Experience of and predictors of response to dapagliflozin in a real-life cohort of people with type 2 diabetes

Feicong Huang, Jennifer Hayden, Lyndsey MJ McConnell, Christopher AR Sainsbury, Gregory C Jones

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Article points

1. In randomised controlled trials, sodium–glucose cotransporter 2 inhibitors are known to improve glycaemic control and reduce weight and blood pressure.
2. In this real-world cohort, the authors observed improved glycaemic control and reduced weight and blood pressure with dapagliflozin, consistent with these clinical trials.
3. In clinical practice, adding dapagliflozin seems to produce similar reductions in HbA_{1c} irrespective of the regimen it is added to.

Key words

- Dapagliflozin
- SGLT2 inhibitors
- Type 2 diabetes

Authors

Author details can be found at the end of the article.

In clinical trials, dapagliflozin has been shown to lower blood glucose and reduce weight and blood pressure in people with type 2 diabetes. However, there are limited published data on the use and efficacy of this drug in routine clinical practice. Therefore, this observational, retrospective study was performed to assess the impact of dapagliflozin on blood glucose, weight and blood pressure, and to identify factors predictive of glycaemic response, in a large, unselected cohort of primary and secondary care patients. The findings confirm the efficacy of dapagliflozin in the real-world setting and show that the agent has similar effects regardless of BMI at baseline or concurrent use of other glucose-lowering therapies. People with higher HbA_{1c} at baseline experienced the greatest reductions in HbA_{1c}.

Sodium–glucose cotransporter 2 (SGLT2) inhibitors are a class of oral antidiabetes drugs that exert their action by blocking the SGLT2 receptor in the proximal convoluted tubule of the kidney, thereby increasing renal glucose excretion and lowering plasma glucose levels (Filippatos et al, 2015; Liakos et al 2015). Dapagliflozin was the first SGLT2 inhibitor to gain approval in Europe for the management of type 2 diabetes, and was first introduced in UK clinical practice in December 2012 (McGovern et al, 2014). NICE guidance recommending dapagliflozin for use in combination therapy for treatment of type 2 diabetes was published in June 2013 (NICE, 2013).

Many clinical trials have shown improvement in glycaemic control with dapagliflozin, either as monotherapy or in combination with metformin, sulfonylureas, dipeptidyl peptidase-4 (DPP-4) inhibitors or insulin. In addition, clinically significant weight loss is common, secondary to the calorie deficit resulting from renal glucose excretion. SGLT2 inhibitors also promote sodium and water loss, lowering blood pressure. The mechanism of dapagliflozin is independent of insulin secretion and action, and thus does not predispose to hypoglycaemia when the agent is used alone (Bailey et al, 2013).

While data from clinical trials are promising, there is less published information on the real-life use and efficacy of this drug. Therefore, this study was conducted to assess the impact of dapagliflozin on glycaemic control, weight and blood pressure in a "real-life" setting, in a large, unselected cohort of primary and secondary care patients. We hypothesised that the effect of dapagliflozin in clinical practice would reflect those reported in randomised control trials.

Aim

Our aim was to examine whether the documented clinical efficacy of dapagliflozin in patients from NHS Greater Glasgow and Clyde Trust and NHS Highland Trust reflected the data from clinical trials, and to explore factors predictive of glycaemic response.

Methods

The data source for this audit was the SCI-Diabetes database and the NHS SCI-Store laboratory and clinical document database. All people in NHS Greater Glasgow and Clyde and NHS Highland who were prescribed dapagliflozin between January 2013 and January 2015 were included in the audit. People found to have no identifiable data on the SCI-Diabetes database were excluded. The agreed data set comprised the following:

- Dapagliflozin prescription start date.
- Dapagliflozin prescription stop date, if applicable, along with reason for discontinuation, if recorded.
- Dose of dapagliflozin.
- Concomitant therapy with metformin, sulfonylureas, pioglitazone, DPP-4 inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists or insulin.
- Initial estimated glomerular filtration rate (eGFR).
- Starting weight (data from up to 180 days prior to dapagliflozin initiation were accepted).
- Starting BMI.
- Weight at 6–18 months after starting dapagliflozin.
- Comments.
- HbA_{1c} readings for each participant.
- Blood pressure readings for each participant.

This study was designed as a clinical audit to improve patient care. Community Health Index (CHI) numbers, NHS Scotland's national patient identifier numbers, were generated and released from the general practice prescription database, following ethical approval from the Caldicott Guardians in both Trusts.

All measurements were taken at routine diabetes reviews. Where participants had been on treatment for less than 6 months of the study timeline, the most recent available measurements were used.

Data on HbA_{1c} and blood pressure were extracted from SCI-Diabetes. HbA_{1c} response by intention to treat was investigated up to 2 years post-initiation, with the response at 6 months compared with baseline analysed by subgroups defined by concomitant treatment, baseline BMI and baseline HbA_{1c} (by quartile). Weight and blood pressure at 12 months were compared with baseline.

Measurements were allocated to time bins to allow analysis over time. Time bins (relative to date of initiation of dapagliflozin) were as follows: –180 to –1 days (6-month run-in period); 0–89 days; 90–179 days; 180–364 days; and 365–730 days. To prevent undue influence of those individuals with multiple data points in their results, only a single value was taken for each time bin: the last (latest) result within that time window.

A *t*-test was applied to the log of HbA_{1c} values, comparing the values within the run-in period to those within the 90–179-day time bin (response at 6 months). This comparison was chosen because the 6-month time bin contained the most data points. Transforming HbA_{1c} values to a log scale is common practice and allows better detection of differences between groups whose within-group variances are very different. Overall HbA_{1c} response at 6 months was tested, along with HbA_{1c} response within a number of subgroups, including GLP-1 analogue users, insulin users and those with prespecified ranges of initial BMI and initial HbA_{1c}.

Weight change was investigated at 1 year, with a *t*-test performed on measured systolic and diastolic blood pressure during a 1-year run-in period and at 1 year post-initiation. Weight and blood pressure changes at 12 months were recorded and compared with baseline. Participants who had not completed a full 12 months' therapy were excluded.

Data were extracted from the two electronic systems detailed above. Primary care records were not available. Not all data points were available for every participant. Where no baseline measurement was available for weight or blood pressure, the most recent measurement within the preceding 3 months was used.

All collected data were sense-checked and apparently anomalous values were rechecked in the clinical records.

Results

A total of 597 people were identified as having been prescribed dapagliflozin between January 2013 and September 2014. Those with no follow-up data were excluded (n=76), leaving a total of 521 subjects for analysis. Overall, 54% were male,

Page points

1. In this clinical audit, the records of all people from two Trusts in Scotland who received dapagliflozin were evaluated to assess the agent's effectiveness in a real-world cohort.
2. HbA_{1c} at 6 months, 12 months and 2 years was compared with baseline, along with weight and blood pressure change at 12 months.
3. Participants were also analysed by subgroups including concurrent medication types and initial BMI and HbA_{1c} levels.
4. A total of 521 people were included in the final analysis.

Table 1. Median HbA_{1c}, blood pressure and weight values over time (*n*=521).

	Median value (interquartile range)			
	Baseline	**6 months**	**12 months**	**24 months**
HbA_{1c} (mmol/mol)	80 (67–94)	68 (57–77)	66 (56–78)	67 (57–76)
HbA_{1c} (%)	9.5 (8.3–10.8)	8.4 (7.4–9.2)	8.2 (7.3–9.3)	8.3 (7.4–9.1)
Systolic blood pressure (mmHg)	136 (124–146)		131 (120–142)	
Diastolic blood pressure (mmHg)	80 (72–84)		77 (70–82)	
Weight (kg; *n*=181)	100 (88–118)		97 (84–114)	

Page points

1. Dapagliflozin was used in combination with one or two other oral medications in the majority of cases.
2. After 12 months of treatment, median HbA_{1c} fell by 14 mmol/mol (1.3%). Higher HbA_{1c} at baseline was associated with greater reductions.
3. Median blood pressure also fell by 5/3 mmHg at 12 months, and median weight reduced by 3 kg, although the latter change was of borderline significance.

and the mean age was 57.5 years. In total, 36 participants (6.9%) discontinued treatment.

Data on median HbA_{1c} at baseline, 6 months, 12 months and 24 months, and on blood pressure and weight at baseline and 12 months, are shown in *Table 1*. Median HbA_{1c} fell significantly from 80 mmol/mol (9.5%) at baseline to 68 mmol/mol (8.4%) at 6 months ($P<0.001$). Median blood pressure fell significantly from 136/80 mmHg at baseline to 131/77 mmHg at 12 months ($P<0.001$).

Median weight fell from 100 kg at baseline to 97 kg at 12 months, although the difference failed to meet statistical significance ($P=0.07$).

Differences in HbA_{1c} over time for all participants

Median HbA_{1c} fell over time from the run-in period until 180–365 days post-dapagliflozin initiation. There was then a small rise in HbA_{1c} in the 365–730-day period. This difference may have been because of the smaller population of participants included within this group (*Figure 1*).

Compared with baseline, median HbA_{1c} was significantly reduced at 6 months (–12 mmol/mol), 12 months (–14 mmol/mol) and 24 months (–13.5 mmol/mol; $P=0.07$ for trend; *Figure 1*).

Dapagliflozin was used as monotherapy in one participant, as an add-on to one or two oral agents in 424 and as an add-on to insulin in 96. Notably, 59 participants received dapagliflozin in conjunction with a GLP-1 analogue, an unlicensed indication.

Changes in HbA_{1c} from baseline to 6 months according to initial HbA_{1c} and BMI are shown in *Table 2*. Higher HbA_{1c} at baseline was associated with the greatest reduction in HbA_{1c}.

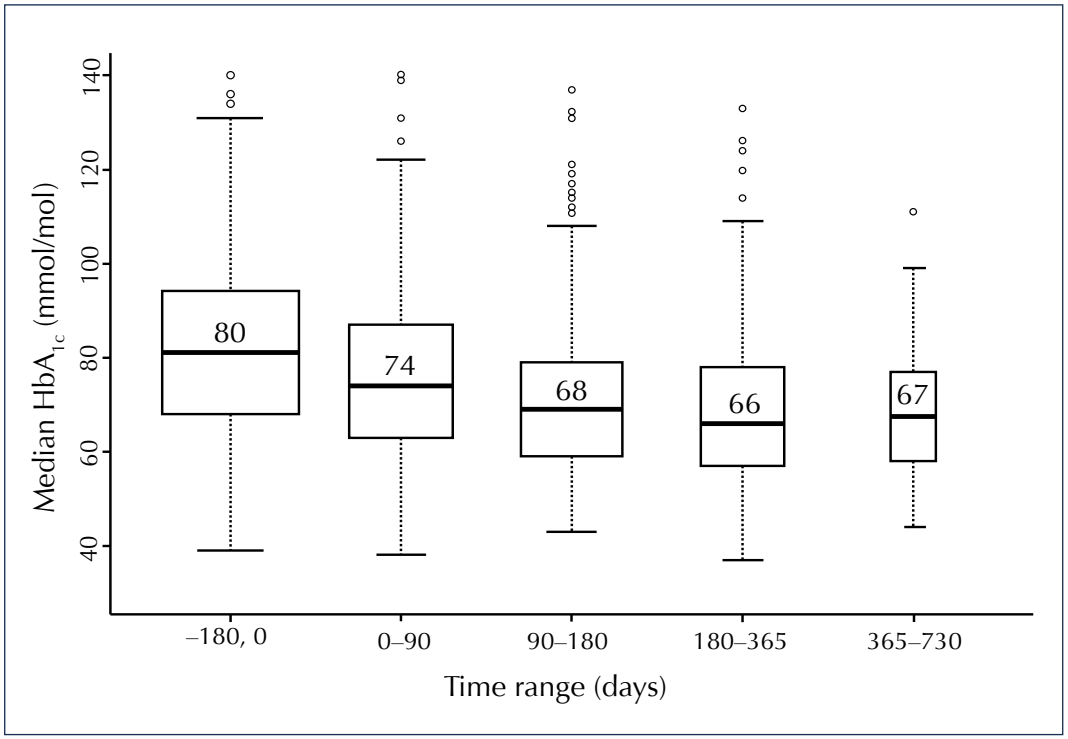

Figure 1. Trends in HbA_{1c} over the study period.

Table 2. Changes in HbA_{1c} between baseline and 6 months according to baseline HbA_{1c} and BMI.

	n	Change in HbA_{1c} (mmol/mol)	*P* value
All participants	521	–12.0	<0.001
HbA_{1c} range (mmol/mol):			
<69	121	–5.0	0.56
>69–81	136	–11.0	<0.001
>81–94	127	–17.0	<0.001
>94	137	–22.0	<0.001
BMI range (kg/m^2):			
<25	23	–6.5	0.011
25–<30	98	–14.5	<0.001
30–<35	159	–13.0	<0.001
35–<40	125	–13.5	<0.001
>40	116	–7.5	0.018

Table 3. Changes in HbA_{1c} from baseline to 6 months according to type of concurrent medication.

Medication	*n*	Change in HbA_{1c} (mmol/mol)	*P* value
One oral agent	200	–10.5	<0.001
Two oral agents	224	–14.0	<0.001
GLP-1	79	–8.0	0.01
Insulin	148	–10.5	0.001

Dapagliflozin was found to be effective in participants at any level of BMI.

Changes in HbA_{1c} according to the type of concomitant medication are shown in *Table 3*. Reductions in HbA_{1c} were significant in all concomitant medication subgroups.

In 181 participants with weight data available, the median weight loss at 12 months was 3.3 kg. *Figure 2* shows the difference between baseline HbA_{1c} and those with a follow-up measurement between 6 and 12 months after initiation of therapy.

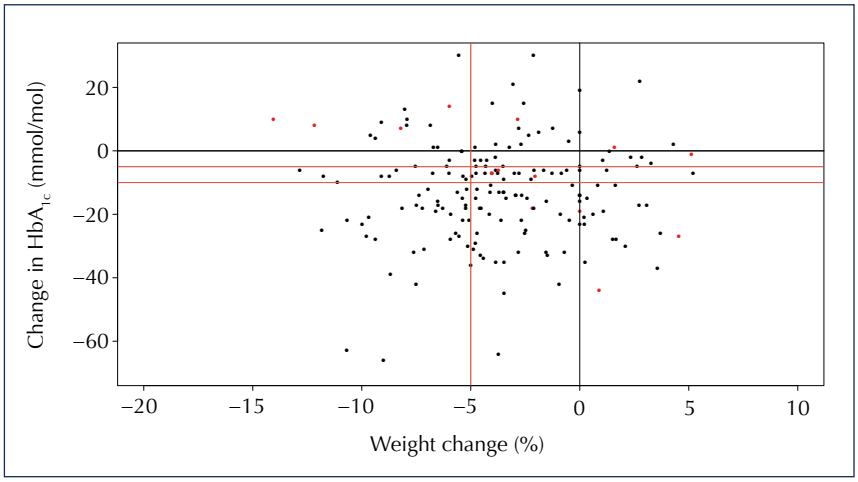

Figure 2. Percentage changes in weight and HbA_{1c} from baseline at 6 and 12 months. The plots in red represent those in whom treatment was discontinued during the period of follow up.

Ten participants were initiated on dapagliflozin with an eGFR of <60 mL/min/1.73 m^2, which is contrary to the licence at this time.

Adverse outcomes and discontinuation

A total of 36 participants discontinued dapagliflozin in the study period. Of these, 13 had recorded adverse outcomes in either their diabetes specialist documentation or GP letters, leading to discontinuation. Weight loss and light-headedness were the most common adverse effects (occurring in two people), followed by poor response, muscle aches, worsening renal function, osmotic symptoms, poor appetite, a urinary tract infection, thrush, genital infection and breathlessness, all of which were single events. Two participants switched to canagliflozin, one because of worsening renal function.

Discussion

This study demonstrates that dapagliflozin is effective at reducing HbA_{1c} at up to 2 years in the real-life setting. Both systolic and diastolic blood pressure were significantly reduced at 12 months. Weight was less commonly measured but a trend towards a reduction was seen at 12 months. As would be expected from its mode of action and

Page points

1. Dapagliflozin was found to be effective in participants at all levels of BMI and irrespective of the type of concomitant medication.
2. Overall, 36 participants (7%) discontinued dapagliflozin. The 13 documented adverse events were generally in line with adverse events reported in clinical trials.

Page points

1. This study confirms that dapagliflozin should be used cautiously in people at risk of volume depletion as it has a known diuretic effect, and users should take steps to mitigate the increased risk of genitourinary infection.
2. In this real-world cohort, dapagliflozin was initiated with number of people with a BMI <30 kg/m^2. This is not recommended as it may increase the risk of diabetic ketoacidosis in such people; however, no case of DKA occurred during the study period.
3. The study is limited by its retrospective nature and incomplete recording of data; however, the results confirm the findings of clinical trials of dapagliflozin.

randomised trials of its use, dapagliflozin showed efficacy independent of BMI and the type and number of medications used at initiation. The effect of therapy was greatest in participants with the highest starting HbA_{1c}.

The discontinuation rate was low (6.9%), with the most common reported adverse effects being osmotic symptoms and genital infections. Dapagliflozin has a known diuretic effect and it should be used with caution in those at risk of volume depletion. The glycosuric mode of action of dapagliflozin is known to increase the risk of candidal genital infection. Patients should be warned of adverse side effects and the importance of personal hygiene prior to initiation of therapy. Should infections arise, they should be treated in the conventional manner.

NICE (2013) guidelines recommend dapagliflozin as an add-on to metformin, sulfonylureas, DPP-4 inhibitors or insulin. However, the agent is not recommended for use in people with moderate to severe renal impairment. Ten participants were also initiated on dapagliflozin despite having an eGFR of <60 mL/min/1.73 m^2. This is not recommended.

It is interesting to note that 98 people had dapagliflozin initiated with a BMI <30 kg/m^2. SGLT2 inhibitor therapy is not usually recommended in such people as, at lower levels of BMI, there is potential for pancreatic insulin reserves to be low, which may predispose them to the reported side effect of euglycaemic diabetic ketoacidosis (DKA).

DKA has been reported as a rare complication (0.01% of users) of SGLT2 inhibitor use. This has mainly occurred in people with type 1 diabetes who received the drugs class off-licence or those with type 2 diabetes treated with insulin (Rosenstock and Ferrannini, 2015). We found no recorded evidence of DKA in our study.

A meta-analysis of 10 randomised controlled trials showed that the mean reduction in HbA_{1c} achieved with dapagliflozin ranged from 4.3 mmol/mol (0.39%) to 22.4 mmol/mol (2.05%), which was superior to placebo (Zhang et al, 2014). All trials demonstrated reductions in body weight, ranging from 0.69 kg to 8.54 kg. Seated systolic and diastolic blood pressure decreased by 3.57 mmHg (95% confidence interval, 2.77–5.38; P<0.001) in the dapagliflozin group compared with placebo. Our data demonstrated an improvement in HbA_{1c} of 13 mmol/mol (1.2%) at 24 months. Mean weight loss was 3.3 kg on average, and reductions in blood pressure of 3–5 mmHg were observed. It is reassuring that in real-life clinical use, people had a similar clinical response to dapagliflozin as in randomised controlled trials.

In clinical trials, common side effects included genital infections (9.7% of participants), urinary tract infections (8.1%) and hypotension (1.1%; Zhang et al, 2014). Dapagliflozin monotherapy did not lead to hypoglycaemic episodes; however, when it was combined with other hypoglycaemic drugs, the risk was higher (risk ratio, 1.16; Aylsworth et al, 2014; Zhang et al, 2014). In people taking concurrent insulin and dapagliflozin, polyuria was reported in 8.3%. In our study, the discontinuation rate was low and the adverse effects were similar to those observed in randomised controlled trials.

Our study has some limitations. Retrospective electronic data collection has its weaknesses, including incomplete documentation of side effects, their frequency and the reasons for discontinuation. Measurements such as weight, blood pressure and HbA_{1c} were subject to personal error and missing values. However, efforts were made to ensure that the latest/most appropriate results were recorded during data collection.

As this was a retrospective cohort study, glycaemic control and weight change may have been partly due to lifestyle and other medication alterations. These confounders cannot be minimised due to the lack of a control group.

Finally, data on insulin doses were not available. Many areas have difficulty prescribing newer agents because of costs. It would have been helpful to know whether using dapagliflozin had any effect on the dose requirements of insulin or other agents, data which could be used to determine the cost-effectiveness of this newer drug.

Conclusions

These findings confirm the efficacy of dapagliflozin in the real-life setting. The results

of the EMPA-REG OUTCOME study, the first cardiovascular safety trial of an SGLT2 inhibitor, demonstrated a reduction in cardiovascular events, heart failure and all-cause mortality among individuals at high risk of cardiovascular events treated with empagliflozin compared with placebo (Zinman et al, 2015). While further study is needed to determine whether these findings can be replicated in people with lower cardiovascular risk and with other drugs in the class, it is likely that this important study will increase the use SGLT2 inhibitors in people with type 2 diabetes.

Our data describe people with a long duration of treatment and probably with a higher rate of comorbidities and baseline HbA_{1c} levels than those who were recruited in the published clinical trials. The results presented here are reassuring as they show that the effects of dapagliflozin observed in randomised controlled trials translate to clinical practice. ■

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Authors

Feicong Huang is Core Medical Trainee at Gartnavel General Hospital, Glasgow; Jennifer Hayden is Medical Student at Gartnavel General Hospital; Lyndsey McConnell is GP at Kinlochleven Medical Practice, Kinlochleven; Christopher Sainsbury is Consultant Physician at Gartnavel General Hospital; Gregory Jones is Consultant Physician at Gartnavel General Hospital.