Hospitalization for acute heart failure syndromes (AHFS) heralds a grim prognosis: More than one third of patients will be dead or rehospitalized within 90 days post-discharge. Although total hospitalizations for AHFS have decreased over the past decade, rehospitalization rates have not. With 1 million hospitalizations annually at an estimated cost exceeding $20 billion, AHFS is a major public health problem.

One of the possible contributors to these poor outcomes is our approach to patients with AHFS in the emergency department (ED). Approximately 80% of hospitalized patients initially present to the ED, highlighting the pivotal role of the ED in initial AHFS management. Yet there are no class I, level A guideline recommendations for the initial pharmacological treatment of AHFS. ED treatment today is largely the same as it was 40 years ago and is similar across all patients with AHFS despite the heterogeneity of patients in terms of precipitant, presentation (eg, pulmonary edema, hypertension), phenotype (eg, reduced or preserved ejection fraction), or etiology (ischemic versus nonischemic). This management approach and lack of progress is not the fault of frontline caregivers; rather it reflects our limited understanding of the pathophysiology of AHFS and the need for further research, especially in the ED setting.

In this issue of *Circulation: Heart Failure*, Drexler et al address the hypothesis that ED patients with AHFS with an underlying ischemic etiology have a distinct pathophysiology compared to patients with AHFS with a nonischemic etiology. Specifically, they tested whether higher brain natriuretic peptide and troponin levels are present in patients with AHFS than in patients with AHFS with an ischemic etiology versus nonischemic etiology for patients with AHFS cannot be determined based on these biomarkers alone, despite evidence that patients with AHFS with an ischemic etiology have greater hemodynamic stress and cardiac damage. Drexler et al are to be commended for investigating the use of biomarkers to better classify patients with AHFS. Their study highlights an important question: Would careful classification and selection of patients with AHFS, potentially resulting in novel strategies of care, tailored therapy of existing therapies, and novel therapies, lead to improved outcomes? Although their well-designed study was not positive, it is an important step in moving the science of classification of patients with AHFS forward. Several aspects of their study, however, merit further discussion.

Central to the hypothesis of Drexler et al is that higher troponin levels will be found in patients with an underlying ischemic etiology, yet the exact mechanism underlying troponin release in AHFS is unknown. Previous studies demonstrated that troponin release in AHFS occurs independent of an ischemic etiology, a fact acknowledged by the authors. Although Drexler et al did not study troponin levels over time, other authors recently confirmed the phenomenon of serial troponin release in patients with AHFS irrespective of underlying coronary artery disease (CAD), finding a sizable number of patients with abnormal troponin levels during hospitalization despite normal baseline troponin levels (a finding associated with worse outcomes). Taken together, baseline troponin level alone lacks the specificity needed to identify patients with AHFS at the time of presentation with an ischemic etiology.
Further discussion of the patient population classified with an ischemic etiology is also warranted; the authors themselves highlight the potential for misclassification despite careful adjudication. The majority of patients whose condition is classified as ischemic was based on a history of CAD, myocardial infarction, or both. The total number of patients who underwent angiography (or the proportion who received percutaneous coronary intervention) during the index hospitalization was not reported, only the number of patients with >75% stenosis in 2 vessels (n = 50 [13%]). Although intimate knowledge of the burden of CAD in this study would have been impractical, there may be differences in biomarker levels by extent and severity of CAD in AHFS. Similarly, 5% of the ischemic subgroup had evidence of scar by myocardial perfusion imaging, but whether this was reversible or irreversible was not reported. In addition, ~40% of the overall ischemic subgroup had de novo or new-onset heart failure. These patients comprise a distinct clinical entity.15 Whether their results would have been different if stratified by de novo versus chronic heart failure (HF) with AHFS would be intriguing because the clinical management of these patients often differs. Finally, Drexler et al included patients with ST-segment elevation or non-ST-segment elevation myocardial infarction (~12% of their ischemic AHFS population); if these patients were excluded, the strength of their finding that patients with an ischemic etiology had a greater evidence of troponin release may have been attenuated. Each of these points highlights that even within the subgroup of patients with AHFS with an ischemic etiology, further subclassification may be necessary.

The question of terminology is thus raised. Not all studies use the same definition of ischemic HF or CAD.16,17 Because the prevalence of CAD in AHFS may be underreported, this could influence results that associate with an ischemic HF etiology.16 In the context of AHFS, the term ischemic AHFS itself is potentially confusing as follows: (1) Ischemia may precipitate AHFS; (2) ischemia may be a result of the adverse milieu present in patients with AHFS (and untoward effects of AHFS therapies); or (3) CAD may be the underlying etiology of HF, but there is an alternate reason for acute decompensation.18 To add to the complexity, all 3 could be present simultaneously, ischemia may occur even in the absence of underlying CAD, or the manifestations might be similar (eg, troponin release) but occur by different mechanisms.13

We advocate for the consensus terminology put forth by Flaherty et al,14 dividing patients with AHFS who have CAD into those who present primarily with acute coronary syndromes and AHFS versus those with AHFS with underlying CAD.

AHFS and CAD

Approximately 60% of patients with AHFS have underlying CAD.5,15,16,19 In patients with HF, the extent and severity of CAD independently predicts worse outcomes.16,20 Secondary analysis of patients with AHFS and CAD from the OPTIMIZE-HF (Organized Program to Initiate Lifesaving Treatment in Patients Hospitalized for Heart Failure) registry found a significantly reduced risk of death and rehospitalization in patients who underwent in-hospital angiography, resulting in higher rates of revascularization and uptake of evidence-based therapies.19 Importantly, in-hospital angiography was not associated with improved outcomes in patients whose condition was classified as nonischemic, despite the presence of elevated troponin levels, supporting the hypothesis that knowledge of the underlying HF etiology is important.19 Prospective studies, however, are needed to determine whether therapies for CAD in AHFS improve outcomes.

The challenge in identifying patients with AHFS and CAD is that on presentation to the ED, the exact etiology of AHFS often is unknown. History alone may be unreliable, patients may have undiagnosed CAD, the extent and severity of CAD may not be fully known, the degree of reversible versus irreversible dysfunctional myocardium may vary, or CAD is present, but other factors may have contributed to the development/progression of HF (eg, valvular disease, hypertension).16,21 Before we can determine whether differential management of patients with AHFS and CAD versus those without CAD can influence outcomes, we must first develop ways of distinguishing these patients acutely in the ED setting. The study by Drexler et al demonstrates that the use of troponin and brain natriuretic peptide levels alone will not improve the classification of patients with AHFS in the ED.

Future Directions

Despite the challenges, improved classification of patients with AHFS at the time of presentation to the ED is critical and involves more than etiology alone.3,15; it is a concept supported by the European Society of Cardiology and highlighted in a recent scientific statement from the American Heart Association as well as by a working group convened by the National Heart, Lung, and Blood Institute.8,22,23 It is also an approach advocated by AHFS clinical trialists. Failure to target specific patient subgroups has been suggested as a possible contributor to the disappointing results of AHFS clinical trials seen to date.9,24,25 Although we have focused on patients with AHFS and CAD, classifying patients without CAD as nonischemic may also be too broad. A multifaceted approach to classifying ED patients is key because targeting only the etiology may be insufficient.7,9,18

One proposal by Drexler et al to improve classification of patients with AHFS is worth reinforcing: the early use of cardiac imaging. Cardiac phenotyping with echocardiography has been proposed for this purpose.23 Advanced echocardiographic techniques allow for detailed assessments of structure, function, hemodynamics, and mechanics. Importantly, repeat assessments at the bedside are possible, capturing the dynamic nature of AHFS. However, the standardization and interpretation of advanced echocardiographic indices will be necessary and presents a potential challenge for the early use of echocardiography in AHFS.26 Another cardiac imaging modality, coronary CT angiography, would allow for direct visualization of coronary anatomy and, depending on the technique, would assess both cardiac structure and function. Another potential benefit would be the ability to identify other comorbidities (eg, pulmonary embolism) that might be the precipitant of the AHFS episode, a contributor to the patient’s presentation, or an alternative diagnosis. The value of comprehensive echocardiography and coronary CT angio-
graph in the ED-AHFS setting, with careful evaluation of its risks, benefits, and costs, requires further study. Importantly, such studies should combine imaging with clinical, laboratory, and a multibiomarker approach, rather than in isolation.

Conclusion
Postdischarge morbidity and mortality rates after hospitalization for AHFS are high. Classifying patients with AHFS in the ED would facilitate both current management and research focused on improving care and might lead to improved outcomes. Patients with AHFS and CAD comprise a key subgroup to target for future research, given the prevalence of CAD in AHFS, the evidence base supporting CAD management, and the availability of multiple modalities for the in-depth assessment of AHFS and CAD. Within this subgroup, further subclassification may be necessary. In addition, elucidating the pathophysiological mechanisms that occur before, during, and after an AHFS episode is critical. The early use of advanced cardiac imaging combined with multibiomarker assessment is one approach that may yield important insights. Ultimately, whether improved classification of patients with AHFS in the ED setting will facilitate successful therapeutic development or strategies to improve outcomes remains to be determined, but it is an exciting and promising hypothesis.

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References


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