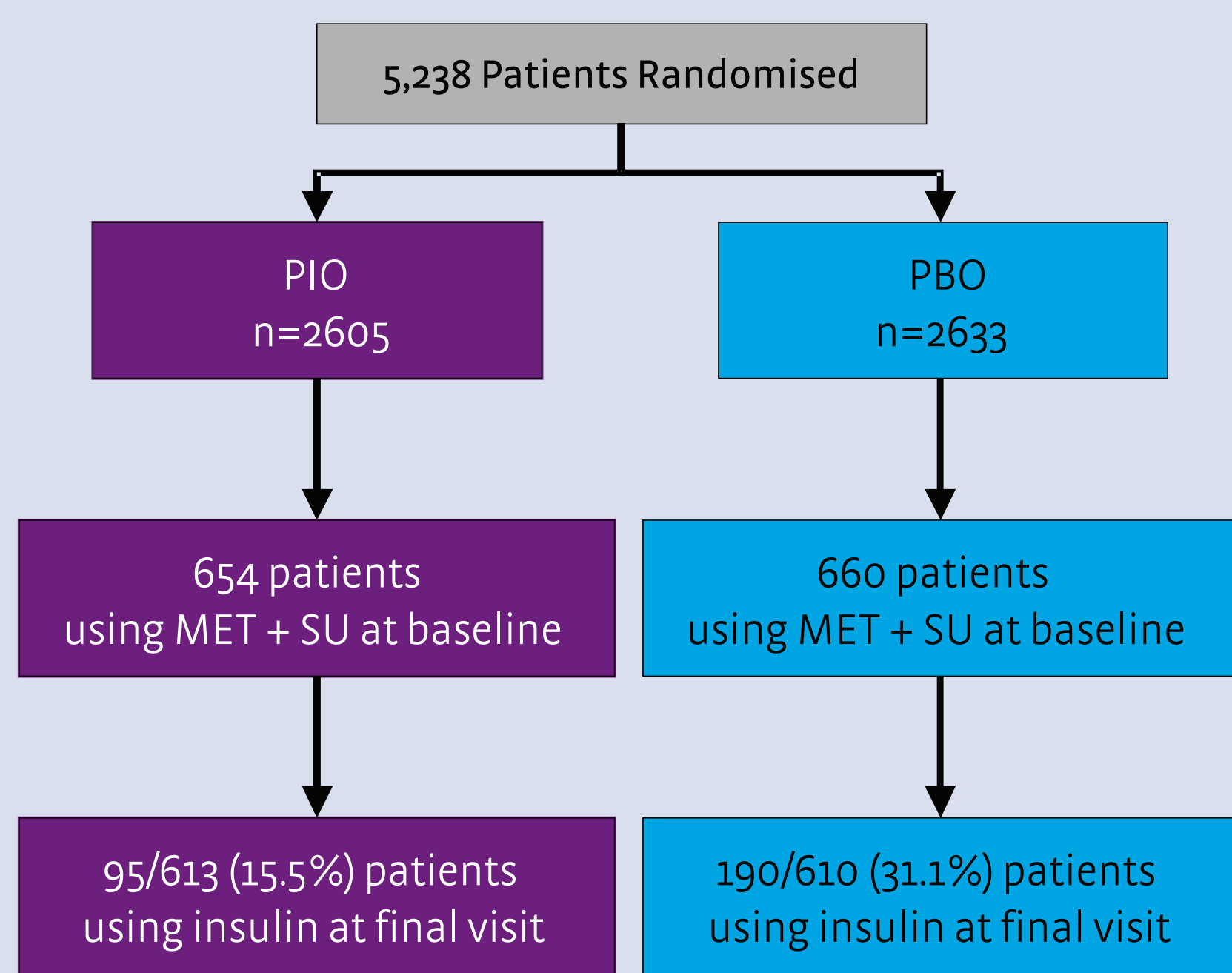
Exclusion criteria:

- Signs of type 1 diabetes; patient taking insulin; myocardial infarction, stroke, coronary artery bypass graft, or percutaneous coronary intervention in the 6 months prior to enrollment; heart failure defined as NYHA class II or above; significantly impaired hepatic function; and hypersensitivity to or current use of a TZD

Statistical methods:

- Efficacy analyses: patients taking ≥1 dose of study medication (intent-to-treat [ITT] population); treatment-group differences analysed with log rank test without covariates; hazard ratios estimated with Cox proportional hazards model; Kaplan-Meier estimates of survival functions used to characterise treatment effects
- Safety analyses: ITT population; adverse events reported by preferred term, system organ class, treatment group, and relationship to study medication

Patient Disposition



RESULTS

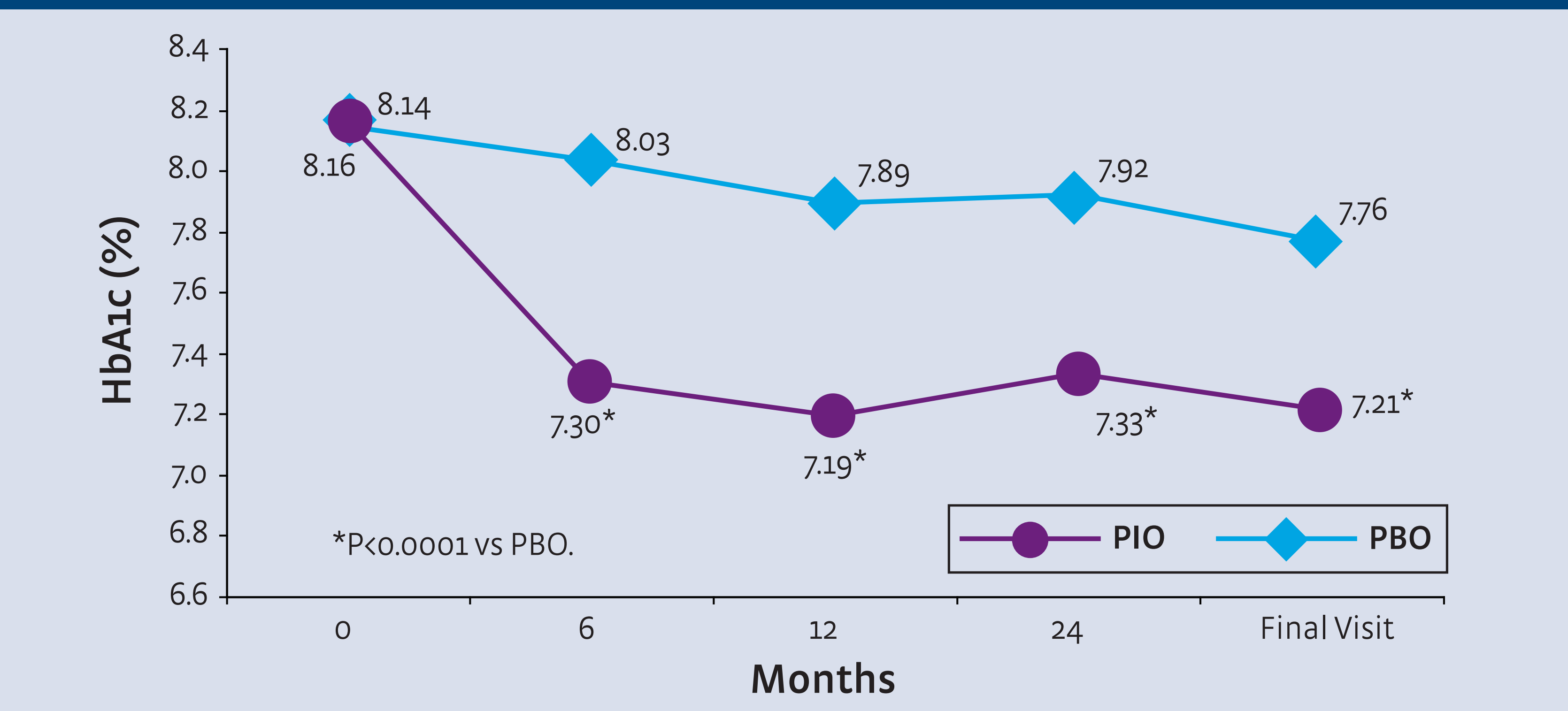
- Presented here are the results for the subgroup of PROactive patients receiving MET and SU at baseline (PIO, n=654; PBO, n=660).
- The randomised treatment groups were well matched with regard to demographic characteristics.
- There were no differences between groups with regard to their glucose-lowering regimens.

Table 1. Characteristics of Patients Receiving MET and SU at Baseline

	PIO n=654	PBO n=660	TOTAL N=1314
Male	472 (72.2)	434 (65.8)	906 (68.9)
Race			
White	639 (97.7)	651 (98.6)	1290 (98.2)
Black	5 (0.8)	1 (0.2)	6 (0.5)
Asian	10 (1.5)	7 (1.1)	17 (1.3)
Age			
<65 years	395 (60.4)	389 (58.9)	784 (59.7)
≥65 years	259 (39.6)	271 (41.1)	530 (40.3)
Duration of Diabetes			
<5 years	157 (24.0)	168 (25.5)	325 (24.8)
≥5 to <10 years	217 (33.2)	207 (31.4)	424 (32.3)
≥10 years	280 (42.8)	284 (43.1)	564 (43.0)
Weight (kg), mean (SD)	87.99 (15.859)	88.12 (15.808)	88.05 (15.828)
BMI (kg/m ²)			
<27	150 (23.0)	148 (22.6)	298 (22.8)
27 – <30	188 (28.9)	171 (26.1)	359 (27.5)
30 – <33	159 (24.4)	154 (23.5)	313 (24.0)
≥33	154 (23.7)	182 (27.8)	336 (25.7)

All data are presented as number of patients (%) unless otherwise indicated.

Figure 1. Time Course of HbA1c in Patients Receiving MET and SU at Baseline



- Glycaemic control improved over the course of the study in both the PIO and PBO groups, however, the PIO group showed significantly greater improvements throughout most of the duration of the study (P<0.0001).
- At the final visit, the PIO group mean HbA1c was 7.21% whereas the PBO group had a mean HbA1c of 7.76% (P<0.0001).

Table 2. Changes in Treatment Regimens in Patients Receiving MET and SU at Baseline

Scheduled visit	Month 1 (attended)		Month 18 (attended)		Final visit (attended)	
	PIO n=652	PBO n=653	PIO n=631	PBO n=625	PIO n=613	PBO n=610
Treatment regimen						
MET only	6	8	58	25	58	28
SU only	6	6	37	23	40	23
MET + SU	636	637	466	460	402	365
Insulin only	0	0	23	23	34	54
Insulin + MET	0	0	13	40	34	78
Insulin + SU	1	0	9	12	7	10
Insulin + MET + SU	2	1	14	38	20	48
None of above	1	1	11	4	18	4
Any insulin	3	1	59	113	95	190

- At study entry, no patients were receiving insulin and all were receiving MET and SU combination. Of these patients, 16% in the PIO group and 31% in the PBO group began to use insulin permanently (defined as insulin use for 90 days or more, or insulin use at death or end of study) during the course of the study.
- Relative to baseline, the number of patients that required insulin therapy at the end of 36 months was 50% less in the PIO group than PBO group.
- More PIO patients had either MET or SU dropped from their regimen (16%) and fewer had insulin added to their regimen (16%) than PBO patients (8% and 31%, respectively).

Table 3. Changes in MET Dosage in Patients Receiving MET and SU at Baseline

Change from baseline (mg)	PIO n=654	PBO n=660
Baseline	1661.4 (601.26)	1636 (631.72)
Month 18	-15.6 (477.12)	150.2 (556.25)
Month 30	0.6 (541.18)	211.3 (624.67)
Final visit	18.9 (567.83)	227.7 (615.90)

Data are presented as mean (standard deviation).

- MET doses decreased in the PIO group and increased in the PBO group.

Table 4. Effect of PIO vs. Placebo on Lipid Subtypes in Patients Receiving MET and SU at Baseline

	PIO n=654	PBO n=660	P-Value*
Triglycerides (mmol/L)			
Baseline	2.25 (1.774)	2.39 (2.168)	0.3761
%CFB Final Visit	-1.10 (51.221)	8.34 (55.089)	0.0003
HDL (mmol/L)			
Baseline	1.15 (0.311)	1.15 (0.309)	0.9597
%CFB Final Visit	21.15 (23.789)	12.60 (32.510)	<0.0001
LDL (mmol/L)			
Baseline	2.86 (0.873)	2.90 (0.923)	0.6118
%CFB Final Visit	12.31 (41.964)	6.09 (32.806)	0.0281
LDL/HDL Ratio			
Baseline	2.59 (0.851)	2.64 (0.980)	0.9093
%CFB Final Visit	-4.36 (39.603)	-2.59 (33.284)	0.0192

CFB = Change from baseline. Data are presented as mean (standard deviation) of the ITT population.

*PIO vs placebo.

- PIO reduced triglycerides and significantly increased HDL cholesterol levels compared with PBO.
- Levels of LDL cholesterol were increased in both groups; however, the ratio of LDL to HDL cholesterol was decreased for PIO compared with PBO throughout the study.

SAFETY

Table 5. Non-serious Adverse Events of Special Interest and Serious Cardiac Adverse Events

n (%)	PIO n=654	PBO n=660
Non-serious AEs of special interest	318 (48.6)	222 (33.6)
Cardiac failure	41 (6.3)	22 (3.3)
Oedema	187 (28.6)	109 (16.5)
Hypoglycaemia	179 (27.4)	131 (19.8)
All serious AEs	298 (45.6)	318 (48.2)
Cardiac disorders	110 (16.8)	125 (18.9)
Acute coronary syndrome	4 (0.6)	12 (1.8)
Angina pectoris	21 (3.2)	32 (4.8)
Angina unstable	19 (2.9)	25 (3.8)
Atrial fibrillation	9 (1.4)	11 (1.7)
Cardiac failure	29 (4.4)	21 (3.2)
Cardiac failure congestive	15 (2.3)	8 (1.2)
Myocardial infarction	27 (4.1)	28 (4.2)

- The percentage of patients within this triple therapy subgroup that experienced a non-serious adverse event was 48.6% for the PIO group and 33.6% for the PBO group.
- The percentage of patients that experienced a serious adverse event was 45.6% for the PIO group and 48.2% for the PBO group.

CONCLUSIONS

- Adding PIO to a dual therapy regimen of MET and SU resulted in a sustained improvement in glycaemic control.
- Pioglitazone improved triglycerides and HDL cholesterol levels.
- PIO delayed the progression to insulin therapy while providing better glycaemic control than PBO.
- The overall safety profile of PIO in a triple oral therapy regimen was similar to that of PBO, with differences in non-serious events of cardiac failure, oedema, and hypoglycaemia.

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