European Journal of Heart Failure (2018) **20**, 842–850
doi:10.1002/ejhf.1169

VIEWPOINT

Acute heart failure: lessons learned, roads ahead

Roberto Ferrari[1,2]*, Héctor Bueno[3], Ovidiu Chioncel[4], John G. Cleland[5], Wendy Gattis Stough[6], Maddalena Lettino[7], Marco Metra[8], John T. Parissis[9], Fausto Pinto[10], Piotr Ponikowski[11], Frank Ruschitzka[12], and Luigi Tavazzi[2]

[1]Department of Cardiology and LTTA Centre, University Hospital of Ferrara, Ferrara, Italy; [2]Maria Cecilia Hospital, GVM Care & Research, E.S. Health Science Foundation, Cotignola, Italy; [3]Department of Cardiology, Hospital 12 de Octubre, Madrid, Spain; [4]University of Medicine Carol Davila Bucuresti, Institutul de Urgente Boli Cardiovasculare CC, Iliescu, Romania; [5]National Heart & Lung Institute, Harefield Hospital, Imperial College, London, UK; [6]Departments of Pharmacy Practice and Clinical Research, Campbell University College of Pharmacy and Health Sciences, Cary, NC, USA; [7]IRCCS Istituto Clinico Humanitas, Milan, Italy; [8]Cardiology, Department of Medical and Surgical Specialties, Radiological Sciences and Public Health, University of Brescia, Brescia, Italy; [9]Heart Failure Unit, Attikon University Hospital, Athens, Greece; [10]Departamento de Cardiologia, CCUL, CAML, Faculdade de Medicina, Universidade de Lisboa, Lisbon, Portugal; [11]Medical University, Centre for Heart Disease, Clinical Military Hospital, Wroclaw, Poland; and [12]Department of Cardiology, University Heart Center, Zürich, Switzerland

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.[1–4] 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.[5–7] 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.[8,9] The available treatment options (primarily diuretics or vasodilators in normo/hypertensive patients) provide symptomatic relief,[1,10] 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.[10–12]

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*).[13–23] 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.[23,24] 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.[21,25,26]

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.[27] A total of 2157 patients were enrolled, and no benefit was observed for ularitide vs. placebo in either of the co-primary endpoints.[23]

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

*Corresponding author. Department of Cardiology and LTTA Centre, University Hospital of Ferrara, Via Aldo Moro 8, 44124 Cona (FE), Italy. Tel: +39 0532 239882, Fax: +39 0532 237841, Email: fri@unife.it

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[13] 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)
SURVIVE[14] 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, $P = 0.4$	Active controlled study
REVIVE[15] Levosimendan vs. placebo (on top of standard care)	$n = 600$, ADHF, dypnoeic 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[16] 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[17] 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[18] Rolofylline 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[19] 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[20] Aliskiren vs. placebo (on top of standard care)	$n = 1639$, ADHF after haemodynamic stabilization, history of chronic HF, LVEF ≤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)
RELAX-AHF[21] Serelaxin vs. placebo (on top of standard care)	$n = 1161$, ADHF, presented within 16 h, treated with ≥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, $P = 0.028$	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-2[22] Serelaxin vs. placebo (on top of standard care)	$n = 6545$, ADHF, randomized within 16 h, SBP ≥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[23] 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 ≥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, Aliskiren 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 Tezosentan 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) ≥500 pg/mL or N-terminal proBNP (NT-proBNP) ≥2000 pg/mL, treated with intravenous furosemide ≥40 mg before screening, estimated glomerular filtration rate 30–75 mL/min/1.73 m^2, and systolic blood pressure > 125 mmHg]. Patients were randomized 1:1 to serelaxin 30 μg/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, $P = 0.10$).[24]

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*).[13–23]

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.[28,29] A large proportion of deaths and hospitalizations may be non-cardiovascular or, at least, not related to heart failure.[30–33] 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.[34] 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%).[34] Other important factors include infection, poor nutrition, or deconditioning.[35,36] 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.[37–42]

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.[7] 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.[43]

Heterogeneity in acute heart failure pathophysiology and clinical phenotypes

It is accepted that multiple pathophysiologic pathways can lead to acute heart failure.[44] 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.[45] However, the optimum criteria for determining phenotype have not been defined. They may include purely clinical variables[44] 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.[1,10,46] 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.[1,10,47] Additional variables, such as time since the first diagnosis of heart failure,[48] precipitating factors of the acute episode,[34,49] and co-morbidities[50–53] 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.[53]

However, clinical criteria may be insufficient to detect the underlying predominant pathophysiology and differentiate long-term outcomes.[6,44]

Heterogeneity by geography

Geographical differences have influenced the results of clinical trials in acute heart failure.[7,54–57] 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%).[58] Geographic disparity in use of inotropes has also been reported (United States 15%, Europe 22–30%, Japan 19%).[58] 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.[58]

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.[5,23,54,59–61]

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.[62] 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[63]), 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,[26,64] 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),[26] and reduced worsening heart failure and cardiovascular and all-cause mortality in the RELAX-AHF trial.[21]

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.[65] 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.[65] 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.[62,66,67]

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.[1,46]

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,[68–72] and the role of genomic and proteomic analyses are under investigation.[73] 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.[72] 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.[17–19,23,74] Thus, a better pathophysiological 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.[28,75] 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.[24] 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.[1,46] 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.[76] 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.[77] 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.[77] 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.[14,15,78,79]

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.[25,80,81] Worsening heart failure is also sensitive to drug treatment.[15,21,80,82] However, it is also highly dependent on the investigator or patient reporting events, as well as the specific definition used.[82] 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.[21,26] 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.[83,84] 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.

Acknowledgements

The authors would like to thank Sarah Novack, PhD, Servier, France, for medical writing assistance during the preparation of this document.

Conflict of interest: R.F. reported that he received honorarium from Servier for steering committee membership consulting and speaking, and support for travel to study meetings from Servier. In addition, he received personal fees from Boehringer Ingelheim, Novartis, Merck Serono and Irbtech. H.B. reports having received consulting/speaking fees from Abbott, AstraZeneca, Bayer, BMS-Pfizer, Daiichi Sankyo, Eli Lilly, Ferrer, Menarini, Novartis, Sanofi, Servier, and research grants from AstraZeneca. O.C. reported steering committee membership of Novartis. He has also received research support from Servier, Vifor, Roche, and Novartis. J.G.C. reported that he received honoraria and research funding from Servier and Novartis and participates in studies of ivabradine (EDIFY) and LCZ696 (PARAGON) in patients with HFpEF. He has also received research support from Roche, which manufactures amino-terminal pro-brain natriuretic peptide that has an important diagnostic role in this context. M.L. has received consulting fees or honoraria, or travel support from Servier and Boehringer, and consulting or lecture fees from Aspen, Sanofi, AstraZeneca, BMS, Daiichi Sankyo, Eli Lilly, and Bayer. M.M. has received fees for board membership from Bayer, Novartis, and Servier, and lecture fees and/or manuscript preparation from Servier and Abbott Vascular. J.T.P. received honoraria for advisory boards and lectures from Roche Diagnostics, Servier, Novartis and Orion Pharma. F.P. has received consulting, manuscript preparation, and/or lecture fees from Bayer, Novarits, Pfizer and Servier. P.P. has received

grants, consulting fees or honoraria, and travel support from Vifor Pharma, Amgen, Servier, Novartis, Bayer, Abbott Vascular, Boehringer Ingelheim, Respicardia, Coridea, Celladon, and Cardiorentis. F.R. received payment for lectures including service on speakers' bureaus from St Jude Medical, Servier, Zoll, AstraZeneca and HeartWare. L.T. is trial committee member and member of the speaker bureau for Servier, and trial committee member for Boston Scientific, Medtronic, Cardiorentis, CVIE Therapeutics, ZS Pharma, St Jude Medical.

References

1. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, Gonzalez-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2016;**18**:891–975.
2. Heidenreich PA, Albert NM, Allen LA, Bluemke DA, Butler J, Fonarow GC, Ikonomidis JS, Khavjou O, Konstam MA, Maddox TM, Nichol G, Pham M, Pina IL, Trogdon JG. Forecasting the impact of heart failure in the United States: a policy statement from the American Heart Association. *Circ Heart Fail* 2013;**6**:606–619.
3. Christ M, Stork S, Dorr M, Heppner HJ, Muller C, Wachter R, Riemer U. Heart failure epidemiology 2000–2013: insights from the German Federal Health Monitoring System. *Eur J Heart Fail* 2016;**18**:1009–1018.
4. Omersa D, Farkas J, Erzen I, Lainscak M. National trends in heart failure hospitalization rates in Slovenia 2004–2012. *Eur J Heart Fail* 2016;**18**:1321–1328.
5. Solomon SD, Dobson J, Pocock S, Skali H, McMurray JJ, Granger CB, Yusuf S, Swedberg K, Young JB, Michelson EL, Pfeffer MA. Influence of nonfatal hospitalization for heart failure on subsequent mortality in patients with chronic heart failure. *Circulation* 2007;**116**:1482–1487.
6. Kristensen SL, Jhund PS, Kober L, Preiss D, Kjekshus J, McKelvie RS, Zile MR, Anand IS, Wikstrand J, Wedel H, Komajda M, Carson PE, Cleland JG, McMurray JJ. Comparison of outcomes after hospitalization for worsening heart failure, myocardial infarction, and stroke in patients with heart failure and reduced and preserved ejection fraction. *Eur J Heart Fail* 2015;**17**:169–176.
7. Crespo-Leiro MG, Anker SD, Maggioni AP, Coats AJ, Filippatos G, Ruschitzka F, Ferrari R, Piepoli MF, Delgado Jimenez JF, Metra M, Fonseca C, Hradec J, Amir O, Logeart D, Dahlstrom U, Merkely B, Drozdz J, Goncalvesova E, Hassanein M, Chioncel O, Lainscak M, Seferovic PM, Tousoulis D, Kavoliuniene A, Fruhwald F, Fazlibegovic E, Temizhan A, Gatzov P, Erglis A, Laroche C, Mebazaa A; Heart Failure Association (HFA) of the European Society of Cardiology (ESC). European Society of Cardiology Heart Failure Long-Term Registry (ESC-HF-LT): 1-year follow-up outcomes and differences across regions. *Eur J Heart Fail* 2016;**18**:613–625.
8. Skali H DE, Goldstein R, Haigney M, Krone R, Kukin M, Lichstein E, McNitt S, Moss AJ, Pfeffer MA, Solomon SD. Prognosis and response to therapy of first inpatient and outpatient heart failure event in a heart failure clinical trial: MADIT-CRT. *Eur J Heart Fail* 2014;**16**:560–565.
9. Okumura N, Jhund PS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Swedberg K, Zile MR, Solomon SD, Packer M, McMurray JJ; PARADIGM-HF Investigators and Committees. 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 in Heart Failure Trial (PARADIGM-HF). *Circulation* 2016;**133**:2254–2262.
10. Mebazaa A, Yilmaz MB, Levy P, Ponikowski P, Peacock WF, Laribi S, Ristic AD, Lambrinou E, Masip J, Riley JP, McDonagh T, Mueller C, deFilippi C, Harjola VP, Thiele H, Piepoli MF, Metra M, Maggioni A, McMurray J, Dickstein K, Damman K, Seferovic PM, Ruschitzka F, Leite-Moreira AF, Bellou A, Anker SD, Filippatos G. Recommendations on pre-hospital & early hospital management of acute heart failure: a consensus paper from the Heart Failure Association of the European Society of Cardiology, the European Society of Emergency Medicine and the Society of Academic Emergency Medicine. *Eur J Heart Fail* 2015;**17**:544–558.
11. Bueno H, Ross JS, Wang Y, Chen J, Vidan MT, Normand SL, Curtis JP, Drye EE, Lichtman JH, Keenan PS, Kosiborod M, Krumholz HM. Trends in length of stay and short-term outcomes among Medicare patients hospitalized for heart failure, 1993–2006. *JAMA* 2010;**303**:2141–2147.
12. Vidan MT, Bueno H. Trends in heart failure: going in the right direction? *Eur J Heart Fail* 2016;**18**:1019–1020.
13. Cuffe MS, Califf RM, Adams KF Jr, Benza R, Bourge R, Colucci WS, Massie BM, O'Connor CM, Pina I, Quigg R, Silver MA, Gheorghiade M; Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF) Investigators. Short-term intravenous milrinone for acute exacerbation of chronic heart failure: a randomized controlled trial. *JAMA* 2002;**287**:1541–1547.
14. Mebazaa A, Nieminen MS, Packer M, Cohen-Solal A, Kleber FX, Pocock SJ, Thakkar R, Padley RJ, Poder P, Kivikko M; SURVIVE Investigators. Levosimendan vs dobutamine for patients with acute decompensated heart failure: the SURVIVE randomized trial. *JAMA* 2007;**297**:1883–1891.
15. Packer M, Colucci W, Fisher L, Massie BM, Teerlink JR, Young J, Padley RJ, Thakkar R, Delgado-Herrera L, Salon J, Garratt C, Huang B, Sarapohja T; REVIVE Heart Failure Study Group. Effect of levosimendan on the short-term clinical course of patients with acutely decompensated heart failure. *JACC Heart Fail* 2013;**1**:103–111.
16. Konstam MA, Gheorghiade M, Burnett JC Jr, Grinfeld L, Maggioni AP, Swedberg K, Udelson JE, Zannad F, Cook T, Ouyang J, Zimmer C, Orlandi C; Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan (EVEREST) Investigators. Effects of oral tolvaptan in patients hospitalized for worsening heart failure: the EVEREST Outcome Trial. *JAMA* 2007;**297**:1319–1331.
17. McMurray JJ, Teerlink JR, Cotter G, Bourge RC, Cleland JG, Jondeau G, Krum H, Metra M, O'Connor CM, Parker JD, Torre-Amione G, van Veldhuisen DJ, Lewsey J, Frey A, Rainisio M, Kobrin I; VERITAS Investigators. Effects of tezosentan on symptoms and clinical outcomes in patients with acute heart failure: the VERITAS randomized controlled trials. *JAMA* 2007;**298**:2009–2019.
18. Massie BM, O'Connor CM, Metra M, Ponikowski P, Teerlink JR, Cotter G, Weatherley BD, Cleland JG, Givertz MM, Voors A, DeLucca P, Mansoor GA, Salerno CM, Bloomfield DM, Dittrich HC; PROTECT Investigators and Committees. Rolofylline, an adenosine A1-receptor antagonist, in acute heart failure. *N Engl J Med* 2010;**363**:1419–1428.
19. O'Connor CM, Starling RC, Hernandez AF, Armstrong PW, Dickstein K, Hasselblad V, Heizer GM, Komajda M, Massie BM, McMurray JJ, Nieminen MS, Reist CJ, Rouleau JL, Swedberg K, Adams KF Jr, Anker SD, Atar D, Battler A, Botero R, Bohidar NR, Butler J, Clausell N, Corbalan R, Costanzo MR, Dahlstrom U, Deckelbaum LI, Diaz R, Dunlap ME, Ezekowitz JA, Feldman D, Felker GM, Fonarow GC, Gennevois D, Gottlieb SS, Hill JA, Hollander JE, Howlett JG, Hudson MP, Kociol RD, Krum H, Laucevicius A, Levy WC, Mendez GF, Metra M, Mittal S, Oh BH, Pereira NL, Ponikowski P, Tang WH, Tanomsup S, Teerlink JR, Triposkiadis F, Troughton RW, Voors AA, Whellan DJ, Zannad F, Califf RM. Effect of nesiritide in patients with acute decompensated heart failure. *N Engl J Med* 2011;**365**:32–43.
20. Gheorghiade M, Bohm M, Greene SJ, Fonarow GC, Lewis EF, Zannad F, Solomon SD, Baschiera F, Botha J, Hua TA, Gimpelewicz CR, Jaumont X, Lesogor A, Maggioni AP; ASTRONAUT Investigators and Coordinators. Effect of aliskiren on postdischarge mortality and heart failure readmissions among patients hospitalized for heart failure: the ASTRONAUT randomized trial. *JAMA* 2013;**309**:1125–1135.
21. Teerlink JR, Cotter G, Davison BA, Felker GM, Filippatos G, Greenberg BH, Ponikowski P, Unemori E, Voors AA, Adams KF Jr, Dorobantu MI, Grinfeld LR, Jondeau G, Marmor A, Masip J, Pang PS, Werdan K, Teichman SL, Trapani A, Bush CA, Saini R, Schumacher C, Severin TM, Metra M; RELAXin in Acute Heart Failure (RELAX-AHF) Investigators. Serelaxin, recombinant human relaxin-2, for treatment of acute heart failure (RELAX-AHF): a randomised, placebo-controlled trial. *Lancet* 2013;**381**:29–39.
22. ESC Press Office. Serelaxin fails to meet primary endpoints in phase 3 RELAX-AHF-2 trial [press release, 29 April 2017]. https://www.escardio.org/The-ESC/Press-Office/Press-releases/serelaxin-fails-to-meet-primary-endpoints-in-phase-3-relax-ahf-2-trial (20 November 2017).
23. Packer M, O'Connor C, McMurray JJ, Wittes J, Abraham WT, Anker SD, Dickstein K, Filippatos G, Holcomb R, Krum H, Maggioni AP, Mebazaa A, Peacock WF, Petrie MC, Ponikowski P, Ruschitzka F, van Veldhuisen DJ, Kowarski LS, Schactman M, Holzmeister J; TRUE-AHF Investigators. Effect of ularitide on cardiovascular mortality in acute heart failure. *N Engl J Med* 2017;**376**:1956–1964.
24. Teerlink JR, Voors AA, Ponikowski P, Pang PS, Greenberg BH, Filippatos G, Felker GM, Davison BA, Cotter G, Gimpelewicz C, Boer-Martins L, Wernsing M, Hua TA, Severin T, Metra M. Serelaxin in addition to standard therapy in acute heart failure: rationale and design of the RELAX-AHF-2 study. *Eur J Heart Fail* 2017;**19**:800–809.
25. Metra M, Cotter G, Davison BA, Felker GM, Filippatos G, Greenberg BH, Ponikowski P, Unemori E, Voors AA, Adams KF Jr, Dorobantu MI, Grinfeld L, Jondeau G, Marmor A, Masip J, Pang PS, Werdan K, Prescott MF, Edwards C, Teichman SL, Trapani A, Bush CA, Saini R, Schumacher C, Severin T, Teerlink JR; RELAX-AHF Investigators. Effect of serelaxin on cardiac, renal, and hepatic biomarkers in the Relaxin in Acute Heart Failure (RELAX-AHF) development program: correlation with outcomes. *J Am Coll Cardiol* 2013;**61**:196–206.

26. Teerlink JR, Metra M, Felker GM, Ponikowski P, Voors AA, Weatherley BD, Marmor A, Katz A, Grzybowski J, Unemori E, Teichman SL, Cotter G. Relaxin for the treatment of patients with acute heart failure (Pre-RELAX-AHF): a multicentre, randomised, placebo-controlled, parallel-group, dose-finding phase IIb study. *Lancet* 2009;**373**:1429–1439.
27. Packer M, Holcomb R, Abraham WT, Anker S, Dickstein K, Filippatos G, Krum H, Maggioni AP, McMurray JJ, Mebazaa A, O'Connor C, Peacock F, Ponikowski P, Ruschitzka F, van Veldhuisen DJ, Holzmeister J; TRUE-AHF Investigators and Committees. Rationale for and design of the TRUE-AHF trial: the effects of ularitide on the short-term clinical course and long-term mortality of patients with acute heart failure. *Eur J Heart Fail* 2017;**19**:673–681.
28. Anker SD, Schroeder S, Atar D, Bax JJ, Ceconi C, Cowie MR, Crisp A, Dominjon F, Ford I, Ghofrani HA, Gropper S, Hindricks G, Hlatky MA, Holcomb R, Honarpour N, Jukema JW, Kim AM, Kunz M, Lefkowitz M, Le Floch C, Landmesser U, McDonagh TA, McMurray JJ, Merkely B, Packer M, Prasad K, Revkin J, Rosano GM, Somaratne R, Stough WG, Voors AA, Ruschitzka F. Traditional and new composite endpoints in heart failure clinical trials: facilitating comprehensive efficacy assessments and improving trial efficiency. *Eur J Heart Fail* 2016;**18**:482–489.
29. Filippatos GS, de Graeff P, Bax JJ, Borg JJ, Cleland JG, Dargie HJ, Flather M, Ford I, Friede T, Greenberg B, Henon-Goburdhun C, Holcomb R, Horst B, Lekakis J, Mueller-Velten G, Papavassiliou AG, Prasad K, Rosano GM, Severin T, Sherman W, Stough WG, Swedberg K, Tavazzi L, Tousoulis D, Vardas P, Ruschitzka F, Anker SD. Independent academic Data Monitoring Committees for clinical trials in cardiovascular and cardiometabolic diseases. *Eur J Heart Fail* 2017;**19**:449–456.
30. Dharmarajan K, Hsieh AF, Lin Z, Bueno H, Ross JS, Horwitz LI, Barreto-Filho JA, Kim N, Bernheim SM, Suter LG, Drye EE, Krumholz HM. Diagnoses and timing of 30-day readmissions after hospitalization for heart failure, acute myocardial infarction, or pneumonia. *JAMA* 2013;**309**:355–363.
31. Krumholz HM, Lin Z, Keenan PS, Chen J, Ross JS, Drye EE, Bernheim SM, Wang Y, Bradley EH, Han LF, Normand SL. Relationship between hospital readmission and mortality rates for patients hospitalized with acute myocardial infarction, heart failure, or pneumonia. *JAMA* 2013;**309**:587–593.
32. O'Connor CM, Miller AB, Blair JE, Konstam MA, Wedge P, Bahit MC, Carson P, Haass M, Hauptman PJ, Metra M, Oren RM, Patten R, Pina I, Roth S, Sackner-Bernstein JD, Traver B, Cook T, Gheorghiade M; Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan (EVEREST) Investigators. Causes of death and rehospitalization in patients hospitalized with worsening heart failure and reduced left ventricular ejection fraction: results from Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan (EVEREST) program. *Am Heart J* 2010;**159**:841–849.e1.
33. Felker GM, Teerlink JR, Butler J, Hernandez AF, Miller AB, Cotter G, Davison BA, Filippatos G, Greenberg BH, Ponikowski P, Voors AA, Hua TA, Severin TM, Unemori E, Metra M. Effect of serelaxin on mode of death in acute heart failure: results from the RELAX-AHF study. *J Am Coll Cardiol* 2014;**64**:1591–1598.
34. Fonarow GC, Abraham WT, Albert NM, Stough WG, Gheorghiade M, Greenberg BH, O'Connor CM, Pieper K, Sun JL, Yancy CW, Young JB; OPTIMIZE-HF Investigators and Hospitals. Factors identified as precipitating hospital admissions for heart failure and clinical outcomes: findings from OPTIMIZE-HF. *Arch Intern Med* 2008;**168**:847–854.
35. Krumholz HM. Post-hospital syndrome—an acquired, transient condition of generalized risk. *N Engl J Med* 2013;**368**:100–102.
36. Parikh KS, Felker GM, Metra M. Mode of death after acute heart failure hospitalization—a clue to possible mechanisms. *Circ J* 2016;**80**:17–23.
37. Luttik ML, Jaarsma T, van Geel PP, Brons M, Hillege HL, Hoes AW, de Jong R, Linssen G, Lok DJ, Berge M, van Veldhuisen DJ. Long-term follow-up in optimally treated and stable heart failure patients: primary care vs. heart failure clinic. Results of the COACH-2 study. *Eur J Heart Fail* 2014;**16**:1241–1248.
38. Guder G, Stork S, Gelbrich G, Brenner S, Deubner N, Morbach C, Wallenborn J, Berliner D, Ertl G, Angermann CE. Nurse-coordinated collaborative disease management improves the quality of guideline-recommended heart failure therapy, patient-reported outcomes, and left ventricular remodelling. *Eur J Heart Fail* 2015;**17**:442–452.
39. Bohm M, Lloyd SM, Ford I, Borer JS, Ewen S, Laufs U, Mahfoud F, Lopez-Sendon J, Ponikowski P, Tavazzi L, Swedberg K, Komajda M. Non-adherence to ivabradine and placebo and outcomes in chronic heart failure: an analysis from SHIFT. *Eur J Heart Fail* 2016;**18**:672–683.
40. Hawkins NM, Virani SA, Sperrin M, Buchan IE, McMurray JJ, Krahn AD. Predicting heart failure decompensation using cardiac implantable electronic devices: a review of practices and challenges. *Eur J Heart Fail* 2016;**18**:977–986.
41. Komajda M, Cowie MR, Tavazzi L, Ponikowski P, Anker SD, Filippatos GS; QUALIFY Investigators. Physicians' guideline adherence is associated with better prognosis in outpatients with heart failure with reduced ejection fraction: the QUALIFY international registry. *Eur J Heart Fail* 2017;**19**:1414–1423.
42. Dierckx R, Inglis SC, Clark RA, Prieto-Merino D, Cleland JG. Telemedicine in heart failure: new insights from the Cochrane meta-analyses. *Eur J Heart Fail* 2017;**19**:304–306.
43. Zannad F, Garcia AA, Anker SD, Armstrong PW, Calvo G, Cleland JG, Cohn JN, Dickstein K, Domanski MJ, Ekman I, Filippatos GS, Gheorghiade M, Hernandez AF, Jaarsma T, Koglin J, Konstam M, Kupfer S, Maggioni AP, Mebazaa A, Metra M, Nowack C, Pieske B, Pina IL, Pocock SJ, Ponikowski P, Rosano G, Ruilope LM, Ruschitzka F, Severin T, Solomon S, Stein K, Stockbridge NL, Stough WG, Swedberg K, Tavazzi L, Voors AA, Wasserman SM, Woehrle H, Zalewski A, McMurray JJ. Clinical outcome endpoints in heart failure trials: a European Society of Cardiology Heart Failure Association consensus document. *Eur J Heart Fail* 2013;**15**:1082–1094.
44. Chioncel O, Mebazaa A, Harjola VP, Coats AJ, Piepoli MF, Crespo-Leiro MG, Laroche C, Seferovic PM, Anker SD, Ferrari R, Ruschitzka F, Lopez-Fernandez S, Miani D, Filippatos G, Maggioni AP; ESC Heart Failure Long-Term Registry Investigators. Clinical phenotypes and outcome of patients hospitalized for acute heart failure: the ESC Heart Failure Long-Term Registry. *Eur J Heart Fail* 2017;**19**:1242–1254.
45. Mebazaa A, Longrois D, Metra M, Mueller C, Richards AM, Roessig L, Seronde MF, Sato N, Stockbridge NL, Gattis Stough W, Alonso A, Cody RJ, Cook Bruns N, Gheorghiade M, Holzmeister J, Laribi S, Zannad F. Agents with vasodilator properties in acute heart failure: how to design successful trials. *Eur J Heart Fail* 2015;**17**:652–664.
46. Metra M, Teerlink JR. Heart failure. *Lancet* 2017;**390**:1981–1995.
47. Gheorghiade M, Abraham WT, Albert NM, Greenberg BH, O'Connor CM, She L, Stough WG, Yancy CW, Young JB, Fonarow GC. Systolic blood pressure at admission, clinical characteristics, and outcomes in patients hospitalized with acute heart failure. *JAMA* 2006;**296**:2217–2226.
48. Greene SJ, Hernandez AF, Dunning A, Ambrosy AP, Armstrong PW, Butler J, Cerbin LP, Coles A, Ezekowitz JA, Metra M, Starling RC, Teerlink JR, Voors AA, O'Connor CM, Mentz RJ. Hospitalization for recently diagnosed versus worsening chronic heart failure: from the ASCEND-HF trial. *J Am Coll Cardiol* 2017;**69**:3029–3039.
49. Arrigo M, Gayat E, Parenica J, Ishihara S, Zhang J, Choi DJ, Park JJ, Alhabib KF, Sato N, Miro O, Maggioni AP, Zhang Y, Spinar J, Cohen-Solal A, Iwashyna TJ, Mebazaa A; GREAT Network. Precipitating factors and 90-day outcome of acute heart failure: a report from the intercontinental GREAT registry. *Eur J Heart Fail* 2017;**19**:201–208.
50. Triposkiadis F, Giamouzis G, Parissis J, Starling RC, Boudoulas H, Skoularigis J, Butler J, Filippatos G. Reframing the association and significance of co-morbidities in heart failure. *Eur J Heart Fail* 2016;**18**:744–758.
51. Targher G, Dauriz M, Laroche C, Temporelli PL, Hassanein M, Seferovic PM, Drozdz J, Ferrari R, Anker S, Coats A, Filippatos G, Crespo-Leiro MG, Mebazaa A, Piepoli MF, Maggioni AP, Tavazzi L; ESC-HFA HF Long-Term Registry Investigators. In-hospital and 1-year mortality associated with diabetes in patients with acute heart failure: results from the ESC-HFA Heart Failure Long-Term Registry. *Eur J Heart Fail* 2017;**19**:54–65.
52. Nunez J, Garcia-Blas S, Comin-Colet J. Iron deficiency and risk of early readmission following hospitalization for acute heart failure. Reply. *Eur J Heart Fail* 2016;**18**:881.
53. Jankowska EA, Tkaczyszyn M, Suchocki T, Drozd M, von Haehling S, Doehner W, Banasiak W, Filippatos G, Anker SD, Ponikowski P. Effects of intravenous iron therapy in iron-deficient patients with systolic heart failure: a meta-analysis of randomized controlled trials. *Eur J Heart Fail* 2016;**18**:786–795.
54. Ferreira JP, Girerd N, Rossignol P, Zannad F. Geographic differences in heart failure trials. *Eur J Heart Fail* 2015;**17**:893–905.
55. Blair JE, Zannad F, Konstam MA, Cook T, Traver B, Burnett JC Jr, Grinfeld L, Krasa H, Maggioni AP, Orlandi C, Swedberg K, Udelson JE, Zimmer C, Gheorghiade M; EVEREST Investigators. Continental differences in clinical characteristics, management, and outcomes in patients hospitalized with worsening heart failure results from the EVEREST (Efficacy of Vasopressin Antagonism in Heart Failure: Outcome Study with Tolvaptan) program. *J Am Coll Cardiol* 2008;**52**:1640–1648.
56. Mentz RJ, Cotter G, Cleland JG, Stevens SR, Chiswell K, Davison BA, Teerlink JR, Metra M, Voors AA, Grinfeld L, Ruda M, Mareev V, Lotan C, Bloomfield DM, Fiuzat M, Givertz MM, Ponikowski P, Massie BM, O'Connor CM. International differences in clinical characteristics, management, and outcomes in acute heart failure patients: better short-term outcomes in patients enrolled in Eastern Europe and Russia in the PROTECT trial. *Eur J Heart Fail* 2014;**16**:614–624.
57. Metra M, Mentz RJ, Hernandez AF, Heizer GM, Armstrong PW, Clausell N, Corbalan R, Costanzo MR, Dickstein K, Dunlap ME, Ezekowitz JA, Howlett JG, Komajda M, Krum H, Lombardi C, Fonarow GC, McMurray JJ, Nieminen MS, Swedberg K, Voors AA, Starling RC, Teerlink JR, O'Connor CM. Geographic differences in patients in a global acute heart failure clinical trial (from the ASCEND-HF Trial). *Am J Cardiol* 2016;**117**:1771–1778.

58. Ambrosy AP, Fonarow GC, Butler J, Chioncel O, Greene SJ, Vaduganathan M, Nodari S, Lam CS, Sato N, Shah AN, Gheorghiade M. The global health and economic burden of hospitalizations for heart failure: lessons learned from hospitalized heart failure registries. *J Am Coll Cardiol* 2014;**63**:1123–1133.
59. Khan H, Greene SJ, Fonarow GC, Kalogeropoulos AP, Ambrosy AP, Maggioni AP, Zannad F, Konstam MA, Swedberg K, Yancy CW, Gheorghiade M, Butler J; EVEREST Trial Investigators. Length of hospital stay and 30-day readmission following heart failure hospitalization: insights from the EVEREST trial. *Eur J Heart Fail* 2015;**17**:1022–1031.
60. Cotter G, Davison BA, Milo O, Bourge RC, Cleland JG, Jondeau G, Krum H, O'Connor CM, Metra M, Parker JD, Torre-Amione G, van Veldhuisen DJ, Kobrin I, Rainisio M, Senger S, Edwards C, McMurray JJ, Teerlink JR; VERITAS Investigators. Predictors and associations with outcomes of length of hospital stay in patients with acute heart failure: results from VERITAS. *J Card Fail* 2016;**22**:815–822.
61. Pfeffer MA, Claggett B, Assmann SF, Boineau R, Anand IS, Clausell N, Desai AS, Diaz R, Fleg JL, Gordeev I, Heitner JF, Lewis EF, O'Meara E, Rouleau JL, Probstfield JL, Shaburishvili T, Shah SJ, Solomon SD, Sweitzer NK, McKinlay SM, Pitt B. Regional variation in patients and outcomes in the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT) trial. *Circulation* 2015;**131**:34–42.
62. Greene SJ, Hernandez AF, Sun JL, Metra M, Butler J, Ambrosy AP, Ezekowitz JA, Starling RC, Teerlink JR, Schulte PJ, Voors AA, Armstrong PW, O'Connor CM, Mentz RJ. Influence of clinical trial site enrollment on patient characteristics, protocol completion, and end points: insights from the ASCEND-HF Trial (Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure). *Circ Heart Fail* 2016;**9**:e002986.
63. de Denus S, O'Meara E, Desai AS, Claggett B, Lewis EF, Leclair G, Jutras M, Lavoie J, Solomon SD, Pitt B, Pfeffer MA, Rouleau JL. Spironolactone metabolites in TOPCAT – new insights into regional variation. *N Engl J Med* 2017;**376**:1690–1692.
64. Anker SD, Ponikowski P, Mitrovic V, Peacock WF, Filippatos G. Ularitide for the treatment of acute decompensated heart failure: from preclinical to clinical studies. *Eur Heart J* 2015;**36**:715–723.
65. Gheorghiade M, Vaduganathan M, Greene SJ, Mentz RJ, Adams KF Jr, Anker SD, Arnold M, Baschiera F, Cleland JG, Cotter G, Fonarow GC, Giordano C, Metra M, Misselwitz F, Muhlhofer E, Nodari S, Frank Peacock W, Pieske BM, Sabbah HN, Sato N, Shah MR, Stockbridge NL, Teerlink JR, van Veldhuisen DJ, Zalewski A, Zannad F, Butler J. Site selection in global clinical trials in patients hospitalized for heart failure: perceived problems and potential solutions. *Heart Fail Rev* 2014;**19**:135–152.
66. Butler J, Subacius H, Vaduganathan M, Fonarow GC, Ambrosy AP, Konstam MA, Maggioni A, Mentz RJ, Swedberg K, Zannad F, Gheorghiade M; EVEREST Investigators. Relationship between clinical trial site enrollment with participant characteristics, protocol completion, and outcomes: insights from the EVEREST (Efficacy of Vasopressin Antagonism in Heart Failure: Outcome Study with Tolvaptan) trial. *J Am Coll Cardiol* 2013;**61**:571–579.
67. Metra M, Davison BA, Gimpelewicz C, Carubelli V, Felker GM, Filippatos G, Greenberg BH, Hua TA, Liu Z, Pang PS, Ponikowski P, Severin TM, Voors AA, Wang Y, Cotter G, Teerlink JR. Site enrollment rate, outcomes, and study drug effects in a multicenter trial. Results from RELAX-AHF. *Int J Cardiol* 2018;**253**:91–96.
68. Meijers WC, de Boer RA, van Veldhuisen DJ, Jaarsma T, Hillege HL, Maisel AS, Di Somma S, Voors AA, Peacock WF. Biomarkers and low risk in heart failure. Data from COACH and TRIUMPH. *Eur J Heart Fail* 2015;**17**:1271–1282.
69. Demissei BG, Valente MA, Cleland JG, O'Connor CM, Metra M, Ponikowski P, Teerlink JR, Cotter G, Davison B, Givertz MM, Bloomfield DM, Dittrich H, van der Meer P, van Veldhuisen DJ, Hillege HL, Voors AA. Optimizing clinical use of biomarkers in high-risk acute heart failure patients. *Eur J Heart Fail* 2016;**18**:269–280.
70. Ovchinnikova ES, Schmitter D, Vegter EL, Ter Maaten JM, Valente MA, Liu LC, van der Harst P, Pinto YM, de Boer RA, Meyer S, Teerlink JR, O'Connor CM, Metra M, Davison BA, Bloomfield DM, Cotter G, Cleland JG, Mebazaa A, Laribi S, Givertz MM, Ponikowski P, van der Meer P, van Veldhuisen DJ, Voors AA, Berezikov E. Signature of circulating microRNAs in patients with acute heart failure. *Eur J Heart Fail* 2016;**18**:414–423.
71. Jackson CE, Haig C, Welsh P, Dalzell JR, Tsorlalis IK, McConnachie A, Preiss D, Anker SD, Sattar N, Petrie MC, Gardner RS, McMurray JJ. The incremental prognostic and clinical value of multiple novel biomarkers in heart failure. *Eur J Heart Fail* 2016;**18**:1491–1498.
72. Demissei BG, Cotter G, Prescott MF, Felker GM, Filippatos G, Greenberg BH, Pang PS, Ponikowski P, Severin TM, Wang Y, Qian M, Teerlink JR, Metra M, Davison BA, Voors AA. A multimarker multi-time point-based risk stratification strategy in acute heart failure: results from the RELAX-AHF trial. *Eur J Heart Fail* 2017;**19**:1001–1010.
73. Voors AA, Anker SD, Cleland JG, Dickstein K, Filippatos G, van der Harst P, Hillege HL, Lang CC, Ter Maaten JM, Ng L, Ponikowski P, Samani NJ, van Veldhuisen DJ, Zannad F, Zwinderman AH, Metra M. A systems BIOlogy Study to TAilored Treatment in Chronic Heart Failure: rationale, design, and baseline characteristics of BIOSTAT-CHF. *Eur J Heart Fail* 2016;**18**:716–726.
74. Chen HH, Redfield MM. Dopamine vs nesiritide for acute heart failure with renal dysfunction—reply. *JAMA* 2014;**311**:1565–1566.
75. Cowie MR, Filippatos GS, Alonso Garcia MLA, Anker SD, Baczynska A, Bloomfield DM, Borentain M, Bruins Slot K, Cronin M, Doevendans PA, El-Gazayerly A, Gimpelewicz C, Honarpour N, Janmohamed S, Janssen H, Kim AM, Lautsch D, Laws I, Lefkowitz M, Lopez-Sendon J, Lyon AR, Malik FI, McMurray JJ, Metra M, Figueroa Perez S, Pfeffer MA, Pocock SJ, Ponikowski P, Prasad K, Richard-Lordereau I, Roessig L, Rosano GMC, Sherman W, Stough WG, Swedberg K, Tyl B, Zannad F, Boulton C, De Graeff P. New medicinal products for chronic heart failure: advances in clinical trial design and efficacy assessment. *Eur J Heart Fail* 2017;**19**:718–727.
76. Fonarow GC, Abraham WT, Albert NM, Stough WG, Gheorghiade M, Greenberg BH, O'Connor CM, Sun JL, Yancy C, Young JB; OPTIMIZE-HF Investigators and Coordinators. Carvedilol use at discharge in patients hospitalized for heart failure is associated with improved survival: an analysis from Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF). *Am Heart J* 2007;**153**:82.e1–11.
77. Gayat E, Arrigo M, Littnerova S, Sato N, Parenica J, Ishihara S, Spinar J, Muller C, Harjola VP, Lassus J, Miro O, Maggioni AP, AlHabib KF, Choi DJ, Park JJ, Zhang Y, Zhang J, Januzzi JL Jr, Kajimoto K, Cohen-Solal A, Mebazaa A. Heart failure oral therapies at discharge are associated with better outcome in acute heart failure: a propensity-score matched study. *Eur J Heart Fail* 2018;**20**:345–354.
78. Greene SJ, Maggioni AP, Fonarow GC, Solomon SD, Bohm M, Kandra A, Prescott MF, Reimund B, Hua TA, Lesogor A, Zannad F, Gheorghiade M; ASTRONAUT Investigators and Coordinators. Clinical profile and prognostic significance of natriuretic peptide trajectory following hospitalization for worsening chronic heart failure: findings from the ASTRONAUT trial. *Eur J Heart Fail* 2015;**17**:98–108.
79. Greene SJ, Fonarow GC, Solomon SD, Subacius HP, Ambrosy AP, Vaduganathan M, Maggioni AP, Bohm M, Lewis EF, Zannad F, Butler J, Gheorghiade M; ASTRONAUT Investigators and Coordinators. Influence of atrial fibrillation on post-discharge natriuretic peptide trajectory and clinical outcomes among patients hospitalized for heart failure: insights from the ASTRONAUT trial. *Eur J Heart Fail* 2017;**19**:552–562.
80. Butler J, Gheorghiade M, Kelkar A, Fonarow GC, Anker S, Greene SJ, Papadimitriou L, Collins S, Ruschitzka F, Yancy CW, Teerlink JR, Adams K, Cotter G, Ponikowski P, Felker GM, Metra M, Filippatos G. In-hospital worsening heart failure. *Eur J Heart Fail* 2015;**17**:1104–1113.
81. Davison BA, Metra M, Cotter G, Massie BM, Cleland JG, Dittrich HC, Edwards C, Filippatos G, Givertz MM, Greenberg B, Ponikowski P, Voors AA, O'Connor CM, Teerlink JR; PROTECT and RELAX-AHF Executive Committees. Worsening heart failure following admission for acute heart failure: a pooled analysis of the PROTECT and RELAX-AHF studies. *JACC Heart Fail* 2015;**3**:395–403.
82. Fonseca C, Maggioni AP, Marques F, Araujo I, Bras D, Langdon RB, Lombardi C, Bettencourt P. A systematic review of in-hospital worsening heart failure as an endpoint in clinical investigations of therapy for acute heart failure. *Int J Cardiol* 2018;**250**:215–222.
83. Ambrosy AP, Pang PS, Khan S, Konstam MA, Fonarow GC, Traver B, Maggioni AP, Cook T, Swedberg K, Burnett JC Jr, Grinfeld L, Udelson JE, Zannad F, Gheorghiade M; EVEREST Trial Investigators. 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**:835–843.
84. Gheorghiade M, Follath F, Ponikowski P, Barsuk JH, Blair JE, Cleland JG, Dickstein K, Drazner MH, Fonarow GC, Jaarsma T, Jondeau G, Sendon JL, Mebazaa A, Metra M, Nieminen M, Pang PS, Seferovic P, Stevenson LW, van Veldhuisen DJ, Zannad F, Anker SD, Rhodes A, McMurray JJ, Filippatos G; European Society of Cardiology; European Society of Intensive Care Medicine. Assessing and grading congestion in acute heart failure: a scientific statement from the acute heart failure committee of the heart failure association of the European Society of Cardiology and endorsed by the European Society of Intensive Care Medicine. *Eur J Heart Fail* 2010;**12**:423–433.