SGLT2 Inhibitors Increase the Risk of Diabetic Ketoacidosis Developing in the Community and During Hospital Admission

Peter S. Hamblin,[1,2] Rosemary Wong,[3] Elif I. Ekinci,[4,5] Spiros Fourlanos,[6,7] Sonali Shah,[8] Alicia R. Jones,[1] Matthew J. L. Hare,[9] Genevieve L. Calder,[10] Dilan Seneviratne Epa,[10] Elizabeth M. George,[11] Rinky Giri,[12,13] Mark A. Kotowicz,[11,14] Mervyn Kyi,[6,7] Nicole Lafontaine,[3] Richard J. MacIsaac,[10,15] Brendan J. Nolan,[4,16] David N. O'Neal,[12,15] Debra Renouf,[17,18] Suresh Varadarajan,[16] Jennifer Wong,[8] Sylvia Xu,[17] and Leon A. Bach[9,19]

[1]Department of Endocrinology and Diabetes, Western Health, St. Albans, Victoria 3021, Australia; [2]Department of Medicine, Western Precinct, University of Melbourne, St Albans, Victoria 3021, Australia; [3]Department of Endocrinology and Diabetes, Eastern Health, Box Hill, Victoria 3128, Australia; [4]Department of Endocrinology, Austin Health, Heidelberg, Victoria 3084, Australia; [5]Department of Medicine, Austin Health, University of Melbourne, Heidelberg 3084, Australia; [6]Department of Diabetes and Endocrinology, Royal Melbourne Hospital, Parkville, Victoria 3050, Australia; [7]Department of Medicine, Royal Melbourne Hospital, University of Melbourne, Parkville, Victoria 3050, Australia; [8]Department of Endocrinology and Diabetes, Monash Health, Clayton, Victoria 3168, Australia; [9]Department of Endocrinology and Diabetes, Alfred Health, Melbourne, Victoria 3004, Australia; [10]Department of Diabetes and Endocrinology, St. Vincent's Hospital Melbourne, Fitzroy, Victoria 3065, Australia; [11]Department of Endocrinology and Diabetes, University Hospital Geelong, Barwon Health, Geelong, Victoria 3220, Australia; [12]Werribee Mercy Hospital, Werribee, Victoria 3030, Australia; [13]Diabetes Technology Research Group, St. Vincent's Hospital Melbourne, Fitzroy, Victoria 3065, Australia; [14]School of Medicine, Faculty of Health, Deakin University, Geelong, Victoria 3220, Australia; [15]Department of Medicine, St. Vincent's Hospital Melbourne, University of Melbourne, Fitzroy, Victoria 3065, Australia; [16]Department of Endocrinology and Diabetes, Northern Health, Epping, Victoria 3076, Australia; [17]Department of Endocrinology and Diabetes, Peninsula Health, Frankston, Victoria 3199, Australia; [18]Peninsula Clinical School, Monash University, Frankston, Victoria 3199, Australia; and [19]Department of Medicine, Central Clinical School, Monash University, Melbourne, Victoria 3004, Australia

ORCiD numbers: 0000-0002-6280-865X (P. S. Hamblin); 0000-0003-2372-395X (E. I. Ekinci); 0000-0002-5153-8324 (S. Fourlanos); 0000-0002-8094-1411 (M. A. Kotowicz); 0000-0001-8058-6977 (R. J. MacIsaac); 0000-0002-9062-1518 (L. A. Bach).

Context: Diabetic ketoacidosis (DKA) has been associated with the use of sodium glucose cotransporter 2 inhibitors (SGLT2is).

Objective: To determine the incidence, characteristics, and outcomes of DKA in SGLT2i users vs nonusers with type 2 diabetes.

Design: Retrospective, multicenter, controlled cohort study.

Setting: All public hospitals in Melbourne and Geelong (combined population of 5 million), Australia, from 1 September 2015 to 31 October 2017.

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in USA

Received 18 January 2019. Accepted 27 February 2019.
First Published Online 5 March 2019

Abbreviations: ADA, American Diabetes Association; DHS, Department of Human Services; DKA, diabetic ketoacidosis; eGFR, estimated glomerular filtration rate; ICD-10, *International Statistical Classification of Diseases and Related Health Problems*, *Tenth Revision*; ICU, Intensive Care Unit; IQR, interquartile range; LADA, latent autoimmune diabetes in adults; NDSS, National Diabetes Services Scheme; PBS, Pharmaceutical Benefits Scheme; RPBS, Repatriation Pharmaceutical Benefits Scheme; SGLT2i, sodium glucose cotransporter 2 inhibitor.

Patients: Consecutive cases of DKA that developed in the community, or during the course of hospital admission, in patients with type 2 diabetes

Main Outcome Measures: In SGLT2i users vs nonusers: (i) OR of DKA developing during hospital admission, and (ii) incidence of DKA.

Results: There were 162 cases of DKA (37 SGLT2i users and 125 non-SGLT2i users) with a physician-adjudicated diagnosis of type 2 diabetes. Of these, DKA developed during the course of inpatient admission in 14 (38%) SGLT2i users vs 2 (2%) non-SGLT2i users (OR, 37.4; 95% CI, 8.0 to 175.9; $P < 0.0001$). The incidence of DKA was 1.02 per 1000 (95% CI, 0.74 to 1.41 per 1000) in SGLT2i users vs 0.69 per 1000 (95% CI, 0.58 to 0.82 per 1000) in non-SGLT2i users (OR, 1.48; 95% CI, 1.02 to 2.15; $P = 0.037$). Fifteen SGLT2i users (41%) had peak blood glucose <250 mg/dL (14 mmol/L) compared with one (0.8%) non-SGLT2i user ($P < 0.001$).

Conclusions: SGLT2i users were more likely to develop DKA as an inpatient compared with non-SGLT2i users. SGLT2i use was associated with a small but significant increased risk of DKA. (***J Clin Endocrinol Metab*** **104: 3077–3087, 2019)**

Sodium glucose cotransporter 2 inhibitors (SGLT2is) have changed the management of type 2 diabetes, especially for those with established cardiovascular disease. The potential risk of diabetic ketoacidosis (DKA), first highlighted in 2015 with a Food and Drug Administration safety warning (1), remains a concern. The pathophysiology of SGLT2i-associated DKA is not fully understood but relates in part to an elevated glucagon/insulin ratio favoring lipolysis (2, 3). SGLT2is decrease insulin requirements by decreasing blood glucose concentrations as they promote glycosuria. Moreover, insulin concentrations may be further decreased by acute reductions in carbohydrate intake such as occur during fasting (4). Additionally, it has been suggested that SGLT2is may reduce renal excretion of ketones (5) and increase ketone production (6).

Whereas several studies found no increased risk of DKA with SGLT2i use (7–9), others have reported an increase (10–15). The totality of the peer-reviewed literature, as well as data analyses by regulatory agencies, supports the conclusion that there is some degree of increased risk of DKA in SGLT2i users with type 2 diabetes.

The incidence, presentation, and detailed risk factors of SGLT2i-associated DKA have not been compared with patients with type 2 diabetes who developed DKA, but were not using SGLT2is. Additionally, the OR of developing DKA during the course of hospital admission in SGLT2i users compared with nonusers has not been reported.

To address these issues, we undertook a large retrospective multicenter, controlled, physician-adjudicated cohort study across all public hospitals in the cities of Melbourne and Geelong, with a combined population of 5 million, in the state of Victoria, Australia.

Methods

Eleven public hospital networks serve Melbourne and Geelong, with each network managing up to five acute hospitals. A retrospective medical records audit was conducted at each of these networks to collect data from all episodes of DKA in type 2 diabetes associated with the use of SGLT2is in the 26-month period from 1 September 2015 to 31 October 2017. Only patients with physician-adjudicated type 2 diabetes and verified DKA (either presenting to the emergency department with DKA or where DKA developed during the course of the hospital admission) were included. SGLT2i nonusers with verified DKA and physician-adjudicated type 2 diabetes were used as a comparator group. The study was approved by each of the hospital networks' Human Ethics Committees.

To maximize the likelihood of capturing all relevant cases of DKA, the initial search criteria were very broad. The Health Information Service at each site searched for multiple diagnoses according to the *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* (ICD-10), Australian Modification codes (Table 1).

Every medical record was then individually examined by study physicians to confirm that a history of type 2 diabetes was recorded in the medical notes and that DKA was present as defined by the American Diabetes Association (ADA) criteria (blood pH <7.30, HCO_3 ≤18 mmol/L, and elevated ketones) (16). In view of the recognized phenomenon of "euglycemic" DKA with SGLT2is, patients (both users and nonusers of SGLT2i) who had blood glucose concentrations <250 mg/dL (14 mmol/L) were also included when they met the other criteria (17). The cohort-defining event was a diagnosis of DKA, and thus the index date was the date of diagnosis of DKA. Although it was theoretically possible for an individual patient to enter the cohort more than once, no such cases were identified during the audit period. Patients were excluded when the admission diagnosis was type 1 diabetes or diabetes caused by chronic pancreatitis, or when ADA criteria for DKA were not met. Duplicate entries covering the same admission were also excluded.

Each DKA case was further examined to determine whether the diagnosis of type of diabetes changed from type 2 diabetes to type 1, latent autoimmune diabetes in adults (LADA), or

Table 1. Diagnostic Codes Searched: ICD-10, Australian Modification

ICD-10 Code	Diagnosis
E1010	Type 1 diabetes mellitus with ketoacidosis without coma
E1012	Type 1 diabetes mellitus with ketoacidosis with coma
E1015	Type 1 diabetes mellitus with ketoacidosis/lactic acidosis without coma
E1016	Type 1 diabetes mellitus with ketoacidosis/lactic acidosis with coma
E1111	Type 2 diabetes mellitus with ketoacidosis, without coma
E1112	Type 2 diabetes mellitus with ketoacidosis, with coma
E1115	Type 2 diabetes mellitus with ketoacidosis/lactic acidosis, without coma
E1116	Type 2 diabetes mellitus with ketoacidosis/lactic acidosis with coma
E1311	Other specified diabetes mellitus with ketoacidosis, without coma
E1312	Other specified diabetes mellitus with ketoacidosis, with coma
E1411	Unspecified diabetes mellitus with ketoacidosis, without coma
E1412	Unspecified diabetes mellitus with ketoacidosis with coma
E1415	Unspecified diabetes mellitus with ketoacidosis/lactic acidosis without coma

chronic pancreatitis as a result of investigations and clinical reevaluation during the admission. After excluding cases where the admission diagnosis was changed from type 2 diabetes, the number of confirmed cases with type 2 diabetes DKA was then obtained. Only these cases of physician-adjudicated type 2 diabetes were included in the analyses.

Demographic, clinical, and biochemical data were obtained from each medical record. For those who developed DKA prior to hospital admission, the time from arrival in the emergency department to initiation of insulin therapy was captured. When surgery occurred during the admission, the type of surgery was recorded, and any other potential precipitating factors for the development of DKA were noted, including the presence of infection, myocardial infarction, and stroke. Durations of planned fasting for surgery or procedures, or unplanned fasting, for example due to medical illness, were extracted when these data were available. Medical records and medication charts were examined to extract data regarding the baseline use of insulin, oral hypoglycemic agents, and/or glucagon-like peptide 1 analogs. Deidentified data were transferred to the coordinating center (Western Health) where data from individual sites were merged for analysis.

SGLT2i drugs in Australia are almost entirely obtained on an Australian Government–subsidized basis through the Pharmaceutical Benefits Scheme (PBS) or, for veterans, the Repatriation Pharmaceutical Benefits Scheme (RPBS). These schemes only subsidize SGLT2is for use in people with type 2 diabetes. The two drugs available through PBS/RPBS during the audit period were dapagliflozin (available from 1 December 2013) and empagliflozin (available from 1 January 2015). Canagliflozin was not available during the audit period, but some patients may have had residual supplies, as it had previously been available on the PBS/RPBS from 1 December 2013 to 31 July 2015.

To calculate the incidence of SGLT2i-associated DKA, prescription dispensing data for empagliflozin and dapagliflozin, either as single agents or in fixed dose combinations with metformin, in the Greater Melbourne and Geelong areas during the audit period were obtained from the Australian Government Department of Human Services (DHS). Unique patient data were obtained to prevent double counting if, for example, a patient started using an SGLT2i and then subsequently changed to a fixed dose combination prescription of SGLT2i and

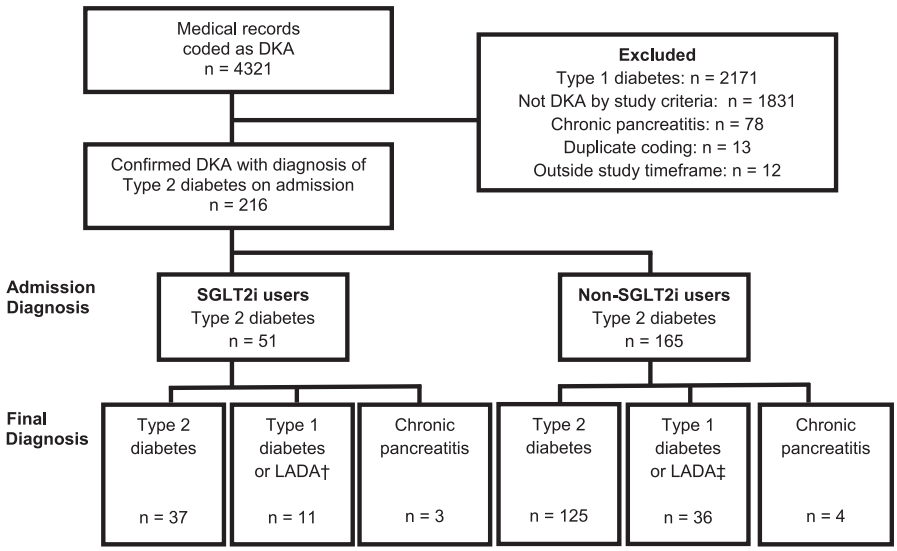

Figure 1. Flowchart of DKA cases in 26-mo audit period. †As a result of DKA admission, 11 of 51 patients previously diagnosed with type 2 diabetes had a change in diagnosis to type 1 diabetes or LADA. Nine had positive anti–glutamic acid decarboxylase (GAD) antibodies and the other two were reassessed by their treating physicians as having type 1 diabetes. ‡As a result of DKA admission, 36 of 165 patients previously diagnosed with type 2 diabetes had a change in diagnosis to type 1 diabetes or LADA. Twenty had positive anti-GAD antibodies and the other 16 were reassessed by their treating physicians as having type 1 diabetes.

Table 2. Characteristics of Patients With DKA

	SGLT2i (n = 37)	Non SGLT2i (n = 125)	*P* Value
Age, y	64 (52, 71)	65 (53, 77)	0.22
Male, n (%)	20 (54)	74 (59)	0.58
Ethnicity, n (%)	(n = 36)	(n = 120)	0.42
White	27 (75)	95 (80)	
Asian	7 (19)	12 (10)	
African	2 (6)	7 (6)	
Pacific Islander	0 (0)	3 (3)	
Indigenous Australian	0 (0)	3 (3)	
Duration of diabetes, y	15 (9, 22) (n = 31)	15 (6, 20) (n = 98)	0.42
Body mass index, kg/m^2	28.7 (23.7, 32.2) (n = 20)	26.9 (23.9, 30.9) (n = 64)	0.96
HbA1c			<0.001
HbA1c, %	9.3 ± 2.1 (n = 36)	11.9 ± 2.7 (n = 112)	
HbA1c, mmol/mol	78 ± 23	107 ± 29	
Diabetes medications, n (%)			
SGLT2i	37 (100)	0 (0)	
Dapagliflozin	18 (49)		
Empagliflozin	18 (49)		
Canagliflozin	1 (3)		
Insulin	24 (65)	70 (56)	0.45
Metformin	32 (87)	81 (65)	0.014
Sulfonylurea	7 (19)	28 (22)	0.82
DPP4 inhibitor	6 (16)	14 (11)	0.40
GLP-1 analog	2 (5)	1 (1)	0.13
Thiazolidinedione	1 (3)	2 (2)	0.54
α-Glucosidase inhibitor	2 (5)	1 (1)	0.13
Duration SGLT2i use, d			
Median	90 (36, 365) (n = 19)	Not applicable	
Range	4–420		

Results are shown as n (%) and mean ± SD or median (IQ range) when not normally distributed.

Abbreviations: DPP4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide 1.

metformin. The DHS data did not indicate duration of SGLT2i therapy or medication adherence. Data were suppressed for smaller geographical locations within Melbourne and Geelong where fewer than six prescriptions were dispensed, as part of DHS policy to preserve patient confidentiality. The data release was approved by the DHS External Request Evaluation Committee.

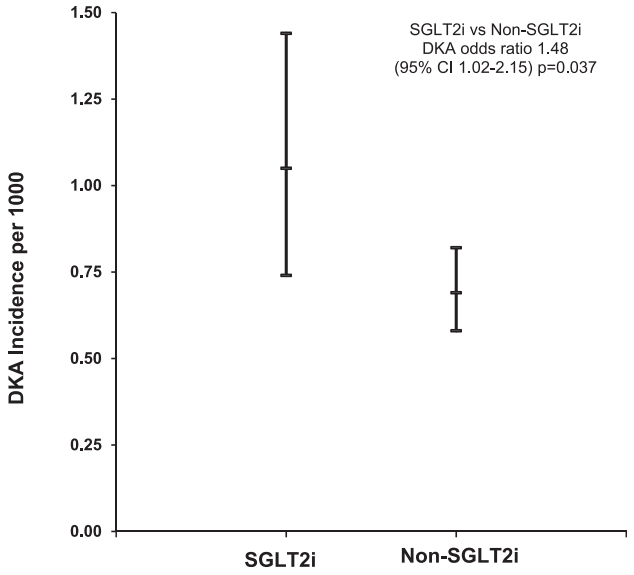

Figure 2. Incidence of DKA in confirmed type 2 diabetes in those exposed to dapagliflozin and empagliflozin and those unexposed (95% CI) during a 26-mo audit period. Confirmed type 2 diabetes cases were determined after reevaluation during the hospital admission.

The number of people living in the Greater Melbourne and Geelong areas registered as having type 2 diabetes with the National Diabetes Services Scheme (NDSS) was obtained from publicly available sources (18). The NDSS, an initiative of the Australian Government, delivers education and information services to people with diabetes and also provides a range of diabetes products at a subsidized cost. Although registration is voluntary, a large community diabetes study in Fremantle, Western Australia, reported that 87.4% of respondents stated they were registered (19).

The number of people with type 2 diabetes who were not being treated with SGLT2is was then estimated by subtracting the number of unique SGLT2i users (as ascertained from the DHS data) from the total number of people registered with type 2 diabetes. The number of nonusers of SGLT2i includes all people registered with type 2 diabetes treated with any non-SGLT2i diabetes medication or diet alone. The incidences of type 2 diabetes DKA in SGLT2i and non-SGLT2i users were then assessed. Incidence data have not been reported in patient-years, as the duration of medication exposure for either of the two groups was not precisely known.

Statistical analysis

Results are shown as mean ± SD when data were normally distributed or median (interquartile range) when not. Continuous variables were analyzed using unpaired *t* tests not assuming equal variances when data were normally distributed,

Table 3. Biochemical and Hospital Stay Characteristics

	SGLT2i (n = 37)	Non-SGLT2i (n = 125)	*P* Value
Timing of DKA development, n (%)			<0.001
Preadmission	23 (62)	123 (98)	
During inpatient stay	14 (38)	2 (2)	
Time (min) from arrival in ED until insulin started for preadmission DKA (SGLT2i, n = 21; non-SGLT2i, n = 110)	230 (62, 300)	114 (60, 240)	0.21
Range	14–1260	10–2040	
Length of inpatient stay, d	9 (5, 18)	7 (4, 13)	0.11
Range	2–83	1–62	
ICU admission, n (%)	25 (68)	64 (51)	0.092
ICU length of stay, d	2 (0, 3)	1 (0, 3)	0.55
Deaths, n (%)	2 (5)	11 (9)	0.73
Lowest pH	7.21 (7.13, 7.25)	7.16 (7.07, 7.26)	0.26
Lowest bicarbonate, mmol/L	11 (6, 14)	11 (7, 15)	0.76
Peak blood glucose, mg/dL	282 (213, 377)	594 (487, 773) (n =123)	<0.001
(mmol/L)	15.7 (11.8, 20.9)	33.0 (27.0, 42.9)	
Peak blood glucose <250 mg/dL (14 mmol/L), n (%)	15 (41)	1 (0.8) (n = 123)	<0.001
Peak β-hydroxy butyrate, mmol/L	5.9 (4.4, 6.5)	5.6 (4.4, 6.9)	0.94
Time to resolution of ketosis (β-hydroxybutyrate <0.6 mmol/L), d	1.0 (1.0, 2.0)	1.0 (1.0, 2.0) (n =113)	0.16
Recurrence of ketosis (β-hydroxybutyrate ≥2 mmol/L after falling to <0.6 mmol/L), n (%)	5 (14)	17 (15) (n =116)	1.0
Number of recurrent episodes of elevated β-hydroxybutyrate (after initial return to normal)	2 (1, 2.5) (n = 5)	1 (1, 2) (n = 17)	0.377
Lowest eGFR, mL/min/1.73 m^2	62 (51, 90)	41 (29, 59) (n = 122)	<0.001
Peak lactate, mmol/L	2.1 (1.6, 3.4) (n = 36)	2.7 (2.0, 4.2) (n = 124)	0.16
SGLT2i recommenced (SGLT2i users) or initiated (in non-SGLT2i users), n (%)	8 (22)	4 (3)	

Results are shown as n (%) and median (IQR).

Abbreviation: ED, Emergency Department.

or Mann–Whitney tests when they were not. The 2 × 2 contingency tables were analyzed using a two-sided Fisher's exact test. Other categorical data were analyzed using χ^2 tests. ORs were calculated from incidence data. Analyses were performed using IBM SPSS Statistics version 25 or MedCalc Software (https://www.medcalc.org/calc/odds_ratio.php).

Results

The search of the ICD-10 codes yielded 4321 medical records (Fig. 1). After exclusion of cases of type 1 diabetes, diabetes due to chronic pancreatitis, misclassifications, and where the diagnosis changed from type 2 diabetes as a result of the admission, there remained 37 patients with a final diagnosis of type 2 diabetes in SGLT2i users and 125 in non-SGLT2i users (Fig. 1). A similar proportion of patients in each group had a change in diagnosis of diabetes type as a result of the DKA admission: 11 (22%) SGLT2i users and 36 (22%) non-SGLT2i users changed from type 2 diabetes to either type 1 diabetes or LADA. There were no differences in the proportions having positive glutamic acid decarboxylase or tyrosine phosphatase–related islet antigen 2 antibodies, or low C-peptide concentrations. All SGLT2i users had continued to take SGLT2i up to the day of hospital admission, with 14 (38%) continuing to take SGLT2i during the inpatient admission.

The characteristics of the SGLT2i users and nonusers are shown in Table 2. HbA1c was significantly lower in SGLT2i users [9.3% ± 2.1% (78 ± 23 mmol/mol)] compared with nonusers [11.9% ± 2.7% (107 ± 29 mmol/mol), $P < 0.001$]. There were no differences in age, sex, ethnicity, body mass index, duration of diabetes, or co-prescribed diabetes medications between SGLT2i users and non-SGLT2i users, with the exception of metformin, which was prescribed in 32 (87%) SGLT2i users and 81 (65%) non-SGLT2i users ($P < 0.001$). The duration of SGLT2i use was only documented in the medical records for 19 of the 37 SGLT2i cases. The median duration was 90 days [interquartile range (IQR), 36 to 365] with a range of 4 to 420 days. Dapagliflozin was used in 18 cases (49%), empagliflozin in 18 (49%), and canagliflozin in 1 (3%).

The total number of unique individuals in Melbourne and Geelong with at least one prescription dispensed for either dapagliflozin or empagliflozin was 35,294, and the total number of NDSS registrants with type 2 diabetes was 217,164. The estimated number of non-SGLT2i users was therefore 181,870. Using these figures, the incidence of DKA in patients with a final diagnosis of type 2 diabetes was 1.02 per 1000 (95% CI, 0.74 to 1.41 per 1000) in SGLT2i users and 0.69 per 1000 (95% CI, 0.58 to 0.82 per 1000) in non-SGLT2i users, resulting in an OR of DKA in

Table 4. Characteristics of the SGLT2i Users and Nonusers Who Developed DKA as Inpatients

SGLT2i	Age	Sex	Duration diabetes (y)	Duration SGLT2i Use (d)	HbA1c % (mmol/mol) During Admission	Inpatient Day DKA Diagnosed
Dapagliflozin	55	F	15	Not documented	9.4 (79)	3
Dapagliflozin	63	M	13	90	7.4 (57)	8
Dapagliflozin	60	F	40	Not documented	10.5 (91)	4
Empagliflozin	69	F	15	Not documented	7.2 (55)	1 (12 h postoperatively)
Empagliflozin	66	F	20	41	6.6 (49)	1 (6 h postoperatively)
Dapagliflozin	47	M	6	365	8.9 (74)	12
Empagliflozin	70	M	Not documented	Not documented	6.7 (50)	3
Empagliflozin	73	F	9	210	7.5 (58)	4
Canagliflozin	48	F	19	420	7.0 (52)	3
Dapagliflozin	40	M	6	Not documented	8.3 (67)	7
Empagliflozin	72	F	11	68	5.9 (41)	3
Empagliflozin	74	F	31	365	7.1 (54)	4
Dapagliflozin	78	M	Not documented	Not documented	8.0 (64)	3
Empagliflozin	70	F	30	Not documented	6.7 (50)	3
Not SGLT2i treated	82	M	Not documented	Not Applicable	7.1 (54)	3
Not SGLT2i treated	80	F	30	Not Applicable	6.9 (52)	3

(*Continued*)

SGLT2i users of 1.48 (1.02 to 2.15), $P = 0.037$ (Fig. 2). DKA incidence was similar in the context of dapagliflozin (1.03 per 1000) or empagliflozin (1.01 per 1000) use.

Peak blood glucose concentration was significantly lower in SGLT2i users (median, 282 mg/dL [IQR, 213 to 377] [15.7 mmol/L (IQR, 11.8 to 20.9)] vs 594 mg/dL [IQR, 487 to 773] [33.0 mmol/L (IQR, 27.0 to 42.9)], $P < 0.001$, Table 3), and more SGLT2i users had a peak blood glucose <250 mg/dL (14 mmol/L) than did non-SGLT2i users [15 (41%) vs 1 (0.8%), $P < 0.001$]. For those who presented to the emergency department, median time to initiation of insulin was 230 minutes (IQR, 62 to 300) in SGLT2i users and 114 minutes (IQR, 60 to 240) in nonusers, but this difference was not statistically significant ($P = 0.21$). There were no differences between the two groups in the severity of acidosis or ketosis, the time for blood β-hydroxybutyrate to normalize, or the number of recurrences of elevated blood ketones after initial return to normal (Table 3). The lowest estimated glomerular filtration rate (eGFR) in the SGLT2i users [median, 62 (IQR, 51 to 90) mL/min/1.73 m^2] was higher than in the non-SGLT2i users [median, 41 (IQR, 29 to 59) mL/min/1.73 m^2, $P < 0.001$]. Blood lactate levels did not differ between the groups. Length of hospital stay was similar in both groups, and there were no differences in the proportion admitted to the Intensive Care Unit (ICU) or length of ICU stay (Table 3).

More SGLT2i users developed DKA during the course of their hospital inpatient stay compared with non-SGLT2i users: 14 (38%) vs 2 (2%), $P < 0.001$ [OR 37.4 (8.0 to 175.9), $P < 0.0001$, Table 3]. All were adjudicated to have type 2 diabetes. Details of these patients are summarized in Table 4. Median blood glucose concentration in the 14 SGLT2i users who developed DKA as inpatients was 243 mg/dL (IQR, 189 to 282) [13.5 mmol/L (IQR, 10.5 to 15.7)] and 457 mg/dL (25.4 mmol/L) in the two non-SGLT2i users. More SGLT2i users had a period of planned fasting [15 (41%) vs 3 (2%), $P < 0.001$, Table 5], mostly related to surgery (13 of the 15 SGLT2i users with a period of planned fasting had surgery, as did two of the three non-SGLT2i users). The proportion of DKA cases with unplanned fasting due to concurrent medical illness was similar in each group (37% of SGLT2i users and 46% of non-SGLT2i users, $P = 0.44$). The most common probable precipitating factor for DKA in non-SGLT2i users was infection, which was present in 51 cases (41%) compared with 10 (27%) in SGLT2i users ($P = 0.18$).

Table 4. Characteristics of the SGLT2i Users and Nonusers Who Developed DKA as Inpatients (Continued)

Surgery	Medical Illness	Fasting	SGLT2i Management During Admission	Insulin Treated Prior to Hospital	Insulin Management as Inpatient Before DKA
Coronary artery bypass	No	Yes	Continued usual dose	Yes	Insulin ceased
Coronary artery bypass	No	Yes	Continued usual dose	Yes	Insulin ceased
Coronary artery bypass	No	Yes	Continued usual dose	Yes	Insulin ceased
Coronary artery bypass	No	Yes	Ceased day of admission	No	No insulin administered
Coronary artery bypass	No	Yes	Ceased day of admission	Yes	Insulin ceased
Pericardial window	Pneumonia	Yes	Continued usual dose	No	No insulin administered
Laparotomy for duodenal perforation	No	Yes	Ceased day of admission	No	No insulin administered
Endoscopic repair of esophagus	No	Yes	Continued usual dose	Yes	Insulin ceased
Craniotomy for middle cerebral artery aneurysm	No	Yes	Continued usual dose	Yes	Insulin reduced
Pancreatic neuroendocrine tumor	No	Yes	Ceased day of admission, restarted day 3 postoperatively	Yes	Insulin ceased
Infected finger washout	No	Yes	Ceased day of admission	Yes	Insulin ceased
No	Subdural hematoma	Yes	Continued usual dose	Yes	Insulin ceased
No	Glucocorticoids; pneumonia	No	Continued usual dose	Yes	Insulin unchanged
No	Carcinoma esophagus	Yes	Ceased day of admission	Yes	Insulin ceased
Colectomy for carcinoma	No	Yes	Not applicable	Yes	Insulin ceased
No	Small bowel obstruction	Yes	Not applicable	Yes	Insulin ceased

Deaths occurred during hospital admission in 2 of 37 (5%) SGLT2i users and 11 of 125 (9%) non-SGLT2i users ($P = 0.73$, Table 3). Only one death (in a non-SGLT2i user) was thought to be directly due to DKA, with the remainder being related to comorbidities. The two deaths in SGLT2i users and one death in non-SGLT2i users were due to cancer. The remaining deaths in non-SGLT2i users were due to sepsis in four, acute myocardial infarction in three, stroke in one, and complications associated with coronary artery bypass graft surgery in one.

Conclusions

Key finding

The novel finding of this study is that the OR of developing DKA as an inpatient was 37.4 (95% CI, 8.0 to 175.9), $P < 0.0001$, in SGLT2i users compared with non-SGLT2i users in those with a final diagnosis of type 2 diabetes. Although previously suspected clinically, to our knowledge this is the first study to quantify this association. Most cases that developed during the admission occurred in the context of surgery and fasting.

Other study findings

First, in keeping with other studies, there was a small but significant increase in absolute risk of DKA associated with SGLT2i use in type 2 diabetes [OR, 1.48 (95% CI, 1.02 to 2.15), $P = 0.037$). The estimates of DKA incidence in SGLT2i users and nonusers did not take into account the duration of exposure to these drugs because of the lack of high-quality data. However, for those who developed DKA either before or during hospital admission, it is likely that the duration of non-SGLT2i use was longer than SGLT2i use, which may lead to an underestimate of the DKA risk associated with SGLT2i. Second, the absolute number of DKA cases in non-SGLTi users was threefold that of SGLT2i users. This is an important finding, as it suggests that clinicians should consider the possibility of DKA in all unwell patients with type 2 diabetes, not just those who are SGLT2i users. Third, 22% of patients who were thought to have type 2 diabetes when initially admitted were reclassified as having type 1 diabetes or LADA in both SGLT2i users and non-SGLT2i users, indicating admission with DKA is an opportunity to question whether a diagnosis of type 2 diabetes is accurate. Fourth, there was no difference in the mortality rate between SGLT2i users and non-SGLT2i users, and death due to DKA itself occurred in only one non-SGLT2i user.

It is noteworthy that the SGLT2i users had a substantially lower mean HbA1c [9.6% (82 mmol/mol) vs 11.9% (107 mmol/mol)], suggesting that the SGLT2i-treated

patients had better chronic glycemic control. In that context, one might have expected them to be less likely to develop ketoacidosis as compared with the non-SGLT2i–treated patients, but this was not the case. A possible explanation is that because these drugs led to better glycemic control, it is more likely that in insulin users their doses were reduced, leading to an increased likelihood of developing DKA.

Another interesting finding was the similarity in severity of acidosis and ketonemia between SGLT2i users and nonusers. This was unexpected given that SGLT2i users often lack the clue of marked hyperglycemia that may prompt testing of ketones and therefore earlier recognition of the diagnosis of DKA.

Comparison with other studies

Studies using the FAERS database (10, 11), although not measuring actual rates of DKA, estimated higher rates of DKA associated with SGLT2i use than was found in this study. Although such databases are very important to detect safety signals, the voluntary nature of reporting may result in potential bias. Our study avoided this by ensuring that we captured every DKA episode managed in all the public hospitals in Melbourne and Geelong, with each case (SGLT2i users and non-SGLT2i users) included only when it satisfied ADA criteria for diagnosis of DKA after careful adjudication by medical staff.

Data from most randomized clinical trials have not demonstrated an increased incidence of DKA in patients with SGLT2i-treated type 2 diabetes (9). The DECLARE study was an exception, demonstrating a hazard ratio for DKA of 2.18 (95% CI, 1.10 to 4.30, $P = 0.02$) (13). Increased incidence rates of DKA were also reported with canagliflozin at 100 mg and 300 mg vs comparator drugs (0.522, 0.763, and 0.238 per 1000 patient-years, respectively), but the diagnosis of DKA was unadjudicated and likely to have been underreported (20). Participants are highly screened and regularly monitored during trials and, unlike our study, they may not necessarily be representative of the population using SGLT2is in the community. Administrative database studies (7, 8) lack granularity in terms of patient characteristics, accuracy of DKA admission diagnoses, and the correct designation of the type of diabetes.

Although DKA in type 2 diabetes is well described (21, 22), increased efforts are needed to ensure that this message reaches the wider medical community. Until recently there were few data available regarding the incidence of non-SGLT2i DKA. In Denmark, the estimated prevalence of DKA in type 2 diabetes, in the era before SGLT2is, was 0.5 to 1.3 per 1000 patient-years depending on the decade of diagnosis (23). Data from a Japanese medical claims database reported an incidence of 0.48 per 1000 patient-years (24).

Consistent with other studies (20, 25), our data show that surgery and fasting represent particular risks for the development of SGLT2i-associated DKA. Other findings from our study in keeping with previous reports included peak blood glucose concentrations that were lower in SGLT2i users, as well as the similar DKA incidences in dapagliflozin and empagliflozin users.

Clinical implications

With the rapidly escalating use of SGLT2is worldwide, it is important for all clinicians and patients to be aware of the risk of developing DKA. Our data support the arguments that these drugs should not be prescribed to inpatients or those who are unwell until they are eating and drinking normally. Note that for most of our study period, no guidelines regarding withholding SGLT2is existed. Guidelines now recommend withholding SGLT2is at least 2 days prior to surgery (26–28), and the results of this study support these recommendations to withhold SGLT2is before major surgery. However, there were no SGLT2i-associated DKA cases linked to day procedures such as gastroscopy, colonoscopy, or coronary angiography in our study. The three minor surgical cases where DKA occurred in SGLT2i users were each complicated by infection: dental abscess in two and an infected finger washout in the third. From review of the medical records, it was not possible to estimate how many SGLT2i users were familiar with "sick day rules." Unfortunately, even with the advent of guidelines and regulatory advice, cases of SGLT2i-associated DKA are still occurring regularly in our hospitals, and therefore the key messages of this study remain relevant.

Nearly all of those who developed DKA as an inpatient were managed with insulin prior to hospital admission. In most cases, insulin was ceased in hospital when patients were fasting, and those involved in patient management may have been falsely reassured by blood glucose levels that were not particularly elevated. This may have contributed to the development of DKA and highlights the need to educate medical staff who are responsible for perioperative diabetes care.

Importantly, also note that there is a significant risk of DKA in type 2 diabetes unrelated to SGLT2i use. These patients had broadly similar demographic, clinical, and biochemical features to SGLT2i users with the notable exceptions of higher HbA1c levels and lower eGFR. The reduced eGFR in non-SGLT2i users may explain the lower use of metformin in that group. Additionally, it is not surprising that SGLT2i users had higher eGFR levels than did non-SGLT2i users, as SGLT2is are not recommended in patients with low eGFR.

Table 5. Fasting Status and Potential Precipitating Factors for the Development of DKA

	SGLT2i (n = 37)	Non-SGLT2i (n = 125)	*P* Value
Period of planned fasting			
Yes, n (%)	15 (41)	3 (2)	<0.001
Duration, h	26.0 (19.5, 48.0)	Insufficient data	
Reason for planned fasting (SGLT2i, n = 15; non-SGLT2i, n = 3)			
Surgery, n (%)	13 (87)	2 (67)	
Nonsurgical reasons, n (%)	2 (13)	1 (33)	
Period of unplanned fasting (SGLT2i, n = 35; non-SGLT2i, n = 122)			
Yes, n (%)	13 (37)	56 (46)	0.44
Duration, h	26 (20, 48)	72 (48, 96)	0.19
Reason for unplanned fasting (SGLT2i, n = 13; non-SGLT2i, n = 56)			
Medical illness, n (%)	12 (92)	55 (98)	
Postoperative nausea, n (%)	1 (8)	1 (2)	
Potential precipitating factors, n (%)			
Surgery	15 (41)	3 (2)	<0.001
Major[a]	12	2	
Minor[b]	3	1	
Infection	10 (27)	51 (41)	0.18
Nonadherence to medication	5 (14)	19 (15)	1.0
Illness (*e.g.*, AMI, stroke)	4 (11)	19 (15)	0.61
Alcohol	1 (3)	5 (4)	1.0
Glucocorticoids	1 (3)	3 (2)	1.0
None apparent	4 (11)	23 (18)	0.33

Results are shown as n (%) and median (IQR). Surgery and infection coexisted in some patients.

Abbreviation: AMI, acute myocardial infarction.

[a]Major surgery included coronary artery bypass, pericardial window, craniotomy, abdominal surgery, thoracotomy, fractured neck of femur, and shoulder surgery.

[b]Minor surgery included: SGLT2i, dental abscess requiring tooth extraction in two patients, infected finger washout in one; non-SGLT2i, carpal tunnel surgery complicated by perioperative myocardial infarction.

It is noteworthy that SGLT2is were restarted after DKA resolution in 22% of SGLT2i users, and SGLT2i were initiated in 4 (3%) nonusers after DKA recovery. This may suggest a lack of physician awareness about the risk of SGLT2i-associated DKA and that ongoing education efforts for medical staff are required. Fortunately, no recurrences of DKA occurred during the audit period.

Strengths/limitations

This is a well-characterized adjudicated cohort study of type 2 diabetes DKA in SGLT2i users. To our knowledge, it is the first detailed clinical study to use non-SGLT2i users as a comparator (as opposed to administrative database studies), which adds considerable strength as well as defining specific characteristics of DKA associated with their use. It comprises a cohort of patients from a range of local and tertiary hospitals reflecting "real-world" clinical experience. The case records of each patient were carefully scrutinized to maximize data availability and minimize inclusion of patients with misclassified diabetes.

There are several methodological limitations of this study. First, limitations inherent in the retrospective design include incomplete data that, however, were proportionately similar for both SGLT2i users and non-SGLT2i users, as well as the issue of unknown and unmeasured confounders. Second, although the vast majority of emergency admissions (92%) in Victoria are managed by public hospitals, 62% of elective surgery is performed in private hospitals (29), so DKA in the perioperative setting could be underreported. Third, it is possible that some of the patients who were adjudicated as having type 2 diabetes may in fact have type 1 diabetes. It was recently reported that 3.5% of people with ketosis-prone diabetes who were negative for traditional type 1 diabetes antibodies were positive for an occult tyrosine phosphatase islet antigen (islet antigen 2) antibody directed against the extracellular domain (30). Fourth, the estimate of the number of people with type 2 diabetes in the community is reliant on NDSS data, which may underestimate the true number of people with type 2 diabetes even though it is the most robust database available in Australia. Our findings are therefore likely to be conservative with respect to the excess risk in patients taking SGLT2is.

In conclusion, SGLT2i users were more likely to develop DKA as an inpatient than non-SGLT2i users. Particular vigilance is necessary in patients who have not

temporarily withheld SGLT2is when potential triggers such as surgery and fasting are present.

Acknowledgments

Author Contributions: P.S.H. designed the study, coordinated the 11 sites, analyzed data, and wrote the manuscript. R.W. helped in the study design, coordinated the local site, and wrote the manuscript. E.I.E. helped in the study design, coordinated the local site, and wrote the manuscript. S.F. coordinated the local site, analyzed the data, and wrote the manuscript. S.S. researched data and helped write the manuscript. A.R.J. helped in the study design, researched data, and critically revised the manuscript. M.J.L.H. helped in the study design, researched data, and critically revised the manuscript. G.L.C. researched data and critically revised the manuscript. D.S.E. researched data and critically revised the manuscript. E.M.G. researched data and critically revised the manuscript. R.G. researched data and critically revised the manuscript. M.A.K. coordinated the local site and critically revised the manuscript. M.K. researched data and critically revised the manuscript. N.L. researched data and critically revised the manuscript. R.J.M. coordinated the local site and critically revised the manuscript. B.J.N. researched data and critically revised the manuscript. D.N.O. coordinated the local site and critically revised the manuscript. D.R. coordinated the local site and critically revised the manuscript. S.V. coordinated the local site and critically revised the manuscript. J.W. coordinated the local site and critically revised the manuscript. S.X. researched data and critically revised the manuscript. L.A.B. designed the study, coordinated the local site, analyzed data, performed the statistical analysis, and wrote the manuscript. All authors gave final approval to publish this manuscript. P.S.H. takes responsibility for the contents of this article.

Correspondence and Reprint Requests: Peter S. Hamblin, Department of Endocrinology and Diabetes, Western Health, 176 Furlong Road, St. Albans, Victoria 3021, Australia. E-mail Peter.Hamblin@wh.org.au.

Disclosure Summary: E.I.E. is an investigator in FIGARO, FIDELIO, Rainbow, T1DGKT137831, and SCORED clinical trials. S.S. has received an educational travel grant from Novo Nordisk. A.R.J. has received an educational travel grant from Novo Nordisk. D.S.E. has received an educational travel grant from Novo Nordisk and meeting registration fee support from Merck Sharp & Dohme. E.M.G. has received an educational travel grant from Novo Nordisk. M.A.K. has received speaker fees from Astra Zeneca, Boehringer Ingelheim, Sanofi, and Novo Nordisk and travel support from Novo Nordisk. R.J.M. has received research grants from Novo Nordisk, Servier, Medtronic, and Grey Innovation. He has received honoraria for lectures from Eli Lilly, Novo Nordisk, Sanofi, Astra Zeneca, Merck Sharp & Dohme, Novartis, and Boehringer Ingelheim and is on the Advisory Boards of the Boehringer Ingelheim–Eli Lilly Diabetes Alliance and Astra Zeneca. He has received travel support from Novo Nordisk, Sanofi, Boehringer Ingelheim, and Astra Zeneca. He has also been a principal investigator for industry-sponsored clinical trials run by Novo Nordisk, Bayer, Janssen, and Abbive. D.N.O. reports Advisory Boards and receiving research support from Sanofi, Novo Nordisk, Abbott, and Medtronic and travel support from Novo Nordisk and Merck Sharp & Dohme. D.R. has received honoraria for talks from Astra Zeneca and Boehringer Ingelheim. S.V. has received honoraria for talks from Astra Zeneca. J.W. has received honoraria for talks from Astra Zeneca, Novo Nordisk, Boehringer Ingelheim, Eli Lilly, Sanofi, and Merck Sharp & Dohme. She has also received a regional support grant from Novo Nordisk. S.X. has received educational travel grants from Novo Nordisk and Merck Sharp & Dohme. L.A.B. was an investigator in DECLARE. The remaining authors have nothing to disclose.

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