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Original Research Article

Impact of Early SGLT2 Inhibitor Initiation on Mortality and Rehospitalization in Patients with Acute Decompensated Heart Failure

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Abstract:

Background: Sodium-glucose cotransporter 2 (SGLT2) inhibitors have demonstrated substantial cardiovascular benefits in chronic heart failure. However, the optimal timing of initiation during acute decompensated heart failure (ADHF) hospitalization and its impact on short-term and intermediate-term clinical outcomes remain insufficiently characterized. This study aimed to evaluate the effect of early in-hospital SGLT2 inhibitor initiation on all-cause mortality and heart failure rehospitalization in patients admitted with ADHF.

Methods: A retrospective cohort study was conducted across two tertiary cardiac centers. A total of 742 patients hospitalized with ADHF were included: 318 who received SGLT2 inhibitors within 48 hours of admission (early initiation group) and 424 who received standard heart failure therapy without SGLT2 inhibitors during hospitalization (standard care group). The primary composite endpoint was all-cause mortality or first heart failure rehospitalization at 180 days. Secondary endpoints included individual components of the composite, in-hospital worsening heart failure events, change in N-terminal pro-B-type natriuretic peptide (NT-proBNP), length of hospital stay, and renal safety outcomes.

Results: The primary composite endpoint occurred in 22.3% of the early initiation group versus 33.5% of the standard care group (hazard ratio [HR] 0.61, 95% CI 0.47–0.79, $p < 0.001$). All-cause mortality at 180 days was 8.2% versus 13.4% (HR 0.58, 95% CI 0.38–0.89, $p = 0.012$). Heart failure rehospitalization occurred in 16.4% versus 24.3% (HR 0.63, 95% CI 0.47–0.85, $p = 0.002$). The early initiation group demonstrated significantly greater NT-proBNP reduction at discharge (−48.2 ± 22.6% vs. −34.7 ± 24.1%, $p < 0.001$) and shorter median length of stay (6.3 ± 2.8 vs. 7.9 ± 3.4 days, $p < 0.001$). No significant differences in acute kidney injury, diabetic ketoacidosis, or urinary tract infections were observed between groups.

Conclusion: Early in-hospital initiation of SGLT2 inhibitors within 48 hours of admission for ADHF was associated with significantly reduced all-cause mortality, lower heart failure rehospitalization rates, and greater neurohormonal decongestion without increased adverse events. These findings support the paradigm of prompt SGLT2 inhibitor initiation during acute heart failure hospitalization.

Keywords: SGLT2 inhibitors; acute decompensated heart failure; mortality; rehospitalization; early initiation; dapagliflozin; empagliflozin; heart failure outcomes.

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Introduction

Heart failure (HF) represents a global cardiovascular epidemic affecting an estimated 64 million individuals worldwide, with acute decompensated heart failure constituting the leading cause of hospitalization among adults over 65 years of age [1]. Despite considerable advances in pharmacological and device-based therapies, ADHF continues to carry a dismal prognosis, with in-hospital mortality rates of 4–10%, 30-day rehospitalization rates approaching 25%, and one-year mortality rates exceeding 30% [2]. The post-discharge period following ADHF hospitalization represents a particularly vulnerable phase characterized by heightened risks of recurrent decompensation, progressive organ dysfunction, and death [3].

Sodium-glucose cotransporter 2 inhibitors, originally developed as glucose-lowering agents for type 2 diabetes mellitus, have emerged as a transformative therapeutic class in heart failure management. The DAPA-HF and EMPEROR-Reduced trials established the efficacy of dapagliflozin and empagliflozin, respectively, in reducing cardiovascular death and heart failure hospitalization among patients with chronic heart

failure with reduced ejection fraction (HFrEF), irrespective of diabetes status [4], [5]. Subsequently, the EMPEROR-Preserved and DELIVER trials extended these benefits to patients with heart failure with preserved ejection fraction (HFpEF), thereby positioning SGLT2 inhibitors as a universal pillar of heart failure therapy across the ejection fraction spectrum [6], [7].

While the evidence base for SGLT2 inhibitors in chronic, stable heart failure is robust, their role in the acute setting has only recently been explored. The SOLOIST-WHF trial was among the first to demonstrate that sotagliflozin, a dual SGLT1/SGLT2 inhibitor, initiated before or shortly after discharge in patients with worsening heart failure and diabetes, significantly reduced cardiovascular deaths and heart failure events [8]. More recently, the EMPULSE trial demonstrated that empagliflozin initiated during hospitalization for acute heart failure produced a statistically significant net clinical benefit at 90 days, encompassing reductions in death, heart failure events, and improvements in patient-reported outcomes [9]. The DAPA ACT HF-TIMI 68 trial further contributed evidence supporting in-hospital initiation of dapagliflozin, though with somewhat mixed results regarding its primary endpoint [10].

Despite these landmark trials, several important knowledge gaps persist. First, the optimal timing of SGLT2 inhibitor initiation relative to admission—whether within the first 24–48 hours versus later during hospitalization—has not been explicitly investigated in comparative effectiveness studies [11]. Second, real-world data examining the safety and efficacy of early SGLT2 inhibitor initiation across heterogeneous patient populations, including those with varying ejection fractions, renal function, and comorbidity burdens, remain limited [12]. Third, the impact of early initiation on surrogate markers of decongestion, including natriuretic peptide trajectory and weight reduction, during the index hospitalization requires further characterization [13]. Fourth, concerns regarding hemodynamic instability, acute kidney injury, and euglycemic diabetic ketoacidosis during the acute phase continue to temper clinician enthusiasm for early adoption in hemodynamically fragile patients [14].

The aim of this study was to evaluate the impact of early SGLT2 inhibitor initiation (within 48 hours of hospital admission) on the composite endpoint of all-cause mortality and heart failure rehospitalization at 180 days in patients hospitalized with ADHF, compared to standard heart failure therapy without in-hospital SGLT2 inhibitor initiation. Secondary objectives included assessment of in-hospital clinical trajectories, neurohormonal biomarker changes, length of stay, and safety outcomes.

Materials and Methods

Study Design and Setting: This was a multicenter retrospective cohort study conducted at two tertiary cardiac care centers.

Study Population: Consecutive adult patients (≥18 years) admitted with a primary diagnosis of ADHF were screened for inclusion. ADHF was defined as the acute or subacute worsening of heart failure signs and symptoms requiring urgent or emergent therapy including intravenous diuretics. Patients were required to have at least one of the following: NT-proBNP ≥1600 pg/mL or BNP ≥400 pg/mL at admission, radiographic evidence of pulmonary congestion, or clinical evidence of volume overload (peripheral edema, jugular venous distension, or pulmonary rales).

The early initiation group comprised patients who received an SGLT2 inhibitor (empagliflozin 10 mg or dapagliflozin 10 mg) within 48 hours of hospital admission. The standard care group included patients who did not receive any SGLT2 inhibitor during hospitalization or within 30 days of discharge. Patients who initiated SGLT2 inhibitors between 48 hours after admission and discharge were excluded to ensure clear temporal separation between groups.

Exclusion Criteria: Exclusion criteria included: (1) cardiogenic shock requiring mechanical circulatory support or vasopressor therapy at admission; (2) estimated glomerular filtration rate (eGFR) <20 mL/min/1.73 m²; (3) history of diabetic ketoacidosis within the preceding 12 months; (4) type 1 diabetes mellitus; (5) systolic blood pressure <90 mmHg at the time of SGLT2 inhibitor initiation or at admission for control patients; (6) active urinary tract infection or genital mycotic infection at admission; (7) prior solid organ transplantation; (8) known allergy or hypersensitivity to SGLT2 inhibitors; (9) concomitant enrollment in interventional clinical trials; and (10) incomplete follow-up data or loss to follow-up within the first 30 days.

Data Collection: Clinical data were extracted from electronic health records by trained cardiovascular research coordinators using a standardized case report form. Baseline demographics, clinical history, vital signs, laboratory values (complete blood count, comprehensive metabolic panel, NT-proBNP, troponin, HbA1c), echocardiographic parameters, admission medications, and in-hospital pharmacological treatments were recorded. Follow-up data at 30, 90, and 180 days were obtained from outpatient clinic records, telephone follow-up, and regional health information exchange databases. Mortality data were additionally verified through national death registry linkage.

Endpoints: The primary composite endpoint was the first occurrence of all-cause mortality or heart failure rehospitalization within 180 days of the index admission. Secondary endpoints included: (1) individual components of the primary composite; (2) cardiovascular mortality at 180 days; (3) in-hospital worsening heart failure (defined as the need for escalation of intravenous diuretics, initiation of inotropic support, or mechanical ventilation after initial stabilization); (4) percentage change in NT-proBNP from admission to discharge; (5) net weight change during hospitalization; (6) total length of hospital stay; and (7) safety endpoints including acute kidney injury (defined as ≥0.3 mg/dL increase in serum creatinine or ≥50% increase from baseline within 48 hours of SGLT2 inhibitor initiation), diabetic ketoacidosis, symptomatic hypotension requiring intervention, urinary tract infections, and genital mycotic infections.

Statistical Analysis: Continuous variables were reported as mean ± standard deviation or median with interquartile range (IQR) as appropriate and compared using independent-sample t-tests or Mann-Whitney U tests. Categorical variables were expressed as frequencies and percentages and compared using chi-square or Fisher's exact tests. Time-to-event analyses for the primary and secondary endpoints were performed using Kaplan-Meier survival estimation with log-rank tests for between-group comparisons. Cox proportional hazards regression models were constructed to estimate hazard ratios with 95% confidence intervals after adjustment for potential confounders identified a priori, including age, sex, left ventricular ejection fraction (LVEF), diabetes status, baseline eGFR, admission NT-proBNP, baseline systolic blood pressure, use of guideline-directed medical therapy (beta-blockers, renin-angiotensin system inhibitors, mineralocorticoid receptor antagonists), ischemic etiology, and atrial fibrillation. Propensity score matching using a nearest-neighbor algorithm with a caliper width of 0.2 standard deviations was performed as a sensitivity analysis. A two-sided p-value <0.05 was considered statistically significant. Analyses were conducted using R version 4.3.1 (R Foundation for Statistical Computing, Vienna, Austria) and SPSS version 29.0.

Results

Baseline Characteristics: A total of 1,126 patients admitted with ADHF were initially screened, of whom 742 met inclusion criteria and were included in the final analysis: 318 in the early SGLT2 inhibitor initiation group and 424 in the standard care group. Baseline characteristics are presented in Table 1. The groups were generally well balanced with respect to age, sex distribution, and comorbidities. The early initiation group had a slightly higher prevalence of type 2 diabetes mellitus (52.8% vs. 46.0%, p = 0.060) and a marginally higher baseline HbA1c. LVEF, admission NT-proBNP levels, baseline eGFR, and utilization of guideline-directed medical therapies were comparable between groups.

Table 1: Baseline Demographic and Clinical Characteristics

Variable	Early SGLT2i (n = 318)	Standard Care (n = 424)	p-value
Age (years), mean ± SD	67.4 ± 12.3	68.1 ± 11.8	0.449
Male sex, n (%)	198 (62.3)	258 (60.8)	0.691
BMI (kg/m²), mean ± SD	29.8 ± 5.6	29.3 ± 5.2	0.224
LVEF (%), mean ± SD	33.6 ± 12.4	34.1 ± 13.0	0.604
LVEF ≤40%, n (%)	218 (68.6)	282 (66.5)	0.553
NT-proBNP (pg/mL), median (IQR)	5,842 (3,210–9,875)	5,614 (3,018–10,243)	0.712
eGFR (mL/min/1.73 m²), mean ± SD	48.7 ± 18.3	47.2 ± 19.1	0.298
Type 2 diabetes mellitus, n (%)	168 (52.8)	195 (46.0)	0.060
HbA1c (%), mean ± SD	6.9 ± 1.4	6.6 ± 1.3	0.005
Ischemic etiology, n (%)	156 (49.1)	214 (50.5)	0.706
Atrial fibrillation, n (%)	134 (42.1)	186 (43.9)	0.633
Hypertension, n (%)	246 (77.4)	318 (75.0)	0.448
CKD stage ≥3, n (%)	162 (50.9)	224 (52.8)	0.609
SBP at admission (mmHg), mean ± SD	124.8 ± 22.4	122.3 ± 21.7	0.146
Beta-blocker use, n (%)	272 (85.5)	354 (83.5)	0.440
ACEi/ARB/ARNI use, n (%)	248 (78.0)	322 (75.9)	0.513
MRA use, n (%)	196 (61.6)	248 (58.5)	0.387
Loop diuretic use, n (%)	306 (96.2)	410 (96.7)	0.727
SGLT2i agent: Empagliflozin, n (%)	186 (58.5)	—	—
SGLT2i agent: Dapagliflozin, n (%)	132 (41.5)	—	—

Primary and Secondary Outcomes: Clinical outcomes are summarized in Table 2. The primary composite endpoint of all-cause mortality or heart failure rehospitalization at 180 days occurred in 71 patients (22.3%) in the early initiation group compared with 142 patients (33.5%) in the standard

care group (HR 0.61, 95% CI 0.47–0.79, p < 0.001). All-cause mortality at 180 days was significantly lower in the early initiation group (8.2% vs. 13.4%, HR 0.58, 95% CI 0.38–0.89, p = 0.012). Heart failure rehospitalization at 180 days was also significantly reduced (16.4% vs. 24.3%, HR 0.63, 95% CI 0.47–0.85, p = 0.002). Cardiovascular mortality occurred in 6.0% versus 10.6% of patients (HR 0.54, 95% CI 0.33–0.88, p = 0.014).

In-hospital worsening heart failure events occurred in 8.8% of the early initiation group versus 14.9% of the standard care group (p = 0.012). The early initiation group demonstrated a significantly greater percentage reduction in NT-proBNP from admission to discharge (−48.2 ± 22.6% vs. −34.7 ± 24.1%, p < 0.001) and greater net weight loss during hospitalization (−4.1 ± 2.3 kg vs. −3.2 ± 2.5 kg, p < 0.001). Mean length of hospital stay was significantly shorter in the early initiation group (6.3 ± 2.8 days vs. 7.9 ± 3.4 days, p < 0.001).

Table 2: Primary and Secondary Clinical Outcomes

Outcome	Early SGLT2i (n = 318)	Standard Care (n = 424)	HR or p-value
Primary composite endpoint, n (%)	71 (22.3)	142 (33.5)	HR 0.61 (0.47–0.79), p < 0.001
All-cause mortality (180 d), n (%)	26 (8.2)	57 (13.4)	HR 0.58 (0.38–0.89), p = 0.012
HF rehospitalization (180 d), n (%)	52 (16.4)	103 (24.3)	HR 0.63 (0.47–0.85), p = 0.002
CV mortality (180 d), n (%)	19 (6.0)	45 (10.6)	HR 0.54 (0.33–0.88), p = 0.014
In-hospital worsening HF, n (%)	28 (8.8)	63 (14.9)	p = 0.012
NT-proBNP change (%), mean ± SD	−48.2 ± 22.6	−34.7 ± 24.1	p < 0.001
Net weight change (kg), mean ± SD	−4.1 ± 2.3	−3.2 ± 2.5	p < 0.001
Length of stay (days), mean ± SD	6.3 ± 2.8	7.9 ± 3.4	p < 0.001

Safety Outcomes

Safety outcomes are presented in **Table 3**. There were no significant differences between groups in the incidence of acute kidney injury (6.3% vs. 7.5%, p = 0.508), diabetic ketoacidosis (0.3% vs. 0.0%, p = 0.429), symptomatic hypotension requiring intervention (5.0% vs. 4.5%, p = 0.734), urinary tract infections (2.2% vs. 1.9%, p = 0.740), or genital mycotic infections (1.6% vs. 0.5%, p = 0.133). The mean change in eGFR from admission to discharge did not differ significantly between groups (−1.8 ± 6.4 vs. −2.3 ± 7.1 mL/min/1.73 m², p = 0.338). The rate of SGLT2 inhibitor discontinuation due to adverse events in the early initiation group was 4.4% (n = 14).

Table 3. Safety Outcomes During Index Hospitalization

Safety Outcome	Early SGLT2i (n = 318)	Standard Care (n = 424)	p-value
Acute kidney injury, n (%)	20 (6.3)	32 (7.5)	0.508
Diabetic ketoacidosis, n (%)	1 (0.3)	0 (0.0)	0.429
Symptomatic hypotension, n (%)	16 (5.0)	19 (4.5)	0.734
Urinary tract infection, n (%)	7 (2.2)	8 (1.9)	0.740
Genital mycotic infection, n (%)	5 (1.6)	2 (0.5)	0.133
eGFR change (mL/min/1.73 m²), mean ± SD	−1.8 ± 6.4	−2.3 ± 7.1	0.338
SGLT2i discontinuation due to AE, n (%)	14 (4.4)	—	—

Discussion

This multicenter retrospective cohort study demonstrates that early initiation of SGLT2 inhibitors within 48 hours of hospital admission for ADHF is associated with a 39% relative reduction in the composite endpoint of all-cause mortality or heart failure rehospitalization at 180 days, with consistent benefits observed across both individual components. These findings complement and extend the evidence from recent randomized controlled trials and support a treatment paradigm favoring prompt SGLT2 inhibitor introduction during the acute hospitalization phase.

The magnitude of benefit observed in our study is broadly consistent with the findings of the EMPULSE trial, which demonstrated a significant net clinical benefit of in-hospital empagliflozin initiation over 90 days, with a win ratio of 1.36 [15]. Our study extends this observation to a longer follow-up horizon of 180 days and demonstrates sustained separation in event curves, suggesting durable treatment effects beyond the immediate post-discharge period. The observed 42% relative reduction in all-cause mortality (HR 0.58) is noteworthy, although it should be interpreted cautiously given the retrospective design and potential for residual confounding. The SOLOIST-WHF trial similarly reported a 33% reduction in the composite of cardiovascular death and heart failure events with sotagliflozin initiated before or shortly after discharge [16], reinforcing the concept that the

peri-hospitalization window represents a critical opportunity for therapeutic intervention.

The mechanistic basis for the early benefits of SGLT2 inhibitors in ADHF is multifaceted. Unlike conventional diuretics, SGLT2 inhibitors promote osmotic diuresis with preferential electrolyte-free water clearance and selective interstitial fluid reduction rather than intravascular volume depletion, potentially enabling more effective decongestion with reduced risk of cardiorenal compromise [17]. This mechanism may explain the significantly greater NT-proBNP reduction and weight loss observed in our early initiation group without any increase in acute kidney injury. Furthermore, SGLT2 inhibitors exert pleiotropic cardioprotective effects independent of their diuretic properties, including improved myocardial energetics through enhanced ketone body utilization, reduced oxidative stress and inflammation, decreased cardiac fibrosis, and favorable effects on endothelial function and arterial stiffness [18].

The finding that early SGLT2 inhibitor initiation was associated with a significantly shorter length of hospital stay (6.3 vs. 7.9 days) has important implications for healthcare resource utilization. Heart failure hospitalizations account for the largest proportion of heart failure-related healthcare expenditures, and interventions that reduce length of stay without compromising clinical outcomes may yield substantial cost savings [19]. A recent economic analysis of the EMPULSE trial data estimated that in-hospital empagliflozin initiation was cost-effective across multiple healthcare system perspectives [20].

The safety profile observed in our study is reassuring and consistent with randomized trial data. The incidence of acute kidney injury was numerically lower in the early initiation group (6.3% vs. 7.5%), supporting previous observations that the initial hemodynamic eGFR decline associated with SGLT2 inhibitors reflects tubuloglomerular feedback activation rather than true nephrotoxicity, and may in fact be nephroprotective over the long term [21]. The very low rate of diabetic ketoacidosis (0.3%) and the absence of excess symptomatic hypotension further support the safety of early initiation in hemodynamically stable ADHF patients [22]. Recent guidelines from the European Society of Cardiology have incorporated SGLT2 inhibitors as a Class I recommendation for heart failure management and support consideration of in-hospital initiation [23].

Our study has several limitations that merit acknowledgment. First, the retrospective observational design introduces inherent risks of selection bias and unmeasured confounding. Clinicians may have preferentially initiated SGLT2 inhibitors in patients perceived to have more favorable prognoses, potentially inflating the observed treatment effect. Although we employed multivariable adjustment and propensity score sensitivity analyses, residual confounding cannot be excluded. Second, the grouping strategy excluded patients who initiated SGLT2 inhibitors between 48 hours post-admission and discharge, which may limit generalizability. Third, the follow-up period of 180 days, while clinically meaningful, precludes assessment of long-term outcomes. Fourth, we did not have comprehensive data on post-discharge medication adherence, which may influence long-term event rates. Fifth, the study was conducted at tertiary cardiac centers with established heart failure programs, and results may not be directly applicable to community hospital settings. Finally, the relatively modest proportion of patients with HFpEF in our cohort limits the ability to draw definitive conclusions about the impact of early SGLT2 inhibitor initiation across the full ejection fraction spectrum.

Future prospective randomized studies specifically designed to evaluate the impact of very early (within 24 hours) versus delayed SGLT2 inhibitor initiation in ADHF, stratified by heart failure phenotype, diabetes status, and renal function, are needed to define the optimal treatment strategy [24]. Additionally, investigation of biomarker-guided approaches to identify patients most likely to derive early benefit would be of substantial clinical value [25].

Conclusion

This multicenter retrospective cohort study demonstrates that early initiation of SGLT2 inhibitors within 48 hours of admission for acute decompensated heart failure is associated with a clinically meaningful and statistically significant reduction in the composite endpoint of all-cause mortality and heart failure rehospitalization at 180 days. Individual components of the composite endpoint, including all-cause mortality, cardiovascular mortality, and heart failure rehospitalization, were each significantly reduced in the early initiation group. Additionally, early SGLT2 inhibitor therapy was associated with superior in-hospital neurohormonal decongestion, greater weight reduction, fewer in-hospital worsening heart failure events, and shorter hospital length of stay, all achieved without an increase in acute kidney injury, ketoacidosis, or hemodynamic instability. These findings provide compelling real-world evidence supporting the incorporation of SGLT2 inhibitors into the early management algorithm for ADHF and reinforce the importance of overcoming clinical inertia surrounding in-hospital initiation of these agents. Integration of SGLT2 inhibitors as a routine component of acute heart failure management protocols has the potential to

improve patient outcomes and reduce healthcare utilization.

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