The PROactive study: some answers, many questions

The insulin-sensitising glitazones, which are selective ligands of the nuclear transcription factor peroxisome proliferator-activated receptor γ (PPARγ), ameliorate the basic problem of insulin resistance and have therefore been thought to reduce the risk of cardiovascular disease in patients with type 2 diabetes.[1] Glitazones are currently approved for treatment of hyperglycaemia. These drugs lower glucose concentrations by ameliorating insulin resistance, especially in the liver, but their mechanism of action, at least in vitro, involves changes in the expression of hundreds of genes. This action is ligand-specific, which implies that results obtained with one glitazone might not be applicable to others. Findings in mice have given mixed messages about the effects of PPARγ agonists on atherogenesis and on colon and bladder cancer, raising questions about the safety and potential benefits of the drugs in human beings. Despite such uncertainties, glitazones account for 21% of oral antihyperglycaemic drugs used in the USA and 5% in Europe.[2] This fact exemplifies the power of marketing compared with evidence-based medicine in guiding treatment practices.

The PROactive study,[3] reported in today's *Lancet*, addresses the role of pioglitazone in the prevention of macrovascular events in patients with type 2 diabetes. The inclusion criteria of the study were brave, as 5238 patients who had extensive evidence of macrovascular disease participated. A third of the patients were treated with insulin. The patients were already using many drugs known to reduce the risk of cardiovascular disease—85% were on antiplatelet medications, 70% on blockers of the renin-aldosterone-angiotensin axis, and 43% on statins. Exclusion criteria included concentrations of serum alanine aminotransferase elevated 2·5-fold above the upper limit of normal. This principle might have excluded patients who respond best to glitazones, as the main mechanism of action of these drugs is a reduction in the fat content of the liver and in hepatic insulin resistance.[1]

The primary endpoint in PROactive was a composite that included both disease endpoints, such as death, myocardial infarction, and stroke, and procedure endpoints such as coronary and leg revascularisations. The secondary endpoint only included disease endpoints. Pioglitazone did not affect the number of patients reaching the primary endpoint, but significantly reduced the number that reached the secondary endpoint. Inclusion of procedure endpoints in the primary endpoint was unfortunate, since procedure endpoints are less specific and less sensitive than disease endpoints, and bias treatment effect towards the null value of 1. In PROactive, pioglitazone reduced all disease endpoints, whereas the number of coronary revascularisations was the same in both groups and the number of leg revascularisations greater in the pioglitazone than the placebo group. Paradoxically, it was also unfortunate that recruitment was faster than anticipated and the decision to close the trial (after 34·5 instead of 48 months) was endpoint driven, because this might have reduced the likelihood of achieving a positive result with respect to the primary endpoint, assuming that the Kaplan-Meier curves continued to diverge as a function of time.

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Pioglitazone reduced the number of primary composite endpoints by 58, but its use was associated with an increase in oedema not attributable to heart failure (221 events more in the pioglitazone than the placebo group) and in heart failure (115 events more in the pioglitazone than the placebo group; figure). There was also a significant increase in the incidence of pneumonia, which is sometimes misdiagnosed as heart failure, a marginally significant increase in bladder cancer (p=0·069)

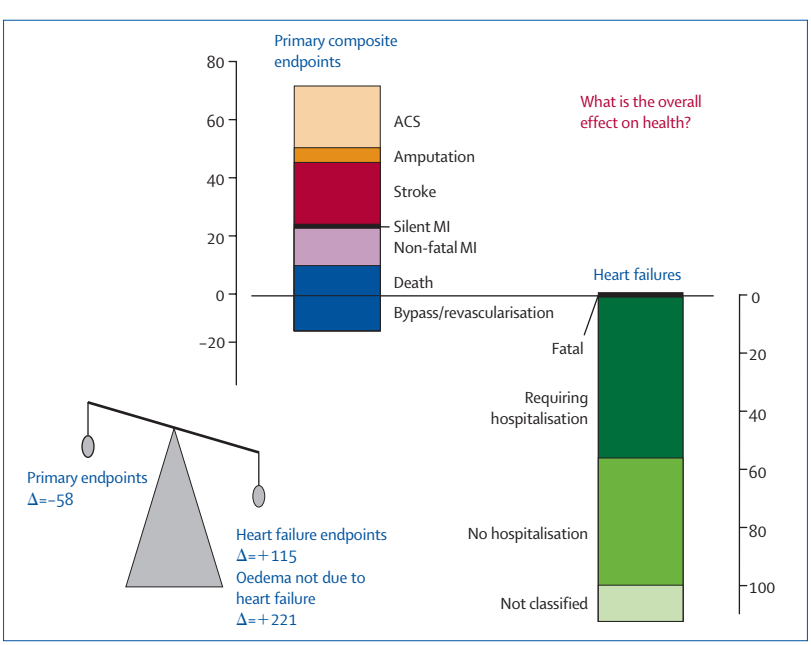

Figure: **Effect of pioglitazone compared with placebo on primary endpoint and on incidence of oedema diagnosed as heart failure in PROactive**
ACS=acute coronary syndrome. MI=myocardial infarction.

***Panel:* Pros, cons, and unknowns of pioglitazone**

Good news

Pioglitazone reduces composite of all-cause mortality, non-fatal myocardial infarction, and stroke in patients with type 2 diabetes with pre-existing cardiovascular disease by about 16%

Bad news

Incidence of oedema not attributable to heart failure is four times greater, and that of heart failure two times greater, than reduction in incidence of cardiovascular events by pioglitazone

Body weight increases more than with other antihyperglycaemic therapies, including insulin

Unknowns

What is prognosis of heart failure?

Who is at greatest risk of developing oedema not attributable to heart failure and who is at risk of developing heart failure?

Is it safe to use insulin with pioglitazone?

Why does pioglitazone reduce cardiovascular events?

—although after exclusion of tumours judged by blinded review to be unrelated to the treatment, the difference was not significant (p=0.309)—and a significant decrease in the number of breast cancers in the pioglitazone group compared with placebo. From the patient's perspective, is it better to have healthy arteries in the heart than a failing heart? The prognosis of heart failure is particularly poor in patients with type 2 diabetes. When presenting the results, the investigators emphasised that heart failure was not a centrally adjudicated event and that increased reporting of heart failure was at least partly caused by a diagnostic bias because of increased oedema. The cardiologists were keen to comment that heart failure induced by pioglitazone is not as dangerous as other types of heart failure, although no data are presented to support this comment in the study. Weight gain was 4 kg greater with pioglitazone than placebo; four times greater than would be expected on the basis of improved glycaemic control.[4] Common sense would suggest that anything that causes weight gain increases the risk of heart failure. Even if half the patients were misclassified, the number of heart failures (115/2=58) would still equal the number of primary endpoints that were reduced by pioglitazone (n=58). Since combination therapy with glitazones and insulin is contraindicated in Europe because of an increased risk of heart failure, it would have been important, by stratification at randomisation, to know whether heart failure was more common in patients who used insulin than in those who did not. The article lists hazards associated with relevant baseline characteristics for the main secondary endpoint.[3] For the practising physician it would be more important to identify predictors of heart failure.

Overall, PROactive is an important study that leaves us with some good news, some bad news, and some unknowns (summarised in the panel). The clinician, of course, wants to know who should be treated with pioglitazone. Unfortunately, the study does not provide such answers. It showed that pioglitazone is beneficial in patients with type 2 diabetes and pre-existing macrovascular disease who do not develop heart failure.

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I have been a consultant for Lilly-Amylin, Sanofi-Aventis, Merck Sharpe and Dohme, Merck, and Astra-Zeneca. I have received speaker's fees from Glaxo (Finland), Lilly, and Sanofi-Aventis, research funding from Lilly-Amylin, Astra-Zeneca, and Sanofi-Aventis, and travel or accomodation payments for consultancies and lectures.

1 Yki-Järvinen H. Thiazolidinediones. *N Engl J Med* 2004; **351:** 1106–18.
2 IMS Health, IMS MIDAS. http://www.imshealth.com (accessed Sept 28, 2005).
3 Dormandy JA, Charbonnel B, Eckland DJA, on behalf of the PROactive investigators. 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. *Lancet* 2005; **366:** 1279–89.
4 Yki-Järvinen H. Combination therapies with insulin in type 2 diabetes. *Diabetes Care* 2001; **24:** 758–67.

Suicide in prison

Published online September 15, 2005
DOI:10.1016/S0140-6736(05)67327-8

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In *The Lancet* today, Seena Fazel and co-workers express concern about increasing numbers of suicides in custody in England and Wales.[1] They compared standardised mortality ratios for men in eight age groups, and found a five-fold excess of suicide mortality in prisons. It is a major strength of this study that prisons were investigated over a quarter of a century. A second strength is the use of age-specific information, which has not been recorded in previous studies.

Sadly, the core message of this paper is not new. It is a consistent finding worldwide that suicide rates in custody exceed those in the general male population.[2–6]