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In the EMPA REG OUTCOME trial empediate reduced the risk of		Table 1. Pooled patient characteristics during a 12-month baseline period prior to drug initiation from 3 databases							
cardiovascular death by 38% all-cause mortality by 32% and hosnitalization		Before PS-matching Before PS-mat							
for heart failure (HHF) by 35% in pa established cardiovascular disease	atients with type 2 diabetes (T2D) and	Baseline characteristics	Empagliflozin (N = 136 937)	DPP4i (N = 599 537)	Standardized mean differences	Empagliflozin (N = 115 116)	DPP4i (N = 115 116)	Standardized mea	
 EMPRISE aims to assess compara 	tive effectiveness, safety, health care	Age, mean (SD)	62.00 (8.65)	67.48 (9.09)	0.62	62.52 (8.64)	62.51 (8.65)	0.00	
utilization and cost of empagliflozin in patients with T2D		Sex female, n (%)	60,000 (43.8%)	312,601 (52.1%)	0.17	51,729 (44.9%)	51,661 (44.9%)	0.00	
(NCT03363464; EUPAS20677)		CVD history, n (%) ¹	47,179 (34.5%)	226,622 (37.8%)	0.07	38,379 (33.3%)	38,381 (33.3%)	0.00	
 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 		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 (%) Heart failure, n (%)	3,482 (2.5%) 11,913 (8.7%)	13,461 (2.2%) 67,900 (11.3%)	-0.02 0.09	2,538 (2.2%) 9,706 (8.4%)	2,520 (2.2%) 9,727 (8.4%)	0.00	
Obiective		Chronic kidney disease, n (%)	12,879 (9.4%)	109,377 (18.2%)	0.26	11,391 (9.9%)	11,636 (10.1%)	0.01	
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		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	
spectrum of CV disease.		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 infarctio	on, unstable angina, o	ther ischemic heart dise	ease, transient ischem	nic attack, stroke, ath	erosclerotic peripheral		
Me	thods	vascular disease, or h ² Available for a subse	eart failure. et (~20%) of patients, t	hus not included in in	the PS model				
Study design: New-user active-comparator cohort study (Figure 1).		Figure 1. EMPRISE study design overview			Figure 3. effectiver	Figure 3. Hazard ratios and rate differences for empagliflozin and effectiveness outcomes			
Data sources: US Medicare, Optum Clinformatics and IBM Marketscan databases (August 1, 2014-September 30, 2019).		Exposure-based Cohort Entry Date (First prescription of empagliflozin or a comparator) Day 0 Exclusion Assessment Window (e.g., no T2D)				Empagliflozin DPP-4i			
						N event N event HRs RD per 1000 PY			
Study population: Adults ≥18 years ≥65 years in Medicare) with T2D (Figure 2). Exposure and comparator: Initiators of empagliflozin relative to DPP-4i. Outcomes		(Intermittent medical and drug coverage) Days [-365, 0]1Patients with 12DWashout Window (exposure) (No SGLT2i, DPP-4i) Days [-365, -1]2New user designExclusion Assessment Window (Age<18 (<65 for Medicare), initiate both empagliflozir & DPP-4i) Days [0, 0]3Active comparator (DPP-4i)Covariate Assessment Window (Age, sex) Days [0, 0]1:1 propensity score matching (143 covariates)		th T2D Outcome HHF – primary	(IRS/1000 PY) (IRS/1000 PY) (dx 397 (5.0) 804 (10.3)	0.50	(95% CI) -5.35 (-6.22,-4.49)		
				2 New user of Active com	HHF – any dx	1,871 (23.6) 2651 (34.5)	0.71 (0.67, 0.75)	-10.83 -10.83	
				3 (DPP-4i) 1:1 proper	MI or stroke	1,080 (14.0) 1,228 (16.2)	0.88 (0.81, 0.96)	-2.20 (-3.43,-0.97)	
				143 covariates) MI Stroke	657 (8.3) 755 (9.7) 400 (5.0) 435 (5.6)	(0.78, 0.96) 0.92	-1.45 (-2.39,-0.52) -0.56		
Cardiovascular effectiveness outcomes	Safety outcomes	Covariate Assessment (Baseline conditio	t Window ons)	5 As treated	analysis		(0.80, 1.05)	(-1.28,0.15) -3 90	
Hospitalization for heart failure (HHF) ¹ (HHF-primary dx)	Lower limb amputations ¹	Days [-365, 0]] Follow up Days [+1.0	Window Censor*1	ACM – all ACM – Medica	485 (6.1) 779 (10.0) are only 347 (12.1) 599 (20.2)	(0.56, 0.70) 0.60	(-4.78,-3.01) -8.15	
HHF in any discharge position (HHF-any dx)	Non-vertebral fractures	Time			IR: incidence ra Mean follow-up	ates; PY: person-years o of 8.3 months	0.4 <u>0.8</u> Favours Favour Empagliflozin DPP-4	-13 -13 Favours Favour i Empagliflozin DPP-4i	
Composite of myocardial infarction (MI) or stroke	Renal cancer								
Hospitalization for MI ¹	Bladder cancer Under the study population (2014-2019) from Medicar			edicare, Figure 4.	Hazard ratios and	rate differences fo	r empagliflozin and		
Hospitalization for stroke ¹ All-cause mortality ²	Acute kidney injury requiring dialysis ¹	Optum and Marketscan databases				safety outcomes			
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		810,543 patients <u>></u> 18 years initiating empagliflozin or a	s (≥65 years for Medicare) a DPP-4i between August		Outcome	N event N event	HRs I	RD per 1000 PY	
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.		2014 - September 2019, and with 12 months of continuous enrollment prior to cohort entry40,044 Excluded • 5,933 Patients without a diagnosis of T2D • 23,326 Patients with a diagnosis of type 1		ed sis of T2D is of type 1 amputation	252 (3.2) 233 (3.0) 1.07	(0.89, 1.28)	0.17 (-0.37,0.72)		
				 diabetes, secondary or gestation 35,096 Patients with malignancy transplant 8,451 Patients with a pursing bo 	y, ESRD, HIV, or Non-vertebral fractures	330 (4.1) 303 (3.9) 1.08	3 (0.92, 1.26)	.25 (-0.37,0.88)	
		737,714 12D patients≥: Medicare) old initiating e	18 years (≥65 years for mpagliflozin or a DPP-4i	 1 Patients with missing age or ge 22 Patients who initiated >1 DPF cohort entry 	ender information P-4i agents on Renal cancer	69 (0.86) 69 (0.86) 1.00	0 (0.70, 1.43)	0.02 (-0.31,0.27)	
		230,232 T2D patie	ents after 1:1 PS-		Bladder cancer	75 (0.94) 67 (0.86) 1.03	3 (0.72, 1.49)	0.08 (-0.21,0.38)	
Subgroups: Baseline history of cardiovascular disease, defined as baseline atherosclerotic cardiovascular diseases and/or heart failure		matching based of characte	on 143 patient eristics		Hospitalization for diabetic ketoacidosis	273 (3.4) 143 (1.8) 1.78	3 (1.44, 2.19)	59 (1.08,2.09)	
		115,116 empagliflozin	115,116 DPP-4i		Acute kidney injury	2,037 (25.7) 2,831 (36.8) 0.71	L (0.67, 0.76) -11	10 (-12.86,-9.34)	
		initiators	initiators				0.6 1.2	-13 -3	
					IR: incidence rates Mean follow-up of	; PY: person-years 8.3 months	Favours Favours Empagliflozin DPP-4i	Favours Favou Empagliflozin DPP-4	

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

Tables and figures







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, nonvertebral 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.

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