Perspectives

Sulphonylureas and cardiovascular risk

The use of sulphonylureas has previously been linked with increased risk of cardiovascular disease, but studies in the area have been inconsistent. Since type 2 diabetes is itself associated with an increased risk of cardiovascular disease, there is a particular imperative to attempt to tease out any potential effects of antidiabetes medications in this regard.

In a recent meta-analysis of 12 randomised controlled trials, 17 cohort studies and four case–control studies (including a total of 1 325 446 individuals followed for between 0.46 and 10.4 years), Phung et al compared sulphonylureas with other oral antidiabetes drugs. Across all studies, sulphonylureas were found to be associated with a significantly increased risk of cardiovascular death (relative risk [RR], 1.27; 95% confidence interval [CI], 1.18–1.34) and a composite of fatal and non-fatal major cardiovascular events (RR, 1.10; 95% CI, 1.04–1.16). Neither of these were statistically significant when the analysis set was restricted to randomised controlled trials, but this is plausibly attributable to the increased width of the confidence intervals (especially for cardiovascular death, where the point estimate [1.22] hinted at a greater increase in risk than for the all-studies analysis).

Below, in the first instalment of a new series in the Journal, we bring you viewpoints from different healthcare professionals on what these findings might mean for clinical practice in the UK.

Reference: Phung OJ, Schwartzman E, Allen RW et al (2013) Sulphonylureas and risk of cardiovascular disease: systematic review and meta-analysis. *Diabet Med* **30**: 1160–71

Citation: Hall G, Munro N, Feher M et al (2013) Perspectives: Sulphonylureas and cardiovascular risk. *Diabetes & Primary Care* **15**: 288–90

About this series

In this series we present a selection of viewpoints on a current hot topic in primary care diabetes.

Perspective Diabetes specialist nursing

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I am not a scientist. I know little of confidence intervals, risk-of-bias tools and weighted regression statistics. What I do know is that the people I look after with diabetes fear hypos and welcome any therapy that does not encourage weight gain. They tend not to know the statistics on cardiovascular disease in diabetes: they are busy getting on with the day-to-day management of their condition. If they read the abstract of this systematic review, they might question what they are being asked to take.

For several years I have listened to experts confirming that sulphonylureas would never get a licence if they arrived now. I have played devil's advocate at many lectures and conferences asking the audience what they would prescribe after metformin for themselves or their family. The answer is rarely sulphonylureas.

I have highlighted some content on my own copy of this paper, including: the approved package labels for all sulphonylureas bear a warning for increased cardiovascular risk; a statistically significant association between sulphonylurea use and cardiovascular mortality was seen in the analyses of all studies; and sulphonylurea use was associated with a statistically significant increase in myocardial infarction in the analyses of all studies.

We are charged with keeping people out of hospital, and on this point I have highlighted another quote: "Sulphonylurea use was associated with statistically significant increases in the risk of hospitalization for cardiovascular causes."

I get the feeling that if we were to prescribe with our hearts rather than our wallets, things might be different. The paper states knowledge of the potential long-term effects of diabetes medications is important for clinicians to make treatment decisions. We have choice. So should our patients. ■

"The paper states knowledge of the potential long-term effects of diabetes medications is important for clinicians to make treatment decisions. We have choice. So should our patients."

Perspective Clinical pharmacology

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"The paper by Phung et al adds weight to the notion that it is time for the regulators to be advising on old, as well as new, drugs."

Sulphonylureas remain one of the most commonly prescribed glucose-lowering medications despite their recognised potential to cause hypoglycaemia and weight gain. Their use as either first- or second-line drugs in the management of hyperglycaemia in type 2 diabetes is endorsed by NICE (2009) guidelines and promoted by prescribing advisors in the UK. Newer classes of glucose-lowering drugs such as the thiazolidinediones, dipeptidyl peptidase-4 inhibitors and glucagon-like peptide-1 receptor agonists have been closely scrutinised for adverse cardiovascular effects. In addition to concerns about the cardiovascular safety of these newer drugs, there is a significant focus on cost and long-term outcome data.

Sulphonylureas have long been available as generic preparations and have low unit (acquisition) costs. The recent review and meta-analysis by Phung and colleagues acts as a timely reminder of the need to constantly review the evidence base for drugs irrespective of economic considerations or the length of time they have been in clinical use.

The possible specific adverse cardiovascular effects of sulphonylurea therapy were first brought into the public domain in the 1970s, following the publication of the University Group Diabetes Programme study (Salsburg, 1971). Since that time, there have been several observational and interventional studies suggesting a possible link between sulphonylurea therapy and cardiovascular risk. The review by Rao and colleagues in 2008, as well as the review discussed here that has an updated meta-analysis of both randomised controlled trials and additional observational data, should make regulators and the healthcare community seriously reappraise the widespread use of these drugs.

Sulphonylureas were developed after an incidental observation that sulphonamide drugs could cause hypoglycaemia (Loubatières-Mariani, 2007). They were introduced into the UK in the late 1950s and have maintained their position as common treatments for type 2 diabetes. Following the results of UKPDS (the UK Prospective Diabetes Study; UKPDS Group, 1998), their inclusion early in the treatment algorithm for type 2 diabetes has been further enhanced by low acquisition costs and new preparations with rapid onset of action and improved pharmacology.

There are several putative mechanisms to explain the adverse cardiovascular effects observed in sulphonylurea studies. Structural differences between drugs within the class lead to altered binding to the sulphonylurea receptor on the beta-cell (SUR1), affecting the individual duration of action of each agent. First-generation sulphonylureas (e.g. tolbutamide and chlorpropamide) exhibit low-affinity binding and require larger doses to achieve their glucose-lowering effect. The second generation of sulphonylureas (e.g. glibenclamide, glipizide, gliclazide and glimepiride) exhibit higher SUR1 binding affinity and are prescribed in lower doses. Potential adverse cardiovascular effects of the second-generation group may occur through the cardiac- and smooth-muscle SUR2A/B receptor, altering vascular adaptation to ischaemia. Sulphonylureas' well-described adverse effect of weight gain may worsen key vascular processes. The cardiovascular effects of sulphonylurea-associated hypoglycaemia may be mediated via QT-interval prolongation and be linked to the duration of action and presence of active sulphonylurea metabolites.

Since the publicity surrounding rosiglitazone, regulators have required extensive cardiovascular safety data for new glucose-lowering drugs. The paper by Phung et al adds weight to the notion that it is time for the regulators to be advising on old, as well as new, drugs. This, in turn, should make clinicians and prescribing advisers think carefully about "doing no harm" in the context of sulphonylurea therapy in type 2 diabetes. ■

Loubatières-Mariani MM (2007) [The discovery of hypoglycemic sulfonamides]. *J Soc Biol* **201**: 121–5

NICE (2009) *Type 2 Diabetes – newer agents (partial update of CG66) (CG87)*. NICE, London. Available at: http://www.nice.org.uk/cg87 (accessed 14.11.13)

Rao AD, Kuhadiya N, Reynolds K, Fonseca VA (2008) Is the combination of sulfonylureas and metformin associated with an increased risk of cardiovascular disease or all-cause mortality?: a meta-analysis of observational studies. *Diabetes Care* **31**: 1672–8

Salsburg DS (1971) The UGDP study. *JAMA* **218**: 1704–5

UK Prospective Diabetes Study Group (1998) 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

Perspective General practice

Roger Gadsby

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This is a large, well-designed systematic review and meta-analysis covering over 1.3 million individuals from 33 studies. The authors conclude that their meta-analysis expands the pool of studies evaluating cardiovascular disease (CVD) mortality compared with prior observations, while using adjusted estimates and assessing an additional outcome – a composite of cardiovascular events. They feel that their results warrant consideration in clinical practice when other treatment options may be available. I agree with these conclusions.

In my opinion, if a new glucose-lowering agent was submitted for marketing approval today and caused the levels of weight gain and hypoglycaemia that sulphonylureas do, it would be unlikely to get a licence. These data on CVD risk also suggest that sulphonylureas would struggle to pass the current test for CVD safety applied to all new glucose-lowering therapies.

The place of sulphonylurea therapy in glucose-lowering treatment guidelines clearly now needs to be re-assessed. It will be very interesting to see what the updated NICE guideline on type 2 diabetes will say about the position of sulphonylurea therapy in the treatment pathway when it is published in 2015.

Until that is published, prescribers following current NICE (2009) recommendations can prescribe a dipeptidyl peptidase-4 inhibitor, pioglitazone or dapagliflozin second line to metformin in place of a sulphonylurea for anyone they feel is at increased risk from hypoglycaemia. In my view, that represents a significant percentage among people with type 2 diabetes needing an agent to be added to metformin, especially when driving is considered. ■

NICE (2009) *Type 2 Diabetes – newer agents (partial update of CG66) (CG87)*. NICE, London. Available at: http://www.nice.org.uk/cg87 (accessed 14.11.13)

Perspective Prescribing advisors

Philip Newland-Jones

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"This meta-analysis gives an opportunity for prescribing advisors to modernise their formularies and ensure that three-dimensional, patient-centred approaches are developed."

As an Advanced Specialist Pharmacist Practitioner in Diabetes and Endocrinology, I have a role both in the clinical delivery of diabetes care and in the prescribing guidelines set in our region. In recent years, the emphasis on treatment individualisation in diabetes has increased, with clinicians understanding the differing needs of people with the condition throughout disease progression. When considering prescribing options in the NHS, there has always been a need to think of cost, which is why sulphonylureas have been considered as first- and second-line treatment for hyperglycaemia in type 2 diabetes.

The results and conclusions drawn from the Phung et al meta-analysis should not be taken outside of the context of patient-focused care. It adds to the ever-growing evidence that, very simply put, hypoglycaemia (which may contribute to increased cardiovascular disease risk) is bad for people. When considering the use of sulphonylureas, prescribing advisors and formulary developers should take into account the risk of hypoglycaemia, as any savings achieved in the prescribing of sulphonylureas (inappropriately) can instantly be annihilated by the cost of ambulance call-outs or admissions to hospital.

Leaving people with diabetes on sulphonylureas as their condition becomes more complex may be inappropriate. People with diabetes need annual reviews as a minimum, where medications can be reviewed in the context of changes in health and lifestyle.

Does this mean that sulphonylureas should be removed from formularies? Certainly not: there are people for whom the use of sulphonylureas is still appropriate. For "mild" hyperglycaemia associated with steroids, as one example, there are very few choices besides insulin and sulphonylureas.

This meta-analysis gives an opportunity for prescribing advisors to modernise their formularies to ensure that linear treatment algorithms become a thing of the past, and that three-dimensional, patient-centred approaches are developed. ■