INTRODUCTION

The emergency department (ED) accounts for 80% of hospital admissions due to acute heart failure (AHF).1-3 Further, because of their multiple comorbidities, approximately 80% of ED patients with AHF are admitted to the hospital, the majority to a telemetry floor. Most of these patients present with worsening chronic heart failure, requiring and benefiting from urgent ED-based intravenous therapy. A minority of patients present as de novo or end-stage heart failure patients, where ED-based therapy is also important, but other factors often determine disposition (etiologic work-up, bridge to destination therapy, etc). As a direct result, emergency physicians and hospitalists deliver acute therapy to the majority of patients hospitalized with AHF. Improved survival from myocardial infarction, an aging population, and hospital overcrowding have also resulted in an increased ED burden of acute heart failure management.4, 5 Accordingly, early management decisions made in the ED will continue to have a significant impact on the acute care of these patients.

Chronic heart failure management has improved dramatically over the last decade. While the introduction of beta-blockers and ACE-inhibitors has led to tremendous advances in chronic heart failure management, clinical trial results for novel therapies treating AHF have shown limited success with regard to efficacy and/or safety.6-9 Furthermore, these trials tend to enroll a highly select group of patients with systolic dysfunction long after ED presentation, resulting in poor generalizability to the ED population. Recently, AHF registries have highlighted the dichotomy between the patients seen and treated in the ED and hospital and those enrolled in clinical trials (Table 1).

Despite extensive ED involvement during the initial phase of AHF management, the potential impact of early therapy has not been accounted for in the design of therapeutic trials. The majority of trials have enrolled patients up to 48 hours after initial therapy, well after most patients have experienced significant improvement in symptoms. A recent
ADVANCING THE STANDARD OF CARE: Cardiovascular and Neurovascular Emergencies

ED-based prospective, international study of dyspnea suggests that dyspnea improves dramatically within 6 hours of ED treatment, and by 24 hours if it is less than 40% of its original magnitude.10, 11 Because many trials require dyspnea for inclusion, enrolling patients 24-48 hours into their hospital course may select for a unique subset of AHF patients with refractory or minimal symptoms. As a direct result of enrolling highly select patients long after ED therapy has been initiated, there has been little or no change in the therapeutic repertoire available to ED physicians when managing patients with AHF.

### ED Management of AHF

**Emergency Medicine and Cardiology Collaboration**

The acute care of the patient with AHF has changed very little in the past two decades. This starkly contrasts with that of the acute coronary syndrome (ACS) patient. While ACS care has seen the introduction of fibrinolytic therapy in the ED, glycoprotein IIb/IIIa inhibitors and the door-to-balloon initiative, AHF care continues to revolve around the administration of diuretics.12 The advancement in ACS care was largely the result of strong collaborations between emergency medicine and cardiology as well as the introduction and study of acute therapy early in the course of ACS, at the time of ED presentation. Similar collaborations between emergency medicine and cardiology researchers are now occurring. The Emergency Management and Research Group in Acute Heart Failure (EMERG-HF) was established to promote heart failure collaboration between emergency medicine and cardiology. As a result, several ongoing and upcoming clinical trials have received significant emergency medicine input with the goal of studying the impact of novel agents earlier in the course of AHF presentation.

Traditionally, AHF clinical trials have identified patients 24-48 hours after their initial presentation, long after the majority of patients experience considerable improvement in symptoms and have received several medications for their acute symptoms.10, 11 For agents targeting acute symptom improvement, patients should be enrolled when symptoms are maximal, if the effect

### Table 1. Demographics and Clinical Characteristics of Patients Enrolled in Registries and Clinical Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Age (yrs)</th>
<th>Women (%)</th>
<th>White (%)</th>
<th>Prior Heart Failure (%)</th>
<th>Renal Dysfunction (%)</th>
<th>Reduced LVEF (% with EF &lt;40% or Mean EF)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VMAC⁷</td>
<td>61</td>
<td>31</td>
<td>58</td>
<td>84</td>
<td>21</td>
<td>85</td>
</tr>
<tr>
<td>EVEREST⁶</td>
<td>66</td>
<td>26</td>
<td>85</td>
<td>79</td>
<td>27</td>
<td>Mean EF 27%</td>
</tr>
<tr>
<td>VERITAS³⁴</td>
<td>70</td>
<td>40</td>
<td>86</td>
<td>73</td>
<td>36</td>
<td>Mean EF 29%</td>
</tr>
<tr>
<td>ADHERE³⁵</td>
<td>72</td>
<td>52</td>
<td>74</td>
<td>76</td>
<td>30</td>
<td>Mean EF 29%</td>
</tr>
<tr>
<td>OPTIMIZE³⁶</td>
<td>73</td>
<td>52</td>
<td>-</td>
<td>63</td>
<td>-</td>
<td>Mean EF 31%</td>
</tr>
</tbody>
</table>

Table 1. Demographics and Clinical Characteristics of Patients Enrolled in Registries and Clinical Trials

While ACS care has seen the introduction of fibrinolytic therapy in the ED, glycoprotein IIb/IIIa inhibitors and the door-to-balloon initiative, AHF care continues to revolve around the administration of diuretics.
of a novel agent is to be determined. For optimal success, the effect of acute therapy on symptoms and/or outcomes should be matched with an enrollment strategy which targets patients at the appropriate phase of the heart failure disease continuum. Specifically, the pathophysiologic or mechanistic target, such as renal impairment, hypertension, low cardiac output, cardioprotection, or lusitropy, needs to be considered. Furthermore, capturing ED patients will not only facilitate enrollment of a more representative sample of AHF patients that is unbiased by admission decisions, it will also allow emergency physicians to evaluate the impact of early investigational therapy on AHF symptoms. As a direct result, in the near future emergency physicians can expect to see trial results about therapeutic agents studied in their population of patients. Thus, it is important that emergency physicians have some knowledge of these new agents.

A Change in Approach to Acute Heart Failure Therapy

While the availability of novel therapeutic agents continues to be limited, the approach to acute management continues to evolve. Traditional AHF treatment focused on relief of congestion via the use of diuretics. However, registry data have confirmed what has been apparent to many emergency physicians: 40-50% of patients with AHF will present with a systolic blood pressure > 140 mm Hg. Secondly, the results of several trials have suggested that early aggressive blood pressure control improves near-term event rates. Subsequently, the importance of blood pressure control and fluid maldistribution in AHF patients presenting with elevated blood pressure has been emphasized. Consensus recommendations suggest early aggressive vasodilator administration should be the cornerstone of therapy in those AHF patients with elevated blood pressure. Patients are reevaluated after the initial use of sublingual nitroglycerin to determine whether additional blood pressure control is needed in the form of intravenous vasodilators (Figure 1).

Approximately 40% of patients with AHF will present with relatively normal blood pressure (≤140 mm Hg). Their symptoms tend to be less acute and often are consistent with systemic fluid overload such as weight gain and abdominal and leg edema. Blood pressure control is less of an issue, and in fact, some of these patients may “run out” of blood pressure if they are concurrently managed aggressively with both diuretics and vasodilators. Adequate relief of congestion is gauged by improvement in dyspnea, jugular venous distension, pulmonary rales and adequate urine output (Figure 2). Further measures to reduce congestion without adversely impacting blood pressure or renal function are necessary in this cohort of patients. Vasopressin antagonists are one group of drugs that may prove to have these qualities.

The Potential Role of Vasopressin Antagonists in Acute Heart Failure

Vasopressin Receptor Subtypes

Vasopressin affects free water reabsorption by the kidney, body fluid osmolality, blood volume, vasoconstriction and myocardial contractile function.
Figure 1. Suggested Treatment Pathway for Those Patients With AHF and Concomitant Elevated Blood Pressure

HYPERTENSIVE PATHWAY

SBP >140 mm Hg (Includes patients with APE)

Immediate topical or sublingual NTG

Start IV diuretic

Reassess VS: BP >160/100?

Add IV vasodilator

Estimate severity of illness

Non high-risk features:
- Good response
- Adequate urine output
- SBP <90 mm Hg
- SBP <210 mm Hg
- Troponin negative

Admit to ED observation unit or in-hospital telemetry floor

Admit ICU

High-risk features:
- Poor response
- Inadequate urine output
- SBP <90 mm Hg
- SBP >210 mm Hg
- Troponin elevated
- Tachycardia
- High respiratory rate
- ↑ BUN or creatinine
- Persistent hypoxia despite initial treatment with non-invasive ventilation

If good response

If worsens

If no improvement

If continued improvement and adequate social support and follow-up anticipated

Consider discharge

Consider additional therapy

Figure 2. Suggested Treatment Pathway for Those Patients With AHF and Concomitant Elevated Blood Pressure

NORMOTENSIVE PATHWAY

SBP 90-140 mm Hg (Includes patients with APE)

IV diuretics

Estimate severity as described in Figure 1 along with:
- History of multiple AHF admits
- BUN>43, Cr>2.75, SBP<115
- Weight above normal dry weight
- ECG with LVH, ischemia, or infarction
- Hypotension
- Known low ejection fraction

Initial work-up and treatment

Non-high-risk features:
- Good response/adequate urine output
- Adequate renal function
- Normal SBP
- Troponin negative

Add IV vasodilator (NTG, NES, NTP)

Admit to ED observation unit or in-hospital telemetry floor

Follow pathway for hypotensive AHF (Figure 6)

High-risk features:
- Poor response/adequate urine output
- Poor renal function
- Diuretic resistant
- Elevated SBP
- Troponin elevated

If good response

If worsens

If no improvement

If continued improvement and follow-up anticipated

Consider additional therapy

Admit ICU

Consider discharge

APE-acute pulmonary edema
There are three types of receptors which help mediate the physiologic effects of vasopressin (Table 2). The V1a receptors can be thought of as the vascular receptors and mediate the hemodynamic effects of vasopressin. They are found on several cell types including vascular smooth muscle and cardiomyocytes. The V1b receptors are found in the anterior pituitary, adrenal medulla, and pancreas. Some of the effects the V1a receptor mediates include ACTH release and platelet aggregation. The V2 receptor, the target of many of the vasopressin antagonists, is expressed in the renal collecting system and mediates the antidiuretic effects. Interestingly, in heart failure patients vasopressin levels appear to be exaggerated in response to osmotic loads, suggesting a greater role for homeostasis in pathologic states.

**Vasopressin Physiology**

Based on the location and mechanism of action of the V1 and V2 receptors, we can expect two direct effects from vasopressin antagonism: 1) reduced vascular tone leading to reduced blood pressure (V1) and 2) loss of free water as a result of aquaretics, leading to increased serum sodium levels (V2). As a direct result of these effects, they would be considered potentially ideal agents to combat several of the adverse effects of AHF: 1) high blood pressure and increased vascular tone; 2) systemic congestion and volume overload; and 3) hyponatremia. Several trials have investigated the impact of vasopressin antagonism in adults with AHF.

**Trials of Vasopressin Antagonists**

The largest trial to date of vasopressin antagonists is the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan (EVEREST) program. This trial was designed after preliminary success with the use of tolvaptan in patients with AHF in the ACTIV in CHF trial. The ACTIV in CHF trial examined three oral doses of tolvaptan (30, 60, 90 mg) or placebo in patients with AHF and systolic dysfunction. There was a decrease in body weight and increase in urine volume in patients treated with tolvaptan. Though not powered to assess differences in mortality, there was a trend toward increased survival in the tolvaptan group.

The EVEREST study was a double blind, placebo controlled, multicenter international trial designed to evaluate...
two endpoints: 1) the efficacy of tolvaptan with regard to global clinical status and body weight reduction through day seven or at the time of discharge; 2) the long-term mortality difference between tolvaptan and placebo. Enrolled patients were required to have AHF as defined by clinical criteria, an ejection fraction of 40% or less and were excluded for significant comorbidities such as hemoglobin < 9 g/dL, creatinine > 3.5 mg/dL or blood pressure less than 90 mm Hg. Patients were randomized within 48 hours of presentation to receive tolvaptan 30 mg daily or placebo for a minimum of 60 days. The trial was set up to be event driven and ultimately enrolled 4,133 patients. The efficacy endpoint was a composite score encompassing: 1) a visual analog scale to capture patient reported global clinical status and 2) change in body weight. The composite primary endpoint showed significantly greater improvement in the tolvaptan group compared to placebo. However, this was largely driven by reduction in body weight [Table 3]. Importantly, despite removing a greater volume of fluid and reducing body weight there was no change in renal function in the tolvaptan group. Changes in patient assessed dyspnea were modestly better with tolvaptan compared to placebo [Figure 3]. There were no differences in the two co-primary mortality endpoints: 1) mortality (Kaplan-Meier 1-year estimates were 25% in the tolvaptan group and 26% in the placebo group, p=0.68) or 2) cardiovascular mortality or heart failure hospitalization - Kaplan-Meier 1-year estimates were 42% in the tolvaptan group and 40.2% in the placebo group between tolvaptan and placebo, p=0.55.

Conivaptan, another vasopressin antagonist, has been studied in patients with AHF as well. In this double blind, placebo controlled, multicenter trial 162 patients with AHF were randomized to conivaptan 20 mg intravenous bolus followed by 40, 80 or 120 mg/day of conivaptan or placebo [Table 4]. Initiation or change in the infusion rate of intravenous diuretics, vasodilators or positive inotropes was not allowed. Compared to placebo, conivaptan produced significant changes in urinary output and body weight, but no significant difference in dyspnea improvement. There were no major differences in adverse events between the patients randomized to conivaptan or placebo. This study suggested conivaptan is safe and reduces body weight via increased urine output, and indicates a larger trial is necessary to determine whether conivaptan improves symptoms when compared to standard care.

The Potential Role of Vasopressin Antagonists in the ED
Patients with continued congestion despite acute ED therapy present a dilemma. The goal of further therapy is to reduce congestion while simultaneously avoiding detrimental hypotension or renal insufficiency. In those patients with continued symptoms, initial therapy (diuretics and inotropes) may have deleterious downstream effects. Previous studies of diuretics suggest not only an association with adverse outcomes, but perhaps a direct cause and effect. In particular, the development of in-hospital renal dysfunction, a common consequence of over-diuresis, has been associated with increased in-hospital mortality. Vasopressin antagonists, through their ability to increase urine output and decrease body weight without impacting renal function, may be a reasonable alternative to diuretics in this difficult subset of patients with AHF.

Prior to ED implementation of vasopressin antagonists several questions will need to be answered. 1) If a vasopressin antagonist is given early in the treatment course, while the patient is still in the ED, would this be in addition to diuretics or in place of diuretics? 2) In ED patients with acute symptoms and intestinal congestion, what are the pharmacokinetics and bioavailability of an oral vasopressin antagonist? and 3) What is the benefit, both regarding symptoms and mortality, if the vasopressin antagonist is started within 6-12 hours of ED presentation, rather than 48 hours? The answers to these questions will be obtained by prospectively studying these agents in a randomized, placebo controlled, blinded fashion with variable study designs revolving around timing and dosing of the study drug in question.
Table 3. Changes From Baseline in Secondary Efficacy End Points

<table>
<thead>
<tr>
<th></th>
<th>Trial A</th>
<th>Trial B</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tolvaptan (n=894)</td>
<td>Placebo (n=915)</td>
</tr>
<tr>
<td>Changes in patient-assessed global clinical status at day 7, mean VAS score (SD) [No.], kg</td>
<td>18.25 (22.26) [903]</td>
<td>17.73 (22.47) [910]</td>
</tr>
<tr>
<td>Changes in body weight at day 1, mean (SD) [No.], kg</td>
<td>-1.71 (1.80) [978]</td>
<td>-0.99 (1.83) [997]</td>
</tr>
<tr>
<td>Changes in body weight at day 7, mean (SD) [No.], kg</td>
<td>-3.35 (3.27) [997]</td>
<td>-2.73 (3.34) [1007]</td>
</tr>
<tr>
<td>Change in patient-assessed dyspnea at day 1, % showing improvement in dyspnea score (No.)*</td>
<td>76.74 (894)</td>
<td>70.61 (915)</td>
</tr>
<tr>
<td>Change in edema scores at day 7, % showing at least a 2-grade improvement (No.)*</td>
<td>73.83 (722)</td>
<td>70.25 (790)</td>
</tr>
</tbody>
</table>

Abbreviation: VAS, visual analog scale.
*Assessed at discharge if before day 7.
†Based on analysis of covariance model.
‡Based on van Elteren test.
§For patients with symptoms at baseline.

Figure 3. Change in Patient-Assessed Dyspnea at Day 1 for Patients Manifesting Dyspnea at Baseline

**P value represents between-group comparison by van Elteren test.**
Table 4. Changes in Key Efficacy Variables at 72 hours.

<table>
<thead>
<tr>
<th>Efficacy variable</th>
<th>Placebo (n = 40)</th>
<th>Conivaptan 40 mg/d (n = 40)</th>
<th>Conivaptan 80 mg/d (n = 40)</th>
<th>Conivaptan 120 mg/d (n = 42)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC change in respiratory VAS*</td>
<td>2135</td>
<td>2199</td>
<td>2166</td>
<td>2036</td>
</tr>
<tr>
<td>AUC change in urine output (mL)</td>
<td>110,931</td>
<td>160,865†</td>
<td>169,274‡</td>
<td>170,229§</td>
</tr>
<tr>
<td>Change in body weight (kg)</td>
<td>−2.5</td>
<td>−3.2</td>
<td>−3.3</td>
<td>−1.8</td>
</tr>
</tbody>
</table>

*At hour 48.
†P = .016.
‡P = .002.
§P = .001.
AUC = area under the curve

SUMMARY

While the outpatient management of AHF has improved dramatically with the implementation of beta-blockers and ACE inhibitors, acute management has changed very little. A new ED approach, based on blood pressure and systemic congestion, has been suggested to improve acute therapy. Over the last decade therapeutic trials of novel agents for patients with AHF have been universally disappointing. The vasopressin antagonists present a promising option for those patients with continued congestion in the ED. Prior, however, to their widespread implementation several questions will need to be answered via prospective ED-based therapeutic trials.

REFERENCES


