EDITORIAL

Heart Failure With Preserved Ejection Fraction
Time for a Reset

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Of the estimated 5 million patients in the US diagnosed with heart failure (HF), approximately 50% have HF with preserved ejection fraction (HFpEF),[1,2] and its prevalence is increasing by about 1% annually relative to that of heart failure with reduced ejection fraction (HFrEF).[3] The mortality associated with HF is substantial, and HF was estimated to account for more than 80 000 deaths annually in the US as of 2017.[4] In addition, because HF is projected to account for an estimated $69.8 billion in annual health care spending by 2030, HFpEF represents an important public health issue that will increase as the population ages, with a concurrent increasing prevalence of associated risk factors, including hypertension, obesity, and diabetes.[4]

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However, the science underpinning the management of HFrEF and HFpEF is quite different. Patients with HFrEF are treated with an armamentarium of guideline-directed medical therapies, which is pathophysiologically linked to mitigating adverse neurohormonal activation and remodeling and is well-established by mortality-driven end point randomized clinical trials.[5] Alternatively, physicians have no such treatment algorithm for patients with HFpEF, which lacks a similar grounding in foundational principles.

Despite universal agreement for the need for therapies that alter the trajectory of HFpEF, clinical trials that have enrolled patients with HFpEF have not led to new therapies that meaningfully improve morbidity or mortality. Rather, current HFpEF guidelines focus on alleviating vascular congestion with diuretics; controlling comorbidities; and excluding alternative diagnoses, such as ischemic heart disease or infiltrative cardiomyopathies.[6] Whether due to a limited syndromic classification and understanding of the pathophysiology, the approach to therapeutic discovery, or the choice of trial end points, it appears that progress on treatment development remains stagnant.

For HFpEF, a reasonable approach for research efforts may be to shift from creating a single group of patients to focus instead on improved patient stratification while evaluating the effect of treatments on phenotypically defined cohorts within the population. From the perspective of care delivery and therapeutic development, the initial premise that HFpEF was a uniform clinical syndrome managed with a singular approach is incorrect. In reality, it is a combination of multiple disease states that necessitate unique approaches. Multiple HFpEF definitions with varying clinical-based, imaging-based, and laboratory-based criteria have influenced widely variable inclusion criteria in clinical trials. This reinforces the need to pivot to more well-defined HFpEF cohorts to refine care, evaluate new therapeutics, and improve outcomes.[7] As an example of this challenge, a study demonstrated that 122 of 187 patients (65%) with HFpEF had an abnormal left ventricular global longitudinal strain on echocardiographic imaging.[8] Although these results were found to correlate with biomarkers of increased myocardial wall stress and fibrosis, they did not corelate with functional capacity or quality of life.[8]

It has been hypothesized that elements of the HFpEF clinical trajectory may be modifiable by agents proven beneficial in HFrEF.[7] Numerous agents already established through randomized clinical trials as guideline-directed medical therapies for HFrEF have now been tested in patients with HFpEF, including renin-angiotensin-aldosterone system inhibitors, spironolactone, and sacubitril-valsartan.[7] These trials enrolled thousands of patients, but they may have missed the mark by failing to meet their primary end points because the study drugs were tested in undifferentiated patients with HFpEF.[2] It remains unknown if choosing patients with HFpEF based on demonstrable deficits in myocardial performance could have led to improved outcomes using these agents. Alternatively, for a likely significant proportion of this population, symptoms do not align with a myocardial performance deficiency. Instead, an abnormal vascular response involving endothelial dysfunction and nitric oxide (NO) signaling may predominate as the key symptom-driving pathophysiology. These patients represent a potentially large and high-risk component of the HFpEF population, and the investigation strategy should be reoriented to define this cohort better and evaluate therapeutic options to mitigate this specific pathophysiology to move the field forward.

In this issue of *JAMA*, the VITALITY-HFpEF trial[9] and the CAPACITY-HFpEF trial[10] evaluated the use of direct soluble guanylate cyclase (sGC) stimulators, vericiguat in VITALITY-HFpEF and praliciguat in CAPACITY-HFpEF, to increase cyclic guanosine monophosphate (cGMP). In HFpEF, endothelial inflammation leading to reduced NO bioavailability is hypothesized to culminate in decreased production of cGMP by sGC. This pathway is understood to regulate myocardial contractility and relaxation, as well as relax smooth muscle and have antiproliferative effects, and impairments of this signaling pathway have been associated with ventricular remodeling, stiffening, and hypertrophy, as well as vascular stiffening and inflammation.[11] Accordingly, several studies have attempted to increase NO by using oral and inhaled nitrates and phosphodiesterase inhibitors.[7] Compared with prior attempts, the sGC stimulators evaluated

in these 2 well-performed studies are novel because they increase cGMP independently of NO.[12]

In the VITALITY-HFpEF trial, Armstrong and colleagues[9] enrolled 789 patients with chronic HFpEF, a left ventricular ejection fraction of at least 45%, and New York Heart Association class II to III symptoms within 6 months of a recent decompensation event (HF hospitalization or intravenous diuretics for HF without hospitalization) and elevated natriuretic peptides. Patients were randomized to receive vericiguat uptitrated to a daily dose of 15 mg (n = 264) or 10 mg (n = 263) or placebo (n = 262). At 24 months, the primary outcome, change in physical performance, as assessed by the mean change in the physical limitation score of the Kansas City Cardiomyopathy Questionnaire (range, 0-100; higher scores indicate better health), was 5.5 points in the 15-mg group, 6.5 points in the 10-mg group, and 6.9 points in the placebo group; differences between either vericiguat dose and placebo were not statistically significant.

In the CAPACITY-HFpEF trial, Udelson and colleagues[10] enrolled 196 patients with HF and a left ventricular ejection fraction of at least 40%, impaired peak rate of oxygen consumption ($\dot{V}O_2$), and at least 2 conditions associated with NO deficiency (diabetes, hypertension, obesity, or advanced age). Patients were randomized to receive 40 mg of praliciguat daily (n = 91) or placebo (n = 90). At 12 weeks, there was no significant difference in the primary outcome, change in peak $\dot{V}O_2$ from baseline to week 12, in the 40-mg praliciguat group compared with the placebo group (−0.26 vs 0.04 mL/kg/min).

Although the agents in both trials target the cGMP pathway, neither trial directly studied physiological end points of impaired vascular response, such as change in brachial reactivity or noninvasive or invasive hemodynamics. The potential effect of these drugs on diminishing an impaired vascular response has not been previously studied in patients with HFpEF and can only be inferred by the hypotensive effects in patients.[13] Vericiguat appears to have a modest effect in reducing cardiovascular hospitalization in patients with HFrEF,[14] but when examined in a previous study in patients with HFpEF, it did not reduce the primary end points of N-terminal fragment of brain natriuretic peptide or left atrial volume compared with placebo.[12] Post hoc analyses from that trial suggested improvements in the Kansas City Cardiomyopathy Questionnaire physical limitation score, which influenced the choice of the primary end point in VITALITY-HFpEF.[15] On the other hand, praliciguat has had only limited in vivo human experience prior to CAPACITY-HFpEF.[16]

Both groups of study investigators chose physical function changes as the primary end points: the physical limitation score and 6-minute walk test distance in VITALITY-HFpEF and a change in peak $\dot{V}O_2$ and 6-minute walk test distance in CAPACITY-HFpEF. Because HFpEF predominantly affects older patients, impairment in exercise capacity and dyspnea on exertion can significantly affect their activities of daily life. Yet, it remains an open question as to whether a change in physical functioning can meaningfully discriminate among effective therapies in patients with HFpEF, many of whom have multiple comorbidities that lead to chronic deconditioning.

However, neither trial found that sCG stimulators improved measures of physical functioning. Given the challenge of defining HFpEF, key limitations of these studies involve the inclusion criteria. Although patients were required to have a prior HFpEF decompensation, the natriuretic peptide levels at baseline were relatively low, even more so in CAPACITY-HFpEF. Also, natriuretic peptide level might not be a reliable biomarker in HFpEF, because levels do not necessarily correlate with decompensation or disease severity, especially among patients with obesity.[7] Obesity was relatively prevalent in both study cohorts, with a mean body mass index of approximately 30 in VITALITY-HFpEF and 34 in CAPACITY-HFpEF. This is not unexpected because more than 80% of patients with HFpEF have overweight or obesity,[17] but it raises the question of whether the physical functioning end points chosen can be improved independent of weight loss.[18]

Overall, the results of these 2 randomized clinical trials of sGC stimulators in patients with HFpEF reported in this issue of *JAMA*, as well as previous studies that have attempted to modify cGMP by other means, suggest that targeting this pathway is not an effective population-based strategy to improve physical functioning for patients with HFpEF in the short term. However, due to the approaches for patient selection, the length of follow-up, and the end points chosen, these studies do not negate the potential that these agents may have to improve outcomes. Future studies should select patients with HFpEF based on demonstrable endothelial dysfunction, and patients should be followed up longer for an end point such as a reduction in HF hospitalization.

Establishing effective therapies for HFpEF will require improved patient characterization and enhanced understanding of the underlying pathophysiology.[2] Proposed patient subgroups to potentially study include those with abnormal myocardial performance, obesity and metabolic disorders, and abnormal endothelial dysfunction.[7] Informatics and machine-learning techniques may be helpful to facilitate a subphenotype classification, based on statistically clustered clinical and biological characteristics.[19] Although improving physical performance and quality of life are no doubt important treatment goals, these outcomes may not be sensitive or specific enough to evaluate for the efficacy of novel therapies. Rather, future research may need to prioritize linkage between pathophysiology defined cohorts and end points to ultimately reduce morbidity and mortality associated with HFpEF.

ARTICLE INFORMATION

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Conflict of Interest Disclosures: Dr Velazquez reported receiving grants and personal fees from Novartis outside the submitted work. No other disclosures were reported.

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