Type 2 diabetes: increased risk of hypoglycaemia with combined use of dipeptidyl peptidase-4 (DPP-4) inhibitors and sulfonylureas

A systematic review and meta-analysis found that adding a dipeptidyl peptidase-4 (DPP-4) inhibitor (or gliptin) to a sulfonylurea increased the risk of hypoglycaemia by around 50%. The NICE guideline on type 2 diabetes recommends the combination of a sulfonylurea and DPP-4 inhibitor as an option for intensification of treatment in certain circumstances. The guideline recommends 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.

Overview and current advice

The management of type 2 diabetes is complex. It needs an individualised multifactorial approach addressing blood glucose, blood pressure, blood lipids and lifestyle issues (for example, smoking cessation, exercise, losing weight and a healthy diet). Controlling blood glucose needs a careful balance between the intensity of the treatment regimen and avoiding hypoglycaemia. Hypoglycaemia can be a potentially life-threatening event associated with hospital admission, cardiovascular disease, and mortality. A Cochrane review (CD008143) compared intensive glycaemic control with conventional glycaemic control and found that intensive control did not reduce the risk of death from any cause, cardiovascular death, nonfatal stroke, or cardiac or peripheral revascularisation. Intensive control did reduce the risk of nonfatal myocardial infarction (MI), amputation of a lower extremity, and microvascular complications (including nephropathy and retinopathy) but it also increased the risk of severe adverse events and hypoglycaemia.

The NICE guideline on type 2 diabetes recommends adopting an individualised approach to diabetes care, which takes into account personal preferences, comorbidities, risks from polypharmacy, and the ability to benefit from long-term interventions because of reduced life expectancy. Importantly, the person's needs and circumstances should be reassessed at each review and consideration given to stopping any medicines that are not effective. NICE also recommends that people with type 2 diabetes should be involved in decisions about their individual glycated haemoglobin (HbA1c) target, which should reflect their own particular circumstances and preferences, and be supported to achieve and maintain this. When intensification of drug treatment is required the guideline recommends that additional treatments should be introduced in a stepwise manner, checking for tolerability and effectiveness of each drug. The choice of medicine should be made following a discussion with the individual person about the benefits and risks of drug treatment, and the options available. Choice
should also take into account the medicine's efficacy (based on metabolic response), safety and tolerability, licensed indications or combinations available, and cost of the medicine.

The study reviewed here investigated the risk of hypoglycaemia with the combined use of DPP-4 inhibitors and sulfonylureas. The summaries of product characteristics for all the DPP-4 inhibitors state that when these drugs are used in combination with a sulfonylurea, a lower dose of the sulfonylurea may be required to reduce the risk of hypoglycaemia. Sulfonylureas are known to cause hypoglycaemia, and when DPP-4 inhibitors are used with sulfonylureas, an increased incidence of hypoglycaemia has been seen.

**New evidence**

A systematic review and meta-analysis was carried out to quantify the risk of hypoglycaemia with the combined use of DPP-4 inhibitors and sulfonylureas, compared with placebo and sulfonylureas (Salvo et al. 2016). The analysis included 10 studies and a total of 6456 people with type 2 diabetes mellitus; 4020 people received DPP-4 inhibitors plus sulfonylureas and 2526 people received placebo plus sulfonylureas. The DPP-4 inhibitors used in the studies were alogliptin 6.5–25 mg daily, linagliptin 5 mg daily, saxagliptin 2.5–5 mg daily, sitagliptin 100 mg daily, and vildagliptin 50–100 mg daily. The sulfonylureas used were not specified in 4 studies and the others included glimepiride or glibenclamide. Four of the studies also allowed treatment with metformin, and 2 studies allowed use of insulin. All of the studies were double-blind, randomised controlled trials. Most of the studies had a follow up of 24 weeks or less (9 out of 10 studies). One longer study followed participants for a median drug use time of 76 weeks.

A total of 479/4020 people who were receiving DPP-4 inhibitors and sulfonylureas developed hypoglycaemia, corresponding to an absolute risk of 11.9%. Out of the 2526 people receiving placebo plus sulfonylureas, 169 developed hypoglycaemia, corresponding to an absolute risk of 6.7%. The relative risk (RR) of hypoglycaemia for DPP-4 inhibitors at any dose plus sulfonylureas compared with placebo plus sulfonylureas was 1.52 (95% confidence interval [CI] 1.29 to 1.80). The number needed to harm (NNH) was 17 (95% CI 11 to 30) for a treatment duration of 6 months or less, 15 (95% CI 9 to 26) for a treatment duration of 6.1 to 12 months, and 8 (95% CI 5 to 15) for a treatment duration of more than 12 months.

When trials that allowed use of insulin were excluded from the analyses the results were also statistically significant (RR 1.61, 95% CI 1.30 to 2.00). The risk of hypoglycaemia was statistically significantly increased with full dose DPP-4 inhibitors plus sulfonylureas compared with placebo plus sulfonylureas (RR 1.66, 95% CI 1.34 to 2.06) but not with low dose DPP-4 inhibitors plus sulfonylureas (RR 1.33, 95% CI 0.92 to 1.94). However, in subgroup analysis, no difference was found between low and full dose DPP-4 inhibitors for the risk of hypoglycaemia ($I^2=0\%$, $p=0.32$).

The strengths of this meta-analysis include its large size (nearly 6500 people). The quality of the included studies was high according the Cochrane collaboration tool for assessing risk of bias. Despite some studies having a high risk of detection and reporting bias, results were still statistically significant when these studies were excluded from the analyses. The authors state that there was no clear evidence of publication bias and the strength of evidence of the meta-analysis was evaluated as high according to GRADE. The included studies investigated all of the currently available DPP-4 inhibitors at varying doses.

As discussed by the authors, the meta-analysis had some limitations. Three studies accounted for more than 80% of the pooled results; however sensitivity analyses which excluded these studies did not change the findings. The definition of hypoglycaemia differed amongst the included studies and...
6 studies did not define hypoglycaemia. These differences in the definition of hypoglycaemia raise questions about the appropriateness of performing a meta-analysis on hypoglycaemia risk. However the findings did not differ between the studies that included a definition of hypoglycaemia and those that did not. Additionally, despite variability between the studies in terms of incidence of hypoglycaemia the authors state that no statistical heterogeneity was found for the estimation of pooled risk of hypoglycaemia and this did not impact on the NNH calculation. The systematic review and meta-analysis gave mean HbA1c levels at baseline for the population in the included studies but no mean HbA1c levels after treatment, and no individual patient data of HbA1c levels were given.

**Commentary**

This meta-analysis found that adding a DPP-4 inhibitor to a sulfonylurea increased the relative risk of hypoglycaemia by around 50%. The NNH was 17 over 6 months, indicating that for every 17 people treated with a DPP-4 inhibitor in addition to a sulfonylurea, there will be 1 extra case of hypoglycaemia in the first 6 months of treatment compared with treatment with a sulfonylurea alone. Although the results suggested a dose effect, a larger sample would be required to confirm these findings. The results confirm warnings in the summaries of product characteristics that adding a DPP4-inhibitor to a sulfonylurea increases the risk of hypoglycaemia, and also highlight the more general point about the increased risk of hypoglycaemia when blood glucose control is intensified.

The risk of hypoglycaemia when combining blood glucose lowering therapies is not unique to DPP4-inhibitors and sulfonylureas. Many of the summaries of product characteristics for blood glucose lowering therapies warn about the increased risk of hypoglycaemia when combining treatments, particularly with a sulfonylurea or insulin. In some cases, a lower dose of insulin or sulfonylurea is recommended when combining these treatments with other blood glucose lowering therapies.

The NICE guideline on type 2 diabetes recommends that HbA1c targets and blood glucose lowering treatment should be individualised to reflect people’s own particular circumstances and preferences. People should be supported to achieve and maintain their target HbA1c unless any resulting adverse effects including hypoglycaemia impair their quality of life. In addition, for people with a high risk of the consequences of hypoglycaemia such as those at risk of falling, people who have impaired awareness of hypoglycaemia, and people who drive or operate machinery as part of their job, consideration should be given to relaxing the individual HbA1c target on a case-by-case basis.

Triple therapy with a DPP-4 inhibitor, a sulfonylurea and metformin is recommended as one option by NICE at second intensification of therapy for people whose initial treatment was metformin. For people who have a contraindication to metformin, or who cannot tolerate it, dual therapy with a sulfonylurea and a DPP-4 inhibitor is recommended as one option at first intensification of therapy.

Clinicians should be aware of the risk of hypoglycaemia when considering intensifying a person’s glucose lowering medicines. This is particularly important when combining medicines which together carry a risk of hypoglycaemia, such as a DPP-4 inhibitor and a sulfonylurea, but also more generally when any intensification of therapy is considered. The potential benefits of tighter control of blood glucose should be weighed against the potential risks of striving for HbA1c levels that may be inappropriately low for some people. A NICE patient decision aid has been developed which helps people with type 2 diabetes think about the advantages and disadvantages of different treatment options for controlling their blood glucose to try to reduce the long-term risks of diabetes.

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References


2. Hemmingsen B, Lund SS, Gluud C et al. (2013) Targeting intensive glycaemic control versus targeting conventional glycaemic control for type 2 diabetes mellitus. Cochrane Database of Systematic Reviews 2013, Issue 11. Art. No.: CD008143. DOI: 10.1002/14651858.CD008143.pub3. This review has been withdrawn because of the involvement of 2 authors being employed in pharmaceutical companies. The authors of the review and the Cochrane Metabolic and Endocrine Disorders Group did not find that this was a breach of the rules of the Cochrane Collaboration at the time when it was published. However, after the publication of the review, the Cochrane Collaboration requested withdrawal of the review due to the employment of the 2 authors. A new protocol for a review to cover this topic will be published. This will have a new title and a markedly improved protocol fulfilling new and important developments and standards within the Cochrane Collaboration as well as an improved inclusion and search strategy making it necessary to embark on a completely new review project.

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