Real-world Evidence of Efficacy and Safety of SGLT2 Inhibitors as Adjunctive Therapy in Adults With Type 1 Diabetes: A European Two-Center Experience

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OBJECTIVE

To evaluate real-world efficacy and safety of sodium–glucose cotransporter 2 inhibitor (SGLT2i) use in combination with insulin in people with type 1 diabetes.

RESEARCH DESIGN AND METHODS

We conducted a retrospective cohort European two-center study. Data on demographics, HbA_{1c}, weight, insulin use, renal function, and adverse events were collected for 199 adults with type 1 diabetes who initiated a SGLT2i adjunct to insulin. Subgroup analyses were performed to identify who benefited most and who was more at risk for adverse events.

RESULTS

Overall, significant reductions in mean HbA_{1c} (−0.5%), weight (−2.9 kg), and daily insulin (−8.5%) were achieved after 12 months. The greatest reduction in HbA_{1c} was obtained in individuals with baseline HbA_{1c} >8% (−0.7% [64 mmol/mol]). The most weight loss was observed in subjects with BMI >27 kg/m^2 (−3.5 kg). Individuals with baseline estimated glomerular filtration rate (eGFR) <90 mL/min/1.73 m^2 showed an increase in eGFR (4.5 mL/min/1.73 m^2), whereas those with urinary albumin-to-creatinine ratio (UACR) >15 mg/g showed a decrease in UACR (−16.6 mg/g). Fifty-seven individuals (28.6%) reported adverse events: 45 with genital infections (22.6%), 5 ketosis episodes (2.5%), and 7 diabetic ketoacidosis (DKA) (3.5%). No severe hypoglycemia events were reported.

CONCLUSIONS

Our real-world data on SGLT2i showed promising results in reductions in HbA_{1c}, weight, and insulin requirements in type 1 diabetes. Benefits were more pronounced in individuals with higher baseline HbA_{1c} and BMI. DKA remained a major concern, despite educational measures. Further real-life evidence is still required for evaluation of SGLT2i longer-term effects and their impact on reno-cardiovascular outcomes.

Global incidence of type 1 diabetes, a chronic disease mediated by autoimmune β-cell destruction, increased over the last decades, with an estimated annual rise of ∼3% in Europe (1). Landmark studies such as the Diabetes Control and Complications Trial

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(DCCT) and the Epidemiology of Diabetes Interventions and Complications (EDIC) study have demonstrated that achieving optimized glycemic control through education and intensive insulin therapy reduces the risk of long-term complications, making it the mainstay of type 1 diabetes management (2,3). However, despite substantial advances in glucose-monitoring devices, improved insulin formulations, and new insulin delivery technologies, achieving the recommended glycemic targets remains a significant challenge (4,5). Indeed, although recent data from the Better Control in Pediatric and Adolescent diabeteS: Working to crEate CEnTers of Reference (SWEET) registry and a real-world study in Belgium have shown improvements in glycemic control with the increasing use of glucose sensors and insulin pumps (continuous subcutaneous insulin infusion [CSII]) in young people, reaching optimal glycemic goals across all the type 1 diabetes spectrum still remains an issue (6,7). Hypoglycemia risk, weight gain, treatment complexity, and significant self-management burden are still barriers to insulin therapy intensification (8,9). Therefore, an unmet need exists to find effective and safe treatment options to complement insulin replacement in individuals with type 1 diabetes.

Sodium–glucose cotransporter (SGLT)2 inhibitors (SGLT2i) reduce the renal threshold for glucose, increasing glycosuria and decreasing plasma glucose levels independently of remaining insulin secretion (10). SGLT2i have demonstrated efficacy and safety in combination with noninsulin therapies and/or insulin in patients with uncontrolled type 2 diabetes (11). Additionally, evidence from extensive cardiovascular outcome studies with SGLT2i has proven substantial cardiovascular and renal benefits in type 2 diabetes (12,13).

In addition, adding an SGLT2i to insulin therapy for type 1 diabetes has been shown to improve glycemic control without increasing hypoglycemic events and reduce glycemic variability with some weight loss. Results from recent phase III trials in type 1 diabetes demonstrated that SGLT2i as adjunctive treatment to intensified insulin therapy significantly improved overall glycemic control while reducing insulin dose, body weight, and blood pressure (14–16). Likewise, increased time in range and reduced glycemic variability were also found for closed loop insulin delivery systems in a recent single-center pilot study (17). However, the use of SGLT2i has also been associated with an increased risk for diabetic ketoacidosis (DKA), including euglycemic DKA, especially in type 1 diabetes (18).

In 2019, despite concerns regarding the increased risk for DKA, the European Medicines Agency (EMA) approved the use of dapagliflozin, a SGLT2i, and sotagliflozin, a dual SGLT1/2 inhibitor that additionally delays dietary glucose absorption through SGLT1 inhibition in the gastrointestinal tract, as adjunctive therapy to insulin treatment in adults with type 1 diabetes and a BMI $\geq$27 kg/m^2, based on their risk/benefits profile (19,20).

Real-world evidence about SGLT2i use in type 1 diabetes outside of phase III controlled clinical trials environments is limited. The aim of this collaborative study was to analyze the efficacy and safety of the use of SGLT2i in adults with type 1 diabetes in a clinical setting based on the data from two European centers.

RESEARCH DESIGN AND METHODS

Study Design and Population

We conducted a retrospective cohort study in two European centers based on medical records from individuals attending the Diabetes Unit at the University Clinic Hospital of Valencia (UCHV) in Spain and the University Hospital Leuven (UHL) in Belgium, evaluating the efficacy and safety of coadjunct SGLT2i treatment in people with type 1 diabetes.

For this study, a query was made in each university hospital's electronic data management system to identify adults diagnosed with type 1 diabetes who had used or were currently using an SGLT2i in combination with insulin therapy (multiple daily injections [MDI] or insulin pump [CSII]). All resulting files were opened manually and checked for validity. Individuals with type 2 diabetes, secondary diabetes, or monogenetic forms of diabetes were excluded. A total of 199 adults were included in the analysis: 128 from UCHV and 71 from UHL.

Among the 199 adults included in the analysis, 13 from UCHV had previously participated in the analysis, and 13 from the UCHV had previously participated in the EASE trial (Empagliflozin as Adjunctive to Insulin Therapy in Type 1 Diabetes), whereas 16 from the UHL had participated in the EASE, the inTandem (Efficacy, Safety, and Tolerability Study of Sotagliflozin as Adjunct Therapy in Adult Patients With Type 1 Diabetes Mellitus Who Have Inadequate Glycemic Control With Insulin Therapy), and the DEPICT (Dapagliflozin Evaluation in Patients with Inadequately Controlled Type 1 Diabetes) trials.

Clinical and Laboratory Data

The medical history was reviewed for each participant who had initiated a SGLT2i between December 2013 and May 2020. Data on participant characteristics, SGLT2i type and dosage prescribed, and individual changes in HbA_{1c}, weight, daily insulin doses, estimated glomerular filtration rate (eGFR), and urinary albumin-to-creatinine ratio (UACR) in a morning sample were collected retrospectively starting with the SGLT2i prescription date and over a 12-month follow-up period. All reported adverse events, and their type and frequency, were also registered for each individual during treatment with an SGLT2i for a year following the prescription date.

SGLT2i Prescription and Off-label Use

The prescribed SGLT2i in the studied cohort included empagliflozin (5, 10, 12.5, and 25 mg), dapagliflozin (5 and 10 mg), and canagliflozin (50 and 100 mg). Of note, 22 individuals included in the analysis were treated with metformin in combination with SGLT2i. All of these participants were taking metformin for at least 1 year before starting the SGLT2i.

As per standard clinical practice, the potential benefits, risks, and off-label use (if this was the case) were discussed, and verbal consent was obtained for each individual before initiation of treatment with SGLT2i.

Ketosis/DKA Risk Mitigation Strategies Under Real-life Conditions

Participants were thoroughly instructed beforehand on early recognition and treatment of ketosis episodes, how to prevent DKA events, and when to seek immediate medical care. All subjects, at both sites, received serum and/or urine ketone meters and instructions on how to monitor ketones levels at home. At UHL, all subjects were given a card des-

cribing the STICH protocol (21) and had blood ketones meters. At HCUV, all participants were provided with specific instructions and had blood ketones meters if they were CSII users and urine ketone strips if they were on MDI, since blood ketones meters were not reimbursed.

Individuals with a positive history of DKA within the previous 12 months who were not willing to comply with or did not understand the medical recommendations did not initiate the SGLT2i.

Data Collection and Handling

The data points were collected into a joined database in Microsoft Excel, with the visit where the SGLT2i was prescribed selected as the baseline visit. All data points were ordered by month and checked for clusters. To ensure enough data points were available, we chose to include the data points of every participant every 4 ± 2 months for a follow-up period of 12 months. For the data on renal function, data points ±12 months from baseline and 12 months were used. This time line was selected because the eGFR and UACR were routinely measured only once per year.

To identify which types of people benefited most from the treatment, we performed subgroup analyses according to HbA_{1c} levels, BMI, and renal function, including eGFR and UACR, at baseline. We also performed subgroup analyses to identify those at higher risk for adverse events. For evaluation of risk factors for DKA, participants were grouped by sex, time since diagnosis, type of insulin administration, BMI, and SGLT2i dose.

Statistical Analysis

Results are shown as mean ± SD for the continuous variables and *n* (%) for the categorical variables. *P* values of <0.05 (two tailed) were chosen to indicate statistical significance.

We evaluated HbA_{1c}, weight, daily insulin dosage, eGFR, and UACR using a linear mixed model as a function of time, with an unstructured covariance matrix for the four or two repeated measurements in the same participant (for eGFR and UACR, only two measurements were used). By using a linear mixed model, we ensured that case subjects with missing data contributed to the analyses. For evolution of HbA_{1c}, weight, and daily insulin dosage, values at 4, 8, and 12 months were compared with the baseline mean value at the baseline visit. For the evolution of the eGFR and the UACR, the mean values at baseline were compared with the mean values at month 12.

For evaluation of the effect of sex, duration of diabetes, type of insulin administration, BMI, and SGLT2i dosage on the risk of DKA, a χ^2 test was performed. *P* values were calculated with Fisher exact test. The linear mixed-model analysis and the χ^2 test were performed with SPSS statistical software, version 27.

RESULTS

A total of 199 individuals with type 1 diabetes (113 women and 86 men) starting treatment with SGLT2i were included in the analysis. Of subjects, 113 were treated with empagliflozin (56.8%), 66 with dapagliflozin (33.2%), and 20 with canagliflozin (10.0%) (Table 1). Baseline characteristics are described in Table 1. Mean ± SD age was 48.1 ± 10.1 years, duration of diabetes 25.5 ± 11.2 years, and baseline HbA_{1c} 8.2% ± 0.87% (mean 66 mmol/mol). A total of 136 individuals (68.3%) had a BMI >27 kg/m^2. Most individuals were treated with MDI ($n = 134$ [67.3%]), while 65 individuals were pump users (32.7%). Mean total daily insulin dose at baseline was 0.67 ± 0.27 IU/kg. Regarding renal function at baseline, eGFR was >90 mL/min/1.73 m^2 in almost two-thirds of the cohort ($n = 104$ [64.2%]), whereas no subjects had eGFR values <60 mL/min/1.73 m^2. In addition, almost all subjects had UACR values <30 mg/g ($n = 144$ [96.0%]) (Table 1).

Efficacy

HbA_{1c} Values

The overall HbA_{1c} mean reduction from baseline was -0.5% ($P = 0.000$) at 12 months. The maximal HbA_{1c} reduction was achieved after 8 months and was maintained thereafter (Table 2). This reduction was highest in those with baseline HbA_{1c} $>8.0\%$ (-0.7% [64 mmol/mol]) ($P = 0.000$). No statistically significant difference was found among individuals with baseline HbA_{1c} $>7.0\%$ (53 mmol/mol) ($n = 10$) (mean reduction -0.1%; $P = 0.525$). Importantly, for subjects with a baseline BMI >27 kg/m^2, the mean HbA_{1c} reduction after 12 months of treatment was greater than for those with lower BMI (-0.6%, $P = 0.000$, and -0.3%, $P = 0.000$, respectively) (Table 2).

Body Weight

Mean body weight reduction at month 12 was -2.9 kg ($P = 0.000$). The largest reduction in weight was observed at month 8 and sustained up to month 12 (Table 2). The most impressive weight loss was observed in those with a baseline BMI >27 kg/m^2 (-3.5 kg; $P = 0.000$) (Table 2). Of interest, the most weight loss was observed in those with a baseline HbA_{1c} between 7.0% and 8.0% (53 and 64 mmol/mol) (-3.1 kg; $P = 0.000$) and baseline HbA_{1c} $>8.0\%$ (64 mmol/mol) (-2.9 kg; $P = 0.000$). Weight loss in those with a baseline HbA_{1c} $<7\%$ (53 mmol/mol) was <1 kg (not significant) (Table 2).

Total Daily Insulin Requirements

At 12 months, the total daily requirements for insulin were significantly reduced from baseline by -8.5% ($P = 0.000$) (Table 2). The largest reduction in daily insulin dose was observed in individuals with baseline HbA_{1c} between 7.0% and 8.0% (53 and 64 mmol/mol) (-12.5%; $P = 0.000$) and baseline HbA_{1c} $>8.0\%$ (64 mmol/mol) (-7.3%; $P = 0.002$). Individuals with BMI >27 kg/m^2 showed a higher reduction in daily insulin requirements as compared with those with BMI ≤ 27 kg/m^2 (-10.2%, $P = 0.000$, vs. -7.9%, $P = 0.000$, respectively) (Table 2).

In individuals on MDI, both basal and prandial insulin doses decreased at month 12 (-12.2%, $P = 0.000$, and -7.4% $P = 0.004$, respectively) (Supplementary Table 1). Individuals on CSII ($n = 65$) showed a decrease in total daily insulin requirements of 7.2% ($P = 0.035$) (Supplementary Table 1).

Renal Outcomes

Data on eGFR and UACR were available for 162 and 150 subjects, respectively (Table 3).

The overall increase in eGFR observed from baseline to 12 months was not statistically significant (1.1%; $P = 0.214$). However, among individuals with eGFR <90 mL/min/1.73 m^2 at baseline ($n = 58$), mean eGFR increased from 80.1 to 84.6 mL/min/1.73 m^2 ($P = 0.008$) at month 12 (Table 3). To the same extent,

Table 1—Demographic and baseline characteristics

	All (n = 199)***	Empagliflozin (n = 113)	Dapagliflozin (n = 66)	Canagliflozin (n = 20)
Female	113 (56.8)	66 (58.4)	36 (54.6)	11 (55)
Age, years	48.13 ± 10.11	47.38 ± 10.32	48.01 ± 9.67	52.75 ± 9.56
Spain	128 (64.3)	77 (68.1)	33 (50)	18 (90)
Belgium	71 (35.7)	36 (31.9)	33 (50)	2 (10)
Duration of diabetes, years	25.5 ± 11.2	24.8 ± 11.1	25.5 ± 11.7	29.4 ± 8.9
HbA_{1c}, % (mmol/mol)	8.2 ± 0.88 (66)	8.1 ± 0.81 (65)	8.3 ± 0.94 (67)	8.4 ± 1.03 (68)
HbA_{1c} <7.0% (53 mmol/mol)	10 (5.0)	7 (6.2)	2 (3.0)	1 (5)
HbA_{1c} 7.0–8.0% (53–64 mmol/mol)	79 (39.7)	45 (39.8)	28 (42.4)	6 (30)
HbA_{1c} >8.0% (64 mmol/mol)	110 (55.3)	61 (54.0)	36 (54.6)	13 (65)
Weight, kg	83.6 ± 14.8	81.9 ± 15.6	85.9 ± 12.9	86.2 ± 15.0
BMI, kg/m^2	28.9 ± 3.7	28.3 ± 3.5	29.7 ± 3.5	30.6 ± 4.9
BMI ≤27 kg/m^2	63 (31.7)	41 (36.3)	18 (27.3)	4 (20)
BMI >27 kg/m^2	136 (68.3)	72 (63.7)	48 (72.7)	16 (80)
eGFR, mL/min/1.73 m^2	97.17 ± 15.26	96.91 ± 15.67	100.32 ± 13.84	89.62 ± 14.99
eGFR <60 mL/min/1.73 m^2*	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
eGFR 60–90 mL/min/1.73 m^2*	58 (35.8)	33 (36.7)	14 (26.4)	11 (57.9)
eGFR >90 mL/min/1.73 m^2*	104 (64.2)	57 (63.3)	39 (73.6)	8 (42.1)
UACR, mg/g	9.6 ± 15.9	8.3 ± 14.4	7.3 ± 6.3	20.6 ± 28.7
UACR <30 mg/g**	144 (96.0)	82 (97.6)	46 (100)	16 (80)
UACR ≥30 mg/g**	6 (4.0)	2 (2.4)	0 (0)	4 (20)
TDI, IU	55.27 ± 26.6	53.0 ± 24.7	55.1 ± 23.3	68.9 ± 41.3
TDI, IU/kg	0.668 ± 0.271	0.643 ± 0.226	0.666 ± 0.221	0.815 ± 0.515
MDI	134 (67.3)	69 (61.1)	50 (75.8)	13 (65.0)
CSII	65 (32.7)	44 (38.9)	16 (24.2)	7 (35.0)

Data are means ± SD, means ± SD (mean), or n (%). TDI, total daily insulin dose. *Data for eGFR were available for 162 subjects. **Data for UACR were available for 150 subjects. ***Of 199, 14 individuals with ongoing SGLT2i treatment had not yet completed a full year of treatment, and their data were incorporated until the last observation visit.

the overall change in UACR from baseline to 12 months was not statistically significant (−11.3%; P = 0.216). However, a significant mean reduction in UACR of −16.6 mg/g was observed (−52.2%; P = 0.006) for individuals with baseline UACR ≥15 mg/g (n = 17) after 12 months (Table 3).

Change in eGFR stage from baseline to month 12 was analyzed for participants with baseline and 12-month measurements (n = 142) (Supplementary Table 2). In those with eGFR at baseline <90 mL/min/1.73 m^2, 10 participants of 47 (21.3%) had eGFR improved to normal after 12 months. Change in UACR status was also analyzed for individuals with baseline and 12-month measurements (n = 134). Of the 14 participants with UACR ≥15 mg/g at baseline, 2 (−14.3%) had UACR improved to <15 mg/g at month 12 (Supplementary Table 2).

Safety Outcomes

Over the 12-month study period, 57 participants of 199 (28.6%) experienced at least one adverse event. Among these, one individual had two adverse events (Table 4). A total of 58 adverse events were registered at month 12: 45 genital infections, 5 elevated ketone levels without acidosis, 7 DKA, and 1 severe polyuria. No severe hypoglycemia events were registered during the study period. Women experienced more adverse events than men (33.6% vs. 22.1%, respectively). Likewise, participants with lower BMIs at baseline experienced an adverse event more frequently than participants with BMIs >27 kg/m^2 (32.1% vs. 26.4%). The proportion of individuals experiencing an adverse event in the group of those on lower-dose SGLT2i was higher than among individuals treated with higher-dose SGLT2i (32.1% vs. 26.4%) (Table 4). Discontinuation due to adverse events occurred for 15 of 199 participants (7.5%) (Table 4), whereas 4 participants discontinued SGLT2i due to insufficient effect (2%).

Overall, the most common adverse events were genital infections, which occurred in nearly one in four subjects (Table 4). A higher proportion of women experienced genital infections compared with men (25.7% vs. 18.6%, respectively). Genital infections also occurred more frequently among individuals with baseline BMI ≤27 kg/m^2 than among those with BMI >27 kg/m^2 (25.4% vs. 21.3%). On the other hand, the proportion of individuals on lower-

Table 2—Change from baseline in HbA_{1c}, weight, and total daily insulin dose

	All, *n* = 199	Participants with HbA_{1c} <7.0% (53 mmol/mol), *n* = 10	Participants with HbA_{1c} 7.0–8.0% (53–64 mmol/mol), *n* = 79	Participants with HbA_{1c} >8.0% (64 mmol/mol), *n* = 110	Participants with BMI ≤27 kg/m^2, *n* = 63	Participants with BMI >27 kg/m^2, *n* = 136
HbA_{1c} at baseline, % (mmol/mol)	8.2 ± 0.87 (66)	6.7 ± 0.23 (50)	7.6 ± 0.29 (60)	8.8 ± 0.65 (73)	8.1 ± 0.84 (65)	8.3 ± 0.89 (67)
HbA_{1c} at 4 months, % (mmol/mol)	8.0 ± 0.78 (64) (*P* = 0.61)	6.7 ± 0.47 (50) (*P* = 0.84)	7.2 ± 0.38 (55) (*P* = 0.000)	8.0 ± 0.80 (64) (*P* = 0.000)	7.6 ± 0.76 (60) (*P* = 0.000)	8.2 ± 0.80 (66) (*P* = 0.971)
HbA_{1c} at 8 months, % (mmol/mol)	7.7 ± 0.74 (61) (*P* = 0.000)	6.6 ± 0.40 (49) (*P* = 0.64)	7.4 ± 0.47 (57) (*P* = 0.001)	8.0 ± 0.76 (64) (*P* = 0.000)	7.6 ± 0.74 (60) (*P* = 0.000)	7.7 ± 0.74 (61) (*P* = 0.000)
HbA_{1c} at 12 months, % (mmol/mol)	7.7 ± 0.72 (61) (*P* = 0.000)	6.6 ± 0.25 (49) (*P* = 0.525)	7.4 ± 0.47 (57) (*P* = 0.001)	8.1 ± 0.68 (65) (*P* = 0.000)	7.8 ± 0.66 (62) (*P* = 0.000)	7.7 ± 0.75 (61) (*P* = 0.000)
Mean HbA_{1c} difference at 12 months, % (% difference)	−0.5 (−6.1)	−0.1 (−1.5)	−0.2 (−2.6)	−0.7 (−8.0)	−0.3 (−3.7)	−0.6 (−7.2)
Weight at baseline, kg	83.6 ± 14.8	85.0 ± 13.4	82.5 ± 15.0	84.2 ± 14.8	71.1 ± 8.3	89.4 ± 13.4
Weight at 4 months, kg	81.6 ± 14.4 (*P* = 0.000)	83.3 ± 12.2 (*P* = 0.246)	80.3 ± 15.0 (*P* = 0.000)	82.3 ± 14.3 (*P* = 0.000)	69.7 ± 8.8 (*P* = 0.000)	87.1 ± 13.2 (*P* = 0.000)
Weight at 8 months, kg	80.7 ± 14.5 (*P* = 0.000)	82.8 ± 13.5 (*P* = 0.204)	79.8 ± 14.9 (*P* = 0.000)	81.3 ± 14.4 (*P* = 0.000)	69.1 ± 8.8 (*P* = 0.000)	86.2 ± 13.5 (*P* = 0.000)
Weight at 12 months, kg	80.7 ± 15.0 (*P* = 0.000)	84.1 ± 12.8 (*P* = 0.692)	79.4 ± 15.0 (*P* = 0.000)	81.3 ± 15.2 (*P* = 0.000)	69.4 ± 9.4 (*P* = 0.000)	85.9 ± 14.4 (*P* = 0.000)
Mean weight difference at 12 months, kg (% difference)	−2.9 (−3.5)	−0.9 (−1.1)	−3.1 (−3.8)	−2.9 (−3.4)	−1.7 (−2.4)	−3.5 (−3.9)
TDI at baseline, IU/kg	0.668 ± 0.27	0.631 ± 0.29	0.648 ± 0.23	0.687 ± 0.30	0.623 ± 0.22	0.689 ± 0.29
TDI at 12 months, IU/kg	0.611 ± 0.22 (*P* = 0.000)	0.578 ± 0.33 (*P* = 0.211)	0.567 ± 0.18 (*P* = 0.000)	0.637 ± 0.24 (*P* = 0.002)	0.574 ± 0.21 (*P* = 0.000)	0.619 ± 0.23 (*P* = 0.000)
Mean TDI difference at 12 months, IU/kg (% difference)	−0.057 (−8.5)	−0.053 (−8.4)	−0.081 (−12.5)	−0.050 (−7.3)	−0.049 (−7.9)	−0.070 (−10.2)

Data, some presented with *P* values, are means ± SD or means ± SD (mean) unless otherwise indicated. TDI, total daily insulin dose.

dose SGLT2i with genital infections was 24.4% vs. 21.5% among individuals receiving higher-dose SGLT2i (Table 4).

During the 12-month study period, a total of seven DKA cases (3.5%) and five episodes of ketosis (2.5%) were registered (Table 4). DKA events were observed more frequently among CSII users (6.2% vs. 2.2% among MDI users), women (5.3% vs. 1.2% among men), and individuals with BMI ≤27 kg/m^2 (4.8% vs. 2.9% among individuals with BMI >27 kg/m^2) (Table 5). A trend toward more DKA in individuals treated with higher-dose SGLT2i was also observed (4.1% vs. 2.6% among lower-dose SGLT2i users). However, these differences were not statistically significant (Table 5).

Finally, in analyses of the risk of DKA for those where the label of dapagliflozin in Europe was followed (dapagliflozin 5 mg once daily and BMI >27 kg/m^2; *n* = 20), none of those treated presented with DKA (Supplementary Table 6).

CONCLUSIONS

In this study we assessed the efficacy and safety of SGLT2i as an adjunct to insulin in adults with type 1 diabetes in real-life clinical conditions from two tertiary European centers. Over 12 months, the use of an SGLT2i was associated with significant reductions in HbA_{1c}, body weight, and daily insulin requirements among individuals with baseline HbA_{1c} >8.0%. Furthermore, we found a beneficial effect on kidney function for individuals with baseline eGFR <90 mL/min and UACR >15 mg/g. Regarding safety, genital infections were the most frequent adverse events, whereas no severe hypoglycemic events were registered. To our knowledge, this is the largest and longest real-world study showing the benefit-risk profile of SGLT2i use in combination with insulin in people with type 1 diabetes.

To date, robust studies investigating the glycemic response over time of add-on SGLT2i to insulin in type 1 diabetes under real-life conditions are missing. In this real-world study, clinically relevant and significant reductions in HbA_{1c} were achieved and sustained over a 12-month period (−0.5%). Moreover, improvements in glycemic control were achieved alongside significant reductions in daily insulin dose (−8.5%) and body weight (−2.9 kg) without an increase in severe hypoglycemia events (22). These data are consistent with, or better than, those from large phase III controlled trials,

Table 3—Change from baseline to 12 months in eGFR and UACR

eGFR, mL/min/1.73 m^2	All, n = 162	Baseline eGFR ≥90 mL/min/1.73 m^2, n = 104	Baseline eGFR <90 mL/min/1.73 m^2, n = 58
At baseline	97.2 ± 15.3	105.5 ± 9.7	80.1 ± 8.5
At 12 months	98.3 ± 16.0 (P = 0.214)	104.6 ± 12.3 (P = 0.386)	84.6 ± 14.4 (P = 0.008)
Difference (% difference)	1.1 (1.1)	−0.9 (−0.9)	4.5 (5.6)
UACR, mg/g	All, n = 150	Baseline UACR ≥15 mg/g, n = 17	Baseline UACR <15 mg/g, n = 133
At baseline	9.7 ± 15.9	31.8 ± 34.2	5.7 ± 3.1
At 12 months	8.6 ± 8.2 (P = 0.216)	15.2 ± 15.5 (P = 0.006)	7.0 ± 3.9 (P = 0.001)
Difference (% difference)	−1.1 (−11.3)	−16.6 (−52.2)	1.3 (22.8)

Data are means ± SD unless otherwise indicated.

suggesting that these benefits could be transferable into real-life scenarios (14–16). Insulin intensification to optimize glycemic control can be complex and often leads to weight gain and a higher risk of hypoglycemia (23). Thus, based on our results, complementary SGLT2i might represent an effective option to improve glycemic control while tackling unmet needs and preventing chronic complications of type 1 diabetes.

In our analysis, the largest reduction in HbA_{1c} was achieved among individuals with baseline HbA_{1c} >8.0% (64 mmol/mol) (−0.7% at week 52), as seen in EASE-2 (16). In addition, subjects with BMI >27 kg/m^2 not only had significant reductions in HbA_{1c} (−0.6%) but also showed the largest 12-month decrease in body weight (−3.5 kg). Indeed, data from the DEPICT trials demonstrated that participants with ≥27 kg/m^2 showed greater effects than the overall DEPICT population (24, 25). And as mentioned, SGLT2i were approved for individuals with type 1 diabetes with BMI ≥27 kg/m^2 by the EMA in 2019 (19,20). In light of these findings, the importance of identifying individuals who would benefit the most from the use of coadjuvant SGLT2i, in particular individuals with diabetes inadequately controlled and those with higher BMI, is emphasized.

SGLT2i have demonstrated renal protection in people with and without type 2 diabetes and reduced eGFR and/or increased albuminuria (26,27). In post hoc analysis from randomized trials including participants with albuminuria it was shown that adding a SGLT2i to insulin reduced baseline UACR, suggesting some kidney protection in type 1 diabetes (28,29). In the current analysis, we did not find significant changes in eGFR or UACR after 12 months. However, most of our participants had normal kidney function and were normoalbuminuric. In fact, we observed a significant small increase in eGFR <90 mL/min/1.73 m^2 in subjects with eGFR <90 mL/min/1.73 m^2 and decrease in UACR (−16.6 mg/g) in those with UACR >15 mg/g. Thus, our data may suggest some renal protection of SGLT2i in type 1 diabetes. However, further and larger real-life studies including all stages of kidney function are warranted to draw definitive conclusions.

As expected, genital infections were the most common adverse events in our study, especially among women, as seen in other studies (14,25,30). Surprisingly, we found that the proportion of individuals experiencing genital infections was up to two times higher than those reported in randomized trials (14, 25,30). The question of whether this higher incidence was related to greater patient awareness about this complication and a more focused interview on this phenomenon during clinical visits should be investigated further.

DKA represents a major acute complication of diabetes that can lead to premature death. In our real-life study, DKA

Table 4—Adverse events with SGLT2i

	All, n = 199	Female, n = 113	Male, n = 86	BMI ≤27 kg/m^2, n = 63	BMI >27 kg/m^2, n = 136	Lower-dose SGLT2i, n = 78**	Higher-dose SGLT2i, n = 121**
Any adverse events*	57 (28.6)	38 (33.6)	19 (22.1)	21 (33.3)	36 (26.5)	25 (32.1)	32 (26.4)
Two adverse events*	1 (0.5)	1 (0.9)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	1 (0.8)
Genital infection	45 (22.6)	29 (25.7)	16 (18.6)	16 (25.4)	29 (21.3)	19 (24.4)	26 (21.5)
Ketosis	5 (2.5)	4 (3.5)	1 (1.2)	2 (3.2)	3 (2.2)	3 (3.9)	2 (1.7)
DKA	7 (3.5)	6 (5.3)	1 (1.2)	3 (4.8)	4 (2.9)	2 (2.6)	5 (4.1)
Severe hypoglycemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Severe polyuria	1 (0.5)	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.5)	1 (0.5)	0 (0.0)
Adverse events leading to discontinuation of treatment	15 (7.5)	9 (8.0)	6 (7.0)	6 (9.5)	9 (6.6)	7 (9.0)	8 (6.6)

Data are n (%). Higher-dose SGLT2i: empagliflozin 10, 12.5, and 25 mg, dapagliflozin 10 mg, canagliflozin 100 mg. Lower-dose SGLT2i: empagliflozin 5 mg, dapagliflozin 5 mg, canagliflozin 50 mg. *Fifty-seven subjects had 58 adverse events (1 subject reported 2 adverse events: genital infection and DKA). **The SGLT2i (type and dose) registered corresponded to the dose received at the time of the adverse event.

Table 5—DKA and individuals' characteristics (n = 199)

	DKA event, n = 7	No DKA events, n = 192	P
Female, n = 113	6 (5.3)	107 (94.7)	0.143
Male, n = 86	1 (1.2)	85 (98.8)	
Long-duration diabetes (≥10 years), n = 187	6 (3.2)	181 (96.8)	0.357
Short-duration diabetes (<10 years), n = 12	1 (8.3)	11 (91.7)	
MDI, n = 134	3 (2.2)	131 (97.8)	0.219
CSII, n = 65	4 (6.2)	61 (93.8)	
BMI ≤27 kg/m^2, n = 63	3 (4.8)	60 (95.2)	0.681
BMI >27 kg/m^2, n = 136	4 (2.9)	132 (97.1)	
Lower-dose SGLT2i, n = 78*	2 (2.6)	76 (97.4)	0.707
Higher-dose SGLT2i, n = 121*	5 (4.1)	116 (95.9)	

Data are n (%). *Higher-dose SGLT2i: empagliflozin 10, 12.5, and 25 mg; dapagliflozin 10 mg; canagliflozin 100 mg. Lower-dose SGLT2i: empagliflozin 5 mg, dapagliflozin 5 mg, canagliflozin 50 mg.

occurrence was similar to the rates reported in randomized trials (16,30,31). As observed previously, DKA occurred most often in women, CSII users, and leaner individuals, albeit no statistical significance was reached (16). Lack of a relevant subcutaneous insulin depot in CSII therapy and a reduction in carbohydrate intake may explain the higher DKA incidence and ketosis episodes in these individuals. Also, an excessive reduction in insulin dose to mitigate the anticipated incidence of hypoglycemia could represent a potential contributor to associated DKA risk and, thus, should be done with caution (32). In line with reported data on empagliflozin and sotagliflozin suggesting a dose-dependent DKA risk, in our analysis we found a higher proportion of the DKA cases occurred in people with type 1 diabetes receiving higher doses versus lower doses of SGLT2i, although this difference was not statistically significant, most likely due to a small number of events (16,30). Likewise, no significant differences were found in relation to duration of diabetes. Of note, in analyses of individuals who received 5 mg dapagliflozin and had BMI >27 kg/m^2, none had DKA, while the metabolic effects were comparable with those in the rest of the participants. This finding supports the EMA's indication of low-dose dapagliflozin for individuals with type 1 diabetes and BMI ≥27 kg/m^2 (20). Importantly, all participants with DKA recovered completely without sequelae.

Our results underline the importance of case selection, close monitoring, and appropriate training before SGLT2i is initiated to mitigate the risk of DKA as well as the need to keep improving our clinical practice through best practice clinical guidelines (31,33). Having said that, despite increased awareness for the risk of DKA and risk mitigation strategies being introduced, no temporal pattern in the adverse events with DKA and ketosis was observed, likely due to the small number of events. Interestingly, despite the potential risks associated with SGLT2i that were explained before initiation of treatment, the large majority of individuals accepted this challenge well and were willing to start treatment with these agents, as has been reported (34,35). Discontinuation of SGLT2i due to adverse events in our real-world study occurred only in 7.5% of individuals and was mainly due to recurrent genital infections and not because of DKA. These results are in line with those from randomized clinical trials, which ranged up to 9% for dapagliflozin 5 mg in DEPICT-2 (25).

Limitations of this real-world study are summarized here. First, we did a retrospective cohort analysis, and so we lacked a control group for comparisons with SGLT2i coadjuvant therapy. The lack of data from continuous glucose monitoring (CGM) devices represents an additional limitation. Unfortunately, glucose sensors were not available for many participants when SGLT2i were added. Recently, we have witnessed an exponential increase in the use of CGM; thus, further real-life studies including CGM data would be required. Self-reported events, such as genital infections, could have been inaccurately reported by participants on some occasions, and microbiology confirmation was not done systematically. Individuals with poor residual β-cell function are known to be at higher risk for DKA (36). Unfortunately, C-peptide levels at SGLT2i prescription were not available for most participants. Therefore, DKA occurrence and its link to residual pancreatic status could not be explored. Regarding the potential benefits of SGLT2i for renal function, we assume that the observation period was too short and that a longer follow-up is required for assessment of the potential long-term beneficial effects of SGLT2i in this population. Finally, an even larger sample size might have helped us to better identify who may benefit the most from SGLT2i and those who are less prone to develop DKA.

In summary, this real-world study shows that SGLT2i combined with insulin is associated with significant glucose lowering and other metabolic benefits in type 1 diabetes. As previously reported, DKA remains a matter of concern. Careful case selection for best balance between benefits and risks remains paramount. Individuals with type 1 diabetes should be informed about the risks of DKA in advance and given in-depth instruction on early recognition and treatment of evolving ketosis episodes, thereby minimizing DKA risk. Further real-life evidence is still needed for investigation of the long-term effects of SGLT2i and their impact on renal and

cardiovascular protection in people with type 1 diabetes.

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