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MINI-FOCUS: HEART FAILURE OUTCOMES AND ENDPOINTS

STATE-OF-THE-ART REVIEW

# Endpoints in Heart Failure Drug Development

## History and Future

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### HIGHLIGHTS

- HF patients experience a high burden of symptoms and functional limitations.
- There remains an unmet need for new HF drugs, despite successful therapies that improve morbidity and mortality.
- The majority of HF drugs in the United States are approved for reducing hospitalization and mortality, with only a few having an indication for improving quality of life, physical function, or symptoms.
- Improvements in symptoms, physical function, or quality of life are potentially approvable endpoints in drug development.
- Drug development should include a focus on symptomatic and functional benefit in HF patients, in addition to drugs that improve survival or reduce hospitalization.

### ABSTRACT

Heart failure (HF) patients experience a high burden of symptoms and functional limitations, and morbidity and mortality remain high despite successful therapies. The majority of HF drugs in the United States are approved for reducing hospitalization and mortality, while only a few have indications for improving quality of life, physical function, or symptoms. Patient-reported outcomes that directly measure patient's perception of health status (symptoms, physical function, or quality of life) are potentially approvable endpoints in drug development. This paper summarizes the history of endpoints used for HF drug approvals in the United States and reviews endpoints that measure symptoms, physical function, or quality of life in HF patients. (J Am Coll Cardiol HF 2020;8:429-40) © 2020 Published by Elsevier on behalf of the American College of Cardiology Foundation.

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**ABBREVIATIONS AND ACRONYMS**

**6MWT** = 6-min walk test

**ACE** = angiotensin-converting enzyme

**ADHF** = acute decompensated heart failure

**ARB** = angiotensin II receptor antagonist

**CPX** = cardiopulmonary exercise testing

**FDA** = U.S. Food and Drug Administration

**HF** = heart failure

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

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

**KCCQ** = Kansas City Cardiomyopathy Questionnaire

**MLHFQ** = Minnesota Living with Heart Failure Questionnaire

**MRAs** = mineralocorticoid receptor antagonists

**PRO** = patient reported outcome

Heart failure (HF) is a global epidemic, with a burden of disease projected to increase significantly in the next decade (1). In addition to high morbidity and mortality, patients with HF experience a substantial burden of symptoms and functional limitations. Despite the need for new treatments, there has been a decline in discovery of relevant new pathophysiologic pathways, new molecular targets, and investment in heart failure therapeutics (2–4). In part, this may reflect an emphasis on clinical outcomes and misconception that U.S. Food and Drug Administration (FDA) approval for HF drugs requires a favorable effect on morbidity and mortality. Because of a number of factors, generating the necessary evidence to demonstrate efficacy and safety is costly and often inefficient, and may be driving innovation and investment into other therapeutic areas.

Currently, few drugs are approved for symptom relief in chronic or acute decompensated HF (ADHF) or congestion, and to date not a single drug has been approved for the treatment of HF with preserved ejection fraction (HFpEF). However, the clinical community has long recognized the importance of improving symptoms, functional capacity, and quality of life and believes these to be valid therapeutic goals in treating HF, in the absence of reductions in death and hospitalization. The concept of patient driven outcomes has been the subject of much research advancement and interest in the clinical trial community.

Sponsors have historically designed trials focusing on endpoints of hospitalization and mortality. This began because of safety concerns in the 1980s when several drugs (e.g., milrinone and flosequinan) with clearly beneficial early effects on symptoms and exercise capacity were subsequently shown to have adverse effects on survival. This dichotomy led to a requirement for cardiovascular outcome studies of sufficient size to exclude an increase in adverse outcomes. Fortunately, many of these outcome studies demonstrated reductions in morbidity and mortality, including trials of beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor antagonists (ARBs), mineralocorticoid receptor antagonists (MRAs), and isosorbide/hydralazine. The utilization of novel study designs and innovative endpoints may improve study efficiency and accelerate development of treatments for HF (5). The FDA has long taken a flexible approach to clinical trial design, urging that trials be designed as efficiently as possible while taking into account the severity and relevance of the disease and the degree of unmet need. The FDA recently issued

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC: Heart Failure* author instructions page.

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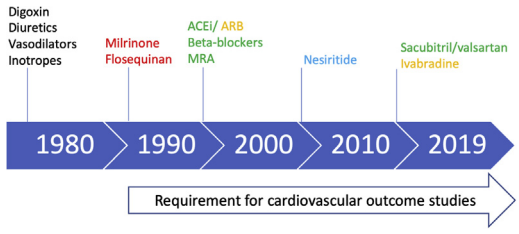
**FIGURE 1 Timeline of Approved Drugs to Treat Heart Failure**




ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker.

a draft guidance, *Treatment for Heart Failure: Endpoints for Drug Development*, clearly stating that an improvement in symptoms or physical function, even without a documented favorable effect on survival or hospitalization, can be a basis for approving drugs to treat HF (6).

The goal of this paper is to provide a historical review of the endpoints used for HF drug approvals in the United States and consider endpoints that measure symptomatic and functional benefit in drug development.

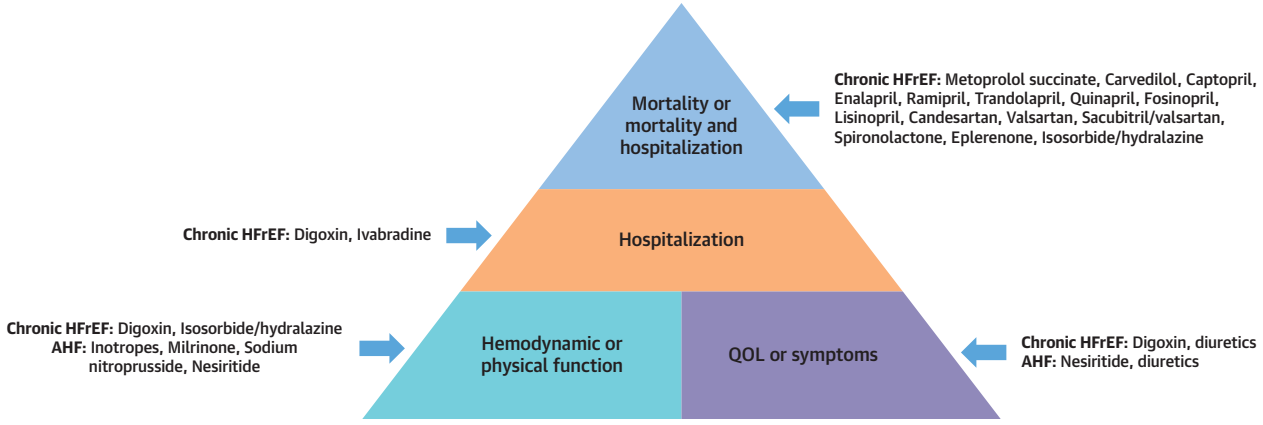
## HISTORICAL REVIEW OF APPROVED HF DRUGS

For the historical review, we examined labels of all drugs with approved indications for HF in the United States and the trials used to support their approval. Drugs were categorized by effects on survival and hospitalization, quality of life, symptoms, or functional status. We did not consider guideline recommendations or clinical use. Although guideline committees carefully consider labeling, the methodology for guideline recommendations covers a broader range which include literature reviews, evolving technologies, and other factors. The scope of the current manuscript is focused on regulatory approvals and considerations.

### ENDPOINTS AND INDICATIONS.

**Mortality and hospitalization.** Following early experience with drugs for HF that showed adverse effects on survival (e.g., milrinone and flosequinan), development programs for drugs used to treat HF were expected to include outcome studies to evaluate their safety (Figure 1). Many drugs led to improvements in rates of hospitalization and/or death. However, clinical trials with those endpoints have significant challenges, including cost and time, particularly in light of a reduction in mortality rates over time and greater barriers to recruitment. Clearly, beneficial effects on hospitalization or mortality are the most significant impact desired, particularly if a drug improves symptoms or function in addition to improving survival. The Central Illustration is a summary of drugs by approved indications. Fifteen drugs have been approved for improving survival or a combination of reducing the risk of hospitalization plus survival.

**CENTRAL ILLUSTRATION Drugs Approved in Heart Failure by Indication**




AHF = acute heart failure; HFrEF = heart failure with reduced ejection fraction; QOL = quality of life.

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AHF = acute heart failure; HFrEF = heart failure with reduced ejection fraction; QOL = quality of life.

**TABLE 1 Drugs Approved for Reducing Mortality or the Composite of Morbidity and Mortality in HF**

| Drug | Labeled Indication | HF Phenotype | Pivotal Trials Supporting Indication |
|---|---|---|---|
| Metoprolol succinate extended release | • Treatment of stable, symptomatic (NYHA functional class II or III) HF of ischemic, hypertensive, or cardiomyopathic origin.<br>• Decreased mortality plus hospitalization, largely through a reduction in CV mortality and HF hospitalizations | Chronic HFrEF (EF ≤40%)<br>NYHA functional class II-IV | MERIT-HF |
| Carvedilol | • CHF: mild-to-severe HF of ischemic or cardiomyopathic origin, to increase survival and reduce the risk of hospitalization<br>• Left ventricular dysfunction following MI: reduce CV mortality in clinically stable patients who have survived acute MI and have an LVEF of ≤40% (with or without symptomatic HF) | Chronic HFrEF (EF ≤40%)<br>NYHA functional class II-IV | COMET<br>COPERNICUS<br>CAPRICORN |
| Captopril | • CHF<br>• Left ventricular dysfunction after MI: improve survival following MI in clinically stable patients with LVEF≤40%; reduce the incidence of overt HF and HF hospitalizations. | Chronic HF<br>HFrEF (EF ≤40%) after acute MI | SAVE |
| Enalapril | • Treatment of symptomatic CHF<br>• Improve symptoms, increase survival, and decrease the frequency of hospitalization<br>• LVEF ≤35%: decrease the rate of development of overt HF and decrease incidence of HF hospitalization | Symptomatic CHF;<br>Asymptomatic LV dysfunction (EF<35%) | SOLVD-Treatment<br>SOLVD-Prevention<br>CONSENSUS |
| Fosinopril | • Management of HF as adjunctive therapy | HFrEF<br>EF≤35%<br>NYHA functional class II-III | |
| Lisinopril | • Adjunctive therapy in the management of HF in patients who are not responding adequately to diuretics and digitalis. | Chronic HFrEF (EF≤30%)<br>NYHA functional class II -IV | ATLAS |
| Quinapril | • Management of HF as adjunctive therapy | Chronic HFrEF<br>NYHA functional class II-IV | |
| Ramipril | • Treatment of stable patients who have clinical signs of CHF within the first few days after acute MI, to decrease the risk of death (principally CV death) and decrease the risks of failure-related hospitalization and progression to severe/resistant HF. | HF after MI | AIRE |
| Trandolapril | • Treatment of stable patients who have evidence of LV systolic dysfunction (identified by wall motion abnormalities) or symptomatic CHF within the first few days after acute MI.<br>• In white patients decrease the risk of death (principally CV death) and decrease the risk of HF-related hospitalization | LV systolic dysfunction after MI or symptomatic CHF after MI in white patients | TRACE |
| Candesartan | • Treatment of HF (NYHA functional class II-IV) in adults LVEF ≤40%) to reduce CV death and reduce HF hospitalizations. | Chronic HFrEF (EF ≤40%)<br>NYHA functional class II-IV | CHARM-Added<br>CHARM-Alternative |
| Valsartan | • Treatment of HF (NYHA functional class II-IV); reduced HF hospitalization<br>• Reduction of CV mortality in clinically stable patients with left ventricular failure or left ventricular dysfunction following MI | Chronic HFrEF (EF<40%) NYHA functional class II-IV<br>HF and/or LVEF≤35%) post-MI | Val-HeFT<br>VALIANT |
| Sacubitril/valsartan | • Reduce the risk of CV death and HF hospitalization in CHF (NYHA functional class II-IV) and reduced EF | Chronic HFrEF (EF ≤40%)<br>NYHA functional class II-IV | PARADIGM-HF |
| Spironolactone | • Edematous conditions for patients with CHF.<br>• Management of edema and sodium retention when the patient is only partially responsive to, or intolerant of, other therapeutic measures.<br>• Also indicated for patients with CHF taking digitalis when other therapies are considered inappropriate.<br>• Severe HF (NYHA functional class III-IV): to increase survival, and to reduce the need for HF hospitalization | Chronic HFrEF (EF ≤35%)<br>NYHA functional class III-IV | RALES |
| Eplerenone | • Improve survival of stable patients with LVEF ≤40% and clinical evidence of CHF after acute MI. | 1) HFrEF (EF ≤40%) after acute MI<br>2) Chronic HFrEF (EF ≤30% or ≤35% if QRS >130 ms), NYHA functional class II | EPHESUS |
| Isosorbide dinitrate/ hydralazine | • Treatment of HF as an adjunct to standard therapy in self-identified black patients to improve survival, to prolong time to HF hospitalization, and to improve patient-reported functional status. | Chronic HFrEF (EF ≤35% or <45% if LV dilation)<br>Self-identified black patients<br>NYHA functional class III-IV | A-HeFT |

In general, drugs that reduce mortality are also effective in reducing hospitalizations. The majority of trials have used a composite endpoint of death (cardiovascular or all-cause) and hospitalizations (cardiovascular, HF, or all-cause) as a primary endpoint. Two drugs, ivabradine and digoxin, are approved only for reducing hospitalization without an indication for improving survival. Table 1 outlines drugs approved to reduce mortality, or a composite endpoint of mortality and hospitalization. If a drug does not show an improvement in morbidity or mortality endpoints but improves feeling or function, morbidity and mortality should be considered to evaluate safety. Table 2 outlines

**TABLE 2 Drugs Approved for Symptom Relief or Other Indications in HF**

| Drug | Labeled Indication | HF Phenotype | Pivotal Trials Supporting Indication |
|---|---|---|---|
| Nesiritide | Treatment of patients with acutely decompensated CHF who have dyspnea at rest or with minimal activity. In this population, the use of nesiritide reduced pulmonary capillary wedge pressure and improved dyspnea. | Acute HF | VMAC |
| Ivabradine | Reduce the risk of hospitalization for worsening HF in adult patients with stable, symptomatic CHF with LVEF ≤35%, in sinus rhythm with resting heart rate ≥70 beats/min and either on maximally tolerated doses of beta-blockers or contraindication to beta-blocker use. | Chronic HFrEF (EF ≤35%)<br>NYHA functional class II-IV;<br>Resting heart rate ≥70 beats/min | SHIFT |
| Digoxin | Treatment of mild to moderate HF. Digoxin increases LVEF and improves HF symptoms as evidenced by exercise capacity and HF-related hospitalizations and emergency care, while having no effect on mortality. | Chronic HF<br>NYHA functional class II-III | RADIANCE<br>PROVED<br>DIG |
| Loop diuretics | Treatment of edema associated with CHF, cirrhosis of the liver, and renal disease, including the nephrotic syndrome.<br>Adjunctive therapy in acute pulmonary edema | Congestive HF | |
| Thiazide diuretics | Treatment of edema. | Congestive HF | |
| Potassium-sparing diuretics | Treatment of edema. | Congestive HF | |
| Sodium nitroprusside | Treatment of acute HF to reduce left ventricular end-diastolic pressure, pulmonary capillary wedge pressure, peripheral vascular resistance and mean arterial blood pressure. | Acute HF | |
| Milrinone | For short-term intravenous treatment of patients with acute decompensated HF. | Acute HF | |
| Dopamine | Hemodynamic support for acute HF | AHF with need for hemodynamic support | |
| Dobutamine | Hemodynamic support for acute HF | AHF with need for hemodynamic support | |

drugs approved for symptom relief or other endpoints.

**Feeling and function: The era of patient reported outcomes.** HF-related symptoms and functional limitations have a significant impact on quality of life. Tools that directly measure patient's perception of health status (symptoms, functional limitation, and quality of life), known as patient reported outcomes (PROs), are potentially approvable endpoints in drug development. However, few PROs have been utilized in clinical trials aiming to obtain regulatory approval for HF drugs. The importance of PROs for clinical decision-making may have been unintentionally undermined by omission from Class I guideline recommendations except for diuretics, which are recommended for improvement of HF symptoms in both heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF). Improvement in symptoms was clearly demonstrated along with decreased hospitalizations and mortality as a positive outcome in blinded, randomized trials for both cardiac resynchronization and the hydralazine/nitrate combination (7). Although this is the subject of ongoing research, we need more evidence in establishing common tools, defining clinically meaningful changes, and setting standard methods of administration.

The FDA published a guidance document that defines the critical elements of PROs, including content validity, construct validity, reproducibility, internal consistency, ability to detect change, and responder definition (8). However, many PRO instruments have limitations in these domains. Table 3 provides a summary of PRO examples, along with noted advantages and limitations of these measures.

## HEART FAILURE SYMPTOMS.

**Dyspnea.** More than one-half of patients discharged after a HF hospitalization suffer persistent symptoms, including dyspnea (9). Dyspnea is the most common and debilitating symptom of HF and correlates to some extent with risk of hospitalization and death (10). Additionally, dyspnea triggers pain/panic cortical centers (11). However, objective quantification of a patient's dyspnea is challenging, and the use of dyspnea as an endpoint has evolved over time. Although multiple tools with differing characteristics are available to assess dyspnea (e.g., single vs. multidimensional questionnaire vs. scale, self-reported vs. interview), there is no consensus on the best measure. Existing tools may quantify the level of dyspnea but not the change in dyspnea during hospitalization. In general, these tools have important limitations in acute HF trials, such as quantification based on activities of daily living or exercise testing. Most acute heart failure trials utilize dyspnea assessment via categorical, 5-point-based Likert or a continuous visual analog scale, without standardization of conditions (oxygen use or position), which may modify dyspnea severity and

**TABLE 3 Examples of Symptom and Functional Endpoint Measurements**

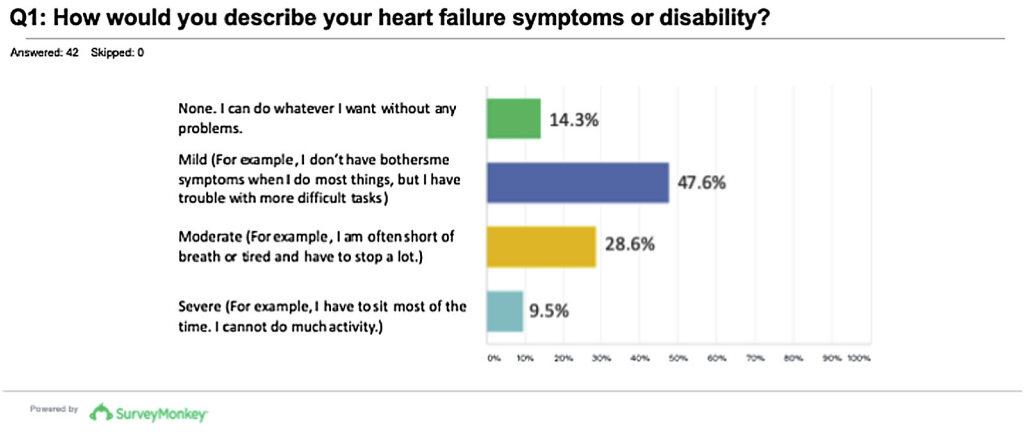
| Endpoint Measurement | Advantages | Limitations |
|---|---|---|
| Functional capacity | • Easy to understand<br>• Tracks to activities<br>• Impact on health-related quality of life | • Activity intensity influences<br>• Variable responsiveness<br>• Overlaps with physical measures and non-heart failure diseases |
| 6MWT | • Inexpensive<br>• Reproducible<br>• Mimics everyday activities<br>• Correlation with cardiopulmonary exercise testing<br>• Correlation with heart failure severity, morbidity, and mortality | • Not able to assess maximal exercise capacity<br>• Frequent intertest variability between subsequent tests<br>• Influenced by patient's motivation, coaching and familiarity of the test |
| 2MWT | • Simple and short | • Not yet validated in heart failure |
| 60ftWT | • Simple and short | • Not yet validated in heart failure |
| 4-m walk test (gait speed test) | • Good choice in advanced heart failure studies | • More a measure of frailty than endurance |
| CPX | • Assessment of multiorgan response to physical activity<br>• Possible association to cardiac imaging or invasive measurements<br>• Maximal exercise test<br>• Correlation with 6MWT<br>• Correlation with heart failure severity, morbidity, and mortality | • More influenced by other medical conditions<br>• Cost and time-consuming<br>• Need for trained personnel and a core lab for interpretation and quality control |
| Accelerometer | • Continuous measurement of effective physical activity<br>• Portable tools<br>• Can assess physical activity, posture and movement functional classification, estimation of energy expenditure, fall detection and balance control evaluation | • Not validated for heart failure patients yet<br>• Measures not standardized between different devices |
| Symptom status | • Easy to understand<br>• Linked to disease<br>• Possibly burdensome<br>• Self-administered tool | • Variable importance<br>• Modifiable by patient<br>• Variable perceptions<br>• Overlaps with non-heart failure diseases (e.g., pulmonary disease) |
| Dyspnea Likert scale | • Variable number of categories, definition, and time of administration | • Minimal clinical relevant change not clear<br>• Variable correlation with other dyspnea tools |
| Dyspnea, visual analog scale | • Continuous variable<br>• Easier to understand (visual comprehension) | • Minimal clinical relevant change not clear<br>• Variable correlation with other dyspnea tools |
| Quality of life | • Integrates all components<br>• Key target of treatment | • Hard to understand<br>• Defining clinical meaningfulness<br>• Overlaps with non-heart failure diseases |
| MLHFQ | • Explores physical symptoms and signs of HF, physical/social functions, psychosocial and cognitive function, and overall adverse impact on quality of life | • Social dimension missing |
| KCCQ | • Explores symptoms, physical function, quality of life, social limitation, self-efficacy, and symptom stability | • Length |

2MWT = 2-min walk test; 6MWT = 6-min walk test; 60ftWT = 60-ft walk test; CPX = cardiopulmonary exercise testing; KCCQ = Kansas City Cardiomyopathy Questionnaire; MLHFQ = Minnesota Living with Heart Failure Questionnaire; VAS = visual analog scale.

change in scores over time. Additionally, patients are typically enrolled hours or days after presentation, after treatment has been initiated and symptoms are improved, rather than at presentation when dyspnea is most severe. This further limits the sensitivity of conventional tools to detect an improvement. Some have proposed a novel provocative dyspnea severity score for use in acute heart failure trials (12). Standardizing scales such as the Likert in terms of category (5 vs. 7 points) and time of assessment could potentially help interpretation across trials (13,14). Importantly, the minimal clinically important difference in dyspnea is not clear (15,16). Other possible approaches may include enrolling patients very early, and incorporate an endpoint of worsening HF in clinical trials. Some of these concepts are already incorporated in clinical trials for ADHF that use dyspnea as a prominent component of an efficacy endpoint (17).

**Quality of life.** Quality of life is typically assessed using a patient-completed questionnaire, which may be general (e.g., Short Form Health Survey [SF-36]; Rand Health Care, Santa Monica, California]), or disease-specific. There are a growing number of instruments to capture various aspects of health status, with 5 general approaches: global, generic, disease-specific, battery, or preference-based (18). Important psychometric properties to consider in selecting an instrument include validity, reliability, responsiveness, and interpretability. The 2 most

**FIGURE 2** Patient-Reported Severity of Heart Failure Symptoms or Disability

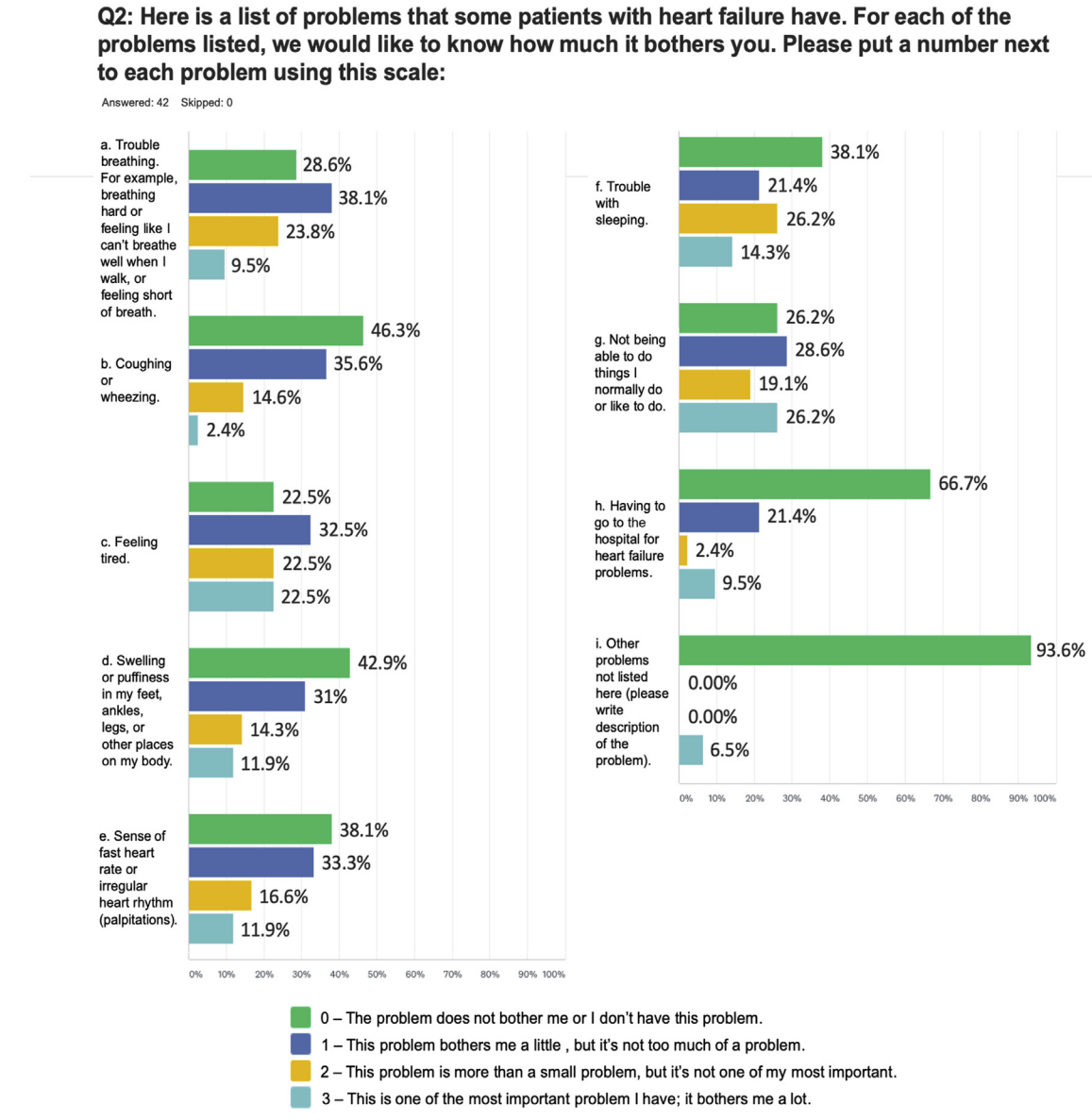



commonly used and validated HF disease-specific instruments are the Kansas City Cardiomyopathy Questionnaire (KCCQ) and the Minnesota Living with Heart Failure Questionnaire (MLHFQ). KCCQ captures how the patient feels through a 23-item questionnaire that explores six domains: symptoms, physical function, quality of life, social limitation, self-efficacy, and symptom stability. Similarly, MLHFQ captures the consequences of HF on a patient's life exploring 4 domains: physical symptoms and signs of HF, physical/social functions, psychosocial and cognitive function, and overall adverse impact on quality of life, through a 21-item questionnaire. Both KCCQ and MLHFQ score allow detection of treatment response and correlate with hospitalization and mortality (19,20). However, in one study, it was shown that no instrument fully assessed all of the quality of life domains that the HF patient experiences, including physical and mental/emotional symptoms, physical limitations, and social limitations. Nonetheless, PROs have shown to be more reproducible than other clinical trial measures, such as assessment of ejection fraction or valve gradients (21).

**Functional capacity and hemodynamics.** Various measures of functional capacity have been used to evaluate treatment effects in clinical trials, including the 6-min walk test (6MWT) and cardiopulmonary exercise testing (CPX or CPET). Assessment of exercise performance may serve as a clinical efficacy measure (intermediate endpoint) and/or as a predictor of clinical outcome (surrogate endpoint). Previous studies have shown that an increase of as little as 10% in functional capacity may be an acceptable marker of efficacy, and correlates with improvement in symptoms, activity of daily living, and quality of life. Metabolic exercise testing has been considered the "gold standard" for exercise assessment in HF patients. Studies have shown that peak $VO_2$ ($pVO_2$) can help to risk stratify HF patients, and may independently predict HF severity, death, HF hospitalizations, and serve as a basis for selection of transplant candidates (22). In addition to giving detailed insights on the pathophysiology of exercise limitation, CPX measures (e.g., $pVO_2$ and minute ventilation [VE]/$CO_2$ production [$VCO_2$] slope) are also accepted prognostic variables in HF (23). Recent studies have used these assessments as primary endpoints (24). However, important limitations have resulted in decreased use of CPX in clinical trials, including patient acceptability, need for costly equipment and specially trained personnel (25). The 6MWT is commonly used in clinical trials because of its simplicity, low cost, and strong correlation with HF outcome (HF severity, HF hospitalization) (26). This test is feasible in the majority of patients with HF, but can be influenced by several factors (e.g., patients' motivation and coaching). Cardiac resynchronization therapy trials used 6MWT in addition to other endpoints including New York Heart Association (NYHA) functional class, quality of life, exercise measures, and EF for premarket approval (27).

Additionally, simpler tests are under development. The 2-min hall walk test has shown good correlation with the 6MWT, but it is not yet validated in HF (28). The 4-meter walk test (Gait speed test) is another simple test that captures the risk of frailty rather than functional capacity and may be more appropriate for advanced HF studies (29). A 60-foot walk test has also

**FIGURE 3** Patient-Reported Perception of Heart Failure Symptoms

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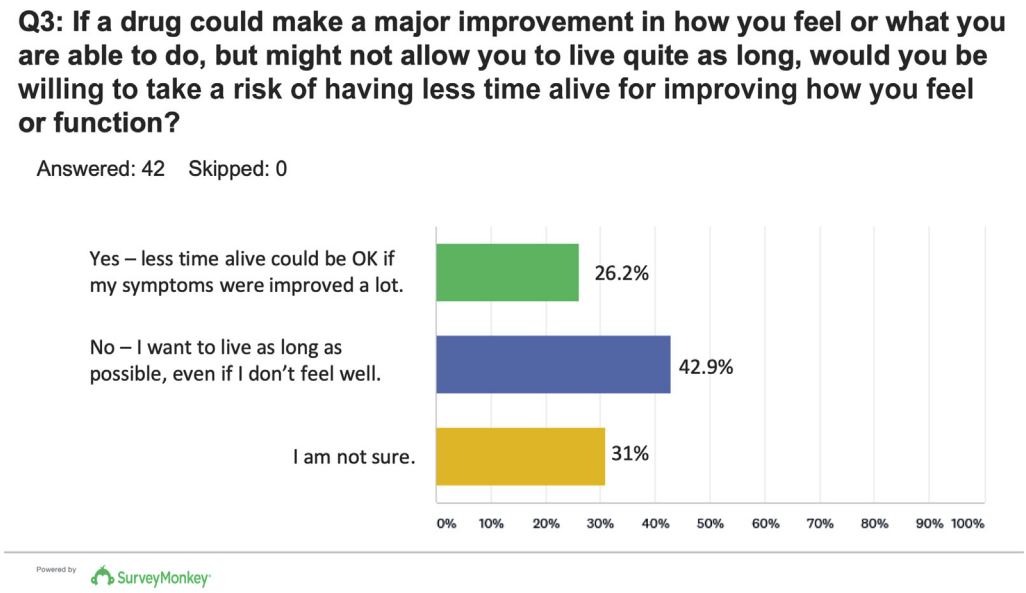
been proposed (30). There are a number of other key measures, such as frailty index measures and scores, grip strength, and other tools that may offer advantages in acutely ill, elderly, or frail populations.

Wearable devices such as accelerometers can be used to measure aspects of a patient's ordinary everyday activity (e.g., steps, intensity of activity, and METs) over long periods of time. Activity, as measured by these devices is influenced by motivation, including state of mind, as well as physical ability and thus represents an interesting potential endpoint in future trials. While activity determined by wearable accelerometers requires further study as a HF endpoint, data derived from cardiac implantable

**FIGURE 4** Patient Reported Perception of Quality Versus Quantity Trade-Off for Heart Failure Drugs




electronic devices (pacemakers and defibrillators) show a strong correlation between continuous measurement of activity changes and risk for HF hospitalization (31). With the influx of data from new technologies, standard methods for analysis are needed.

**Surrogate and intermediate endpoints.** A surrogate endpoint is a measure of a treatment effect that is expected to correlate with and predict a clinical benefit (i.e., how patients feel, function, or survive). For example, biomarkers such as natriuretic peptide levels and left ventricular EF are commonly used surrogate endpoints in HF. Hemodynamic improvements have supported short-term indications for inotropic drugs, although these are controversial because treatments exhibiting short-term hemodynamic benefits have sometimes led to an increased risk of death in the long-term (32). The challenge of using surrogate markers in HF is in part due to difficulty with validation. Unlike blood pressure in hypertension trials, biomarkers including natriuretic peptides have not been validated but appear promising (33–35).

Surrogate endpoints can be useful in small trials with multiple treatment groups and relatively short follow-up, where it can be difficult to power a trial for an endpoint based on symptoms, function, or survival. Thus, use of surrogate endpoints is not unusual in phase 2 trials—to evaluate early signals of benefit and to inform the dose selection and design of phase 3 trials. However, despite apparently beneficial effects on surrogate endpoints, many treatments have shown a neutral effect on morbidity and mortality in subsequent phase 3 trials (e.g., aliskiren) (36).

**The patient voice: HFSA/FDA survey results.** To inform our discussion on endpoints related to symptoms and function, the FDA collaborated with the Heart Failure Society of America (HFSA) to conduct a 3-question survey of patients who access the HFSA mobile application ("App") (Supplement). The survey explored patients' perceptions of: 1) overall HF symptoms and disability; 2) specific HF symptoms; and 3) the possible trade-off between quantity and quality of life. A 4-point scale was used for the first two questions on HF symptoms and quality of life (ranging from no symptoms to severe symptoms). The final question evaluated patients' preferences with respect to a potential trade-off between quantity and quality of life through three choices (yes; no; not sure).

Of a potential 650 patients who received the survey, there were 149 clicks of the link, and 42 patients completed the survey. About one-half the patients described their symptoms or disability as "mild," 30% as "moderate," and 10% as severe (**Figure 2**). The symptom reported most frequently as "one of the most important" was not being able to do activities of daily living. Second was "being tired" (**Figure 3**). This should be taken in the context of a majority of patients who completed the survey with mild or no disability or symptoms.

Patients were asked about perceptions regarding quality and quantity of life; that is, if a drug could make major improvements in how they feel, would they accept the risk that their life might be shortened for this improvement. Forty-three percent responded they wanted to live as long as possible, even if a drug could improve symptoms a lot (**Figure 4**). Twenty-seven percent responded that they would consider less time alive if their symptoms were improved a lot. Thirty-one percent responded that they were not sure about this potential trade-off. The finding that more than one-half of patients *might* consider a scenario of improved symptoms with a possible risk of reduced survival is notable, considering the relatively mild severity of symptoms in these patients, and supports previous literature on this subject (37).

These contemporary data align with results of similar studies reported during earlier eras of HF therapies, which show that, generally, the distribution of patient decisions regarding time trade-off is relatively bimodal. Most patients describe willingness to trade a large majority of their remaining time, particularly in sicker patients, or conversely, almost no time in exchange for better health (37–39). Few patients are undecided or between these positions. For hospitalized patients, the preference often increases toward survival after discharge but is relatively stable thereafter (37).

Individual patient preferences help to frame the margin of uncertainty that patients might accept around potential reduced survival associated with a drug that improves symptoms, function, and quality of life. For severely limited patients, it is unlikely that the difference between a 2% and 15% increased mortality would be meaningful in an informed decision to take a therapy to improve symptoms. On the other hand, for patients with NYHA functional class II symptoms, small differences in mortality risk might be highly important when considering a therapy to improve symptoms at this level (38).

## EVOLVING OPPORTUNITIES AND NEW DIRECTIONS

The new guidance reflects FDA's thinking regarding the importance of drugs that improve symptoms or physical function in HF. The guidance is intended to stimulate development of drugs for HF utilizing the totality of endpoints, and accelerate the availability of new therapies for patients in need. The HF community is hopeful that payers will recognize the importance of drugs that may demonstrate these improvements, and facilitate coverage and access for patients. Patient access to drugs following regulatory approval is controlled by complex interactions between governmental and third-party payers, pharmacy benefit managers, distributers, manufacturers, health systems, and pharmacies, but is a critical component of implementation and access for vulnerable populations. In addition to novel endpoints, the guidance reflects recommendations on assessing mortality in clinical trials, and highlights factors that will be considered in determining whether and when (pre- or post-approval) additional mortality data would be needed. For example, consideration will be given to the mortality and other safety findings of pharmacologically-similar drugs. The safety of certain drug classes such as ACE inhibitors, ARBs, beta blockers, mineralocorticoid receptor antagonists, and digoxin are well established. The safety of a new drug in these classes could be supported by existing data, and additional information on mortality might not be needed. In general, drugs with novel mechanisms of action will require greater reassurance with respect to mortality. Another consideration is planned duration of exposure. If the planned treatment is for short-term use (typically fewer than 10 days; e.g., treatment of acute exacerbations), there would generally be no requirement for long-term data. Finally, consideration will be given to mortality and other safety findings of the drug in a closely related population with HF or at risk of HF. For example, patients with coronary artery disease or long-standing diabetes are at risk for HF. Outcome studies in such populations could therefore be reassuring with respect to treatment of a HF population.

In addition to novel endpoints, novel study designs concepts such as Bayesian borrowing, risk-based monitoring, pooling doses, randomized withdrawal designs, and nested studies may improve the efficiency and speed of drug development and ultimately, increase availability of new therapies for HF patients.

## CONCLUSIONS

This review, we presented a summary of endpoints used for HF drugs approved in the United States. Drugs have been primarily approved on the basis of improved survival and reduced hospitalization, with only a few drugs approved on the basis of improvement in HF symptoms such as dyspnea and edema. Yet, HF patients experience a high burden of symptoms and functional limitations and report that improving their quality of life is something they value. In some cases, HF patients may consider

a possible risk of reduced time alive, or unknown risk, for improved quality of life. There remains an unmet need, despite successful therapies that improve morbidity and mortality. Drug development should include a focus on symptomatic and functional benefit in patients with HF, in addition to drugs that improve survival or reduce hospitalization.

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