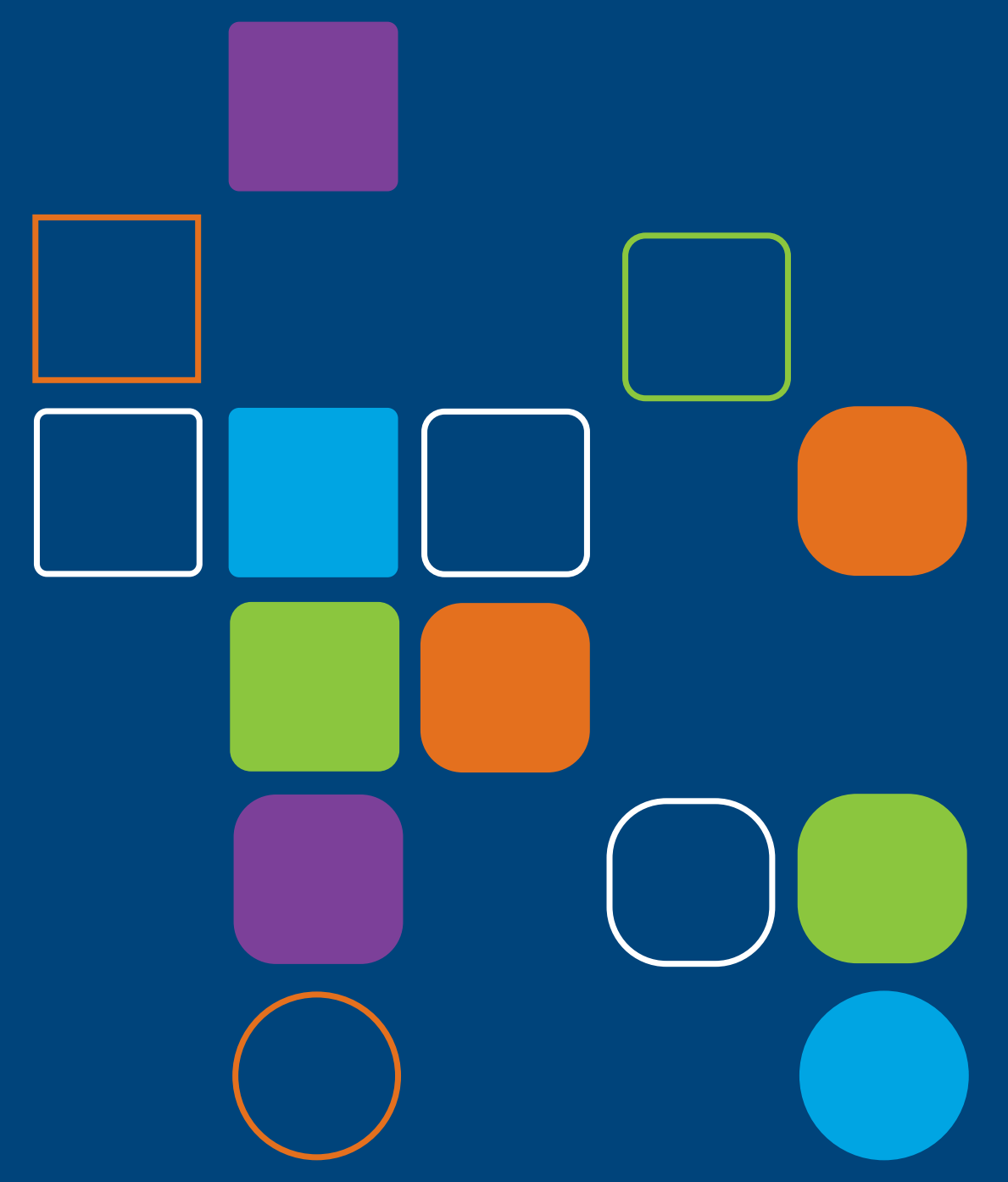


Pioglitazone Treatment Delays the Need for Permanent Insulin Use: Results from PROactive



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ABSTRACT

Aims: Management of type 2 diabetes typically involves multiple agents and many patients eventually require insulin. This subgroup analysis from PROactive assessed time to permanent insulin use in patients not receiving insulin at baseline.

Methods: PROactive randomised 5238 patients with type 2 diabetes and macrovascular disease to pioglitazone (up to 45 mg) or placebo (mean follow-up=34.5 months). Two thirds of the study population (pioglitazone=1741; placebo=1737) were not receiving insulin at baseline. Permanent insulin use was defined as daily use for ≥90 days or ongoing use at death/final visit.

Results: In this cohort, twice as many placebo (n=362) as pioglitazone (n=183) patients had progressed to permanent insulin use by final visit (Kaplan-Meier rates of 11% [pioglitazone] versus 21% [placebo] after 3 years; HR=0.47; 95%CI:0.39,0.56; P<0.0001). There were significantly greater improvements in HbA1c with pioglitazone versus placebo in patients not on insulin at baseline (HbA1c=7.9% at baseline in both groups; HbA1c=6.97% pioglitazone versus 7.49% placebo at final visit; P<0.0001 between groups at all timepoints). The 2-fold increase in insulin use in the placebo group was irrespective of the baseline oral regimen. Half as many pioglitazone patients (58 [3.6%]) as placebo patients (117 [7.2%]) were on insulin without metformin or sulphonylurea at final visit.

	Baseline oral treatment n (%)		Permanent insulin use n (%)	
	Pioglitazone n=1741	Placebo n=1737	Pioglitazone	Placebo
Metformin only	253 (14.5)	261 (15.0)	9 (3.6)	20 (7.7)
Sulphonylurea only	508 (29.2)	493 (28.4)	35 (6.9)	78 (15.8)
Metformin+sulphonylurea	654 (37.6)	660 (38.0)	113 (17.3)	204 (30.9)
Other ^a	326 (18.7)	323 (18.6)	26 (8.0)	60 (18.6)

^aNo medication, or acarbose or repaglinide (+/-metformin +/-sulphonylurea).

More pioglitazone patients had oedema (26% versus 15%; P<0.0001) and hypoglycaemia (21% versus 16%; P<0.0001), with no other between-group differences in adverse events.

Conclusions: Progression to permanent insulin use was reduced by 50% at 3 years with pioglitazone versus placebo and better glycaemic control was seen with pioglitazone. The decreased need for insulin with pioglitazone was irrespective of baseline treatment.

INTRODUCTION

- Type 2 diabetes (T2D) is a disease that encompasses both core defects of insulin resistance and beta-cell dysfunction that lead to insulin deficiency. These defects make it progressively more difficult for patients with T2D to achieve and maintain glycaemic control.
- As the disease advances, exogenous insulin therapy in addition to oral glucose-lowering agents is usually required for adequate glycaemic control [1].
- It has been shown previously that further improvement in glycaemic control is achieved when thiazolidinediones are added to insulin therapy in patients with T2D and that insulin dosage requirements can be reduced with the addition of pioglitazone (PIO) [1,2].
- In this prespecified analysis of PROactive (PROspective pioglitazone Clinical Trial In macroVascular Events), we aimed to determine if progression to permanent insulin therapy could be delayed by initiating thiazolidinedione therapy.

STUDY DESIGN AND METHODS

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

- The primary PROactive methods and results have been described previously [3,4].
- 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 New York Heart Association (NYHA) class II or above; significantly impaired hepatic function; and hypersensitivity to or current use of a TZD.

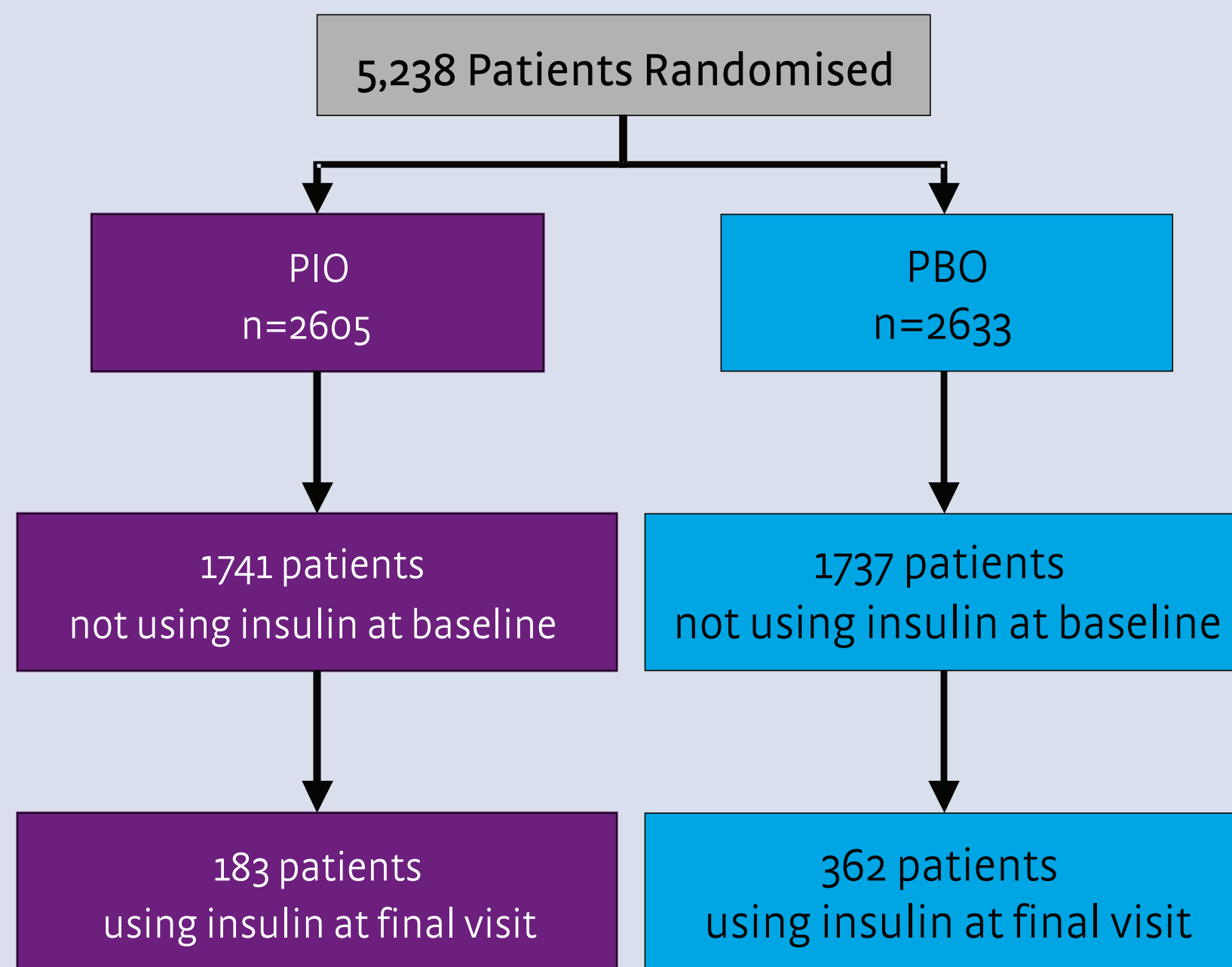
Clinical laboratory measures and safety:

- Additional measures of pharmacologic activity were also collected periodically throughout the study, including HbA1c, triglycerides, HDL cholesterol, and LDL cholesterol.
- As part of the safety assessment, information related to all serious adverse events and non-serious adverse events of special interest (ie, new or worsening heart failure, hypoglycaemia, oedema, and any adverse event that lead to permanent cessation of study drug dosing) were collected.

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 notable differences between groups who were not taking insulin at baseline.
- There were no differences between groups with regard to their glucose-lowering regimens in those not using insulin at baseline.

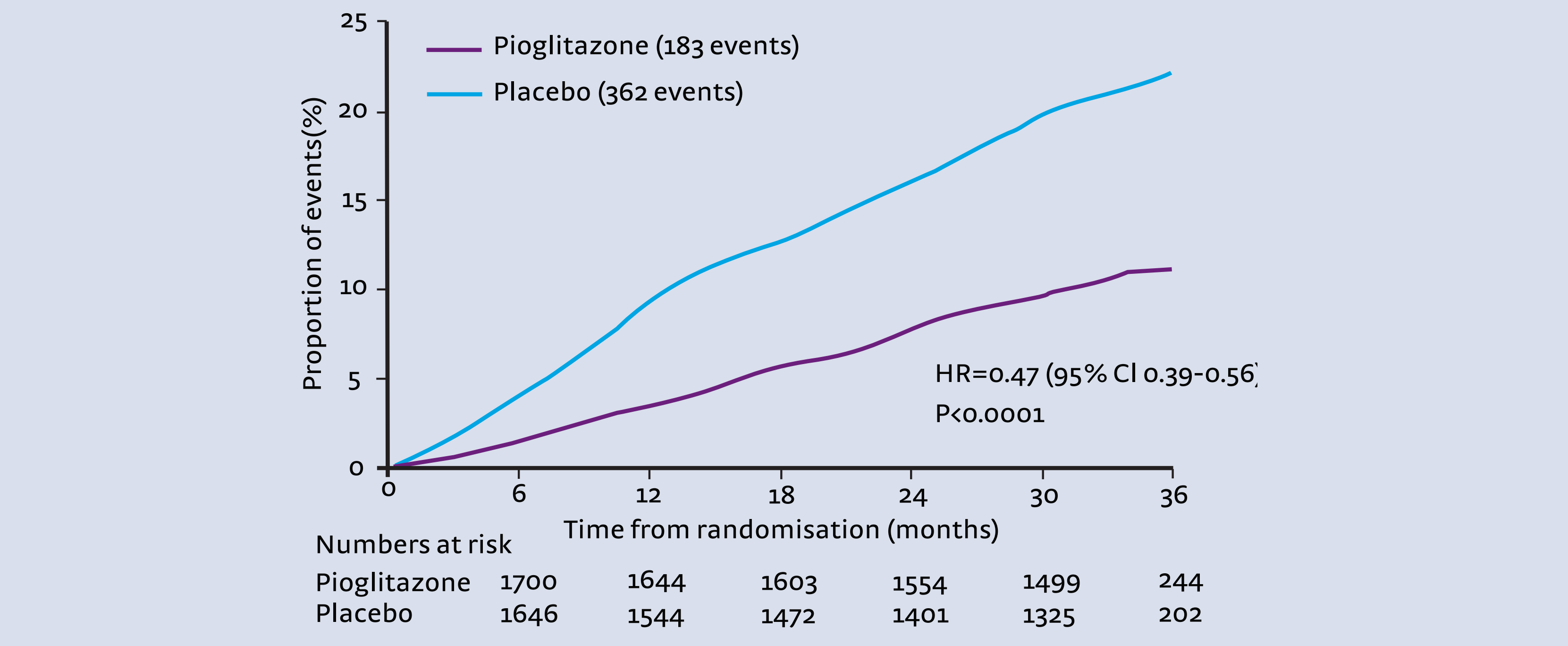
Table 1. Characteristics of Patients not Receiving Insulin at Baseline

	PIO n=1741	PBO n=1737	TOTAL n=3478
Male	1232 (70.8)	1181 (68.0)	2413 (69.4)
Race			
White	1710 (98.2)	1713 (98.6)	3423 (98.4)
Black	7 (0.4)	5 (0.3)	12 (0.3)
Asian	24 (1.4)	18 (1.0)	42 (1.2)
Age			
<65 years	1013 (58.2)	1022 (58.8)	2035 (58.5)
≥65 years	728 (41.8)	715 (41.2)	1443 (41.5)
Duration of Diabetes			
<5 years	652 (37.4)	680 (39.2)	1332 (38.3)
≥5 to 10 years	527 (30.3)	504 (29.0)	1031 (29.7)
≥10 years	562 (32.3)	552 (31.8)	1114 (32.0)
Weight (kg), mean (SD)	86.97 (15.405)	87.45 (15.554)	87.21 (15.479)
BMI (kg/m ²)			
<27	419 (24.1)	387 (22.4)	806 (23.3)
27 to <30	496 (28.6)	463 (26.8)	959 (27.7)
30 to <33	409 (23.6)	433 (25.1)	842 (24.3)
≥33	412 (23.7)	445 (25.8)	857 (24.7)

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

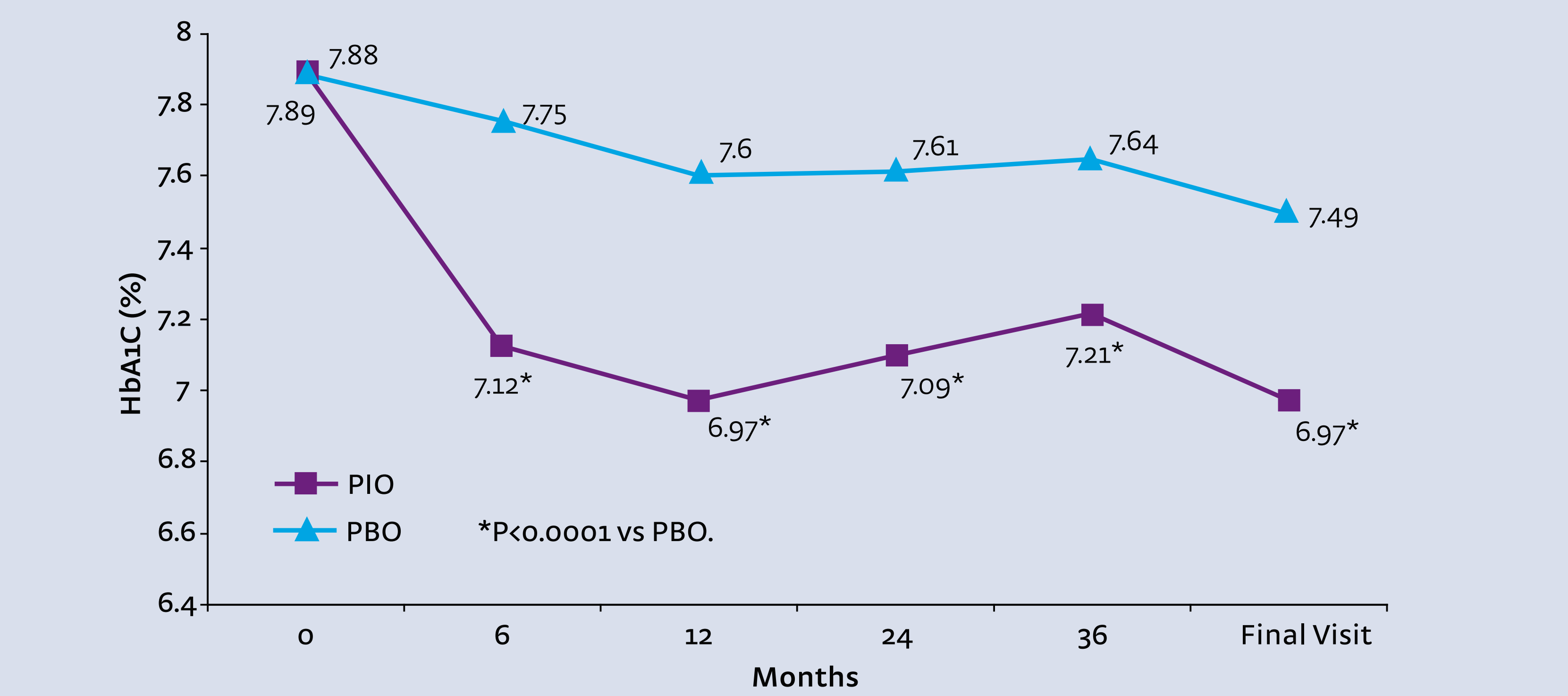
- At study entry, two thirds of patients were not receiving insulin (n=3478). Of these patients, 183 of 1741 (11%) in the PIO group and 362 of 1737 (21%) in the PBO group began to use insulin permanently (defined as insulin use for 90 days or more, or insulin use at death or end of study) during the course of the study.
- Relative to baseline, the number of patients that required additional insulin therapy at the end of 36 months was 50% less in the PIO group than PBO group.

Figure 1. Time to Permanent Insulin Use



- In the PIO group, progression to permanent insulin therapy was delayed by initiating thiazolidinedione therapy when compared with the PBO group.

Figure 2. Time Course of HbA1c in Patients Not Using Insulin at Baseline



- Glycaemic control, as measured by HbA1c, improved over the course of the study in both the PIO and PBO groups, however, the PIO group showed significantly (P<0.0001) greater improvements throughout the duration of the study.
- At the final visit, mean HbA1c in the PIO group was 6.97%, whereas the mean HbA1c in the PBO group was 7.94% (P<0.0001).

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

	PIO n=1741	PBO n=1737	P-Value*
Triglycerides (mmol/L)			
Baseline	2.18 (1.519)	2.25 (1.762)	0.359
%CFB Final Visit	-1.41 (60.954)	11.71 (61.610)	<0.0001
HDL (mmol/L)			
Baseline	1.15 (0.306)	1.16 (0.298)	0.193
%CFB Final Visit	21.60 (23.826)	11.93 (27.422)	<0.0001
LDL (mmol/L)			
Baseline	2.95 (0.889)	2.99 (0.957)	0.861
%CFB Final Visit	10.62 (38.373)	6.53 (37.006)	0.0031
LDL/HDL Ratio			
Baseline	2.68 (0.909)	2.69 (0.964)	0.568
%CFB Final Visit	-6.06 (36.792)	-2.45 (32.874)	<0.0001

CFB = Change from baseline.

Data are the mean (standard deviation) of the ITT population.

*PIO vs PBO.

- In addition to glycaemic effects, PIO showed significantly (P<0.0001) greater improvements in triglycerides and HDL cholesterol throughout the duration of the study in all therapy groups.

SAFETY:

Table 3. Serious Adverse Events

n (%)	PIO n=1741	PBO n=1737
Any SAE	770 (44.2)	791 (45.5)
Cardiac-related SAE	302 (17.3)	315 (18.1)
Heart failure	95 (5.5)	61 (3.5)
Myocardial infarction	55 (3.2)	73 (4.2)
Nervous system disorders	114 (6.5)	125 (7.2)
Cerebrovascular accident	38 (2.2)	42 (2.4)
Transient ischemic attack	29 (1.7)	21 (1.2)
Hepatobiliary disorders	19 (1.1)	17 (1.0)
Death	100 (5.7)	107 (6.2)

Table 4. Non-Serious Adverse Events of Special Interest

n (%)	PIO n=1741	PBO n=1737
Cardiac-related AE	92 (5.3)	58 (3.3)
Heart failure	92 (5.3)	54 (3.1)
Hypoglycaemia	368 (21.1)	270 (15.5)
Oedema	447 (25.7)	256 (14.7)

- The most commonly reported serious adverse events that occurred during the study were related to cardiac disorders. Events of cardiac ischemia and cerebrovascular disorders were reported more frequently for the PBO group, whereas heart failure was more frequently reported for the PIO group.
- The most commonly reported non-serious adverse events were cardiac failure, oedema, and hypoglycaemia, which were reported more frequently in the PIO group.

CONCLUSIONS

- Pioglitazone increased the time that patients could be managed without the need for permanent insulin therapy and significantly improved other important parameters such HbA1c, triglycerides, and HDL cholesterol levels.
- Progression to permanent insulin use was reduced by 50% at 3 years with PIO vs PBO and better glycaemic control was seen with PIO.

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