# Assessing CV risk in people with type 2 diabetes on oral antidiabetes drugs

***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 cohort study that investigated the cardiovascular risk associated with oral antidiabetes drug therapy in people with type 2 diabetes.***

*Roger Gadsby, GP and Associate Clinical Professor, Warwick Medical School, Warwick*

This is a retrospective audit study from the UK research database between 1990 and 2005 of 91 521 people with diabetes.

A total of 3588 incident cases of myocardial infarction, 6900 of congestive cardiac failure and 18 548 deaths occurred. Person–time intervals for drug treatment were categorised by drug class, excluding non-drug intervals and intervals for insulin.

Compared with metformin, monotherapy with sulphonylureas (SUs) was associated with a significant 24–61% excess risk for all-cause mortality. Pioglitazone was associated with a significant 31–39% lower risk of all-cause mortality compared with metformin. Rosiglitazone was associated with a 34–41% higher risk of all-cause mortality compared with pioglitazone. This study tried to account for as many confounders as possible, but is still open to the criticism that residual confounding or confounding by indication (differences in prognostic factors between drug groups) may have influenced the results.

The unfavourable risk of SUs compared with metformin, however, is striking, as is the favourable risk of pioglitazone compared with metformin, and the favourable risk of pioglitazone compared with rosiglitazone. Pioglitazone comes off patent in around 12 months and then may reduce in price to around the cost of generic SU.

Given this evidence of its favourable risk profile, one wonders if pioglitazone might actually replace SU as the recommended agent to be added second to metformin in many people with type 2 diabetes.

*Naveed Sattar is Professor in Metabolic Medicine at University of Glasgow and Honorary Consultant in Clinical Biochemistry, Glasgow Royal Infirmary*

There is a growing interest regarding the vascular and mortality risks associated with oral antidiabetes drugs (OADs), yet there is a scarcity of relevant trials to inform on such risk, especially for the older agents. Moreover, even for some of the newer agents, trials have generally been underpowered due to far lower than anticipated event rates. As a result, investigators have sought other means to establish risks of OADs, including data from large cohorts of people with detailed follow-up of events.

The UK General Practice Research Database is perhaps one of the largest and best databases to address questions related to health risk on a range of conditions over a relatively long period. It has therefore been widely used by many investigators worldwide to determine health risk associated with a variety of conditions (e.g. vascular risk in psoriasis) and to examine potential long-term effects of a range of drugs in differing disease areas (e.g. dementia risk with statins, reported to be lower). However, it is not an easy database to work with and requires careful analyses and strong statistical expertise.

With this in mind, Tzoulaki et al (summarised alongside) sought to investigate the long-term vascular and mortality effects of a range of OADs in this database, making certain to account for a vast range of potential confounding factors. At face value, the findings seem to concur with prior data with evidence for: i) adverse effects of sulphonylureas compared with metformin on vascular risk and mortality; and ii) vascular benefit of pioglitazone compared with rosiglitazone, but interestingly with both thiazolidinediones (TZDs) being associated with lower mortality risk than metformin.

These results are of interest, but how robust are the findings? And can we be certain that all confounding factors that may lead doctors to prescribe one drug against another have been accounted for? Perhaps the key sentence in the entire article comes in the abstract where the investigators admit that "the possibility of residual confounding or confounding by indication (differences in prognostic factors between groups) cannot be excluded."

Of interest, some prior results from the same database have so far failed to be confirmed in randomised trials (e.g. statins versus cognitive benefit). Thus, while the results of the present report are of interest, they cannot be taken as read and a heavy dose of circumspection is needed; the results are hypothesis-generating and should stimulate more randomised trials, however difficult these may be.

A head-to-head TZD trial has just begun but it will likely take many years to reach a conclusion. In the meantime, at best the present work seems to align with favourable benefits of metformin, which clearly remains the primary agent of choice in our patients. Beyond metformin, ongoing and future trials, including those with newer agents, are needed to help clarify the most appropriate therapeutic choice(s) in terms of benefits and safety, with attention to differing patient characteristics.

***Risk of cardiovascular disease and all cause mortality among patients with type 2 diabetes prescribed oral antidiabetes drugs: retrospective cohort study using UK general practice research database.***

Tzoulaki I, Molokhia M, Curcin V et al (2009) *BMJ* **339**:b4731

BMJ

## Sulphonylureas associated with increased risk of all-cause mortality

1 The authors of this retrospective cohort study were investigating an association of the prescription of oral antidiabetes drugs with risk of incident myocardial infarction, congestive heart failure and all-cause mortality.

2 Data were obtained from the UK General Practice Database, which contains anonymised clinical and prescribing data for 5 million people.

3 Only those aged between 35 and 90 years with an episode of care between 1 January 1990 and 31 December 2005, and a diagnostic Read code for diabetes, were included in the study ($n$=91 521).

4 Events were identified by Read codes. The primary events were first occurrence of incident myocardial infarction, congestive heart failure and all-cause mortality.

5 The unit of observation was an interval of drug treatment. This was defined as the period of time from initiation of treatment until the next drug was initiated, or until data was censored, or until the event of interest occurred.

6 There were 2 843 007 intervals of treatment with oral antidiabetes drugs. Periods where people received insulin therapy and events throughout those periods were excluded.

7 The mean age of the cohort was 65 years and the mean follow-up per individual was 7.1 years. There were 3588 myocardial infarctions, 6900 cases of congestive heart failure and 18 548 deaths.

8 Results were adjusted for sex and diabetes duration (model 1); plus previous complications of diabetes, previous peripheral artery disease, previous cardiovascular disease, and co-prescribed drugs (model 2); plus BMI, cholesterol concentration, systolic blood pressure, $HbA_{1c}$ level, creatinine concentration, albumin concentration and smoking status (model 3).

9 Compared with metformin there was a significant association between treatment with a first- or second-generation sulphonylurea and an excess risk that ranged from 24% to 61% for all-cause mortality across all three models ($P<0.001$).

10 The analysis did not find an association between thiazolidinediones and increased myocardial infarction risk. However, pioglitazone was significantly associated with a 31–39% lower risk of all-cause mortality ($P=0.02$ to $P<0.001$).

11 Compared with pioglitazone, rosiglitazone was associated with a 34–41% higher risk of all cause mortality ($P=0.14$ to $P=0.01$).

12 The findings of this analysis suggest that, compared with metformin, sulphonylureas have an unfavourable risk profile. Pioglitazone was associated with reduced all-cause mortality compared with metformin and a favourable risk profile compared with rosiglitazone.

*Jonathan Levy, Clinical Director and Diabetes Research Fellow, Oxford Centre for Diabetes, Endocrinology and Metabolism, Oxford*

Tzoulaki et al (2009; summarised alongside) examined the risk of myocardial infarctions (MI), congestive heart failure (CHF) and all-cause mortality on various oral antidiabetes drugs (OADs), using the records of 91 521 patients from the GP Research Database.

Around 3 million intervals of time when individual patients were taking a set of predefined OAD mono or combination therapies were identified, and this was used to calculate relative risks compared with metformin monotherapy. Excess risk, compared with metformin of first- or second-generation sulphonylureas (SUs), rosiglitazone, pioglitazone and other non-thiazolidinedione (TZD) combination therapies was calculated.

Three models were used in the analysis: in model 1, adjustments were made for sex, duration of diabetes and calendar year; in model 2, previous complications and co-prescriptions were taken into account; model 3 also adjusted for risk factors for cardiovascular (CV) disease. For this full adjustment, only 30% of intervals was available for analysis, reducing the significance of the estimates.

The results showed that there was an excess risk MI of over 30% with SUs compared with metformin, but no excess was evident for rosiglitazone. The excess risk for the SUs did not diminish in the fully adjusted model, although the statistical significance was lost.

For CHF, a significant excess risks of 36–45% was seen with SUs, 29% with rosiglitazone and 17% with other drug combinations, but these diminished when all covariates were taken into account and only remained significant at 18% for SUs.

The excess risk of for all-cause mortality was over 55% for SUs but rosiglitazone and pioglitazone had a reduced risk of 20% and 40% in the simple model. These associations diminished to 25% higher and 12% and 30% lower when all risk factors were taken into account, but remained significant for SUs and pioglitazone. The well recognised excess risk of non-hip fractures with the TZDs was confirmed.

This well conducted and carefully analysed retrospective observational study complements similar population-based studies in Saskatchewan and Tayside (Johnson et al, 2005; Evans et al, 2006), but extends them by including comparisons with the TZDs. Metformin was chosen as the reference group as it was the most widely prescribed now the recommended first-line OAD, and the reported risks are relative and not absolute.

The UKPDS (UK Prospective Diabetes Study) was the first trial to demonstrate the completely unexpected and, to-date, unexplained major protective effect of metformin for MI and total mortality (UKPDS Group, 1998a). It also found no excess risk in the intensively treated group, of which 60% were assigned to SUs and 40% to basal insulin (UKPDS Group, 1998b), and this group had significantly reduced rates of MI and total mortality in the 10-year follow-up analysis (Holman et al, 2008).

While the present study adds to the evidence that SUs have worse CV outcomes than metformin, this does not imply that SUs are in fact dangerous. On the other hand, the TZDs, in particular rosiglitazone, showed no increased risk of MI, and pioglitazone was associated with a lower risk of mortality compared with metformin. The excess risk of fractures with this class supports other evidence (Kahn et al, 2006; Dormandy et al, 2009).

Overall, this study adds to previous knowledge of the relative risks of the currently used OAD therapy and supports current guideline recommendations that metformin should be used as first-line therapy. However, it will also contribute to the more troublesome question of the choice of a preferred second-line therapy.

Dormandy J, Bhattacharya M, van Troostenburg de Bruyn AR (2009) Safety and tolerability of pioglitazone in high-risk patients with type 2 diabetes: an overview of data from PROactive. *Drug Saf* **32**: 187–202

Evans JM, Ogston SA, Emslie-Smith A, Morris AD (2006) Risk of mortality and adverse cardiovascular outcomes in type 2 diabetes: a comparison of patients treated with sulfonylureas and metformin. *Diabetologia* **49**: 930–6

Holman RR, Paul SK, Bethel MA et al (2008) 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med* **359**: 1577–89

Johnson JA, Simpson SH, Toth EL, Majumdar SR (2005) Reduced cardiovascular morbidity and mortality associated with metformin use in subjects with Type 2 diabetes. *Diabet Med* **22**: 497–502

Kahn SE, Haffner SM, Heise MA et al (2006) Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. *N Engl J Med* **355**: 2427–43

UKPDS Group (1998a) Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet* **352**: 854–65

UKPDS Group (1998b) Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* **352**: 837–53