Cardiorenal Effectiveness of Empagliflozin vs. GLP-1 Receptor Agonists in Patients with Advanced Chronic Kidney Disease: Results from the EMPRISE study

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Background

- Patients with chronic kidney disease (CKD) are at an increased risk of cardiovascular disease, heart failure, and mortality.
- We reported the final results of the EMPRISE study program in patients with type 2 diabetes (T2D) and advanced CKD.
- EMPRISE aims to assess the comparative effectiveness, safety, health care utilization and cost of empagliflozin in patients with T2D (NCT03363464; EUPAS20677).
- EMPRISE uses real-world data from the U.S. and collects accumulating data on empagliflozin for a period of 5 years.

Objective

We aimed to assess the cardiovascular effectiveness of empagliflozin compared to glucagon-like peptide-1 receptor agonists (GLP-1RA) in patients with T2D and CKD stages 3-4.

Methods

- **Study design:** New-user active-comparator cohort study.
- **Data sources:** US Medicare, Optum's de-identified Clinformatics® Data Mart Database, and IBM Marketscan (August 1, 2014-September 30, 2019).
- **Study population:** Adults ≥18 years ≥65 years in Medicare) with T2D and diagnoses for CKD stages 3-4.
- **Exposure and comparator:** Initiators of empagliflozin relative to GLP-1RA.
- **Outcomes:** Hospitalizations for myocardial infarction, ischemic or hemorrhagic stroke, and heart failure, were identified using validated claims-based algorithms with high specificity. End-staged kidney disease (ESKD) includes CKD stage 5, dialysis, kidney transplant, and replacement therapy.

Cardiorenal effectiveness outcomes
Composite of myocardial infarction (MI) or stroke[1]
Hospitalization for heart failure (HHF)[1]
End-stage kidney disease (ESKD)[1]
Secondary outcomes
Hospitalization for MI[1]
Hospitalization for stroke[1]
All-cause mortality[2]

[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. Paik et al. PDS 2022.
[2] Only in Medicare

Statistical analyses:

- Confounding was addressed via 1:1 propensity score (PS) matching adjusting for 143 baseline patient characteristics.
- PS was estimated as the predicted probability of initiating empagliflozin vs. GLP-1RA using multivariable logistic regression, and PS estimation and matching were conducted separately within each data source
- Hazard ratios (HR) and rate differences (RD), accounting for mortality as a competing risk, were estimated in the final database pooled across 3 data sources.

Tables and figures

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

	After 1:1 PS-matching		
Baseline characteristics	**Empagliflozin (N = 10,930)**	**GLP1RA (N = 10,930)**	**Standardized mean differences**
Age, mean (SD)	72.15 (7.37)	72.12 (7.39)	-0.0041
Gender male, n (%)	4,823 (44.1%)	4,771 (43.7%)	-0.0081
Cardiovascular disease history, n (%)[1]	6,683 (61.1%)	6,703 (61.3%)	0.0041
Acute myocardial infarction, n (%)	533 (4.9%)	544 (5.0%)	0.0046
Stroke, n (%)	1,616 (14.8%)	1,596 (14.6%)	-0.0056
Heart failure, n (%)	2,743 (25.1%)	2,799 (25.6%)	0.0115
Acute kidney injury, n (%)	1,643 (15.0%)	1,746 (16.0%)	0.0276
Number of diabetes medications at index date, mean (SD)	1.48 (0.96)	1.52 (0.95)	0.0419
Current use of metformin; n (%)	4,992 (45.7%)	5,079 (46.5%)	0.0160
Current use of insulin; n (%)	2,659 (24.3%)	2,753 (25.2%)	0.0209
HbA1c, mean (SD)[2]	8.83 (2.30)	8.80 (2.25)	-0.01319
eGFR, mean (SD)[2]	53.38 (16.00)	49.92 (15.88)	-0.21706

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

Table 2. Hazard ratios and rate differences for cardiorenal outcomes

Outcomes	Empagliflozin N events (IR/1000 PY)	GLP-1RA N events (IR/1000 PY)	HR (95% CI)	RD (95% CI)
MI or stroke	176 (26.9)	208 (30.7)	0.88 (0.72-1.07)	-3.84 (-9.60, 1.93)
MI	107 (16.3)	144 (21.2)	0.78 (0.61-1.00)	-4.93 (-9.56, -0.29)
Stroke	73 (11.1)	65 (9.5)	1.16 (0.83-1.62)	1.59 (-1.85, 5.02)
Mortality	143 (21.6)	137 (20.0)	1.08 (0.86-1.36)	1.66 (-3.21, 6.53)
HHF	132 (20.1)	200 (29.5)	0.68 (0.55-0.85)	-9.44 (-14.78, -4.10)
ESRD	130 (19.8)	195 (28.8)	0.70 (0.56-0.87)	-9.01 (-14.30, -3.72)

Figure 2. Cumulative incidence of hospitalization for heart failure

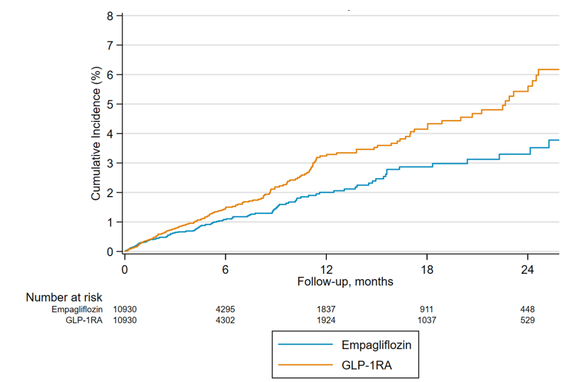


Figure 1. Cumulative incidence of Myocardial Infarction or Stroke

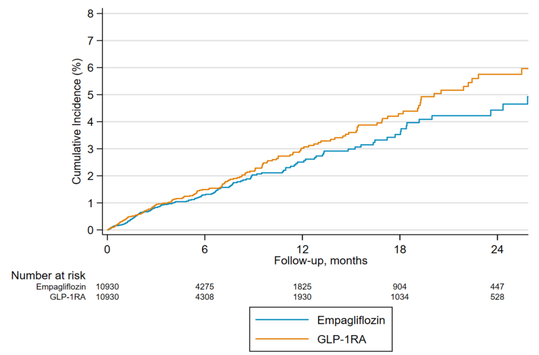
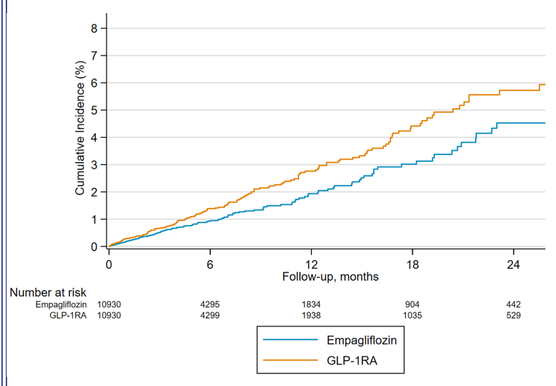


Figure 3. Cumulative incidence of end-stage kidney disease



Results

We identified 10,930 1:1 PS-matched pairs of patients with T2D between August 1, 2014 and September 30, 2019 (**Table 1**).

Cardiorenal effectiveness outcomes

- In patients with CKD stages 3-4, compared with GLP-1RA, empagliflozin was associated with a trend towards reduced risk of a composite outcome of MI or stroke (12% risk reduction and 3.8 fewer events per 1000 person-years), compared with GLP-1RA **(Table 2 and Figure 1).**
- Empagliflozin was associated with a 32% reduction in the risk of HHF (corresponding to 9.4 fewer events per 1000 person-years), over a mean follow-up time of 8.3 months (**Table 2 and Figure 2**).
- Empagliflozin was associated with a 30% relative risk reduction of ESKD (9.0 fewer events per 1000 person-years), compared with GLP-1RA.
- Regarding the secondary outcomes, the risk of all-cause mortality, which was only estimated in the subset of the population with complete information, i.e., Medicare, was similar between empagliflozin vs. GLP-1RA initiators.
- Estimates for the MI and stroke (individually measured) were also similar between empagliflozin and GLP-1RA.

Conclusions

- In this final analysis from EMPRISE (2014-2019), restricting to patients with advanced CKD stages 3-4, the initiation of empagliflozin was associated with a trend towards reduced risk of a composite outcome of myocardial infarction or stroke and a reduction in the risk of HHF, ESRD, relative to GLP-1RA.
- In Medicare patients (≥65 years), the risk of all-cause mortality was similar between treatment groups.
- These findings complement randomized clinical trial data in patients with T2D and advanced CKD in routine clinical practice.

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