Effectiveness and safety of empagliflozin in routine care: Results from the EMPagliflozin compaRative effectIveness and SafEty (EMPRISE) study

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Background

- In the EMPA-REG OUTCOME trial, empagliflozin reduced the risk of cardiovascular death by 38%, all-cause mortality by 32%, and hospitalization for heart failure (HHF) by 35% in patients with type 2 diabetes (T2D) and established cardiovascular disease
- EMPRISE aims to assess comparative effectiveness, safety, health care utilization and cost of empagliflozin in patients with T2D (NCT03363464; EUPAS20677)
- EMPRISE uses real-world data from two commercial insurance claims data and federal Medicare data in the U.S. and collects accumulating data on empagliflozin for a period of 5 years, starting from empagliflozin launch in the U.S., i.e.. August 1, 2014

Objective

Using real-world data from August 2014 through September 2019, we aimed to assess the cardiovascular effectiveness and safety of empagliflozin compared to dipeptidyl peptidase 4 inhibitors (DPP-4i) in patients with T2D across the spectrum of CV disease.

Methods

Study design: New-user active-comparator cohort study (**Figure 1**).

Data sources: US Medicare, Optum Clinformatics and IBM Marketscan databases (August 1, 2014-September 30, 2019).

Study population: Adults ≥18 years ≥65 years in Medicare) with T2D (**Figure 2**).

Exposure and comparator: Initiators of empagliflozin relative to DPP-4i.

Outcomes

Cardiovascular effectiveness outcomes	Safety outcomes
Hospitalization for heart failure (HHF)[1] (HHF-primary dx)	**Lower limb amputations[1]**
HHF in any discharge position (HHF-any dx)	**Non-vertebral fractures**
Composite of myocardial infarction (MI) or stroke	**Renal cancer**
Hospitalization for MI[1]	**Bladder cancer**
Hospitalization for stroke[1]	**Hospitalization for diabetic ketoacidosis[1]**
All-cause mortality[2]	**Acute kidney injury requiring dialysis[1]**

[1] Validated claims-based algorithms: Kiyota et al. AHJ 2004. Wahl et al. PDS 2010. Tirschwell et al. Stroke 2002. Saczynski et al. PDS 2012. Hudson et al. J Clin Epi 2013. Bobo et al. BMC Med Res Methodol. 2011. Waikar et al. JASN 2006.
[2] Only in Medicare

Statistical analyses: Confounding was addressed via 1:1 propensity score (PS) matching adjusting for over 140 baseline patient characteristics. Hazard ratios (HR) and rate differences (RD), accounting for mortality as a competing risk, separately within each database and pooled across databases by fixed-effects meta-analysis.

Subgroups: Baseline history of cardiovascular disease, defined as baseline atherosclerotic cardiovascular diseases and/or heart failure

Tables and figures

Table 1. Pooled patient characteristics during a 12-month baseline period prior to drug initiation from 3 databases

	Before PS-matching			After PS-matching		
Baseline characteristics	**Empagliflozin (N = 136,937)**	**DPP4i (N = 599,537)**	**Standardized mean differences**	**Empagliflozin (N = 115,116)**	**DPP4i (N = 115,116)**	**Standardized mean differences**
Age, mean (SD)	62.00 (8.65)	67.48 (9.09)	0.62	62.52 (8.64)	62.51 (8.65)	0.00
Sex female, n (%)	60,000 (43.8%)	312,601 (52.1%)	0.17	51,729 (44.9%)	51,661 (44.9%)	0.00
CVD history, n (%)[1]	47,179 (34.5%)	226,622 (37.8%)	0.07	38,379 (33.3%)	38,381 (33.3%)	0.00
Frailty index, mean (SD)	0.16 (0.04)	0.17 (0.05)	0.22	0.16 (0.04)	0.16 (0.04)	0.00
Acute MI, n (%)	3,482 (2.5%)	13,461 (2.2%)	-0.02	2,538 (2.2%)	2,520 (2.2%)	0.00
Heart failure, n (%)	11,913 (8.7%)	67,900 (11.3%)	0.09	9,706 (8.4%)	9,727 (8.4%)	0.00
Chronic kidney disease, n (%)	12,879 (9.4%)	109,377 (18.2%)	0.26	11,391 (9.9%)	11,636 (10.1%)	0.01
Current use of insulin; n (%)	21,281 (15.5%)	56,808 (9.5%)	-0.18	14,682 (12.8%)	14,637 (12.7%)	0.00
HbA1C, %, mean (SD)[2]	9.0 (2.3)	8.8 (2.3)	0.09	9.0 (2.3)	8.9 (2.3)	0.04
eGFR, mean (SD)[2]	85.2 (22.0)	78.5 (24.7)	0.29	85.1 (22.0)	83.7 (23.0)	0.06

[1] Defined as a history of myocardial infarction, unstable angina, other ischemic heart disease, transient ischemic attack, stroke, atherosclerotic peripheral vascular disease, or heart failure.
[2] Available for a subset (~20%) of patients, thus not included in in the PS model

Figure 1. EMPRISE study design overview

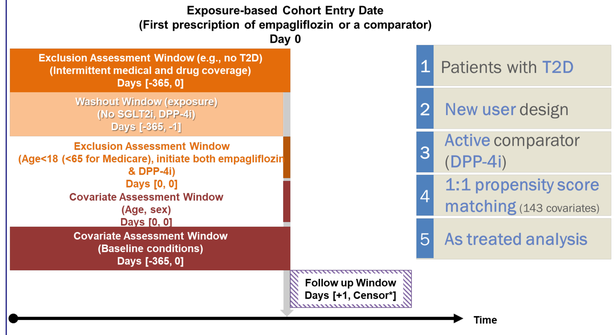


Figure 2. EMPRISE study population (2014-2019) from Medicare, Optum and Marketscan databases

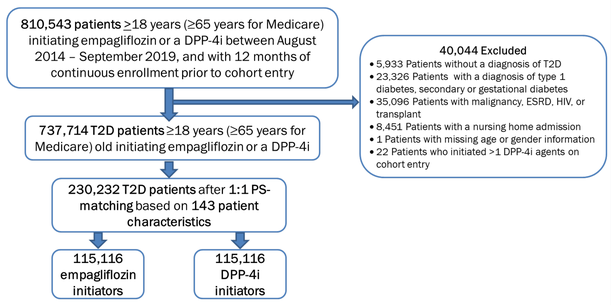
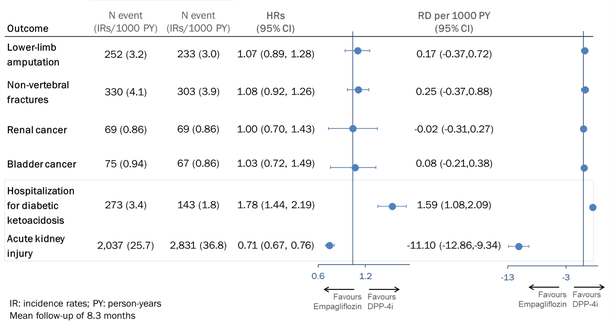


Figure 3. Hazard ratios and rate differences for empagliflozin and effectiveness outcomes

Figure 4. Hazard ratios and rate differences for empagliflozin and safety outcomes



Results

We identified 43,244 PS-matched pairs of patients with T2D in Medicare, 39,164 in Marketscan, and 32,708 in Optum, who initiated empagliflozin or a DPP-4i between August 1, 2014 and September 30, 2019 (**Figure 2 and Table 1**).

Effectiveness outcomes

- Compared with DPP-4i, empagliflozin was associated with a 29-50% reduction in the risk of HHF (corresponding to 5.4-10.8 fewer events per 1000 person-years), over a mean follow-up time of 8.3 months (**Figure 3**).
- Empagliflozin was associated with a 12% reduction in the risk of a composite outcome of myocardial infarction or stroke (2.2 fewer events per 1000 person-years), compared with DPP-4i.
- The risk of all-cause mortality, which was only estimated in the subset of the population with complete information, i.e., Medicare, was lower in empagliflozin vs. DPP-4i initiators.
- Results were consistent in subgroup analyses by history of cardiovascular disease, though the absolute cardiovascular benefit of empagliflozin was greater in patients with history of cardiovascular disease compared to those without it.

Safety outcomes

- Empagliflozin was associated with a reduction in the risk of acute kidney injury, an increased risk of hospitalization with diabetic ketoacidosis, and a similar risk of lower limb amputations, non-vertebral fracture, and renal and bladder cancer (**Figure 4**).

Conclusions

- In this final analysis from EMPRISE (2014-2019), including over 230,000 PS-matched U.S. patients, the initiation of empagliflozin was associated with a reduction in the risk of HHF, a slightly lower risk of a composite outcome of myocardial infarction or stroke, relative to DPP-4i, and, in Medicare patients (≥65 years), a reduction in the risk of all-cause mortality.
- Results were consistent in patients with and without history of cardiovascular disease, though the absolute benefits of empagliflozin were greater in patients with cardiovascular disease.
- Empagliflozin was associated with an increased risk of diabetic ketoacidosis, in line with documented safety information.
- These results complement cardiovascular outcome trial data and reinforce the notion of the beneficial effects of empagliflozin on cardiovascular outcomes, particularly heart failure, regardless of the baseline history of cardiovascular diseases.

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. The authors retained the right of publication and determined the final wording of the poster.
- Dr. Htoo is supported by the grant (4-22-PDFPM-15) from the American Diabetes Association.
- Dr Patorno is supported by grants from the National Institute on Aging (K08AG055670) and the Patient Centered Outcomes Research Institute (DB-2020C2-20326).

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SC-US-74430