Cohort study

High-dose sulphonylurea treatment in patients with renal impairment should be considered with caution

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Commentary on: van Dalem J, Brouwers MC, Stehouwer CD, *et al*. Risk of hypoglycaemia in users of sulphonylureas compared with metformin in relation to renal function and sulphonylurea metabolite group: population based cohort study. *BMJ* 2016;354: i3625.

Context

Type 2 diabetes mellitus (T2DM) is one of the most serious health problems worldwide.[1] Strict glycaemic control has been emphasised, and the number of patients with the risk of hypoglycaemia has increased.[2] Hypoglycaemia is a serious side effect of treatment with sulphonylureas, which stimulate insulin secretion regardless of blood glucose level. It is more common in patients using long-acting sulphonylureas with renally excreted active metabolites.[3] Therefore, an increasing number of patients with renal impairment may currently live with the risk of hypoglycaemia. However, the incidence of hypoglycaemia when treating with sulphonylureas in patients with impaired renal function has remained unclear.

Methods

This was a population-based cohort study of the association between the use of sulphonylureas and the risk of hypoglycaemia in relation to renal function and sulphonylurea metabolite compared with the use of metformin only. Data for this study were derived from the Clinical Practice Research Datalink (CPRD) database, 2004–2012. Participants were new users of a non-insulin antidiabetic agent. A first ever hypoglycaemic event was defined as the first 'read code' recording for hypoglycaemia or a blood glucose level of <3.0 mmol/L. Sensitivity analyses by stratification of current users of metformin only by renal function were assessed, as well as stratification of current users of sulphonylureas only by daily dose and haemoglobin A1c level.

Findings

The 120 803 participants (mean age 67.4 years) were followed-up for a mean duration of 3.7 years. The current users of sulphonylureas only showed a significant increased risk of a hypoglycaemic event compared with current users of metformin only (HR=2.50, 95% CI 2.23 to 2.82) after the adjustment of the use of other non-insulin antidiabetic agents. The risk of a hypoglycaemic event was dose-dependent in this comparison. The increase in risk of hypoglycaemia was also observed in patients with current metformin and sulphonylurea use, as well as in patients with current sulphonylurea and non-insulin antidiabetic agent use. In patients with an estimated glomerular filtration rate (eGFR) of <30 mL/min/1.73 m^2, the risk of hypoglycaemia in current users of sulphonylureas only was markedly increased (HR=4.96, 95% CI 3.76 to 6.55). The use of glibenclamide was associated with the highest risk of hypoglycaemic events compared with the current use of metformin; other sulphonylureas including gliclazide were also associated with increased risk.

Commentary

This study highlights the important debate on the use of sulphonylureas and the risk of hypoglycaemia. It indicates that current users of sulphonylureas only have a significantly increased risk of hypoglycaemic events compared with users of metformin only, and this is worsened in renal impairment, and with increasing doses. Gliclazide, mainly excreted as inactive metabolites, is the first choice sulphonylurea for T2DM because it is thought to have a lower risk of hypoglycaemia.[4] However, in this study, the use of gliclazide did not show a decreased risk of hypoglycaemia compared with glimepiride. As this study was based on real life data in general clinical practice, unlike previous randomised controlled trials (RCTs), there is the potential for selection bias with important differences in patient characteristics observed between groups. As mentioned in the limitations of this study, patients with renal impairment tended to be treated with gliclazide rather than other sulphonylureas with active metabolites, limiting the power to be able to make comparisons.

Implications for practice

This study provided evidence that care should be taken in increasing doses of sulphonylureas and that high-dose sulphonylurea treatment in patients with renal impairment and an eGFR <30 mL/min/1.73 m^2 should be considered with caution. Gliclazide, the first choice for sulphonylurea in many countries based on presumption of lower risk of hypoglycaemia, showed no different risks of hypoglycaemia compared with other sulphonylureas in this study, highlighting the need for further investigation.

Competing interests None declared.

Provenance and peer review Commissioned; internally peer reviewed.

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Notes