Management & prevention of type 2 diabetes

Rosiglitazone and risk of CVD

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

Rosiglitazone and pioglitazone were launched in the late 1990s as members of a new class of agents, the glitazones, that effectively lowered blood glucose and dealt with the underlying pathophysiological abnormality in type 2 diabetes, that of insulin resistance. There were high hopes that they would reduce CVD risk in people with type 2 diabetes, in the same way as metformin. This is why the meta-analysis by Nissen and colleagues, summarised to the right, which suggested that not only does rosiglitazone not reduce CKD risk, but that it might actually increase CHD risk, has become so controversial.

The Nissen meta-analysis is of 42 trials with 15 560 people treated with rosiglitazone compared with 12 283 people treated with placebo or other oral agents. In the rosiglitazone group, the odds ratio for myocardial infarction was 1.43 compared with the control group (86 people having infarcts in the rosiglitazone group versus 72 in the comparator group). For deaths from cardiovascular causes, the odds ratio was 1.64 (39 deaths from cardiovascular causes in the rosiglitazone group compared with 22 deaths in the comparator group). The authors conclude by stating that rosiglitazone was associated with a significant risk of myocardial infarction and with an increase in the risk of death from cardiovascular causes that had borderline significance.

The paper was accompanied not by several editorials discussing the strengths and weaknesses of the review, but by just one editorial that questioned the whole rationale for prescribing rosiglitazone, and whether or not the procedures of the USA drug licensing authority, the FDA, were robust enough. It is perhaps therefore not surprising that the whole debate hit the front pages of newspapers in the USA.

The Cochrane review of rosiglitazone, which was published in July, did not receive any media attention. It reviewed 18 studies and concluded that these did not provide evidence that patient-oriented outcomes such as morbidity and mortality are positively influenced by this compound. In my opinion, the debate about rosiglitazone and CKD risk is likely to continue for some time to come.

NEW ENGLAND JOURNAL OF MEDICINE

The impact of payment-by-results schemes on diabetes care in England

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓
WOW! factor	✓✓✓

1 The authors of this study collected data from 42 primary care practices in England to examine how the quality of care they provide changed over time and whether or not this could be related to the introduction of pay-for-performance programmes in 2004.

2 Care quality was assessed by a validated set of criteria in 1998, 2003 and 2005.

3 In their analysis of data, the authors used the change between the 1998 and 2003 data to calculate predictions for 2005. These predictions were then compared to the observed scores in 2005.

4 In 1998, the mean score for practice-level quality of care for type 2 diabetes was 61.6 %. In 2003 this was 70.4 % and by 2005 this had increased to 81.4 %. The increase in improvement of care between 2003 and 2005 was significantly greater than predicted (P=0.002).

5 As well as type 2 diabetes, other areas of care were investigated. These data showed no significant difference in the rate of improvement in clinical indicators for which financial incentives were provided compared to those which were not financially rewarded.

6 However, overall the study does support previous findings that payment-by-results can be useful in improving quality of care.

Campbell S, Reeves D, Kontopantelis E et al (2007) Quality of primary care in England with the introduction of pay for performance. *New England Journal of Medicine* **357**: 181–90

NEW ENGLAND JOURNAL OF MEDICINE

Rosiglitazone associated with increase in MI

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓✓
WOW! factor	✓✓✓✓✓

1 In this highly influential study, the authors investigated the safety of rosiglitazone in the treatment of type 2 diabetes, with regards to cardiovascular morbidity and mortality.

2 A meta-analysis was conducted using published literature from the FDA website and a clinical trials registry maintained by GlaxoSmithKline.

3 Studies were included if: their duration was more than 24 weeks; they used a randomised control group not receiving rosiglitazone; and they included data on MI and death from cardiovascular causes. This criteria was met by 42 trials.

4 The mean age of trial participants was 56 years and mean baseline HbA_{1c} was 8.2 %.

5 Compared with controls, the odds ratio for people using rosiglitazone was 1.43 (95 % CI: 1.03–1.58; P=0.03) for MI and 1.64 (95 % CI: 0.98–2.74; P=0.06) for death from cardiovascular diseases.

6 This study demonstrates a risk of MI associated with rosiglitazone use, and also a borderline significant risk of death from cardiovascular causes.

7 It is important to note that this study was limited by a lack of access to original data; therefore, time-to-event analysis could not be performed. Despite this, people prescribing or taking rosiglitazone should be aware of the potential serious side effects.

Nissen SE, Wolski K (2007) Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *New England Journal of Medicine* **356**: 2457–71

DIABETIC MEDICINE

Guidelines on conducting a physical activity consultation

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓
WOW! factor	✓✓✓✓

1 The trans-theoretical model of behaviour change suggests that people move through five stages when changing a behaviour: pre-contemplation, contemplation, preparation, action and maintenance. Research is emerging supporting its use in promoting physical activity in people with type 2 diabetes.

2 The model proposes that different intervention strategies should be used at each stage to avoid relapse and help the individual progress.

3 Certain variables such as self-efficacy (confidence in ability to change), perceived benefits, outcome expectations, motivation and physical activity knowledge have been identified in the literature as being important in the design of intervention strategies.

4 The authors recommend a one-to-one discussion with a guiding, rather than directing, style allowing the patient to make their own decisions about their behaviour change.

5 For people in the early stages of behaviour change, the healthcare professional should focus on enhancing motivation, overcoming barriers and developing an activity plan.

6 A decision balance table is a good way of weighing up the perceived pros and cons of being more physically active and encouraging people that exercise is beneficial. Barriers to physical activity and ways to overcome them can then be discussed.

7 The person's self-efficacy should be assessed continuously and specific and measurable physical activity goals, both short and long term, should be set.

8 It is also important to focus on ways to prevent relapse, especially during high-risk times, such as a busy work schedule or holidays.

Kirk AF, Barnett J, Mutrie N (2007) Physical activity consultation for people with Type 2 diabetes: evidence and guidelines. *Diabetic Medicine* **24**: 809–16

DIABETIC MEDICINE

DOQ: A questionnaire to assess obstacles in living with diabetes

Readability	✓✓✓
Applicability to practice	✓✓✓✓
WOW! factor	✓✓✓✓

1 The authors developed and validated an easy-to-use questionnaire (Diabetes Obstacles Questionnaire [DOQ]) to identify obstacles in diabetes self-management.

2 The 113-item DOQ was completed by 180 people with type 2 diabetes from 22 practices throughout the UK. For comparison, the participants also completed a quality-of-life questionnaire (ADDQoL) and the Problem Areas in Diabetes (PAID) scale.

3 Fifty per cent of participants were male; 91% were white British; mean age was 62.2 years (SD: 10.4 years); mean duration of diabetes was 7.25 years (SD 8.3 years).

4 Analysis of the 176 usable completed questionnaires (>20 % completion) deemed 36 of the 113 items redundant.

5 The remaining 77 items were classified into eight subscales: medication, self-monitoring, knowledge and beliefs, diagnosis, relationships with healthcare professionals, lifestyle changes, coping, and advice and support. Each of these subscales had a Cronbach's alpha >0.75.

6 Criterion validity was demonstrated by significant correlations between each subscale and the PAID scale ($P<0.01$ for each subscale).

7 Construct validity was demonstrated by correlations between HbA_{1c} and the four subscales relating to blood glucose levels.

8 In conclusion, the authors state that the subscales incorporated into this questionnaire provide more detailed identification of obstacles in diabetes self-management (including mental health problems) and help clinicians and people with diabetes identify and focus on specific barriers.

Hearnshaw H, Wright K, Dale J et al (2007) Development and validation of the Diabetes Obstacles Questionnaire (DOQ) to assess obstacles in living with Type 2 diabetes. *Diabetic Medicine* **24**: 878–82

COCHRANE DATABASE

No evidence of a positive influence of rosiglitazone on mortality

Readability	✓✓✓
Applicability to practice	✓✓✓✓✓
WOW! factor	✓✓✓✓

1 Many previous trials have not identified a reduction in cardiovascular end points despite improved metabolic control.

2 This meta-analysis assessed the effect of rosiglitazone on adverse events and cardiovascular risk factors in people with type 2 diabetes.

3 The inclusion criterion was that they were randomised controlled trials of at least 24 weeks' duration looking at treatment outcomes of adults with type 2 diabetes.

4 In total, 18 trials were included that randomised 3888 people to rosiglitazone. The median therapy duration was 26 weeks, and the longest 4 years.

5 The published articles did not provide any evidence of a positive influence on adverse events, morbidity, mortality, costs or health-related quality of life associated with rosiglitazone use.

6 HbA_{1c} as an end point was not significantly different to other oral antidiabetic drugs.

7 There was a significantly raised occurrence of oedema with rosiglitazone (OR: 2.27; 95 % CI: 1.83–2.81).

8 In addition, one large trial (ADOPT) suggested an increase in cardiovascular risk.

9 The authors recommend that all safety data and adverse events from any trial are made available to the public.

Richter B, Bandeira-Echtler E, Bergerhoff K et al (2007) Rosiglitazone for type 2 diabetes mellitus. *Cochrane Database Systematic Review* CD006063

'For people in the early stages of behaviour change, the healthcare professional should focus on enhancing motivation, overcoming barriers and developing an activity plan.'

'There was a significantly raised occurrence of oedema with rosiglitazone.'

'Combination of insulin with rosiglitazone and metformin enabled more people to reach glycaemic targets with less insulin, and this was generally well tolerated.'

'Pioglitazone has more beneficial effects on atherogenic diabetic dyslipidemia than other oral glucose-lowering agents and improves a number of atherosclerotic risk markers.'

DIABETES CARE

Liraglutide improves glycaemic control

Readability	✓✓✓
Applicability to practice	✓✓✓✓
WOW! factor	✓✓✓✓✓

1 This 14-week study assessed the safety and efficacy of liraglutide, a long-acting glucagon-like peptide-1 analogue in people with type 2 diabetes.

2 People were aged ≥18 years with an HbA_{1c} of ≥7.5 and ≤10.0 % for diet treated or ≥7.0 and ≤9.5 % for oral antidiabetic drugs. Previous treatment was discontinued.

3 Liraglutide was administered at a dose of 0.65, 1.25 or 1.90 mg.

4 Estimated HbA_{1c} change was as follows: placebo: +0.29 %; 1.90 mg: -1.45 %; 1.25 mg: -1.40 %; and 0.65 mg: -0.98 %. The change for any liraglutide dose versus placebo was significantly different ($P<0.0001$ for all).

5 In total, 46 % of people receiving the 1.90 mg dose achieved an HbA_{1c} <7 % compared with 48 % (1.25 mg), 38 % (0.65 mg) and 5 % (placebo).

6 Fasting plasma glucose was reduced significantly (1.90 mg versus placebo: -3.4 mmol/l; 1.25 mg versus placebo: -3.4 mmol/l; and 0.65 mg versus placebo: -2.7 mmol/l; $P<0.0001$ for all).

7 Despite an increase in glycaemic control often associated with increased body weight, this decreased dose dependently. The highest dose of 1.90 mg reduced weight by 1.21 kg compared with placebo ($P=0.0390$).

8 The most frequently reported adverse events were headaches and gastrointestinal complaints. There were no hypoglycaemic episodes.

9 An improvement in ß-cell function, triglyceride levels and blood pressure was also observed with liraglutide.

Vilsbøll T, Zdravkovic M, Le-Thi T et al (2007) Liraglutide, a long-acting human glucagon-like peptide-1 analog, given as monotherapy significantly improves glycemic control and lowers body weight without risk of hypoglycemia in patients with type 2 diabetes. *Diabetes Care* **30**: 1608–10

DIABETIC MEDICINE

Addition of insulin to rosiglitazone and metformin is effective

Readability	✓✓✓✓
Applicability to practice	✓✓
WOW! factor	✓✓✓

1 This study compared the effect of continuing or discontinuing rosiglitazone and metformin therapy when insulin is initiated.

2 In total, 324 people with type 2 diabetes inadequately controlled on rosiglitazone and metformin were randomly assigned to twice-daily premix insulin in addition to their current therapy or in addition to placebo.

3 At week 24, the insulin dose required was significantly lower with rosiglitazone and metformin (33.5 ± 1.5 U/day) than with placebo (59.0 ± 3.0 U/day; $P<0.001$).

4 In addition, there was better improvement in glycaemic control. HbA_{1c} for rosiglitazone plus metformin was 6.8 ± 0.1 % versus 7.5 ± 0.1 % ($P<0.001$).

5 A greater percentage of people using rosiglitazone and metformin (60 %) also achieved the target HbA_{1c} of <7.0 % compared with placebo (34 %; $P<0.001$).

6 Occurrence of hypoglycaemic events was similar between the two treatments; however compared with placebo, a greater number of people experienced oedema (7 vs 3 %) and weight gain (3.7 vs 2.6 kg; $P=0.02$) when on combination therapy.

7 Despite this, greater treatment satisfaction was reported for people who continued with rosiglitazone and metformin.

8 In conclusion, combination therapy enabled more people to reach glycaemic targets with less insulin, and this was generally well tolerated.

Home PD, Bailey CJ, Donaldson J et al (2007) A double-blind randomized study comparing the effects of continuing or not continuing rosiglitazone + metformin therapy when starting insulin therapy in people with Type 2 diabetes. *Diabetic Medicine* **24**: 618–25

INTERNATIONAL JOURNAL OF CLINICAL PRACTICE

Synergistic effect of pioglitazone plus glimepiride in treatment of type 2 diabetes

Readability	✓✓✓
Applicability to practice	✓✓✓✓
WOW! factor	✓✓✓

1 Long-term glycaemic control is improved by combining drugs that target both insulin secretory dysfunction and insulin resistance.

2 Pioglitazone and glimepiride are now available in the US as a combination tablet.

3 Pioglitazone's mode of action is to act as an agonist for peroxisome proliferator-activated receptor-γ, improving insulin sensitivity and augmenting hepatic glucose uptake.

4 Glimepiride acts by increasing insulin release from ß-cells.

5 Combined, these therapies have a synergistic effect in the treatment of type 2 diabetes. Glimepiride reduces HbA_{1c} rapidly and pioglitazone enables long-term glycaemic control.

6 In addition, pioglitazone has more beneficial effects on atherogenic diabetic dyslipidemia than other oral glucose-lowering agents and improves a number of atherosclerotic risk markers.

7 There is also evidence that glimepiride may improve atherosclerotic risk markers and lipoproteins.

8 This combination therapy is beneficial in patient adherence, targeting the dual effects of insulin resistance and ß-cell dysfunction, and affecting a number of metabolic and cardiovascular parameters.

Derosa G (2007) Pioglitazone plus glimepiride: a promising alternative in metabolic control. *International Journal of Clinical Practice* **61**: 28–36