If sulphonylureas are more harmful than rosiglitazone, why has the latter been withdrawn, and the former has not?

As readers will be aware, one of the longest running questions in the field of type 2 diabetes is whether oral anti-diabetes drugs (OADs) reduce cardiovascular disease risk and all-cause mortality as well as reducing blood glucose levels. The UKPDS (UK Prospective Diabetes Study) answered this question positively with regard to metformin when the trial reported in 1998 (UKPDS Study Group, 1998). For other drugs, an answer has been awaited ever since. It is indeed an answer that takes many years to achieve because a drug has to be in use for a considerable period of time before it can be categorically stated that it does (or does not) reduce cardiovascular disease and all-cause mortality.

An article published in the *BMJ* bravely attempted to answer this question and it has raised remarkably few waves in view of the sensational results it reported (Tzoulaki et al, 2009). It was a retrospective cohort study, in which only data from individual's past records are examined. These are subject to the problems of all observational studies, although the authors did make every attempt to exclude possible confounding issues by looking at several models.

Tzoulaki et al examined records from the general practice database of over 90 000 people with diabetes taking OADs. The outcomes of people taking sulphonylureas, rosiglitazone or pioglitazone were compared with metformin with respect to the incidence of myocardial infarction, congestive cardiac failure and all-cause mortality.

The authors were critical of previous articles suggesting an increased risk with rosiglitazone, which they did not confirm, although a subsequent continuing controversy has led to the withdrawal of rosiglitazone from the market. This was discussed by the Editor of this journal, Colin Kenny, at the end of last year (Kenny, 2010).

Looking at all-cause mortality, which is the area of most interest to a person with diabetes, rosiglitazone showed a modest reduction compared with metformin. Pioglitazone showed a much greater reduction of 20–30% compared with metformin in both myocardial infarction and all-cause mortality.

However, the really dramatic findings were in respect to sulphonylureas: both first generation (all of these have now been withdrawn for other reasons) and second generation (including all the commonly used ones). These showed an increase of over 50% in all-cause mortality compared with metformin, and second generation sulphonylureas were associated with a 30% excess risk for congestive heart failure. There is always the possibility that people taking sulphonylureas may have been at risk for other reasons. Model 2 adjusted the figures for existing cardiovascular disease and treatment. Model 3 adjusted the figures for other possible risk factors such as cholesterol levels, BMI, and so on. In neither case were the overall figures very different (Tzoulaki et al, 2009).

From these momentous findings, there are two questions that, I think, need to be answered:

- Why has rosiglitazone been withdrawn and the sulphonylureas have not?
- Why are sulphonylureas still recommended as one of two "first choice" drug categories (the other being metformin) in both the two major guidelines (NICE, 2009; SIGN, 2010)?

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Yours sincerely,
Paul Sheldon

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Tzoulaki I, Molokhia M, Curcin V et al (2009) Risk of cardiovascular disease and all cause mortality among patients with type 2 diabetes prescribed oral antidiabetes drugs: retrospective cohort study using UK general practice research database. *BMJ* **339**: b4731

UK Prospective Diabetes Study (UKPDS) 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

If you would like to write a response to this letter, please send an email to dpc@sbcommunications group.com or call 0207 627 1510 for more information.

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