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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.\textsuperscript{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.\textsuperscript{5-7} Similarly, unplanned visits for worsening symptoms requiring intravenous diuretic treatment are also associated with poor prognosis, with a greater than 4-fold increase in subsequent mortality.\textsuperscript{8, 9}

The available treatment options (primarily diuretics or vasodilators in normo/hypertensive patients) provide symptomatic relief,\textsuperscript{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.\textsuperscript{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. The contrast between the advances made in acute heart failure compared to other cardiovascular conditions (e.g., heart failure with reduced ejection fraction, acute coronary syndrome) is striking. This experience calls for critical examination of past trials and application of lessons learned to guide new directions in the field.
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).\textsuperscript{13-23} A comprehensive review of the results of all major trials is beyond the scope of this manuscript, but two recent trials involving vasodilators are discussed, the results from which were unexpected.

The Trial of Ularitide Efficacy and Safety in Acute Heart Failure (TRUE-AHF) was a randomized, double-blind, parallel-group, placebo-controlled trial evaluating the effects of a 48-hour 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 from presentation. The study had two co-primary endpoints: cardiovascular mortality during long-term follow-up (median 15 months) and the early clinical course (during first 48 hours) assessed through a composite endpoint including death, worsening heart failure and symptom relief.\textsuperscript{24} A total of 2,157 patients were enrolled, and no benefit was observed for ularitide versus placebo in either of the co-primary endpoints.\textsuperscript{23}

The Efficacy, Safety, and Tolerability of Serelaxin When Added to Standard Therapy in Acute Heart Failure trial-2 (RELAX-AHF-2) was a randomized, double-blind, placebo controlled study that enrolled 6,545 patients with acute heart failure (defined as dyspnea at rest or with minimal exertion, pulmonary congestion on chest radiograph, and BNP $\geq$500 pg/mL or NT-proBNP $\geq$2000 pg/mL, treated with intravenous furosemide $\geq$40 mg before screening, estimated glomerular filtration rate 30-75 ml/min/1.73 m$^2$, 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). 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 to understand whether the drugs were truly 
ineffective, if characteristics inherent to the acute heart failure population or the 
clinical settings where they receive care could have played a role, or if flaws in 
clinical trial design or execution may have contributed. Importantly, these clinical 
trial results can influence future research strategies and may ultimately enable 
discovery of effective treatment options for patients with acute heart failure.

Key Lessons Learned from Completed Clinical Trials

The lack of progress in identifying effective therapies for the treatment of
acute heart failure has been disappointing, but a large body of evidence from 
prospective, randomized clinical trials conducted over the past decade is now 
available and can provide substantial insight into the clinical characteristics and 
outcomes of patients with acute heart failure (Table 1). Heterogeneity across 
many aspects relevant to acute heart failure has been proposed as a major factor 
influencing clinical trial results to date.

Heterogeneity in Causes of Rehospitalization or Death

Rehospitalizations and deaths that occur following an episode of acute heart 
failure are attributed to several different causes. A large proportion may be non-
cardiovascular or, at least, not related with heart failure.\textsuperscript{26-29} In the OPTIMIZE-HF registry, 42\% of patients had at least 1 factor that precipitated the hospitalization for acute heart failure.\textsuperscript{30} The most common contributors were pneumonia or respiratory condition (15.3\%), acute coronary syndrome or ischemia (14.7\%), arrhythmia (13.5\%), and uncontrolled hypertension (10.7\%).\textsuperscript{30} Other important factors include infection, poor nutrition, or deconditioning.\textsuperscript{31, 32} Social support, education of the patient and her/his relatives, home monitoring, and increasing patients’ 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.\textsuperscript{33-38}

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 were related to non-cardiovascular causes, while the cause of death was unknown in slightly over a third (34.7\%) of patients.\textsuperscript{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.\textsuperscript{39}

\textbf{Heterogeneity in Acute Heart Failure Pathophysiology and Clinical Phenotypes}

It is accepted that multiple pathophysiologic pathways can lead to acute heart failure.\textsuperscript{40} Treatment strategies applied to the broad population of patients with acute heart failure have not yielded improvements in outcome. This experience suggests that phenotyping patients hospitalized for acute heart failure and administering treatments specific for the phenotype may be a more effective approach.\textsuperscript{41} The optimum criteria for determining phenotype has not been defined. They may include
purely clinical variables or also incorporate more sophisticated strategies (e.g., bioprofiling, multimarker panels).

Current treatment algorithms always recommend investigation of potential specific causes of decompensation. Possible etiologies of acute heart failure include acute coronary syndromes, hypertensive emergencies, arrhythmias, or mechanical factors (e.g., acute valve regurgitation, septal rupture, aortic dissection, pulmonary embolism). Specific treatment targeting these underlying causes may dramatically improve both symptoms and clinical outcomes.

After evaluation of specific aetiologies, patients are further classified based on the presence of signs of congestion and/or peripheral hypoperfusion. In addition, blood pressure remains the most important clinical variable to consider when making treatment choices. Variables, such as duration of heart failure diagnosis, precipitating factors of the acute decompensation, and comorbidities also influence subsequent outcomes. 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.

Despite the exceptions noted above, clinical criteria may be insufficient to reflect the underlying predominant pathophysiology. Moreover, clinical classifications alone in patients with acute heart failure have failed to differentiate long-term outcomes. Use of multiple biomarkers may provide more comprehensive characterization of pathophysiology and the role of genomic and proteomic analyses are under investigation. A multimarker approach that included high sensitivity cardiac troponin, N-terminal pro-B-type natriuretic peptide, 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.
However, it is important to recognize that while these markers can indicate patients at high risk of poor outcome, they do not necessarily indicate that the outcome can be impacted by the treatment under study. Single or multi-biomarkers can reflect a high-risk population, but in order to achieve better precision in clinical trials, it is important to match the pathophysiology reflected by the biomarker with a treatment that can interrupt the underlying pathophysiological processes. Using biomarkers to identify a high-risk population is insufficient if the biomarker does not also provide information on the likelihood of response or non-response to treatment. Development of biomarker approaches that identify a predominant pathophysiology may help promote precision medicine by enabling therapies to be selected that match the prevailing pathophysiology. However, this concept remains a hypothesis that needs to be validated in clinical trials.

**Heterogeneity by Geography**

Geographical differences have influenced the results of clinical trials in acute heart failure. 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%). Geographic disparity in use of inotropes has also been reported (United States 15%, Europe 22-30%, Japan 19%). 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.
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.\textsuperscript{5, 23, 56, 61-63}

**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 lower risk of 30-day death or rehospitalization.\textsuperscript{64} Low performing centres with poor protocol adherence or inadequate clinical trial experience may introduce “noise” and decrease the ability to detect treatment effects. 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\textsuperscript{65}), rather than to intrinsic differences in patient populations.

Critical processes have been described to achieve optimal site selection in acute heart failure trials.\textsuperscript{66} 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 key factors that determine the success of sites in a clinical trial.\textsuperscript{66}

**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 patients’ 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,\textsuperscript{67, 68} although it is
acknowledged that phase 2 results can be unstable due to the relatively small number
of patients or events usually reflected in phase 2 trials. Specifically, serelaxin
improved multiple endpoints in a first phase IIb trial, pre-RELAX,\textsuperscript{68} and reduced
worsening heart failure and cardiovascular and all-cause mortality in the RELAX-AHF trial.\textsuperscript{21E}

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 suboptimal matching of study drug to patient
phenotype or selecting the wrong timepoint to assess study endpoints. Addressing
these considerations in future trials, along with the previously mentioned
heterogeneity among patients with acute heart failure, may help generate future
successes.

\textbf{Matching Drugs to Pathophysiology}

Investigators in acute heart failure have drawn parallels between acute heart
failure and acute coronary syndromes, since in both cases an acute event is followed
by an increase in mortality. In acute coronary syndromes, drugs acting on the primary pathophysiology (i.e., thrombus formation) improve long-term outcomes. In acute heart failure, it was hypothesized that a drug administered in the acute setting could also exert long-term effects on outcome. Unfortunately, the critical difference between acute coronary syndrome and acute heart failure is that acute heart failure can originate from many different pathophysiologic processes. The equivalent of a “clot” for acute heart failure has not yet been identified. The targeted pathophysiology model has also worked well for patients with chronic heart failure and reduced ejection fraction, where mechanisms responsible for disease progression such as neurohormonal activation, tachycardia, or dyssynchrony are identified and treated with neurohormonal antagonists, ivabradine, or cardiac resynchronization.¹,⁴²

Better patient phenotyping has also been proposed as a solution to increase the likelihood of a successful trial. This approach assumes that patient phenotype might correlate with the relevant pathophysiology (e.g., matching drugs with renal protective effects to patients with worsening renal function, vasodilators in patients with normal to high blood pressure). Although a logical idea, these trials have also failed to identify a clinical benefit of treatment.¹⁷-¹⁹,²³,⁶⁹ Thus, current clinical and laboratory based approaches to phenotyping patients with acute heart failure is not effective to select and target treatment. 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.⁷⁰,⁷¹ 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. 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 hours) 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. 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. 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 (HR 0.56, 95% CI 0.46-0.69) and 1-year mortality (HR 0.62, 95% CI 0.55-0.71) than untreated patients. 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. 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 patients’ outcomes and have often been used as surrogates for outcomes. However, the relationship between the effect of drug therapy on natriuretic peptides and outcomes have been inconsistent across trials.14, 15, 74, 75

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.76-78 Worsening heart failure is also sensitive to drug treatment.15, 21, 76, 79 However, it is also highly dependent on the investigator or patient reporting events, as well as the specific definition used to identify worsening heart failure events.79 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, 68 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. 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.

Conflicts of interest
R. Ferrari 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. Bueno reports having received consulting/speaking fees from Abbott, Astra-Zeneca, Bayer, BMS-Pfizer, Daichii-Sankyo, Eli-Lilly, Ferrer, Menarini, Novartis, Sanofi, Servier, and research grants from Astra-Zeneca. O. Chioncel reported steering committee membership of Novartis. He has also received research support from Servier, Vifor, Roche, and Novartis. J.G. Cleland 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. Lettino 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. Metra has received fees for board membership from Bayer, Novartis, and Servier, and lecture fees and/or manuscript preparation from Servier and Abbot Vascular. J.T. Parissis received honoraria for advisory boards and lectures from Roche diagnostics. Servier, Novartis and Orion Pharma. F. Pinto has received consulting, manuscript preparation, and/or lecture fees from Bayer, Novartis, Pfizer and Servier. P. Ponikowski has received grants, consulting fees or honoria, and travel support from Vifor Pharma, Amgen, Servier, Novartis, Bayer, Abbott Vascular, Boehringer Ingeheim, Resplicardia, Coridea, Celladon, and Cardiorentis. F. Ruschitzka received payment for lectures including service on speakers' bureaus from SJM, Servier, Zoll, AstraZeneca and HeartWare. L. Tavazzi 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.

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References


first inpatient and outpatient heart failure event in a heart failure clinical trial:


43. 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(18):2217-2226.


from the ESC-HFA Heart Failure Long-Term Registry. Eur J Heart Fail 2017;19(1):54-65.


Antagonism in Heart Failure: Outcome Study with Tolvaptan) program. J Am Coll Cardiol 2008;52(20):1640-1648.


<table>
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<tr>
<th>Trial</th>
<th>Study drug vs. comparator</th>
<th>Patient Population</th>
<th>Primary Endpoint</th>
<th>Duration of Treatment</th>
<th>Primary Results (Study Drug vs. Control)</th>
<th>Potential Contributors to Results</th>
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</thead>
<tbody>
<tr>
<td>OPTIME13</td>
<td>Milrinone vs. placebo (on top of standard care)</td>
<td>N=949, ADHF, &lt;48 hours since admission, LVEF &lt;40%</td>
<td>Number of days hospitalized for CV causes or dead within 60 days after randomization</td>
<td>48 hours</td>
<td>Median 6 days vs. 7 days, P=0.71</td>
<td>Mismatch of patient population to drug mechanism of action (patients congested, not low output)</td>
</tr>
<tr>
<td>SURVIVE14</td>
<td>Levosemidan vs. dobutamine</td>
<td>N=1,327, ADHF, need inotropic support, LVEF &lt;30%, SBP ≥85 mmHg</td>
<td>180-day all-cause mortality</td>
<td>24 hours (min)</td>
<td>26% vs. 28%, HR 0.91, 95% CI 0.74-1.13, P=0.4</td>
<td>Active controlled study</td>
</tr>
<tr>
<td>REVIVE15</td>
<td>Levosemidan vs. placebo (on top of standard care)</td>
<td>N=600, ADHF, dypneic at rest despite IV diuretic treatment, LVEF ≤35%, SBP ≥90 mmHg</td>
<td>Clinical classification of improved, unchanged, or worse during first 5 days</td>
<td>24 hours</td>
<td>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</td>
<td>Hypotension</td>
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<tr>
<td>EVEREST16</td>
<td>Tolvaptan vs. placebo (on top of standard care)</td>
<td>N=4,133, ADHF, volume overload, NYHA class III/IV, &lt;48 hours since admission, LVEF ≤40%</td>
<td>Co-primary: all-cause mortality; composite of CV death or hospitalization for HF (median follow-up)</td>
<td>60 days</td>
<td>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</td>
<td>Mismatch of patient population to drug mechanism of action (i.e., patients may not have had elevated...</td>
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Table 1. Overview of Major Randomized, Controlled Trials with new drugs in Acute Heart Failure\textsuperscript{13-23} (continued)

<table>
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<tr>
<th>Trial Study drug vs. comparator</th>
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<tr>
<td>VERITAS program\textsuperscript{17} Tezosentan vs. placebo (on top of standard care)</td>
<td>N=1,448, ADHF, persistent dyspnea at rest, &lt;24 hours since admission, SBP $\geq$100 mmHg (or $\geq$120 mmHg if concomitant vasodilator)</td>
<td>Individual studies: Change from baseline in dyspnea over first 24 hours Combined studies: incidence of death or worsening HF at 7 days</td>
<td>up 9.9 months)</td>
<td>P=0.55</td>
<td>vasopressin levels, only 8% had hyponatremia)</td>
</tr>
<tr>
<td>PROTECT\textsuperscript{18} Rolofylline vs. placebo (on top of standard care)</td>
<td>N=2,033, ADHF, persistent dyspnea at rest or minimal activity, estimated CrCl 20-80 ml/min, &lt;24 hours since admission, SBP</td>
<td>Treatment success, failure or no change in clinical condition</td>
<td>Up to 3 days</td>
<td>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</td>
<td>Inadequate understanding of contribution of cardiorenal syndrome to ADHF pathophysiology (i.e., role of psuedoworsening)</td>
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<td>Trial Study drug vs. comparator</td>
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<tr>
<td>ASCEND-HF&lt;sup&gt;19&lt;/sup&gt; Nesiritide vs. placebo (on top of standard care)</td>
<td>≥95 mmHg</td>
<td>Co-primary: Change in self-reported dyspnea at 6 and 24 hours; composite of all-cause mortality or HF hospitalization at 30 days</td>
<td>24 hours to 7 days</td>
<td>Moderate or marked improvement in dyspnea at 6 hours: 44.5% vs. 42.1% (P=0.03, did not meet pre-specified criteria for significance) Moderate or marked improvement in dyspnea at 24 hours: 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)</td>
<td>Co-administration of other therapies that relieve congestion; limitations of dyspnea assessment instruments (i.e., minimal clinically important differences); lower than expected event rate</td>
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<tr>
<td>ASTRONAUT&lt;sup&gt;20&lt;/sup&gt; Aliskiren vs. placebo (on top of standard care)</td>
<td>N=7,141, ADHF; dyspnea at rest with minimal activity, &lt;24 hours after first intravenous treatment for ADHF, SBP ≥100 mmHg (or ≥110 if concomitant intravenous nitroglycerin)</td>
<td>First occurrence of CV death or HF rehospitalization at 6 months</td>
<td>12 months</td>
<td>24.9% vs. 26.5%, HR 0.92, 95% CI 0.76-1.12, P=0.41</td>
<td>Limited potential for beneficial treatment effect of additional RAAS blockade; influence of comorbidities (i.e., diabetes mellitus); influence of adverse effects (e.g., hyperkalemia, renal impairment,</td>
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<td>RELAX-AHF\textsuperscript{21} Serelaxin vs. placebo (on top of standard care)</td>
<td>N=1,161, ADHF, presented within 16 hours, treated with $\geq$40 mg intravenous furosemide before screening, SBP $&gt;$125 mmHg</td>
<td>Co-primary: Change in patient-reported dyspnea quantified by area under curve of visual analogue scale scores through day 5; moderately or markedly improved patient reported dyspnea using 7-point Likert scale at 6, 12, and 24 hrs (responders were those with moderate or marked improvement at all timepoints)</td>
<td>Up to 48 hours</td>
<td>Area under curve of visual analogue scale: Greater change from baseline for serelaxin (2756 mm x hr vs. 2308 mm x hr, $P=0.007$) Likert scale marked or moderate improvement: 35.8% vs. 31.4% at 6 hrs ($P=0.113$), 50.3% vs. 44.6% at 12 hrs ($P=0.051$), 67.9% vs. 63.1% at 24 hrs ($P=0.086$) 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, $P=0.028$</td>
<td>Lower risk population (based on placebo group 30-day all-cause mortality of 3%, lower than VERITAS and ASCEND); limitations of dyspnea assessment instruments (i.e., minimal clinically important differences);</td>
</tr>
<tr>
<td>RELAX-AHF-2\textsuperscript{22} Serelaxin vs. placebo (on top of standard care)</td>
<td>N=6,545, ADHF, randomized within 16 hours,</td>
<td>Co-primary: CV mortality at 180 days; worsening</td>
<td>48 hours</td>
<td>No difference in CV mortality at 180 days between groups</td>
<td>Short-term drug administration unlikely to impact</td>
</tr>
</tbody>
</table>
Table 1. Overview of Major Randomized, Controlled Trials with new drugs in Acute Heart Failure\textsuperscript{13-23} (continued)

<table>
<thead>
<tr>
<th>Trial Study drug vs. comparator</th>
<th>Patient Population</th>
<th>Primary Endpoint</th>
<th>Duration of Treatment</th>
<th>Primary Results (Study Drug vs. Control)</th>
<th>Potential Contributors to Results</th>
</tr>
</thead>
</table>
| TRUE-HF\textsuperscript{23}  | Ularitide vs. placebo (on top of standard care) | N=2,157, ADHF (ER or hospitalization), study drug initiation within 12 hours, persistent dyspnea 2 hours after \( \geq 40 \) mg intravenous furosemide, SBP 116-180 mmHg | Co-primary: CV death (median follow-up 15 months); hierarchical clinical composite during first 48 hours | 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 hemodynamic improvement and reduction in wall stress, no benefit on long-term outcomes suggesting that rapid cardiac decongestion does not influence that natural history of heart failure progression |

SBP \( \geq 125 \) mmHg | HF through day 5 | Non-significant trend towards reduction in worsening HF through day 5 | long-term outcomes; small number of deaths in RELAX-AHF may explain discrepancy in findings between two studies |