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Sodium–Glucose Cotransporter-2 Inhibitors and the Risk for Diabetic Ketoacidosis

A Multicenter Cohort Study

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Background: Sodium–glucose cotransporter-2 (SGLT-2) inhibitors could increase the risk for diabetic ketoacidosis (DKA).

Objective: To assess whether SGLT-2 inhibitors, compared with dipeptidyl peptidase-4 (DPP-4) inhibitors, are associated with an increased risk for DKA in patients with type 2 diabetes.

Design: Population-based cohort study; prevalent new-user design between 2013 and 2018. (ClinicalTrials.gov: NCT04017221)

Setting: Electronic health care databases from 7 Canadian provinces and the United Kingdom.

Patients: 208 757 new users of SGLT-2 inhibitors were matched by using time-conditional propensity scores to 208 757 recipients of DPP-4 inhibitors.

Measurements: Cox proportional hazards models estimated site-specific hazard ratios (HRs) with 95% CIs of DKA comparing receipt of SGLT-2 inhibitors with receipt of DPP-4 inhibitors, which were pooled by using random-effects models. Secondary analyses were stratified by molecule, age, sex, and prior receipt of insulin.

Results: Overall, 521 patients were diagnosed with DKA during 370 454 person-years of follow-up (incidence rate per 1000 person-years, 1.40 [95% CI, 1.29 to 1.53]). Compared with DPP-4 inhibitors, SGLT-2 inhibitors were associated with an increased risk for DKA (incidence rate, 2.03 [CI, 1.83 to 2.25] versus 0.75 [CI, 0.63 to 0.89], respectively; HR, 2.85 [CI, 1.99 to 4.08]). Molecule-specific HRs were 1.86 (CI, 1.11 to 3.10) for dapagliflozin, 2.52 (CI, 1.23 to 5.14) for empagliflozin, and 3.58 (CI, 2.13 to 6.03) for canagliflozin. Age and sex did not modify the association; prior receipt of insulin appeared to decrease the risk.

Limitations: There was unmeasured confounding and no laboratory data were available for the majority of patients, and molecule-specific analyses were conducted at a limited number of sites.

Conclusion: SGLT-2 inhibitors were associated with an almost 3-fold increased risk for DKA, with molecule-specific analyses suggesting a class effect.

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* For a list of the CNODES Investigators, see the **Appendix** (available at Annals.org).

Sodium–glucose cotransporter-2 (SGLT-2) inhibitors are a newer class of medications for type 2 diabetes (1). Randomized controlled trials (RCTs) have demonstrated that they reduce the risk for myocardial infarction, heart failure, renal failure, cardiovascular mortality, and potentially all-cause mortality in patients with type 2 diabetes at high cardiovascular risk (2–5). However, there are several important safety concerns related to their use, including a possible increased risk for diabetic ketoacidosis (DKA), a potentially fatal diabetic complication (6).

In 2015, the U.S. Food and Drug Administration issued a safety warning on the risk for DKA with SGLT-2 inhibitors on the basis of spontaneous reports (6). In addition, RCTs have linked SGLT-2 inhibitors to DKA, albeit with strong variation in the magnitude of the potential effect (hazard ratios [HRs] ranging from 1.99 [95% CI, 0.22 to 17.80] for empagliflozin to 10.80 [CI, 1.39 to 83.65] for canagliflozin) (2–5, 7). There is an urgent need to evaluate the "real-world" safety of SGLT-2 inhibitors.

Observational studies of SGLT-2 inhibitors and the risk for DKA have yielded conflicting results (8–12). Some studies had methodological limitations (9, 11), whereas others included mostly younger patients (8, 12), and only 1 study was powered to provide molecule-specific estimates (11). Given the conflicting results and the knowledge gaps in the literature, further studies with adequate sample size are needed to better characterize this potential drug safety issue in a real-world setting. The Canadian Network for Observational Drug Effect Studies (CNODES) (13) conducted a large, population-based cohort study to assess the risk for DKA associated with SGLT-2 inhibitors, compared with dipeptidyl peptidase-4 (DPP-4) inhibitors, in patients with type 2 diabetes.

Methods

Study Design and Data Sources

We performed a retrospective cohort study using administrative health care data from 7 Canadian prov-

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inces (Alberta, British Columbia, Manitoba, Nova Scotia, Ontario, Quebec, and Saskatchewan) and a primary care clinical database from the United Kingdom, the Clinical Practice Research Datalink (CPRD) (14), which was linked to the Hospital Episode Statistics and Office for National Statistics databases. The study was done according to a prespecified common protocol (https://clinicaltrials.gov/ct2/show/NCT04017221).

Study Cohort Definition

We first assembled a base cohort including all patients receiving an antidiabetic medication (metformin, sulfonylureas, thiazolidinediones, DPP-4 inhibitors, SGLT-2 inhibitors, glucagon-like peptide-1 [GLP-1] receptor agonists, α-glucosidase inhibitors, meglitinides, insulin, or combinations of these drugs) between 1 January 2006 and 30 June 2018 (or the latest date of data availability at each site; exact dates are provided in Supplement Table 1, available at Annals.org). The date of the first dispensation (or prescription in the CPRD) for an antidiabetic drug defined base cohort entry.

From this base cohort, we assembled a study cohort including patients initiating therapy with an SGLT-2 inhibitor or receiving a DPP-4 inhibitor between 1 January 2013 (the year the first prescription for an SGLT-2 inhibitor was observed in our data) and 30 June 2018 (or the latest date of data availability at each site). We excluded patients younger than 18 years (<19 years in Alberta and <66 years in Ontario), patients with fewer than 365 days of health coverage before study cohort entry, patients initiating therapy with an SGLT-2 inhibitor and a DPP-4 inhibitor on the same date, patients receiving DPP-4 inhibitors who had previously received SGLT-2 inhibitors, and patients with a hospitalization or emergency department visit for DKA in the year before study cohort entry. Using a prevalent new-user design with time-based exposure sets (Supplement Figure 1, available at Annals.org) (15), each new user of an SGLT-2 inhibitor (canagliflozin, dapagliflozin, or empagliflozin [the molecules approved in Canada and the United Kingdom during the study period], alone or in combination with other antidiabetic drugs) was matched to a recipient of a DPP-4 inhibitor (alogliptin, linagliptin, saxagliptin, sitagliptin, or vildagliptin, alone or in combination with other non–SGLT-2 inhibitor antidiabetic drugs). Exposure sets were defined by the combination of matching factors. Incident new users of SGLT-2 inhibitors were matched to incident new users of DPP-4 inhibitors, defined as no use of DPP-4 inhibitors in the prior 365 days. They were matched on 1) level of antidiabetic therapy (defined as third-line if there had been 1 or more prescriptions for insulin in the prior 365 days, second-line if 2 or more noninsulin antidiabetic drug classes were received in the prior 365 days, or first-line if 1 noninsulin antidiabetic drug class or no antidiabetic drugs were received in the prior 365 days), 2) use of GLP-1 receptor agonists (not covered by Ontario's provincial drug plan and thus not used as a matching criterion in Ontario) in the prior 365 days, 3) calendar time (DPP-4 inhibitor prescription within 120 days of SGLT-2 inhibitor initiation), and 4) time-conditional propensity scores (TCPSs). Prevalent new users of SGLT-2 inhibitors (patients switching to an SGLT-2 inhibitor from a DPP-4 inhibitor) were matched to patients who had been using DPP-4 inhibitors for the same amount of time in their exposure sets but who did not add or switch to an SGLT-2 inhibitor. Prevalent new users were matched on time on DPP-4 inhibitors in addition to the 4 criteria described earlier (Supplement Figure 2, available at Annals.org).

Study cohort entry was defined as the date of the SGLT-2 inhibitor prescription or the corresponding date of the matched DPP-4 inhibitor prescription. Patients entering the study cohort were followed until occurrence of the study outcome, discontinuation of the study cohort entry drug, death, end of coverage, or end of study period (30 June 2018 or the latest date of data availability at each site), whichever occurred first.

Time-Conditional Propensity Scores

We performed conditional logistic regression separately for incident and prevalent new users and stratified by exposure set (therefore "conditional" on exposure set) to calculate TCPSs (propensity scores estimated by using the patient characteristics measured at the time of the time-based exposure sets—that is, conditional on the time of the exposure set). The TCPSs predicted the probability (propensity) of treatment with an SGLT-2 inhibitor versus a DPP-4 inhibitor on the basis of prespecified covariates. We then matched, within each site, patients treated with SGLT-2 inhibitors chronologically (starting with the patient with the "earliest" calendar date) without replacement in a 1:1 ratio to patients treated with DPP-4 inhibitors in their exposure set on closest TCPS. Matching without replacement, where a DPP-4 inhibitor recipient can be matched only once to an SGLT-2 inhibitor recipient, was preferred over matching with replacement, where a DPP-4 inhibitor recipient can be matched to multiple SGLT-2 inhibitor recipients, because matching potentially "atypical" DPP-4 inhibitor recipients by using the latter approach could affect the generalizability of the results. However, if matching without replacement resulted in a loss of exposure sets greater than 10% after positivity assumption testing (that is, exclusion of exposure sets that did not satisfy the assumption that any member of the study cohort has a positive probability of receiving either treatment) at a given site, matching with replacement was allowed. For matching with replacement, we used a caliper width of 0.2 SD of the TCPS on the logarithmic scale (Supplement Table 1) (16).

We included the following covariates in the TCPS, defined by using the International Classification of Diseases, Ninth Revision (ICD-9) or 10th Revision with Canadian Enhancements (ICD-10-CA) diagnostic codes (ICD-10 codes and Read codes in the CPRD) and measured at study cohort entry: age (modeled flexibly by using restricted cubic splines to account for potential nonlinear associations), sex, socioeconomic status (site-specific definition; see Supplement Table 2, available at Annals.org), and duration of diabetes (modeled flexibly by using restricted cubic splines; time since first diagnosis of type 2 diabetes or first-ever antidiabetic treatment).

We also included the following comorbid conditions measured in the 3 years before study cohort entry: alcohol-related disorders, cancer (excluding nonmelanoma skin cancer), macrovascular diabetic complications (myocardial infarction, ischemic stroke, peripheral arterial disease), microvascular diabetic complications (retinopathy, neuropathy, diabetic nephropathy), other kidney disease, and dialysis. Moreover, we considered receipt of the following medications, measured in the year before study cohort entry: metformin, sulfonylureas, thiazolidinediones, GLP-1 receptor agonists, α-glucosidase inhibitors, meglitinides, insulin, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, β-blockers, calcium-channel blockers, thiazide diuretics, loop diuretics, other diuretics, direct renin inhibitors, aldosterone antagonists, digitalis-like agents, statins, other lipid-lowering therapy, acetylsalicylic acid, other antiplatelet agents, nonsteroidal anti-inflammatory drugs, and oral anticoagulants, as well as oral glucocorticoids and atypical antipsychotics, 2 drug classes previously linked to DKA (17, 18).

Finally, we considered proxies of overall health, including the number of different classes of nonantidiabetic medications, hospitalizations, and physician visits in the year before study cohort entry. In the CPRD analysis, we also included the following in the TCPS: body mass index (<30 kg/m^2, ≥30 kg/m^2, or unknown), smoking (ever, never, or unknown), race, hemoglobin A_{1c} (≤7%, 7.1% to 8%, >8%, or unknown), blood pressure (diastolic blood pressure ≥90 mm Hg or systolic blood pressure ≥140 mm Hg, diastolic blood pressure <90 mm Hg and systolic blood pressure <140 mm Hg, or unknown), and estimated glomerular filtration rate (<60 mL/min per 1.73 m^2, ≥60 mL/min per 1.73 m^2, or unknown).

Exposure Definition

We used an as-treated exposure definition, in which patients were considered continuously exposed if the duration of one prescription overlapped with the date of the subsequent prescription. In the case of nonoverlap, we allowed for a 30-day "grace period" between successive prescriptions to account for reduced adherence and the plasma half-life of the drugs. Drug discontinuation was defined by a gap between successive prescriptions of more than 30 days or the initiation of an SGLT-2 inhibitor for patients in the DPP-4 inhibitor group.

Outcome Definition

The study outcome was DKA, defined by a hospitalization with a primary diagnosis of DKA (or an emergency department visit for sites with available data: Alberta, British Columbia, Nova Scotia, Ontario, Quebec, and Saskatchewan) by using the following ICD-10-CA diagnostic codes: E11.10, E11.12, E13.10, E13.12, E14.10, and E14.12 (or E11.1, E13.1, and E14.1 in the CPRD). The event date was defined by the date of hospital admission (or emergency department visit).

Statistical Analysis

We calculated the incidence rates of DKA for the overall cohort and the 2 exposure groups (SGLT-2 inhibitor recipients and DPP-4 inhibitor recipients) on the basis of the Poisson distribution and expressed them as number of events per 1000 person-years. Moreover, we used a Cox proportional hazards model to estimate the HR and 95% CI of DKA associated with receipt of SGLT-2 inhibitors compared with receipt of DPP-4 inhibitors. In addition to matching, we decided a priori to also adjust for age, sex, duration of diabetes, and TCPS deciles to further control for confounding. Because SGLT-2 inhibitor recipients and DPP-4 inhibitor recipients were matched on incident or prevalent new-user status, we did not account for it in our primary analysis, which included all matched pairs. In sites where matching with replacement was used, a robust sandwich estimator was used to estimate the variance.

Each participating site conducted the analyses (including descriptive analyses and Cox proportional hazards models) independently according to a common analytical protocol. We subsequently combined data summaries and meta-analyzed the site-specific estimates by using DerSimonian–Laird random-effects models with inverse variance weighting (19). We chose to use a random-effects model because although all sites used a common protocol, there are still several potential sources of heterogeneity within CNODES, which may include differences in populations, formulary restrictions, or data capture. Only sites with more than 5 events in each of the exposure groups were included in the meta-analyses (sites included in the primary analysis were Alberta, British Columbia, Manitoba, Ontario, Quebec, and Saskatchewan; **Supplement Table 3**, available at Annals.org, lists the sites contributing to each meta-analysis).

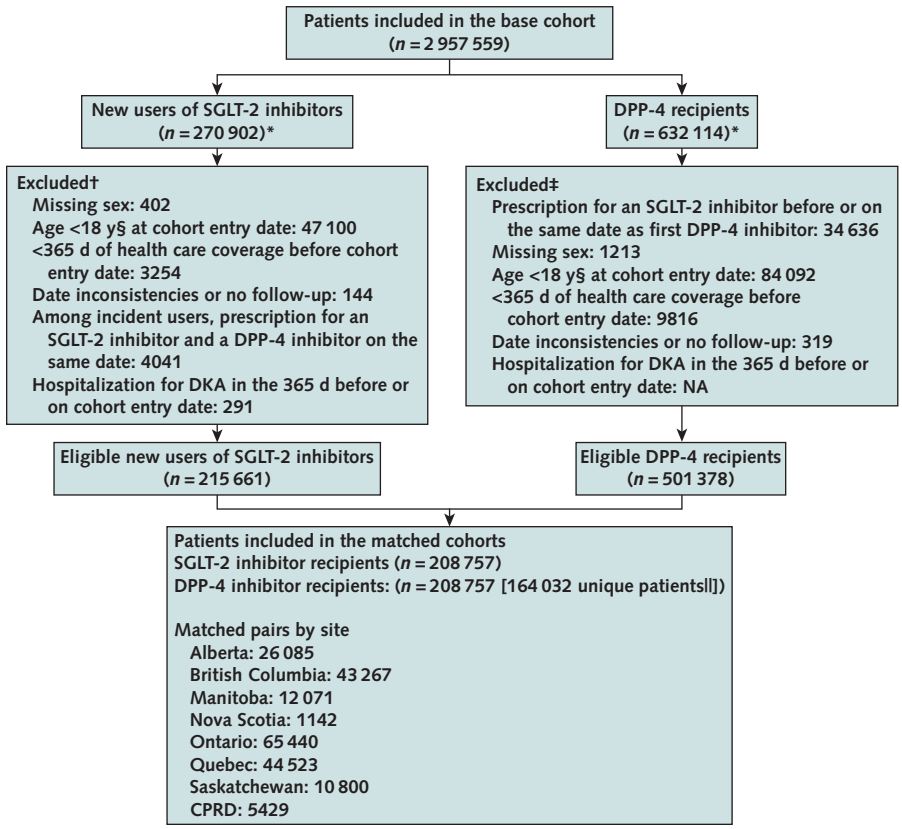
We conducted 5 secondary analyses. First, we obtained molecule-specific estimates for the 3 SGLT-2 inhibitors that were available in the databases: canagliflozin, dapagliflozin, and empagliflozin. Second, we stratified by age (≥70 years versus <70 years), sex, and receipt of insulin (present versus absent) in the year before study cohort entry. Finally, we stratified recipients of SGLT-2 inhibitors and their matched comparators according to the status of DPP-4 inhibitor receipt at study cohort entry (incident new user versus prevalent new user).

We also conducted 4 sensitivity analyses. To account for potential exposure misclassification, we used alternate 0- and 60-day grace periods to define continuous exposure. Second, in a post hoc analysis, we did not exclude patients with prior DKA, including prior DKA as an additional covariate in the TCPS. Finally, in another post hoc analysis, we combined the site-specific estimates by using a fixed-effects meta-analysis model instead of a random-effects model. All survival analyses were conducted by using the PHREG procedure in various versions of SAS statistical software (SAS Institute).

Role of the Funding Source

CNODES is a collaborating center of the Drug Safety and Effectiveness Network and is funded by the Canadian Institutes of Health Research (grant DSE-146021). The sponsors were not directly involved in the

Figure 1. Study flow diagram.



Exclusion criteria were applied slightly differently between the SGLT-2 inhibitor and the DPP-4 inhibitor groups owing to use of the prevalent new-user design, where 1) patients with a previous prescription for an SGLT-2 inhibitor were excluded from the DPP-4 inhibitor group, but no patients were excluded for this reason in the SGLT-2 inhibitor group, and 2) exclusion criteria were applied at the time of treatment initiation among SGLT-2 inhibitor recipients but were applied to each DPP-4 inhibitor prescription during follow-up. CPRD = Clinical Practice Research Datalink; DKA = diabetic ketoacidosis; DPP-4 = dipeptidyl peptidase-4; NA = not applicable; SGLT-2 = sodium–glucose cotransporter-2.

* Patients could enter the study cohort a maximum of twice, the first time with DPP-4 inhibitors and the second time initiating treatment with an SGLT-2 inhibitor.

† Numbers regarding the exclusions in the SGLT-2 inhibitor group do not add up because of small cells (<6 patients) at individual sites that were suppressed owing to privacy restrictions.

‡ In the DPP-4 inhibitor cohort, we applied the exclusion criterion regarding prior DKA at the prescription and not the patient level when constructing the exposure sets (numbers not listed). Thus, the numbers regarding the exclusions in the DPP-4 inhibitor group do not add up (also because of small cells that were suppressed owing to privacy restrictions at specific sites).

§ Younger than 19 y in Alberta and <66 y in Ontario.

‖ Because of matching with replacement in some sites (see also **Supplement Table 1**).

design and conduct of the study; the collection, management, analysis, and interpretation of the data; or the preparation, review, or approval of the manuscript.

RESULTS

We identified 903 016 patients with type 2 diabetes who received an SGLT-2 inhibitor (n = 270 902) or a DPP-4 inhibitor (n = 632 114) during the study period (**Figure 1**). Of those, we matched 208 757 SGLT-2 inhibitor recipients to 208 757 DPP-4 inhibitor recipients (164 032 unique DPP-4 inhibitor recipients owing to matching with replacement) (**Supplement Table 1**). Among SGLT-2 inhibitor recipients, 88 287 (42.3%) received canagliflozin, 64 076 (30.7%) received dapagliflozin, and 56 394 (27.0%) received empagliflozin. Matching resulted in 2 well-balanced groups regarding baseline patient characteristics (**Table 1**). **Supplement Table 4** (available at Annals.org) provides patient characteristics before and after matching; **Supplement Table 5** (available at Annals.org) shows additional baseline characteristics in the CPRD; and **Supplement Tables 6** to **13** (available at Annals.org) show site-specific key baseline characteristics, stratified by incident and prevalent new users.

During a total of 370 454 person-years of follow-up (mean, 0.9 year [SD, 0.8]), 521 patients were hospitalized with DKA (incidence rate, 1.41 per 1000 person-years). **Table 2** shows that compared with DPP-4 inhibitors, SGLT-2 inhibitors were associated with an almost 3-fold increase in the risk for DKA (incidence rates, 2.03 versus 0.75 per 1000 person-years; HR, 2.85 [CI, 1.99 to 4.08]; I^2 = 50%) (**Figure 2**). **Supplement Table 14** (available at Annals.org) shows site-specific incidence rates.

Table 1. Baseline Sample Characteristics*

Characteristic	SGLT-2 Inhibitor Group (*n* = 208 757)	DPP-4 Inhibitor Group (*n* = 208 757)
Mean age (SD), *y*	63.8 (9.5)	64.0 (9.5)
Female, *n (%)*	86 476 (41.4)	86 766 (41.6)
Year of study cohort entry, *n (%)*		
2013	323 (0.2)	344 (0.2)
2014	6973 (3.3)	7351 (3.5)
2015	51 693 (24.8)	51 207 (24.5)
2016	66 572 (31.9)	66 589 (31.9)
2017	61 565 (29.5)	61 364 (29.4)
2018	21 631 (10.4)	21 902 (10.5)
New user status, *n (%)*		
Incident new users	102 807 (49.2)	102 807 (49.2)
Prevalent new users	105 950 (50.8)	105 950 (50.8)
SGLT-2 inhibitor molecule, *n (%)*		
Canagliflozin	88 287 (42.3)	–
Dapagliflozin	64 076 (30.7)	–
Empagliflozin	56 394 (27.0)	–
Mean diabetes duration (SD), *y*	12.6 (6.6)	12.5 (6.6)
Diabetes duration, *n (%)*		
<1 y	7129 (3.4)	7431 (3.6)
1–4.9 y	25 261 (12.1)	25 715 (12.3)
5–10 y	52 670 (25.2)	52 696 (25.2)
>10 y	123 697 (59.3)	122 915 (58.9)
Comorbid conditions, *n (%)*†		
Alcohol-related disorders	3642 (1.7)	3710 (1.8)
Cancer	21 833 (10.5)	22 148 (10.6)
Myocardial infarction	5411 (2.6)	5299 (2.5)
Ischemic stroke	2494 (1.2)	2534 (1.2)
Peripheral arterial disease	4845 (2.3)	4880 (2.3)
Diabetic retinopathy	5394 (2.6)	5439 (2.6)
Diabetic neuropathy	3997 (1.9)	4095 (2.0)
Diabetic nephropathy	7619 (3.6)	7709 (3.7)
Other kidney diseases	10 407 (5.0)	11 231 (5.4)
Dialysis	301 (0.1)	323 (0.2)
Antidiabetic comedications, *n (%)*†		
Metformin	181 458 (86.9)	181 438 (86.9)
Sulfonylureas	108 893 (52.2)	108 888 (52.2)
Thiazolidinediones	5181 (2.5)	4944 (2.4)
Glucagon-like peptide-1 receptor agonists	8508 (4.1)	8508 (4.1)
α-Glucosidase inhibitors	3048 (1.5)	2924 (1.4)
Meglitinides	4698 (2.3)	4688 (2.2)
Insulin	57 623 (27.6)	57 623 (27.6)
Other comedications, *n (%)*†		
Angiotensin-converting enzyme inhibitors	95 069 (45.5)	94 664 (45.3)
Angiotensin II receptor blockers	66 994 (32.1)	66 581 (31.9)
β-Blockers	59 269 (28.4)	58 524 (28.0)
Calcium-channel blockers	63 688 (30.5)	63 845 (30.6)
Loop diuretics	21 549 (10.3)	21 791 (10.4)
Thiazide diuretics	45 226 (21.7)	45 111 (21.6)
Other diuretics	18 605 (8.9)	18 558 (8.9)
Direct renin inhibitors	102 (0.0)	99 (0.0)
Aldosterone antagonists	6186 (3.0)	6071 (2.9)
Digitalis-like agents	2621 (1.3)	2622 (1.3)
Statins	160 551 (76.9)	159 869 (76.6)
Other lipid-lowering therapy	23 626 (11.3)	22 773 (10.9)
Acetylsalicylic acid	37 142 (17.8)	37 010 (17.7)
Other antiplatelet agents	14 210 (6.8)	13 752 (6.6)
Nonsteroidal anti-inflammatory drugs	40 544 (19.4)	40 244 (19.3)
Oral anticoagulants	13 577 (6.5)	13 736 (6.6)
Oral glucocorticoids	13 032 (6.2)	12 994 (6.2)
Atypical antipsychotics	8746 (4.2)	8689 (4.2)

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Table 1–Continued

Characteristic	SGLT-2 Inhibitor Group (*n* = 208 757)	DPP-4 Inhibitor Group (*n* = 208 757)
Proxies of overall health, *n* (%)†		
Classes of non-antidiabetic drugs received		
0 or 1	8477 (4.1)	8613 (4.1)
2–5	66 097 (31.7)	66 961 (32.1)
≥6	134 183 (64.3)	133 183 (63.8)
Inpatient hospitalizations		
0	177 486 (85.0)	176 999 (84.8)
1 or 2	28 902 (13.8)	29 240 (14.0)
≥3	2368 (1.1)	2517 (1.2)
Physician visits		
0–2	14 998 (7.2)	15 075 (7.2)
3–5	31 949 (15.3)	32 088 (15.4)
≥6	161 810 (77.5)	161 594 (77.4)

DPP-4 = dipeptidyl peptidase-4; SGLT-2 = sodium–glucose cotransporter-2.
* Numbers may not add up because small cells were suppressed owing to privacy restrictions at specific sites. SGLT-2 inhibitor recipients were matched to DPP-4 inhibitor recipients from their exposure set (defined on level of antidiabetic therapy, prior receipt of glucagon-like peptide-1 receptor agonists, time receiving DPP-4 inhibitors for prevalent new users, and calendar time) on time-conditional propensity score.
† Comorbidities were assessed in the 3 years before study cohort entry, and medications and proxies of overall health were assessed in the year before study cohort entry.

There was some variation in the point estimate of the HR for each individual SGLT-2 inhibitor: 1.86 (CI, 1.11 to 3.10) for dapagliflozin, 2.52 (CI, 1.23 to 5.14) for empagliflozin, and 3.58 (CI, 2.13 to 6.03) for canagliflozin (Table 2). Stratifying by age, sex, or recipient type (incident versus prevalent new user) at study cohort entry did not modify the association between SGLT-2 inhibitors and risk for DKA (Supplement Table 15, available at Annals.org, shows incidence rates in the different subgroups from all sites, and Supplement Table 16, available at Annals.org, shows incidence rates and HRs from the sites included in each meta-analysis). However, the risk for DKA associated with SGLT-2 inhibitors was higher among patients without prior receipt of insulin (HR, 3.96 [CI, 2.74 to 5.72]) than among those with prior receipt of insulin (HR, 2.24 [CI, 1.40 to 3.61]) (Supplement Table 16). The results of sensitivity analyses were consistent with those of the primary analysis (Supplement Table 17, available at Annals.org).

DISCUSSION

Our population-based cohort study of over 350 000 adults with type 2 diabetes demonstrated a nearly 3-fold increased risk for DKA with SGLT-2 inhibitors compared with DPP-4 inhibitors. Except for a lower risk in patients with prior receipt of insulin than in those without, results were consistent regardless of sex, age, or recipient type (incident versus prevalent new user) and were robust across sensitivity analyses. Furthermore, the increased risk was observed with all 3 SGLT-2 inhibitors available in our data, with canagliflozin showing the highest effect estimate.

Table 2. Crude and Adjusted HRs for the Association Between Receipt of SGLT-2 Inhibitors and Risk for Diabetic Ketoacidosis in Patients With Type 2 Diabetes

Study Group	Patients, *n**	Events, *n*	Person-Years	Crude IR (95% CI)†	Crude HR (95% CI)	Adjusted Models‡		Sites Included, *n*§
						HR (95% CI)	I^2, %	
SGLT-2 inhibitors	202 186	372	183 374	2.03 (1.83–2.25)	2.83 (1.93–4.14)	2.85 (1.99–4.08)	50	6
DPP-4 inhibitors	202 186	133	177 615	0.75 (0.63–0.89)	Reference	Reference		
Specific SGLT-2 analyses								
Canagliflozin	78 779	200	88 731	2.25 (1.96–2.59)	3.65 (2.06–6.48)	3.58 (2.13–6.03)	58	4
DPP-4 inhibitors	78 779	58	87 125	0.67 (0.51–0.86)	Reference	Reference		
Dapagliflozin	36 746	58	28 528	2.03 (1.57–2.63)	1.87 (1.12–3.13)	1.86 (1.11–3.10)	0	3
DPP-4 inhibitors	36 746	32	27 187	1.18 (0.83–1.66)	Reference	Reference		
Empagliflozin	26 728	25	16 970	1.47 (1.00–2.18)	2.32 (1.14–4.72)	2.52 (1.23–5.14)	–	1
DPP-4 inhibitors	26 728	11	17 575	0.63 (0.35–1.13)	Reference	Reference		

DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; HR = hazard ratio; IR = incidence rate; SGLT-2 = sodium–glucose cotransporter-2.
* Recipients of SGLT-2 inhibitors were matched to DPP-4 inhibitor recipients from their exposure set (defined by level of antidiabetic therapy, prior use of GLP-1 receptor agonists, time on DPP-4 inhibitors for prevalent new users, and calendar time) on time-conditional propensity score.
† Per 1000 person-years.
‡ Adjusted for age (continuous), sex, diabetes duration (continuous), and deciles of time-conditional propensity score.
§ In the primary analysis, Alberta, British Columbia, Manitoba, Ontario, Quebec, and Saskatchewan were included. In the canagliflozin-specific analysis, Alberta, British Columbia, Ontario, and Quebec were included. In the dapagliflozin-specific analysis, Alberta, Quebec, and Saskatchewan were included. In the empagliflozin-specific analysis, only Ontario was included.

A potential link between inhibitors of sodium–glucose cotransporters and the risk for DKA was first hypothesized in 19th-century Germany, when the ketogenic potential of phlorizin, a phytochemical with a molecular structure similar to the SGLT-2 inhibitors available today, was described (20). More recently, it was shown that SGLT-2 inhibition promotes lipid oxidation and ketogenesis, possibly via volume depletion, providing a pathophysiologic mechanism for SGLT-2 inhibitor–related DKA (21). These suspicions have been reinforced by signals from RCTs (2–4, 7). However, the effect estimates from RCTs were based on very few events, with the overall number ranging from 5 in EMPA-REG OUTCOME (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients-Removing Excess Glucose) to 39 in the DECLARE-TIMI 58 (Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58) trial (2–4, 7).

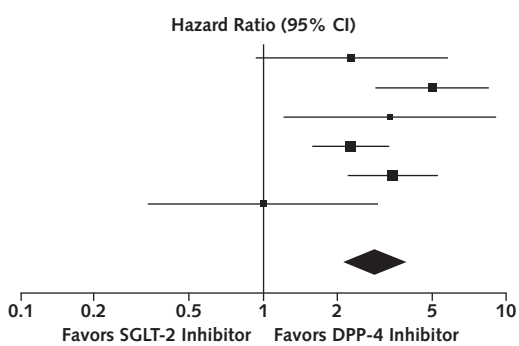
Observational studies assessing the association between SGLT-2 inhibitors and risk for DKA have yielded conflicting results (8–12). Three studies showed an increased risk or a nonsignificant but similar trend (HRs ranging from 1.91 to 2.14) (8–10), 1 study showed no increased risk (HR, 0.96 [CI, 0.58 to 1.57]) (12), and 1 study using multiple active comparators and different definitions for type 2 diabetes reported HRs ranging from 0.70 (CI, 0.50 to 1.00) versus insulin to 1.53 (CI, 1.31 to 1.79) versus sulfonylureas (11).

Of note, 2 of the previous observational studies had important limitations, including immortal time bias (9), potential exposure misclassification (9, 11), residual confounding (9), and poor reporting (such as missing patient characteristics) (11). Moreover, 2 other studies included mostly younger patients (mean ages of 53 and 55 years) (8, 12), which could potentially decrease the generalizability of their results to older adults typically seen in real-world practice. Finally, most studies were limited by their modest number of events, which precluded molecule-specific analyses (8–10, 12). This knowledge gap is important, considering the intraclass differences among SGLT-2 inhibitors in pharmacodynamics (SGLT-2 receptor selectivity) and pharmacokinetics (degree of renal elimination) (22), the recent emergence of canagliflozin-specific signals for the risk for fractures and lower-extremity amputations (2), and the methodological limitations of the only study that provided molecule-specific estimates to date (11).

Our results based on a study cohort of more than 350 000 patients and more than 500 DKA events corroborate existing concerns about DKA as a potential adverse effect of SGLT-2 inhibitors, showing an almost 3-fold increased risk (6). That being said, with a crude rate difference of 1.2 per 1000 person-years, the increase in the absolute risk was relatively low. Our results also argue for a class effect, because all 3 SGLT-2 inhibitors studied were associated with an increased risk. Given that the respective HRs ranged from 1.86 for dapagliflozin to 3.58 for canagliflozin, some heterogeneity in the magnitude of this risk among individual compounds seems possible. Indeed, canagliflozin has a lower SGLT-2/SGLT-1 selectivity compared with empagliflozin and dapagliflozin, and it has been shown to also inhibit SGLT-1, a glucose and galactose transporter mainly expressed in small-intestine enterocytes (22). Intestinal SGLT-1 inhibition could potentially lead to osmotic diarrhea and volume depletion, a predisposing factor for DKA. However, canagliflozin-associated diarrhea is not common. Ultimately, additional mechanistic studies are needed to verify this hypothesis. Finally, the increase in the risk for DKA associated with SGLT-2 inhibitors appears to be greater among patients without than in those with prior receipt of insulin, a potential proxy of more advanced type 2 diabetes. Thus, our results suggest that the risk for this adverse drug effect could be higher among patients with less advanced disease.

Our study has several strengths. First, the population-based design and few exclusion criteria make the study results highly generalizable to adults with type 2 diabetes in routine care. Second, the prevalent new-user design allowed us to include almost 80% of patients initiating SGLT-2 inhibitors that were available in the databases, which further enhanced generalizability and statistical power. Finally, because of the large sample

Figure 2. Hazard ratios (95% CIs) for diabetic ketoacidosis associated with receipt of SGLT-2 inhibitors versus DPP-4 inhibitors.



Because there were fewer than 5 events in at least 1 of the 2 exposure groups, Nova Scotia and the United Kingdom Clinical Practice Research Datalink were not included in the main analysis. The meta-analysis used a DerSimonian–Laird random-effects model with inverse variance weighting. DPP-4 = dipeptidyl peptidase-4; SGLT-2 = sodium–glucose cotransporter-2.

size, we could calculate precise estimates for the risk for DKA. We were also able to assess molecule-specific risks, albeit in a limited number of sites.

Our study also has limitations. First, because it is observational, some residual confounding is possible. However, use of DPP-4 inhibitors, a drug class also recommended as second-line treatment in adults with type 2 diabetes during the study period, as an active comparator helped to decrease confounding while also providing a clinically meaningful comparison (23). Moreover, we matched on TCPS including many potential confounders, which led to 2 well-balanced groups.

Second, we did not have access to baseline laboratory data, such as hemoglobin A_{1c}, for the majority of patients in our study, which could be an additional source of confounding with respect to the level of diabetes control. However, other proxies of diabetes control, such as duration of diabetes, history of microvascular and macrovascular diabetic complications, and prior receipt of antidiabetic drugs, were almost identical between the 2 exposure groups.

Third, misclassification of exposure is possible owing to decreased patient adherence. Although the decrease in patient adherence could be differential between SGLT-2 inhibitor and DPP-4 inhibitor recipients owing to potential differences in the tolerability of these 2 drug classes, sensitivity analyses using alternate grace periods yielded consistent results.

Fourth, the results in some of the subgroups (empagliflozin, prevalent new users, and no prior receipt of insulin) are mainly driven by the site-specific findings in Ontario. Given that this site did not include patients younger than 66 years, these results could have limited generalizability to younger adults.

Fifth, the distribution of the different SGLT-2 inhibitor molecules varied by site. Thus, it also varied across meta-analyses depending on which sites were included in each analysis.

Finally, with the mean duration of follow-up being 0.9 year, we were not able to assess the long-term safety of SGLT-2 inhibitors with respect to DKA.

In conclusion, our results provide robust evidence that SGLT-2 inhibitors are associated with an increased risk for DKA. Of note, increased risks were observed in all molecule-specific analyses, with canagliflozin showing the highest effect estimate. Because the beneficial effects of SGLT-2 inhibitors in the prevention of cardiovascular and renal disease will probably increase their uptake in the following years, physicians should be aware of DKA as a potential adverse effect.

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Reproducible Research Statement: *Study protocol:* Available from Dr. Filion (e-mail, kristian.filion@mcgill.ca). *Statistical code and data set:* Not available.

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