

# Acute heart failure: lessons learned, roads ahead

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Acute heart failure remains a major challenge for clinicians and healthcare systems. The number of annual hospitalizations for acute heart failure is rising due to the aging of the general population and the increasing prevalence of heart failure. Heart failure is the leading cause of unplanned hospitalizations for patients older than 65 years in developed countries.<sup>1–4</sup> These acute events impact the natural history of heart failure progression, as demonstrated by the dramatic increase in the rate of death and rehospitalizations after an acute heart failure episode.<sup>5–7</sup> Similarly, unplanned visits for worsening symptoms requiring intravenous diuretic treatment are also associated with poor prognosis, with a greater than four-fold increase in subsequent mortality.<sup>8,9</sup> The available treatment options (primarily diuretics or vasodilators in normo/hypertensive patients) provide symptomatic relief,<sup>1,10</sup> but no therapies for acute heart failure have been shown to improve clinical outcomes in prospective, randomized trials. Thus, reducing morbidity and prolonging survival remain major unmet needs for patients with acute heart failure.<sup>10–12</sup>

Acute heart failure is an ideal target for development of new therapeutic interventions given its high frequency and negative impact on clinical outcomes. However, substantial investments in research and development have not yielded proof of efficacy and safety for any of the therapies tested.

## Results of recent mega-trials in acute heart failure

The goal of improving outcomes for patients with acute heart failure has fostered an emphasis on mega-trials, designed to enrol a sufficiently large number of patients to detect improvements in

survival and/or major outcomes (*Table 1*).<sup>13–23</sup> A comprehensive review of the results of all major trials is beyond the scope of this paper, but two recent trials involving vasodilators are discussed, the results from which were unexpected. These two trials had unique characteristics. First, it was the first time that the effects of a short-term 48 h drug infusion on long-term mortality, at 180 days in RELAX-AHF-2 (Efficacy, Safety, and Tolerability of Serelaxin When Added to Standard Therapy in Acute Heart Failure trial-2) and until the end of the study in TRUE-AHF (Trial of Ularitide Efficacy and Safety in Acute Heart Failure), were assessed as primary endpoint.<sup>23,24</sup> Second, both RELAX-AHF-2 and TRUE-AHF required early randomization from the time of admission to the hospital and had the most accurate criteria as possible for patient enrolment, including normal to high blood pressure and clinical and laboratory signs of congestion. Third, RELAX-AHF-2 was preceded by two trials and a meta-analysis, showing a reduction in mortality with serelaxin vs. placebo.<sup>21,25,26</sup>

TRUE-AHF was a randomized, double-blind, parallel-group, placebo-controlled trial evaluating the effects of a 48 h infusion of ularitide (15 ng/kg/min) on the short- and long-term clinical course of patients with acute heart failure enrolled within 12 hours of presentation. The study had two co-primary endpoints: cardiovascular mortality during long-term follow-up (median 15 months) and the early clinical course (first 48 h) of the patient, assessed through a composite endpoint including death, worsening heart failure and symptom relief.<sup>27</sup> A total of 2157 patients were enrolled, and no benefit was observed for ularitide vs. placebo in either of the co-primary endpoints.<sup>23</sup>

RELAX-AHF-2 was a randomized, double-blind, placebo controlled study that enrolled 6545 patients with acute heart

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**Table 1** Overview of major randomized controlled trials with new drugs in acute heart failure

Trial and study drug vs. comparator	Patient population	Primary endpoint	Duration of treatment	Primary results (study drug vs. control)	Potential contributors to results
OPTIME-CHF <sup>13</sup> Milrinone vs. placebo (on top of standard care)	n = 949, ADHF; <48 h since admission, LVEF <40%	Number of days hospitalized for CV causes or death within 60 days after randomization	48 h	Median 6 days vs. 7 days, P = 0.71	Mismatch of patient population to drug mechanism of action (patients congested, not low output) Active controlled study
SURVIVE <sup>14</sup> Levosimendan vs. dobutamine	n = 1327, ADHF; need for inotropic support, LVEF <30%, SBP ≥85 mmHg	180-day all-cause mortality	24 h (min)	26% vs. 28%, HR 0.91, 95% CI 0.74–1.13, P = 0.4	
REVIVE <sup>15</sup> Levosimendan vs. placebo (on top of standard care)	n = 600, ADHF; dyspnoeic at rest despite i.v. diuretic treatment, LVEF ≤35%, SBP ≥90 mmHg	Clinical classification of improved, unchanged, or worse during first 5 days	24 h	Improved: 58% vs. 44% Worse: 58% vs. 82% P = 0.015 for between-group difference HR for 90-day all-cause mortality: 1.33, 95% CI 0.85–2.06	Hypotension
EVEREST <sup>16</sup> Tolvaptan vs. placebo (on top of standard care)	n = 4133, ADHF; volume overload, NYHA class III/IV, <48 h since admission, LVEF ≤40%	Co-primary: all-cause mortality; composite of CV death or hospitalization for HF (median follow-up 9.9 months)	60 days	All-cause mortality: 25.9% vs. 26.3%, HR 0.98, 95% CI 0.87–1.11, P = 0.68 (superiority) CV death or HF hospitalization: 42% vs. 40.2%, HR 1.04, 95% CI 0.95–1.14, P = 0.55	Mismatch of patient population to drug mechanism of action (i.e. patients may not have had elevated vasopressin levels, only 8% had hyponatraemia)
VERITAS <sup>17</sup> Tezosentan vs. placebo (on top of standard care)	n = 1448, ADHF; persistent dyspnoea at rest, <24 h since admission, SBP ≥100 mmHg (or ≥120 mmHg if concomitant vasodilator)	Individual studies: change from baseline in dyspnoea over first 24 h Combined studies: incidence of death or worsening HF at 7 days	24–72 h	Dyspnoea: no difference in AUC for change in dyspnoea from baseline Death or worsening HF at day 7: 26.3% vs. 26.4%, P = 0.95	Challenges associated with dyspnoea assessment (e.g. rapid response of dyspnoea to standard therapy, knowledge of haemodynamics, uncertain sensitivity of dyspnoea assessment instruments); adverse effects (hypotension)
PROTECT <sup>18</sup> Roflofylline vs. placebo (on top of standard care)	n = 2033, ADHF; persistent dyspnoea at rest or minimal activity, estimated CrCl 20–80 mL/min, <24 h since admission, SBP ≥95 mmHg	Treatment success, failure or no change in clinical condition	Up to 3 days	No difference in distribution of primary composite endpoint; more patients in rolofylline group met criteria for treatment success (OR 1.22, 95% CI 1.01–1.47, P = 0.04) but also for treatment failure (OR 1.13, 95% CI 0.90–1.42, P = 0.30); numerical excess of rolofylline treated patients who met criteria for worsening renal function (12.7% vs. 11.1%, P = 0.31)	Inadequate understanding of contribution of cardiorenal syndrome to ADHF pathophysiology (i.e. role of pseudo-worsening renal function in the setting of ADHF) Co-administration of other therapies that relieve congestion
ASCEND-HF <sup>19</sup> Nesiritide vs. placebo (on top of standard care)	n = 7141, ADHF; dyspnoea at rest with minimal activity, <24 h after first i.v. treatment for ADHF, SBP ≥100 mmHg (or ≥110 mmHg if concomitant i.v. nitroglycerin)	Co-primary: change in self-reported dyspnoea at 6 and 24 h; composite of all-cause mortality or HF hospitalization at 30 days	24 h to 7 days	Moderate or marked improvement in dyspnoea at 6 h: 44.5% vs. 42.1% (P = 0.03, did not meet pre-specified criteria for significance) Moderate or marked improvement in dyspnoea at 24 h: 68.2% vs. 66.1% (P = 0.007, did not meet pre-specified criteria for significance) All-cause mortality or HF hospitalization at 30 days: 9.4% vs. 10.1% (HR 0.93, 95% CI 0.8–1.08)	Co-administration of other therapies that relieve congestion; limitations of dyspnoea assessment instruments (i.e. minimal clinically important differences); lower than expected event rate

Table 1 Continued

Trial and study drug vs. comparator	Patient population	Primary endpoint	Duration of treatment	Primary results (study drug vs. control)	Potential contributors to results
ASTRONAUT <sup>20</sup> Alikiren vs. placebo (on top of standard care)	n = 1639, ADHF after haemodynamic stabilization, history of chronic HF, LVEF $\leq$ 40%	First occurrence of CV death or HF rehospitalization at 6 months	12 months	24.9% vs. 26.5%, HR 0.92, 95% CI 0.76–1.12, P = 0.41	Influence of co-morbidities (i.e. diabetes mellitus); influence of adverse effects (e.g. hyperkalaemia, renal impairment, hypotension) Lower risk population (based on placebo group 30-day all-cause mortality of 3%, lower than VERITAS and ASCEND-HF); limitations of dyspnoea assessment instruments (i.e. minimal clinically important differences)
RELAX-AHF <sup>21</sup> Serelaxin vs. placebo (on top of standard care)	n = 1161, ADHF, presented within 16 h, treated with $\geq$ 40 mg i.v. furosemide before screening, SBP $>$ 125 mmHg	Co-primary: change in patient-reported dyspnoea quantified by AUC of visual analogue scale scores through day 5; moderately or markedly improved patient reported dyspnoea using 7-point Likert scale at 6, 12, and 24 h (responders were those with moderate or marked improvement at all time-points)	Up to 48 h	AUC of visual analogue scale: greater change from baseline for serelaxin (2756 mm x h vs. 2308 mm x h, P = 0.007) Likert scale marked or moderate improvement: 35.8% vs. 31.4% at 6 h (P = 0.113), 50.3% vs. 44.6% at 12 h (P = 0.051), 67.9% vs. 63.1% at 24 h (P = 0.086) Secondary efficacy (days alive and out of hospital to day 60): 48.3 days vs. 47.7 days, P = 0.37 CV death or hospitalization for HF or renal failure to day 60: 13.2% vs. 13%, HR 1.02, 95% CI 0.74–1.41, P = 0.89 CV death: 6.1% vs. 9.6%, HR 0.63, 95% CI 0.41–0.96, P = 0.028	
RELAX-AHF <sup>22</sup> Serelaxin vs. placebo (on top of standard care)	n = 6545, ADHF, randomized within 16 h, SBP $\geq$ 125 mmHg	Co-primary: CV mortality at 180 days; worsening HF through day 5	48 h	No difference in CV mortality at 180 days between groups Non-significant trend towards reduction in worsening HF through day 5	Short-term drug administration unlikely to impact long-term outcomes; small number of deaths in RELAX-AHF may explain discrepancy in findings between two studies
TRUE-AHF <sup>23</sup> Ularitide vs. placebo (on top of standard care)	n = 2157, ADHF (ER or hospitalization), study drug initiation within 12 h, persistent dyspnoea 2 h after $\geq$ 40 mg i.v. furosemide, SBP 116–180 mmHg	Co-primary: CV death (median follow-up 15 months); hierarchical clinical composite during first 48 h	48 h	CV death: 21.7% vs. 21%, HR 1.03, 96% CI 0.85–1.25, P = 0.75 Hierarchical composite: improved 48.6% vs. 47.5%; unchanged 44.8% vs. 44.2%; worse 6.6% vs. 8.3%, P = 0.82 for distribution	Despite evidence of haemodynamic improvement and reduction in wall stress, no benefit on long-term outcomes suggesting that rapid cardiac decongestion does not influence the natural history of HF progression

ADHF, acute decompensated heart failure; ASCEND-HF, Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure; ASTRONAUT, Alikiren Trial in Acute Heart Failure; Outcomes: AUC, area under the curve; CI, confidence interval; CrCl, creatinine clearance; CV, cardiovascular; ER, emergency room; EVEREST, Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan; HF, heart failure; HR, hazard ratio; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; OPTIME-CHF, Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure; OR, odds ratio; PROTECT, 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; RELAX-AHF, Relaxin in Acute Heart Failure; SBP, systolic blood pressure; SURVIVE, Survival of Patients With Acute Heart Failure in Need of Intravenous Inotropic Support; TRUE-AHF, Trial of Ularitide Efficacy and Safety in Acute Heart Failure; VERITAS, Value of Endothelin Receptor Inhibition With Terazosin in Acute Heart Failure Studies.

failure [defined as dyspnoea at rest or with minimal exertion, pulmonary congestion on chest radiograph, and B-type natriuretic peptide (BNP)  $\geq 500$  pg/mL or N-terminal proBNP (NT-proBNP)  $\geq 2000$  pg/mL, treated with intravenous furosemide  $\geq 40$  mg before screening, estimated glomerular filtration rate 30–75 mL/min/1.73 m<sup>2</sup>, and systolic blood pressure  $> 125$  mmHg]. Patients were randomized 1:1 to serelaxin 30  $\mu$ g/kg/day or placebo. No difference between treatment groups was observed in the co-primary endpoints of cardiovascular mortality at 180 days after enrolment (8.7% serelaxin vs. 8.9% placebo,  $P = 0.39$ ) or worsening heart failure events during the first 5 days of hospitalization (6.9% serelaxin vs. 7.7% placebo,  $P = 0.10$ ).<sup>24</sup>

These results raise pertinent questions regarding why these and other acute heart failure trials have not identified beneficial treatment effects for the therapies tested. It is critical to dissect these trials and understand whether the drugs were truly ineffective or if characteristics inherent to the acute heart failure population or the clinical settings and/or if flaws in clinical trial design or execution may have contributed (Table 1).<sup>13–23</sup>

## Key lessons learned from completed clinical trials

Heterogeneity across many aspects relevant to acute heart failure has been proposed as a major factor influencing clinical trial results. Such heterogeneity may increase differences in the results of treatment and the lack of significant results.

## Heterogeneity in causes of rehospitalization or death

Mortality and hospitalizations are by far the most important and, actually, the more frequently assessed clinical endpoints in randomized controlled trials. Their importance is obvious. The value of hospitalizations as a major cause of reduced quality of life and increased costs for healthcare is also clear. Lastly, these events are relatively easy to detect and adjudicate. Unfortunately, their causes and mechanisms may differ substantially.<sup>28,29</sup> A large proportion of deaths and hospitalizations may be non-cardiovascular or, at least, not related to heart failure.<sup>30–33</sup> In the OPTIMIZE-HF (Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure) registry, 42% of patients had at least one factor that precipitated the hospitalization for acute heart failure.<sup>34</sup> The most common contributors were pneumonia or respiratory condition (15.3%), acute coronary syndrome or ischaemia (14.7%), arrhythmia (13.5%), and uncontrolled hypertension (10.7%).<sup>34</sup> Other important factors include infection, poor nutrition, or deconditioning.<sup>35,36</sup> Social support, education of the patient and her/his relatives, home monitoring, and increasing patient adherence to therapy may therefore have a major impact on decreasing rehospitalizations, even in the absence of any direct impact on the progression of cardiac dysfunction.<sup>37–42</sup>

Regarding the mode of death, the European Society of Cardiology Heart Failure Long-Term Registry reported that cardiovascular causes accounted for the greatest proportion of deaths (51.7%)

among patients with acute heart failure. A smaller proportion (13.7%) of deaths was related to non-cardiovascular causes, while the cause of death was unknown in slightly over a third (34.7%) of patients.<sup>7</sup> This heterogeneity in precipitants of rehospitalization and mechanisms of death may obscure the treatment effect of an intervention if the therapy only influences a single mode of death or cause of hospitalization.<sup>43</sup>

## Heterogeneity in acute heart failure pathophysiology and clinical phenotypes

It is accepted that multiple pathophysiologic pathways can lead to acute heart failure.<sup>44</sup> Treatment strategies applied to the broad population of patients with acute heart failure have not yielded improvements in outcome. This suggests that phenotyping patients hospitalized for acute heart failure and administering treatments specific for the phenotype may be a more effective approach.<sup>45</sup> However, the optimum criteria for determining phenotype have not been defined. They may include purely clinical variables<sup>44</sup> or also incorporate more sophisticated strategies (e.g. bioprofiling, multimarker panels).

Current treatment algorithms always recommend investigation of potential causes of decompensation, such as acute coronary syndromes, hypertensive emergencies, arrhythmias, or mechanical factors (e.g. acute valve regurgitation, septal rupture, aortic dissection, pulmonary embolism). A treatment targeting specific causes may dramatically improve symptoms and clinical outcomes.<sup>1,10,46</sup> When a specific cause is not present, assessment of clinical signs is mandatory. These include signs of congestion and/or peripheral hypoperfusion as well as blood pressure.<sup>1,10,47</sup> Additional variables, such as time since the first diagnosis of heart failure,<sup>48</sup> precipitating factors of the acute episode,<sup>34,49</sup> and co-morbidities<sup>50–53</sup> also influence subsequent outcomes and therapeutic choices. For example, the specific treatment of iron deficiency has been associated with improved quality of life and reduced hospitalizations in clinical trials and meta-analyses.<sup>53</sup>

However, clinical criteria may be insufficient to detect the underlying predominant pathophysiology and differentiate long-term outcomes.<sup>6,44</sup>

## Heterogeneity by geography

Geographical differences have influenced the results of clinical trials in acute heart failure.<sup>7,54–57</sup> Heart failure trials have become increasingly global in order to achieve the requisite number of patients and to compensate for lower enrolment rates in many Western countries, particularly the United States. The criteria for hospital admission, treatment approaches, and discharge practices can vary substantially among countries. For example, registry data indicate that vasodilators are less commonly used in the United States (9%), whereas they are used more frequently in other parts of the world (Europe 33–41%, Japan 78%).<sup>58</sup> Geographic disparity in use of inotropes has also been reported (United States 15%, Europe 22–30%, Japan 19%).<sup>58</sup> Length of stay in the hospital for patients with acute heart failure is much shorter in the United States compared to Europe, and it is much longer in Japan.<sup>58</sup>

These differences in length of hospitalization across geographically diverse study centres affect post-discharge outcomes, primarily early rehospitalization rates, and it can confound the interpretation of clinical trial results.<sup>5,23,54,59–61</sup>

## Heterogeneity among clinical investigative sites

Site characteristics may also have a major influence on outcomes. An analysis from ASCEND-HF (Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure) showed that high site enrolment rate was associated with a greater likelihood of patients completing the study protocol. High study centre enrolment was also independently associated with a lower risk of 30-day death or rehospitalization.<sup>62</sup> In some cases, geographic differences may be explained by differences in execution of study protocols by investigative sites (e.g. enrolment of ineligible patients, study drug non-adherence<sup>63</sup>), rather than to intrinsic differences in patient populations.

## Strategies for future acute heart failure clinical trials

The most straightforward explanation for the neutral results of acute heart failure clinical trials completed to date is simply that the treatments tested were not effective. Taking this view, the trials accomplished their primary aim, which is to determine whether or not a drug is more effective than placebo on patient symptoms or, preferably, outcomes.

However, some evidence casts doubt on this reasoning. First, the mechanism of action of drugs like serelaxin and ularitide should favourably impact the pathophysiologic mechanisms of acute heart failure. Second, all the major prospective, multicentre randomized trials were preceded by smaller phase 2 trials that demonstrated beneficial effects of the investigational drugs,<sup>26,64</sup> although it is acknowledged that phase 2 results can be unstable due to the relatively small number of patients or events. Specifically, serelaxin improved multiple endpoints in a first phase IIb trial (Pre-RELAX),<sup>26</sup> and reduced worsening heart failure and cardiovascular and all-cause mortality in the RELAX-AHF trial.<sup>21</sup>

Thus, it is plausible that therapies for acute heart failure that have 'failed' in randomized controlled trials actually have beneficial effects that remained undetected. A variety of factors could contribute to this inability to identify a treatment effect (if one exists), including inadequate site selection and monitoring, suboptimal matching of study drug to patient phenotype, selection of the wrong time-point to assess study endpoints (e.g. long-term for short-term administrations).

## Site selection and monitoring

Critical processes have been described to achieve optimal site selection in acute heart failure trials and their in-depth discussion goes beyond the aims of this article.<sup>65</sup> Assessing sites' interest in the topic, creating a sense of 'ownership' among investigative sites,

and providing sites with adequate resources to hire experienced clinical research staff are among the key factors that determine the success of sites in a clinical trial.<sup>65</sup> Geographical heterogeneity and differences in enrolment rates between sites have been variables influencing the results of the study in some trials but not in others.<sup>62,66,67</sup>

## Matching drugs to pathophysiology

Treatments shown to be effective for cardiovascular disease are all targeted to specific mechanisms of disease progression. This has been the case with acute coronary syndromes where thrombolysis and, then, coronary angioplasty dissolve the coronary thrombus, as well as with chronic heart failure with reduced ejection fraction where we administer treatments targeted to neurohormonal activation, tachycardia, and left ventricular dyssynchrony. Unfortunately, acute heart failure can originate from many different pathophysiologic processes and it seems that we cannot address them satisfactorily, yet.<sup>1,46</sup>

Better patient phenotyping has been proposed as a solution to increase the likelihood of a successful trial. Use of multiple biomarkers may provide more comprehensive characterization of pathophysiology,<sup>68–72</sup> and the role of genomic and proteomic analyses are under investigation.<sup>73</sup> A multimarker approach including high-sensitivity cardiac troponin, NT-proBNP, soluble ST2, and growth differentiation factor-15 on top of known prognostic markers provided the best prediction of 180-day cardiovascular mortality in an analysis of data from RELAX-AHF.<sup>72</sup> However, it is important to recognize that the finding that these markers have a prognostic value does not necessarily mean that a treatment changing their levels may have an impact on outcomes.<sup>17–19,23,74</sup> Thus, a better pathophysiologic characterization of patients with acute heart failure is urgently needed.

## Timing of endpoint assessment

### Long-term endpoints

Clinical trial endpoints have been extensively discussed elsewhere.<sup>28,75</sup> A major hallmark of acute heart failure is its high mortality and readmission rates. Correspondingly, morbidity and mortality endpoints have been predominantly used in clinical trials. However, these endpoints can be problematic in acute heart failure trials. First, in order to achieve the number of events needed for adequate statistical power, a large number of patients (i.e. many thousands) must be enrolled and long-term follow-up is needed, at least 6 months.<sup>24</sup> The potential limitations and challenges previously discussed (e.g. inappropriate inclusion of ineligible patients, geographic differences, poor clinical site performance) are magnified in large trials. Second, consistent with the recognition that a single pathophysiologic process does not fully explain heart failure progression in the setting of an acute event, it seems unlikely that short-term (e.g. 48 h) administration of a drug would have long-term effects on outcomes.

The most effective therapy for acute episodes of decompensation seems to be prevention. Treatments effective in chronic heart



failure have also reduced heart failure related hospitalizations.<sup>1,46</sup> It remains, however, to be shown whether the initiation of an appropriate treatment at the time of discharge, or shortly thereafter, and its continuation post-discharge may have beneficial effects on long-term outcomes. Observational data suggest that beta-blocker use at the time of hospital discharge is associated with better survival 60–90 days post-discharge.<sup>76</sup> A propensity matched analysis of 19 980 patients with acute heart failure enrolled in the GREAT network registry showed that patients receiving a beta-blocker at discharge had a lower 90-day mortality [hazard ratio (HR) 0.56, 95% confidence interval (CI) 0.46–0.69] and 1-year mortality (HR 0.62, 95% CI 0.55–0.71) than untreated patients.<sup>77</sup> Similar findings were reported for 90-day (HR 0.53, 95% CI 0.42–0.66) and 1-year mortality (HR 0.62, 95% CI 0.53–0.72) in patients discharged on a renin–angiotensin system inhibitor compared to those not treated.<sup>77</sup> These findings, while observational, are strengthened by the knowledge that these drug classes have been shown to prolong survival and reduce hospitalizations in prospective, randomized trials in patients with chronic heart failure with reduced ejection fraction. Thus, optimizing the use of chronic, guideline-recommended evidence-based therapies before discharge in patients hospitalized for acute heart failure should be a priority.

### Short-term endpoints

Short-term endpoints may be less ambitious but are potentially more likely to succeed. However, which endpoints are most suitable is a topic of debate. Biomarkers, specifically natriuretic peptides, are associated with patient outcomes and have often been used as surrogates for outcomes. However, the relationship between the effect of drug therapy on natriuretic peptides and outcomes has been inconsistent across trials.<sup>14,15,78,79</sup>

Short-term clinical endpoints may be more attractive. Worsening heart failure is defined as worsening symptoms requiring reinitiation or increasing doses of intravenous treatment or mechanical devices during the hospitalization for heart failure. It occurs in 4% to 37% of patients hospitalized for heart failure, and it is associated with higher plasma levels of natriuretic peptides and troponin, worsening renal function, longer length of the hospital stay, increased post-discharge hospitalizations, deaths, and higher healthcare costs post-discharge.<sup>25,80,81</sup> Worsening heart failure is also sensitive to drug treatment.<sup>15,21,80,82</sup> However, it is also highly dependent on the investigator or patient reporting events, as well as the specific definition used.<sup>82</sup> The occurrence of worsening heart failure events has declined in recent trials, possibly due to the increased complexity of case report forms and resultant underreporting.

Length of stay for the initial hospitalization for acute heart failure may also be reduced with appropriate treatment.<sup>21,26</sup> It is clinically relevant and significantly impacts on the costs of healthcare. However, it also has marked geographical differences and is strongly influenced by local treatment patterns. Evaluating proportional rather than absolute length of stay may be one approach to overcome the limitations of regional/cultural differences in length of stay. Symptom relief is clinically meaningful, but its subjectivity

results in substantial variability in large multicentre trials. Furthermore, current treatment (e.g. intravenous diuretics) is generally effective for symptomatic relief in most patients. Because of this treatment response, demonstrating additional treatment effects on symptoms for a new therapy is difficult. Additionally, a new therapy may not be considered valuable to health systems and payers if the symptomatic improvement is the same or only marginally greater than inexpensive standard therapy (i.e. diuretics) without some evidence of other clinical benefit. Signs of congestion are related with outcomes, and they may persist at the time of discharge.<sup>83,84</sup> Thus, better congestion relief may be a meaningful endpoint, but accurate assessment tools and validation studies are lacking.

## Conclusions

Acute heart failure remains a major challenge for clinical practice. Current treatment is insufficient as patients continue to have poor outcomes. Short-term treatment is unlikely to affect long-term mortality and/or rehospitalization rates. Thus, composite endpoints based on symptom relief and short-term events may be better suited to gauge the effects of drug treatment. Long-term outcomes are more likely to be improved by adherence to evidence-based therapies for chronic heart failure to prevent new episodes of decompensation.

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