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ORIGINAL ARTICLE

Effect of Dapagliflozin on Glycemic Control, Weight, and Blood Pressure in Patients with Type 2 Diabetes Attending a Specialist Endocrinology Practice in Canada: A Retrospective Cohort Analysis

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Abstract

Background: In randomized clinical trials, dapagliflozin has been shown to improve glycemic control, weight, and blood pressure. However, there is little real-world evidence of the effectiveness of dapagliflozin. The objective of this study is to investigate the real-world treatment outcomes of patients with type 2 diabetes (T2D) who initiated dapagliflozin in a referral-based endocrinology practice.

Methods: This study was a retrospective cohort analysis of patients with T2D who initiated dapagliflozin in 2015, using data from a large, specialist diabetes registry in Canada.

Results: 1520 patients were eligible for analysis. Following 3 to 6 months of treatment, hemoglobin A1c (HbA1c) decreased by a mean of $0.9\% \pm 1.3\%$ (9.8 ± 14.2 mmol/mol) ($P < 0.01$), weight decreased 2.2 ± 3.1 kg ($P < 0.01$), and systolic blood pressure decreased 3.7 ± 14.3 mmHg ($P < 0.01$). The proportion of patients who achieved glycemic control (HbA1c ≤7.0%) increased from 7.0% at baseline to 27.0% during follow-up. There was also a statistically significant decrease from baseline in body mass index, diastolic blood pressure, fasting glucose, total cholesterol, low-density lipoprotein cholesterol, triglycerides, alanine aminotransferase, and the proportion of patients with microalbuminuria ($P < 0.01$). A higher baseline HbA1c, shorter duration of diabetes, male gender, and greater weight loss were each independently associated with a greater reduction in HbA1c ($P < 0.01$).

Conclusions: In a real-world clinical setting in Canada, dapagliflozin produced significant improvements in HbA1c, weight, and blood pressure in patients with T2D, comparable to that seen in randomized clinical trials.

Keywords: Type 2 diabetes mellitus, Dapagliflozin, Hemoglobin A1c, Real-world evidence, Retrospective analysis, Tertiary healthcare.

Introduction

Nearly 1 in 10 Canadian adults have been diagnosed with diabetes, posing a significant public health issue and financial burden on the healthcare system.[1] Effective therapies are needed to prevent the microvascular and macrovascular complications that are associated with diabetes.[2] Sodium-glucose cotransporter 2 inhibitors (SGLT2i) are a newer class of diabetes therapy that reduces hyperglycemia through the reduction of glucose reabsorption in the kidney, independent of insulin.[3] One of the agents in this class, dapagliflozin, has been shown in randomized clinical trials (RCTs) to significantly improve glycemic control compared to placebo when used as monotherapy,[4] or when added to metformin,[5] sulfonylurea (SU),[6] sitagliptin,[7] or insulin.[8] Dapagliflozin has also been shown to reduce body weight[8] and blood pressure.[4]

Although randomized controlled trials are the gold standard to determine drug efficacy and safety, it is important to investigate the effectiveness of a drug in a real-world setting with a broader patient population. Recent evidence has demonstrated that canagliflozin, another SGLT2i, is associated with significant improvements in hemoglobin A1c

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(HbA1c) in real-world settings.[9–11] A retrospective analysis of patients from routine clinical practice demonstrated that patients initiating an SGLT2i (canagliflozin, dapagliflozin, or empagliflozin) had a significantly lower risk of heart failure or death compared to patients initiating another diabetes therapy.[12] However, there is currently limited data regarding the real-world effectiveness of dapagliflozin on clinical outcomes. The purpose of this study was to conduct a retrospective observational analysis of a large representative diabetes registry in Canada to investigate the real-world outcomes in patients with type 2 diabetes (T2D) who were initiated on dapagliflozin.

Materials and Methods

Data source

This study was a retrospective observational analysis of adult patients with T2D from the LMC Patient Registry, which represents the active health records of one of the largest endocrine practice groups globally, LMC Diabetes & Endocrinology. There are 9 LMC clinics in Canada, representing 40 endocrinologists, 25 diabetes educators, and ~29,000 patients with diabetes actively being treated by the healthcare team. The registry contains medical information for all patients cared for by LMC healthcare professionals, including sociodemographic information, medical history, prescriptions, and laboratory investigations. A detailed description of this registry has been provided.[13] Patients provided written informed consent for their electronic medical record data to be used for research purposes, and this study was approved by a local ethics review board.

Patients were eligible for inclusion in the analysis if they had a clinical diagnosis of T2D for at least 6 months and if they had at least one prescription from an LMC physician for dapagliflozin, as either a single or combination therapy, between January 2015 and January 2016. Patients were excluded if they were prescribed dapagliflozin by their primary care physician, were switched to dapagliflozin from another SGLT2i, or were currently participating in a research study with an investigational product. The first prescription for dapagliflozin was considered the medication index date. The preindex (baseline) time period was defined as up to 4 months before the index date. Available follow-up information was retrieved between 3 and up to 6 months (±6 weeks) after the medication index date (April 2015 to June 2016).

Patient characteristics and outcomes

Age, sex, duration of T2D, ethnicity, education, and private health coverage were recorded at baseline. Clinical characteristics at baseline included history of macrovascular complications (any of myocardial infarction, stroke, angioplasty, transient ischemic attack, cerebrovascular accident, angina, coronary artery disease, or coronary artery bypass graft), hypertension, dyslipidemia, and diabetic kidney disease (estimated glomerular filtration rate [eGFR] <60 mL/min/1.73 m^2 or urinary albumin–creatinine ratio [uACR] ≥2.0 mg/mmol). Concomitant classes of antihyperglycemic and antihypertensive medications were assessed at baseline and during the follow-up period. Incidence of hypoglycemia and severe hypoglycemia (requiring the assistance of another individual) was self-reported during the patient's clinic visits.

For all clinical outcomes, the last evaluable value within 3–6 months follow-up was used to calculate change from baseline. The primary outcome was the change in HbA1c. Secondary outcomes included change in body weight, blood pressure, body mass index (BMI), fasting plasma glucose (FPG), eGFR, sodium, potassium, alanine aminotransferase (ALT), lipids, and proportion of patients with diabetic kidney disease. The proportion of patients achieving ≥5% body weight loss and incidence of nonsevere and severe hypoglycemia, the proportion of patients who discontinued dapagliflozin, and clinical predictors of change in HbA1c, body weight, and blood pressure were also evaluated.

Statistical analyses

Baseline characteristics are presented as mean ± standard deviation or as *n* (%). All outcome analyses included patients with evaluable baseline and follow-up data. Patients who discontinued dapagliflozin before the analyzed time point were not included in the respective analysis. Paired t-tests were used to evaluate the change in HbA1c, body weight, blood pressure, BMI, FPG, eGFR, sodium, potassium, ALT, and lipids between baseline and follow-up. McNemar's test was used to assess the change in proportion of patients with diabetic kidney disease. Multiple regression models were used to investigate clinical predictors of change in HbA1c, body weight, and systolic blood pressure (SBP) between baseline and last evaluable follow-up within 6 months. Variables that were included in the models as potential predictors were baseline value, age, gender, duration of diabetes, weight change, concomitant therapy, macrovascular complications, chronic kidney disease, hypertension, and dyslipidemia. Alpha was set at 0.05 for statistical significance and all statistical analyses were performed with SAS 9.4 (SAS Institute, Cary, NC).

Results

Between January 2015 and January 2016, there were 2498 patients with T2D who had at least one prescription for dapagliflozin. Of these patients, 384 did not meet the eligibility criteria described above. Patients were further excluded from the primary analytic dataset if they did not have an HbA1c value at both baseline and during the follow-up period ($n = 451$) and if they used dapagliflozin for less than 6 weeks before discontinuing treatment ($n = 143$), leaving a final analytic cohort of 1520 patients.

Baseline characteristics of the study sample are presented in Table 1. The mean age of the patients was 57.6 ± 9.8 years, approximately half of the sample were male, and 40% were Caucasian. The dose of the first prescription for dapagliflozin was 5 mg for 45% of the patients and 10 mg for the remaining patients.

Primary outcome

Between baseline and follow-up, there was a statistically significant decrease in HbA1c of −0.9 ± 1.3% (9.8 ± 14.2 mmol/mol) ($P < 0.01$) (Table 2). The proportion of patients who achieved different levels of HbA1c at baseline and last available follow-up within 6 months are presented in Figure 1. During follow-up, 27% of patients achieved an HbA1c of ≤7.0%, compared to only 7% of patients at baseline.

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Table 1. Baseline Characteristics of 1520 Patients with Type 2 Diabetes Who Initiated Dapagliflozin

Age (years)	57.6 ± 9.8
Duration of diabetes (years)	11.6 ± 7.6
Sex (males)	866 (57)
Prescription	
Dapagliflozin 5 mg	680 (45)
Dapagliflozin 10 mg	840 (55)
HbA1c (%)	8.6 ± 1.4
HbA1c (mmol/mol)	70.0 ± 15.3
Weight (kg)	91.0 ± 21.3
BMI (kg/m^2)	32.1 ± 6.0
SBP (mmHg)	127.3 ± 13.3
Ethnicity	
Caucasian	628 (41)
Asian	491 (32)
Other	253 (17)
Not specified	148 (10)
Private health insurance	628 (41)
Comorbidity	
Macrovascular complications	129 (8)
Hypertension	1013 (67)
Dyslipidemia	1243 (82)
Diabetic kidney disease	455 (32)
Concomitant medications	
No. of antihyperglycemic medications	2.8 ± 1.0
No. of antihypertensive medications	1.3 ± 1.1
Diabetes therapy	
Drug naïve	8 (0.6)
Metformin monotherapy	109 (7)
Insulin (±metformin)	183 (12)
DPP-4i (±metformin)	208 (14)
SU (±metformin)	89 (6)
Other combinations	923 (61)
Order of dapagliflozin therapy	
Second line (excluding insulin)	121 (8.0)
Third line (excluding insulin)	324 (21.3)
Fourth line (excluding insulin)	435 (28.6)
Prescribed following insulin	632 (41.6)
Antihypertensive therapy	1134 (75)
ACE inhibitor	629 (41)
ARB	434 (28)
Calcium channel blocker	354 (23)
Diuretic	320 (21)
Beta Blocker	238 (16)
Lipid lowering therapy	
Statin medication	1326 (87)
Rosuvastatin	837 (56)
Atorvastatin	421 (28)
Simvastatin	43 (3)
Pravastatin	21 (1)
Fluvastatin	5 (0.3)
Other lipid lowering medications	145 (10)
Ezetimibe	111 (7)
Fibrates	36 (2)
Niacin	4 (0.3)
Colesevelam	1 (0.1)

Data are presented as mean ± standard deviation, or as *n* (%).

ACE, angiotensin-converting enzyme; BMI, body mass index; ARB, angiotensin receptor blocker; DPP-4i, dipeptidyl peptidase-4 inhibitors; SBP, systolic blood pressure; SU, sulfonylurea.

Secondary outcomes

Body weight was significantly lower during follow-up (−2.2 ± 3.1 kg; $P < 0.01$) (Table 2), and 18% of patients achieved a clinically significant weight loss of ≥5% of baseline body weight. There was also a significant reduction in SBP (−3.7 ± 14.4 mmHg) and diastolic blood pressure (DBP, −1.3 ± 9.2 mmHg) ($P < 0.01$) (Table 2). Compared to baseline, BMI, FPG, total cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, high-density lipoprotein (HDL) cholesterol, non-HDL cholesterol, ALT, and the proportion of patients with microalbuminuria (uACR ≥2.0 mg/mmol) significantly improved during follow-up (Table 2) ($P < 0.01$). In addition, there was a small reduction in eGFR (0.5 ± 9.1 mL/min/1.73 m^2, $P = 0.03$) and a small increase in creatinine (1.6 ± 8.5 μmol/L, $P < 0.01$).

Predictors of change in HbA1c, body weight, and blood pressure

Higher baseline HbA1c, shorter duration of T2D, male sex, and greater weight loss from baseline were all independently associated with a significantly lower HbA1c during follow-up (Supplementary Table S1; Supplementary Data are available online at www.liebertpub.com/dia). Every 1% higher HbA1c at baseline was associated with a 0.67% decrease in HbA1c during follow-up. The adjusted mean reduction in HbA1c in patients adding dapagliflozin to metformin (−0.96%) was significantly greater compared to the adjusted mean reduction in HbA1c in patients adding dapagliflozin to insulin ± metformin (−0.53%) ($P < 0.01$).

Three variables were also predictive of body weight change during follow-up—a higher baseline body weight, longer duration of T2D ($P < 0.05$), and not having chronic kidney disease at baseline (Supplementary Table S2). Every 1 kg higher baseline body weight was associated with a 0.03 kg reduction in body weight during follow-up. Addition of dapagliflozin to metformin monotherapy had a significantly greater adjusted mean reduction in body weight (−2.6 kg) than patients adding dapagliflozin to insulin ± metformin (−1.6 kg) ($P < 0.01$).

A higher baseline SBP, greater weight change, no prior antihypertensive therapy, and no prior history of hypertension were all associated with a significantly greater reduction in SBP during follow-up (Supplementary Table S3). Every 1 mmHg higher baseline SBP was associated with a 0.59 mmHg decrease in SBP during follow-up.

Concomitant therapy

Patients were using a mean of 2.8 ± 1.0 antihyperglycemic medications at baseline and 2.5 ± 0.9 antihyperglycemic medications during follow-up. The proportion of patients using different antihyperglycemic medication classes at baseline and follow-up is shown in Figure 2a. The most common antihyperglycemic medications in use at baseline were metformin (93%), dipeptidyl peptidase-4 inhibitor (DPP-4i, 59%), and SUs (49%). During follow-up, 7.4% of patients discontinued SU and 4.1% of patients discontinued a DPP-4i.

Patients were using a mean of 1.3 ± 1.1 antihypertensive medications at baseline and 1.2 ± 1.0 antihypertensive medications during follow-up. The proportion of patients

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Table 2. Change in Clinical Outcomes from Baseline to 3–6 Months Follow-up in Patients with Type 2 Diabetes Initiating Dapagliflozin

	n	*Baseline*	*Follow-up*	*Δ*	P
HbA1c (%)	1520	8.6 ± 1.4	7.7 ± 1.1	−0.9 ± 1.3	<0.01
HbA1c (mmol/mol)	1520	70.0 ± 15.3	61.0 ± 12.0	9.8 ± 14.2	<0.01
Body weight (kg)	1408	91.0 ± 21.3	88.8 ± 21.0	−2.2 ± 3.1	<0.01
SBP (mmHg)	1415	127.3 ± 13.3	123.6 ± 13.2	−3.7 ± 14.4	<0.01
DBP (mmHg)	1415	73.2 ± 8.7	71.8 ± 8.2	−1.3 ± 9.2	<0.01
BMI (kg/m^2)	1382	32.2 ± 6.0	31.4 ± 6.0	−0.8 ± 1.4	<0.01
FPG (mmol/L)	964	9.6 ± 3.1	7.8 ± 2.2	−1.8 ± 3.3	<0.01
Sodium (mmol/L)	550	138.6 ± 2.8	139.2 ± 2.5	0.6 ± 2.8	<0.01
Potassium (mmol/L)	670	4.5 ± 0.4	4.5 ± 0.4	0.0 ± 0.4	0.88
Total cholesterol (mmol/L)	903	4.03 ± 1.47	3.81 ± 0.97	−0.23 ± 1.37	<0.01
LDL-C (mmol/L)	831	2.05 ± 0.88	1.91 ± 0.77	−0.13 ± 0.80	<0.01
Triglycerides (mmol/L)	928	1.96 ± 1.69	1.78 ± 1.39	−0.17 ± 1.50	<0.01
Non-HDL (mmol/L)	873	2.87 ± 1.19	2.64 ± 0.93	−0.22 ± 1.07	<0.01
HDL-C (mmol/L)	930	1.14 ± 0.32	1.17 ± 0.32	0.03 ± 0.20	<0.01
eGFR (mL/min/1.73 m^2)	1324	93.4 ± 16.2	92.9 ± 16.0	−0.5 ± 9.1	0.03
Creatinine (μmol/L)	1293	69.8 ± 16.3	71.3 ± 16.9	1.6 ± 8.5	<0.01
uACR (≥2.0 mg/mmol)	909	386 (42.5)	333 (36.6)	−53 (−5.9)	<0.01
ALT (U/L)	804	32.5 ± 22.4	28.3 ± 18.5	−4.1 ± 15.1	<0.01
Diabetic kidney disease (%)	1395	31.4	29.2	−2.2	0.07

Diabetic kidney disease is defined as eGFR <60 mL/min/1.73 m^2 or uACR ≥2.0 mg/mmol.

ALT, alanine aminotransferase; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; uACR, urinary albumin–creatinine ratio.

using different antihypertensive medications at baseline and during follow-up is presented in Figure 2b. The most common antihypertensive classes at baseline were angiotensin-converting enzyme inhibitors (41%) and angiotensin receptor blockers (28%). During follow-up, 4.5% of patients discontinued a diuretic.

At baseline, 87% of patients used a statin medication (Table 1), and this proportion was maintained throughout the follow-up period. The most common statin medications used at baseline were rosuvastatin (56%) and atorvastatin (28%). Also, 9.5% of patients used other lipid-lowering therapies at baseline, including ezetimibe (7%) and fibrates (2%).

Other outcomes

The incidence of any self-reported hypoglycemia was low, with 7% of patients reporting at least one incidence/month at both baseline and follow-up. The incidence of self-reported severe hypoglycemia was negligible (six patients at baseline and three patients at follow-up). The three patients who reported severe hypoglycemia at follow-up were all using insulin and one was also using SU.

Of the total 2114 patients who initiated dapagliflozin at LMC, 303 (14%) patients discontinued dapagliflozin within a 6-month follow-up period, with an even distribution

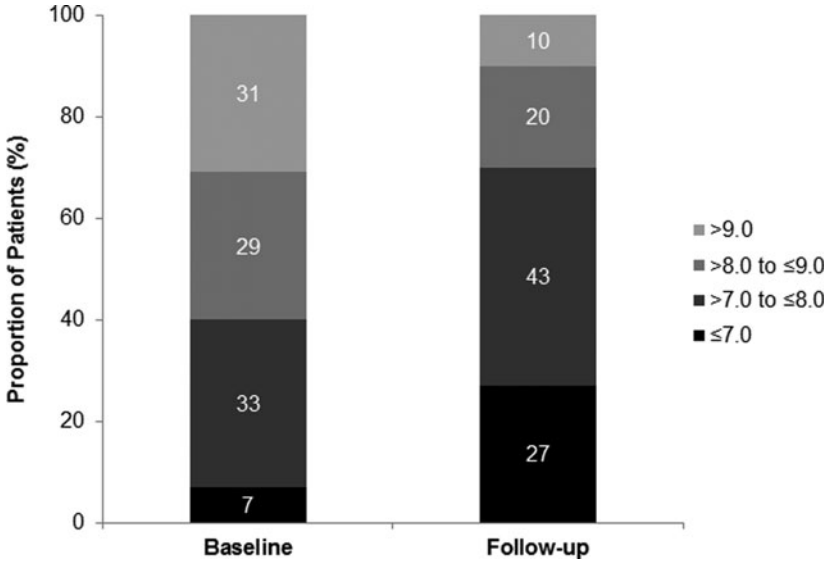

FIG. 1. Proportion of patients achieving different levels of HbA1c at baseline and 3–6 months follow-up. HbA1c, hemoglobin A1c.

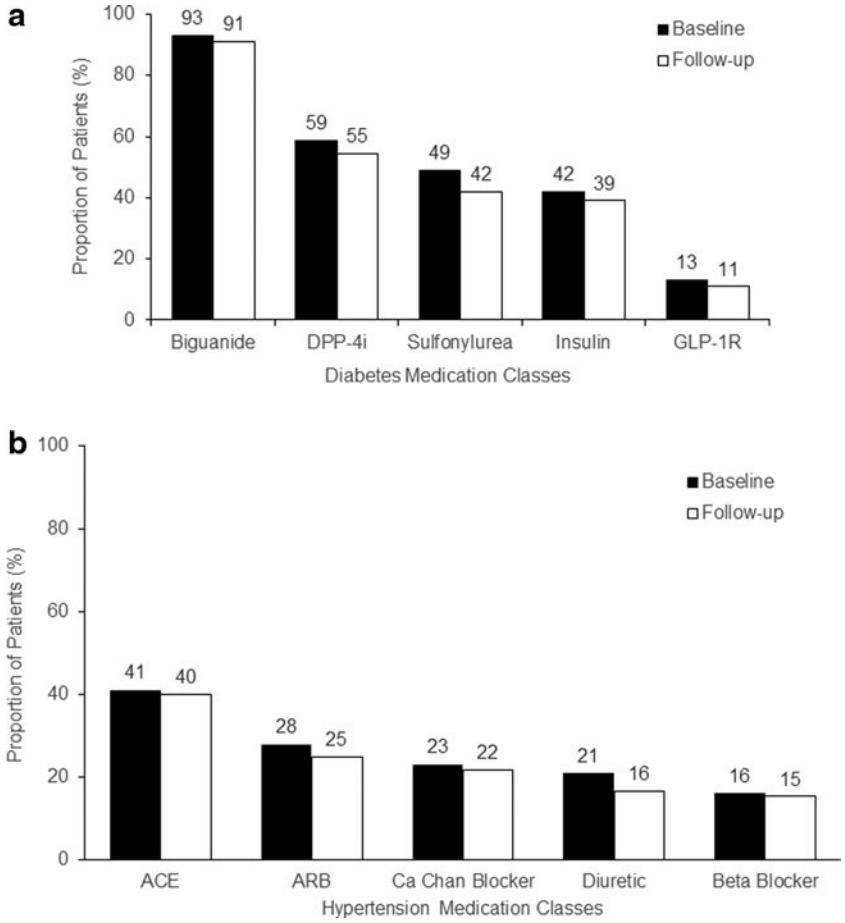

FIG. 2. **(a)** Proportion of patients using different classes of diabetes therapy at baseline (black bars) and follow-up (white bars). **(b)** Proportion of patients using different classes of hypertension therapy at baseline (black bars) and follow-up (white bars). ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; DPP-4i, dipeptidyl peptidase-4 inhibitor.

between men and women. Patients who discontinued the medication had completed a mean of 3.7 ± 2.0 months.

Discussion

This retrospective cohort study confirms the clinical trial findings of clinically significant improvements in glycemic control, body weight, and blood pressure following initiation of dapagliflozin in patients with T2D in a real-world clinical setting. The magnitude of reduction in these parameters was comparable to that observed in the RCTs. Patients also had significant reductions in other clinical endpoints, including BMI, FPG, lipids, and ALT. Thus, dapagliflozin was associated with improvements in various clinical parameters in patients with T2D who attend a referral-based endocrinology group practice in Canada.

A central aim of T2D management is to achieve glycemic control, with the goal for most patients being an HbA1c $\leq 7.0\%$.[2] In this study, the proportion of patients at target HbA1c increased from only 7% at baseline to 27% at follow-up. Importantly, the proportion of patients with very poor glycemic control (HbA1c >9.0%) decreased from 31% at baseline to only 10% during follow-up. The greatest improvement in HbA1c was seen in those with the poorest control at baseline. Although the observed glycemic response was independent of age, a shorter duration of diabetes was significantly associated with HbA1c reduction, which is unexpected as SLGT2i's primary mechanism of action is independent of beta cell function and therefore the duration of diabetes. Patients adding dapagliflozin to insulin (±metformin) had a smaller A1c reduction compared to patients adding dapagliflozin to metformin. It is possible that the insulin dose was downtitrated at the time of dapagliflozin initiation, but unfortunately such information is not available.

One interesting finding was that the reduction in HbA1c was greater in men compared to women. Genital and urinary tract infections are the most frequently reported side effects of dapagliflozin and are more commonly reported in women than men.[14,15] Although we did not have information for adverse events, if women did experience a higher rate of these infections, one might hypothesize that there may have been greater nonadherence with dapagliflozin among women, potentially explaining the greater observed glycemic benefit than in men. However, the proportion of patients whom we know discontinued dapagliflozin was similar between men and women. Thus, this gender difference cannot be fully explained at this time and warrants further investigation.

In this particular cohort of patients, many were prescribed dapagliflozin as a third- or fourth-line therapy. Given the

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clinical effects of dapagliflozin, it would be expected that more patients would be using this medication as a second-line therapy following metformin. However, it is important to highlight that the patients observed in this study were from a referral-based endocrinology practice, had a mean diabetes duration of 12 years, and had poorly controlled glycemia. Accordingly, many of the patients in this cohort were already using multiple oral medications at baseline and 40% were already on insulin therapy, which may explain why few patients in this cohort were prescribed dapagliflozin as a second-line agent.

Hypertension and dyslipidemia are common in patients with T2D.[16] In this study, the reductions in both SBP and DBP were similar to what have been reported in clinical trials,[7,15] and in an observational cohort study from the United Kingdom.[17] According to regression analyses, a higher SBP at baseline, greater weight loss, not using antihypertensive therapy, and not having a history of hypertension were all associated with a greater reduction in SBP. These results build upon the findings of a small study of fewer than 100 patients using dapagliflozin, which reported that only baseline blood pressure was a significant predictor of blood pressure change.[18] With respect to lipid profile, there were significant reductions in both LDL cholesterol and total cholesterol, which is in contrast to some clinical trials that reported an increase in LDL and total cholesterol in patients using dapagliflozin.[5,15] Of note, in this study population, between baseline and follow-up, the proportion of patients using statins was unchanged (87%), and the dosage of statins was similar (data not shown). Thus the reason for these contradictory findings is not clear.

Weight loss is an important strategy for glycemic management in T2D. Previous evidence suggests that dapagliflozin-induced glucosuria leads to a urinary loss of 200–300 kcal/day[3] and weight loss with dapagliflozin is primarily due to reductions in fat mass, visceral adipose tissue, and subcutaneous adipose tissue.[8] In this study, the mean weight loss of −2.2 kg was comparable to the weight loss observed in clinical trials at 24 weeks.[5–8] Also, 18% of patients achieved a clinically significant weight loss of ≥5%. A longer duration of diabetes was associated with greater weight loss, which is consistent with a report that patients with late-stage T2D have a greater reduction in weight with dapagliflozin compared to patients with early-stage T2D.[19] Furthermore, our finding that weight loss was significantly associated with the improvement in HbA1c and SBP is similar to a recent pooled analysis of patients using dapagliflozin.[20]

A strength of this study is the use of the LMC Patient Registry, which provides comprehensive patient information updated in real time, allowing the simultaneous assessment of important variables that may contribute to changes in metabolic control, such as demographics, comorbidities, and concomitant medications. Unlike most patient registries, the LMC Patient Registry collects information regarding incidence of hypoglycemia at every clinic visit. Although these data are somewhat limited by self-reported incidence of hypoglycemia, findings from this study suggest that there is no increase in either nonsevere or severe hypoglycemia following initiation of dapagliflozin. Furthermore, because patients had a wide range of HbA1c at baseline, and many had multiple comorbidities and were using various combinations of diabetes therapies, findings from this real-world study may be more generalizable to clinical practice than results emerging from randomized controlled trials.

Limitations also warrant mention. Despite the large sample of patients prescribed dapagliflozin, only 80% of the study sample had an evaluable outcome for HbA1c. Furthermore, we were unable to assess medication compliance, and it is likely that patients in this study were less compliant with taking dapagliflozin than patients in RCTs. Although we were able to determine if a patient discontinued dapagliflozin during follow-up, this information was only available for patients who saw their endocrinologist within 6 months of dapagliflozin initiation. Thus, the discontinuation rate may be underestimated. It is also important to acknowledge that the sample for this study came from patients attending a referral-based diabetes specialist practice, and thus results may not be generalizable to all patients with T2D. Finally, as this was an observational study, causality cannot be inferred.

Conclusions

In conclusion, this study provides further evidence that dapagliflozin is effective in improving glycemic control, weight, and blood pressure in patients with T2D in a real-world clinical setting.

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