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Introduction

Sodium-glucose cotransporter-2 inhibitors (SGLT2i) are now recommended for the management of heart failure with preserved ejection fraction (HFpEF), but little is known about their in-class comparative effectiveness in real-world settings. To fill this knowledge gap, we assessed the comparative effectiveness of SGLT2i for preventing HF-related and all-cause hospitalizations among patients with HFpEF.

Methods

- **Study Design:** Active comparator cohort study
- **Data Source:** MarketScan® claims databases
- **Study Period:** 2012 - 2020
- **Inclusion Criteria:** Patients with diagnosed HFpEF who initiated SGLT2i were included if they were aged ≥18 years and had six months of continuous enrolment in the health plan before the prescription fill date.
- **Exclusion Criteria:** Patients who had any HF-related diagnosis before HFpEF diagnosis
- **Index date:** Prescription fill date of SGLT2i
- **Exposure:** Cohort 1 (dapagliflozin vs. canagliflozin); Cohort 2 (empagliflozin vs. canagliflozin); Cohort 3 (dapagliflozin vs. empagliflozin)
- **Outcome:** HF-related hospitalization
All-cause hospitalizations
- **Statistical Analysis:** Stabilized inverse probability treatment weighted Cox proportional hazards regression was used to compare HF-related and all-cause hospitalizations in three pairwise comparisons: dapagliflozin vs. canagliflozin; empagliflozin vs. canagliflozin; and dapagliflozin vs. empagliflozin.

Results

- 3,629 users with SGLT2i (881 dapagliflozin, 1,120 canagliflozin, and 1,628 empagliflozin) were identified. The baseline characteristics of study populations included in the three pairwise comparisons of patients were well-balanced among groups (standardized mean differences for each pairwise comparison <0.10) (**Table 1**).
- Empagliflozin had 50% and 55% less risk of HF-related hospitalization compared with Dapagliflozin and Canagliflozin, respectively (**Table 2**).

Table1: Baseline characteristics of patients with heart failure with preserved ejection fraction (N=3,629)

Characteristics	Cohort 1			Cohort 2			Cohort 3		
	Dapagliflozin n=881	Canagliflozin n=1,120	SMD*	Empagliflozin n=1,628	Canagliflozin n=1,120	SMD*	Dapagliflozin n=881	Empagliflozin n=1,628	SMD*
Age, Mean (SD), y	60.4 (9.8)	64.2 (10.1)	0.02	62.2 (10.8)	64.2 (10.1)	<0.01	60.4 (9.8)	62.2 (10.8)	<0.01
Gender, n (%)	0.03			0.01			0.01		
Men	494 (56.1)	619 (55.3)		954 (58.5)	620 (55.2)		494 (56.1)	954 (58.5)	
Women	387 (44.0)	501 (44.7)		678 (41.5)	503 (44.8)		387(43.9)	678 (41.5)	
Selected Comorbid Conditions, n (%)									
Dyslipidemia	654(74.2)	785 (70.1)	<0.01	1,205 (73.8)	788 (70.2)	0.01	654 (74.2)	1,205 (73.8)	0.01
Diabetes mellitus	840 (95.4)	1,098 (98.0)	-0.01	1,589 (97.4)	1,101 (98.0)	-0.02	840 (95.4)	1,589 (97.4)	<0.01
Hypertension	728 (82.6)	937 (83.7)	0.01	1,375 (84.3)	939 (83.6)	0.01	728 (82.6)	1,375 (84.3)	<0.01
Renal disease	111 (12.6)	175 (15.6)	0.02	248 (15.2)	176 (15.7)	<0.01	111 (12.6)	248 (15.2)	<0.01

Table 2: Risk of heart failure–related and all-cause hospitalization among patients with heart failure with preserved ejection fraction in inverse probability treatment weighting adjusted analyses

Analysis	Cohort 1		Cohort 2		Cohort 3	
	Dapagliflozin n=881	Canagliflozin n=1,120	Empagliflozin n=1,628	Canagliflozin n=1,120	Dapagliflozin n=881	Empagliflozin n=1,628
HF-related hospitalization n	65	124	95	124	65	95
Crude incidence rate per 100 person-months	0.63	1.38	0.54	1.38	0.63	0.54
HR (95%CI)	0.75 (0.56-1.01)	Ref	0.45 (0.34-0.59)	Ref	1.50 (1.09-2.07)	Ref
All-cause hospitalization n	334	516	554	516	334	554
Crude incidence rate per 100 person-months	3.63	5.17	3.63	5.17	3.63	3.63
HR (95%CI)	0.84 (0.73-0.97)	Ref	0.82 (0.73-0.93)	Ref	1.05 (0.92-1.20)	Ref

Abbreviations: CI = confidence interval; HF = heart failure; HR = hazard ratio; n = number of patients; SMD = standardized mean difference Ref = reference

* calculated and reported after stabilized inverse probability treatment weighting

Strengths

- First study to directly compare in-class effectiveness of empagliflozin, dapagliflozin, and canagliflozin for the treatment of patients with HFpEF
- Stabilized IPTW for adjustment of differences in baseline demographic and clinical characteristics in the treatment groups
- Large commercial administrative claims databases

Limitations

- No information on lab values and ejection fraction
- No information on the actual consumption of the medication
- Generalizable to patients with commercial insurance plans
- Majority of the population with comorbid diabetes



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Conclusion: Compared with canagliflozin or dapagliflozin use, empagliflozin use was associated with decreased risk of HF-related and all-cause hospitalizations. Compared with canagliflozin, dapagliflozin was associated with decreased risk of HF-related and all-cause hospitalizations.