PROactive™

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pioglitazone HCl
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Pioglitazone Treatment in Patients with Type 2 Diabetes and a History of Myocardial Infarction: Subgroup Analyses from PROactive Stratified by Gender, Age, and Duration of Diabetes

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ABSTRACT

Background and Aims: Compared with the general population, individuals with type 2 diabetes (T2D) have an increased incidence of myocardial infarction (MI). PROactive studied the effects of pioglitazone on top of standard therapy on a composite macrovascular endpoint, which included non-fatal MI. This exploratory subanalysis of the larger PROactive study assessed 1,804 male and 641 female patients with a previous MI (≥6 months prior to randomisation).

Materials and Methods: PROactive was a double-blind, placebo-controlled study in 5,238 patients with type 2 diabetes and macrovascular disease randomised to pioglitazone or matching placebo in addition to existing glucose-lowering and cardiovascular medications, including antihypertensive, antiplatelet, and lipid-modifying drugs. The starting dose of pioglitazone was 15 mg/day, which was titrated to a dose of 45 mg/day, if tolerated. Mean follow-up was 34.5 months. Investigators were encouraged to treat diabetes, dyslipidaemia, and hypertension optimally according to the International Diabetes Federation guidelines. Analyses were performed according to gender, age (<65 years [n=1452], ≥65 years [n=993]), and duration of diabetes (<5 years [n=731], ≥5-<10 years [n=673], ≥10 years [n=1040]).

Results: The occurrence of a secondary MI (fatal or non-fatal, excluding silent MI) in patients with previous MI was significantly lower in those treated with pioglitazone than in those treated with placebo (5.3% vs 7.2%, HR=0.72, P=0.045). Interaction tests showed that there was no significant impact of gender (P=0.53), age <65 years/≥65 years (P=0.43), or diabetes duration <5 years/≥5- <10 years/≥10 years (P=0.46) on the hazards ratio for time to fatal/non-fatal MI (excluding silent MI). This suggests that the best estimate for the reduction in risk of recurrent MI for each subgroup is given by that for the entire previous MI cohort. Median HbA1c and triglycerides decreased and HDL-C increased to a greater extent in the pioglitazone group than in the placebo group in the total cohort of patients with previous MI and also in all of the gender, age, and diabetes duration subgroups (P<0.0001 for all comparisons except triglycerides in the ≥5-<10 years duration subgroup, P<0.03).

Conclusion: Pioglitazone has been shown to have beneficial effects on hyperglycaemia as well as diabetic dyslipidaemia and pleiotropic markers associated with macrovascular disease. In this exploratory subset, pioglitazone had a consistently better effect on recurrent MI and metabolic parameters than placebo did, irrespective of gender, age, and duration of diabetes.

INTRODUCTION

- The PROactive study is the first prospective study designed to evaluate whether pioglitazone (PIO) vs placebo (PBO) in combination with other glucose-lowering agents might reduce the incidence of cardiovascular (CV) events in patients with type 2 diabetes, thus improving CV outcome. [1]
- Pioglitazone was shown to prevent recurrent MI in the subgroup of patients entering PROactive with MI. [2]
- Fewer events of recurrent MI were observed among pioglitazone users (5.3% vs 7.2% in the placebo group), indicating a significant risk reduction of 28% (P=0.045) for secondary MI. [2]
- Previous studies show that MI occurs more frequently in older male patients with a long duration of diabetes. [3–6]

PURPOSE

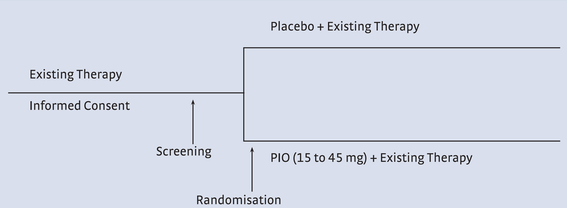
1) The PROactive study was designed to determine whether PIO reduces total mortality and macrovascular morbidity in high-risk patients with type 2 diabetes.

2) This subgroup *post-hoc* analysis looks at the effect of PIO on patients with type 2 diabetes and a history of MI stratified by gender, age, and duration of diabetes.

METHODS

- Multicentre, randomised, double-blind, placebo-controlled, parallel-group study design.

Study Design



Subjects were:

- Between the ages of 35 to 75 years.
- Diagnosed with type 2 diabetes and had an HbA_{1c} level above the upper limit of normal (ie, the local equivalent of 6.5%).
- Required to have had an established history of macrovascular disease.

Event Adjudication Process:

An independent and treatment-blinded Endpoint Adjudication Committee reviewed all events that could potentially contribute to the primary endpoint.

An event was adjudicated as an MI if at least 2 criteria of the following were met:

Ischaemic symptoms ≥30 min
ECG evidence
Cardiac enzyme evidence

Assessments

The following prespecified composite CV endpoints were evaluated in both cohorts (patients with previous MI and patients without previous MI):

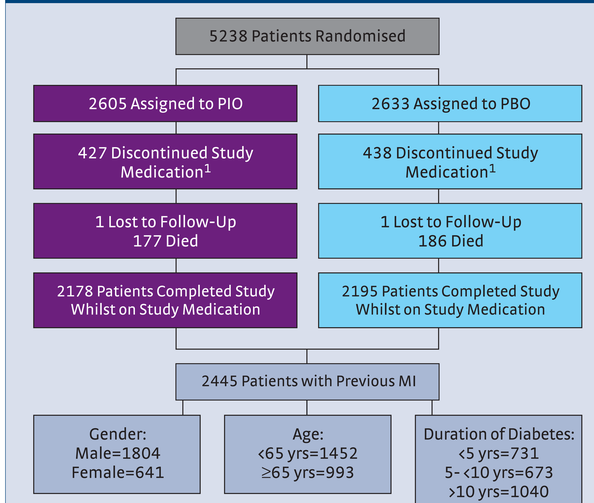
- CV death, non-fatal MI (excluding silent MI), or stroke
- CV death or non-fatal MI (excluding silent MI)
- Fatal or non-fatal MI (excluding silent MI)

The subgroups evaluated were stratified by gender, age (<65 years and ≥65 years), and duration of diabetes (<5 years, 5 to <10 years, and ≥10 years). A test for interaction between treatment and these subgroups was used.

RESULTS

Subject disposition was similar between treatment groups.

Patient Disposition



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

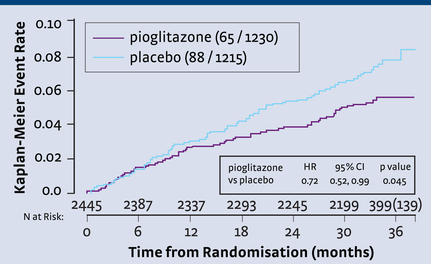
Table 1. Demographic and Baseline Characteristics

Characteristic	With Prior MI N=2445	Without Prior MI N=2793
Gender, n (%)		
Male	1804 (73.8)	1659 (59.4)
Age (years), mean (SD)		
<65	56.8 (5.6)	56.7 (5.5)
≥65	69.2 (2.9)	69.2 (2.9)
Race, n (%)		
Caucasian	2409 (98.5)	2755 (98.6)
Body mass index (kg/m^2), mean (SD)	31.0 (4.7)	30.7 (4.8)
Duration of diabetes (years), median (IQR)	8 (4, 13)	8 (4, 14)
<5	2 (1, 3)	2 (1, 3)
5- <10	7 (6, 8)	7 (5, 8)
≥10	15 (11,19)	15 (12, 19)
Blood pressure: systolic (mm Hg), mean (SD)	141.5 (17.6)	145.1 (17.7)
Blood pressure: diastolic (mm Hg), mean (SD)	82.6 (9.9)	83.4 (9.5)
History of hypertension, n (%)	1759 (71.9)	2193 (78.5)
Microvascular disease[1], n (%)	972 (39.8)	1217 (43.6)
Smoking status, n (%)		
Current smoker	300 (12.3)	421 (15.1)
Past smoker	1231 (50.3)	1127 (40.4)

SD=standard deviation; IQR=interquartile range.
[1]Retinopathy, nephropathy, neuropathy.

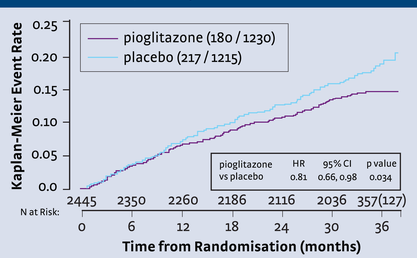
- There were some differences in baseline characteristics and previous macrovascular morbidity data between those with and those without previous MI.
  - In particular, the proportion of men, history of hypertension, and mean systolic blood pressure differed between groups (Table 1).
- Within the subgroup of patients with previous MI, demographic and baseline characteristics between the treatment groups (PIO vs PBO) were similar.

Figure 1: Time to Fatal/Non fatal MI (excluding silent MI) in Patients with Prior MI



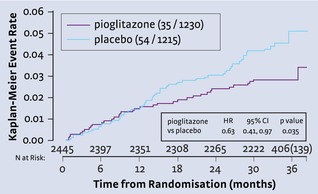
- Pioglitazone had a statistically significant beneficial effect on time to fatal or non-fatal MI (28% risk reduction relative to placebo; P=0.045).

Figure 2: Time to Composite Cardiac Endpoint (Cardiac Death, Non-fatal MI, Coronary Revascularisation, or ACS) in Patients with Prior MI



- There was a 19% risk reduction with pioglitazone relative to placebo in the cardiac composite endpoint of non-fatal MI (excluding silent MI), coronary revascularisation, ACS, and cardiac death (P=0.033).

Figure 3: Time to ACS in Patients with Prior MI



- Pioglitazone also significantly reduced the occurrence of acute coronary syndrome in patients with previous MI (37% risk reduction relative to placebo; P=0.035)

Analysis of Treatment Effect by Subgroup

- Interaction tests showed that there was no significant impact of gender (P=0.53), age <65 years/≥65 years (P=0.43), or diabetes duration <5 years/≥5-<10 years/≥10 years (P=0.46) on the hazards ratio for time to fatal/non-fatal MI (excluding silent MI).

Table 2. Changes from Baseline to Final Visit in HbA1c and Lipid Parameters in Patients with Prior MI

By gender	PIO	PBO	P-Value
Male, N	909	895	
HbA1c, change in % (IQR)	-0.7 (-1.5, -0.1)	-0.3 (-1.1, 0.3)	<0.0001
Triglycerides, % change (IQR)	-10.2 (-34.6, 19.6)	1 (-27.6, 36.1)	<0.0001
HDL-cholesterol, % change (IQR)	18.8 (6.7, 32.9)	10.1 (-2, 21.5)	<0.0001
LDL-cholesterol, % change (IQR)	7.9 (-12, 26.6)	4.2 (-14.8, 22.8)	0.0492
Female, N	321	320	
HbA1c, change in % (IQR)	-0.9 (-1.7, -0.4)	-0.4 (-1.2, 0.4)	<0.0001
Triglycerides, % change (IQR)	-13.5 (-35.5, 14.1)	1.3 (-21.4, 30.2)	<0.0001
HDL-cholesterol, % change (IQR)	18.6 (6.1, 34.6)	9.4 (-1.8, 21.7)	<0.0001
LDL-cholesterol, % change (IQR)	7.8 (-9.9, 31.8)	5.5 (-13.4, 26.8)	0.2767
By age	**PIO**	**PBO**	**P-Value**
<65 Years, N	724	728	
HbA1c, change in % (IQR)	-0.8 (-1.6, -0.1)	-0.4 (-1.2, 0.3)	<0.0001
Triglycerides, % change (IQR)	-11.7 (-35.5, 19.8)	2.3 (-25.5, 40.2)	<0.0001
HDL-cholesterol, % change (IQR)	19.4 (7.1, 34.5)	10.7 (-1.6, 21.6)	<0.0001
LDL-cholesterol, % change (IQR)	9.9 (-9.2, 31.7)	6.6 (-12.4, 26.8)	0.0928
≥65 Years, N	506	487	
HbA1c, change in % (IQR)	-0.8 (-1.5, -0.1)	-0.4 (-1.1, 0.3)	<0.0001
Triglycerides, % change (IQR)	-9.5 (-32.2, 16.3)	-0.1 (-25.3, 29.5)	0.0001
HDL-cholesterol, % change (IQR)	18.2 (5.1, 32.0)	8.9 (-2.2, 21.6)	<0.0001
LDL-cholesterol, % change (IQR)	3.2 (-16, 23.2)	-0.3 (-18.4, 18.5)	0.1341
By duration of diabetes	**PIO**	**PBO**	**P-Value**
<5 Years, N	361	370	
HbA1c, change in % (IQR)	-0.7 (-1.4, 0)	-0.3 (-1.0, 0.3)	<0.0001
Triglycerides, % change (IQR)	-12.8 (-34.6, 15.2)	4.1 (-22.9, 34.9)	<0.0001
HDL-cholesterol, % change (IQR)	18.7 (6.8, 34.7)	10 (-1.4, 19.0)	<0.0001
LDL-cholesterol, % change (IQR)	8 (-8.5, 28.3)	3.3 (-14.6, 20)	0.0051
5 to <10 Years, N	347	326	
HbA1c, change in % (IQR)	-0.9 (-1.7, -0.3)	-0.4 (-1.3, 0.4)	<0.0001
Triglycerides, % change (IQR)	-10.2 (-32.7, 13.4)	-3.5 (-30.1, 34.6)	0.0262
HDL-cholesterol, % change (IQR)	18.6 (6.8, 31.7)	10.1 (-0.8, 22.1)	<0.0001
LDL-cholesterol, % change (IQR)	4.4 (-15.6, 24.7)	4.1 (-15.5, 21.8)	0.8337
≥10 Years, N	522	518	
HbA1c, change in % (IQR)	-0.8 (-1.5, -0.2)	-0.4 (-1.2, 0.3)	<0.0001
Triglycerides, % change (IQR)	-11.2 (-36.8, 23.4)	1.9 (-25.5, 36.1)	<0.0001
HDL-cholesterol, % change (IQR)	18.9 (6.1, 34.3)	9.4 (-3.1, 22.2)	<0.0001
LDL-cholesterol, % change (IQR)	9.1 (-11.1, 29.8)	5.8 (-13.8, 27.2)	0.3474

IQR=inter-quartile range

- Median HbA_{1c} and triglycerides decreased and high-density lipoprotein (HDL)-cholesterol increased to a greater extent in the PIO group than in the PBO group across all subgroups (ie, gender, age, and duration of diabetes).

CONCLUSIONS

- The results from PROactive showed that pioglitazone had a consistently better effect on recurrent MI than placebo did.
- In this exploratory analysis, the beneficial effect on secondary MI was shown to be independent of gender, age, and duration of diabetes.

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