Evaluation of a combination of SGLT2 inhibitor and GLP-1 receptor agonist treatment in type 2 diabetes

Jennifer Hayden, Feicong Huang, Lyndsey M McConnell, Christopher A Sainsbury, Gregory C Jones

Sodium–glucose cotransporter 2 (SGLT2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists both improve glycaemic control and can lead to weight loss, so it would seem logical to use them in combination. We aimed to evaluate clinical experience with this regimen. Retrospective clinical data were collected from electronic patient records of all individuals prescribed a SGLT2 inhibitor (dapagliflozin in this case) as an addition to a GLP-1 receptor agonist across two Scottish health board areas. Clinical data were collected at baseline and at 6–18 months after SGLT2 inhibitor initiation. Discontinuation of therapy and adverse events were recorded. The authors describe their findings and consider their wider impact on clinical practice.

Sodium–glucose cotransporter 2 (SGLT2) inhibitors are agents that competitively inhibit the reabsorption of glucose from the renal proximal tubule, and in doing so increase urinary glucose excretion by about 100 g glucose daily (Day and Bailey, 2015). The class improves both fasting and post-prandial glucose and there are now three SGLT2 inhibitors available in the UK: dapagliflozin, canagliflozin and empagliflozin. Dapagliflozin was the first SGLT2 inhibitor to be licensed in the UK in 2012. At the time of this study, it was the only available SGLT2 inhibitor; canagliflozin and empaglifozin are now also licensed.

The SGLT2 inhibitor class is generally well tolerated; the most reported common adverse events are female genital mycotic and urinary tract infections (Scheen, 2015). Trial data for dapagliflozin have shown a reduction of HbA_{1c}, weight and blood pressure (BP) in people with type 2 diabetes (Ferrannini et al, 2010). The NICE type 2 guidelines recommend that dapagliflozin can be used as part of dual therapy with metformin or in combination with other drugs or with insulin for the treatment of type 2 diabetes (NICE, 2015).

Glucagon-like peptide-1 (GLP-1) receptor agonists are a class of peptides that bind and activate receptors for the incretin hormone GLP-1 (Day and Bailey, 2015). They encourage insulin secretion and exert satiety effects that facilitate weight loss (Drucker and Nauck, 2006). At the time of writing, there are six available GLP-1 receptor agonists licensed in the UK with different doses and regimens (exenatide twice daily, lixisenatide, liraglutide, exenatide once weekly, dulaglutide and albiglutide once weekly). NICE guidelines recommended that GLP-1 receptor agonists can be used if triple therapy including metformin is not effective or tolerated. In this situation, a combination of metformin, a sulfonylurea and a GLP-1 receptor agonist can be considered (NICE, 2015). The individual should have a BMI of ≥35 kg/m^2 and specific psychological or other medical problems associated with obesity, or have a BMI of <35 kg/m^2 and for whom insulin would not be a suitable intensification due to their occupation

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Article points

1. Both sodium–glucose cotransporter 2 (SGLT2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists improve glycaemic control and reduce weight.
2. The modes of action of GLP-1 receptor agonists and SGLT2 inhibitors would suggest they would have an additive benefit on glucose control and weight.
3. In clinical practice, adding the SGLT2 inhibitor to a GLP-1 receptor agonist appears to reduce HbA_{1c} with a trend towards reductions of weight and blood pressure.

Key words

- Glucagon-like peptide-1 receptor agonists
- Real-world data
- Sodium–glucose cotransporter 2 inhibitors

Authors

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Page points

1. Sodium–glucose cotransporter 2 inhibitors lower blood glucose through insulin-independent mechanisms, whilst glucagon-like peptide-1 receptor analogues lower blood glucose levels through insulin-dependent mechanisms.
2. The potential benefit of this combination has led to their combined use in clinical practice. The authors aimed to evaluate the clinical experience of this regimen.

or weight loss would benefit other significant obesity-related comorbidities.

To date there are no randomised control trials of the combination of SGLT2 inhibitors and GLP-1 analogues in the treatment of type 2 diabetes. However, the mode of action of the two therapies suggest they would be a logical therapeutic combination. SGLT2 inhibitors lower blood glucose through insulin-independent mechanisms, whilst GLP-1 receptor analogues lower blood glucose levels through insulin-dependent mechanisms. This two-pronged attack to lowering blood glucose through one insulin-dependent and one insulin-independent method may have a potential therapeutic effect. SGLT2 and GLP-1 receptor agonists are also the only glucose-lowering medications associated with weight loss. The potential benefit of this combination has led to their combined use in clinical practice. We aimed to evaluate the clinical experience of this regimen.

Methods

The study included all eligible patients from Greater Glasgow & Clyde and Highland Health Boards in Scotland. Greater Glasgow & Clyde serves a population of over 1 million people in a mainly urban setting and has over 60 000 people who are registered as having diabetes. Highland Health Board serves over 300 000 people, many of whom are in remote and rural settings, with over 16 000 registered as having diabetes.

Observational retrospective data were collected from electronic patient records across the two health boards (SCI-diabetes) on all individuals prescribed an SGLT2 inhibitor (dapagliflozin) as an addition to GLP-1 receptor agonists liraglutide or exenatide twice daily. HbA_{1c}, weight, BP, total cholesterol, HDL-cholesterol, alanine aminotransferase (ALT), aspartate aminotransferase (AST)/ALT ratio and estimated glomerular filtration rate (eGFR) change at 6–18 months were compared to baseline. Discontinuation of therapy and adverse events were also recorded.

Results

Data were gathered for all eligible individuals between January 2013 and September 2014. In total, 85 people were prescribed a GLP-1 receptor agonist and then were prescribed an SGLT2 inhibitor (47 male; mean age, 57 years; mean diabetes duration, 13 years). In our cohort, 74 people were on liraglutide and 11 on exenatide twice-daily preparations, and all the individuals had an eGFR of >60 mL/min/1.73 m^2 at initiation of dapagliflozin. Dapagliflozin was used for between 3 and 18 months among the cohort, and five people (8.5%) stopped dapagliflozin therapy during the study period.

Median HbA_{1c} at initiation was 76 mmol/mol (9.1%; interquartile range [IQR], 67.5–88 mmol/mol [6.2–10.2%]) and at 12 months was 64 mmol/mol (8%; IQR, 56–71.5 mmol/mol [7.3–8.7%], P=<0.001). Systolic BP at baseline was 132 mmHg (IQR, 120–143 mmHg) and at 12 months was 128 mmHg (IQR, 120–135 mmHg). Median diastolic BP at baseline was 79 mmHg (IQR, 73–83 mmHg) and at 12 months was 77 mmHg (IQR, 72–86 mmHg). Neither reduction in BP was statistically significant. There was also a non-significant reduction in weight from 107.8 kg (IQR, 90.4–121.4 kg) at baseline to 102.7 kg (IQR, 86.4–120 kg) at 12 months. No significant change in total cholesterol, HDL-cholesterol, ALT, AST/ALT ratio and eGFR were observed post treatment. Adverse events documented included genital mycosis in 9 people (9.4%) and volume depletion in 4 people (4.7%).

Figure 1 shows the effect of dapagliflozin on HbA_{1c} and weight in the 35 people (41.1%) where data were available at 6–12 months' post-initiation for both parameters. Of this group, 22 people (62.8%) had a reduction in both weight and HbA_{1c} and 12 people (34.2%) had both a 5% reduction in weight and a ≥5 mmol/mol (0.46%) reduction in HbA_{1c}.

Discussion

The SGLT2 inhibitor class is known to be effective as a monotherapy in type 2 diabetes or as an add-on therapy with metformin (Nauck et al, 2011), dipeptidyl-peptidase 4 (DPP-4) inhibitors (Jabbour et al, 2012) or insulin (Wilding et al, 2012). The results of these combination therapies with dapagliflozin are well described by Fioretto et al (2015) in terms of reduction of HbA_{1c},

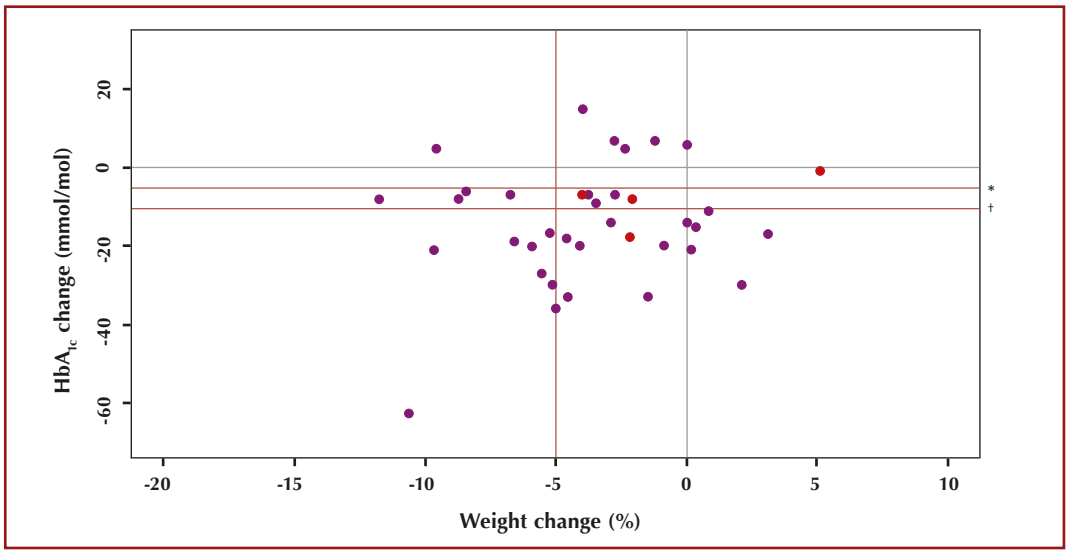

*Figure 1. A graph to show HbA_{1c} change (mmol/mol) compared to weight change (%) after 6–12 months of dapagliflozin added to glucagon-like peptide-1 receptor agonist in 35 people. The red dots represent people who discontinued dapagliflozin therapy. *5 mmol/mol HbA_{1c} reduction threshold; †10 mmol/mol HbA_{1c} reduction threshold.*

BP and weight loss. The Scottish Medicines Consortium (2014) accepts dapagliflozin (and canagliflozin and empagliflozin) for use in adults with type 2 diabetes to improve glycaemic control in combination with metformin, when metformin alone is inadequate and the addition of a sulfonylurea is seen as inappropriate.

Our results show that the addition of dapagliflozin to GLP-1 agonist therapy appears to effectively reduce HbA_{1c} in people with type 2 diabetes. A non-significant reduction in weight and blood pressure was also found.

This study also looked at the adverse effects associated with dapagliflozin. Those reported included genital mycosis and volume depletion, which is in keeping with previous reports (Scheen, 2015). The results from this small study suggest that this combination therapy is tolerated well by people with diabetes.

In people with type 2 diabetes, reduction of cardiovascular mortality and morbidity is a key goal. Treatment should aim to reduce weight, BP and total cholesterol as well as HbA_{1c}. Initial results from this study are encouraging and suggest that dapagliflozin in combination with GLP-1 receptor agonists may be capable of reducing HbA_{1c} whilst possibly lowering weight, which may have a beneficial impact on cardiovascular risk.

Hypoglycaemia is a common and dangerous complication of diabetes and is a safety issue in any medication that aims to lower blood glucose levels. Previous studies looking at dapagliflozin combined with insulin showed an increase in the number of hypoglycaemic events encountered compared to placebo (without dapagliflozin; Wilding et al, 2012). This is similar for concurrent therapy with a sulfonylurea alongside dapagliflozin (Nauck et al, 2011). Combining SGLT2 inhibition with GLP-1 receptor agonists without using insulin or sulfonylurea should avoid hypoglycaemia and may well have potential safety advantages over the former combinations described. GLP-1 receptor agonists and SGLT2 inhibitors are more expensive than other available anti-diabetes drug classes, particularly sulfonylurea. However, with the potential for a reduced incidence of hypoglycaemia, a reduced need for monitoring and a possible reduction in excess weight, using this combination may result in lower overall costs.

The results of the EMPA-REG OUTCOME study, the first cardiovascular safety trial of an SGLT2 inhibitor, demonstrated a reduction in cardiovascular events and death from all-cause mortality among individuals at high-risk of cardiovascular events treated with empagliflozin against placebo (Zinman et al, 2015). While more

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"In conclusion, we have demonstrated that dapagliflozin in combination with liraglutide or exenatide twice daily led to a significant reduction in HbA_{1c} in people with type 2 diabetes."

data are needed on whether these findings can be replicated in people with lower cardiovascular risks and with other drugs in the class, it is likely that this seminal study will increase the use of the SGLT2 inhibitor class.

In conclusion, we have demonstrated that dapagliflozin in combination with liraglutide or exenatide twice daily led to a significant reduction in HbA_{1c} in people with type 2 diabetes. This combined with the observed low withdrawal rate and side-effect profile make this a promising long-term combination for people with type 2 diabetes. Formal randomised controlled trials are necessary to further assess the role of SGLT2 inhibitors in combination with GLP-1 receptor agonists in the treatment of type 2 diabetes. ■

Day C, Bailey CJ (2015) Pharmacotherapies to manage diabesity: An update. *Diabesity in Practice* **4**: 14–22

Drucker DJ, Nauck MA (2006) The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. *Lancet* **368**: 1696–705

Ferrannini E, Ramos SJ, Salsali A et al (2010) Dapagliflozin Monotherapy in Type 2 Diabetic Patients With Inadequate Glycemic Control by Diet and Exercise: A randomized, double-blind, placebo-controlled, phase 3 trial. *Diabetes Care* **33**: 2217–24

Fioretto P, Giaccari A, Sesti G (2015) Efficacy and safety of dapagliflozin, a sodium glucose cotransporter 2 (SGLT2) inhibitor, in diabetes mellitus. *Cardiovasc Diabetol* **14**: 142–55

Jabbour S, Hardy E, Sugg JE et al (2012) Dapagliflozin as add-on therapy to sitagliptin with or without metformin: a randomized, double-blind, placebo controlled study. Abstract 1071-P. *72nd Scientific Sessions of the American Diabetes Association*. Philadelphia, PA. 8–12 June 2012

Nauck MA, Del Prato S, Meier JJ et al (2011) Dapagliflozin versus glipizide as add-on therapy in patients with type 2 diabetes who have inadequate glycemic control with metformin: a randomized, 52-week, double-blind, active-controlled non inferiority trial. *Diabetes Care* **34**: 2015–22

NICE (2015) *Type 2 diabetes in adults: management* (NG28). NICE, London. Available at: https://www.nice.org.uk/guidance/ng28 (accessed 28.04.16)

Scheen AJ (2015) Pharmacodynamics, efficacy and safety of sodium-glucose co-transporter type 2 (SGLT2) inhibitors for the treatment of type 2 diabetes mellitus. *Drugs* **75**: 33–59

Scottish Medicines Consortium (2014) *Briefing Note: dapagliflozin (Forxiga)*. SMC, Edinburgh. Available at: http://bit.ly/XRMhiv (accessed 19.11.15)

Wilding JPH, Woo V, Soler NG et al (2012) Long-term efficacy of dapagliflozin in patients with type 2 diabetes mellitus receiving high doses of insulin. *Ann Intern Med* **156**: 405–15

Zinman B, Wanner C, Lachin JM et al (2015) Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* **373**: 2117–28