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Review Paper

In-Hospital Empagliflozin Therapy for Congestion Relief and Renal Function in Patients with Acute Decompensated Heart Failure: A Structured Review

E. D. Rivadeneira[1]*, J. T. Alvarez[2], M. L. Jaraba[3], A. C. Montiel[4], A. M. Baquero[5]

[1,5]*General Physician, Universidad del Sinu, Cartagena*
[2]*General Physician, Universidad Industrial de Santander, Bucaramanga*
[3]*General Physician, Universidad del Sinu, Montería*
[4]*General Physician, Universidad de Sucre, Sincelejo.*

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ABSTRACT

Acute decompensated heart failure is associated with substantial morbidity, mortality, recurrent hospitalization, and healthcare utilization. Persistent congestion is a major determinant of adverse outcomes, while worsening renal function may complicate decongestive therapy. Empagliflozin, a sodium-glucose cotransporter-2 inhibitor, has emerged as a disease-modifying therapy for heart failure, with evidence supporting its initiation during hospitalization after clinical stabilization. This structured review critically synthesizes evidence regarding in-hospital empagliflozin initiation in patients hospitalized with acute decompensated heart failure, focusing on decongestion, diuretic response, renal function, safety, and short-term clinical outcomes. Randomized controlled trials, observational studies, post hoc analyses, systematic reviews, meta-analyses, and contemporary clinical guidelines were considered. Current evidence indicates that early in-hospital initiation is associated with enhanced decongestion and improved diuretic efficiency without increasing clinically significant renal injury. A modest and transient decline in estimated glomerular filtration rate may occur after initiation, followed by stabilization of renal function. Clinical trials also indicate favorable effects on symptoms, quality of life, and heart failure events, with no significant increase in hypotension, acute kidney injury, or serious adverse events. Overall, the available evidence supports early initiation of empagliflozin during hospitalization after clinical stabilization in appropriately selected patients

***Corresponding Author:** Esteban Diaz Rivadeneira
Address: *Universidad del Sinú - Elías Bechara Zainúm, Seccional Cartagena, Campus Santillana, Av. al Bosque, Transversal 54 No. 30-453, Cartagena, Colombia*
Email ✉: juancho251997@hotmail.com

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INTRODUCTION

Acute decompensated heart failure (ADHF) is one of the leading causes of hospitalization among adults worldwide and remains associated with high rates of mortality, recurrent hospitalizations, and healthcare expenditures despite substantial therapeutic advances [1,2]. Persistent congestion is the predominant cause of hospital admission and the principal determinant of early readmission, emphasizing the importance of achieving effective decongestion before hospital discharge [3,4]. However, conventional decongestive strategies relying primarily on intravenous loop diuretics are frequently complicated by diuretic resistance, electrolyte disturbances, neurohormonal activation, and worsening renal function, creating a therapeutic dilemma for clinicians managing patients hospitalized with ADHF [5,7].

Renal dysfunction is present in approximately one-third to one-half of patients admitted with acute heart failure and represents one of the strongest independent predictors of adverse clinical outcomes, including prolonged hospitalization, recurrent heart failure, and mortality [8–10]. The close interaction between cardiac and renal dysfunction, commonly referred to as the cardiorenal syndrome, contributes to impaired sodium excretion, persistent congestion, neurohormonal activation, and progressive organ dysfunction [11]. Importantly, transient declines in renal function observed during aggressive decongestive therapy do not necessarily indicate structural kidney injury but frequently reflect reversible hemodynamic changes associated with effective plasma volume reduction [12,13]. Consequently, achieving adequate decongestion while preserving renal function has become one of the principal therapeutic goals in the contemporary management of hospitalized patients with ADHF [3,5].

The introduction of sodium–glucose cotransporter-2 (SGLT2) inhibitors has transformed the therapeutic landscape of heart failure over the last decade [14,17]. Initially developed as glucose-lowering agents for patients with type 2 diabetes mellitus, these drugs have consistently demonstrated reductions in cardiovascular mortality, heart failure hospitalization, and progression of chronic kidney disease across diverse patient populations, irrespective of diabetes status or left ventricular ejection fraction [14,18]. Their benefits extend beyond glycemic control through multiple complementary mechanisms, including osmotic diuresis, natriuresis, restoration of tubuloglomerular feedback, improvement of renal hemodynamics, attenuation of sympathetic nervous system and renin–angiotensin–aldosterone system activation, reduction of interstitial congestion, enhancement of myocardial energetics, and anti-inflammatory and antifibrotic effects [19,23].

Among the available SGLT2 inhibitors, empagliflozin has become one of the most extensively investigated agents in both chronic and acute heart failure [15,18]. Evidence from the EMPEROR-Reduced and EMPEROR-Preserved trials established its efficacy across the spectrum of heart failure phenotypes, while the EMPULSE trial demonstrated that initiation of empagliflozin during hospitalization, following clinical stabilization, significantly improved the hierarchical composite outcome of all-cause mortality, heart failure events, and health-related quality of life at 90 days compared with placebo [16,17,24]. Subsequent prespecified analyses further demonstrated enhanced decongestion, improved diuretic efficiency, and preservation of renal function without increasing the incidence of acute kidney injury or clinically significant hypotension [25,26].

The favorable renal profile of empagliflozin deserves particular attention. Although treatment initiation is commonly associated with a modest and transient decline in estimated glomerular filtration rate (eGFR), extensive clinical and mechanistic evidence indicates that this phenomenon reflects restoration of physiological tubuloglomerular feedback rather than structural renal injury [22,25,27]. Long-term follow-up studies have consistently demonstrated slower progression of chronic kidney disease and reduced risk of major renal events among patients receiving SGLT2 inhibitors [18,27,28].

Despite these encouraging findings, several clinically relevant questions remain unanswered. The magnitude of empagliflozin induced decongestion, its effects on renal function during the acute hospitalization period, the optimal timing of treatment initiation, patient selection, and integration with other components of guideline-directed medical therapy continue to be areas of active investigation [24,27,29]. Furthermore, emerging evidence from randomized clinical trials, observational studies, post hoc analyses, and recent meta-analyses warrants comprehensive synthesis to better define the role of early empagliflozin initiation during the vulnerable post-hospitalization period.

Therefore, the aim of this structured review is to critically evaluate the current evidence regarding the effects of in-hospital initiation of empagliflozin on congestion and renal function in patients hospitalized with acute decompensated heart failure, with particular emphasis on the underlying pathophysiological mechanisms, clinical efficacy, renal safety, and implications for contemporary inpatient heart failure management.

MATERIALS AND METHODS

Study Design

This structured review was conducted to critically evaluate the available evidence regarding the effects of in-hospital initiation of empagliflozin on congestion and renal function in patients hospitalized with acute decompensated heart failure (ADHF). The methodology was developed following the principles of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) statement to ensure transparency and reproducibility throughout the review process.

Literature Search Strategy

A comprehensive literature search was performed in the electronic databases PubMed/MEDLINE, Embase, Scopus, and the Cochrane Library. The search included studies published from January 2015 through June 2026, encompassing the period during which the principal clinical trials evaluating sodium-glucose cotransporter-2 (SGLT2) inhibitors in heart failure were conducted.

The search strategy combined Medical Subject Headings (MeSH) and free-text terms using Boolean operators. The primary search terms included:

- "empagliflozin"
- "acute decompensated heart failure"
- "acute heart failure"
- "hospitalization"
- "in-hospital initiation"
- "SGLT2 inhibitor"
- "congestion"
- "decongestion"
- "diuretic response"
- "renal function"
- "kidney function"
- "estimated glomerular filtration rate"
- "cardiorenal syndrome"

The complete search strategy was adapted according to the indexing system of each database.

Eligibility Criteria

Studies were considered eligible if they met the following criteria:

Inclusion Criteria

• Randomized controlled trials.
• Prospective or retrospective observational studies.
• Post hoc analyses of randomized clinical trials.
• Systematic reviews and meta-analyses.
• Clinical practice guidelines and expert consensus documents from major cardiovascular societies.
• Adult patients (≥18 years) hospitalized with acute decompensated heart failure.
• Studies evaluating empagliflozin initiated during hospitalization or immediately before hospital discharge.
• Studies reporting at least one outcome related to congestion, renal function, diuretic response, safety, or clinical outcomes.

Exclusion Criteria

• Case reports or case series involving fewer than ten patients.
• Editorials, narrative commentaries, conference abstracts without full-text publication, and letters lacking original data.
• Animal or in vitro studies.
• Studies evaluating chronic outpatient initiation of empagliflozin without specific inpatient data.
• Articles not published in English.

Study Selection

All identified records were screened by title and abstract. Full-text articles were subsequently reviewed for eligibility according to the predefined inclusion and exclusion criteria. Duplicate publications were removed before full-text assessment. Disagreements regarding study eligibility were resolved through discussion and consensus among the reviewers.

Data Extraction

Relevant information was extracted using a standardized data collection form. The following variables were recorded:
• First author and year of publication.
• Study design.
• Country of origin.
• Sample size.
• Patient characteristics.
• Heart failure phenotype.
• Timing of empagliflozin initiation.
• Comparator therapy.
• Duration of follow-up.
• Congestion-related outcomes.
• Renal outcomes, including estimated glomerular filtration rate (eGFR), serum creatinine, acute kidney injury, and need for renal replacement therapy.
• Diuretic efficiency.
• Heart failure rehospitalization.
• All-cause mortality.
• Adverse events.

Outcomes

The primary outcomes of this review were:
1. Improvement in clinical and biochemical markers of congestion.
2. Changes in renal function following in-hospital initiation of empagliflozin.
Secondary outcomes included:
• Diuretic efficiency.
• Length of hospital stay.
• Worsening renal function.
• Acute kidney injury.
• Rehospitalization for heart failure.
• Cardiovascular mortality.
• All-cause mortality.
• Safety outcomes, including hypotension, volume depletion, ketoacidosis, hypoglycemia, and genitourinary infections.

Quality Assessment

The methodological quality of the included randomized controlled trials was assessed using the Cochrane Risk of Bias 2 (RoB 2) tool, whereas observational studies were evaluated using the Newcastle–Ottawa Scale (NOS). The quality of evidence supporting the principal outcomes was interpreted considering study design, consistency of findings, risk of bias, and clinical applicability.

Data Synthesis

Given the expected clinical and methodological heterogeneity among the included studies, a qualitative narrative synthesis was performed. Findings were organized according to the principal domains of interest, including mechanisms of action, decongestion, renal function, safety profile, and clinical outcomes. Whenever available, results from randomized controlled trials were prioritized over observational evidence, while current international guideline recommendations were incorporated to contextualize the findings within contemporary clinical practice.

RESULTS

Evidence from Randomized Clinical Trials

The management of acute decompensated heart failure (ADHF) has evolved considerably over the last decade with the introduction of therapies capable of modifying disease progression beyond symptomatic relief. Traditionally, pharmacological treatment during hospitalization focused almost exclusively on stabilization through intravenous diuretics, vasodilators, and, when necessary, inotropic agents. Although these therapies improve congestion and hemodynamic status, they have demonstrated limited ability to reduce long-term mortality or recurrent heart failure hospitalization [30,32]. Consequently, increasing attention has been directed toward initiating guideline-directed medical therapy during hospitalization, a period now recognized as a unique opportunity to improve long-term cardiovascular outcomes [2,30,33].

Hospitalization for ADHF represents a particularly vulnerable period characterized by profound neurohormonal activation, persistent inflammation, endothelial dysfunction, and progressive renal impairment. Approximately 20–30% of patients require rehospitalization within the first month after discharge, while nearly one-third experience death or recurrent heart failure events within 90 days [34,35]. This vulnerable phase has become an important therapeutic target because initiation of evidence-based therapies before discharge has been associated with improved treatment adherence, earlier achievement of target doses, and lower rates of adverse cardiovascular events [33,36].

EMPA-RESPONSE-AHF Trial

The EMPA-RESPONSE-AHF trial represented the first randomized clinical study specifically designed to evaluate the feasibility and safety of initiating empagliflozin during hospitalization for acute heart failure [37]. This multicenter, randomized, double-blind, placebo-controlled pilot trial enrolled 80 patients admitted with ADHF irrespective of diabetes status. Participants were randomized within 24 hours after hospital admission to receive empagliflozin 10 mg once daily or placebo in addition to guideline-directed therapy for 30 days [37].

The primary endpoint consisted of changes in visual analogue dyspnea score, diuretic response, natriuretic peptide concentrations, and hospital length of stay. Although the study was not powered to detect significant differences in mortality or rehospitalization, important physiological observations emerged [37].

Patients treated with empagliflozin demonstrated significantly greater cumulative urine output

during the first four days of hospitalization, indicating enhanced natriuresis and osmotic diuresis without evidence of excessive intravascular volume depletion [37,38]. Moreover, body weight decreased more rapidly in the empagliflozin group, suggesting more efficient removal of excess extracellular fluid. These findings supported the hypothesis that SGLT2 inhibition preferentially mobilizes interstitial rather than intravascular fluid, a mechanism fundamentally different from conventional loop diuretics [19,20,38].

Despite the increased diuretic effect, renal safety remained reassuring. No significant differences were observed between treatment groups regarding serum creatinine, estimated glomerular filtration rate (eGFR), symptomatic hypotension, electrolyte disturbances, ketoacidosis, or acute kidney injury [37]. Interestingly, empagliflozin was associated with a lower combined incidence of worsening heart failure, rehospitalization, or death at 60 days, although this secondary endpoint should be interpreted cautiously because of the limited sample size [37].

Although EMPA-RESPONSE-AHF was primarily a proof-of-concept study, its results established the biological plausibility and clinical safety of initiating empagliflozin during hospitalization and provided the rationale for larger randomized outcome trials.

EMPULSE Trial

The EMPULSE trial constitutes the landmark randomized clinical trial evaluating empagliflozin initiated during hospitalization for acute heart failure [17,24]. Conducted across 118 hospitals in 15 countries, this multicenter, randomized, double-blind, placebo-controlled trial enrolled 530 clinically stabilized patients hospitalized with either de novo acute heart failure or acute decompensation of chronic heart failure, regardless of diabetes status or left ventricular ejection fraction [17].

Patients became eligible after achieving clinical stabilization, defined by systolic blood pressure ≥100 mmHg, absence of intravenous vasodilators during the preceding six hours, no intravenous inotropes for at least 24 hours, and no recent escalation of intravenous diuretic therapy [17]. This design reflected real-world clinical practice while ensuring adequate hemodynamic stability before treatment initiation.

Unlike previous heart failure trials, EMPULSE used a hierarchical composite endpoint analyzed through the win-ratio method, integrating all-cause mortality, number of heart failure events, time to first heart failure event, and change in Kansas City Cardiomyopathy Questionnaire Total Symptom Score (KCCQ-TSS) at 90 days [17,39]. This innovative statistical approach allowed simultaneous evaluation of mortality, morbidity, and patient-reported outcomes.

Empagliflozin demonstrated a statistically significant clinical benefit compared with placebo across the hierarchical composite endpoint, with a win ratio of 1.36 (95% confidence interval 1.09–1.68; P=0.0054) [17]. Importantly, treatment benefits were remarkably consistent across predefined subgroups, including patients with reduced or preserved ejection fraction, diabetic and non-diabetic patients, elderly individuals, and those with baseline renal impairment [17,40].

One of the most clinically relevant observations was the rapid onset of therapeutic benefit. Improvements in health status measured by the KCCQ became evident within weeks after treatment initiation, suggesting that empagliflozin exerts favorable physiological effects almost immediately following stabilization [17,41]. This rapid response contrasts with many traditional disease-modifying therapies whose clinical benefits generally require several months to become apparent.

Effects on Decongestion

Persistent congestion remains the strongest predictor of early readmission after hospitalization for ADHF [3,13]. Accordingly, prespecified analyses from EMPULSE investigated whether empagliflozin could enhance decongestion beyond conventional intravenous diuretic therapy [25].

Patients receiving empagliflozin exhibited significantly greater reductions in body weight throughout hospitalization and follow-up, reflecting more effective fluid removal [25]. Furthermore, weight loss normalized according to loop diuretic dose, an accepted surrogate of diuretic efficiency, was consistently greater among patients treated with empagliflozin [25]. These findings suggest that SGLT2 inhibition potentiates the natriuretic response to loop diuretics without increasing their dosage requirements.

Similarly, empagliflozin produced larger reductions in plasma NT-proBNP concentrations, improved composite congestion scores, and increased the proportion of patients achieving complete clinical decongestion before discharge [25,42]. Notably, these improvements occurred without increased rates of symptomatic hypotension, excessive hemoconcentration, or deterioration of renal function, reinforcing the concept that empagliflozin preferentially mobilizes interstitial fluid while preserving effective circulating volume [19,25].

Renal Outcomes

Preservation of renal function represents a major therapeutic challenge during hospitalization for ADHF because aggressive decongestion may transiently reduce glomerular filtration [8,11]. A prespecified renal analysis of EMPULSE demonstrated the characteristic modest early decline in eGFR following empagliflozin initiation, typically occurring during the first two weeks of therapy [26].

Importantly, renal function subsequently stabilized, and eGFR trajectories became similar between treatment groups by 90 days [26]. Rates of investigator-reported acute kidney injury did not differ significantly between empagliflozin and placebo, providing strong evidence that the initial reduction in eGFR reflects restoration of physiological tubuloglomerular feedback rather than structural nephrotoxicity [22,26,43].

These findings are consistent with previous observations from EMPEROR-Reduced, EMPEROR-Preserved, and EMPA-KIDNEY, all of which demonstrated long-term preservation of renal function despite an early hemodynamic decline in eGFR following treatment initiation [15,16,18].

Safety Profile of In-Hospital Empagliflozin

The introduction of new pharmacological therapies during hospitalization for acute decompensated heart failure (ADHF) requires careful evaluation of their safety profile because these patients frequently present with hemodynamic instability, impaired renal function, electrolyte abnormalities, and multiple concomitant medications. Historically, concerns regarding the use of sodium–glucose cotransporter-2 (SGLT2) inhibitors during acute illness focused on the potential risk of symptomatic hypotension, excessive volume depletion, acute kidney injury (AKI), diabetic ketoacidosis (DKA), and genitourinary infections [55,56]. However, accumulating evidence from randomized clinical trials and real-world studies has consistently demonstrated that empagliflozin can be safely initiated during hospitalization after clinical stabilization.

In the EMPULSE trial, the incidence of serious adverse events was numerically lower in the empagliflozin group than in the placebo group [17,57]. No significant differences were observed in symptomatic hypotension, electrolyte

disturbances, hypoglycemia, urinary tract infections, genital mycotic infections, ketoacidosis, or treatment discontinuation [17,57]. These findings are particularly relevant because hospitalized patients commonly receive high-dose intravenous loop diuretics, vasodilators, beta-blockers, renin–angiotensin system inhibitors, mineralocorticoid receptor antagonists, and angiotensin receptor-neprilysin inhibitors simultaneously, theoretically increasing the risk of cumulative adverse effects [47,58].

Renal Safety

Renal dysfunction remains one of the principal challenges during aggressive decongestive therapy. In EMPULSE, empagliflozin induced the characteristic early decline in estimated glomerular filtration rate (eGFR), typically occurring within the first two weeks after treatment initiation [54]. Nevertheless, renal function stabilized during follow-up, and by 90 days eGFR trajectories were comparable between empagliflozin and placebo [54].

Importantly, rates of investigator-reported AKI did not differ significantly between groups [54]. These observations support previous mechanistic studies demonstrating that the initial decline in eGFR reflects restoration of physiological tubuloglomerular feedback rather than structural nephron injury [31,54,59]. Similar findings have been consistently observed in EMPEROR-Reduced, EMPEROR-Preserved, EMPA-KIDNEY, and DAPA-HF, reinforcing the concept that transient hemodynamic changes should not be interpreted as nephrotoxicity [15,16,18,60].

Hypotension and Volume Depletion

Because SGLT2 inhibitors induce osmotic diuresis and natriuresis, concerns initially arose regarding excessive intravascular volume depletion during acute hospitalization. However, randomized evidence has demonstrated that empagliflozin preferentially mobilizes interstitial fluid while largely preserving effective circulating volume [33,34]. Consequently, symptomatic hypotension has remained uncommon across clinical trials [17,37,57].

This physiological distinction from loop diuretics likely explains why empagliflozin improves congestion without triggering marked neurohormonal activation or compromising renal perfusion [20,34].

Diabetic Ketoacidosis and Hypoglycemia

Diabetic ketoacidosis represents one of the most recognized adverse effects of SGLT2 inhibitors, particularly among patients with type 1 diabetes or severe insulin deficiency [61]. Nevertheless, euglycemic ketoacidosis remains exceedingly uncommon in patients hospitalized with ADHF following clinical stabilization [17,37]. Current recommendations advise temporary avoidance of empagliflozin in patients with active ketoacidosis, prolonged fasting, severe sepsis, or cardiogenic shock [2,61].

Similarly, empagliflozin does not increase the incidence of clinically significant hypoglycemia when administered as monotherapy or in combination with non–insulin-based glucose-lowering therapies [14,61]. Most hypoglycemic events occur only among patients receiving intensive insulin therapy or sulfonylureas.

Evidence from Recent Meta-Analyses

The publication of EMPULSE stimulated several systematic reviews and meta-analyses evaluating the efficacy and safety of SGLT2 inhibitors initiated during hospitalization for acute heart failure [62,65].

The largest contemporary meta-analysis pooled randomized controlled trials investigating empagliflozin initiated during hospitalization for ADHF and demonstrated significant reductions in

all-cause mortality, cardiovascular mortality, worsening heart failure, and composite cardiovascular events compared with placebo [62]. Importantly, treatment benefits were observed regardless of diabetes status, baseline renal function, or left ventricular ejection fraction.

Pooled analyses also demonstrated significantly greater reductions in body weight, NT-proBNP concentrations, and congestion scores among patients receiving empagliflozin [62,63]. These findings are consistent with mechanistic studies demonstrating enhanced natriuretic efficiency and improved interstitial fluid mobilization.

From a renal perspective, meta-analyses consistently reported no increase in acute kidney injury despite the expected transient reduction in eGFR [62,64]. Likewise, no excess risk of symptomatic hypotension, urinary tract infection, genital infection, diabetic ketoacidosis, or severe hypoglycemia was identified [62,65].

Although statistical heterogeneity exists because of differences in study populations, timing of drug initiation, and follow-up duration, sensitivity analyses have consistently confirmed the robustness of these findings [62,64].

Collectively, current meta-analytic evidence strongly supports the early in-hospital initiation of empagliflozin as a safe intervention capable of improving both short-term clinical stabilization and long-term cardiovascular outcomes.

Current Guideline Recommendations

The consistent evidence generated during the last decade has fundamentally changed international heart failure guidelines. Both the 2022 American Heart Association/American College of Cardiology/Heart Failure Society of America (AHA/ACC/HFSA) guideline and the 2023 European Society of Cardiology (ESC) Focused Update recognize SGLT2 inhibitors as one of the four foundational therapies for heart failure with reduced ejection fraction regardless of diabetes status [1,2].

The ESC guideline further emphasizes that initiation should occur as early as clinically feasible, including before hospital discharge whenever patients have achieved hemodynamic stabilization [1]. This recommendation reflects growing evidence that hospitalization provides an ideal opportunity to initiate disease-modifying therapies under close medical supervision.

Several observational studies have demonstrated that patients started on guideline-directed medical therapy before discharge are more likely to remain on treatment, achieve target doses, and experience lower rates of early rehospitalization than those whose therapy is deferred until outpatient follow-up [47,66].

Nevertheless, careful patient selection remains essential. Current consensus documents recommend initiating empagliflozin only after resolution of cardiogenic shock, discontinuation of intravenous vasoactive agents, stabilization of blood pressure, and confirmation of adequate renal function and volume status [1,2,58]. Patients with severe hypotension, active diabetic ketoacidosis, or rapidly progressive renal failure remain underrepresented in randomized clinical trials and therefore require individualized decision-making.

Another important consideration involves integration with contemporary quadruple therapy. Recent expert consensus statements advocate simultaneous early initiation of SGLT2 inhibitors together with beta-blockers, renin–angiotensin system inhibitors or angiotensin receptor-neprilysin inhibitors, and mineralocorticoid receptor antagonists during hospitalization whenever clinically feasible [67]. This strategy may shorten the time required to achieve optimal guideline-directed therapy while reducing therapeutic inertia after discharge.

DISCUSSION

The present review summarizes the available evidence supporting the early initiation of empagliflozin during hospitalization for acute decompensated heart failure (ADHF). Collectively, current randomized clinical trials, mechanistic investigations, and recent meta-analyses indicate that empagliflozin provides clinically meaningful benefits extending beyond glycemic control, including enhanced decongestion, improved diuretic efficiency, preservation of renal function, and reduction in early heart failure events [17,25,62,64]. These findings support a paradigm shift in the inpatient management of ADHF, moving from a strategy focused exclusively on hemodynamic stabilization toward the early implementation of disease-modifying therapies.

One of the most important observations emerging from the available evidence is the rapid onset of clinical benefit following empagliflozin initiation. Unlike several traditional heart failure therapies that require weeks or months before significant reductions in cardiovascular events become apparent, improvements in symptoms, congestion, and health-related quality of life were observed within days to weeks after treatment initiation in EMPULSE [17,52]. This rapid therapeutic effect is particularly relevant because the early post-discharge period represents the highest-risk phase for recurrent decompensation, emergency department visits, and cardiovascular mortality [44,68].

The mechanisms responsible for these early benefits are likely multifactorial. Osmotic diuresis and natriuresis induced by SGLT2 inhibition improve sodium excretion while preferentially mobilizing interstitial fluid, thereby reducing systemic and pulmonary congestion without substantial depletion of effective intravascular volume [33,34]. This contrasts with loop diuretics, whose aggressive intravascular volume contraction frequently triggers activation of the renin–angiotensin–aldosterone system (RAAS), sympathetic nervous system, and vasopressin pathways [17,18]. Consequently, empagliflozin appears to complement rather than replace conventional diuretic therapy by enhancing decongestion while minimizing maladaptive neurohormonal responses.

Renal preservation constitutes another clinically relevant aspect of SGLT2 inhibition. Historically, transient deterioration in renal function during aggressive decongestive therapy has prompted clinicians to reduce diuretic intensity or discontinue potentially beneficial therapies. However, contemporary evidence suggests that modest declines in estimated glomerular filtration rate (eGFR) frequently reflect physiological restoration of tubuloglomerular feedback rather than structural kidney injury [31,54,59]. In EMPULSE and previous chronic heart failure trials, the initial decline in eGFR was consistently followed by stabilization and slower long-term renal function decline compared with placebo [15,16,18,54]. These findings support the concept that clinicians should distinguish transient hemodynamic adaptations from clinically meaningful acute kidney injury when evaluating renal function after initiation of empagliflozin.

Another noteworthy finding involves the consistency of treatment benefit across diverse patient populations. EMPULSE demonstrated similar efficacy irrespective of diabetes status, age, baseline renal function, or left ventricular ejection fraction [17,51]. This observation reinforces the notion that the cardiovascular and renal effects of empagliflozin are largely independent of glucose lowering and instead derive from pleiotropic mechanisms involving renal hemodynamics, myocardial metabolism, endothelial function, inflammation, and oxidative stress [20,35,39]. Such consistency has facilitated incorporation of SGLT2 inhibitors into contemporary guideline-

directed medical therapy (GDMT) regardless of diabetic status.

The concept of initiating comprehensive GDMT before hospital discharge has gained increasing acceptance during recent years [2,47,67]. Hospitalization provides an opportunity to optimize therapy under direct medical supervision, assess tolerability, educate patients, and improve long-term adherence. Observational studies consistently demonstrate that therapies initiated before discharge are more likely to be continued after hospitalization and are associated with improved clinical outcomes compared with delayed outpatient initiation [47,66]. Empagliflozin appears particularly well suited for inpatient initiation because of its favorable safety profile, absence of dose titration requirements, minimal effect on blood pressure, and low incidence of electrolyte disturbances [17,57].

Despite these encouraging findings, several important limitations should be acknowledged. First, existing randomized trials enrolled clinically stabilized patients and therefore excluded individuals with cardiogenic shock, persistent hypotension, severe metabolic instability, or advanced multiorgan failure [17,37]. Consequently, the safety and efficacy of empagliflozin in these high-risk populations remain uncertain. Second, although EMPULSE demonstrated significant improvements in a hierarchical composite endpoint, longer-term randomized studies powered specifically for cardiovascular mortality remain limited [17]. Third, most available evidence concerns empagliflozin; direct head-to-head comparisons with other SGLT2 inhibitors have not been performed, making it difficult to determine whether observed benefits represent class effects or drug-specific characteristics [63,65].

Finally, important questions remain regarding the optimal timing of treatment initiation, interactions with sequential nephron blockade strategies, and integration with emerging therapies such as acetazolamide, intravenous iron supplementation, soluble guanylate cyclase stimulators, and device-based congestion monitoring. These issues represent promising areas for future investigation.

FUTURE PERSPECTIVES

Future research should focus on expanding the evidence base supporting early inpatient use of empagliflozin. Large pragmatic randomized clinical trials evaluating treatment initiation immediately after emergency department presentation or during the earliest stages of hospitalization would clarify whether even earlier administration provides additional clinical benefit [69].

Similarly, studies involving patients with cardiogenic shock, advanced chronic kidney disease (eGFR <20–25 mL/min/1.73 m²), mechanical circulatory support, or severe right ventricular failure are urgently needed because these populations remain underrepresented in current clinical trials [70].

The development of precision medicine strategies may further optimize patient selection. Integration of biomarkers such as NT-proBNP, high-sensitivity troponin, soluble ST2, galectin-3, and urinary kidney injury biomarkers with advanced imaging modalities including lung ultrasound, venous excess ultrasound score (VExUS), renal Doppler ultrasonography, and bioimpedance analysis may improve identification of patients most likely to benefit from early SGLT2 inhibition [71,72].

Artificial intelligence and machine-learning algorithms also offer opportunities for individualized risk stratification, prediction of diuretic response, and optimization of congestion management during hospitalization [73]. These technologies may facilitate personalized therapeutic strategies integrating empagliflozin with other components of guideline-directed therapy.

Finally, health economic analyses performed across different healthcare systems are required to determine the cost-effectiveness of routine inpatient empagliflozin initiation. Given the substantial economic burden associated with recurrent heart failure hospitalization, even modest reductions in readmission rates may translate into significant healthcare savings [74].

CONCLUSION

Acute decompensated heart failure remains a major cause of hospitalization, morbidity, and mortality despite continuous advances in cardiovascular medicine. Persistent congestion and worsening renal function continue to represent major therapeutic challenges during inpatient management.

Current evidence indicates that early initiation of empagliflozin during hospitalization constitutes a safe and effective therapeutic strategy capable of enhancing decongestion, improving diuretic efficiency, preserving long-term renal function, improving health-related quality of life, and reducing early heart failure events without increasing clinically significant adverse effects [17,25,62].

The benefits observed appear to extend beyond glucose lowering and are mediated through multiple complementary mechanisms involving osmotic diuresis, restoration of tubuloglomerular feedback, attenuation of neurohormonal activation, improvement of myocardial energetics, reduction of inflammation, and preservation of renal hemodynamics.

Collectively, these findings support current international guideline recommendations advocating early in-hospital initiation of SGLT2 inhibitors following clinical stabilization. Although additional studies are required to refine patient selection and define the optimal timing of therapy, the available evidence strongly suggests that empagliflozin should become an integral component of contemporary inpatient management for appropriately selected patients hospitalized with acute decompensated heart failure.

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CONFLICT OF INTEREST

TO BE DECLARED BY THE AUTHORS.

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