Empagliflozin and the risk of Gout: Analysis from the EMPagliflozin compaRative effectIveness and SafEty (EMPRISE) study

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Background

Hyperuricemia is frequently observed in patients with type 2 diabetes (T2D) and is associated with increased risk of gout. Empagliflozin lowers serum urate levels by enhancing its urinary excretion. There is limited evidence that use routinely collected data to evaluate the association between empagliflozin and its effect on gout incidence.

Objective

To compare initiators of empagliflozin vs. dipeptidyl peptidase-4 inhibitor (DPP4i) (cohort 1) and initiators of empagliflozin vs. glucagon-like peptide-1 receptor agonist (GLP-1RA) (cohort 2) with respect to the risk of incident gout events.

Methods

Data Sources: Two commercial claims datasets (Optum Clinformatics (CDM) and IBM® MarketScan®) and Medicare fee-for-service data (2014-2019).

Study design: New user, active comparator cohort study

Outcome: Our primary outcome was incident gout diagnosis defined as the occurrence of an inpatient gout diagnosis or an outpatient gout diagnosis co-occurring with a prescription claim or an outpatient medication administration to treat gout flares within 14 days of the recorded diagnosis. In a secondary analysis, incident gout was defined only based on a hospital inpatient discharge diagnosis in any position.

Statistical analysis: We estimated hazard ratios (HRs), rate differences (RD) and their 95% confidence intervals (CI) in 1:1 propensity score (PS) matched cohorts that adjusted for 141 baseline covariates in the PS model. Subgroup analyses were conducted by sex, age (<65 and ≥65 years), BMI (30-39 and ≥40 kg/m^2), heart failure, CKD, ASCVD, and concurrent use of loop and thiazide diuretics.

Tables and figures

Table 1. Selected baseline characteristics in 1:1 propensity score-matched population from 3 databases[1]

	Cohort 1			Cohort 2		
Pooled patient characteristics[2]	**Empagliflozin (N=102,262)**	**DPP4i (N=102,262)**	**St. diff**	**Empagliflozin (N=131,216)**	**GLP-1RA (N=131,216)**	**St. diff**
Age, mean (SD)	61.98 (9.15)	61.98 (9.12)	0.00	62.07 (9.07)	62.10 (9.05)	0.00
Gender male; n (%)	54,815 (53.6%)	54,571 (53.4%)	0.00	69,181 (52.7%)	64,494 (53.0%)	0.00
Hyperlipidemia; n (%)	80,077 (78.3%)	79,929 (78.2%)	0.00	103,655 (79.0%)	103,695 (79.0%)	0.00
Heart failure; n (%)	7,824 (7.7%)	7,761 (7.6%)	0.00	9,462 (7.2%)	9,699 (7.4%)	0.01
Chronic kidney disease (CKD), stages 3-4; n (%)	6,034 (5.9%)	6,020 (5.9%)	0.00	8,196 (6.2%)	8,196 (6.2%)	0.00
Kidney and urinary stone; n (%)	3,712 (3.6%)	3,690 (3.6%)	0.00	4,740 (3.6%)	4,763 (3.6%)	0.00
Psoriasis; n (%)	1,892 (1.9%)	1,878 (1.8%)	0.01	2,352 (1.8%)	2,393 (1.8%)	0.00
Number of diabetes medications at index date, mean (SD)	1.25 (0.84)	1.25 (0.83)	0.00	1.44 (0.94)	1.46 (0.96)	0.02
Thiazide or thiazide like diuretics; n (%)	13,517 (13.2%)	13,464 (13.2%)	0.00	17,124 (13.1%)	17,172 (13.1%)	0.00
Loop diuretics; n (%)	10,974 (10.7%)	11,003 (10.8%)	0.00	13,826 (10.5%)	13,967 (10.6%)	0.00
HbA1C, %, mean (SD)	8.99 (2.32)	8.96 (2.33)	0.01	9.03 (2.29)	9.06 (2.38)	0.01
Serum urate, mg/dL, mean (SD)	5.38 (1.58)	5.56 (1.55)	0.12	5.38 (1.55)	5.47 (1.48)	0.06

PS: propensity score; GLP-1RA: glucagon-like peptide-1 receptor agonist; DPP4i: dipeptidyl peptidase-4 inhibitors; SD: standard deviation; St. diff.: standardized difference; RD: Rate difference; PY: person-years; HR: hazard ratio; CI: confidence interval; BMI: Body mass index; HF: Heart failure; ASCVD: atherosclerotic cardiovascular disease

[1]For each cohort, results were pooled across three databases (Optum CDM, IBM® MarketScan®, and Medicare fee-for-service). Follow-up started one day following treatment initiation and ended at the occurrence of a study outcome, insurance disenrollment, treatment switch/discontinuation, or end of the study period, whichever came first. [2]Patient characteristics were measured during the 12 months (365 days) preceding (and including) date of treatment initiation.

Figure 1. Primary Outcome and Subgroup Analyses

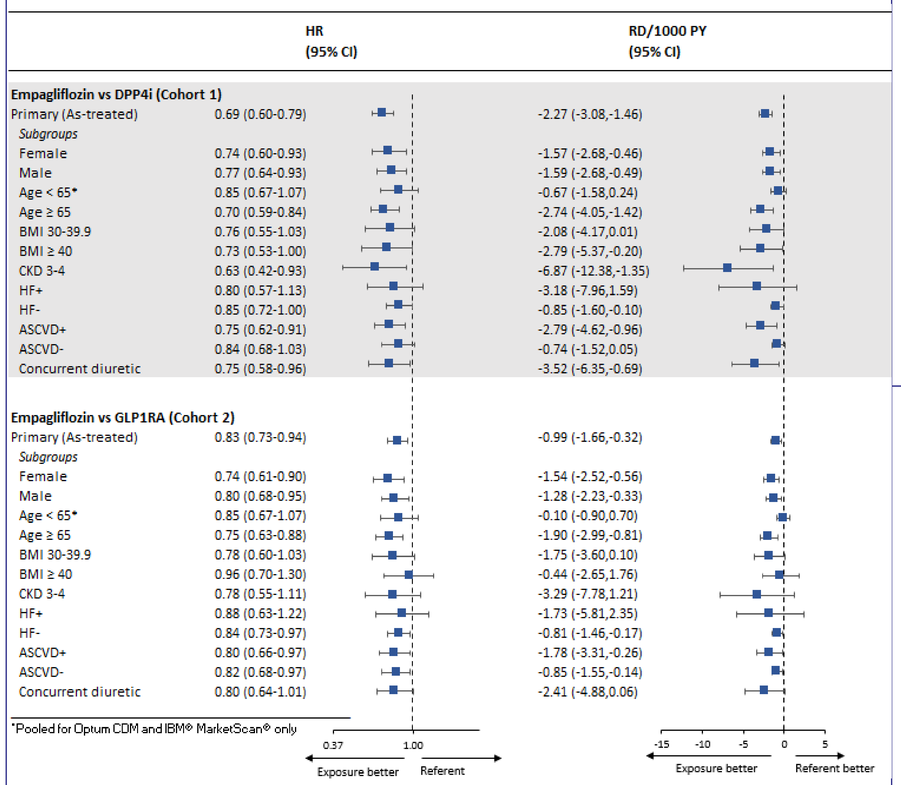
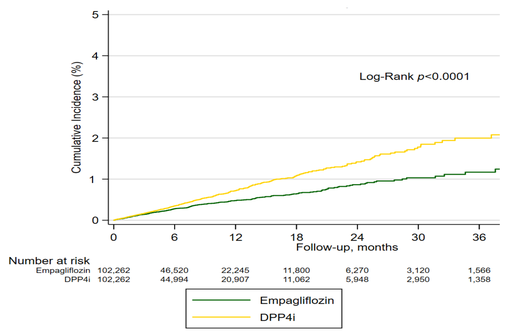
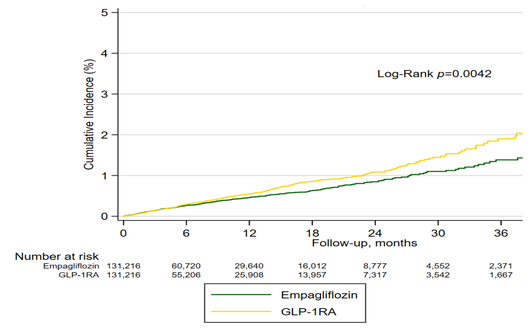


Figure 2. Kaplan-Meier Curves for Incidence of Gout within Matched Groups of empagliflozin vs DPP4i



DPP4i: dipeptidyl peptidase-4 inhibitors

Figure 3. Kaplan-Meier Curves for Incidence of Gout within Matched Groups of empagliflozin vs GLP-1RA



GLP-1RA: glucagon-like peptide-1 receptor agonist

SC-US-76215

Results

After 1:1 PS matching, we identified 102,262 pairs with type 2 diabetes (T2D) aged ≥ 18 years (≥ 65 in Medicare) and without history of gout or gout medications initiating empagliflozin or a DPP4i and 131,216 pairs initiating empagliflozin or a GLP-1RA. In both cohort 1 and cohort 2, the mean age was 62 (SD 9) years and 53% were male (**Table 1**).

For cohort 1, there were 342 incident gout events among patients initiating empagliflozin and 490 events among patients initiating a DPP4i. In cohort 2, there were 445 events among patients initiating empagliflozin and 493 events among patients initiating a GLP-1RA.

Over a mean follow-up of ~8 months on treatment, the risk of incident gout was lower in the empagliflozin group compared with the DPP4i group (HR 0.69 [95% CI 0.60-0.79]; RD/1,000 PY -2.27 [95% CI, -3.08, 1.46]) and the GLP-1RA group (HR 0.83 [95% CI 0.73-0.94]; RD/1,000 PY -0.99 [95% CI, -1.66, -0.32]) (**Figures 1, 2 and 3**).

Subgroup analyses (**Figure 1**) produced consistent results.

Conclusions

In routine care, empagliflozin use was associated with a reduced risk of incident gout, compared to DPP4i and GLP-1RA use in patients with T2D.

Funding & Disclosures

This study was supported by a research grant to the Brigham and Women's Hospital from Boehringer-Ingelheim. The authors had full control of the design and conduction of the study and interpretation of the study's findings.

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