Dapagliflozin: Clinical practice compared with pre-registration trial data

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Abstract

Background: **Dapagliflozin is the first sodium-glucose co-transporter 2 (SGLT2) inhibitor to be approved in Europe and represents a new class of agents developed as oral diabetes medications. Improved glycaemic control and weight loss have been demonstrated in clinical trials but effectiveness outside of the trial environment has not yet been reported.**

Method: **A systematic clinical case note audit of type 2 diabetes patients initiated on dapagliflozin in a diabetes specialist outpatient centre of a London teaching hospital.**

Results: **Of the 96 people included, 42% had a reduction in glycated haemoglobin (HbA_{1c}) of ≥1%, 29% had no reduction; 15% had weight loss ≥5kg, 3% had weight loss ≥10kg and 24% had no weight reduction. Improvements in HbA_{1c}, weight, and blood pressure were consistent with those reported in clinical trials. The rate of discontinuation of dapagliflozin due to side effects (22%) was higher than reported in trials (3-4%), but 52% of people tolerating dapagliflozin were able to stop or reduce one or more other diabetes medications.**

Conclusions: **Dapagliflozin is effective at improving glycaemic control. It also reduces blood pressure, results in weight loss, and reduces the need for concomitant diabetes medications. However, it is not as well tolerated in real-world patients as in participants of clinical trials.**

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Key words: dapagliflozin, real-world, SGLT2, type 2 diabetes

Introduction

Dapagliflozin is the first SGLT2 inhibitor drug to gain approval in Europe for the management of type 2 diabetes and was introduced into UK clinical practice in December 2012.

The pre-registration clinical trials of dapagliflozin have demonstrated improvements in glycaemic control when used as monotherapy[1] and with metformin,[2-4] sulfonylureas,[5,6] or insulin.[7,8] There have also been clinically meaningful reductions in weight and blood pressure. However, these clinical trials were performed on selected patient groups and therefore the trial results may not be matched in "real-world" clinical practice. The Association of British Clinical Diabetologists nationwide exenatide audit demonstrated a differing real-world efficacy profile from that reported in registration clinical trials.[9]

We hypothesised that routine use of dapagliflozin in clinical practice may vary in efficacy and side effect rates from those reported in clinical trials. We present the results of a phase 4 clinical study in the form of treatment observation of type 2 diabetes patients treated with dapagliflozin.

Abbreviations and acronyms

BMI	body mass index
GLP-1ra	glucagon-like peptide-1 receptor agonist
GP	general practitioner
HbA_{1c}	glycated haemoglobin
OAD	oral antidiabetic drug
SEM	standard error of the mean
SGLT2	sodium glucose co-transporter 2
UTI	urinary tract infection

Methods

The design was a real-world, observational, non-randomised single centre study. The study comprised of a systematic clinical audit of notes and electronic records from people with type 2 diabetes with dapagliflozin initiated in the diabetes specialist outpatient centre of a London teaching hospital.

The records of all people prescribed dapagliflozin before 14th May 2014 were analysed (n=122). People with no follow-up data were excluded (n=26).

Anonymised data were collected on patient demographics, disease profile, concurrent medications, and outcomes. The demographic and disease information collected comprised patient age, gender, diabetes type and duration, renal function, and baseline measurement of HbA_{1c}, weight, BMI, and blood pressure. All recorded clinical measurements were taken from routine data. Where no baseline measurement was available for HbA_{1c}, weight, or blood pressure, the most recent available measurement within the preceding three months was used.

A small number of people had dapagliflozin stopped by their

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Table 1 Changes in outcome measures at final follow-up visit in patients with type 2 diabetes treated with dapagliflozin

Outcome measure (units)	n (%)	Mean baseline value (SEM)	Mean change from baseline (SEM)	95% confidence interval
HbA_{1c} (%)	79 (82)	9.51 (0.19)	**-0.84 (0.23)**	-1.30 to -0.38
HbA_{1c} (mmol/mol)	79 (82)	80.4 (2.1)	**-9.2 (2.5)**	-14.2 to -4.2
Weight (kg)	88 (92)	94.3 (2.6)	**-2.2 (0.5)**	-3.2 to -1.2
Systolic BP (mmHg)	68 (71)	135 (2)	**-3.9 (2.3)**	-8.5 to 0.8
Diastolic BP (mmHg)	68 (71)	78 (1)	**-3.9 (1.3)**	-6.5 to -1.2

GP and there was no documented reason for this discontinuation in the secondary care notes. In these cases the GP was contacted for additional information and asked about any drug related adverse effects. Where people stopped taking dapagliflozin, data from subsequent visits were excluded from the analysis here.

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

Statistical analyses

To evaluate change in the outcome parameters of HbA_{1c}, weight, and blood pressure over time, patient follow-up data were grouped by three month periods; 0-3, 4-6, 7-9, and 10-12 months. The median change in each outcome parameter was calculated for each three month group. Where people attended more than one follow-up appointment in a single three month period, the last appointment data was used.

We performed a linear regression analysis to identify predictors of reduction in HbA_{1c}, weight, and blood pressure in people taking dapagliflozin. People who failed to start dapagliflozin or who stopped taking it during the follow-up period were excluded. Change from baseline for the outcome measures of HbA_{1c}, weight, and blood pressure were calculated. We assume a significance level of $p < 0.05$ and report model performance using R-square and adjusted R-square values. The analysis was undertaken using SPSS version 20.0.

Ethical considerations

This study was designed as a clinical audit of routine practice for the purpose of improving patient management and as such did not require ethics committee review.[10]

Results

All people (n=122) who had been prescribed dapagliflozin were initially included for analysis. Three people were excluded as their notes were unavailable. Four people were excluded as they failed to attend any follow-up appointments. One person was excluded as they had type 1 diabetes initially misdiagnosed as type 2, and dapagliflozin was then stopped. Fourteen people were excluded because they were not yet due to attend follow-up and four were excluded because they chose not to start taking dapagliflozin. The majority of participants had complete data (an initial value and follow-up measurements) on HbA_{1c} (n=79; 82%), weight (n=88; 92%), and blood pressure (n=68; 71%). Those with incomplete data for an outcome measure were excluded from the analysis of that outcome measure.

The included cohort (n=96) attended one or more follow-up appointments and comprised 43% women, mean age 58.9 (range 31-85) years, with a mean duration of type 2 diabetes of 15.1 (range 1-37) years. The mean weight of the cohort was 94.7 (range 49-154) kg and BMI 33.7 (range 22-52) kg/m^2.

The mean duration of follow-up was 152 (range 7-431; standard deviation 115) days. The shortest duration of follow-up was an urgent appointment requested because the patient had developed a widespread rash. Dapagliflozin was stopped at this visit. The mean number of follow-up appointments included was 1.57 (range 1-4).

Efficacy

Of the included people, 72 (75%) had follow-up within the first three months of starting dapagliflozin, 50 (52%) at 4-6 months, 22 (23%) at 7-9 months, and 12 (13%) at 10-12 months. Average changes at the follow-up visit are shown in Table 1. Seven people had no response to dapagliflozin with no improvement in HbA_{1c} and no weight reduction (Table 2). The HbA_{1c} response was sustained (Figure 1). Weight and blood pressure continued to improve during the year of follow-up (Figure 2).

Of those people who tolerated dapagliflozin through the follow-up period, 36 (52%) were able to stop or reduce one or more other diabetes medications, whereas 18 (26%) patients had medication

Table 2 Response to dapagliflozin treatment in patients with type 2 diabetes ('real-world data')

Outcome measures	n (%)	Response	%
HbA_{1c} reduction	79 (82)	No response	29
		Reduction < 1%	29
		Reduction ≥ 1%	42
Weight loss	88 (92)	No response	24
		Weight loss < 5kg	58
		Weight loss ≥ 5kg and <10kg	15
		Weight loss ≥ 10kg	3
Systolic BP (mmHg) reduction	68 (71)	No response	43
		Reduction < 5mmHg	16
		Reduction ≥ 5mmHg	41
Diastolic BP (mmHg) reduction	68 (71)	No response	40
		Reduction < 5mmHg	12
		Reduction ≥ 5mmHg	48

Figure 1. Changes over time in HbA_{1c} in patients with type 2 diabetes following initiation of dapagliflozin

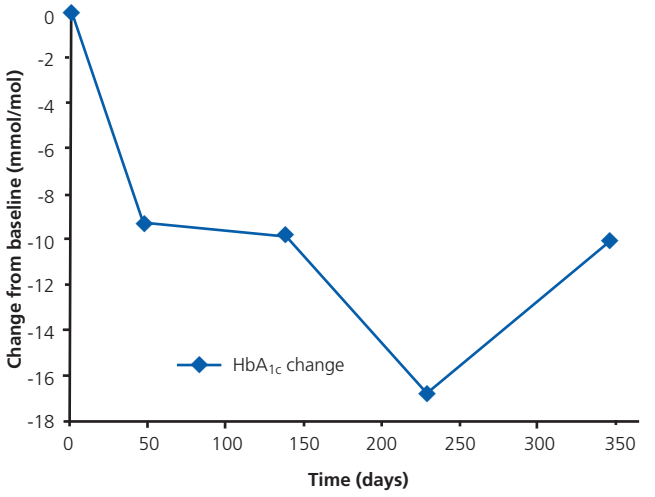

Figure 2. Changes over time in weight and blood pressure in patients with type 2 diabetes following initiation of dapagliflozin

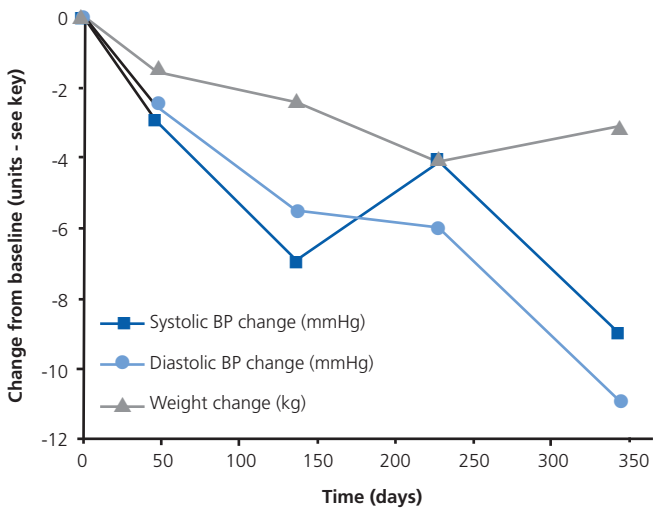

Table 3 Changes in concurrent diabetes medications during the follow-up period in patients who tolerated dapagliflozin

Concurrent medication type	n (%)	Dose decreased	Medication stopped	Dose increased	Medication started
Total	*69 (100)*	*17**	*21**	*10**	*3*
OADs	69 (100)	7*	9*	2*	1
GLP-1ra	33 (48)	1	6	2	1
Insulin	36 (52)	9*	6	6	1

*Includes patients with changes to >1 medication.

Table 4 Clinical predictors of change in HbA_{1c} in patients taking dapagliflozin (n=79)

Clinical characteristic	Coefficient (95% confidence limits)	p value
Age (years)	-0.007 (-0.023 to 0.009)	0.668
Female	-0.437 (-0.747 to -0.126)	0.164
Diabetes duration (years)	0.010 (-0.015 to 0.034)	0.693
BMI (kg/m²)	0.014 (-0.010 to 0.037)	0.561
Baseline HbA_{1c} (%)	-0.598 (-0.686 to -0.511)	<0.001
Model R-square 0.459, adjusted R-square 0.419		

Table 5 Clinical predictors of weight change in patients taking dapagliflozin (n=88) (kg)

Clinical characteristic	Coefficient (95% confidence limits)	p value
Age (years)	0.011 (-0.031 to 0.052)	0.795
Female	-0.480 (-1.288 to 0.328)	0.554
Diabetes duration (years)	0.002 (-0.061 to 0.065)	0.976
BMI (kg/m²)	-0.144 (-0.208 to -0.081)	0.026
Baseline HbA_{1c} (%)	-0.165 (-0.409 to 0.079)	0.502
Model R-square 0.072, adjusted R-square 0.006		

doses increased or an additional medication added (Table 3).

Higher HbA_{1c} at baseline was associated with a greater reduction in HbA_{1c} whilst taking dapagliflozin (Table 4). Reduction in HbA_{1c} was independent of age, gender, duration of diabetes. Higher BMI at baseline was associated with greater weight loss (Table 5). Baseline weight was not associated with the degree of weight loss (results not shown). Weight loss was independent of age, gender, duration of disease, and baseline HbA_{1c}. Higher baseline blood pressure was associated with a greater reduction in both systolic and diastolic blood pressure (Tables 6 and 7). Older age was weakly associated with a greater reduction in diastolic blood pressure.

Adverse effects

Adverse effects were recorded for 36 (38%) people. Increased urine flow (nocturia and polyuria) was the most common adverse

Table 6 Clinical predictors of reduction in systolic blood pressure (mmHg) in patients taking dapagliflozin (n=68)

Clinical characteristic	Coefficient (95% confidence limits)	p value
Age (years)	-0.169 (-0.404 to 0.066)	0.475
Female	2.186 (-2.029 to 6.401)	0.606
Diabetes duration (years)	-0.065 (-0.378 to 0.248)	0.837
BMI (kg/m^2)	-0.241 (-0.572 to 0.090)	0.470
Baseline HbA_{1c} (%)	-0.826 (-2.009 to 0.358)	0.489
Baseline systolic BP (mmHg)	-0.528 (-0.664 to -0.392)	<0.001
Model R-square 0.261, adjusted R-square 0.175		

Table 7 Clinical predictors of reduction in diastolic blood pressure (mmHg) in patients taking dapagliflozin (n=68)

Clinical characteristic	Coefficient (95% confidence limits)	p value
Age (years)	-0.312 (-0.462 to -0.161)	0.043
Female	-0.885 (-3.435 to 1.665)	0.730
Diabetes duration (years)	0.175 (-0.018 to 0.368)	0.368
BMI (kg/m^2)	-0.209 (-0.410 to -0.008)	0.304
Baseline HbA_{1c} (%)	-0.445 (-1.169 to 0.279)	0.541
Baseline diastolic BP (mmHg)	-0.274 (-0.406 to -0.143)	0.042
Model R-square 0.146, adjusted R-square 0.048		

effect (occurring in 17 people) followed by genital candidiasis (10), postural hypotension (3), UTI (3), dyspepsia (2), thirst (2), dry mouth (2), rash (2), erectile dysfunction (1), fatigue (1), back pain (1), palpitations (1), and urinary incontinence (1). The person reporting urinary incontinence had a previous history of incontinence which returned whilst taking dapagliflozin. The two people reporting rash had developed a widespread erythematous rash with associated pruritus within the first three days of taking dapagliflozin necessitating discontinuation. One person was admitted to hospital with a confirmed *E. coli* UTI and bacteraemia whilst taking dapagliflozin. This person had a history of multiple UTIs although none had previously required hospital admission. This suggests a history of recurrent UTIs may limit the use of this drug.

Tolerability

A total of 27 (28%) people stopped taking dapagliflozin during the follow-up period. Four people were advised to stop because of deterioration in their renal function (three of these had an improvement in glucose control prior to stopping), two because they felt it added to an already large pill burden (which may be improved in future by fixed dose combinations) and 21 because of adverse effects. The most common adverse effect leading to discontinuation of dapagliflozin was genital candidiasis (4 of 10 people affected). Most people with reported polyuria (6 of 8) elected to continue taking dapagliflozin. Similarly, most people with nocturia (8 of 9) elected to continue.

Discussion

This study of real-world data demonstrates that dapagliflozin is effective at reducing HbA_{1c} with 42% of the people who tolerated dapagliflozin achieving a reduction in HbA_{1c} >1%. Significant reductions in weight and blood pressure were also confirmed in our study. The clinical response to dapagliflozin was independent of age and duration of diabetes and the greatest improvement in HbA_{1c} was seen in those with the poorest control at baseline. Similarly the greatest reduction in weight and blood pressure was seen in those with the highest BMI and blood pressure at baseline. BMI and not baseline weight was associated with weight loss, which suggests that the degree of obesity is the predictor of weight loss. As considerable numbers could either reduce or stop other oral therapies or insulin, there may be additional cost benefits from a pharmaco-economic perspective.

Dapagliflozin improves glycaemic control by preventing glucose reuptake by SGLT2 in the proximal tubule of the kidney.[11,12] Inhibition of SGLT2 prevents renal reabsorption of

Table 8 Outcomes in clinical trials compared with real-world data in patients with type 2 diabetes treated with dapagliflozin

	Real-word data (Current study)	Ferrannini *et al.*[1]	Bailey *et al.*[2]	Strojek *et al.*[6]	Wilding *et al.*[7]
Duration of follow-up (weeks)	22 (mean)	24	24	24	12
Concomitant therapy	Various	None	Metformin	Glimepiride	Insulin
Participant demographics					
Total participants (n)	96	558	546	592	71
Mean age (years)	58.9	52.0	53.9	59.8	56.7
Mean duration of diabetes (years)	15.1	0.5	6.1	7.4	12.3
Mean BMI (kg/m^2)	33.7	32.6	31.5	-	35.5
Outcomes (means)					
HbA_{1c} change (%)	-0.84	-0.89	-0.84	-0.82	-0.70
Weight change (kg)	-2.2	-3.1	-2.9	-2.3	-4.5
Systolic BP change (mmHg)	-3.9	-2.3	-5.1	-5.0	-5.5
Diastolic BP change (mmHg)	-3.9	-1.0	-1.8	-2.8	-5.8

glucose. The resulting glucosuria also promotes weight loss.[4] The action is independent of insulin secretion and insulin action and does not predispose to hypoglycaemia.[3] Inhibition of SGLT2 can promote urinary sodium loss[13,14] which, along with weight reduction and an osmotic diuresis, may be responsible in part for the blood pressure lowering effects observed.[15]

People who experienced polyuria or nocturia were likely to continue to take the agent, although several adverse effects were observed leading to 22% of the cohort discontinuing dapagliflozin therapy. The glycosuria induced by dapagliflozin can potentially lead to UTIs and genital infections, predominantly candidiasis[12,16] - the adverse effect most likely to lead to discontinuation.

Comparison with pre-registration trial results

Our patient cohort was a similar in age to people included in clinical trials, although the mean duration of diabetes was longer than that of trial participants (Table 8). The effectiveness of dapagliflozin, despite the longer duration of diabetes, in our study was similar to that reported in clinical trials of similar duration (Table 8).

In pre-registration trial patients taking dapagliflozin 10mg single agent therapy, genital infections were reported in 9.7%, UTIs in 8.1%, nocturia in 1.6%, hypotension in 1.1%, and any adverse event leading to discontinuation in 4.3%.[1] In patients taking concurrent metformin and dapagliflozin (10mg), genital infections were reported in 8.8%, UTIs in 8.1%, and any adverse event leading to discontinuation in 3.0%.[2] In patients taking concurrent insulin and dapagliflozin (10mg), polyuria was reported in 8.3%, and any adverse effect leading to discontinuation in 4.2%.

By contrast, the current study had slightly higher rates of genital infections (10.4%) and postural hypotension (3.1%), and higher rates of increased urine flow (polyuria/nocturia) (17.7%) than reported in these trials. The most substantial discrepancy was the rate of discontinuation due to side effects which we found to be 22%.

Limitations of this real-world study

Using routinely collected data to assess the prevalence of side-effects is likely to lead to some underestimation of their frequency, as minor side effects may not be reported in clinics. However major adverse events or effects that lead to patients wanting to discontinue dapagliflozin are almost certainly documented. The routinely collected data also had some missing values for the outcome measures of HbA_{1c}, weight, and blood pressure. We cannot determine retrospectively if there was a bias towards missing data in a particular subpopulation although we suspect that missing data are mostly random.

Our real-world data are confounded by changes to other medications and there is no control group for comparison. However the general trend observed during the follow-up period was towards less concomitant medication, suggesting that the beneficial effects seen in this group of patients are mostly attributable to dapagliflozin.

The linear regression analysis of factors associated with HbA_{1c}, weight, and blood pressure changes is limited by small sample size and heteroskedacity in both outcome measures. The higher variability in HbA_{1c}, weight, and blood pressure change with higher initial values is likely to be an intrinsic property of the data.

Key messages

In a 'real world' setting:

- Dapagliflozin responders had a marked reduction in glucose, weight and BP
- The greatest benefit occurred in those with the poorest glucose control, highest BMI and BP
- Increased urine flow (polyuria and nocturia) was the most common side effect although genital candidiasis was most likely to lead to discontinuation

Conclusions

The real-world data presented here may have greater generalisability to clinical practice, than data from clinical trials as patients with multiple co-morbidities or on multiple oral antidiabetic agents were included in the population analysed and are usually excluded from clinical trials. This study looked at a population of patients with diabetes referred for specialist management in secondary care and therefore may not be applicable to all patients in the primary care setting.

These data confirm that dapagliflozin is effective for use in clinical practice but clinicians should account for a higher level of intolerance to the side effects of dapagliflozin in clinical practice than that which is reported in clinical trials. In those who tolerated dapagliflozin, the commonly clustered metabolic risk factors of poor glycaemic control, obesity, and hypertension were all significantly improved. There was also a reduction in the use of other oral antidiabetic agents and insulin in this population.

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