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EDITORIAL COMMENT

Patient-Reported Outcome Instruments in Heart Failure

Are They Preserved?*

Mitchell A. Psotka, MD, PhD,[a] John R. Teerlink, MD[b,c]

Despite constituting approximately one-half of all patients with a heart failure (HF) syndrome, HF with preserved ejection fraction (HFpEF) remains understudied and enigmatic compared to its sibling, HF with reduced EF (HFrEF). Improved care for patients with HFpEF has been impeded by multiple issues including the absence of a unified definition, poor comprehension of its underlying pathophysiology, and a relative inability to even understand the patients' experience. Because investigational therapeutic interventions have been unable to reduce mortality for patients with HFpEF, the focus has shifted to target patient symptoms and well-being evaluated principally by using patient-reported outcomes (PRO) instruments.

PRO instruments collect data directly from patients without adulteration or interpretation by clinicians or other individuals. Validated PRO questionnaires for HFpEF could facilitate development and implementation of novel therapeutics and increase clinical trial efficiency by proving that an intervention improves health-related quality of life (HRQoL). Two of the most robustly evaluated heart failure disease-specific PROs are the Kansas City Cardiomyopathy Questionnaire (KCCQ) and the Minnesota Living with Heart Failure Questionnaire (MLHFQ), both of which were initially developed for patients with HFrEF (1). PROs and the KCCQ in particular are slated for a larger role in HF outcomes assessment with the recent U.S. Food and Drug Administration (FDA) Centers for Devices and Radiological Health qualification decision allowing the KCCQ to be used as a medical device development tool (2). Nonetheless, the utility of these PROs in the evaluation and management of patients with HFpEF remains uncertain (1,3).

Full evaluation of PRO tools for clinical utility and research purposes and for regulators involves psychometric testing and examination of evidence across numerous domains. These domains include content validity (that the PRO measures the concept of interest), construct validity (evidence that PRO predictably correlates with similar alternative assessment tools), reproducibility (includes test-retest reliability), internal consistency (the extent to which items within a PRO measure the same concept, measured by Cronbach's alpha), ability to detect change (evidence that the PRO can detect change or responsiveness), and whether there is a responder definition (empirically determined PRO change that can be interpreted as a treatment benefit) (1). Because the pathophysiology of symptoms in HFpEF may be distinct from those in HFrEF, PRO tools may not be transferable between the disease states; the validity of extrapolating PRO measures to HFpEF should be appraised based on structured examination of the aforementioned domains.

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To address whether the most robust HFrEF PROs may be useful for HFpEF, in this issue of *JACC: Heart Failure* Napier et al. (4) evaluated some of the instruments' important attributes in

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From the [a]Inova Heart and Vascular Institute, Falls Church, Virginia; [b]School of Medicine, University of California-San Francisco, San Francisco, California; and the [c]Section of Cardiology, San Francisco Veterans Affairs Medical Center, San Francisco, California. Dr. Psotka has consulted for Amgen and Cytokinetics. Dr. Teerlink has received research grants and personal fees from Abbott, Amgen, Bayer, Bristol-Myers Squibb, Novartis, and scPharmaceuticals; and has consulted for Amgen, Bayer, Cytokinetics, Novartis, and Stealth Health.

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a well-characterized, small HFpEF clinical trial population. These patients were >50 years of age, had a left ventricular ejection fraction of >50%, and had objective evidence of heart failure with either hospitalization (including radiographic evidence of pulmonary congestion, elevated left ventricular filling pressures quantitated by invasive hemodynamics, or elevated natriuretic peptides) or echocardiographic evidence of diastolic dysfunction. All 110 patients from the NEAT (Nitrate Effect on Activity Tolerance in Heart Failure) trial were included in this secondary analysis, but only 78 completed baseline and 6-week follow-up MLHFQ assessments, whereas 108 patients provided KCCQ data.

The 2 PRO assessments were frequently not in agreement, with only fair κ value of 0.36. Nonetheless, both the KCCQ and the MLHFQ demonstrated good internal consistency (Cronbach α: >0.9) overall, and within most subdomains. The summary or total scores either inversely or directly correlated with New York Heart Association (NYHA) functional class with absolute Pearson correlation coefficients ≥0.3; however, the KCCQ scores for the 6-min walk distance were better correlated. Unsurprisingly, neither correlated well with N-terminal pro-B-type natriuretic peptide concentrations, which are typically insensitive for diagnosis and for therapy in patients with HFpEF, and further reinforces the fact that changes in natriuretic peptides and myocardial stretch do not appropriately represent the patients' experience or symptom severity for people with HFpEF. There was a statistically significant correlation between the KCCQ clinical summary score and accelerometry, but the association was modest. Unfortunately, as seen for patients with HFrEF, the PROs were able to measure functional improvements better than worsenings. In this regard to responsiveness, the MLHFQ appeared slightly superior to the KCCQ.

The work of Napier et al. (4) recapitulates prior results for the KCCQ within a prospective registry of 200 patients with HFpEF defined by left ventricular ejection fraction ≥50% (3). Patients were younger those than in the study by Napier et al. (4) (mean 60 vs. 69 years of age), fewer patients were white (76% vs. 89%, respectively), more patients were taking diuretic drugs (79% vs. 65%, respectively), fewer patients had hypertension (63% vs. 90%, respectively), and fewer patients had ischemic heart disease (14% vs. 62%, respectively), although other baseline variables were similar. This work evaluated criterion standards of NYHA functional class as well as deaths and all-cause hospitalization to establish internal and construct validity for patients with HFpEF. The Cronbach alpha values were 0.96 for the overall summary score and >0.80 for all but the self-efficacy scores. Notably, removal of self-efficacy items in a separate study appeared not to affect the psychometric performance for a short version of the KCCQ (5). The correlation coefficient between KCCQ and NYHA functional class results was −0.62 for patients with HFpEF, and KCCQ discriminated between subjects with higher and lower 1-year mortality and hospitalization rates. The predictive validity of KCCQ scores for heart failure outcomes suggested that the KCCQ meaningfully captured at least some essential aspect of the HFpEF disease trajectory.

Strengths of the study by Napier et al. (4) include the well-defined patient population, uniform implementation and capture of PRO measurements, direct comparison of the 2 most robust PRO assessment tools available for HF, and the use of multiple criterion standards. The studies by Joseph et al. (3) and Napier et al. (4) remain somewhat limited because the KCCQ and the MLHFQ were designed for use with HFrEF rather than HFpEF. Neither study used qualitative methods to ensure concept saturation for patients with HFpEF, experiments to determine content validity by identifying symptoms and functional limitations that unique impair health status with HFpEF. Demonstration of test-retest reliability is lacking, there is no clear anchored responder definition for these PROs for patients with HFpEF, and these tools are poorly responsive to worsening in health status. Nonetheless, the paper by Napier et al. (4) adds to current reports that support using established PROs for the study and monitoring of patients with HFpEF.

It has been well demonstrated that few biochemical, echocardiographic, or functional parameters appropriately define HFpEF, and the futility of developing a definition may stem from the heterogeneity of phenotypes and presentations of HFpEF (6). Whether HFpEF should even be considered a type of heart failure is a frequent question. However, this fruitful foray into HRQoL for patients with HFpEF suggests that heart failure is a key component of the syndrome, even if more work needs to be done. Moving toward an improved and measurable definition of the patients' experience for those with HF without reduced ejection fraction is the way forward, and this is a welcome next step.

ADDRESS FOR CORRESPONDENCE: Dr. Mitchell A. Psotka, Inova Heart and Vascular Institute, 3300 Gallows Road, Falls Church, Virginia 22042. E-mail: Mitchell.Psotka@inova.org.

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