

Pioglitazone Treatment in Patients with Type 2 Diabetes and a History of MI: Subgroup Analyses From PROactive Stratified by Gender, Age, and Duration of Diabetes

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Background and aims: Compared with the general population, individuals with type 2 diabetes 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).

Material 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 anti-hypertensive, 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 recurrent fatal or non-fatal MI (excluding silent MI) in patients with previous MI was significantly lower in those treated with pioglitazone than in those treated with placebo (5.3% *versus* 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 HbA_{1c} 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 hyperglycemia as well as diabetic dyslipidemia 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.