Cardiovascular journals

Rosiglitazone: the debate continues...

Marc Evans, Consultant Physician, Llandough Hospital, Cardiff

Rosiglitazone is a member of the thiazolidenidione (TZD) class of blood glucose-lowering therapies, and has been removed from use in routine clinical practice due to concerns over its potential cardiovascular safety. These cardiovascular safety concerns were based on a meta-analysis (Nissen and Wolski, 2007) of clinical trial data in relatively low-risk patients experiencing few events.

The only large, completed outcome study – the RECORD (Rosiglitazone Evaluated for Cardiovascular Outcomes and Regulation of Glycaemia in Diabetes) study – revealed no evidence of an increase in cardiovascular risk associated with rosiglitazone. Such considerations have thus fuelled an ongoing controversy over both the cardiovascular safety of rosiglitazone and the withdrawal of its marketing authorisation in 2010 by the European Medicines Agency (EMA). The BARI 2D (Bypass Angioplasty Revasularisation In type 2 Diabetes) study (summarised alongside) examined any association between rosiglitazone-based therapy and cardiovascular events in 2368 individuals with type 2 diabetes and established coronary artery disease, a cohort not represented in either the RECORD study or the cardiovascular safety meta-analysis.

Total mortality, and composite of death, myocardial infarction and stroke, were compared over 4.5 years for individuals receiving rosiglitazone compared to those not receiving a TZD by means of a Cox proportional hazard model and Kaplan-Meier survival analysis, which included propensity score matching. The individual incidences of death, myocardial infarction, stroke, congestive heart failure and bone fractures were also compared in the two groups. After multivariable adjustment among individuals treated with rosiglitazone, mortality was similar, whereas the incidence of composite of death, myocardial infarction and stroke was lower. While the incidence of fractures was higher, there was no significant difference in the incidence of myocardial infarction or congestive heart failure between the rosiglitazone-exposed individuals and those not receiving a TZD, both before and after propensity score matching.

This study, while confirming the well-described association between TZD therapy and bone fractures, demonstrated no association between rosiglitazone and an increased risk of cardiovascular events in a high-risk group of patients with type 2 diabetes. Due to the controversy relating to the cardiovascular safety of rosiglitazone, two analytical approaches were used; the first used Cox regression models to evaluate drug exposure as a time-dependent variable using treatment event rates, and the second used propensity score matching to address any potential confounding factors. It is noteworthy that, with both approaches, there was no detrimental effect of rosiglitazone with respect to adjusted cardiovascular events.

There are some important limitations to this study that need to be appreciated prior to definitively revising prior concerns over the cardiovascular safety of rosiglitazone. Firstly, the effects of unmeasured confounders could not be estimated, and, secondly, due to the complex nature of the study design, blood glucose-lowering therapy was complex with multiple treatment modifications taking place in order to achieve an HbA_{1c} of <53 mmol/mol (<7%). The majority of individuals received more than one agent and some individuals were only transiently exposed to rosiglitazone. Thus, due to the high degree of investigator flexibility in relation to therapy use, it is possible that the lack of a cardiovascular safety signal in the rosiglitazone-treated cohort could reflect the relative under use of rosiglitazone in individuals perceived to be at the highest risk.

Despite such considerations, it is noteworthy to add that rosiglitazone therapy demonstrated no adverse cardiovascular safety signal in this high-risk group of individuals. Furthermore, this study highlights the need for a detailed evaluation of all available data prior to definitively assessing the safety of any specific therapy.

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

CIRCULATION

Rosiglitazone and its outcomes in BARI 2D

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

1 Rosiglitazone was withdrawn in 2010 because of concerns with its cardiovascular safety.

2 As part of the BARI 2D (Bypass Angioplasty Revascularization In type 2 Diabetes) study, the cardiovascular events of high-risk individuals taking or not taking rosiglitazone were analysed post-hoc.

3 Mean follow-up was 4.5 years and data from 2368 participants with T2D and established coronary artery disease were used. In total, 42% of the participants received rosiglitazone at some point in the trial.

4 The primary end-point of the BARI 2D study was death of any cause, and the secondary end-point was composite of death, myocardial infarction (MI) or stroke.

5 The all-death rate was similar for those receiving and not receiving rosiglitazone (1.88 versus 2.56 per 100 patient-years, respectively; hazard ratio [HR]=0.77, P=0.08).

6 Those that received rosiglitazone had lower composite incidence of death, MI and stroke (P=0.002), and a lower incidence of stroke alone (P=0.008), but the rate of MI was not significantly different compared with those not receiving rosiglitazone.

7 There was a significantly higher bone fracture risk among those who received rosiglitazone.

8 The authors concluded that there was no evidence of an association between rosiglitazone and increased rates of major adverse cardiovascular events among the high-risk individuals in the study.

Bach RG, Brooks MM, Lombardero M et al (2013) Rosiglitazone and outcomes for patients with diabetes mellitus and coronary artery disease in the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial. *Circulation* **128**: 785–94

THE AMERICAN HEART JOURNAL

Undiagnosed diabetes in individuals with ACS

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

1 The authors examined the prevalence of undiagnosed diabetes and prediabetes among those with non-ST segment elevation (NSTE) acute coronary syndrome (ACS), and investigated its association to ischaemic outcomes.

2 In total, 8795 individuals from the EARLY ACS trial were put into one of four groups: "known diabetes" (*n*=2870), "undiagnosed diabetes" (*n*=1069) "prediabetes" (*n*=947) or "normal" (no diabetes; *n*=3919).

3 Associated adjustments were made for "known diabetes", "undiagnosed diabetes" and "prediabetes" (versus "normal") to compare short- (30 days) and intermediate-term (1 year) ischaemic outcomes.

4 The primary outcome was the 30-day composite of all-cause death or myocardial infarction (MI).

5 The "undiagnosed diabetes" group had a greater 30-day death and a greater MI outcome rate than the "normal" group, which were primarily driven by a greater 30-day mortality.

6 There was no significant difference between those with "known diabetes" and "prediabetes" and individuals in the "normal" group for 30-day death or MI outcomes, but 30-day mortality was higher.

7 The authors concluded that undiagnosed diabetes and prediabetes are common among individuals with high-risk NSTE ACS, and undiagnosed and known diabetes are associated with worse short-term outcomes.

Giraldez RR, Clare RM, Lopes RD et al (2013) Prevalence and clinical outcomes of undiagnosed diabetes mellitus and prediabetes among patients with high-risk non-ST-segment elevation acute coronary syndrome. *Am Heart J* **165**: 918–25

THE AMERICAN JOURNAL OF CARDIOLOGY

Novel paradigm for diabetes risk factors

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

1 The authors aimed to identify the risk factors for diabetes progression in people with impaired glucose tolerance (IGT) and high cardiovascular disease (CVD) risk and to create predictive models for the 5-year incidence of diabetes.

2 Participant data from the NAVIGATOR (Nateglinide and Valsartan in Impaired Glucose Tolerance Outcome Research) trial were used.

3 In total, 9306 people participated in the NAVIGATOR trial and 3254 (35%) developed diabetes over the 5-year follow-up.

4 Multivariate Cox proportional hazards models were used to estimate the 5-year diabetes incident risk.

5 The full 5-year prediction model created by the authors weighed the contribution of three different measures of glycaemia (fasting and 2-hour glucose and HbA_{1c}) and took into consideration the ten traditional diabetes risk factors that are all known to give a statistically significant contribution to the development of diabetes.

6 Fasting and 2-hour glucose levels were measured annually, and HbA_{1c} was measured at baseline only. The date of diabetes onset was the date of the first elevated glucose level.

7 The model demonstrated only moderate discrimination for diabetes (C-statistics=0.70).

8 The results confirmed that, in a population with IGT and high CVD risk, the traditional risk factors are appropriate predictors of diabetes development, and glucose values are a better predictor than HbA_{1c} levels.

Bethel MA, Chacra AR, Deedwania P et al (2013) A novel risk classification paradigm for patients with impaired glucose tolerance and high cardiovascular risk. *Am J Cardiol* **112**: 231–7

INTERNATIONAL JOURNAL OF CARDIOLOGY

All-cause and CVD mortality with and without diabetes

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

1 The differences in all-mortality and cardiovascular disease (CVD) mortality among individuals with and without diabetes were assessed using data from three large Finnish cohorts.

2 The three large cohorts were made from six independent cross-sectional population surveys that were carried out over a 25-year period: cohort 1 comprised two surveys from 1972 and 1977; cohort 2 comprised two surveys from 1982 and 1987; and cohort 3 comprised two surveys from 1992 and 1997.

3 The three cohorts had a baseline assessment 10 years apart and were followed-up for 10 years. In total, from all three cohorts, the final sample comprised 16 223 men and 17 503 women.

4 All-cause mortality in men without diabetes was significantly lower in the latest two cohorts than the earliest cohort. All-cause mortality in men and women with diabetes also decreased, but not significantly.

5 Both men and women without diabetes had a lower risk of CVD mortality in the two later cohorts compared to the first, and, in the most recent cohort, CVD mortality decreased both in men and women with diabetes.

6 There was a decrease in CVD mortality in people with diabetes, which the authors suggested was due to improvements over the last decade in the treatment of diabetes and cardiovascular risk factors in patients with diabetes, e.g. improvements in emergency care and transport to coronary care units.

Barengo NC, Antikainen R, Peltonen M, Tuomilehto J (2013) Changes in all-cause and cardiovascular disease mortality in three different Finnish population cohorts with and without diabetes. *Int J Cardiol* **168**: 4734–8

> *"The results confirmed that, in a population with impaired glucose tolerance and high cardiovascular risk, the traditional risk factors are appropriate predictors of diabetes development."*