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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ALI1

AKI

84,917 95,697 NA

194,488 201,751 NA

34,064 35,019

UTI

NA

ALI2

41,770

110,759

NA 247,019 NA

CKD

NA

NA

187,599

70,853

359.710

618,162

97,616

43,443

116,347

257,406

Meet all outcome-specific exclusion criteria

75,507 71,035 97,413 55,876 41,740 94,490 71,766



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 (Gls) (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 \geq 18 years, and with \geq 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:

- 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)

- GI in females: 3.24 (2.81-3.74);

and GIH in females: 3.34

(2.83-3.95) (Table 2)

- DKA: 2.19 (1.74-2.76) (Figure 2A)
- ALI1: 0.77 (0.50-1.19)
- (Figure 2B)
- AKI: 0.54 (0.41-0.73) (Figure 2D)
- (Figure 2C)

- ALI2: 0.70 (0.56-0.88)

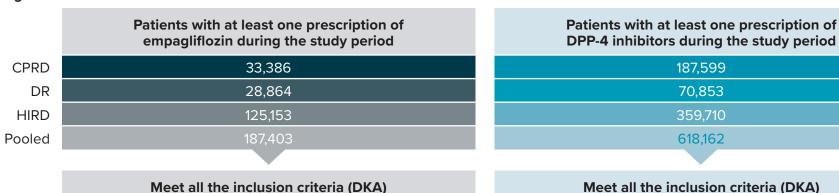
 The consistency of results using alternative exposure duration windows did not support exposure misclassification.

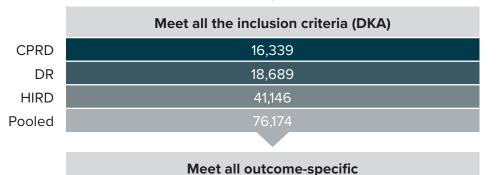
(Table 2)

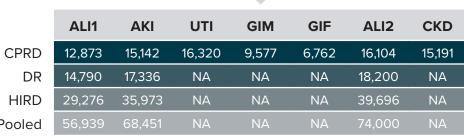
 Results were consistent across data sources and all subgroup and sensitivity analyses (data not shown). Although some variations in the IRRs were observed, they were likely related to the small numbers of events in some analyses.

Figure 1. Cohort Attrition

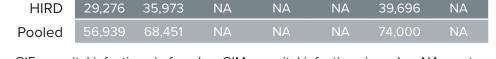
V DKV







exclusion criteria

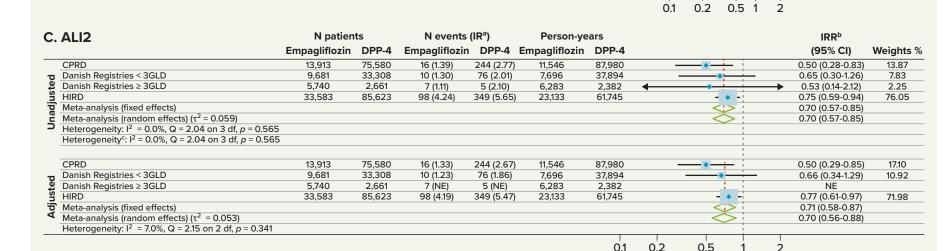


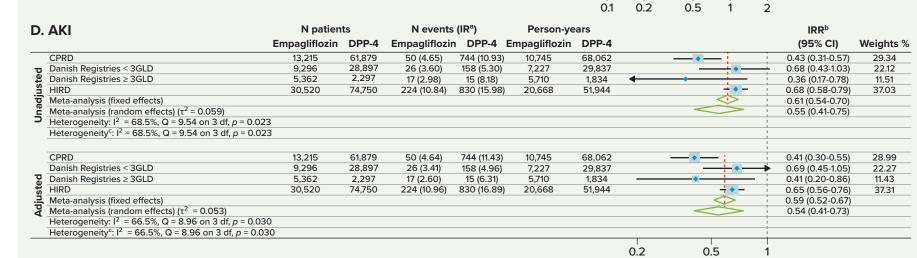
GIF = genital infections in females; GIM = genital infections in males; NA = not applicable.

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

| A. DKA | 14 patien | ıs | 14 events | ('''') | i erson-ye | ais | | | | | IKK | |
|---|---------------|--------|---------------|------------|---------------|--------|----------|-----|---------------|----------|------------------|-----------|
| | Empagliflozin | DPP-4 | Empagliflozin | DPP-4 | Empagliflozin | DPP-4 | | | | | (95% CI) | Weights % |
| CPRD | 14,086 | 77,408 | 33 (2.82) | 94 (1.04) | 11,686 | 90,183 | | - : | \rightarrow | | 2.71 (1.76-4.07) | 31.51 |
| Danish Registries < 3GLD | 9,923 | 33,973 | 13 (1.65) | 33 (0.86) | 7,872 | 38,592 | | - | -•- | _ | 1.93 (0.93-3.77) | 18.07 |
| Danish Registries ≥ 3GLD | 5,905 | 2,742 | 13 (2.01) | 7 (2.89) | 6,482 | 2,426 | ← | | _: | | 0.69 (0.26-2.06) | 10.00 |
| HIRD | 34,685 | 89,192 | 88 (3.68) | 119 (1.86) | 23,893 | 64,142 | | - 1 | - • - | | 1.99 (1.49-2.64) | 40.42 |
| Meta-analysis (fixed effects) | | | | | | | | | \Diamond | | 2.06 (1.65-2.56) | |
| Meta-analysis (random effects) (τ2 = 0.059) | | | | | | | | - | $\overline{}$ | • | 1.96 (1.36-2.82) | |
| Heterogeneity: $I^2 = 49.6\%$, Q = 5.95 on 3 df, p = 0.114 | | | | | | | | | | | | |
| Heterogeneity ^c : I^2 = 49.6%, Q = 5.95 on 3 df, p = 0.114 | | | | | | | | 1 | | | | |
| | | | | | | | | | | | | |
| CPRD | 14,086 | 77,408 | 33 (2.57) | 94 (0.92) | 11,686 | 90,183 | | - 1 | - | → | 2.78 (1.77-4.36) | 26.19 |
| Danish Registries < 3GLD | 9,923 | 33,973 | 13 (1.50) | 33 (0.70) | 7,872 | 38,592 | | - : | • | | 2.14 (1.11-4.12) | 12.29 |
| Danish Registries ≥ 3GLD | 5,905 | 2,742 | 13 (NE) | 7 (NE) | 6,482 | 2,426 | | - 1 | | | NE | |
| HIRD | 34,685 | 89,192 | 88 (3.62) | 119 (1.82) | 23,893 | 64,142 | | | - • - | | 1.99 (1.48-2.66) | 61.52 |
| Meta-analysis (fixed effects) | | | | | | | | | | | 2.19 (1.74-2.76) | |
| Meta-analysis (random effects) ($\tau^2 = 0.053$) | | | | | | | | | \Diamond | | 2.19 (1.74-2.76) | |
| Heterogeneity: $I^2 = 0.0\%$, Q = 1.50 on 2 df, p = 0.471 | | | | | | | | | | | | |
| | | | | | | | | | Ţ | <u> </u> | | |
| | | | | | | | 0.5 | 1 | 2 | 3 5 | | |
| | | | | | | | | | | | | |

| В. | ALI1 | N patien | ts | N events | IR ^a) | Person-ye | ars | | IRR ^b | |
|--------------|---|---------------|--------|---------------|-------------------|---------------|--------|-------------------------|------------------|-----------|
| | | Empagliflozin | DPP-4 | Empagliflozin | DPP-4 | Empagliflozin | DPP-4 | | (95% CI) | Weights % |
| _ | CPRD | 11,189 | 61,254 | 6 (0.65) | 80 (1.14) | 9,204 | 70,065 | | 0.57 (0.20-1.30) | 20.36 |
| σ | Danish Registries < 3GLD | NR | 27,404 | NR (0.32) | 34 (1.10) | NR | 30,788 | • | 0.29 (0.03-1.13) | 5.67 |
| ţ. | Danish Registries ≥ 3GLD | NR | NR | NR (0.57) | NR (1.62) | NR | NR | • | 0.35 (0.05-2.65) | 4.32 |
| .sn | HIRD | 24,864 | 65,896 | 22 (1.32) | 81 (1.77) | 16,702 | 45,790 | - • - | 0.74 (0.44-1.21) | 69.65 |
| <u> </u> | Meta-analysis (fixed effects) | | | | | | | \Diamond | 0.65 (0.43-0.98) | |
| na L | Meta-analysis (random effects) ($\tau^2 = 0.059$) | | | | | | | | 0.65 (0.43-0.98) | |
| _ | Heterogeneity: $I^2 = 49.6\%$, Q = 1.51 on 3 df, p = 0.679 | | | | | | | | | |
| | Heterogeneity ^c : $I^2 = 49.6\%$, Q = 1.51 on 3 df, p = 0.679 | | | | | | | | | |
| | | | | | | | | | | |
| | CPRD | 11,189 | 61,254 | 6 (0.60) | 80 (1.09) | 9,204 | 70,065 | | 0.55 (0.23-1.32) | 24.11 |
| 7 | Danish Registries < 3GLD | NR | 27,404 | NR (NE) | 34 (NE) | NR | 30,788 | | NE | |
| ě | Danish Registries ≥ 3GLD | NR | NR | NR (NE) | NR (NE) | NR | NR | : : | NE | |
| Sn | HIRD | 24,864 | 65,896 | 22 (1.21) | 81 (1.41) | 16,702 | 45,790 | - • - | 0.86 (0.52-1.41) | 75.89 |
| . | Meta-analysis (fixed effects) | | | | | | | \Diamond | 0.77 (0.50-1.19) | |
| ⋖ | Meta-analysis (random effects) ($\tau^2 = 0.053$) | | | | | | | | 0.77 (0.50-1.19) | |
| | Heterogeneity: $I^2 = 0.0\%$, Q = 0.75 on 1 df, p = 0.388 | | | | | | | | | |





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

^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**

| 1 5-11 mined study conorts, or Kb | | | | | | |
|--------------------------------------|-------------------|---------------------|--|--|--|--|
| | 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 | | | | |
| evere 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

| | Mal | es | 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.

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