Oral antidiabetes drugs: A retrospective analysis of risk

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Recent studies have precipitated intense discussion regarding the safety of oral antidiabetes drugs (OADs) with regard to cardiovascular morbidity and mortality, with the relative benefits and harms not well established. This has occurred in the context of a number of new OADs.

In a recent retrospective cohort study, the authors of this editorial set out to investigate the risk of incident myocardial infarction, congestive heart failure, and all cause mortality associated with prescription of OADs in people with type 2 diabetes (Tzoulaki et al, 2009). The study, which included 91 521 people with the condition, represents one of the largest diabetes cohorts in the UK with "real" data. Person–time intervals for drug treatment were categorised by drug class, excluding non-drug intervals and intervals for insulin. The study had a number of strengths, including the examination of 3 million drug intervals of drug treatments with ascertainment of drug co-prescriptions and covariates at the beginning of each interval.

While we tried to address most possible sources of confounding in the study, it is not possible to control for residual confounding or for confounding by indication (prognostic factor differences that vary between different drug groups), which may result in spurious associations. Dose–response calculations (and drug usage patterns) are challenging to investigate using longitudinal data due to inaccuracies in recording and variation in patient behaviour patterns, although a proxy of diabetes duration and cumulative past prescriptions of antidiabetes drugs were used in this study. Ongoing studies adjusting for cancer diagnoses are also examining possible contribution to risk.

What are the findings?

Our findings suggest a relatively unfavourable risk profile of sulphonylureas compared with metformin; however, this is not a new finding. Concerns about sulphonylurea safety were first raised by the University Group Diabetes Study, which showed increased cardiovascular mortality with tolbutamide (Meinert et al, 1970), and similar results have been demonstrated by other groups, including intensive sulphonylurea therapy in an obese subgroup in the UKPDS (UK Prospective Diabetes Study Group, 1998). However, no differences between these groups was found in ADOPT (A Diabetes Outcome Progression Trial; Kahn et al, 2006), although this study was underpowered. The findings were also confirmed in a meta-analysis, which showed that a combination of metformin and sulphonylurea was associated with a significant increased risk of composite endpoint of hospitalisation due to cardiovascular disease and mortality (Rao et al, 2008).

What this means for prescribers

Type 2 diabetes is a progressive chronic condition and good glycaemic control is associated with significant reduction in microvascular and macrovascular complications (Holman et al, 2008).

The findings support recommendations of the NICE (2009) guideline on the management of type 2 diabetes and the American Diabetes Association/European Association for the Study of Diabetes guidelines (Nathan et al, 2009) that favour metformin as the initial treatment for type 2 diabetes. The sulphonylureas, along with metformin, are well established drug treatments for type 2 diabetes.

Furthermore, we do not confirm previous reports of excess risk of myocardial infarction with rosiglitazone compared with metformin. Additionally, pioglitazone was associated with reduced all-cause mortality compared with metformin and a favourable risk profile compared with rosiglitazone, which requires replication elsewhere; however, this should not normally be considered for first-line anti-diabetes therapy, and may have implications for prescribing within this class of drugs.

The findings of this current study need to be evaluated in larger ongoing prospective studies or in sub-analyses of recent large diabetes trials. Until then, clinicians should consider metformin as first-line therapy and continue tailoring second-line therapies on an individualised basis. ■

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