Clinical Investigations

Trends in Heart Failure Clinical Trials From 2001−2012

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ABSTRACT

Background: A systematic assessment of the temporal trends in heart failure (HF) clinical trials is lacking.

Methods and Results: A total of 154 phase II−IV HF trials including 162,725 patients published from 2001 to 2012 in 8 high-impact-factor journals were reviewed. The median number of participants and sites per trial were 367 (interquartile range [IQR] 133-1450) and 38 (5−101), respectively. Median enrollment duration was 2.2 (1.5−3.3) years. The majority of studies investigated treatment for chronic HF (82.5%) and investigated HF with reduced ejection fraction (EF) (71.4%), whereas 27 trials (17.5%) enrolled patients with mixed EF and 9 (5.8%) enrolled HF with preserved EF patients alone. Enrollment rates did not significantly change over time (median 0.49 patients site^{-1} month^{-1}, IQR 0.34−0.98; $P = .53$). Trials meeting their primary end point decreased over time from 73.5% in 2001−2003 to 52.5% in 2010−2012 ($P = .08$) and were more often smaller and used nonmortality end points. Industry trials were larger with shorter enrollment duration, more concentrated in North America, and more likely to be positive. Trials conducted exclusively outside North America and Western Europe had the highest enrollment rates (median 1.95 patients site^{-1} month^{-1}, IQR 1.34−4.11).

Conclusions: Contemporary HF clinical trials display slow enrollment rates and decreased rates of positive outcomes over time. Positive trials tended to be smaller size with a higher proportion of surrogate end points. (*J Cardiac Fail 2016;22:171−179*)

Key Words: Clinical trials, heart failure, outcomes, temporal trends.

Heart failure (HF) constitutes a tremendous health care burden and is the leading cause of hospitalizations among older adults in the United States.[1−3] Despite recent national attempts at reform of HF care, mortality and readmission rates among HF patients remain suboptimal.[4] There remains an unmet need to develop new therapies for these patients.[5] Recent HF clinical trials, however, have faced hurdles, particularly sluggish patient recruitment and retention. For example, in the EVEREST (Efficacy of Vasopressin Antagonism in Heart Failure: Outcome Study With Tolvaptan) trial, more than one-fifth of North American sites failed to enroll any patients, and even enrolling sites recruited only an average of 7 patients per site over the 28-month follow-up.[6] In a recent study of the ClinicalTrials.gov registry, the major reason for early termination of cardiovascular clinical trials was lower than expected recruitment.[7] Failing to meet enrollment targets delay clinical trials, drive up costs, and pose threats to both internal and external validity. Moreover, baseline characteristics, treatment patterns, protocol completion rates, and outcomes may differ by site enrollment rate, potentially influencing overall trial results.[6]

Comprehensive data characterizing recent trends and experience in enrollment patterns of HF clinical trials are limited. To this end, we sought to describe operational

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characteristics of HF trials published from 2001 to 2012 in the 8 highest-impact-factor medical journals in the categories of general medicine and cardiology.

Methods

Identification of Clinical Trials

All HF trials published in 2001−2012 in the 8 highest-impact-factor journals in the ''General and Internal Medicine'' and ''Cardiology'' categories of the 2013 Journal Citation Reports, including *New England Journal of Medicine* (NEJM), *Journal of the American Medical Association* (JAMA), *Lancet*, *Annals of Internal Medicine* (AIM), *Circulation*, *European Heart Journal* (EHJ), *Journal of the American College of Cardiology* (JACC), and *British Medical Journal* (BMJ), were reviewed. We identified 154 phase II−IV randomized controlled trials (RCT) by means of an electronic search of the Pubmed database with the use of the key words ''trial*'' and ''random*'' restricted to the aforementioned high-impact journals. To ensure that no trials were missed, a subsequent manual search of each individual journal edition from January 2001 to December 2012 was performed. The following studies were excluded: (1) pilot or phase I trials, (2) pediatric trials, (3) trials including hospitals as units of intervention, and (4) publications reporting interim, secondary, or post hoc analyses. We followed PRISMA guidelines for all procedures and reporting.

Data Abstraction

The following data were abstracted: (1) journal, (2) year of publication, (3) HF type, (4) recruitment setting and acuity, (5) intervention, (6) duration (estimated from starting and ending dates), (7) total patients enrolled, (8) total number of sites, (9) number of participating countries, (10) number of participating sites in each country, (11) primary outcomes, and (12) funding sources. For incomplete data fields, additional data were extracted from secondary publications identified in ClinicalTrials.gov. Trials were divided into trials including HF with reduced ejection fraction (HFrEF) and with preserved ejection fraction (HFpEF) and trials recruiting both types. Trials were also classified into acute and chronic (stable, ambulatory) subsets. EF cutoff points used for enrollment criteria also were collected. The trials were further divided into (1) acute HF from hospital units with short-term intervention, (2) chronic outpatient HF, (3) chronic HF recruited from the inpatient setting but with post-discharge long-term intervention, and (4) chronic HF recruited from both inpatient and outpatient settings or recruitment setting not clearly designated.

Trials were divided into 6 categories based on the intervention: (1) medications, (2) devices (pacemakers, left ventricular assist devices, implantable cardioverter-defibrillators, biventricular pacemakers, intra-aortic balloon pumps), (3) surgical procedures (coronary artery bypass surgery, ventricular reconstruction), (4) nonsurgical procedures (intracoronary gene therapy, ultrafiltration), (5) others (exercise training, continuous positive airway pressure, multidisciplinary management, patient education, behavioral and lifestyle interventions), and (6) testing/imaging. Based on the ClinicalTrials.gov designations, funding source was assessed as (1) industry, (2) government, or (3) university or other nonprofit or nonfederal organizations.

Trials were further classified according to the primary end point measured: (1) all-cause mortality, (2) cardiovascular or HF-related death, (3) nonmortality intermediate end point (subjective measures that may be dependent on patient motivation or clinical judgment, such as symptom scores, hospitalizations, exercise tolerance tests), and (4) ''surrogate'' end points as indirect measures for clinically meaningful outcomes (eg, assessment of left ventricular function or biomarkers). The most common nonmortality intermediate and surrogate end points used in the included sample of trials are summarized in Table 1.

A ''positive'' trial was defined when the null hypothesis was rejected for the primary end point (intervention was either superior or equivalent/noninferior according to the primary hypothesis). Reported outcomes were divided into mortality as primary outcome vs trials using surrogate end points (eg, dyspnea relief, wedge pressure, B-type natriuretic peptide, etc). Regions were divided into (1) exclusively in North America (NA), including the United States, Canada, and Mexico; (2) exclusively in Western Europe (WE), including Austria, Belgium, Bermuda, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Israel, Italy, Luxembourg, the Netherlands, Norway, Portugal, Spain, Sweden, Switzerland, and United Kingdom; (3) exclusively outside of NA and WE (rest of the world [ROW]); and (4) mixed/multiregional.

Statistical Analysis

Trials were divided into four 3-year periods on the basis of publication date (2001−2003, 2004−2006, 2007−2009, and 2010−2012). Continuous variables were described as mean and SD or as median and interquartile range (IQR), categoric variables as number and percentage. Enrollment rates were estimated based on the reported study duration (completion date minus start date). Continuous variables were compared across nominal categories with the use of the Kruskal-Wallis test and Bonferroni-adjusted post hoc pairwise comparisons to maintain the family-wise error $\alpha = 0.05$. Categoric variables were compared with the use of chi-square testing. A second investigator rereviewed trials conducted from 2001 to 2003 for the percentage of trials meeting their primary end point. Proportion of agreement was 0.94 (0.85−0.98) and Cohen unweighted κ coefficient was 0.88 (0.77−0.99) between the 2 reviewers for this sample. Analyses were performed with the use of IBM SPSS 21 (IBM Corp, Armonk, New York).

Results

Trial Characteristics

A total of 154 trials that collectively enrolled 162,725 patients were identified (Fig. 1). Forty (26%) were published in JACC, 35 (22.7%) in NEJM, and 29 (18.8%) in Circulation. The median number of participants was 367 (IQR 133−1,450), the median number of participating sites per trial was 38 (IQR 5−101), and the median duration of enrollment was 2.2 (IQR 1.5−3.3) years. The distributions of other characteristics are presented in Table 2. The majority of studies (127 trials, 82.5%) investigated chronic HF, and only 27 trials (17.5%) tested therapy in acute HF. Most chronic HF trials recruited patients from the outpatient setting; only 12 trials (7.8%) recruited chronic HF participants from the inpatient setting. For acute HF trials, only 5 of the 27 trials (18.5%) included natriuretic peptides as a key enrollment criteria. B-Type natriuretic peptide cutoffs ranged from 350 to 500 pg/