Management & prevention of type 2 diabetes

Rosiglitazone and cardiovascular risk: New results from the RECORD trial

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There has been considerable debate on the cardiovascular (CV) safety of rosiglitazone since the publication in June 2007 of an article by Nissen and Wolski.

The meta-analysis of 42 trials compared 15 560 people treated with rosiglitazone with 12 283 people treated with placebo or other oral antidiabetes agents. In the rosiglitazone group, as compared with the control group, the odds ratio for myocardial infarction (MI) was 1.43 (86 people having infarcts in the rosiglitazone group against 72 in the comparator group.

Nissen and Wolski's paper received criticism, particularly as the studies in the meta-analysis were largely trials of short duration and were not powered to look for CV outcomes. Around 9–10 years ago the RECORD (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes) trial was planned – designed and powered to specifically answer these questions regarding CV protection in people taking rosiglitazone.

In response to the Nissen and Wolski controversy, an unplanned interim analysis of the RECORD study was published by Home et al (2007). Mean follow-up was 3.75 years and the primary endpoint was hospitalisation or death from CV causes. A total of 217 people in the rosiglitazone group and 202 in the control group reached the adjudicated endpoint. There were no statistically significant differences between the rosiglitazone and control groups regarding MI and death from coronary heart disease causes or any cause. The authors concluded that the interim analysis was inconclusive regarding the effect of rosiglitazone on the primary endpoint. The RECORD study continued, and the final results are summarised alongside (Home et al, 2009).

After 5.5 mean years of follow-up the primary outcome was reached by 321 people in the rosiglitazone group and 323 in the control group. The conclusion is that rosiglitazone does not increase the risk of overall CV morbidity or mortality. It does not, however, show any CV protection. (It was hoped at their launch, and in the first few years of being marketed, that both pioglitazone and rosiglitazone would offer protection from ischaemic CV events.)

> *"The conclusion is that rosiglitazone does not increase the risk of overall CV morbidity or mortality. It does not, however, show any CV protection."*

So, the results of RECORD show no increase in overall CV morbidity or mortality compared with combined metformin and sulphonylurea treatment. Overall, CV event rates were much lower than were expected when the study was designed, perhaps suggesting that the multifactorial interventions to lower CV risk in people with type 2 diabetes used in the interim have been exerting beneficial CV effects.

Home PD, Pocock SJ, Beck-Nielsen H et al (2007) Rosiglitazone evaluated for cardiovascular outcomes – an interim analysis. *N Engl J Med* **357**: 28–38

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

LANCET

Rosiglitazone does not increase risk of overall CV morbidity or mortality

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

1 The authors of this study investigated the effects of addition of rosiglitazone to either metformin or sulphonylurea compared with the combination of the two on cardiovascular morbidity and mortality over a mean 5.5 years of follow-up.

2 This multicentre, open-label study enrolled 4447 people with type 2 diabetes and a mean HbA_{1c} level of 7.9% (63 mmol/mol) on metformin or sulphonylurea monotherapy.

3 Particpants were randomly assigned to addition of rosiglitazone (n=2220) or to a combination of metformin and sulphonylurea (n=2227).

4 The primary outcome was time to first occurrence of cardiovascular (CV) hospitalisation or CV death.

5 During 5.5 mean years of follow-up, the primary outcome was experienced by 321 people in the rosiglitazone arm and 323 in the dual therapy arm.

6 Heart failure causing hospitalisation or death occurred in 61 people in the rosiglitazone group and 29 in the dual therapy group. Fracture rates were increased mainly in women in the rosiglitazone arm.

7 The authors concluded that, while rosiglitazone does appear to increase risk of heart failure and fracture, it does not increase risk of overall CV morbidity or mortality compared with dual metformin and sulphonylurea therapy.

Home PD, Pocock SJ, 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

DIABETES

Increased risk of T2D in older twins

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

1 Low birth weight is common in twins, and is also a factor in the development of type 2 diabetes (T2D). This study was undertaken to determine whether being a twin is associated with an increased risk of developing T2D.

2 Same-sex elderly monozygotic (MZ) and dizygotic (DZ) twins were enrolled, and anthropometry and glucose tolerance were measured. In addition, T2D incidence cases in twins (n=626) and controls (n=553) were identified.

3 Twins were more abdominally obese, insulin resistant, and glucose intolerant, with a higher HbA_{1c} level than non-twin controls (P=0.004).

4 Twins also had a higher prevalence of T2D (P=0.03) and a 60% higher incidence rate compared with controls.

5 The authors concluded that the fetal environment has a significant impact on the risk of T2D.

Poulsen P, Grunnet LG, Pilgaard K et al (2009) Increased risk of type 2 diabetes in elderly twins. *Diabetes* **58**: 1350–5

DIABETES CARE

Human once-weekly GLP-1 analogue plus metformin therapy

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

1 This double-blind, placebo-controlled study aimed to determine the efficacy and safety of the human glucagon-like peptide-1 (GLP-1) analogue taspoglutide in people with type 2 diabetes inadequately controlled on metformin.

2 A total of 306 participants were randomised to receive either placebo or taspoglutide for 8 weeks.

3 Reductions in HbA_{1c} levels from baseline were significantly greater in all taspoglutide groups compared with placebo (P<0.0001) at study end.

4 Weight reduction by study end was significantly greater in the 10 and 20 mg once-weekly groups (P=0.0035, P<0.0001, respectively), and the 20 mg once every 2 weeks group (P=0.0083).

5 The authors concluded that combination use of taspoglutide and metformin was well tolerated and associated with significantly improved glycaemic control and weight loss.

Nauck MA, Ratner RE, Kapitza C et al (2009) Treatment with the human once-weekly glucagon-like peptide-1 analog taspoglutide in combination with metformin improves glycemic control and lowers body weight in patients with type 2 diabetes inadequately controlled with metformin alone: a double-blind placebo-controlled study. *Diabetes Care* **32**: 1237–43

ANNALS OF INTERNAL MEDICINE

Need for a refocus in T2D treatment?

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

1 Tight glycaemic control is widely advocated as an integral part of treatment for type 2 diabetes (T2D) to prevent or delay the development of diabetes-related complications.

2 The authors of this review evaluated large trials that compared clinical outcomes in people with T2D randomly assigned to either tight or less tight glycaemic targets using contemporary treatment approaches.

3 Trials evaluated in the review were ADAVANCE, ACCORD, VADT and UKPDS.

4 The authors concluded that tight glycaemic control burdens people with complex regimens, hypoglycaemia, weight gain and costs, while offering uncertain benefits. Instead, the authors suggest that clinicians should proritise wellbeing, healthy lifestyles, preventative care and cardiovascular risk reduction.

Montori VM, Fernández-Balsells M (2009) Glycaemic control in type 2 diabetes: Time for an evidence-based about-face? *Ann Intern Med* **150**: 803–8

ARCHIVES OF INTERNAL MEDICINE

Pioglitazone may carry a higher fracture risk than rosiglitazone

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

1 This Canadian study was undertaken to determine the association between thiazolidinedione use and occurrence of fractures in people with type 2 diabetes.

2 Using a prospective cohort study design, the authors analysed the data of 84339 people with type 2 diabetes who had begun treatment with either a thiazolidinedione or a sulphonylurea between 1 January 1998 and 31 December 2007.

3 The average age of participants was 59 years, with individuals in the thiazolidinedione group being 3.8 years younger than those taking sulphonylurea (P<0.001). Fourty-three per cent were female. The primary outcome was occurrence of a peripheral fracture or fracture of any kind.

4 The results indicated that treatment with a thiazolidinedione was associated with a 28% increased risk of peripheral fractures compared with sulphonylurea therapy.

5 Compared with sulphonylureas, use of pioglitazone was associated with more peripheral fractures in men and women with type 2 diabetes. However, no such association was observed when rosiglitazone was used instead of pioglitazone.

6 The authors concluded that pioglitazone carries a greater fracture risk than rosiglitazone, and that larger scale trials need to be conducted to further enhance safety with regard to fractures in people with type 2 diabetes.

Dormuth CR, Carney G, Carleton B ET AL (2009) Thiazolidinediones and fractures in men and women. *Arch Intern Med* **169**: 1395–402

"Combination use of taspoglutide and metformin was well tolerated and associated with significantly improved glycaemic control and weight loss."

"Hypoglycaemic events in those using oral antidiabetes drugs was associated with an increase in the length of inpatient stay, but not with acute coronary syndrome."

DIABETES CARE

Lispro mix showed HbA_{1c} improvement and weight gain against basal insulin

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

1 The authors sought to compare the safety and efficacy of two insulin starter regimens (lispro mix 75/25 [LM75/25], glargine [GL]) as add-ons to oral antidiabetes agents in people with type 2 diabetes.

2 Participants were randomised to receive either twice-daily LM75/25 (n=1045) or daily GL (n=1046). Existing oral regimens were maintained.

3 HbA_{1c} levels were similar across the groups at baseline (P=0.414): LM75/25 group 9.1±1.3% (76±14 mmol/mol) and GL group 9.0±1.2% (75±13 mmol/mol).

4 By week 24, the LM75/25 group had achieved a greater reduction in HbA_{1c} than the GL group (–1.8±1.3 vs. –1.7±1.3% [–20±14 vs. –19±14 mmol/mol]; P=0.005) and had a lower HbA_{1c} level (P=0.005). A higher percentage of the LM75/25 group achieved the HbA_{1c} target of <7.0% (<53 mmol/mol) than those in the GL group (P<0.001).

5 LM75/25 was associated with higher insulin dose (0.47±0.23 vs. 0.40±0.23 unit/kg/day; P<0.001) and more weight gain (3.6±4.0 vs. 2.5±4.0 kg; P<0.0001) than GL.

6 Participants receiving LM75/25 experienced a lower rate of nocturnal hypoglycaemic (P=0.009), but a higher rate of overall hypoglycaemia (P=0.007) than those randomised to receive GL.

Buse JB, Wolffenbuttel BH, Herman WH et al (2009) DURAbility of basal versus lispro mix 75/25 insulin efficacy (DURABLE) trial 24-week results: safety and efficacy of insulin lispro mix 75/25 versus insulin glargine added to oral antihyperglycemic drugs in patients with type 2 diabetes. *Diabetes Care* **32**: 1007–13

BMJ

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

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

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

2 Participants comprised 39 736 Ontario residents aged ≥66 years who started treatment with rosiglitazone (n=22 785) or pioglitazone (n=16 951) between 1 April 2002 and 31 March 2008.

3 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.

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

5 A lower risk of death (adjusted hazard ratio [AHR] 0.86, confidence interval [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).

6 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.

Juurlink D, Gomes T, Lipscombe L et al (2009) Adverse cardiovascular events during treatment with pioglitazone and rosiglitazone: population based cohort study. *BMJ* **339**: b2942

DIABETES RESEARCH & CLINICAL PRACTICE

OAD-induced severe hypoglycaemia results in longer hospital stays

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

1 The authors of this study aimed to describe the clinical characteristics of, and long-term mortality following, severe iatrogenic hypoglycaemia in people with type 2 diabetes, with attention to their glycaemic drug regimen.

2 Hypoglycaemic episodes resulting in hospitalisation were retrospectively analysed. Data were collected on the event, on the duration of hospital stay and on acute coronary syndrome.

3 Participants were divided into those taking oral antidiabetes drugs (OADs; n=63) and those taking two or more insulin injections daily (n=63).

4 Participants on OADs were significantly older (P=0.009) and had lower HbA_{1c} levels (P<0.001) than those on insulin, were more likely to enter a coma due to the event (P=0.002) and their event had a longer duration (P=0.001).

5 Hypoglycaemic events in those using OADs were associated with an increase in the length of inpatient stay (P=0.05), but not with acute coronary syndrome (P=0.85).

6 At follow-up (median 2 years), overall mortality was 42.1%, with no significant difference in mortality between the OAD and insulin groups.

7 While severe iatrogenic hypoglycaemia in OAD-treated people had a worse presentation, this was not associated with higher long-term mortality than people receiving ≥two insulin injections daily.

Fadini GP, Rigato M, Tiengo A, Avogaro A (2009) Characteristics and mortality of type 2 diabetic patients hospitalized for severe iatrogenic hypoglycemia. *Diabetes Res Clin Pract* **84**: 267–72

ANNALS OF INTERNAL MEDICINE

Long-term candesartan therapy fails to prevent microalbuminuria

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

1 Microalbuminuria in people with diabetes predicts high morbidity and mortality, and preventative therapies are a clinical priority.

2 The angiotensin-receptor blocker candesartan was compared with placebo to determine its relationship with new onset microalbuminuria and rate of change in albuminuria.

3 Participants (n=5231) had either type 1 or 2 diabetes and were mostly normotensive. All were normoalbuminuric (median urinary excretion rate 5.0 µg/min).

4 Participants were assigned at random to receive candesartan (16 mg/day increasing to 32 mg/day) or placebo. The primary endpoint was new-onset microalbuminuria.

5 Urinary albumin excretion rate was assessed by two overnight collections annually. Where a sample was ≥20 µg/min, two more samples were taken.

6 Candesartan did not reduce the risk of microalbuminuria compared with placebo by study end (P=0.60; median follow-up 4.7 years). A 5.53% reduction in the rate of change in albuminuria was found in the candesartan group compared with placebo (P=0.024).

7 In a patient population that was largely normotensive and at low overall vascular risk, candesartan failed to prevent microalbuminuria. The authors concluded that a longer follow-up period may be necessary to see clinical benefits in this group.

Bilous R, Chaturvedi N, Sjølie AK et al (2009) Effect of candesartan on microalbuminuria and albumin excretion rate in diabetes: three randomized trials. *Ann Intern Med* **151**: 11–20

DIABETES CARE

Intensifying therapy improves HbA_{1c} without anxiety

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

1 The predictors of intensification of antihyperglycaemic therapy were assessed in this retrospective analysis of survey, medical record and health plan administrative data collected in the Translating Research into Action for Diabetes (TRIAD) study.

2 Participants of the TRIAD study were ≥18 years of age with diabetes and data were taken from 10 health plans and 68 provider groups serving around 180 000 people with diabetes.

3 Data were selected if people had type 2 diabetes and it was managed using diet or lifestyle or oral antidiabetes drugs at baseline with an HbA_{1c} level of >7.2% (>55 mmol/mol), who stayed with or intensified therapy over 18 months.

4 During the study, 520 of the 1093 participants intensified their therapy with oral medications or insulin.

5 Characteristics of participants who had intensified their therapy were: 58±12 years of age, diabetes duration of 11±9 years and an HbA_{1c} level of 9.1±1.5% (76±16.4 mmol/mol).

6 Therapy intensification was associated with younger age and higher HbA_{1c} levels. Those who intensified their therapy experienced a 0.49% (5.4 mmol/mol) reduction in HbA_{1c} (P<0.0001), an increase in weight by 3 pounds (P=0.003) and no change in anxiety/depression (P=0.2) compared with those who did not.

7 Intensifying treatment resulted in improved glycaemic control with no increase in anxiety/depression. Healthcare professionals should ensure treatment is intensified when required.

McEwan L, Bilik D, Johnson SL et al (2009) Predictors and impact of intensification of antihyperglycaemic therapy in type 2 diabetes. *Diabetes Care* **32**: 971–6

DIABETES & METABOLISM

DIABASIS survey reveals views of people with diabetes

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

1 A questionnaire was sent to 20 000 members of the general population of France, aged ≥45 years, to explore knowledge of diabetes.

2 A total of 14 201 people responded, 1092 of which had type 2 diabetes, making the prevalence of the condition in this population 7.7%.

3 A large proportion (85%) of respondents with type 2 diabetes reported that they wanted more information at diagnosis about at least one aspect of the condition. These respondents also reported feeling anxious (30%), frightened (13%), angry (4%), or that the condition was unfair (12%), at diagnosis.

4 Most respondents with type 2 diabetes knew about HbA_{1c} (84%), but only 58% knew what it was used for.

5 The most common treatment was oral antidiabetes drugs (OADs; 81%) with 19% receiving insulin (alone or in combination with OADs).

6 Average weight gain in those who reported is since diagnosis of their type 2 diabetes (23%) was 7.3 kg.

7 Many respondents marked insulin initiation as a turning point in their condition. When they realised its severity, they were more willing to follow advice and take more responsibility for the management of their diabetes. The mean time from diagnosis to insulin initiation was 13.8 years.

8 The authors concluded that this survey provides important information to improve diabetes care by highlighting people with diabetes' perception of their condition.

Mosnier-Pudar H, Hochberg G, Eschwege E et al (2009) How do patients with type 2 diabetes perceive their disease? Insights from the French DIABASIS survey. *Diabetes Metab* **35**: 220–7

"Many respondents marked insulin initiation as a turning point in their condition. When they realised its severity, they were more willing to follow advice and take more responsibility for the management of their diabetes."