

Debate & Analysis

Time to be cautious about prescribing sulfonylureas?

Type 2 diabetes increases the risk of cardiovascular disease (CVD) and reducing this disease burden through glycaemic control has long been the principal objective of treating the disease. No treatment has yet succeeded in reaching this objective. There are concerns that sulfonylurea (SU) medications may increase, rather than decrease this risk.

SUs have been central to the management of type 2 diabetes for many decades. Every month, more than 600 000 prescriptions for SUs are dispensed in England and current National Institute for Health and Care Excellence (NICE) guidelines recommend them for second-line use after metformin. The American College of Endocrinologists downgraded this role for SUs in 2009 and the European Association for the Study of Diabetes (EASD) did likewise in 2012.

WELL-ESTABLISHED SU CONCERNS

There are three major concerns regarding SUs. Firstly their widely acknowledged and indisputable tendency to cause hypoglycaemia.

Second is the belief that they accelerate beta pancreatic cell failure. This was demonstrated by their marked lack of durability in maintaining glycaemic control in the UK Prospective Diabetes Study (UKPDS) and ADOPT (A Diabetes Outcome Progression Trial) study. This was highlighted by Ralph de Fronzo in his 2008 American Diabetes Association's Banting lecture, in which he declared that:

*'Sulfonylureas are not recommended because, after an initial improvement in glycaemic control, they are associated with a progressive rise in HbA1c and progressive loss of beta cell function.'*¹

DEBATABLE SU CONCERNS

The third and most worrying concern regarding SUs relates to questions regarding their cardiovascular safety. These questions have remained unanswered for more than 40 years.

The University Group Diabetes Programme, the first randomised control study in diabetes, compared the effects of insulin, the SU tolbutamide, and placebo. The tolbutamide arm was stopped prematurely in 1969 when it was believed to be associated with increased cardiovascular mortality (12.7% versus

4.9%).² The study's conduct was much criticised and its findings disputed.

The controversy continued until the UKPDS reported in 1998 that intensive glycaemic control showed significant benefits regarding microvascular endpoints. The modest benefits for macrovascular outcomes (16% reduction in myocardial infarction [MI]) were not statistically significant. Interestingly, these cardiovascular benefits did become significant after an additional 10 years of follow-up, suggesting a legacy effect of good early glycaemic control soon after diagnosis. The authors reported that:

*'... the UKPDS data do not support the suggestion of adverse cardiovascular effects from sulphonylureas [chlorpropamide and glibenclamide] ...'*³

Rather disconcertingly, when a small subset of patients in the UKPDS allocated to metformin had a SU added to their treatment, a worrying 96% increase in diabetes-related death was seen. This anomaly was attributed to 'differences in the patients studied'. Given that metformin and SU combination was and remains the commonest dual therapy used in type 2 diabetes, this anomaly was a concern. Several studies subsequently explored the issue further. A meta-analysis of nine of these was published by Rao *et al.*⁴ Of 101 000 patients, 25 000 had been prescribed combination SU and metformin and these showed a significant 43% increased risk of composite CVD hospitalisation or mortality.

Several observational studies have retrospectively compared metformin and SU monotherapy. These include Johnson *et al* (12 000 new users of oral hypoglycaemic agents [OHA] in Saskatchewan),⁵ Evans *et al* (6000 new users of OHAs in Tayside),⁶ Tzoulaki *et al* (92 000 patients from the UK General Practice Research Database),⁷ Roumie *et al* (254 000 US Veterans),⁸ and Wheeler *et al*, (190 000 US Veterans).⁹ All

found worryingly increased risk (21% to 70%) of cardiovascular mortality associated with SU use and the latter showing 27% higher mortality for glipizide than for rosiglitazone (since withdrawn because of concerns regarding CVD risk).

More recently, a meta-analysis by Phung *et al* including 33 studies comprising 1.3 million patients, found that, compared with other OHAs, SUs were associated with significantly increased risk of cardiovascular death (relative risk [RR] 1.27) and composite cardiovascular event (including MI, stroke, cardiovascular-related hospitalisation or cardiovascular death) (RR 1.10).¹⁰

In contrast to the alarming evidence from these observational studies, in which the treatment groups will undoubtedly have had differing patient characteristics, many randomised controlled trials (RCTs) have included SUs as an active comparator or as part of a treatment strategy. Almost all were designed to target a level of glycaemic control and none were designed or powered to demonstrate CV risk or benefit. However, none of these indicated that SUs were associated with increased CVD risk.

Of interest, therefore, is the meta-analysis by Monami and colleagues who looked at 62 RCTs which compared SU with non-SU agents.¹¹ They found that the use of SUs was associated with increased mortality (odds ratio [OR] 1.22, $P = 0.047$) and a higher risk of stroke (OR 1.28, $P = 0.026$) whereas the overall incidence of major coronary events appeared to be unaffected. However they advised caution in the interpretation of this meta-analysis because of concerns regarding possibly insufficient sample size, trial quality, and the possible under-reporting of cardiovascular events and mortality.

Therefore, there is some discrepancy between these RCTs designed for other research purposes and the observational studies specifically looking at CV risk. The observational studies can only be 'hypothesis generating'. But surely, the

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only hypothesis that can be generated is that SUs are cardiovascularly unsafe? This hypothesis can only be tested by a dedicated prospective RCT, but there is no prospect of such a trial ever taking place. The closest we will get is the CAROLINA (Cardiovascular Outcome Study of Linagliptin Versus Glimperide in Patients With Type 2 Diabetes) study (commenced in 2010 and due to end in 2018), a double blind RCT comparing the dipeptidyl peptidase-4 inhibitor (DPP4i) linagliptin with the SU glimepiride in patients with type 2 diabetes at high cardiovascular risk. The results will be very interesting.

If these studies suggest that SUs may be less safe than metformin and may incur increased cardiovascular morbidity, perhaps metformin is cardiovascularly protective while the SUs are neutral? A small subgroup of 342 obese patients in the UKPDS did indeed demonstrate a 39% reduced risk of MI, but few would accept that such a small study is truly informative. No other study has convincingly showed cardiovascular benefits from metformin use, although several have failed to do so. These include two meta-analyses by Hemmingsen and colleagues¹² and Bousageon and colleagues.¹³

Prescribers of alternative, newer drugs will be heartened by a study recently published by Morgan and colleagues.¹⁴ Using the UK’s Clinical Practice Research Database, 34 000 patients taking metformin–SU dual therapy were compared with 8000 patients taking metformin–DPP4i (gliptin) dual therapy. Conscious that this was yet another observational study, participants were matched by age, sex, diabetes duration, BMI, renal status, and HbA1c. In the directly matched group, there was an astonishing 85% increase in mortality in the SU group.

Surely we need to be more cautious about prescribing SUs? NICE should endorse newer guidance, such as the 2012 American Diabetes Association/European Association for the Study of Diabetes position statement.¹⁵ SUs will continue to have small but specific indications, such as in certain monogenic forms of diabetes

and in newly-diagnosed hyperglycaemic patients. GPs should now question the demands of commissioners seeking to compel them to use SUs in preference to newer and better drugs in the majority of their patients.

The nation’s 600 000 users of SUs will be bewildered that so many decades have passed without an appropriate clinical trial to demonstrate SU safety and will wonder if regulators have adequately sought an answer to such an important question. They will be astonished that in today’s safety-obsessed health environment, so much uncertainty has been tolerated for so long.

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If the UK’s SU users were all to change to a DPP4i, the cost to the NHS would be around £200 million per annum. Let us hope this appalling vista does not discourage further examination of the issue.

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Provenance

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