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RESEARCH LETTER

Real-world data of 12-month adjunct sodium-glucose co-transporter-2 inhibitor treatment in type 1 diabetes from the German/Austrian DPV registry: Improved HbA1c without diabetic ketoacidosis

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1 | INTRODUCTION

Sodium-glucose co-transporter-2 inhibitors (SGLT2is) represent a class of oral antidiabetic drugs that are used in the treatment of type 2 diabetes (T2D), and more recently have been approved for therapy of heart and kidney failure independent of T2D.[1] Importantly, SGLT2is have shown the capacity to induce reverse cardiac remodelling,[2] together with impressive reductions in cardiovascular, heart failure, and kidney endpoints in outcome trials.[3] SGLT2is lower blood glucose levels independently of insulin action by inhibiting reabsorption of filtered glucose in the proximal tubule to increase urinary glucose excretion.[4] Therefore, this mode of action is also effective in absolute insulin deficiency in type 1 diabetes (T1D). Consequently, similar to the clinical effects in T2D, clinical trials of SGLT2i use in patients with T1D as an oral adjunct to insulin therapy have shown reductions in HbA1c, body weight, and blood pressure. Moreover, reductions in insulin doses despite improvements in HbA1c, and most importantly, improvements of daily glucose excursions with reduced hypoglycaemia rates and increased time in

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physiological glucose range, have been observed.[5] However, recognized as a rare side effect in T2D, SGLT2is significantly increased the risk for comparatively normoglycaemic diabetic ketoacidosis (DKA) in T1D trials.[5,6] In addition, no outcome trial results are available for the use of SGLT2is in T1D.

To date, little is known about patient selection, and the risks and benefits of SGLT2is in T1D in the real world.[6,7] In Europe, the SGLT2i dapagliflozin, at a reduced dose of 5 mg, was licensed in 2019 for use in adults with T1D as an adjunct to insulin therapy for selected patients with a body mass index (BMI) of 27 kg/m^2 or higher. The licensing of dapagliflozin in Europe for T1D was mandatorily associated with a risk mitigation strategy for the prevention of DKA, including patient and provider education programmes, provision of self-measurement meters for ketone bodies, and intense patient surveillance.[6] Of note, off-label use of SGLT2is in T1D in clinical practice had been observed earlier, well before official licensing.[7] The criteria upon which healthcare providers selected patients with T1D for treatment with SGLT2is in the real world are not well characterized. Further, therapeutic effects and adverse events of SGLT2is in T1D in daily clinical practice have not been substantially reported.

Therefore, in this trial, we collected data on the characteristics of patients with T1D selected for SGLT2i treatment, and analysed efficacy and safety in clinical practice.

2 | METHODS

The Diabetes Prospective Follow-up Registry DPV (Diabetes-Patienten-Verlaufsdokumentation) has followed patients with diabetes from 1995. DPV data on patients with all types of diabetes (regardless of their disease stage and treatment strategy) are collected every 6 months from centres in Germany, Austria, and Switzerland using DPV software, and the anonymized data are sent to the University of Ulm. Detailed information on the documentation was published previously.[8] The DPV initiative was approved by the ethics committee of the University of Ulm, and data collection was approved by the review boards of the participating centres.

Data for this study were collected from 2012 to 2020. Inclusion criteria were diagnosis of T1D, age at diabetes onset of 6 months or older, and current age 18 years or older. Characteristics in the year before SGLT2i initiation were compared with patients not selected for SGLT2i treatment. Further, the therapeutic effects of SGLT2is after an average treatment period of 12 months were analysed. The SGLT2is used were dapagliflozin (5-10 mg QD [once daily]) and empagliflozin (10-25 mg QD). Repeated measures (autoregressive [Toeplitz] covariance structure) linear regression models were used for continuous outcomes and logistic regression models for binary outcomes. Models were adjusted for sex, categorized time-dependent age (<40, 40-<60, ≥60 years), diabetes duration (<2, 2-<5, ≥5 years), and respective baseline variables. As a sensitivity analysis we used an unstructured covariance structure for repeated measures models.

3 | RESULTS

3.1 | Characteristics of patients with T1D selected for SGLT2i treatment

In total, 50 795 patients with T1D were included in this study. Of these, only 431 patients (0.85%) had initiated an SGLT2i (89% of those off-label) (Table 1); 56% were male, the mean age was 50.2 (standard deviation [SD] 15.3) years, mean BMI was 29.6 kg/m^2 (SD 6.5 kg/m^2, 63% with BMI ≥ 27 kg/m^2), mean diabetes duration was 15.5 (SD 13.1) years, average HbA1c at initiation was 8.58% (SD 1.80%) and mean insulin dose/kg body weight was 0.65 (SD 0.37) IU/kg, and the average overall insulin dose was 57.3 (SD 36.6) IU.

Adjusted linear regression models revealed significantly higher baseline mean HbA1c, BMI, overall daily insulin dose, systolic and diastolic blood pressure, and frequency of albuminuria in patients selected for SGLT2i treatment compared with patients not selected for SGLT2i treatment (Table 1). No differences in baseline average daily insulin dose/kg or estimated glomerular filtration rate (eGFR) were observed.

3.2 | Outcomes after 12 months of SGLT2i treatment in T1D

Data on 12 months of SGLT2i treatment were available for 233 patients (mean age 46.9 [SD 15.4] years, and diabetes duration 15.7 [SD 12.8] years, at SGLT2i initiation). Compared with the year before SGLT2i initiation, after an average of 12 months of treatment, a significant decrease in mean HbA1c, as well as small reductions in systolic and a significant decrease in diastolic blood pressure, were observed (Table 2). Moreover, total cholesterol and LDL-cholesterol decreased significantly during follow-up. An average of 12 months of SGLT2i treatment in T1D did not result in significant changes in mean BMI, mean insulin dose/kg, HDL-cholesterol, triglyceride, eGFR, and the proportion of individuals with microalbuminuria (Table 2). Using an unstructured instead of autoregressive covariance structure did not change the results.

The proportion of patients with at least one severe hypoglycaemia in the year prior to SGLT2i initiation and in the first 12 months with an SGLT2i was low (3%), as were other safety variables (Table S1). Of note, none (0%) of the patients had a DKA in the year before or during the 12 months of SGLT2i treatment.

4 | DISCUSSION

Based on this nationwide observational trial in Germany, Austria, and Switzerland, we conclude that overall use of SGLT2is in adults with T1D is rare in real-world clinical practice. In the prospective randomized licensing trials for dapagliflozin in T1D, the major clinical outcomes were substantial reductions in HbA1c, BMI, insulin

TABLE 1 Characteristics of patients with type 1 diabetes selected for SGLT2i therapy versus no SGLT2i

Outcome	Total cohort (n = 50 795)		*P* value
	No SGLT2i (n = 50 364)	SGLT2i (n = 431)	
HbA1c (%)	8.20 (8.18-8.21)	8.58 (8.39-8.77)	**<.001**
BMI (kg/m^2)	25.75 (25.70-25.79)	29.08 (28.57-29.60)	**<.001**
Daily insulin dose (IU/kg)	0.70 (0.69-0.70)	0.72 (0.67-0.76)	.437
Overall daily insulin dose (IU)	52.07 (51.77-52.36)	61.31 (58.10-64.53)	**<.001**
Systolic blood pressure (mmHg)	129.30 (129.16-129.44)	131.28 (129.68-132.89)	**.016**
Diastolic blood pressure (mmHg)	76.54 (76.45-76.63)	79.82 (78.81-80.84)	**<.001**
eGFR (mL/min/1.73m^2)	92.00 (91.70-92.28)	91.15 (88.01-94.28)	.598
Microalbuminuria (%)	18.0 (17.6-18.5)	27.8 (22.4-34.0)	**<.001**

Note: Data are shown as adjusted means or percentages and 95% confidence interval.
Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate (CKD-EPI formula); IU, international units; mmHG, millimetre mercury; SGLT2i, sodium-glucose co-transporter-2 inhibitor.
P values in bold are significant.

TABLE 2 Changes in outcomes with an average of 12 months of SGLT2i treatment in type 1 diabetes

Outcome	Cohort with an average of 12 months on SGLT2is (n = 233)		*P* value
	Baseline	Follow-up	
HbA1c (%)	8.44 (8.29-8.58)	7.81 (7.66-7.95)	**<.001**
BMI (kg/m^2)	29.89 (29.77-30.01)	29.94 (29.82-30.06)	.591
Daily insulin dose (IU/kg)	0.69 (0.67-0.70)	0.70 (0.68-0.71)	.348
Overall daily insulin dose (IU)	61.12 (59.64-62.61)	62.02 (60.49-63.56)	.413
Systolic blood pressure (mmHg)	132.93 (131.43-134.43)	130.78 (129.24-132.32)	.077
Diastolic blood pressure (mmHg)	80.94 (79.99-81.89)	79.07 (78.09-80.04)	**.017**
Cholesterol (mg/dl)	198.49 (195.03-201.94)	189.78 (186.02-193.54)	**.004**
LDL-cholesterol (mg/dl)	113.90 (110.88-116.92)	108.32 (105.01-111.64)	**.026**
HDL-cholesterol (mg/dl)	54.90 (53.95-55.85)	55.38 (54.33-56.43)	.528
Triglyceride (mg/dl)	164.13 (152.67-175.59)	149.48 (137.00-161.96)	.137
eGFR (mL/min/1.73m^2)	86.47 (85.02-87.92)	85.86 (84.32-87.40)	.581
Microalbuminuria (%)	30.2 (22.5-39.1)	27.8 (21.0-35.9)	.641

Note: Data are shown as adjusted means or percentages and 95% confidence interval.
Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate (CKD-EPI formula); IU, international units; mmHG, millimetre mercury; SGLT2i, sodium-glucose co-transporter-2 inhibitor.
P values in bold are significant.

requirements, blood pressure, and glucose excursions.[5] Therefore, if healthcare providers in the real world may have chosen patients with T1D for SGLT2i treatment according to these results, it could be envisioned that the selection criteria would have been inadequate glycaemic control with high HbA1c, elevated BMI, high insulin requirements and large glucose excursions, and maybe also accompanying arterial hypertension. Indeed, in this observational trial in clinical practice, the selection of patients with T1D for SGLT2i treatment appears to be primarily triggered by the presence of higher HbA1c and BMI in combination with requirements of higher insulin doses, higher blood pressure, and the presence of microalbuminuria. This preselection of patients may also explain in part the somewhat larger HbA1c reductions in this real-world evidence study compared with the results of controlled licensing trials of SGLT2is in T1D. Of note, 89% of patients with T1D in this observational cohort received SGLT2i treatment off-label, that is, before official licensing of dapagliflozin for the use in T1D. Therefore, we conclude that the criteria for selection of patients with T1D for SGLT2i treatment may have been translated from the well-known clinical results in patients with T2D to similarly 'expected' outcomes in selected patients with T1D. Similar results were recently observed in a trial within the US type 1 diabetes exchange registry (T1DX) in adults.[9] There, SGLTi use was also rare and reported by less than 3% of adults. Compared with non-users, those who used SGLTis were more probably of an older age, with a longer diabetes duration, of white race, had private insurance, the use of an insulin pump or continuous glucose monitor,

higher BMI, and used other adjuvant diabetes medication, which mirrors the observations in our DPV study.

In contrast to the significant results from prospective trials of SGLT2i treatment in T1D, in real-world practice after 1 year of treatment in routine care, a clinically relevant but smaller improvement in HbA1c, and more importantly negligible changes in BMI or insulin requirements, were observed. In addition, effects on blood pressure, eGFR, or frequency of microalbuminuria were not substantiated after 1 year of treatment either, indicating that clinical responses of these variables to SGLT2i treatment in T1D in real-world practice may be more heterogeneous than implied by randomized trials. As a limitation to this statement, we acknowledge that the overall number of patients with T1D in this population receiving SGLT2i treatment in this observational trial was small, and the treatment interval was only 12 months. Further, 1-year follow-up data were only available for a subset of 233 SGLT2i users of the overall group of 431 patients. We cannot exclude that results for systolic blood pressure and body weight would change if 1-year follow-up data were available for the whole subset of 431 patients.

As an additional limitation, in this real-world trial, we were unable to acquire sufficient data for continuous glucose monitoring during the course of SGLT2i treatment. Therefore, we are unable to report any treatment effects on glucose excursions in response to SGLT2i therapy, and cannot report times in ranges, as were published for the randomized trial in this patient population.[5]

Before dapagliflozin was officially licensed for use in T1D, it was known that DKA is a rare but significant adverse clinical complication of SGTL2i treatment in T2D over the observational time interval analysed in this real-world trial.[1] As a higher DKA rate is generally envisioned in T1D, the fear of this complication in these patients in response to SGLT2i therapy may have prevented healthcare providers from using this type of treatment in more patients with T1D in clinical practice. Of note, in contrast to results from randomized trials with SGLT2is in T1D, this observational trial revealed no increase in the rate of DKA in response to SGLT2i treatment in real-world practice. While this may indicate that the risk of DKA as a side effect of SGLT2i therapy in T1D may be overestimated in daily clinical practice, the overall low DKA rate in this patient population may also reflect a highly restrictive patient selection for this treatment or an intense surveillance of patients during the course of the treatment. This is somewhat different to the observations of the T1DX trial,[9] in which participants with SGLT2i therapy experienced a minimal non-significant increase in DKA, but unexpectedly, also a higher rate of severe hypoglycaemia.

It should be noted that no data exist from outcome trials of SGLT2i use in T1D, despite the fact that prevention of cardiovascular and kidney endpoints would be similarly desired in patients with T1D, as in those patients with T2D. However, we do not know whether wishfully anticipated cardioprotective and nephroprotective effects may have triggered, to some extent, the selection of patients with T1D in this trial for SGLT2i therapy.

In summary, SGLT2i therapy in T1D may represent an effective and safe oral adjunct therapy in highly selected patients with T1D not reaching their glycaemic goals by insulin therapy alone. While the effects of SGLTis on blood pressure, BMI, and albuminuria may be smaller in T1D versus T2D, and to date no results of outcome trials exist, it may be envisioned that SGLT2is also reduce cardiovascular and kidney outcomes in T1D in longer duration therapy.

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CONFLICT OF INTEREST

The authors report no conflicts of interest with respect to this study.

AUTHOR CONTRIBUTIONS

SL and JS wrote the manuscript and analysed the data; SL, JS, and RWH researched and analysed the data, reviewed and edited the paper; and TD, PB, SMS, FK, SK, PF, and CS contributed to discussions and reviewed/edited the manuscript. SL is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

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