Clinical profiles in acute heart failure: an urgent need for a new approach

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Abstract

Acute heart failure (HF) is a major public health concern, responsible for >26 million hospitalizations per year worldwide. Many trials have investigated new therapeutic options for acute HF, with most revealing equivocal results. Successful innovations in therapy for acute HF have remained limited, and standard of care has remained largely unchanged over the past decade, suggesting the need for a new approach for therapeutic decision making and clinical trial design in acute HF. This manuscript focuses on one approach that could prove useful in the development and application of novel therapies: classification of patients based on clinical profiles. While previous attempts at developing clinical profiles were successful in stratifying patients based on clinical and laboratory variables, they have not been utilized for personalized treatment strategies that improve patient outcomes. We suggest a new approach to the creation of clinical profiles that could stratify patients based on their underlying aetiology and their response to novel interventions. We also investigate novel analytic approaches to the creation of new clinical profiles that both investigators and clinicians alike could utilize to inform clinical trial design and the application of new therapies. Despite a large number of clinical trials for new therapeutic options, the treatment of acute HF has seen few advances over the past decades. Innovative approaches to patient selection through the use of clinical profiles could help to identify patients most likely to benefit from novel interventions and lead to the discovery of new therapeutic options.

Keywords Acute heart failure; Classification; Clinical trials

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Introduction

Acute heart failure (HF) is a major public health issue. It is associated with >1 million hospitalizations per year in the USA, >1 million hospitalizations per year in Europe, and >26 million hospitalizations per year worldwide.\(^1\)\(^,\)\(^2\) The 1 year mortality rate after an acute HF hospitalization has remained high at 20–30%,\(^3\) and there is additive risk with each subsequent hospitalization.\(^4\)\(^,\)\(^5\) The costs of acute HF care are also staggering and expected to rise as the prevalence of HF increases.\(^6\) Many initially promising therapies have been tested in this patient population without success,\(^7\)\(^–\)\(^9\) and as a result, acute HF care remains largely homogenous and unchanged over the past 40 years.\(^10\)\(^–\)\(^12\) The majority of acute HF patients are treated with intravenous loop diuretics, a subset receive inotropic or vasodilator therapies or non-invasive ventilation, and a minority require mechanical support.\(^2\) This review seeks to achieve the following: review findings from recent acute HF clinical trials, summarize previous research utilizing clinical profiles and frameworks in acute HF, and outline a new approach to the identification and use of clinical profiles that could inform future research.

A case study in promising but unsuccessful therapies

Given the paucity of new treatments for patients hospitalized with acute HF, a large amount of interest was generated when serelaxin, a recombinant form of human relaxin-2 with vasodilating properties, demonstrated beneficial effects in...
the initial RELAX-AHF trial in patients with the following criteria: acute HF, a normal-to-high systolic blood pressure, and mild-to-moderate renal dysfunction. The promising findings of this trial on cardiovascular death at 180 days reinvigorated the hope that new therapeutic targets for patients with acute HF could be identified and manipulated to improve outcomes. In an attempt to reproduce the findings of the initial trial, the multicentre phase III RELAX-AHF-2 was undertaken. Though the final manuscript has not yet been published, a presentation at the 2017 European Society of Cardiology (ESC) World Conference on acute HF revealed that serelaxin compared with placebo had no impact on the primary endpoint of reduction in cardiovascular death through 180 days of follow-up or reduced worsening HF through Day 5. Despite the initial excitement surrounding serelaxin, it appears that treatment for patients with acute HF will continue to focus on symptom relief, decongestion, and initiation of chronic therapies for HF with reduced ejection fraction (HFrEF) unless a new approach is undertaken in both study design and treatment selection.

Acute heart failure is a unique clinical syndrome with limited treatment options

The lack of progress in the pharmacologic treatment of acute HF is in contrast to treatment advances for patients with chronic HFrEF. There are currently a plethora of treatment options for patients with chronic HFrEF, and this potentially affords a more personalized approach to care on the basis of clinical profiles. For one, the left ventricular ejection fraction (LVEF) is a measurement that defines a large group of patients with chronic HF in whom evidence-based therapies can be used. Further subsets are then defined in these patients and can be used to inform therapeutic choices. Persistence of high heart rate despite optimal medical treatment with neurohormonal antagonists is an indication for ivabradine treatment, a medication that acts on the I_{Kr} channel in the sinoatrial node to lower a patient’s heart rate and has been shown to have a survival benefit in patients with HFrEF. A wide QRS complex, a marker of left ventricular dyssynchrony, is an indication for cardiac resynchronization therapy in order to electrically restore synchrony in these patients. Further treatments are indicated on the basis of severity and clinical stage of illness in both the European and US guidelines.

Similarly, and probably to a larger extent than patients with chronic HFrEF, patients hospitalized with acute HF are an extremely heterogeneous population, and tailored treatment seems mandated. However, similar to the case of RELAX-AHF-2, trials have generally failed to yield favourable results despite efforts for better patient selection. Most of these trials were based on tailored treatments in patients with concomitant renal dysfunction, a subgroup known to be at higher risk of events. For example, the PROTECT (Placebo-Controlled Randomized Study of the Selective A2 Adenosine Receptor Antagonist Rolofylline for Patients Hospitalized with Acute Decompensated HF and Volume Overload to Assess Treatment Effect on Congestion and Renal Function) trial assessing adenosine antagonism in patients with renal dysfunction was neutral with respect to a primary clinical composite endpoint. Also, CARRESS-HF (Cardiorenal Rescue Study in Acute Decompensated HF) demonstrated that in patients with worsening renal function, ultrafiltration led to worse renal function without additional benefit when compared with stepped pharmacologic care. Finally, no benefit with low-dose dopamine or low-dose nesiritide, compared with placebo, was shown in a similar patient population in the ROSE (Renal Optimization Strategies Evaluation) trial.

One trial that did not explicitly target patients with concomitant renal dysfunction was the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) trial, which specifically assessed if therapy guided by pulmonary artery catheters, compared with clinical assessment alone, would improve outcomes in a cohort of patients with acute HF without concomitant advanced renal disease (Cr > 3.5) or prior use of inotropes. Patients randomized to the pulmonary artery catheter intervention had increased anticipated adverse events, and there was no difference in mortality and hospitalization.

A number of other trials have revealed disappointing data among patients with acute HF (Table 1): the OPTIME-CHF trial revealed that i.v. milrinone did not improve in-hospital mortality, 60 day mortality, or readmission rates among patients hospitalized with acute HF; the VERITAS trial failed to show an improvement in clinical outcomes or symptomatic relief from using the endothelin receptor antagonist tezosentan in patients with acute HF; REVIVE I and II showed that treatment with the calcium sensitizer levosimendan reduced symptoms but led to increased adverse cardiovascular events in patients with acute HF; the TRUE-AHF trial showed no difference in cardiovascular outcomes among patients with acute HF who had received the vasodilator ularitide, despite markedly improved intravascular congestion. While this is certainly not an exhaustive list of trials investigating novel interventions for acute HF, it is certainly a representative sample of the disheartening results seen in many such trials.

Based on these results, it has become clear that there is a need for a new method of stratifying patients on the basis of their underlying pathology and subsequent likelihood to benefit from different therapies. In fact, subgroup analyses have hinted that patients meeting specific criteria may have benefitted from some of these novel therapies. In the PROTECT trial, there was a trend toward improved clinical
Table 1  Examples of acute heart failure trials with negative or equivocal results

| Trial          | Year published | Major inclusion criteria                                                                 | Findings                                                                 |
|---------------|----------------|------------------------------------------------------------------------------------------|--------------------------------------------------------------------------|
| OPTIME-CHF²³  | 2002           | - LVEF < 40%  
- sCr > 3.0 mg/dL  
- SBP > 80 mmHg  
- No active myocardial ischaemia  
- No atrial fibrillation with tachycardia (HR > 110 b.p.m.)  
- No VT or SVT | - Number of days hospitalized for cardiovascular causes was no different between milrinone and placebo  
- Patients receiving milrinone, compared with placebo, had more frequent sustained hypotension and new atrial arrhythmias  
- Milrinone, when compared with placebo, did not improve in-hospital mortality, 60 day mortality, or the composite incidence of death or readmission |
| ESCAPE²¹      | 2005           | - Severely symptomatic HF patients  
- At least 3 months of symptoms despite ACE inhibitor and diuretic usage  
- LVEF < 30%  
- SBP < 125 mmHg  
- 1 sign + 1 symptom of congestion  
- sCr < 3.5 mg/dL  
- No prior milrinone use  
- No prior use of dobutamine or dopamine < 3 µg/kg/min | - The pulmonary artery catheterization group, when compared with the placebo group, had increased adverse events without improvements in overall mortality or hospitalizations |
| VERITAS²⁴     | 2007           | - Hospitalized within 24 h for acute HF  
- Dyspnoeic at rest (RR > 24/min at rest)  
- sCr < 2.5 mg/dL  
- SBP > 100 mmHg without vasodilator or SBP > 120 with vasodilator  
- Hb > 10 g/dL, Hct > 30%  
- No STEMI or ongoing cardiac ischaemia  
- No cardiogenic shock within 48 h | - Tezosentan, when compared with placebo, did not improve dyspnoea  
- Tezosentan, compared with placebo, did not reduce the incidence of death or worsening HF |
| PROTECT⁹      | 2010           | - Hospitalized for acute HF  
- Dyspnoea at rest  
- Impaired renal function  
- Ongoing loop diuretic usage | - No difference in the proportion of patients who achieved treatment success when rolofylline was compared with placebo  
- Rolofylline did not improve readmission rates or death from cardiovascular or renal causes at Day 60 |
| ASCEND²⁸      | 2011           | - Hospitalized for acute HF  
- Dyspnoea at rest or with minimal activity  
- 1 or more signs of acute HF (RR ≥ 20, pulmonary congestion or oedema with rales)  
- 1 or more objective measures of heart failure (evidence of congestion or oedema on chest radiography, BNP ≥ 400 pg/mL or NT-proBNP level ≥ 1000 pg/mL, PCWP > 20 mmHg, or LVEF < 40% in the previous 12 months)  
- SBP > 100 mmHg  
- Concurrent treatment with dobutamine or previous use of dobutamine or levosimendan in the past 30 days | - Nesiritide did not significantly improve dyspnoea at 6 or 24 h  
- Nesiritide did not improve rehospitalization rates for heart failure or cardiovascular causes at 30 days  
- Nesiritide did not improve death rates at 30 days from either cardiovascular causes or any cause  
- A greater proportion of patients receiving nesiritide had an episode of hypotension |
| CARRRESS-HF¹⁹ | 2012           | - Hospitalized for acute HF  
- Renal dysfunction within 12 weeks before or 12 weeks after index admission for HF with sCr < 3.5  
- Evidence of persistent congestion  
- No inotrope usage | - sCr increased in the ultrafiltration group, compared with sCr decrease in the placebo group  
- No difference between groups in worsening of condition, amount of diuretic usage, or crossover to alternate therapy  
- More patients receiving ultrafiltration had adverse events  
- Neither nesiritide nor dopamine, compared with placebo, changed cystatin C levels or 72 h urine volume  
- Neither nesiritide nor dopamine had an effect on end-points reflective of decongestion, renal function, or clinical outcomes |
| ROSE²⁰        | 2013           | - Hospitalized for acute HF  
- Evidence of renal dysfunction (eGFR 15–60 mL/min/1.73 m²) | - (Continues)
Proposed clinical profiles at admission for acute heart failure

Authors have proposed multiple different clinical profile frameworks for patients presenting with acute HF (Table 2). In our experience, the haemodynamic profiles based on work by Forrester\textsuperscript{27,36} in patients with acute myocardial infarction and then translated into an advanced HF population by Nohria and colleagues\textsuperscript{28,38} have proven to be useful constructs for evaluating patients. These profiles are based on data from a routine history and physical examination. They can be easily obtained at the bedside during routine clinical practice, unlike other profiles that rely on an echocardiogram or invasive testing. However, to our knowledge, these profiles have not been prospectively assessed in a randomized fashion in the design of therapies that alter the natural history of acute HF, and some evidence exists that there is inaccuracy in the bedside use of physical exam to estimate haemodynamic status,\textsuperscript{39,40} which is then used in therapeutic decision making.

In 2004 and 2005, investigators, clinicians, and regulatory and industry representatives convened the International Workshop on Acute HF Syndrome.\textsuperscript{41} This group outlined three major categories of patients with acute HF (i.e. new-onset HF, acute decompensation of chronic HF, and advanced HF), with this last category encompassing ~5% of all the patients and a very poor clinical course. Further classification was proposed on the basis of clinical findings with a list of eight different clinical presentations. These clinical profiles were based mainly on initial blood pressure, a major

| Trial          | Year published | Major inclusion criteria                                                                 | Findings                                                                                             |
|---------------|----------------|------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------|
| REVIVE I and II\textsuperscript{25} | 2013 | - Hospitalized with acute HF - Dyspnoea at rest despite diuretic therapy - LVEF ≤ 35% within last year - SBP > 90 mmHg, HR < 110 b.p.m. - sCr ≤ 5 g/dL, potassium > 3.3 - No hepatic dysfunction - No stroke, TIA, or cardiac revascularization within 90 days - No COPD - No acute bleeding or anaemia (Hb > 10 g/L) - No active infection - No history of torsades de pointes - Emergency-department visit or hospitalization for acute HF - Dyspnoea at rest, worsening over the past week - SBP between 116 and 180 mmHg - Persistent dyspnoea despite treatment with at least 40 mg intravenous furosemide | - More levosimendan patients, compared with the placebo group, were symptomatically improved at all measured time points - The levosimendan group had more frequent hypotension and cardiac arrhythmias during infusion than did the placebo group - The levosimendan group had increased risk of death than did the placebo group |
| TRUE-AHF\textsuperscript{26} | 2017 | - Ularitide did not improve cardiovascular mortality - Ularitide was associated with greater decreases in SBP and NT-proBNP as well as fewer in-hospital heart failure events | - Serelaxin, compared with placebo, did not reduce cardiovascular mortality at 180 days - Serelaxin showed a trend toward reduction of worsening heart failure at 5 days, though this difference was not statistically significant - Serelaxin did not show benefit in all-cause mortality at 180 days, length of initial hospital stay, or the combined endpoint of cardiovascular death and rehospitalizations due to heart or renal failure through Day 180 |
| RELAX-AHF-2\textsuperscript{15} | 2017 | - More levosimendan patients, compared with the placebo group, were symptomatically improved at all measured time points - The levosimendan group had more frequent hypotension and cardiac arrhythmias during infusion than did the placebo group - The levosimendan group had increased risk of death than did the placebo group | - Serelaxin, compared with placebo, did not reduce cardiovascular mortality at 180 days - Serelaxin showed a trend toward reduction of worsening heart failure at 5 days, though this difference was not statistically significant - Serelaxin did not show benefit in all-cause mortality at 180 days, length of initial hospital stay, or the combined endpoint of cardiovascular death and rehospitalizations due to heart or renal failure through Day 180 |

b.p.m., beats per minute; COPD, chronic obstructive pulmonary disorder; eGFR, estimated glomerular filtration rate; Hb, haemoglobin; Hct, haematocrit; HF, heart failure; HR, heart rate; LVEF, left ventricular ejection fraction; PCWP, pulmonary capillary wedge pressure; RR, respiratory rate; SBP, systolic blood pressure; sCr, serum creatinine; STEMI, ST-elevation myocardial infarction; SVT, sustained ventricular tachycardia; TIA, transient ischaemic attack; VT, ventricular tachycardia.

outcomes as baseline renal function worsened; in the OPTIME-CHF trial, ischaemic cardiomyopathy patients responded significantly worse to milrinone than did their non-ischaemic counterparts. Clinical profiles may be one way of stratifying these patients to guide therapeutic choices.
prognostic factor in acute HF, but included also pulmonary oedema, as a separate category, acute coronary syndrome, right ventricular failure, and post-cardiac surgery HF. This is a comprehensive list of different acute HF phenotypes and has had a major impact in subsequent guidelines. With the previously outlined exception of acute coronary syndrome, its main legacy resides in the use of systolic blood pressure to select patients for treatment with vasodilating drugs or inotropic agents.

Guidelines have also outlined clinical profiles for patients with acute HF. The ESC first proposed distinct profiles in 2005 and updated these in 2008 and 2009. In general, these profiles incorporate various clinical data and are based on physiologic concepts, precipitating causes for an HF exacerbation, and cardiac structure and function. Some of these profiles necessitate specific testing for verification, such as right heart catheterization for high-output HF. The prognostic value of these clinical profiles was assessed in the EuroHeart Failure Survey II. A better prognosis was shown for the patients with new-onset HF than for the patients with an acute decompensation of chronic HF as well as for the patients with hypertensive HF, compared with the other clinical classes. Patients with cardiogenic shock had a higher in-hospital and 3 month mortality but a similar long-term outcome than did the other clinical classes. These clinical profiles are not included in the most recent guidelines.

The utility of these profiles was tested in the ESC-HF-LT Registry; 16012 patients with chronic HF were included in the registry, and 6629 of these patients were hospitalized with acute HF during the year after enrolment in the trial. Differences in both therapeutic decision making and in-hospital all-cause mortality were seen among the six categories of acute HF.

### Table 2 Examples of clinical profiles at admission for acute heart failure

| Title | Description |
|-------|-------------|
| **Bedside Assessment of Congestion and Perfusion**<sup>27,28</sup> | Hemodynamic profiles for patients presenting with advanced HF |
| 2005 ESC Guidelines<sup>29</sup> | 1. Warm and dry 2. Warm and wet 3. Cold and dry 4. Cold and wet Clinical categories 1. Acute decompensated HF (de novo or as chronic HF) 2. Pulmonary oedema 3. Hypertensive 4. Cardiogenic shock 5. Isolated right HF 6. High-output failure |
| 2008 ESC Guidelines (not present in 2012)<sup>11,30</sup> and EuroHeart Failure Survey II<sup>31</sup> | Clinical categories (with potential overlap between the 6 categories) 1. Worsening or decompensated chronic HF 2. Pulmonary oedema 3. Hypertensive HF 4. Cardiogenic shock 5. Isolated right HF 6. Acute coronary syndrome and HF<sup>b</sup> |
| 2009 Update to 2005 ACCF/AHA Guidelines (not present in 2013)<sup>12,32</sup> | Clinical profiles 1. Volume overload frequently precipitated by acute increase in BP 2. Profound depression of cardiac output 3. Both fluid overload and shock |
| International Working Group on Acute HF Syndromes<sup>33</sup> | Clinical Presentations of acute HF syndromes 1. Hypertensive acute HF 2. Normotensive acute HF 3. Hypotensive acute HF (systolic BP < 90 mmHg) 4. Cardiogenic shock 5. Pulmonary oedema (gradual or abrupt) 6. Isolated right HF 7. Acute coronary syndromes 8. Post-cardiac surgery HF |
| Framework utilizing ACCF/AHA Stages of HF Development<sup>34</sup> | Profiles based on cardiac structure and function 1. Worsening chronic HF (Stage C) 2. Advanced HF (Stage D) 3. De novo HF (Stage B, Stage A, or neither) |
| Breathlessness at Rest<sup>35</sup> | Symptom-based profiles on presentation to the emergency department 1. SOBAR: short of breath at rest 2. CARBOSE: comfortable at rest but breathless on slight exertion |

ACCF, American College of Cardiology Foundation; AHA, American Heart Association; BP, blood pressure; ESC, European Society of Cardiology; HF, heart failure.

*Does not include either the Killip or Forrester classifications in patients with heart failure and recent acute myocardial infarction.<sup>27,36,37</sup> *Not included in the profiles utilized by EuroHeart Failure Survey II investigators.<sup>31</sup>
profile groups, with cardiogenic shock having the highest in-hospital and 1 year mortality, though all clinical profiles were noted to have similar outcomes between 6 and 12 months post-discharge. Interestingly, distinction based on systolic blood pressure at baseline, when compared with stratification based on clinical profiles, allowed for similar, if not better, risk stratification. While the study recognized the poor prognosis seen in cardiogenic shock and the high readmission rate seen in right HF, it also acknowledged the sizable overlap in clinical characteristics between the profiles and the problem posed by misclassification based on these profiles.

Relatedly, the American College of Cardiology Foundation/American Heart Association (ACCF/AHA) guidelines proposed separate categories in 2009 that were based largely on the ACCF/AHA stages of HF.32 These categories also do not appear in the most recent guidelines.12,46,47 The removal of these clinical profiles from the ESC and ACCF/AHA clinical practice guidelines parallels the move toward evidence-based recommendations and provides additional support to the notion that, aside from the case of concomitant acute coronary syndromes and the use of blood pressure to guide treatment, current clinical profiles are not adequate for use in isolation to guide treatment in acute HF.

**Are there data to support clinical profiles of acute heart failure?**

Prior analyses have demonstrated the applicability of various clinical profiles to patients with acute HF. The bedside haemodynamic assessment popularized by Nohria and colleagues28,38 was reproducible by both cardiologists and emergency medicine physicians.38,48 Application of these profiles to routine clinical practice suggests that a majority of patients presenting with acute HF have adequate perfusion and are volume overloaded (i.e. warm and wet).38,39,48 In a single-centre study, patients presenting with other profiles (i.e. cold and wet) were shown to have higher mortality and need for cardiac transplant at 1 year than do patients in the warm and wet categories.38 With the use of blood pressure as a surrogate for perfusion, these data are consistent with large registry data, which show that many patients hospitalized with acute HF have elevated blood pressure on presentation (systolic > 140 mmHg) and exam findings of volume overload such as peripheral oedema.41 Thus, these clinical profiles as described may not be sufficient to identify unique populations of patients to guide individual therapies.

There also exists difficulty in evaluating the severity of acute HF and monitoring improvement in symptoms, as represented by an assessment of the utility of dyspnoea. A majority of patients also report symptoms of dyspnoea on presentation, but conflicting data are available on the prognosis of patients when profiling by dyspnoea. One analysis suggested patients comfortable at rest but breathless on slight exertion had worse outcomes than had those with shortness of breath at rest.35 The authors suggested that while profound dyspnoea at rest is an alarming clinical condition, patients without dyspnoea until they exert themselves may actually have worse outcomes related to right ventricular dysfunction. However, an analysis of US registry data suggested patients presenting with dyspnoea at rest had worse in-hospital outcomes and fewer days alive and out of the hospital than had those with less severe dyspnoea.49 And in addition to this problem of the uncertainty regarding the prognostic utility of one of the central symptoms in acute HF, there also remains the question of how best to assess, standardize, and utilize dyspnoea as a symptom of HF. Numerous struggles with using dyspnoea as a primary endpoint for clinical trials, such as the potential for increased use of standard therapies by physicians in control groups and the impact that bias and blinding may have on results, have been discussed in the literature,50 and troubles developing and implementing a standardized dyspnoea scale have also been well documented.51,52

These collective data suggest that clinical profiles can be applied to clinical care and may provide prognostic value, but no data exist to suggest that treating clinical Profile A with Therapy A improves outcomes above standard care; thus, all patients with acute HF are initially treated with minor variations of the same standard of care, with routine reassessment of therapeutic efficacy in an attempt to optimize management of acute HF. The major reason for failure of clinical profiles to guide treatment of acute HF resides in the lack of a clear, evidence-based treatment, targeted to a specific clinical profile that results in improved outcomes. At present, no trials have used clinical profiles to identify and selectively enroll patients hypothesized to derive the most benefit from an intervention, and this could be contributing in part to the numerous equivocal trials for new acute HF therapies. If a set of useful clinical profiles is identified among the heterogeneous population of acute HF patients and appropriate treatment strategies applied to the various patient subgroups based on their underlying pathology, perhaps new, successful therapies for acute HF will emerge.

An example of using a constellation of lab values and symptoms to target a single underlying mechanism can be found in the literature surrounding metabolic syndrome. While the criteria for metabolic syndrome are quite nonspecific (e.g. waist circumference, blood pressure, triglyceride level, HDL level, and fasting blood glucose), when used in constellation, they can identify patients with an increased risk of atherosclerotic disease and insulin resistance, which ultimately allows them to undergo the appropriate therapy to reduce their future risk of developing these chronic
Acute HF is a clinical syndrome defined as a change in HF signs or symptoms resulting in the need for urgent therapy. The clinical manifestations of acute HF are the end product of multiple different diseases (many still unknown or idiopathic) that lead to chronic HF syndromes. There are a myriad of conditions that lead to an exacerbation, many of which are also unknown. The underlying causes of myocardial dysfunction and systemic adaptations remain poorly understood, and current clinical profiles based on this limited understanding are unlikely to succeed.

To utilize clinical profiles to guide treatments in acute HF—a paradigm shift in acute HF—it is necessary to know the specific mechanisms, be able to detect them with simple but reproducible clinical tools, and have targeted treatments shown to be effective in appropriate clinical trials. Profiles of acute HF that drive treatment strategies should ideally be based on fundamental disorders of the myocyte and improved molecular phenotyping that complement readily available clinical information. This approach was outlined in a report by the National Research Council.

### Table 3 Clinical profiles identified in chronic heart failure with reduced ejection fraction and acute heart failure patients57,58

| Cluster           | Description                                                                                           | Lab and imaging findings                                      |
|-------------------|--------------------------------------------------------------------------------------------------------|---------------------------------------------------------------|
| **Chronic HFrEF** |                                                                                                       |                                                               |
| Cluster 1         | Older, Caucasian men with ischaemic cardiomyopathy, advanced NYHA functional class, numerous co-morbidities, and highest use of ICDs and CRT |                                                               |
|                   | Often current or former smokers                                                                      |                                                               |
|                   | Young, African American men (with the second highest percent of women) with non-ischaemic cardiomyopathy, highest BMI, highest rates of previous CVA, COPD, and prior hospitalizations |                                                               |
|                   | Low rates of other co-morbidities, prior ICD or CRT use, and second lowest QOL scores                 |                                                               |
| Cluster 2         | Second highest levels of 3 HF biomarkers (NT-proBNP, galectin-3, ST2)                                 |                                                               |
|                   | Lowest median peak VO₂                                                                                |                                                               |
|                   | Highest VEVO2 slope                                                                                    |                                                               |
| Cluster 3         | Second highest median levels of 3 HF biomarkers                                                       |                                                               |
|                   | Second lowest median peak VO₂                                                                          |                                                               |
|                   | Second highest VEVO2 slope                                                                             |                                                               |
| Cluster 4         | Second lowest NT-proBNP and galectin-3; ST2 was similar to Cluster 4                                   |                                                               |
|                   | Highest median peak VO₂                                                                               |                                                               |
| **Acute HF**      |                                                                                                       |                                                               |
| Cluster 1         | Caucasian men with ischaemic cardiomyopathy.                                                          |                                                               |
|                   | Highest median BMI, prevalence of AF, ICD use, and prior CVA                                          |                                                               |
|                   | Second lowest QOL                                                                                     |                                                               |
| Cluster 2         | Women (both Caucasian and minority) with non-ischaemic cardiomyopathy and normal renal function        |                                                               |
|                   | Lowest rates of ICD placement, peripheral oedema                                                       |                                                               |
|                   | Second lowest rates of co-morbidities (besides AF), and prior hospitalizations                         |                                                               |
|                   | Highest QOL                                                                                           |                                                               |
|                   | Most likely to be non-smokers                                                                          |                                                               |
| Cluster 3         | Second highest median levels of 3 HF biomarkers                                                       |                                                               |
|                   | Second lowest median peak VO₂                                                                          |                                                               |
|                   | Second highest VEVO2 slope                                                                             |                                                               |
| Cluster 4         | Second lowest NT-proBNP and galectin-3; ST2 was similar to Cluster 4                                   |                                                               |
|                   | Highest median peak VO₂                                                                               |                                                               |

AF, atrial fibrillation; CABG, coronary artery bypass graft; CI, cardiac index; COPD, chronic obstructive pulmonary disorder; CRT, cardiac resynchronization therapy; CVA, cerebrovascular accident; HFrEF, heart failure with reduced ejection fraction; ICD, implantable cardiac defibrillator; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; PCWP, pulmonary capillary wedge pressure; QOL, quality of life.

A similar approach may be utilized to identify a high-risk profile of patients with acute HF.

### A new approach to identifying clinical profiles

A new approach to identifying clinical profiles involved the use of molecular phenotyping that complement readily available clinical information. This approach was outlined in a report by the National Research Council.
An example of this was seen with the 2015 I-PRESERVE study,\textsuperscript{55} which used a latent-class analysis approach to 4113 patients with HF with preserved ejection fraction (HFrEF) to identify subgroups of patients with similar characteristics. This study revealed six unique HFrEF clinical profiles that were differentiated on the basis of a variety of prospective variables. These profiles were then applied to 3203 CHARM-Preserved patients, which revealed that subgroup type was a significant predictor of all-cause mortality or cardiovascular hospitalization. Similarly, in the BEST study, >1100 patients with HFrEF from the Beta-blocker Evaluation of Survival Trial were analysed with latent-class analysis, which revealed several different phenotypes of patients. The authors used two models of latent-class analysis, one that incorporated features associated with HF pathogenesis and another that incorporated markers of HF prognosis and severity. Ultimately, these groups of patients had differential responses to treatment with bucindolol as well as differences in prognosis and LVEF,\textsuperscript{56} factors that are highly clinically relevant.

Comparably, another study in patients with chronic HF was recently completed using baseline information from a clinical trial to identify several distinct phenotypes of patients with HFrEF.\textsuperscript{57} A similar approach using cluster analysis was then applied to 172 acute HF patients from the ESCAPE trial, which also revealed several distinct phenotypes (Table 3)\textsuperscript{58} that were similar to the ones found in patients with HFrEF, though not identical. Cluster analysis does not require a hypothesis to drive an investigation and conclusion, as past investigations into clinical profiles have; instead, it uses an agnostic approach to modelling to cluster patients with similar objective variables, allowing the data itself to guide the investigation. Latent-class analysis operates in a similar fashion to identify subgroups of similar patients.

Interestingly, the phenotypes identified via cluster analysis among patients with acute HF had no discernable relationship to the haemodynamic profiles currently used in clinical practice. Given the divergence of these new phenotypic profiles from prior clinical profiles that as of yet have been unable to successfully guide therapy, this raises the question as to whether these new phenotypic profiles can be effectively applied to therapeutic decision making. These unique cluster analysis-derived acute HF phenotypes are deserving of future research to elucidate their contribution to therapeutic decision making and clinical utility.

Compared with prior acute HF phenotypes or clinical profiles that have failed to identify patient groups who similarly benefit from a more targeted therapy, cluster analysis-derived profiles are defined by data rather than clinician observation. In this way, it instead reverses the paradigm of what has previously tried (and failed) to identify targetable patient phenotypes: instead of relying on the clinician to identify patients who would benefit from Therapy A and subsequently test the hypothesis using data-driven methods, we instead identify the patients who may benefit from Therapy A using data-driven methods such as cluster analysis and allow clinicians to assess their utility in clinical practice.

Perhaps a first step toward elucidating these patient subgroups that derive therapeutic benefit from varying interventions would be the performance of secondary analyses on large datasets including those collected during clinical trials and registries. Additional large-scale datasets collected from clinical encounters through the electronic medical record and biorepositories that exist in parallel to clinical care would also be a valuable step toward identifying distinct patient phenotypes and their associated responses to various interventions. In taking these first steps toward stratifying patients with similar disease processes based on clinical and laboratory phenotype, distinct clinical profiles may be identified and ultimately used to inform future clinical trial design with the hopes of identifying properly targeted therapeutic interventions.

**Conclusions**

Acute HF remains a common syndrome associated with poor outcomes and high health care expenditures. Utilizing clinical profiles to guide treatment decisions is an attractive solution to this public health problem, but current data have failed to provide the necessary evidence base to support this approach. An emerging area of research in acute HF has identified novel clusters that share phenotypic similarities, though these clusters have not yet been studied prospectively in acute HF as therapeutic decision-making aids. The abundance of neutral trials in acute HF that have applied broad strokes to this heterogeneous group of patients implores a new approach; perhaps clinical profile-guided therapy is the answer.

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