Metformin does not increase risk of GI side effects during GLP-1 RA initiation and titration

Metformin use during initiation and titration of GLP-1 receptor agonists (GLP-1 RAs) does not increase the frequency or severity of gut-related adverse events, or the likelihood of discontinuing the GLP-1 RA, according to this study published in *Diabetes Care*. Since gastrointestinal (GI) adverse events are common with both metformin and with GLP-1 RAs, data from four major clinical trials of liraglutide and subcutaneous and oral semaglutide were used to explore whether those treated with metformin suffered more GI side effects. The results suggest that pausing metformin therapy during GLP-1 RA initiation, as has been recommended by some, is not required. There was in fact a higher rate of GI adverse events and GLP-1 RA discontinuations in those not taking metformin, which the authors postulate could reflect an increased susceptibility to gut side effects with any drug. They recommend that increased counselling and consideration of slower titration may be helpful in this group. This is useful information to guide practice as a recently published National Drug Safety Alert states that supplies of oral semaglutide are now adequate to support new initiations of this drug, following the mandatory cessation of new initiations of any GLP-1 RA that has been in place since June 2023 due to manufacturing shortages.

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Gastrointestinal (GI) side effects are common in people with diabetes treated both with metformin and with GLP-1 receptor agonists (GLP-1 RAs), and they are the commonest reason for discontinuation of these drugs in clinical practice. Metformin can cause abdominal pain, bloating and diarrhoea, which can be minimised by slow titration. GLP-1 RAs can also cause these and other GI side effects due to their mechanisms of action, including slowing of gastric emptying, and again the effects are generally temporary, mild to moderate in severity and most likely to occur during dose titration; usually they do not result in the need to discontinue the GLP-1 RA. However, finding ways to minimise discontinuations remains important, due to the significant benefits these drugs can have on blood glucose, weight and cardiovascular events. Slow titration, counselling regarding the possibility and temporary nature of these side effects, and recommendations to eat smaller meals can be helpful.

A multidisciplinary expert consensus published in 2022 suggested pausing or reducing the dose of metformin therapy during initiation of a GLP-1 RA as an option to reduce GI side effects (Gorgojo-Martínez et al, 2022), although this is not widely practised in the UK. Guidance such as the ADA/EASD Management of hyperglycaemia in type 2 diabetes consensus report (Davies et al, 2022) recommends early initiation of GLP-1 RAs or SGLT2 inhibitors along with metformin in those with established or high risk of cardiovascular disease, and it is usual practice to titrate one drug up fully before adding the second class, without waiting for further glycaemic assessment.

In the present *post hoc* analysis published in *Diabetes Care*, Klein and colleagues examined data on the 16 996 adults participating in four large randomised, double-blind, placebo-controlled clinical trials assessing the safety and efficacy of GLP-1 RAs: the LEADER trial of liraglutide, the STEP 2 and

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Occurrence of Gastrointestinal Adverse Events Upon GLP-1 Receptor Agonist Initiation With Concomitant Metformin Use: A Post Hoc Analysis of LEADER, STEP 2, SUSTAIN-6, and PIONEER 6

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SUSTAIN 6 trials of subcutaneous semaglutide, and the PIONEER 6 trial of oral semaglutide. The primary endpoint was the percentage of people with at least one GI adverse event during the initiation and titration observation period, stratified by whether they were also taking metformin.

Results

Between 73.2% (SUSTAIN 6) and 89.6% (STEP 2) of participants in the four studies were taking metformin. As expected, participants randomised to the GLP-1 RAs were more likely to develop GI adverse events than those treated with placebo across all four trials; however, concomitant metformin therapy was not associated with an increased risk of GI symptoms, or an increased likelihood of GLP-1 RA discontinuation, compared to those who were not taking metformin. Interestingly, GI adverse events and GLP-1 RA discontinuations were more common in participants not treated with metformin, which may represent increased susceptibility of this group to gut-related adverse events, resulting in intolerance to metformin previously as well as to GLP-1 RAs in the trials.

Metformin is not recommended when eGFR is consistently less than 30 mL/min/1.73 m^2, and in LEADER, SUSTAIN 6 and PIONEER 6, some of those who were not taking metformin had lower eGFRs. The authors recommend providing in-depth counselling and possibly slower titration of GLP-1 RAs during initiation in these groups, particularly those who are known to have discontinued metformin previously, in order to decrease discontinuation rates.

Implications for practice

Following more than 6 months where initiation of GLP-1 RAs was not permitted in the UK, clinicians will have been pleased to read the National Drug Safety Alert published earlier this month, which confirms that there are now sufficient supplies of daily oral semaglutide (Rybelsus®) available in the UK to allow new initiations as well as supplying those already on treatment. However, our local pharmacies report intermittent supplies from distributors, so prescribers are urged to ensure consistent local supplies prior to full-scale implementation of this new guidance, in order to avoid jeopardising supplies to those already receiving Rybelsus treatment.

Prescribers are reminded of the importance of this drug being taken exactly as directed: swallowed whole, first thing in the morning, with a sip (up to 120 mL) of water and with no food, drink or other medication for at least 30 minutes to ensure absorption and, therefore, efficacy (note that, although the Summary of Product Characteristics states that Rybelsus can be taken at any time of day provided it is taken on an empty stomach, since GLP-1 RAs delay gastric emptying it is likely that the best time to ensure the stomach is empty is first-thing in the morning, and this is usually recommended).

GLP-1 RAs offer improved glycaemia, weight loss and cardiovascular benefits in those for whom they are recommended by the guidelines, so it is important that we facilitate their initiation and continuation in as many appropriate people as possible. These findings should help us to do so. ■

Davies MJ, Aroda VR, Collins BS et al (2022) Management of hyperglycemia in type 2 diabetes, 2022. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care* **45**: 2753–86

Gorgojo-Martínez JJ, Mezquita-Raya P, Carretero-Gómez J et al (2022) Clinical recommendations to manage gastrointestinal adverse events in patients treated with GLP-1 receptor agonists: A multidisciplinary expert consensus. *J Clin Med* **12**: 145