Addition of SGLT2 inhibitor to GLP-1 agonist therapy in people with type 2 diabetes and suboptimal glycaemic control

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Abstract
This study aimed to observe the effect of the novel combination of dual add-on therapy of a sodium-glucose co-transporter-2 (SGLT2) inhibitor to a glucagon-like peptide-1 receptor agonist (GLP-1 RA) on glycaemic control and weight in patients with suboptimal diabetes control who are already on antidiabetic treatment after failure of a GLP-1 RA therapy alone.

We conducted a retrospective observational case note review of patients who had a minimum of 12 weeks’ treatment with a GLP-1 RA added onto their previous regimen followed by the addition of an SGLT2 inhibitor. HbA1c and weight were measured routinely.

Dual therapy with a GLP-1 RA and an SGLT2 inhibitor was associated with a significantly larger reduction in HbA1c than therapy with a GLP-1 RA (25.5mmol/mol vs 8mmol/mol; p<0.05) on the background of the usual diabetic regimen at week 20; this effect was sustained at week 48. There was an additional benefit of further weight loss in 58% of the patients on dual add-on therapy compared to single GLP-1 therapy at 48 weeks.

In conclusion, patients with type 2 diabetes who require further improvement in glycaemic control despite the addition of a GLP-1 RA to their regimen can be considered for an SGLT2 inhibitor. The mechanism of action may be synergistic and has the advantage of promoting further weight loss. Copyright © 2016 John Wiley & Sons.

Key words
SGLT2 inhibitor; GLP-1 analogues; type 2 diabetes; weight loss

Introduction
Diabetes is estimated to cost 10% of total health resource expenditure in 2010/2011 in the UK, with estimates rising to 17% in 2034/2035 if care regimens do not adapt.1 This necessitates ongoing efforts by patients and health care providers to curb these frightening trends.

Available data support early intervention to achieve appropriate glycaemic control in order to minimise complications.2 Despite this, only 64.8% of people with type 2 diabetes are achieving NICE recommended glucose control (HbA1c ≤58mmol/mol).3

Patients with type 2 diabetes often require multiple antidiabetic agents to achieve and maintain glycaemic control4 due to the progressive nature of the disease.2 Few studies have looked at the benefits of using multiple agents with complementary mechanisms of action.6,7 With the expanding armamentarium of treatment for type 2 diabetes, prescribing choices for the treatment of hyperglycaemia need to be within a multifactorial risk reduction framework where the impact on weight is carefully considered.

Injectable glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have been licensed in the UK for type 2 diabetes since 2007. They mimic the effects of endogenous GLP-1 – thereby stimulating pancreatic insulin secretion in a glucose-dependent fashion, suppressing pancreatic glucagon output, slowing gastric emptying and decreasing appetite.8 Their efficacy has been proven and they have an established role in treatment. Not only do they improve glycaemic control but they also do so in line with weight reduction.9,10

Sodium-glucose co-transporter 2 (SGLT2) inhibitors are a novel class of antidiabetic agent first licensed for use in 2012. Improvements in glycaemic control were reported but also beneficial effects on weight loss and blood pressure are seen.11 The mechanism of action is at the proximal convoluted tubule where they block the reabsorption of glucose.12 Several studies and meta-analyses, including the recent EMPA-REG study, have established the safety,
efficacy and mortality benefits of SGLT2 inhibitors.\textsuperscript{13–16} Real-world data further confirm their reported benefits.\textsuperscript{17}

The objective of this study was to observe the impact on glycaemic control and weight of the novel combination of add-on therapy of a GLP-1 RA and an SGLT2 inhibitor, compared to GLP-1 RA add-on therapy alone, in patients with suboptimal diabetes control on routine antidiabetic treatment which included insulin in some cases.

**Methods**

We carried out a retrospective observational case note review of patients with type 2 diabetes who were started on an SGLT2 agent in addition to their diabetic regimen which previously included a GLP-1 analogue. Other inclusion criteria were suboptimal glycaemic control (HbA\textsubscript{1c} >88mmol/mol) on their initial therapy and an eGFR >60. All of these patients were commenced on an SGLT2 inhibitor if there was ongoing suboptimal control after a minimum of 24 weeks following a GLP-1 analogue addition to their diabetic regimen. This treatment regimen was decided during consultation at a specialty diabetes clinic.

Regular assessments of patients’ weight and HbA\textsubscript{1c} done during routine clinical visits were recorded. All patients were counselled about the unlicensed use of this combination of treatment and verbal consent was gained. All females of child-bearing age were advised of the need for reliable contraception while using either agent and for six months after their discontinuation, and they were also counselled regarding the lack of evidence on the safety of these classes of drugs in pregnancy. This was reiterated at each follow-up visit and continues to be discussed at each consultation.

A retrograde analysis of patients’ weight and HbA\textsubscript{1c} was done at the start of their GLP-1 analogue treatment, and a change in weight and HbA\textsubscript{1c} was noted at 24 weeks following the start of this treatment. Similarly, the data about weight and HbA\textsubscript{1c} of all these patients was calculated at the start of their SGLT2 inhibitor treatment, and a subsequent analysis of the change in weight and HbA\textsubscript{1c} was done at weeks 20 and 48. The patients were continued on their baseline diabetic treatment and the treatment regimen was reviewed at each clinic visit.

Statistical calculations were performed with Microsoft Excel 2010.

**Results**

A total of 14 patients meeting the inclusion and exclusion criteria were enrolled into this study. Population age was median 54 years (IQR 47.3–66.25) and 50% were male. The duration of type 2 diabetes was median 18.5 years (IQR 10–20); baseline HbA\textsubscript{1c} was 86.5mmol/mol (76.5–95.5) and weight was 113.3kg (95.6–120.1). The baseline treatment regimen included two or more oral hypoglycaemic agents in use at the start of SGLT2 inhibitor therapy in the study population.

Table 1. List of all hypoglycaemic agents used in the study population (n=14)

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Metformin</th>
<th>Sulphonylureas</th>
<th>GLP-1 agonists</th>
<th>Insulin regimen</th>
<th>SGLT2 inhibitors</th>
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<tr>
<td>1</td>
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<td>Liraglutide</td>
<td>Lantus</td>
<td>Dapagliflozin</td>
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<tr>
<td>2</td>
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<td>–</td>
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<td>Premix insulin</td>
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<tr>
<td>3</td>
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<td>–</td>
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<td>MDI</td>
<td>Dapagliflozin</td>
</tr>
<tr>
<td>4</td>
<td>Yes</td>
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<td>Dapagliflozin</td>
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<td>–</td>
<td>Dapagliflozin</td>
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<tr>
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<tr>
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<td>–</td>
<td>Bydureon</td>
<td>Premix insulin</td>
<td>Dapagliflozin</td>
</tr>
</tbody>
</table>

MDI = multiple daily insulin injection.

The addition of an SGLT2 inhibitor to the GLP-1 therapy occurred between January 2014 and November 2015. The list of all hypoglycaemic agents in use at the start of SGLT2 inhibitor therapy in the study population is shown in Table 1.

In addition to hypoglycaemic agents, all of the patients were also on statins and at least one antihypertensive agent. The HbA\textsubscript{1c} and weight were analysed initially at 20 weeks (range 8–46) and then at 48 weeks (range 46–84). With the addition of an SGLT2 inhibitor, the subsequent mean reduction from the baseline in HbA\textsubscript{1c} and weight at week 20 was -25.5mmol/mol (-20.75 to -29.0; p=0.0005) and -2.6kg (-0.9 to -3.4; p=0.11), respectively. Analysis at week 48 of 11/14 patients (one had been lost to follow up, one passed away and one patient underwent bariatric surgery) showed that the reduction in HbA\textsubscript{1c} and weight from the baseline was -24.5mmol/mol (-30 to -20.75; p=0.001) and -5.47kg (-5 to -2.29; p=0.32), respectively.
Addition of SGLT2 inhibitor to GLP-1 agonist therapy in suboptimally controlled type 2 diabetes

The effects of adding SGLT2 inhibitor therapy to GLP-1 treatment in terms of HbA1c and weight loss are outlined in Figures 1 and 2.

Weight loss was noticed in 58% of the patients after the addition of an SGLT2 inhibitor.

The most common side effects included urinary tract infections (in three patients) and polydipsia (in one patient).

Discussion
In this small observational study we have found that a combination of a GLP-1 RA and an SGLT2 inhibitor results in a greater HbA1c reduction than a GLP-1 RA alone.

This is not a comment on the efficacy of GLP-1 agonists. However, due to the complex involvement of multiple metabolic defects in the pathogenesis of type 2 diabetes, the use of different antidiabetic medications with different and complementary modes of action could result in improved glycaemic control, and with favourable metabolic changes.

This study showed that there was a significant reduction in HbA1c in patients who had had an SGLT2 added to their diabetic regimen which previously included a GLP-1 analogue. The improvement was noted: it was found to be statistically significant at week 20 and was maintained at week 48. There was also some reduction in weight noticed in 58% of the patients (range -1.9 to -30) at week 48.

The American Diabetes Association/European Association for the Study of Diabetes Joint Task Force recommends that addition of a third non-insulin agent can be considered as a treatment option in some patients. They advise that, in triple combinations, agents with complementary mechanisms of action should be used. However, they acknowledge that increasing the number of drugs heightens the potential for side effects and drug–drug interactions, raises costs, and negatively impacts on patient adherence. The rationale, benefits and side effects of each new medication should be discussed with the patient.

A recent study has shown that the glucosuric effect of SGLT2 inhibitors may be at the expense of increased endogenous glucose production via increased plasma glucagons. As GLP-1 RAs reduce plasma glucagon, the combination of GLP-1 agonists and SGLT2 inhibitors may have an additive or synergistic effect with potential favourable outcomes in terms of improvement in glycaemic control and weight reduction.

Rosenstock et al investigated concurrent dual add-on therapy to metformin of a dipeptidyl peptidase-4 (DPP-4) inhibitor and an SGLT2 inhibitor compared to single add-on therapy in different groups of patients, and demonstrated greater reductions in HbA1c from baseline in the group taking dual add-on therapy. However, there was no significant difference in weight loss between the two groups. DPP-4 inhibitors also act via increasing GLP-1 concentrations and are therefore insulin dependent.

In relation to weight loss and glycaemic control, McGovern et al studied the effects of adding an SGLT2 inhibitor to a regimen that includes a GLP-1 RA versus the addition of an SGLT2 inhibitor to a regimen without a GLP-1 RA. Forty patients had dapagliflozin therapy added to a GLP-1 RA and 48 had no GLP-1 agonist. After a mean of 154 days they demonstrated a weight loss of -2.8 kg with both agents compared to -1.4 kg with SGLT2 inhibitor add-on alone. There was no difference in glycaemic control.

Our study reflects real-life experience and demonstrates that dual add-on therapy with a GLP-1 RA and an SGLT2 inhibitor caused significantly reduced HbA1c levels.
when compared to single add-on therapy with a GLP-1 RA. While physicians must embrace the additions to the formulary for treating type 2 diabetes mellitus, they must also weigh the risk–benefit in selecting the appropriate patients for specific treatments.

However, when it is necessary to use triple therapy, the use of agents with different/synergetic mechanisms of action should be considered, particularly in relation to those agents with the additional benefit of weight loss. The EMPA-REG study16 has shown the favourable cardiovascular outcomes and mortality benefits, and this has led to further interest in the use of SGLT2 inhibitors. Therefore, this combination of medications associated with multiple metabolic benefits is attractive when there are real or perceived barriers to commencing insulin therapy.

This study has some limitations in relation to its retrospective nature and small sample size. In addition, some other important characteristics, such as compliance and side effects’ profile, could not be assessed for the present analysis. In this study, we only used those patients who tolerated GLP-1 RA and SGLT2 inhibitor therapy very well; however, in real life, our experience shows that a significant number of such patients cannot tolerate this intervention due to side effects or compliance issues relating to polyparmacy as the majority of them are also on other multiple medications, for example, statins and antihypertensives. However, these limitations did not significantly affect the importance of the analysis performed.

### Conclusion

Patients with type 2 diabetes who require further improvement in glycaemic control despite the addition of a GLP-1 RA to their regimen can be considered for an SGLT2 inhibitor. The mechanism of action is synergistic and has the advantage of promoting further weight loss.

### Declaration of interests

There are no conflicts of interest declared.

### References