The PROactive study

In this new section, a panel of multidisciplinary team members give their opinions on a recently published diabetes paper. In this issue, the focus is on the results of the PROspective pioglitAzone Clinical Trial In macroVascular Events.

John Nolan, Consultant Endocrinologist, St James's Hospital, Dublin

The recently reported findings of the PROactive study will be a disappointment to patients with type 2 diabetes, their doctors, and those involved in this field of clinical investigation. After an average period of nearly 3 years, pioglitazone treatment, when added to all other standard therapies, resulted in only a marginal benefit in terms of a secondary endpoint, which comprised all-cause mortality, non-fatal myocardial infarction and stroke. The effect on the primary endpoint did not reach significance.

This was a large and adequately powered study. The study design and inclusion criteria raise important questions. The patient population represented a very late phase in the metabolic and cardiovascular complications of type 2 diabetes. With an average duration of diabetes of 8 years (and a true biological duration of hyperglycaemia of 15–20 years), all participants had evidence of macrovascular complications. Nearly half the cohort had micro- or macroalbuminuria. Clinical evidence to date for the glitazones has been most promising in the very early stages of dysglycaemia and type 2 diabetes – at the opposite end of the disease process to the patient cohort chosen in this study.

The most optimistic interpretation of the PROactive study would be that the metabolic, cellular and vascular effects of these drugs are maximal in the early stages of the disease and much less effective in the advanced phase of diffuse atherosclerosis. LDL-cholesterol was far from optimal in this population (2.9 mmol/l at baseline, disimproving after pioglitazone). Based on evidence from the Heart Protection Study and CARDS (Collaborative AtoRvastatin Diabetes Study), and current guidelines for lipid lowering therapy, it is likely that aggressive LDL-cholesterol reduction to target in this same cohort would have had far greater benefit than pioglitazone in terms of the endpoints chosen.

'Based on current evidence and guidelines it is likely that aggressive LDL-cholesterol reduction would have had far greater benefit than pioglitazone in terms of the endpoints chosen.'

Roger Gadsby, GP, Nuneaton and Senior Lecturer, Centre for Primary Healthcare Studies, Warwick University

This was a well-executed placebo-controlled study with a large number of subjects in a high-risk population. The hard endpoint of death plus non-fatal stoke and myocardial infarction reached statistical significance.

I think the data on reduced need to start insulin in the pioglitazone group are also interesting and important.

The participants studied were similar to those seen in UK general practice and the results are therefore generalisable.

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The reductions in risk in the intervention group were perhaps less impressive than had been hoped. However, I do feel that this study does give me hard endpoint data to promote the use of pioglitazone, as the first addition to metformin montherapy, instead of a using a sulphonylurea, which is known not to lower cardiovascular risk, in the people I look after who have type 2 diabetes.

Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study: a randomised controlled trial

Dormandy JA, Charbonnel B, Eckland DJA et al (2005) *The Lancet* **366**: 1279–89

THE LANCET

Pioglitazone reduces specific vascular events in type 2 diabetes

1 It is well established that people with type 2 diabetes are at high risk of fatal and non-fatal myocardial infarction and stroke. These macrovascular events are the principal cause of the reduced life expectancy associated with the condition.

2 Pioglitazone, an agonist of peroxisome proliferator-actived receptor gamma, is used in the treatment of type 2 diabetes. Several of its metabolic effects suggest that it may reduce the macrovascular risk associated with the condition.

3 In this paper, the investigators report on a prospective, multicentre, randomised controlled trial in which 5238 people with type 2 diabetes and evidence of established macrovascular disease were randomised to receive either pioglitazone (maximum of 45 mg/day,→

→ titrated up from 15 mg/day; n=2605) or placebo (n=2633) in addition to their existing medications. Participants were included if they were aged 35–75 years with HbA_{1c} >6.5 % and were treated with diet alone or with oral hypoglycaemic agents (with or without insulin in addition). The study groups were well matched in their baseline characteristics.

4 The study's primary endpoint was the time from randomisation to a composite of all-cause mortality, non-fatal myocardial infarction (MI), stroke, acute coronary syndrome plus endovascular and surgical interventions.

5 The main secondary endpoint was the time to the composite of all-cause mortality, stroke or non-fatal MI.

6 The proportion of participants reaching the composite primary endpoint was lower at the end of the study in the pioglitazone group (n=514/2605) compared with placebo (n=572/2633), but failed to reach statistical significance (hazard ratio [HR]: 0.90; 95 % confidence interval [CI]: 0.80–1.02; *P*=0.095).

7 The proportion of patients reaching the main composite secondary endpoint was also lower in the pioglitazone group (n=301/2605) compared with the placebo group (n=358/2633). In this case the difference was statistically significant (HR: 0.84; 95 % CI: 0.72–0.98; *P*=0.027).

8 At the start of the study, two-thirds of patients were not using insulin. During the course of the trial 11 % of the non-insulin users treated with pioglitazone (n=183/1741) began to use insulin compared with 21 % of the non-insulin users in the placebo group (n=362/1737; HR: 0.47; 95 % CI: 0.39–0.56; *P*<0.0001).

9 The authors concluded that, in patients with type 2 diabetes who are at high risk of cardiovascular events, pioglitazone treatment can reduce the composite of all-cause mortality, non-fatal MI and stroke. Furthermore, pioglitazone treatment reduces the need for insulin in addition to other glucose-lowering regimens.

Marc Evans
Consultant Physician, Llandough Hospital, Cardiff

This was an event-driven study which showed that pioglitazone therapy in this context would avoid 21 myocardial infarctions, strokes or deaths per 1000 patients treated over 3 years.

In the pioglitazone group there were also notable reductions in systolic blood pressure (around 3 mmHg), serum transaminase levels, frequency of angina and a 50 % reduction in need for insulin therapy. Furthermore, the pioglitazone cohort demonstrated a 0.5 % greater reduction in HbA_{1c}. The lack of significance in terms of the primary endpoint may represent the selection of too broad an endpoint, but may also be a function of relatively short exposure to pioglitazone. The outcome benefits in terms of the secondary endpoint may be accounted for by the metabolic changes associated with pioglitazone therapy when these are incorporated into the UK Prospective Diabetes Study (UKPDS) risk engine analysis.

The mean duration of diabetes in this study was 8 years, suggesting potential benefits of glitazone-based therapy even when used late in the natural history of type 2 diabetes. Of note was a significant incidence of oedema and fluid retention in the pioglitazone group suggesting that careful assessment of cardiac failure status should be made prior to initiation of glitazone therapy.

In summary, the PROactive study suggests that pioglitazone-based therapy may influence the natural history of type 2 diabetes from the perspective of both metabolic control and cardiovascular risk.

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Sue Cradock, Consultant Nurse – Diabetes, Portsmouth Hospitals/ Portsmouth City tPCT, Portsmouth

The glitazones are now very much part of the treatment armoury for those with type 2 diabetes. This study had been expected to provide further data about the expected benefits of this group of drugs on cardiovascular disease prevention, as well as their known impact on glycaemic control. Searches on the internet show the words 'landmark' and 'groundbreaking' as adjectives being applied to the study in its press releases.

However, as with the UK Prospective Diabetes Study, the high expectations were not quite met. The PROactive study showed some benefits, but its primary endpoints were not individually affected – only a composite of primary endpoints (all-cause mortality, non-fatal MI and stroke) reached significance when the data were analysed. It is also interesting that the investigators report including 82 patients (20 with no previous macrovascular event) who did not meet the study entry criteria. The fact that they were included in the primary analysis, and we are not told how they are distributed between the intervention and control groups, makes me wonder how their inclusion affects the significance of the results.

The issue of heart failure being identified in more patients in the pioglitazone arm of the study is unclear, as the definition and diagnosis of heart failure was not specific. Possibly some patients could have just had ankle oedema rather than heart failure – no diagnostic tests such as ultrasounds were used.

The challenges of this study for me as a clinical practitioner are that, despite the reported 95 % 'compliance' with the drug, only a small number of patients benefited. But what will be the significance of this in the real world of UK health care, where 'compliance' with medication is actually between 30 and 40 % (as shown in tracked prescription studies; Evans et al, 2002).

I am interested in the high profile of this study, which may be more about good marketing rather than clear clinical outcomes. I have no doubt in the value of glitazones for some of our patients, but am not sure about the specific messages from this study adding more to our knowledge base. It does provide some increased confidence in their use, which no doubt will be capitalised upon!

Evans JM, Donnan PT, Morris AD (2002) Adherence to oral hypoglycaemic agents prior to insulin therapy in Type 2 diabetes. *Diabetic Medicine* **19**(8): 685–8