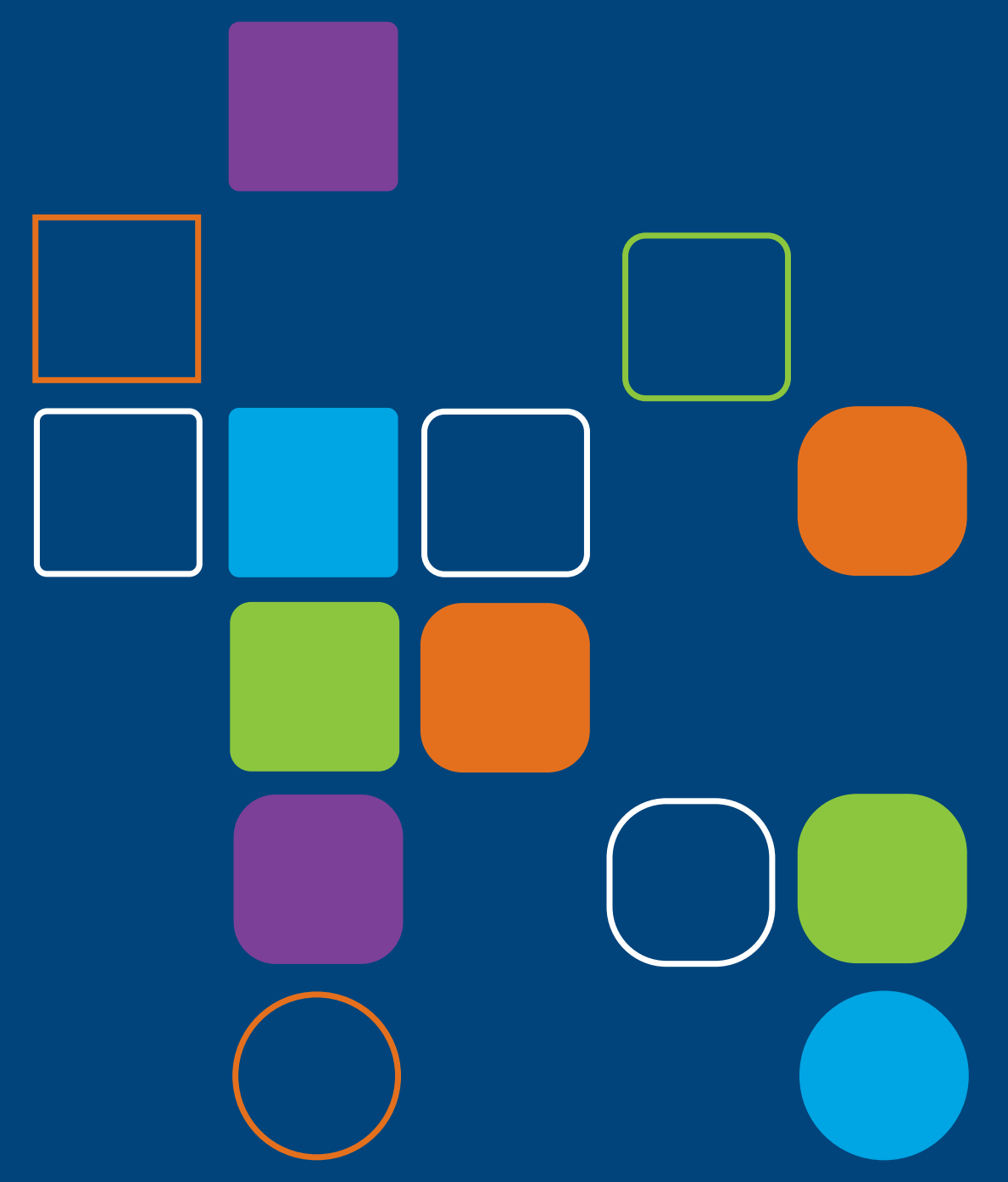


# Reduced Insulin Requirements and Improved Glycaemic Control with Pioglitazone in Insulin-treated Patients with Type 2 Diabetes: Results from PROactive

André Scheen<sup>1</sup>, Ole Schmitz<sup>2</sup>, Bernard Charbonnel<sup>3</sup> on behalf of the PROactive investigators.  
<sup>1</sup>Liege, Belgium; <sup>2</sup>Aarhus, Denmark; <sup>3</sup>Nantes, France

pioglitazone HCl  
 IDF 2006



## ABSTRACT

**Aim & Methods:** Management of type 2 diabetes (T2D) typically requires multiple agents, including insulin. We examined insulin requirements and glycaemic control in the one-third of patients (PIO=864; PBO=896) who were treated with insulin at baseline in PROactive (mean follow-up=34.5 months).

**Results:** Within this cohort, baseline HbA1c values and mean daily insulin doses were similar between treatment groups (PIO=8.4% and 47 U/d; PBO=8.5% and 47 U/d). In both groups at baseline, insulin was combined with oral monotherapy with metformin (MET) in 53% and sulfonylurea (SU) in 24% of patients and with dual therapy with MET+SU in 12%.

A rapid and sustained decrease in insulin doses was observed with PIO (force-titrated up to 45 mg/day), contrasting with a progressive increase with PBO. By study end, the mean insulin dose was lower with PIO (42 U/d) than with PBO (55 U/d; P<0.0001); nevertheless, there were statistically significant differences in HbA1c between PIO and PBO (HbA1c = 7.45% for PIO vs 8.06% for PBO at final visit; P<0.0001 at all time points). At final visit, insulin had been discontinued in 9% of patients in the PIO group vs 2% in the PBO group (P<0.0001 between-group difference). The proportion of patients on oral/insulin combined therapy remained similar in both groups: MET alone in 47% vs 52%, SU alone in 16% vs 16%, and MET+SU in 10% vs 11%, in the PIO group vs the PBO group, respectively (P=NS).

There were differences in oedema (PIO=31%; PBO=18%; P<0.0001) and hypoglycaemia (PIO=41%; PBO=29%; P<0.0001), but there were no other differences in the safety profiles between the PIO and PBO groups (with or without other treatments).

**Conclusions:** PIO reduced the number of patients on insulin and the mean daily insulin dose, while providing better glycaemic control than PBO.

## INTRODUCTION

- Type 2 diabetes (T2D) is a disease that encompasses both core defects of insulin resistance and beta-cell dysfunction [1]. These defects make it increasingly difficult for patients with T2D to achieve and maintain glycaemic control.
- T2D is a progressive disease and patients eventually require insulin, mostly in combination with oral glucose-lowering agents, to achieve and maintain glycaemic goals [2].
- PIO is a thiazolidinedione (TZD), an insulin-sensitising agent used in the treatment of T2D. It increases insulin sensitivity in peripheral tissues, adipocytes, and liver tissue, thus reducing circulating glucose levels. Moreover, in animal models it has been shown to cause regeneration of beta cells [3].
- In combination therapy studies, treatment with PIO significantly reduced mean insulin dose in as little as two weeks after treatment initiation. These reductions were sustained through the 24-week study [4].

## 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 and results have been described previously [5,6].
- In the total patient population, patients were treated for 2.5 to 3.5 years, mean study 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.

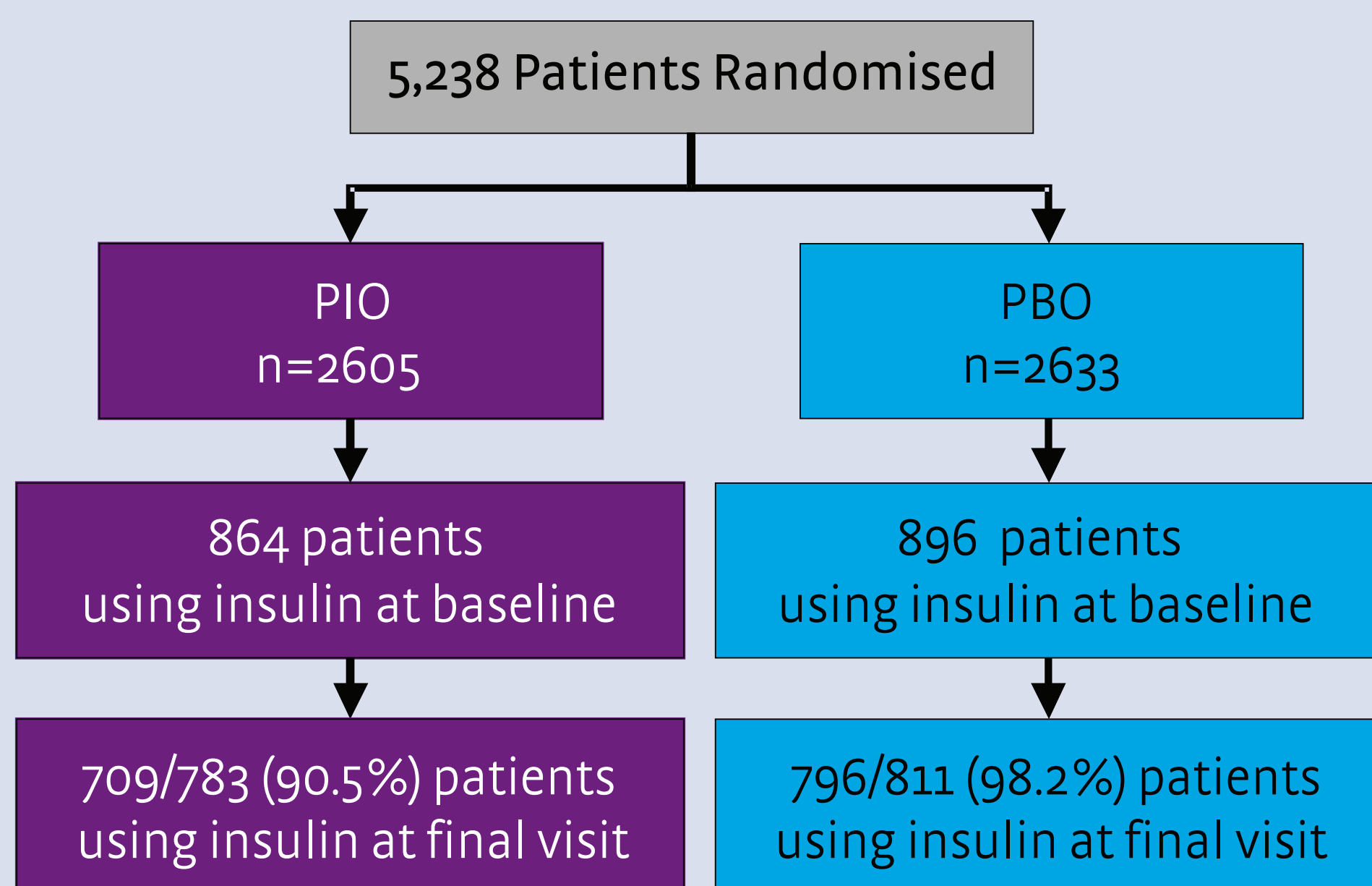
- Inclusion criteria:**
- Male or female patients, 35 to 75 years of age, inclusive
  - HbA1c above the upper limit of normal
  - Established history of macrovascular disease

- Exclusion criteria:**
- 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

- The randomised treatment groups were well matched with regard to demographic characteristics.
- There were no relevant differences between groups who were taking insulin at baseline.
- Over one-third of all patients in this study received insulin (with or without glucose-lowering medication) as part of their treatment regimen at baseline — 33.2% in the PIO group and 34.0% in the PBO group.

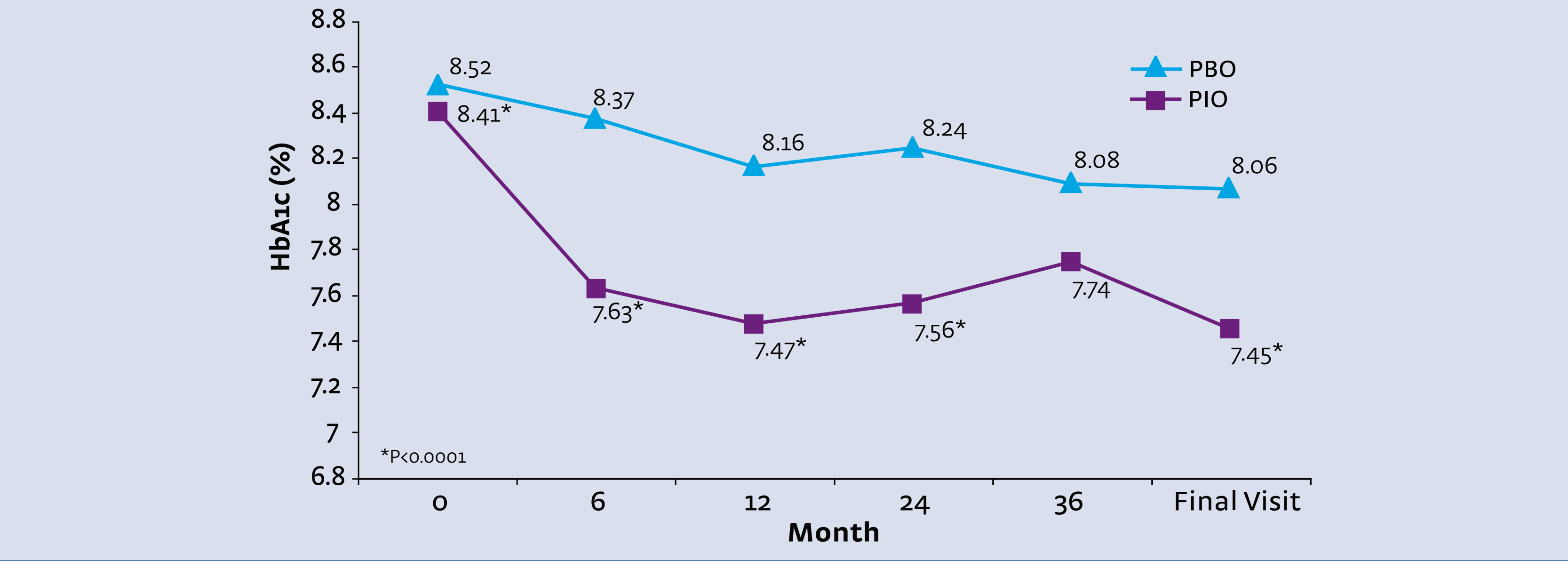
**Table 1. Characteristics of Patients Receiving Insulin at Baseline**

	PIO n=864	PBO n=896	TOTAL N=1760
Male	503 (58.2)	547 (61.0)	1050 (59.7)
Race			
White	854 (98.8)	887 (99.0)	1741 (98.9)
Black	3 (0.3)	2 (0.2)	5 (0.3)
Asian	5 (0.6)	5 (0.6)	10 (0.6)
Age			
<65 years	524 (60.6)	556 (62.1)	1080 (61.4)
≥65 years	340 (39.4)	340 (37.9)	680 (38.6)
Duration of diabetes			
<5 years	91 (10.5)	80 (8.9)	171 (9.7)
≥5 to <10 years	194 (22.5)	211 (23.5)	405 (23.0)
≥10 years	579 (67.0)	605 (67.5)	1184 (67.3)
Weight (kg), mean (SD)	88.80 (15.59)	90.57 (15.59)	89.70 (15.61)
BMI (kg/m <sup>2</sup> )			
<27	141 (16.4)	122 (13.6)	263 (15.0)
27–<30	206 (23.9)	210 (23.4)	416 (23.7)
30–<33	220 (25.5)	209 (23.3)	429 (24.4)
≥33	295 (34.2)	355 (39.6)	650 (37.0)
Insulin, mean (SD)			
No. of injections/day	2.3 (1.11)	2.3 (1.11)	2.3 (1.11)
Daily dose (units)	46.5 (31.18)	46.7 (30.62)	46.6 (30.89)
Therapies			
Insulin + MET	456 (52.8)	475 (53.0)	931 (52.9)
Insulin + SU	209 (24.2)	219 (24.4)	428 (24.3)
Insulin + MET + SU	105 (12.2)	107 (11.9)	212 (12.0)

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

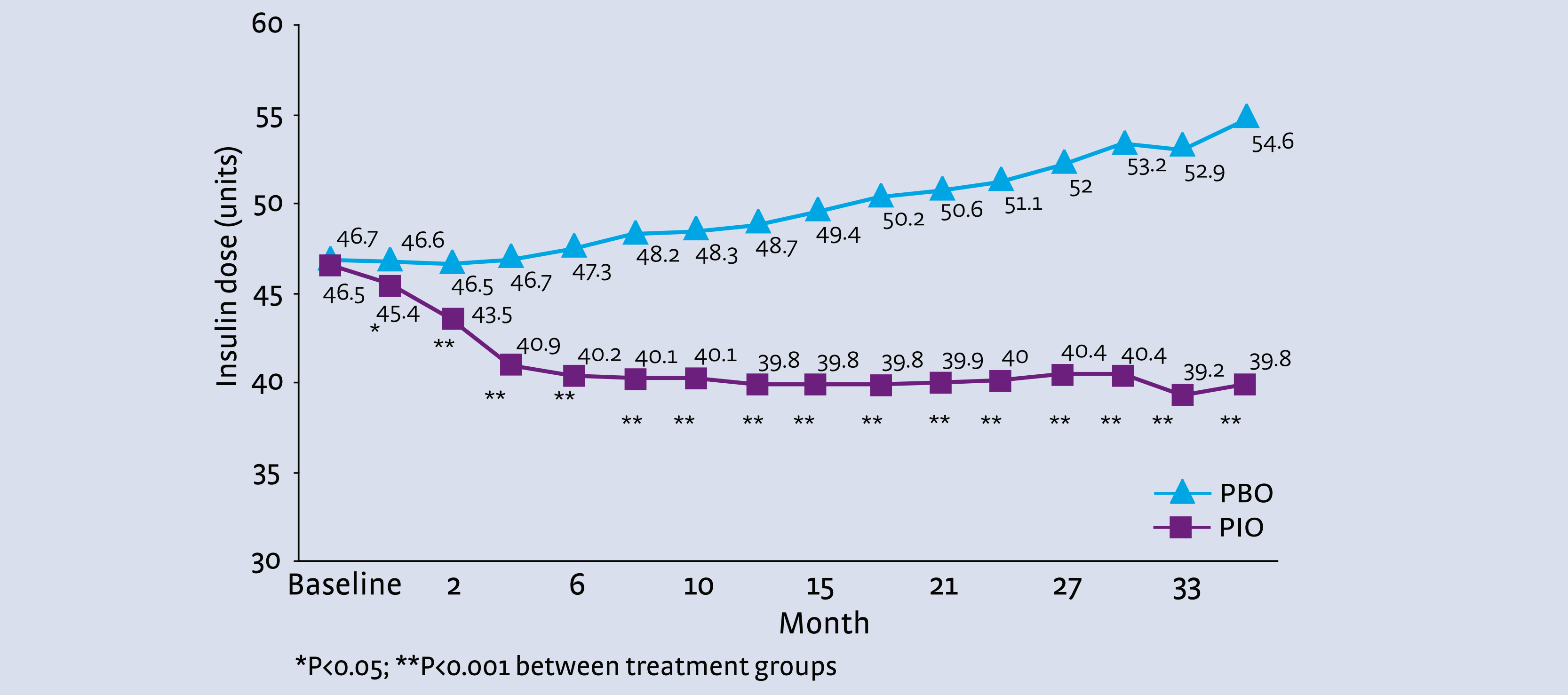
- At final visit, insulin had been discontinued in 74 patients in the PIO group vs 15 in the PBO group.

**Figure 1. Time Course of HbA1c in Patients Using Insulin 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 mean was 7.45% in the PIO group, whereas the mean was 8.06% in the PBO group (P<0.0001).

**Figure 2. Change in Insulin Dose (Units) in Patients Using Insulin at Baseline**



- Mean daily insulin dose (units) decreased steadily over the 36 months in the PIO group while the units of insulin steadily increased in the PBO group.

**Table 2. Effect of PIO vs. Placebo on Lipid Subtypes**

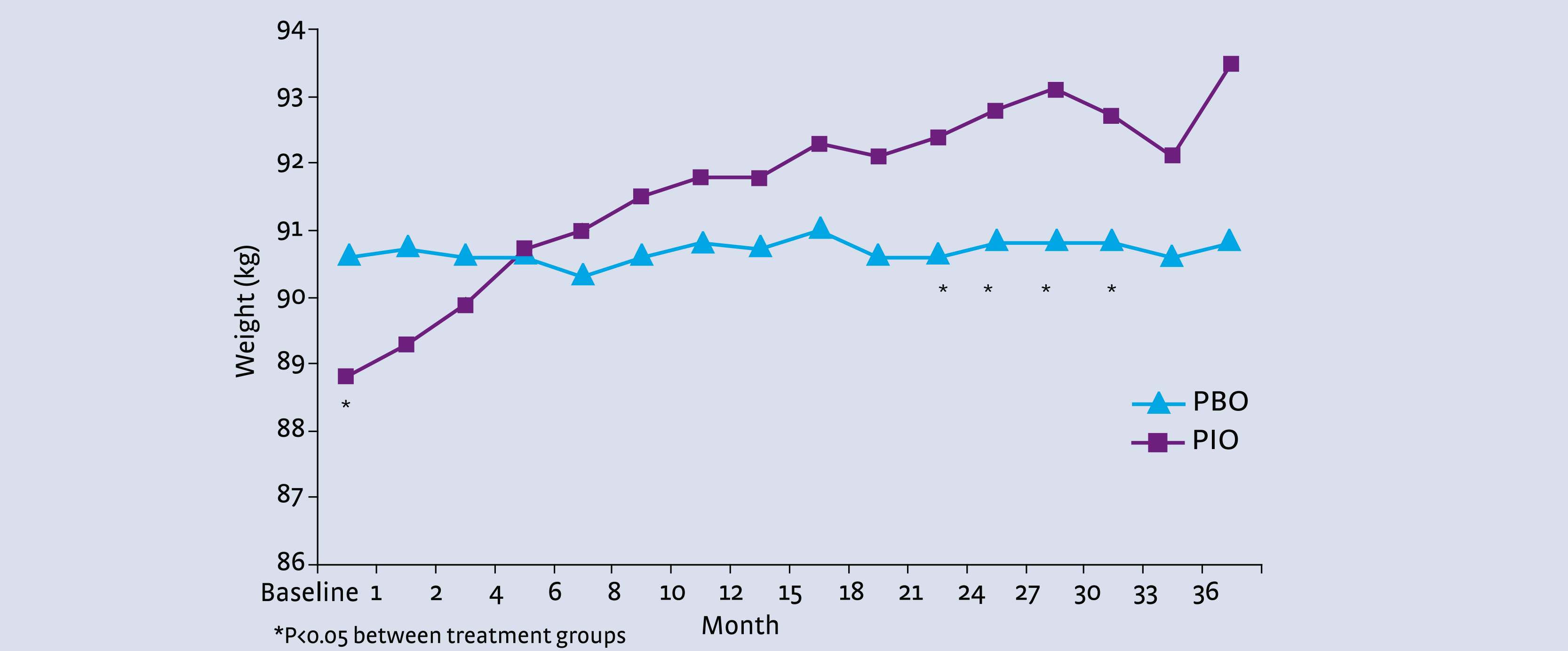
	PIO n=864	PBO n=896	P-Value*
Triglycerides (mmol/L)			
Baseline	2.34 (2.372)	2.24 (1.826)	0.847
%CFB Final Visit	-2.21 (52.886)	14.11 (59.306)	<0.0001
HDL (mmol/L)			
Baseline	1.17 (0.338)	1.16 (0.320)	0.949
%CFB Final Visit	20.45 (28.163)	10.09 (21.916)	<0.0001
LDL (mmol/L)			
Baseline	2.96 (1.012)	2.29 (1.005)	0.736
%CFB Final Visit	15.13 (43.605)	12.08 (38.147)	0.293
LDL/HDL Ratio			
Baseline	2.68 (1.078)	2.67 (1.093)	0.701
%CFB Final Visit	-0.95 (41.274)	4.66 (38.432)	0.0002

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

\* PIO vs placebo.

- PIO also significantly reduced triglycerides and increased HDL cholesterol levels in comparison 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.

**Figure 3. Time Course of Body Weight in Patients Using Insulin at Baseline**



## SAFETY:

**Table 3: Serious adverse events**

n (%)	PIO n=864	PBO n=896
Any SAE	434 (50.2)	484 (54.0)
Cardiac-related SAE	168 (19.4)	200 (22.3)
Heart failure	54 (6.3)	47 (5.2)
Myocardial infarction	39 (4.5)	53 (5.9)
Hypoglycaemia	15 (1.7)	7 (0.8)
Peripheral oedema	3 (0.3)	0 (0.0)
Death	77 (8.9)	79 (8.8)

**Table 4: Adverse events**

n (%)	PIO n=864	PBO n=896
Any AE	731 (84.6%)	748 (83.5%)
Cardiac-related AE	248 (28.7%)	258 (28.8%)
Hypoglycaemia	365 (42.2%)	261 (29.1%)
Oedema	265 (30.7%)	163 (18.2%)
Weight gain	38 (4.4%)	12 (1.3%)

## CONCLUSIONS

- In the PIO group, more patients discontinued insulin therapy and the mean daily insulin dose was reduced. Despite this, PIO-treated patients experienced better glycaemic control than patients in the PBO group.
- Pioglitazone significantly improved HbA1c, triglycerides, and HDL cholesterol levels.
- Adding insulin therapy did not negate the beneficial lipid effects seen with PIO.
- Overall numbers of SAEs were similar between groups.
- Overall numbers of AEs were similar between groups with significantly higher AEs of hypoglycaemia and oedema in the PIO group.

## REFERENCES

1. American Diabetes Association. Standards of medical care in diabetes. Diabetes Care. 2006;29(Suppl 1):S4-S42.
2. DeFronzo RA. Pharmacological therapy for type 2 diabetes mellitus. Ann Intern Med. 1999;131:281-303.
3. Diani AR, Sawada C, Wyse B, Murray FT, Khan M. Pioglitazone preserves pancreatic islet cell structure and insulin secretory function in three murine models of type 2 diabetes. Am J Physiology Endocrinol Metab. 2004;286:116-122.
4. Perez A, Khan M, Johnson T, Karunarante M. Effects of pioglitazone on lipid subtypes and subparticle profiles: results from a double-blind, randomized study of pioglitazone HCl vs placebo in reducing or eliminating insulin requirement in subjects with type 2 diabetes. American Diabetes Association Scientific Sessions 2004.
5. Charbonnel B, Dormandy J, Erdmann E, Massi-Benedetti M, Skene A. The prospective pioglitazone clinical trial in macrovascular events (PROactive): can pioglitazone reduce cardiovascular events in diabetes? Study design and baseline characteristics of 5238 patients. Diabetes Care. 2004;27:1647-1653.
6. Dormandy JA, Charbonnel B, Eckland DJA, et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitazone Clinical Trial In macroVascular Events): a randomised controlled trial. Lancet. 2005;366:1279-1289.