

## **Pioglitazone reduces insulin requirements and improves glycaemic control in insulin-treated patients with type 2 diabetes: results from PROactive**

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on behalf of the PROactive investigators;

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**Background and Aims:** Type 2 diabetes is a progressive disease with associated insulin resistance and diminished insulin production. Treatment typically requires multiple agents, including insulin. PROactive was a study designed to evaluate the effects of pioglitazone on cardiovascular outcomes in 5,238 high-risk patients with type 2 diabetes. We examined insulin requirements and glycaemic control in the one-third of patients (n=864 in the pioglitazone group; n=896 in the placebo group) who were treated with insulin at baseline in PROactive.

**Materials and Methods:** PROactive was a randomised, double-blind, placebo-controlled outcome study in patients with type 2 diabetes and macrovascular disease randomised to pioglitazone or matching placebo, in addition to their existing glucose-lowering and cardiovascular medication. Doses of pioglitazone were force-titrated to a dose of 45 mg, if tolerated. Mean follow-up was 34.5 months. Within the cohort of patients receiving insulin at baseline, baseline mean daily insulin doses and HbA1c values were similar between treatment groups (pioglitazone: 47 U/d and 8.4%; placebo: 47 U/d and 8.5%). In both groups at baseline, insulin was combined with oral monotherapy with metformin in 53% and sulfonylurea in 24% of patients and with dual therapy with metformin+sulfonylurea in 12%.

**Results:** There was a rapid and sustained decrease in insulin dose with pioglitazone, whereas there was a progressive increase with placebo. By study end, the mean insulin dose was lower with pioglitazone (42 U/d) than with placebo (55 U/d;  $P<0.0001$ ); nevertheless, a greater decrease in HbA1c was observed with pioglitazone (0.93%) compared with placebo (0.45%;  $P<0.0001$ ). At final visit, insulin had been discontinued in 9% of patients in the pioglitazone group versus 2% in the placebo

group ( $P < 0.0001$ ). The distribution of patients on oral/insulin combined therapy remained similar in both groups: metformin alone in 47% versus 52%, sulfonylurea alone in 16% versus 16%, and metformin+sulfonylurea in 10% versus 11%, in the pioglitazone group versus the placebo group, respectively ( $P = \text{NS}$ ). There were differences in oedema (pioglitazone: 31%; placebo: 18%;  $P < 0.0001$ ) and hypoglycaemia (pioglitazone: 41%; placebo: 29%;  $P < 0.0001$ ), but there were no other differences in the safety profiles between the pioglitazone and placebo groups (with or without other treatments).

**Conclusion:** Pioglitazone reduced the number of patients on insulin and the mean daily insulin dose while providing better glycaemic control than placebo.

