Cardiovascular outcomes with pioglitazone compared with rosiglitazone

In this 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 a retrospective, population-based study comparing the cardiovascular outcomes of treatment with either rosiglitazone or pioglitazone.

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This research can be said to have the theoretical weaknesses of any retrospective cohort-type study. However, it does have a very large number of participants (39736 people with type 2 diabetes) who initiated either rosiglitazone or pioglitazone.

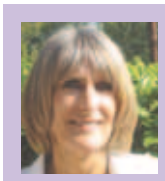
Significant numbers of participants (895 taking pioglitazone and 1563 taking rosiglitazone) reached the composite endpoint of death or hospital admission for acute myocardial infarction or heart failure. The fact that the setting of the study was in Ontario, Canada, and the age of the participants was 66 years and older means that the findings are likely to be generalisable to older people with type 2 diabetes who are taking thiazolidinediones (TZDs) in the UK. The study authors seem to have been very thorough and thoughtful in their data analysis.

The results show a significantly lower risk of heart failure and death in those taking pioglitazone rather than rosiglitazone. With one additional composite outcome predicted each year for every 93 people treated with pioglitazone rather than rosiglitazone, this gives new fuel to the debate about the possible benefits of using pioglitazone over rosiglitazone.

Before I read this study, my take on the vast amount of data already published was that both TZDs could cause heart failure, that this was not associated with increased mortality, that pioglitazone has data to suggest it could protect against myocardial ischaemic events and that, at best, rosiglitazone has no benefit on myocardial ischaemic events, and at worst, it increases the risk of myocardial ischaemic events.

The results of this study give further support to the American Diabetes Association/European Association for the Study of Diabetes recommendation that when TZD therapy is required, pioglitazone should be the therapy to use (Nathan et al, 2009).

Nathan DM, Buse JB, Davidson MB et al (2009) Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* **32**: 193–203



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Diabetes treatment is rather confusing at the moment; new therapies abound and controversy remain regarding the use of rosiglitazone.

In 2007, Nissen and Wolski suggested that rosiglitazone was associated with a significant increase in the risk of myocardial infarction plus an increased risk of death from cardiovascular disease, although the latter had borderline significance. This was refuted in the RECORD (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes) study (Home et al, 2009), showing that while rosiglitazone did increase the risk of heart failure, it did not increase the risk of overall cardiovascular morbidity or mortality compared with other glucose-lowering drugs.

Both studies have limitations and experts may give differing opinions. Now we have to consider this latest publication. Again, at first inspection, the evidence seems damning to rosiglitazone, with pioglitazone apparently demonstrating a significantly lower risk of heart failure and death. The authors state that continued use of rosiglitazone may not be justified.

Professor Russell-Jones and Corinne de Vries (2009) advise people to ask themselves two questions: do the findings reflect a true difference in risk between the two drugs, and if so, should this lead to changes in clinical practice?

Increased duration of diabetes in the rosiglitazone group in the study may have affected the findings. The thiazolidinediones, they confirm, are useful drugs with a proven track-record over years. We know their side-effects, we know their limitations. We do not know, they assert, the long-term effects of the newer agents.

As a specialist nurse, this controversy confirms my view that, more than ever, we need to involve people with diabetes in *their* choice of medication and, as NICE (2009) advises, prescribe what is appropriate for each individual.

Home P, Pocock S, Beck-Nielsen H et al (2009) Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomised, open-label trial. *Lancet* **373**: 2125–35

NICE (2009) *Type 2 Diabetes. The Management of Type 2 Diabetes. (NICE Clinical Guideline 87).* NICE, London. Available at: http://tiny.cc/lyJrG (accessed 02.09.09)

Nissen MD, Wolski MP (2007) Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *N Engl J Med* **356**: 2457–71

Russell-Jones D, de Vries C (2009) Rosiglitazone or pioglitazone in type 2 diabetes? *BMJ* **339**: b3076

Adverse cardiovascular events during treatment with pioglitazone and rosiglitazone: population based cohort study

Juurlink DN, Gomes T, Lipscombe LL et al (2009) *BMJ* **339**: b2942

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Rosiglitazone associated with greater risk of heart failure and death than pioglitazone

1 The authors of this retrospective population-based study looked at people with type 2 diabetes treated with rosiglitazone or pioglitazone to compare the risk of acute myocardial infarction, heart failure and death as a result of either treatment.

2 Participants were 39 736 Ontario residents aged ≥66 years who started treatment with rosiglitazone or pioglitazone between 1 April 2002 and 31 March 2008.

3 Data were obtained from the computerised prescription records of the Ontario Public Drug Benefit Program. All participants had access to hospital care, physician services, and prescription drugs.

4 The primary outcome was a composite of death or hospital

admission for either acute myocardial infarction or heart failure. Each outcome was also examined separately in a secondary analysis.

5 Over the 72-month study period, 39 736 people who started treatment with either thizolidinedione were identified: 22 785 (57.3%) with rosiglitazone, and 16 951 (42.7%) with pioglitazone.

6 After 6 years, 895 people (5.3%) treated with pioglitazone reached the composite outcome compared with 1563 taking rosiglitazone (6.9%).

7 Participants taking rosiglitazone were followed for a median of 292 days (interquartile range 124–448 days) and those on pioglitazone for a median of 294 days (interquartile range 87–487 days). Collectively, participants were followed for a total of 38 752 person years of treatment.

8 Extensive adjustment for demographic and clinical factors and drug doses was performed and pioglitazone-treated participants were found to be at lower risk of reaching the primary outcome than those treated with rosiglitazone (adjusted hazard ratio [AHR] 0.83, 95% confidence interval [CI] 0.76–0.90).

9 A lower risk of death (AHR 0.86, CI 0.75–0.98) and a lower risk of heart failure (AHR 0.77, CI 0.69–0.87) was associated with pioglitazone treatment, but there was no significant difference between pioglitazone and rosiglitazone use in terms of the risk of acute myocardial infarction (AHR 0.95, CI 0.81–1.11).

10 The authors of the study estimate that, in terms of absolute risk, approximately one more composite outcome would be expected to occur each year for every 93 people treated with rosiglitazone rather than pioglitazone.

11 In this sample of older people with type 2 diabetes, rosiglitazone was associated with a greater risk of adverse cardiovascular events and death than pioglitazone.

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Rosiglitazone and pioglitazone are insulin sensitising agents that improve glycaemic control and are widely used in clinical practice. Weight gain, fluid retention and an increased risk of heart failure are recognised adverse effects of both agents. Although the mechanisms are not clearly understood, PPAR-gamma receptor activation, which is the primary glucose-lowering mechanism of these agents, is thought to play a role via the promotion of renal tubular salt and water absorption. Whereas both agents appear to have similar effects in terms of these adverse events and their glucose-lowering potential, there has recently been considerable debate surrounding whether rosiglitazone and pioglitazone carry a differential adverse cardiovascular risk.

To shed further light on this issue, this retrospective cohort study compared the risk of acute myocardial infarction, heart failure and death in people with type 2 diabetes treated with either rosiglitazone or pioglitazone, using data derived from the Ontario Public Drug Benefit Program. A total of 39 736 participants aged 66 years or older who initiated rosiglitazone or pioglitazone were identified during the period from 1 April 2002 until 31 March 2008. During the 6-year study period, the composite outcome was reached in 895 (5.3%) of people taking pioglitazone and 1563 (6.9%) of people taking rosiglitazone.

After extensive adjustment for demographic and clinical factors, and drug doses, pioglitazone-treated participants had a lower risk of developing the primary outcome than did people treated with rosiglitazone (adjusted hazard ratio [AHR] 0.83, 95% confidence interval [CI] 0.76–0.90). Secondary analyses revealed a lower risk of death (AHR 0.86, 95% CI 0.75–0.98) and heart failure (AHR 0.77, 95% CI 0.69–0.87) with pioglitazone but no significant difference in the risk of acute myocardial infarction (AHR 0.95, 95% CI 0.81–1.11). One additional composite outcome would be predicted to occur annually for every 93 people treated with rosiglitazone rather than pioglitazone.

The clinical implications of these observations are unclear. It is noteworthy that there is no definitive direct randomised controlled trial data comparing the cardiovascular effects of rosiglitazone and pioglitazone. Additionally, the biological plausibility of the observations seen in this study is not entirely clear, as the reported small differences in lipid profiles seen between the two agents is unlikely to account for the observed differences in cardiovascular safety profile. Furthermore, the results of the recently reported RECORD (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes) trial showed no increase in cardiac mortality or all cause mortality for rosiglitazone. It is also noteworthy that this is a retrospective cohort study, which, despite multiple statistical adjustments, may still be confounded by allocation bias. Furthermore, the data used for this study was derived from people aged 66 years and older and therefore generalisability to younger people is unclear.

While the observations from this study may be of interest, as long as both agents are used in line with their current licence recommendations then this study should not significantly impact clinical practice.

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The thiazolidinediones (TZDs) remain controversial treatments for type 2 diabetes. There is clear and compelling evidence from double-blind randomised controlled trails (RCTs) that rosiglitazone and pioglitazone have different effects on lipids and lipid sub-fractions (Deeg et al, 2007; Berneis et al, 2008). While this is scientifically interesting, the important clinical question is whether there are differences in hard cardiovascular (CV) outcomes comparing the two available drugs from the TZD class. There are currently no completed RCTs comparing CV endpoints, so we are compelled to examine the next level of evidence that comes from cohort studies.

This well-conducted, retrospective cohort study from Canada uses a large computerised register of 22 785 people who initiated rosiglitazone and 16 951 people who initiated pioglitazone. A composite outcome of death or hospital admission for either myocardial infarction or heart failure was significantly less common in people who had been started on pioglitazone when adjusted for confounding factors.

The authors freely acknowledge the limitations of their findings and place the results alongside the previous literature. They suggest that, as rosiglitazone lacks a distinct clinical advantage over pioglitazone, continued use of rosiglitazone may not be justified. It is very hard to argue with this carefully worded conclusion – if rosiglitazone were the only available TZD, cautious continued use would be possible, but as there is an alternative that appears to be safer and to have greater benefits, then continued use of rosiglitazone may indeed not be justified.

Berneis K, Rizzo M, Stettler C et al (2008) *Expert Opin Pharmacother* **9**: 343–9

Deeg MA, Buse JB, Goldberg RB et al (2007) *Diabetes Care* **30**: 2458–64