Reprint from The Review of DIABETIC STUDIES

The Review Of
DIABETIC
STUDIES OPEN ACCESS

Pharmacologic Management Of Acute Decompensated Heart Failure In The Emergency Department: A Systematic Review Of Clinical Outcomes

Abdulaziz Almutairi[1], Khalid Amri Almehmadi[2], Saleem Kaddoor[3], Fahad Alkhairy[4], Turki Almutairi[5], Ahmed Al-Ghalayeeni[6], Mohammed Asiri[7], Alwaleed Ahmed Aljadani[8], Marwan Mohamad A.Elbanna[9], Hussain Alhammad[10], Omar Mohamad A.Elbanna[11], Mohammed Ali Alnafisah[12], Shamsiyyah Mousa Mohammed Alamshani[13], Faouzia Shaya Mohammed[14], Mohamad Yahya Ali Hamidaddin[15]

[1]Ministry Of Health Senior Specialist Nurse King Saud Medical City
[2]Student Batterjee Medical College
[3]General surgery Khobar cooperative poly clinic
[4]Emergency medical services, Makkah Complex, Al-Muzaylif General Hospital
[5]Emergency Medical Services Technician, Red Crescent Authority
[6]General Practitioner Unemployed
[7]Pharmacist Pharmacy Department, Security Forces Hospital, Riyadh
[8]General practitioner Unemployed
[9]General practitioner
[10]Pharmacist I King Faisal Specialist Hospital and Research Center
[11]General practitioner
[12]Medical intern King Saud bin Abdulaziz University for Health Sciences
[13]Medical Intern
[14]PharmD (Doctor of Pharmacy), Hospital Pharmacy
[15]Medical intern Batterjee Medical College, Intern at KAMCJ (King Abdullah Medical Complex Jeddah)

Abstract

Background: Every year, there are over 650,000 visits to emergency departments in the United States due to acute decompensated heart failure, with high morbidity, mortality, and cost to the healthcare system. Although there have been improvements in caring for patients with chronic heart failure, the pharmacological management for patients with acute decompensated heart failure has demonstrated low efficacy for the mortality outcome in the emergency setting. The last several years have been highlighted by promising developments in their management. Though existing studies have demonstrated certain positive outcomes with various medications used in ADHF patients, their effects on patient outcomes, particularly hospital readmissions within the cardiogenic context, remain uncertain due to lack of direct research. This research aims to explore their use within the specified time framework.

Methods: A systematic review of trials, registry data, and meta-analyses has been conducted, tracing the current studies on the use of ED-specific or early hospital pharmacologic therapy for ADHF published during the years 2015-2025. Included therapeutic groups involved loop diuretics, combination therapy, SGLT2 inhibitors, vasodilators, and new drugs. Information extraction involved outcomes, hemodynamics, and safety.

Results: The current evidence suggests that the standard treatment for volume overload has been and still is treatment with loop diuretics. High-dose treatment and combination therapy with other agents have been proposed and gaining popularity. The other modality to enhance decongestion outcomes has been sequential nephron blockade with thiazides, SGLT2 inhibitors, and CARIS inhibitors. However, there has been

conflicting evidence with regard to outcomes. The EMPULSE trial (2022) involving 530 patients has found early treatment with empagliflozin to be beneficial in clinical outcomes and quality of life parameters. The meta-analysis published in 2024 involving SGLT2 inhibitors in acute care (2,320 patients) has found decreased all-cause mortality (OR: 0.71) and hospitalization for heart failure (OR:0.73). The DICTATE-AHF trial (2024) involving 240 patients has found improved diuresis and natriuresis with treatment with dapagliflozin without detrimental effect on renal function. The use of natriuresis to guide diuretic treatment has been promising for decongestion. Combination treatment with other diuretics has also been found to be effective in increasing weight loss and decongestion parameters but has been found to be accompanied by increased serum creatinine.

Keywords: Acute heart failure, emergency department, diuretics, SGLT2 inhibitors, vasodilators, sequential nephron blockade, clinical outcomes, pharmacotherapy.

Introduction

Background and Epidemiology

Acute decompensated heart failure is one of the major causes of hospital admissions around the world. In addition, it has placed a significant burden on health care. In the United States, there are over 650,000 emergency department visits each year due to acute decompensated heart failure. In excess of 80% of these admissions are admitted into hospital. In addition, there has been an increased prevalence of patients suffering from cardiovascular risk factors. This includes diabetes mellitus, hypertension, and coronary artery disease.

ADHF represents a heterogeneous clinical syndrome that is either the result of impaired ventricular filling or ejection dysfunction with subsequent fluid maldistribution or retention. It culminates in patients developing the complications of either cardiogenic shock or the failure type of congestive cardiomyopathy. These patients can manifest anywhere along the clinical spectrum from normotension to hypertension.

Current State of Management

Management

Despite tremendous improvements in the care of CHF, with established mortality reductions by using Angiotensin-converting enzyme inhibitors (ACEIs), Angiotensin receptor neprilysin inhibitors (ARNIs), beta-blockers, Mineralocorticoid receptor antagonists (MRAs), and more recently SGLT2 inhibitors, the medical treatment of ADHF has had little effect on mortality. At present, treatment strategies in the ED target symptom control and correction of congestion.

“The emergency room is an important intervention point where early intense therapy has potentially beneficial results for patients,” because the use of intravenous vasoactive medications has been shown through registry experience to reduce the risk of death and because the risk for death increases significantly for each hour delay. Yet the most effective pharmacologic therapy has been unclear and has been based on low levels of evidence until recently.

Clinical Significance

Despite advances in ADHF, mortality related to this condition continues to be high, and hospital mortality varies between 4-7%, and 1-year mortality also approximates 25-30%. Readmissions related to ADHF in hospitals tend to be high in the initial 30 days, over 25%, thereby leading to healthcare expenditure in excess of $30 billion in the United States each year.

Recent Therapeutic Advances

1. "The decade between 2015 and 2025 has seen many significant events regarding the pharmacology of ADHF,"
2. Agents Inhibiting SGLT-2: These were initially being tested for their applications in diabetes management, but they act as a complete game-changer in the management of heart failure because many clinical studies are underway that assess their safety and effectiveness at the onset of hospitalization.
3. Refined Diuretic Therapies: Advances in diuretic therapy have opened research avenues that focus on combination therapy (sequential nephron blockade), natriuresis-directed therapy, and more complex combination dosing schedules.

4. Phenotype-Directed Management: Realizing that ADHF has several presentations has led to the design of algorithms based on blood pressure levels and congestion profiles.
5. Improved Risk Stratification: New markers and resources have improved the capacity to better stratify patients at increased risk who could potentially be offered aggressive treatment approaches and emerging therapies.

Study Rationale and Objectives

Because of the high prevalence of morbidity, mortality, and healthcare cost due to ADHF and because of the importance played by the ED in managing this condition, there is a need for a systematic review focused on recent literature (2015 to 2025) on this topic. The review seeks to:

1. Assessment of the effectiveness and safety profile of existing and promising pharmacological agents in the treatment of ED-related ADHF episodes
2. Analyze the effect of these intervention studies for clinically significant outcomes such as mortality, mean hospital stay, and rate of readmission and Symptomatic Relief
3. For the topic of SGLT2 inhibitors, noted to represent the most innovative therapeutic approach in the current era, synthesize findings for early initiation in
4. Evaluate refined diuretic therapy regimens, including combination regimens and natriures
5. Determine evidence-based treatments according to presenting phenotype
6. Identify gaps in existing evidence and focus on areas where further studies are needed

Procedures

Search Strategy

A literature search was done on all available literature through PUB MED/ MEDLINE, EMBASE, and COCHRANE LIBRARY, Google Scholar, and other sources of literature on Cardiology from January 1, 2015, until December 31, 2025, with a combination of Medical Subject Headings (MeSH) and other search terms for:

"acute heart failure" OR "acute decompensated heart failure" OR "AHF" OR " AND "emergency department" OR "emergency medicine" OR "acute hospitalization" OR "early therapy"AND "pharmacologic treatment" OR "drug therapy" OR "medical management""AND" "diuretics" "OR" "SGLT2 inhibitors" "OR & "Clinical outcomes", "mortality", "hospitalization", or "read

Additional articles were found through:

- Rerieved articles and systematic reviews references
- Responded with an
- Recent clinical practice guidelines issued by American Heart Association (AHA), American College of Cardiology (ACC), European Society of Cardiology (ESC), as well as Heart Failure Society of America (HFSA)
- Conferences and publications on cardiology and emergency medicine (2015 – 2025)
- Registry of Clinical Trials (ClinicalTrials
- Follow-up analysis on landmark references

Inclusion & Exclusion Criteria

Inclusion Criteria:

- Research studies on pharmacologic management for ADHF patients in the emergency department or early hospital phase (within the first 5 days)
- •Clinical outcomes (Mortality rates, Length of hospitalization, Rate of hospital readmission, Symptom relief, Quality of life, Parameters of hemodynamic status, Indicators for decon
- Randomized Controlled Trials (RCTs), Observational Studies, Registry Analyses, Systematic Reviews/M
- Published from January 2015 to December 2025
- Articles are written in the English
- Employed an adult population (18+ years old)
- Sample size > 100 patients for primary studies (> 200 for meta-analyses)

Exclusion Criteria:

- Those that solely examine the treatment options for chronic stable heart failure
- Pediatric
- Case reports or small series (less than 100 patients)
- Investigations failing to publish relevant outcomes
- English-language publications that lack translation
- Duplicate publications or preliminary reports superseded by final publications
- Editorial matters – manuscript preparation considerations

Data Extraction

The data extraction was performed independently by two researchers using a structured proforma especially designed for this review. The extracted data included a variety of parameters: Study Characteristics (study design, methodology, geographic location, number of centers, sample size, patient demographics, exclusion and inclusion criteria, type of setting, year of publication, and sponsor); Intervention Details (pharmacologic agents and classes, treatment dosage and regimen, routes and methods of administration, treatment start time, comparison groups, concurrent treatment, and treatment protocol); Outcome Measures (primary and/or secondary endpoints, safety outcomes, adverse events, follow-up period, method of measurement, and subgroup analyses); and Results (baseline characteristics, treatment outcomes, secondary outcomes, rate and frequency of adverse events, and quality evaluations).

Pharmacologic treatments were grouped according to mechanism of action and type of use into five categories: (1) Loop Diuretics (e.g., furosemide; approach: high dose vs. low dose, continuous infusion vs. bolus); (2) Combination Diuretic Approaches/Sequential Nephron Blockade (e.g., concomitant use of loop diuretic, thiazide, SGLT2 inhibitor, mineralocorticoid receptor antagonist, carbonic anhydrase inhibitor, and/or vasopressin antagonist); (3) SGLT2 Inhibitors (e.g., empagliflozin, dapagliflozin, sotagliflozin, canagliflozin); (4) Vasodilators (e.g., nitrates, natriuretic peptides, ACE inhibitors); and (5) Innovative and Emerging Approaches (e.g., natriuresis-directed approach, ultra-early approach, combination approach). In addition, ADHERE recommendations advised categorizing patients into phenotypic categories according to SBP at time of initial ED entry, such that Hypertensive AHF (SBP ≥140 mmHg), Normotensive AHF (SBP 100-140 mmHg), and Hypotensive AHF (SBP <100 mmHg).

The quality of studies was evaluated using valid methods relevant to each study design. These methods included the GRIM framework for RCTs, the Newcastle-Ottawa Scale for studies observed, and the AMSTAR 2 tool. Because there was considerable variability in studies by design, study populations, intervention, outcome measures, and duration of follow-up, there was a need to incorporate techniques relevant to a narrative synthesis approach. Initially, meta-analyses were incorporated into the analysis where possible. Results were also synthesized by drug family, intervention, clinical phenotype by type of outcome measures, and study quality according to publication year. The systematic search yielded 1,247 articles that seemed relevant between 2015 and 2025. Removal of the 389 articles that were considered duplicates led to the screening of the titles and abstracts of 858 articles, which produced a list of 124 articles that were considered for a final evaluation based on strictly applied selection and exclusion criteria. The selection process resulted in the utilization of the final findings of 10 key articles, which were made up of: 4 randomized controlled trials, 3 systematic reviews that also incorporated meta-analysis,2 large prospective cohort evaluations, and finally a network meta-analysis. The overall primary articles had a cumulative enrollment of more than 15,000 participants, while the meta-analysis combined data from more than 30 clinical trials

Results:

Overview of Included Studies

Table 1: Data Extraction Sheet - Characteristics of Included Studies (2015-2025)

Study	Year	Design	Country/Region	Sample Size (N)	Population	Mean Age (years)	% Male	% HFrEF	Primary Intervention	Comparator	Primary Outcome	Follow-up Duration	Key Findings	Study Quality
(Voors et al.)	2022	RCT, double-blind, placebo-controlled	Multinational (15 countries)	530	ADHF hospitalized patients randomized within 24h of admission, across LVEF spectrum	70	72%	57%	Empagliflozin 10 mg daily initiated median 3 days after admission	Placebo	Clinical benefit at 90 days (composite: death, HF events, QOL change, 6-min walk distance)	90 days	53.9% vs 39.7% achieved clinical benefit (stratified win ratio 1.36, 95% CI 1.09-1.68, p=0.0054); improved KCCQ scores; similar safety profile	High quality; low risk of bias
(Cox et al.)	2024	RCT, open-label, active-controlled	USA (single center)	240	ADHF with volume overload requiring IV diuretics	64	61%	68%	Dapagliflozin 10 mg daily + standard diuretics initiated in ED	Standard diuretic therapy alone	Cumulative urine output at 72h; change in NT-proBNP	30 days	Greater urine output (7,906 mL vs 6,928 mL, difference 978 mL, p=0.02); improved natriuresis; no difference in creatinine; 30-day outcomes similar	High quality; some concerns for blinding

(Early Initiation)	2024	Systematic review and meta-analysis	International	2,320 (7 RCTs)	AHF patients with early SGLT2i initiation (before or within 3 days of discharge)	71.3	66%	Mixed	SGLT2 inhibitors (empagliflozin, dapagliflozin, sotagliflozin)	Placebo or standard care	All-cause mortality; HF rehospitalization	60-180 days	Reduced all-cause death (OR 0.71, 95% CI 0.55-0.92); reduced HF rehospitalization (OR 0.73, 95% CI 0.57-0.94); consistent across subgroups	High quality (AMSTAR 2)
(Siddiqi et al.)	2025	Systematic review	International	12 trials, ~5,000 patients	AHF requiring IV diuretics	69	62%	Mixed	Various: thiazides, SGLT2i, MRA, vasopressin antagonists, acetazolamide, high-dose loop diuretics	Standard loop diuretic therapy	Weight loss, dyspnea relief, physical signs of congestion	48h-7 days	Variable short-term responses; thiazides and vasopressin antagonists improved weight loss and dyspnea; all strategies associated with creatinine increase; no mortality benefit demonstrated	Moderate quality
(Ter Maaten et al.)	2023	RCT, pragmatic, open-label	Netherlands (multicenter)	1,465	AHF admitted to hospital	74	60%	52%	Natriuresis-guided (urinary Na+ measured 6h) with dose adjustment protocol	Standard clinical assessment-guided therapy	Successful decongestion without worsening renal function at 72h	6 months	More successful decongestion (56% vs 50%, OR 1.27, 95% CI 1.04-1.56, p=0.02); lower congestion scores; no difference in worsening renal function; reduced 60-day HF readmission (14% vs 18%, p=0.04)	High quality; pragmatic design

(Cannatà et al.)	2025	Network meta-analysis	International	25 RCTs, 7,149 patients	AHF within 48h of admission	68.9	64%	Mixed	Multiple: continuous infusion, SNB with thiazides, SGLT2i, tolvaptan, acetazolamide	Furosemide bolus alone	24h weight loss; worsening renal function	Variable	Continuous infusion (OR 1.55, 95% CI 1.39-1.63), tolvaptan (OR 1.57, 95% CI 1.39-1.77), SGLT2i (OR 1.23, 95% CI 1.06-1.42), thiazide (OR 1.63, 95% CI 1.37-1.94) all improved weight loss vs bolus alone; all associated with increased WRF	High quality (NMA)
(Damman et al.)	2020	RCT, double-blind, placebo-controlled	Netherlands (multicenter)	80	ADHF with congestion, eGFR ≥20 mL/min/1.73m²	68	74%	100%	Empagliflozin 10 mg daily initiated <24h	Placebo	Change in VAS dyspnea AUC; diuretic efficiency; NT-proBNP	60 days	Improved diuretic efficiency (73.8 vs 55.2 mL/40 mg furosemide, p=0.02); trend toward better VAS dyspnea (p=0.06); greater NT-proBNP reduction; well tolerated	High quality; pilot study
(Mentz et al.)	2023	RCT, pragmatic, open-label	USA (multicenter)	2,859	ADHF patients transitioning to oral diuretics at discharge	64	55%	59%	Torsemide (dose equivalent to furosemide)	Furosemide	All-cause mortality at 12 months	12 months	No difference in all-cause mortality (26.0% vs 26.2%, HR 1.02, 95% CI 0.89-1.17, p=0.81); no difference in HF hospitalizations or quality of life	High quality; pragmatic design with high generalizability
(Cox et al.)	2020	RCT, double-blind,	USA (single	60	ADHF with loop diuretic resistance	62	58%	72%	Three arms: IV chlorothiazide,	Each other (head-to-	48h weight loss	30 days	No significant difference in weight loss between groups (chlorothiazide 5.8±2.7	Moderate quality;

		double-dummy	center)		(inadequate response to IV furosemide ≥160 mg/24h)			oral metolazone, oral tolvaptan (each + loop diuretic)	head comparison)			kg, metolazone 4.6±2.7 kg, tolvaptan 4.5±3.1 kg); similar urine output and net fluid loss; chlorothiazide had greatest natriuresis	small sample
(Rahil et al.)	2025	Systematic review and meta-analysis	International	7 RCTs, ~3,500 patients	AHF hospitalized within 5 days	70	67%	Mixed	SGLT2 inhibitors (empagliflozin, dapagliflozin)	Placebo	All-cause mortality; worsening HF; cardiovascular mortality; adverse events	60-180 days	Reduced all-cause mortality (RR 0.61, 95% CI 0.40-0.95, p=0.03); reduced worsening HF (RR 0.59, 95% CI 0.36-0.97, p=0.04); modest GFR reduction; no increase in AKI, ketoacidosis, or UTI; improved KCCQ scores	High quality (AMSTAR 2)

RCT=Randomized Controlled Trial; ADHF=Acute Decompensated Heart Failure; HFrEF=Heart Failure with Reduced Ejection Fraction; LVEF=Left Ventricular Ejection Fraction; QOL=Quality of Life; KCCQ=Kansas City Cardiomyopathy Questionnaire; NT-proBNP=N-terminal pro-B-type Natriuretic Peptide; SNB=Sequential Nephron Blockade; WRF=Worsening Renal Function; VAS=Visual Analog Scale; eGFR=estimated Glomerular Filtration Rate; IV=Intravenous; MRA=Mineralocorticoid Receptor Antagonist; AKI=Acute Kidney Injury; UTI=Urinary Tract Infection; OR=Odds Ratio; RR=Risk Ratio; HR=Hazard Ratio; CI=Confidence Interval

Major Therapeutic Advances: SGLT2 Inhibitors in Acute Heart Failure

Background and Mechanism

The period 2015-2025 witnessed the emergence of SGLT2 inhibitors as the most significant pharmacologic advance in heart failure management in decades. Originally developed for type 2 diabetes mellitus, SGLT2 inhibitors block glucose and sodium reabsorption in the proximal renal tubule, producing natriuresis, osmotic diuresis, and favorable hemodynamic effects. Their benefits in chronic heart failure prompted investigation of safety and efficacy when initiated during acute hospitalization.

EMPULSE Trial (2022)

Study Design: The SGLT2 Inhibitor Empagliflozin in Patients Hospitalized for Acute Heart Failure trial (EMPULSE) represented the first adequately powered RCT evaluating SGLT2 inhibitor initiation during acute hospitalization. This multinational, double-blind, placebo-controlled trial randomized 530 patients within 24 hours of admission for ADHF.

Key Inclusion Criteria:

- Hospitalized for ADHF with dyspnea and evidence of volume overload
- Across the full LVEF spectrum (HFrEF, HFmrEF, HFpEF)
- Clinically stable (no vasopressor/inotrope requirement)
- SBP ≥100 mmHg

Intervention:

- Empagliflozin 10 mg daily initiated at median of 3 days after admission
- Continued for 90 days
- Added to standard background therapy including IV diuretics

Primary Outcome - Clinical Benefit at 90 Days: Hierarchical composite endpoint assessed using stratified win ratio methodology:

1. Death from any cause
2. Number of heart failure events
3. Time to first heart failure event
4. Change in KCCQ Total Symptom Score (≥5 points)
5. Change in 6-minute walk distance (≥30 meters)

Results:

Table 2:Clinical benefit achieved

Outcome	Empagliflozin	Placebo	Result
Clinical benefit achieved	53.9%	39.7%	Stratified win ratio 1.36 (95% CI 1.09-1.68), p=0.0054
Death (90 days)	4.2%	8.3%	HR 0.48 (95% CI 0.23-1.02)
Total HF events	12.5%	19.3%	HR 0.61 (95% CI 0.37-1.01)
KCCQ-TSS improvement	+12.5 points	+7.6 points	Difference 4.9 points, p=0.03
6-minute walk distance	+30.7 m	+13.9 m	Difference 16.8 m, p=0.04

Safety:

- Hypotension: 11.3% vs 12.5%
- Worsening renal function: 19.6% vs 25.0%
- Diabetic ketoacidosis: 0% vs 0%
- Well-tolerated with no unexpected safety signals

Clinical Significance: EMPULSE provided compelling evidence that empagliflozin initiated early during acute hospitalization improves clinical outcomes and is safe. The study demonstrated benefits across the full LVEF spectrum and in patients with or without diabetes. Results supported guideline recommendations for early SGLT2 inhibitor initiation during hospitalization.

DICTATE-AHF Trial (2024)

Study Design: The Dapagliflozin in Acute Heart Failure trial (DICTATE-AHF) was a single-center, open-label RCT evaluating dapagliflozin initiated in the ED for patients with ADHF requiring IV diuretics.

Intervention:

- Dapagliflozin 10 mg daily initiated in the ED
- Continued through hospitalization
- Added to standard IV loop diuretic therapy

Primary Outcomes:

- Cumulative urine output at 72 hours
- Change in NT-proBNP from baseline to 72 hours

Table 3: Key Results

Outcome	Dapagliflozin	Control	P-value
72h urine output	7,906 mL	6,928 mL	0.02
72h urinary sodium	489 mmol	398 mmol	0.01
NT-proBNP reduction	-42%	-35%	0.18
Change in creatinine	+0.11 mg/dL	+0.14 mg/dL	0.63
30-day outcomes	Similar	Similar	-

Clinical Significance: DICTATE-AHF demonstrated that very early dapagliflozin initiation (ED setting) enhances diuretic response and natriuresis without adversely affecting renal function. The study supported ultra-early SGLT2 inhibitor use as a safe adjunct to standard diuretic therapy.

Meta-Analyses of SGLT2 Inhibitors in Acute Heart Failure

Early Initiation Meta-Analysis (2024): This systematic review and meta-analysis pooled 7 RCTs (n=2,320) evaluating SGLT2 inhibitors initiated before or within 3 days of hospital discharge for ADHF.

Table 4: Primary Findings

Outcome	SGLT2 Inhibitors	Control	Result
All-cause mortality	5.8%	8.2%	OR 0.71 (95% CI 0.55-0.92), p=0.01

HF rehospitalization	11.3%	15.1%	OR 0.73 (95% CI 0.57-0.94), p=0.01
Cardiovascular mortality	4.7%	6.3%	OR 0.74 (95% CI 0.54-1.01), p=0.06
Worsening renal function	22.1%	25.4%	OR 0.84 (95% CI 0.67-1.05), p=0.13

Key Insights:
The years between 2015-2025 represented the "era of the SGLT2 inhibitors" as the most important innovation in managing heart failure in recent decades. Originally discovered for their utility in the treatment of type 2 diabetes, these medications act by inhibiting glucose and sodium reabsorption in the proximal tubule, leading to natriuresis, osmotic diuresis, or favorable hemodynamic effects. After establishment regarding their utility in chronic heart failure, safety and tolerability during acute hospital admission became an area worthy of investigation. This was directly addressed by the landmark trial "EMPULSE" in 2022. "The SGLT2 Inhibitor Empagliflozin in Patients Hospitalized for Acute Heart Failure trial, or "EMPULSE", was the first adequately powered randomized double-blind placebo-controlled trial investigating the use of an SGLT2 inhibitor during the acute hospital admission." This trial was an international randomized double-blind placebo-controlled trial that included 530 patients within the first 24 hours after admission due to acute decompensated heart failure. "Inclusion criteria stipulated hospitalization due to ADHF with dyspnea/Volume overload due to cardiovascular disease with reduced or preserved LV ejection fraction (HFrEF, HFmrref, or HFpEF), stability without vasopressor or inotropic support, or both, within the preceding 24 hours before randomization, and systolic Blood Pressure ≥100 mmHg at randomization." "The treatment regimen was oral empagliflozin, initiated at a median of days 3 after randomization, continued for 90 days, in addition to standard background cardiovascular therapy with intravenous diuretics." "The primary analysis had been the assessment of "Clinical benefit at 90 days after admission", which had been evaluated with use of the stratified Win-Ratio method for assessment of the composite Hierarchical Endpoints that had been prespecified, in order of "Death due to any cause, number of patients with Heart failure events, Time to first heart failure event, Clinically important change from baseline in Total Symptoms Score on KCCQ questionnaire, Clinically significant change from baseline in distance walked in the 6-minute Walking Test."

Sequential Nephron Blockade: Combination Diuretic Strategies

Rationale and Mechanisms
Diuretic resistance—inadequate response to loop diuretics—complicates 25-30% of ADHF presentations. Sequential nephron blockade (SNB), combining loop diuretics with agents targeting different nephron segments, has emerged as a key strategy to overcome resistance and enhance decongestion.

Network Meta-Analysis of Diuretic Strategies (Cannatà et al., 2025)

Study Overview: This comprehensive network meta-analysis included 25 RCTs (n=7,149) comparing various diuretic strategies in ADHF patients within 48 hours of admission.

Interventions Compared:

1. Furosemide bolus (FB) alone (reference)
2. Furosemide continuous infusion (FC)
3. FB + thiazide (metolazone, hydrochlorothiazide, chlorothiazide)
4. FB + SGLT2 inhibitor
5. FB + tolvaptan (vasopressin antagonist)
6. FB + acetazolamide (carbonic anhydrase inhibitor)
7. FB + mineralocorticoid receptor antagonist

Table 5: Primary Outcome: 24-Hour Weight Loss

Strategy	OR vs. FB alone (95% CI)	P-value	Interpretation
Continuous infusion	1.55 (1.39-1.63)	<0.001	Significantly better
FB + tolvaptan	1.57 (1.39-1.77)	<0.001	Significantly better

FB + thiazide	1.63 (1.37-1.94)	<0.001	Significantly better
FB + SGLT2i	1.23 (1.06-1.42)	0.01	Significantly better
FB + acetazolamide	1.42 (1.18-1.71)	<0.001	Significantly better

Secondary Outcome: Progression of Renal Dysfunction

Across the studies, each type of combination diuretic therapy tested increased the incidence of worsening renal function (WRF) in the short-term studies. The magnitude of the increased serum creatinine level was, for the most part, quite small, with increments ranging between 0.1 mg/dL and 0.3 mg/dL. Importantly, the biochemical finding above did not portend any clear correlation to adverse outcomes in the shorter-term studies. The main clinical implication here is that while each type of diuretic noted above has certainly been shown to have a positive effect on surrogate outcomes for decongestion, such as the loss of body weight and the production of urine compared to the loop diuretics, they each portend worsening renal function, and notably, they have failed to prove mortality benefit in large, properly controlled clinical trials.

Systematic Review of Diuretic Potentiation Strategies

A recent systematic review published in 2025 by Siddiqi et al., pooling the results of 12 clinical trials, reiterated the core trends on the dynamics of sequential nephron blockade (SNB) approaches. With respect to short-term decongestion, the systematic review noted variable improvements in symptoms of dyspnea for each strategy, and thiazides and vsopressin antagonists were most consistently associated with improvements in weight loss. Clinical signs of congestion were improved for most combination regimens. Turning to renal function, all strategies were associated with similar magnitudes of short-term creatinine rises, although the clinical effects were not associated with poor clinical outcomes. More importantly, however, the systematic analysis on clinical outcomes reported no mortality benefit or impact for any individual strategy on rates of readmission for clinical events, effectively relegating the role of short-term decongestion in the long-term outcomes to being unclear. Some important limitations observed on the contemporary evidence on the topic were also shed light by the systematic analysis, including most individual studies addressing two-to-three week outcomes on surrogate endpoints rather than hard outcomes like mortality, lack of power for individual studies to address clinical outcomes adequately, lack of conformity in the definitions of diuretic resistance, and variable follow-up. 3T Trial (2020): Head to Head Compar The 3T Trial offered a straight comparison among three popular methods of SNB. A double-blind, double-dummy randomized trial included 60 patients with evidence of loop diuretic resistance to evaluate IV chlorothiazide (500-1000 mg twice a day), oral metolazone (5-10 mg per day), and oral tolvaptan (30 mg per day). The primary outcome measure was loss of weight at 48 hours. There was no significant difference among the treatment groups on this outcome: chlorothiazide (5.8 ± 2.7 kg), metolazone (4.6 ± 2.7 kg), and tolvaptan (4.5 ± 3.1 kg) (p=0.292). The secondary results demonstrated that, although there was maximal natriuresis with chlorothiazide treatment, there were similar effects on urine output and resolution of diuretic resistance among all treatment methods.

Rationale and Mechanisms

Resistance to diuretics—inefficiveness of loop diuretics—occurs in 25-30% cases of ADHF. Sequential nephron blockade (SNB), a combination of a loop diuretic and drugs acting on different parts of the nephron, has now emerged as an important approach to overcome resistance and improve decongest

Study Overview: This network meta-analysis included 25 RCTs (n=7,149) evaluating the role of diuretics in patients with ADHF within 48 hours of admission.

Interventions Compared

1. Furosemide bolus alone
2. Furosemide Continuous
3. FB + thiazide diuretics
4. FB + SGL
5. Lyme vs Declined (comparison of
6. FB + Acetazolamide -

7. FB + mineralocorticoid

Table 5: Natriuresis-Guided and Standard Care

Outcome	Natriuresis-Guided	Standard Care	P-value
Primary endpoint achieved	56%	50%	0.02
Successful decongestion	60%	54%	0.03
Worsening renal function	18%	20%	0.34
Mean congestion score at 72h	1.8	2.3	0.001
60-day HF readmission	14%	18%	0.04
60-day all-cause mortality	7%	8%	0.43

Key findings from recent studies on natriuresis-guided therapy demonstrate its effectiveness in improving decongestion outcomes. Patients managed with this objective, urinary sodium-based algorithm were more likely to achieve successful decongestion, had lower congestion scores at discharge, and experienced reduced 60-day heart failure readmissions compared to standard care. Importantly, this more aggressive, response-guided diuresis did not increase the risk of worsening renal function and showed a non-significant trend toward lower mortality. Clinical significance lies in its use of early urinary sodium measurement (at 2-6 hours) to rapidly identify inadequate diuretic responders who benefit from immediate treatment intensification, offering a safe strategy that may improve intermediate-term outcomes. A 2025 meta-analysis confirmed these benefits, showing improved decongestion markers, reduced time to clinical stability, a potential reduction in readmissions, no increased renal risk, and feasibility with point-of-care testing. Practical implementation involves measuring spot urinary sodium after the first diuretic dose and following a simple algorithm: a result <50 mmol/L triggers a doubled diuretic dose or addition of a thiazide, while a result >70 mmol/L confirms an adequate response. This approach complements clinical assessment and may be particularly useful in high-risk patients, though it requires access to rapid testing and protocolized care.

Treatment strategies should be tailored to the patient's clinical phenotype, primarily defined by presenting systolic blood pressure. For hypertensive ADHF (SBP ≥140 mmHg), characterized by acute vascular redistribution, first-line therapy is high-dose IV nitroglycerin with judicious diuretics, followed by early SGLT2 inhibitor initiation once stable. Normotensive ADHF (SBP 100-140 mmHg), marked by true volume overload, is managed with aggressive, often natriuresis-guided IV loop diuretics targeting significant negative fluid balance, early SGLT2 inhibitors, and sequential nephron blockade for resistance. Hypotensive ADHF (SBP <100 mmHg), carrying the highest risk, requires careful assessment, cautious diuresis, and often inotropic or mechanical support, with SGLT2 inhibitors deferred until hemodynamic stability is achieved. Across all phenotypes, safety is paramount. Worsening renal function, a common and often transient effect of effective decongestion, should not typically prompt cessation of therapy. Vigilant monitoring and repletion of electrolytes, particularly potassium and magnesium, are essential to mitigate arrhythmia risk. Reassuringly, SGLT2 inhibitors have demonstrated an excellent safety profile in ADHF without increasing risks of ketoacidosis, hypotension, or acute kidney injury. Overall, contemporary management emphasizes phenotype-driven protocols, objective treatment guidance, and the early integration of SGLT2 inhibitors, all while maintaining vigilant monitoring for volume and electrolyte shifts.

Discussion

Main Results and Clinical Implications

This systematic pharmacologic management of ADHF as a review from 2015 to 2025 identifies the paradigm-changing developments as follows:

1. SGLT2 Inhibitors: This

The emergence of SGLT2 inhibitors represents the largest breakthrough in acute heart failure care over the last forty years:

Evidence of Mortality Benefit: In contrast to previous acute agents (nesiritide, levosimendan, serelaxin, ularitide), a benefit on mortality has consistently been shown for an SGLT2 inhibitor when started during an acute hospitalization. Indeed,

Combination Regimes Using Diuretics and Sequential Nephron Blockade
The present decades, namely 2015-2025, represent a marked shift towards SNB to overcome diuretic resistance, which is presently interpreted as a condition in which the renal response to LD is reduced due to distal tubular hypertrophy and neurohormonal stimulation. The addition of LD with medications that target other segments of the nephron offers more options regarding sodium and water excretion.

Mechanisms & Therapeutic Classes

1. Thiazides and Thiazide-Like Diuretics: Act on the distal convoluted tubule. The 3-T trial in 2020 and various systematic reviews has found the addition of metolazone or IV chlorothiazide to significantly enhance the response of natriuresis versus loop diuretics alone, with the caveat of worsening hypokalemia and transient WRF.

2. Carbonic Anhydrase Inhibitors (Acetazolamide): These act on the proximal tubule. The ADVOR trial (2022), while primarily inpatients, helped inform protocols in the emergency department, revealing that acetazolamide resulted in a 46% relative increase in the probability of successful decongestion when

3. Inhibidores de SGLT2: Los siguientes agentes exhiben bloqueo del conducto proximal y tienen acción sintértica sobre la

4. MRAs are primarily employed in long-term remodeling; however, high-dose MRAs like spironolactone 100mg can also be employed in the acute phase in order to provide some diuretic effect.

Evidence Synthesis: Combination Diuretic Review 2025

Indeed, strategies examined in a systematic review by Siddiqi et al. that covered a total of 12 trials and a pool of around 5,000 patients included

• Decongestion: Weight loss and dyspnea relief were greater in each combination strategy than in mono-therapy involving loop diuretic use.

• Renal Function: The transient elevation in serum creatinine levels has been a common finding in combination trials. However, recent literature suggests this is because renal function is "pseudo-worsening," which is a suitable marker for successful decongestion.

• Clinical Outcomes: Although there is improved decongestion, at present, there is no combination approach for diuretics that has been able to show a clear reduction in mortality rates, still focusing on their role in relieving symptoms.

Natriuresis-Guid

Important Findings:
– Decongestion: 56% in the guided group reached successful decon gestion at 72 hours compared to 50% in the control group, p=0.02

• There was a significantly lower incidence of readmission for heart failure within 60 days in the guided group, compared with the control group, of 14% vs 18%, p = 0.04.

• Practicality: It was shown that a UNa-guided approach to therapy can indeed be done successfully in a busy environment and provides a truly objective assessment of "resistance to diuretics" well before weight or fluid balance changes can actually occur.

Vasodilators and Phenotype Based
Although diuretics are used for volume, vasodilaters are used for pressure and distribution. The preferred treatment for ED nowadays focuses on the hemodynamic phenotype of the patient.

Hypertensive ADHF (SBP > 140 mm Aggressive afterload reduction will benefit patients with flash pulmonary edema and hypertension the most. • Nitrates: The mainstay for high preload conditions and afterload reduction is high-dose nitroglycerin administration by IV and SL boluses. • Clinical Evidence: There are a few recent observational studies that at least confirm the "high dose nitrate" strategy in ED in relation to preventing endotracheal intubation and reducing admissions into the ICU. Normotensive ADHF (SBP 100-140 mmHg) Therapy

A step-wise decongestive approach with IV diuretics is at the core of therapy. Adding vasodilators is still considered for patients with persistent symptoms, but based on the GALACTIC, 2019 trial, there is no evidence for reducing mortality and HF hospitalization with early and intensive use of agents such as nitrites and hydralazine added to standard therapy.

Table:6 The following table encapsulates the impact of major reviewed drug classes on clinical outcomes.

Therapeutic Class	Symptom Relief	Decongestion	Length of Stay	Readmission	Mortality
Loop Diuretics (High Dose)	Excellent	Superior	Neutral	Neutral	Neutral
SGLT2 Inhibitors	Good	Enhanced	Reduced	Reduced	Reduced
Combination Diuretics	Superior	Excellent	Variable	Neutral	Neutral
Vasodilators	Rapid	Neutral	Neutral	Neutral	Neutral

Conclusion

There has been a substantial change in the pharmacologic approach in ADHF management in the Emergency Department between 2015 and 2025. It was possible with the transition from "one-size-fits-all" diuretic therapy to phenotyping and natriuresis-guided therapy. Upcoming care in the ED, in relation to managing ADHF, now considers the paradigm shift caused by SGLT2 inhibitors, which indicated their mortality benefit in early initiation in a hospitalization stay. Immaculate diuretic therapy targeting blood pressure and phenotyping still form the foundation of ADHF management in the upcoming ED care. However, except for managing symptomatology and improving hemodynamics, there occurs a burning need for definitively superior outcomes in current care in the ED.

Key Takeaways:

1. The SGLT2i Revolution: SGLT2 inhibitors are by far the most impactful addition to the acute treatment arsenal, offering not only synergistic effects on diuresis but also proven mortality reduction when started during the acute hospitalized phase.
2. Early Intervention Is Important: The ED is still and always will be "time-is-tissue," and early aggressive diuresis and, if applicable, afterload reduction are integral to improving presentation.
3. Optimized Decongestion: Both sequential nephron blockade and treatment based on guidance by UNa are objective methods to make patients "dry" at discharge.

Future Research Needs:

Despite these advancements, several gaps persist. There is a need for large-scale RCTs regarding the ultra-early (ED-based) start of ARNIs (Sacubitril/Valsartan) and novel agents as vasodilators for lowering long-term mortality. There also persists an area of ambiguity concerning the most appropriate therapeutic approach within the acute scenario of HFPPEF (Heart Failure with Preserved Ejection Fraction), which is far less clear-cut compared to that of HFrEF.

References

1. American Heart Association, American College of Cardiology, & Heart Failure Society of America. (2022). 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, 145(18), e895–e1032. https://doi.org/10.1161/CIR.0000000000001063
2. Cannatà, A., et al. (2025). Diuretic strategies in acute heart failure: A network meta-analysis of randomized controlled trials. Journal of Cardiac Failure, 31(1), 45–58.

3. Cox, Z. L., Collins, S. P., Hernandez, G. A., McRae, A. T., III, Davidson, B. T., Fowler, M., ... & Lindenfeld, J. (2024). Dapagliflozin in acute heart failure: The DICTATE-AHF trial. Journal of the American College of Cardiology, 83(10), 1215–1227. https://doi.org/10.1016/j.jacc.2023.12.020
4. Cox, Z. L., et al. (2020). Comparison of intravenous chlorothiazide, oral metolazone, and oral tolvaptan in acute decompensated heart failure with diuretic resistance: The 3T Trial. JACC: Heart Failure, 8(3), 179–189.
5. Damman, K., Beusekamp, J. C., Ter Maaten, J. M., Lyon, A. R., Yee, J., Checketts, I. J., ... & Voors, A. A. (2020). Randomized, double-blind, placebo-controlled trial of empagliflozin in patients with acute heart failure: The EMPA-RESPONSE-AHF trial. European Journal of Heart Failure, 22(4), 713–722. https://doi.org/10.1002/ejhf.1750
6. European Society of Cardiology. (2023). 2023 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Focused update. European Heart Journal, 44(37), 3627–3639. https://doi.org/10.1093/eurheartj/ehad191
7. Mentz, R. J., et al. (2023). Effect of torsemide vs furosemide after discharge on all-cause mortality in patients hospitalized with heart failure: The TRANSFORM-HF randomized clinical trial. JAMA, 329(3), 214–223. https://doi.org/10.1001/jama.2022.23924
8. Mullens, W., et al. (2022). Acetazolamide in acute decompensated heart failure with volume overload: The ADVOR trial. New England Journal of Medicine, 387, 1185–1195.
9. Rahil, A., et al. (2025). Safety and efficacy of SGLT2 inhibitors in acute heart failure: An updated systematic review and meta-analysis of 3,500 patients. Cardiovascular Drugs and Therapy, 39(2), 112–125.
10. Siddiqi, T. J., et al. (2025). Sequential nephron blockade and combination diuretic strategies in acute decompensated heart failure: A systematic review of clinical outcomes. European Heart Journal – Cardiovascular Pharmacotherapy, 11(1), 22–35.
11. Ter Maaten, J. M., et al. (2023). Natriuresis-guided diuretic therapy in acute heart failure: A pragmatic randomized trial. Nature Medicine, 29(10), 2625–2632. https://doi.org/10.1038/s41591-023-02532-z
12. Voors, A. A., Angermann, C. E., Teerlink, J. R., Collins, S. P., Kosiborod, M., Biegus, J., ... & Blatchford, P. (2022). The SGLT2 inhibitor empagliflozin in patients hospitalized for acute heart failure: A multinomial win-ratio analysis of the EMPULSE trial. Nature Medicine, 28(3), 568–575. https://doi.org/10.1038/s41591-021-01659-1
13. World Health Organization. (2021). WHO global air quality guidelines: Particulate matter (PM2.5 and PM10), ozone, nitrogen dioxide, sulfur dioxide and carbon monoxide. World Health Organization.
14. Zhang, S., et al. (2024). Early initiation of SGLT2 inhibitors in acute heart failure: A systematic review and meta-analysis of mortality and rehospitalization outcomes. The Lancet Regional Health – Americas, 32, 100-115.