Kirby pg 66-70 28/6/06 2:42 pm Page 1

Heart disease prevention – what place for the glitazones?

In this article Professor Michael Kirby analyses the first major outcome study with glitazones, the PROactive study, and looks at the role for glitazones in the light of its findings.

Abstract

This paper considers the role for glitazones in the treatment of type 2 diabetes following publication of the PROactive study, the first major outcome study with this class of agents. The macrovascular benefits of glitazones are discussed. Recent guidance for glitazone prescribing from the Association of British Clinical Diabetologists is also given.

Key words: PROactive study, glitazones, type 2 diabetes.

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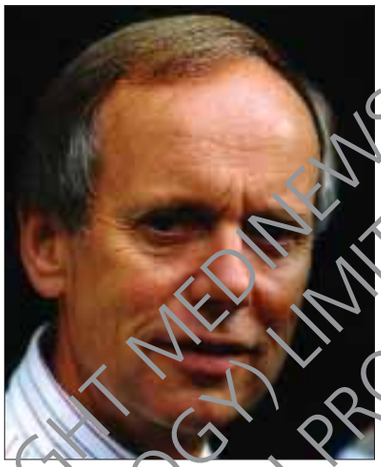
Introduction

The long-awaited publication of the PROactive (PROspective pioglitAzone Clinical Trial in macroVascular Events) study[1] has once again focused our clinical attention on glitazones.

This 5,000-patient, prospective, randomised trial investigated whether the addition of pioglitazone could reduce macrovascular morbidity and mortality in type 2 diabetes patients who were receiving optimal pharmacotherapy, and had already suffered a cardiovascular event.[1]

The key findings of the study were that adding pioglitazone to optimal therapy in these high-risk patients:[1]

- evokes a significant reduction in the number of deaths, heart attacks and strokes (16% reduction in this composite end point; p=0.027)
- achieves significantly better glycaemic control (HbA_{1C} absolute change from baseline: -0.8% *vs.* -0.3%, p<0.0001)
- significantly reduces dyslipidaemia (percentage change in low density lipoprotein [LDL]/high density lipoprotein [HDL] ratio: -9.5% *vs.* -4.2%, p<0.0001; percentage change in triglycerides: -11.4% *vs.* -1.8%, p<0.0001)
- significantly delays the progression to insulin (53% reduced risk of permanent insulin use, p<0.001).



'As the data-set builds, the arguments for earlier glitazone use are becoming stronger'

Michael Kirby

Study limitations

Although the study indicated an increased rate of oedema and heart failure in the pioglitazone group, mortality due to heart failure did not differ between groups. The investigators concluded that the increased reporting of heart failure in the pioglitazone group might, at least in part, indicate a diagnostic bias because of the increased oedema in the pioglitazone group. They also noted that heart failure was not a centrally adjudicated event.[1] Neither was it diagnosed by echocardiography. It was simply reported by the physician involved in the study.

In my own practice when we reviewed our own diagnoses of heart failure, we found we were wrong 50% of the time and this has been demonstrated in many studies subsequently. It is not biologically plausible that an increased incidence of heart failure can occur alongside a reduction in cardiovascular mortality. Certainly the development of oedema during glitazone therapy has been previously well documented and is not a new finding. The study was conducted in a very high risk population and further analysis of the subgroups on statin therapy and those patients on maximal secondary prevention therapy for cardiovascular disease will be very interesting.

It should also be recorded that the study's primary end point (the composite of all-cause mortality, non-fatal myocardial infarction [including silent myocardial infarction], stroke, acute coronary syndrome, endovascular or surgical intervention in the coronary or leg arteries, and amputation above the ankle) showed no statistically significant inter-group differences. This was mainly due to an increased number of leg revascularisations in the pioglitazone group, when compared to placebo.[1]

The investigators have since admit-

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Kirby pg 66-70 28/6/06 2:42 pm Page 2

ted that their rationale for including these subjective, clinician-reliant measures (i.e. that the need for amputation or cardiac/leg revascularisation was likely to indicate macrovascular deterioration and would respond to therapy in a similar way to stroke and myocardial infarction) was inherently flawed.[1]

Study benefits

Notwithstanding these weaknesses in the study design, Kaplan-Meier estimates indicate that administering pioglitazone over a three-year period prevents 21 myocardial infarctions (MIs), strokes, or deaths for every 1,000 patients treated. In other words, one major cardiovascular event is avoided for every 48 patients treated.[1]

Two further PROactive sub-analyses have reinforced this potential. In patients who had suffered an MI as their 'prior cardiovascular event' entry criterion, the addition of pioglitazone significantly reduced the likelihood of experiencing a further fatal or non-fatal MI (28% risk reduction; p=0.045), and significantly reduced the likelihood of developing acute coronary syndrome (37% risk reduction; p=0.035).

Although this is the first major outcome study involving a glitazone, these results are encouraging. The macrovascular benefits of glitazones have long been postulated, and investigations of their molecular mechanisms have often suggested a cardioprotective effect.

Table 1. A summary of the molecular effects of PPARγ-receptor agonists

Vascular smooth muscle	Endothelium	Macrophages
↓ Growth	↓ Migration	↓ Endothelial cell attachment
↓ Migration	↓ Growth	↓ Migration
↓ MMP production	↓ Angiogenesis	↓ Inflammation
↓ PAI-1 production		↑ Reverse cholesterol transportation

Key: MMP = matrix metalloproteinase; PAI = plasminogen activator inhibitor

Table 2. The effect of glitazones on the clinical components of the metabolic syndrome[15-31]

Component	Effect
Central obesity[14-17]	↓ Visceral fat ↑ Subcutaneous fat ↓ Hepatic fat ↑ Muscular fat Small initial increases in weight gain which stabilise after six months
Hypertension[18]	↓ Systolic blood pressure (slight) ↓ Diastolic blood pressure (slight)
Dyslipidaemia[19] (more marked improvements with pioglitazone)	↓ Triglycerides ↑ HDL-C ↓ LDL particle concentration ↑ LDL-C
Pro-coagulation[20-23]	↓ Platelet aggregation ↑ Time to intra-arterial thrombus formation ↓ PAI-1 expression ↓ PAI-1 release
Endothelial dysfunction, inflammation and atherosclerosis[24-30]	↓ C-reactive protein ↓ TNFα ↑ Adiponectin ↓ Intima-media thickness

Key: HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; PAI = plasminogen activator inhibitor; TNF = tumour necrosis factor

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Mechanism of action

At the molecular level, glitazones stimulate peroxisome proliferator-activated receptors (PPARs), specifically PPARγ, a ligand-activated nuclear transcription factor that modulates the expression of the gene-regulated proteins which control glucose and lipid metabolism.[2]

Rosiglitazone has also recently been shown to reduce clinical inflammatory responses in patients with type 2 diabetes with coronary artery disease after coronary angioplasty. Patients were randomised to receive 4 mg rosiglitazone a day for six months and compared with placebo. Diabetic control was improved in the rosiglitazone group and markers of inflammation, including C-reactive protein, were much improved. High-density lipoprotein cholesterol levels rose significantly and the occurrence of coronary events was reduced. Although this was a small study with 35 patients in each group, the findings are consistent with our current knowledge of the mechanisms of atherosclerosis.[2]

PPARγ receptors are most strongly expressed in adipose tissue and the vascular wall, and have secondary insulin-sensitising benefits in skeletal muscle fibres and liver cells.[3] A summary of these molecular effects is provided in table 1.[4]

The net effect of this complex molecular mechanism is that glitazones enhance glucose uptake in muscle and adipose tissue, whilst reducing levels of circulating free fatty-acids.[3] There is also evidence to suggest that they improve short- and long-term pancreatic beta-cell function.[5-7]

Implications for practice

So, given that the PROactive study now provides solid outcome data to rein-

Kirby pg 66-70 28/6/06 2:42 pm Page 3

force pioglitazone's proven hypoglycaemic benefits, is it now time to review the position of glitazones in type 2 diabetes? Certainly, as the data-set builds, the arguments for earlier glitazone use are becoming stronger.

We now have several long-term studies which demonstrate the glitazones' hypoglycaemic benefits, and these data show that they evoke reductions in HbA_{1C} equivalent to that of metformin and the sulphonylureas.[6,8-13] Data also indicate that when glitazones are used in combination with metformin or a sulphonylurea, they reduce mean HbA_{1C} by a further 0.8% and 1.1% respectively, compared to either agent alone.[14]

However, with PROactive confirming their biological plausibility, the main argument for using glitazones is that in addition to their glucose-lowering properties, they also evoke beneficial effects on each of the other cardiovascular risk factors of the metabolic syndrome (table 2).[15-31]

Of course, until cardiovascular outcome data involving other commercially available glitazones are published, it is impossible to predict whether the morbidity and mortality benefits seen in PROactive are a class effect of the PPAR agonists. Certainly, rosiglitazone and pioglitazone have subtly different effects on lipid profile. In a head-to-head study, when compared to rosiglitazone, pioglitazone was associated with significant improvements in the levels of triglycerides, HDL cholesterol, non-HDL cholesterol, LDL particle size and LDL particle concentration.[19]

Another interesting development is that a recent study has shown for the first time that a glitazone can improve exercise function in type 2 diabetes.[32] Although exercise is recommended as a cornerstone of treatment for type 2 diabetes, it is often poorly adopted by patients. Even in the absence of apparent cardiovascular disease, patients with type 2 diabetes have an impaired ability to carry out maximal exercise. This impairment is correlated with insulin resistance and endothelial dysfunction. The fact that a glitazone may actually improve exercise function in type 2 diabetes may be due to the observed improvements in insulin sensitivity and/or endothelial function. It is clearly an area that requires future research as exercise will remain at the heart of good management for these patients.

Another recent review in *JAMA*, however, which looked at the safety of muraglitazar, the first dual PPAR agonist which targets both alpha and gamma families of receptors, suggests the need for caution. Compared with placebo or pioglitazone, muraglitazar was associated with an excess incidence of the composite end point of death, major adverse cardiovascular events and heart failure. However, there were important limitations to the comparative study which did not have access to original documents, and the number of events was small in a population highly likely to suffer cardiovascular events. Caution needs to be exercised with this drug until further dedicated studies to evaluate this drug are conducted.[33]

Table 3. Post-NICE ABCD recommendations for glitazone use[34]

Monotherapy

- glitazones should be considered as monotherapy in patients who are unable to take metformin
- glitazones should be considered in place of metformin in patients with renal impairment

Combination therapy

- glitazones are the preferred second-line oral antidiabetic agent (following metformin) in obese patients with type 2 diabetes
- carefully monitored triple therapy comprising metformin, a sulphonylurea, and a glitazone, should be considered in patients who are severely obese and/or who are unable to take insulin
- glitazones should not be a substitute for insulin in patients on maximum tolerated doses of metformin and sulphonylureas who still have poor glycaemic control
- use of glitazones with insulin cannot currently be recommended – however, if such use is considered by the clinician, it is essential to screen for oedema, heart failure, and significant left ventricular dysfunction, and to ensure that the patient fully understands and accepts the increased risks
- when using glitazones, caution is needed to monitor for fluid retention and heart failure, particularly in patients with renal disease and/or those on insulin

Key messages

- Glitazones stimulate the peroxisome proliferator-activated receptors-gamma (PPARγ). Their complex molecular mechanism has macrovascular benefits enhancing glucose uptake and reducing circulating free fatty acids
- This gives glitazones hypoglycaemic benefits and also beneficial effects on the clinical components of the metabolic syndrome
- The cardiovascular benefits of glitazones are being assessed in various clinical outcome studies

Guidelines

Rather unhelpfully, the latest National Institute for Health and Clinical Excellence (NICE) guidance on glitazone use[34] was published just six days before the European Medicines Evaluation Agency (EMEA) announced changes to the glitazone licences. In 2004, in an attempt to clarify prescribing practice, the Association of British Clinical Diabetologists (ABCD) issued a position paper on glitazones. Its main recommendations for glitazone use are summarised in table 3.[35]

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Kirby pg 66-70 28/6/06 2:42 pm Page 4

The addition of the glitazones to our type 2 diabetes treatment armoury seems to provide a number of important cardiovascular benefits. The value of these benefits will be further assessed following the publication of future cardiovascular outcome studies such as ADOPT (A Diabetes Outcome Prevention Trial) in 2006,[36] ORIGIN (Outcome Reduction with Initial Glargine Intervention) in 2008,[37] RECORD (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes) in 2009,[38] and BARI-2D (Bypass Angioplasty Revascularization Investigation 2 Diabetes) in 2012.[39] However, the continuing emergence of new antidiabetic agents suggests that innovative pharmacotherapy will play a vital part in diabetes management for years to come.

Conflict of interest

MK has received honoraria for speaking at meetings sponsored by a variety of pharmaceutical companies including GSK and Takeda.

Michael Kirby
General Practitioner and Director of HertNet, Visiting Professor at the University of Hertfordshire
The Nevells Road Surgery, Nevells Road, Letchworth, Herts, SG6 4TS.
(email: kirbym@globalnet.co.uk)

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Kirby pg 66-70 28/6/06 2:42 pm Page 5

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Life planner

Author: Percival J
Publisher: Word of Mouth Publishing, Herts, 2004
ISBN: 0 9545671 0 2 Price: £12.99 (reader offer £8.50 inc. p+p from www.thought-catcher.com)

I have never read a self-help book in my life. My personal opinion has always been that if you think a book is going to get you through life then either you either need to get some friends or you are beyond help. So although I approached *Life planner* with a degree of cynicism, I also tried to keep an open mind.

The book is described as a self-help workbook containing thought-provoking text and exercises to complete, helping you to reflect on your life as it is in the present, how you want to change and what skills you need to achieve this change. I was pleasantly surprised to find I enjoyed the first section. It raised some interesting points which I had not previously considered, particularly when looking at what makes you happy in life.

On the whole, the book is well written and easy to read, although I did find the exercises slightly simplistic and I am not wholly convinced as to just how much insight into real life the book actually provides.

I feel the book could provide a good start in terms of assessing the major influences in one's life and it is a useful generic guide in the practical decision-making process. This may be helpful for a one-off change, but I can't see it having much of an impact on anyone's life as a whole.

Catherine Walker
National Heart & Lung Institute,
Dovehouse Street,
London, SW3 6LY

An introduction to cardiovascular physiology, 4th edition

Author: Levick JR
Publisher: Hodder Education, London, 2003
ISBN: 0 340809213 Price: £24.99

The physiology of the cardiovascular system advances at a frightening rate, and keeping up requires a flat-footed pursuer. Rodney Levick, doyen of physiology, teaches at St George's Hospital, and has kept up by writing four editions of his 'Introduction' in 12 years. It is a remarkable book which re-invents itself in each edition: this, the fourth, has 38 new illustrations and 70 refurbished old ones. At the same time, the text is actually shorter than the third edition.

Levick's own research centres on the microcirculation, so it is not surprising that this provides the book's core. The law of chemistry and physics that play a key role in understanding the capillary are conspicuous; it is a rigorous approach that allows Levick to return to first principles whenever things demand them. This all sounds rather dry and scholarly, but it is not, for he has a light touch. He quotes, for example, Flanders and Swann's hippopotamus song ('Mud, glorious mud') to illustrate the function of atrio-venous anastomoses. Then again, he tells us of the first recorded ECG (a trace from Augustus Waller's bulldog) and the bizarre debate in the House of Commons, produced by a public demonstration of bulldog Jimmie's cardiac potentials.

In true modern mode, each chapter begins with a list of learning objectives; there are 'concept boxes' scattered in the text, and a summary at the end of each chapter. Moreover, at the end of the book, there are 'clinical cases for problem-based learning'. There is political correctness here – the student has absolutely no excuse for not getting the hang of it all. Many textbooks now rely heavily on this apparent over-kill.

This reviewer has one reservation, and this is aesthetic. The text is printed in black and bright (oxygenated?) red. On the first page of each chapter is a lurid sheet of red, almost needing sunglasses. The previous edition had no such eyesores and it isn't clear what the designer wanted to achieve, apart from forcefully reminding the reader that he is launching himself into another chapter.

But this is carping. It is hard to imagine a better all-round introduction to cardiovascular physiology whose range and readability recommend it to both preclinical and clinical readers.

John Henderson
Physician
Surrey

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