Cardiovascular Effectiveness Of Empagliflozin Vs. Glucagon-like Peptide-1 Receptor Agonists Or Liraglutide In The EMPRISE Study

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Background

- In the EMPA-REG OUTCOME trial, empagliflozin reduced the risk of cardiovascular (CV) death, all-cause mortality, and hospitalization for heart failure (HHF) in patients with type 2 diabetes (T2D) and **established CV disease**
- EMPRISE is a monitoring program aimed to assess comparative effectiveness and safety of empagliflozin in T2D patients in routine care with a broad spectrum of baseline CV risk (NCT03363464; EUPAS20677)
- Uses real-world data from two commercial insurance claims data and federal Medicare data in the U.S.
- Collects accumulating data on empagliflozin for a period of 5 years: August 2014 - September 2019.

Objective

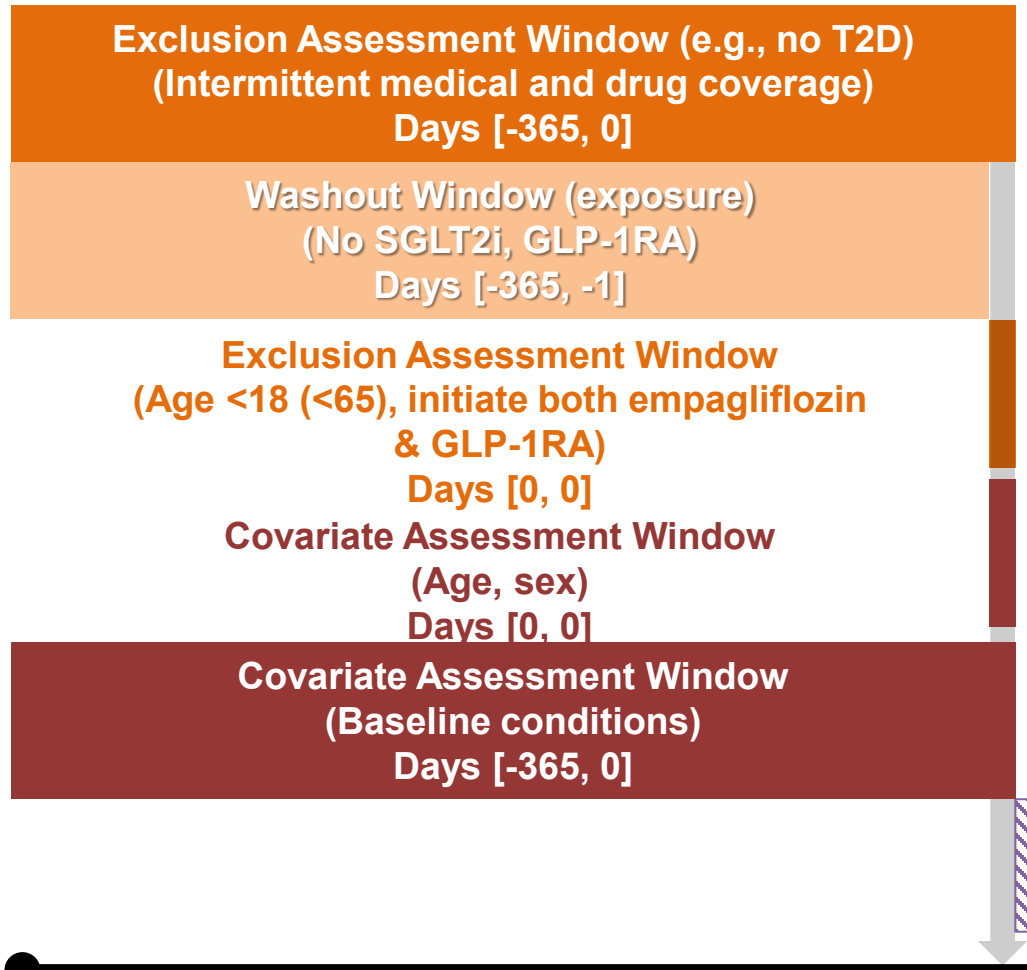
- Objective: To assess the cardiovascular effectiveness and safety of empagliflozin compared to glucagon-like peptide-1 receptor agonists (GLP1RA) or liraglutide in patients with T2D across the spectrum of CV disease, using three electronic healthcare databases (2014-2019)

Methods

Methods

- **Study design:** New-user active-comparator cohort study
- **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
- **Exposure and comparator:** Initiators of (i) empagliflozin compared to GLP1RA (ii) empagliflozin compared to liraglutide.

Exposure-based Cohort Entry Date
(First prescription of empagliflozin or a comparator)
Day 0



1. Patients with T2D
2. New user design
3. Active comparator (GLP-1RA/liraglutide)
4. 1:1 propensity score matching (143 covariates)
5. As treated analysis

* Earliest of: outcome of interest, switching or discontinuation of study drugs, death, disenrollment, end of the study period

Outcomes

Cardiovascular effectiveness outcomes
Hospitalization for heart failure (HHF)[1] in primary discharge position
Hospitalization for MI[1]
Hospitalization for stroke[1]
All-cause mortality (ACM) (all 3 databases)[2]
ACM (Medicare only)

[1] Validated claims-based algorithms: Kiyota et al. AHJ 2004. Jones et al. Stroke. 2014. Kucharska-Newton et al. JCF. 2016.
[2] Mortality data is incomplete in Optum and Marketscan

Statistical analyses

- Hazard ratios (HR) and rate differences (RD), with 95% confidence intervals (CI) accounting for mortality as a competing risk
- Analyses conducted in each of the three data sources separately and then pooled across data sources using fixed-effects meta-analysis.
- **Subgroups:** Baseline history of cardiovascular disease, [defined as baseline **atherosclerotic cardiovascular diseases** and/or **heart failure**]

EMPRISE study population 2014-2019 (GLP-1RA)

Medicare, MarketScan, and Optum

581,535 patients ≥18 years (≥ 65 years in Medicare) initiating empagliflozin or a GLP-1RA between August 2014 – September 2019, and with 12 months of continuous enrollment prior to cohort entry

40,765 Excluded

- 9,660 Patients without a diagnosis of T2D
- 18,195 Patients with a diagnosis of type 1 diabetes, secondary or gestational diabetes
- 19,885 Patients with malignancy, ESRD, HIV, or transplant
- 3,552 Patients with a nursing home admission
- 1 Patients with missing age or gender information
- 18 Patients who initiated >1 GLP-1RA agents on cohort entry
- 114 Patients who initiated Saxenda

530,110 T2D patients ≥ 18 years old (≥ 65 years in Medicare) initiating empagliflozin or a GLP-1RA

260,816 T2D patients after **1:1 PS-matching** based on **143 patient characteristics**

130,408 empagliflozin initiators

130,408 GLP-1RA initiators

EMPRISE study population 2014-2019 (liraglutide)

Medicare, MarketScan, and Optum

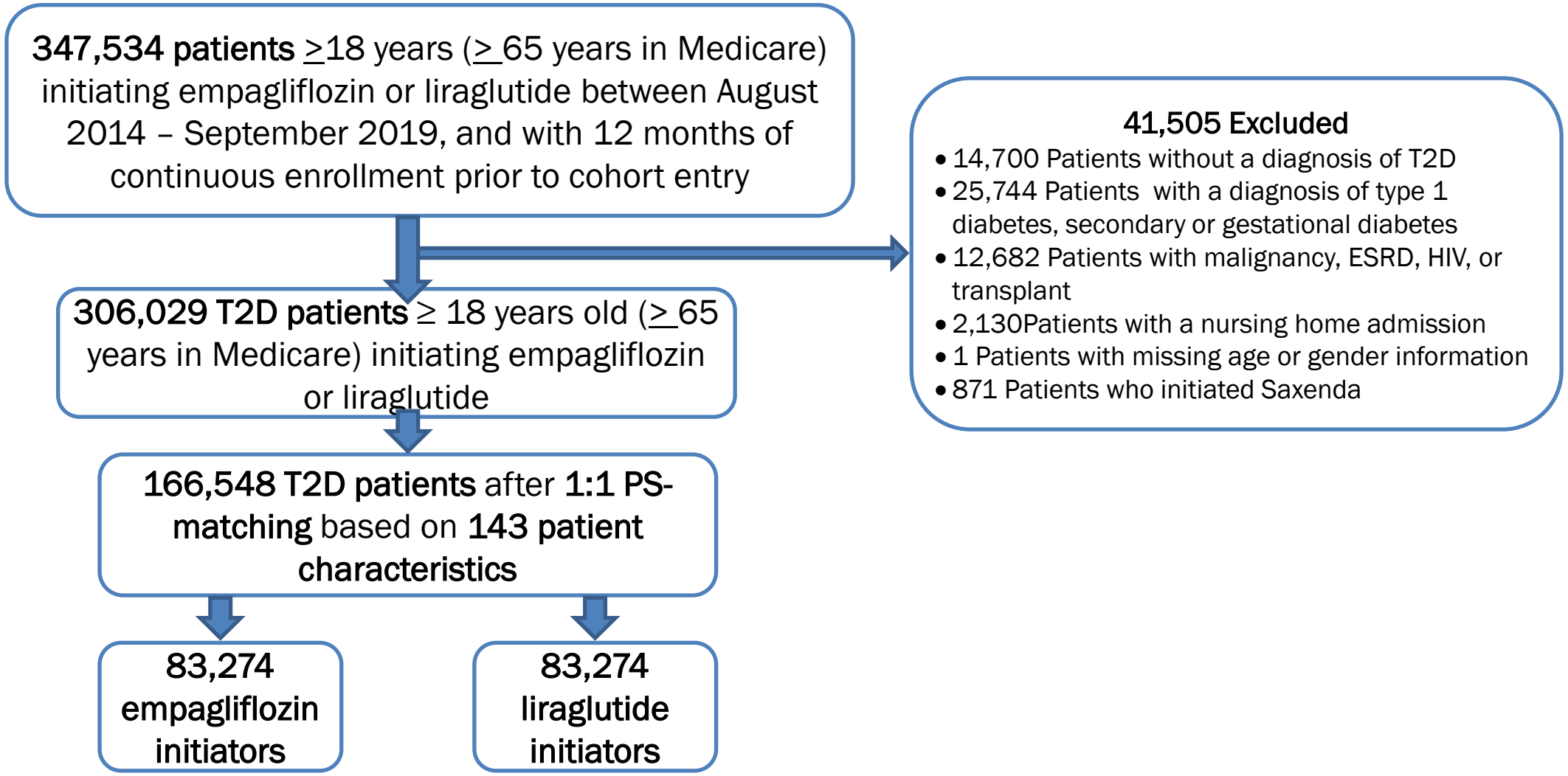


Table 1. Pooled patient characteristics during a 12-month baseline period prior to drug initiation from 3 databases after 1:1 PS matching

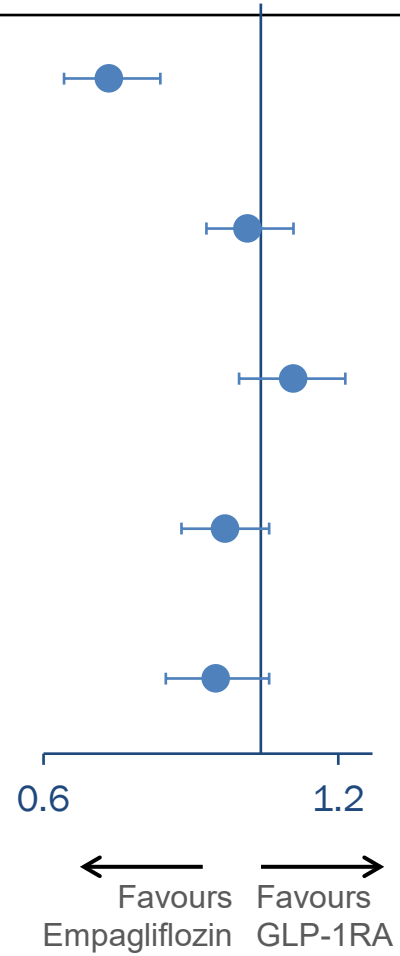
	Empagliflozin vs. GLP-1RA (After matching)			Empagliflozin vs. Liraglutide (After matching)		
	Empagliflozin (N = 130,408)	GLP-1RA (N = 130,408)		Empagliflozin (N = 83,274)	Liraglutide (N = 83,274)	
Patient characteristics	Mean (SD) or n (%)	Mean (SD) or n (%)	Stand. Diff.	Mean (SD) or n (%)	Mean (SD) or n (%)	Stand. Diff.
Age, mean (SD)	63.83 (8.60)	63.87 (8.61)	0.00	62.13 (8.59)	62.09 (8.69)	0.00
Sex female, n (%)	59,837 (45.9%)	59,497 (45.6%)	-0.01	42,795 (51.4%)	42,799 (51.4%)	0.00
CVD history, n (%)[1]	45,837 (35.1%)	45,841 (35.2%)	0.00	27,678 (33.2%)	27,677 (33.2%)	0.00
Chronic kidney disease, n (%)	14,594 (11.2%)	15,102 (11.6%)	0.01	10,170 (12.2%)	10,372 (12.5%)	0.01
No. diabetes medications on index date, mean (SD)	1.44 (0.94)	1.46 (0.96)	0.02	1.39 (0.94)	1.39 (0.96)	0.00
Current use of metformin, n (%)	83,248 (63.8%)	83,507 (64.0%)	0.00	50,093 (60.2%)	49,957 (60.0%)	0.00
Current use of insulin, n (%)	22,530 (17.3%)	23,157 (17.8%)	0.01	19,822 (23.8%)	20,107 (24.1%)	0.01
HbA1C, %, mean (SD)[2]	9 (2.3)	9 (2.3)	0.00	9.0 (2.3)	8.9 (2.4)	0.04
eGFR, mean (SD)[2]	84.6 (22.1)	83.1 (23.2)	0.07	84.7 (22.6)	83.0 (23.8)	0.07

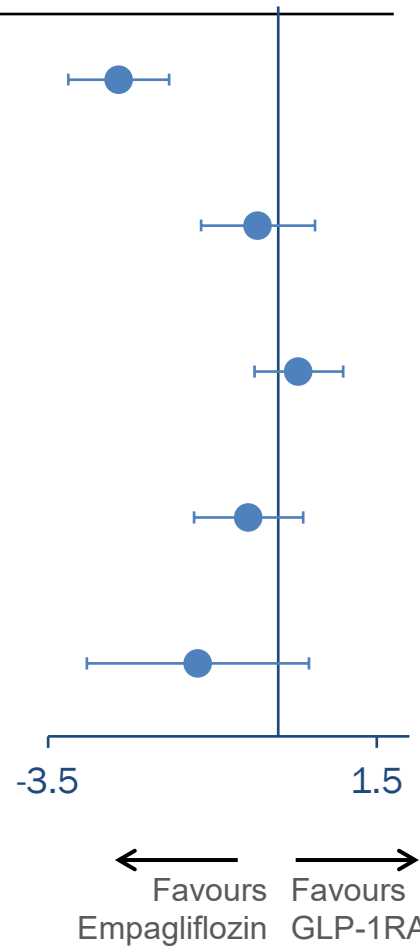
[1] CVD history includes both atherosclerotic cardiovascular diseases and heart failure.

[2] Available for a subset (~20%) of the population so not used to estimate PS.

Hazard ratios and rate differences for empagliflozin vs. GLP-1RA

Outcome	Empagliflozin N event (IRs/1000 PY)	GLP-1RA N event (IRs/1000 PY)	HRs (95% CI)	RD per 1000 PY (95% CI)
HHF – primary dx	515 (5.6)	685 (8.0)	0.70 (0.63, 0.79)	-2.42 (-3.19,-1.66)
MI	788 (8.5)	757 (8.8)	0.97 (0.88, 1.08)	-0.31 (-1.17,0.56)
Stroke	509 (5.5)	445 (5.2)	1.08 (0.95, 1.22)	0.31 (-0.36,0.99)
ACM – all[1]	722 (7.8)	708 (8.2)	0.92 (0.83, 1.02)	-0.45 (-1.28,0.38)
ACM – Medicare only	538 (13.6)	552 (14.8)	0.90 (0.80, 1.02)	-1.22 (-2.91,0.47)

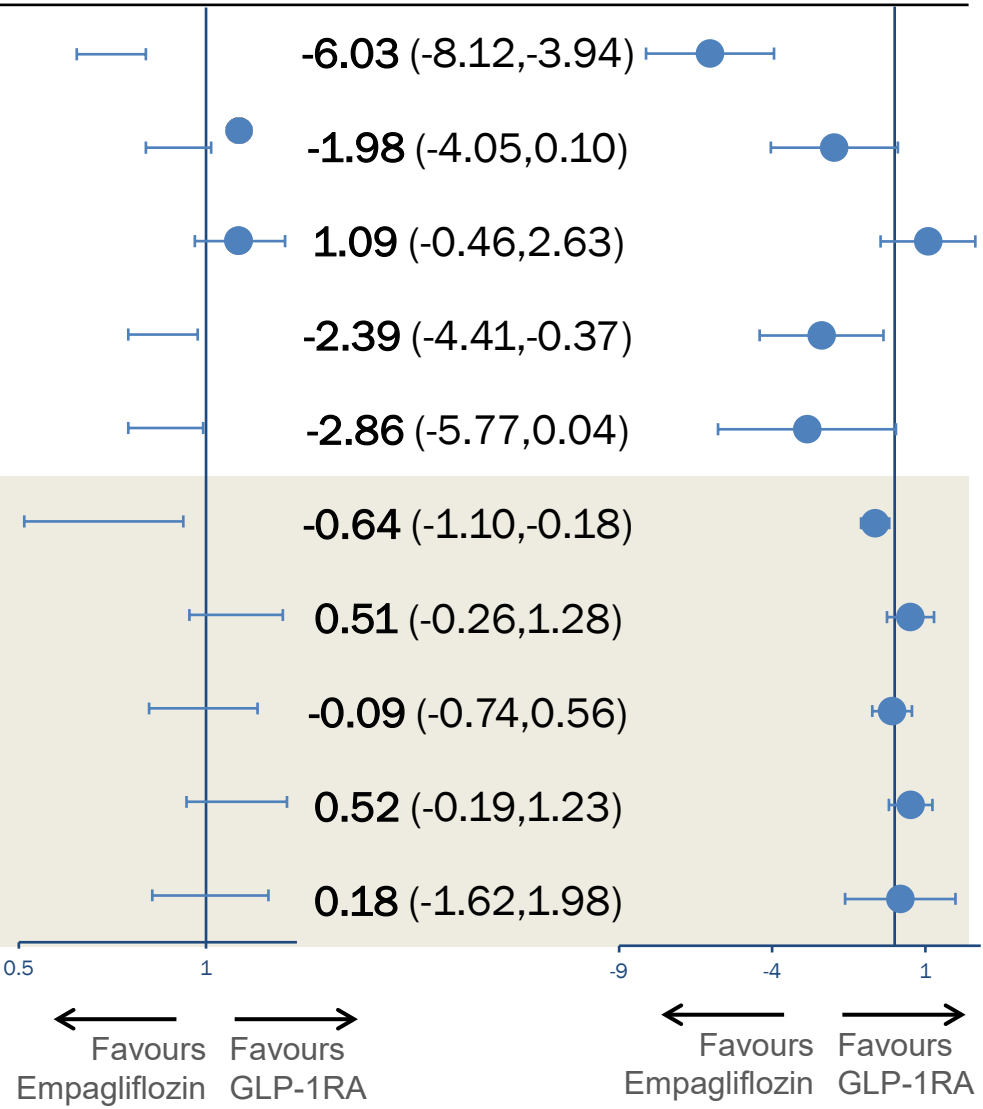




IR: incidence rates; PY: person-years; HR: hazard ratios; RD: rate differences
Mean follow-up ~8.9 months
[1]All-cause mortality data from Optum and Marketscan are incomplete

Hazard ratios and rate differences for empagliflozin vs. GLP-1RA by subgroups

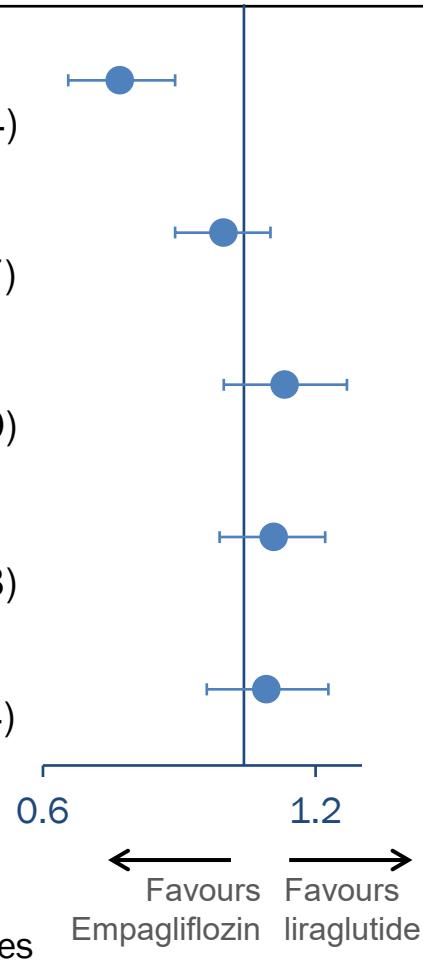
	Outcome	Empagliflozin N event (IRs/1000 PY)	GLP-1RA N event (IRs/1000 PY)	HRs (95% CI)	RD per 1000 PY (95% CI)
Baseline CV (+)	HHF – primary dx	436 (13.9)	575 (20.0)	**0.70** (0.62, 0.80)	**-6.03** (-8.12,-3.94)
	MI	494 (15.8)	513 (17.8)	**0.90** (0.80, 1.02)	**-1.98** (-4.05,0.10)
	Stroke	311 (9.9)	256 (8.8)	**1.13** (0.96, 1.34)	**1.09** (-0.46,2.63)
	ACM – all[1]	466 (14.8)	500 (17.2)	**0.85** (0.75, 0.97)	**-2.39** (-4.41,-0.37)
	ACM – Medicare only	370 (19.1)	395 (22.0)	**0.86** (0.75, 0.99)	**-2.86** (-5.77,0.04)
Baseline CV (-)	HHF – primary dx	79 (1.3)	110 (1.9)	**0.68** (0.51, 0.92)	**-0.64** (-1.10,-0.18)
	MI	294 (4.8)	244 (4.3)	**1.12** (0.94, 1.33)	**0.51** (-0.26,1.28)
	Stroke	198 (3.2)	189 (3.3)	**0.99** (0.81, 1.21)	**-0.09** (-0.74,0.56)
	ACM – all[1]	256 (4.2)	208 (3.6)	**1.12** (0.93, 1.35)	**0.52** (-0.19,1.23)
	ACM – Medicare only	168 (8.4)	157 (8.2)	**1.02** (0.82, 1.26)	**0.18** (-1.62,1.98)

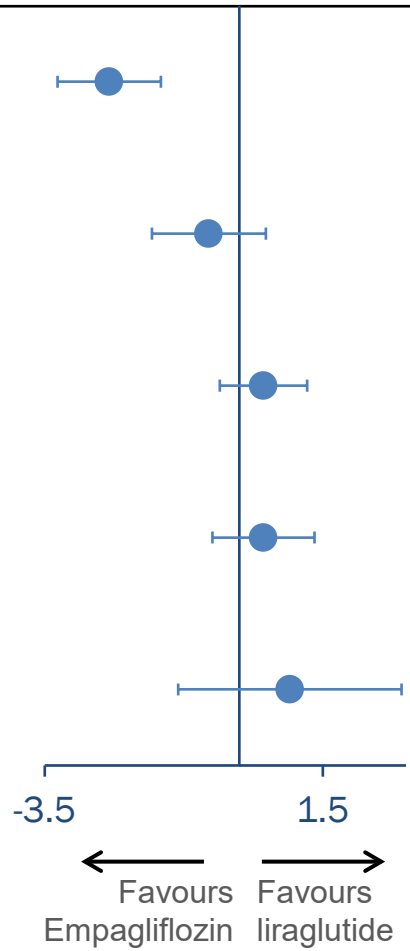


IR: incidence rates; PY: person-years; HR: hazard ratios; RD: rate differences
Mean follow-up ~8-9 months
[1]Mortality data is incomplete in Optum and Marketscan

Figure 3. Hazard ratios and rate differences for empagliflozin vs. liraglutide

Outcome	Empagliflozin N event (IRs/1000 PY)	Liraglutide N event (IRs/1000 PY)	HRs (95% CI)	RD per 1000 PY (95% CI)
HHF – primary dx	384 (5.8)	490 (8.2)	0.73 (0.64, 0.84)	-2.34 (-3.27,-1.41)
MI	547 (8.3)	531 (8.8)	0.95 (0.84, 1.07)	-0.55 (-1.57,0.48)
Stroke	350 (5.3)	293 (4.9)	1.11 (0.95, 1.30)	0.43 (-0.35,1.22)
ACM – all[1]	471 (7.1)	403 (6.7)	1.08 (0.94, 1.23)	0.43 (-0.48,1.35)
ACM – Medicare only	345 (13.5)	304 (12.6)	1.06 (0.91, 1.24)	0.91 (-1.10,2.92)

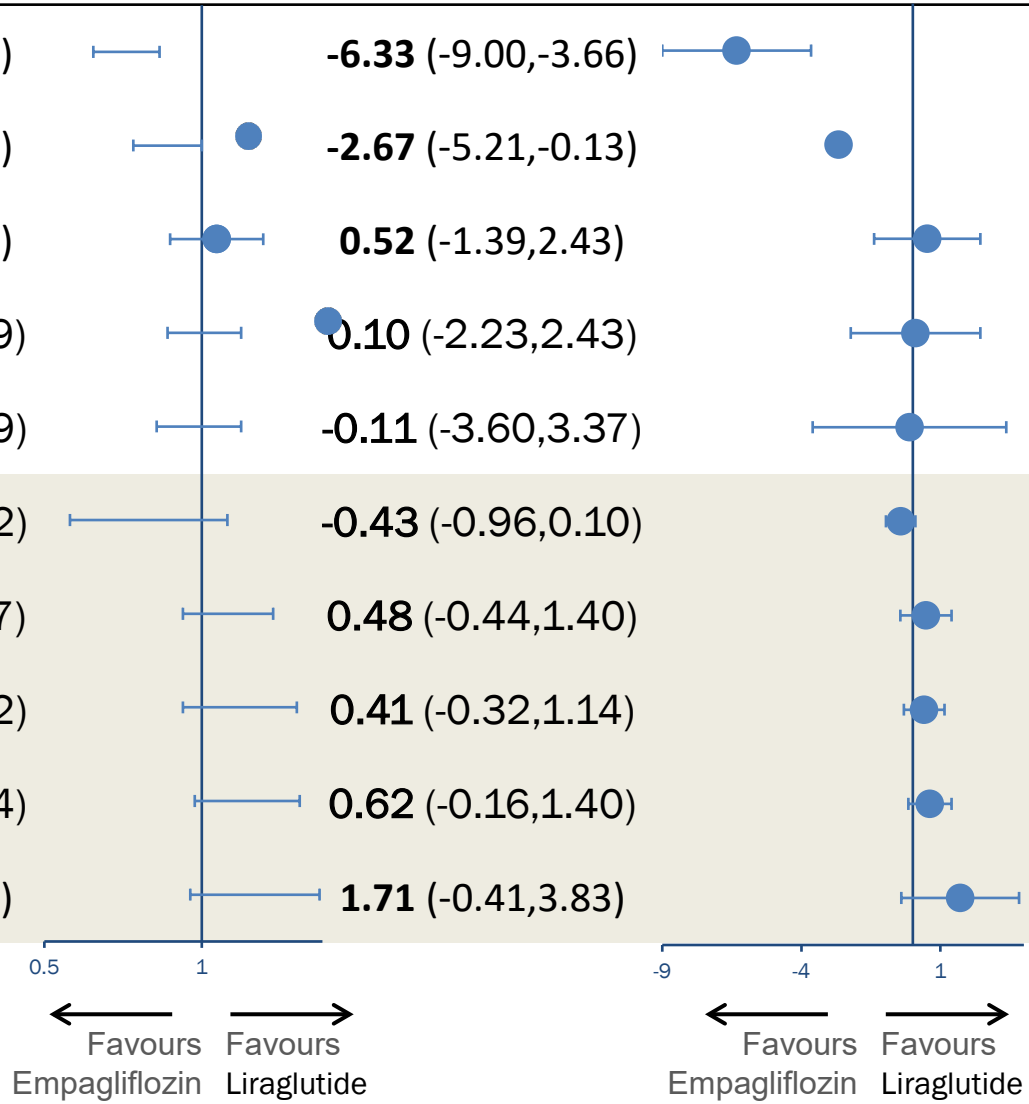




IR: incidence rates; PY: person-years ; HR: hazard ratios; RD: rate differences
Mean follow-up ~8-10 months
[1]Mortality data is incomplete in Optum and Marketscan

Hazard ratios and rate differences for empagliflozin vs. liraglutide by subgroups

	Outcome	Empagliflozin N event (IRs/1000 PY)	Liraglutide N event (IRs/1000 PY)	HRs (95% CI)	RD per 1000 PY (95% CI)
Baseline CV (+)	HHF – primary dx	323 (15.4)	417 (21.7)	**0.72** (0.62, 0.83)	**-6.33** (-9.00,-3.66)
	MI	325 (15.5)	349 (18.2)	**0.86** (0.74, 1.00)	**-2.67** (-5.21,-0.13)
	Stroke	207 (9.8)	180 (9.3)	**1.07** (0.87, 1.31)	**0.52** (-1.39,2.43)
	ACM – all[1]	303 (14.3)	276 (14.2)	**1.01** (0.86, 1.19)	**0.10** (-2.23,2.43)
	ACM – Medicare only	236 (18.9)	221 (19.1)	**0.99** (0.82, 1.19)	**-0.11** (-3.60,3.37)
Baseline CV (-)	HHF – primary dx	61 (1.4)	73 (1.8)	**0.79** (0.56, 1.12)	**-0.43** (-0.96,0.10)
	MI	222 (4.9)	182 (4.5)	**1.12** (0.92, 1.37)	**0.48** (-0.44,1.40)
	Stroke	143 (3.2)	113 (2.8)	**1.18** (0.92, 1.52)	**0.41** (-0.32,1.14)
	ACM – all[1]	168 (3.7)	127 (3.1)	**1.22** (0.97, 1.54)	**0.62** (-0.16,1.40)
	ACM – Medicare only	109 (8.4)	83 (6.6)	**1.26** (0.95, 1.68)	**1.71** (-0.41,3.83)



IR: incidence rates; PY: person-years ; HR: hazard ratios; RD: rate differences
Mean follow-up ~8-10 months
[1]Mortality data is incomplete in Optum and Marketscan

Conclusions

- In this final analysis from EMPRISE (2014-2019), including over 260,000 PS-matched U.S. patients, the initiation of empagliflozin was associated with a reduction in the risk of HHF, a similar risk of MI, stroke, and all-cause mortality, relative to both GLP-1RA as a class, and liraglutide, over a short follow-up.
- Results were consistent in patients with T2D, with and without history of cardiovascular disease, though the absolute benefits of empagliflozin were greater in patients with cardiovascular disease.
- 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.