Major journals

An interim analysis of rosiglitazone evaluated for cardiovascular outcomes: The RECORD study group

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The Rosiglitazone Evaluated for Cardiovascular and Regulation of Glycaemia in Diabetes (RECORD) trial is a long-term multicentre, randomised, open-label study that compares cardiovascular outcomes in people with type 2 diabetes treated with rosiglitazone plus metformin or sulphonylurea with outcomes in people treated with metformin plus sulphonylurea. The results of the UKPDS suggested that the comparators metformin and sulphonylurea reduced myocardial infarction by 39 % and 16 %, respectively, compared with conventional treatment and diet. Following the recent meta-analysis of the cardiovascular safety of rosiglitazone, an interim report evaluating the cardiovascular outcomes from this study has been presented.

A total of 4447 people who had inadequate glycaemic control (baseline HbA_{1c}: 7.9 %) while receiving metformin or sulphonylurea monotherapy were randomly assigned to receive add-on rosiglitazone (n = 2220) or a combination of metformin plus sulphonylurea (n = 2220). If the HbA_{1c} exceeded 7.0 % after 8 weeks of treatment, the doses of study agents were increased to maximum (8 mg rosiglitazone; 2550 mg metformin; 15 mg glyburide; 240 mg gliclazide and 4 mg glimepiride). If HbA_{1c} exceeded 8.5 %, a third agent was added in the rosiglitazone group, while insulin was initiated for people in the control group. If people in the rosiglitazone group receiving triple therapy had HbA_{1c} levels above 8.5 % then rosiglitazone was discontinued and insulin commenced. The primary end point was hospitalisation or death from cardiovascular causes, with a mean follow up of 3.75 years. A total of 217 people in the rosiglitazone group and 202 in the control group had the adjudicated primary end point (hazard ratio: 1.08; 95% CI: 0.89–1.31) with no statistical difference between the rosiglitazone and control groups regarding myocardial infarction and death from cardiovascular causes.

Approximately 10 % of individuals in both groups were lost to follow up, coupled with the low event rate (3.1 % per year), which may reflect the impact of concomitant cardioprotective therapies or potential difficulties with event ascertainment.

The statistical power of this analysis was limited, as reflected by the relatively wide 95 % confidence intervals. People in the rosiglitazone group had a significantly higher risk of congestive heart failure, with 32 versus 17 adjudicated events. In total, 6.5 % of people in the rosiglitazone group began to receive insulin compared with 10.9 % in the control group. Furthermore, 1476 people in the rosiglitazone group and 1476 in the control group were still receiving their allocated therapy at 3.75 years. The results of this analysis at least partly address some of the cardiovascular safety concerns raised by Nissen and Wolski (2007).

The RECORD study has several strengths in that it was a large, randomised, long-term study designed to assess the cardiovascular safety of rosiglitazone in the context of dual-agent combination therapy, with all reported cardiovascular end points undergoing independent adjudication. This study also has some deficiencies. It is non-blinded, with a low event rate and significant drop-out rate (around 10 %), and is designed as a non-inferiority study. Each of these may limit the statistical power of the study to detect differences. Thus, while the data from this interim analysis may be reassuring, they must be viewed with some degree of caution.

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

NEW ENGLAND JOURNAL OF MEDICINE

No evidence that rosiglitazone is linked to MI or death

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

1 Following a recent meta-analysis indicating that rosiglitazone treatment is associated with an increased risk of myocardial infarction (MI) and death from cardiovascular complications, the authors of this paper set out to investigate whether or not these statements are well founded.

2 They conducted an interim analysis of a randomised, multicentre, open-label trial on 4447 individuals with type 2 diabetes who were receiving metformin or sulphonylurea and had inadequate glycaemic control.

3 Participants were assigned to receive either add-on rosiglitazone (n = 2220) or a combination of metformin and sulphonylurea (control; n = 2227).

4 The primary end point was hospitalisation or death from cardiovascular complications. This was reached by 217 people in the rosiglitazone group and 202 controls (hazard ratio [HR]: 1.08; 95 % CI: 0.89–1.31).

5 MI and death from any cause were not significantly different between the groups; however, there were more people with heart failure in the rosiglitazone group than the control group (HR: 2.15; 95 % CI: 1.30–3.57).

6 The authors conclude that although rosiglitazone is associated with an increased risk of heart failure, there was no effect on MI incidence. It is clear that further investigation into the side effects of rosiglitazone is neccessary.

Home PD, Pocock SJ, Beck-Nielsen H et al (2007) Rosiglitazone evaluated for cardiovascular outcomes – an interim analysis. *New England Journal of Medicine* **357**: 28–38

JAMA

Ranolazine is a safe and effective antianginal therapy for people with acute coronary syndromes

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

1 This study aimed to assess the safety and efficacy of ranolazine treatment of chronic angina in people with acute coronary syndromes (ACSs).

2 Within 48 hours of ischaemic symptoms, 6560 people were randomly assigned to receive ranolazine (initiated intravenously, followed by oral extended-release 1000 mg twice daily; n=3279) or placebo (n=6560).

3 They were followed up for 348 days in the Metabolic Efficiency with Ranolazine for Less Ischaemia in non-ST elevation acute coronary syndromes (MERLIN-TIMI 36) trial.

4 Cardiovascular death or MI occurred in 338 (10.4%) people in the ranolazine group and 343 (10.5%) in the placebo group (HR: 0.99; 95% CI: 0.85–1.15; *P*=0.87).

5 Recurrent ischaemia was reduced in 430 (13.9%) people in the ranolazine group and 494 (16.1%) in the placebo group (HR: 0.87; 95% CI: 0.76–0.99; *P*=0.03).

6 Symptomatic documented arrhythmias were similar between ranolazine treatment (99 [3.0%] and placebo (102 [3.1%]; *P*=0.84).

7 There was also no difference in total mortality (P=0.91) between the groups.

8 In conclusion, the addition of ranolazine to standard ACS treatment does not increase the risk of death or arrhythmia. While it is not effective in reducing major cardiovascular events, it is safe and effective as antianginal therapy.

Morrow DA, Scirica BM, Karwatowska-Prokopczuk E et al (2007) Effects of ranolazine on recurrent cardiovascular events in patients with non-ST-elevation acute coronary syndromes: the MERLIN-TIMI 36 randomized trial. *JAMA* **297**: 1775–83

ARCHIVES OF INTERNAL MEDICINE

Regular aerobic exercise increases HDL cholesterol

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

1 A meta-analysis was conducted on randomised, controlled trials examining how serum levels of high-density lipoprotein cholesterol (HDL-c) are affected by exercise.

2 A search of electronic database identified 25 articles, in which the mean increase in HDL-c was significant but modest (0.065 mmol/l; *P*=0.001).

3 In order to increase HDL-c, minimum energy expenditure was 900 kcal or 120 minutes of exercise a week.

4 Univariate regression analysis indicated that an additional 10 minutes exercise per session raised HDL-c by 0.036 mmol/l.

5 Exercise frequency and intensity was not associated significantly with HDL-c.

6 A BMI of <28 and total cholesterol of ≥5.7 mmol/l was associated with an approximately 0.054 mmol/l larger increase in HDL-c.

Kodama S, Tanaka S, Saito K (2007) Effect of aerobic exercise training on serum levels of high-density lipoprotein cholesterol: a meta-analysis. *Archives of Internal Medicine* **167**: 999–1008

NEW ENGLAND JOURNAL OF MEDICINE

Very low birth weight predicts components of metabolic syndrome

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

1 Very-low-birth-weight young adults (age: 18–27 years; n=163) were compared with 169 people who were not small for gestational age at birth with regards their glucose regulation.

2 A 75g oral glucose tolerance test demonstrated that compared with those born at term, very-low-birth-weight individuals had a 6.7% increase in 2-hour glucose concentration, a 16.7% increase in fasting insulin concentration and a 40.0% increase in the 2-hour insulin concentration.

3 There was also an 18.9% increase in the insulin-resistance index and increase of 4.8 mmHg in systolic blood pressure for those born prematurely or with very low birth weight.

4 The authors concluded that individuals who were born with very low birth weight have greater insulin resistance and glucose intolerance, and higher blood pressure than those born at term, leaving them more susceptible to the metabolic syndrome.

Hovi P, Andersson S, Eriksson JG et al (2007) Glucose regulation in young adults with very low birth weight. *New England Journal of Medicine* **356**: 2053–63

ARCHIVES OF INTERNAL MEDICINE

Aspirin lowers mortality risk

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

1 Women (n=79439) with no history of cancer or cardiovascular disease (CVD) provided data on medication use biennially since 1980.

2 The relative risk (RR) of death was assessed with respect to aspirin use.

3 Over a 24-year period, there were 9477 deaths. The multivariate RR of all-cause mortality for current aspirin takers was 0.75 (95% CI: 0.71–0.81) compared with women who were not regular aspirin users.

4 There was a greater risk reduction for death from CVD (0.62 [0.55–0.71]) than cancer (0.88 [0.81–0.96]).

5 Use of aspirin for 1–5 years reduced the risk of CVD (0.75 [0.61–0.92]) while a significant effect of aspirin use on cancer risk was only seen with 10 years of aspirin use (*P*=0.005).

6 Aspirin benefit in CVD was demonstrated with low and moderate doses and was greater in older participants (*P*<0.001) and those with more cardiac risk factors (*P*=0.02).

Chan AT, Manson JE, Feskanich D et al (2007) Long-term aspirin use and mortality in women. *Archives of Internal Medicine* **167**: 562–72

'Individuals who were born with very low birth weight have greater insulin resistance and glucose intolerance, and higher blood pressure than those born at term.'

'Use of aspirin for 1–5 years reduced the risk of cardiocascular disease while a significant effect of aspirin use on cancer risk was only seen with 10 years of aspirin use.'