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THE PRESENT AND FUTURE

STATE-OF-THE-ART REVIEW

# Patient Selection in Heart Failure With Preserved Ejection Fraction Clinical Trials

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## ABSTRACT

Recent clinical trials in patients with heart failure with preserved ejection fraction (HFpEF) have provided important insights into participant selection strategies. Historically, HFpEF trials have included patients with relatively preserved left ventricular ejection fraction ranging from 40% to 55% and a clinical history of heart failure. Contemporary HFpEF trials have also incorporated inclusion criteria such as hospitalization for HFpEF, altered functional capacity, cardiac structural and functional abnormalities, and abnormalities in neurohormonal status (e.g., elevated natriuretic peptide levels). Careful analyses of the effect of these patient selection criteria on outcomes in prior trials provide valuable lessons for future trial design. We review recent and ongoing HFpEF clinical trials from a patient selection perspective and appraise trial patient selection methodologies in relation to outcomes. This review reflects discussions between clinicians, scientists, trialists, regulators, and regulatory representatives at the 10th Global CardioVascular Clinical Trialists Forum in Paris, France, on December 6, 2013. (J Am Coll Cardiol 2015;65:1668–82) © 2015 by the American College of Cardiology Foundation.

Heart failure with preserved ejection fraction (HFpEF) currently represents almost one-half of all heart failure (HF) patients and, with the growing elderly population, is projected to become the predominant form of HF in the future (1,2). HFpEF represents a large unmet need in cardiovascular medicine. Over 5 million Americans and 23 million people worldwide have HF, of which patients with HFpEF constitute more than 50%, and this percentage will continue to rise with our aging population (1,3–5). In general, outcomes in HFpEF are similarly poor as those in patients with heart failure with reduced ejection fraction (HFrEF) with respect to hospitalization and mortality risk. Despite the therapeutic advances for patients with HFrEF through landmark clinical trials on neurohormonal modulation and device therapy, clinical trials in patients with HFpEF have been challenging, and results

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have been neutral. Important lessons can be learned from these prior trials. In this paper, we summarize recent and ongoing HFpEF clinical trials and appraise trial methodologies from the perspective of patient selection to critically inform the design of future randomized clinical trials for clinicians, researchers, and patients.

## GUIDELINE DEFINITIONS FOR HFpEF

Recommendations for the diagnosis of patients with HFpEF are similar in scope and depth across the most recent U.S. and European guidelines (6–9). The most recent American College of Cardiology/American Heart Association guidelines defined HFpEF as patients with ejection fraction (EF) ≥50% with symptoms suggestive of HF and exclusion of other potential noncardiac etiologies of HF. The guidelines also include subpopulations of borderline HFpEF with EF 41% to 49% and HFpEF with improved EF >40% for patients who previously had reduced EF (6). The 2012 European Society of Cardiology guidelines defined 4 requirements to diagnose HFpEF, including: 1) symptoms typical of HF; 2) signs typical of HF; 3) normal or only mildly reduced left ventricular EF without left ventricular dilation; and 4) relevant structural heart disease (left ventricular hypertrophy/left atrial enlargement) and/or diastolic dysfunction (**Table 1**) (8,9). The underlying pathophysiologic mechanisms behind HFpEF involve, in part, a diffuse inflammatory state that develops from the constellation of such frequently coexisting comorbidities as chronic obstructive lung disease, anemia, diabetes mellitus, renal dysfunction, and obesity in patients with HFpEF (10,11). The proinflammatory state limits the available nitric oxide in the coronary microvasculature and shifts cardiac remodeling toward hypertrophy and interstitial fibrosis, which increases left ventricular diastolic stiffness and the conditions for HFpEF (12).

## DEFINITIONS IN CLINICAL TRIALS

The first large clinical trial that focused on patients with HFpEF, the CHARM (Candesartan in Heart Failure-Assessment of Reduction in Mortality and Morbidity) Preserved trial, required an EF >40%, New York Heart Association (NYHA) functional class II to IV symptoms for >4 weeks, and any prior hospital admission for a cardiac reason (13). This definition was analogous to HFrEF trials at the time, where EF cutpoints <35% and <45% were used in addition to HF symptoms or known history of HF (14,15). As the results from clinical trials and secondary analyses in these HFpEF populations without use of guideline criteria revealed low event rates and limited benefits from traditional HF therapies, clinical trialists subsequently adjusted entry criteria (16). The EF criterion was increased, echocardiographic parameters were incorporated, and eventually, natriuretic peptide (NP) levels were included in a combined definition that also required HF symptoms (**Table 2**). Preserved EF ≥50%, symptoms and/or hospitalization for HF, echocardiographic findings, and elevated NP levels exemplified the prevailing thought that HFpEF was primarily a disease of elderly women with stiff left ventricles from longstanding hypertension and concomitant diabetes mellitus. However, clinical trials, cohort studies, and registry analyses have demonstrated that the HFpEF population is heterogeneous, particularly with respect to comorbidities (11). Future clinical trials in HFpEF may benefit from further refinement of these key patient selection criteria to optimize the potential for success.

## EJECTION FRACTION

EF was the first inclusion criterion used to differentiate patients with HFrEF from HFpEF. The first 3 large HFpEF trials studied renin-angiotensin aldosterone system inhibition with EF cutoffs of 40% to 45% (13,17,18). More recent trials have split between using an EF cutoff ≥45% and ≥50%. The PARAMOUNT (Prospective comparison of ARNI with ARB on Management Of heart failUre with preserved ejectioN fracTion) and TOPCAT (Treatment of

### ABBREVIATIONS AND ACRONYMS

**EF** = ejection fraction

**HF** = heart failure

**HFpEF** = heart failure with preserved ejection fraction

**HFrEF** = heart failure with reduced ejection fraction

**NP** = natriuretic peptide

**PASP** = pulmonary artery systolic pressure

**PCWP** = pulmonary capillary wedge pressure

**VAS-AUC** = visual analog scale area under the curve

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