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A study on the utilization of canagliflozin in type 1 diabetes mellitus using real-world data from four European countries

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Abstract

Aims: Sodium-glucose co-transporter-2 (SGLT2) inhibitors are not approved for glycaemic control in type 1 diabetes mellitus (T1DM), and concerns exist around off-label use in this patient population. The objective of this study was to investigate whether and how canagliflozin, an SGLT2 inhibitor, has been used in patients with T1DM, and whether the off-label use of canagliflozin for T1DM has changed over time.

Materials and Methods: This observational, retrospective cohort study utilized real-world data from 2016 to 2022 in four European countries (Belgium, Italy, Spain and United Kingdom) with high cumulative exposure to canagliflozin. Analyses were conducted to identify canagliflozin users with T1DM and estimate the prevalence and incidence of off-label use during the entire study period and by year.

Results: The overall prevalence and incidence of off-label use of canagliflozin in T1DM were consistently low, ranging from 0.0% to 0.2% across six healthcare databases, using both primary and sensitivity definitions of patients with T1DM. A trend analysis of new users of canagliflozin with T1DM over time was not feasible given that the annual prevalence and incidence calculations for many years were censored. Few (number censored) to no diabetic ketoacidosis (DKA) events were reported among canagliflozin users with T1DM in each database.

Conclusion: Real-world data analyses from four European countries showed that off-label use of canagliflozin for T1DM was rare.

KEYWORDS

canagliflozin, cohort study, European, incidence, observational data, off-label use, prevalence, type 1 diabetes

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1 | INTRODUCTION

Canagliflozin is an oral anti-hyperglycaemic medication in the sodium-glucose co-transporter-2 (SGLT2) inhibitor drug class. This drug is approved for the treatment of paediatric patients ≥ 10 years (in the United States), and adult patients with insufficiently controlled type 2 diabetes mellitus (T2DM) as an adjunct to diet and exercise.¹ Canagliflozin lowers blood glucose levels through an insulin-independent mechanism by inhibiting SGLT2 receptors, which lowers the renal threshold for glucose and results in an increased urinary glucose excretion. Canagliflozin also provides cardio- and renal-protective effects for patients with T2DM.^{1,2} Similarly in patients with type 1 diabetes mellitus (T1DM), a retrospective cohort study of medical records showed that SGLT2 inhibitors, as adjunctive agents to insulin, were associated with cardio- and renal-protective effects.³ Specifically, the treatment was associated with preservation of the estimated glomerular filtration rate over a 5-year period, including in patients with established chronic kidney disease. Further, the treated patients were less likely to develop heart failure, chronic kidney disease and be hospitalized for any cause. The study also found that treatment provided clinically meaningful reductions in haemoglobin A1C. However, the SGLT2 inhibitor-treated patients had higher rates of diabetes ketoacidosis (DKA) than the comparator, glucagon-like peptide-1 receptor agonists (GLP-1 RAs).

Since a proportion of the T1DM patient population does not achieve sufficient glycaemic control by using insulin alone, resulting in a high risk of acute and chronic complications, there is a need for adjunct treatments.² In 2019, two SGLT2 inhibitors (dapagliflozin⁴ and sotagliflozin⁵) were approved by the European Medicines Agency (EMA) as adjuncts to insulin for glycaemic control in patients with T1DM and a body mass index >27 kg/m². However, AstraZeneca withdrew the marketing authorization of dapagliflozin for T1DM in 2021,⁶ and Guidehouse Germany GmbH withdrew the marketing authorization of sotagliflozin for T1DM in 2022.⁷

Canagliflozin is not approved for the treatment of patients with T1DM.¹ The safety and efficacy of canagliflozin, as an add-on to insulin, has been evaluated in a randomized controlled trial of patients with T1DM.⁸ The treatment was associated with a reduction in haemoglobin A1C, body weight and insulin dose without any increase in hypoglycaemia; however, an increase in ketone-related adverse events including DKA was observed.

The off-label use of canagliflozin and other SGLT2 inhibitors for T1DM has been observed in clinical practice in Europe.^{9–11} Due to concerns about the risk of DKA associated with SGLT2 inhibitors, the EMA requested that the market authorization holder conduct a drug utilization study of canagliflozin use in patients with T1DM. The objective of this study was to determine the overall and annual prevalence and incidence of canagliflozin use for T1DM using real-world data from 2016 to 2022. In addition, the data were analysed to elucidate whether off-label use of canagliflozin in patients with T1DM had increased, decreased or remained the same over time. Lastly, the occurrence of DKA events among canagliflozin users with T1DM was also explored.

2 | MATERIALS AND METHODS

2.1 | Databases

After feasibility assessments, six real-world databases with large canagliflozin cumulative exposure were identified, including two UK databases (Clinical Practice Research Datalink [CPRD] GOLD and AURUM),¹² 3 IQVIA longitudinal patient databases (LPD) with data from Belgium, Italy and Spain, and the Information System for the Development and Research in Primary Care (SIDIAP) database¹³ with data from Catalonia, Northeast Spain. Throughout this document, we refer to these databases as “real-world databases” to highlight that the data are collected from routine clinical practice. All the databases have been standardized to the Observation Medical Outcomes Partnership Common Data Model (OMOP CDM).^{14–18}

The CPRD GOLD and AURUM databases contain patient data from over 985¹⁹ and 738²⁰ UK general practitioners (GPs), respectively. Overlap for the same patient, during the same observation period, is unlikely based on the data collection software used. The UK databases are linked to hospital episode statistic files, enabling hospitalizations due to DKA to be identified. However, the hospital episode statistics from the CPRD were limited up to March 2021.

The IQVIA LPDs contain outpatient data from GPs gathered from patient management software and there is no linkage with hospitalization records. IQVIA LPD Belgium sampled electronic medical record data of 300 GPs, IQVIA LPD Italy collected data from a panel of 900 GPs, and IQVIA LPD Spain included data from over 3000 GPs and office-based specialists across three regions of Spain.

The SIDIAP database contains data collected from $>30\,000$ healthcare professionals during routine visits to primary care centres of the Catalan Institute of Health.²¹ The population served by the centres includes around 80% of the Catalan population. Some but not all patients in SIDIAP have linkage with hospital discharge records in Catalonia.

Due to licensing agreements, all the databases required censoring when low counts of patients were identified to maintain confidentiality. Specifically, patient counts >0 and <5 were censored. Additionally, when patients were stratified (e.g., by age), if patient counts in one of the subgroups was <5 , all counts in the entire set were censored.

The use of CPRD GOLD and AURUM was approved by the Research Data Governance process (protocol 22-002098). IQVIA LPD datasets did not require patient permission on the use of the data for research purposes because all patient data are deidentified. For the SIDIAP, IDIAP Jordi Gol received internal review board approval for use of data in the current study (22/176-Eom).

2.2 | Setting and patient cohorts

The study period ranged from 01 January 2016 to 31 December 2022. In each of the six databases, to be eligible for analysis, patients (all ages and both sexes) had to have both ≥ 1 canagliflozin exposure record during the study period and ≥ 180 days of continuous

observation before the first exposure to canagliflozin (the index date). Data from patients meeting these criteria were used to calculate the overall and annual prevalence and incidence of off-label use in T1DM among all canagliflozin users.

Two definitions were used in this study to identify canagliflozin users with T1DM, a primary and a sensitivity definition. The primary definition criteria included 1) ≥ 1 diagnosis of T1DM on or before the first exposure to canagliflozin; 2) a record of insulin therapy for $>90\%$ of observation time from the first T1DM diagnosis until study end; 3) no diagnosis of T2DM or secondary diabetes mellitus on or after the first T1DM diagnosis; and 4) the absence of non-insulin antidiabetic treatment apart from SGLT2 inhibitor on or after the first T1DM diagnosis. The sensitivity definition criteria included the first three primary definition criteria along with a less stringent fourth criterion: the absence of non-insulin antidiabetic treatment apart from metformin and SGLT2 inhibitor on or after the first T1DM diagnosis, in which patients who received metformin treatment in addition to insulin were retained as patients with T1DM. The sensitivity definition was included to assess the robustness of the primary definition and related results.²² In each database, patients meeting the primary or sensitivity definition criteria were used to calculate the respective overall and annual prevalence and incidence of canagliflozin users with T1DM.

2.3 | Drug utilization and exploratory analysis

Characteristics of canagliflozin use included total number of prescriptions, total days of supply, and days of continuous treatment after the first prescription/dispensing (with a gap of ≤ 90 days allowed between exposure records). Continuous variables were summarized using mean $\pm$ standard deviation, median and range. The availability of information on days of supply associated with a prescription or dispensing record varied notably across data sources. In CPRD databases, only a limited number of prescription records had valid days supplied or duration values. For records without this information, an imputation was implemented, and result validation has been published previously.¹⁶ In IQVIA LPD Belgium, the days of supply for the prescribed medications were either directly recorded in the source data or computed from the prescription start and end dates. In IQVIA LPD Italy, the days of supply information were not directly available from the source data, and were computed from the prescription dosage, prescriptions per period, pack number and dose number, or imputed if impossible to compute. In IQVIA LPD Spain, the days of supply were obtained from the duration of days in the prescription record that were directly available in the source data. In SIDIAP, all records have prescription start and end dates, and the number of days of drug supply was calculated as the number of days from the initial date to final date of prescription.

For the exploratory analysis, among new users of canagliflozin with T1DM, events of DKA that occurred after initiation of canagliflozin treatment were identified based on diagnosis codes. It is important to note that our analysis primarily utilized databases from primary care settings, whereas DKA is generally managed within inpatient or emergency care contexts. To enhance data completeness, we obtained

hospitalization records when available. Given the potential incomplete capture of DKA events in these GP databases, we consider the analysis of DKA only exploratory.

In addition to the aforementioned exploratory analysis, baseline patient demographics and clinical characteristics observed within the 180 days prior to the first canagliflozin exposure were also explored.

2.4 | Prevalence and incidence calculation

The unadjusted prevalence and incidence of patients with T1DM among canagliflozin users were calculated in each database for the overall study period as well as by year. The prevalence was calculated as the proportion of canagliflozin users who were patients with T1DM among all existing canagliflozin users within the specified time periods. The incidence was calculated as the proportion of new canagliflozin users who were patients with T1DM among all new canagliflozin users within the specified time periods. For the estimates within each calendar year, the study period was from 01 January to 31 December of that year. For the overall estimates, the study period was from 01 January 2016 to 31 December 2022.

2.5 | Federated data network analysis

For this study, the Johnson & Johnson Global Epidemiology Organization developed the programming code and made it available on a private GitHub repository that all data partners could access. The data partners included analysts at Johnson & Johnson who licensed the CPRD databases, IQVIA, which owns the LPD databases and IDIAP Jordi Gol, which owns and manages the SIDIAP database. Programming code was developed to build the patient populations, assess the population characteristics using CohortDiagnostics,^{23,24} and generate output. Prior to analysis, all data were converted to the OMOP CDM,¹⁶ which guaranteed vocabulary consistency and enabled standardized analysis across the databases. All analyses were conducted in R version 4+²⁵ and package versions were managed with renv (an R package to manage package dependencies for a project).²⁶

2.6 | Study registration

A protocol describing the study design and methods was reviewed and approved by the EMA, and the study was registered in the European Union Electronic Register of Post-Authorization Studies (EU PAS Register) under the number EUPAS47585.²⁷

3 | RESULTS

3.1 | New canagliflozin users with T1DM

Table 1 (primary definition) and Table 2 (sensitivity definition) present the stepwise attrition of new users of canagliflozin with T1DM using

TABLE 1 Attrition: total number of canagliflozin new users with type 1 diabetes mellitus (primary definition).

Attrition steps	CPRD databases		IQVIA databases			SIDIAP
	AURUM	GOLD	Belgium	Italy	Spain	Catalonia Spain
Identify patients with ≥ 1 prescription fill or dispensing for canagliflozin during the study period	37 144	11 076	463	2127	3296	6669
≥ 180 days of observation prior to the exposure to canagliflozin	36 175	10 828	444	2057	3284	6640
≥ 1 diagnosis of T1DM on or before the exposure to canagliflozin	388	128	95	24	189	223
Have no diagnosis of T2DM and no diagnosis of SDM on or after the first T1DM diagnosis	134	70	13	19	39	57
Absence of non-insulin antidiabetic treatment apart from SGLT2 inhibitor on or after the first T1DM diagnosis	24	12	<5	12	12	19
No record of canagliflozin exposure in all prior periods	17	5	<5	11	7	7
Record of insulin therapy >90% of observation time from the first T1DM diagnosis until study end	5	<5	0	<5	<5	<5

Abbreviations: CPRD, Clinical Practice Research Datalink; SDM, secondary diabetes mellitus; SGLT2, sodium-glucose co-transporter-2; SIDIAP, Information System for the Development and Research in Primary Care; T1DM, Type 1 diabetes mellitus; T2DM, Type 2 diabetes mellitus.

TABLE 2 Attrition: total number of canagliflozin new users with type 1 diabetes mellitus (sensitivity definition).

Attrition Steps	CPRD databases		IQVIA databases			SIDIAP
	AURUM	GOLD	Belgium	Italy	Spain	Catalonia Spain
Identify patients with ≥ 1 prescription fill or dispensing for canagliflozin during the study period	37 144	11 076	463	2127	3296	6669
≥ 180 days of observation prior to the exposure to canagliflozin	36 175	10 828	444	2057	3284	6640
≥ 1 diagnosis of T1DM on or before the exposure to canagliflozin	388	128	95	24	189	223
Have no diagnosis of T2DM and no diagnosis of SDM on or after the first T1DM diagnosis	134	70	13	19	39	57
Absence of non-insulin antidiabetic treatment apart from metformin and SGLT2 inhibitor on or after the first T1DM diagnosis	80	21	11	14	27	27
No record of canagliflozin exposure in all prior periods	43	11	8	12	14	13
Record of insulin therapy >90% of observation time from the first T1DM diagnosis until study end	11	6	0	<5	<5	<5

Abbreviations: CPRD, Clinical Practice Research Datalink; SDM, secondary diabetes mellitus; SGLT2, sodium-glucose co-transporter-2; SIDIAP, Information System for the Development and Research in Primary Care; T1DM, Type 1 diabetes mellitus; T2DM, Type 2 diabetes mellitus.

the respective definitions. During the study period, the number of new users of canagliflozin with T1DM was consistently low in all six databases. Across the databases, using the primary definition, between nil new users (out of 463 in the IQVIA-Belgium database) and five new users (out of 37 144 in the CPRD AURUM database) were identified to be patients with T1DM. Using the sensitivity definition, between nil new users and 11 new users, respectively, were identified to be patients with T1DM.

3.2 | Drug utilization and patient baseline demographics and characteristics

Given the low numbers of new canagliflozin users with T1DM that were identified in the six databases, the data on drug utilization are only descriptive and should be interpreted with caution. Using the primary definition, canagliflozin prescribing in patients with T1DM

varied across databases: the median number of prescriptions ranged from eight (range: 1 to 15, IQVIA-Italy) to 20 (range: 15 to 25, SIDIAP); the median total days of supply ranged from 376 (range: 1 to 751, IQVIA-Italy) to 1210 (range: 671 to 1749, SIDIAP) days; and the median days of continuous treatment after the first prescription ranged from 197 (range: 79 to 606, CPRD GOLD) to 1210 (range: 671 to 1749, SIDIAP) days (Table 3). Similar results were reported across the databases using the sensitivity definition for T1DM (Table 4).

Regarding patient baseline demographics and clinical characteristics, across the databases, the majority of data were censored due to low counts of patients, or there were no new users of canagliflozin with T1DM identified. Using the primary and sensitivity definitions, very few new canagliflozin users with T1DM had prespecified conditions relating to diabetes, were exposed to non-insulin diabetic medications, or had undergone major surgeries within 180 days prior to the first exposure to canagliflozin (data not shown).

TABLE 3 Drug utilization among canagliflozin new users with type I diabetes mellitus (primary definition).

Drug utilization characteristics	CPRD databases		IQVIA databases			SIDIAP
	AURUM	GOLD	Belgium	Italy	Spain	Catalonia Spain
N of patients	5	<5	0	<5	<5	<5
Number of prescriptions						
Median	12.0	11.0	N/A	8.0	15.5	20.0
Range	4.0–74.0	2.0–12.0	N/A	1.0–15.0	9.0–22.0	15.0–25.0
Total days of supply						
Median	655.0	587.0	N/A	376.0	515.0	1210.0
Range	109.0–2502.0	79.0–606.0	N/A	1.0–751.0	296.0–734.0	671.0–1749.0
Days of continuous treatment after the first prescription/dispensing						
Median	655.0	197.0	N/A	376.0	515.0	1210.0
Range	109.0–2502.0	79.0–606.0	N/A	1.0–751.0	296.0–734.0	671.0–1749.0

Abbreviations: CPRD, Clinical Practice Research Datalink; LPD, longitudinal patient database; N/A, not applicable; N=Number; SIDIAP, Information System for the Development and Research in Primary Care.

TABLE 4 Drug utilization among canagliflozin new users with type I diabetes mellitus (sensitivity definition).

Drug utilization characteristics	CPRD databases		IQVIA databases			SIDIAP
	AURUM	GOLD	Belgium	Italy	Spain	Catalonia Spain
N of patients	11	6	0	<5	<5	<5
Number of prescriptions						
Median	12.0	11.5	N/A	8.0	22.0	20.0
Range	4.0–74.0	1.0–30.0	N/A	1.0–15.0	9.0–35.0	15.0–25.0
Total days of supply						
Median	522.0	596.5	N/A	376.0	734.0	1210.0
Range	109.0–2502.0	30.0–1074.0	N/A	1.0–751.0	296.0–1126.0	671.0–1749.0
Days of continuous treatment after the first prescription/dispensing						
Median	522.0	401.5	N/A	376.0	734.0	1210.0
Range	109.0–2502.0	30.0–1074.0	N/A	1.0–751.0	296.0–1126.0	671.0–1749.0

Abbreviations: CPRD, Clinical Practice Research Datalink; LPD, longitudinal patient database; N, Number; N/A, not applicable; SIDIAP, Information System for the Development and Research in Primary Care.

No new canagliflozin users with T1DM (using either the primary or sensitivity definitions) had DKA recorded after initiation of canagliflozin in the CPRD GOLD, the three IQVIA and the SIDIAP databases. In the CPRD AURUM database, using either the primary or sensitivity definitions, <5 but >0 new canagliflozin users with T1DM had a DKA event recorded after the index date. The hospital episode statistics linkage files associated with the CPRD databases were also reviewed for DKA events. Among these data, no new canagliflozin users with T1DM, identified using either the primary or sensitivity definitions, had a DKA event recorded after the initiation of canagliflozin treatment.

3.3 | Overall and annual prevalence of canagliflozin users with T1DM

For each database, the denominator for the prevalence calculation was all canagliflozin users (inclusive of T1DM, T2DM and unspecified

patients). Using the primary definition, from 2016 to 2022, the overall prevalence of users with T1DM among all canagliflozin users was 0.000% (0 out of 444) in the IQVIA-Belgium database, 0.017% (6 out of 36 175) in the CPRD AURUM database, and 0.055% (6 out of 10 828) in the CPRD GOLD database. In the IQVIA-Italy, IQVIA-Spain, and SIDIAP databases, since the number of canagliflozin users with T1DM was censored, the overall prevalence could not be calculated.

Using the sensitivity definition, the overall prevalence was 0.000% (0 out of 444) in the IQVIA-Belgium database, 0.102% (11 out of 10 828) in the CPRD GOLD database, 0.053% (19 out of 36 175) in the CPRD AURUM database, and 0.152% (5 out of 3284) in the IQVIA-Spain database. In the IQVIA-Italy and SIDIAP databases, since the number of canagliflozin users with T1DM was censored, the overall prevalence could not be calculated. In all databases, due to low counts of users with T1DM and data censorship, the demographic breakdown of overall prevalence and annual prevalence could not be calculated in full (data not shown).

3.4 | Overall and annual incidence of new canagliflozin users with T1DM

For each database, the denominator for the incidence calculation was all new canagliflozin users (inclusive of T1DM, T2DM and unspecified patients). Using the primary definition, the overall incidence of new users with T1DM among all new canagliflozin users ranged from 0.000% (0 out of 379) in the IQVIA-Belgium database to 0.018% (5 out of 28 236) in the CPRD AURUM database. In the CPRD GOLD, IQVIA-Italy, IQVIA-Spain, and SIDIAP databases, since the number of new users with T1DM was censored, the overall incidence could not be calculated.

Using the sensitivity definition, the overall incidence was 0.000% (0 out of 379) in the IQVIA-Belgium database, 0.039% (11 out of 28 236) in the CPRD AURUM database, and 0.068% (6 out of 8850) in the CPRD GOLD database. In the IQVIA-Italy, IQVIA-Spain and SIDIAP databases, since the number of new users with T1DM was censored, the overall incidence could not be calculated. In all databases, due to low counts of new users with T1DM and data censorship, the demographic breakdown of overall incidence and annual incidence could not be calculated in full (data not shown).

3.5 | Time-trend analysis

The originally planned time-trend analysis of the annual prevalence and incidence in each database was not feasible given that the data were either zero or censored.

4 | DISCUSSION

This observational, retrospective cohort study, using real-world data from Belgium, Italy, Spain and the United Kingdom, showed that the off-label use of canagliflozin in patients with T1DM is rare. This was consistent regardless of which criteria (primary or sensitivity definitions) were used to identify patients with T1DM.

Similar to our study, other studies of real-world data from large medical record databases have reported that off-label use of SGLT2 inhibitors in patients with T1DM was rare. The first real-world study evaluated data from the TRiNetX, a global collaborative network that provides access to real-time electronic medical records primarily from North America and Western Europe.³ A total of 196 691 patients with T1DM was identified in the database, of which only 992 (0.5%) received a SGLT2 inhibitor. In addition, an analysis of the Diabetes Prospective Follow-up Registry, Diabetes-Patienten-Verlaufsdokumentation (DPV) that contains real-world data from participating centres in Germany, Austria and Switzerland, also found that the off-label use of SGLT2 inhibitors was rare.¹¹ During the period of 2012 to 2020, a total of 50 795 patients with T1DM was identified, and among these, only 431 (<1%) were treated with a SGLT2 inhibitor. Similarly, an analysis of data from the United States T1D Exchange Registry, a multi-institutional consortium of clinical and patient-reported data, found that off-label

use of a SGLT2 inhibitor occurred in <3% of patients with T1DM.²⁸ Within the registry, 204 patients with T1DM were identified to be treated with a SGLT2 inhibitor, while 7124 were not. The SGLT2 inhibitors used included canagliflozin (50%), dapagliflozin (27%) and empagliflozin (27%).

In our study, the overall off-label use of canagliflozin in T1DM during the period from 2016 to 2022 was rare and this finding was consistent across the six databases. The annual prevalence and incidence could not be estimated for most of the individual calendar years and, therefore, the trend of prevalence and incidence over time could not be determined. However, it is reasonable to conclude that the potential off-label use of canagliflozin in patients with T1DM has been consistently low from year to year over the study period. Thus, the approval (2019)^{4,5} and withdrawal (2021–2022)^{6,7} of other SGLT2 inhibitors for treatment of T1DM did not seem to have meaningful impact on the low use pattern of canagliflozin in patients with T1DM.

Our study also found that among new canagliflozin users with T1DM, DKA events were rarely observed. However, this finding should be interpreted with caution given the very low number of new canagliflozin users with T1DM identified in the six databases and the limitations of these databases in identifying DKA events. No inferences can be drawn from the data regarding DKA rates. Similar to our finding, the analysis of data from the Diabetes Prospective Follow-up Registry DPV found that none of the 431 patients with T1DM treated with a SGLT2 inhibitor had a DKA event in the year before or during the 12 months of treatment.¹¹

A unique feature and strength of this study was its implementation as a federated network study. In this approach, multiple organizations collaborate on an observational study without the need to share their raw data. Data sharing is unnecessary because all participating databases have standardized their data to the OMOP CDM. This standardization allows institutions to maintain control over their own data while still contributing to a unified analysis. This study utilized a single code set that ran across all databases, which enhanced accuracy, consistency and reproducibility. With a single code set, institutions do not need to independently develop the study statistical analysis plan, which minimized variability. This single code set also ensured consistency in reporting output by generating all necessary reporting elements.

This study is subject to several limitations inherent in observational database research. First and foremost, misclassification is a concern in all studies utilizing real-world databases. The data analysed in this study were collected primarily for administrative purposes, which means there was no standardized methodology in place to ensure the accuracy of recorded clinical conditions, drug exposures and other relevant covariates. Moreover, it is assumed that patients receiving prescriptions or dispensations of certain medications have adhered to their prescribed regimen; however, there is no reliable way to verify this adherence.

Second, due to limitations inherent in the CPRD databases, the days of drug supply are often unavailable and are imputed based on other available data. This limitation may influence patient identification, particularly when applying our criterion requiring patients with

T1DM to have at least 90% of time exposed to insulin during the study period. It also may influence our characterization of the duration of canagliflozin treatment. Nevertheless, we believe that the risk of significant bias is minimal, given the validated methodology.¹⁶

Third, the databases utilized in this study capture only the information recorded during routine clinical practice, primarily from GPs, leaving out critical information related to care provided by specialists. Specifically, as DKA events often necessitate emergency visits or hospitalization for treatment, relying solely on diagnosis codes recorded during GP visits may lead to an underestimation of the actual occurrence of these events. Given this limitation, DKA events were assessed only as exploratory analysis in this study.

Fourth, the databases utilized in this study are geographically specific, and the findings should be interpreted within the context of the countries where the analysis was performed. While other countries, such as the United States represented in the Merative™ MarketScan® Commercial Database, may provide larger patient populations,²⁹ this current study concentrated exclusively on European data and provided real-world evidence in this setting specifically.

Fifth, the possibility of misclassification of T1DM versus T2DM remains in this study despite that two definitions were used to identify T1DM. This is potentially due to the different clinical practices in the four European countries. In addition, the existence of inconsistent or incomplete data may vary by databases, potentially leading to misclassification of T1DM versus T2DM. However, given the finding of low prevalence and incidence in all databases, using both definitions, the potential misclassification is expected to have limited impact on the conclusion that off-label use of canagliflozin in T1DM is rare.

Lastly, to maintain confidentiality, all the databases required censoring when low counts (>0 and <5) of patients occurred. Due to low patient counts across various outcomes analysed in this study, including patient demographics and characteristics, clinical measurements, DKA events, and overall and annual prevalence and incidence, results from some databases had to be censored. While censorship was necessary to maintain confidentiality, it added uncertainty to our interpretations of the analysis results.

In conclusion, based on the analyses of real-world data from the six databases in Belgium, Italy, Spain and the UK, the use of canagliflozin for patients with T1DM in a European setting during the study period was rare.

AUTHOR CONTRIBUTIONS

EAV, ZY and LW contributed to the study design, conducted the research and performed the analysis. SRA and CJ developed important intellectual content and contributed to the interpretation of data. SF developed important intellectual content. RB made contributions to the study design, statistical analysis plan and interpretation of data. EE made substantial contributions to the interpretation of the data. JB conducted the research, statistical programming and data extraction, generation and analysis. BV conducted the analysis and contributed to the interpretation of data. BFC contributed to the interpretation of data. SFB conducted the data conversion of the SIDIAP database and ensured the correct interpretation of and use of the transformed data.

LW had primary responsibility for the final content and all authors developed, reviewed and approved the final content.

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CONFLICT OF INTEREST STATEMENT

EAV, ZY, SRA, SF, CJ and LW are employees of Johnson & Johnson and shareholders of Johnson & Johnson stock. RB, EE and JB are employees of IQVIA, Inc., which provides contract research services to Johnson & Johnson. BV, BFC and SFB have no conflicts of interest associated with this study.

PEER REVIEW

The peer review history for this article is available at <https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/dom.16574>.

DATA AVAILABILITY STATEMENT

Data from CPRD and IQVIA are available via license. Outside the license data previously described, this study was performed as a federated network study, meaning the data remained with the data partner (SIDIAP). Individual organizations would need to be contacted in order to gain access to those data assets.

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