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CLINICAL TRIALS (J. BUTLER, SECTION EDITOR)

Evolving Landscape of Clinical Trials in Heart Failure: Patient Populations, Endpoint Selection, and Regions of Enrollment

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Abstract
Purpose of Review Clinical trial design and execution are evolving as increasingly important considerations with respect to the success of heart failure trials. The current review highlights temporal trends in characteristics of heart failure clinical trials.
Recent Findings Recent trials in heart failure have required longer recruitment phases, displayed inefficient enrollment rates, increased use of composite and nonfatal endpoints, undergone rapid globalization, and gradually increased focus on heart failure with preserved ejection fraction.
Summary Understanding patterns and trends in clinical trial design and execution may inform future planning and conduct of trials of heart failure therapeutics.

Keywords Clinical trials · Heart failure · Endpoints · Enrollment · Temporal trends

Introduction

Randomized controlled trials (RCTs) form the foundation of evidence generation for the management of heart failure (HF) and have been instrumental in the development of safe and effective new therapies. Data derived from these trials influence clinical practice guidelines, regulatory decisions, and patient care. Indeed, largely secondary to these trial experiences, national guidelines in HF have undergone substantial evolution over the last decade, as compared with other cardiovascular professional guidelines [1]. However, despite their critical role towards advancing care and evaluating therapies, challenges in the execution and timely completion of HF clinical trials are becoming increasingly well recognized [2••, 3]. Specifically, trial cohorts are becoming increasingly difficult to enroll and potentially less generalizable to routine practice. Furthermore, the costs required and complexity of data generated from contemporary HF clinical trials continue to increase. In efforts to design and implement strategies to best meet these challenges, careful appraisal of emerging patterns in the design and conduct of recent HF trials is critical, including understanding variation in enrollment efficiency and duration, trial size, funding mechanism, interventions tested, endpoints selected, and regions of enrollment. These factors may have important implications with respect to timeliness of trial completion, representativeness of the patient population enrolled, and potentially the ultimate success of the trial program. We review recent patterns and trends in trial design and execution in contemporary HF clinical trials and discuss their implications on future planning and conduct of trials of HF therapeutics (Fig. 1).

This article is part of the Topical Collection on *Clinical Trials*

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Trends in Trial Enrollment and Size

HF clinical trials are taking longer to complete with poor enrollment efficiency, especially in certain regions of the

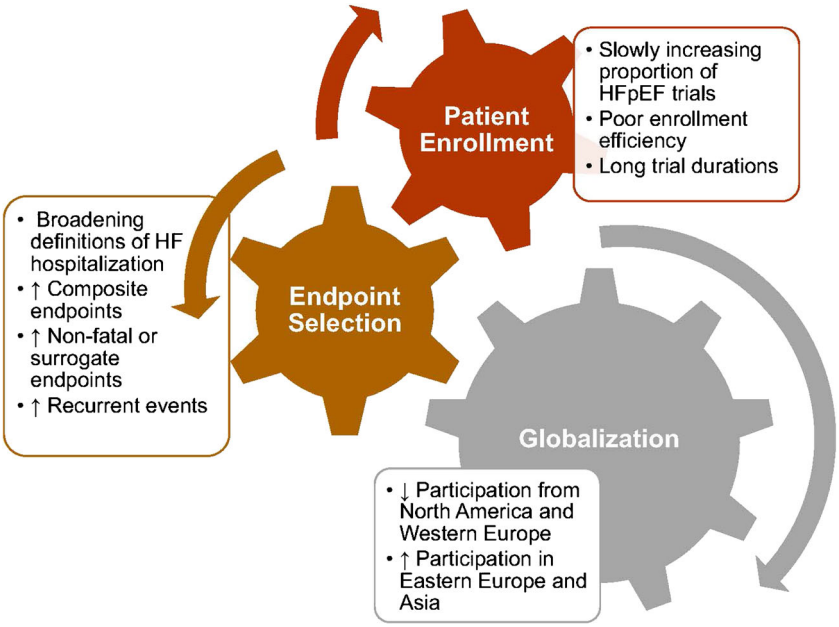

Fig. 1 Trends in patient enrollment, endpoint selection, and globalization of heart failure trials

world. Accrual in HF clinical trials remains a major challenge and represents the leading factor contributing to trial termination [4•]. Poor trial enrollment delays study completion, depletes resources, and limits the generalizability of the results. Despite the tremendous prevalence of HF in the general population, enrollment rates in HF trials appear to be even lower than in general cardiovascular trials without much improvement over the last decade. A trial-level analysis of 150 HF clinical trials published in high-impact journals between 2001 and 2012 showed that the median enrollment rate was 0.5 patients/site/month, as compared with 1.1 patients/site/month in an analysis of more than 1200 general cardiovascular clinical trials [5••, 6•]. In a recent analysis using a database of more than 300 HF clinical trials published between 2001 and 2016, these sluggish enrollment rates remained unchanged while the enrollment duration prolonged over the 16-year period (Fig. 2a, b).

In addition to potential effects on excess trial costs and resource utilization, enrollment efficiency may also influence the profile of enrolled cohorts, trial outcomes, and overall performance. Despite uniform trial inclusion criteria across all sites, data from hospitalized HF trials strongly suggest that patient characteristics differ between sites enrolling few versus many patients [7•, 8••]. In the EVEREST (Efficacy of Vasopressin Antagonism in Heart Failure: Outcome Study with Tolvaptan) trial, patients from sites with poor enrollment had distinct patient profiles and a greater risk of post-discharge cardiovascular mortality or HF hospitalization compared with patients enrolled from more efficient sites [7•]. Over 60% of sites enrolled 10 or fewer patients in EVEREST. More recently, an analysis from ASCEND-HF (Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure) found that lower site enrollment was independently predictive of worse 30-day clinical outcomes after rigorous adjustment for traditional factors. Moreover, the ASCEND-HF investigators found patients from poorly enrolling sites carried greater likelihood of not competing the study protocol (e.g., protocol deviation, adverse event), thus generating the hypothesis that such sites may present quality control issues in conjunction with their minimal contribution towards trial enrollment [8••].

Clinical trials aim to efficiently enroll a representative sample of patients, and hurdles in patient recruitment may require increased number of sites and longer trial durations. Enrollment rates differ substantially depending on HF subtype, clinical indication, intervention type, funding mechanism, selected primary endpoint, and geographic region. Multiple factors limiting study enrollment have been identified. These include intrinsic characteristics of patients with HF such as advanced age, disease characteristics, comorbid conditions, and socioeconomic status. Additionally, increasingly stringent inclusion and exclusion criteria can limit participant eligibility and study enrollment [9, 10]. Healthcare patterns in the USA may also impact ability of site investigators to enroll patients. Focus on providing more efficient healthcare, with more patients seen by fewer providers in a shorter time, has made enrollment in trials more difficult.

Strategies designed to improve trial accrual have been investigated and proposed including close monitoring of recruitment progress, identifying failures by a multidisciplinary team, allocating a sufficient budget for recruitment, financial incentives for recruitment, and improving patient and provider awareness of HF [2••, 8••, 11, 12, 13•]. In addition, pragmatic and registry-based trials may be increasingly considered, as well as use of a

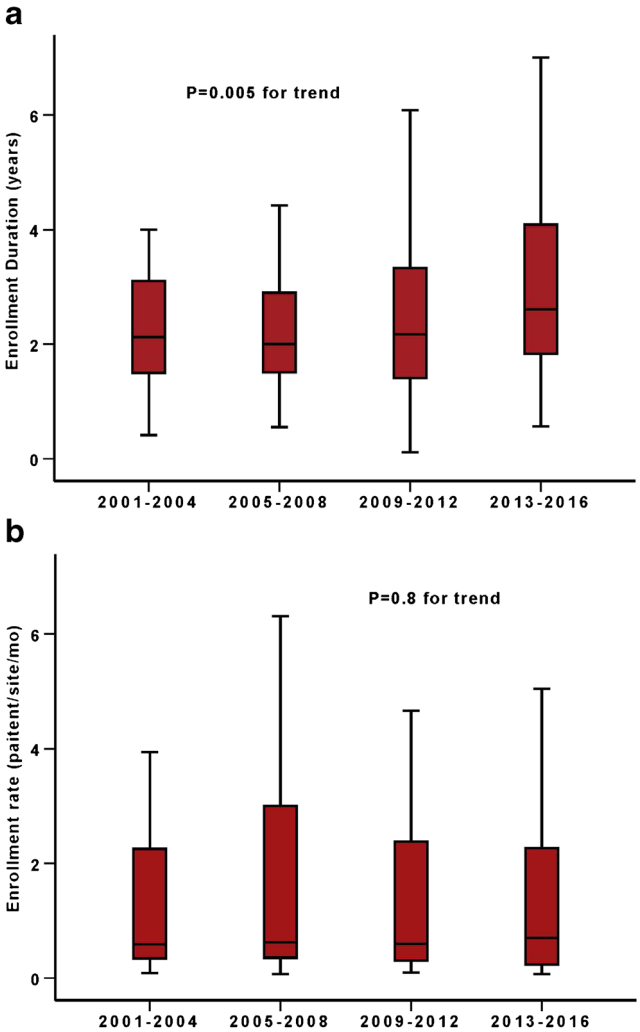

Fig. 2 Trends in **a** enrollment duration and **b** enrollment rate in heart failure trials with sample sizes over 100 between 2001 and 2016

pre-trial registry upstream of clinical trial enrollment to identify efficient and reliable sites with an adequate exposure to the targeted HF population [3].

Trends in Trial Endpoints and Outcomes

Over time, there has been increasing use of non-fatal trial endpoints, composite outcomes (e.g., cardiovascular mortality or hospitalization for HF), and recurrent events as primary efficacy measures [14]. Some examples of commonly used non-fatal endpoints include functional status improvement, patient-reported symptoms, exercise time, and hospitalization for HF. As more patients are being treated for worsening chronic HF as outpatients, trial endpoint definitions for worsening HF have evolved to include not only hospitalization for HF, but also emergency department visits, short stay unit says, and outpatient intensification of HF care [15, 16]. Major advantages of using composite outcomes, which often include both fatal and non-fatal events, include a comprehensive picture of important treatment-related benefits or harms and the ability to improve statistical power and reduce the sample size required. However, they often require close examination since fatal and non-fatal events may occur on differing timelines, and treatment effects may be driven by one component over the other. For example, in SHIFT (Systolic Heart Failure Treatment with the If Inhibitor Ivabradine Trial), the primary endpoint was a composite of cardiovascular death or HF hospitalization, where the treatment effect was driven solely by a reduction in HF hospitalization [17]. In addition, composite endpoints may not always fully capture patient-centered differences between interventions. For example, a patient with short uncomplicated HF hospitalization after enrollment with a subsequent uneventful course might be viewed similarly as a patient who had a long, complicated HF hospitalization later in follow-up. In chronic conditions such as HF, appropriate statistical accounting for recurrent events may improve overall power and robustness of the analysis, and potentially shorten trial duration [18]. Several approaches to recurrent event analyses have been tested instead of time-to-first event analyses. The ongoing PARAGON-HF (Prospective Comparison of ARNI with ARB Global Outcomes in Heart Failure With Preserved Ejection Fraction) trial is designed with the primary endpoint of cumulative number of HF hospitalizations and cardiovascular death [19]. Likewise, some trials have included "days alive and out of the hospital" as an exploratory endpoint, which intrinsically captures repeated events and the duration of each event [20, 21].

Although the overall utility and role of surrogate endpoints in HF trials have not been entirely defined, surrogate endpoints are used in a third of all HF clinical trials, a proportion that has remained constant over the past decade [5••]. Surrogate endpoints are commonly used in early phase or mechanistic studies where they may be viewed as a proxy for more clinically oriented outcomes [22•]. Among other factors, effects on these surrogate measures in early phase studies may dictate "go/no go" decisions for proceeding with late phase registration trials. Nonetheless, interpretation of surrogate endpoints in HF drug development requires cautious interpretation, as the literature carries numerous examples where promising effects on surrogate endpoints have failed to translate to valuable clinical benefits in subsequent clinical outcomes trials [22•]. As such, the use of surrogate endpoints in HF drug development remains challenging. Future research is required to validate single or combination surrogate endpoints for use in HF clinical trials.

Despite the evolution in endpoint selection and definition, the number of clinical trials reporting positive results has declined over time such that positive clinical outcome trials have decreased by more than 20% from 2001 to 2012 [5••]. While the explanation for this trend is unclear, possibilities include

the fact that trials are testing incremental clinical benefit of novel therapies over standard care or due to an incomplete understanding of the mechanism of therapeutic interventions, or to an increasing degree of mismatch between therapies tested and target HF subgroups.

Globalization of Heart Failure Clinical Trials

Over the last two decades, there has been rapid globalization of HF trials. A recent systematic review of published contemporary HF trials confirmed the pattern of rapid globalization with greater trial participation in regions outside North America and Western Europe [6•, 23••]. Challenges in efficient enrollment and excess costs of site initiation and maintenance in North America and Western Europe may have driven these patterns [24, 25]. Globalization of trials with greater representation of Central/South America, Eastern Europe, and other developing countries is associated with increased heterogeneity of the HF trial cohort and may present challenges for guideline writers, regulators, and practicing clinicians who must decide whether trial results are applicable to their respective populations. Numerous HF clinical trials have noted substantial regional variation in patient profiles and clinical outcomes [26, 27]. The TOPCAT (Spironolactone for Heart Failure with Preserved Ejection Fraction) trial provides an example of how regional differences in the quality of the study execution can influence overall trial results [28]. The primary endpoint was not met in the overall trial population, but marked regional differences in treatment effects were observed between the Americas and Russia/Georgia [29, 30]. Concerns have since arisen that the diagnosis of HF with preserved ejection fraction (HFpEF) in Russia/Georgia may have tended to be less accurate and that patients in those countries may have been inconsistently receiving study therapy [29, 31]. Thus, the TOPCAT trial serves as an example of how globalization may influence trial outcomes irrespective of potential differences in regional HF biology, but via quality control and site-specific factors.

Trends in Funding Mechanisms

Funding for biomedical research worldwide comes largely from three main sources (governmental agencies, private non-profit organizations, and industry). Based on contemporary estimates, non-profit organizations and research networks have increasingly funded a larger proportion of cardiovascular trials over the last decade while the rates of government- and industry-based trials have significantly declined [32•]. Using a database of more than 300 HF clinical trials published between 2001 and 2016 as previously described [23], similar trends were observed in HF trials (Fig. 3). This trend could also be a sign of financial constraints and restructuring of these funding bodies. Industry is the lead sponsor in more than half of HF trials and tends to design trials with large sample sizes enrolled over shorter durations and are more likely to report favorable results compared with other funding sources [6•, 33–36]. There are major methodological differences across trials funded by different mechanisms. Industry may preferentially fund later phase investigations, which set the stage for new drug/device approval, and thus less likely to engage in head-to-head drug or device comparisons [37].

Trends in Trials of HFpEF

HFpEF accounts for over half the cases of prevalent HF and is expected to become the predominant form of HF as the population ages [38, 39]. Particularly alarming, despite a mortality rate comparable to HFrEF, contemporary HFpEF management remains devoid of a definitively proven therapy and remains limited to empiric optimization of comorbidities and use of diuretics. The number of trials focused on HFpEF has increased gradually overtime but still represents a very small proportion compared with HFrEF. For example, the HFpEF clinical trial enterprise is still dominated by small clinical trials with non-mortality endpoints. Most HFpEF trials are single-center experiences and often enroll half as many participants as trials conducted in HFrEF. Given the increasing prevalence of HFpEF and unmet therapeutic need, larger, more rigorous studies in HFpEF are greatly needed [40].

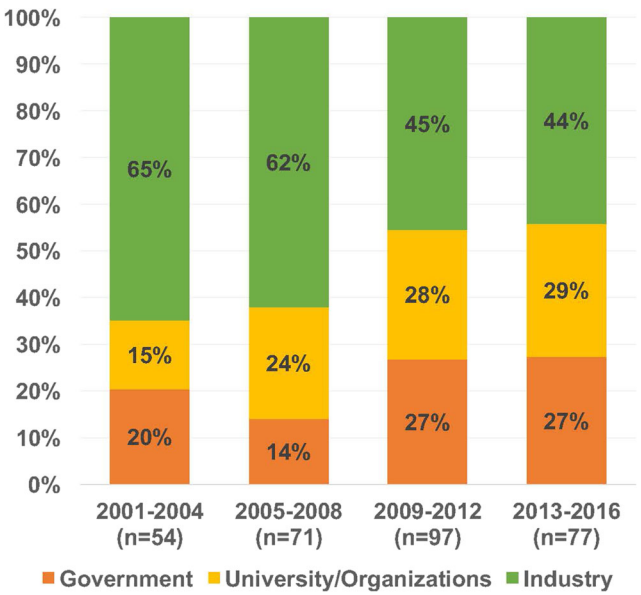

Fig. 3 Proportion of 305 HF trials with sample size over 100 stratified by funding sources between 2001 and 2016. Proportion of trials funded by industry trended down over time, while there was an increase in the proportion of trials funded by non-profit organizations or universities

Historically, HFpEF trials have enrolled those with preserved EF and a clinical history of HF. More recent HFpEF trials have also incorporated other "enrichment" criteria such as biomarkers (e.g., elevated natriuretic peptide levels), prior HF hospitalization, reduced functional capacity, abnormal hemodynamic measurements, and altered cardiac structural or functional abnormalities [41]. Although these enrichment criteria may identify patients at higher risk for an endpoint of interest, it is important to recognize these selected patients may not necessarily be more likely to respond to the investigational therapy. Indeed, the effects of irbesartan and spironolactone in HFpEF appear to be more prominent in subgroups of patients with lower, not higher, natriuretic peptide levels [42, 43]. EF cutoffs used to select patients with HFpEF vary broadly across trials with a range from ≥ 40 to > 55%. There has been a trend to use of higher EF cutoffs to define HFpEF which is in line with contemporary US and European HF guidelines [44–46].

EF cutoffs as low as 40% may increase patient heterogeneity and obscure significant results by including different patient populations. It is also important to note that EF values and normal ranges depend on the imaging technique used, method of analysis, and reader [47]. Standardization of HFpEF definitions in clinical trials is necessary to reduce the heterogeneity of enrolled populations.

Conclusion

In conclusion, our review highlights rapidly evolving trends in HF clinical trial design and conduct, including increased trial durations, broadening endpoint selection (beyond all-cause mortality alone), and accelerated globalization with emergence of sites outside North American and Western Europe. There has been more modest progress in trials testing therapeutics in patients with HFpEF. These findings reinforce the need for significant improvements across the HF clinical trial enterprise, such as greater consideration of site and investigator-level incentivizes for enrollment, design of pragmatic study protocols with careful endpoint selection, identification of high-quality study sites, and development of strategies to address geographic heterogeneity in trial performance. Examination of prior trends in trial design and performance may support development of targeted strategies for improving the efficiency and execution of future HF clinical trials and the likelihood of therapeutic advancement.

Compliance with Ethical Standards

Conflict of Interest Sonali Kumar and Maureen Okafor declare no conflicts of interest.

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Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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