Medicines Evidence Commentary

commentary on important new evidence from Medicines Awareness Weekly

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Type 2 diabetes: meta-analysis finds no increased risk of mortality, MI or stroke with sulfonylureas

A meta-analysis has found that second- and third-generation sulfonylureas (for example, gliclazide, glipizide, glimepiride and glibenclamide) are not associated with a clinically significant increased risk of all-cause mortality, cardiovascular mortality, myocardial infarction (MI) or stroke compared with placebo, diet or other active comparators in adults with type 2 diabetes. Subgroup analyses of mortality found that the results were irrespective of the comparator drug class or stage of treatment. Healthcare professionals should continue to follow NICE guidance on managing type 2 diabetes in adults.

Overview and current advice

Sulfonylureas are widely used for treating type 2 diabetes and recommended throughout NICE guidance. However, concerns have been raised that they may increase the risk of cardiovascular events and death, and results of studies have been conflicting.

The NICE guideline on type 2 diabetes in adults recommends an individualised approach to diabetes care that takes into account personal preferences, comorbidities, risks from polypharmacy, and the ability to benefit from long-term interventions because of reduced life expectancy. Controlling blood glucose levels requires a careful balance between the intensity of the treatment regimen and avoiding hypoglycaemia. The choice of treatment should be made following a discussion with the individual person about the benefits and risks of drug treatment, and the options available.

The NICE guideline recommends offering metformin as the initial drug treatment for adults with type 2 diabetes. If metformin is contraindicated or not tolerated, a dipeptidyl peptidase-4 (DPP-4) inhibitor (gliptin), pioglitazone or sulfonylurea should be considered instead. Repaglinide may be an option for some people.

The guideline recommends considering dual therapy if initial drug treatment does not continue to control HbA1c to below the person's individually agreed threshold for intensification of treatment. In people already taking metformin, a DPP-4 inhibitor, pioglitazone or sulfonylurea should usually be considered. A sodium-glucose cotransporter-2 (SGLT-2) inhibitor may be used in certain circumstances. If metformin is contraindicated or not tolerated, treatment with 2 of the following 3 medicines should be considered: a DPP-4 inhibitor, pioglitazone and a sulfonylurea.
If dual therapy does not continue to control HbA1c to below the person's individually agreed threshold for intensification, the guideline recommends considering either triple therapy with oral drugs or starting insulin-based treatment. For triple therapy the following are recommended:

- metformin, a DPP-4 inhibitor and a sulfonylurea or
- metformin, pioglitazone and a sulfonylurea or
- metformin, pioglitazone or a sulfonylurea, and an SGLT-2 inhibitor in certain circumstances.

If an adult with type 2 diabetes is symptomatically hyperglycaemic at any stage of treatment, the NICE guideline recommends considering insulin or a sulfonylurea as rescue therapy. Treatment should be reviewed when blood glucose control has been achieved.

The NICE pathway on diabetes brings together all related NICE guidance and associated products in a set of interactive topic-based diagrams. The NICE quality standards on diabetes in adults describe concise sets of prioritised statements designed to drive measurable quality improvements within this area. A NICE key therapeutic topic discusses the evidence for managing blood glucose to support medicines optimisation.

**New evidence**

Following suggestions that results of earlier meta-analyses may have been contradictory because of the inclusion of observational studies, short-term studies and first-generation sulfonylureas (for example, chlorpropamide and tolbutamide), a recent meta-analysis of randomised controlled trials (RCTs: published between 1986 and 2014) has assessed the safety of second- and third-generation sulfonylureas (for example, gliclazide, glipizide, glimepiride and glibenclamide) for treating adults with type 2 diabetes.

The meta-analysis included 47 RCTs (37,650 adults, mean age 57.3 years, mean baseline HbA1c 55.2 mmol/mol [7.2%]) comparing sulfonylureas with diet, placebo or other antihyperglycaemic medication for at least 12 months (range 12–133 months). The primary outcomes were all-cause and cardiovascular mortality. Secondary outcomes included MI and stroke.

The meta-analysis found that sulfonylureas were not associated with statistically significant increases in all-cause mortality (37 RCTs, n=34,723: number of deaths 320/14,841 [2.2%] compared with 570/19,882 [2.9%] with control; odds ratio [OR] 1.12, 95% confidence interval [CI] 0.96 to 1.30) or cardiovascular mortality (21 RCTs, n=17,966: number of deaths 113/7749 [1.5%] compared with 241/10217 [2.4%] with control: OR 1.12, 95% CI 0.87 to 1.42). Although the number of events in those taking and those not taking sulfonylureas was not reported, there was also no significant difference between the groups in MI (23 RCTs, n=26,521: total number of events 589: OR 0.92, 95% CI 0.76 to 1.12) or stroke (23 RCTs, n=26,175: total number of events 275: OR 1.16, 95% CI 0.81 to 1.66).

Subgroup analyses also found no statistically significant increases in the risk of all-cause mortality or cardiovascular mortality when sulfonylureas were:

- compared with different types of control treatment (for example, placebo or diet, all active comparators combined, individual drug classes for treating type 2 diabetes or metformin)
- assessed according to the stage of treatment (for example, first-line, second-line or addition to metformin).

The meta-analysis was not designed to compare different sulfonylureas.

The reliability of the results was assessed using trial sequential analysis. This found that the meta-analysis included sufficient information to conclude that fewer than 1 in 200 people (0.05%, the amount considered by the researchers to be the minimum clinically significant difference) were likely to have been harmed by using sulfonylureas rather than placebo, diet or another active treatment.
The meta-analysis has some limitations. Thirty six identified RCTs could not be included in the study because mortality outcomes were not available, even after trying to contact the authors. Also, the study only included RCTs, which are generally not designed to evaluate long-term safety outcomes, and although only RCTs with at least 12 months’ follow-up were included, this may be too short to reliably assess mortality. Nevertheless, an analysis including only RCTs with at least 2 years duration (number not reported) had similar results to the primary analyses. In most RCTs it was unclear whether random sequence generation, allocation concealment and blinding of outcome assessment were used. However, the authors reported that the GRADE quality of evidence was high for all-cause and cardiovascular mortality, and moderate for MI and stroke.

Commentary
Commentary provided by NICE

The authors of the meta-analysis concluded that their study suggests that the use of second- and third-generation sulfonylureas in adults with type 2 diabetes is not associated with increased cardiovascular risk and all-cause mortality, irrespective of comparator or background medication. They consider that sulfonylureas should, therefore, still be used but that it is important to weigh their efficacy in controlling hyperglycaemia and low cost against the risks of hypoglycaemia and weight gain.

The study supports the NICE guideline on type 2 diabetes in adults, which recommends sulfonylureas as an option at each stage of treatment and for rescue treatment. In their assessment of the evidence for initial therapy for type 2 diabetes, the NICE Guideline Development Committee noted that although sulfonylureas were associated with clinically important reductions in blood glucose levels in the short-term at 3 and 6 months, they were consistently associated with more hypoglycaemic events and weight gain at 12 and 24 months. NICE advises that the choice of medicine for managing blood glucose levels should be made following a discussion with the individual person about the benefits and risks of drug treatment, and the options available.

NICE also recommends that people with type 2 diabetes should be involved in decisions about their individual HbA1c target and be supported to achieve and maintain this. Different targets are recommended in the guideline depending on the stage of treatment and which drugs are used. A higher HbA1c target than usual may be considered in people who are taking sulfonylureas because they are associated with hypoglycaemia. The target HbA1c can be relaxed on a case-by-case basis, with particular consideration for people who are older or frail, those with a reduced life expectancy, those for whom tight blood glucose control poses a high risk of the consequences of hypoglycaemia, and those for whom intensive management would not be appropriate, such as people with significant comorbidities. The NICE patient decision aid for adults with type 2 diabetes can support the implementation of the guideline recommendations on the individualised agreement of HbA1c targets and the pharmacological management of blood glucose.

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References
1. Rados DV, Pinto LC, Remonti LR et al. (2016) The association between sulfonylurea use and all-cause and cardiovascular mortality: a meta-analysis with trial sequential analysis of randomized clinical trials. PLOS Medicine DOI:10.1371/journal.pmed.1001992
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