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Early Treatment in Emergency Department Patients with Acute Heart Failure: Does Time Matter?

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Abstract

Purpose of Review Acute heart failure accounts for over one million hospital discharges annually. Current guidelines suggest treatments for AHF should begin "without delay" but this time interval has not been clearly defined.

Recent Findings Data suggest that certain treatments such as earlier treatment with diuretics and vasodilators may improve patient symptom relief, morbidity, and mortality. Secondary analyses of clinical trials of novel treatments under development have not shown similar results.

Summary The data are equivocal regarding the impact of early treatment in AHF on in-hospital and long-term morbidity and mortality. Improved clinical trial designs will help answer when and if "early" treatment should begin and whether it impacts short- and long-term outcomes in AHF.

Keywords Acute heart failure · Emergency medicine · Treatments for AHF

Introduction

Chronic heart failure (HF) afflicts nearly six million Americans, resulting in over one million emergency department (ED) visits [1] and over one million annual hospital discharges for acute HF (AHF) [2]. AHF is a secondary diagnosis in over three million hospitalizations [3]. An aging population and improved survival from cardiovascular diseases will lead to increased chronic HF prevalence by 25% heading into the next decade. Costs will also increase; over $39 billion was spent on HF care in the USA in 2010 and will almost double by 2030 [4].

Despite this growing burden, pharmacologic treatment of AHF has not changed significantly in more than 40 years [3]. Targeted time to treatment definitions now exist for multiple other disease states, including acute coronary syndrome (ACS), stroke, sepsis, and trauma (Table 1) no similar time definitions exist for AHF. The 2013 ACCF/AHA Heart failure guidelines do recommend diuretic therapy should begin "without delay", but this time interval is not clearly defined [10]. Unlike these other disease entities, signs and symptoms of AHF are neither sensitive nor specific. Diagnosis often remains a challenge for both emergency physicians and cardiologists [11].

Whether "time to therapy" matters in patients with AHF is debatable [12–16]. Unlike ACS or stroke, there is no "clot" or single defined treatment target. Rather, the goals of therapy in AHF are multi-faceted: to relieve congestion, achieve euvolemia, improve hemodynamics, and

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Table 1 Time to treatment definitions in other acute diseases

Condition	Goal	Time to goal
Chest pain	ECG	10 min of presentation
Chest pain	Serial troponins	At presentation, and 3–6 h after symptom onset
ST elevation MI	First medical provider to balloon deployment	90 min
Trauma	Definitive trauma care	60 min of injury
Ischemic stroke	Administration of intravenous tissue-type plasminogen activator (IV tPA)	4.5 h of stroke onset
Sepsis	Measure lactate level and blood cultures prior to administration of antibiotics, administer broad spectrum antibiotics, and 30 mL/kg crystalloid for hypotension or lactate ≥ 4 mmol/L	Within 3 h for those with sepsis
Sepsis	Start vasopressors to maintain a mean arterial pressure (MAP) ≥ 65 mmHg	Within 6 h

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transition to life-saving chronic HF therapies [10]. Early intervention may help achieve some of these goals, but given the underlying multifactorial physiology that contributes to AHF, it may not impact post-discharge outcomes.

Given both the increased public health burden of AHF and the lack of AHF therapies proven to improve outcomes, we outline three overarching goals of this review. The first is to describe how the definition and timing of early therapy may impact the type of patients and interventions that need to be studied. The second is to describe the available data regarding the association of the timing of AHF treatment with subsequent outcomes in both standard care and novel therapies. The third goal is to highlight how addressing the limitations of current study design could inform subsequent studies to provide better evidence about the timing and type of therapy.

Defining "Early" Treatment: a Balance of Timely Therapy and Accurate Diagnosis

The definition of "early" in AHF treatment can be interpreted in several ways and is often viewed as an absolute time from hospital or ED presentation to treatment or randomization. Historically, clinical trials defined this time frame as up to 48 h after ED presentation [17–19]. However, recent phase III clinical trials have defined this as 12 [20] or 16 [12, 21] h from the initial hospital or ED presentation. These times are not "early" compared with delivering typical acute care therapy such as thrombolytics or percutaneous coronary intervention for an ST elevation MI, which sometimes can occur in the ambulance or within the first 3 h of ED evaluation. In the last 10 years, only one AHF trial attempted to randomize patients within 3 h of ED arrival at the time of initial therapy and receive study drug within 30 min [22]. Finally, from a practical standpoint, early could also be defined based on a transition period during clinical care, such as transitions of care from emergency medical services to the ED, or from the ED to inpatient management.

Patients can present with a myriad of symptoms that are attributable to AHF. Thus, early and accurate diagnosis of AHF can be difficult, unless the patient has readily identifiable findings such as congestion on chest radiograph, lung ultrasound, or jugular venous distension [23]. Patients treated expeditiously for AHF are those with obvious signs and symptoms, and may respond differently than those with more subtle presentations. Further, when symptoms of abdominal swelling and peripheral edema predominate over dyspnea they may be perceived as lower acuity, and providers may feel less compelled to treat them immediately [24]. Importantly, when there is a delay due to diagnostic uncertainty or overlapping comorbidities, the in-hospital and short-term outcomes may be affected. Prior studies suggest a delay in obtaining natriuretic peptide (BNP) levels correlated with delay to treatment, including time to diuretic. The delay in obtaining a BNP likely reflects a dearth of AHF signs or symptoms of a lack of early consideration of AHF as a primary diagnosis, resulting in treatment delays associated with increased in-hospital mortality [13]. In the URGENT-Dyspnea study at 6 h, only 68% of patients had a confirmed diagnosis of AHF and 22% of patients had an unclear diagnosis [25]. Thus, while it would be important to enroll patients as early as possible to avoid confounding by therapy delivered prior to randomization, it is equally important to ensure a timely and accurate diagnosis prior to randomization.

Studies of the Timing of Early Standard Therapy

Non-invasive Ventilation

Early non-invasive ventilation (NIV) benefits AHF patients with respiratory distress and pulmonary edema. This patient phenotype demonstrating benefit includes significantly elevated blood pressure on presentation and is rapidly identified, leading to early intervention with NIV, sometimes even in the pre-hospital setting. Across thousands of patients and pooled analyses, when compared with standard oxygen therapy, both continuous positive airway pressure (CPAP) and non-invasive intermittent positive-pressure ventilation (NIPPV) decreases the need for intubation and time to symptom resolution [26]. While a pre-hospital randomized trial suggested no improvement in mortality or intubation with NIV over standard oxygen therapy, greater reductions in heart rate, acidosis, and hypercapnia were demonstrated [26]. While NIV is beneficial, and it seems intuitive that earlier use is better than later use, there are no studies that have evaluated the timing of NIV and its impact on the use of other treatments and outcomes.

Vasoactive Therapy

Intravenous vasoactive drugs are used in more than a third of AHF admissions [5] and early administration may be important. An ADHERE registry analysis compared patients who received IV vasoactive therapy with vasodilators and inotropes early and late during hospital admission. These agents were used early (within 6 h) in 64% ($n = 22{,}788$) of hospitalizations and late (between 6 and 48 h) in 36% of hospitalizations. Median time to initiation was 1.7 and 14.7 h in the early versus late group. In adjusted analysis, there was lower mortality in those with early vasodilator and inotrope treatments [6]. In addition, a higher proportion of patients who received early vasodilator therapy were asymptomatic at discharge. This analysis is limited by a number of confounders as patients were not randomized. Further, those who were diagnosed in a more rapid manner would have been identified earlier as candidates for vasoactives and were more likely to be hypertensive and evidence of acute congestion [6].

In addition to the registry analysis above, a systematic review evaluated the safety and efficacy of IV vasodilators across 36 studies in ED patients with AHF treated within 24 h of presentation [7]. Of five studies evaluating nitroglycerin, one study suggested patients who received repeated high-dose nitroglycerin boluses over the initial 30 min of treatment, when compared with concurrent nitroglycerin infusion, were less likely to require intubation, NIV, and intensive unit care admission compared with those who did not receive high-dose nitroglycerin [8]. Two studies evaluated the early use of furosemide with high-dose bolus isosorbide dinitrate versus intravenous treatment and found high-dose isosorbide dinitrate was safe and patients were less likely to require mechanical ventilation [26]. While some trials focused on patient outcomes with IV vasoactives, the timing of administration has not been carefully studied. The lack of trials randomizing patients to an early vasoactive strategy limits the conclusions that can be drawn from prior studies. While preliminary data suggests timing may matter, vigorously designed pragmatic studies of IV vasoactives are needed to inform clinical practice and improve the evidence base.

Diuretics

Diuretics are a mainstay of AHF treatment, and delivered in over 80% of ED presentations for AHF [3, 9]. Despite their ubiquitous use, there is only one randomized trial evaluating initial diuretic dosing [27], and while they are recommended in most HF guidelines, the level of evidence is C. Four non-randomized cohort studies evaluated time to furosemide treatment and its association with inpatient outcomes. In the first study patients' time to diuretic was divided into quartiles. The later the treatment took place, the smaller the proportion of patients who were asymptomatic at discharge. In the quartiles of highest BNP, increased time to diuretic was associated with an increased mortality [18]. In the second analysis, ADHERE registry data were linked to Medicare claims data and suggested that most older patients received IV diuretics promptly, with a median time to treatment of 2.3 h. The quartile of time to treatment was associated with a small impact on the in-hospital mortality rate (adjusted OR 1.01 per hour delay) and length of stay (adjusted estimate 0.057 day per hour delay) [5]. More recently, the association between time to diuretic treatment and clinical outcome was evaluated in a cohort of 1291 patients treated with intravenous furosemide within 24 h of ED arrival. Median time to furosemide treatment was 90 min. Of these, 481 patients received furosemide within 60 min, defined as the "early" group. In both multivariate and propensity score-matched analysis, in-hospital mortality was lower in the early furosemide group when compared with the late group [6]. The fourth cohort study was similarly designed but suggested that early diuretic administration was not associated with differences in-hospital or 30-day mortality [16]. There is still equipoise regarding the ideal timing of diuretic therapy, and whether a delay in treatment to ensure an accurate diagnosis outweighs the potential benefit of early therapy. A trial stratifying patients based on time of randomization, conducted at the time of initial ED evaluation is needed to better inform clinical practice.

Dose Early Treatment Matter in AHF Clinical Trials of Novel Therapeutic Agents?

It is important to consider how the choice of the outcome evaluated in clinical trials of novel therapeutic agents may influence the impact of treatment timing on outcome trajectory. In addition to reductions in cardiovascular morbidity and mortality, dyspnea became an endpoint of interest in the 2000s in clinical trials of novel therapeutic agents. In addition, global assessments of worsening heart failure and congestion have also been evaluated. Composite outcomes capturing morbidity and mortality, safety, symptoms, functional capacity, and patient-reported outcomes have all been used. The choice of the outcome impacts whether early treatment matters, as dyspnea relief occurs earlier in the course of treatment than congestion relief. The data on whether dyspnea relief translates to morbidity and mortality benefits are unclear.

Early Clinical Trials

In the last 20 years, investigators and clinicians have shortened the window on time to enrollment for novel AHF therapies. Early trials did not report time of arrival to hospital to first study drug infusion. The Survival of Patients With Acute Heart Failure in Need of Intravenous Inotropic Support (SURVIVE) trial did not report time from presentation to randomization or infusion of either levosimedan or dobutamine [28]. EVEREST (Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan), ASCEND-HF (Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure), and OPTIME-CHF (Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure) required enrollment within 48 h of presentation. ASCEND-HF suggested some improvement in dyspnea with earlier enrollment [29]. However, dyspnea relief did not translate to improvement in 30-day clinical outcomes. A post-hoc analysis of the EVEREST trial placebo group showed that over 70% of patients had a significantly improved congestion score by discharge. However, those with no congestion at discharge still had almost a 20% mortality rate in the follow-up period [14].

The next phase of studies including VERITAS (Value of Endothelin Receptor Inhibition With Tezosentan in Acute Heart Failure Studie) [17], PROTECT (Placebo-Controlled Randomized Study of the Selective A1 Adenosine Receptor Antagonist Rolofylline for Patients Hospitalized with Acute Decompensated Heart Failure) [18], DOSE (Diuretic Optimization Strategies), and ROSE (Renal Optimization Strategies Evaluation in Acute Heart Failure) [30] required enrollment within 24 h of presentation. Despite decreasing the time to enrollment, most of the studies still failed to achieve meaningful differences in short- and long-term outcomes. Tezosentan failed to improve symptoms or clinical outcomes. Rolofylline also did not impact death, worsening heart failure, or rates of early readmission for heart failure [18]. In a post-hoc analysis, infusion of rolofylline did provide early dyspnea relief in almost half of patients and those had decreased mortality [31]. Varying strategies of bolus or infusion dose furosemide in the DOSE-HF trial did not clinically impact dyspnea scores [27], in-hospital outcomes or length of stay. In the ROSE trial, neither low-dose dopamine nor nesiritide had an effect on congestion or renal function [30]. It is unclear whether the agents used were ineffective or perhaps other factors led to the lack of efficacy in the trials.

Earlier Enrollment Times in Trials of Novel Therapeutic Agents—Mixed Results

The program of serelaxin studies further tested the early treatment hypothesis. In pre-RELAX-AHF, patients were randomized a median of 6.6 h from hospital presentation [12]. At the highest dose of serelaxin, more patients had improvement of dyspnea compared with placebo, though some resolution of dyspnea and reduction of increased blood pressure also occurred with standard therapy. Based upon the favorable results on dyspnea and long-term clinical outcomes in pre-RELAX, over 1100 patients were randomized to placebo versus serelaxin infusion in RELAX-AHF [32]. This study had a mean time of 7.9 h from time of presentation until randomization and also found serelaxin resulted in early improvements in dyspnea scores, general well-being, and cardiovascular mortality. RELAX-AHF-2 followed a similar protocol and enrolled over 6500 patients, but in contrast to the prior studies, did not meet its primary endpoints including worsening heart failure through day five or cardiovascular mortality [33]. Evidence of congestion relief including exertional dyspnea, orthopnea, rales, and edema were similar across the serelaxin and placebo subjects. Despite similar enrollment criteria, the findings of the serelaxin series of studies were disparate, and the lack of effectiveness in RELAX-2.

TRUE-AHF evaluated the natriuretic peptide analogue ularitide for a clinical composite endpoint comprised of signs and symptoms of AHF at 6, 24, and 48 h. Given the positive findings from RELAX-AHF [32], the additional co-primary endpoint of cardiovascular mortality was added after enrollment had begun. Patients were randomized in a median of 6.7 h from hospital presentation. In the overall study, there was no difference in cardiovascular mortality or the composite clinical endpoint. In both the placebo and treatment arms, over 45% of patients had moderate or marked improvement in their signs and symptoms.

BLAST-AHF was a phase IIb dose-ranging study, randomizing patients with AHF to placebo or four varying doses of TRV027, a selective ligand of the angiotensin II type 1 receptor [21]. This study also had a primary composite endpoint of 30-day death, rehospitalization, worsening HF, change in dyspnea score, and length of hospitalization. Overall, 621 patients were enrolled, with a median time of enrollment of 5.7 h from presentation. While there was no specific analysis comparing early with late enrollment, despite this overall early enrollment in all patients, there was no benefit seen with TRV027 compared with placebo in any of the endpoints. Thus, despite recent clinical trials decreasing the duration of time to randomization, there are still mixed results of dyspnea relief.

The PRONTO study was a randomized non-blinded trial of clevidipine versus standard-of-care in patients with hypertensive AHF. The study enrolled 104 dyspneic patients with AHF and a systolic blood pressure ≥ 160 mmHg and co-primary endpoints included median time and percent attaining a 30-min target SBP range. Secondary endpoints included dyspnea at each time point through study drug termination. At 45 min after treatment, the dyspnea VAS decrease from baseline was greater with clevidipine than usual care, an effect maintained at 3 h. However, both groups had significant decreases in dyspnea [22]. Mean time to study drug from arrival to the ED was 3.2 h in the clevidipine arm and 2.7 h in the standard of care arm. This door-to-treatment time of 149 min is shorter than any previous trials. The study was small and nonblinded and thus may not be ideal. However, this adds to the body of literature that vasodilators may be most efficacious when used early in the hypertensive AHF phenotype and utilized the collaboration between emergency physicians and cardiologists.

Summary: Timing in AHF Clinical Trials

Patients with AHF often have subclinical congestion developing for days and weeks, eventually leading to symptoms and signs prompting emergency care [34]. Given this long prelude, a therapy given for only a few hours or even 48, may have limited impact. However, standard therapy in all of these clinical trials was poorly structured, introducing significant variability into both arms. This variability would impact both the standard care and investigational arm throughout the study, as well as pre-randomization. While randomization plus a sufficient sample size hopefully balances these differences, such heterogeneity of treatment may have a significant impact. Patient phenotypes may also differ in those who received a smaller dose of diuretics versus higher doses, and those who required vasoactives prior to enrollment than those who did not.

Future Directions—Structured Standard Therapy: Better Defining Timing, Type and Duration Will Inform both Clinical Trials and Practice

Past lessons learned will hopefully inform subsequent trial design. Prior studies have differed in study location, methodology, region of the world, and the medications considered to be part of routine clinical practice. This will have a significant impact on study results and generalizability. First, future trials should study the optimal approach to early standard therapy such as diuretics or noninvasive ventilation. Once standard therapy is well delineated it can be structured as the control arm in randomized trials of novel investigational agents. Further delineation of when patients have "failed" standard therapy based on objective criteria is needed. This may include a standardized dyspnea instrument or a clinical congestion score [24, 28, 31]. Efforts should seek to determine how standardization of therapy in the ED and during hospitalization impacts outcomes in patients with different phenotypes and AHF precipitants, and to standardize the usual care arm in trials of investigational agents. While there is no clear direction on how to determine phenotypes of patients, a large pragmatic trial with several pre-defined patient categories would be an important first step.

Second, future trials should align AHF characteristics, patient types, and HF precipitants with the mechanism of novel investigational agents. When these are aligned, it will be crucial to study both patient-centric (e.g., dyspnea and well-being), mechanistic (e.g., biomarkers, echocardiography, and lung ultrasound), and clinical (e.g., worsening HF, mortality) outcomes to better understand the impact of each agent. Inclusion and exclusion criteria (Table 2) have been similar for many prior AHF trials without consideration for unique patient phenotypes. Patients with hypertension and AHF may benefit from earlier vasodilator intervention, as has been seen with both randomized and non-randomized trials [8, 22, 35]. Currently, many of these patients with SBP > 160 mmHg are excluded from clinical trials of vasoactive agents, yet may benefit the most. A TRUE-AHF subgroup analyses reported numerical trends in favor of active treatment in patients with baseline SBP > 140 mmHg and EF > 40% [36]. In the BLAST-AHF study, patients who had baseline SBP > 127 mmHg, and especially > 140 mmHg, showed trends towards a beneficial effect of TRV027 in longer-term kidney function and 180-day outcomes [21]. Guidelines outline differences in treatment of chronic HFrEF and HFpEF, and studies have suggested trends towards differences in these populations [30, 37]. Hence, consideration may need to be given in phase 2 AHF studies to further assess not only the dose–response of the intervention but also explore preferential response in patient phenotypes. Innovative study designs capitalizing on increased collaboration between ED and inpatient

Table 2 Recent AHF clinical trials with inclusion requirements

	OPTIME-CHF	EVEREST [30]	REVIVE I and II	SURVIVE [31]	VERITAS 1 and 2 [14]	PROTECT	ASCEND-HF [32]
Treatment	Milrinone: placebo	Tolvaptan: placebo	Levosimendan: placebo	Levosimendan: dobutamine	Tezosentan: placebo	Rolofylline: placebo	Nesiritide: placebo
Time from presentation to randomization	< 48	< 48 h	"hospitalized for the treatment of ADHF"	"hospitalized with ADHF"	< 24	< 24	< 48
Median time to drug initiation	15.3	NR	NR	NR	11	NR	15.3 (5.4–21.9)
Number of patients	949	4133 (2048 trial A and 2085 trial B)	700 (100 REVIVE I and 600 in REVIVE II)	1327	1435	2033	7141
LVEF	< 40	≤ 40	≤ 35	≤ 30	< 40	NR	< 40
SBP requirement	80–150 mmHg	< 90 mmHg	> 90 mmHg	< 85 mmHg (persistently lower)	> 100 mmHg	95–160 mmHg	100–180 mmHg
BNP requirement	NR	None	None	None	3× URL	BNP > 500 pg/mL or NT-proBNP > 2000	≥ 400 pg/mL or NT-proBNP ≥ 1000
Diuretic required before randomization	No	No	Yes	Yes	Yes	Yes	No
Dyspnea requirement	In "HF score"	Yes (≥ 2 of the following: dyspnea, JVD, or peripheral edema)	At rest despite treatment with IV diuretics	Dyspnea at rest or mechanical ventilation	At rest + RR > 24	At rest	At rest

	RELAX-AHF [13]	BLAST-AHF [17]	TRUE-AHF [27]	PRONTO [12]	STAND-UP
Treatment	Serelaxin: placebo	TRV027: placebo	Ularitide: placebo	Clevidipine: standard care IV antihypertensive	Nitroxyl donor: placebo
Time from presentation to randomization	< 16	< 16 h	< 12 h	As soon as possible	< 18 h
Median time to drug initiation	7.8 (4.7)	5.7 (IQR 4.2–8.5)	6.1 (4.6–8.4)	3.2 ± 1.9 and 2.7 ± 1.8	*
Number of patients	1161	621	2157	104	*
LVEF	< 40	NR	NR	NR	< 40
SBP requirement	≥ 125 mmHg	120–200 mmHg	110–80 mmHg	≥ 160 mmHg	mmHg
BNP requirement	≥ 350 pg/mL or NT-proBNP ≥ 1400	≥ 400 pg/mL or NT-proBNP ≥ 1600	BNP ≥ 500 pg/mL or NT-pro BNP ≥ 2000	None	BNP ≥ 400 pg/mL or NT-pro BNP ≥ 1600
Diuretic required before randomization	Yes	Yes	Yes	No	Yes > 40 mg intravenous furosemide
Dyspnea requirement	At rest	At rest	At rest	At rest	At rest or minimal exertion

clinicians may improve patient enrollment and increase the potential of novel agents.

Third, optimal therapy duration has not been clearly defined. Phase IIb and III studies have evaluated the duration of novel therapy from 24 to 120 h of the inpatient stay [9, 16, 27]. The optimal time of medication delivery may depend on the endpoint being targeted, including dyspnea or blood pressure control may only require therapy for 24 h. Improving renal dysfunction or myocardial injury may require intervention for the entire inpatient hospitalization. With an improved ability to remotely detect worsening HF pathophysiology in the outpatient setting, perhaps intervention with novel agents when congestion is present, but prior to symptom onset, should be the next direction. While some episodes of AHF are "acute", many may be more insidious in onset. Fluid shifts occur up to 2 weeks prior to admission, including evidence of edema, weight gain, and shortness of breath [34]. Some patients may have had symptoms building for weeks, but only get admitted once detected by a medical provider. In order to correct these slowly building changes, perhaps therapy needs to start even prior to hospitalization, and continue for a longer duration. Symptomatic relief and cardiovascular mortality are both important endpoints but may be impacted differently by therapies that preferentially affect neurohormones and hemodynamics during an AHF presentation. Our understanding of the causes of AHF is poor relative to the compendium of data we have regarding "clot" pathophysiology in patients with ACS and stroke [38].

Last, current clinical trials often utilize new treatment as "add-ons" to background therapy compared with current existing therapies (i.e., active control trials). Active control trials allow a direct comparison of new therapies with existing ones; this has not been done in most AHF trials. Current inclusion criteria often require patients still be short of breath despite standard therapy. Thus, we are potentially missing an opportunity to evaluate the efficacy and safety of a drug, as current standard therapy often successfully relieves dyspnea [13, 23]. There may also be bias since subjects, even in the placebo arm, get more monitoring and intensification of standard therapy. In the absence of an active comparator and dual phase trial design, even if a trial of early intervention is positive, it will be impossible to ascertain if the benefit was related to early intervention or to the investigational agent. This issue therefore needs to be addressed in clinical trial design as it has major cost implications in clinical practice.

Conclusions

The data are equivocal regarding the impact of early treatment in AHF on in-hospital and long-term morbidity and mortality. We believe improvements in clinical trial design are the next most important step to further evaluate the impact of timing of AHF treatment on outcomes. Answering the questions previously proposed will be a necessary first step if we aim to address the question of precisely when and if "early" treatment should begin and whether it impacts short- and long-term outcomes in AHF.

Compliance with Ethical Standards

Conflict of Interest Alan Storrow: Consultant for Quiedel, Siemens, Novartis. Grant support from NIH, AHRQ, and PCORI.

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References

1. Storrow AB, Jenkins CA, Self WH, Alexander PT, Barrett TW, Han JH, et al. The burden of acute heart failure on U.S. emergency departments. JACC Heart Fail. 2014;2(3):269–77. https://doi.org/10.1016/j.jchf.2014.01.006.
2. Benjamin EJ, Blaha MJ, Chiuve SE, Cushman M, Das SR, Deo R, de Ferranti SD, Floyd J, Fornage M, Gillespie C, Isasi CR, Jiménez MC, Jordan LC, Judd SE, Lackland D, Lichtman JH, Lisabeth L, Liu S, Longenecker CT, Mackey RH, Matsushita K, Mozaffarian D, Mussolino ME, Nasir K, Neumar RW, Palaniappan L, Pandey DK, Thiagarajan RR, Reeves MJ, Ritchey M, Rodriguez CJ, Roth GA, Rosamond WD, Sasson C, Towfighi A, Tsao CW, Turner MB, Virani SS, Voeks JH, Willey JZ, Wilkins JT, Wu JH, Alger HM, Wong SS, Muntner P, Subcommittee On behalf of the AHASC and SS. Heart Disease and Stroke Statistics—2017 Update: a report from the American Heart Association. Circulation. 2017;CIR.0000000000000485. https://doi.org/10.1161/CIR.0000000000000485.
3. Adams KF, Fonarow GC, Emerman CL, LeJemtel TH, Costanzo MR, Abraham WT, et al. Characteristics and outcomes of patients hospitalized for heart failure in the United States: rationale, design, and preliminary observations from the first 100,000 cases in the Acute Decompensated Heart Failure National Registry (ADHERE). Am Heart J. 2005;149(2):209–16. https://doi.org/10.1016/j.ahj.2004.08.005.

4. Heidenreich PA, Albert NM, Allen LA, Bluemke DA, Butler J, Fonarow GC, et al. Forecasting the impact of heart failure in the United States. Circ Heart Fail. 2013;6(3):606–19. https://doi.org/10.1161/HHF.0b013e318291329a.
5. Nieminen MS, Brutsaert D, Dickstein K, Drexler H, Follath F, Harjola V-P, et al. EuroHeart Failure Survey II (EHFS II): a survey on hospitalized acute heart failure patients: description of population. Eur Heart J. 2006;27(22):2725–36. https://doi.org/10.1093/eurheartj/ehl193.
6. Peacock WF, Emerman C, Costanzo MR, Diercks DB, Lopatin M, Fonarow GC. Early vasoactive drugs improve heart failure outcomes. Congest Heart Fail. 2009;15(6):256–64. https://doi.org/10.1111/j.1751-7133.2009.00112.x.
7. Alexander P, Alkhawam L, Curry J, Levy P, Pang PS, Storrow AB, et al. Lack of evidence for intravenous vasodilators in ED patients with acute heart failure: a systematic review. Am J Emerg Med. 2015;33(2):133–41. https://doi.org/10.1016/j.ajem.2014.09.009.
8. Levy P, Compton S, Welch R, Delgado G, Jennett A, Penugonda N, et al. Treatment of severe decompensated heart failure with high-dose intravenous nitroglycerin: a feasibility and outcome analysis. Ann Emerg Med. 2007;50(2):144–52. https://doi.org/10.1016/j.annemergmed.2007.02.022.
9. Gheorghiade M, Abraham WT, Albert NM, Greenberg BH, O'Connor CM, She L, et al. OPTIMIZE-HF Investigators and Coordinators for the. Systolic blood pressure at admission, clinical characteristics, and outcomes in patients hospitalized with acute heart failure. JAMA. 2006;296(18):2217. https://doi.org/10.1001/jama.296.18.2217.
10. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Drazner MH, et al. 2013 ACCF/AHA guideline for the management of heart failure a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2013;128(16):e240–327. https://doi.org/10.1161/CIR.0b013e31829e8776.
11. Wang CS, FitzGerald JM, Schulzer M, Mak E, Ayas NT. Does this dyspneic patient in the emergency department have congestive heart failure? JAMA. 2005;294(15):1944–56. https://doi.org/10.1001/jama.294.15.1944.
12. Teerlink JR, Metra M, Felker GM, Ponikowski P, Voors AA, Weatherley BD, et al. 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(9673):1429–39. https://doi.org/10.1016/S0140-6736(09)60622-X.
13. Maisel AS, Peacock WF, McMullin N, Jessie R, Fonarow GC, Wynne J, et al. Timing of Immunoreactive B-type natriuretic peptide levels and treatment delay in acute decompensated heart failure: an ADHERE (Acute Decompensated Heart Failure National Registry) analysis. J Am Coll Cardiol. 2008;52(7):534–40. https://doi.org/10.1016/j.jacc.2008.05.010.
14. Ambrosy AP, Pang PS, Khan S, Konstam MA, Fonarow GC, Traver B, et al. Clinical course and predictive value of congestion during hospitalization in patients admitted for worsening signs and symptoms of heart failure with reduced ejection fraction: findings from the EVEREST trial. Eur Heart J. 2013;34(11):835–43. https://doi.org/10.1093/eurheartj/ehs444.
15. Matsue Y, Damman K, Voors AA, Kagiyama N, Yamaguchi T, Kuroda S, et al. Time-to-furosemide treatment and mortality in patients hospitalized with acute heart failure. J Am Coll Cardiol. 2017;69(25):3042–51. https://doi.org/10.1016/j.jacc.2017.04.042.
16. Park JJ, Kim S-H, Oh I-Y, Choi D-J, Park H-A, Cho H-J, et al. The effect of door-to-diuretic time on clinical outcomes in patients with acute heart failure. JACC Heart Fail. 2018;6(4):286–94. https://doi.org/10.1016/j.jchf.2017.12.017.
17. McMurray JJV, Teerlink JR, Cotter G, Bourge RC, Cleland JGF, Jondeau G, et al. Effects of tezosentan on symptoms and clinical outcomes in patients with acute heart failure: the VERITAS randomized controlled trials. JAMA. 2007;298(17):2009. https://doi.org/10.1001/jama.298.17.2009.
18. Massie BM, O'Connor CM, Metra M, Ponikowski P, Teerlink JR, Cotter G, et al. Rolofylline, an adenosine A1-receptor antagonist, in acute heart failure. N Engl J Med. 2010;363(15):1419–28. https://doi.org/10.1056/NEJMoa0912613.
19. O'Connor CM, Starling RC, Hernandez AF, Armstrong PW, Dickstein K, Hasselblad V, et al. Effect of nesiritide in patients with acute decompensated heart failure. N Engl J Med. 2011;365(1):32–43. https://doi.org/10.1056/NEJMoa1100171.
20. Packer M, Holcomb R, Abraham WT, Anker S, Dickstein K, Filippatos G, et al. 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(5):673–81. https://doi.org/10.1002/ejhf.698.
21. Pang PS, Butler J, Collins SP, Cotter G, Davison BA, Ezekowitz JA, et al. Biased ligand of the angiotensin II type 1 receptor in patients with acute heart failure: a randomized, double-blind, placebo-controlled, phase IIB, dose ranging trial (BLAST-AHF). Eur Heart J. 2017;38(30):2364–73. https://doi.org/10.1093/eurheartj/ehx196.
22. Peacock WF, Chandra A, Char D, Collins S, Der Sahakian G, Ding L, et al. Clevidipine in acute heart failure: results of the A study of blood pressure control in acute heart failure—a pilot study (PRONTO). Am Heart J. 2014;167(4):529–36. https://doi.org/10.1016/j.ahj.2013.12.023.
23. Martindale JL, Wakai A, Collins SP, Levy PD, Diercks D, Hiestand BC, et al. Diagnosing acute heart failure in the emergency department: a systematic review and meta-analysis. Acad Emerg Med. 2016;23(3):223–42. https://doi.org/10.1111/acem.12878.
24. Lala A, McNulty SE, Mentz RJ, Dunlay S, Vader JM, AbouEzzeddine OF, et al. Relief and recurrence of congestion during and after hospitalization for acute heart failure: insights from DOSE-AHF and CARRESS-HF. Circ Heart Fail. 2015;8(4):741–8. https://doi.org/10.1161/CIRCHEARTFAILURE.114.001957.
25. Mebazaa A, Pang PS, Tavares M, Collins SP, Storrow AB, Laribi S, et al. The impact of early standard therapy on dyspnoea in patients with acute heart failure: the URGENT-dyspnoea study. Eur Heart J. 2010;31(7):832–41. https://doi.org/10.1093/eurheartj/ehp458.
26. Gray A, Goodacre S, Newby DE, Masson M, Sampson F, Nicholl J. Noninvasive ventilation in acute cardiogenic pulmonary edema. N Engl J Med. 2008;359(2):142–51. https://doi.org/10.1056/NEJMoa0707992.
27. Felker GM, Lee KL, Bull DA, Redfield MM, Stevenson LW, Goldsmith SR, et al. Diuretic strategies in patients with acute decompensated heart failure. N Engl J Med. 2011;364(9):797–805. https://doi.org/10.1056/NEJMoa1005419.
28. Mebazaa A, Nieminen MS, Packer M, Cohen-Solal A, Kleber FX, Pocock SJ, et al. Levosimendan vs dobutamine for patients with acute decompensated heart failure: the SURVIVE randomized trial. JAMA. 2007;297(17):1883. https://doi.org/10.1001/jama.297.17.1883.
29. Wong YW, Mentz RJ, Felker GM, Ezekowitz J, Pieper K, Heizer G, et al. Nesiritide in patients hospitalized for acute heart failure: does timing matter? Implication for future acute heart failure trials. Eur J Heart Fail. 2016;18(6):684–92. https://doi.org/10.1002/ejhf.487.
30. Chen HH, Anstrom KJ, Givertz MM, Stevenson LW, Semigran MJ, Goldsmith SR, et al. Low-dose dopamine or low-dose nesiritide in acute heart failure with renal dysfunction: the ROSE acute heart failure randomized trial. JAMA. 2013;310(23):2533–43. https://doi.org/10.1001/jama.2013.282190.
31. Metra M, O'Connor CM, Davison BA, Cleland JGF, Ponikowski P, Teerlink JR, et al. Early dyspnoea relief in acute heart failure: prevalence, association with mortality, and effect of rolofylline in the

PROTECT study. Eur Heart J. 2011;32(12):1519–34. https://doi.org/10.1093/eurheartj/ehr042.

32. Teerlink JR, Cotter G, Davison BA, Felker GM, Filippatos G, Greenberg BH, et al. Serelaxin, recombinant human relaxin-2, for treatment of acute heart failure (RELAX-AHF): a randomised, placebo-controlled trial. Lancet. 2013;381(9860):29–39. https://doi.org/10.1016/S0140-6736(12)61855-8.
33. Efficacy, safety and tolerability of serelaxin when added to standard therapy in AHF - study results - ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/results/NCT01870778. Accessed July 24, 2018.
34. Zile MR, Bennett TD, St John Sutton M, Cho YK, Adamson PB, Aaron MF, et al. Transition from chronic compensated to acute decompensated heart failure: pathophysiological insights obtained from continuous monitoring of intracardiac pressures. Circulation. 2008;118(14):1433–41. https://doi.org/10.1161/CIRCULATIONAHA.108.783910.
35. Cotter G, Metzkor E, Kaluski E, Faigenberg Z, Miller R, Simovitz A, et al. Randomised trial of high-dose isosorbide dinitrate plus low-dose furosemide versus high-dose furosemide plus low-dose isosorbide dinitrate in severe pulmonary oedema. Lancet. 1998;351(9100):389–93. https://doi.org/10.1016/S0140-6736(97)08417-1.
36. Packer M, O'Connor C, McMurray JJV, Wittes J, Abraham WT, Anker SD, et al. Effect of ularitide on cardiovascular mortality in acute heart failure. N Engl J Med. 2017;376(20):1956–64. https://doi.org/10.1056/NEJMoa1601895.
37. Butler J, Anstrom KJ, Felker GM, Givertz MM, Kalogeropoulos AP, Konstam MA, et al. Efficacy and safety of spironolactone in acute heart failure: the ATHENA-HF randomized clinical trial. JAMA Cardiol. 2017;2(9):950–8. https://doi.org/10.1001/jamacardio.2017.2198.
38. Hamo CE, Gheorghiade M, Butler J. Novel endpoints for heart failure clinical trials. Curr Heart Fail Rep. 2017;14(4):210–6. https://doi.org/10.1007/s11897-017-0334-z.