Received: 18 September 2023 | Revised: 29 November 2023 | Accepted: 7 December 2023

DOI: 10.1111/dom.15429

ORIGINAL ARTICLE

WILEY

Liver, renal, genitourinary and diabetic ketoacidosis risks among new users of empagliflozin versus dipeptidyl peptidase-4 inhibitors in patients with type 2 diabetes: Post-authorization safety study based on multinational cohorts

Cristina Rebordosa MD[1] | Reimar W. Thomsen MD[2] | Arlene K. Tave MA[3] | Morten Madsen MSc[2] | Daniel C. Beachler PhD[3] | David Martinez MSc[1] | Raquel Garcia-Esteban MSc[1] | Estel Plana MSc[1] | Anita Tormos MPH[1] | Soulmaz Fazeli Farsani PharmD[4] | Susana Perez-Gutthann MD[1] | Manel Pladevall-Vila MD[1,5]

[1]RTI Health Solutions, Barcelona, Spain

[2]Department of Clinical Epidemiology, Aarhus University and Aarhus University Hospital, Aarhus, Denmark

[3]Carelon Research, Wilmington, Delaware, USA

[4]Boehringer Ingelheim International GmbH, Ingelheim am Rhein, Germany

[5]The Center for Health Policy and Health Services Research, Henry Ford Health System, Detroit, Michigan, USA

Correspondence
Cristina Rebordosa, MD, RTI Health Solutions, Av. Diagonal, 605, 9-1, 08028 Barcelona, Spain.
Email: crebordosa@rti.org

Funding information
Boehringer Ingelheim & Eli Lilly and Company Diabetes Alliance

Abstract

Aim: To estimate risks of diabetic ketoacidosis (DKA), acute liver injury (ALI), acute kidney injury (AKI), chronic kidney disease (CKD), severe complications of urinary tract infection (UTI) and genital infection (GI) among patients with type 2 diabetes initiating empagliflozin versus those initiating a dipeptidyl peptidase-4 (DPP-4) inhibitor.

Materials and Methods: In this large multinational, observational, new-user cohort study in UK, Danish and US healthcare data sources, patients initiated empagliflozin or a DPP-4 inhibitor between August 2014 and August 2019, were aged ≥18 years, and had ≥12 months' continuous health plan enrolment. Incidence rates by exposure and incidence rate ratios, adjusted for propensity-score deciles, were calculated.

Results: In total, 64 599 empagliflozin initiators and 203 315 DPP-4 inhibitor initiators were included. There was an increased risk [pooled adjusted incidence rate ratios (95% confidence interval)] of DKA [2.19 (1.74-2.76)] and decreased risks of ALI [0.77 (0.50-1.19) in patients without predisposing conditions of liver disease; 0.70 (0.56-0.88) in all patients] and AKI [0.54 (0.41-0.73)]. In the UK data, there was an increased risk of GI [males: 4.04 (3.46-4.71); females: 3.24 (2.81-3.74)] and decreased risks of CKD [0.53 (0.43-0.65)] and severe complications of UTI [0.51 (0.37-0.72)]. The results were generally consistent in subgroup and sensitivity analyses.

Conclusions: Compared with DDP-4 inhibitor use, empagliflozin use was associated with increased risks of DKA and GI and decreased risks of ALI, AKI, CKD and severe complications of UTI. These associations are consistent with previous studies and known class effects of sodium-glucose cotransporter 2 inhibitors, including renoprotective effects and beneficial effects on alanine aminotransferase levels.

KEYWORDS
antidiabetic drug, empagliflozin, pharmacoepidemiology, real-world evidence

1 | INTRODUCTION

Jardiance (empagliflozin), a highly potent and selective inhibitor of sodium-glucose cotransporter 2 (SGLT2), was approved in Europe and the United States in 2014 for the treatment of type 2 diabetes (T2D) to improve glycaemic control in adults.[1,2] Empagliflozin improves glycaemic control in patients with T2D by reducing renal glucose reabsorption.[3]

We conducted a preplanned, large, multinational post-authorization safety study, beginning at the empagliflozin launch date in 2014 in the United Kingdom, United States and Denmark [-European Union Register of Post-Authorization Studies (EU PAS) no. ENCEPP/SDPP/13413; category 3].[4] This observational, new-user cohort study evaluated the risks of acute liver injury (ALI), acute kidney injury (AKI) and chronic kidney disease (CKD) associated with empagliflozin. The hepatic safety of empagliflozin was of predefined interest because of a higher frequency of serious hepatic events in clinical trials, and its renal safety was of interest because of empagliflozin's mechanism of action.[3] The study was also designed to evaluate the risks of genital infection (GI) and severe complications of urinary tract infection (UTI). The rationale for evaluating these risks is related to the mechanism of action of empagliflozin: the inhibition of SGLT2 in patients with T2D leads to excess glucose excretion in the urine,[3] which, together with hyperglycaemia and T2D-related comorbidities and complications, may increase the susceptibility of patients with diabetes to GI and UTI. Finally, although not initially planned before empagliflozin authorization, the assessment of the risks of diabetic ketoacidosis (DKA) was added to the study because of initial spontaneous adverse event reporting of DKA events occurring in patients taking SGLT2 inhibitors for T2D; a number of these events were atypical (i.e. with blood sugar levels not as high as expected or even in the normal range).[5] These outcomes have been evaluated previously in clinical trials and observational studies.[6–25]

Our aim was to estimate, among patients with T2D, the risks of ALI, AKI, CKD, severe complications of UTI, GI and DKA among patients treated with empagliflozin compared with patients treated with dipeptidyl peptidase-4 (DPP-4) inhibitors.

2 | METHODS

The study protocol, available in the EU PAS Register (ENCEPP/SDPP/13413), describes the study methods in detail.[4]

2.1 | Study design and setting

This was a multinational, observational, population-based, new-user cohort study using existing data in the Clinical Practice Research Datalink (CPRD) in the United Kingdom [both the General Practitioner Online Database (GOLD) and Aurum], the Danish Population Registries (Danish Registries) in Denmark, and the HealthCare Integrated Research Database (HIRD) in the United States. CPRD data were used for the evaluation of all study outcomes, and data from the Danish Registries and HIRD were used for evaluation of the rarest outcomes (i.e. DKA, ALI and AKI). Appendix S1 describes the data sources in detail.

The study employed a new-user design and compared initiators of empagliflozin with initiators of DPP-4 inhibitors. The index date was defined as the date on which each identified initiator received the index prescription for empagliflozin or a DPP-4 inhibitor. The study period started on 1 August 2014, the date of empagliflozin launch in the United Kingdom, United States and Denmark, and ended 1 August 2019 (31 July 2019 in HIRD).

2.2 | Participants

The study population included all eligible adult patients with T2D initiating treatment with empagliflozin or with a DPP-4 inhibitor during the study period. Appendix S2 describes the eligibility criteria in detail. Briefly, eligible patients were aged ≥18 years and had ≥12 months of continuous registration in the data source before the index date. Empagliflozin-exposed patients had ≥1 prescription/dispensing for empagliflozin, and patients exposed to a DPP-4 inhibitor had ≥1 prescription/dispensing for a DPP-4 inhibitor. Outcome-specific exclusion criteria were applied to the overall study population, to create distinct analysis populations for each outcome (see Figure 1).

Follow-up started the day after the index date (date of qualifying prescription/dispensing of empagliflozin or a DPP-4 inhibitor) and, for each specified outcome, continued until the occurrence of the study outcome, the date during follow-up on which specific exclusion criteria were met, the end date of the first continuous treatment episode of empagliflozin or DPP-4 inhibitor plus a defined grace period (30 days after the end of the days' supply for the last prescription in the main analyses), the date on which a new treatment episode with the other type of study drug or other SGLT2 inhibitors started, or the end of the study period.

2.3 | Exposures

The exposures were empagliflozin [including fixed-dose combination (FDC) with metformin] and the DPP-4 inhibitors sitagliptin, saxagliptin, linagliptin, vildagliptin, or alogliptin (including FDCs of these drugs with metformin).[4] DPP-4-inhibitors were selected as the comparator because of their similar indications and target population to SGLT2 inhibitors, as well as to the fact that they are the most common second-line regimens after metformin with sulphonylurea. FDCs of SGLT2 inhibitors with DPP-4 inhibitors were excluded. Current use

FIGURE 1 Cohort attrition, all data sources. AKI, acute kidney injury; ALI1, acute liver injury in patients with no predisposing conditions (primary outcome); ALI2, acute liver injury in patients with or without predisposing conditions (secondary outcome); CKD, chronic kidney disease; CPRD, Clinical Practice Research Datalink; DKA, diabetic ketoacidosis; DPP-4i, dipeptidyl peptidase-4 inhibitor; DR, Danish Registries; GIF, genital infections in females; GIM, genital infections in males; HIRD, HealthCare Integrated Research Database; NA, not applicable; SGLT2i, sodium-glucose cotransporter 2 inhibitor; T1D, type 1 diabetes; T2D, type 2 diabetes; UTI, urinary tract infection. [a]Different exclusion criteria were applied according to each outcome of interest (e.g. patients with CKD were excluded from the analysis of AKI), which resulted in different outcome-specific populations.

was defined from the index date to the end of days' supply for the qualifying prescription, plus a period of 30 days. Recent use was defined from the end of current use plus a period of 90 days (i.e. 120 days after the end of days' supply). Days' supply was estimated according to prescription instructions in CPRD or based on available information on the duration of dispensing (e.g. number of packages bought, strength and number of pills) in Danish Registries.

2.4 | Outcomes

The primary study outcomes evaluated in all data sources were DKA [hospitalization or emergency department (ED) visit], ALI in patients without predisposing conditions (hospitalization, ED visit, or specialist visit) (ALI1) and AKI (hospitalization, ED visit, or specialist visit). Primary outcomes evaluated only in CPRD were severe complications of UTI (inpatient and outpatient) and GIs (inpatient and outpatient). Secondary outcomes were ALI in patients with and without predisposing conditions (hospitalization, ED visit, or specialist visit) (ALI2), evaluated in all data sources, as well as CKD (inpatient and outpatient) and severe GI (hospitalization or ED visit or required systemic treatment), both evaluated only in CPRD.

2.5 | Validation

Validation of identified events was implemented for all outcomes in the three data sources (see Table D1 in Appendix S4 for results). Events identified in CPRD and Hospital Episode Statistics were

validated through questionnaires sent to general practitioners (GPs), complemented with available laboratory results. Events identified in HIRD were validated through medical record data abstraction and/or laboratory test results when available. In CPRD and HIRD, with the aim of validating 100 events per outcome for each outcome-specific population in each data source, when there were >200 events, a random sample of up to 200 events of each outcome were targeted for validation via questionnaires or medical record abstraction; otherwise, all events were selected for validation. In the Danish Registries, validation was attempted for all identified outcome events via laboratory test results.

2.6 | Statistical methods

For each outcome-specific population and in each data source, logistic regression was used to estimate propensity scores (PSs) based on the information before or at the index date, to account for potential confounding. Appendix S3 describes the PS modelling process in detail, including examination of PS distributions and trimming of extreme values.

For each outcome, incidence rates (IRs) adjusted for PS decile were generated for empagliflozin and DPP-4 inhibitor cohorts along with adjusted IR ratios (IRRs) (empagliflozin vs. DPP-4 inhibitors) overall. These estimates with corresponding 95% confidence intervals (CIs) were generated through the application of a Poisson regression model, where the outcome was modelled as a function of treatment cohort (empagliflozin or DPP-4 inhibitors) and PS decile (specified as a categorical variable) with the log of time of exposure (in years) as the offset.[26] Where possible, DerSimonian and Laird random-effects meta-analysis methods were used to combine IRRs and 95% CIs of the outcomes across the data sources,[27,28] and heterogeneity was analysed using the Cochran Q test and the I^2 index.

Subgroup analyses evaluated outcomes by sociodemographic, clinical and treatment characteristics, and sensitivity analyses explored how robust the results were to variations in the definitions of outcomes, exposures and the positive predictive values (PPVs) of the outcome-identification algorithms from the validation substudies. A sensitivity analysis that added outpatient primary care events to the ALI and AKI primary outcomes was conducted in CPRD and HIRD, where primary care data are available. A quantitative bias analysis was conducted to evaluate potential unmeasured confounding.[29]

3 | RESULTS

3.1 | Study population

After applying all common inclusion and exclusion criteria, and before trimming extreme PS values, 76 174 initiators of empagliflozin and 257 406 initiators of DPP-4 inhibitors were included in the DKA populations, which were the largest populations because of the lack of outcome-specific exclusion criteria (Figure 1). The numbers of patients included in the other outcome-specific populations were smaller, with the exclusion criteria for ALI1 being the most restrictive. Most patients (71%-87%) initiated empagliflozin and DPP-4 inhibitors as add-on therapy, and >70% of the initiators of empagliflozin and of DPP-4 inhibitors were also concomitant users of metformin. The most relevant difference in treatment patterns observed between the two exposure cohorts in all data sources was concomitant use of insulin, which was consistently more frequent in empagliflozin initiators (range across data sources, 14.2%-31.2%) than in DPP-4 inhibitor initiators (range across data sources, 4.7%-10.6%). The mean duration of exposure to the study drug was shorter among initiators of empagliflozin (range across data sources, 242.3-336.5 days) than among initiators of DPP-4 inhibitors (range across data sources, 275.2-446.5 days).

Baseline characteristics before trimming and before PS adjustment showed that empagliflozin initiators were younger than initiators of DPP-4 inhibitors (Table 1). Approximately 60% of patients were males in both cohorts and in all data sources. Patients in the empagliflozin cohort were more frequently obese than those in the DPP-4 inhibitors cohort. There was a higher proportion of initiators of DPP-4 inhibitors in the initial years and a higher proportion of empagliflozin initiators in later years of the study in all data sources. The average pretreatment glycated haemoglobin (HbA1c) was higher in empagliflozin than DPP-4 inhibitor initiators, and the proportion of patients with poor diabetes control (i.e. HbA1c >74.9 mmol/mol or HbA1c >9.0%) was higher in the empagliflozin cohort than in the DPP-4 inhibitors cohort in CPRD and Danish Registries. The proportions of patients with diabetes complications were similar between cohorts in all data sources, except for 'other diabetes complications' (such as diabetic arthropathy, and complications recorded as unspecified or as 'multiple'), which were more frequent in the empagliflozin cohort than in the DPP-4 inhibitors cohort in HIRD and in Danish Registries. The distribution of other baseline comorbidities was similar between exposure cohorts in all data sources. When evaluating PS distributions, non-overlapping PS curves were observed in Danish Registries. Non-comparability was solved by stratifying the Danish study population into patients with fewer than three glucose-lowering drug (GLDs) and patients with three or more GLDs (see Appendix S3 for further details). After trimming, a good balance in the distribution of all variables was achieved in all data sources (see Appendix S3).

3.2 | Outcomes

The total number of outcome events identified across all data sources was the lowest for ALI1 (<70 in the empagliflozin cohort), followed by DKA, ALI2 and AKI; for other outcomes evaluated only in CPRD (CKD, severe complications of UTI and GI outcomes), a total of >1000 events were identified for each outcome (Table D1, Appendix S4). The response for GP questionnaires in CPRD was low (<8%), and retrieval rates of medical records in HIRD were modest (approximately 50%), both of which impacted the precision of the PPVs, particularly for rare outcomes, in those two data sources (Table D1).

TABLE 1 Patient sociodemographics and lifestyle characteristics at the index date, comorbidities and diabetes severity before or on the index date, and medications within 6 months before or on the index date in the DKA study population before trimming.

	CPRD			HIRD			Danish Registries		
Characteristics	Empagliflozin (N = 16 339)	DPP-4 inhibitors (N = 97 616)	SB[a]	Empagliflozin (N = 41 146)	DPP-4 inhibitors (N = 116 347)	SB[a]	Empagliflozin (N = 18 689)	DPP-4 inhibitors (N = 43 443)	SB[a]
Sociodemographic characteristics									
Age (years)									
n	16 339	97 616		41 146	116 347		18 689	43 443	
Mean (SD)	57.8 (10.9)	65.5 (13.2)	0.58	55.4 (9.9)	58.1 (12.0)	0.23	60.8 (11.5)	65.3 (12.9)	0.35
Median (Q1, Q3)	58.0 (51.0, 66.0)	66.0 (56.0, 75.0)		56.0 (49.0, 61.9)	58.0 (50.3, 64.8)		61.4 (53.3, 69.4)	66.3 (56.2, 74.5)	
P1, P99	31, 81	34, 91		30, 80	30, 88		31, 84	33, 92	
Female, n (%)	6762 (41.4)	41 740 (42.8)	0.03	17 053 (41.4)	51 407 (44.2)	0.06	6959 (37.2)	17 507 (40.3)	0.06
BMI >30, obesity diagnosis or obesity surgery, n (%)	12 141 (74.3)	52 734 (54.0)	−0.41	NA	NA		5373 (28.7)	7667 (17.6)	−0.29
Smoking history (CPRD), n (%)									
Current	3544 (21.7)	21 173 (21.7)	0.00	NA	NA		NA	NA	
Former	7395 (45.3)	45 669 (46.8)	0.03	NA	NA		NA	NA	
Never	5371 (32.9)	30 507 (31.3)	−0.03	NA	NA		NA	NA	
Unknown/missing	29 (0.2)	267 (0.3)	0.02	NA	NA		NA	NA	
History of smoking (Danish Registries), n (%)	NA	NA		NA	NA		710 (3.8)	1300 (3.0)	−0.05
Alcohol consumption (CPRD), n (%)									
Non-drinker	2210 (13.5)	13 608 (13.9)	0.01	NA	NA		NA	NA	
Low to moderate intake	7363 (45.1)	41 433 (42.4)	−0.05	NA	NA		NA	NA	
Heavy or very heavy intake	721 (4.4)	3985 (4.1)	−0.02	NA	NA		NA	NA	
Drinker, unknown quantity	5202 (31.8)	33 425 (34.2)	0.05	NA	NA		NA	NA	
Unknown/missing	843 (5.2)	5165 (5.3)	0.01	NA	NA		NA	NA	
History of alcohol abuse/dependence or alcohol-related diseases (HIRD, Danish Registries), n (%)	NA	NA		746 (1.8)	2012 (1.7)	−0.01	793 (4.2)	1984 (4.6)	0.02
Comorbidities and diabetes severity									
Time since first diagnosis of T2D (months)									
Mean (SD)	117.0 (74.1)	117.4 (78.4)	0.01	50.6 (40.2)	44.0 (37.6)	−0.18	111.9 (78.3)	90.2 (71.0)	−0.31
Median (Q1, Q3)	106.7 (59.8, 164.1)	105.8 (58.4, 162.5)		39.7 (19.2, 71.3)	32.1 (15.8, 62.7)		101.8 (47.1, 167.1)	77.0 (32.2, 134.8)	
P1, P99	2, 330	2, 351		0, 154	0, 146		0, 294	0, 277	

(Continues)

TABLE 1 (Continued)

Characteristics	CPRD			HIRD			Danish Registries		
	Empagliflozin (N = 16 339)	DPP-4 inhibitors (N = 97 616)	SB[a]	Empagliflozin (N = 41 146)	DPP-4 inhibitors (N = 116 347)	SB[a]	Empagliflozin (N = 18 689)	DPP-4 inhibitors (N = 43 443)	SB[a]
HbA1c in the 12 months before or on the index date, n, (%)									
Number of patients with available information on HbA1c	16 099	95 603		14 592	39 052		18 091	40 038	
HbA1c ≤53 mmol/mol or ≤7%, n (%[c])	850 (5.2)	8958 (9.2)	0.14	2829 (6.9)	8086 (6.9)	0.03	2280 (12.2)	8229 (18.9)	0.17
HbA1c >53 mmol/mol and ≤ 63.9 mmol/mol or >7% and ≤8%. n (%[c])	2821 (17.3)	24 153 (24.7)	0.17	3661 (8.9)	10 662 (9.2)	0.05	5241 (28.0)	13 398 (30.8)	0.06
HbA1c >63.9 mmol/mol and ≤74.9 mmol/mol or >8% and ≤9%. n (%[c])	4147 (25.4)	27 709 (28.4)	0.07	2958 (7.2)	7334 (6.3)	−0.04	4731 (25.3)	8751 (20.1)	−0.13
HbA1c >74.9 mmol/mol or >9%. n (%[b])	8286 (50.7)	34 835 (35.7)	−0.31	5144 (12.5)	12 970 (11.1)	−0.04	5839 (31.2)	9660 (22.2)	−0.22
HbA1c missing, n (%[c])	235 (1.4)	1961 (2.0)	0.04	26 554 (64.5)	77 295 (66.4)	0.04	598 (3.2)	3405 (7.8)	0.17
Renal complications, n (%)	355 (2.2)	3103 (3.2)	0.06	4649 (11.3)	12 814 (11.0)	−0.01	1110 (5.9)	2336 (5.4)	−0.02
Ophthalmic complications, n (%)	6545 (40.1)	38 979 (39.9)	0	5576 (13.6)	14 044 (12.1)	−0.05	2762 (14.8)	3665 (8.4)	−0.23
Neurological complications, n (%)	1088 (6.7)	7076 (7.2)	0.02	8774 (21.3)	21 059 (18.1)	−0.08	1666 (8.9)	1990 (4.6)	−0.21
Amputations, n (%)	185 (1.1)	1348 (1.4)	0.02	258 (0.6)	821 (0.7)	0.01	218 (1.2)	539 (1.2)	0.01
Cerebrovascular disease, n (%)	1077 (6.6)	11 803 (12.1)	0.17	4274 (10.4)	16 134 (13.9)	0.10	1863 (10.0)	5185 (11.9)	0.06
Peripheral circulatory complications, n (%)	5534 (33.9)	38 515 (39.5)	0.11	2838 (6.9)	7390 (6.4)	−0.02	1961 (10.5)	3894 (9.0)	−0.05
Other diabetes complications,[d] n (%)	164 (1.0)	1184 (1.2)	0.02	26 465 (64.3)	53 863 (46.3)	−0.36	5241 (28.0)	7352 (16.9)	−0.30
Coronary heart disease,[e] n (%)	2776 (17.0)	21 798 (22.3)	0.13	9483 (23.0)	26 921 (23.1)	0.00	4538 (24.3)	9065 (20.9)	−0.08
Recent myocardial ischaemia/infarction (in the 6 months before index date), n (%)	151 (0.9)	905 (0.9)	0	585 (1.4)	1595 (1.4)	0.00	267 (1.4)	365 (0.8)	−0.06
High blood pressure/hypertensive disease, n (%)	10 636 (65.1)	69 886 (71.6)	0.14	35 435 (86.1)	98 781 (84.9)	−0.03	8389 (44.9)	18 117 (41.7)	−0.06
Heart failure, n (%)	769 (4.7)	9106 (9.3)	0.16	3851 (9.4)	13 048 (11.2)	0.06	1534 (8.2)	3914 (9.0)	0.03
Liver and biliary disease, n (%)	2617 (16.0)	15 449 (15.8)	−0.01	10 451 (25.4)	26 055 (22.4)	−0.07	2748 (14.7)	6249 (14.4)	−0.01
Chronic renal disease or renal dialysis, n (%)	1050 (6.4)	23 301 (23.9)	0.41	4926 (12.0)	19 375 (16.7)	0.13	383 (2.0)	2965 (6.8)	0.19
Kidney and genitourinary stones, n (%)	755 (4.6)	4986 (5.1)	0.02	4366 (10.6)	11 725 (10.1)	−0.02	1112 (6.0)	2541 (5.8)	0.00
Crohn's disease, n (%)	106 (0.6)	562 (0.6)	−0.01	272 (0.7)	800 (0.7)	0.00	135 (0.7)	251 (0.6)	−0.02
Ulcerative colitis, n (%)	193 (1.2)	1224 (1.3)	0.01	461 (1.1)	1255 (1.1)	0.00	277 (1.5)	565 (1.3)	−0.02
Pancreatic diseases, n (%)	404 (2.5)	1902 (1.9)	−0.04	1344 (3.3)	2945 (2.5)	−0.05	529 (2.8)	982 (2.3)	−0.04
Pancreatitis, n (%)	361 (2.2)	1595 (1.6)	−0.05	1065 (2.6)	1998 (1.7)	−0.07	507 (2.7)	908 (2.1)	−0.04
	3257 (19.9)	22 599 (23.2)	0.08	15 298 (37.2)	42 726 (36.7)	−0.01	2894 (15.5)	7020 (16.2)	0.02

TABLE 1 (Continued)

Characteristics	CPRD			HIRD			Danish Registries		
	Empagliflozin (N = 16 339)	DPP-4 inhibitors (N = 97 616)	SB[a]	Empagliflozin (N = 41 146)	DPP-4 inhibitors (N = 116 347)	SB[a]	Empagliflozin (N = 18 689)	DPP-4 inhibitors (N = 43 443)	SB[a]
Gastro-oesophageal reflux, gastroesophagitis and peptic ulcer disease, n (%)									
Autoimmune and connective tissue diseases, n (%)	1191 (7.3)	9695 (9.9)	0.09	10 804 (26.3)	32 192 (27.7)	0.03	920 (4.9)	2323 (5.3)	0.02
Rheumatoid arthritis, n (%)	327 (2.0)	2578 (2.6)	0.04	1188 (2.9)	3889 (3.3)	0.03	279 (1.5)	762 (1.8)	0.02
Polymyalgia rheumatica, n (%)	151 (0.9)	2144 (2.2)	0.09	188 (0.5)	717 (0.6)	0.02	133 (0.7)	573 (1.3)	0.05
Other autoimmune and connective tissue diseases, n (%)	871 (5.3)	6343 (6.5)	0.05	10 314 (25.1)	30 662 (26.4)	0.03	699 (3.7)	1716 (4.0)	0.01
Osteoarthrosis and osteoarthritis, n (%)	4328 (26.5)	34 267 (35.1)	0.18	13 073 (31.8)	37 568 (32.3)	0.01	3714 (19.9)	8692 (20.0)	0.00
Immunosuppressive diseases,[f] n (%)	194 (1.2)	1845 (1.9)	0.05	877 (2.1)	3248 (2.8)	0.04	131 (0.7)	510 (1.2)	0.04
Dementia, n (%)	110 (0.7)	3332 (3.4)	0.15	654 (1.6)	3883 (3.3)	0.10	126 (0.7)	792 (1.8)	0.09
COPD/emphysema/respiratory insufficiency, n (%)	1186 (7.3)	10 503 (10.8)	0.11	7520 (18.3)	20 732 (17.8)	−0.01	1274 (6.8)	3647 (8.4)	0.06
Asthma, n (%)	3545 (21.7)	19 330 (19.8)	−0.05	6394 (15.5)	17 403 (15.0)	−0.02	1211 (6.5)	2281 (5.3)	−0.06
Prior history of diabetic ketoacidosis, n (%)	119 (0.7)	667 (0.7)	−0.01	579 (1.4)	1549 (1.3)	−0.01	330 (1.8)	547 (1.3)	−0.05
Psychological stress, n (%)	3574 (21.9)	18 731 (19.2)	−0.07	14 309 (34.8)	35 579 (30.6)	−0.09	1297 (6.9)	2694 (6.2)	−0.03
Thyroid problems (e.g. thyroid storm and thyrotoxicosis), n (%)	1916 (11.7)	12 893 (13.2)	0.04	11 157 (27.1)	30 140 (25.9)	−0.03	1275 (6.8)	3018 (6.9)	0.00
Chronic disease score[g]									
Score 0 or 1, n (%[c])	11 225 (68.7)	55 367 (56.7)	−0.24	14 417 (35.0)	42 791 (36.8)	0.04	14 683 (78.6)	31 435 (72.4)	−0.14
Score 2, n (%[c])	2721 (16.7)	16 321 (16.7)	0	11 735 (28.5)	28 387 (24.4)	−0.10	2292 (12.3)	5838 (13.4)	0.03
Score ≥3, n (%[c])	2393 (14.6)	25 928 (26.6)	0.27	14 994 (36.4)	45 169 (38.8)	0.05	1714 (9.2)	6170 (14.2)	0.14
Prior history of AKI <6 months before index date, n (%)	84 (0.5)	3401 (3.5)	0.16	536 (1.3)	4393 (3.8)	0.13	48 (0.3)	797 (1.8)	0.12
Acute illness (infections, trauma, surgery) <6 months before index date, n (%)	5097 (31.2)	34 955 (35.8)	0.1	10 642 (25.9)	34 575 (29.7)	0.08	1290 (6.9)	4459 (10.3)	0.11
Hypovolaemia, reduced caloric and fluid intake <6 months before index date, n (%)	86 (0.5)	1004 (1.0)	0.05	526 (1.3)	2909 (2.5)	0.08	33 (0.2)	518 (1.2)	0.09
Hypoxaemia <6 months before index date, n (%)	6 (0.0)	67 (0.1)	0.01	507 (1.2)	2616 (2.2)	0.07	54 (0.3)	189 (0.4)	0.02
Acute alcohol intoxication <6 months before index date, n (%)	8 (0.0)	31 (0.0)	−0.01	0 (0.0)	NR		NR	NR	
Medication use									
Drugs used in diabetes, n (%)	16 339 (100.0)	97 616 (100.0)		37 368 (90.8)	97 204 (83.5)	−0.20	17 971 (96.2)	39 400 (90.7)	−0.19
Insulin, n (%)	3272 (20.0)	6842 (7.0)	−0.51	9448 (23.0)	13 101 (11.3)	−0.37	6233 (33.4)	4235 (9.7)	−0.80

(Continues)

TABLE 1 (Continued)

Characteristics	CPRD			HIRD			Danish Registries		
	Empagliflozin (N = 16 339)	DPP-4 inhibitors (N = 97 616)	SB[a]	Empagliflozin (N = 41 146)	DPP-4 inhibitors (N = 116 347)	SB[a]	Empagliflozin (N = 18 689)	DPP-4 inhibitors (N = 43 443)	SB[a]
Any oral glucose-lowering drug, n (%)	16 339 (100.0)	97 616 (100.0)		37 368 (90.8)	97 204 (83.5)	−0.20	17 288 (92.5)	38 130 (87.8)	−0.14
Thiazides, n (%)	1313 (8.0)	9451 (9.7)	0.06	11 612 (28.2)	32 995 (28.4)	0.00	2286 (12.2)	5420 (12.5)	0.01
Systemic glucocorticosteroids, n (%)	852 (5.2)	7137 (7.3)	0.08	4453 (10.8)	12 984 (11.2)	0.01	765 (4.1)	2645 (6.1)	0.08
Immunosuppressants, n (%)[h]	223 (1.4)	1337 (1.4)	0.00	589 (1.4)	1959 (1.7)	0.02	171 (0.9)	440 (1.0)	0.01
Anti-inflammatory and antirheumatic products, n (%)[i]	2787 (17.1)	17 054 (17.5)	0.01	7082 (17.2)	19 368 (16.6)	−0.02	2880 (15.4)	6301 (14.5)	−0.03
Clozapine, n (%)	NR	20 (0.0)		0 (0.0)	0 (0.0)		37 (0.2)	85 (0.2)	0.00
Olanzapine, n (%)	73 (0.4)	523 (0.5)	0.01	60 (0.1)	237 (0.2)	0.01	108 (0.6)	282 (0.6)	0.01
Lithium, n (%)	33 (0.2)	240 (0.2)	0.01	86 (0.2)	223 (0.2)	0.00	49 (0.3)	130 (0.3)	0.01
Pentamidine, n (%)	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Terbutaline, n (%)	87 (0.5)	510 (0.5)	0.00	NR	0 (0.0)		6 (0.0)	31 (0.1)	0.01
Cocaine, n (%)	0 (0.0)	NR		15 (0.0)	66 (0.1)	0.01	0 (0.0)	0 (0.0)	

Note: Statistics were based on non-missing values unless otherwise specified.

Abbreviations: AKI, acute kidney injury; ATC, Anatomical Therapeutic Chemical (classification system); BMI, body mass index; COPD, chronic obstructive pulmonary disease; CPRD, Clinical Practice Research Datalink; DKA, diabetic ketoacidosis; DPP-4, dipeptidyl peptidase-4; HbA1c, glycated haemoglobin; HIRD, HealthCare Integrated Research Database; NR, not reportable because of small cell count(s); P1, P99, first and 99th percentiles; Q1, Q3, first and third quartiles; SB, standardized bias; SD, standard deviation; T2D, type 2 diabetes.

[a]Standardized bias versus empagliflozin cohort.

[b]The Index of Multiple Deprivation (IMD) combines information from seven domains: (a) income, (b) employment, (c) education, (d) skills and training, (e) health and disability, (f) crime and (g) barriers to housing and services, to produce an overall relative measure of deprivation. In this study, IMD was categorized as quintiles of the IMD at the patient level, if available, or at the practice level otherwise.

[c]Percentage over the total number of patients with available information for the specific covariate.

[d]Includes other specified complications such as diabetic arthropathy and complications recorded as unspecified or as 'multiple'.

[e]Coronary heart disease, including revascularization procedures.

[f]Including HIV/AIDS; transplants; malignant neoplasms of lymphoid, haematopoietic and related tissue; and other immunodeficiency disorders.

[g]Charlson comorbidity index.

[h]Numbers and proportions are reported for the selected medications listed in the indented categories, i.e. numbers and proportions do not sum up to all the medications included in the higher-level categories.

[i]Includes all drugs under ATC code C02, except antihypertensives for pulmonary arterial hypertension (C02KX), i.e. antiadrenergic agents, agents acting in arteriolar smooth muscle and other antihypertensives.

3.2.1 | Diabetic ketoacidosis

DKA was more frequent among initiators of empagliflozin (adjusted IR per 1000 person-years, range, 1.50-3.62) than among initiators of DPP-4 inhibitors (adjusted IR per 1000 person-years, range, 0.70-1.82). Initiators of empagliflozin had more than double the risk of DKA compared with initiators of DPP-4 inhibitors (pooled adjusted IRR, 2.19; 95% CI, 1.74-2.76) (Figure 2A). Results for DKA were consistent across the individual data sources, with clearly increased risk (IRRs) with empagliflozin use, except among the small subset of patients using three or more GLDs in Danish Registries, although the small number of DKA events in this group led to very imprecise estimates.

3.2.2 | Acute liver injury

ALI events were less common among initiators of empagliflozin (adjusted IR per 1000 person-years, range, 0.60-1.21 for ALI1 and 1.23-4.19 for ALI2) than among initiators of DPP-4 inhibitors (adjusted IR per 1000 person-years, range, 1.09-1.41 for ALI1 and 1.86-5.47 for ALI2). A decreased risk of these liver outcomes was observed among initiators of empagliflozin compared with initiators of DPP-4 inhibitors (ALI1 pooled adjusted IRR, 0.77; 95% CI, 0.50-1.19; ALI2 pooled adjusted IRR, 0.70; 95% CI, 0.56-0.88) (Figure 2B,C). The results for ALI1 and ALI2 were similar and consistent across all data sources and in both Danish population subsets. When including outpatient ALI events, ALI became slightly more frequent (<9 per 1000 person-years) but was still less frequent among initiators of empagliflozin, and the decreased risk persisted when compared with initiators of DPP-4 inhibitors (Figure E2, Appendix S5). The analysis evaluating the elevation of liver enzymes, irrespective of ALI diagnosis, showed that more patients in the DPP-4 inhibitors cohort had elevated liver enzymes during follow-up than patients in the empagliflozin cohort, in all data sources (Table E1, Appendix S5).

3.2.3 | Acute kidney injury

AKI was less frequent among initiators of empagliflozin (adjusted IR per 1000 person-years, range, 2.60-10.96) than among initiators of DPP-4 inhibitors (adjusted IR per 1000 person-years, range, 4.96-16.89) and was more frequent in HIRD than in the other data sources. A decreased risk of AKI was observed among initiators of empagliflozin compared with initiators of DPP-4 inhibitors (pooled adjusted IRR, 0.54; 95% CI, 0.41-0.73) (Figure 2D). When including outpatient AKI events, the IRs increased slightly among initiators of empagliflozin (<1 per 1000 person-years increase), but there was still a lower risk when compared with initiators of DPP-4 inhibitors (Figure E4, Appendix S5).

3.2.4 | Chronic kidney disease

CKD was evaluated only in CPRD and the IR among initiators of empagliflozin (adjusted IR, 9.32 per 1000 person-years) was roughly half that among initiators of DPP-4 inhibitors (IR, 17.73 per 1000 person-years). The lower risk in the empagliflozin cohort is also seen in the adjusted IRR of 0.53 (95% CI, 0.43-0.65) (Table 2).

3.2.5 | Severe complications of urinary tract infection

Severe complications of UTI were also evaluated only in CPRD. As with CKD, the IR of severe complications of UTI among initiators of empagliflozin (adjusted IR, 3.32 per 1000 person-years) was about half the corresponding IR among initiators of DPP-4 inhibitors (adjusted IR, 6.47 per 1000 person-years). The lower risk of severe complications of UTI among initiators of empagliflozin compared with initiators of DPP-4 inhibitors is also seen in the adjusted IRR of 0.51 (95% CI, 0.37-0.72) (Table 2).

3.2.6 | Genital infection

GIs were also evaluated only in CPRD. Overall, these infections were more frequent among females than among males in both therapy groups. Among males, adjusted IRs per 1000 person-years among empagliflozin initiators were roughly four times the corresponding IRs among initiators of DPP-4 inhibitors (47.23 vs. 11.70 for GI, 43.35 vs. 10.72 for severe GI). In females, GI adjusted IRs per 1000 person-years were about three times higher for empagliflozin initiators than for DPP-4 initiators (79.65 vs. 24.58 for GI, 58.42 vs. 17.48 for severe GI) (Table 3). Adjusted IRRs were 4.04 (95% CI, 3.46-4.71) for GI in males; 4.04 (95% CI, 3.44-4.75) for severe GI in males; 3.24 (95% CI, 2.81-3.74) for GI in females; and 3.34 (95% CI, 2.83-3.95) for severe GI in females.

3.3 | Subgroup, sensitivity and bias analyses

The results were consistent across subgroups and sensitivity analyses, except for the ALI outcomes, for which data were sparse (Figures E2 and E3, Appendix S5). Results from the quantitative bias analysis showed that residual confounding was unlikely to account for the decreased relative risk observed among empagliflozin patients for severe complications of UTI, their increased relative risk observed for DKA, or other negative or positive associations observed. Appendix S5 presents the results of the subgroup and sensitivity analyses in detail.

4 | DISCUSSION

In the databases included in this post-authorization safety study, use of empagliflozin compared with the use of DPP-4 inhibitors was associated with increased risks of DKA (approximately two-fold) and GI (approximately three-fold among females and four-fold among males).

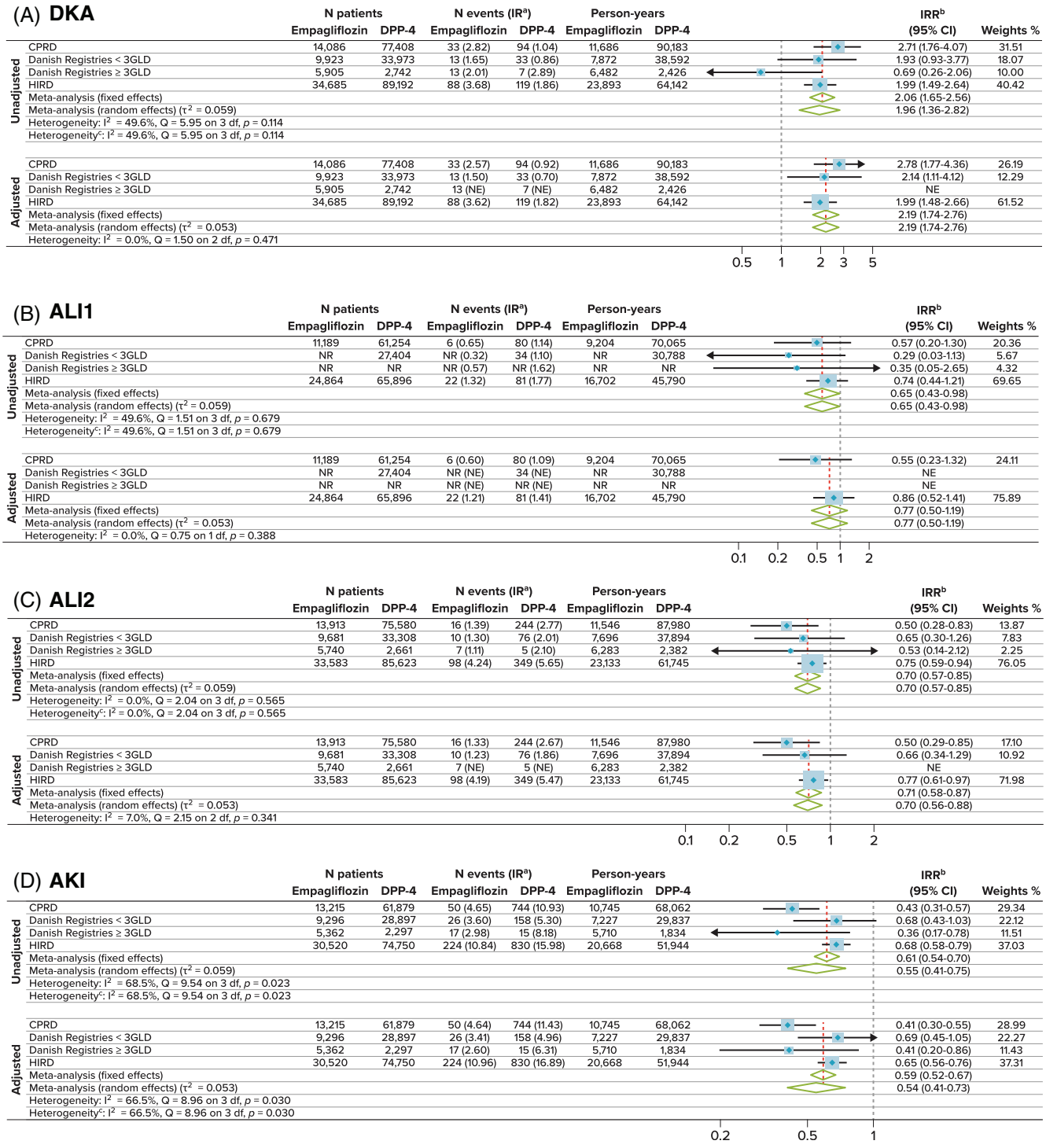

FIGURE 2 Incidence rates and incidence rate ratios for primary outcomes among initiators of empagliflozin and of DPP-4 inhibitors in propensity score–trimmed study cohorts, all data sources and meta-analysis. AKI, acute kidney injury; ALI1, acute liver injury in patients with no predisposing conditions (primary outcome); ALI2, acute liver injury secondary outcome; CI, confidence interval; df, degrees of freedom; CPRD, Clinical Practice Research Datalink; DKA, diabetic ketoacidosis; DPP-4, dipeptidyl peptidase-4; DR, Danish Registries; GLD, glucose-lowering drug; HIRD, HealthCare Integrated Research Database; I^2, heterogeneity statistic; IR, incidence rate; IRR, incidence rate ratio; N, number; NE, not estimable; NR, not reportable because of small cell count(s); Q, Cochran's Q statistic. IRR <1.0 is the reduced risk of the outcome of interest among initiators of empagliflozin compared with initiators of DPP-4 inhibitors. IRRs by propensity score deciles are presented in Appendix S6. [a]Per 1000 person-years. [b]Both unadjusted and adjusted IRRs for empagliflozin relative to DPP-4 inhibitors were derived from a Poisson regression model within the propensity score–trimmed populations, where outcome was modelled as a function of treatment cohort, with the log of years of exposure as the offset. The adjusted IRR also includes propensity score decile categories as explanatory variables. [c]Heterogeneity statistics from the meta-analysis exclude users of three or more GLDs in Danish Registries.

TABLE 2 Incidence rates and incidence rate ratios for CKD and severe complications of UTI among initiators of empagliflozin and of DPP-4 inhibitors in propensity score–trimmed study cohorts, Clinical Practice Research Datalink.

	Empagliflozin	DPP-4 inhibitors
CKD		
Number of patients	13 256	62 435
Number of events	104	1368
Person-years	10 8949	705 038
Unadjusted IR[a] (95% CI)	9.55 (7.80-11.57)	19.40 (18.39-20.46)
Adjusted IR[a] (95% CI)	9.32 (7.68-11.31)	17.73 (16.16-19.45)
Unadjusted IRR[b] (95% CI)	0.49 (0.40-0.60)	Reference
Adjusted IRR[b] (95% CI)	0.53 (0.43-0.65)	Reference
Severe complications of UTI		
Number of patients	14 050	77 330
Number of events	39	578
Person-years	116 413	893 615
Unadjusted IR[a] (95% CI)	3.35 (2.38-4.58)	6.47 (5.95-7.02)
Adjusted IR[a] (95% CI)	3.32 (2.42-4.54)	6.47 (5.64-7.42)
Unadjusted IRR[b] (95% CI)	0.52 (0.36-0.72)	Reference
Adjusted IRR[b] (95% CI)	0.51 (0.37-0.72)	Reference

Note: IRR <1.0 means reduced risk of the outcome of interest among initiators of empagliflozin compared with initiators of DPP-4 inhibitors.
Abbreviations: CI, confidence interval; CKD, chronic kidney disease; DPP-4, dipeptidyl peptidase-4; IR, incidence rate; IRR, incidence rate ratio; UTI, urinary tract infection.
[a]Per 1000 person-years.
[b]Both unadjusted and adjusted IRRs for empagliflozin relative to DPP-4 inhibitors were derived from a Poisson regression model, within the propensity score–trimmed populations where outcome was modelled as a function of treatment cohort, with the log of years of exposure as the offset. The adjusted IRR also includes propensity score decile categories as explanatory variables.

Both of these outcomes are identified risks in empagliflozin's risk-management plan.[30] Use of empagliflozin compared with the use of DPP-4 inhibitors was associated with a decreased risk of ALI among patients with and without predisposing conditions, of AKI and CKD, and of severe complications of UTI, all potentially explained by the beneficial effects of empagliflozin on fat metabolism and on renal function.

The results were consistent across data sources and across all subgroup and sensitivity analyses, although some variations in the IRRs, probably related to small numbers of events in some analyses, were observed.

Our findings are broadly consistent with those of published studies evaluating the safety of SGLT2 inhibitors. Increased risks of DKA have been found among users of SGLT2 inhibitors relative to users of DPP-4 inhibitors and other GLDs in some large observational studies,[6–9] while other studies have observed no increased DKA risk.[10–12] Future research could explore the effect of other potential risk factors (e.g. elevated HbA1c) on DKA outcomes with SGLT2 inhibitor use,[31] as well as whether DKA events are atypical and occur without hyperglycaemia. ALI events were rare in our study, and the decreased risk of ALI observed was in line with the evidence from clinical trials suggesting that SGLT2 inhibitors may have potentially beneficial effects on alanine aminotransferase levels, potentially because of reductions in glucose levels and body fat stores that in turn improve liver function.[13–15] The observed decreased risk of AKI and the renoprotective effect observed among initiators of empagliflozin compared with initiators of DPP-4 inhibitors may be because of decreased sodium reabsorption[21] and are in line with a meta-analysis of seven randomized controlled trials showing a 25% decreased risk of AKI among users of SGLT2 inhibitors compared with placebo,[16] as well as with observational studies in the United States, the United Kingdom and Taiwan.[6,17,18] The observed decreased risk of CKD is also in line with multiple studies showing a decrease in CKD progression among users of SGLT2 inhibitors.[19,20] The evidence from long-term trials and postmarketing studies has shown that estimated glomerular filtration rate declines in the long-term at a slower rate among users of SGLT2 inhibitors than among patients treated with placebo.[21] Observational studies have generally reported no increased risk of severe complications of UTI,[22] except with high doses of dapagliflozin,[23] even when evaluating less severe UTIs that do not require hospitalization.[32] Finally, elevated risks of GIs, a known class effect of SGLT2 inhibitors that is caused by glycosuria, have been observed in a meta-analysis of 56 clinical trials[23] and in several observational studies comparing SGLT2 inhibitors with DPP-4 inhibitors or glucagon-like peptide 1 analogues.[24,25] Taken together, our results align with the safety evidence from clinical trials of empagliflozin, suggesting that observational studies can yield results consistent with those from clinical programmes.[33]

These results must be interpreted with potential limitations and biases in mind. Although some degree of bias and confounding cannot be completely discarded, the study design sought to avoid these by employing a new-user design with an active comparator (DPP-4 inhibitors); by including all potential confounders and variables associated with the outcome in the respective PS models; by balancing exposure cohorts in all baseline characteristics; and by analysing (a) the potential impact of calendar year in the distribution of baseline confounders, (b) the association of the exposure with the outcome by calendar year, and (c) the effect of calendar year in several PS models. While PSs were estimated to account for potential confounding, residual confounding because of unmeasured variables cannot be discarded. However, results from a quantitative bias analysis showed that residual confounding was unlikely to account for most negative or positive associations observed.

Misclassification of exposure and outcome is a risk in all studies conducted using routinely collected data from population-based data sources. However, the consistency of results in sensitivity analyses using alternative exposure duration windows does not support exposure misclassification. Outcome misclassification is possible, and the validation process had severe limitations because of the low response rate to GP questionnaires and the unavailability of

TABLE 3 Incidence rates and incidence rate ratios for genital infections and severe genital infections among initiators of empagliflozin and of DPP-4 inhibitors in propensity score–trimmed study cohorts, Clinical Practice Research Datalink.

	Males		Females	
	Empagliflozin	DPP-4 inhibitors	Empagliflozin	DPP-4 inhibitors
Genital infections				
Number of patients	8272	45 683	5802	31 940
Number of events	319	550	354	689
Person-years	6749.9	538 092	4459.2	353 907
Unadjusted IR[a] (95% CI)	47.26 (42.22-52.74)	10.22 (9.38-11.11)	79.39 (71.33-88.10)	19.47 (18.04-20.98)
Adjusted IR[a] (95% CI)	47.23 (42.28-52.76)	11.70 (10.45-13.10)	79.65 (71.72-88.45)	24.58 (22.28-27.13)
Unadjusted IRR[b] (95% CI)	4.62 (4.02-5.32)	Reference	4.08 (3.58-4.64)	Reference
Adjusted IRR[b] (95% CI)	4.04 (3.46-4.71)	Reference	3.24 (2.81-3.74)	Reference
Severe genital infections				
Number of patients	8272	45 683	5802	31 940
Number of events	293	506	263	494
Person-years	67 699	538 463	4522.7	35593.1
Unadjusted IR[a] (95% CI)	43.28 (38.47-48.53)	9.40 (8.60-10.25)	58.15 (51.33-65.62)	13,88 (12.68-15.16)
Adjusted IR[a] (95% CI)	43.35 (38.63-48.65)	10.72 (9.53-12.07)	58.42 (51.73-65.97)	17.48 (15.57-19.64)
Unadjusted IRR[b] (95% CI)	4.61 (3.97-5.33)	Reference	4.19 (3.59-4.88)	Reference
Adjusted IRR[b] (95% CI)	4.04 (3.44-4.75)	Reference	3.34 (2.83-3.95)	Reference

Note: IRR <1.0 means reduced risk of the outcome of interest among initiators of empagliflozin compared with initiators of DPP-4 inhibitors.
No cases of Fournier's gangrene were identified.
Abbreviations: CI, confidence interval; DPP-4, dipeptidyl peptidase-4; IR, incidence rate; IRR, incidence rate ratio.
[a]Per 1000 person-years.
[b]Both unadjusted and adjusted IRRs for empagliflozin relative to DPP-4 inhibitors were derived from a Poisson regression model within the PS-trimmed populations, where outcome was modelled as a function of treatment cohort, with the log of years of exposure as the offset. The adjusted IRR also includes propensity score decile categories as explanatory variables.

inpatient laboratory results in CPRD; the low number of events (and the low number of validated events) for some outcomes, which impacted the precision of PPVs, particularly for ALI outcomes; and the unavailability, for some patients, of specific test results required for validation (e.g. ketosis measurements for the DKA outcome). Furthermore, estimates for sensitivity were not calculated in the validation studies, and it is assumed that any false-negative errors were non-differential in this study. For some rarer outcomes, such as ALI1 and DKA, the precision of the adjusted IRRs was low, particularly for some subgroup analyses. Despite these limitations, in most sensitivity analyses performed on only confirmed events or corrected by the PPV, results were in line with the main analysis and with all other sensitivity analyses, with notable exceptions for the ALI1 outcome, for which data were sparse.

In conclusion, empagliflozin compared with the use of DPP-4 inhibitors is associated with increased risks of DKA (approximately two-fold) and GI (approximately four-fold), both of which are class effects for SGLT2 inhibitors. For ALI, AKI, CKD and severe complications of UTI, the beneficial effects of empagliflozin compared with the use of DPP-4 inhibitors are compatible with previous observations of the pleiotropic effects of SGLT2 inhibitors on body weight, diuresis, blood pressure, alanine aminotransferase and estimated glomerular filtration rate,[34] potentially mediating in part the improvement of the cardiometabolic disease risks of patients with T2D.

ACKNOWLEDGMENTS

The authors wish to thank Anahit Papazian of Carelon Research, Inc. for project management and Diana Hedevang Christensen of Aarhus University for her work on this study in its early phases. Kate Lothman of RTI Health Solutions provided medical writing services, which were funded by the Boehringer Ingelheim & Eli Lilly and Company Diabetes Alliance. The study was supported and funded by the Boehringer Ingelheim & Eli Lilly and Company Diabetes Alliance.

CONFLICT OF INTEREST STATEMENT

The study was supported and funded by the Boehringer Ingelheim & Eli Lilly and Company Diabetes Alliance, including a contract with RTI Health Solutions granting the research team independent publication rights. CR, DM, RGE, EP, AT, SPG, and MPV are employees of RTI Health Solutions. RWT and MM are employees of Aarhus University. AKT and DCB are employees of Carelon Research. SFF is an employee of Boehringer Ingelheim.

DATA AVAILABILITY STATEMENT

Study data are confidential due to the privacy policies of each of the data sources.

ORCID

Cristina Rebordosa https://orcid.org/0000-0002-8064-5997

REFERENCES

1. EMA. *European Medicines Agency, Committee for Medicinal Products for Human Use. Assessment Report: Jardiance. EMA/CHMP/137741/2014*. EMA; 2014. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002677/WC500168594.pdf. Accessed 09 October 2014.
2. FDA. Drug approval package: Jardiance (empagliflozin) tablets. 8 September 2014. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/204629Orig1s000TOC.cfm. Accessed 11 September 2023.
3. Boehringer Ingelheim International GmbH. *Jardiance (Empagliflozin) Summary of Product Characteristics*. Boehringer Ingelheim International GmbH; 2014. http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002677/human_med_001764.jsp&mid=WC0b01ac058001d124. Accessed 09 October 2014.
4. ENCePP. ENCEPP/SDPP/13413: Post-authorisation safety study in patients with type 2 diabetes mellitus to assess the risk of acute liver injury, acute kidney injury and chronic kidney disease, severe complications of urinary tract infection, genital infections, and diabetic ketoacidosis among patients treated with empagliflozin compared to patients treated with other SGLT2 inhibitors or DPP-4 inhibitors. 21 Oct 2015. https://www.encepp.eu/encepp/openAttachment/fullProtocol/16192. Accessed 19 Jun 2023
5. Rosenstock J, Ferrannini E. Euglycemic diabetic ketoacidosis: a predictable, detectable, and preventable safety concern with SGLT2 inhibitors. *Diabetes Care*. 2015;38(9):1638-1642. doi:10.2337/dc15-1380
6. Patorno E, Pawar A, Wexler DJ, et al. Effectiveness and safety of empagliflozin in routine care patients: results from the EMPagliflozin compaRative effectIveness and SafEty (EMPRISE) study. *Diabetes Obes Metab*. 2022;24(3):442-454. doi:10.1111/dom.14593
7. Fralick M, Schneeweiss S, Patorno E. Risk of diabetic ketoacidosis after initiation of an SGLT2 inhibitor. *N Engl J Med*. 2017;376(23):2300-2302. doi:10.1056/NEJMc1701990
8. Hamblin PS, Wong R, Ekinci EI, et al. SGLT2 inhibitors increase the risk of diabetic ketoacidosis developing in the community and during hospital admission. *J Clin Endocrinol Metab*. 2019;104(8):3077-3087. doi:10.1210/jc.2019-00139
9. Wang L, Voss EA, Weaver J, et al. Diabetic ketoacidosis in patients with type 2 diabetes treated with sodium glucose co-transporter 2 inhibitors versus other antihyperglycemic agents: an observational study of four US administrative claims databases. *Pharmacoepidemiol Drug Saf*. 2019;28(12):1620-1628. doi:10.1002/pds.4887
10. Wang Y, Desai M, Ryan PB, et al. Incidence of diabetic ketoacidosis among patients with type 2 diabetes mellitus treated with SGLT2 inhibitors and other antihyperglycemic agents. *Diabetes Res Clin Pract*. 2017;128:83-90. doi:10.1016/j.diabres.2017.04.004
11. Kim YG, Jeon JY, Han SJ, Kim DJ, Lee KW, Kim HJ. Sodium-glucose co-transporter-2 inhibitors and the risk of ketoacidosis in patients with type 2 diabetes mellitus: a nationwide population-based cohort study. *Diabetes Obes Metab*. 2018;20(8):1852-1858. doi:10.1111/dom.13297
12. Laursen HVB, Roikjer JB, Dal J, Jensen MH. Sodium glucose Cotransporter-2 inhibitor treatment and the risk of diabetic ketoacidosis in Denmark: a retrospective cohort study of five years of use. *Curr Drug Saf*. 2021;16(1):73-81. doi:10.2174/1574886315666200819114629
13. Chrysavgis L, Papatheodoridi AM, Chatzigeorgiou A, Cholongitas E. The impact of sodium glucose co-transporter 2 inhibitors on non-alcoholic fatty liver disease. *J Gastroenterol Hepatol*. 2021;36(4):893-909. doi:10.1111/jgh.15202
14. Pokharel A, Kc S, Thapa P, et al. The effect of empagliflozin on liver fat in type 2 diabetes mellitus patients with non-alcoholic fatty liver disease. *Cureus*. 2021;13(7):e16687. doi:10.7759/cureus.16687
15. Chehrehgosha H, Sohrabi MR, Ismail-Beigi F, et al. Empagliflozin improves liver steatosis and fibrosis in patients with non-alcoholic fatty liver disease and type 2 diabetes: a randomized, double-blind. *Placebo-Controlled Clin Trial Diabetes Ther*. 2021;12(3):843-861. doi:10.1007/s13300-021-01011-3
16. Qiu M, Ding LL, Zhang M, Zhou HR. Safety of four SGLT2 inhibitors in three chronic diseases: a meta-analysis of large randomized trials of SGLT2 inhibitors. *Diab Vasc Dis Res*. 2021;18(2) 14791641211011016. doi:10.1177/14791641211011016
17. Johannes CB, Beachler DC, Layton JB, et al. Post-authorization safety study of hospitalization for acute kidney injury in patients with type 2 diabetes exposed to dapagliflozin in a real-world setting. *Drug Saf*. 2023;46(2):157-174. doi:10.1007/s40264-022-01263-3
18. Lee YT, Hsu CN, Fu CM, Wang SW, Huang CC, Li LC. Comparison of adverse kidney outcomes with empagliflozin and linagliptin use in patients with type 2 diabetic patients in a real-world setting. *Front Pharmacol*. 2021;12:781379. doi:10.3389/fphar.2021.781379
19. Wanner C, Inzucchi SE, Lachin JM, et al. Empagliflozin and progression of kidney disease in type 2 diabetes. *N Engl J Med*. 2016;375(4):323-334. doi:10.1056/NEJMoa1515920
20. Packer M, Anker SD, Butler J, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. *N Engl J Med*. 2020;383(15):1413-1424. doi:10.1056/NEJMoa2022190
21. Bailey CJ, Day C, Bellary S. Renal protection with SGLT2 inhibitors: effects in acute and chronic kidney disease. *Curr Diab Rep*. 2022;22(1):39-52. doi:10.1007/s11892-021-01442-z
22. Danysh HE, Johannes CB, Beachler DC, et al. Post-authorization safety studies of acute liver injury and severe complications of urinary tract infection in patients with type 2 diabetes exposed to dapagliflozin in a real-world setting. *Drug Saf*. 2023;46(2):175-193. doi:10.1007/s40264-022-01262-4
23. Liu J, Li L, Li S, et al. Effects of SGLT2 inhibitors on UTIs and genital infections in type 2 diabetes mellitus: a systematic review and meta-analysis. *Sci Rep*. 2017;7(1):2824. doi:10.1038/s41598-017-02733-w
24. Dave CV, Schneeweiss S, Patorno E. Comparative risk of genital infections associated with sodium-glucose co-transporter-2 inhibitors. *Diabetes Obes Metab*. 2019;21(2):434-438. doi:10.1111/dom.13531
25. Lega IC, Bronskill SE, Campitelli MA, et al. Sodium glucose cotransporter 2 inhibitors and risk of genital mycotic and urinary tract infection: a population-based study of older women and men with diabetes. *Diabetes Obes Metab*. 2019;21(11):2394-2404. doi:10.1111/dom.13820
26. Wyss R, Girman CJ, LoCasale RJ, Brookhart AM, Sturmer T. Variable selection for propensity score models when estimating treatment effects on multiple outcomes: a simulation study. *Pharmacoepidemiol Drug Saf*. 2013;22(1):77-85. doi:10.1002/pds.3356
27. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7(3):177-188. doi:10.1016/0197-2456(86)90046-2
28. DerSimonian R, Laird N. Meta-analysis in clinical trials revisited. *Contemp Clin Trials*. 2015;45(Pt A):139-145. doi:10.1016/j.cct.2015.09.002
29. Lash TL, Fox MP, Fink AK. *Applying Quantitative Bias Analysis to Epidemiologic Data*. Springer; 2009.
30. Boehringer Ingelheim International GmbH. Summary of the risk management plan for Jardiance (empagliflozin). European Medicines Agency 20 June 2022. https://www.ema.europa.eu/en/medicines/human/EPAR/jardiance. Accessed 21 September 2022
31. Fralick M, Redelmeier DA, Patorno E, et al. Identifying risk factors for diabetic ketoacidosis associated with SGLT2 inhibitors: a Nationwide

cohort study in the USA. *J Gen Intern Med*. 2021;36(9):2601-2607. doi:10.1007/s11606-020-06561-z
32. Alkabbani W, Zongo A, Minhas-Sandhu JK, et al. Sodium-glucose Cotransporter-2 inhibitors and urinary tract infections: a propensity score-matched population-based cohort study. Can. *J Diabetes*. 2022;46(4):392-403 e13. doi:10.1016/j.jcjd.2021.12.005
33. Franklin JM, Patorno E, Desai RJ, et al. Emulating randomized clinical trials with nonrandomized real-world evidence studies: first results from the RCT DUPLICATE initiative. *Circulation*. 2021;143(10):1002-1013. doi:10.1161/CIRCULATIONAHA.120.051718
34. Shao SC, Chang KC, Chien RN, et al. Effects of sodium-glucose co-transporter-2 inhibitors on serum alanine aminotransferase levels in people with type 2 diabetes: a multi-institutional cohort study. *Diabetes Obes Metab*. 2020;22(1):128-134. doi:10.1111/dom.13875

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Rebordosa C, Thomsen RW, Tave AK, et al. Liver, renal, genitourinary and diabetic ketoacidosis risks among new users of empagliflozin versus dipeptidyl peptidase-4 inhibitors in patients with type 2 diabetes: Post-authorization safety study based on multinational cohorts. *Diabetes Obes Metab*. 2024;1-14. doi:10.1111/dom.15429.