Comparative Genitourinary Safety of In-Class Sodium Glucose Co-Transporter-2 Inhibitors among Patients with Heart Failure with Preserved Ejection Fraction

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BACKGROUND

Sodium-glucose cotransporter-2 inhibitors (SGLT2i) have received an expanded indication for heart failure with preserved ejection fraction (HFpEF) by the Food and Drug Administration, but little is known about their real-world in-class comparative safety in patients with HFpEF.

We aimed to compare in-class safety of SGLT2i for the risk of genitourinary infections, a composite of urinary tract infections (UTI) or genital infections, among patients with HFpEF.

Methods

- **Study Design:** Retrospective New-user Active Comparator Cohort Study
- **Data Source:** IBM® MarketScan® claims databases
- **Study Period:** 01-01-2012 to 12-31-2020
- **Study Population:** Patients aged ≥18 years diagnosed with HFpEF who initiated an SGLT2i (canagliflozin, dapagliflozin or empagliflozin) were included.
- **Index Date:** The first prescription fill date of SGLT2i
- **Study Exposures:** Three pairwise comparisons of patients including cohort 1 (dapagliflozin vs. canagliflozin), cohort 2 (empagliflozin vs. canagliflozin), and cohort 3 (dapagliflozin vs. empagliflozin).
- **Study Outcomes:** A composite of urinary tract infections (UTI) or genital infections; Individual components outcomes
- **Statistical Analysis:** After stabilized inverse probability treatment weighting, Cox proportional hazards regression was used to compare the composite outcome and each individual component outcome in each cohort. Several subgroup and sensitivity analyses were performed to check the robustness of the findings.

Table 1. Baseline demographic and clinical characteristics of patients with HFpEF after stabilized inverse probability treatment weighting

Characteristic	Cohort 1			Cohort 2			Cohort 3		
	Dapagliflozin n=422	Canagliflozin n=522	SMD	Empagliflozin n=849	Canagliflozin n=511	SMD	Dapagliflozin n=413	Empagliflozin n=849	SMD
Age, Mean (SD), y	62.2 (9.8)	62.1 (10.5)	0.01	62.6 (10.9)	62.4 (10.4)	0.02	61.0 (10.2)	61.2 (10.6)	0.01
Sex, n (%)			0.07			0.01			<0.01
Male	208 (50.1)	266 (51.9)		445 (52.5)	266 (51.9)		208 (50.1)	445 (52.5)	
Female	207 (49.9)	247 (48.2)		403 (47.5)	247 (48.1)		207 (49.9)	403 (47.5)	
Type of health plan, n (%)			0.06			0.09			<0.01
PPO	259 (62.9)	254 (49.8)		487 (57.4)	256 (49.9)		259 (62.4)	487 (57.4)	
US Region, n (%)			0.10			0.08			<0.01
South	220 (53.0)	227 (44.3)		391 (46.1)	227 (44.3)		220 (53.0)	391 (46.1)	
Comorbid Condition, n (%)									
Coronary artery syndrome	132 (31.8)	200 (39.0)	0.05	377 (44.5)	200 (39.0)	0.04	132 (31.8)	377 (44.5)	0.02
Diabetes	390 (94.0)	501 (97.7)	0.01	819 (96.6)	501 (97.7)	0.03	390 (94.0)	819 (96.6)	0.01
Dyslipidemia	281 (67.7)	347 (67.6)	0.02	605 (71.3)	347 (67.6)	0.02	281 (67.7)	605 (71.3)	0.01
Hypertension	327 (78.8)	410 (79.9)	0.03	685 (80.8)	410 (80.0)	0.01	327 (78.8)	685 (80.8)	0.02
Renal disease	36 (8.7)	55 (10.7)	0.01	85 (10.0)	55 (10.7)	0.05	36 (8.7)	85 (10.0)	0.02
Medications, n (%)									
Oral antidiabetic	331 (80.3)	427 (83.7)	0.02	699 (82.4)	430 (83.8)	0.07	331 (79.8)	699 (82.4)	0.01
Insulin	154 (37.1)	209 (40.7)	<0.01	209 (38.2)	324 (40.7)	<0.01	154 (37.1)	324 (38.2)	0.01
Steroid	46 (11.1)	65 (12.7)	0.04	114 (13.4)	65 (12.7)	0.04	46 (11.1)	114 (13.4)	<0.01

Table 2. Risk of UTI or genital infection as composite (primary) or separate outcomes in inverse probability treatment weighting–adjusted analyses

Analysis	Cohort 1		Cohort 2		Cohort 3	
	Dapagliflozin n=422	Canagliflozin n=522	Empagliflozin n=849	Canagliflozin n=511	Dapagliflozin n=413	Empagliflozin n=849
Composite (UTI or genital infection) outcome						
No. of patients with event	24	27	66	27	24	66
Person-months	4,774	3,397	8,628	3,337	4,583	8,735
Incidence rate per 100 person-months	0.50	0.79	0.76	0.81	0.52	0.76
HR (95% CI)	0.64 (0.36 – 1.14)	Ref	1.25 (0.77 – 2.05)	Ref	0.76 (0.48 - 1.21)	Ref
UTI						
No. of patients with event	20	21	48	21	20	48
Person-months	4,837	3,437	8,818	3,364	4,647	8,935
Incidence rate per 100 person-months	0.41	0.61	0.54	0.62	0.43	0.54
HR (95% CI)	0.64 (0.33 – 1.24)	Ref	1.24 (0.70 – 2.21)	Ref	0.86 (0.50 - 1.49)	Ref
Genital Infection						
No. of patients with event	6	7	21	7	6	21
Person-months	4,959	3,523	9,103	3,439	4,780	9,204
Incidence rate per 100 person-months	0.12	0.20	0.23	0.20	0.13	0.23
HR (95% CI)	0.73 (0.26 – 2.09)	Ref	1.35 (0.55 – 3.28)	Ref	0.68 (0.30 - 1.55)	Ref

Abbreviations: HFpEF = heart failure with preserved ejection fraction; PPO = preferred provider organization; SD = standard deviation; SMD = standardized mean difference; US = United States; CI = confidence interval; HR = hazard ratio; n = number of patients; Ref = reference; UTI, urinary tract infection

- Our study using large administrative claims databases found that **empagliflozin, dapagliflozin, and canagliflozin do not differ significantly in the risk of genitourinary infections for patients with heart failure and preserved ejection fraction.**
- Our study provides evidence for the genitourinary safety of sodium-glucose cotransporter-2 inhibitors and recommends their use based on effectiveness and tolerability for patients with heart failure and preserved ejection fraction.

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