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Observational Study

Comparative efficacy of sodium glucose cotransporter-2 inhibitors in the management of type 2 diabetes mellitus: A real-world experience

Islam L *et al.* Comparative efficacy of SGLT-2i in T2DM

Abstract

BACKGROUND

Sodium glucose cotransporter-2 inhibitors (SGLT-2i) are a class of drugs with modest antidiabetic efficacy, weight loss effect, and cardiovascular benefits as proven by multiple randomised controlled trials (RCTs). However, real-world data on the comparative efficacy and safety of individual SGLT-2i medications is sparse.

AIM

To study the comparative efficacy and safety of SGLT-2i using the real-world clinical data.

METHODS

We evaluated the comparative efficacy data of 3 SGLT-2i drugs (dapagliflozin, canagliflozin, and empagliflozin) used for treating patients with type 2 diabetes mellitus. Data on the reduction of glycated hemoglobin (HbA1c), body weight, blood pressure (BP), urine albumin creatinine ratio (ACR), and adverse effects were recorded retrospectively.

RESULTS

Data from 467 patients with median age 64 (14.8) years, 294 (62.96%) males and 375 (80.5%) Caucasians were analysed. Median diabetes duration was 16.0 (9.0) years, and the duration of SGLT-2i use was 3.6 (2.1) years. SGLT-2i molecules used were dapagliflozin 10 mg ($n = 227$; 48.6%), canagliflozin 300 mg ($n = 160$; 34.3%), and empagliflozin 25 mg ($n = 80$; 17.1). Baseline median (interquartile range) HbA1c in mmol/mol were: dapagliflozin - 78.0 (25.3), canagliflozin - 80.0 (25.5), and empagliflozin - 75.0 (23.5) respectively. The respective median HbA1c reduction at 12 months and the latest review (just prior to the study) were: 66.5 (22.8) & 69.0 (24.0), 67.0 (16.3) & 66.0 (28.0), and 67.0 (22.5) & 66.5 (25.8) respectively ($P < 0.001$ for all comparisons from baseline). Significant improvements in body weight (in kilograms)

from baseline to study end were noticed with dapagliflozin - 101 (29.5) to 92.2 (25.6), and canagliflozin 100 (28.3) to 95.3 (27.5) only. Significant reductions in median systolic and diastolic BP, from 144 (21) mmHg to 139 (23) mmHg; ($P = 0.015$), and from 82 (16) mmHg to 78 (19) mmHg; ($P < 0.001$) respectively were also observed. A significant reduction of microalbuminuria was observed with canagliflozin only [ACR 14.6 (42.6) at baseline to 8.9 (23.7) at the study end; $P = 0.043$]. Adverse effects of SGLT-2i were as follows: genital thrush and urinary infection - 20 (8.8%) & 17 (7.5%) with dapagliflozin; 9 (5.6%) & 5 (3.13%) with canagliflozin; and 4 (5%) & 4 (5%) with empagliflozin. Diabetic ketoacidosis was observed in 4 (1.8%) with dapagliflozin and 1 (0.63%) with canagliflozin.

CONCLUSION

Treatment of patients with SGLT-2i is associated with statistically significant reductions in HbA1c, body weight, and BP were observed better than those reported in RCTs, with low side effect profiles. Review of large-scale real-world data is needed to inform better clinical decision making.

Key Words: Sodium glucose cotransporter-2 inhibitors; Empagliflozin; Canagliflozin; Dapagliflozin; Type 2 diabetes mellitus; Cardiovascular disease; Albumin creatinine ratio; Diabetesity

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Core Tip: Treatment of type 2 diabetes mellitus with sodium glucose cotransporter-2 inhibitors (SGLT-2i) is associated with significant glycated hemoglobin (HbA1c) reduction, body weight loss, and cardiovascular benefits as proven by multiple randomised controlled trials (RCTs). Our real-world data analysis of the efficacy and

safety of individual SGLT-2i revealed better reduction of HbA1c with dapagliflozin, canagliflozin and empagliflozin, while better body weight reduction was seen only with dapagliflozin and canagliflozin when compared to RCTs. Blood pressure reduction, and side effect profiles were comparable to previous studies. Significant improvement of albuminuria was obvious only with canagliflozin, presumably because of the low number of participants in this study. Analyses of various large-scale real-world data are expected to inform better clinical decision making in future.

INTRODUCTION

Sodium glucose cotransporter-2 inhibitors (SGLT-2i) belong to a class of new antidiabetic drugs with mainly extra-pancreatic mechanism of actions to control hyperglycemia predominantly by enhancing renal glycosuria. Even in nondiabetic individuals, these agents can cause a daily loss of about 80 g of glucose through the kidneys, which is much higher in individuals with hyperglycemia, and therefore, SGLT-2i possess moderate antidiabetic efficacy^[1]. Glycosuria also results in a net body energy deficit (the reason why SGLT-2i causes weight loss), and osmotic diuresis as consequence - the additional benefits of these medications. The weight loss benefit makes this class of drugs an attractive treatment option for patients with type 2 diabetes mellitus (T2DM) and diabetes - diabetes because of obesity^[2,3]. Moderate improvement in glycemic control with a reduction in glycated hemoglobin (HbA1c) is seen with the use of these drugs^[1-11]. Multiple randomised controlled trials (RCTs) and meta-analyses have proven that SGLT-2i use is associated with cardiovascular benefits not only for primary prevention but also for the management of established cardiovascular disease^[4-11]. Multiple studies also revealed the remarkable nephroprotective effects of this class of medications^[10-14].

Although there are multiple clinical trials and prospective cohort studies examining the cardiovascular, renal, and diabetes outcomes of individual SGLT-2i molecules, making them drugs of choice in day-to-day management of patients with T2DM and multiple comorbidities related to diabetes, the comparative data on the efficacy of each

molecule are rather sparse in the global scientific literature. As clinical trial and prospective cohort study settings are appropriately supervised and often rigorously controlled by the study teams, the data captured by these methods may not always reflect the actual real-world clinic picture when we consider the study outcomes. Therefore, we should have adequate real-world data from our own day-to-day clinical practice to truly appraise the actual long-term benefits of SGLT-2i and to help therapeutic decision making for our T2DM patients with multi-comorbidities. The current study was designed to suit this purpose in a large academic teaching hospital in the United Kingdom.

MATERIALS AND METHODS

Study design & settings

This is a retrospective clinical study by review of the data of all patients treated with any one of the SGLT-2i drug, empagliflozin, canagliflozin or dapagliflozin between 1st July 2016 and 30th June 2022 at Lancashire Teaching Hospitals NHS Trust. The diabetes service of this hospital provides comprehensive diabetic care for patients in the Central Lancashire and South Cumbria regions of United Kingdom, catering a population of about 0.4 million people. The study was approved by the institutional research committee (No: KB/PB/SE-387/2022).

SGLT-2i molecules used and the dosages

The standard practice of using the SGLT-2i molecules in the hospital was to start with lower doses (daily dose of dapagliflozin at 5 mg, empagliflozin at 10 mg and canagliflozin at 100 mg) and subsequently to increase the dose to full strength of the drug (dapagliflozin 10 mg, empagliflozin 25 mg, and canagliflozin 300 mg, respectively) after a month with monitoring of renal functions just prior to the dose increment.

Participants

All adult patients (age ≥ 18 years) with T2DM treated by one of the above three SGLT-2i molecule for management of their diabetes were considered for inclusion in the study.

Data capture

Electronic records were searched for all patients with a diagnosis of DM treated with antidiabetic medications of the SGLT-2i class during the study period. The total number of cases in this category were further reviewed for inclusion in the study.

Inclusion criteria

Patients with a diagnosis of T2DM managed with one of the SGLT-2i. Participants with predefined primary outcome measures (HbA1c alteration from baseline values at follow-up) and/or secondary outcomes such as alterations in body weight \pm body mass index (BMI), blood pressure (BP), renal functions, and urine albumin creatinine ratio (ACR) - all these outcomes with meaningful data in at least one of the follow-up period (6 months, 12 months and/or at the last follow up just prior to the study), and/or the development of adverse events [such as genital thrush, urinary tract infections (UTI) or diabetic ketoacidosis (DKA)].

Exclusion criteria

Patients with T1DM. Incomplete study data to obtain meaningful outcome measures as specified above. Follow up duration less than 6 months. SGLT-2i commenced primarily for patients for other indications (such as heart failure or CKD) without T2DM or diet controlled T2DM. Discontinuation of SGLT-2i within 6 months of initiation for any reason including major adverse events such as DKA, recurrent genital thrush, allergy reactions or UTI.

Data management

Two junior doctors, under the supervision of a senior academic, recorded the relevant study information using a Microsoft Excel data sheet by entering the demographic,

clinical, biochemical, and follow-up data of all study subjects from their electronic case records retrieved with the help of a senior data scientist of the hospital.

Statistical analysis

Initially, each quantitative trait was tested for normality of distribution using the Shapiro-Wilk normality test. Continuous variables were expressed as median and interquartile range (IQR), and categorical variables as numbers and percentages. The nonparametric Wilcoxon signed-rank test was used for within-group quantitative differences, whereas the two-tailed Fisher's exact test was used to compare proportions. Spearman's rank correlation analysis was used to explore the correlation between the safety and efficacy of SGLT-2 inhibitors with clinical and biochemical parameters. Kruskal Wallis nonparametric test was used to compare the relationship between continuous variables in different SGLT2 drugs. The χ^2 test is used for finding the association between two categorical variables. A *P*-value of < 0.05 (two-tailed) was considered statistically significant. Data were analyzed with Jamovi Software, Version 2.3.21.0 (based on the R program) and BlueSky Statistics Version 10.0, R package version 8.0.

RESULTS

Clinical and biochemical baseline characteristics of SGLT-2i-treated patients

Among a total of 562 patients treated with SGLT-2i during the study period, 467 T2DM patients had meaningful data for analysis of primary and or secondary outcomes. Table 1 shows the main clinical and biochemical characteristics of these subjects. Out of these patients, 160 (34.3%) were on canagliflozin, 227 (48.6%) on dapagliflozin, and 80 (17.1%) on empagliflozin. All these patients were using the full standard recommended doses of individual SGLT-2i molecules.

Efficacy of SGLT-2i on glycemic control (primary outcome)

The median duration of SGLT-2i therapy was 3.6 (2.1) years. An overall median HbA1c reduction from 78 (26) mmol/mol to 68 (26) mmol/mol ($P < 0.001$) was observed with the drug treatment. In other words, we observed a median HbA1c reduction of -10 (IQR 25) mmol/mol, with a percentage of decrease of 12.82% from the baseline value, indicating moderate antidiabetic efficacy of this class of oral agents. During this treatment period, a significant reduction in HbA1c levels were observed, with a more pronounced decrease in HbA1c during the first six months of SGLT-2i use.

Secondary outcomes of SGLT-2i treatment

Considering the secondary outcomes, a median body weight reduction from 99 (29) kg to 95.5 (30.3) kg; ($P < 0.001$) at first 6 months, with a further reduction to 92.4 kg (median with IQR 27.3) at the latest measurement, and this decrease paralleled the median reduction in BMI: from 34 (7.58) to 33 (7.47) kg/m² ($P < 0.001$). Significant reductions in median systolic BP, from 144 (21) mmHg to 139 (23) mmHg ($P = 0.015$), and median diastolic BP from 82 (16) mmHg to 78 (19) mmHg ($P < 0.001$) were also observed. Although a significant reduction in median estimated glomerular filtration rate (eGFR) from 88 (17) mL/min to 86.5 (18) mL/min ($P < 0.001$) at the 6 months' follow up after the SGLT-2i commencement, an improvement to 87 (18) mL/min at 12 months, and maintenance at that level median eGFR: 87 (21) mL/min at latest follow up was noticed. No statistically significant differences were observed in other biochemical parameters like serum creatine and gamma glutamyl transpeptidase were observed at any follow up periods.

Treatment outcomes with individual SGLT-2i molecules

The primary outcome (HbA1c reduction) with each SGLT-2i drug is shown in Figure 1 and the composite treatment outcomes in Tables 2-4. The median weight changes with the individual SGLT-2i drug molecule are shown in Figure 2 and the gender-specific latest weight is shown in the Figure 3.

Subgroup analysis

Only 98 participants had microalbuminuria at baseline and meaningful follow up data of urine ACR for analysis. Of these subjects, only those on canagliflozin showed a statistically significant reduction of albuminuria at the latest follow up, though dapagliflozin showed a significant reduction in ACR at 6 and 12 months follow up periods (Figure 4).

Adverse events of treatment

A total of 64 (13.7%) participants developed adverse events with the use of SGLT-2i therapy [genital thrush in 46 (9.9%), UTI in 11 (2.36%), and DKA in 5 (1.07%) cases]. Adverse effects of individual SGLT-2i molecules were as follows: genital thrush and urinary infection - 20 (8.8%) & 17 (7.5%) participants with dapagliflozin; 9 (5.6%) & 5 (3.13%) participants with canagliflozin; and 4 (5%) & 4 (5%) participants with empagliflozin. DKA was observed in 4 (1.8%) participants with dapagliflozin and 1 (0.63%) participant with canagliflozin. No participant on empagliflozin developed DKA.

Risk factor for DKA

Explanatory data analysis using box plot showed that a high baseline and follow-up HbA1c levels were correlated with higher risk for DKA (Figure 5A and B). While a baseline median HbA1C of ≥ 109 (18) mmol/mol was associated with higher risk of DKA, an HbA1C of < 78 (25) mmol/mol is appeared to confer protection from DKA. Similarly, median HbA1c at 12 months ≥ 81 (4) mmol/mol was associated with DKA, HbA1c level at 12 months < 67 (20) mmol/mol was associated with protection from DKA.

DISCUSSION

In this retrospective cohort study involving 467 participants with a median duration of T2DM of 16 (9) years treated for a median duration of 3.6 (2.1) years with various

SGLT2i medications, we observed statistically significant improvements in glycemic, metabolic, and other cardiovascular outcomes known to occur with the use of this class of drugs in previous clinical studies. The median HbA1c reduction observed from baseline was 10-14 mmol/mol with these drug use at various follow up periods. Significant and persistent improvements in body weight from baseline to the study end were noticed with dapagliflozin (8.8 kg) and canagliflozin (4.7 kg). Though empagliflozin use was associated with significant weight loss at six (6 kg) and 12 months (9.2 kg) there was a regain of weight (see Table 4) at latest follow up. Significant reduction of microalbuminuria was observed with canagliflozin only [ACR 14.6 (42.6) at baseline to 8.9 (23.7) at study end]. The observed adverse effects with the use of SGLT-2i were not unacceptably high in our study. High baseline and follow up HbA1c levels predicted the risk of ketoacidosis.

Dapagliflozin was the commonest SGLT-2i molecule used in our cohort. A recent meta-analysis using pooled data from 8 clinical trials involving 3747 patients showed that its use is associated with a mean HbA1c reduction of 0.59% (approximately 7 mmol/mol)^[15] though the first clinical trial (as an add-on therapy to metformin) with the molecule showed a better HbA1c reduction of 0.84% (approximately 9.5 mmol/mol)^[16]. We observed a median HbA1c reduction of 10, 11.5 and 9 mmol/mol respectively at 6, 12 and last (median 3.6 years) follow up periods indicating a better treatment response than that were seen in the clinical trials. The better efficacy in glycemic control we observed may be related to the poorer baseline glycemic control (high baseline HbA1c) in our patients, a usual feature in the real-world settings compared to the strictly controlled clinical trial settings where some degree of selection bias is expected with participants likely having better baseline glycemic parameters. Moreover, a significant chunk of our patients was already on multiple antidiabetic agents at the time of addition of dapagliflozin where some drug synergism is expected. The efficacy of dapagliflozin appears to be better even in the clinical trial settings when baseline glycemic control is poor (with an observed mean HbA1c reduction of 12

mmol/mol at 24 wk), and the drug is used as an add-on therapy as observed in a recent study^[17].

We observed much better weight reduction with the use of dapagliflozin in our cohort (median -8.8 kg at last follow up) compared to a weight reduction observed in the meta-analysis (-1.88 kg) by Pinto *et al*^[15]. More profound weight loss observed in our study may be related to the poor baseline glycemic control in our cohort and multicomination antidiabetic drug therapy. Patients with poorer diabetes control are likely to have more profound glycosuria and the related negative energy balance from SGLT-2i as evidenced by previous studies with greater weight loss and better average HbA1c reduction as a consequence^[18-20], supporting our observations. Although the systolic BP reduction following treatment did not reach statistical significance ($P = 0.08$) possibly because of the low number of participants in our cohort, a tendency towards significance in this study supports the beneficial effects of dapagliflozin as shown by other studies^[21,22]. The significant reduction in diastolic BP observed in this cohort is also in agreement with the observations from other studies^[23,25]. Although we observed significant reduction of albuminuria as observed by the DAPA-CKD trial^[25], at 6 months and 12 months of follow up, the ACR reduction at the latest follow up did not reach statistical significance ($P = 0.06$) presumably because of the relatively low number of participants in the cohort. The adverse events such as genital thrush and UTI were relatively high from dapagliflozin use as shown by a recent meta-analysis^[26]. The tendency for DKA in those with poorer glycemic control observed in the dapagliflozin cohort is highly important in choosing this molecule for managing patients with T2DM. Patients with poor T2DM control are usually insulinopenic and often behave metabolically like those with T1DM^[27]. Dapagliflozin use in T1DM patients was associated with a 3.4-fold higher risk of DKA compared to those T2DM patients treated with drug^[28]. Therefore, as we observed in our cohort, anyone with a high HbA1c indicating poor glycemic control are at a greater risk of DKA, and clinicians should exercise caution in prescribing dapagliflozin in such patients.

Canagliflozin

As shown in various studies, canagliflozin use was associated with the maximum HbA1c reduction compared to the other 2 SGLT-2i agents in our study^[15,29,30]. However, the median HbA1c reduction was higher than that observed in clinical trials and meta-analyses presumably from the reasons as mentioned above (see dapagliflozin section). Similarly, the weight reduction was also higher than those seen in various studies^[15,29-31]. The reason for this also could same as explained above under dapagliflozin section. Interestingly, we found statistically significant reductions in both the systolic and diastolic BP in the canagliflozin group compared to the other 2 molecules.

Canagliflozin use also showed better and consistent reduction in albuminuria compared to the other two SGLT-2i molecules in our study. This could partly be explained by higher baseline ACR in those with albuminuria in the canagliflozin sub-cohort and low numbers of participants in the individual cohorts of the other two drugs in our study (would not have reached significance). Canagliflozin also possesses some inhibitory effect on SGLT-1 receptors which would have potentially helped to improve albuminuria in this cohort as suggested by a recent study^[32]. Although ketoacidosis related to SGLT-2i therapy was found to be highest with canagliflozin use compared to other drugs in this class in a recent study^[33], we found a lower risk compared to dapagliflozin use in our cohort. Data from more real-world studies might shed light on to the reason for this interesting new observation.

Empagliflozin

Compared to the other two SGLT-2i molecules, the number of participants in the empagliflozin cohort was lower, and therefore some of the outcomes might not have reached statistical significance in the present study. Even then the HbA1c reduction was better for empagliflozin compared to the previous studies^[15,29,34], possibly for the same reasons mentioned in the previous sections. For some unexplained reason, the tendency for weight reduction observed in this group at 6 and 12 months of follow up periods did not sustain at the latest follow up. The absence of significant BP reduction,

improvement of albuminuria, and DKA in this group may be explained by low numbers in the sub-cohort.

Limitations and strengths of the study

Our study has several limitations as seen in any retrospective data analysis. High attrition rate of cases during follow-up, incomplete data of several of the clinical and biochemical parameters studied, dissimilar numbers of participants in the treatment arms with the three SGLT-2i drugs (downgrading quality of statistical comparisons), and higher baseline HbA1c compared to many previously reported studies, might have reduced the overall quality at least some of the outcome analyses.

Although SGLT-2i drugs have shown to alter lipid parameters with a reduction in triglycerides and improvement of high-density lipoprotein, with a resultant improvement of metabolic syndrome^[35], which may be one among the several reasons for their cardiovascular benefits, we could not procure adequate data on lipid parameters (baseline and during follow up period) for inclusion in this study. However, significant improvements in other cardiometabolic parameters like BP, body weight, BMI, and albuminuria make our study results impressive in predicting remarkable future cardiovascular benefits for our cohort.

Moreover, the study results show several unique features such as relatively long period of follow up of our cohort, reasonable record of many of the study parameters and the real-world data with some good comparative and contrasting features with previously reported studies makes our study reasonably robust and should help to inform evidence-based clinical decision-making process by physicians.

CONCLUSION

The real-world use of SGLT-2i medications dapagliflozin, canagliflozin and empagliflozin is associated with significant improvements diabetes, cardiovascular outcomes such as BP reduction and improvement of microalbuminuria, all of which are expected to improve the cardiovascular morbidity and possibly mortality. The adverse

effects are relatively low as observed in various clinical trials and meta-analyses. Caution should be exercised while treating T2DM patients with poor glycemic control and high baseline HbA1c with SGLT-2i because of higher risk of developing DKA. Data from larger real-world clinical studies are expected to inform clinical decision making in using SGLT-2i by practitioners more judiciously.

ARTICLE HIGHLIGHTS

Research background

Sodium glucose cotransporter-2 inhibitors (SGLT-2i) are antidiabetic medications with moderate efficacy in glycemic control, and a potential for weight loss through their glycosuric effects, which are helpful for patients with diabetes - diabetes consequent to obesity. Marked cardiovascular and reno-protective effects with the use of SGLT-2i were proven by multiple randomised controlled trials (RCTs), observational studies and various systematic reviews.

Research motivation

Head-to-head comparison of the real-world data on the comparative efficacy and safety of individual SGLT-2i medications is rather sparse and needs more reports to appraise the benefits shown by the above studies.

Research objectives

To procure the comparative efficacy, safety, and adverse effect profiles of SGLT2i drugs in the clinical practice settings to make better therapeutic decision making as RCTs and prospective observational studies are often biased with rigorous monitoring of patients and the study results that wouldn't always reflect the real-world medical practice.

Research methods

We evaluated the comparative efficacy data of 3 SGLT-2i drugs (dapagliflozin, canagliflozin, and empagliflozin) at full doses, used for treating patients with type 2

diabetes mellitus (T2DM) only. Reduction of glycated hemoglobin, body weight, blood pressure, and urine albumin creatinine ratio were recorded, and the adverse effects were documented retrospectively from the clinical records.

Research results

This real-world data from 467 patients with T2DM showed remarkable improvements in diabetes and cardiometabolic outcomes with all the three SGLT-2i agents with a tendency for renal protection (improvement of albuminuria) in those on canagliflozin. These drugs are reasonably safe with acceptably mild side effects profiles when used judiciously in patients with diabetes.

Research conclusions

We found that SGLT-2i class of medications are very useful for the management of diabetes with improvements cardiometabolic outcomes in the real-world settings as proven by previous RCTs and observational studies.

Research perspectives

Management of diabetes is often a clinical dilemma in the context of optimal glycemic control as several antidiabetic agents including insulins tend to cause weight gain with a potential for worsening of diabetes in a vicious cycle. SGLT-2i group of drugs improves glycemic control and cause weight loss when used in patients with diabetes. Moreover, SGLT-2i medications are useful in improving cardiometabolic outcomes and renal protection in patients with T2DM. We studied the comparative efficacy of dapagliflozin, empagliflozin and canagliflozin using a retrospective data from our hospital which revealed significant improvements in body weight, blood pressure, and glycated hemoglobin, with canagliflozin also showing improvement in albuminuria. They were also reasonably safe with acceptable side effect profile when used in the appropriate clinical context.

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