Clinical reviews

Our panel of GPs review recent research papers in their specialist areas that may influence the way you practise

Reviewers

Addiction
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Diabetes

Sulfonylureas raise risk of CHD in women

The use of sulfonylureas in women with type 2 diabetes is associated with a significant increase in the risk of coronary heart disease (CHD), but not stroke, a large prospective cohort study has shown. The longer the drugs were used the higher the risk.

The Nurses' Health Study cohort was established in 1976, when 121,700 female registered nurses aged 30 to 55 years were enrolled across the US. The participants filled in a detailed postal questionnaire on their medical history and lifestyle. Every two years follow-up questionnaires have been sent to update information on potential risks and to identify newly diagnosed cases of type 2 diabetes and cardiovascular events. This cohort of patients was used in the current study published in *Diabetes Care*.

In 2000 and 2005, 5,536 women with type 2 diabetes responded to the supplemental questionnaire about their diabetes treatment and any complications. The 634 respondents with prevalent cardiovascular disease at the time of the supplemental questionnaires were excluded from the analysis. This left 4,902 eligible women who were followed until the end of June 2010 for incident cardiovascular disease. Their mean age was 68 years and mean duration of diabetes was 11 years.

Although the diagnoses of diabetes and cardiovascular disease were based on self-reporting, checks on the medical notes of a sample of patients confirmed a high level of accuracy, consistent with the findings of similar earlier studies. The medical records of patients with CHD and stroke were assessed against the WHO definitions of non-fatal MI and the Perth Community Stroke Study.

The risk of cardiovascular disease was examined according to duration of sulfonylurea use. The categories were: nonuser, 1-5 years, 6-10 years and > 10 years. The information from the questionnaires allowed detailed statistical analysis for confounding variables, and was able to isolate the risk of incident cardiovascular disease associated with using sulfonylureas.

There were 191 cases of CHD and 148 strokes diagnosed in the study population over 5-10 years' follow-up. A longer duration of sulfonylurea use was significantly associated with an increased risk of CHD. Compared with nonusers the relative risks (RR) were:

- 1-5 years RR 1.24 (95% CI:0.85-1.81)
- 6-10 years RR 1.51 (95% CI:0.94-2.42)
- > 10 years RR 2.15 (95% CI:1.31-3.54).

The trend for increasing risk with length of use was significant, P = 0.002.

No similar increase in stroke risk was associated with the use of sulfonylureas.

Compared with patients treated with metformin alone, the RR for CHD was 3.27 (95% CI:1.31-8.17) for those treated with a combination of metformin and sulfonylurea.

The authors conclude that long-term use of sulfonylureas was associated with a significantly higher risk of CHD in women with type 2 diabetes.

Sulfonylureas are associated with weight gain and hypoglycaemia, both of which might be associated with adverse cardiovascular outcomes. However, at a molecular level, sulfonylureas bind to ATP-sensitive potassium channels on pancreatic cells, resulting in the subsequent opening of voltage gated calcium channels that stimulate the movement of insulin-containing secretory granules from beta cells into the circulation. Sulfonylureas bind to the same channels in the myocardium and this may be one mechanism by which they interfere with myocardial function. This might explain the absence of an increase in strokes.

Although the study population is highly selected, this is an important study for primary care. Of the older oral hypoglycaemic drugs metformin has a consistently demonstrated cardioprotective effect, but the sulfonylureas have never been able to demonstrate a similar property. In fact there has always been a question mark over their potential to cause adverse cardiovascular outcomes: the UKPDS sub-group analysis suggested this. In the US, the approved package labels for sulfonylureas include a warning about increased cardiovascular risk.

Newer oral agents, such as DPP-IV inhibitors and SGLT2 inhibitors are significantly more expensive than sulfonylureas. The newer agents do not carry the same risks of hypoglycaemia and weight gain as the sulfonylureas, but GPs are still encouraged to use sulfonylureas in the treatment of type 2 diabetes because of their low acquisition cost.

One of the arguments offered to support this is that newer agents have no long-term outcome data. However, the long-term outcome data suggesting a worsening of cardiovascular outcomes with sulfonylureas is likely to spark further debate about the optimum treatment of type 2 diabetes.

DR MATTHEW LOCKYER

● **Li Y, Hu Y, Ley SH et al. Sulfonylurea use and incident cardiovascular disease among patients with type 2 diabetes: Prospective cohort study among women. *Diabetes Care* 2014;37:3106-13**

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