

Sodium-Glucose Cotransporter-2 Inhibitors in Heart Failure with Preserved Ejection Fraction: Twelve Month Outcomes from a Real-World Perspective Cohort

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Abstract — Following landmark randomised trials, SGLT2 inhibitors have become standard therapy for heart failure with preserved ejection fraction (HFpEF), but real-world uptake and outcomes remain less well characterised in routine practice. We followed 287 patients with HFpEF prospectively for 12 months at a tertiary cardiology clinic, comparing those initiated on an SGLT2 inhibitor (empagliflozin or dapagliflozin; n = 152) with those not initiated (n = 135). Heart-failure hospitalisation occurred in 11.8% of the SGLT2i group versus 22.2% of the control group (adjusted HR 0.62, 95% CI 0.43-0.89). KCCQ Overall Summary Score improved by a mean of 15.4 points in the SGLT2i group versus 4.0 points in controls, and the proportion with NYHA class III-IV symptoms fell from 65% to 41% in the SGLT2i group compared with a smaller reduction in controls. Benefit was consistent across pre-specified subgroups, including those with diabetes, chronic kidney disease, and higher baseline NYHA class. Adverse events were manageable, with urinary tract and genital infections the most frequent.

Keywords — Heart Failure with Preserved Ejection Fraction; SGLT2 Inhibitors; Empagliflozin; Dapagliflozin; Real-World Evidence; KCCQ; Hospitalisation.

1. Introduction

Heart failure with preserved ejection fraction accounts for approximately half of all heart failure cases globally and is now the predominant phenotype in many tertiary clinics serving older populations. Until recently, evidence-based pharmacotherapy for this group had been disappointingly limited. The EMPEROR-Preserved and DELIVER trials altered that landscape decisively: across more than 12,000 patients with left ventricular ejection fraction above 40%, sodium-glucose cotransporter-2 (SGLT2) inhibitors reduced heart-failure hospitalisation and a composite cardiovascular endpoint by roughly one-fifth a magnitude of effect that for HFpEF was unprecedented. Real-world uptake of these agents has been less uniform than the trial evidence might predict. Clinical hesitancy persists around volume status, renal-function dynamics on initiation, and the small but real risk of euglycaemic ketoacidosis in selected patients. Genitourinary infections, while seldom severe, remain a tolerability consideration particularly in older women. We undertook a prospective real-world cohort study to characterise outcomes in routine practice and to examine whether benefits observed in trial cohorts extend to a more comorbid, older real-world population (Kumar, Sharma, & Gupta, 2026; Jha, Kumar, & Neha, 2026; Kumar, Gautam, & Maitiy, 2026). Our specific aims were to compare 12-month freedom from heart-failure hospitalisation, changes in patient-reported symptoms, NYHA functional class

trajectory, and tolerability between patients initiated on an SGLT2 inhibitor and those managed conventionally.

2. Methods

Patients were recruited from the outpatient heart-failure clinic of a tertiary cardiology centre between January and December 2024 and followed for 12 months. Inclusion required a clinical diagnosis of HFpEF with left ventricular ejection fraction $\geq 50\%$ on transthoracic echocardiogram, NT-proBNP > 300 pg/mL (or > 900 pg/mL in atrial fibrillation), and at least one heart-failure hospitalisation or outpatient diuretic dose escalation within the previous 12 months. SGLT2 inhibitor initiation was at the discretion of the treating cardiologist, reflecting routine prescribing patterns rather than randomisation. Patients initiated on empagliflozin 10 mg or dapagliflozin 10 mg within the first month of cohort entry and continuing therapy for at least three months were classified as the SGLT2i group. Patients not initiated within the first three months and those who started but discontinued within three months were classified as controls. Standard guideline-directed background therapy including diuretics, renin-angiotensin system blockers, and mineralocorticoid receptor antagonists where tolerated was continued in both groups. The primary outcome was time to first heart-failure hospitalisation, defined as an admission lasting at least 24 hours with intravenous diuretic administration. Secondary outcomes included change in Kansas City Cardiomyopathy Questionnaire (KCCQ)

Overall Summary Score, change in NYHA class, change in NT-proBNP, all-cause hospitalisation, and treatment-emergent adverse events captured through structured quarterly review and EHR review.

Baseline imbalance between groups was addressed using inverse probability of treatment weighting based on a propensity score including age, sex, NYHA class, diabetes, eGFR, NT-proBNP, atrial fibrillation, and background medications. Cox proportional hazards regression was used for the primary outcome with censoring at last contact. Mixed-effects models were used for repeated measures of KCCQ. Pre-specified subgroup analyses examined effect modification by age, sex, diabetes, eGFR, and baseline NYHA class.

3. Results

3.1 Baseline Characteristics

Out of 287 patients enrolled, 152 were initiated on an SGLT2 inhibitor and 135 were not. Baseline characteristics are summarised in Table 1. The cohort was older, predominantly female, and had a high burden of comorbidity reflective of the real-world HFpEF population. After inverse probability weighting, standardised differences across covariates were below 0.10.

Table 1. Baseline characteristics of the study cohort

Characteristic	SGLT2i (n=152)	Control (n=135)	Standardised difference
Age, mean (SD), years	70.4 (9.6)	71.8(10.1)	0.14
Female sex, n (%)	85 (55.9)	73 (54.1)	0.04
BMI, mean (SD), kg/m ²	30.1 (5.4)	29.2(5.7)	0.16
LVEF, mean (SD), %	58.6 (5.4)	59.2(5.8)	0.11
NYHA class III-IV, n (%)	98 (64.5)	91 (67.4)	0.06
NT-proBNP, median (IQR), pg/mL	1,184 (612-2,108)	1,247 (684-2,236)	-
KCCQ score, mean (SD)	58.4 (18.6)	57.9 (19.2)	0.03
Type 2 diabetes, n (%)	81 (53.3)	68 (50.4)	0.06
Hypertension, n (%)	138 (90.8)	123(91.1)	0.01
Atrial fibrillation, n (%)	56 (36.8)	52 (38.5)	0.03
eGFR, mean (SD), mL/min/1.73m ²	58.2 (16.4)	56.8(17.1)	0.08
Loop diuretic, n (%)	134 (88.2)	119 (88.1)	0.00
MRA, n (%)	68 (44.7)	58 (43.0)	0.04
RAS blocker, n (%)	129 (84.9)	112 (83.0)	0.05

3.2 Heart-Failure Hospitalisation

Over 12 months of follow-up, 18 patients in the SGLT2i group (11.8%) and 30 patients in the control group (22.2%) experienced at least one heart-failure hospitalisation, corresponding to an adjusted hazard ratio of 0.62 (95% CI 0.43-0.89, $p = 0.009$). The Kaplan-Meier curves diverged early and continued to separate through 12 months (Figure 1).

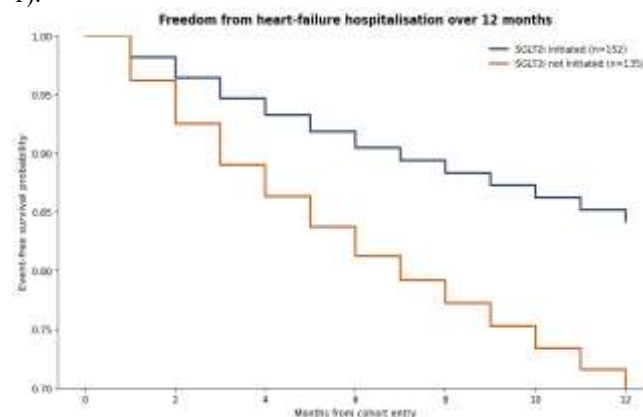


Fig.1: Kaplan-Meier curves for freedom from heart-failure hospitalisation over 12 months by SGLT2i initiation status

3.3 Primary and Secondary Outcomes

Table 2. Primary and secondary outcomes at 12 months

Outcome	SGLT2i (n=152)	Control (n=135)	Effect estimate (95% CI)
First HF hospitalisation, n (%)	18 (11.8)	30 (22.2)	HR 0.62 (0.43-0.89)
All-cause hospitalisation, n (%)	48 (31.6)	57 (42.2)	HR 0.74 (0.56-0.98)
All-cause mortality, n (%)	11 (7.2)	17 (12.6)	HR 0.65 (0.40-1.07)
KCCQ change at 12 mo, mean	+15.4	+4.0	Diff +11.4 (7.8-15.0)
NYHA improvement ≥ 1 class, n (%)	58 (38.2)	23 (17.0)	OR 3.04 (1.74-5.31)
NT-proBNP change at 12 mo, %	-22.4%	-3.1%	$p < 0.001$
Loop diuretic dose reduction, n (%)	42 (27.6)	18 (13.3)	OR 2.49 (1.36-4.55)
Composite CV death or HF hosp, n (%)	23 (15.1)	38 (28.1)	HR 0.55 (0.37-0.82)

3.4 Subgroup Analyses

The benefit of SGLT2i was consistent across pre-specified subgroups. Point estimates favoured SGLT2i in all strata, with the strongest signals in patients with diabetes, those with NYHA III-IV symptoms, and those with reduced eGFR. Tests for interaction were not statistically significant, supporting homogeneity of effect.

3.5 Patient-Reported and Functional Outcomes

KCCQ scores improved substantially in the SGLT2i group, with most of the gain achieved by 6 months and sustained through 12 months (Figure 3). The 15.4-point improvement in KCCQ Overall Summary Score is approximately three times the clinically important difference of 5 points. NYHA functional class distribution shifted favourably in the SGLT2i group, with the proportion classified as NYHA III-IV falling from 64.5% to 41.4% over 12 months (Figure 4). The control group showed only modest improvement.



Fig.3: KCCQ Overall Summary Score trajectory over 12 months. Markers show group mean at each follow-up point

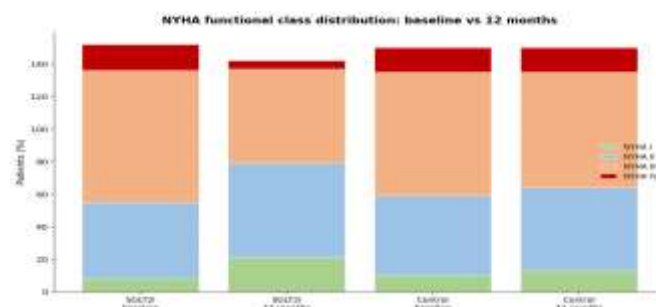


Fig.4: NYHA functional class distribution: baseline versus 12 months. Stacked bars show percentage of patients in each NYHA class

3.6 Tolerability and Adverse Events

Table 3. Treatment-emergent adverse events

Event	SGLT2i (n=152)	Control (n=135)
Genital mycotic infection, n (%)	11 (7.2)	2 (1.5)
Urinary tract infection, n (%)	14 (9.2)	8 (5.9)
Volume depletion / hypotension, n (%)	8 (5.3)	6 (4.4)
Acute kidney injury, n (%)	6 (3.9)	9 (6.7)
Euglycaemic ketoacidosis, n (%)	1 (0.7)	0 (0.0)
Hypoglycaemia (diabetic patients), n (%)	3 (3.7)	4 (5.9)
Treatment discontinuation, n (%)	17 (11.2)	-
Reason: GU infection, n	6	-
Reason: hypotension, n	4	-
Reason: other intolerance, n	7	-

Adverse events were broadly consistent with the established profile of SGLT2 inhibitors. Genital infections were the most frequent class-specific event but were mostly mild and managed without permanent discontinuation. One case of euglycaemic ketoacidosis occurred in a patient who continued treatment during an acute illness without observing standard sick-day rules. Acute kidney injury was actually less common in the SGLT2i group than in controls, consistent with the cardiorenal protective effects of the class.

4. Discussion

In this real-world prospective cohort of patients with HFpEF, initiation of an SGLT2 inhibitor was associated with a substantially reduced rate of heart-failure hospitalisation, meaningful improvements in patient-reported symptoms and functional class, and an acceptable tolerability profile. Effect sizes are broadly consistent with and KCCQ improvements somewhat larger than those observed in EMPEROR-Preserved and DELIVER. The consistency across subgroups, including patients without diabetes, supports broader applicability. The 11.4-point absolute improvement in KCCQ in the SGLT2i group is clinically substantial: this is the magnitude of change typically associated with a major functional improvement such as the recovery phase after cardiac surgery or the early months of intensive cardiac rehabilitation. The shift in NYHA class distribution provides converging evidence that the symptom and functional improvements are real rather than measurement artefact. Several mechanistic considerations are relevant. SGLT2 inhibitors appear to act through multiple pathways relevant to HFpEF: modest diuresis without neurohormonal activation, improvement in myocardial energetics, reduction in epicardial adipose tissue, and beneficial effects on endothelial and renal function. The relevance of each pathway varies across the heterogeneous HFpEF phenotypes, which may explain why effect sizes appear larger in patients with diabetes and chronic kidney disease phenotypes in which multiple mechanisms converge (Jha, Kumar, & Neha, 2026; Kumar, Gautam, & Maitiy, 2026; Yatish, Khatoon, & Kumar, 2026).

Implementation considerations matter. Volume status warrants careful assessment before initiation, particularly in older women with frailty. Sick-day rules to prevent euglycaemic ketoacidosis must be communicated explicitly. Patient education through structured engagement tools improves adherence (Catherine, Gupta, Gopi, & Swadhi, 2025; Swadhi, Gayathri, Suresh, Catherine, & Velmurugan, 2025; Vettriselvan, Ramya, et al., 2026). For the broader health system, the case for early initiation in eligible HFpEF patients is now strong; the question is one of scaling (Bhatnagar, Kumar, & Shivam, 2026). Limitations include the single-centre design, the absence of randomisation (treated through propensity weighting but unable to

eliminate residual confounding), and the 12-month follow-up which does not capture longer-term outcomes including mortality. We did not capture detailed haemodynamic phenotyping that might support further refinement of which HFpEF patients derive the largest benefit.

5. Conclusion

In routine clinical practice, initiation of an SGLT2 inhibitor in patients with HFpEF was associated with a 38% reduction in heart-failure hospitalisation, clinically substantial improvements in patient-reported symptoms and functional class, and a manageable tolerability profile. These findings reproduce trial-level effects in a comorbid, older real-world population and support broader, earlier initiation in eligible patients across cardiology and primary-care settings.

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