

This house believes that sulphonylureas should not be used routinely as second-line treatments for patients with Type 2 Diabetes

A debate between Dr Robert EJ Ryder^a (for the motion) and Professor Rury R Holman^b (against the motion).

Mike Gwilt was there.

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Setting the scene

Sulphonylureas have received a terrible press in recent years. A series of publications over many years have told us that SU increase the risk of adverse cardiovascular outcomes in diabetes patients (usually relative to metformin in observational studies),¹ analyses from ACCORD and other megatrials have heightened concern over severe hypoglycaemia as a risk factor for premature mortality² and it is not uncommon to hear that sulphonylureas induce β -cell exhaustion.³

The place of metformin (with lifestyle intervention) looks secure at the head of the management algorithm for type 2 diabetes, for the time being at least.^{4,5} But, most type 2 diabetes patients will need the addition of a second pharmacologic agent to their regimen at some point, as their β -cell function continues to wane. Is it time we finally said goodbye to SU as a second-line management option with metformin, or have their limitations been overstated?

Two distinguished diabetologists and clinical trialists (Figure 1) went head-to-head recently to address this important question.⁶ Read on for an overview of the ground they covered (Figure 2).

For the motion (Dr REJ Ryder)

From the UK Prospective diabetes Study to the present day

The Diabetes Control and Complications Trial (DCCT), conducted in a type 1 diabetes population proved in 1993 that improving blood glucose control reduces the risk of developing microvascular complications of diabetes.⁷ The UK Prospective Diabetes Study (UKPDS), arguably the greatest trial of all time, confirmed five years later that improved microvascular outcomes follow improved glycaemia in type 2 diabetes over ten years of randomised follow-up.⁸ This trial also helped to cement the place of metformin as the

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preferred first option for antidiabetic pharmacotherapy (for patients without contraindications), a role it continues to fulfil today.⁹

But what to prescribe next, once glycaemic control deteriorates? Only sulphonylureas, metformin and insulin were available for prescription for diabetes at the time that the UKPDS was designed. Average HbA1c, and the incidence of complications such as neuropathy continued to rise as the trial progressed,^{8,9} which has emphasised the continuing need for more effective antidiabetic therapies.

Physicians continually stress the need for their patients with diabetes to commit to a healthier lifestyle, with weight loss an important route to improved metabolic control, although most will need additional pharmacologic antidiabetic therapy.^{4,5} Meanwhile, guideline writers urge physicians to individualise the antidiabetic regimen.^{4,5} New classes of antidiabetic therapy have arrived on the scene since the days of the UKPDS, with pioglitazone, α -glucosidase inhibitors, DPP4 inhibitors, GLP-1 agonists and SGLT2 inhibitors available for therapeutic use. The range of options for individualised diabetes care is larger than ever.

Choose the treatments with the best overall therapeutic profile

Weight

If so many diabetes patients need to lose weight, why give them a drug that increases weight? Well-designed randomised trials in type 2 diabetic populations have shown that GLP-1 agonists or SGLT2 inhibitors induce weight loss, while sulphonylureas lead to increased weight.¹⁰ Moreover, the greater the patient's initial weight, the more they are likely to lose during treatment with a GLP-1 agonist.¹¹ DPP4 inhibitors are a weight-neutral alternative.¹⁰

Hypoglycaemia

All of the newer classes of antidiabetic agents mentioned above have a lower risk of hypoglycaemia than SU; indeed, incretin-based agents only induce clinically significant incidence of hypoglycaemia when co-prescribed with SU or insulin (see Figure 3).^{10,12} It is particularly important to avoid hypoglycaemia for the many frail, elderly diabetes patients, who are at risk of life-limiting trauma from falls. Emergency admissions for SU-related hypoglycaemia are a frequent and an unnecessary burden on healthcare systems.¹³

Cardiovascular outcomes – don't forget pioglitazone

Which antidiabetic agents improve long-term cardiovascular outcomes, besides metformin in patients at high risk of these adverse outcomes (especially patients with prior myocardial infarction (MI) or stroke)? Recent reconsideration of the PROactive trial (a randomised, placebo-controlled evaluation of pioglitazone in 5,283 patients at high cardiovascular risk) has enabled us to see beyond the limitations of the design of that trial.^{14,15} Initial discussion of PROactive focussed on the flawed primary endpoint of that trial; this was not affected significantly by pioglitazone but which contained an outcome related to a procedure, which likely confounded the outcome. The principal secondary outcome (all-cause mortality, non-

fatal MI or stroke) was reduced by pioglitazone (by 16% vs. placebo) and is highly relevant to the cardiovascular events suffered by diabetes patients. Further analyses from PROactive have confirmed significant protection by pioglitazone from recurrent MI or stroke.¹⁵

The efficacy of pioglitazone must be balanced against its tolerability: be cautious in prescribing pioglitazone where risk of fractures is of particular concern (women at risk of osteoporosis) and watch carefully for oedema – excess fluid can often be unloaded successfully by co-prescribing a diuretic (which also reduces the risk of the congestive heart failure that has been associated with pioglitazone).¹⁵ Further research has shown that there is no increased risk of bladder cancer with pioglitazone, as had been suggested.¹⁵

Cardiovascular outcomes – don't forget incretin agents and SGLT2 inhibitors

New regulations in the USA require a post-marketing cardiovascular outcomes trial for most new diabetes therapies. As a result, a steady stream of cardiovascular safety studies continues to add to the list of incretin-based agents and SGLT2 inhibitors that have *not* been associated with an increased risk of adverse cardiovascular outcomes.

Durability of action

The short-term effects of sulphonylureas, pioglitazone, DPP4 inhibitors and GLP-1 agonists on HbA1c are broadly similar.¹² Newer classes of antidiabetic agents (TZD,¹⁶ GLP-1 agonists¹⁷ or SGLT2 inhibitors¹⁸) appear to have a more durable effect on HbA1c than SU, however, implying superior long-term control of glycaemia.

Closing remarks

Patients presenting with type 2 diabetes with BMI <30 kg/m², symptoms of hypoglycaemia and fasting glucose of 15–20 mmol/L may well be candidates for initial treatment with a sulphonylurea. But, a sulphonylurea should not be used routinely for the majority of patients: newer antidiabetic agents bring at least equivalent antihyperglycaemic efficacy without the burden of sulphonylurea-associated weight gain and hypoglycaemia. Moreover, pioglitazone may improve cardiovascular prognosis.

Against the motion (Professor RR Holman)

Current status of SU in management guidelines for type 2 diabetes

Guidance from the National Institute for Health and Care Excellence (NICE) is unambiguous: SU can be used as second-line therapy in a patient already receiving metformin, and treatment can be continued if other agents are subsequently added.⁵ Low-cost agents are preferred, with once-daily treatment preferred for patients who find it difficult to comply with treatment.

This and other guidance may change with time, and the results of new randomised, controlled trials, but moving to wider use of the newer agents today may represent a leap into the

unknown. Pioglitazone has potentially serious side-effects (increased risk of heart failure or fractures)¹⁹ and regulators either side of the Atlantic are considering reports of increased risk of heart failure with some DPP4 inhibitors²⁰ or of euglycaemic diabetic ketoacidosis with SGLT2 inhibitors.²¹ We should look beyond second-line therapy: as blood glucose levels continue to rise, patients may need a third, fourth or fifth therapy, and beyond the promotional activities of pharmaceutical sponsors of newer drugs who may naturally tend to extol the benefits of newer vs. older therapies.

Addressing the claims made against sulphonylureas

Sulphonylureas do not worsen cardiovascular prognosis

Many observational studies have reported worse outcomes in patients receiving a sulphonylurea vs. metformin, or other therapies (e.g. ref 1). Most of these are inherently confounded by the presence of more advanced diabetes in patients who require combination therapy.²² Suppression by some sulphonylurea of “ischaemic preconditioning”, where repeated minor episodes of myocardial ischaemia protect the heart against a subsequent major ischaemic episode, is often cited as a mechanism for the supposed adverse cardiovascular effects of sulphonylureas.²³ This can be demonstrated readily in the laboratory, but its clinical significance is less certain.²³ The UKPDS remains the only long-term, randomised evaluation of a sulphonylurea (mostly glibenclamide) in diabetes: there was no indication of any tendency towards an increased risk of cardiovascular events in patients receiving intensive glycaemic management with a sulphonylurea, compared with the diet-treated control group (Figure 4).⁸

Measuring case fatality during acute MI provides a way to assess the clinical importance of ischaemic preconditioning: having a sulphonylurea on board that blocks this phenomenon should worsen outcomes in this setting, if it is truly important. Further data from the UKPDS provided no evidence for such an exacerbation by sulphonylureas of case fatality during an evolving MI.²⁴

The observation of increased mortality after addition of SU to metformin in the UKPDS has caused much controversy over the years.⁹ The diminution of this effect during post-trial epidemiological follow-up of the UKPDS population (it was no longer significant after a further 10 years of follow-up) helps to confirm the original finding as a statistical artifact.^{25,26}

Sulphonylureas do not exhaust the β -cell

Plasma insulin tracked similarly over time for patients randomised to glibenclamide or to the control group in the UKPDS.⁸ Moreover, the rate of the steady rise in HbA1c, caused by progressive loss of β -cells, was no different for any of the randomised treatments in the UKPDS, including the control group.⁸ The ADOPT trial demonstrated a minor but statistically significant reduction in the rate of increase in HbA1c for a thiazolidinedione vs. glibenclamide over five years in type 2 diabetes patients, but β -cell function was similar at study end for patients randomised to each treatment.^{Error! Bookmark not defined.} In any event,

differences in the slope of HbA1c over time have been demonstrated for different sulphonylureas.²⁷ There is no reason to believe that treatment with a sulphonylurea hastens the demise of the pancreas in people with type 2 diabetes.

The problem of sulphonylurea-induced weight gain is overstated

Body weight increases modestly following prescription of a sulphonylurea and then levels out and was similar for patients randomised to glibenclamide or to the control group after ten years of treatment in the UKPDS.⁸ Similarly, mean weight gain on glibenclamide in the ADOPT trial was only 1.6 kg, and remained stable after the first year of treatment.¹⁶ Type 2 diabetes is largely driven by obesity and the effectiveness of treatments differs little across the continuum of body weight among the type 2 diabetes population. Fear of increased weight with sulphonylureas is not sufficient to prevent the second-line use of a sulphonylurea in a patient likely to benefit from this treatment.

Hypoglycaemia – choose your patients carefully

Hypoglycaemia is a genuine concern with sulphonylureas but can be mitigated by careful patient selection. Patients with higher HbA1c at before treatment are less likely to develop hypoglycaemia, and titrating the dose based on plasma glucose helps to avoid undue hypoglycaemia.²⁸ There were fewer hypoglycaemic events on liraglutide vs. glimepiride in the LEAD-2 study, but event rates were modest in either group (0.03–0.14 events/year for placebo or liraglutide and 1.23 events/year for glimepiride).²⁹

Closing remarks

Sulphonylureas remain widely prescribed because they are an effective, cost-effective (at a time of restricted healthcare budgets), safe and proven antidiabetic therapy. Many of the accusations levelled against these drugs are overstated, are of limited relevance to clinical practice or can be mitigated by careful patient selection. Sulphonylureas remain a valuable therapeutic option within the patient-centred management of type 2 diabetes.

The people speak

A vote was taken among the audience before and after the debate (Table 1). There was a swing to against the motion on the day, but it is clear that this question will remain controversial for the foreseeable future.

Funding and conflict of interest

MG has previously provided medical communications consultancy and writing services to pharmaceutical companies that market product(s) containing a sulphonylurea. No payment was received in relation to this article.

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Table 1. Voting before and after the debate.

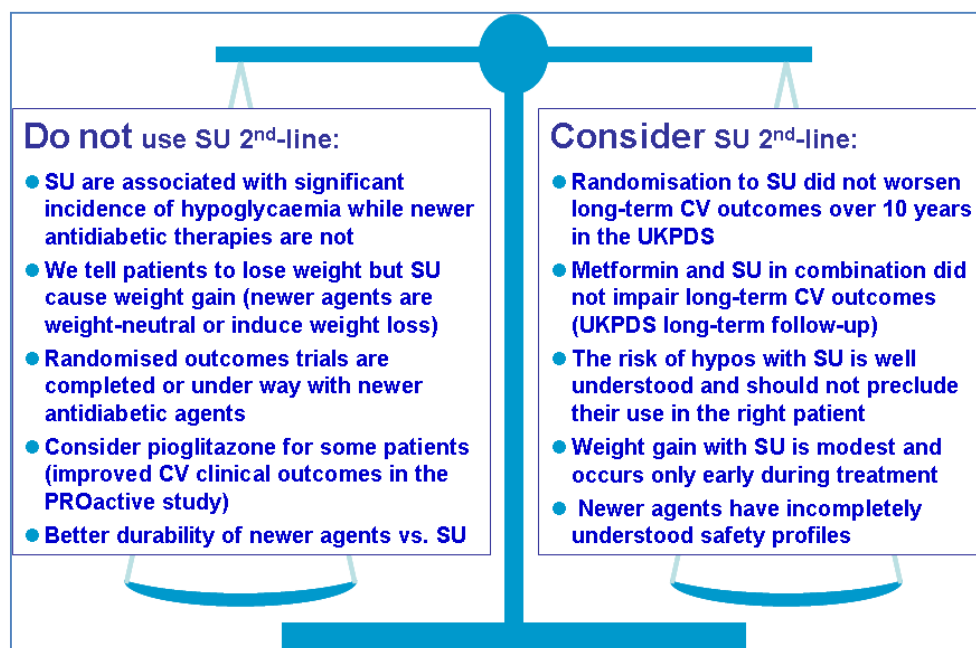
	For the motion (no more use of SU^a)	Against the motion (retain SU^a)	Abstain/don't know
Before the debate (% voting)	50	24	26
After the debate (% voting)	38	42	20

^aAs 2nd-line therapy for type 2 diabetes. SU: sulphonylureas.

Figure 1. Our protagonists: Professor RR Holman (left) and Dr REJ Ryder (right).

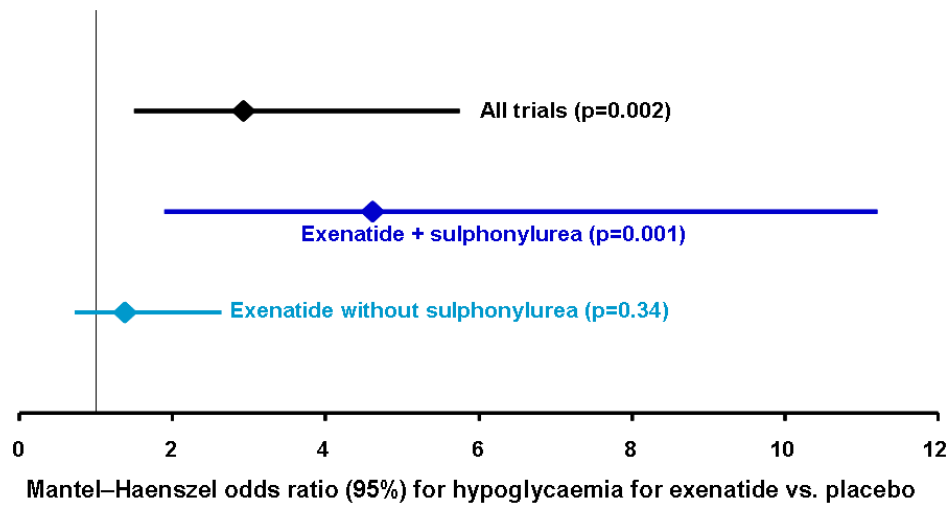


Figure 2. Summary of key points made.



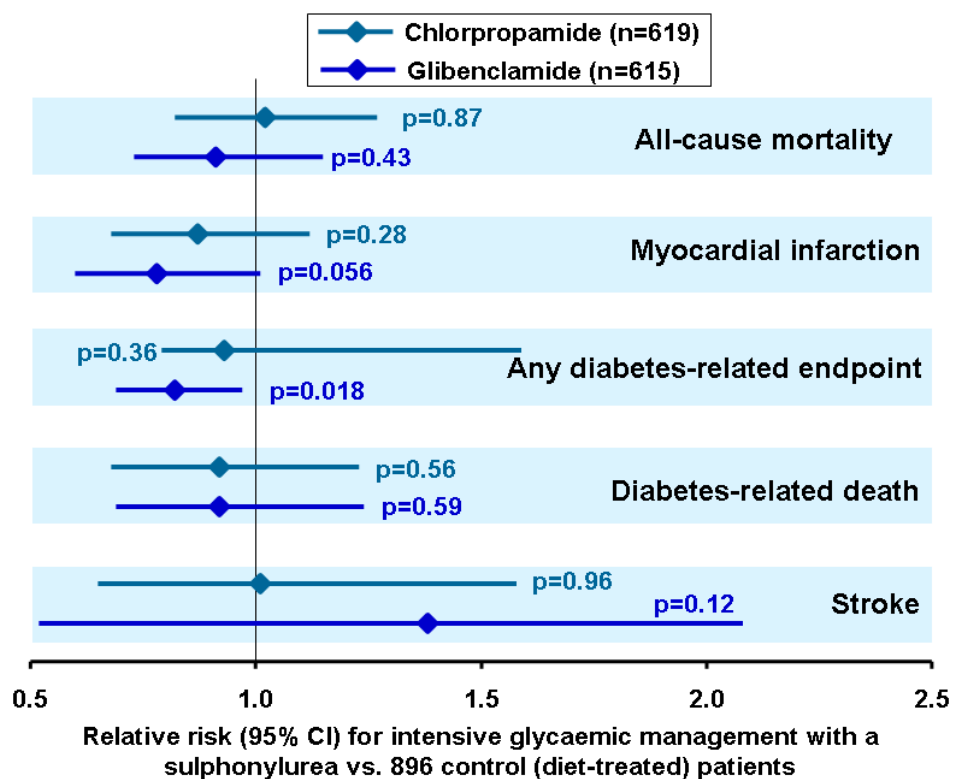
CV: cardiovascular; UKPDS: UK Prospective diabetes study; SU: sulphonylurea(s).

Figure 3. Incidence of hypoglycaemia with exenatide vs. placebo with or without background sulphonylurea treatment in a meta-analysis of randomised, controlled trials in type 2 diabetes patients.



Drawn from data presented by Monami et al.¹²

Figure 4. Clinical outcomes from 10 years of intensive glycaemic management with sulphonylureas in the UK Prospective diabetes study.



Drawn from data presented by the UK prospective Diabetes study Group.⁸