

RAPID APPRAISAL

Name of Trial: 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

Reference: Dormandy JA, Charbonnel B, Eckland DJA et al Lancet 2005;366:1279-89

Question: Does pioglitazone reduce macrovascular morbidity and mortality in high-risk patients with type 2 diabetes?

Summary: Pioglitazone was compared with placebo in patients with type 2 diabetes who were taking a number of blood-glucose lowering treatments and insulin. This trial provides some preliminary evidence that pioglitazone may reduce the risk of death, myocardial infarction (MI) and stroke in diabetic patients who are at high risk of such events. These results were based on a secondary endpoint which appears to have been defined post hoc. The primary endpoint of the study did not reach statistical significance. The pioglitazone group also demonstrated an increased risk of heart failure. There is a known risk of heart failure associated with pioglitazone, especially in patients taking insulin; for this reason the UK licence does not permit use with insulin or use in patients with pre-existing disease. Further research is required to determine the absolute benefit of using pioglitazone in high-risk patients.

Did the study ask a clearly focussed question?

Yes - the study was designed to assess the effect of pioglitazone on cardiovascular events in patients with type 2 diabetes who already had evidence of macrovascular disease.¹ The composite primary endpoint was time from randomisation to the occurrence of a new macrovascular event or death. Macrovascular events included were non-fatal myocardial infarction (MI) (including silent MI), stroke, leg amputation above the ankle, acute coronary syndrome, coronary revascularisation and leg revascularisation.^{1,2} Secondary endpoints included the individual components of the primary endpoint plus cardiovascular mortality.²

Was the study design appropriate?

Yes - the study was prospective, randomised, double-blind and placebo-controlled. Patients with evidence of macrovascular disease were defined by one or more of the following: MI or stroke at least 6 months before entry to the trial, percutaneous coronary intervention or coronary artery bypass surgery at least 6 months before recruitment, acute coronary syndrome at least 3 months before recruitment, or objective evidence of coronary artery disease or obstructive arterial disease in the leg. Exclusion criteria included

patients with any signs of type 1 diabetes, patients on insulin monotherapy (although patients taking insulin in combination with an oral antihyperglycaemic drug were included), planned coronary or peripheral revascularisation, symptomatic heart failure (New York Heart Association class II or above) and significantly impaired hepatic function. Allocated patients were given 15 mg pioglitazone for the first month, 30 mg for the second, and 45 mg for the third to achieve the maximum tolerated dose. The dose could be adjusted within this range at any time if clinically indicated. The study was funded by Takeda Pharmaceutical Company and Eli Lilly and Company.

Were participants appropriately allocated to intervention and control groups?

Yes – allocation of patients to treatment groups was done by the method of randomised permuted blocks within centre. The randomisation sequence was generated by a member of the contracted statistical team. The two groups were well matched with regard to baseline characteristics. 82 randomised patients (2%) were later discovered not to have met the inclusion criteria relating to previous macrovascular disease, and 13 patients (0.2%) were recruited despite fulfilling exclusion criteria

(insulin monotherapy). All were included in the intention-to-treat analysis.

Were participants, staff and study personnel 'blind' to participants study group?

Yes – the authors state that all investigators and study personnel were unaware of the treatment assignment for the duration of the study although they do not go into detail as to how this was achieved.

Were all of the participants who entered into the trial accounted for at its conclusion?

Yes - all patients received the intended treatment although 16% of those in the pioglitazone group and 17% of those assigned placebo discontinued study medication before death or final visit. Only two patients were lost to follow up; reasons were given (moved away).

Were the participants in all groups followed up and data collected in the same way?

Yes - all patients were followed up until the end of the study. Patients were seen monthly for the first two months, then every two months for the first year, then every three months until the final visit. No details of any missed appointments were given. The treatment code was broken for three patients.

Was the study large enough?

Yes - the study had 91% power to detect a 20% reduction in hazard of the primary endpoint with a type I error of 0.05. In order to do this, all patients had to be followed up until at least 760 patients had one endpoint event or more, which was achieved. As the event rate was higher than expected and the recruitment rate was faster than planned, the protocol was amended so that follow-up had to be at least 30 months.

How are the results presented and what is the main result?

The average time of observation was 34.5 months. The hazard ratios (HRs) of the composite primary and secondary endpoints were determined using Kaplan-Meier curves. There was a non-significant reduction in the HR for the composite primary endpoint (HR = 0.90, $p = 0.095$). A composite of death, MI (excluding silent MI) and stroke was described as the main secondary endpoint. This composite showed a statistically significant reduction in HR (HR = 0.84, $p = 0.027$). However, although the original protocol specified the individual endpoints as secondary endpoints, it did not specify the composite secondary endpoint used in the final analysis, which therefore appears to have been decided 'post hoc'. The HRs of the individual components of the primary and secondary endpoints did not reach significance. Reductions

in the composite secondary endpoint were also presented as number needed to treat (NNT) using the mean HR and it was estimated that allocation of 1000 patients to pioglitazone would avoid 21 first MIs, strokes or deaths over 3 years (or 48 patients would need to be treated for 3 years to avoid one first event). The four most frequent endpoints were death, MI, stroke and coronary revascularisation. Concentrations of triglycerides decreased and high density lipoproteins (HDL) increased significantly in the pioglitazone group relative to placebo. The ratio of low density lipoprotein (LDL) to HDL also decreased significantly in the pioglitazone group, despite a slight increase in the LDL concentration.

How safe were the regimens?

There were more reports of heart failure, including patients requiring hospital admission, in the pioglitazone group than the placebo group. The difference between the total number of reports of heart failure was significant ($p < 0.0001$); when expressed as numbers needed to harm (NNH), treating approximately 31 patients for 3 years would be expected to result in one case of heart failure. However, the numbers of deaths attributed to heart failure in the two groups were similar (approximately 1% of patients). There were also more reports of oedema without heart failure in patients taking pioglitazone. Symptoms compatible with hypoglycaemia were more common in the pioglitazone group ($p < 0.0001$), whereas slightly more patients in the placebo group needed to be admitted to hospital for management of diabetes (3% versus 2% respectively). There were more reports of bladder cancer in the pioglitazone group (14 versus 6). The authors concluded that the imbalance was unlikely to have been due to pioglitazone treatment.

How precise are the results?

This was a large randomised controlled trial. The HR for the primary endpoint was non-significant ($p = 0.095$; 95% CI 0.8-1.02). The HR for the secondary composite endpoint (death, MI (excluding silent MI), or stroke) was significant ($p = 0.027$; 95% CI 0.72-0.98), but the CI was broader than that for the primary endpoint and the upper limit was close to the no effect value of 1. The reliability of using the secondary endpoint in drawing conclusions is questionable, as the study was powered only for analysis of the primary endpoint.³ Excluding the procedure endpoints from the overall composite primary endpoint was sufficient for the result to reach significance. This may be because procedure endpoints are less sensitive and less specific than disease endpoints.⁴

Can the results be applied to the local population?

This study population comprised of patients at high risk of macrovascular conditions as determined by a history of existing disease. Patients were taking a number of different blood-glucose lowering treatments and insulin. Of the initial study population, 4% were not receiving any drug therapy, 29% were taking metformin or a sulphonylurea as monotherapy, 25% were taking metformin and a sulphonylurea and approximately 30% were taking insulin in combination with metformin or sulphonylureas or both. Of the patients not receiving insulin, 11% in the pioglitazone group and 21% in the placebo group began using insulin permanently during the course of the study.

Pioglitazone is licensed for use in the UK as monotherapy, or in combination with a sulphonylurea or metformin. Use with insulin or in heart failure is contraindicated.⁵ NICE guidance currently states: *The present UK licence does not allow the Institute to recommend the use of glitazones in triple combination therapy (with other oral antidiabetic agents), as monotherapy, or in combination with insulin. The use of a glitazone in triple combination (with other oral antidiabetic agents) is classified in the licence under 'special warnings and special precautions for use'. This precaution is based on the fact that at the time the licence was issued there was no clinical experience of triple combination therapy.*⁶ This guidance was issued prior to the licensing of pioglitazone as monotherapy. Review of NICE guidance is due in 2006, and recommendations will take into account extensions to the licences for the use of glitazones. Using current recommendations however, at least 60% of patients in this study would not be considered for treatment with pioglitazone in the UK.

An increased incidence of heart failure in the pioglitazone group was demonstrated in this study. It is not clear whether this risk applies equally to all patients, or is more likely in subgroups already at high risk of heart failure. Oedema and heart failure are recognised adverse

effects when pioglitazone is taken in conjunction with insulin.⁵ This raises the question of whether the increased risk of heart failure is outweighed by the benefit of a small decrease in risk of macrovascular events, and which is more acceptable to the patient.

How pioglitazone affected cardiovascular outcome is unclear. Glycaemic control was better in the pioglitazone group, despite investigators being required to increase all therapy to an optimum. Intensive blood-glucose control (by sulphonylureas or insulin) has been shown to decrease the risk of microvascular complications, but not macrovascular events, in patients with type 2 diabetes.⁷ Better blood pressure control was achieved in the pioglitazone group (median change - 3 mmHg versus 0 mmHg systolic, $p=0.03$) and some favourable effects on metabolic markers were also observed. Throughout the study, optimisation of antihypertensive, lipid lowering and anti-platelet drugs was required.

This study only investigated patients at high risk of macrovascular events, i.e. previous history of MI, stroke, percutaneous coronary intervention, coronary artery bypass surgery, acute coronary syndrome or evidence of coronary artery disease or obstructive arterial disease in the leg. In these cases, management may be best reserved for specialists in a secondary care setting. NNT values for patients at lower risk are not known and may be substantially higher than those for these high risk patients.

Does pioglitazone reduce macrovascular morbidity and mortality in high risk patients with type 2 diabetes?

This trial provides some preliminary evidence that pioglitazone may reduce the risk of death, MI and stroke in diabetic patients who are at high risk of such events. However, the known risk of heart failure associated with the use of pioglitazone, particularly in patients taking insulin, precludes the drawing of firm conclusions of the overall benefit of pioglitazone in these patients.

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RCT-randomised controlled trial, U-unpublished, E-editorial G-guideline

Regional Drug and Therapeutics Centre (Newcastle)
Wolfson Unit, Claremont Place, Newcastle upon Tyne NE2 4HH
Tel: 0191 232 1525 Fax 0191 260 6192 E-mail: nyrdtc.di@ncl.ac.uk
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