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### What's Next for Acute Heart Failure Research?

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### **Abstract**

Each year over one million patients with acute heart failure (AHF) present to a United States emergency department (ED). The vast majority are hospitalized for further management. The length of stay and high post-discharge event rate in this cohort has changed little over the last decade. Therapeutic trials have failed to yield substantive improvement in post-discharge outcomes, subsequently, AHF care has changed little in the last 40 years. Prior research studies have been fragmented as either “inpatient” or “ED-based”. Recognizing the challenges in identification and enrollment of ED patients with AHF, and the lack of robust evidence to guide management, an AHF

clinical trials network was developed. This network has demonstrated, through organized collaboration between cardiology and emergency medicine, that many of the hurdles in AHF research can be overcome. The development of a network that supports the collaboration of acute care and HF researchers, combined with the availability of federally funded infrastructure, will facilitate more efficient conduct of both explanatory and pragmatic trials in AHF. Yet many important questions remain, and in this document our group of emergency medicine and cardiology investigators have identified four high priority research areas.

Each year over one million patients with acute heart failure (AHF) present to an emergency department (ED) in the United States.<sup>1</sup> The vast majority are admitted to the hospital for further management.<sup>2,3</sup> While a minority may be discharged from the ED after a short stay *and prior recommendations suggest who may be safe for management in an observation unit*<sup>4</sup>, no definitive guidelines exist to aid clinicians in identifying patients who don't require hospitalization. The length of stay and high post-discharge event rate for AHF patients admitted through the ED and discharged from the inpatient setting have changed little over the last decade.<sup>5,6</sup> Therapeutic trials in this clinical syndrome have thus far failed to yield any improvement in post-discharge outcomes, including recent neutral results from 3 studies evaluating improvements in clinical endpoints such as worsening heart failure, dyspnea and mortality.<sup>7-10</sup> Since AHF admissions are the number one cause of hospitalization for Medicare beneficiaries, accounting for the majority of over 30 billion dollars in direct costs, continued research is imperative to improve outcomes of these patients.<sup>5</sup> Prior studies in patients with AHF were often fragmented as either "inpatient" or "ED-based". Improved collaboration between acute care and HF researchers and the availability of federally funded acute care and HF network infrastructure can change this, facilitating the conduct of both pragmatic and explanatory trials. Herein, we outline important questions related to the current management of AHF whose answers are needed to both inform national guidelines, and improve patient care.

### **Challenges and Opportunities in Emergency Department Management of Acute Heart Failure**

Finding safe and effective treatments for AHF is a worldwide priority.<sup>11,12</sup> AHF care has changed little in the last 40 years, and 80% of patients with AHF are uniformly treated with intravenous (IV) diuretics, despite significant heterogeneity of both HF etiology and acute precipitants.<sup>13</sup> Management of AHF is largely based on opinion and experience rather than evidence,<sup>14,15</sup> yet is associated with extensive resource utilization and persistently poor outcomes.<sup>16-20</sup> The experience

with AHF is contrasted with patients with chronic HF with reduced ejection fraction where national guidelines give strong I-A recommendations for oral therapies like angiotensin converting enzyme inhibitors (ACEI) or angiotensin receptor antagonists (ARB), angiotensin receptor neprilysin inhibitors (ARNI), beta blockers, and mineralocorticoid receptor antagonists.<sup>21-25</sup> Moreover, after an ED visit over 80% of patients with AHF are hospitalized, despite recent studies describing low-risk patients being safe for discharge after short-term therapy.<sup>1, 26-29</sup> Safely transitioning a larger proportion of patients to the outpatient setting is an unmet need.

### **Priority Topics for Future Research in Acute Heart Failure: Necessary Emergency Medicine and Cardiology Collaboration**

Completion of ED-based AHF clinical trials requires a coordinated effort at multiple centers with access to patients with AHF. *There are challenges in identification and enrollment of ED patients with AHF and the lack of evidence guiding their management. It would be crucial for HF and emergency medicine investigators to develop local collaborations to help answer these questions by facilitating clinical trial enrollment.* One example of this has originated from multidisciplinary partnerships that capitalize on robust local site infrastructures at select institutions, creating the first US-based AHF clinical trials network.<sup>30</sup> The Emergency Medicine Research and Outcomes Consortium (EMROC) network requires each participating institution to have a collaborative model, where both an emergency medicine physician and cardiology investigator have an ongoing relationship that facilitates implementation of clinical care pathways and research initiatives.<sup>31</sup> Seamless transition from the ED to the inpatient setting also remains an important goal of this network as optimal transition ensures patient safety, complete data capture, and ideal interaction between the study team and clinical team. This also ensures competitive trials are not separately initiated by the emergency medicine and the cardiology investigators, resulting in poor enrollment in both. As new studies are considered, the emergency medicine and cardiology investigators determine by consensus who will lead the study, whether the population of patients is adequate, and how each protocol will be implemented. Obtaining informed consent in a chaotic ED environment, utilizing exception from informed consent, and the early enrollment of patients at the time of initial ED evaluation are all concepts familiar to EM research teams, but can be challenging for cardiology-based investigators. Conversely, while it is routine for the cardiology team to manage a study patient on the hospital floor or in the intensive care unit, and in the post-discharge clinic environment, this is often unfamiliar to many emergency medicine investigators.

Having infrastructure already in place engenders timely contract and IRB submission, study start up and enrollment, and results in rapid implementation of industry supported and federally funded trials by site investigators. Although ED-based teams screen the electronic medical record in a similar manner as other hospital based research teams, the most successful ED teams place research staff physically in the ED and work with the ED clinical team to identify and approach potential participants to gauge their interest. Once a subject candidate is identified to fulfill the inclusion and exclusion criteria, and expresses interest in the study, the ED team then confirms the availability of the cardiology team to assume inpatient study responsibilities. This model has been successful in several AHF studies, accounting for a high volume of enrolled patients relative to the number of participating EMROC centers in each study (**Table**). Given the unique expertise the EMROC network provides, it also provides additional opportunities for its participants to serve on steering and executive committees for studies.

While there remain ample opportunities to further understand the epidemiology, taxonomy, pathophysiology, treatment options, and approach to disposition for the management of patients with AHF, we believe the following targeted topics are of highest priority to advance care. *The author group held an in-person meeting at the Heart Failure Society of America meeting in 2016 (Orlando, FL) where ideas were solicited for both our next manuscript topic and the content to be contained in the manuscript. We used a nominal group technique (consensus-building methodology involving structured, iterative rounds of input to identify, review, prioritize, discuss, and reprioritize research domains and questions) to develop the research topics proposed in this consensus document.*

**1) Does Early Bolus Vasodilator Use Improve Symptoms In Patients With Hypertensive Acute Heart Failure?**

Emerging data suggest variable hemodynamic derangements underlie similar clinical presentations among AHF patients. In particular, patients with hypertensive AHF have exaggerated vasoconstrictive physiology,<sup>32, 33</sup> are more likely to have greater fluid redistribution than net fluid gain, and appear to benefit from IV vasodilators. Despite this understanding, vasodilators remain underutilized.<sup>34, 35</sup> Recent trials of IV vasoactive agents have produced neutral results, but have largely excluded patients with significant blood pressure elevations.<sup>7, 10, 36</sup> Preliminary data in hypertensive AHF patients suggests targeting this pathophysiology with IV vasodilators improves symptoms, as well as decreases length of stay and resource use.<sup>37-41</sup> In patients with chronic HF, national guidelines give a strong I-A recommendation for use of oral vasodilators including ACEI and

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nitrates in select patients. Conversely, in the setting of AHF there are far weaker II-B recommendations for the use of nitroglycerin (NTG) or other IV vasodilators, and the precise patients in whom this therapy needs to be utilized is poorly characterized.<sup>21-25</sup> The lack of robust data, combined with the additional monitoring and titration necessary for continuous vasodilator infusions, leads to their infrequent use in AHF, even when hypertension is a predominant component. Early vasodilator use in hypertensive AHF seems logical, and IV boluses instead of continuous drips may facilitate improved outcomes and resource use. A rigorously designed study is necessary to provide strong evidence for their appropriate and safe use, and ultimately to drive practice change.<sup>22, 34, 42, 43</sup> Preliminary data suggest the early use of bolus IV ACEI and bolus high-dose (HD) NTG would benefit patients with hypertensive AHF.<sup>38-40</sup> Despite promising preliminary data, a randomized trial comparing bolus IV ACEI and IV HD NTG with structured standard therapy is needed to determine the clinical impact and safety of this approach.

## **2) Can Utilization of Objective Targets of Decongestion Lead to Improve Clinical Outcomes?**

Mortality and symptoms have been the focus of AHF clinical trials, irrespective of mechanism of action or phase of therapy development. However, it is not clear what the optimal combination should be for a primary endpoint. Symptoms related to congestion, due to fluid gain and/or redistribution, are the primary reason patients with AHF present to the ED. For many, symptoms can often be reduced with the use of standard IV diuretics, but failure to completely relieve congestion is associated with worse outcomes. Up to 50% of patients with AHF leave the hospital with persistent congestion.<sup>44-46</sup> Both the assessment and treatment of congestion is based on limited evidence<sup>11, 12, 47-49</sup> and current guidelines state that “the treatment of AHF remains largely opinion-based with little good evidence to guide therapy.”<sup>48</sup>

Combining an objective measure of decreased congestion with subjective improvement, such as dyspnea assessment, may lead to better identification of optimal treatment endpoints. Following changes in natriuretic peptides during hospitalization to identify treatment endpoints have not proven beneficial.<sup>50</sup> However, lung ultrasound can identify congestion and pulmonary edema with high sensitivity<sup>51</sup> and discriminate AHF from other causes of dyspnea. Beyond its diagnostic value, lung ultrasound demonstrates changes in pulmonary edema in real time.<sup>52-54</sup> Improvement in sonographic pulmonary edema has been shown during dialysis<sup>53, 54</sup> and in response to inpatient AHF treatment.<sup>52, 55-57</sup> Incomplete resolution of pulmonary edema visualized on lung ultrasound following

inpatient treatment predicts the need for re-hospitalization.<sup>57, 58</sup> Given the prognostic value of residual sonographic pulmonary edema, its resolution may be a valuable therapeutic target for both routine and investigational AHF therapy and merits further investigation.

Other metrics such as inferior vena cava ultrasound also deserve study. A prospective, multi-center study comparing length of stay, 30-day readmission and mortality between patients randomized to: 1) routine clinical treatment or 2) treatment directed by serial lung ultrasound measures of congestion, or other objective measures, would determine if these strategies better define therapeutic endpoints. A large, clinically heterogeneous cohort would allow for subgroup analyses of patients with heart failure and reduced vs. preserved ejection fraction, those presenting with differences in initial blood pressure, and relevant comorbidities such as diabetes and chronic kidney disease. ED lung fluid assessment may facilitate optimal disposition to the observation unit, or the medical floor, vs. other inpatient settings, and repeated assessment may provide an objective measure of ‘readiness for discharge’.<sup>59-61</sup>

### **3) Can Use of Non-Invasive Physiological Monitoring Facilitate Emergency Department Care and Safe Discharge?**

Remote monitoring technologies can help engage subjects, inform caregivers, and facilitate timely intervention. These technologies have been utilized to manage patients with HF in an effort to improve quality of life and prevent readmissions.<sup>62-64</sup> However, most of these studies have utilized indwelling sensors in chronic ambulatory patients to acquire and relay the information to the patient and their providers.<sup>65</sup> This limits the utility and generalizability of this technology to patients with implanted devices, and their utility in the ED patient with AHF is unclear. There are currently available external monitoring devices that collect data such as chest impedance, radar volume detection, heart rate variability, cardiac index, arrhythmia burden, positionality, and activity levels, similar to the implantable devices.<sup>60, 66, 67</sup> However, these devices have not yet been broadly and systematically studied in the context of AHF in the ED and this represents a tremendous knowledge gap and opportunity.

To accurately utilize such information in ED patients with AHF, it is important to obtain data along a continuum from ED presentation through hospitalization and into the post-discharge period. These data are critical to quantify decongestion during hospitalization, identify decompensation, and predict subsequent re-hospitalization. HF rehospitalization shortly after hospital discharge is a unique problem caused by a combination of the disease state and the patient’s ability to navigate the

outpatient setting. This may be strongly influenced by patient factors such as medication and dietary adherence, health literacy, access to follow-up and socio-economic conditions.<sup>2</sup> It would be important to test the feasibility of treatment adjustment based on physiologic data from an external device applied in the ED and utilized throughout hospitalization and during post-discharge follow-up. This would require ED, inpatient, and outpatient providers to establish protocols to ensure consistent treatment as a response to changes in the physiologic data. We hypothesize that management based on physiologic parameters will result in a decrease in ED visits and hospital re-admissions compared to patients managed without this information. This type of study could also incorporate not only diagnostic data but also therapeutic options whose intensity would be based on the severity of physiologic disturbances as indicated by the monitoring. For example, a device able to administer subcutaneous diuretic may safely increase the proportion of ED and OU patients who are discharged without hospitalization and facilitate symptom improvement in the outpatient setting. In addition, combining an external device with an intervention while engaging the patient and their caregiver to improve self-care may address the socioeconomic and demographic barriers contributing to rehospitalization.<sup>68</sup>

#### **4) Do All AHF Patients With a Troponin Elevation Absent Suspected Acute Coronary Syndrome Require Admission to the Hospital?**

With the development of increasingly sensitive assays, only a minority of patients with AHF will have a cardiac specific troponin (cTn) concentration below the 99<sup>th</sup> percentile of a normal population.<sup>69,70</sup> The detection of cTn above this cutpoint in the setting of AHF is indicative of some degree of underlying myocardial cell death, though release from cytosolic pools in damaged but viable cardiomyocytes and other mechanisms have been proposed.<sup>71-74</sup> While the presence of serum troponin above the 99<sup>th</sup> percentile occurs in the setting of an acute coronary syndrome (ACS), many other causes of cell death are common as well, and may reflect processes more chronic in nature involving remodeling with cardiomyocyte turnover.<sup>75,76</sup> cTn concentrations exceeding normal values do portend worse prognosis.<sup>26,29,77,78</sup> As a result, clinicians are compelled to treat such patients as high-risk, often admitting them to a monitored hospital setting for presumed management of possible ACS. However, few such patients actually undergo diagnostic evaluation for potential myocardial ischemia and most spend several days in the hospital receiving treatment primarily with diuretics.<sup>1,79</sup>



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It is unclear what the incremental value of hospital admission is in patients who present to the ED with AHF, whose symptoms resolve yet are admitted solely due to an elevated cTn. For those with new-onset HF, hospitalization to search for underlying, undetected coronary artery disease is appropriate, but many patients with AHF have an established diagnosis of chronic HF with known previous coronary disease evaluation. Similarly, whether and when such repeat evaluations are needed in the presence of a cTn elevation where ACS is unlikely, especially those patients with known normal coronary arteries on prior cardiac catheterization, is not clear. In reality, invasive studies are often not conducted despite hospitalization for such concerns.<sup>80</sup> Moreover, it is not clear that hospitalization mitigates risk of outcomes for patients with chronic HF. Prior studies suggest few in-hospital cardiac arrest events among those admitted for acute decompensation,<sup>81</sup> and no difference in 30-day outcome between those admitted compared with those discharged from the ED.<sup>82</sup>

Given these many unanswered questions regarding optimal disposition decision making, a trial focused on safe discharge of ED patients with AHF and stable cTn elevations could alter the current clinical practice of hospital admission in many of these patients. Patients with an elevated cTn whom the treating ED provider intended to admit, who didn't have ACS or another acute indication for hospital admission, would be randomized to: 1) a usual care arm, which would continue with inpatient admission; or 2) an investigational arm prompting discharge from the ED after serial cTn assessments prove to be stable. To alleviate clinician concerns about safety, the latter would need to include early outpatient follow-up and initiation, re-initiation, or uptitration of appropriate, guideline directed medical therapy. To avoid imbalance, case matching or stratified randomization may also be needed to account for other risk modifiers such as renal function, blood pressure, and psychosocial support. Given the known trepidation and conservative approach that emergency physicians apply to AHF disposition,<sup>83</sup> the results of this trial could have a significant impact on clinical care.

### **Answers Require Emergency Medicine and Cardiology Collaboration**

### **Conclusion**

Over the last decade, emergency physicians and cardiologists have partnered to conduct AHF clinical trials. This partnership ensures: 1) early patient identification and enrollment; 2) a smooth transition for clinical care; and 3) data collection and follow-up for both the inpatient and outpatient setting.

This clinical trial infrastructure has been utilized to evaluate novel therapies and optimal ED-based management strategies. Such partnerships should continue to be encouraged and further strengthened. The outcomes for patients with AHF remain sub-optimal and management guidelines remain largely opinion based. Many important questions need to be answered. In this document, our AHF Working Group has identified four high priority areas for research including defining optimal endpoints of therapy, defining risk and management strategies in AHF patients with elevated cTn, and early therapeutic approaches in patients with elevated blood pressure and AHF. Results from these studies will inform clinical practice and national guidelines by significantly advancing the limited current evidence base.

**Table.** EMROC participation in AHF studies, study design and number of patients enrolled.

<b>RELAX AHF 2</b>	Novartis	Phase III RCT	Complete	6610	712	115
<b>TRUE</b>	Cardiorentis	Phase III RCT	Complete	2152	301	62
<b>STAND UP</b>	BMS	Phase IIb RCT	Started 5/2017	6 (Approx. 200 planned)	6	3
<b>GUIDED</b>	PCORI	Phase III RCT	Ongoing	700 planned	290	250
<b>AHF Registry</b>	EMROC	Cohort	Ongoing	1300	1300	1300
<b>BLUSHED AHF</b>	NHLBI	Phase III RCT	Started 8/1/17	135 planned	4	4
<b>Obs Unit vs Inpatient Admission in ED patients with AHF</b>	AHRQ	Phase III RCT	Pending	Pending	Pending	Pending

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