Post-Authorisation Safety Study Assessing the Risk of Liver, Renal, Genitourinary, and Diabetic Ketoacidosis Outcomes Among Users of Empagliflozin Versus DPP-4 Inhibitors in Patients With Type 2 Diabetes

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DISCLOSURES

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BACKGROUND

- Empagliflozin, a sodium-glucose cotransporter 2 (SGLT2), improves glycaemic control among patients with type 2 diabetes (T2D) by reducing renal glucose reabsorption.[1,2]
- Given empagliflozin's mechanism of action, the risks of liver and renal injury, genitourinary infection/injury, and diabetic ketoacidosis are of interest.[2]

OBJECTIVE

- In patients with T2D, to estimate the risks for empagliflozin initiators compared with dipeptidyl peptidase-4 (DPP-4) inhibitor initiators of the following:
  - Diabetic ketoacidosis (DKA) (hospitalisation or emergency department [ED] visit)
  - Acute liver injury in patients without predisposing conditions (ALI1) and in all patients with ALI (ALI2) (hospitalisation, ED visit, or specialist visit)
  - Acute kidney injury (AKI) (hospitalisation, ED visit, or specialist visit) and chronic kidney disease (CKD) (hospitalisation or outpatient)
  - Severe complications of urinary tract infections (UTIs) (hospitalisation or outpatient)
  - Genital infections (GIs) (hospitalisation or outpatient) and severe GIs (GIHs) (hospitalisation, ED visit, or requiring systemic treatment)

METHODS

- A non-interventional cohort study was conducted in the United Kingdom's Clinical Practice Research Datalink (CPRD), the Danish Population Registries (DR), and HealthCare Integrated Research Database (HIRD) (United States).
- The study population comprised patients with T2D initiating empagliflozin or a DPP-4 inhibitor between August 2014 and August 2019 (index date), aged ≥ 18 years, and with ≥ 12 months of continuous health plan registration immediately preceding their index date.
- Incidence rates (IRs) by exposure and corresponding IR ratios (IRRs) were adjusted for deciles of propensity scores (PSs). PSs were separately calculated within outcome-specific analysis populations.
- IRRs from all data sources were pooled via meta-analysis using random-effects methods.

RESULTS

- Prior to PS-trimming, the overall study population comprised 76,174 empagliflozin initiators (Figure 1) with a mean age of 57.2 years and 257,406 DPP-4 inhibitor initiators (Figure 1) with a mean age of 62.1 years. Approximately 60% of all initiators were male.
- After PS-trimming to remove patients with extreme values, the total analysis population comprised 64,599 empagliflozin and 203,315 DPP-4 inhibitor initiators, and most covariates were balanced.
- Pooled adjusted IRRs (95% confidence interval) for the outcomes of interest were:
  - DKA: 2.19 (1.74-2.76) (Figure 2A)
  - ALI1: 0.77 (0.50-1.19) (Figure 2B)
  - ALI2: 0.70 (0.56-0.88) (Figure 2C)
  - AKI: 0.54 (0.41-0.73) (Figure 2D)
  - CKD: 0.53 (0.43-0.65) (Table 1)
  - UTI: 0.51 (0.37-0.72) (Table 1)
  - GI in males: 4.04 (3.46-4.71); GIH in males: 4.04 (3.44-4.75) (Table 2)
  - GI in females: 3.24 (2.81-3.74); and GIH in females: 3.34 (2.83-3.95) (Table 2)
- The consistency of results using alternative exposure duration windows did not support exposure misclassification.
- Results were consistent across data sources and all subgroup and sensitivity analyses (data not shown). Although some variations in the IRRs were observed, they were likely related to the small numbers of events in some analyses.

Figure 1. Cohort Attrition

	Patients with at least one prescription of empagliflozin during the study period	Patients with at least one prescription of DPP-4 inhibitors during the study period
CPRD	33,386	187,599
DR	28,864	70,853
HIRD	125,153	359,710
Pooled	187,403	618,162
	Meet all the inclusion criteria (DKA)	**Meet all the inclusion criteria (DKA)**
CPRD	16,339	97,616
DR	18,689	43,443
HIRD	41,146	116,347
Pooled	76,174	257,406

	Meet all outcome-specific exclusion criteria						
	ALI1	AKI	UTI	GIM	GIF	ALI2	CKD
CPRD	12,873	15,142	16,320	9,577	6,762	16,104	15,191
DR	14,790	17,336	NA	NA	NA	18,200	NA
HIRD	29,276	35,973	NA	NA	NA	39,696	NA
Pooled	56,939	68,451	NA	NA	NA	74,000	NA

	Meet all outcome-specific exclusion criteria						
	ALI1	AKI	UTI	GIM	GIF	ALI2	CKD
CPRD	75,507	71,035	97,413	55,876	41,740	94,490	71,766
DR	34,064	35,019	NA	NA	NA	41,770	NA
HIRD	84,917	95,697	NA	NA	NA	110,759	NA
Pooled	194,488	201,751	NA	NA	NA	247,019	NA

GIF = genital infections in females; GIM = genital infections in males; NA = not applicable.

Figure 2. IR and IRR for Primary Outcomes Among Initiators of Empagliflozin and DPP-4 Inhibitors in PS-Trimmed Study Cohorts, All Data Sources and Meta-analysis

CI = confidence interval; df = degrees of freedom; GLD = glucose-lowering drug; I^2 = heterogeneity statistic; N = number; NE = not estimable; NR = not reportable due to small cell count(s); Q = Cochran's Q statistic.

Note: IRR below 1.0 means reduced risk of the outcome of interest among initiators of empagliflozin compared with initiators of DPP-4 inhibitors.

[a] Per 1,000 person-years.

[b] Both unadjusted and adjusted IRRs for empagliflozin relative to DPP-4 inhibitors are derived from a Poisson regression model within the PS-trimmed population that includes the exposure and the natural logarithm of person-years at risk as the offset. The adjusted IRR also controls for the PS deciles in the Poisson regression model.

[c] Heterogeneity statistics from the meta-analysis exclude users of 3 or more GLDs in Danish Registries.

Table 1. IRs and IRRs for CKD and UTI Among Initiators of Empagliflozin and DPP-4 Inhibitors in PS-Trimmed Study Cohorts, CPRD

	Empagliflozin	DPP-4 inhibitors
CKD		
Number of patients	13,256	62,435
Number of events	104	1,368
Person-years	10,894.9	70,503.8
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	11,641.3	89,361.5
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 below 1.0 means reduced risk of the outcome of interest among initiators of empagliflozin compared with initiators of DPP-4 inhibitors.

[a] Per 1,000 person-years.

[b] Both unadjusted and adjusted IRRs for empagliflozin relative to DPP-4 inhibitors are derived from a Poisson regression model within the PS-trimmed population that includes the exposure and the natural logarithm of the person-years at risk as the offset. The adjusted IRR also controls for the PS deciles in the Poisson regression model.

Table 2. IR and IRR for GI and GIH Among Initiators of Empagliflozin and DPP-4 Inhibitors in PS-Trimmed Study Cohorts, by Sex, CPRD

	Males		Females	
	Empagliflozin	DPP-4 inhibitors	Empagliflozin	DPP-4 inhibitors
GI				
Number of patients	8,272	45,683	5,802	31,940
Number of events	319	550	354	689
Person-years	6,749.9	53,809.2	4,459.2	35,390.7
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
GIH				
Number of patients	8,272	45,683	5,802	31,940
Number of events	293	506	263	494
Person-years	6,769.9	53,846.3	4,522.7	35,593.1
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]	4.04 (3.44-4.75)	Reference	3.34 (2.83-3.95)	Reference

Note: IRR below 1.0 means reduced risk of the outcome of interest among initiators of empagliflozin compared with initiators of DPP-4 inhibitors.

[a] Per 1,000 person-years.

[b] Both unadjusted and adjusted IRRs for empagliflozin relative to DPP-4 inhibitors are derived from a Poisson regression model within the PS-trimmed population that includes the exposure and the natural logarithm of the person-years at risk as the offset. The adjusted IRR also controls for the PS deciles in the Poisson regression model.

LIMITATIONS

- PSs were estimated to account for potential confounding, but residual confounding due to unmeasured variables cannot be discarded.
- Outcome misclassification was possible, and the validation substudy had limitations due to low response rate and/or the unavailability of laboratory results in some cases.

CONCLUSIONS

- Empagliflozin initiators compared with initiators of DPP-4 inhibitors was associated with increased risks of DKA (approximately 2-fold) and GI (approximately 4-fold). Both are known class effects for SGLT2 inhibitors and identified in empagliflozin's risk management plan and in previous studies.[3-7]
- Decreased risks of ALI, AKI, CKD, and UTI observed among users of empagliflozin compared with users of DPP-4 inhibitors may reflect beneficial metabolic effects of empagliflozin.

REFERENCES

1. EMA. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002677/WC500168594.pdf.
2. Boehringer Ingelheim. http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002677/human_med_001764.jsp&mid=WC0b01ac058001d124.
3. Boehringer Ingelheim. https://www.ema.europa.eu/en/medicines/human/EPAR/jardiance.
4. Qiu M et al. Diab Vasc Dis Res. 2021;18(2):14791641211011016.
5. Patorno E et al. Diabetes Obes Metab. 2022;24(3):442-54.
6. Fralick M et al. N Engl J Med. 2017;376(23):2300-2.
7. Liu J et al. Sci Rep. 2017;7(1):2824.

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