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Comprehensive Review

Patient Selection and End Point Definitions for Decongestion Studies in Acute Decompensated Heart Failure: Part 2

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ABSTRACT

Congestion is the most common manifestation of acute decompensated heart failure (ADHF). Residual congestion despite initial medical therapy is common and is recognized to be associated with worse outcomes; however, there are currently no standardized definition regarding decongestion end point. In the second part of this 2-part review, we provide a critical appraisal of decongestion definitions previously used in ADHF studies, review alternative metrics to define severity of volume overload, and propose a more granular 4-class congestion grading scheme and decongestion end point definitions that could potentially be included in future ADHF trials and consensus definitions.

Introduction

The first part of this 2-part review on congestion in acute decompensated heart failure (ADHF) focused on defining high-risk patients regarding the evaluation and use of novel device therapies. In particular, we (1) explored patient-related risk factors for residual congestion and adverse events, (2) reviewed recent trials on ADHF and their key inclusion criteria, (3) described patient population targeted by investigational ADHF devices, and (4) proposed potential criteria to identify patients at high-risk of residual congestion in future studies. Among patients presenting with ADHF, residual congestion at discharge has been shown to be a strong predictor of mortality.[1-4] Although therapeutic strategies should aim at complete decongestion, it remains unclear how fluid status should be measured and what defines adequate/optimal decongestion.

In the second part of this review, we provide a critical appraisal of currently available definitions of decongestion and proposed novel definitions, which could potentially be included in future versions of Heart Failure Collaboratory and Academic Research Consortium (HFC-ARC) standardized definitions.[5] In particular, we (1) examine how decongestion has been defined in key trials, (2) discuss alternative metrics used to assess fluid status, (3) propose a more granular staged approach to defining congestion, and (4) define potential standardized end point definitions for use in future ADHF trials to compare safety and efficacy of decongestive strategies (Central Illustration).

Current decongestion end point definitions

Many large-scale prospective trials have evaluated the effect of therapy on decongestion parameters (eg, weight loss, urine output, and clinical congestion score)[6,7] or the influence of decongestion targets on hard outcomes[8,9]; however, only a few studies on decongestive strategies in ADHF have defined an optimal decongestion end point using specific criteria.[2,10,11] A summary of these key ADHF trials is presented in Table 1.[2,11–13]

The DOSE (Diuretic Strategies in Patients with Acute Decompensated Heart Failure) trial was the first large, prospective, randomized trial to include successful decongestion as an end point and defined decongestion as jugular venous pressure of <8 cm H_2O, with no orthopnea and with no or trace peripheral edema at 72 hours.[2] Other markers of decongestion (change in weight, net fluid loss, and change in N-terminal pro-B-type natriuretic peptide [NT-proBNP]) were also assessed at the same time point but were not incorporated in the definition. Only a minority of patients were free from congestion at 72 hours, with a trend

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Abbreviations: ADHF, acute decompensated heart failure; WRF, worsening renal function.

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

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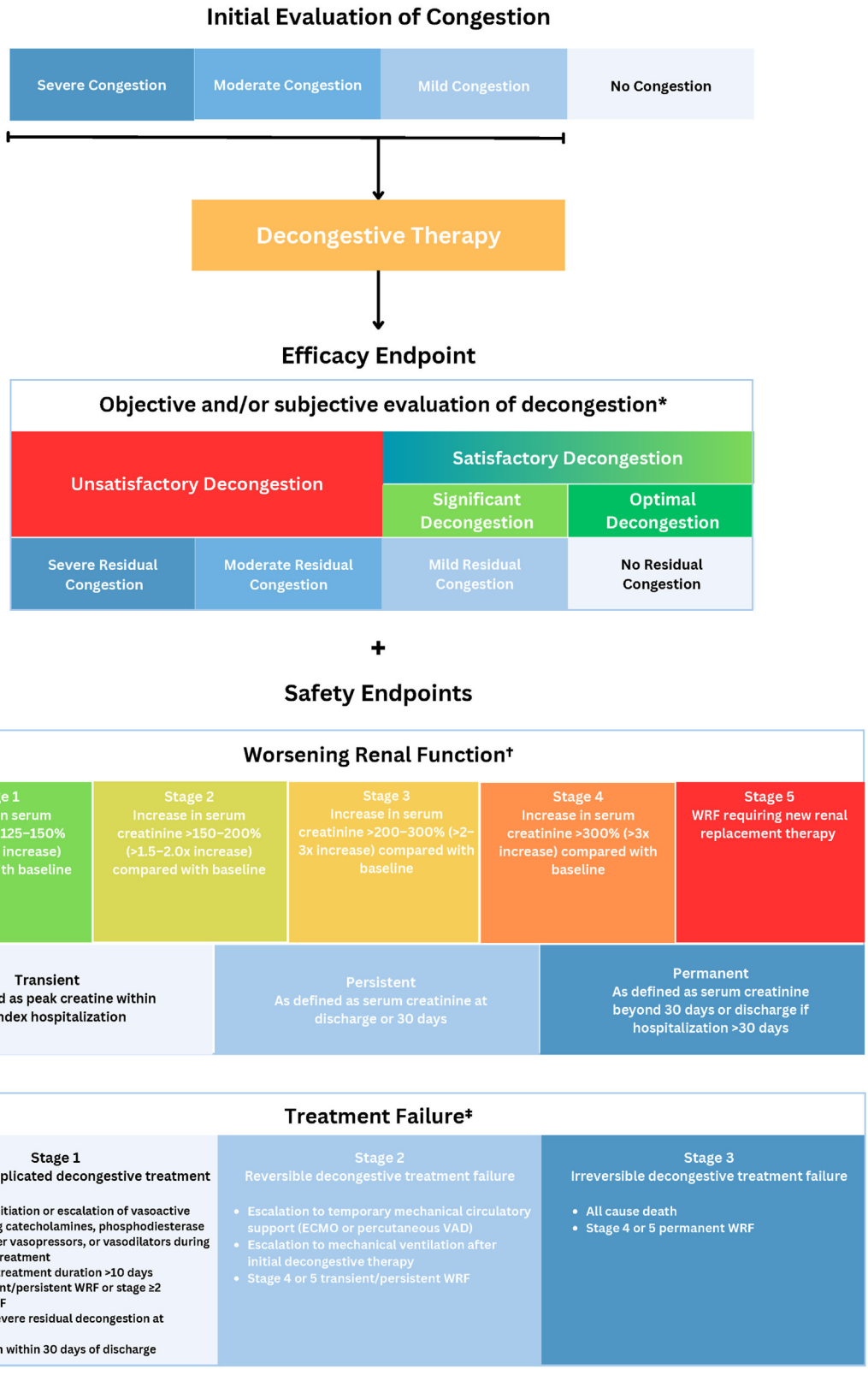

Central Illustration.

Proposed nomenclature and definitions of major end points for future decongestion trials in the context of acute decompensated heart failure: (1) novel standardized 4-class grading of congestion, (2) decongestion end points based on objective and subjective assessment, and (3) safety end points related to worsening kidney function and worsening of heart failure or treatment failure. *Refer to Table 3; †refer to Table 4; ‡refer to Table 5. ECMO, extracorporeal mechanical circulatory support; VAD, ventricular assist device; WRF, worsening renal function.

Table 1. Summary of clinical trials in acute heart failure using decongestion as an efficacy end point.

Study	Intervention	Decongestion end point	Criteria for decongestion	Assessment time	Proportion of patients meeting decongestion end point
DOSE (2011)[2]	Bolus vs continuous infusion and high-dose vs low-dose furosemide	Freedom from congestion (secondary end point)	Jugular venous pressure of <8.0 cm H_2O, with no orthopnea and no more than trace peripheral edema	72 h	11% in low-dose vs 18% in high-dose group ($P = .09$)
CARRESS-HF (2012)[12]	Ultrafiltration vs stepped pharmacologic care	Clinical decongestion (secondary end point)	Pulmonary wedge pressure <18 mm Hg (if available), jugular venous pressure <8.0 cm H_2O, or central venous pressure <8 mm Hg (if available), no orthopnea, and no more than trace peripheral edema	96 h	10% in ultrafiltration vs 9% in pharmacologic therapy ($P = .83$)
ADVOR (2022)[11]	High-dose loop diuretic and placebo vs acetazolamide	Successful decongestion (primary end point)	Absence of signs of volume overload (no more than trace edema, no pleural effusion, and no ascites) and without an indication for escalation of decongestive therapy	≤72 h	42% in acetazolamide group vs 31% in placebo group ($P < .001$)
ENACT-HF (ongoing)[13]	Standard care vs standardized diuretic protocol	Euvolemia (secondary end point)	No more than trace edema, no pleural effusion, and no ascites	2 d	Ongoing study

toward more frequent decongestion in the high-dose diuretic group (11% vs 18%; $P = .09$).

The CARRESS-HF (Ultrafiltration in Decompensated Heart Failure with Cardiorenal Syndrome) study defined successful decongestion in the same way as the DOSE trial but added criteria for invasive pressure measurements when available (pulmonary capillary wedge pressure [<18 mm Hg] and central venous pressure [<8 mm Hg]).[10] The evaluation was made 24 hours later than in the DOSE trial, at 96 hours. Decongestion rates were relatively similar to those in the DOSE trial, considering the differences between the 2 studies (eg, diuretic dose adjustment protocols).[2,12]

The ADVOR (Acetazolamide in Acute Decompensated Heart Failure with Volume Overload) trial introduced a new decongestion definition as their primary end point.[14] The ADVOR investigators abandoned jugular venous pressure <8 cm H_2O and absence of orthopnea as criteria for decongestion. Instead, they defined successful decongestion as the absence of signs of volume overload (ie, no more than trace edema, no pleural effusion, and no ascites) and the absence of indication for escalation of decongestive therapy on the morning of day 3.[14] The ADVOR trial was powered based on a control group rate of decongestion similar to that of the high-dose group in the DOSE trial (~15%) and a net superiority of 10 percentage points in the acetazolamide group; however, using their decongestion criteria, 42% of patients in the acetazolamide group and 31% of patients in the control group achieved the primary end point.[11] Although the slight differences in diuretic protocol and patient characteristics may explain some discrepancy between the 2 studies, the alternative definition of decongestion most likely played a major role. Indeed, in the DOSE trial, both orthopnea and jugular venous pressure >8 cm H_2O were found in >90% of patients at baseline (baseline prevalence of the third criteria [more than trace lower extremity edema] is not reported).[2] In the ADVOR trial, more than trace lower extremity edema was the only criteria present in most patients at baseline (>90%), whereas pleural effusion was present in ~50% of patients at randomization and <10% presented with ascites.[11] Clearly, replacing jugular vein distension and orthopnea by less-frequent/more-severe volume overload manifestations resulted in a greater proportion of patients meeting the decongestion end point. However, not all clinical markers of congestion are equivalent markers of prognosis. In fact, jugular venous distension has been found to be the most useful indicator of elevated left ventricular filling pressures during patient history and physical examination[15] and has been associated with increased 30-day, 1-year, and 10-year all-cause mortality.[16] Apart from jugular venous distension, orthopnea was the only other finding independently associated with elevated pulmonary capillary wedge pressure in the ESCAPE trial.[17] However, although a greater proportion of patients were decongested in the acetazolamide arm according to the criteria defined in the ADVOR trial, there was no difference in all-cause mortality or rehospitalization for heart failure between the 2 groups.

Among upcoming studies in acute heart failure, the ENACT-HF (Efficacy of a Standardized Diuretic Protocol in Acute Heart Failure) study will evaluate a standardized diuretic protocol vs the current standard of care and will provide insights into more contemporary rates of decongestion using a similar definition to the one used in the DOSE trial.[13]

Alternative measures of decongestion

In the first part of this review, we described how dynamic changes in congestion parameters during diuretic therapy can provide valuable insights on patient prognosis; however, conceptually, not all measurements captured in the course of decongestive therapy can be translated into decongestion end points. For example, it would be difficult to set target values of total urine output and net fluid loss to define adequate decongestion because these are patient specific and largely dependent on the initial level of volume overload. Similarly, although a greater weight loss has been associated with better outcomes, a common target or weight loss percentage cannot be defined[18,19]; however, reaching an euvolemic baseline state, previously known for a given patient, could be seen as a more appropriate and practical strategy. Indeed, achieving a known dry weight is already a common goal in ADHF therapy and could serve as a criterion of complete decongestion if this information is available. Nevertheless, potential loss of significant fat/lean body mass as can occur in patients with chronic heart failure and malnutrition limits the validity of a previously recorded dry weight over time. Similar to achieving a dry weight, the concept of achieving an individualized "dry" natriuretic peptide level before discharge rather than targeting a certain percentage in reduction or standardized level has been previously proposed.[9,20] In this study, we explore alternative measures of congestion (other than gold-standard invasive pressure measurements and clinical assessment) as targets of optimal decongestion.

Natriuretic peptides

Mechanistically, natriuretic peptides are directly related to intracardiac filling pressures and, in this regard, are superior to many subjective signs/symptoms of congestion. Natriuretic peptide levels are quantitative and dynamic, measurable at reasonable cost, and are an established marker of prognosis.[21,22] The GUIDE-IT (Guiding Evidence Based

Therapy Using Biomarker Intensified Treatment in Heart Failure) trial enrolled patients with chronic heart failure with reduced ejection fraction (<40%), a history of hospitalization for ADHF in the last 12 months, and elevated natriuretic peptide levels in the last 30 days (NT-proBNP level >2000 pg/mL or BNP >400 pg/mL).[9] Patients were randomized to either NT-proBNP–guided management (target of <1000 pg/mL) or usual care. This cutoff was chosen based on the positive PROTECT (ProBNP Outpatient Tailored Chronic Heart Failure Therapy) study and evidence of a significant increase in risk above this threshold.[23] Enrollment in the GUIDE-IT trial was halted for futility (n = 894) after the primary end point of time-to-first heart failure hospitalization or cardiovascular-related mortality occurred in 37% of each group at a median follow-up of 15 months. Another important finding from the GUIDE-IT trial was that patients in both groups achieved similar rates of target NT-proBNP levels and neurohormonal treatment titration, which had not been the case in previous positive studies. Moreover, patients in the usual care group were scheduled for ~10 visits over 15 months, which may not have been representative of common practice. Importantly, the GUIDE-IT trial did not target particularly hospitalized patients with ADHF.

More recently, a retrospective analysis of large, prospective ADHF cohorts have shown that a reduction in NT-proBNP levels during hospitalization is associated with significantly improved outcomes.[4,24] Salah et al [4] assembled data from 6 prospective ADHF cohorts (n = 1232) and showed that a reduction of >30% in NT-proBNP during hospitalization was the only predictor for both death (hazard ratio [HR], 1.81; 95% CI, 1.32-2.50) and for the composite end point of all-cause mortality and readmission for cardiovascular cause (HR, 1.36; 95% CI, 1.13-1.64) within 180 days. Of note, outcomes were improved with significant decrease in NT-proBNP regardless of baseline renal function or worsening renal function (WRF) during decongestive treatment. Similarly, a post hoc analysis of AKINESIS (Acute Kidney Injury NGAL Evaluation of Symptomatic Heart Failure Study) showed that a reduction of ≥30% in NT-proBNP levels was associated with lower in-hospital and 1-year mortality, again, regardless of the occurrence of WRF.[24] However, when the >30% reduction in NT-proBNP levels at discharge target was prospectively evaluated in patients with ADHF in the PRIMA II trial (Can NT-proBNP-Guided Therapy During Hospital Admission for Acute Decompensated Heart Failure Reduce Mortality and Readmissions?), there was no significant improvement in the combined event rate for all-cause mortality and heart failure readmission although the target was reached in more patients of the NT-proBNP-guided group.[8] Consequently, although natriuretic peptide levels remain important tools in guiding management of ADHF, they should not replace clinical assessment.

Hemoconcentration

Hemoconcentration can be assessed using changes in routinely measured parameters, such as hemoglobin, hematocrit, serum albumin, or total protein, or using indicator-dilution techniques. No prospective trial has evaluated the use of hemoconcentration as a target to guide diuretic therapy in patients with ADHF, but its association with better outcomes has been repeatedly demonstrated. In a post hoc analysis of the PROTECT trial, anemia was present in ~50% of patients with ADHF, and hemoglobin level increased in 69% of patients during hospitalization. Hemoconcentration was independently associated with lower mortality at 180 days (HR, 0.66; 95% CI, 0.51-0.86; $P = .002$), despite more deterioration of renal function during decongestive therapy.[25] Baseline hemoglobin levels did not predict outcomes. Darawsha et al[26] evaluated 704 patients with ADHF and volume overload for changes in a congestion score and hemoconcentration, defined as an increase in hemoglobin and hematocrit between admission and discharge. Hemoconcentration was associated with improved survival at a mean follow-up of 14 months (adjusted HR, 0.70; 95% CI, 0.54-0.90; $P = .006$), whereas persistent congestion at discharge was associated with worse survival. However, hemoconcentration was only weakly correlated with clinical assessment of decongestion. Hemoconcentration provides a surrogate for intravascular volume contraction. With aggressive diuresis, intravascular volume depletion exceeds plasma refill from the extravascular space but does not indicate that the patient has achieved euvolemia. Testani et al[27] demonstrated that early decongestion (likely indicating volume contraction without excess extravascular volume depletion) was not associated with a mortality benefit, whereas late hemoconcentration (more likely associated with sustained decongestion and euvolemia) predicted improved survival (HR, 0.74; 95% CI, 0.59-0.93; $P = .009$). Late hemoconcentration was also associated with greater weight loss, higher cumulative diuretic dose, and shorter length of stay.

A standardized quantitative blood volume analysis has been discussed in the first part of this review. Importantly, this technique provides direct measurement of volume in contrast with pressure measurements and has the potential to provide clear individualized targets to define satisfactory decongestion.[28] Consequently, this technique may help in guiding volume management and improve ADHF outcomes.[29] Prospective evaluation is underway.[30]

Clinical congestion scores

Multiple congestion scores, such as the Lucas, Rohde, EVEREST, and Gheorgiade scores, have been developed and reviewed elsewhere.[1] The EVEREST score was derived from the placebo arm of the Efficacy of Vasopressin Antagonism in Heart Failure: Outcome Study With Tolvaptan is the most contemporary evidence-based score. The score is calculated at discharge and evaluates 6 signs and symptoms (dyspnea, fatigue, orthopnea, jugular venous distension, rales, and pedal edema) on a scale from 0 to 3 depending on severity, for a total between 0 and 18.[31] Patients with a discharge EVEREST score of 0 showed the best outcomes, with a readmission for heart failure rate of 26% at ~10 months and all-cause mortality rate of 19%, whereas patients with a score ≥3 showed the worst prognosis, with a rehospitalization rate of 35% and all-cause mortality of 43% during the same period. Integrative assessments combining several signs and symptoms such as the EVEREST score can easily be performed at bedside, standardize intrinsically subjective parameters, and outperform single indicators.[1,32]

Imaging tools

Standard imaging in a patient with ADHF included chest x-ray and echocardiography. Signs of pulmonary congestion on chest radiography offer high specificity for ADHF, but sensitivity is suboptimal (signs lacking in ~1 in 5 ADHF patients).[33] Comprehensive echocardiography remains the gold standard to evaluate de novo heart failure and ADHF episodes. It provides crucial information to determine heart failure etiology, classify heart failure based on ventricular function, and evaluate filling pressures; however, when assessing dynamic changes in severity of congestion, performing daily echocardiography is unrealistic. Recently, vascular and lung ultrasound have been demonstrated as reliable and rapid tools to evaluate fluid status.[34-38] The techniques are simple to use, detect subclinical congestion, and can provide serial assessment throughout the course of decongestive therapy. In particular, assessment of inferior vena cava diameter is the quickest to obtain, can be measured using handheld ultrasonic devices, and correlates well with right atrial pressure.[35,39-41] Right atrial pressure can be classified as normal (0-5 mm Hg), intermediate (5-10 mm Hg), or high (10-20 mm Hg) based on maximal inferior vena cava expiratory diameter (≤21.0 mm vs >21.0 mm) and sniff-test collapsibility (>50% vs <50%).[42] In a small prospective trial evaluating the ability of different metrics of congestion

to predict rehospitalization in patients with ADHF, inferior vena cava diameter and collapsibility at discharge were statistically significant predictors of readmission, along with discharge natriuretic peptide levels.[43] Baseline comorbidities, symptoms/signs of persistent congestion, length of stay, and net fluid loss did not accurately predict readmissions; however, results are inconsistent across studies, and randomized controlled trials evaluating ultrasound to guide decongestive therapy are ongoing.[44-46]

Lung ultrasound is the most powerful tool to detect pulmonary congestion and has been used routinely in critical care medicine.[38,47,48] Simplified protocols make for quicker assessments (eg, 4-zone or 8-zone vs 28-zone scan), and images are simple to interpret (ie, presence of B-lines, pleural sliding, aspect of anterior pleural line, and pleural effusion). Lung ultrasound in the emergency department can also allow more timely initiation of decongestive therapy in patients with ADHF by enhancing diagnostic accuracy compared with natriuretic peptide or chest radiography in conjunction with clinical evaluation.[37,38,49] Randomized trials evaluating the role of lung ultrasound outside of the acute setting have provided encouraging results, but the role of ultrasound markers of pulmonary congestion as a target to guide ADHF therapy remains uncertain.[50-53] A systematic review on the prognosis utility of B-lines in acute and chronic heart failure demonstrated that B-lines were a dynamic marker of congestion (change in B-line number occurring within a few hours of diuretic treatment) and that patients who were discharged with ≥15 B-lines on 28-zone lung ultrasound demonstrated at least a 5-fold increase in the risk of heart failure rehospitalization or death.[54]

Current status and recommendations

Congestion grading

Clinical assessment continues to provide essential information on fluid status and patient prognosis. The incremental value of objective parameters to guide diuretic therapy, although conceptually appealing, has yet to be demonstrated in randomized trials.[8,50] Ultrasound of the inferior vena cava for congestion assessment provides rapid, accessible, noninvasive, semiquantitative data and can be serially performed to evaluate dynamic changes in fluid status. Findings from ongoing randomized trials on the additive value of ultrasound parameters in the management of patients with ADHF are awaited.[44,45,54]

In a recent position statement from the European Society of Cardiology, a congestion scale is provided.[55] Although it provides valuable guidance, the scale lacks clear categorization of congestion severity, does not integrate key congestion parameters such as right heart catheterization measurements, and is not particularly designed to concur with a residual congestion scale in response to decongestive therapy. Similar to what has been seen in other fields,[56] dedicated and more granular definitions are required to provide a framework and guidance in the conduct of decongestion studies and randomized trials. We propose a new 4-class grading scheme of decongestion for the evaluation of ADHF therapies. Table 2[57,58] summarizes the grading scheme with suggested criteria for key clinical and objective parameters. As depicted in the Central Illustration, this grading scheme can be used to assess initial degree of fluid overload in patients presenting with ADHF.

Satisfactory decongestion end point definition

Once decongestive therapy is initiated, the level of residual congestion is assessed until the decongestive target is met or treatment failure occurs. Recently, the HFC-ARC released their first standardized definitions for the evaluation of heart failure therapies.[5] The consensus statement included clear recommendations focused on mortality, hospitalization, worsening heart failure, and quality of life end points; however, optimal decongestion was not defined. Decongestion is an important end point in the evaluation of ADHF therapies because it determines prognosis,[1-4] and the lack of clear guidance on the adequate

Table 2. Proposed grading of congestion.

Proposed 4-class grading scheme	Severe congestion	Moderate congestion	Mild congestion	No congestion
Clinical congestion parameters				
Self-reported symptoms				
NYHA functional class	4	3	1-2	1
Orthopnea (≥2 pillows)	Present	Present	None	None
Physical examination				
Jugular venous pressure, cm H_2O	>16	≤16 and >10	≤10 and >8	≤8
Pedal edema[a]	+4	+2/+3	+1	None
Hepatomegaly	Massive enlargement and tender	Moderate enlargement	Liver edge palpable	None
Ascites[b]	IAC grade 3 (severe)	IAC grade 2 (moderate)	IAC grade 1 (mild)	None
Congestion score				
EVEREST score[c]	>6	3-6	2	0-1
Objective congestion parameters				
Invasive pressure measurement				
CVP (mm Hg)	>15	≤15 and >10	≤10 and >5	≤5
PCWP (mm Hg)	>25	≤25 and >18	≤18 and >12	≤12
Biomarkers				
NT-proBNP (pg/mL)	>3000	≤3000 and >1000	≤1000 and >400	≤400
Hemoglobin[d] (g/L)	<11	≥11 and <13 in men or 12 g/L in women	No dilutional anemia	
Blood volume analysis[e]				
Blood volume/plasma volume	≥30% expansion	≥20% and <30% expansion	≥10% and <20% expansion	<10% expansion
Red blood cell volume	≥24% reduction	≥16% and <24% reduction	≥8% and <16% reduction	<8% reduction
Imaging				
IVC ultrasound	Diameter >21.0 mm and no collapsibility	Diameter >21.0 mm and <50% collapsibility	Diameter <21.0 mm and ≥50% collapsibility	
B-lines on 28-point lung ultrasound	>30	≤30 and >15	≤15	

Adapted from Girerd et al,[1] Bozkurt et al,[57] and Mullens et al.[55]
CVP, central venous pressure; IAC, International ascites club; IVC, inferior vena cava; NYHA, New York Heart Association; PCWP, pulmonary capillary wedge pressure.
[a] Refer to Supplemental Table S1. [b] Refer to Supplemental Table S2. [c] Refer to Supplemental Table S3. [d] Without evidence of bleeding. [e] Measured using Daxor BVA-100 or equivalent. Criteria defined per manufacturer guidance and Feldschuh et al.[58]

Table 3. Objective and subjective decongestion end point definition[a]

Decongestion end point	Unsatisfactory decongestion		Satisfactory decongestion	
			Significant decongestion	Optimal decongestion
Four-class grading scheme	Severe residual congestion	Moderate residual congestion	Mild residual congestion	No residual congestion
Class features	Severe volume overload with no or slight improvement in volume status	Improvement in volume status with clear residual signs of congestion	Meaningful improvement in volume status. Adequate target based on clinical judgment	Complete resolution of signs and symptoms of congestion. Ultimate target
Objective decongestion end point definition[b]				
Left-sided pressures				
PCWP (mm Hg)	>25	≤25 and >18	≤18 and >12 or >20% reduction	≤12
		OR		
NT-proBNP (pg/mL)	>3000	≤3000 and >1000	≤1000 and >400 or ≥30% reduction	≤400
Right-sided pressures				
CVP (mm Hg)	>15	≤15 and >10	≤10 and >5 or >20% reduction	≤5
		OR		
IVC ultrasound	Diameter >21 mm and no collapsibility	Diameter >21 mm and <50% collapsibility	Diameter <21 mm and ≥50% collapsibility	
Blood volume analysis[c]				
Blood volume/ plasma volume	≥30% expansion	≥20% and <30% expansion	or ≥10% and <20% expansion	<10% expansion
		OR		
Red blood cell volume	≥24% reduction	≥16% and <24% reduction	≥8% and <16% reduction	<8% reduction
Subjective decongestion end point definition				
Self-reported symptoms				
NYHA functional class	4	3	1-2	1
Orthopnea (≥2 pillows)	Present	Present	None	None
Physical examination				
Jugular venous pressure, cm H_2O	>16	≤16 and >10	≤10 and >8	≤8
Pedal edema[d]	+4	+2/+3	+1	None
Hepatomegaly	Massive enlargement and tender	Moderate enlargement	Liver edge palpable	None
Ascites[e]	IAC grade 3 (severe)	IAC grade 2 (moderate)	IAC grade 1 (mild)	None
Congestion score				
EVEREST score[f]	>6	3-6	2 or reduction in ≥3 points	0-1

CVP, central venous pressure; IAC, International ascites club; IVC, inferior vena cava; NYHA, New York Heart Association; PCWP, pulmonary capillary wedge pressure.
[a] Adapted from Girerd et al,[1] Bozkurt et al,[57] and Mullens et al.[55] [b] The use of objective decongestion end point definition is recommended over the use of subjective definition [c] Measured using Daxor BVA-100 or equivalent. Criteria defined per manufacturer guidance and Feldschuh et al.[58] [d] Refer to Supplementary Table S1. [e] Refer to Supplementary Table S2. [f] Refer to Supplementary Table S3.

level of decongestion can lead to overtargeting or undertargeting.[5,32,55] In addition, achieving optimal decongestion can serve as a valuable mechanistic and surrogate end point to investigate novel decongestive therapies. This is of particular importance in smaller heart failure device studies, which may lack the power to demonstrate treatment effect based on hard outcomes.

To standardize the evaluation of decongestive treatment efficacy, we propose decongestion end point definitions based on a residual congestion scale similar to our 4-class congestion grading scheme (Table 3). Optimal decongestion is the ultimate target of decongestion therapy and refers to a "dry" state with resolution of signs and symptoms of congestion. Although this end point should be reported, it may not be realistic to achieve in a significant number of patients. This may become problematic in smaller device studies that lack the statistical power of larger trials. To address this reality, satisfactory decongestion definition is extended to include optimal decongestion and significant decongestion. Significant decongestion is defined as a marked improvement in signs of congestion without achieving euvolemia (mild residual congestion). Significant decongestion can be achieved by reaching absolute criteria or significant relative improvement in decongestion compared with baseline. For example, targets such as a 30% reduction in NT-proBNP levels compared with admission or a decrease in EVEREST congestion score can be used as criteria to determine satisfactory decongestion. When moderate or severe signs of residual congestion persist, decongestion is defined as being unsatisfactory.

A caveat of current decongestion end points is that they mainly rely on subjective assessment of symptoms and physical examination, which may introduce potential bias, particularly in device trials where sham procedure and blinding are not always feasible. We believe that in dedicated decongestion studies, degree of decongestion should be assessed using objective criteria as defined in Table 3, which could be adjudicated by a central core laboratory to avoid bias. However, because guiding decongestion based on objective parameter targets has failed to demonstrate superiority to clinical assessment in previous trials, we also include subjective parameter criteria to define satisfactory decongestion. It should also be noted that the proposed definitions represent one of the first attempts to improve homogeneity in the reporting/adjudication of events and comparison between ADHF therapeutic strategies. Hence, they may serve as a steppingstone for future consensus definitions, such as HFC-ARC.[5] Although our definitions regroup a comprehensive list of key clinical and objective parameters, limitations include the use of potentially unfamiliar grading scales (eg, ascites grading scheme) in an attempt to standardize subjective parameters and the still-uncertain added value of objective decongestion metrics.

Worsening renal function

The evaluation of new decongestive therapies should also include assessment of its effect on renal function. The HFC-ARC defines WRF as

Table 4. Worsening renal function end point definition[a]

WRF severity
Stage 1
WRF with an increase in serum creatinine ≥125–150% (≥1.25–1.5× increase) compared with baseline
Stage 2
WRF with an increase in serum creatinine >150–200% (>1.5–2.0× increase) compared with baseline
Stage 3
WRF with an increase in serum creatinine >200–300% (>2–3× increase) compared with baseline
Stage 4
WRF with an increase in serum creatinine >300% (>3× increase) compared with baseline
Stage 5
WRF requiring new temporary or permanent renal replacement therapy
Timing of assessment
Transient
Peak creatine within the index hospitalization
Persistent
Serum creatinine at discharge or 30 d
Permanent
Serum creatinine beyond 30 days or discharge if hospitalization >30 days

Adapted from Clinical Practice Guidelines for Acute Kidney Injury 2012[61] and VARC-3[56] definitions.
WRF, worsening renal function.
[a] Given the variability of baseline renal impairment in patients with acute decompensated heart failure, WRF should be defined based on relative increase in serum creatinine values. Absolute criteria, such as an increase of ≥0.3mg/dL in serum creatinine compared with baseline, are of uncertain significance and should be avoided. Baseline is defined as serum creatinine value on admission.

Table 5. Decongestive treatment failure end point[a]

Stage 1: Prolonged or complicated decongestive treatment
Initiation, re-initiation or escalation of vasoactive agent including catecholamines, phosphodiesterase inhibitors, other vasopressors, or vasodilators during decongestive treatment
Decongestive treatment duration >10 d
Stage 3 WRF or stage 2 permanent WRF
Moderate or severe residual decongestion at discharge
HF readmission within 30 days of discharge
Stage 2: Reversible decongestive treatment failure
Escalation to temporary mechanical circulatory support (ECMO or percutaneous VAD)
Escalation to mechanical ventilation after initial decongestive therapy
Stage 4 or 5 transient/persistent WRF
Stage 3: Irreversible decongestive treatment failure
All-cause death
Stage 4 or 5 permanent WRF

ADHF, acute decompensated heart failure; ECMO, extracorporeal mechanical circulatory support; NT-proBNP, *N*-terminal pro-B-type natriuretic peptide; VAD, ventricular assist device; WRF, worsening renal function.
[a] Adapted from HF-ARC[5] definition.

an increase in creatinine to ≥125% of baseline or increase ≥0.3 mg/dL (26.4 mmol/L) within 48 hours.[5] As discussed in the first part of this review, similar definitions have been widely used in the past. However, in an acutely decompensated patient, small transient increases in creatinine have been shown not to be associated with adverse prognosis,[4,59,60] and it may be challenging to compare treatment safety without more granular definitions. Most importantly, current definitions do not acknowledge the dynamic nature of cardiorenal syndrome in patients with ADHF and the variable degree of renal function recovery. We propose that temporality/reversibility of renal injury may hold important prognostic value for the comparison of decongestive strategies and should be captured in the conduct of future decongestive trials.

In Table 4, we propose a new staging of WRF based on the well-defined and validated Kidney Disease: Improving Global Outcomes (KDIGO) criteria,[61] with the addition of temporality/reversibility in the assessment of renal injury. Transient WRF is assessed using the peak serum creatinine value during decongestive therapy; persistent WRF is defined according to serum creatinine at 30 days, and irreversible/permanent WRF is evaluated at beyond 30 days. In line with the current HF-ARC definition, we have also adapted the KDIGO criteria to capture smaller increases in serum creatinine (stage 1 WRF: 125%-150% baseline level vs stage 1 KDIGO: 150-190% baseline level). In doing so, we ensure continuity between previously and currently proposed WRF definitions and avoid overlooking potentially meaningful renal injuries until a consensus over the long-term prognostic value of these smaller increases in serum creatinine levels is reached.

Our proposed definition also moves away from criteria based on absolute increases in serum creatinine values, given the variability in baseline renal impairment in ADHF. For example, it is unknown whether a 0.3-mg/dL increase in serum creatinine (KDIGO stage 1) has equivalent prognostic value in a patient with a baseline creatinine of 1 or 3 mg/dL. Similarly, WRF leading to a serum creatinine of 4 mg/dL (KDIGO stage 3) during decongestive treatment should be reported separately in a patient with a baseline creatinine of 3.5 mg/dL compared with a patient with normal renal function at baseline. Further analysis of the prognostic effect of WRF with variable severity in ADHF is warranted to refine WRF qualification in future consensus definitions.

Decongestive treatment failure

Beyond renal dysfunction, ineffective or failed decongestive therapy may lead to serious adverse events ranging from less severe adverse events, such as prolonged length of stay or the need to initiate vasoactive agents, to more-severe events such as escalation to mechanical circulatory support and death. Currently, many of these events are encompassed in a broad definition of worsening heart failure.[5] However, because of the varying degree of severity of these events, we propose a more granular staging of decongestive treatment failure for future use in ADHF trials. Treatment failure stages are detailed in Table 5. Stage 1 includes prolonged or complicated decongestive treatment; stage 2 describes patients with decongestive treatment failure who maintain a potential for recovery; stage 3 represents treatment failure with severe and irreversible end-organ damage or death. Importantly, small increases in baseline creatinine levels during decongestive therapy or the initiation/titration of heart failure medication (transient or persistent WRF stage 1) should be reported but are not included in the treatment failure definitions because their prognostic value is uncertain.[4,59,60]

Conclusion

Therapies in ADHF have lagged behind the remarkable progress in chronic heart failure management. Various novel therapies targeting more efficient and complete decongestion are currently in development. Concurrent refinement in patient selection and standardization of decongestion end points are required. In this 2-part review, we explored high-risk patient factors, proposed a new granular 4-class grading of decongestion, and defined end points for future use in ADHF research to improve medical therapy and device comparison.

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

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

Supplementary material

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