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Research Article

Dapagliflozin Therapy in Adult Patients with Type 2 Diabetes: Hong Kong Data from the Association of British Clinical Diabetologists (ABCD) Nationwide Dapagliflozin Audit

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Abstract

Introduction: In this ABCD dapagliflozin audit subset, data of adult patients with type 2 diabetes from four Hong Kong local clinics initiating dapagliflozin treatment from February 2015 to January 2017 were routinely collected. Descriptive analysis was performed and expressed as frequency (%) and mean ± SD. Changes in HbA1c, body weight and other cardiometabolic parameters at Week 24 and 52 were calculated. Information on concurrent medications and adverse events was also documented.

Summary of the Results: Of all 167 patients, mean change of HbA1c from baseline (8.0 ± 1.3%) was the same at Week 24 (n = 105) and Week 52 (n = 53) at -0.8% (95% CI -1.1, -0.5). Mean change of body weight from baseline (80.9 ± 17.4 kg) was -4.0 kg (95% CI -8.3, 0.3) and -5.2 kg (95% CI -10.8, 0.4) at Week 24 and Week 52 respectively. Patients with higher baseline HbA1c (≥ 8.5%) and younger patients (< 60 years old) showed greater reduction in HbA1c compared with those with lower baseline HbA1c (< 8.5%) and older patients (≥ 60 years old) respectively at Week 52. Patients with baseline triple (or more) therapy showed a clinically meaningful reduction in HbA1c from baseline: -1.0% (95% CI -1.3, -0.7) at Week 52 (n = 42). Dapagliflozin treatment related adverse events were considered as uncommon, with genital infection being the most frequent treatment-emergent event (8%).

Conclusion: Dapagliflozin as an add-on therapy reduced HbA1c and body weight by clinically significant amounts in real-world patients with type 2 diabetes. It is effective in both young patients and those with advanced stage diabetes due to the insulin independent effect, and may allow the delay in insulin usage.

Keywords: *Sodium-Glucose Co-Transporter-2 (SGLT2); Type 2 Diabetes; Association of British Clinical Diabetologists (ABCD); Dapagliflozin*

Introduction

In recent years, several new drugs have been approved to provide additional options for the management of type 2 diabetes. In particular, dapagliflozin belongs to a new class of antidiabetic medications known as sodium-glucose co-transporter-2 (SGLT2) inhibitors. This class of drugs acts by blocking glucose reabsorption at the proximal convoluted tubule of the nephron, improving glycaemic control through decrease in renal threshold and increase in renal glucose excretion, a mechanism independent of insulin secretion and insulin action [1]. This unique mechanism of action allows dapagliflozin to be used in combination with any other existing antidiabetic drug classes, by providing synergistic effects of further reducing blood glucose level with an overall effect size of -0.52% [2,3]. Indeed, phase 3 double-blind, placebo-controlled trials have demonstrated that dapagliflozin, when used alone or with another antidiabetic agent, significantly and dose dependently reduced glycated haemoglobin (HbA1c) in treatment-naïve patients with type 2 diabetes [4], as well as treatment-experienced patients whose glycaemic control was not adequately controlled with metformin [5-8], insulin [9], pioglitazone [10], and dipeptidyl peptidase-4 inhibitors (DPP4i) [11]. The trials also consistently showed extra benefits of dapagliflozin in terms of reduction in body weight and blood pressure [3,12]. Dapagliflozin is generally considered as well tolerated, demonstrating a similar frequency of most adverse events seen in patients receiving placebo [12]. It was also proved to be safe in subgroup patients with type 2 diabetes such

as the elderly and those with coexistent liver disease and cardiovascular disease [12,13], although an increase in mild genital infections and urinary tract infections has been reported in patients probably due to glucosuria [14].

In 2012, dapagliflozin became the first approved SGLT2 inhibitor in Europe for the management of type 2 diabetes based on the positive clinical trial data [15]. It can be recommended as monotherapy, or second/third line agent in combination with any other antidiabetic agent in adult patients [1]. Although randomised placebo-controlled clinical trials are considered as the gold standard of assessing drug efficacy and safety, they mainly involve selected patient groups with strict inclusion and exclusion criteria, and therefore the trial results may not reflect those obtained in routine primary care. With an aim to assess its use in real world clinical setting, the Association of British Clinical Diabetologists (ABCD) initiated a nationwide audit on dapagliflozin starting in September 2014.

There are several major objectives of this observational study, including summarising the characteristics of patients with type 2 diabetes receiving dapagliflozin in primary care, assessing its effectiveness on glycaemic control, and evaluating its cardiometabolic effects and safety.

Methods

This was a retrospective observational study of treatment-experienced patients with T2D aged >18 years receiving dapagliflozin therapy from four Hong Kong local clinics.

T2DM on drug with regular follow-up in specialist out-patient clinic in a pubic hospital and 3 private specialist clinics were recruited. The only exclusion criteria was drug treatment less than one year. From February 2015 to January, adult treatment-experienced patients (> 18 years old) with type 2 diabetes who initiated add-on dapagliflozin treatment were included in this retrospective observational study. Data of eligible patients were entered in a set of questionnaires designed by ABCD [16]. The original design of the audit form was meant to be simple and using modern technologies on the NHS N3 computer network to facilitate easy gathering of anonymised data. ABCD is setting up a nationwide audit of dapagliflozin (Forxiga) in real clinical use.

The on-line audit tool is so easy to use that live data entry in clinic is a real option to be considered. However, to facilitate data collection in our aduit, we used two paper forms which exactly match the data that can be entered into the audit tool. The questionnaires were then collected from the clinics at a regular interval for data entry via on line system of the ABCD webpage. Upon completion of the study these data were downloaded for analysis.

At baseline, demographic data, body mass index (BMI), and cardiometabolic parameters: HbA1c, systolic and diastolic blood pressure, lipids, alanine aminotransferase (ALT), and serum creatinine were recorded, and subsequent values at two different time points since dapagliflozin initiation were then measured: week 18 up to week 30 (grouped and denoted as Week 24) and week 44 up to week 60 (grouped and denoted as Week 52). Descriptive analysis on baseline characteristics and follow-up parameters for those who attended follow-up appointments at least up to Week 24 was performed and expressed as frequency (%) and mean ± standard deviation (SD). Other information including diabetes medications prescribed over time and dosage changes (if any) for each patient, adverse events such as urinary tract infection and genital infection, and treatment discontinuation was also documented.

After collecting all the data, mean changes in each parameter with 95% confidence interval (CI) for the difference were calculated. Subgroup analysis stratified by patients' baseline HbA1c values, baseline BMI values, age, type 2 diabetes duration, and number of therapies received was performed to further assess the effect of dapagliflozin in different patient subgroups. All analyses were performed using SPSS Statistics Version 20.0 (IBM Corp., Armonk, NY, USA).

Results

During the study period, 4 centres submitted data on a total of 167 patients. Of this intent-to-treat population, 65% were males and 97% were Han Chinese, with a mean age of 56.1 ± 9.2 years and mean diabetes duration of 12.0 ± 6.9 years. Before initiating dapagliflozin, triple therapy with metformin + pioglitazone + DPP4i (n = 22) was the most common regimen prescribed for the patients, followed by dual therapy with metformin + DPP4i (n = 18). Prior therapies adopted by the patients are described in figure 1. After dapagliflozin initiation, 158 patients had follow-up clinic visits up to Week 24, and 44 patients were able to stop or decrease the dose of at least one concurrent diabetes medication at the end of the follow-up period.

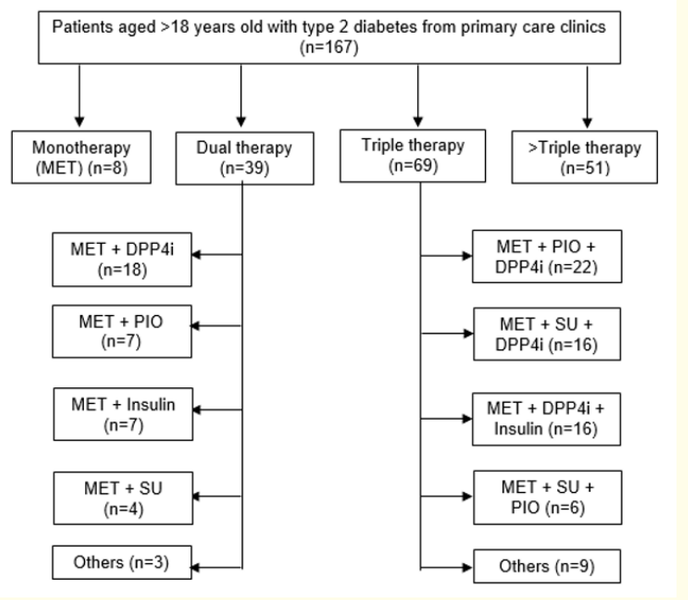

Figure 1: *Baseline antidiabetic medication prescription breakdown. MET: Metformin; DPP4i: Dipeptidyl Peptidase-4 Inhibitor; PIO: Pioglitazone; SU: Sulphonylurea.*

At Week 24 and Week 52, mean change of body weight from baseline (80.9 ± 17.4 kg) was -4.0 kg (95% CI -8.3, 0.3; n = 105) and -5.2 kg (95% CI -10.8, 0.4; n = 53) respectively, and mean change of HbA1c from baseline (8.0 ± 1.3%) was identical at both time points at -0.8% (95% CI -1.1, -0.5). Values and changes of other parameters at both time points were listed in table 1 and 2.

Baseline characteristics	**N=167**		
Male, n (%)	108 (64.7%)		
Mean age (years)	56.1 ± 9.2		
Mean duration of type 2 diabetes (years)	12.0 ± 6.9		
Mean dapagliflozin treatment duration (weeks)	35.0 ± 22.1		
Parameter	**Baseline (N = 167)**	**Week 24 (n = 105)**	**Week 52 (n = 53)**
Mean body weight (kg)	80.9 ± 17.4	76.9 ± 17.0	75.7 ± 18.1
Mean BMI (kg/m^2)	29.6 ± 5.2	28.2 ± 5.1	27.8 ± 5.4
Mean HbA_{1c} (%)	8.0 ± 1.3	7.2 ± 0.9	7.2 ± 0.8
Mean SBP (mmHg)	135.8 ± 14.1	129.4 ± 13.1	130.2 ± 12.4
Mean DBP (mmHg)	83.5 ± 10.2	79.4 ± 9.7	80.2 ± 9.1
Mean TG (mmol/L)	1.73 ± 2.39	1.50 ± 0.87	1.38 ± 0.77
Mean HDL (mmol/L)	1.28 ± 0.34	1.28 ± 0.35	1.30 ± 0.33
Mean TC (mmol/L)	4.03 ± 0.86	4.02 ± 0.76	4.14 ± 0.85
Mean ALT (IU/L)	35.2 ± 26.0	31.2 ± 22.1	29.0 ± 17.3
Mean serum Cr (μmol/L)	72.0 ± 18.0	72.6 ± 18.4	73.9 ± 20.6

Table 1: *Baseline characteristics of patients receiving dapagliflozin. Data reported as mean ± SD; "Week 24" included data measured at week 18 up to week 30; "Week 52" included data measured at week 44 up to week 60.*
BMI: Body Mass Index; HbA_{1c}: Haemoglobin A_{1c}; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; TG: Triglyceride; HDL: High-Density Lipoprotein; TC: Total Cholesterol; ALT: Alanine Aminotransferase; Cr: Creatinine.

Parameter	Mean change at Week 24	95% CI for the difference	Mean change at Week 52	95% CI for the difference
Body weight (kg)	-4.0	-8.3, 0.3	-5.2	-10.8, 0.4
BMI (kg/m^2)	-1.4	-2.7, -0.1	-1.8	-3.5, -0.1
HbA_{1c} (%)	-0.8	-1.1, -0.5	-0.8	-1.1, -0.5
SBP (mmHg)	-6.4	-9.7, -3.1	-5.6	-9.6, -1.6
DBP (mmHg)	-4.1	-6.5, -1.7	-3.3	-6.2, -0.4
TG (mmol/L)	-0.23	-0.67, 0.21	-0.35	-0.84, 0.14
HDL (mmol/L)	0	-0.10, 0.10	0.02	-0.12, 0.16
TC (mmol/L)	-0.01	-0.25, 0.23	0.11	-0.26, 0.48
ALT (IU/L)	-4.0	-11.9, 3.9	-6.2	-17.2, 4.8
Serum Cr (μmol/L)	0.6	-5.1, 6.3	1.9	-8.6, 12.4

Table 2: *Change in different parameters after dapagliflozin treatment.*

Data analysis was further carried out for various patient subgroups, and it was found that patients with higher baseline HbA1c (≥ 8.5%) showed greater reduction in HbA1c compared with those with lower baseline HbA1c (< 8.5%) at Week 52: -2.3% (95% CI -3.0, -1.6) vs. -0.3% (95% CI -0.5, 0) respectively (Figure 2A). Younger patients (< 60 years old) also showed greater reduction in HbA1c compared with older patients (≥ 60 years old) at Week 52: -1.2% (95% CI -1.5, -0.8) vs. -0.4% (95% CI -0.8, 0) respectively (Figure 2B). There was no apparent difference in terms of HbA1c reduction in those who had diabetes for 1-10 years versus those who had diabetes for >10 years: -0.9% (95% CI -1.4, -0.4) for those who had diabetes for 1-10 years vs. -0.9% (95% CI -1.2, -0.5) for those who had diabetes for >10 years (Figure 2A) and those who were obese versus those who were not at baseline: -0.9% (95% CI -1.2, -0.6) for baseline BMI ≥ 25 kg/m^2 (obese patients) vs. -0.5% (95% CI -1.1, 0.1) for baseline BMI < 25 kg/m^2 (non-obese patients) (Figure 2B). Number of therapies received by patients also seemed to exert no impact on HbA1c reduction at Week 52: -1.1% (95% CI -1.5, -0.7) for those treated with quadruple therapy or more vs. -0.9% (95% CI -1.4, -0.4) for those treated with triple therapy (Figure 2C).

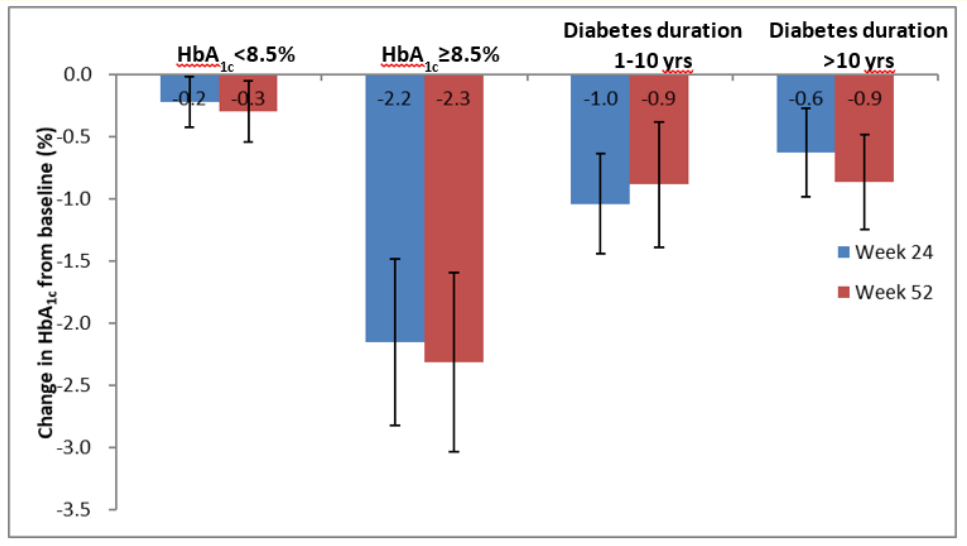

Figure 2A: *Change in HbA1c from baseline in subgroup patients stratified by baseline HbA1c and diabetes duration.*

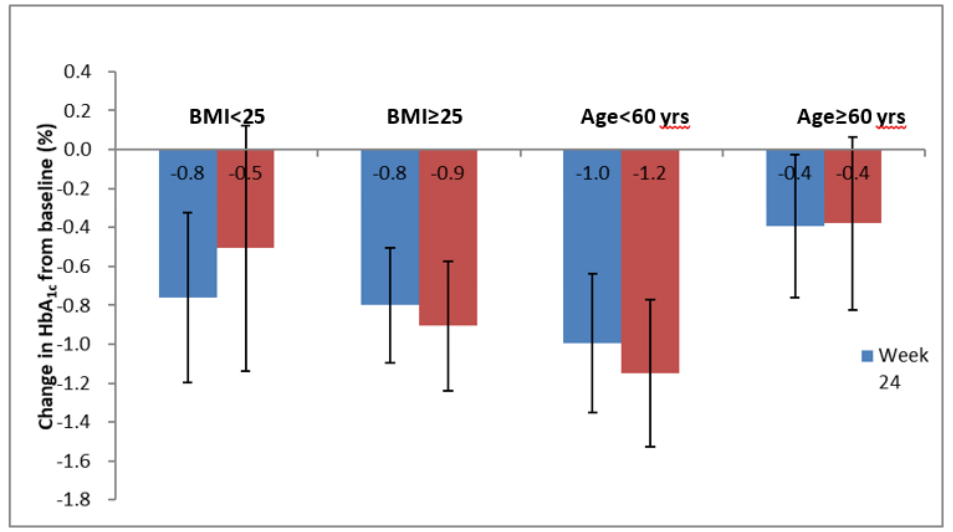

Figure 2B: *Change in HbA1c from baseline in subgroup patients stratified by baseline BMI and age.*

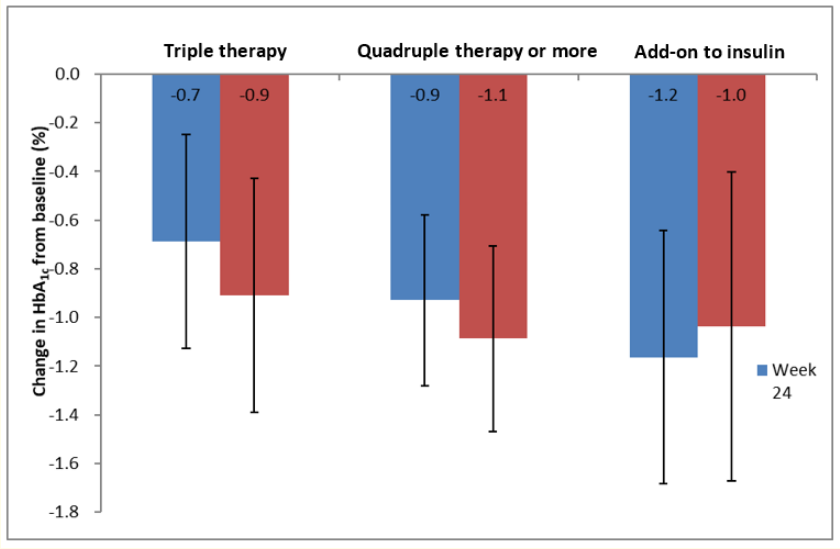

Figure 2A: *Change in HbA1c from baseline in subgroup patients stratified by baseline HbA1c and diabetes duration.*

Further analysis indicated that patients treated with baseline triple (or more) therapy showed a drop of -1.0% (95% CI -1.3, -0.7; n = 42) in HbA1c at Week 52 after adding dapagliflozin, and the reduction did not appear to differ from that observed in the overall study population at Week 52. In addition, the odds of achieving HbA1c < 7% (glycaemic control) at Week 52 was independent of baseline HbA1c level, duration of diabetes, baseline BMI and age (Table 3).

	A1C to target (< 7.0%)		
	N (%) (< 7%)	OR (95% CI)	P value
Baseline A1C			
≥ 8.5%	46 (28.3%)	1.00	
< 8.5%	116 (71.7%)	1.50 (0.377, 5.965)	0.563
Diabetes duration			
> 10 yrs	87 (52.1 %)	1.00	
1 - 10 yrs	80 (47.9%)	0.578 (0.177, 1.882)	0.361
Baseline BMI			
> 25 kg/m^2	135(83.3%)	1	0.319
< 25 kg/m^2	27(16.7%	0.474 (0.698 to 7.647)	
Age			
> 60	61(36.5%)	1 (0.377 to 5.965)	0.166
< 60	106(63.5%	2.311	

Table 3: *Odds ratios of various subgroup patients achieving glycaemic target of HbA_{1c} < 7.0% at Week 52 was independent of baseline HbA_{1c} level, duration of diabetes, baseline BMI and age.*

Out of the 167 patients, 22 (13%) stopped dapagliflozin treatment after an average of 14.6 ± 11.7 weeks Dapagliflozin treatment related adverse events were considered as uncommon, with genital infection being the most frequent treatment-emergent event (8%). For patients who experienced genital infection, 4 were males and 10 were females. For patients who experienced hypoglycaemia (n = 23), 4 received concomitant therapy with sulphonylurea, 18 received concomitant therapy with insulin, and 1 received concomitant therapy with sulphonylurea plus insulin. Two patients showed hyperkalaemia and their serum potassium levels returned to normal during the follow-up period.

Discussion

In this real world retrospective observational study, treatment-experienced patients with type 2 diabetes (majority treated with metformin, sulphonylurea, pioglitazone, DPP4i, and/or insulin) were prescribed with add-on dapagliflozin. Results from this study showed an overall 0.8% reduction in HbA1C after treatment with dapagliflozin, comparable to the pooled results obtained in clinical trials of which SGLT2 inhibitors were able to reduce HbA1C up to ~1% as an add-on therapy from a baseline of ~8% [17]. Patients from this study with a higher baseline HbA1C level were associated with a greater reduction in HbA1C after treatment with dapagliflozin, and this observation was also consistent with a pooled analysis of five phase 3 studies with dapagliflozin demonstrating similar results [18]. These results therefore confirmed the point that SGLT2 inhibitors can be added to any other class of antidiabetic agents to further improve glycaemic control [19]. An additional advantage of this new drug class is that it does not appear to show significant drug-drug interactions with other oral antidiabetic drugs, including the commonly used metformin, pioglitazone, sitagliptin and glimepiride, or with some common cardiovascular drugs [12], implying that no major dosage adjustment is required when combining dapagliflozin with these drugs.

In terms of other added benefits, our study showed a clinically meaningful decrease in body weight and blood pressure (both systolic and diastolic) in patients treated with dapagliflozin. The weight reduction in this study was comparable to that (-4.7 kg) observed in phase 2 and 3 clinical trials when SGLT2 inhibitors were administered as monotherapy or as add-on therapy to metformin, sulphonylurea, or insulin up to 104 weeks [17]. The blood pressure reduction was also comparable to that observed in clinical trials, which demonstrated a drop of systolic blood pressure of ~2 - 10 mmHg in those treated with SGLT2 inhibitors [17]. This blood pressure lowering effect by

the addition of dapagliflozin may result from a mechanism different from that of common antihypertensive drugs, as a randomised controlled study recently showed that the magnitude of blood pressure reduced by an SGLT2 inhibitor was similar regardless of whether the patients received antihypertensive treatment or not [20]. On the other hand, the weight reducing effect of SGLT2 inhibitors is probably due to caloric loss through glucosuria (approximately 200-300 kilocalories per day [21]) and glucose-induced osmotic diuresis [12,22]. The osmotic diuretic effect together with the urinary sodium loss due to SGLT2 inhibition could potentially explain the blood pressure lowering effects [23,24], although the exact mechanism has not been fully elucidated [21]. It has been known that elevation in body weight and blood pressure could raise the risk of developing cardiovascular complications in patients with type 2 diabetes [25], and the ability of dapagliflozin in controlling these two risk factors may provide added values to patients.

On the other hand, adding dapagliflozin did not seem to impact lipid levels significantly. Nonetheless, the baseline levels of total cholesterol (4 mmol/L), triglycerides (1.7 mmol/L), and high-density lipoprotein (1.3 mmol/L) were all considered normal [26] before dapagliflozin initiation. Our results simply demonstrated that adding dapagliflozin did not further reduce a lipid level that was already normal. Review data indicated that lipid changes by SGLT2 inhibitors were indeed small and whether the changes are clinically relevant require further investigation [21].

With the unique mechanism of SGLT2 inhibitors that act independently of insulin, dapagliflozin should have a low intrinsic propensity to induce hypoglycaemia unlike insulin or sulphonylureas [27]. In this study, a total of 23 patients reported to have hypoglycaemia, but all of these patients received concomitant therapy with sulphonylurea and/or insulin - medications that have been known to induce hypoglycaemia [28]. Therefore, hypoglycaemia experienced by those patients was more likely to be induced by insulin and/or sulphonylurea rather than dapagliflozin, although this requires further investigation. Another advantage of the insulin-independent mechanism of action of SGLT2 inhibitors renders them effective in any stage of diabetes with any degree of insulin resistance or β-cell function [17]. Our results indeed agree with this assumption as no apparent difference in HbA1c reduction was observed in patients with baseline diabetes duration < 10 years versus those who had diabetes for > 10 years. It is noteworthy that patients treated with baseline triple (or more) therapy showed a similar drop in HbA1c at Week 52 after adding dapagliflozin, when compared with the overall study population. This finding suggests that patients who are already on an aggressive treatment regimen can still benefit from the addition of dapagliflozin, and further reinforces the concept in the recent statement from the American Diabetes Association/the European Association for the Study of Diabetes that adding SGLT2 inhibitors to the background therapy of metformin or sulphonylurea plus metformin can be beneficial if glycaemic goals are not met [2,29].

In this real world cohort, add-on dapagliflozin was considered well tolerated, with 9 patients discontinuing treatment due to side effects. The most common adverse event recorded was nocturia (34%). Although the frequency was no doubt high compared with those reported in pre-registration trials [30], none of the episode was considered treatment-related. Glycosuria induced by dapagliflozin can potentially lead to urinary tract infection and genital infection [31], probably due to the excreted glucose providing a favourable environment for bacterial or fungal growth, and 4.8% and 8.4% of patients indeed experienced these side effects in this study respectively. These percentages appear to be either equal or lower compared to those reported in previous clinical trials [30].

Limitation of the Study

There are several limitations, in this study. Firstly, adherence rate was not able to be estimated in this patient cohort, and therefore drug efficacy could be underestimated. Secondly, as an inherent problem of any retrospective studies there are missing data. Thirdly, this analysis is mostly focused on the first year of treatment with dapagliflozin, and its longer term effect is therefore not evaluated. Lastly, using routinely collected data may lead to underreporting of the frequency of adverse effects, as very often minor side effects were ignored and not reported.

For patients with type 2 diabetes, treatment goals include reaching glycaemic targets while reducing common side effects of current medications such as hypoglycaemia and weight gain. Despite the aforementioned limitations, the findings in this study confirmed the point that dapagliflozin can provide synergistic benefits when combining with other current antidiabetic medications.

Conclusion

Dapagliflozin as an add-on therapy reduced HbA1c and body weight by clinically significant amounts in real-world patients with type 2 diabetes. It is effective in both young patients and those with advanced stage diabetes due to the insulin independent effect and may allow the delay in insulin usage.

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Conflict of Interest

No conflict of interest.

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