

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 Ryder¹ (for the motion) and Professor Rury R Holman² (against the motion). Mike Gwilt³ was there

Setting the scene

Sulphonylureas (SU) have received a terrible press in recent years. A series of publications over many years have told us that SUs increase the risk of adverse cardiovascular outcomes in diabetes patients (usually relative to metformin in observational studies),¹ analyses from ACCORD and other mega trials have heightened concern over severe hypoglycaemia as a risk factor for premature mortality² and it is not uncommon to hear that SUs 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 pharmacological agent to their regimen at some point, as their β -cell function continues to wane. Is it time we finally said goodbye to SUs as a second-line management option with metformin, or have their limitations been overstated?

Two distinguished diabetologists and clinical trialists, Professor Rury R Holman and Dr Robert EJ Ryder, went head-to-head recently to address this important question.⁶ Read on for an overview of the ground they covered (Figure 1).

For the motion (Dr REJ Ryder)

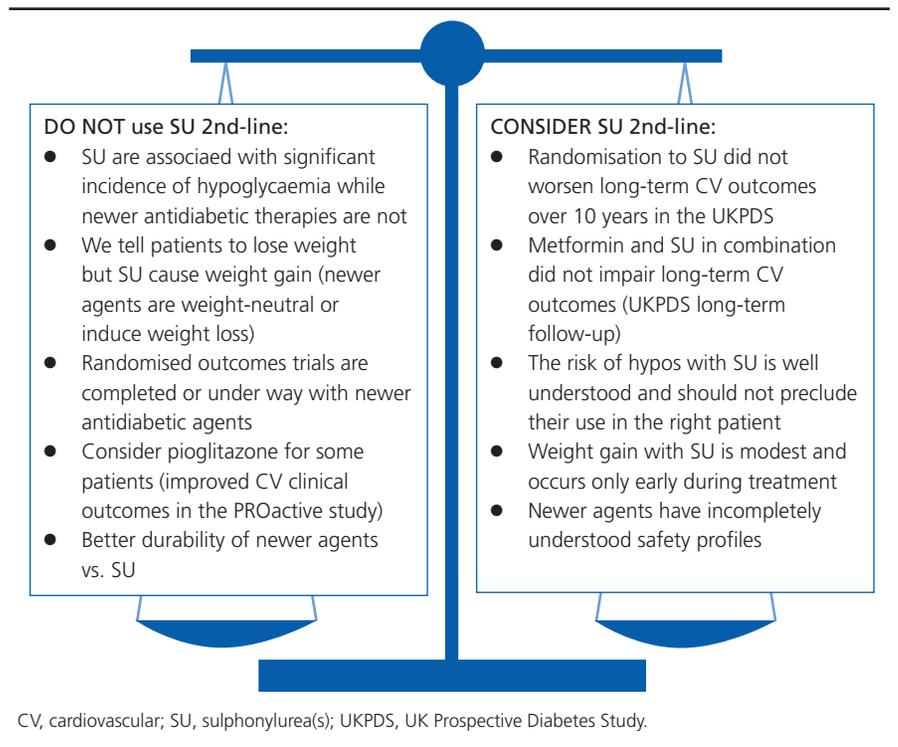
From the UK Prospective Diabetes Study to the present day

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), confirmed five years later that improved microvascular outcomes follow improved glycaemia in type 2 diabetes over 10 years of randomised follow-up.⁸ This trial also helped to cement the place of metformin as the preferred first option for antidiabetic pharmacotherapy (for patients without contraindications), a role it contin-



*Our protagonists:
Professor RR Holman
(left) and
Dr REJ Ryder (right)*

Figure 1. Summary of key points made

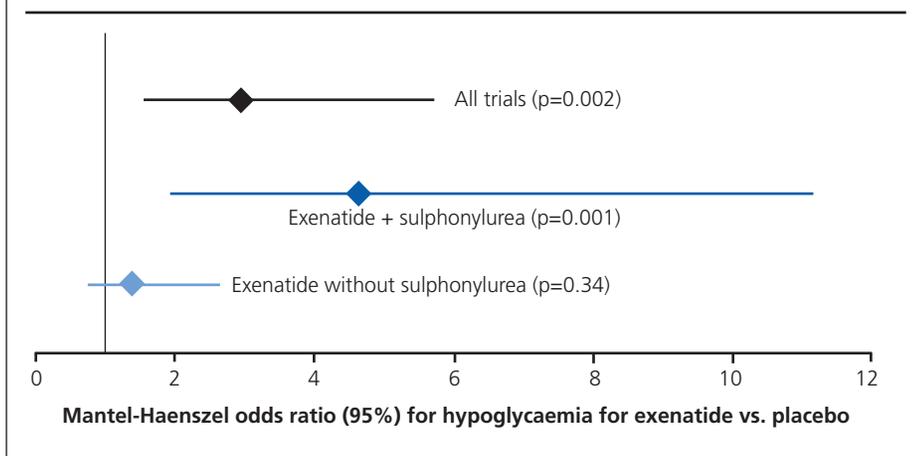


ues to fulfil today.⁹

But what to prescribe next, once glycaemic control deteriorates? Only SUs, metformin and insulin were available for prescription for diabetes at the time that the

UKPDS was designed. Average HbA_{1c} 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.

Figure 2. Incidence of hypoglycaemia with exenatide versus 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



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 pharmacological 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, dipeptidyl peptidase-4 (DPP4) inhibitors, glucagon-like peptide-1 (GLP-1) agonists and sodium-glucose cotransporter 2 (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 SUs 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 SUs; indeed, incretin-based agents only induce a clinically significant incidence of hypoglycaemia when co-prescribed with SU or insulin (see

Figure 2).^{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 focused on the flawed primary endpoint of that trial; this was not affected significantly by pioglitazone but 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 un-

loaded 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 has continued to add to the list of newer antidiabetic agents that have not been associated with an increased risk of adverse cardiovascular outcomes. Since this debate took place, cardiovascular outcomes benefits have been observed in the EMPA-REG OUTCOME trial with empagliflozin¹⁶ and with liraglutide in the LEADER trial (soon to be presented at the time of writing).

Durability of action

The short-term effects of SUs, pioglitazone, DPP4 inhibitors and GLP-1 agonists on HbA_{1c} are broadly similar.¹² Newer classes of antidiabetic agents (thiazolidinediones,¹⁷ GLP-1 agonists¹⁸ or SGLT2 inhibitors¹⁹) appear to have a more durable effect on HbA_{1c} than SUs, 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 SU. But a SU should not be used routinely for the majority of patients: newer antidiabetic agents bring at least equivalent antihyperglycaemic efficacy without the burden of SU-associated weight gain and hypoglycaemia. Moreover, pioglitazone may improve cardiovascular prognosis.

Against the motion

(Professor RR Holman)

Current status of SUs in management guidelines for type 2 diabetes

Guidance from the National Institute for Health and Care Excellence (NICE) is unambiguous: SUs can be used as second-line therapy in patients with type 2 diabetes (T2DM) already receiving metformin, and they can be continued if other glucose-lowering agents are added subsequently.⁵ Low-cost agents are preferred, as are once-daily agents for patients who find it difficult

to comply with treatment.

This and other guidance may change with time, as the results of new randomised, controlled trials are incorporated into the guidelines, but moving to wide spread use of newer agents today may represent a leap into the unknown. Pioglitazone has potentially serious side-effects (increased risk of heart failure or fractures)²⁰ and regulators either side of the Atlantic are considering reports of increased risk of heart failure with some DPP-4 inhibitors²¹ as well as euglycaemic diabetic ketoacidosis with SGLT-2 inhibitors.²² We should look beyond second-line therapy as blood glucose levels continue to rise, patients may need a third, fourth or fifth therapy, and also beyond the promotional activities of the pharmaceutical companies who may naturally tend to extol the benefits of newer vs. older therapies.

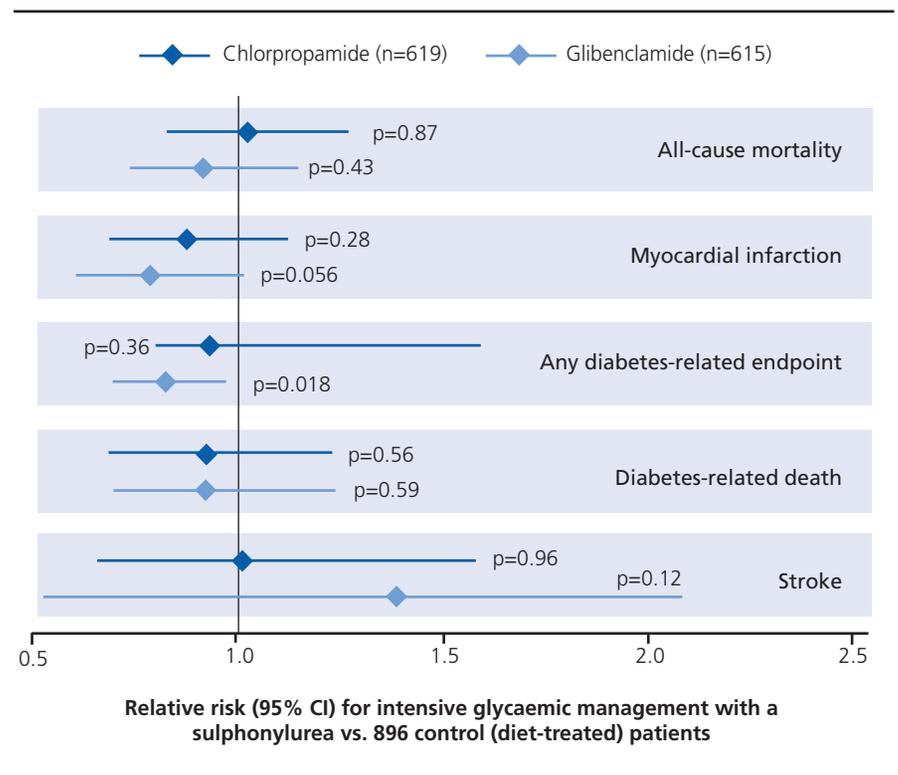
Addressing the claims made against SUs

SUs do not worsen cardiovascular prognosis

Many observational studies have reported worse outcomes in patients receiving a SU vs. metformin, or other therapies (e.g. ref 1). However, most such analyses are inherently confounded by the presence of more advanced diabetes in those patients who clinically require combination therapy.²³ Suppression by some SUs of "ischaemic preconditioning", whereby repeated minor episodes of myocardial ischaemia can protect the heart against a subsequent major ischaemic episode, is often cited as a mechanism for the supposed adverse cardiovascular effects of SUs.²⁴ This phenomenon can be demonstrated in animal studies, but its clinical significance is uncertain.²⁴ The UKPDS, the only long-term, randomised evaluation of cardiovascular outcomes with SUs in T2DM (predominately with chlorpropamide and glibenclamide), showed no indication of any tendency towards an increased risk of cardiovascular events in patients allocated to intensive glycaemic control with a SU, compared with the diet-treated conventional control group (Figure 3).⁸

Measuring case fatality during acute MI provides a way to assess the clinical importance of ischaemic preconditioning: having a SU on board that may block this phenomenon should worsen outcomes in this setting, if it is truly important. Further data from the UKPDS provided no evidence for such an effect with no difference in case fatality rates for those taking or not taking a SU during an evolving MI.²⁵

Figure 3. Clinical outcomes from 10 years of intensive glycaemic management with sulphonylureas in the UK Prospective Diabetes Study (UKPDS). Drawn from data presented by the UKPDS⁸



The observation of increased mortality after addition of a SU to metformin therapy in a UKPDS 6-year sub study has caused much controversy over the years.⁹ The diminution of this effect to become no longer statistically significant during the 10-year observational post-trial monitoring period suggests that the original finding was likely a statistical artefact.^{26,27}

SUs do not exhaust the β -cell

Plasma insulin levels tracked similarly over time for patients randomised to SUs or to the dietary control group in the UKPDS.⁸ Moreover, the steadily rising mean HbA_{1c} values, secondary to progressive loss of β -cell functions, did not differ between randomised treatments in the UKPDS, including the dietary control group.⁸ The ADOPT trial demonstrated a modest but statistically significant lower rate of increase in HbA_{1c} with a thiazolidinedione (rosiglitazone), compared with a SU (glibenclamide) in T2DM patients, but at study end (five years), β -cell function did not differ between treatments and was numerically highest with glibenclamide.¹⁷ UKPDS also showed that the rate of increase of HbA_{1c} was greater over time with glibenclamide than with chlorpropamide.²⁸ There is no rea-

son to believe that SU treatment hastens the demise of the β -cell function in people with T2DM.

The problem of SU-induced weight gain is overstated

In UKPDS, mean body weight increased modestly (~2kg) following prescription of a SU to patients with newly-diagnosed diabetes and then levelled out.⁸ Similarly, mean weight gain with glibenclamide in the ADOPT trial was ~1.6 kg, and remained stable after the first year of treatment.¹⁷ T2DM can be exacerbated by obesity, but the effectiveness of SUs therapy differs little across the continuum of body weight. Fear of increased weight with SU should not be sufficient to prevent their second-line use if a patient likely to benefit from this treatment.

Hypoglycaemia – choose your patients carefully

Hypoglycaemia is a genuine concern with SUs, but can be mitigated by careful patient selection. Those with a higher HbA_{1c} before treatment are less likely to develop hypoglycaemia, and titrating the dose based on fasting plasma glucose levels helps to avoid undue hypoglycaemia.²⁹ There were fewer hypoglycaemic events on liraglutide vs. glimepiride in the LEAD-2

Table 1 Voting before and after the debate

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

*As second-line therapy for type 2 diabetes. SU, sulphonylureas.

study, but event rates were modest in both groups (0.03–0.14 events/year for placebo or liraglutide and 1.23 events/year for glimepiride).³⁰

Closing remarks

SUs remain widely prescribed because they are an effective, cost-effective (at a time of restricted healthcare budgets), safe and proven glucose-lowering 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. They remain a valuable therapeutic option within the patient-centred management of T2DM.

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.

References

1. Monami M, Genovese S, Mannucci E. Cardiovascular safety of sulphonylureas: a meta-analysis of randomized clinical trials. *Diabetes Obes Metab* 2013;**15**:938-53. <http://dx.doi.org/10.1111/dom.12116>
2. Giorgino F, Leonardini A, Laviola L. Cardiovascular disease and glycemic control in type 2 diabetes: now that the dust is settling from large clinical trials. *Ann N Y Acad Sci* 2013;**1281**:36-50. <http://dx.doi.org/10.1111/nyas.12044>
3. Del Prato S, Pulizzi N. The place of sulphonylureas in the therapy for type 2 diabetes mellitus. *Metabolism* 2006;**55**(5 Suppl 1):S20-7. <http://dx.doi.org/10.1016/j.metabol.2006.02.003>
4. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycaemia in type 2 diabetes: a patient-centered approach. Position statement of the American Diabetes Associ-

ation (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetologia* 2012;**55**:1577-96. <http://dx.doi.org/10.1007/s00125-012-2534-0>

5. National Institute for Health and Care Excellence. Type 2 diabetes: the management of type 2 diabetes. Guideline CG87. Available at <https://www.nice.org.uk/guidance/cg87> (accessed June 2015).
6. Debate held at a meeting of the Midlands Endocrine and Diabetes Club, Friday 8th May 2015.
7. Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 1993;**329**:977-86. <http://dx.doi.org/10.1056/NEJM199309303291401>
8. UK Prospective Diabetes Study Group. Intensive blood glucose control with sulphonylurea or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998;**352**:837-53. [http://dx.doi.org/10.1016/S0140-6736\(98\)07019-6](http://dx.doi.org/10.1016/S0140-6736(98)07019-6)
9. UK Prospective Diabetes Study Group. Effect of intensive blood glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet* 1998;**352**:854-65. [http://dx.doi.org/10.1016/S0140-6736\(98\)07037-8](http://dx.doi.org/10.1016/S0140-6736(98)07037-8)
10. Mearns ES, Sobieraj DM, White CM, et al. Comparative efficacy and safety of antidiabetic drug regimens added to metformin monotherapy in patients with type 2 diabetes: a network meta-analysis. *PLoS One* 2015;**10**:e0125879. <http://dx.doi.org/10.1371/journal.pone.0125879>
11. Thong KY, Gupta PS, Cull ML, et al. GLP-1 Receptor agonists in type 2 diabetes – NICE guidelines versus clinical practice. *Br J Diabetes Vasc Dis* 2014;**14**:52-9. <http://dx.doi.org/10.15277/bjdv.2014.015>
12. Monami M, Marchionni N, Mannucci E. Glucagon-like peptide-1 receptor agonists in type 2 diabetes: a meta-analysis of randomized clinical trials. *Eur J Endocrinol* 2009;**160**:909-17. <http://dx.doi.org/10.1530/EJE-09-0101>
13. Rajendran R, Hodgkinson D, Rayman G. Patients with diabetes requiring emergency department care for hypoglycaemia: characteristics and long-term outcomes determined from multiple data sources. *Postgrad Med J* 2015;**91**:65-71. <http://dx.doi.org/10.1136/postgradmedj-2014-132926>
14. Dormandy JA, Charbonnel B, Eckland DJ, et

al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. *Lancet* 2005;**366**:1279-89. [http://dx.doi.org/10.1016/S0140-6736\(05\)67528-9](http://dx.doi.org/10.1016/S0140-6736(05)67528-9)

15. Ryder REJ, Defronzo RA. Rehabilitation of pioglitazone. *Br J Diabetes Vasc Dis* 2015;**15**:46-9. <http://dx.doi.org/10.15277/bjdv.2015.021>
16. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* 2015;**373**:2117-28. <http://dx.doi.org/10.1056/NEJMoa1504720>
17. Kahn SE, Haffner SM, Heise MA, et al. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. *N Engl J Med* 2006;**355**:2427-43. <http://dx.doi.org/10.1056/NEJMoa066224>
18. Gallwitz B, Guzman J, Dotta F, et al. Exenatide twice daily versus glimepiride for prevention of glycaemic deterioration in patients with type 2 diabetes with metformin failure (EUREXA): an open-label, randomised controlled trial. *Lancet* 2012;**379**:2270-8. [http://dx.doi.org/10.1016/S0140-6736\(12\)60479-6](http://dx.doi.org/10.1016/S0140-6736(12)60479-6)
19. Del Prato S, Nauck M, Durán-García S, et al. Long-term glycaemic response and tolerability of dapagliflozin versus a sulphonylurea as add-on therapy to metformin in patients with type 2 diabetes: 4-year data. *Diabetes Obes Metab* 2015;**17**:581-90. <http://dx.doi.org/10.1111/dom.12459>
20. Scherthamer G, Currie CJ, Scherthamer GH. Do we still need pioglitazone for the treatment of type 2 diabetes? A risk-benefit critique in 2013. *Diabetes Care* 2013;**36**(Suppl 2):S155-61. <http://dx.doi.org/10.2337/dcS13-2031>
21. Ault A. FDA panel backs new safety warnings on two diabetes drugs. Medscape Medical News. Available at <http://www.medscape.com/viewarticle/843179> (accessed July 2015).
22. Medicines and Healthcare Products Regulatory Agency. Drug Safety Update. SGLT2 inhibitors (canagliflozin, dapagliflozin, empagliflozin): risk of diabetic ketoacidosis. Available at <https://www.gov.uk/drug-safety-update/sgl2-inhibitors-canagliflozin-dapagliflozin-empagliflozin-risk-of-diabetic-keto-acidosis> (accessed July 2015).
23. Turner RC, Holman RR. Metformin and risk of cardiovascular disease. *Cardiology* 1999;**91**:203-04. <http://dx.doi.org/10.1159/000006910>
24. Valensi P. Sulphonylureas and cardiovascular risk: facts and controversies. *Br J Diabetes Vasc Dis* 2006;**6**:159-65. <http://dx.doi.org/10.1177/14746514060060040301>
25. Stevens RJ, Coleman RL, Adler AI, Stratton IM, Matthews DR, Holman RR. Risk factors for myocardial infarction case fatality and stroke case fatality in type 2 diabetes: UKPDS 66. *Diabetes Care* 2004;**27**:201-07. <http://dx.doi.org/10.2337/1201>
26. UK Prospective Diabetes Study Group. Correspondence. *Lancet* 1998;**352**:1932-4.
27. Holman RR. Post trial monitoring results of the UKPDS sulphonylurea plus metformin sub-

- study. Presentation at the 49th Annual Meeting of the European Association for the Study of Diabetes, Barcelona, Spain, 23–27 September 2013. Available at <http://www.easdvirtualmeeting.org/resources/post-trial-monitoring-results-of-the-ukpds-sulfonylurea-plus-metformin-substudy> (accessed July 2015).
28. Matthews DR, Cull CA, Stratton IM, Holman RR, Turner RC. UKPDS 26: Sulphonylurea failure in non-insulin-dependent diabetic patients over six years. UK Prospective Diabetes Study (UKPDS) Group. *Diabet Med* 1998;**15**:297-303. [http://dx.doi.org/10.1002/\(SICI\)1096-9136\(199804\)15:4<297::AID-DIA572>3.3.CO;2-N](http://dx.doi.org/10.1002/(SICI)1096-9136(199804)15:4<297::AID-DIA572>3.3.CO;2-N)
29. Wright AD, Cull CA, Macleod KM, Holman RR. Hypoglycemia in type 2 diabetic patients randomized to and maintained on monotherapy with diet, sulfonylurea, metformin, or insulin for 6 years from diagnosis: UKPDS73. *J Diabetes Complications* 2006;**20**:395-401. <http://dx.doi.org/10.1016/j.jdiacomp.2005.08.010>
30. Nauck M, Frid A, Hermansen K, et al. Efficacy and safety comparison of liraglutide, glimepiride, and placebo, all in combination with metformin, in type 2 diabetes: the LEAD (liraglutide effect and action in diabetes)-2 study. *Diabetes Care* 2009;**32**:84-90. <http://dx.doi.org/10.2337/dc08-1355>

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