Sodium-glucose co-transporter 2 inhibitors and the risk of diabetic ketoacidosis: A multicenter cohort study

Running title: SGLT2 inhibitors and the risk of DKA

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ABSTRACT

Background: Sodium-glucose co-transporter 2 (SGLT2) inhibitors could increase the risk of diabetic ketoacidosis (DKA).

Objective: To assess whether SGLT2 inhibitors, compared with dipeptidyl peptidase-4 (DPP-4) inhibitors, are associated with an increased risk of DKA in patients with type 2 diabetes.

Design: Population-based cohort study; prevalent new-user design between 2013 and 2018.

Setting: Electronic healthcare databases from seven Canadian provinces and the United Kingdom.

Patients:.208,757 new users of SGLT2 inhibitors were matched with time-conditional propensity scores to 208,757 users of DPP-4 inhibitors .

Measurements: Cox proportional hazards models estimated site-specific hazard ratios (HRs) with 95% confidence intervals (CIs) of DKA comparing use of SGLT2 inhibitors to use of DPP-4 inhibitors, which were pooled using random-effects models. Secondary analyses stratified by molecule, age, sex, and prior insulin use. .

Results: Overall, 521 patients were diagnosed with DKA during 370,454 person-years of follow-up (incidence rate per 1,000 person-years [95% CI]: 1.40 [1.29-1.53]). Compared with DPP-4 inhibitors, SGLT2 inhibitors were associated with an increased risk of DKA (incidence rates [95% CI], 2.03 [1.83-2.25] versus 0.75 [0.63-0.89]; HR, 2.85; 95% CI, 1.99-4.08). Molecule-specific HRs (95% CIs) were 1.86 (1.11-3.10) for dapagliflozin, 2.52 (1.23-5.14) for empagliflozin, and 3.58 (2.13-6.03) for canagliflozin. Age and sex did not modify the association; prior insulin use appeared to decrease the risk.

Limitations: Unmeasured confounding; no laboratory data for the majority of patients, molecule-specific analyses conducted at a limited number of sites.

Conclusion: SGLT2 inhibitors were associated with an almost threefold increased risk of DKA, with molecule-specific analyses suggesting a class effect.

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INTRODUCTION

Sodium-glucose co-transporter 2 (SGLT2) inhibitors are a newer class of medications for type 2 diabetes.(1) Randomized controlled trials (RCTs) have demonstrated that they reduce the risk of 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 of diabetic ketoacidosis (DKA), a potentially fatal diabetic complication.(6)

In 2015, the US Food and Drug Administration issued a safety warning on the risk of DKA with SGLT2 inhibitors based on spontaneous reports.(6) RCTs have also linked SGLT2 inhibitors to DKA, albeit with strong variation in the magnitude of the potential effect (hazard ratios [HRs] and 95% confidence intervals [CIs] ranging from 1.99 [0.22-17.80] for empagliflozin to 10.80 [1.39-83.65] for canagliflozin).(2-5, 7) There is an urgent need to evaluate the "real-world" safety of SGLT2 inhibitors.

Observational studies of SGLT2 inhibitors and the risk of DKA have yielded conflicting results.(8-12) Some studies had methodological limitations,(9, 11) while others included mostly younger patients,(8, 12) and only one 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 of DKA associated with SGLT2 inhibitors, compared with dipeptidyl peptidase-4 (DPP-4) inhibitors, in patients with type 2 diabetes.

METHODS

Study design and data sources

We conducted a retrospective cohort study using administrative healthcare data from seven Canadian provinces (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. This study was conducted according to a pre-specified 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, SGLT2 inhibitors, glucagon-like peptide-1 [GLP-1] receptor agonists, alpha-glucosidase inhibitors, meglitinides, insulin, or combinations of these drugs) between January 1, 2006 and June 30, 2018 (or the latest date of data availability at each site; exact dates in **eTable 1**). 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 an SGLT2 inhibitor or receiving a DPP-4 inhibitor between January 1, 2013 (the year the first prescription for an SGLT2 inhibitor was observed in our data) and June 30, 2018 (or the latest date of data availability at each site). We excluded patients aged <18 years (<19 in Alberta and <66 in Ontario), patients with <365 days of health coverage before study cohort entry, patients initiating an SGLT2 inhibitor and a DPP-4 inhibitor on the same date, DPP-4 inhibitor patients with prior use of SGLT2 inhibitors, and patients with a hospitalization or emergency room visit for DKA in the year before

study cohort entry. Using a prevalent new-user design with time-based exposure sets (see below; also **eFigure 1**),(15) each user of an SGLT2 inhibitor (canagliflozin, dapagliflozin, 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 user of a DPP-4 inhibitor (alogliptin, linagliptin, saxagliptin, sitagliptin, vildagliptin; alone or in combination with other non-SGLT2 inhibitor antidiabetic drugs). Exposure sets were defined by the combination of matching factors. Incident new users of SGLT2 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 (i) level of antidiabetic therapy (defined as third-line if ≥1 prescription for insulin in the prior 365 days, second-line if ≥2 non-insulin antidiabetic drug classes in the prior 365 days, or first-line if 1 non-insulin antidiabetic drug class was used or no use of antidiabetic drugs in the prior 365 days), (ii) 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, (iii) calendar time (DPP-4 inhibitor prescription within 120 days of SGLT2 inhibitor initiation), and (iv) time-conditional propensity scores (TCPS). Prevalent new users of SGLT2 inhibitors (i.e., patients switching to a SGLT2 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 a SGLT2 inhibitor. Prevalent new users were matched on time on DPP-4 inhibitors in addition to the 4 criteria described above (**eFigure 2**).

Study cohort entry was defined as the date of the SGLT2 inhibitor prescription or the corresponding date of the matched DPP-4 inhibitor prescription. Patients entering the study cohort were followed until the occurrence of the study outcome (defined below), discontinuation of the

study cohort entry drug (defined below), death, end of coverage, or end of study period (June 30, 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 TCPS (that is propensity scores estimated using the patient characteristics measured at the time of the time-based exposure sets, i.e., conditional on the time of the exposure set). TCPS predicted the probability (propensity) of treatment with an SGLT2 inhibitor versus a DPP-4 inhibitor based on pre-specified covariates (listed below). We then matched, within each site, patients treated with SGLT2 inhibitors chronologically (i.e., starting with the patient with the 'earliest' calendar date) without replacement 1:1 to patients treated with DPP-4 inhibitors in their exposure set on closest TCPS. Matching without replacement, where a DPP-4 inhibitor user can be matched only once to an SGLT2 inhibitor user, was preferred over matching with replacement, where a DPP-4 inhibitor user can be matched to multiple SGLT2 inhibitor users, because matching potentially 'atypical' DPP-4 inhibitor users with the latter approach could impact the generalizability of the results. However, if matching without replacement resulted in a loss of exposure sets of >10% after positivity assumption testing (i.e., 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 standard deviations of the TCPS on the logarithmic scale (**eTable 1**).(16)

We included the following covariates in the TCPS, defined using International Classification of Diseases, 9th 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 (modelled flexibly using restricted cubic splines to account for potential non-linear associations), sex, socioeconomic status (site-specific definition; see **eTable 2**), and duration of diabetes (modelled flexibly using restricted cubic splines; time since first diagnosis of type 2 diabetes or first-ever antidiabetic treatment).

We also included the following comorbidities measured in the three years before study cohort entry: alcohol-related disorders, cancer (excluding non-melanoma 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 the use of the following medications, measured in the year before study cohort entry: metformin, sulfonylureas, thiazolidinediones, GLP-1 receptor agonists, alpha-glucosidase inhibitors, meglitinides, insulin, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, beta-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, non-steroidal anti-inflammatory drugs, and oral anticoagulants, as well as oral glucocorticoids and atypical antipsychotics, two drug classes previously linked to DKA.(17, 18)

Finally, we considered proxies of overall health including the number of different classes of non-antidiabetic 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, unknown), smoking (ever, never, unknown), race, hemoglobin A1c (≤7%, 7.1-8%, >8%, unknown), blood pressure (diastolic blood pressure ≥90 mmHg or systolic blood pressure ≥140 mmHg, diastolic blood pressure <90 mmHg and systolic blood pressure <140

mmHg, unknown), and estimated glomerular filtration rate (<60 mL/min per 1.73m^2, ≥60 mL/min per 1.73m^2, 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 non-overlap, 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 SGLT2 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) 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 two exposure groups (i.e., SGLT2 inhibitor users and DPP-4 inhibitor users) based on 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 the 95% CI of DKA associated with use of SGLT2 inhibitors

as compared with use of DPP-4 inhibitors. In addition to matching (described above), we decided *a priori* to also adjust for age, sex, duration of diabetes, and TCPS deciles to further control for confounding. Since SGLT2 inhibitor users and DPP-4 inhibitor users were matched on incident/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 estimate 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 using DerSimonian and 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 five events in each of the exposure groups were included in the meta-analyses (sites included in the primary analysis: Alberta, British Columbia, Manitoba, Ontario, Quebec, and Saskatchewan; see also **eTable 3** for the sites contributing to each meta-analysis).

We conducted five secondary analyses. First, we obtained molecule-specific estimates for the three SGLT2 inhibitors that were available in the databases, i.e., canagliflozin, dapagliflozin, and empagliflozin. Second, we stratified by age (≥70 years versus <70 years), sex, and insulin use (present versus absent) in the year before study cohort entry. Finally, we stratified users of SGLT2 inhibitors and their matched comparators according to the status of DPP-4 inhibitor use at study cohort entry (incident new user versus prevalent new user).

We also conducted four 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 using a fixed-effects meta-analysis model instead of random-effects model. All survival analyses were conducted with SAS statistical software (different versions; SAS Institute, Cary, North Carolina) using the PHREG procedure.

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 Number DSE-146021). The sponsors were not directly involved in the 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 used a SGLT2 inhibitor (n=270,902) or a DPP-4 inhibitor (n=632,114) during the study period (**Figure 1**). Of those, we matched 208,757 SGLT2 inhibitor users to 208,757 DPP-4 inhibitor users (164,032 unique DPP-4 inhibitor users due to matching with replacement; **eTable 1**). Among SGLT2 inhibitor users, 88,287 (42.3%) used canagliflozin, 64,076 (30.7%) used dapagliflozin, and 56,394 (27.0%) used empagliflozin. Matching resulted in two well-balanced groups regarding baseline patient characteristics (**Table 1**; see also **eTable 4** with patient characteristics pre-matching and post-matching, **eTable 5** with additional baseline characteristics in the CPRD, and **eTables 6-13** with site-specific key baseline characteristics stratified by incident and prevalent new users).

During a total of 370,454 person-years of follow-up (mean [standard deviation] 0.9 [0.8] years), 521 patients were hospitalized with DKA (incidence rate, 1.41 per 1,000 person-years). **Table 2** shows that, compared with use of DPP-4 inhibitors, use of SGLT2 inhibitors was associated with an almost threefold increase in the risk of DKA (incidence rates 2.03 versus 0.75 per 1000 person-years; HR, 2.85; 95% CI, 1.99-4.08; I^2=50%) (**Figure 2**; see also **eTable 14** for site-specific incidence rates).

There was some variation in the point-estimate of the HR for each individual SGLT2 inhibitor: 1.86 (95% CI, 1.11-3.10) for dapagliflozin, 2.52 (95% CI, 1.23-5.14) for empagliflozin, and 3.58 (95% CI, 2.13-6.03) for canagliflozin (**Table 2**). Stratifying by age, sex, or user type (incident versus prevalent new user) at study cohort entry did not modify the association between SGLT2 inhibitors and risk of DKA (see **eTable 15** for incidence rates in the different subgroups from all sites and **eTable 16** for incidence rates and HRs from the sites included in each meta-analysis). However, the risk of DKA associated with SGLT2 inhibitors was higher among patients

without prior insulin use (HR, 3.96; 95% CI, 2.74-5.72) as compared to those with prior insulin use (HR, 2.24; 95% CI, 1.40-3.61) (**eTable 16**). Finally, the results of sensitivity analyses were consistent with those of the primary analysis (**eTable 17**).

DISCUSSION

Our population-based cohort study of over 350,000 adults with type 2 diabetes demonstrated a nearly three-fold increased risk of DKA with SGLT2 inhibitors compared to DPP4 inhibitors. Except for a lower risk in patients with prior insulin use than in those without, results were consistent regardless of sex, age, user type (incident versus prevalent new user) and robust across sensitivity analyses. Furthermore, the increased risk was observed with all three SGLT2 inhibitors available in our data, with canagliflozin showing the highest effect estimate.

A potential link between inhibitors of sodium-glucose co-transporters and the risk of DKA was first hypothesized in 19th century Germany, when the ketogenic potential of phlorizin, a phytochemical with a molecular structure similar to the SGLT2 inhibitors available today, was described.(20) More recently, it was shown that SGLT2 inhibition promotes lipid oxidation and ketogenesis, possibly via volume depletion, providing a pathophysiologic mechanism for SGLT2 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 the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients-Removing Excess Glucose (EMPA-REG OUTCOME) trial to 39 in the Dapagliflozin Effect on Cardiovascular Events-Thrombolysis in Myocardial Infarction 58 (DECLARE-TIMI 58) trial.(2-4, 7)

Observational studies assessing the association between SGLT2 inhibitors and risk of DKA have yielded conflicting results.(8-12) Three studies showed an increased risk or a non-significant but similar trend (HRs ranging from 1.91 to 2.14),(8-10) one study showed no increased risk (HR, 0.96; 95% CI, 0.58-1.57),(12) and another study using multiple active comparators and different

definitions for type 2 diabetes reported HRs (95% CIs) ranging from 0.70 (0.50-1.00) versus insulin to 1.53 (1.31-1.79) versus sulfonylureas.(11)

Of note, two of the previous observational studies had important limitations including immortal time bias,(9) potential exposure misclassification,(9, 11) residual confounding,(9) and poor reporting (e.g., missing patient characteristics).(11) Moreover, two others 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 intra-class differences among SGLT2 inhibitors in pharmacodynamics (i.e., SGLT2 receptor selectivity) and pharmacokinetics (i.e., degree of renal elimination),(22) the recent emergence of canagliflozin-specific signals for the risk of 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 SGLT2 inhibitors, showing an almost threefold increased risk.(6) That being said, with a crude rate difference of 1.2 per 1,000 person-years, the increase in the absolute risk was relatively low. Our results also argue for a class effect, since all three SGLT2 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 SGLT2/SGLT1 selectivity compared to empagliflozin and dapagliflozin, and it has been shown to also inhibit SGLT1, a glucose and galactose transporter mainly expressed in small intestine enterocytes.(22) Intestinal SGLT1 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 of DKA associated with SGLT2 inhibitors appears to be greater among patients without as compared to those with prior insulin use, a potential proxy of more advanced type 2 diabetes. Thus, our results suggest that the risk of 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 study results highly generalizable to adults with type 2 diabetes in routine care. Second, using the prevalent new-user design, we were able to include the majority (almost 80%) of patients initiating SGLT2 inhibitors that were available in the databases, which further enhanced generalizability and statistical power. Third, based on the large sample size, we could calculate precise estimates for the risk of DKA. We were also able to assess molecule-specific risks, albeit in a limited number of sites.

This study also has some limitations. First, due to its observational nature, some residual confounding is possible. However, using DPP-4 inhibitors, a drug class also recommended as second-line treatment in adults with type 2 diabetes during the study time 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 two well-balanced groups. Second, we did not have access to baseline laboratory data such as hemoglobin A1C 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 use of antidiabetic drugs were almost identical between the two exposure

groups. Third, misclassification of exposure is possible due to decreased patient adherence. While the decrease in patient adherence could be differential between SGLT2 inhibitor and DPP-4 inhibitor users due to potential differences in the tolerability of these two drug classes, sensitivity analyses using alternate grace periods yielded consistent results. Fourth, the results in some of the subgroups (i.e., empagliflozin, prevalent new users, and no prior insulin use) are mainly driven by the site-specific findings in Ontario. Given that this site did not include patients <66 years, these results could have limited generalizability to younger adults. Fifth, the distribution of the different SGLT2 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 years, we were not able to assess the long-term safety of SGLT2 inhibitors with respect to DKA.

Our results provide robust evidence that SGLT2 inhibitors are associated with an increased risk of DKA. Importantly, increased risks were observed in all molecule-specific analyses, with canagliflozin showing the highest effect estimate. Since the beneficial effects of SGLT2 inhibitors in the prevention of cardiovascular and renal disease will likely increase their uptake in the following years, physicians should be aware of DKA as a potential adverse effect.

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DISCLOSURES

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CONTRIBUTIONS OF AUTHORS

AD drafted the manuscript. All authors contributed to the study design and implementation, interpretation of results, and critically reviewed the manuscript for important intellectual content.

LML conducted the meta-analyses. All authors approved the final version of the manuscript. KBF is the guarantor.

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FIGURE LEGENDS

Figure 1. Flowchart of study cohort construction

Abbreviations: CPRD, Clinical Practice Research Datalink; DKA, diabetic ketoacidosis; SGLT2, sodium-glucose co-transporter 2; DPP-4, dipeptidyl peptidase-4.

[a] Patients could enter the study cohort maximum twice, the first time initiating treatment with DPP-4 inhibitors and the second time initiating treatment with an SGLT2 inhibitor.

[b] Numbers regarding the exclusions in the SGLT2 inhibitor group do not add up because of small cells (<6) in individual sites suppressed due to privacy restrictions.

[c] 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 suppressed due to privacy restrictions in specific sites).

[d] Due to matching with replacement in some sites (see also **eTable 1**)

Exclusion criteria were applied slightly differently between SGLT2 inhibitor and DPP-4 inhibitor users due to the use of the prevalent new user design, where (i) 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 (ii) exclusion criteria were applied at the time of treatment initiation among SGLT2 inhibitor users but were applied to each DPP-4 inhibitor prescription during follow-up.

Figure 2. Hazard ratios (95% confidence intervals) of diabetic ketoacidosis associated with the use of SGLT2 inhibitors compared with the use of DPP-4 inhibitors

Abbreviations: CI, confidence interval; SGLT2, sodium-glucose co-transporter 2; DPP-4, dipeptidyl peptidase-4.

Due to less than five events in at least one of the two 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 and Laird random-effects model with inverse variance weighting.