Among the estimated 5.7 million people living with heart failure (HF) in the United States, HF with preserved ejection fraction (HF-PEF) or mildly reduced left ventricular dysfunction represents approximately 90% of women and 70% of men. Although patients with severe left ventricular dysfunction may have worse mortality, other outcomes are similar including impaired quality of life. Although this HF-PEF population has a higher representation of women, elderly and minorities, there is an underrepresentation of randomized clinical trials to determine therapies that may improve outcomes. Thus, trends in mortality have remained unchanged in this population despite improvements in mortality among the patients with HF with low ejection fraction in epidemiology cohorts. The increase in hospitalization rates for acute decompensated HF, overall costs of managing these complex patients, and high prevalence in the general population support the expanded efforts of researchers to determine novel interventions for improving outcomes. In addition to reducing mortality and hospitalizations, increasing exercise capacity, and attenuating disease progression, improving the patient’s sense of well-being is an additional important goal of novel therapy.

The term “quality of life” (QOL) has been used for decades by researchers, clinicians, patients, and health policy experts. The foundation of QOL may date back to 1948 when the World Health Organization expanded the concept of health beyond merely the absence of disease, but included the overall well-being of the patient. Given the logical importance of QOL, there has been a surge of articles with QOL listed as a key word in MEDLINE from 5 articles in 1973 to >4000 articles today when restricting the search to HF. The emergence of standardized metrics for determining the validity, reliability, responsiveness, and interpretability of instruments for measuring QOL (also known as psychometric properties of the instrument) has started to provide some foundation for generalized understanding of relative abstract outcome measures. The Food and Drug Administration Draft Guidance for Patient-Reported Outcome Measures further established criteria to consider in the design of clinical trials that assessed interventions that may improve the sense of well-being. Nevertheless, despite outcomes researchers’ long-held belief that QOL is a concept that can be reliably measured and possibly used to guide therapy and increasing QOL publications in high-impact journals, many clinicians and nonoutcomes researchers remain skeptical and often shy away from targeting QOL as the primary end point in clinical studies. Other potential factors contributing to this broad skepticism include (1) the countless number of available instruments which affects clarity of anchors for “good” and “bad” health status, clinical importance of a change score, and comparative QOL to other populations; (2) simultaneous assessment of multiple domains with superior power to achieve significant probability values with minimal differences between groups; (3) lack of consistency with QOL outcome results; and (4) no standardized approach to the reporting of QOL outcomes. Nevertheless, as the “quality” of QOL studies improves due to better trial design with rigorous methods applied both scientifically and for regulatory purposes, the acceptance of these findings by clinicians and nonoutcomes researchers will expand.

In this issue of Circulation: Heart Failure, Rector et al expand the quality of life component of the Irbesartan in Heart Failure with Preserved Ejection Fraction study (I-PRESERVE) experience beyond that reported in the primary article. Using the Minnesota Living with Heart Failure (MLHF) questionnaire, the authors were able to assess QOL at baseline, 6 months, and 14 months with gradual decline in response rates from 88% at baseline down to 81% by 14 months. Only 60% of patients completed the MLHF instrument by end of study with slightly less than half of the missing data unexplained due to death or another rationale. The summary score of 42 was modestly impaired and similar to other trials of patients with HF. The key finding is that there was clinically meaningful improvement in QOL (on average) in both patients randomized to placebo and those randomized to irbesartan with most of the change occurring between baseline and 6 months; this improvement persisted throughout the study. However, randomization to irbesartan did not confer additional improvements in QOL (using mean adjusted differences in MLHF scores) either during short term or longer-term follow-up. The authors also demonstrated reasonable psychometric properties of the MLHF questionnaire in the HF-PEF population enrolled in I-PRESERVE and thus conclude that the lack of improvement in QOL using irbesartan cannot be explained by inadequacy of the QOL measurement used.

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

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The authors should be commended on a clear article that both describes the outcomes of I-PRESERVE QOL experience and details key metrics supporting the validity and reliability of the MLHF in HF-PEF that may be helpful for researchers who plan to assess QOL in future studies of HF-PEF. Sensitivity of the MLHF instrument to detect differences between patients was evident by large mean differences at baseline (eg, 14-point worse scores for patients with severe edema or diffuse rales, 9-point worse scores for patients with enlarged liver, 9- and 25-point worse scores for those with New York Heart Association Class III and IV, respectively), and supports earlier studies.9 Although there was worse QOL among women as seen in other studies,3 age was not a major factor, which is likely due to the population that did not enroll young people who tend to have worse overall QOL among patients with HF. Moreover, a 10-point improvement in MLHF scores overall suggests responsiveness of the instrument to change. The authors used the path model to confirm retest reliability of the instrument, which is supported by the data collection; this has not been the approach used most recently in the design of novel health status measures.10 Several missing items were likely nonrandom, including the questions related to the impact of HF on sexual activity and ability to work, consistent with other studies. I-PRESERVE was a large, well-characterized population with HF-PEF with clearly defined end points making it a perfect fit for this type of analysis by providing ample power to detect differences between patients and thus further solidifying the lack of effect of irbesartan on a patient’s sense of well-being.

There are limitations with the article. A complete psychometric analysis could not be performed and would have been better served in a small cohort of patients similar to the demographics of I-PRESERVE. This smaller subset would enable formal testing of (1) content validity or patient specifically stating that the items measured constitute the totality of the impact of HF on their lives; (2) minimum important difference or the distinction in responses that convincingly suggests a meaningful difference; and (3) more extensive assessment of convergent validity by determining correlation of MLHF responses to other measures of QOL. The instrument was administered in all 25 countries and there was no mention of the validity, reliability, and responsiveness of the MLHF within the context of the subtle cultural differences in translations of the instrument. This may account for the differences in the responses stratified by countries. Missing data are 1 of the most difficult factors in interpretation of QOL outcomes and this trial had similar missing data rates of other large trials. The lack of data on rationale for missing data potentially introduces bias because this data often are nonrandom. There was also a large gap between the 14-month visit and end of study with potential wide variations in the time it was assessed. Finally, there was no reassessment of QOL scores soon after randomization; thus, it is difficult to discern a true improvement in QOL over the first 6 months or if some of the effect size is due to a true “placebo effect” or optimism for gaining a benefit from being in the clinical study.

The results of this study will join other studies of pharmacological therapies with mixed results, mostly in patients with low left ventricular ejection fraction HF.11 In the Valsartan Heart Failure Trial (Val-HeFT), there were minor QOL differences in favor of angiotensin receptor blocker despite a much better baseline QOL (MLHF=32); however, a small number of patients actually completed instruments at the end of follow-up.12 Using overall treatment evaluation scores, more patients randomized to a angiotensin receptor blocker felt improved with a lower percentage noting a decrement in their sense of well-being13; however, global changes may not be the most accurate assessment of impact of therapy. Although one can argue that a more responsive instrument may have demonstrated improvement with treatment, I contend that clinically meaningful changes in QOL would be captured regardless of the instrument used as was evident with the use of mechanical circulatory support for the treatment of advanced HF that demonstrated dramatic improvements of health status with multiple instruments14 and (to a lesser degree) the use of cardiac resynchronization therapy. Nevertheless, despite a “negative” study for the effects of treatment on QOL, I-PRESERVE serves as a “positive” model for QOL studies in clinical trials.

Future Directions
The paucity of clinical trials that definitively improves QOL will continue to add to skepticism but must not affect our abilities to improve the methodology and to reconsider interventions that may influence this important outcome. As new trials are designed, the expected impact of the intervention on the patient should be considered because this may influence the optimal duration of follow-up and the domains chosen as the primary QOL outcome measure. In addition, researchers need to address multiple challenges: (1) decide on standardized formatting for primary QOL articles that include baseline QOL scores, change scores adjusted for baseline scores, imputation strategies used, and missing data at each follow-up visit; (2) define a priori which domain(s) will be the primary QOL metric used and define the difference that is clinically meaningful; (3) assess health status using a disease-specific instrument for the efficacy measure and a generic instrument that provides a reference point to other populations to define the severity of QOL impairment; (4) consider double-blinded studies whenever possible to avoid introduction of bias when determining effect size of an intervention on QOL; (5) reduce missing values by escalating the importance of completion of validated instruments at the beginning of a clinical trial and thoughtfully consider which countries to include in the QOL study as culturally sensitive instruments are required; and (6) consider the underlying mechanism of QOL improvements as the duration of follow-up is chosen (eg, an intervention that reduces congestion may improve QOL quicker than an agent that leads to reverse remodeling).

In the interim, we should consider novel interventions that can improve a patient’s sense of well-being. Clinically meaningful changes in QOL may occur by an intervention (1) that targets those with more impaired baseline QOL; (2) that has a dramatic influence on physiological factors, symptom burden, functional status, or nonfatal events; or (3) that addresses multiple factors that contribute to impairment in
sense of well-being such as depression, social supports, exercise capacity, or optimism. Although the path to improved QOL is tortuous, the reward is the improvement of a major clinical outcome that is often at least as important to the patient as survival, especially in patients with advanced HF. The semantics of health status, QOL, health-related QOL, or patient-reported outcomes are less important than designing novel interventions that make patients feel better despite their disease.

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References

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