Nomenclature in Heart Failure: A Call for Objective, Reproducible, and Biologically-Driven Terminology

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Abstract

Contemporary clinical trials in heart failure (HF) enroll patients largely based on acuity of presentation, left ventricular ejection fraction (EF), and functional status. These trial programs variably employ certain enrichment criteria such as prior hospitalization for HF or elevated natriuretic peptide levels to reaffirm the HF diagnosis and identify patients at higher risk of clinical events. This approach has yielded heterogenous patient cohorts with distinct biological substrates and varying levels of clinical risk. Indeed, patients with HF have variable clinical trajectories that often depend on comorbidities, congestion, hemodynamics, and underlying etiology. In the past decade, progress has been made in identifying imaging- and biomarker-based signatures of HF and the development of risk scores for prognosis. Although these parameters have advanced the promise of precision-based therapeutic approaches, such tools have been variably incorporated alongside traditional eligibility criteria in contemporary trial design. Over the past 3 decades, since the initial publication of the CONSENSUS (Cooperative North Scandinavian Enalapril Survival Study) trial in 1987 (1), enrollment criteria have remained relatively stagnant and have not evolved in parallel with progress in defining HF as an entity. Similarly, patients early or late in their HF journey are loosely defined and have variable

approaches to care. We explore complexities in the interpretation and application of traditional HF-related nomenclature in clinical practice and in clinical trials (**Table 1**).

Keywords

classification; ejection fraction; functional status; heart failure

Ejection Fraction

EF has been the preferred measure to classify HF patients due to the early availability of imaging methods of its assessment. As a result, EF has become a cornerstone criterion for nearly all contemporary HF trials. Major clinical practice guidelines have also incorporated this metric to classify patients into reduced, borderline or mid-range, and preserved EF phenotypes (2). While convenient, the limitations of EF in terms of measurement variability, lack of etiologic specificity, and dependency on loading conditions and rhythm are well recognized. Importantly however, as EF is a continuous measure, thresholds for EF-based definitions are arbitrarily selected and various trials have used varying definitions to classify HF patients with reduced vs. preserved EF, making generalizability of results and understanding of the disease process difficult. For the purposes of validity, reliability, and generalizability of data, defining EF uniformly across studies is imperative.

New York Heart Association Functional Status

New York Heart Association (NYHA) functional classification remains a major inclusion metric in clinical trials and an important determinant of candidacy for medical and device therapies. While in populations of patients it maintains its prognostic value, for a given individual, NYHA class is variably graded by clinicians and there is no consistent method for its assessment. Cardiologists have only a 54% concordance in assessment of the same patient's functional class, questioning the utility of this metric in individual decision-making (3). Provider-determined NYHA classifications do not correlate well with other objective measures like 6-minute walking distance (4). Functional class may be influenced by comorbidities, frailty, or mental health. NYHA class can be labile in the short-term and this transient and subjective fluctuation may have implications in eligibility for therapies based on current guidelines. Thus, more objective measures for individual decision-making are needed with greater precision.

Stage B Heart Failure

Current American College of Cardiology / American Heart Association guidelines delineate specific management approaches for stages of HF ranging from patients at risk for HF (stage A) to those with refractory HF (stage D). Stage B HF includes patients with structural heart disease who have not yet developed symptoms of HF. This was previously synonymous with asymptomatic left ventricular systolic dysfunction and reduced EF, but with the increased recognition of HF risk substrates, defining a structurally normal versus abnormal heart has become more complex. While purely structural abnormalities like left ventricular hypertrophy or asymptomatic valvular heart disease may be less controversial (though not

completely without argument, e.g. trace regurgitation or borderline ventricular mass), this designation is even more uncertain for functional abnormalities that predispose patients to HF risk, e.g. atrial arrhythmias, changes in diastolic function, and abnormalities in myocardial strain.

Stage D Heart Failure and Advanced Heart Failure

The terms Stage D or "advanced HF" have also gained widespread acceptance but remain vague. Stage D is defined as end-stage, refractory HF requiring specialized interventions (5). However, advanced HF may have significant variation in meaning across providers, institutions, and regions. While trials of novel ventricular assist therapies have defined advanced HF more rigorously to facilitate inclusion and limit subjectivity (6), several aspects of these criteria are based on treatment intensity (rather than objective markers of disease severity), which may vary significantly based on geographic practice-level patterns. For instance, triage classification for heart transplantation, which relies heavily on treatment intensity, may lead to regional variation in the appropriation of heart transplantation (7).

Acute Heart Failure and Worsening Heart Failure

Patients who develop acute decompensated HF represent a vulnerable group of patients, however, the nomenclature surrounding acute HF is poorly defined. Traditionally, acute HF has been synonymous with hospitalized HF. However, due to global variation in thresholds for hospitalization for HF, defining an entity by location of care is problematic (8). Indeed, similar levels of acuity may be managed in the outpatient care setting and the patient or clinician decision to use hospitalization as a care strategy is inherently subjective. With the expansion of the pool of patients being including in the acute decompensated HF category with the inclusion of those who require intravenous diuretics in other practice setting, the term "worsening HF" has been increasingly used. However, substantial overlap and confusion remains as to the definition of the term worsening HF, its categorization between outpatients vs. inpatient worsening, and how to define this entity. This is likely going to become a more important concern if in future more outpatient infusion center-based care is adopted or easier alternatives (e.g. subcutaneous loop diuretic administration) become clinically available.

Conclusions

The traditional characterization of HF phenotypes to date has relied on markers that have either been used variably or are prone to challenges with designation or interpretation. We herein discuss a few of these traditional terminologies, while this field of study is fraught with other examples, e.g. 'idiopathic' or 'dilated' cardiomyopathy. This historical set of terms and classification schema have been widely applied in clinical trials defining current evidence-based HF therapies, and thus will continue to remain important in determining treatment eligibility in practice. However, the development of future HF therapies depends on identification and characterization of cohorts who are most likely to derive benefit. To this aim, utilization of novel biomarker- or imaging-based signatures of HF or robust clinical

risk scores may translate to improved clinical trial selection criteria and classification of HF. There is an unmet need for precise, objective, and reproducible metrics to define HF.

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Table 1.

Complexities with Current HF Nomenclature

Current HF Terminology	Challenges with Use
Ejection Fraction	• Fails to reflect underlying biology or pathophysiology
	• Specific thresholds are arbitrarily selected
	• Depends on loading conditions and arrhythmia status
	• The conventional and widely used 2D echocardiographic assessment subject to intra- and inter-observer variability and variability in the quality of image acquisition
NYHA Functional Class	• Depends on congestive status
	• Symptoms and functional status may be limited by comorbidities
	• Subjective and variably graded by clinicians
	• Dynamic and labile over the short-term
Stage B HF	• Uncertain application to HF with preserved ejection fraction
	• Use of more sensitive imaging modalities may expand this population
	• Non-structural changes may represent clinically-relevant pre-clinical states (e.g., atrial arrhythmias)
Advanced / Stage D HF	• Depends on treatment intensity (i.e., use of inotropes or mechanical circulatory support)
	• Depends on response to therapies (i.e., lack of adequate response or intolerance to evidence-based therapies)
	• May not correlate with cardiopulmonary exercise testing
Acute HF and Worsening HF	• Generally defined as synonymous with a hospitalization for HF and subject to wide regional and practice-based variation in thresholds for hospitalization
	• Similar level of care and acuity may be managed in the outpatient setting in some practices
	• Decision to hospitalize a patient for HF dependent on many factors other than the severity of the HF presentation, including age, comorbidities, and non-clinical factors (e.g., patient preference, patient living/social situation, physician/hospital financial incentives)

Abbreviations: HF = heart failure

NYHA = New York Heart Association