Journal of the Society for Cardiovascular Angiography & Interventions 2 (2023) 101060

JSCAI

The official journal of the Society for Cardiovascular Angiography & Interventions

Comprehensive Review

Patient Selection and End Point Definitions for Decongestion Studies in Acute Decompensated Heart Failure: Part 1

Gabriel Georges, MD, MSc [a], Marat Fudim, MD, MHS [b], Daniel Burkhoff, MD, PhD [c], Martin B. Leon, MD [d], Philippe Généreux, MD [e,*]

[a] Quebec Heart and Lung Institute, Quebec City, Quebec, Canada; [b] Division of Cardiology, Department of Internal Medicine, Duke University School of Medicine, Durham, North Carolina; [c] Cardiovascular Research Foundation, New York, New York; [d] Division of Cardiology, Columbia University Irving Medical Center/NewYork-Presbyterian Hospital, New York; [e] Gagnon Cardiovascular Institute, Morristown Medical Center, Morristown, New Jersey

ABSTRACT

Despite recent advances in the treatment of patients with chronic heart failure, acute decompensated heart failure remains associated with significant mortality and morbidity because many novel therapies have failed to demonstrate meaningful benefit. Persistent congestion in the setting of escalating diuretic therapy has been repeatedly shown to be a marker of poor prognosis and is currently being targeted by various emerging device-based therapies. Because these therapies inherently carry procedural risk, patient selection is key in the future trial design. However, it remains unclear which patients are at a higher risk of residual congestion or adverse outcomes despite maximally tolerated decongestive therapy. In the first part of this 2-part review, we aimed to outline patient risk factors and summarize current evidence for early recognition of high-risk profile for residual congestion and adverse outcomes. These factors are classified as relating to the following: (1) previous clinical course, (2) severity of congestion, (3) diuretic response, and (4) degree of renal impairment. We also aimed to provide an overview of key inclusion criteria in recent acute decompensated heart failure trials and investigational device studies and propose potential criteria for selection of high-risk patients in future trials.

Introduction

Acute decompensated heart failure (ADHF) is associated with significant mortality and morbidity in patients with chronic heart failure.[1] Although considerable progress in the treatment of stable chronic heart failure has been achieved in the past decades, advancements in ADHF therapy has lagged behind.[2] In fact, multiple strategies evaluated in large randomized trials have failed to demonstrate meaningful benefit.[3–9] Hence, several device-based approaches are currently in development.[10–12] These devices act on several important pathways to improve response to decongestive therapy, such as increasing renal perfusion, reducing renal venous and lymphatic congestion (leading to "renal tamponade"), and improving cardiac function (eg, by modulating preload and contractility). Ultimately, a common goal is to achieve successful decongestion in patients before discharge because residual congestion has been repeatedly shown to be associated with worse outcomes.[3,13–15] However, the addition of decongestion as a study end point is recent, and there is no clear consensus regarding a definitive definition of successful decongestion.[3,16,17] There is also a lack of guidance on which patient should be targeted and are at risk for residual congestion despite escalation of diuretic therapy. The latter is key in the development of novel interventional therapies (which inherently involve procedural risk) designed for patients resistant to medical therapy.[11,12]

In the first part of this 2-part review, we aimed to highlight factors associated with a high risk of residual congestion or adverse outcomes in patients with ADHF. The proposed approach includes (1) acknowledging patient risk based on previous clinical course, (2) defining the severity of congestion before initiation/intensification of decongestive therapy, (3) prompt recognition of diuretic resistance, and (4) appreciation of clinically meaningful renal dysfunction (Central Illustration). We also aimed to review key patient inclusion criteria used in recent medical and interventional ADHF studies and provide potential high-risk features for future trial design.

Previous clinical course

For many patients with heart failure, the clinical course is one of the relative stability with punctual episodes of worsening symptoms.[1] ADHF often requires multiple hospitalizations, which is an established

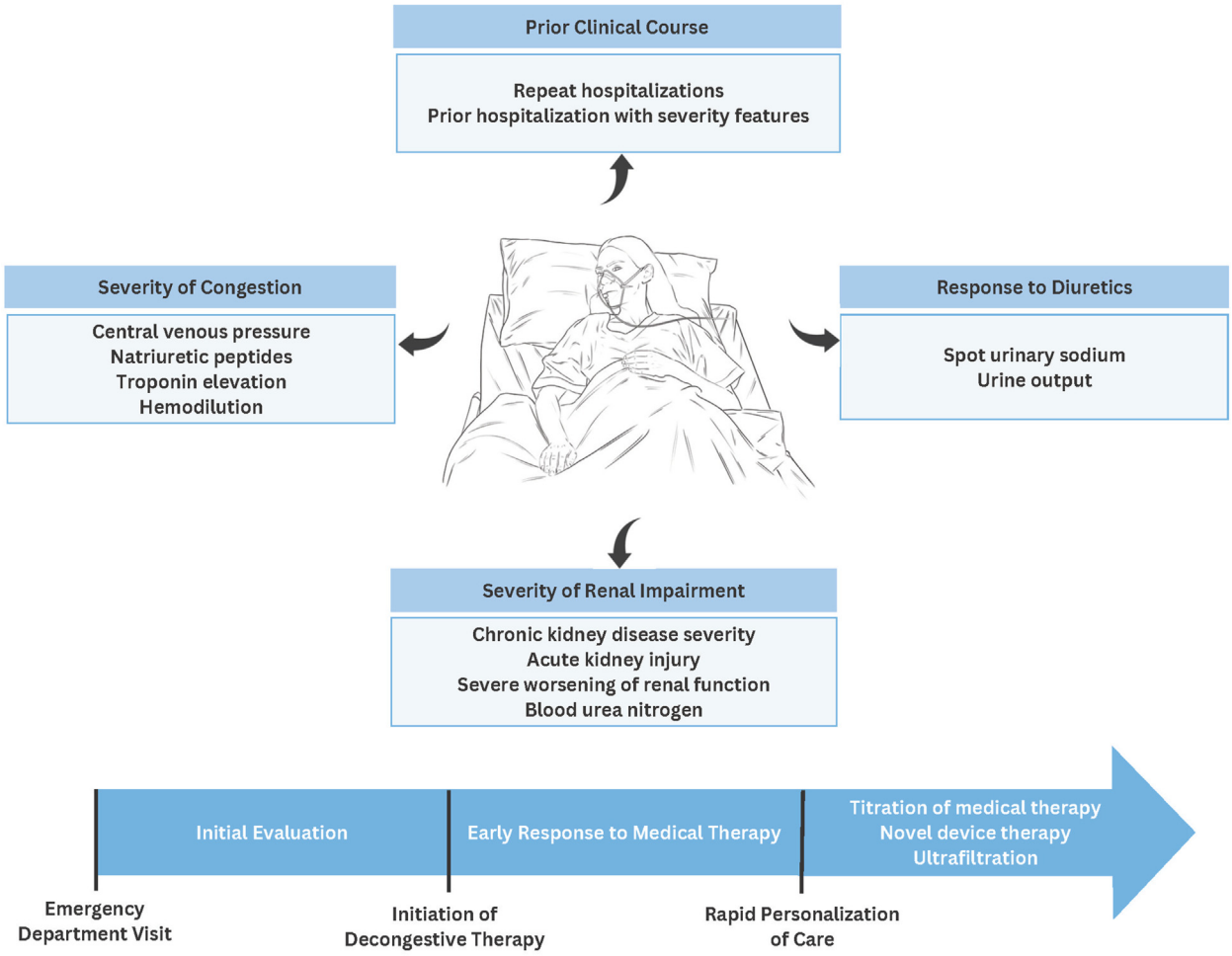
DOI of Part 2: https://doi.org/10.1016/j.jscai.2023.101059.

Abbreviations: ADHF, acute decompensated heart failure; AKI, acute kidney injury; BNP, B-type natriuretic peptide; CVP, central venous pressure; WRF, worsening renal function.

Keywords: cardiorenal syndrome; congestion; diuretic resistance; heart failure.

* Corresponding author: philippe.genereux@atlantichealth.org (P. Généreux).

https://doi.org/10.1016/j.jscai.2023.101060
Received 27 April 2023; Received in revised form 7 June 2023; Accepted 9 June 2023
Available online 8 August 2023



Central Illustration.

Conceptual approach to the identification of high-risk patients with acute decompensated heart failure. Risk factors for residual congestion or adverse outcomes in patients with acute decompensated heart failure can be divided into 4 categories: (1) previous clinical course, (2) severity of congestion, (3) diuretic response, and (4) degree of renal impairment.

predictor of poor prognosis.[1,18–20] Mortality rate in patients hospitalized with ADHF is 3-fold higher than those who are not hospitalized.[20] Even with contemporary medical therapy, almost 1 in 4 patients with heart failure with reduced ejection fraction dies within 2 years of hospitalization, and rehospitalization rates are reported as high as >50% at 30 days.[21] Importantly, each subsequent hospitalization carries incremental risk, and patients on their third hospitalization experience a >50% risk of mortality at 1 year.[19] Although the exact duration of severe vulnerability after hospitalization is unknown, it is generally accepted that risk is higher in the first few months after hospitalization.[1] Accordingly, Pocock et al[18] demonstrated that a previous hospitalization increased the risk of cardiovascular death or readmission by 73% in the first 6 months and 22% otherwise.

It is also being increasingly recognized that ADHF events treated in the emergency department or in the outpatient setting also carry a poor prognosis.[22–26] In a nationwide Danish cohort including 74,990 patients, 1-year mortality rate was 18% after outpatient intensification of diuretic therapy, 23% in patients hospitalized for ADHF, and 10% for those who required neither.[22] A post hoc analysis of the Prospective Comparison of ARNI with ARB Global Outcomes in Heart Failure with Preserved Ejection Fraction (PARAGON-HF) trial demonstrated similar results. In this study, patients who were hospitalized with heart failure showed the highest mortality (19 deaths per 100 patient-years), followed by patients who were treated in the emergency department (10 deaths per 100 patient-years) and patients without ADHF (4 deaths per 100 patient-years).[26] In addition, in a post hoc analysis of the Effect of Nesiritide in Patients with Acute Decompensated Heart Failure (ASCEND-HF) trial, the rate of death at 150 days was 21% in patients who were readmitted for ADHF compared with 11% for patients treated at the emergency department.[23] On the contrary, the Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial (PARADIGM-HF) investigators reported a similar increase in the risk of death after ADHF regardless of treatment location, such as outpatient therapy intensification.[25]

Among others, repeated ADHF events may reflect fragility, end-stage heart failure, or residual congestion. According to clinical judgment, some patients who are readmitted for ADHF and in whom successful decongestion is difficult to achieve by escalating medical therapy should be evaluated for alternative strategies as these become available.[11] In particular, patients who are readmitted within 6 months of discharge or patients with >2 previous hospitalizations are at extreme risk of adverse events.[18,19] Alternative therapies may also be considered in patients who are readmitted with a history of severe congestion with prolonged hospitalization, diuretic resistance, or severe cardiorenal syndrome during their last hospitalization.

Severity of congestion

Degree of congestion can be assessed clinically using a combination of intravascular and extravascular signs of fluid overload. Although the contribution to total excess fluid by the intravascular volume is

limited, the extravascular space can contain large volumes distributed in the interstitium and third spaces. For example, pedal edema provides a rapid and easy to obtain appreciation of interstitial fluid status and has been embedded in almost every congestion score.[3,14,16,17,27,28] Multiparameter congestion scales have also been described but lack standardization and prospective evaluation.[14,29] Invasive pressure measurement (ie, using right heart catheterization) provide objective parameters to inform on intravascular congestion[14,28] but may not provide a significant advantage to the general appreciation of total excess fluid to guide diuretic therapy. In fact, in the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) trial, outcomes were similar between patients who received decongestive therapy guided by right heart catheterization and those by clinical assessment.[30] Similarly, objective natriuretic peptide–guided therapy resulted in similar outcomes compared with standard clinical evaluation in the Guiding Evidence Based Therapy Using Biomarker Intensified Treatment in Heart Failure (GUIDE-IT) and Can NT-ProBNP-Guided Therapy During Hospital Admission for Acute Decompensated Heart Failure Reduce Mortality and Readmissions? (PRIMA-II) trials.[31,32]

These findings suggest that the technique used to evaluate congestion, whether objective or subjective, does not determine patient outcomes. However, the severity of congestion itself may play a role in the early identification of patients at risk of adverse outcomes. Given that subjective physical examination findings are already established in congestion grading scales, this review will focus on objective parameters that could potentially improve patient selection in the development of novel ADHF therapies.[3,16,17] Objective selection criteria also have the advantage of being more easily standardized across studies and centers to facilitate future comparison of decongestive strategies. In this review, we discuss 4 objective markers of congestion associated with ADHF outcomes.

Central venous pressure

Jugular venous pressure provides an estimate of central venous pressure (CVP) and has been shown among history and physical examination findings to be the best parameter to assess left ventricular filling pressures.[33,34] In a study of >2000 patients with acute heart failure enrolled in the Heart Failure Survey in Israel, jugular venous distension on admission was associated with a significant increase in mortality at 30 days, 1 year, and 10 years.[35] These findings are consistent with the previous Study of Left Ventricular Dysfunction (SOLVD), which followed up 2569 patients with symptomatic heart failure for a duration of 32 ± 15 months.[36] In this study, elevated jugular venous pressure was associated with an increased risk of hospitalization for heart failure (relative risk, 1.32; $P < .01$), death or hospitalization for heart failure (relative risk, 1.30; $P < .005$), and death from pump failure (relative risk, 1.37; $P < .05$). CVP on admission has also been associated with worsening renal function (WRF) during hospitalization. Mullens et al prospectively enrolled 145 patients with decompensated severe heart failure requiring intensive medical therapy guided by right heart catheter. They found CVP on admission to be the most important hemodynamic factor driving WRF, outperforming all other measurements including cardiac output.[37] Patients who developed WRF showed higher CVP on admission (18 vs 12 mm Hg) and after medical therapy (11 vs 8 mm Hg) than patients without WRF. Similarly, a retrospective study including 2557 patients who underwent right heart catheterization found that CVP was associated with impaired renal function and was independently related to mortality over a >10-year follow-up.[38] CVP values of >16 and >24 mm Hg were associated with sharp increases in risk of adverse outcomes. One theory behind the association between CVP and the increased risk of WRF is that elevations in CVP increase renal interstitial pressure and renal venous pressure. This in turn leads to reduced renal blood flow and parenchymal hypoxia,[33,34] resulting in "renal tamponade," given the nonexpandible nature of the renal capsule.[39,40] In a position statement from the Heart Failure Association of the European Society of Cardiology, a criterion of >16 mm Hg was used as an indicator of severe congestion.[14] In light of available evidence, this criterion seems reasonable a as potential marker of high-risk ADHF.[37,38]

Elevated natriuretic peptide

Natriuretic peptide levels increase with cardiac stretch and are widely used as a surrogate marker of congestion. Elevated natriuretic peptide on admission is associated with a decline in renal function and worse outcomes.[41–48] In a retrospective analysis of 1083 patients admitted for acute heart failure, Shirakabe et al[48] found a 10-pg/mL increase in B-type natriuretic peptide (BNP) to be independently associated with 1-year mortality. The group also found elevated natriuretic peptide levels to be significantly higher in patients with acute kidney injury (AKI). Taylor et al[49] performed a cohort-based population study of >40,000 patients with a new heart failure diagnosis and natriuretic peptide measurement. Patients with high BNP levels (BNP > 400 pg/mL or *N*-terminal prohormone BNP > 2000 pg/mL) showed a 50% higher risk of heart failure–related death at 1, 5, and 10 years, and 2× the risk of heart failure hospitalization at 1 year compared with patients with moderate natriuretic peptide levels (BNP = 100-400 pg/mL or *N*-terminal prohormone BNP = 400-2000 pg/mL). Although there is no consensus to identify patients at higher risk based on the level of natriuretic peptide,[41,48] cutoff values of 500 pg/mL for BNP and 3000 pg/mL for *N*-terminal prohormone BNP have been proposed to define severe congestion.[14,50] These criteria seem to be appropriate based on the current level of evidence, although higher levels may better discriminate high-risk patients.[15,41,43–46,48,50–54]

Hemodilution

Hemodilution can be defined according to serum sodium, albumin, total protein, or hemoglobin.[55–58] Hemoglobin is a marker of particular interest in evaluating patient risk because (1) anemia can be detected in ~50% of patients with heart failure, (2) anemia has been shown to predict worse outcome in heart failure with chronic heart failure and ADHF, (3) acute hemoconcentration in response to decongestive therapy is associated with improved outcomes, and (4) cardiorenal anemia syndrome, the combination of renal impairment and anemia, has been associated with an even greater increase in mortality.[58–65]

Using data from the Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF) study, Felker et al[60] identified anemia as an independent predictor of rehospitalization or death at 60 days in patients with acute heart failure. In particular, each decrease in hemoglobin of 1 mg/L was associated with a 12% increase of rehospitalization or death. More severe anemia led to worse outcomes. In accordance with these results, an inquiry of the Organized Program to Initiate Lifesaving Treatment in Patients with Heart Failure (OPTIMIZE-HF) registry database showed that anemia was associated with higher in-hospital all-cause mortality and more frequent readmission at 60-90 days.[59] Again, patients with the lowest hemoglobin values were at greater risk. The effects of anemia on longer-term outcomes of patients with ADHF were reported by the investigators of the Atherosclerosis Risk in Communities (ARIC) study. In this study, anemia was associated with twice the risk of death at 1 year in patients with preserved ejection fraction and a 40% increase in the risk of death at 1 year in heart failure with reduced ejection fraction.[58] Thus, anemic patients are at greater risk of adverse outcomes, particularly patients with severe anemia (hemoglobin < 11 mg/dL).[59,60]

Cardiorenal anemia syndrome is defined as an estimated glomerular filtration rate of <60 mL/min/1.73 m^2 and a hemoglobin level of <12 g/dL in women or <13 g/dL in men.[66] In chronic heart failure, renal dysfunction and anemia carry an incremental negative prognostic effect.[67,68] Fewer studies have evaluated the effect of cardiorenal anemia syndrome in ADHF. The Acute Decompensated Heart Failure Syndromes (ATTEND) registry accumulates data on patients with acute heart failure admitted to 53 hospitals in all regions of Japan. Kajimoto et al[64] showed that cardiorenal anemia syndrome was associated with a more than 2-fold increase in in-hospital mortality in patients with reduced and preserved ejection fraction. The combination of anemia and renal dysfunction generally led to a greater risk than either one alone. This additive effect on short-term mortality was also shown in a Spanish registry of 13,307 patients, where patients with cardiorenal anemia syndrome also showed ~2× greater risk of 30-day mortality.[61] van den Berge et al evaluated the effect of cardiorenal anemia syndrome on longer-term outcomes in a prospective registry of 1783 patients with acute heart failure. Anemia was associated with worse outcomes at a follow-up of 10 years and showed an incremental decrease in prognosis in patients with renal dysfunction.[63] Therefore, severe anemia and cardiorenal anemia syndrome are associated with a greater risk of adverse outcomes.

A shortcoming of using naturally occurring blood elements/proteins to derive information on intravascular volume is that the concentration of these parameters can be influenced by a myriad of external factors (eg, bleeding or transfusion for hemoglobin/hematocrit; malnutrition or albuminuria for albumin/total serum protein). In addition, because the dynamic changes in these parameters are more valuable than their absolute values, repeated assessments are required to determine change in volume status, and there is no clear target to define satisfactory decongestion. A quantitative blood volume analysis using a standardized computer-based indicator-dilution technique (ie, Daxor BVA-100) solves most of these issues by providing absolute total blood volume, plasma volume, and red blood cell mass and by offering individualized normal reference ranges.[69] This technique also allows identification of true anemia based on red blood cell mass, therefore reclassifying patients with normal amounts of red blood cells or polycythemia with significant volume expansion. In fact, a recent study demonstrated that true anemia was associated with worst outcomes in acute heart failure, regardless of volume status.[70] The study also suggested that the blood volume analysis may help in guiding volume management and improve ADHF outcomes, although prospective evaluation is underway.[70,71] Importantly, the blood volume analysis provides a direct measurement of volume in contrast with central pressure measurements and may in fact succeed where other strategies have failed in guiding decongestive therapy.[30,32]

However, without specialized tools, it may be challenging to differentiate anemia due to plasma volume increase from other causes of anemia, and hemodilution will most likely remain a retrospective finding. Testani et al[65] found that hemoconcentration occurred in ~50% of patients with congestive heart failure and peak hemoglobin and hematocrit levels were achieved after ~4 days of diuretic treatment. Nevertheless, patients with anemic heart failure remain at greater risk regardless of the underlying etiology and may benefit from more complete decongestion using novel therapies.

Increase in troponin

Increased levels of circulating cardiac troponin are detectable in a significant proportion of patients with acute heart failure.[72] Potential mechanisms leading to cardiac damage in patients with ADHF include supply and demand mismatch with subendocardial ischemia.[72,73] In ADHF, increased myocardial demand due to elevated filling pressures, increased transmural stress, and left ventricular hypertrophy are often met by decreased oxygen supply secondary to hypotension and anemia. Therefore, although troponin is not a marker of congestion per se, because of its association with increased filling pressures, it could be considered in specific clinical situations as a marker of cardiac overload. Other mechanisms for troponin increase in ADHF include renal failure, inflammation, and circulating hormone toxicity.[72,73]

Elevated troponin in patients with ADHF has been consistently associated with worse outcomes.[54,72–76] In a large study (n = 67,924) on data collected in the Acute Decompensated Heart Failure National Registry (ADHERE), Frank Peacock et al[76] found troponin-positive patients to show almost a 3× higher rate of in-hospital mortality than troponin-negative patients. Higher troponin values predicted higher mortality. Similarly, data from the biomarker substudy of the ASCEND-HF trial showed that elevated troponin was associated with worse in-hospital outcomes such as death, worsening heart failure, and a longer length of stay[74]; however, elevated troponin did not predict all-cause mortality at 30 or 180 days. By contrast, investigators in the Relaxin in Acute Heart Failure (RELAX-AHF) study demonstrated that higher baseline and peak troponin levels were strongly associated with death from heart failure or other cardiovascular cause at 180 days.[75] A potential explanation for this discrepancy was that the RELAX-HF study focused only on cardiovascular death. In the Efficacy and Safety of Aliskiren Therapy on Top of Standard Therapy, on Morbidity and Mortality in Patients With Acute Decompensated Heart Failure (ASTRONAUT) trial, troponin elevation at discharge was not associated with 1-year outcomes, but elevated troponin at 1 month after discharge independently predicted all-cause 1-year mortality.[54] When combined with other markers of congestion, such as BNP, elevation in troponin detects high-risk patients with even more accuracy.[50]

Diuretic resistance

Despite intravenous loop diuretics being almost ubiquitously used to treat ADHF and resistance to diuretics being commonly encountered, diuretic resistance remains a vague concept. Diuretic resistance is typically defined as unsatisfactory decongestion despite an adequate/escalating diuretic regimen. The mechanisms of diuretic resistance have been extensively described, and its association with worse outcomes has been repeatedly demonstrated[77–79]; however, there is currently no consensus on quantitative evaluation of diuretic response to define resistance.[13,14] In recent years, various groups have defined adequate and poor diuretic response using different metrics such as natriuresis, urine output, net fluid loss, fractional sodium excretion, and fluid/-weight loss (often indexed to 40 mg of furosemide equivalent). General strength and weaknesses of each metric have been reviewed elsewhere.[13,77]

Urine chemistry parameters

Recently, several studies have evaluated diuretic response using measurement of urinary sodium.[80] Sodium excretion can be evaluated over a period (24-hour urine collection) or using a single spot urine sample. Convenience and rapid assessment allowing risk stratification and early intervention are key considerations in choosing a metric to define diuretic resistance; in this regard, spot urinary sodium has gained interest. It is typically measured 1-2 hours after an appropriate dose of diuretic, thereby avoiding the lag-time of other conventional metrics such as urine output or weight loss over 24 hours and enables timely tailoring of decongestive therapy. Spot urinary sodium at 2 hours after a diuretic dose has also been shown to predict natriuretic response over 6 hours using a simple equation.[81,82] Values <50-70 mEq/L have been proposed to identify patients with high renal sodium avidity and a greater risk of insufficient diuretic response. In addition, of importance

Table 1. Summary of studies using spot urinary sodium as a measure of diuretic resistance.

Reference	Poor diuretic response	Good diuretic response	Outcome with diuretic resistance (low UNa)
Martens et al,[91] 2022	19-40 mmol/L	69-139 mmol/L	Less improvement in decongestive metrics
Biegus et al,[84] 2021	<60 mmol/L	>60 mmol/L	More in-hospital WHF, inotrope use, and rehospitalization
Galluzzo et al,[92] 2022	<50 mmol/L	>50 mmol/L	Lower urine output, higher body weight, higher NT-proBNP, and higher incidence of worsening renal function
Minana et al,[83] 2020	13-65 mmol/L	111-181 mmol/L	UNa inversely related to 24-h diuretic efficiency
Cunningham et al,[89] 2020	≤60 mmol/L	>60 mmol/L	Longer length of stay and less weight loss
Biegus et al,[88] 2019	No increase in UNa after diuretic dose vs baseline	Increase in UNa after diuretic dose vs baseline	No increase in UNa after diuretic dose associated with poor diuretic response and increased mortality at 1 y
Collins et al,[93] 2019	48 mmol/L (median)	80 mmol/L (median)	Increased risk of WHF during hospitalization
Honda et al,[94] 2018	<74 mg/dL	>113 mg/dL	Less improvement in decongestive metrics and increased risk of death and WHF over long-term follow-up
Luk et al,[87] 2018	<60 mmol/L	>60 mmol/L	Increased risk of death at 90 d, mechanical circulatory support during admission, and requirement of inotropic support at discharge
Brinkley et al,[85] 2018	<67 mmol/L	>94 mmol/L	Lower risk of hospitalization or emergency department visit within 30 d
Doering et al,[86] 2017	<50 mmol/L	>50 mmol/L	More likely to be readmitted at 30 d
Ferreira et al,[95] 2016	<60 mmol/L	>100 mmol/L	Increased midterm cardiovascular mortality or rehospitalization
Singh et al,[90] 2014	<2 mmol/mg of furosemide	>4 mmol/mg of furosemide	Increased risk of death, cardiac transplant, or rehospitalization

eGFR, estimated glomerular filtration rate; UNa, urinary sodium; WHF, worsening heart failure.

is that standing up to measure weight or collecting urine output without a foley catheter may be challenging in some patients, but bedridden or incontinent patients are typically capable of providing a urine sample. The simple metric also reduces the annoyance of missing or incorrect measurements that can occur with other metrics requiring serial measurements (eg, weight loss and urine output). It has been demonstrated that low urinary sodium is strongly associated with less effective decongestion, longer hospitalization, and worse short-term and long-term outcomes and performs better than other traditional markers of congestion such as weight loss, urine output, and fluid balance.[80,83–91] Table 1 summarizes the current evidence on spot urinary sodium evaluation of diuretic response in acute heart failure.[83–95] In a recent position statement from the Heart Failure Association, a stepwise pharmacologic diuretic strategy to increase the diuretic response and achieve rapid decongestion is proposed using spot urinary sodium (<50-70 mEq/L cutoff to intensify therapy) and urine output measured (<100-150 mL/h on average for 6 hours cutoff to intensify therapy) after 2 and 6 hours of diuretic dose, respectively.[14] Multiple prospective clinical trials are testing whether spot urinary sodium to guide treatment will lead to more effective decongestion.[96,97] Most interestingly, a post hoc analysis of the Renal Optimization Strategies Evaluation in Acute Heart Failure (ROSE-AHF) trial showed that even a random spot urine sodium measure (not timed 1-2 hours after diuretic dose) can accurately predict decongestion.[91] This may further facilitate translation of spot urinary sodium into clinical practice.

Urine output

Insufficient diuresis is also used to define diuretic resistance and has been shown to correlate with outcomes, but there is significant variability in criteria to characterize poor diuretic response.[98–101] Notably, the stepped pharmacologic approach in the Cardiorenal Rescue Study in Acute Decompensated Heart Failure (CARESS-HF) targeted a urine output of 3-5 L/24 h.[16] Other investigators have identified and validated diuretic response adjusted to loop diuretic dose (ie, per 40 mg of furosemide equivalent) or diuretic efficiency, as a marker of prognosis.[98,102,103] Poor diuretic response has been described, with values ranging from <730 mL/40 mg furosemide to <2 L/40 mg furosemide.[98,100] However, many of these studies did not consider the log-linear relationship between diuretic dose and response.[78] The thresholds suggested by the Heart Failure Association (<100-150 mL/h on average for 6 hours after a diuretic dose) allow for a more rapid assessments but need prospective validation.[14,104] Therefore, from a trial design standpoint, determining a threshold to define urine output may be more arbitrary than other markers, such as spot urinary sodium.

Weight loss

Weight is simple and inexpensive to obtain. The major pitfall with using weight to provide early identification of diuretic resistance is that this is usually performed with measurements obtained over 4-7 days.[53,57,102,103,105] In a post hoc analysis of the Placebo-controlled Randomized Study of the Selective A1 Adenosine Receptor Antagonist Rolofylline for Patients Hospitalized with acute heart failure and Volume Overload to Assess Treatment Effect on Congestion and Renal FuncTion (PROTECT) trial, Valente et al[102] demonstrated a significant interaction between diuretic response (defined as weight loss on day 4 indexed to furosemide dose) and 180-day mortality. Patients in the 2 lowest weight loss quintiles (−0.18 kg/40 mg furosemide and −0.0 kg/40 mg furosemide) showed ~3-fold greater mortality at 6 months than patients in the highest weight loss quintile (−1.33 kg/40 mg furosemide). Change in weight at day 5 indexed to the diuretic dose was associated with a higher risk of cardiovascular-related death or rehospitalization for heart failure in the RELAX-AHF trial.[103] Similar to urine output, evaluation of weight loss also lacks adjustment for the total amount of excess fluid. Therefore, weight loss alone does not inform on the level of decongestion. Although weight loss may help predict outcomes postdischarge, its utility in the early identification of patients at risk of diuretic resistance is limited.

Severity of renal impairment

Acute renal injury and WRF

It is currently under debate whether WRF in the setting of effective decongestion translates into adverse outcomes for patients with ADHF.[14,47,57,78,106,107] Most recent studies have shown that changes in markers of congestion (such as a decrease in BNP, usually by 30%) determine prognosis regardless of changes in renal function.[15,53,57] This is in line with the findings of the landmark Diuretic Strategies in Patients with Acute Decompensated Heart Failure (DOSE) study, which demonstrated similar clinical outcomes, greater decline in

Table 2. Patient selection criteria of recent ADHF randomized controlled trials.

Trial name	Intervention	Time to randomization	Key inclusion criteria	Key findings
CLOROTIC[114]	HCTZ 25-100 mg vs placebo	Within 24 h of hospitalization	Hospitalized for ADHF with: • a history of chronic HF • treatment with an oral loop diuretic for at least 1 mo before hospitalization, at a furosemide dose between 80 and 240 mg daily, or equivalent	Greater weight loss at 3 d, no difference in dyspnea
EMPULSE[115]	Empagliflozin 10 mg/d vs placebo	After at least 24 h and no later than 5 d after admission	Hospitalized for acute HF with: • dyspnea on exertion or at rest and clinical signs of congestion • NT-proBNP $\geq$ 1600 pg/mL or BNP $\geq$ 400 pg/mL • treated with a minimum dose of 40 mg IV furosemide or equivalent	Improvement in the hierarchical composite primary end point of death, number of HF events and time to first HF event, or a - point or greater difference in change in the KCCQ at 90 d
ADVOR[17]	Intravenous (IV) acetazolamide 500 mg once daily vs placebo	—	Admitted to the hospital for ADHF with: • at least 1 clinical sign of volume overload • BNP $\geq$ 250 pg/mL or NT-proBNP $\geq$ 1000 pg/mL • Oral maintenance therapy with at least 40 mg of furosemide or an equivalent dose for at least 1 mo before randomization	Greater incidence of successful decongestion at 3 d
EMPA-RESPONSE-AHF[116]	Empagliflozin 10 mg/d vs placebo	Within 24 h of presentation to the hospital	Hospitalized for ADHF with: • dyspnea at rest or with minimal exertion • signs of congestion, such as edema, rales, and/or congestion on chest radiograph • BNP $\geq$ 350 pg/mL or NT-proBNP $\geq$ 1400 pg/mL treated with loop diuretics at screening	No difference in any of 4 primary end points at day 4
ATHENA-HF[117]	100 mg spironolactone vs placebo or 25 mg spironolactone	Within 24 h of first dose of IV diuretics	Clinical diagnosis of ADHF with: • At least 1 sign and 1 symptom of acute HF • BNP $\geq$250 pg/mL or NT pro-BNP $\geq$1000 pg/mL	No change in primary end point of reduction in NT pro-BNP levels at 4 d
TRUE-AHF[8]	IV infusion of ularitide vs placebo	Within 12 h of initial evaluation	Unplanned emergency department visit or hospitalization for acute HF with: • dyspnea at rest that had worsened during the previous week • evidence of HF on chest radiography • BNP $\geq$ 500 pg/mL or NT-proBNP $\geq$ 2000 pg/mL • dyspnea at rest for at least 2 h after IV administration of at least 40 mg of furosemide • systolic blood pressure between 116 mm Hg and 180 mm Hg	No effect on composite end point
ROSE[7]	Low-dose dopamine or low-dose nesiritide vs placebo	Within 24 h of hospitalization	Hospitalized for the treatment of acute HF with: • sign and symptoms of heart failure • renal dysfunction (GFR of 15–60 mL/min/1.73 m^2)	Neither low-dose dopamine nor low-dose nesiritide enhanced decongestion or improved renal function
PROTECT[4]	IV rolofylline 30 mg/d vs placebo	Within 24 h of hospitalization	Hospitalized for acute HF with: • persistent dyspnea at rest or with minimal activity • impaired renal function (an estimated CrCl of 20–80 mL/min) • BNP $\geq$ 500 pg/mL or NT-proBNP $\geq$ 2000 pg/mL • Ongoing IV loop diuretic therapy	No effect on primary end point
UNLOAD[118]	Ultrafiltration vs diuretics	Within 24 h of hospitalization	Hospitalized for HF with at least 2 clinical signs and symptoms volume overload	Greater weight loss at 2 d, no difference in dyspnea
ASCEND-HF[5]	Nesiritide vs placebo	Within 24 h before the first IV treatment for heart failure	Hospitalized for HF with: • dyspnea at rest or with minimal activity • 1 or more accompanying signs (respiratory rate $\geq$ 20 breaths/m or pulmonary congestion or edema with rales one-third of the way or more up the lung fields) • 1 or more objective measures of HF (evidence of congestion or edema on chest radiography, BNP $\geq$ 400 pg/mL or NT-proBNP $\geq$ 1000 pg/mL, PCWP >20 mm Hg, or left ventricular ejection fraction <40% in the previous 12 mo)	No effect on dyspnea or composite end point of rehospitalization for HF or death
DOSE[3]	Diuretic therapy administered by bolus vs continuous infusion or high dose vs low dose	Within 24 h of presentation	Presenting with ADHF, with: • at least 1 symptom and 1 sign of heart failure • a history of chronic HF • receipt of an oral loop diuretic for at least 1 mo before hospitalization at a dose between 80 mg and 240 mg daily of furosemide or equivalent	No significant differences in patient global assessment of symptoms or in change in renal function

(*continued on next page*)

Table 2. (*continued*)

Trial name	Intervention	Time to randomization	Key inclusion criteria	Key findings
EVEREST[119]	Tolvaptan 30 mg/d vs placebo	Within 48 h of hospitalization	Hospitalized for worsening congestive HF, with: • a history of chronic HF (minimum of 30 d before hospitalization) • left ventricular ejection fraction of ≤40% • HF symptoms at rest or minimal exertion • clinical signs of congestion	Improvement in weight but not global clinical status at 7 d
CARRESS-HF[6]	Ultrafiltration vs stepped diuretic therapy	Within 24 h of hospitalization	Admitted to hospital with a primary diagnosis of ADHF with: • onset of cardiorenal syndrome (increasing creatinine ≥ 0.3 mg/dL) after or before hospitalization • persistent volume overload (PCWP > 22 mm Hg if available and clinical signs of volume overload)	Worse renal function, more adverse events, and similar decongestion at 96 h

ADHF, acute decompensated heart failure; ADVOR, Acetazolamide in Decompensated Heart Failure with Volume Overload; ATHENA-HF, Aldosterone Targeted Neurohormonal Combined with Natriuresis Therapy in Heart Failure; BNP, B-type natriuretic peptide; CLOROTIC, Combination of Loop with Thiazide Diuretics for Decompensated Heart Failure; CrCl, creatinine clearance; EMPA-RESPONSE-AHF, Effects of Empagliflozin on Clinical Outcomes in Patients With Acute Decompensated Heart Failure; EVEREST, Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study; HCTZ, hydrochlorothiazide; HF, heart failure; KCCQ, Kansas City Cardiomyopathy Questionnaire; NT-proBNP, *N*-terminal prohormone B-type natriuretic peptide; PCWP, pulmonary capillary wedge pressure.

markers of congestion, and greater symptom relief in the high-dose diuretic group vs low-dose group despite a higher incidence of WRF in the high-dose group.[3] Correspondingly, persistent congestion at discharge is now recognized as a strong predictor of adverse outcomes. In a post hoc analysis of 6 prospective cohorts including 1232 patients, Salah et al[15] demonstrated that patients in whom BNP levels failed to decrease by 30% experienced 2.5× greater mortality than the patients who showed an adequate decrease in BNP. Similarly, a post hoc analysis of the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan (EVEREST) trial showed that evidence of decongestion by decline in BNP, weight loss, or hemoconcentration was associated with better outcomes independent of acute declines in renal function.[57]

However, one of the challenges in correlating renal impairment with the risk for adverse events is the lack of a universal definition for WRF and AKI.[47,106,108] Guidelines for standardization of renal injury include the Kidney Disease: Improving Global Outcomes (KDIGO), Acute Kidney Injury Network (AKIN), and Risk, Injury, Failure, Loss of kidney function, and End-Stage disease (RIFLE) criteria. Perhaps, because it is found both in the KDIGO and AKIN criteria definition of stage 1 renal injury, many authors also chose to define WRF simply as an increase in serum creatinine level of ≥0.3 mg/dL within the first few days of admission.[47,106,107] Importantly, most WRF criteria use admission values as baseline. This implies that significant AKI on admission without further deterioration during hospitalization is currently included in the no-WRF group.[48,109] Shirakabe et al[48] clearly illustrated this issue by classifying patients in 4 groups based on the presence of WRF (increase in serum creatinine of ≥0.3 mg/dL within the first 5 days of admission) and AKI (according to the RIFLE criteria and using the lowest serum creatinine value within the last 12 months as baseline) and evaluating mortality and heart failure events at 1 year. Patients without WRF but AKI on admission experienced a ~2-fold increase in mortality at 1 year, and patients with both WRF and AKI showed a ~3.5-fold increase in mortality compared with patients without WRF or AKI. On the contrary, mortality in patients with WRF but without AKI was not significantly different from that in patients without WRF or AKI. A limitation of this classification is that baseline renal function for diagnosis of AKI is not known in all patients; however, a significant advantage of predicting patient risk based on AKI is that high-risk patients can be identified immediately on admission and their therapy can be individualized (vs later developing WRF). Along with the lack of a consensus definition, this may also partly explain the discrepancies seen in the association of WRF and prognosis.

Chronic kidney disease

Another significant risk factor that can be considered on admission is the baseline severity of chronic kidney disease (CKD).[47,110] Approximately 90% of patients hospitalized for heart failure present with some degree of CKD. Mortality is strongly associated in a graded fashion with baseline renal function.[47,110] Patel et al[110] reported that patients with moderate-to-severe CKD (eGFR 30-44 mL/min/1.73 m^2) and severe CKD (eGFR <30 mL/min/1.73 m^2) on admission experience an in-hospital mortality 3× and 6× greater than that of patients with normal CKD (eGFR ≥90 mL/min/1.73 m^2) or mild CKD (eGFR 60-89 mL/min/1.73 m^2). Patients with CKD were also less likely to be optimally treated with guideline-directed medical therapy.[110] A large meta-analysis of 57 studies (1,076,104 patients) also demonstrated increasing long-term mortality in patients with heart failure and increasing severity of CKD.[47]

Blood urea nitrogen

Among other markers of renal function/tubular injury, blood urea nitrogen (BUN) has been demonstrated to be a strong single predictor (surpassing creatinine) of in-hospital and long-term mortality. Investigators from the ADHERE registry identified a BUN level of ≥43 mg/dL as the strongest predictor for mortality, followed by low systolic blood pressure (<115 mm Hg) at admission and a serum creatinine level of ≥2.75 mg/dL.[111] Similar findings were obtained in a post hoc analysis of the Acute and Chronic Therapeutic Impact of a Vasopressin Antagonist in Chronic Heart Failure (ACTIV in CHF) trial. In this study, Flippatos et al[112] stratified patients in 4 quartiles according to BUN levels (quartile 1: ≤18 mg/dL; quartile 2: 19-26 mg/dL; quartile 3: 27-39 mg/dL; and quartile 4: ≥40 mg/dL). Higher BUN levels were predictive of higher mortality and higher rates of death or hospitalization within 60 days. Patients with BUN in the highest quartile showed the highest 60-day mortality rate at 14.3%, compared with 0% in the lowest quartile. On the contrary, creatinine was not independently associated with outcomes. Again, using data from the PROTECT trial, BUN was shown to be the strongest single predictor of 180-day mortality.[113] The highest quartile of risk was associated with significant mortality (15% at 30 days and 40% at 6 months) compared with other quartiles (all less than 1% and 5% at 30 days and 6 months, respectively). The median BUN in the highest quartile was 44 mg/dL (vs Q3: 32 mg/dL, Q2: 28 mg/dL, and Q1: 22 mg/dL).[113] Therefore, patients with elevated BUN,

Table 3. Patient selection for the study of investigational acute heart failure devices.

Device	Description	Theoretical effect	Phase of study	Ongoing study	Inclusion criteria
Aortix (Procyrion)	Intra-aortic pump	↑Renal blood flow ↓Afterload ↑CO	Pilot study underway	NCT04145635	Hospitalized for ADHF and: • Worsening renal function (serum creatinine increase by ≥0.3 mg/dL [≥27 μmol/L]) despite 48 h of intravenous diuretic therapy (increase can be compared with a baseline value taken within 90 d of hospitalization or during hospitalization) • Objective measure of congestion (PCWP ≥20 mm Hg) or elevated CVP (≥12 mm Hg) • Persistent clinical signs and/or symptoms of congestion despite diuretic therapy
Reitan Catheter Pump (Cardiobridge)			Pilot study complete Smaller profile device FIH study complete	—	ADHF with known advanced chronic heart failure and: • requiring inotropic or mechanical circulatory support • left ventricular ejection fraction <30% • cardiac index <2.1 L/min/m^2 as measured by pulmonary artery thermodilution catheter
Second Heart Assist (Second Heart Assist)			FIH study complete	—	—
ModulHeart (Puzzle Medical Devices)			FIH study complete	—	FIH study performed in high-risk patients who underwent PCI as proof of concept
preCARDIA (Abiomed)	Superior vena cava occlusion	↓Preload	EFS underway	NCT03836079	• NYHA class III-IV heart failure • subjects with inadequate diuresis • stage C-D systolic heart failure
Doraya catheter (Revamp Medical)	Inferior vena cava occlusion	↓Preload Renal venous unloading	EFS complete	NCT05206422	Hospitalized for ADHF and: • NT-proBNP ≥ 1000 pg/mL or BNP ≥ 250 pg/mL • Evidence of fluid overload • Subject insufficiently responds to intravenous diuretic therapy
CorInnova Direct Cardiac Compression Device (CorInnova)	Cardiac compression device	↑CO	Preclinical stage	—	—
Cardiac Pulmonary Nerve Stimulation system (Cardionomics)	Cardiac autonomic nerve stimulation	↑Contractility	EFS study underway	NCT04814134	Admitted to hospital for ADHF and: • BMI-adjusted BNP ≥ 500 pg/mL or NT-proBNP ≥ 2000 pg/mL • left ventricular ejection fraction ≤50% • at least 1 sign or symptom of fluid overload despite the administration of IV furosemide (or equivalent) (at least 40 mg or equivalent)
Reprieve Cardiovascular System (Reprieve Cardiovascular)	Fluid management console	Personalized and optimized diuretic and saline infusion	Pivotal study underway	NCT05174312	Hospitalized with a diagnosis of heart failure and: • ≥10 pounds (4.5 kg) above dry weight • Previous use of loop diuretics with a total daily dose of 80-400 mg furosemide for a minimum of 30 d before admission
Whiteswell Catheter (WhiteSwell)	Suction catheter	↑Lymph drainage into intravascular compartment	Feasibility study underway	NCT05747196	Admitted to hospital for ADHF and: • systolic BP ≥90 mg Hg and ≤180 mm Hg without the need for inotropes or vasopressors at the time of enrollment • currently receiving loop diuretics as home therapy for a minimum of 6 mo beforeadmission
AquaPass Microclimate Suit (AquaPass Medical)	Hot body capsule	↑Fluid and salt loss through the sweat glands	FIH study completed	—	Congestive heart failure and: • 2 or more score for pitting edema • taking diuretic medications at home

ADHF, acute decompensated heart failure; BP, blood pressure; BNP, B-type natriuretic peptide; CO, cardiac output; CVP, central venous pressure; EFS, early feasibility study; FIH, first-in-human; NT-proBNP, *N*-terminal prohormone B-type natriuretic peptide; NYHA, New York Heart Association; PCWP, pulmonary capillary wedge pressure.

particularly in the ~40 mg/dL range, should be considered at high risk of adverse outcomes.

Current status and future direction

Many novel therapeutic strategies have failed to demonstrate clinically meaningful benefit in patients with ADHF. In Table 2,[114–119] we summarize key inclusion criteria used in recent ADHF randomized control trials and their main findings.[3–8] Patient selection plays a crucial role in trials evaluating new therapeutic strategies, particularly interventional therapies that may provide substantial improvements in heart failure but at the intrinsic cost of being more invasive. In Table 3, we provide an overview of investigational devices for the treatment of ADHF, their current phase of study, and study population. Of note, most of the studies target patients with some level of diuretic resistance, but no consensus criteria are provided to define poor diuretic response.

This review highlights several patient factors that can be used to guide the definition of high-risk profiles in future trials and clinical practice. Conceptually, we classified these risk factors in 4 categories: (1) previous clinical course, (2) severity of congestion at presentation, (3) diuretic response, and (4) degree of renal impairment (Central Illustration). Of note, this list is not exhaustive and other risk factors (ie, frailty, comorbidities, and etiology of decompensation) should also be considered when evaluating individual patient risk. In the near future, the use of machine learning algorithms, which can process a virtually unlimited number of predictive factors, may help clinicians identify optimal candidates for

Table 4. Potential objective criteria to identify patients with ADHF and at high risk for residual congestion and worse outcomes.

Category	Marker	Suggested criteria
Previous clinical course	Hospitalized for ADHF in the past 6 mo	
	Two or more previous hospitalizations for ADHF in the past 12 mo	
	Hospitalized for ADHF in the past 12 mo with severe congestion, diuretic resistance, or severe cardiorenal syndrome	
Severity of congestion	Central venous pressure	≥16 mm Hg obtained using catheter measurement
	BNP/NT-proBNP	BNP > 500 pg/mL or NT-proBNP > 3000 pg/mL
	Troponin elevation[a]	hs-TnT >40 ng/L
	Severe hemodilution	Hemoglobin <11 g/L[b] ≥30% expansion in blood volume or plasma volume[c] ≥24% reduction in red blood cell volume[c]
	Cardiorenal anemia syndrome	Serum creatinine of >1.5 mg/dL or eGFR of <60 mL/min and hemoglobin of <13 g/L in men or <12 g/L in women on admission or during hospitalization[b]
Diuretic response	Spot urine sodium	<50 mmol/L 2 h after an appropriate dose of intravenous furosemide[d]
	Average urine output	<600 mL over 6 h after an appropriate dose of intravenous furosemide[d]
Degree of renal impairment	Blood urea nitrogen	>40 mg/dL on admission or during hospitalization
	Acute kidney injury on admission	≥2× increase in serum creatinine level on admission compared with that at baseline[e]
	High-risk worsening renal function	≥1.5× increase in serum creatinine levels on admission compared with baseline values[e] and absolute increase of >0.3 mg/dL in serum creatinine level within 5 d of admission
	Severe renal impairment on admission	Serum creatinine of >2 mg/dL or eGFR of <30 mL/min

ADHF, acute decompensated heart failure; BNP, B-type natriuretic peptide; GFR, glomerular filtration rate; NT-proBNP, *N*-terminal prohormone B-type natriuretic peptide.

[a] Without evidence of acute coronary syndrome. [b] Without evidence of bleeding. [c] Measured using Daxor BVA-100 or equivalent. Criteria defined per manufacturer guidance and Feldschuh et al.[128] [d] Defined as ≥2× the oral daily loop diuretic dose at home or 40 to 80 mg of intravenous furosemide or equivalent. [e] Defined as lowest value within the past 12 mo.

interventional therapies. Indeed, there is growing evidence supporting potential future application of machine learning in heart failure patient phenotyping,[120,121] short-term and long-term risk prediction,[122–124] and patient selection for device therapies.[125,126] That said, currently, machine learning algorithms operate as black boxes providing unexplainable output and lack prospective validation that limits their uptake in the clinical setting.[127]

We have also proposed potential inclusion criteria and specific threshold values that could be used to guide the development of future trials (Table 4).[128] These considerations are essential as we approach a tipping point in the development of interventional therapies for ADHF beyond the early feasibility stage.[11,12] It should also be mentioned that although residual congestion and diuretic resistance have been associated with worst outcomes, the effect of more significant decongestion on the modification of hard outcomes remains uncertain. Future studies will help define the degree of residual risk in these high-risk patients despite achieving complete in-hospital decongestion and, thus, inform on the potential role of device-based strategies in modifying outcomes in ADHF.

Peer review statement

Guest Editor Philippe Généreux had no involvement in the peer review of this article and had no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to Associate Editor Andrew M. Goldsweig.

Declaration of competing interest

Gabriel Georges reports equity in Puzzle Medical Devices Inc. Marat Fudim is supported by the American Heart Association and Doris Duke and is a consultant for Abbott, Ajax, Broadview, Shifamed, and Summacor. Daniel Burkhoff has received grant support from Abiomed, Ancora, Axon, and Edwards Lifesciences and has consulted for Aquapass, Axon Therapeutics, BioMind, Corvia Medical, Impulse Dynamics, Orchestra Biomedical, TherOx, and Zoll. Martin Leon reports institutional clinical research support from Abbott, Boston Scientific, Edwards Lifesciences, Abiomed, and Medtronic; Philippe Généreux is a consultant for Abbott Vascular, Abiomed, BioTrace Medical, Boston Scientific, CARANX Medical, Cardiovascular System Inc, Edwards Lifesciences, GE Healthcare, iRhythm Technologies, Medtronic, Opsens, Pi-Cardia, Puzzle Medical, Saranas, Shockwave, Soundbite Medical Inc, Teleflex, and 4C Medical; receives advisor and speaker fees from Abbott Vascular, Abiomed, BioTrace Medical, Edwards LifeSciences: receives speaker fees from Shockwave, Edwards LifeSciences; is a proctor for Edwards Lifesciences; is a principal investigator for EARLY-TAVR trial, PROGRESS trial, ECLIPSE trial, and Feasibility study for 4C Medical; and holds equity in Pi-Cardia, Puzzle Medical, Saranas, and Soundbite Medical Inc.

Funding sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethics statement and patient consent

This manuscript does not report on patient or patient data, so an ethical publication statement is not required.

References

1. Greene SJ, Bauersachs J, Brugts JJ, et al. Worsening heart failure: nomenclature, epidemiology, and future directions: JACC review topic of the week. *J Am Coll Cardiol*. 2023;81(4):413–424. https://doi.org/10.1016/j.jacc.2022.11.023
2. Sacks CA, Jarcho JA, Curfman GD. Paradigm shifts in heart-failure therapy—a timeline. *N Engl J Med*. 2014;371(11):989–991. https://doi.org/10.1056/nejmp1410241
3. Papazian L, Forel J-M, Gacouin A, Penot-Ragon C, et al. Diuretic strategies in patients with acute decompensated heart failure. *N Engl J Med*. 2011;365:687–696.
4. Massie BM, O'Connor CM, Metra M, et al. Rolofylline, an adenosine A 1—receptor antagonist, in acute heart failure. *N Engl J Med*. 2010;363(15):1419–1428. https://doi.org/10.1056/nejmoa0912613
5. O'Connor CM, Starling RC, Hernandez AF, et al. Effect of nesiritide in patients with acute decompensated heart failure. *N Engl J Med*. 2011;365(1):32–43. https://doi.org/10.1056/nejmoa1100171
6. Bart BA, Goldsmith SR, Lee KL, et al. Ultrafiltration in decompensated heart failure with cardiorenal syndrome. *N Engl J Med*. 2012;367(24):2296–2304. https://doi.org/10.1056/NEJMoa1210357

7. Chen HH, Anstrom KJ, Givertz MM, et al. Low-dose dopamine or low-dose nesiritide in acute heart failure with renal dysfunction: The ROSE acute heart failure randomized trial. *JAMA*. 2013;310(23):2533–2543. https://doi.org/10.1001/jama.2013.282190
8. Packer M, O'Connor C, McMurray JJV, et al. Effect of ularitide on cardiovascular mortality in acute heart failure. *N Engl J Med*. 2017;376(20):1956–1964. https://doi.org/10.1056/nejmoa1601895
9. Lee DS, Straus SE, Farkouh ME, et al. Trial of an intervention to improve acute heart failure outcomes. *N Engl J Med*. 2023;388(1):22–32. https://doi.org/10.1056/nejmoa2211680
10. Guzik M, Urban S, Iwanek G, Biegus J, Ponikowski P, Zymliński R. Novel therapeutic devices in heart failure. *J Clin Med*. 2022;11(15):4303. https://doi.org/10.3390/jcm11154303
11. Rosenblum H, Kapur NK, Abraham WT, et al. Conceptual considerations for device-based therapy in acute decompensated heart failure: DRI2P2S. *Circ Heart Fail*. 2020;13(4), e006731. https://doi.org/10.1161/CIRCHEARTFAILURE.119.006731
12. Tang R, Chang Y, Song J. Advances in novel devices for the treatment of heart failure. *Heart Fail Rev*. 2023;28(2):331–345. https://doi.org/10.1007/s10741-022-10293-z
13. Verbrugge FH. Editor's Choice—diuretic resistance in acute heart failure. *Eur Heart J Acute Cardiovasc Care*. 2018;7(4):379–389. https://doi.org/10.1177/2048872618768488
14. Mullens W, Damman K, Harjola VP, et al. The use of diuretics in heart failure with congestion—a position statement from the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail*. 2019;21(2):137–155. https://doi.org/10.1002/ejhf.1369
15. Salah K, Kok WE, Eurlings LW, et al. Competing risk of cardiac status and renal function during hospitalization for acute decompensated heart failure. *J Am Coll Cardiol HF*. 2015;3(10):751–761. https://doi.org/10.1016/j.jchf.2015.05.009
16. Bart BA, Goldsmith SR, Lee KL, et al. Cardiorenal rescue study in acute decompensated heart failure: rationale and design of CARRESS-HF, for the Heart Failure Clinical Research Network. *J Card Fail*. 2012;18(3):176–182. https://doi.org/10.1016/j.cardfail.2011.12.009
17. Mullens W, Dauw J, Martens P, et al. Acetazolamide in acute decompensated heart failure with volume overload. *N Engl J Med*. 2022;387(13):1185–1195. https://doi.org/10.1056/NEJMoa2203094
18. Pocock SJ, Wang D, Pfeffer MA, et al. Predictors of mortality and morbidity in patients with chronic heart failure. *Eur Heart J*. 2006;27(1):65–75. https://doi.org/10.1093/eurheartj/ehi555
19. Setoguchi S, Stevenson W, Schneeweiss S. Repeated hospitalizations predict mortality in the community population with heart failure. *Am Heart J*. 2007;154(2):260–266. https://doi.org/10.1016/j.ahj.2007.01.041
20. Solomon SD, Dobson J, Pocock S, et al. Influence of Nonfatal hospitalization for heart failure heart failure. *Circulation*. 2007;116(3):1482–1487. https://doi.org/10.1161/CIRCULATIONAHA.107.696906
21. Butler J, Yang M, Manzi MA, et al. Clinical course of patients with worsening heart failure with reduced ejection fraction. *J Am Coll Cardiol*. 2019;73(8):935–944. https://doi.org/10.1016/j.jacc.2018.11.049
22. Madelaire C, Gustafsson F, Stevenson LW, et al. One-year mortality after intensification of outpatient diuretic therapy. *J Am Heart Assoc*. 2020;9(14), e016010. https://doi.org/10.1161/JAHA.119.016010
23. Shah A, Mentz RJ, Sun JL, et al. Emergency department visits versus hospital readmissions among patients hospitalized for heart failure. *J Card Fail*. 2022;28(6):916–923. https://doi.org/10.1016/j.cardfail.2021.11.025
24. Docherty KF, Jhund PS, Anand I, et al. Effect of dapagliflozin on outpatient worsening of patients with heart failure and reduced ejection fraction: a prespecified analysis of DAPA-HF. *Circulation*. 2020;142(17):1623–1632. https://doi.org/10.1161/CIRCULATIONAHA.120.047480
25. Okumura N, Jhund PS, Gong J, et al. Heart failure importance of clinical worsening of heart failure treated in the outpatient setting evidence from the prospective comparison of ARNI with ACEI to determine impact on global mortality and morbidity. *Circulation*. 2016:2254–2262. https://doi.org/10.1161/CIRCULATIONAHA.115.020729
26. Vaduganathan M, Cunningham JW, Claggett BL, et al. Worsening heart failure episodes outside a hospital setting in heart failure with preserved ejection fraction. *J Am Coll Cardiol HF*. 2021;9(5):374–382. https://doi.org/10.1016/j.jchf.2021.01.014
27. Thibodeau JT, Drazner MH. The role of the clinical examination in patients with heart failure. *J Am Coll Cardiol HF*. 2018;6(7):543–551. https://doi.org/10.1016/j.jchf.2018.04.005
28. Ambrosy AP, Pang PS, Khan S, et al. Clinical course and predictive value of congestion during hospitalization in patients admitted for worsening signs and symptoms of heart failure with reduced ejection fraction: findings from the EVEREST trial. *Eur Heart J*. 2013;34(11):835–843. https://doi.org/10.1093/eurheartj/ehs444
29. Chioncel O, Mebazaa A, Maggioni AP, et al. Acute heart failure congestion and perfusion status—impact of the clinical classification on in-hospital and long-term outcomes; insights from the ESC-EORP-HFA Heart Failure Long-Term Registry. *Eur J Heart Fail*. 2019;21(11):1338–1352. https://doi.org/10.1002/ejhf.1492
30. Binanay C, Califf RM, Hasselblad V, et al. ESCAPE Investigators and ESCAPE Study Coordinators. Evaluation study of congestive heart failure and pulmonary artery catheterization effectiveness: the ESCAPE trial. *JAMA*. 2005;294(13):1625–1633. https://doi.org/10.1001/jama.294.13.1625
31. Felker GM, Anstrom KJ, Adams KF, et al. Effect of natriuretic peptide–guided therapy on hospitalization or cardiovascular mortality in high-risk patients with heart failure and reduced ejection fraction: a randomized clinical trial. *JAMA*. 2017;318(8):713–720. https://doi.org/10.1001/jama.2017.10565
32. Stienen S, Salah K, Moons AH, et al. NT-proBNP (N-terminal pro-B-type natriuretic peptide)-guided therapy in acute decompensated heart failure PRIMA II randomized controlled trial. *Circulation*. 2018;137(16):1671–1683. https://doi.org/10.1161/CIRCULATIONAHA.117.029882
33. Cohn JN. Jugular venous pressure monitoring: a lost art? *J Card Fail*. 1997;3(2):71–73. https://doi.org/10.1016/s1071-9164(97)90037-3
34. Drazner MH, Hellkamp AS, Leier CV, et al. Value of clinician assessment of hemodynamics in advanced heart failure: the ESCAPE trial. *Circ Heart Fail*. 2008;1(3):170–177. https://doi.org/10.1161/CIRCHEARTFAILURE.108.769778
35. Chernomordik F, Berkovitch A, Schwammenthal E, et al. Short- and long-term prognostic implications of jugular venous distension in patients hospitalized with acute heart failure. *Am J Cardiol*. 2016;118(2):226–231. https://doi.org/10.1016/j.amjcard.2016.04.035
36. Drazner MH, Rame JE, Stevenson LW, Dries DL. Prognostic importance of elevated jugular venous pressure and a third heart sound in patients with heart failure. *N Engl J Med*. 2001;345(8):574–581. https://doi.org/10.1056/NEJMoa010641
37. Mullens W, Abrahams Z, Francis GS, et al. Importance of venous congestion for worsening of renal function in advanced decompensated heart failure. *J Am Coll Cardiol*. 2009;53(7):589–596. https://doi.org/10.1016/j.jacc.2008.05.068
38. Damman K, van Deursen VM, Navis G, Voors AA, van Veldhuisen DJ, Hillege HL. Increased central venous pressure is associated with impaired renal function and mortality in a broad spectrum of patients with cardiovascular disease. *J Am Coll Cardiol*. 2009;53(7):582–588. https://doi.org/10.1016/j.jacc.2008.08.080
39. Hansen D, Mullens W, Cops J, Haesen S, de Moor B. Current animal models for the study of congestion in heart failure: an overview. Heart Fail Rev. Published online 2019;24(3):387-397. https://doi.org/10.1007/s10741-018-9762-4
40. Gnanaraj FJ, von Haehling S, Anker SD, Raj DS, Radhakrishnan J. The relevance of congestion in the cardio-renal syndrome. *Kidney Int*. 2013;83(3):384–391. https://doi.org/10.1038/ki.2012.406
41. Shirakabe A, Hata N, Kobayashi N, et al. Worsening renal failure in patients with acute heart failure: the importance of cardiac biomarkers. *ESC Heart Fail*. 2019;6(2):416–427. https://doi.org/10.1002/ehf2.12414
42. Damman K, Testani JM. The kidney in heart failure: an update. *Eur Heart J*. 2015;36(23):1437–1444. https://doi.org/10.1093/eurheartj/ehv010
43. Ge H, Liang Y, Fang Y, et al. Predictors of acute kidney injury in patients with acute decompensated heart failure in emergency departments in China. *J Int Med Res*. 2021;49(9), 3000605211016208. https://doi.org/10.1177/03000605211016208
44. Lassus JPE, Nieminen MS, Peuhkurinen K, et al. Markers of renal function and acute kidney injury in acute heart failure: definitions and impact on outcomes of the cardiorenal syndrome. *Eur Heart J*. 2010;31(22):2791–2798. https://doi.org/10.1093/eurheartj/ehq293
45. Núñez J, Garcia S, Núñez E, et al. Early serum creatinine changes and outcomes in patients admitted for acute heart failure: the cardio-renal syndrome revisited. *Eur Heart J Acute Cardiovasc Care*. 2017;6(5):430–440. https://doi.org/10.1177/2048872614540094
46. Lee TH, Fan PC, Chen JJ, et al. A validation study comparing existing prediction models of acute kidney injury in patients with acute heart failure. *Sci Rep*. 2021;11(1), 11213. https://doi.org/10.1038/s41598-021-90756-9
47. Damman K, Valente MAE, Voors AA, O'Connor CM, van Veldhuisen DJ, Hillege HL. Renal impairment, worsening renal function, and outcome in patients with heart failure: an updated meta-analysis. *Eur Heart J*. 2014;35(7):455–469. https://doi.org/10.1093/eurheartj/eht386
48. Shirakabe A, Hata N, Kobayashi N, et al. Worsening renal function definition is insufficient for evaluating acute renal failure in acute heart failure. *ESC Heart Fail*. 2018;5(3):322–331. https://doi.org/10.1002/ehf2.12264
49. Taylor CJ, Lay-Flurrie SL, Ordóñez-Mena JM, et al. Natriuretic peptide level at heart failure diagnosis and risk of hospitalisation and death in England 2004–2018. *Heart*. 2022;108(7):543–549. https://doi.org/10.1136/heartjnl-2021-319196
50. Pascual-figal DA, Manzano-Ferna S, Boronat M, et al. Soluble ST2, high-sensitivity troponin T- and N-terminal pro-B-type natriuretic peptide : complementary role for risk stratification in acutely decompensated heart failure. *Eur J Heart Fail*. 2011;13(7):718–725. https://doi.org/10.1093/eurjhf/hfr047
51. Lu X, Xin Y, Zhu J, et al. Diuretic resistance prediction and risk factor analysis of patients with heart failure during hospitalization. *Glob Heart*. 2022;17(1):33. https://doi.org/10.5334/gh.1113
52. Testani JM, Damman K, Brisco MA, et al. A combined-biomarker approach to clinical phenotyping renal dysfunction in heart failure. *J Card Fail*. 2014;20(12):912–919. https://doi.org/10.1016/j.cardfail.2014.08.008
53. Feola M, Testa M, Ferreri C, et al. Role of response-to-diuretic in predicting prognosis in discharged heart failure patients after an acute decompensation. *Arch Med Res*. 2018;49(3):198–204. https://doi.org/10.1016/j.arcmed.2018.08.007
54. Greene SJ, Butler J, Fonarow GC, et al. Pre-discharge and early post-discharge troponin elevation among patients hospitalized for heart failure with reduced ejection fraction : findings from the ASTRONAUT trial. *Eur J Heart Fail*. 2018;20(2):281–291.
55. Verbrugge FH, Steels P, Grieten L, Nijst P, Tang WHW, Mullens W. Hyponatremia in acute decompensated heart failure. *J Am Coll Cardiol*. 2015;65(5):480–492. https://doi.org/10.1016/j.jacc.2014.12.010
56. Aronson D, Darawsha W, Promyslovsky M, et al. Hyponatraemia predicts the acute (type 1) cardio-renal syndrome. *Eur J Heart Fail*. 2014;16(1):49–55. https://doi.org/10.1093/eurjhf/hft123

57. McCallum W, Tighiouart H, Testani JM, et al. Acute kidney function declines in the context of decongestion in acute decompensated heart failure. *J Am Coll Cardiol HF*. 2020;8(7):537–547. https://doi.org/10.1016/j.jchf.2020.03.009
58. Caughey MC, Avery CL, Ni H, et al. Outcomes of patients with anemia and acute decompensated heart failure with preserved versus reduced ejection fraction (from the ARIC Study Community Surveillance). *Am J Cardiol*. 2014;114(12):1850–1854. https://doi.org/10.1016/j.amjcard.2014.09.024
59. Young JB, Abraham WT, Albert NM, et al. Relation of low hemoglobin and anemia to morbidity and mortality in patients hospitalized with heart failure (insight from the OPTIMIZE-HF registry). *Am J Card Imaging*. 2008;101(2):223–230. https://doi.org/10.1016/j.amjcard.2007.07.067
60. Felker GM, Gattis WA, Leimberger JD, et al. Usefulness of anemia as a predictor of death and rehospitalization in patients with decompensated heart failure. *Am J Cardiol*. 2003;92(5):625–628. https://doi.org/10.1016/S0002-9149(03)00740-9
61. Llauger L, Jacob J, Herrero-Puente P, et al. The CRAS-EAHFE study: characteristics and prognosis of acute heart failure episodes with cardiorenal-anaemia syndrome at the emergency department. *Eur Heart J Acute Cardiovasc Care*. 2020;9(5):406–418. https://doi.org/10.1177/2048872620921602
62. Al-Jarallah M, Rajan R, Al-Zakwani I, et al. Incidence and impact of cardiorenal anaemia syndrome on all-cause mortality in acute heart failure patients stratified by left ventricular ejection fraction in the Middle East. *ESC Heart Fail*. 2019;6(1):103–110. https://doi.org/10.1002/ehf2.12351
63. van den Berge JC, Constantinescu AA, van Domburg RT, Brankovic M, Deckers JW, Akkerhuis KM. Renal function and anemia in relation to short- and long-term prognosis of patients with acute heart failure in the period 1985-2008: a clinical cohort study. *PLoS One*. 2018;13(8), e0201714.
64. Kajimoto K, Sato N, Takano T. Association of anemia and renal dysfunction with in-hospital mortality among patients hospitalized for acute heart failure syndromes with preserved or reduced ejection fraction. *Eur Heart J Acute Cardiovasc Care*. 2016:1–4. https://doi.org/10.1177/2048872615593387
65. Testani JM, Brisco MA, Chen J, McCauley BD, Parikh CR, Tang WHW. Timing of hemoconcentration during treatment of acute decompensated heart failure and subsequent survival: Importance of sustained decongestion. *J Am Coll Cardiol*. 2013;62(6):516–524. https://doi.org/10.1016/j.jacc.2013.05.027
66. Silverberg D, Wexler D, Blum M, Wollman Y, Iaina A. The cardio-renal anaemia syndrome: does it exist? *Nephrol Dial Transplant*. 2003;18(Suppl 8):viii7–vii12. https://doi.org/10.1093/ndt/gfg1084
67. Scrutinio D, Passantino A, Santoro D, Catanzaro R. The cardiorenal anaemia syndrome in systolic heart failure: prevalence, clinical correlates, and long-term survival. *Eur J Heart Fail*. 2011;13(1):61–67. https://doi.org/10.1093/eurjhf/hfq167
68. Lu KJ, Kearney LG, Hare DL, et al. Cardiorenal anemia syndrome as a prognosticator for death in heart failure. *Am J Cardiol*. 2013;111(8):1187–1191. https://doi.org/10.1016/j.amjcard.2012.12.049
69. Miller WL. Fluid volume overload and congestion in heart failure: time to reconsider pathophysiology and how volume is assessed. *Circ Heart Fail*. 2016;9(8):e002922. https://doi.org/10.1161/CIRCHEARTFAILURE.115.002922
70. Strobeck JE, Feldschuh J, Miller WL. Heart failure outcomes with volume-guided management. *J Am Coll Cardiol HF*. 2018;6(11):940–948. https://doi.org/10.1016/j.jchf.2018.06.017
71. Jacob J, Bart B, Vardeny O, et al. Evaluation of blood volume analysis—guided management of decompensated heart failure. *NCT04855097*. Updated July 27, 2022. Accessed April 7, 2023. https://clinicaltrials.gov/ct2/show/NCT04855097.
72. Kociol RD, Pang PS, Gheorghiade M, Fonarow GC, Connor CMO, Felker GM. Troponin elevation in heart failure: prevalence, mechanisms, and clinical implications. *J Am Coll Cardiol*. 2010;56(14):1071–1078. https://doi.org/10.1016/j.jacc.2010.06.016
73. Januzzi JL, Filippatos G, Nieminen M, Gheorghiade M. Troponin elevation in patients with heart failure: on behalf of the third Universal Definition of Myocardial Infarction Global Task Force. *Eur J Heart Fail*. 2012;33(18):2265–2271. https://doi.org/10.1093/eurheartj/ehs191
74. Felker GM, Hasselblad V, Tang WHW, et al. Troponin I in acute decompensated heart failure : insights from the ASCEND-HF study. *Eur J Heart Fail*. 2012;14(11):1257–1264. https://doi.org/10.1093/eurjhf/hfs110
75. Felker GM, Mentz RJ, Teerlink JR, et al. Serial high sensitivity cardiac troponin T measurement in acute heart failure: insights from the RELAX-AHF study. *Eur J Heart Fail*. 2015;17(12):262–270.
76. Frank Peacock WIV, De Marco T, Fonarow GC, et al. ADHERE Investigators. Cardiac troponin and outcome in acute heart failure. *N Engl J Med*. 2008;358(20):2117–2126.
77. Cox ZL, Testani JM. Loop diuretic resistance complicating acute heart failure. *Heart Fail Rev*. 2020;25(1):133–145. https://doi.org/10.1007/s10741-019-09851-9
78. Felker GM, Ellison DH, Mullens W, Cox ZL, Testani JM. Diuretic therapy for patients with heart failure: JACC state-of-the-art review. *J Am Coll Cardiol*. 2020;75(10):1178–1195. https://doi.org/10.1016/j.jacc.2019.12.059
79. ter Maaten JM, Valente MAE, Damman K, Hillege HL, Navis G, Voors AA. Diuretic response in acute heart failure—pathophysiology, evaluation, and therapy. *Nat Rev Cardiol*. 2015;12(3):184–192. https://doi.org/10.1038/nrcardio.2014.215
80. Tersalvi G, Dauw J, Gasperetti A, et al. The value of urinary sodium assessment in acute heart failure. *Eur Heart J Acute Cardiovasc Care*. 2021;10(2):216–223. https://doi.org/10.1093/ehjacc/zuaa006
81. Testani JM, Hanberg JS, Cheng S, et al. Rapid and highly accurate prediction of poor loop diuretic natriuretic response in patients with heart failure. *Circ Heart Fail*. 2016;9(1):e002370. https://doi.org/10.1161/CIRCHEARTFAILURE.115.002370
82. Rao VS, Ivey-Miranda JB, Cox ZL, et al. Natriuretic Equation to Predict Loop Diuretic Response in Patients With Heart Failure. *J Am Coll Cardiol*. 2021;77(6):695–708. https://doi.org/10.1016/j.jacc.2020.12.022
83. Miñana G, Llàcer P, Sanchis I, et al. Early spot urinary sodium and diuretic efficiency in acute heart failure and concomitant renal dysfunction. *Cardiorenal Med*. 2020;10(5):362–372. https://doi.org/10.1159/000508178
84. Biegus J, Zymliński R, Testani J, et al. Renal profiling based on estimated glomerular filtration rate and spot urine sodium identifies high-risk acute heart failure patients. *Eur J Heart Fail*. 2021;23(5):729–739. https://doi.org/10.1002/ejhf.2053
85. Brinkley Jr DM, Burpee LJ, Chaudhry S-P, et al. Spot urine sodium as triage for effective diuretic infusion in an ambulatory heart failure unit. *J Card Fail*. 2018;24(6):349–354. https://doi.org/10.1016/j.cardfail.2018.01.009
86. Doering A, Jenkins CA, Storrow AB, et al. Markers of diuretic resistance in emergency department patients with acute heart failure. *Int J Emerg Med*. 2017;10(1):17. https://doi.org/10.1186/s12245-017-0143-x
87. Luk A, Groarke JD, Desai AS, et al. First spot urine sodium after initial diuretic identifies patients at high risk for adverse outcome after heart failure hospitalization. *Am Heart J*. 2018;203:95–100. https://doi.org/10.1016/j.ahj.2018.01.013
88. Biegus J, Zymliński R, Sokolski M, et al. Serial assessment of spot urine sodium predicts effectiveness of decongestion and outcome in patients with acute heart failure. *Eur J Heart Fail*. 2019;21(5):624–633. https://doi.org/10.1002/ejhf.1428
89. Cunningham JW, Sun JL, McCausland FR, et al. Lower urine sodium predicts longer length of stay in acute heart failure patients: insights from the ROSE AHF trial. *Clin Cardiol*. 2020;43(1):43–49. https://doi.org/10.1002/clc.23286
90. Singh D, Shrestha K, Testani JM, et al. Insufficient natriuretic response to continuous intravenous furosemide is associated with poor long-term outcomes in acute decompensated heart failure. *J Card Fail*. 2014;20(6):392–399. https://doi.org/10.1016/j.cardfail.2014.03.006
91. Martens P, Chen HH, Verbrugge FH, Testani JT, Mullens W, Tang WHW. Assessing intrinsic renal sodium avidity in acute heart failure: implications in predicting and guiding decongestion. *ESC Heart Fail*. 2022;24(10):1978–1987. https://doi.org/10.1002/ejhf.2662
92. Galluzzo A, Frea S, Boretto P, et al. Spot urinary sodium in acute decompensation of advanced heart failure and dilutional hyponatremia: insights from DRAIN trial. *Clin Res Cardiol*. 2020;109(10):1251–1259. https://doi.org/10.1007/s00392-020-01617-w
93. Collins SP, Jenkins CA, Baughman A, et al. Early urine electrolyte patterns in patients with acute heart failure. *ESC Heart Fail*. 2019;6(1):80–88. https://doi.org/10.1002/ehf2.12368
94. Honda S, Nagai T, Nishimura K, et al. Long-term prognostic significance of urinary sodium concentration in patients with acute heart failure. *Int J Cardiol*. 2018;254:189–194. https://doi.org/10.1016/j.ijcard.2017.08.053
95. Ferreira JP, Girerd N, Medeiros PB, et al. Spot urine sodium excretion as prognostic marker in acutely decompensated heart failure: the spironolactone effect. *Clin Res Cardiol*. 2016;105(6):489–507. https://doi.org/10.1007/s00392-015-0945-x
96. ter Maaten JM, Beldhuis IE, van der Meer P, et al. Natriuresis-guided therapy in acute heart failure: rationale and design of the Pragmatic Urinary Sodium-based treatment algoritHm in Acute Heart Failure (PUSH-AHF) trial. *Eur J Heart Fail*. 2022;24(2):385–392. https://doi.org/10.1002/ejhf.2385
97. Dauw J, Lelonek M, Zegri-Reiriz I, et al. Rationale and design of the efficacy of a standardized diuretic protocol in acute heart failure study. *ESC Heart Fail*. 2021;8(6):4685–4692. https://doi.org/10.1002/ehf2.13666
98. Maaten JM, Dunning AM, Valente MAE, et al. Diuretic response in acute heart failure—an analysis from ASCEND-HF. *Am Heart J*. 2015;170(2):313–321.e4. https://doi.org/10.1016/j.ahj.2015.05.003
99. Kuroda S, Damman K, ter Maaten JM, et al. Very early diuretic response after admission for acute heart failure. *J Card Fail*. 2019;25(1):12–19. https://doi.org/10.1016/j.cardfail.2018.09.004
100. Aronson D, Burger AJ. Diuretic response: clinical and hemodynamic predictors and relation to clinical outcome. *J Card Fail*. 2016;22(3):193–200. https://doi.org/10.1016/j.cardfail.2015.07.006
101. Buckley LF, Carter DM, Matta L, et al. Intravenous diuretic therapy for the management of heart failure and volume overload in a multidisciplinary outpatient unit. *J Am Coll Cardiol HF*. 2016;4(1):1–8. https://doi.org/10.1016/j.jchf.2015.06.017
102. Valente MAE, Voors AA, Damman K, et al. Diuretic response in acute heart failure: clinical characteristics and prognostic significance. *Eur Heart J*. 2014;35(19):1284–1293. https://doi.org/10.1093/eurheartj/ehu065
103. Voors AA, Davison BA, Teerlink JR, et al. Diuretic response in patients with acute decompensated heart failure: characteristics and clinical outcome—an analysis from RELAX-AHF. *Eur J Heart Fail*. 2014;16(11):1230–1240. https://doi.org/10.1002/ejhf.170
104. McDonagh TA, Metra M, Adamo M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2021;42(36):3599–3726. https://doi.org/10.1093/eurheartj/ehab368
105. ter Maaten JM, Valente MAE, Metra M, et al. A combined clinical and biomarker approach to predict diuretic response in acute heart failure. *Clin Res Cardiol*. 2016;105(2):145–153. https://doi.org/10.1007/s00392-015-0896-2
106. Chávez-Íñiguez JS, Ivey-Miranda JB, de la Vega-Mendez FM, Borges-Vela JA. How to interpret serum creatinine increases during decongestion. *Front Cardiovasc Med*. 2023;9:1098553. https://www.frontiersin.org/articles/10.3389/fcvm.2022.1098553

107. Emmens JE, ter Maaten JM, Matsue Y, et al. Worsening renal function in acute heart failure in the context of diuretic response. *Eur J Heart Fail*. 2022;24(2):365–374. https://doi.org/10.1002/ejhf.2384
108. Sheerin NJ, Newton PJ, Macdonald PS, et al. Worsening renal function in heart failure: the need for a consensus definition. *Int J Cardiol*. 2014;174(3):484–491. https://doi.org/10.1016/j.ijcard.2014.04.162
109. Berra G, Garin N, Stirnemann J, et al. Outcome in acute heart failure: prognostic value of acute kidney injury and worsening renal function. *J Card Fail*. 2015;21(5):382–390. https://doi.org/10.1016/j.cardfail.2014.12.015
110. Patel RB, Fonarow GC, Greene SJ, et al. Kidney function and outcomes in patients hospitalized with heart failure. *J Am Coll Cardiol*. 2021;78(4):330–343. https://doi.org/10.1016/j.jacc.2021.05.002
111. Royston P, Altman DG. Risk stratification for in-hospital mortality in acutely decompensated heart failure. *JAMA*. 2005;293(20):2467–2468. https://doi.org/10.1001/jama.293.20.2468-a
112. Filippatos G, Rossi J, Lloyd-Jones DM, et al. Prognostic value of blood urea nitrogen in patients hospitalized with worsening heart failure: insights from the acute and chronic therapeutic impact of a vasopressin antagonist in chronic heart failure (ACTIV in CHF) study. *J Card Fail*. 2007;13(5):360–364. https://doi.org/10.1016/j.cardfail.2007.02.005
113. Cleland JG, Chiswell K, Teerlink JR, et al. Predictors of postdischarge outcomes from information acquired shortly after admission for acute heart failure: A report from the placebo-controlled randomized study of the selective a1 adenosine receptor antagonist rolofylline for patients hospitalized with Acute Decompensated Heart Failure and Volume Overload to Assess Treatment Effect on Congestion and Renal Function (PROTECT) Study. *Circ Heart Fail*. 2014;7(1):76–87. https://doi.org/10.1161/CIRCHEARTFAILURE.113.000284
114. Trullàs JC, Morales-Rull JL, Casado J, et al. Combining loop with thiazide diuretics for decompensated heart failure: the CLOROTIC trial. *Eur Heart J*. 2023;44(5):411–421. https://doi.org/10.1093/eurheartj/ehac689
115. Voors AA, Angermann CE, Teerlink JR, et al. The SGLT2 inhibitor empagliflozin in patients hospitalized for acute heart failure: a multinational randomized trial. *Nat Med*. 2022;28(3):568–574. https://doi.org/10.1038/s41591-021-01659-1
116. Damman K, Beusekamp JC, Boorsma EM, et al. Randomized, double-blind, placebo-controlled, multicentre pilot study on the effects of empagliflozin on clinical outcomes in patients with acute decompensated heart failure (EMPA-RESPONSE-AHF). *Eur J Heart Fail*. 2020;22(4):713–722. https://doi.org/10.1002/ejhf.1713
117. Butler J, Anstrom KJ, Felker GM, et al. Efficacy and safety of spironolactone in acute heart failure: the ATHENA-HF randomized clinical trial. *JAMA Cardiol*. 2017;2(9):950–958. https://doi.org/10.1001/jamacardio.2017.2198
118. Costanzo MR, Guglin ME, Saltzberg MT, et al. Ultrafiltration versus intravenous diuretics for patients hospitalized for acute decompensated heart failure. *J Am Coll Cardiol*. 2007;49(6):675–683. https://doi.org/10.1016/j.jacc.2006.07.073
119. Gheorghiade M, Konstam MA, Burnett JC, et al. Short-term clinical effects of tolvaptan, an oral vasopressin antagonist, in patients hospitalized for heart failure: the EVEREST clinical status trials. *JAMA*. 2007;297(12):1332–1343. https://doi.org/10.1001/jama.297.12.1332
120. Kyodo A, Kanaoka K, Keshi A, et al. Heart failure with preserved ejection fraction phenogroup classification using machine learning. *ESC Heart Fail*. 2023;10(3):2019–2030. https://doi.org/10.1002/ehf2.14368
121. Gevaert AB, Tibebu S, Mamas MA, et al. Clinical phenogroups are more effective than left ventricular ejection fraction categories in stratifying heart failure outcomes. *ESC Heart Fail*. 2021;8(4):2741–2754. https://doi.org/10.1002/ehf2.13344
122. Kwon JM, Kim KH, Jeon KH, et al. Artificial intelligence algorithm for predicting mortality of patients with acute heart failure. *PLoS One*. 2019;14(7), e0219302. https://doi.org/10.1371/journal.pone.0219302
123. Chen Z, Li T, Guo S, Zeng D, Wang K. Machine learning-based in-hospital mortality risk prediction tool for intensive care unit patients with heart failure. *Front Cardiovasc Med*. 2023;10, 1119699. https://doi.org/10.3389/fcvm.2023.1119699
124. Boehmer JP, Hariharan R, Devecchi FG, et al. A multisensor algorithm predicts heart failure events in patients with implanted devices: results From the MultiSENSE study. *J Am Coll Cardiol HF*. 2017;5(3):216–225. https://doi.org/10.1016/j.jchf.2016.12.011
125. Cikes M, Sanchez-Martinez S, Claggett B, et al. Machine learning-based phenogrouping in heart failure to identify responders to cardiac resynchronization therapy. *Eur J Heart Fail*. 2019;21(1):74–85. https://doi.org/10.1002/ejhf.1333
126. Kalscheur MM, Kipp RT, Tattersall MC, et al. Machine learning algorithm predicts cardiac resynchronization therapy outcomes: lessons from the COMPANION trial. *Circ Arrhythm Electrophysiol*. 2018;11(1), e005499. https://doi.org/10.1161/CIRCEP.117.005499
127. Averbuch T, Sullivan K, Sauer A, et al. Applications of artificial intelligence and machine learning in heart failure. *Eur Heart J*. 2022;3(2):311–322. https://doi.org/10.1093/ehjdh/ztac025
128. Feldschuh J, Katz S. The importance of correct norms in blood volume measurement. *Am J Med Sci*. 2007;334(1):41–46. https://doi.org/10.1097/MAJ.0b013e318063c707