Review Article

Defining Advanced Heart Failure: A Systematic Review of Criteria Used in Clinical Trials

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ABSTRACT

Background: Enrollment criteria used in advanced heart failure (HF) clinical trials might identify a common set of widely accepted quantitative characteristics as the basis of a consensus definition for advanced HF, which is currently lacking.

Methods: We reviewed all clinical trials investigating interventions in patients with advanced HF as of July 31, 2015. Eligible publications (N = 134) reported original data from clinical trials explicitly defining advanced HF in adults.

Results: New York Heart Association (NYHA) class was the most common criterion (119 trials, 88.8%; classes ranged from II to IV), followed by left ventricular ejection fraction (LVEF) (84 trials, 62.7%; cutoff range, 20% to 45%; mode 35%). Other criteria included inotrope-dependent status (12.7%), peak oxygen consumption (10.4%), ≥1 previous HF admissions (10.4%), cardiac index (10.4%), pulmonary capillary wedge pressure (9.0%), left ventricular end-diastolic diameter (6.0%), and transplant listing status (5.2%). Cutoff points for quantitative criteria varied considerably. Previous HF admission was more frequently required in recent trials ($P = .007$ for temporal trend), whereas use of hemodynamic criteria decreased over time ($P = .050$ for temporal trend). Average LVEF among participants increased over time.

Conclusions: There is considerable variation in the definition of advanced HF for clinical trial purposes. Beyond NYHA and LVEF, a wide array of criteria has been used, with little consistency both in criteria selection and quantitative cutoff points. (*J Cardiac Fail 2016;22:569–577*)

Key Words: Heart failure, advanced heart failure, clinical trials, systematic review.

Nearly 6 million Americans have heart failure (HF), with total medical costs approaching $40 billion annually.[1] These numbers will only continue to grow.[2] With the increasing pool of patients with HF, an additional concern is the inevitable increase of patients who will require advanced therapies in the form of heart transplantation or mechanical circulatory support (MCS). Current estimates of patients with advanced HF range from 1 and 10% of the total HF population.[1,3,4] In fact, these wide estimates reflect the lack of an explicit definition or epidemiological criteria for advanced HF. In any case, considering the dramatic deficiency and stagnant numbers of donor hearts[1,3] and the disappointing pace of developments in new pharmacotherapies,[1,3,5] the use of MCS as destination therapy is expected to increase,[6] with considerable impact on costs.[7] Thus, it is becoming increasingly important to be able to identify patients with advanced HF reliably to facilitate (1) referral to advanced HF programs; (2) selection for available advanced therapies, especially as MCS technology evolves[1,8]; and (3) effective enrollment of patients into advanced HF studies.

Although the need for a consensus definition of advanced HF has been long recognized,[9] such uniform definitions are still lacking. Current HF guidelines recognize the need to define advanced HF as a distinct entity.[10,11] However, the suggested definitions are mostly descriptive in nature and characterized by varying degrees of subjectivity. Therefore, application of these systems in practice for the detection of patients reaching advanced HF is limited. On the other hand, clinical trials need to define target populations explicitly in

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order to investigate the effects of new drugs and devices. Therefore, the enrollment criteria used in clinical trials in advanced HF might offer an opportunity to identify a set of quantitative characteristics that might be widely accepted and form the basis of a consensus definition.

In this systematic review of the literature, we evaluated the enrollment criteria used in clinical trials investigating therapies for patients with advanced HF. Our goal was to (1) identify the presence of a common set of quantitative criteria across clinical trials and (2) investigate trends in the thresholds used for quantitative criteria.

Methods

Literature Search

We searched PubMed for English-language articles whose title or abstract contained any of the following terms: "advanced HF," "end-stage HF," "endstage HF," "refractory HF," or "stage D HF," with "clinical trial" as the publication type. No publication date filter was applied. We did not restrict our search to randomized clinical trials; early phase trials were eligible also. The initial search yielded 407 articles as of July 31, 2015. Of these, publications were excluded if (1) the publication was not actually reporting data from a clinical trial but rather observational data or post-hoc analyses (N = 104); (2) the definition of advanced HF was either nonspecific or lacking (N = 116); (3) the investigation was not targeting advanced HF patients or had advanced HF as a nondescript outcome (N = 16); (4) the population was pediatric or consisted of MCS or heart transplant recipients (N = 6); (5) study was conducted in animals (N = 1); or (6) the unit of study was the treatment center rather than the patient (N = 1). In addition, 29 publications were excluded because they were a follow-up or secondary analysis of a previously included study using the same enrollment criteria. Papers describing design and rationale for a clinical trial were considered valid entries. The final analytic data set included 134 publications. If enrollment criteria in a clinical trial were modified over time, the originally stated criteria were used for analysis. The search strategy and yield are summarized in Fig. 1. The complete list of included studies, arranged by trial size, with a brief description of the interventions investigated and corresponding bibliography is provided in the Supplemental Table S1.

We also conducted a subgroup analysis for trials enrolling ambulatory (N = 66) vs hospitalized (N = 42) patients. We excluded from this analysis publications that included both hospitalized and ambulatory patients (N = 4); did not specify status upon enrollment (N = 12); or enrolled patients who were hospitalized electively for procedures or transplant evaluation (N = 10).

Data Extraction

Individual articles were reviewed by two investigators (JBB, KKA) to extract (1) the enrollment criteria used to define the advanced HF population; (2) key publication characteristics (year, journal); and (3) other clinical trial characteristics, including sample size and hospitalized vs ambulatory status at enrollment. The search for explicit advanced HF criteria in each publication included the full text of the article, appendices, and any online references to the study protocol. All publications with questionable or nondescript definitions of advanced HF were reviewed for potential eligibility by an additional investigator (APK), as were all discrepancies after initial data extraction. All criteria used in the eligible publications were included in the analysis if they were directly used to define advanced HF.

Statistical Analysis

To provide approximate measures of patient characteristics, we have extracted measures of location (mean for continuous variables and percentages for discrete variables) for all available baseline characteristics, stratified by arm where applicable (investigational vs control or standard therapy). This analysis included the 122 studies that presented actual data or referred to analyses from original studies; 12 studies were design papers and did not present actual patient characteristics. We then weighted distributional measures by sample size to produce weighted estimates of these characteristics. In addition, we examined for temporal trends in these characteristics using the nonparametric test for trend. To synthesize these data, we used an approach similar to that described in the Cochrane Handbook for Systematic Reviews of Interventions, version 5.1.0 (http://handbook.cochrane.org).

To provide an objective measure of disease severity, we extracted available mortality data, stratified by investigational vs standard treatment arms and by follow-up time. When follow-up time was not a prespecified interval (eg, exactly 1 year), we classified that study into the closest follow-up bin. Although we have calculated weighted average estimates for mortality using the Cochrane methodology, it should be noted that these estimates are an approximation and that exact mortality estimates would require access to individual-level data.

We analyzed both semiquantitative (ordinal, eg, New York Heart Association [NYHA] class), and quantitative (scale, eg, left ventricular ejection fraction [LVEF]) criteria for mode (most frequently encountered value), range, and frequency distribution of the cutoff value. In addition, for quantitative criteria, we have described the location (median) and dispersion (25th–75th percentile) of the cutoff values. For mode calculation and other statistics, we considered inclusive cutoffs ($\geq$ or $\leq$) and corresponding noninclusive cutoffs ($>$ or $<$, respectively) as a single value. To detect temporal trends in criteria usage, we used the nonparametric test for trend. To detect temporal trends in the cutoff values applied for quantitative criteria, we used the Spearman correlation coefficient. We used the Fisher exact and Mann-Whitney tests to compare criteria usage and cutoff points between hospitalized and ambulatory trials. As a sensitivity analysis, we repeated the analysis of criteria including only studies with 200 or more participants. We used STATA 14.0 (StataCorp LP, College Station, Texas) for all statistical analyses.