Acute Decompensated Heart Failure: Update on New and Emerging Evidence and Directions for Future Research

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ABSTRACT

Acute decompensated heart failure (ADHF) is a complex clinical event associated with excess morbidity and mortality. Managing ADHF patients is challenging because of the lack of effective treatments that both reduce symptoms and improve clinical outcomes. Existing guideline recommendations are largely based on expert opinion, but several recently published trials have yielded important data to inform both current clinical practice and future research directions. New insight has been gained regarding volume management, including dosing strategies for intravenous loop diuretics and the role of ultrafiltration in patients with heart failure and renal dysfunction. Although the largest ADHF trial to date (ASCEND-HF, using nesiritide) was neutral, promising results with other investigational agents have been reported. If these findings are confirmed in phase III trials, novel compounds, such as relaxin, omecamtiv mecarbil, and ularitide, among others, may become therapeutic options. Translation of research findings into quality clinical care can not be overemphasized. Although many gaps in knowledge exist, ongoing studies will address issues around delivery of evidence-based care to achieve the goal of improving the health status and clinical outcomes of patients with ADHF. (J Cardiac Fail 2013;19:371–389)

Key Words: Heart failure, clinical trials, diuretics, vasodilators, biomarkers, quality of care, ultrafiltration.

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Heart failure is a complex syndrome that involves both acute and chronic processes. Acute heart failure has various presentations. It can be characterized by rapidly developing symptoms of new-onset or de novo heart failure, or it can be a gradual worsening of chronic heart failure culminating in acute decompensated heart failure (ADHF), sometimes referred to as “acute on chronic” heart failure. Many different terms have been used in the literature to describe this syndrome, including acute heart failure, acute heart failure syndromes, and ADHF. The latter term will be used for this report.

Despite ongoing and intense efforts, clinical trials have not yielded therapeutic strategies that improve outcomes in the ADHF population. Many factors may contribute to inadequate trial results, including the heterogeneity of the condition, the likelihood that multiple triggers or pathophysiologic processes exist and differ among individual patients, the timing of patient enrollment, and inherent challenges such as obtaining informed consent and conducting clinical trials in patients who are acutely symptomatic and may have high adverse event rates. As a result, there are limited data to guide patient management. Of the 44 recommendations relevant to ADHF in the 2010 Heart Failure Society of America (HFSA) heart failure guidelines, 3 were supported by strength of evidence A, 8 by strength of evidence B, and 33 by strength of evidence C. Similarly, in the American College of Cardiology/American Heart Association 2009 heart failure guidelines, only 1 of 25 recommendations related to ADHF was a class I, level of evidence A recommendation.

Despite the paucity of evidence, practicing clinicians routinely seek guidance on the management of patients with ADHF. Since the publication of the 2010 HFSA heart failure guidelines, several trials in ADHF have yielded new data. Although these studies advance knowledge and inform clinical decision making, their results do not warrant a complete revision of the guidelines. The purpose of the present paper is to review new data generated in the broad ADHF population involving therapeutic drugs or strategies, biomarkers, and quality of care initiatives. This paper also highlights gaps in the current evidence base for the diagnosis, prognosis, risk stratification, management and monitoring of ADHF. Future research efforts should focus on these high-priority areas of unmet needs. This paper does not address the management of heart failure in the setting of shock, specific precipitants (eg, acute myocardial infarction or atrial fibrillation), early management with bilevel positive airway pressure, or other agents not approved for use in the United States (eg, levosimendan). Readers interested in these topics should refer to the 2010 HFSA guidelines for further information.

**Epidemiology**

More than 1 million hospitalizations for heart failure occur annually in the USA. Heart failure remains a primary cause of hospitalization among older Americans. An analysis from the Centers for Medicare and Medicaid Services (CMS) revealed a risk-adjusted heart failure hospitalization rate of ~2,000 per 100,000 person-years among Medicare beneficiaries based on 2008 data. A decline in the relative rate of hospitalization from 1998 to 2008 was detected in that study, which the authors primarily attributed to a reduction in the number of unique individuals hospitalized for heart failure rather than to a reduction in repeated hospitalizations. Unfortunately, heart failure is a progressive disease in most patients, and although some therapies slow or reverse progression, only cardiac transplantation is curative for patients with irreversible causes. The prevalence of heart failure is expected to increase in the USA over the next 20 years. Moreover, the risk of hospitalization tends to increase as heart failure progresses, and ADHF admissions increase the risk of subsequent readmission and death.

If the expected increase actually occurs, the burden of heart failure hospitalization will continue to place a major strain on health care resources. Clinicians, hospital administrators, and patients now have access to CMS publicly reported “quality metrics” for ADHF, including 30-day mortality and readmission rates (www.cms.gov/Medicare/Quality-Initiatives-Patient-Assessment-Instruments/HospitalQualityInits/OutcomeMeasures.html). It remains hotly debated whether the ideal end points have been defined for ADHF clinical trials and quality metrics. Event rates were lower than predicted in the Acute Effectiveness of Nesiritide in Decompensated Heart Failure (ASCEND-HF) trial, revealing that emerging therapies must have large treatment effects for an ADHF trial to have the power to detect a mortality benefit (even with >5,000 patients enrolled). Therefore, the process to develop new therapies from small mechanistic trials to large outcome trials will be prolonged and expensive.

**Patient Characteristics**

In general, patients hospitalized for ADHF are elderly, approximately one-half are women, and 25% are non-white. The majority (88% in the OPTIMIZE [Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure] registry) have a history of chronic heart failure rather than a de novo presentation. These patients typically have multiple comorbidities and moderately elevated systolic blood pressure, and approximately one-half have heart failure with preserved ejection fraction (HF-PEF). The majority of patients present with evidence of congestion or volume overload. Increases in body weight are associated with heart failure hospitalization and begin at least a week before presentation. Cardiogenic shock during the initial presentation to the emergency department (ED) is very rare. ADHF is a heterogeneous syndrome, and more focus on presenting characteristics may allow for better-targeted therapies. Clinical characteristics have been proposed to subcategorize patients with ADHF based on parameters such as blood pressure, degree of congestion, time course
of symptoms, presence of cardiogenic shock, or concomitant factors, such as acute coronary syndrome or renal dysfunction. In recent trials, patients were selected on the basis of 1 or more subcategories, such that the known or expected pharmacologic actions of the drug were matched to patient characteristics.17,18

Patients with ADHF present in a variety of settings, and the initial patient assessment and management may differ depending on the presenting location. Patients may develop acute symptoms in the home environment, prompting the use of emergency medical services (EMS) personnel as first responders, or they may present directly to the ED. Patients routinely managed in heart failure clinics may contact the heart failure clinical team to notify them of worsening symptoms. The decision can be made to bring patients in for urgent clinic evaluations and potential treatment on an outpatient basis depending on the severity of symptoms. In this scenario, an ambulatory center or observation unit may be used for administration of intravenous diuretics and laboratory monitoring. As health care reimbursement models change and Accountable Care Organizations and patient-centered medical home models emerge, a shift toward initial management of patients with ADHF in outpatient clinics or observation units is likely to occur, particularly in the USA.19,20

Recent data show that subclinical changes in intracardiac pressures and thoracic impedance occur days before patients generally seek medical attention owing to escalating symptoms (typically dyspnea or volume overload).21—23 Therefore, the typical patient with chronic heart failure presenting with symptoms that require hospitalization most likely has experienced subclinical changes for days, weeks, or even months. It is anticipated that future treatment strategies will include therapies triggered by monitoring devices even before symptoms occur.

**Clinical Outcomes**

Episodes of ADHF are associated with significant short- and long-term morbidity and mortality. In the Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM) trials, patients hospitalized for heart failure had a 3-fold greater risk for all-cause mortality compared with patients who did not have a heart failure hospitalization after adjustment for known baseline predictors of death.24 The in-hospital mortality reported in major registries ranges from 4% to 12%, and it may increase to 20%—25% in high-risk subgroups.10,12,14,25—27 It has not been determined whether the association between an ADHF event and poor prognosis is related to an underlying detrimental process that occurs during the episode, as evidenced by myocardial necrosis, inflammation, or marked neurohormonal activation, or if ADHF is a marker of progressive disease. ADHF episodes are frequent and costly, and they negatively affect overall health status and quality of life.

**New Data in Management of ADHF**

Standard therapies for managing ADHF (in addition to background chronic heart failure therapy) primarily include intravenous loop diuretics for patients with evidence of pulmonary and/or systemic venous congestion, vasodilators for patients with acute dyspnea or elevated filling pressures and evidence of vascular volume redistribution, and positive inotropes for patients with low cardiac output and evidence of end-organ dysfunction or damage. However, robust scientific evidence evaluating the safety and efficacy of current treatment strategies were lacking before the completion of several studies designed to address knowledge gaps. In addition, there have been no new drugs approved for the treatment of ADHF since 2001.

The management of ADHF requires a multifaceted approach that involves strategies or methods of delivering therapy, as well as drug therapies. Recent data will be examined in the context of these distinctions.

**Strategies**

**Diuretics.** The Diuretic Optimization Strategies Evaluation (DOSE) trial was designed to test low- versus high-dose intravenous furosemide administered as a continuous infusion versus intermittent intravenous boluses as the initial treatment strategy (ie, patients were not treatment resistant).28 This relatively small, prospective, double-blind, controlled trial randomized a total of 308 patients in a 1:1:1:1 fashion with the use of a 2×2 factorial design (Table 1). In the low-dose strategy, the total intravenous furosemide dose was equal to the total daily oral loop diuretic dose (in furosemide equivalents). For the high-dose arm, patients received a dose that was 2.5 times greater than their total daily oral loop diuretic dose (in furosemide equivalents). The median time to randomization was 14.6 hours.28 No significant difference was observed for efficacy or safety between the groups (Table 1). Some significant differences were noted across secondary end points for the low versus high dose comparison, including a larger decrease in body weight, greater fluid loss, and more dyspnea relief with higher doses. Length of stay and days alive out of the hospital did not differ between groups.28 However, caution should be used in the interpretation of secondary end points, because the primary efficacy outcome did not detect significant between-group differences.

The DOSE results suggest that high-dose intravenous furosemide (median 773 mg over 72 hours) was not associated with greater increases in serum creatinine compared with a low-dose strategy (median 358 mg over 72 hours), although more patients experienced an increase in serum creatinine of >0.3 mg/dL at 72 hours in the high-dose (23%) compared with the low-dose (14%) strategy (P = .04). The difference in creatinine between the 2 groups had disappeared at 7 days. In earlier retrospective analyses, high-dose diuretics were associated with a greater risk of worsening renal function and subsequent mortality.29—32
### Table 1. Summary of Recently Completed Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Study Arms</th>
<th>Population</th>
<th>Primary End Point</th>
<th>Results</th>
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| **DOSE**28  
* n = 308 | Low- vs high-dose furosemide. Continuous vs intermittent intravenous bolus.  
1:1:1:1 2 × 2 factorial design. | ADHF presented within previous 24 h, ≥1 sign and ≥1 symptom of HF, history of chronic HF treated with 80–240 mg/d furosemide (or equivalent) for ≥1 mo | Coprimary: patient global assessment of symptoms measured by aVAS and quantified as the AUC of serial assessments from baseline to 72 h; change in sCr from baseline to 72 h | Global assessment of symptoms: bolus AUC 4,236 ± 1,440 vs continuous AUC 4,373 ± 1,404 (P = .47); low dose AUC 4,171 ± 1,436 vs high dose AUC 4,430 ± 1,401 (P = .06).  
Mean change in sCr: bolus 0.05 mg/dL vs continuous 0.07 mg/dL (P = .45); low dose 0.04 mg/dL vs high dose 0.08 mg/dL (P = .21). |
| **ASCEND-HF**9  
* n = 7,141 | Nesiritide 0.01 µg kg⁻¹ min⁻¹ with optional 2 µg/kg bolus (from 24 h up to 7 d) vs standard medical therapy | Hospitalized for ADHF, dyspnea at rest or with minimal activity, ≥1 sign and ≥1 objective measure of ADHF, randomized within 24 h of first IV treatment for ADHF | Coprimary: change in self-reported dyspnea at 6 and 24 h; composite of HF rehospitalization or all-cause mortality through day 30 | Self-reported dyspnea moderately or markedly better.  
At 6 h: placebo 42.1% vs nesiritide 44.5%; P = .03.*  
At 24 h: placebo 66.1% vs nesiritide 68.2%; P = .007.*  
Death or rehospitalization for HF at 30 d: placebo 10.1% vs nesiritide 9.4% (HR 0.93, 95% CI 0.8–1.08; P = .31).  
sCr increase >0.3 mg/dL: low-dose dopamine/low-dose furosemide 6.7% vs high-dose furosemide 30%; P = .042.  
>20% decrease in eGFR vs high-dose furosemide 33.3%; P = .057. |
| **DAD-HF**51  
* n = 60 | Dopamine 5 µg kg⁻¹ min⁻¹ plus low-dose furosemide (5 mg/h continuous infusion) vs high-dose furosemide (20 mg/h continuous infusion) | Hospitalized for ADHF with evidence of volume overload and eGFR ≥30 mL min⁻¹ 1.73 m⁻² | Incidence of worsening renal function during the first 24 h after randomization, defined as >0.3 mg/dL rise in sCr from baseline to 24 h and >20% decrease in eGFR from baseline to 24 h | sCr increase >0.3 mg/dL: low-dose dopamine/low-dose furosemide 6.7% vs high-dose furosemide 30%; P = .042.  
>20% decrease in eGFR: low-dose dopamine/low-dose furosemide 10% vs high-dose furosemide 33.3%; P = .057. |
| **PROTECT**18  
* n = 2033 | Rolofylline 30 mg vs placebo for up to 3 d | Hospitalized for ADHF, persistent dyspnea at rest or with minimal activity, estimated CrCl 20–80 mL/min, BNP ≥500 pg/mL or NT-proBNP ≥2,000 pg/mL, IV loop diuretic therapy, and enrollment within 24 h after admission | Treatment success (moderate or marked improvement in dyspnea at both 24 and 48 h), failure (death or readmission for HF through day 7, worsening symptoms requiring intervention by day 7 or discharge, or persistent worsening renal function), or no change in patient’s condition | Treatment success: placebo 36% vs rolofylline 40.6%.  
No change: placebo 44.2% vs rolofylline 37.5%.  
Treatment failure: placebo 19.8% vs rolofylline 21.8%.  
OR for rolofylline: 0.92, 95% CI 0.78–1.09; P = .35. |
| **CARRESS**52  
* n = 188 | Ultrafiltration vs stepped pharmacologic care | Patients hospitalized with ADHF who develop cardiorenal syndrome (defined as increasing sCr (≥0.3 mg/dL) either after hospitalization (within 7 d from admission after receiving intravenous diuretics) or before hospitalization [within 6 wk of the index hospitalization in the setting of escalating doses of outpatient loop diuretics]) | Combined change in SCr and body weight at 96 h | Change in creatinine level: −0.04 ± 0.53 mg/dL in the pharmacologic-therapy group vs +0.23 ± 0.70 mg/dL in the ultrafiltration group; P = .003.  
Weight loss: 5.5 ± 5.1 kg (12.1 ± 11.3 lb) in the pharmacologic-therapy group vs 5.7 ± 3.9 kg (12.6 ± 8.5 lb) in the ultrafiltration group; P = .58.  
Serious adverse events: 72% in the ultrafiltration group vs 57% in the pharmacologic-therapy group; P = .03. |
 change dyspnea to day 5: Seralaxin significantly improved dyspnea compared with placebo by V AS AUC (448 mm h, 95% CI 120/C2 e775); P = .007. 

Patients with dyspnea at rest or on minimal exertion were randomized to a single-blind strategy of hypertonic saline (3%) along with high-dose furosemide and sodium restriction to 1,000 mL/d. These patients were lost to follow-up. Length of stay was shorter (3.5 days vs 5.5 days; P < .0001) and creatinine clearance was higher at discharge for patients in the hypertonic saline arm. Readmissions occurred in 18.5% of the hypertonic saline group and 21.2% of the placebo group (P < .0001). Mortality was also lower in the hypertonic saline group (12.9% vs 23.8%; P < .0001). These data are intriguing, but they are limited by the lack of blinding, the absence of data on short-term outcomes, the proportion of patients lost to follow-up, and the unknown effect that postdischarge management may have had on the study findings. Additionally, in usual practice, clinicians and patients may find it extremely difficult to limit fluid intake to 1,000 mL daily.

In DOSE, there was no significant difference between the low- and high-dose strategies in the clinical composite of death, rehospitalization, or ED visit within 60 days. However, the numbers of patients and events in DOSE were small. The hazard ratio and 95% confidence interval (CI) for the high-dose strategy were 0.83, 0.60—1.16.

The findings from DOSE are not likely to substantially change clinical practice, but they may reduce clinicians’ concerns regarding the safety of using high-dose diuretics in ADHF patients, at least up to the doses studied in the trial. Other recent reports also confirm the safety of higher-dose diuretics in ADHF. In addition, there is no longer a strong rationale for using a continuous infusion of diuretics as an up-front strategy. High-dose therapy may be associated with some clinical advantages regarding response to therapy, but the data are not definitive. There was no evidence that continuous infusions offered an advantage over bolus administration in terms of efficacy or safety, but the study results may be confounded by the rigorous administration of the bolus doses in the clinical trial context, which may not be representative of general clinical practice. In a Cochrane review of earlier studies, a modest benefit of continuous loop diuretic infusion regarding urine output and safety was observed, but the studies involved were small and incompletely blinded. Therefore, clinicians should use their clinical judgment and personal preference when determining mode of administration.

**Hypertonic Saline.** In small trials, administration of hypertonic saline (3%) along with high-dose furosemide and sodium and fluid restriction may be associated with greater diuretic and clinical response. In the SMAC-HF [Sodium Management in Acute and Chronic Heart Failure] study, 1,927 patients hospitalized for ADHF were randomized to a single-blind strategy of hypertonic saline solution plus 250 mg furosemide (intravenous bolus) twice daily and sodium restriction to 120 mmol (2,760 mg) per day, versus 250 mg furosemide (intravenous bolus) twice daily (without hypertonic saline) and sodium restriction to 80 mmol (1,849 mg) per day. Both groups received fluid restriction to 1,000 mL/d. The primary end point was death or first hospitalization for worsening heart failure during a mean follow-up of 57 months. A total of 8% of patients were lost to follow-up. Length of stay was shorter (3.5 days vs 5.5 days; P < .0001) and creatinine clearance was higher at discharge for patients in the hypertonic saline arm. Readmissions occurred in 18.5% of the hypertonic saline and 21.2% of the placebo group (P < .0001). Mortality was also lower in the hypertonic saline group (12.9% vs 23.8%; P < .0001). These data are intriguing, but they are limited by the lack of blinding, the absence of data on short-term outcomes, the proportion of patients lost to follow-up, and the unknown effect that postdischarge management may have had on the study findings. Additionally, in usual practice, clinicians and patients may find it extremely difficult to limit fluid intake to 1,000 mL daily.
Larger prospective blinded trials are needed to further evaluate this therapeutic approach, which cannot be recommended for clinical practice at this time.

**Ultrafiltration.** In the Ultrafiltration Versus Intravenous Diuretics for Patients Hospitalized for Acute Decompensated Heart Failure (UNLOAD) study, ultrafiltration reduced body weight and promoted fluid loss to a greater extent than intravenous diuretics in 200 patients hospitalized for ADHF with signs of volume overload. A reduction in ADHF hospitalizations and unscheduled visits was also observed, but the study was too small to definitively evaluate the effect of ultrafiltration on outcomes. Although the results from UNLOAD and earlier studies were encouraging, 2 recent studies raise concerns about the efficacy and safety of using ultrafiltration as a rescue strategy in high-risk patients with ADHF, persistent congestion, and worsening renal function. In an observational study, Patarroyo et al examined clinical outcomes of slow continuous ultrafiltration (SCUF) in 63 patients with ADHF and refractory congestion. Although 48 hours of SCUF improved hemodynamics and resulted in further weight loss, renal function did not improve in this high-risk cohort, and almost 60% required hemodialysis during their hospital course. The Cardiorenal Rescue Study in Acute Decompensated Heart Failure (CARRESS) randomly assigned (Table 1) 188 patients with ADHF, worsened renal function, and persistent congestion to a strategy of stepped pharmacologic care (intravenous diuretics dosed by the investigator to maintain urine output of 3–5 L/d plus intravenous vasodilators or inotropes if needed to achieve target urine output) or ultrafiltration (target fluid removal rate of 200 mL/h). The primary end point assessed at 96 hours was the bivariate change from baseline in serum creatinine level and weight. Ultrafiltration resulted in similar weight loss (~12 pounds), but it was inferior to pharmacologic care owing to an increase in creatinine levels (\( P = .003 \)). In addition, more patients in the ultrafiltration group had a serious adverse event (72% vs 57%; \( P = .03 \)). CARRESS enrolled a high-risk population with composite rates of death or rehospitalization at 60 days of 61% and 48% in the ultrafiltration and pharmacologic-therapy groups, respectively (\( P = .12 \)). An ongoing trial, the Aquapheresis Versus Intravenous Diuretics and Hospitalizations for Heart Failure (AVOID-HF, ClinicalTrials.gov identifier NCT01474200; Table 2) will further evaluate the role of ultrafiltration in the management of ADHF.

Ultrafiltration is an option that may be considered instead of diuretics for treating volume overload in the setting of ADHF (strength of evidence B, HFSA 2010 guidelines). However, major gaps in knowledge remain and include short- and long-term safety, patient impact, and cost-effectiveness of this approach compared with diuretic management. In particular, issues related to venous access, systemic anticoagulation and bleeding risks, and acute kidney injury need to be explored in larger patient cohorts. Patients with ADHF who are truly refractory to diuretic therapy also deserve further study.

### Existing Pharmacologic Therapies

**Nitrates.** Nitrates may be considered for relief of congestive symptoms in patients with ADHF. Information on their use is provided in the full HFSA guidelines, and no new evidence has been generated since the most recent guidelines publication. Readers are referred to the 2010 HFSA guidelines for more information on the role of nitroglycerin and nitroprusside in ADHF, including a detailed discussion of the Vasodilation in the Management of Acute Congestive Heart Failure (VMAC) study. Addition of comparative effectiveness studies of intravenous nitroglycerin in ADHF are being planned.

**Inotropes.** As recommended in the 2010 HFSA guidelines, intravenous inotropes may be considered to relieve symptoms and improve end-organ function in patients with advanced heart failure, reduced left ventricular ejection fraction (LVEF), and LV dilatation. In particular, positive inotropes may be used when patients are hypotensive despite adequate filling pressures, are unresponsive or intolerant to intravenous vasodilators, or display diminished or worsening peripheral perfusion or renal or other end-organ dysfunction. No new evidence has been generated since the most recent guidelines publication. Readers are referred to the 2010 HFSA guidelines for detailed information on the use of inotropes in ADHF.

**Nesiritide.** Nesiritide (recombinant human B-type natriuretic peptide [BNP]) was approved to relieve dyspnea and to reduce pulmonary capillary wedge pressure in patients with ADHF on the basis of the VMAC study, which was a short-term trial of 498 patients that was not powered to evaluate clinical outcomes. Subsequently, 2 meta-analyses brought the safety and efficacy of the drug into question. The ASCEND-HF trial was designed to prospectively answer the questions raised by the meta-analyses and to respond to the concerns of an expert panel commissioned by the drug sponsor.

The study design and overall results are presented in Table 1. A total of 7,141 patients were randomized 1:1 to nesiritide (0.01 µg kg\(^{-1}\) min\(^{-1}\) infusion for 24 hours to 7 days, with an optional initial 2 µg/kg intravenous bolus) or placebo. In addition, all patients received standard medical therapy. The use of loop diuretics, positive inotropes, and vasodilators after randomization were similar between groups. Self-reported dyspnea improved marginally in the nesiritide group at 6 and 24 hours, but the prespecified criterion for statistical significance (\( P < .005 \)) was not met (although analyses required by the European Medicines Agency did achieve significance). Similarly, there was no significant difference in the outcome of death or heart failure hospitalization between treatment groups. There were no between-group differences in the safety end point of the proportion of patients with a >25% decrease in estimated glomerular filtration rate (eGFR) from baseline (31.4% nesiritide vs 29.5% placebo; odds ratio 1.09, 95% CI 0.98–1.21; \( P = .11 \)). Hypotension was reported more frequently in the nesiritide group (26.6% vs 15.3%);
The end point findings were consistent across a number of prespecified subgroups. What is the current role of nesiritide in light of the ASCEND-HF findings? In patients with signs and symptoms of ADHF within 24 hours after the initial presentation, nesiritide did not provide a meaningful incremental improvement in dyspnea on top of standard therapy at either 6 or 24 hours. Therefore, it is not recommended as an effective therapy in this setting. It is possible that nesiritide may have clinical efficacy in other patient populations or at even lower doses (ROSE-AHF [Renal Optimization Strategies Evaluation in Acute Heart Failure]: Table 2), but that hypothesis remains to be tested.

Dopamine. Dopamine is an adrenergic agonist with dose-dependent pharmacologic effects. At low doses (0.5–2.5 μg kg⁻¹ min⁻¹), dopamine leads primarily to vasodilation through vascular D₁-dopaminergic receptor stimulation, thereby increasing renal blood flow and GFR. At medium doses (5–10 μg kg⁻¹ min⁻¹), dopamine is associated with positive inotropic and chronotropic effects through stimulation of β₁-adrenergic receptors. High doses of dopamine (>10 to 20 μg kg⁻¹ min⁻¹) lead to systemic vasoconstriction via stimulation of α-receptors. Low-dose or “renal-dose” dopamine has been used in critical care settings for the prevention or treatment of acute kidney injury, but the available evidence of efficacy is limited. Although mechanistic data show beneficial renal effects of dopamine in chronic heart failure, few studies have evaluated low-dose dopamine specifically in the ADHF population. The Dopamine in Acute Decompensated Heart Failure (DAD-HF) trial demonstrated that fewer patients randomized to “low-dose” dopamine (actually 5 μg kg⁻¹ min⁻¹) and low-dose furosemide experienced an increase in serum creatinine >0.3 mg/dL or a >20% decrease in eGFR from baseline compared with high-dose furosemide, although the number of patients and absolute numbers of events in this study was small (Table 1). The DAD-HF II (NCT01060293) and ROSE-AHF (NCT 01132846) trials are ongoing (Table 2).

Pharmacologic Agents in Development for ADHF

Rolofylline. Rolofylline is an adenosine A₁ receptor antagonist that has been studied in the setting of ADHF and renal impairment. It was hypothesized that A₁-receptor antagonists would preserve GFR, improve the response to diuretic therapy, and increase sodium excretion by blocking the effects of adenosine on the kidney. In phase II trials, rolofylline produced greater improvements in dyspnea outcomes, and fewer patients experienced worsening renal function. A trend toward improved clinical outcome was also observed. However, these findings were not confirmed in the large 2,033-patient phase III 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 (PROTECT) trial (Table 1).18 No difference in the primary clinical composite outcome was observed between the rololofylline and placebo groups. Persistent worsening renal function did not differ between treatment groups,26 and the incidence of death or readmission for cardiovascular or renal causes at 60 days also was similar between groups.18 Furthermore, rololofylline was associated with an increased rate of adverse neurologic events, including seizures and strokes.57 Based on the data, further development of rololofylline and other adenosine receptor antagonists for ADHF was discontinued.58

Relaxin. Relaxin is an endogenous peptide initially discovered as a hormone that is active in pregnancy.59,60 Through stimulation of the relaxin receptor, relaxin decreases inflammation, decreases fibrosis, increases vasodilation, promotes renal blood flow, and increases vascular endothelial growth factor and angiogenesis.59 In a variety of animal models, relaxin prevented ischemia and reperfusion injury, decreased cardiac fibrosis in hypertension and of animal models, relaxin prevented ischemia and reperfusion injury, decreased cardiac fibrosis in hypertension and cardiomyopathy, and reduced cell death and contractile dysfunction in myocardial infarction.60 Relaxin was studied in a phase II placebo-controlled dose-ranging study of 234 patients with ADHF, evidence of congestion, mild to moderate renal impairment, and preserved systolic blood pressure (>125 mm Hg).17 The Preliminary Study of Relaxin in Acute Heart Failure (Pre-RELAX-AHF) showed improvements in dyspnea scores for patients treated with relaxin, although hypotension and worsening renal function were observed at higher doses. The study was too small to draw conclusions regarding efficacy or clinical outcomes, but hypothesis-generating observations from the trial suggested favorable effects on clinical end points including cardiovascular death or hospitalization for heart or renal failure.17 The larger RELAX-AHF study61 was designed on the basis of previous data, and enrolled 1,161 ADHF patients within 16 hours of presentation who had dyspnea, congestion, mild-moderate renal insufficiency, and systolic blood pressure >125 mm Hg (Table 1). Patients were randomly assigned to receive an infusion of seralaxin (30 μg kg⁻¹ d⁻¹) or placebo for 48 hours with primary efficacy end points being dyspnea improvement over 5 days with the use of a visual analog scale (VAS) and over 24 hours with the use of a 7-point Likert scale. Compared with placebo, seralaxin improved the dyspnea VAS end point (P = .007), but it had no significant effect on the shorter-term end point (P = .70). Seralaxin had no significant effect on the secondary end point of death or heart failure readmission at 60 days (P = .89), but it was associated with reduced 180-day mortality (P = .02). More hypotensive events requiring dose reduction occurred in the seralaxin group (29% vs 18%; P < .0001), and more adverse events due to renal impairment were observed in the placebo group (9% vs 6%; P = .03).61 More data are needed to determine the role of seralaxin in patients with ADHF.

Omecamtiv Mecarbil. The development of positive inotropic agents for the treatment of ADHF has had a history marked by early enthusiasm tempered by concerns for toxicity. Although drugs such as dobutamine, milrinone, vesanerine, enoximone, and levosimendan effectively increase cardiac output, they increase the risk of adverse events, including arrhythmias, ischemia, and hypotension, and, in some cases, mortality.62–67 Omecamtiv mecarbil is the first selective cardiac myosin activator to be studied in humans.68 Through greater binding of myosin to actin during cardiac systole, omecamtiv mecarbil increases the force of myocardial contractions without increasing myocardial oxygen consumption.69 In a phase II, dose-ranging trial in 45 patients with stable heart failure, omecamtiv mecarbil increased LVEF and stroke volume, and decreased end-systolic and end-diastolic volumes. Chest pain, tachycardia, and myocardial ischemia were observed at high plasma concentrations.70 These data were sufficient to proceed with the Acute Treatment With Omecamtiv Mecarbil to Increase Contractility-Acute Heart Failure (ATOMIC-AHF; NCT01300013; Table 2) study to further evaluate the potential role of omecamtiv mecarbil.

Ularitide. Ularitide is a synthetic form of urodilatin, a human natriuretic peptide produced in the kidneys. It induces natriuresis and diuresis by binding to specific natriuretic peptide receptors (NPR-A, NPR-B, and others), thereby increasing intracellular cyclic guanosine monophosphate, relaxing smooth muscle cells, and leading to vasodilation and increased renal blood flow. Ularitide has been studied in patients with ADHF in 2 double-blind placebo-controlled proof-of-concept studies, and it was shown to exert beneficial effects on symptoms and hemodynamics.71,72 The Trial of Ularitide’s Efficacy and Safety in Patients With Acute Heart Failure (TRUE-AHF) is an ongoing phase III randomized clinical trial designed to evaluate the role of ularitide as an intravenous infusion in addition to conventional therapy in patients with ADHF (NCT01661634). The primary end point will be a hierarchic clinical composite variable that includes a patient-centered assessment of clinical progress, an assessment of lack of improvement or worsening of HF requiring a prespecified intervention, and death. The study aims to recruit ~2,116 patients with ADHF from 190 centers in North America, Europe, and Latin America.

Biomarkers

Diagnosis. Natriuretic peptides (plasma BNP or N-terminal pro-BNP [NT-proBNP]) are recommended in the current HFSA guidelines to aid in the diagnosis of ADHF in patients with dyspnea and signs and symptoms of heart failure.2 The biomarker field is constantly evolving, and new biomarkers are being investigated. A complete review of all biomarkers undergoing clinical investigation is outside the scope of this paper. In the Biomarkers in Acute Heart Failure (BACH) trial, midregional pro–A-type natriuretic peptide (MR-proANP) at a prespecified threshold of 120 pmol/L was noninferior to a BNP level of 100 pg/mL for the diagnosis of ADHF.73 The use of both BNP and
MR-proANP slightly, but significantly, enhanced the diagnostic performance of BNP. Similarly to BNP and NT-proBNP, MR-proANP levels may be affected by age, race, sex, body mass index, or comorbidities such as atrial fibrillation. Confirmatory studies are needed to establish the role of MR-proANP as a diagnostic tool for ADHF and to determine its advantages over available biomarkers. Currently, MR-proANP is not recommended for use.

Prognosis. A number of novel markers predict clinical outcomes in ADHF. The soluble ST2 receptor is a member of the interleukin family, and it is up-regulated in response to myocardial stretch. ST2 levels correlate with New York Heart Association (NYHA) functional class and predict 1-year mortality in patients with ADHF. Neutrophil gelatinase-associated lipocalin (NGAL) is a marker of acute kidney injury. When investigated in ADHF, higher levels strongly predicted all-cause death or hospital readmission at 30 days, although some data indicated that NGAL strongly predicted all-cause death or hospital readmission at 30 days. NGAL was not a significant predictor of kidney injury. When investigated in ADHF, higher levels predicted short- and long-term mortality. The absolute differences were small. GWTG-HF performance measure adherence rates were statistically significant, the absolute differences were small. GWTG-HF hospitals had statistically lower 30-day all-cause readmission rates compared with other hospitals. Although the absolute differences again were quite small (24% vs 24.4%; \( P = .0009 \)), these differences may still translate into substantial reductions in hospital readmissions and costs.

Quality of Care

A major component of the economic burden of heart failure is related to hospitalizations. Understanding the level of quality of health care delivered to patients with ADHF and how quality affects clinical outcomes is imperative. The rate of hospital adherence to national performance measures for patients with heart failure is variable but improving, and targeted interventions to improve adherence to core measures have been successful. However, the degree to which adherence correlates with improved outcomes has not been well established. Recent mortality and rehospitalization rates in the Veterans Affairs Health Care System have trended in opposite directions with decreasing mortality and increasing odds for readmission at 30 days. Similar trends were observed in the Hospital Compare database (www.hospitalcompare.hhs.gov), leading some to question the validity of using readmission rate as a quality measure. Measures associated with evidence-based drug therapy at the time of discharge (angiotensin-converting enzyme [ACE] inhibitor or angiotensin receptor blocker [ARB]; or beta-blockade, an emerging performance measure) have been associated with a lower risk of 60–90-day postdischarge mortality or rehospitalization; however, other standard performance measures were not. At 1 year, beta-blocker use at discharge was associated with a lower risk of mortality, but other standard performance measures were not associated with mortality or cardiovascular readmission. Recent analyses from the Get With the Guidelines Heart Failure (GWTG-HF) registry that linked quality measures to Medicare claims data showed poor correlations between hospital ranking and 30-day mortality or readmission. Another study showed that hospitals enrolled in the GWTG-HF program had greater adherence to the composite CMS core performance measures than other hospitals, but CMS-reported 30-day mortality was similar regardless of participation in GWTG-HF. Although the differences in performance measure adherence rates were statistically significant, the absolute differences were small. GWTG-HF hospitals had statistically lower 30-day all-cause readmission rates compared with other hospitals. Although the absolute differences again were quite small (24% vs 24.4%; \( P = .0009 \)), these differences may still translate into substantial reductions in hospital readmissions and costs.
needs to be established through formal evaluation and testing. Key components of transition programs that may promote improved outcomes are: 1) ongoing contact with a care manager and interactions before and after discharge; 2) education that includes assessing understanding of content and comprehensive discharge planning, including early follow-up and medication reconciliation and adherence; 3) access to community resources; and 4) provider-to-provider communication and coordination. Rehospitalization rates may also be influenced more by regional patterns of practice (ie, underlying use of hospital services) than by patient factors. The number of cardiovascular specialists available to manage ADHF may play a role in this variation. Whether or not targeted process-of-care initiatives will overcome such external factors and beneficially influence readmission rates remains to be determined. More evidence is required to determine the effectiveness of many current strategies intended to reduce readmissions.

**Evidence Gaps: Priorities for Future Research**

**Diagnosis**

ADHF is a heterogeneous syndrome that encompasses new-onset heart failure, worsening chronic heart failure, heart failure exacerbated by comorbidities, nonadherence, or contraindicated drugs or toxins, and reduced or preserved ejection fraction. This heterogeneity may cause delays in making the diagnosis of ADHF and instituting appropriate therapies or processes of care. BNP and NT-proBNP are useful tools when the diagnosis is uncertain, but even extremely high or low values do not always rule in or rule out ADHF and must be interpreted with knowledge of the patient’s clinical picture. Chest radiography also may be helpful to identify patterns consistent with ADHF, although other objective measures are needed. Based on preliminary data, limited bedside echocardiography, combined with ultrasound measures of lung water, may be helpful to differentiate ADHF from non-ADHF causes in patients with undifferentiated dyspnea. Use of thoracic bioimpedance to determine increases in lung water associated with decompensation have produced mixed results, although newer devices may be helpful to differentiate hypervolemic and euvolemic patients. Most findings, however, are preliminary, and large-scale studies are needed to determine the additive value of these tests in the acute setting. Ongoing studies will determine if other biomarkers or noninvasive tools will offer advantages to the existing approach to ADHF diagnosis.

Scores have been developed that use NT-proBNP and clinical characteristics to diagnose ADHF. The Pro-BNP Investigation of Dyspnea in the Emergency Department (PRIDE) acute heart failure score had a sensitivity of 96% and a specificity of 84% for the diagnosis of ADHF at a cutoff of \( \geq 6 \) points (Table 3). A mathematical model that included NT-proBNP as a continuous variable, patient
The contribution of cardiorenal syndrome to the pathophysiology of ADHF has garnered significant interest in recent years. Many researchers have established that worsening renal function (using a variety of definitions) was a predictor of mortality and morbidity in patients with both acute and chronic heart failure.\textsuperscript{32,120--122} However, evidence is lacking to determine the interplay (or interaction) between the kidney and the heart in cardiorenal syndrome, ie, whether the kidney contributes to heart failure pathophysiology, poor cardiac function results in renal impairment, or it is some combination of both. Two analyses confirmed the central role that elevated systemic venous pressure plays in worsening renal function in ADHF.\textsuperscript{123,124} Investigators highlighted the important role of vascular redistribution.\textsuperscript{125} In additional analyses, worsening renal function was associated with cardiovascular mortality and heart failure hospitalizations, and it was also associated with greater reductions in body weight, natriuretic peptides, and blood pressure, factors that generally predict favorable outcomes.\textsuperscript{126} Furthermore, transient (vs persistent) worsening renal function during treatment of ADHF may actually be associated with improved outcomes when related to aggressive diuresis.\textsuperscript{127} In addition, several drug classes that improve survival and reduce morbidity in chronic heart failure may also increase serum creatinine, namely, ACE inhibitors, ARBs, and mineralocorticoid receptor antagonists. These data illustrate the complexity of cardiorenal interactions. Clearly, more data are needed to fully characterize the pathophysiologic role of the cardiorenal syndrome in ADHF. Ongoing research is examining the role of dopamine and nesiritide to preserve renal function when treating ADHF (ROSE-AHF).

Heart failure with preserved ejection fraction accounts for almost one-half of all ADHF admissions, yet its underlying pathophysiology is understood even less than heart failure with reduced ejection fraction (HF-REF).\textsuperscript{128} Although limited data exist to characterize patients with ADHF and preserved ejection fraction, registry data suggest that postdischarge mortality and rehospitalization rates are similar to those of patients with reduced ejection fraction,\textsuperscript{129} although the risk of noncardiac mortality and rehospitalization is higher in HF-PEF patients.\textsuperscript{129} The majority of completed or ongoing studies of HF-PEF have not been conducted in the setting of ADHF. Although it is unlikely that therapies for the acute setting will differ substantially among HF-PEF and HF-REF patients, achieving a better understanding of the pathophysiology may allow postdischarge therapies to be specifically tailored to HF-PEF. For example, systemic or pulmonary arterial hypertension may play a greater role in decompensation among patients with HF-PEF and serve as an appropriate target for therapy.

**Risk Stratification: Predicting Early Versus Later Events**

Several prognostic models have been developed from clinical trials or registries in ADHF.\textsuperscript{130--134} Other scores derived from chronic heart failure (Seattle Heart Failure

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**Table 3. PRIDE Score**

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated NT-proBNP ( &gt;450 pg/mL for age &lt;50 y and &gt;900 pg/mL for age ≥50 y)</td>
<td>4</td>
</tr>
<tr>
<td>Intersitial edema on chest x-ray</td>
<td>2</td>
</tr>
<tr>
<td>Orthopnea</td>
<td>2</td>
</tr>
<tr>
<td>Lack of fever</td>
<td>2</td>
</tr>
<tr>
<td>Current loop diuretic use</td>
<td>1</td>
</tr>
<tr>
<td>Age &gt;75 y</td>
<td>1</td>
</tr>
<tr>
<td>Rales on lung exam</td>
<td>1</td>
</tr>
<tr>
<td>Lack of cough</td>
<td>1</td>
</tr>
<tr>
<td>Total possible points</td>
<td>14</td>
</tr>
</tbody>
</table>

Adapted from Baggish et al. Am Heart J 2006;151:48–54.\textsuperscript{144}
Model) were validated in advanced heart failure populations referred for cardiac transplant, though not in the ADHF setting. A novel model has been developed that estimates the combined end point of death and failure to achieve a favorable health status, and it may identify ADHF patients before discharge who may be good candidates for either advanced therapies or palliative care.

Risk stratification may be a valuable tool in the setting of ADHF. Patients identified as high risk for short- or long-term mortality or rehospitalization may benefit from aggressive optimization of drug or device therapy, focused disease management initiatives, or therapies targeting comorbidities or risk factor modification. A stratified treatment approach for patients with ADHF based on risk scores has not been tested in clinical trials and is an area where research is warranted.

Clinical Measures of Patient Improvement

Measures of efficacy should be both clinically relevant and meaningful to patients. Several outcomes have been used to evaluate the efficacy of therapeutic agents for ADHF. In clinical trials, dyspnea is a common end point because it is generally the symptom that prompts patients to seek medical attention. Despite this, clinically meaningful improvements in dyspnea in clinical trials are difficult to demonstrate, particularly on top of standard diuretic therapy. In secondary analyses of both the Pre-RELAX-AHF study and the PROTECT trial, early dyspnea relief was associated with more favorable outcomes. In the RELAX-AHF study (Table 1), treatment with serelaxin improved dyspnea at 5 days, but it had no effect on cardiovascular death or heart failure readmission. The optimal method and timing of dyspnea assessment in clinical trials is controversial, although in the clinical setting it is routinely assessed by physical examination and by querying patients regarding their degree of breathlessness. Whether dyspnea is the most relevant end point to judge patient response in clinical practice (or in clinical trials) has been debated. More research is needed to fill the evidence gap that exists between dyspnea improvement, overall health status, and clinical outcomes. Functional measures, such as 6-minute walk or patient-reported health status measures, or refinements to dyspnea assessment that include response to exertion also may be informative ways to judge patient response to ADHF therapies in the clinical setting.

Monitoring

Devices. The majority of published and ongoing trials of telemonitoring in heart failure were conducted in patients with chronic heart failure. The use of existing or similar devices to prevent recurrent episodes of heart failure in the setting of ADHF has not been well studied. When noninvasive externally applied impedance cardiography (ICG) was studied in 212 patients in the PREDICT (Prospective Evaluation and Identification of Cardiac Decompensation by ICG Test) study, it identified patients at increased near-term risk for recurrent decompensation. Other variables were also important: patient visual analog scale of distress, NYHA functional class, and systolic blood pressure. Furthermore, data from other studies indicated that internally implanted devices that measured intrathoracic impedance values were not highly sensitive to predict hospital admissions, and they did not reduce heart failure hospitalizations, although studies to date have generally been underpowered. In contrast, the observational Program to Access and Review Trending Information and Evaluate Correlation to Symptoms in Patients With Heart Failure (PARTNERS-HF) study showed that internal cardiac device diagnostic data (driven to a large extent by high fluid indices) independently predicted subsequent heart failure hospitalization with pulmonary congestion in patients with NYHA functional class III/IV heart failure who received a cardiac resynchronization therapy defibrillator device with impedance monitoring capabilities (Optivol; Medtronic).

Implantable hemodynamic monitoring systems are currently being investigated for use in heart failure and are capable of monitoring pulmonary artery pressures (CardioMEMS) or left atrial pressures (Heartpod; St Jude Medical). In the CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Functional Class III Heart Failure Patients (CHAMPION) trial, the 270 patients randomized to the CardioMEMS device had a lower rate of heart failure-related hospitalizations at 6 and 15 months than the 280 patients in the control group. The Heartpod device was studied in the Hemodynamically Guided Home Self-Therapy in Severe Heart Failure Patients (HOMEOSTASIS) observational pilot trial. The investigators found that individualized therapy guided by left atrial pressures was associated with reduced left atrial pressures, improved NYHA functional class, and increased LVEF and resulted in higher doses of ACE inhibitors/ARBs and beta-blockers. The Left Atrial Pressure Monitoring to Optimize Heart Failure Therapy (LAPTOP-HF) study is a larger randomized study evaluating the safety and efficacy (heart failure hospitalization) of the Heartpod device in patients with NYHA functional class III heart failure. Although these implantable device studies are not being conducted specifically in the ADHF population, if the devices are approved, they will likely be used clinically in this setting during hospitalization of patients with the devices. Whether used to prevent acute decompensation or in patients currently undergoing treatment for ADHF, a key element of improved outcomes will be how aggressively and thoroughly clinicians respond to data abnormalities. Therefore, studies in the setting of ADHF are warranted so that information on how to interpret the data in this setting can be generated.

Noninvasive monitoring of left ventricular end-diastolic pressure (LVEDP) has also been studied as a mechanism to guide treatment and prevent heart failure rehospitalization.
In a small study of 50 patients hospitalized for ADHF, patients randomized to daily noninvasive monitoring of LVEDP with the use of the Vericor monitor (CVP Diagnostics) had lower estimated LVEDP at discharge and lower rates of rehospitalizations for heart failure at 1, 3, 6, and 12 months. However, the study was too small to draw conclusions regarding clinical outcomes. In the future, noninvasive tools that assess congestion and/or other sensitive factors of decompensation and guide treatment of ADHF may be most useful to the primary health care providers of ADHF patients, including emergency physicians, cardiologists, internists, and hospitalists.

**Biomarkers.** The majority of biomarker-guided therapy studies were performed in the chronic heart failure population. The Pro-B-Type Natriuretic Peptide Outpatient Tailored Chronic Heart Failure Therapy (PROTECT) study reported a reduction in cardiovascular events among 151 patients with chronic heart failure at a single center who were randomized to NT-proBNP-guided therapy compared with standard care. Whether or not biomarker-guided therapy improves outcomes in the setting of ADHF has not been determined. New evidence evaluating this concept is lacking, and more studies are critically needed to advance the field in this area.

Home-based monitoring of biomarkers is another potential strategy that may be useful to identify and treat episodes of worsening heart failure before a patient's signs and symptoms progress to the point that hospitalization is required. The Heart Failure Outpatient Monitoring Evaluation (HOME; NCT01347567) study is enrolling ~ 375 patients hospitalized or treated as an outpatient with ADHF. Participants will be randomized into 1 of 3 arms: BNP home finger-stick monitoring plus health management (investigator will use BNP data to guide management, along with weight, signs, and symptoms), health management alone (BNP levels will be obtained, but results will be blinded to investigator and subject; investigator will use weight, signs, and symptoms to manage care), or usual care. The primary end point is heart failure-related mortality, heart failure readmission, intravenous diuretic or augmented oral diuretic therapy in the ED, or unplanned outpatient treatments for ADHF. The Guiding Evidence Based Therapy Using Biomarker Intensified Treatment (GUIDE-IT; NCT01685840) study is also enrolling subjects with ADHF to determine the efficacy of a strategy of NT-proBNP-guided therapy compared with usual care in high-risk patients with left ventricular systolic dysfunction. The primary outcome measure is the time to cardiovascular death or heart failure hospitalization; all-cause mortality will also be assessed.

**Processes of Care in the Hospital Setting**

A wide variation in quality of care for ADHF persists across the USA. Although multiple initiatives that involve processes of care and outcomes in ADHF have been an intense area of research in recent years, more work is needed to determine the best approaches. Developing standard algorithms and processes to rapidly assess, triage, and implement early therapy in patients in prehospital and ED-based settings (ambulance, ED, or observation units) is one approach where formal testing is warranted. Collaborations among prehospital personnel, cardiologists, hospital-based clinicians, heart failure specialists, and emergency physicians are needed to ensure a smooth transition of care. Preliminary data suggest that collaborative care can result in successful implementation of protocol-driven therapy. Creating networks and integration between emergency personnel and hospital-based personnel decreased treatment delays in patients with acute coronary syndromes. Whether similar strategies, such as door-to-diuretic time or triage of heart failure admissions in the ED, would be feasible and/or effective to improve outcomes in ADHF is unknown.

Additional parameters beyond the door-to-diuretic time (preferably <90 min) could include: 1) clinical assessment of volume status and readiness for discharge on a twice-daily basis; 2) assessment of precipitating factors and measurement of electrolytes and renal function at least every 48 hours in patients receiving intravenous diuretics; 3) assessment of LVEF if not done in the past year; and 4) initiation of an ACE inhibitor (or ARB) and beta-blocker therapy in patients with HF-REF and no contraindications. Further studies are needed to define if these measures improve quality, reduce length of stay, and favorably affect longer-term outcomes in ADHF.

The key evidence gap in this arena is in clarifying the contributions of the individual components of these interventions to determine which are the most effective. Specific predischarge strategies are critically important in enhancing patient knowledge and adherence to postdischarge expectations. Some examples are education (clinician and patient), medication optimization and reconciliation, and plans for postdischarge follow-up. Risk-stratified readmission models that are widely available and have the potential to identify high-risk patients who may benefit from aggressive postdischarge follow-up and management need to be formally evaluated. Examples include the readmission score (http://readmissionscore.org/heart_failure.php) or the score developed by Philbin and DiSalvo based on administrative data. The optimal method of follow-up (in-home, heart failure clinic, telephone) for patients may depend on geography and the availability of clinicians, as well as the underlying physical, emotional, social (including informed caregivers and family), and/or economic risk of an individual patient. New knowledge in these areas would be highly clinically relevant.

Finally, more work is needed to address palliative care and end of life issues, particularly as advanced therapies such as mechanical circulatory support are considered for broader patient populations. Although palliative care should be integrated throughout the course of heart failure care, an episode of ADHF may act as a trigger for
clinicians to assess whether or not goals of care have been addressed and to implement symptom-focused and end of life care as appropriate. A recent study showed that palliative care consultation can be provided in the heart failure clinic after discharge and can result in reduced symptoms and improved quality of life.

**Conclusion**

Recently completed trials answered questions regarding the safety and efficacy of diuretic strategies, vasodilator therapies, and ultrafiltration. Completed trials with neutral or negative results, though disappointing, contribute to overall knowledge pertaining to clinical characteristics and outcomes, and they are informative for the design of future trials. The results of ongoing trials of new therapeutic agents and devices that monitor clinical status will determine if effective and safe therapies are on the horizon. In the future, attempts may be made to match patient clinical characteristics with the expected pharmacologic mechanism of action for new agents or devices, rather than taking the traditional “all comers” approach. Successful translation of this approach into a greater ability to detect effective therapies remains to be seen. The timing of intervention will also be tested to determine the optimal pace and location of treatment. At present, initiatives to improve processes and quality of care may offer the best opportunity to improve patient outcomes. Although advances have been realized, many opportunities remain to reduce the burden of ADHF.

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