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PERSPECTIVE

Design Elements and Enrollment Patterns of Contemporary Trials in Heart Failure With Preserved Ejection Fraction

A Systematic Review

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Despite numerous clinical trials, there remain no definitively proven therapies for patients with heart failure (HF) with preserved ejection fraction (HFpEF). Although this experience may be in part related to the intervention tested, certain other factors related to the design of the clinical trial itself, including size, conduct, enrollment, endpoint selection, and funding source, may have an impact on the results (1). Furthermore, the representation and the temporal trends of participation by the elderly, women, and racial/ethnic minorities in HFpEF clinical trials have not been well characterized. Systematic evaluation of these trial-level factors may inform the future design of efficient and effective drug and device development programs in HFpEF.

Accordingly, we conducted a comprehensive systematic review of operational and patient-level characteristics of contemporary HFpEF trials published over the last 16 years (January 2001 to December 2016) using 2 strategies: 1) PubMed/MEDLINE query with the following limits: publication year, "heart failure," "trial*," and "randomized"; and 2) ClinicalTrials.gov query limited to adult, interventional, phase II to IV, HF trials. We excluded phase I, pilot trials, secondary, interim, or post hoc analyses. The following data were abstracted: 1) year of publication; 2) intervention; 3) enrollment duration; 4) subjects enrolled; 5) number of participating centers and countries; 6) ejection fraction (EF) cut-offs; 7) mean age of the cohort; 8) proportion of women enrolled; 9) race and ethnicity when reported; 10) primary endpoints; and 11) funding sources. Based on ClinicalTrials.gov designations, funding source was classified as industry; government; or university, other nonprofit, or nonfederal organizations. Primary endpoints were classified as mortality, intermediate (e.g., quality of life, dyspnea relief, hospitalization, length of stay), or surrogate (e.g., pulmonary capillary wedge pressure, natriuretic peptides). Regions of enrollment were divided into: 1) exclusively North America (NA); 2) exclusively Western Europe (WE); 3) exclusively outside of NA and WE—the rest of the world; and 4) mixed/multiregional. We compared

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these clinical trial data with epidemiological data in the United States (weighted for sample size) collected from large registries or observational studies of patients with HFpEF (2–5).

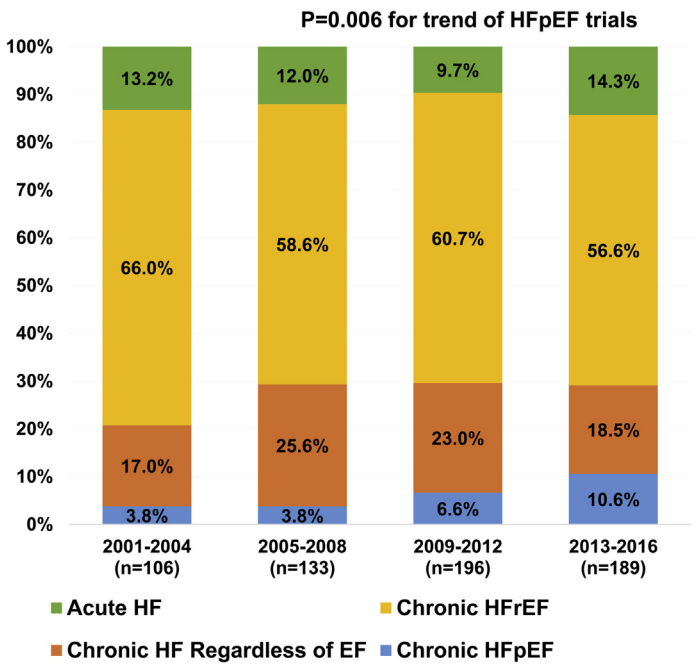
We screened 5,488 studies and identified 624 HF clinical trials of which 374 (60%) studied HF with reduced EF (HFrEF), 42 (7%) focused on HFpEF, 132 trials (21%) enrolled HF participants regardless of their EF, and 76 trials (12%) were conducted in the acute HF setting. Overall, these trials collectively enrolled 12,185 patients from a total of 946 sites; 16 trials enrolled more than 100 subjects. The number of HFpEF trials increased from 4 in 2001 to 2004 to 21 in 2013 to 2016 ($p = 0.006$ for trend) (**Figure 1**). Key characteristics of HFpEF trials are provided in **Table 1**. The left ventricular EF cutoff to define HFpEF increased from a median 45% in trials conducted in 2001 to 2008 to 50% in 2009 to 2016. Median numbers of participants and enrolling sites per HFpEF trial were significantly lower than for HFrEF and acute HF trials, and remained stable over time ($p > 0.05$ for both trends). No differences were observed in regional distribution of HFpEF trials over time ($p = 0.30$).

The weighted mean age of participants in HFpEF trials was 70 ± 9 years compared with the corresponding average age of 73 years of patients with HFpEF in U.S. epidemiological studies. There was a trend toward enrolling younger participants in HFpEF trials over time (72 ± 7 years in 2001 to 2008 vs. 68 ± 9 years in 2009 to 2016). Overall, women constituted 55% of participants; this proportion trended down from 59% in 2001 to 2008 to 53% in 2009 to 2016. Trials conducted exclusively in NA enrolled 63% women, which is consistent with the estimated proportion of 62% in U.S. epidemiological studies (2–5).

Overall, 10% of participants in studies reporting race/ethnicity distribution data ($n = 37$) were nonwhite, which increased from 7% in 2001 to 2008 to 13% in 2009 to 2016. In NA trials with available race/ethnicity data, 21% of participants were nonwhite, which is lower than the proportion of 26% to 34% reported in U.S. epidemiological studies. Trials with sample sizes over 100 were less likely to enroll nonwhite patients (10%) compared with smaller trials (19%). Only 7 studies (17%) reported black race, which constituted 6% of patients enrolled in these studies (increased from 2% in 2001 to 2008 to 10% in 2009 to 2016) (Online Table 1, Online Figure 1).

Overall, mean body mass index in HFpEF trials was 30.3 ± 2.3 kg/m^2, which increased from 27.5 ± 1.0 kg/m^2 in trials conducted in 2001 to 2008 to 30.8 ± 2.1 kg/m^2 in 2009 to 2016. Highest body mass index was observed in trials conducted in NA with mean of 33.2 ± 2.9 kg/m^2 compared with 31.0 ± 0.4 kg/m^2 in multiregional trials, 29.0 ± 1.4 kg/m^2 in WE, and 27.9 ± 3.2 kg/m^2 in trials conducted in the rest of the world ($p = 0.002$).

FIGURE 1 Trends in HF by EF and Hospitalization Status Over 16-Year Study Period



EF = ejection fraction; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction.

Data to calculate enrollment rate were available in 34 trials (81%). Median enrollment rate among HFpEF trials was 0.88 (interquartile range [IQR]: 0.39 to 2.23) patients/site/month, similar to that observed in HFrEF and acute HF trials, but lower than those in HF trials without EF-specific cutoffs ($p < 0.001$) (**Table 1**). Enrollment rate in HFpEF trials enrolling more than 100 participants was significantly lower (median: 0.29, IQR: 0.18 to 0.57 patient/site/month) compared with smaller HFpEF trials (median: 1.47, IQR: 0.85 to 2.59 patients/site/month; $p < 0.001$). Enrollment rates in HFpEF trials stratified by key trial-level characteristics are shown in Online Table 2.

This comprehensive systematic review highlights important aspects of HFpEF trial design and research methodology over a 16-year period. Although the proportion of HFpEF trials conducted over time has increased gradually, these programs represent only ~10% of the contemporary HF trial enterprise. Most HFpEF trials are small, single-center experiences with nonmortality outcomes, and almost exclusively test

TABLE 1 Trial-Level Characteristics of HF Trials Published From 2001 to 2016

	Chronic HFpEF Trials With >100 Patients (n = 16)	All Chronic HFpEF Trials (n = 42)	Chronic HFrEF Trials (n = 374)	Chronic HF Regardless of EF (n = 132)	Acute HF Trials (n = 76)	p Value*
Year published						
2001–2008	5 (31)	8 (19)	148 (40)	52 (40)	30 (39)	
2009–2016	11 (69)	34 (81)	226 (60)	80 (61)	46 (61)	0.14
Trial size						
Patients	220 (147–365)	62 (30–162)	97.5 (41–335)	141.5 (65–277)	106.5 (55.5–326.5)	0.03
Sites	39 (12–65)	1 (1–12)	4 (1–38)	2 (1–7)	8 (1–31)	0.002
Countries	2 (1–8)	1 (1–2)	1 (1–2)	1 (1–1)	1 (1–2)	<0.001
Duration, yrs	3.0 (2.2–4.8)	2.3 (1.3–4.2)	2.1 (1.42–3.33)	1.92 (1.17–3.08)	2.00 (1.17–2.74)	0.23
Enrollment rate, patient/site/month	0.29 (0.18–0.57)	0.88 (0.39–2.23)	0.61 (0.26–2.00)	2.25 (1.13–4.23)	0.68 (0.42–2.02)	<0.001
Ejection fraction cutoff, %	45 (45–50)	50 (45–50)	40 (35–40)	–	–	<0.001
Intervention						
Device	0 (0)	0 (0)	64 (17)	3 (2)	5 (7)	
Medication	15 (94)	34 (81)	180 (48)	43 (33)	57 (75)	
Others	1 (6)	8 (19)	93 (25)	80 (61)	5 (7)	<0.001
Procedure	0 (0)	0 (0)	23 (6)	3 (2)	7 (9)	
Surgery	0 (0)	0 (0)	7 (2)	1 (1)	1 (1)	
Testing/imaging	0 (0)	0 (0)	7 (2)	2 (2)	1 (1)	
Sponsor						
Government	6 (38)	17 (40)	75 (20)	32 (24)	9 (12)	
University/organization	1 (6)	10 (24)	92 (25)	52 (39)	25 (33)	<0.001
Industry	9 (56)	14 (33)	153 (41)	28 (21)	32 (42)	
Region						
Rest of the world	3 (23)	7 (18)	60 (17)	34 (26)	15 (20)	0.003
Multiregional	3 (23)	4 (10)	69 (19)	5 (4)	16 (22)	
North America	3 (23)	15 (39)	103 (29)	46 (35)	23 (31)	
Western Europe	4 (31)	13 (33)	126 (35)	46 (35)	20 (27)	
Multicenter (>3 sites)	13 (93)	21 (50)	178 (50)	47 (37)	41 (54)	
Multinational	10 (67)	13 (32)	112 (30)	9 (7)	22 (29)	<0.001
Primary outcome						
Mortality	4 (25)	4 (10)	102 (27)	38 (29)	12 (16)	
Nonmortality intermediate outcomes	8 (50)	21 (50)	141 (38)	63 (48)	25 (33)	0.001
Surrogate outcomes	4 (25)	17 (40)	130 (35)	31 (23)	39 (51)	

Values are n (%) or median (interquartile range). *Comparison across trials of chronic HFpEF, chronic HFrEF, chronic HF regardless of EF, and acute HF.
EF = ejection fraction; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction.

pharmacotherapies. Elderly and female patients are historically underrepresented in cardiovascular clinical trials; however, these data suggest that the prevalence of these subsets in contemporary HFpEF trials did not markedly differ from those seen in U.S. epidemiological studies. Although the proportion of nonwhite participants among clinical trials for HFpEF appears to be increasing over time, not all trials provided a detailed breakdown of race/ethnicity data, and, therefore, we may have overestimated the proportion of nonwhite participants. Adequate enrollment of these minority populations is essential to ensure the generalizability of study findings to all patients with HFpEF.

In the present study, the median enrollment rate in larger (N > 100) HFpEF trials was less than one-half that in chronic HFrEF trials. Among all HFpEF trials, factors related to the scale and complexity of the trial program were associated with slow enrollment: multicenter, multinational, and trial size >100 patients. Despite large trials likely devoting more trial resources and having greater potential to influence clinical practice, our findings suggest these larger programs are in more need of targeted initiatives to improve enrollment rates. Methods to better identify high-quality sites and improve enrollment incentives are needed to augment efficient patient recruitment, which may potentially shorten trial duration and improve the generalizability of study results. Specific strategies may include use of a pre-trial registry, registry-based trials, application of pragmatic trial designs with less

restrictive selection criteria, provision of incentives for recruitment, and improvement in patient and provider awareness of clinical research.

We observed significant heterogeneity in terms of EF thresholds adopted in HFpEF trials, which increased from a median of 45% to 50% over the study period, which is in keeping with contemporary guidelines in defining HFpEF. Standardization of the HFpEF definition used for research purposes is essential to reduce heterogeneity in this patient population.

There are few large ongoing or planned advanced-phase trials in HFpEF: PARAGON-HF (Efficacy and Safety of LCZ696 Compared to Valsartan, on Morbidity and Mortality in Heart Failure Patients With Preserved Ejection Fraction; NCT01920711); EMPEROR-Preserved (EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure With Preserved Ejection Fraction; NCT03057951); and SPIRRIT (Spironolactone Initiation Registry Randomized Interventional Trial in Heart Failure With Preserved Ejection Fraction; NCT02901184). These trials are anticipated to enroll over 3,000 patients each and will expand our current understanding of this syndrome. There has been little progress in device or procedure innovation for HFpEF or in evaluating interventions targeting patients hospitalized for HFpEF.

This trial-level systematic analysis represents a comprehensive characterization of the HFpEF clinical trial enterprise over the last 16 years and highlights an important mismatch between a limited research pipeline and the large burden of disease. Although the number of trials is slowly increasing over time, the majority of completed HFpEF trials were limited in size and scope, and were not equipped to expand the therapeutic armamentarium for a significant proportion of this population. Enrollment rates across HFpEF programs remains suboptimal, lower than other HF trials, and particularly low among large, multicenter, and multinational trials. There is an unmet need to improve the future execution of HFpEF trial programs to ensure such therapies are well tested and that the evidence generated is generalizable.

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REFERENCES

1. Samman Tahhan A, Vaduganathan M, Kelkar A, et al. Trends in heart failure clinical trials from 2001-2012. J Card Fail 2016;22:171–9.

2. Gerber Y, Weston SA, Redfield MM, et al. A contemporary appraisal of the heart failure epidemic in Olmsted County, Minnesota, 2000 to 2010. JAMA Intern Med 2015;175:996–1004.

3. Gottdiener JS, McClelland RL, Marshall R, et al. Outcome of congestive heart failure in elderly persons: influence of left ventricular systolic function. The Cardiovascular Health Study. Ann Intern Med 2002;137:631–9.

4. Lee DS, Gona P, Vasan RS, et al. Relation of disease pathogenesis and risk factors to heart failure with preserved or reduced ejection fraction: insights from the Framingham Heart Study of the National Heart, Lung, and Blood Institute. Circulation 2009;119:3070–7.

5. Silverman MG, Patel B, Blankstein R, et al. Impact of race, ethnicity, and multimodality biomarkers on the incidence of new-onset heart failure with preserved ejection fraction (from the Multi-Ethnic Study of Atherosclerosis). Am J Cardiol 2016;117:1474–81.

KEY WORDS clinical trials, enrollment, heart failure with preserved ejection fraction, trial design

APPENDIX For supplemental tables and figure, please see the online version of this paper.