

SGLT2 Inhibitors Reduce Urinary Tract Infection Risk in Heart Failure Patients in a Real World Propensity Matched Study

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Abstract

Aims:

Although Sodium-glucose cotransporter-2 (SGLT2) inhibitors have become central to modern heart failure (HF) care, clinical reluctance remains over whether drug-induced glucosuria increases the risk of urinary tract infections (UTIs). This concern is especially relevant in HF management, where fluid restrictions can limit natural urinary flushing. To address this, we examined the real-world risk of both initial and recurrent UTI hospitalizations in patients with chronic HF.

Methods:

We conducted a retrospective cohort study utilizing electronic medical record (EMR) data (2021–2024) from a tertiary academic medical center in Taiwan. Patients with chronic HF on continuous guideline-directed medical therapy (GDMT) for at least 28 days were screened. To rigorously control for confounding, we performed 1:1 propensity score matching (PSM) based on baseline demographics, clinical comorbidities, medications, and key laboratory parameters (NT-proBNP, eGFR, and HbA1c). The primary outcomes were hospitalizations for incident UTI (no prior UTI during a 12-month baseline washout) and recurrent UTI (at least one baseline UTI-related hospitalization). Secondary outcomes included HF hospitalization and 3-point major adverse cardiovascular events (MACE).

Results

Out of 7,094 eligible patients, 1:1 PSM yielded well-balanced cohorts consisting of 550 pairs of SGLT2 inhibitor users and unexposed controls. Longitudinal follow-up revealed that SGLT2 inhibitor initiation was associated with a significantly reduced risk of both incident UTI hospitalizations (HR, 0.64; $P = 0.021$) and recurrent UTI hospitalizations (HR, 0.46; $P = 0.047$). HF hospitalizations showed a similar downward trend (HR, 0.78; $P = 0.059$), and 3-point MACE was significantly lower in multivariable-adjusted models (aHR, 0.72; $P = 0.036$).

Conclusions

In this real-world chronic HF population, SGLT2 inhibitor initiation was associated with fewer incident and recurrent UTI hospitalizations alongside the expected cardiovascular benefit. A history of UTI does not appear to be a reason to withhold or delay SGLT2 inhibitor therapy in this setting.

Introduction

Sodium-glucose cotransporter-2 (SGLT2) inhibitors have revolutionized the management of type 2 diabetes mellitus (T2DM), chronic kidney disease (CKD), and heart failure (HF) across the entire spectrum of left ventricular ejection fraction (1–4). Guidelines from major cardiovascular societies (ESC, AHA/ACC/HFSA) now give SGLT2 inhibitors a Class I recommendation as a foundational pillar of guideline-directed medical therapy (GDMT), reflecting trial evidence of consistent reductions in cardiovascular mortality and heart failure hospitalization (2, 5–7). These cardiorenal protective benefits operate largely independently of glycemic control, making SGLT2 inhibitors indispensable in contemporary cardiometabolic care (4, 8).

Despite these benefits, many clinicians remain hesitant to prescribe SGLT2 inhibitors, largely because of their distinctive mechanism of action (9–11). By blocking glucose reabsorption in the renal proximal tubules, these drugs induce a therapeutic glucosuria (12). Elevated urinary glucose, however, creates a favorable environment for uropathogens, and this has sustained concern about the genitourinary safety of these drugs (1, 9).

This creates a genuine dilemma in HF care. Increased fluid intake is routinely recommended in diabetes to help flush urinary pathogens and lower UTI risk (13), yet fluid restriction is a cornerstone of HF management, needed to maintain euvolemia and prevent congestion (14). Because infections, including UTIs, are known to precipitate acute HF decompensation, hospitalization, and death (15, 16), even a modest increase in severe UTI risk could meaningfully shift the risk–benefit calculus for SGLT2 inhibitor therapy.

Landmark randomized controlled trials (RCTs) found no overall increase in UTI risk with SGLT2 inhibitors, but these trials were designed primarily to assess cardiovascular outcomes, not infection-related safety (5, 6). They also tended to exclude patients with recurrent or complicated genitourinary infections, and the closely monitored trial setting may not reflect routine clinical practice. Evidence on the risk of severe, hospitalization-requiring UTIs—particularly recurrent infections—in patients with chronic HF therefore remains limited.

To help close this gap, we conducted a large, real-world propensity score–matched cohort study examining the association between SGLT2 inhibitor initiation and incident and recurrent UTI hospitalizations in patients with HF. Because fluid restriction is routinely recommended in this population, it offers a particularly relevant setting for weighing the proven cardiorenal benefits of SGLT2 inhibitors against their potential UTI risk.

Methods

Study Design and Data Source

We conducted a retrospective, observational cohort study utilizing comprehensive electronic medical record (EMR) data from Changhua Christian Hospital (CCH), a premier 1,600-bed tertiary academic medical center in central Taiwan. The study window spanned four years, from January 1, 2021, through

December 31, 2024. Methods were performed in accordance with the relevant guidelines and regulations., including the ethical principles outlined in the Declaration of Helsinki and the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines. The Institutional Review Board of CCH granted the waiver for informed consent and approved the study (IRB No. 241012).

Study Population and Eligibility

We initially screened 7,172 patients with a confirmed diagnosis of heart failure, identified using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes (428.xx) or Tenth Revision (ICD-10-CM) codes (I50.x). To ensure the cohort represented stable, chronic HF patients, eligible individuals were required to have received continuous guideline-directed medical therapy (GDMT) for a minimum of 28 days. After excluding 78 patients who fell outside our pre-specified target age range (18 to 100 years), a final cohort of 7,094 patients was included in the primary analysis.

Exposure Definition

The primary exposure of interest was the initiation of an SGLT2 inhibitor, identified by prescriptions for single-agent SGLT2 inhibitors (Anatomical Therapeutic Chemical [ATC] code: A10BK) or fixed-dose combinations (ATC codes: A10BD15, A10BD16, A10BD19, A10BD20, A10BD21, A10BD23, A10BD24, A10BD25, and A10BD27). The index date was defined as the date of the first SGLT2 inhibitor prescription. To effectively minimize immortal time bias, unexposed controls were assigned a pseudo-index date corresponding to the calendar index date of their matched exposed counterpart.

Outcome Measures

Outcome Measures

Following the index date, patients were followed longitudinally until the first occurrence of a study outcome, death, or the study termination date on December 31, 2024.

Primary Outcomes:

The primary clinical outcomes were hospitalizations for UTI, identified using ICD-9-CM codes (599.0, 590.x, 595.x) and ICD-10-CM codes (N39.0, N10, N30.x). To distinguish patients with different baseline infection risks, UTI hospitalizations were categorized as either incident or recurrent.

Incident UTI was defined as the first UTI-related hospitalization after the index date among patients with no documented UTI diagnosis during the 12-month baseline washout period.

Recurrent UTI was defined as a UTI-related hospitalization after the index date among patients with at least one documented UTI-related hospitalization during the 12-month baseline period.

Secondary Outcomes

Secondary clinical endpoints were hospitalization for HF and 3-point major adverse cardiovascular events (MACE). HF hospitalization was defined as an acute admission with a principal discharge diagnosis of HF (ICD-9-CM: 428.x; ICD-10-CM: I50.x). Three-point MACE comprised cardiovascular death, non-fatal myocardial infarction (ICD-9-CM: 410.x; ICD-10-CM: I21.x, I22.x), and non-fatal stroke (ICD-9-CM: 430–434, 436; ICD-10-CM: I60–I63).

Propensity Score Matching (PSM)

To minimize selection bias and control for potential confounding, we performed 1:1 propensity score matching. Propensity scores were estimated using a multivariable logistic regression model incorporating key clinical baseline covariates: age, sex, HF duration, clinical comorbidities, baseline medications, and vital laboratory parameters (including N-terminal pro-B-type natriuretic peptide [NT-proBNP], estimated glomerular filtration rate [eGFR], and glycated hemoglobin [HbA1c]). Patients were matched using the nearest-neighbor method without replacement, employing a strict caliper width of 0.2 standard deviations of the logit of the propensity score.

Statistical Analysis

Baseline characteristics were summarized using descriptive statistics and compared between groups. Covariate balance after matching was assessed using standardized mean differences (SMDs), with an absolute SMD < 0.1 indicating excellent balance. Time-to-event outcomes were analyzed using Cox proportional hazards regression models to estimate hazard ratios (HRs) and 95% confidence intervals (CIs). Cumulative event incidences were estimated using Kaplan–Meier curves and compared via the log-rank test.

We performed pre-specified subgroup analyses stratified by age (< 65 vs. ≥65 years), renal function (eGFR < 50 vs. ≥50 mL/min/1.73 m²), diabetes status, and HF duration. Interaction terms were included in the Cox models to test for effect modification. All statistical analyses were two-sided, with P < 0.05 considered statistically significant.

Results

Among 7,094 patients with chronic HF, 1,087 initiated SGLT2 inhibitors, while 6,007 remained unexposed. Before propensity score matching, the SGLT2 inhibitor group was younger, predominantly male, had a higher prevalence of diabetes and prior myocardial infarction, and demonstrated better renal function. These patients were also more likely to receive guideline-directed medical therapy, including statins, diuretics, beta-blockers, and RAAS inhibitors. After 1:1 propensity score matching, 550 well-balanced patient pairs were identified. Baseline demographics, comorbidities, laboratory findings, medication use, and Charlson Comorbidity Index scores were comparable between the two groups, with all standardized mean differences below 0.1, indicating excellent covariate balance (Table 1).

Table 1
Demographic and Clinical Variable

	Overall Heart failure patients			After Propensity score matching		
	SGLT2 non-user	SGLT 2 user	P-value	SGLT2 non-user	SGLT 2 user	P-value
Sample size	6007	1087		550	550	
Gender						
Female	2822(47%)	385(35.4%)	< 0.001	221(40.2%)	220(40%)	0.951
Male	3185(53%)	702(64.6%)		329(59.8%)	330(60%)	
Age	71.96 ± 14.7	67.68 ± 14.21	< 0.001	71.11 ± 13.44	70.25 ± 13.34	0.288
Duration of HF	3.38 ± 3.78	2.78 ± 3.7	< 0.001	3.44 ± 4.17	3.54 ± 3.78	0.670
Medicine use at index date						
Statin	3359(55.9%)	758(69.7%)	< 0.001	444(80.7%)	445(80.9%)	0.939
Anti-HPT	769(12.8%)	106(9.8%)	< 0.001	77(14%)	65(11.8%)	0.281
Diuretics	3209(53.4%)	870(80%)	< 0.001	407(74%)	411(74.7%)	0.782
Beta blocking	3984(66.3%)	954(87.8%)	< 0.001	448(81.5%)	456(82.9%)	0.528
CCB	1960(32.6%)	241(22.2%)	< 0.001	175(31.8%)	160(29.1%)	0.326
RAAS inhibitors	4198(69.9%)	1005(92.5%)	< 0.001	494(89.8%)	499(90.7%)	0.611
VASODILATORS	1583(26.4%)	310(28.5%)	0.137	178(32.4%)	193(35.1%)	0.339
Digitalis glycosides	468(7.8%)	108(9.9%)	0.017	48(8.7%)	56(10.2%)	0.410
Aldosterone antagonists	1141(19%)	210(19.3%)	0.802	123(22.4%)	125(22.7%)	0.885
Lab data at index date						
NT-proBNP	7221 ± 10503	4489 ± 6943	< 0.001	5357 ± 8920	4097 ± 6854	0.054
Creatinine	2.1 ± 2.65	1.32 ± 1.05	< 0.001	1.43 ± 1.18	1.39 ± 0.93	0.556
eGFR	59.64 ± 36.07	63.39 ± 28.73	< 0.001	63.39 ± 31.43	59.38 ± 29.12	0.028
Hb	12.2 ± 2.45	13.03 ± 2.27	< 0.001	12.6 ± 2.47	12.82 ± 2.22	0.141
HbA1c	6.43 ± 1.3	6.7 ± 1.39	< 0.001	6.78 ± 1.54	6.74 ± 1.35	0.628
LDL	87.11 ± 31.11	82.64 ± 30.64	< 0.001	82.26 ± 30.85	83.2 ± 31.63	0.617
Triglyceride	134.67 ± 109.68	141.21 ± 96.32	0.134	140.25 ± 138.77	142.49 ± 93.93	0.760
WBC count	8.07 ± 3.83	8.07 ± 3.33	0.993	8.16 ± 3.46	7.88 ± 3.09	0.180
Platelet count	213.26 ± 83.15	219.27 ± 78.29	0.042	215.03 ± 82.94	217.24 ± 74.63	0.655
Comorbidity disease						
DM	2823(47%)	628(57.8%)	< 0.001	394(71.6%)	405(73.6%)	0.457
AMI	1290(21.5%)	374(34.4%)	< 0.001	129(23.5%)	169(30.7%)	0.007
VHD	947(15.8%)	121(11.1%)	< 0.001	87(15.8%)	67(12.2%)	0.082
HPT	4611(76.8%)	769(70.7%)	0.005	463(84.2%)	455(82.7%)	0.516
AF	1649(27.5%)	322(29.6%)	0.141	159(28.9%)	181(32.9%)	0.151
Anemia	1372(22.8%)	142(13.1%)	< 0.001	106(19.3%)	88(16%)	0.154
CCI score	5.56 ± 3.1	5.44 ± 3.18	0.267	6.65 ± 3.36	6.51 ± 3.12	0.497
Propensity score	0.87 ± 0.15	0.63 ± 0.22	< 0.001	0.68 ± 0.2	0.68 ± 0.2	0.999
Note. Results are expressed as mean ± SD or n (%). Abbreviations: Anti-HPT, anti-hypertensive; CCB, calcium channel blocker; RAAS, Renin-Angiotensin-Aldosterone System; N-terminal pro B-type natriuretic peptide (NT-proBNP); eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; DM, diabetes mellitus; HF, heart failure; CAD, coronary artery disease; CVA, cerebrovascular accident; CKD, chronic kidney disease; PVD, peripheral vascular disease.						

Urinary Tract Infection Outcomes

During the longitudinal follow-up, SGLT2 inhibitor initiation was associated with a significantly reduced risk of incident UTI. In the univariate Cox regression model, SGLT2 inhibitor use lowered the risk of incident UTI hospitalizations compared with unexposed (crude hazard ratio [cHR], 0.69; 95% confidence interval [CI], 0.55–0.88; P = 0.003). This protective association remained consistent after multivariable adjustment (adjusted hazard ratio [aHR], 0.75; 95% CI, 0.56–1.00; P = 0.048) and was further pronounced within the propensity score-matched cohort (HR, 0.64; 95% CI, 0.44–0.94; P = 0.021) (Table 2).

Table 2 Impact of SGLT2 inhibitor use on clinical outcomes assessed by univariate and multivariate Cox regression analyses.						
Outcome	cHR (95% CI)	p-value	aHR (95% CI)	p-value	PSM (95% CI)	p-value
UTI incidence	0.69(0.55,0.88)	0.003	0.75(0.56,1.00)	0.048	0.64(0.44,0.94)	0.021
UTI recurrence	0.69(0.43,1.11)	0.128	0.85(0.52,1.38)	0.505	0.46(0.22,0.99)	0.047
Heart failure hospitalization	1.13(0.98,1.29)	0.101	0.85(0.68,1.05)	0.128	0.78(0.61,1.01)	0.059
MACE incidence	0.93(0.73,1.20)	0.591	0.72(0.53,0.98)	0.036	0.76(0.51,1.12)	0.166
Abbreviations: UTI, urinary tract infection; MACE, Major adverse cardiovascular events						

Intriguingly, while SGLT2 inhibitor use was not significantly associated with recurrent UTI risk in the broader univariate or multivariable analyses, a highly significant protective effect emerged within the propensity score-matched cohort (HR, 0.46; 95% CI, 0.22–0.99; P = 0.047) (Table 2). Kaplan–Meier survival curves confirmed a lower cumulative incidence of both incident and recurrent UTI hospitalizations in SGLT2 inhibitor users compared to unexposed controls across the follow-up period.

Cardiovascular Outcomes

For the secondary outcomes, SGLT2 inhibitor use was associated with a lower rate of HF hospitalization in the matched cohort, although the difference did not reach statistical significance (HR, 0.78; 95% CI, 0.61–1.01; P = 0.059) (Table 2). SGLT2 inhibitor use was associated with a lower risk of 3-point MACE in the multivariable-adjusted analysis (aHR, 0.72; 95% CI, 0.53–0.98; P = 0.036), but the association was no longer statistically significant after propensity score matching (Table 2).

Subgroup and Sensitivity Analysis

Stratified analyses showed that, among patients not receiving SGLT2 inhibitors, diabetes was independently associated with a higher risk of incident UTI, HF hospitalization, and 3-point MACE. Notably, among patients with diabetes, initiation of SGLT2 inhibitors was not associated with an increased risk of either incident or recurrent UTI. Instead, SGLT2 inhibitor users consistently exhibited lower estimated risks of both outcomes than non-users (Table 3).

Table 3 Impact of Diabetes status on Clinical Outcomes in Heart Failure Patients Treated with SGLT2 Inhibitors									
DM	SGLT2 use	UTI incidence		UTI recurrence		Heart failure hospitalization		MACE incidence	
		aHR (95% CI)	p-value	aHR (95% CI)	p-value	aHR (95% CI)	p-value	aHR (95% CI)	p-value
No	No	1 (reference)		1 (reference)		1 (reference)		1 (reference)	
No	Yes	0.61(0.29,1.28)	0.195	0.32(0.06,1.70)	0.182	1.10(0.78,1.57)	0.584	0.68(0.32,1.48)	0.332
Yes	No	1.62(1.33,1.97)	< 0.001	1.14(0.79,1.63)	0.484	1.35(1.17,1.56)	< 0.001	1.46(1.18,1.81)	< 0.001
Yes	Yes	1.07(0.75,1.52)	0.719	0.67(0.33,1.32)	0.244	0.92(0.72,1.17)	0.484	0.98(0.67,1.45)	0.928
Abbreviations: UTI, urinary tract infection; MACE, Major adverse cardiovascular events									

Table 3 Impact of Diabetes on Clinical Outcomes in Heart Failure Patients Treated with SGLT2 Inhibitors									
DM	SGLT2 use	UTI incidence		UTI recurrence		Heart failure hospitalization		MACE incidence	
		aHR (95% CI)	p-value	aHR (95% CI)	p-value	aHR (95% CI)	p-value	aHR (95% CI)	p-value
No	No	1 (reference)		1 (reference)		1 (reference)		1 (reference)	
No	Yes	0.61(0.29,1.28)	0.195	0.32(0.06,1.70)	0.182	1.10(0.78,1.57)	0.584	0.68(0.32,1.48)	0.332
Yes	No	1.62(1.33,1.97)	< 0.001	1.14(0.79,1.63)	0.484	1.35(1.17,1.56)	< 0.001	1.46(1.18,1.81)	< 0.001
Yes	Yes	1.07(0.75,1.52)	0.719	0.67(0.33,1.32)	0.244	0.92(0.72,1.17)	0.484	0.98(0.67,1.45)	0.928
Abbreviations: UTI, urinary tract infection; MAC, Major adverse cardiovascular events									

Pre-specified subgroup analyses demonstrated that the association between SGLT2 inhibitor use and a lower risk of incident UTI was consistent across subgroups defined by age, sex, renal function, and diabetes status, with no significant interactions observed (Table 4). Although no significant effect modification was detected, the protective association appeared more pronounced among patients with preserved renal function (eGFR greater than or equal to 50 mL/min/1.73 m²) (Table 4).

Table 4
Subgroup analysis the effect of SGLT2 on clinical outcomes

Outcome Subgroup	Age < 65	Age≥65	P _{interaction}	eGFR < 50	eGFR≥50	P _{interaction}	No DM	DM
UTI incidence	0.70(0.37,1.35)	0.66(0.47,0.92)	0.859	0.79(0.54,1.15)	0.45(0.28,0.72)	0.058	0.62(0.30,1.27)	0.66(0.48,0.91)
UTI recurrence	0.46(0.11,1.90)	0.59(0.31,1.12)	0.739	0.54(0.23,1.27)	0.55(0.26,1.18)	0.984	0.31(0.06,1.69)	0.60(0.32,1.11)
Heart failure hospitalization	0.70(0.49,1.00)	0.82(0.65,1.02)	0.453	0.56(0.43,0.73)	0.89(0.68,1.16)	0.011	1.11(0.78,1.58)	0.69(0.56,0.87)
MACE incidence	0.30(0.12,0.72)	0.82(0.58,1.17)	0.032	0.45(0.28,0.74)	0.86(0.55,1.32)	0.045	0.70(0.32,1.52)	0.67(0.47,0.96)

Outcome Subgroup	NT-proBNP < 1800	NT-proBNP≥1800	P _{interaction}	CHD duration < 1 year	CHD duration≥1 year	P _{interaction}
UTI incidence	0.65(0.39,1.10)	1.22(0.77,1.93)	0.061	0.59(0.36,0.97)	0.76(0.53,1.09)	0.397
UTI recurrence	0.33(0.09,1.25)	0.89(0.36,2.19)	0.207	0.38(0.15,0.94)	0.84(0.40,1.76)	0.162
Heart failure hospitalization	0.61(0.42,0.89)	0.69(0.51,0.91)	0.608	0.66(0.49,0.87)	0.99(0.77,1.26)	0.025
MACE incidence	0.83(0.46,1.49)	0.71(0.42,1.21)	0.685	0.63(0.37,1.09)	0.77(0.52,1.15)	0.554

Outcome Subgroup	Female	Male	P _{interaction}
UTI incidence	0.76(0.52,1.12)	0.56(0.35,0.89)	0.282
UTI recurrence	0.57(0.29,1.15)	0.46(0.17,1.26)	0.711
Heart failure hospitalization	0.73(0.55,0.99)	0.80(0.63,1.03)	0.637
MACE incidence	0.58(0.34,0.99)	0.79(0.52,1.19)	0.351
Abbreviations: UTI, urinary tract infection; NT-proBNP, N-terminal pro-B-type natriuretic peptide ;CHD, Coronary Heart Disease; MACE, Major adverse cardiovascular events			

For cardiovascular outcomes, the benefits of SGLT2 inhibitors appeared more pronounced among patients with diabetes, impaired renal function, and a shorter duration of HF (Table 4). In the sensitivity analysis, we applied a more stringent, guideline-based definition of recurrent UTI requiring a greater number of episodes. Although the protective association remained directionally consistent, it was no longer statistically significant in the matched cohort, likely reflecting the smaller number of events under the stricter definition (HR, 0.79; 95% CI, 0.44–1.42; P = 0.424) (Table 5).

Table 5
For Sensitivity analysis: Clinical guidelines, "recurrent UTI" usually implies a specific frequency (> 2 in 6 months or > 3 in a year)

Outcome Subgroup	Female	Male	P _{interaction}
UTI incidence	0.76(0.52,1.12)	0.56(0.35,0.89)	0.282
UTI recurrence	0.57(0.29,1.15)	0.46(0.17,1.26)	0.711
Heart failure hospitalization	0.73(0.55,0.99)	0.80(0.63,1.03)	0.637
MACE incidence	0.58(0.34,0.99)	0.79(0.52,1.19)	0.351

Outcome	cHR (95% CI)	p-value	aHR (95% CI)	p-value	PSM (95% CI)	p-value	PSM ^{no adjusted PS} (95% CI)	p-value
UTI recurrent based on clinical guideline	0.84(0.57,1.23)	0.3652	0.83(0.56,1.21)	0.3319	0.79(0.44,1.42)	0.4236	0.79(0.44,1.42)	0.4289
No adjusting for the Propensity Score:								

Discussion

This retrospective cohort study provides real-world evidence regarding the association between SGLT2 inhibitor initiation and the risk of serious UTIs in patients with HF. Despite the well-established glucosuric mechanism of these agents (17–19), SGLT2 inhibitor initiation was associated with a significantly lower risk of both incident and recurrent UTI hospitalizations in the propensity score-matched cohort. Concerns about severe UTIs should not, on this evidence, discourage SGLT2 inhibitor use in patients with chronic HF, and these findings add to the favorable safety profile already reported in landmark randomized trials.

The reduced risk of incident UTI we observed is consistent with the DAPA-HF and EMPEROR-Reduced trials, neither of which found excess UTI risk with SGLT2 inhibitors (3, 4), and with observational studies and meta-analyses showing no increased risk of severe UTI despite glucosuria (10, 20). Patients with

HF, however, have been underrepresented in these studies. Our matched analysis also showed a significant reduction in recurrent UTI hospitalizations (HR, 0.46; $P = 0.047$), an outcome rarely examined in HF populations (21). This association weakened in the sensitivity analysis, largely because of the smaller number of recurrent events, but the direction of effect held, which argues against treating a history of recurrent UTI as a contraindication to SGLT2 inhibitor therapy in patients with HF.

The apparent drop in UTI risk despite therapeutic glucosuria is something of a paradox. Urinary glucose could in theory promote bacterial growth, yet SGLT2 inhibitors also induce osmotic diuresis and natriuresis, which may enhance urinary clearance of pathogens and reduce bacterial adherence (22–25). These agents also improve renal hemodynamics by relieving venous congestion, reducing interstitial edema, and restoring renal microvascular perfusion (26–28). Together, these mechanisms could plausibly help preserve local host defenses, which may partly explain the lower incidence of severe UTIs observed in our cohort.

The protective association between SGLT2 inhibitor use and incident UTI held up across prespecified subgroups, with no significant interactions by age, sex, diabetes status, or renal function. The association looked somewhat stronger among patients with preserved renal function, though this interaction was not statistically significant. Notably, even though diabetes is an established UTI risk factor, SGLT2 inhibitor therapy was not associated with any increase in incident or recurrent UTI risk among diabetic patients — a pattern consistent with the drug's cardiorenal benefits outweighing any theoretical infection risk from glucosuria.

Our cardiovascular findings track the established benefits of SGLT2 inhibitors: use was associated with a lower risk of 3-point MACE in multivariable analysis and a trend toward fewer HF hospitalizations after matching. The loss of statistical significance after matching most likely reflects reduced power from cohort balancing rather than a true loss of treatment effect. Subgroup analyses also pointed to greater benefit among patients with shorter HF duration, in line with current guideline recommendations for early initiation of SGLT2 inhibitors as part of guideline-directed medical therapy (2, 7).

Taken together, these observations argue against a history of genitourinary infection as a reason to withhold or delay SGLT2 inhibitor therapy in HF, a population in which prescribing hesitancy has persisted despite strong guideline endorsement. They also carry a practical message for clinicians managing fluid-restricted patients: the theoretical infection risk from glucosuria does not appear to translate into excess hospitalizations in practice, and if anything runs in the opposite direction.

Conclusions

Concerns about genitourinary infections remain a common barrier to SGLT2 inhibitor initiation in patients with heart failure, but our real-world data do not support that caution: SGLT2 inhibitor therapy was not associated with an increased risk of serious UTIs, even among patients with diabetes or a history of recurrent UTIs, and appeared instead to reduce UTI-related hospitalizations. These results may help ease therapeutic inertia and support wider use of SGLT2 inhibitors as a foundational component of guideline-directed medical therapy for HF.

Careful patient selection, counseling, and clinical monitoring remain important nonetheless. Patients should be advised on genital hygiene, early recognition of urinary symptoms, and hydration strategies tailored to their HF-related fluid restrictions. Alongside the established cardiovascular and renal benefits of SGLT2 inhibitors, these measures should support their safe use in routine heart failure care.

Limitations:

Our study has several notable strengths, including its focus on both incident and recurrent UTIs specifically within a heart failure cohort, and the use of propensity score matching to minimize measured confounding. However, several limitations must be acknowledged:

1. The retrospective, observational design precludes the determination of direct causality, leaving a possibility of residual confounding.
2. Our reliance on EMR diagnostic codes introduces a risk of misclassification bias.
3. We only captured severe, hospitalization-requiring UTIs, omitting milder, outpatient-managed infections.
4. The absence of microbiological data, urine culture results, specific antibiotic regimens, and long-term glycemic variability metrics limits our ability to fully verify the proposed biological mechanisms.
5. Lastly, because this study was conducted at a single tertiary academic medical center, the generalizability of our findings to other healthcare settings and distinct ethnic populations remains to be confirmed.

Declarations

Funding

No external funding was received for this study.

Consent to participate

This study was approved after a full ethical review by the Institutional Review Board (IRB) of the Changhua Christian Hospital (approval number 241012), and the IRB waived the need for consent. Those data were accessed anonymously.

Consent for publication

Not applicable.

Data Availability Statement

The dataset utilized in the study is not accessible due to confidentiality regulations outlined in the Personal Information Protection Act enforced by the Taiwanese Government since 2012. For additional details regarding data acquisition, interested parties may contact the primary author upon request.

Clinical trial number

Not applicable.

Ethical Approval

The study protocol was approved by the Institutional Review Board of Changhua Christian Hospital (IRB No. 241012).

Conflict of Interest

The authors declare no conflicts of interest related to this work.

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References

1. Heerspink HJL, Stefánsson BV, Correa-Rotter R, Chertow GM, Greene T, Hou FF, et al. Dapagliflozin in Patients with Chronic Kidney Disease. *N Engl J Med*. 2020;383(15):1436–46.
2. McMurray JJV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. *N Engl J Med*. 2019;381(21):1995–2008.
3. Anker SD, Butler J, Filippatos G, Ferreira JP, Bocchi E, Böhm M, et al. Empagliflozin in Heart Failure with a Preserved Ejection Fraction. *N Engl J Med*. 2021;385(16):1451–61.
4. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. *N Engl J Med*. 2015;373(22):2117–28.
5. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2021;42(36):3599–726.
6. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2022;145(18):e895–1032.
7. Packer M, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P, et al. Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. *N Engl J Med*. 2020;383(15):1413–24.
8. Zannad F, Ferreira JP, Pocock SJ, Anker SD, Butler J, Filippatos G, et al. SGLT2 inhibitors in patients with heart failure with reduced ejection fraction: a meta-analysis of the EMPEROR-Reduced and DAPA-HF trials. *Lancet (London England)*. 2020;396(10254):819–29.
9. Puckrin R, Saltiel MP, Reynier P, Azoulay L, Yu OHY, Filion KB. SGLT-2 inhibitors and the risk of infections: a systematic review and meta-analysis of randomized controlled trials. *Acta Diabetol*. 2018;55(5):503–14.
10. Dave CV, Schneeweiss S, Kim D, Fralick M, Tong A, Paterno E. Sodium-Glucose Cotransporter-2 Inhibitors and the Risk for Severe Urinary Tract Infections: A Population-Based Cohort Study. *Ann Intern Med*. 2019;171(4):248–56.
11. Greene SJ, Pierce JB. Overcoming Barriers to Use of SGLT2 Inhibitor Therapy: The Battle Against Clinical Inertia. *JACC Heart Fail*. 2023;11(8 Pt 1):943–5.
12. Zou H, Zhou B, Xu G. SGLT2 inhibitors: a novel choice for the combination therapy in diabetic kidney disease. *Cardiovasc Diabetol*. 2017;16(1):65.
13. Hooton TM. Clinical practice. Uncomplicated urinary tract infection. *N Engl J Med*. 2012;366(11):1028–37.
14. Hsu SM, Lin YH, Lin YC, Liu SJ, Liu CJ, Hung CL, et al. Fluid intake impact on heart failure: Systematic review and meta-analysis with trial sequential analysis. *J Formos Med Association = Taiwan yi zhi*. 2025;124(7):650–9.
15. Cardoso JN, Del Carlo CH, Oliveira Junior MT, Ochiai ME, Kalil Filho R, Barretto ACP. Infection in Patients with Decompensated Heart Failure: In-Hospital Mortality and Outcome. *Arquivos brasileiros de cardiologia*. 2018;110(4):364–70.
16. Drozd M, Garland E, Walker AMN, Slater TA, Koshy A, Straw S, et al. Infection-Related Hospitalization in Heart Failure With Reduced Ejection Fraction: A Prospective Observational Cohort Study. *Circulation Heart Fail*. 2020;13(5):e006746.
17. Zelniker TA, Wiviott SD, Raz I, Im K, Goodrich EL, Bonaca MP, et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. *Lancet (London England)*. 2019;393(10166):31–9.
18. Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondou N, et al. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. *N Engl J Med*. 2017;377(7):644–57.

19. Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, et al. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med*. 2019;380(4):347–57.
20. Aboukaoud M, Morhi Y, Osher E. Sodium-Glucose Co-Transporter 2 Inhibitors and Severe Urinary Tract Infections: Real-World Meta-Analysis of Cohort Studies. *Annals pharmacotherapy*. 2025;59(10):891–903.
21. Borovac JA, Kurir T, Mustapic I, Kumric M, Bozic J, Glavas D, et al. SGLT2 inhibitors and the risk of urinary tract infections in patients with heart failure: A pooled analysis examining safety endpoints. *Kardiologia Polska*. 2022;80(2):198–201.
22. Dekkers CCJ, Sjöström CD, Greasley PJ, Cain V, Boulton DW, Heerspink HJL. Effects of the sodium-glucose co-transporter-2 inhibitor dapagliflozin on estimated plasma volume in patients with type 2 diabetes. *Diabetes Obes Metab*. 2019;21(12):2667–73.
23. Ferrannini E, Muscelli E, Frascerra S, Baldi S, Mari A, Heise T, et al. Metabolic response to sodium-glucose cotransporter 2 inhibition in type 2 diabetic patients. *J Clin Investig*. 2014;124(2):499–508.
24. Gajewska A, Wasiak J, Sapeda N, Młynarska E, Rysz J, Franczyk B. SGLT2 Inhibitors in Kidney Diseases-A Narrative Review. *Int J Mol Sci*. 2024;25(9).
25. Gorgojo-Martínez JJ, Górriz JL, Cebrián-Cuenca A, Castro Conde A, Velasco Arribas M. Clinical Recommendations for Managing Genitourinary Adverse Effects in Patients Treated with SGLT-2 Inhibitors: A Multidisciplinary Expert Consensus. *J Clin Med*. 2024;13:21.
26. Vallon V, Verma S. Effects of SGLT2 Inhibitors on Kidney and Cardiovascular Function. *Annu Rev Physiol*. 2021;83:503–28.
27. Wallbach M, Ajrab J, Bayram B, Pieper D, Schäfer AK, Lüders S, et al. Effects of SGLT2 inhibitors on parameters of renal venous congestion in intrarenal Doppler ultrasonography. *Clin kidney J*. 2024;17(9):sf234.
28. Iordan L, Gaita L, Timar R, Avram V, Sturza A, Timar B. The Renoprotective Mechanisms of Sodium-Glucose Cotransporter-2 Inhibitors (SGLT2i)-A Narrative Review. *Int J Mol Sci*. 2024;25(13).

Figures

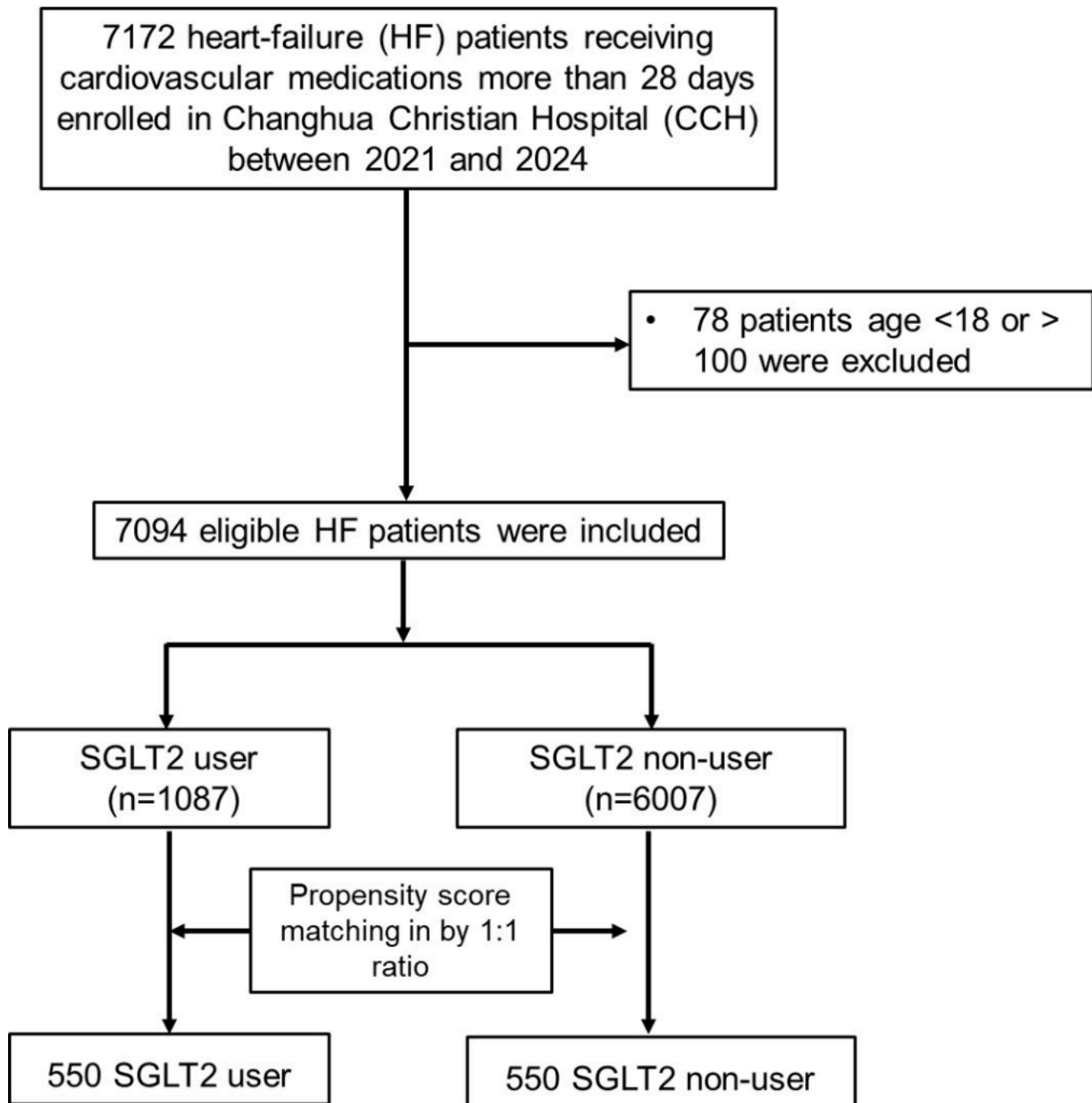


Figure 1

Flow chart

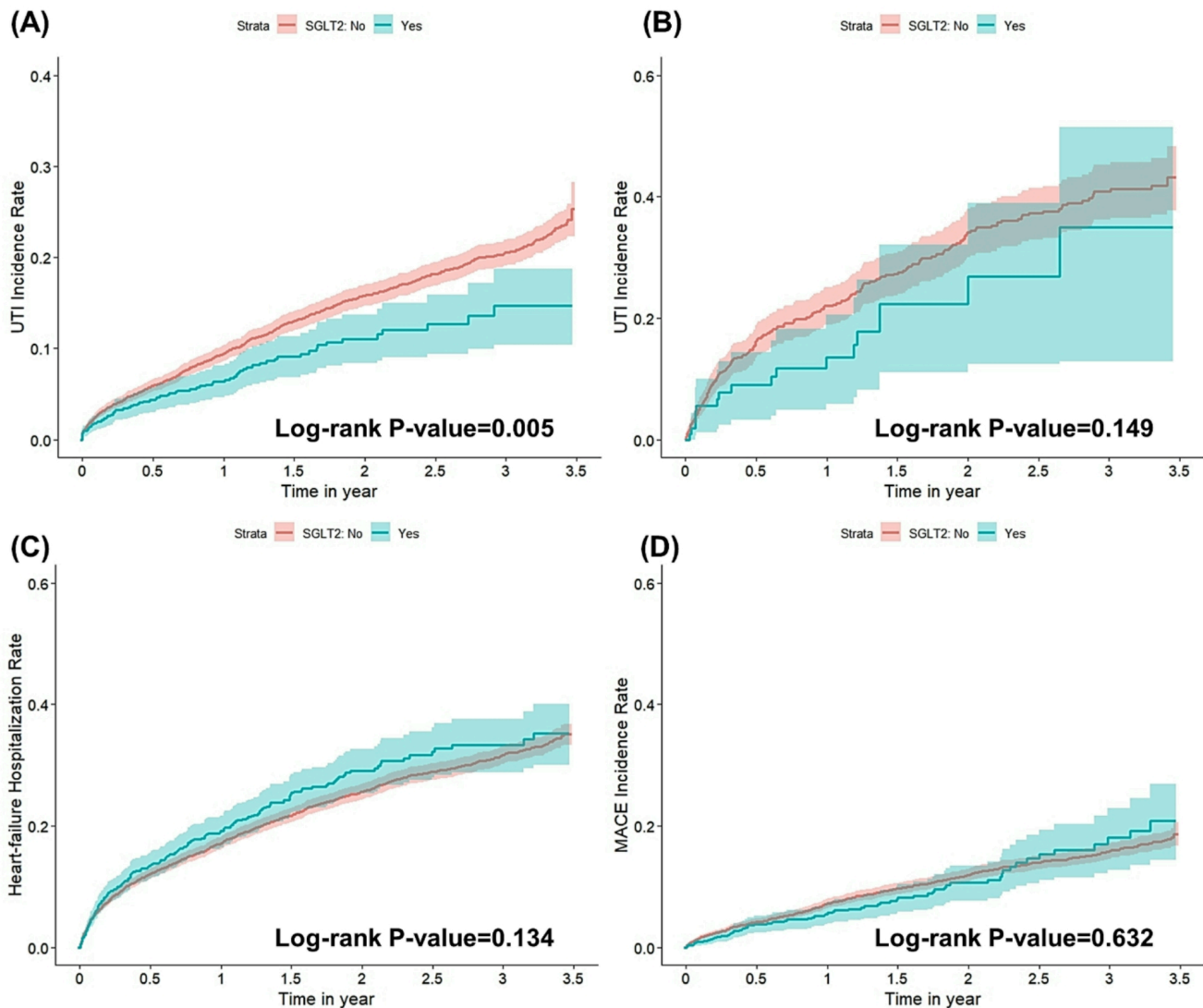


Figure 2

Kaplan-Meier curves comparing clinical outcomes between SGLT2 inhibitor users and non-users.

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