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POSITION STATEMENT

Defining Clinically Meaningful Within-Patient Changes in Heart Failure

JACC: Heart Failure Position Statement

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HIGHLIGHTS

- Develop a framework to understand the relevance and interpretability of various outcomes.
- Synthesize the clinical relevance and interpretability of clinical outcomes to better support their interpretation by clinicians, regulators, industry, and—most importantly—patients.
- As win ratios and similar composite methods become more common in trial design, the paper calls for research into how patients actually weigh outcomes like death, hospitalizations, and quality of life againtst each other when they are combined into 1 ranked endpoint.

ABSTRACT

Heart failure (HF) clinical trials increasingly rely on diverse endpoints beyond mortality, including hospitalizations, imaging, hemodynamic status, biomarkers, functional capacity, and patient-reported outcomes. Although statistically significant differences between treatment groups are commonly reported, interpreting whether these changes are clinically meaningful for individual patients remains challenging. This *JACC: Heart Failure* position statement proposes a pragmatic framework for defining clinically meaningful within-patient change across commonly used HF outcomes by integrating measurement variability, prognostic associations, and patient-anchored evidence where available. Relative and absolute risk reductions should both inform interpretation of clinical events, while imaging, hemodynamic, biomarker, and functional measures require changes exceeding measurement variability and consideration of physiological context. Patient-reported health status measures, particularly the Kansas City Cardiomyopathy Questionnaire, currently have the strongest evidence supporting clinically meaningful thresholds. Many proposed cutpoints remain provisional, reflecting limited validation linking physiological changes to patient-perceived benefit or hard outcomes. Future work should prioritize anchor-based analyses and patient-centered validation to align trial results with shared decision-making. (JACC Heart Fail. 2026;■:103310) © 2026 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

6MWD = 6-minute walk distance

ARR = absolute risk reduction

CMR = cardiac magnetic resonance

CMWPC = clinically meaningful within-patient change

CPET = cardiopulmonary exercise testing

HFH = heart failure hospitalization

HFpEF = heart failure with preserved ejection fraction

HFrEF = heart failure with reduced ejection fraction

NNT = number needed to treat

NT-proBNP = N-terminal pro-B-type natriuretic peptide

PA = pulmonary artery

PADP = pulmonary artery diastolic pressure

PRO = patient-reported outcome

QoL = quality of life

RRR = relative risk reduction

WHF = worsening heart failure

Heart failure (HF) affects ~6.8 million adults in the United States alone, with numbers expected to rise because of an aging population, improved myocardial infarction survival rates, and increasing risk factors, including obesity, hypertension, and diabetes.[1] The impact of HF on patients' lives is profound, reducing their quality of life (QoL) and increasing their mortality and morbidity. As such, HF imposes enormous societal costs.[1,2]

Over the past several decades, there has been an explosion of research identifying novel interventions to improve HF care and outcomes. Although death is such an important outcome, for which any reduction would be considered meaningful, it is economically impractical for most clinical trials to enroll enough participants, and follow them long enough, to use death as a primary outcome. To maximize power and provide pathophysiological insights, myriad surrogate outcomes are used in HF trials. These include measures of resource use (heart failure hospitalizations [HFHs], emergency department visits, and worsening heart failure [WHF] in the outpatient setting), cardiac structural and physiological measures (echocardiography, magnetic resonance imaging, hemodynamic assessments, biomarkers), measures of patients' physical capacity (cardiopulmonary exercise testing [CPET], 6-minute walk distance [6MWD]), and health status measures using either clinicians' (NYHA functional class) or patients' (patient-reported outcomes [PROs], such as the Kansas City Cardiomyopathy Questionnaire [KCCQ]) perspectives. When clinical trials identify a statistically significant difference between treatment groups in these measures, it is important for providers and patients to understand the clinical importance of these differences between groups. However, the clinical significance of these improvements can be challenging to interpret, particularly for patients.[3-6] All measurements have variability and to define clinically meaningful within-patient change (CMWPC) requires separating the "noise" of repeated measurements from the "signal" of what magnitude of change would be considered important. Developing a framework to understand the relevance and interpretability of various outcomes measures is needed to describe the treatment benefits from clinical research to patients during shared decision-making.[7,8]

Accordingly, this position statement was commissioned by *JACC: Heart Failure* to synthesize the clinical relevance and interpretability of clinical outcomes to better support their interpretation by clinicians, regulators, industry, and, most important, patients. *JACC: Heart Failure* leadership identified the most used clinical trial outcomes measures and engaged experts in each outcome to describe the value and minimal CMWPC in these measures. When CMWPCs are not defined, considerations for future research to define these thresholds are provided (**Central Illustration**).

SEPARATING MEAN GROUP DIFFERENCES FROM CLINICALLY MEANINGFUL WITHIN-PATIENT DIFFERENCES

The greatest statistical power for continuous outcomes comes from comparing the mean differences between groups. Importantly, as shown in **Figure 1A**, although some trial participants get much worse (red), others do not change (yellow), and some get much better (green), there is no patient who experiences a blend of all 3 states (red head, yellow body,

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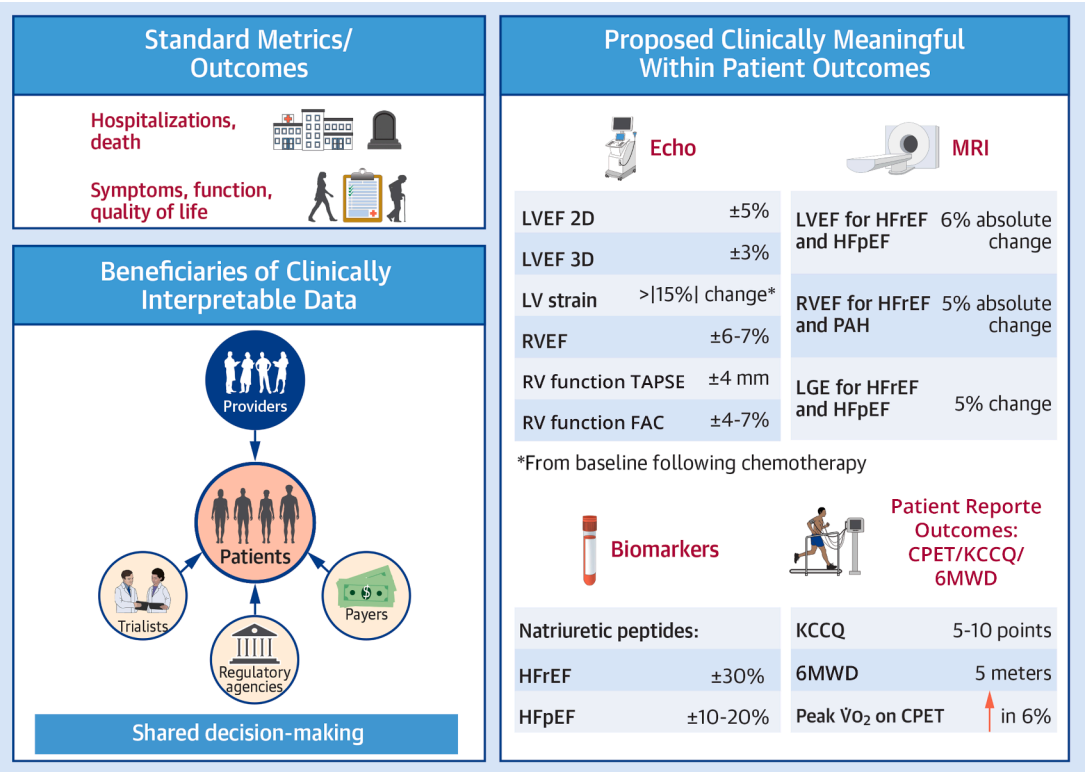
CENTRAL ILLUSTRATION **Clinically Meaningful Change Across Heart Failure Outcomes**



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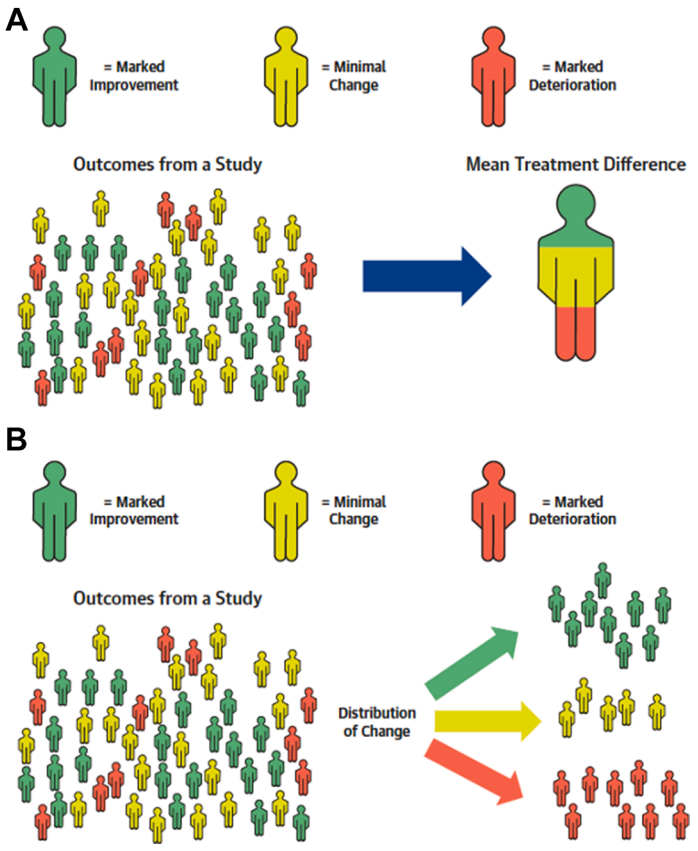
Standard metrics and outcomes in heart failure, including hospitalizations, death, symptoms, functional status, and quality of life, serve multiple beneficiaries of clinically interpretable data, including providers, patients, trialists, regulatory agencies, and payers, all in the context of shared decision-making. Proposed thresholds for clinically meaningful within-patient changes are presented across 4 domains: echocardiography, cardiac magnetic resonance imaging (MRI), biomarkers, and patient-reported outcomes. 2D = 2-dimensional; 3D = 3-dimensional; 6MWD = 6-minute walk distance; CPET = cardiopulmonary exercise testing; FAC = fractional area change; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; KCCQ = Kansas City Cardiomyopathy Questionnaire; LGE = late gadolinium enhancement; LV = left ventricular; LVEF = left ventricular ejection fraction; PAH = pulmonary arterial hypertension; RV = right ventricular; RVEF = right ventricular ejection fraction; TAPSE = tricuspid annular plane systolic excursion; $V\dot{O}_2$ = oxygen uptake.

and green legs). Thus, when providers and patients discuss the benefits of a treatment, it is difficult to explain how these mean differences are likely to affect the patient. In contrast, **Figure 1B** describes the proportions of patients who get better, or worse, from which the absolute risk reduction (ARR) and number needed to treat (NNT) can be calculated. Using the 12-week difference in KCCQ-Clinical Summary Scores (CCSs) between treatment arms of the EMPEROR-Preserved (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure With Preserved Ejection Fraction) as an example, the mean difference was 1.23 points (KCCQ score range: 0-100). Explaining the clinical significance of this to patients is almost impossible. However, the difference in proportions of patients with a clinically important improvement resulted in an NNT of 20 (95% CI: 14-40) and allows the clinician to say that, on average, for every 20 patients treated with empagliflozin, 1 felt significantly better than if they had all been treated with placebo.[9] A recent comparison between mean differences and the underlying distribution of patients experiencing different magnitudes of clinical change highlights this phenomenon.[10]

Defining CMWPC is difficult. A recent U.S. FDA (Food and Drug Administration) guidance document outlines strategies for supporting clinical outcomes assessments in regulatory submissions.[11] When formal anchor-based approaches are unavailable,

FIGURE 1 Mean Treatment Differences vs Distribution of Within-Patient Change



(A) Although mean treatment differences offer the greatest statistical power for continuous outcomes, they obscure the reality of individual patient experience. Although trial participants experience markedly better outcomes (green), minimal change (yellow), or markedly worse outcomes (red), no patient actually experiences a blend of all 3 states, making it difficult for providers and patients to meaningfully discuss the likely impact of treatment. (B) An alternative approach that describes the proportions of patients who improve or worsen, enabling the calculation of clinically intuitive metrics, including absolute risk reduction and number needed to treat, to facilitate shared decision-making.

alternative strategies have been used, such as Cohen's effect size, which considers a proportion of the SD of measurement (eg, 0.5× SD of baseline measures) as clinically important, along with other approaches. Some have used the association between changes in a measure and clinical events, such as mortality or hospitalization.[12] Although these define an association between the measure and clinical events, they are based on mean changes in scores and do not necessarily reflect what patients would consider a clinically important change in their health. In developing the insights collected in this report, distinguishing population-level mean differences and intraindividual differences was challenging. In fact, the estimates provided are often much larger than what is observed when comparing means between groups. For example, the intraindividual difference in left ventricular volume or function by echocardiography may appear very large compared with prior literature demonstrating associations of group-level mean differences with clinical events, until one considers whether they, or the patient, would consider those mean differences to be an important change in a patient's condition.

Any effort to estimate CMWPC is further complicated by the fact that the average changes in those who consider themselves to have had important improvements (or deteriorations) of different clinical magnitudes may differ among individual patients. This is an intractable problem that places increasing pressure on clinicians to have a deep understanding of clinical trial outcomes and their interpretation and how to present them to support patients' decision-making process. However, it also enables clinicians to tailor evidence to individual patients by eliciting patients' perspectives and priorities to improve the patient-centeredness of care.

CLINICAL EVENTS

Clinical events are generally considered the most important outcomes by trialists and regulatory agencies. Although reductions in clinical events often focus upon the relative risk reduction (RRR) associated with treatment, it is important to also consider the ARR, which can be converted into estimates of NNT. A common convention in pivotal trials is to consider a ≥15 to 20% RRR as clinically meaningful (Table 1). However, this approach overlooks the study population's baseline risk, such that the same RRR can reflect markedly different impacts on ARR and NNT. When baseline risk is high, smaller relative reductions (≈8%-12%) may still represent substantial clinical benefit if associated with meaningful ARRs. Across contemporary HF trials, an ARR of ~2% to 5% over 12 to 24 months, corresponding to an NNT of roughly 20 to 50, is generally associated with therapies that receive strong guideline endorsement. Conversely, larger RRRs observed in lower risk populations may yield modest absolute benefit and higher NNTs, underscoring the importance of evaluating treatment effects within the context of baseline risk, event rates, and follow-up duration. For example, the VICTORIA (Vericiguat Global Study in Subjects With Heart Failure With Reduced Ejection Fraction) trial reported a 10% RRR (HR: 0.90) in cardiovascular death or first HFH, which was deemed a modest benefit leading to a

TABLE 1 Primary Endpoints, Target Relative Effect Sizes, and Powering Assumptions in Recent Landmark HF Trials

Study (Year)	Target Population	N	Study Drug	Primary Endpoint	Predicted RRR and Power (β)
TOPCAT (2014)	HFpEF; LVEF ≥45%	3,445	Spironolactone vs placebo	Composite of CV death, aborted cardiac arrest, or HFH	20%; 80% power
FINEARTS-HF (2024)	HFmrEF/HFpEF; LVEF ≥40%	6,001	Finerenone vs placebo	Total (first and recurrent) HF events + CV death	19% (rate reduction); 90% power
PARADIGM-HF (2014)	HFrEF; LVEF ≤40% (amended to ≤35%)	8,442	Sacubitril/valsartan vs enalapril	CV death or HFH[a]	15%; >97% power
PARAGON-HF (2019)	HFpEF; LVEF ≥45%	4,822	Sacubitril/valsartan vs valsartan	Total (first and recurrent) HF events + CV death[b]	~22%; 95% power ~19%; 84% power
DAPA-HF (2019)	HFrEF; LVEF ≤40%	4,744	Dapagliflozin vs placebo	WHF (HFH/urgent visit with IV therapy) or CV death	20%; 90% power
DELIVER (2022)	HFmrEF/HFpEF; LVEF >40%	6,263	Dapagliflozin vs placebo	WHF (HFH/urgent visit with IV therapy) or CV death	20%; 93% power
EMPEROR-Reduced (2020)	HFrEF; LVEF ≤40%	3,730	Empagliflozin vs placebo	CV death or HFH	20%; 90% power
EMPEROR-Preserved (2021)	HFmrEF/HFpEF; LVEF >40%	5,988	Empagliflozin vs placebo	CV death or HFH	20%; 90% power

[a]Powered at 80% to detect a 15% RRR in CV death. [b]Powering based on 2 prespecified effect size scenarios for the primary endpoint.

β = type II error (1 − power); CV = cardiovascular; DAPA-HF = Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure; DELIVER = Dapagliflozin Evaluation to Improve the Lives of Patients With Preserved Ejection Fraction Heart Failure; EMPEROR-Preserved = Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Preserved Ejection Fraction; EMPEROR-Reduced = Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Reduced Ejection Fraction; FINEARTS-HF = Study to Evaluate the Efficacy (Effect on Disease) and Safety of Finerenone in Participants With Heart Failure and Left Ventricular Ejection Fraction (Proportion of Blood Expelled per Heart Stroke) Greater or Equal to 40%; HF = heart failure; HFH = heart failure hospitalization; HFmrEF = heart failure with mildly reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; IV = intravenous; LVEF = left ventricular ejection fraction; PARADIGM-HF = A Multicenter, Randomized, Double-Blind, Parallel Group, Active-Controlled Study to Evaluate the Efficacy and Safety of LCZ696 Compared to Enalapril on Morbidity and Mortality in Patients With Chronic Heart Failure and Reduced Ejection Fraction; PARAGON-HF = Efficacy and Safety of LCZ696 Compared to Valsartan, on Morbidity and Mortality in Heart Failure Patients With Preserved Ejection Fraction; RRR = relative risk reduction; TOPCAT = Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist; WHF = worsening heart failure.

class 2B guideline recommendation.[13] However, because VICTORIA enrolled a higher risk cohort, the 10% RRR translated into an ARR of ~4% and an NNT of 25, similar to other trials for which stronger guidelines' recommendations were endorsed.[14]

MORTALITY

Clearly death is of unquestionable clinical importance. However, depending upon the study population and duration of follow-up, it can be relatively rare. Although any statistically significant difference in mortality would be considered clinically important, many clinical trials are inadequately powered to examine mortality alone. Although some trials focus upon all-cause mortality, others use blinded endpoint adjudication committees to define cardiovascular death, on the basis of the rationale that the intervention is expected to specifically prevent cardiovascular causes of death. Although a focus on cardiovascular death would be ideal for the HF field, narrow endpoints affect power and trial feasibility.

WHF EVENTS

Determining the CMWPC for clinical outcomes such as HFH is challenging. Although HFH clearly represents an acute deterioration of patients' health status, this impact can be transient, with good health status before and after such an event.[15] Moreover, there is marked variability in clinical presentations triggering admissions for HF exacerbation between providers and health systems[16] or among those in clinical trials.[17] Accordingly, natural language processing and other techniques to define WHF are being adopted to capture nonhospitalized clinical encounters for WHF. These can not only potentially improve the consistency of detecting acute worsening of patients' HF but can also be more comprehensive, accounting for up to 50% of WHF events, and have a strong association with subsequent hospitalization or death.[18,19] From a societal perspective, hospitalizations and other forms of health care use, including WHF, such as emergency department visits and ambulatory encounters, are costly.[20] As a result, clinical trials are increasingly considering both HFH and WHF without hospitalization to develop a more consistent approach to capturing the broader spectrum of WHF.[21-24]

PHYSIOLOGICAL OUTCOMES AND CARDIOVASCULAR IMAGING

The advances in imaging techniques and the growing use of noninvasive hemodynamic assessments to supplement invasive hemodynamic measurements provide increasingly nuanced insights into cardiac anatomy and physiology. Although patients do not "feel" their ejection fraction, valvular dysfunction, or

cardiac fibrosis, these measures provide exquisite insights into disease progression and are often incorporated into clinical trials to identify mechanistic explanations for the improvements in other outcomes.

ECHOCARDIOGRAPHY. As a noninvasive imaging modality without appreciable risks or complications, echocardiography has been used in clinical trials for >70 years to better understand patients' anatomy, physiology, and disease severity.[25,26] Adverse remodeling and reverse remodeling reflected in noninvasive measures of left ventricular ejection fraction, left ventricular end-systolic volume, and left ventricular end-diastolic volume, have been the conventional parameters in multiple HF trials.[27,28] Defining a CMWPC in imaging is extremely challenging given the variability in estimates of cardiac structure and function related to: 1) an individual patient's imaging windows; 2) image acquisition techniques; 3) imaging equipment; 3) inconsistencies in measurement during image acquisition; 4) physiological variability over time; and 5) test-retest and interobserver and interobserver variability. Nonetheless, these measures are closely linked to cardiovascular outcomes and have become key surrogate endpoints for evaluating the therapeutic efficacy of contemporary treatments for HF.

It is commonly believed that meaningful changes (the "signal") should exceed measurement variability by ~1.5- to 2-fold to reflect "significant" changes in structure or function. **Table 2** provides proposed CMWPC that considers overall variability for different echocardiographic measurements. Importantly, the group mean differences for echocardiographic changes that have been associated with favorable clinical outcomes are lower than the meaningful patient-level changes in these parameters that are based upon measurement variability (Supplemental Table 1). Given the variability in imaging interpretation described earlier, each trial should explicitly estimate its interobserver variability in the measurements it describes (eg, 10% over-read by interpreters to define the agreement and magnitude of measurement uncertainty). Although the use of between-group differences exceeding the variability of measurement can be useful in understanding the clinical significance of observed differences in a specific trial, it limits the ability to compare such benefits across trials. Despite these limitations, given the low cost, high patient safety, and acceptance, and accessibility, there is a growing use of echocardiography in clinical trials. Cardiac chamber[29] and valvular[28,30-32] quantitation parameters have been advocated by imaging societies as possible trial endpoints. Understanding the variability of measurements, and the source of that variability, is important in trial design and outcome interpretation.

Beyond the challenges of measurement itself, the physiological variability of load-dependent parameters introduces additional challenges in measuring cardiac physiology, such left ventricular ejection fraction or valvular function. For instance, the severity of mitral regurgitation or tricuspid regurgitation is highly dependent on preload, afterload, and the influence of respirophasic or rhythm variability. All societal guidelines require a multiparametric, multimodality (ie, 2-dimensional, 3-dimensional, and Doppler) integration of parameters to result in a qualitative grade of regurgitant severity.[28,30-32] The Academic Research Consortium documents suggest cutoffs for hemodynamic bioprosthetic valve deterioration[33] and optimal reduction parameters for mitral regurgitation[34] and tricuspid regurgitation[35] listed in **Table 2**.

CARDIAC MAGNETIC RESONANCE. Cardiac magnetic resonance (CMR) is the imaging technique of reference for assessing cardiac anatomy. Compared with echocardiography, CMR is more accurate, precise, and reproducible when quantifying cardiac chamber dimensions. In HF trials, the most frequently used CMR markers of cardiac structure and function are left ventricular end-systolic volume and end-diastolic volume, ejection fraction, indexed left ventricular mass, and global longitudinal strain.[49] CMR is especially well suited for the quantifying right ventricular volumes, as the crescentic 3-dimensional shape of this chamber is challenging to assess using 2-dimensional echocardiography. In addition, CMR enables tissue characterization using late gadolinium enhancement and T1 mapping to assess interstitial fibrosis, while T2-weighted imaging and mapping can estimate myocardial edema, and T2* can quantify intramyocardial iron accumulation.[49] In various clinical trials using CMR to assess the therapeutic effect, the magnitude of change that has been reported for left ventricular volumes, function, and myocardial structure are provided in **Table 3**.[49] In **Table 4**, we provide the smallest detectable changes in cardiac remodeling in CMR with the associated clinical implications. However, the prognostic implication of those changes remains unclear and therefore it may be difficult to define a clinically important change of any of those parameters. Although CMR measurements are more reproducible than echocardiographic measurements, the

TABLE 2 Sample of Echocardiographic Parameters in Clinical Trials With Proposed Minimal Significant Change Based on Measurement Variability

	Specific Modality	Specific Parameter	Proposed CMWPD
LV dimensions	2D, 3D	LVIDd, LVIDs (cm)	2-3 mm
LV volumes	2D biplane or 3D[36]	LVEDV, LVESV (mL)	2D LVEDV: ±59 mL 2D LVESV: ±29 mL 3D LVEDV: ±35 mL 3D LVESV: ±14 mL OR Δ20% for LVDV
LV stroke volume[a]	3D	SV index (mL/m^2)[37]	±9 mL/m^2
LV mass	2D, 3D	LVM index (g/m^2)	2D LV mass[38] • ↑ ≥35 g (14.9%) or ≥19.3 g/m^2 (≥95% likelihood of a true ↑) • ↓ ≤32 g (−14.2%) or ≤17.8 g/m^2 (≥95% likelihood of a true ↓)
LV ejection	2D, 3D	LVEF (%)[36]	2D: ±5% 3D: ±3%
LV strain	Speckle tracking	LV GLS (|%|)	>|15%| change from baseline following chemotherapy[39]
LA volume	2D biplane	LA volume index (mL/m^2)[40]	±10 mL/m^2
LA filling pressure	Doppler, TDI, speckle tracking	E/e′ ratio, LA reservoir strain (%)[41]	LA reservoir strain >15% change or >2.5%
RV dimensions[ab]	2D (RV focused view)	$RVID_{base}$, $RVID_{mid}$ (mm)[37,42]	$RVID_{base}$: ±5 mm $RVID_{mid}$: ±4-6 mm
RV volumes[a]	3D	RVEDV, RVESV (mL)[37]	3D RVEDV: ±45 mL 3D LVESV: ±21 mL
RV stroke volume[a]	3D	SV index (mL/m^2)[37]	±11 mL/m^2
RVEF[ab]	3D	RVEF (%)[37,42]	±6%-7%
RV function[ab]	M-mode, 2D, TDI, speckle tracking, 3D	TAPSE (cm), FAC (%), s′ (mm/s), RVFWS (%)[37,42]	TAPSE: ±4 mm FAC: ±4%-7% TDI s′: ±2 mm/s RVFWS: ±4%-5%
RA volume[b]	2D method of discs, 3D (end-systolic)	RA volume index (mL/m^2)[42]	2D: ±6 mL/m^2 3D: ±7 mL/m^2
TR maximum[b]	Continuous-wave Doppler	TR peak velocity (m/s)[42]	±0.4 m/s
Aortic stenosis (native)	Doppler	AVA, V_{MAX}	ΔAVA ≥ 0.15 cm^2/y[43] ΔV_{MAX} ≥ 0.3 m/s/y[44]
Aortic stenosis[c] (bioprosthetic)	Doppler	Mean gradient, AVA, DVI	Stage 2 HVD[33] ↑ Mean gradient >20 mm Hg ↓ AVA ≥0.3 cm^2/m^2 or ≥20% ↓ DVI ≥0.1 or ≥25%
Mitral stenosis[c] (bioprosthetic)	Doppler	MVA, DVI	Stage 2 HVD[33] ↓ MVA ≥0.5 cm^2/m^2 or ≥25% ↓ DVI ≥0.4 or ≥20%
Mitral regurgitation[d]	Doppler	MR reduction	• Optimal reduction to trace or absent • Acceptable reduction of at least 1 class or grade from baseline and to no more than moderate (2+) in severity[34]
Tricuspid regurgitation[d]	Doppler	TR reduction	• Optimal reduction to mild or less [1+]) • Acceptable reduction to moderate or less [2+])[35]

[a]From normative data SD reported by Addetia et al.[45] [b]From normative data and differences between severity grades reported by Mukherjee et al.[42] [c]From the Heart Valve Society consensus documents for bioprosthetic valve dysfunction by Pibarot et al.[46] [d]From the definitions of technical device success of the Academic Research Consortium consensus (Stone et al[47] and Hahn et al[48]).

2D = 2-dimensional; 3D = 3-dimensional; AVA = aortic valve area; CMWPD = clinically meaningful within-patient difference; DVI = Doppler velocity index; E/e′ = ratio of mitral inflow early diastolic velocity to mitral annular early diastolic velocity; FAC = fractional area change; GLS = global longitudinal strain; HVD = hemodynamic valve deterioration; LA = left atrial; LVEDV = left ventricular end-diastolic volume; LVESV = left ventricular end-systolic volume; LVIDd = left ventricular internal diameter at end-diastole; LVIDs = left ventricular internal diameter at end-systole; LVM = left ventricular mass; MR = mitral regurgitation; MVA = mitral valve area; RA = right atrial; RVEDV = right ventricular end-diastolic volume; RVEF = right ventricular ejection fraction; RVESV = right ventricular end-systolic volume; RVFWS = right ventricular free wall strain; $RVID_{base}$ = right ventricular basal internal diameter; $RVID_{mid}$ = right ventricular mid-cavity internal diameter; s′ = tricuspid annular systolic velocity by tissue Doppler imaging; SV = stroke volume; TAPSE = tricuspid annular plane systolic excursion; TDI = tissue Doppler imaging; TR = tricuspid regurgitation; V_{MAX} = maximum aortic jet velocity; other abbreviation as in Table 1.

human test-retest variability of the measurement of wall thickness with CMR, for example, is still inferior to that of artificial intelligence-based tools.[50]

CARDIAC HEMODYNAMIC STATUS. Hemodynamic data remain clinically relevant trial endpoints, as they represent the direct cause of symptoms (affecting congestion and perfusion), and they are associated with morbidity, mortality, and readmission, as well as the pathophysiological insights they can provide to define the mechanism of the HF syndrome. The interpretation of cardiac hemodynamic status varies by HF acuity, severity, and etiology (eg, heart failure with reduced ejection

TABLE 3 Representative Treatment Responses as Assessed With CMR in Clinical Trials

	Disease	Time Horizon, mo	Natural History	Treatment	Difference
LVEDVi, mL/m^2	HFrEF	6-12	+6 to 2	−2 to 24	~10
	HFpEF	12	−3	−2	~0
	Iron overload	12	+1 to 1	−6 to 8	~5
	Cardio-oncology	24	+4 to 1	+8 to 5	~2
LVESVi, mL/m^2	HFrEF	6-12	+6 to 4	−5 to 26	~5
	HFpEF	12	−3	−2	~0
	Iron overload	12	−1	−5 to 6	~5
	Cardio-oncology	24	+2 to +6	0 to +5	~0
LVMi, g/m^2	HFrEF	6-12	+6 to 15	−3 to 15	~2
	HFpEF	12	0	−1	~2
	Amyloidosis	12	+1 to +8	−4 to +6	~5
	HCM	7	−2	−17	~16
	Cardio-oncology	24	0 to +1	0 to +1	~0
EF, %	HFrEF	6-12	+1	+5 to +8	~5
	HFpEF	12	0	+1	~2
	Amyloidosis	12	−3 to 8	0	~3
	Iron overload	12	0 to +1	0 to +3	~2
	HCM	7	0	−5	~6
	Cardio-oncology	24	−2 to 5	−1 to 3	~2
ECV, %	HFrEF	8	−0.7	−0.8	~0
	HFpEF	12	+0.5	−0.7	~1
	Amyloidosis	12	+4 to +5	+2 to 0	~5
	HCM	7	0	0	~0
T2*, ms	Iron overload	12	+1 to +3	+1 to +6	~2

Values are the range of mean change in untreated (natural history) and treated patients (treatment) for the studies listed in Supplemental Table 1. The difference approximates the average treatment response across studies for illustration purposes. Reproduced with permission from Benz et al.[49]

CMR = cardiac magnetic resonance; ECV = extracellular volume; EF = ejection fraction; GLS = global longitudinal strain; HCM = hypertrophic cardiomyopathy; LVEDVi = left ventricular end-diastolic volume index; LVESVi = left ventricular end-systolic volume index; LVMi = left ventricular mass index; other abbreviations as in Table 1.

fraction [HFrEF], heart failure with preserved ejection fraction [HFpEF]), rendering the interpretation of CMWPCs challenging.[59,60] Although the expanse of research in cardiogenic shock in the past decade has contributed greatly to our understanding of the association of cardiopulmonary hemodynamic parameters[61,62] with outcomes in patients with cardiogenic shock due to acute myocardial infarction, fewer prognostic data are available for patients with cardiogenic shock. Patients with long-standing HF, for example, may present with higher mean pulmonary artery (PA) pressures than those with acute HF due to compensatory myocardial adaptations to pulmonary hypertension.[60] Decompensated chronic HF often displays fewer acid-base disturbances than acute HF, as patients with chronic HF often compensate for chronically low cardiac output (CO) through better peripheral oxygen extraction (manifested as mixed venous oxygen saturation) and better acid buffering.[59,60] Thus, establishing absolute thresholds to use as minimally important differences in clinical trials across the spectrum of HF is challenging. Nonetheless, thresholds chosen herein may be clinically relevant, as they signify favorable

TABLE 4 Clinical Implications That Are Associated With the Smallest Detectable Changes in CMR

	Parameter Measured	Smallest Detectable Change	Associated Clinical Outcomes
HFrEF, HFpEF	LVEF	6% absolute change (1 y)	SDC ≥6% linked to risk for cardiac events, mortality, and hospitalization[51,52]
HFrEF, HFpEF	LVEDV	13-mL absolute change (1 y)	SDC ≥13 mL associated with incident HF and adverse prognosis[52-54]
HFrEF, HFpEF	LVESV	7-mL absolute change (1 y)	SDC ≥7 mL associated with mortality risk and HF progression[52-54]
HFrEF, HFpEF	LVM	6-g absolute change (1 y)	SDC ≥6 g associated with mortality and adverse remodeling[52,55]
HFrEF, HFpEF	ECV	2%-3% absolute change	SDC ≥2%-3% associated with incident HF, hospitalization, and mortality[54,56]
HFrEF, HFpEF	Late gadolinium enhancement	5% absolute change in fibrosis extent	SDC ≥5% associated with increased mortality and arrhythmic risk[54,55]
HFrEF, PAH	Right ventricular volume	10- to 17-mL absolute change	SDC ≥10-17 mL associated with functional status and survival[54,57]
HFrEF, PAH	RVEF	5% absolute change	SDC ≥5% associated with mortality and clinical worsening[54,57]
HFpEF	LA volume	8- to 10-mL absolute change	SDC ≥8-10 mL associated with exercise capacity and HFpEF diagnosis[58]
HFpEF	RA volume	8- to 10-mL absolute change	SDC ≥8-10 mL associated with functional status and HF progression[58]

PAH = pulmonary arterial hypertension; SDC = smallest detectable change; other abbreviations as in Tables 1-3.

trajectories in hemodynamic status, but future research is needed to better define what constitutes a CMWPC in each clinical scenario.

METRICS OF CONGESTION AND ASSOCIATED VENOUS HYPERTENSION. In patients admitted with acute decompensated HF, the presence of persistent congestion (high right atrial pressure or pulmonary capillary wedge pressure >20 mm Hg) on final invasive hemodynamic measure was associated with higher rates of readmission or death at 3 to 6 months.[59,63-66] In the ESCAPE (Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness) trial, a final pulmonary capillary wedge pressure >20 mm Hg (HR: 2.0; 95% CI: 1.3-3.2) or elevated right atrial pressure (HR: 1.09 per mm Hg; 95% CI: 1.06-1.12 per mm Hg) were associated with worse HF outcomes at 6 months.[67] In a smaller but more contemporary study restricted to patients with cardiogenic shock, survival to discharge was superior for patients with a greater change in right atrial pressure from baseline to device removal (−6.5 ± 6.9 mm Hg vs −2.5 ± 6.2 mm Hg). In multivariable modeling, the presence of lower right atrial pressure (10 mm Hg vs 16 mm Hg) or lower pulmonary capillary wedge pressure (17 mm Hg vs 24 mm Hg) on final hemodynamic assessment was more important than absolute differences from baseline.[68]

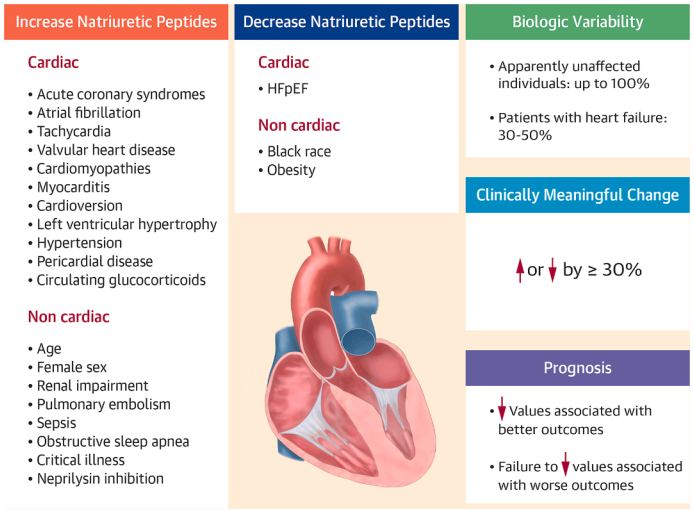
HEMODYNAMIC STATUS IN AMBULATORY PATIENTS WITH HF. Studies have shown that relatively minor increases in pulmonary artery diastolic pressure (PADP) precede acute decompensated HF events by weeks to months, even in the absence of weight changes. In patients with HFrEF, PADP increased from 21 to 24 mm Hg prior to decompensation in HFrEF and from 17 to 22 mm Hg in patients with HFpEF.[69] In a retrospective analysis of 3 implantable hemodynamic monitoring trials, Zile et al[70] demonstrated that each 5 mm Hg increase in estimated baseline PADP was associated with a 38% increase in risk for death. Importantly, changes in PADP were also associated with subsequent mortality. Increases in PADP from baseline to 6 months of 3, 4, and 5 mm Hg were associated with 23.8%, 32.9%, and 42.8% increased risk for death. Conversely, 3, 4, and 5 mm Hg decreases in PADP over 6 months were associated with 19.2%, 24.8%, and 30.0% decreases in the risk for death.[70] In a more recent and much larger analysis from multiple implantable hemodynamic monitoring studies (n = 4,342), a 2 mm Hg or greater decrease in PADP over 6 months was associated with a 14.7% decrease in all-cause mortality, whereas a 2 mm Hg or greater increase in PADP was associated with a 26.7% higher mortality.[71]

Implantable hemodynamic monitoring trials have also shown changes in PADP to be associated with HFH.[72,73] In the EMBRACE (Empagliflozin Evaluation by Measuring Impact on Hemodynamics in Patients With Heart Failure) trial (predominantly HFrEF), a linear relationship was found between change in PADP and patient-reported health status. After adjusting for baseline KCCQ score, each 2 mm Hg reduction in PADP was associated with a 2.1-point (95% CI: 0.2-4 points) improvement in the KCCQ-Total Symptom Score.[74] In patients with HFpEF, treatment with dapagliflozin for 24 weeks decreased pulmonary capillary wedge pressure at rest by −3.5 mm Hg (95% CI: −6.6 to 0.4 mm Hg; $P = 0.029$).[75] In another HFpEF trial enrolling the same phenotype of patients, dapagliflozin for 12 weeks increased KCCQ score by 5.8 points (95% CI: 2.3-9.2 points; $P = 0.001$) and increased 6MWD by 20.1 m (95% CI: 5.6-34.7 m; $P = 0.007$).[76] Whether improvements in KCCQ score are directly attributable to changes in pulmonary capillary wedge pressure or other factors will require further studies.

EXERCISE HEMODYNAMIC STATUS. Clinical trials are increasingly using exercise hemodynamic parameters as primary endpoints to evaluate efficacy for drugs and devices.[75,77-84] Although blood delivery from the heart is quantified by CO and cardiac index, robust studies have failed to demonstrate a significant prognostic association in patients with HF, largely because perturbation in end-organ function can be highly variable at different levels of CO and cardiac index.[59] The ability to increase CO is highly prognostic in HF, in both HFrEF and HFpEF.[85,86] In 1 study of HFrEF, patients with a reduced CO slope relative to oxygen uptake ($pV\dot{o}_2$) during exercise had a 1-year survival of 72%, compared with 95% in those with a normal CO response ($P < 0.0001$). In HFpEF, there was no association between resting CO and risk for death or HFH (HR: 0.89; 95% CI: 0.73-1.08), but each 1-SD increase in the ability to augment CO with exercise was associated with a 50% reduction in risk (HR: 0.50; 95% CI: 0.39-0.64).

Elevations in PA pressure and PA wedge pressure during exercise lead to pulmonary congestion, impairments in exercise capacity, symptoms of dyspnea, and increased risk for HFH or death, making exercise PA pressure an important therapeutic target. Each 5 mm Hg elevation in supine exercise PA wedge pressure in HFpEF is associated with 58% increased

FIGURE 2 Factors That Influence Natriuretic Peptide Levels, Biologic Variability, Clinically Meaningful Change, and Prognostic Implications



Natriuretic peptides (NT-proBNP and BNP collectively) are elevated by numerous cardiac and noncardiac conditions and are reduced in heart failure with preserved ejection fraction (HFpEF), Black race, and obesity. Biological variability ranges up to 100% in apparently unaffected individuals and 30% to 50% in patients with HF. A change of ≥30% in either direction is proposed as the threshold for clinically meaningful within-patient change. Declining values are associated with better outcomes, whereas failure to decrease portends worse prognosis. BNP = B-type natriuretic peptide; HF = heart failure; NT-proBNP = N-terminal pro- B-type natriuretic peptide

risk for HFH or death,[86] while upright exercise PA pressure and PA wedge pressure indexed to CO >3 and 2 mm Hg/L/min predict HFH or death.[87,88] In the CAMEO DAPA (Cardiac and Metabolic Effects of Dapagliflozin in Heart Failure With Preserved Ejection Fraction) trial, dapagliflozin treatment for 6 months reduced PA wedge pressure by −5.7 mm Hg (95% CI: −10.8 to 0.7 mm Hg; $P = 0.027$) at peak exercise,[75] while also decreasing PA wedge pressure at low-level work load, which was coupled with reductions in respiratory rate, minute ventilation, ventilatory drive, and lactate production, objective evidence for symptom relief.[89] A smaller number of trials have included resting or exercise CO as primary or key secondary endpoint, showing statistical significance at effect sizes as low as 0.2 L/min, though the clinical significance for this degree of change remains unknown.[82,83,90]

Thus, on the basis of existing evidence, relatively mild decreases in left heart filling pressures, PA diastolic pressure, or PA mean pressure of only 2 to 4 mm Hg over the course of weeks to months are associated with favorable effects on patient-reported health status, reductions in risk for WHF, and lower mortality rates. As PA pressure and PA wedge pressure are higher during exercise, somewhat higher reductions may be required to realize clinical benefits, on the order of 4 to 6 mm Hg.

Invasive and noninvasive hemodynamic measurements are subject to important technical and interpretative limitations that complicate their use as clinical trial endpoints. Measurements such as intracardiac filling pressures and CO vary by conditions, respiratory variation, catheter positioning, measurement technique, and assumptions used for derived variables, introducing both interobserver and intraobserver variability.[91] Furthermore, single-time point measurements incompletely reflect the dynamic nature of HF physiology, particularly in chronic HF, in which compensatory adaptations alter the relationship between measured hemodynamic parameters and symptoms or end-organ perfusion. Consequently, associations between absolute hemodynamic values and clinical outcomes have been inconsistent across studies and HF phenotypes, emphasizing the need to interpret these parameters within clinical context and to prioritize trajectories or changes over time rather than isolated thresholds.[65]

BIOMARKERS. Biomarkers have emerged as essentials tools for quantifying neurohormonal activation and HF pathophysiological processes. Natriuretic peptides, including B-type natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP),[92] are the most established biomarkers and serve as indicators of elevated intracardiac filling pressures and myocardial wall stress, thereby aiding in the diagnosis, prognostication, and therapeutic guidance of patients with HF.[92] Current guidelines recommend measuring BNP or NT-proBNP to support the diagnosis of HF in patients presenting with dyspnea, for risk stratification in chronic HF, and for establishing prognosis in hospitalized patients.[93-95] Relatively little is known about what represents a CMWPC for most biomarkers, with natriuretic peptides having the most information in this regard and will be the focus herein. In those with established diagnoses of HF, absolute BNP concentrations <200 ng/L or NT-proBNP concentrations <1,000 ng/L are prognostically favorable, with better health status, more reverse cardiac remodeling, and lower event rates.[96-98] Unlike clinical outcome measures such as health status and walking distance, the factors determining CMWPC for biomarkers are far more complex, as there are matters of biological variation that underlie their production or release (Figure 2). Reframing the question to how much change in BNP or

NT-proBNP without a difference in clinical status is a potentially more appropriate way to approach this issue.

In studies that included persons with chronic HF, the reference change value, defined as the percentage reduction from baseline necessary to achieve significance for change in biomarker concentration, for day-to-day and week-to-week measurement was found to be 38% and 71% for BNP and 27% and 47% for NT-proBNP, respectively.[99-104] Despite the variability in these reference change values, the use of a clinical change value of ~30% (increase or decrease) has been supported by data to represent a reasonable prognostic threshold.[104-108] For example, in Val-HEFT (Valsartan Heart Failure Trial), 5,010 patients with chronic stable HFrEF had baseline and 4-month NT-proBNP levels measured.[109] A percentage increase of NT-proBNP >33% represented the highest mortality category.[109] Similar findings were recently demonstrated from the GUIDE-IT HF (Guiding Evidence Based Therapy Using Biomarker Intensified Treatment in Heart Failure) trial, in which NT-proBNP increases ≥30% were seen months ahead of and were significantly associated with, clinical events, independent of measured confounders. For example, each doubling of serially measured NT-proBNP prior to an event was independently associated with an HR of 1.66 (95% CI: 1.50-1.84; $P < 0.0001$) for cardiovascular death or HFH.[110] In HFpEF, even smaller relative changes may be meaningful. In the STEP-HFpEF (Semaglutide Treatment Effect in People With Obesity and Heart Failure With Preserved Ejection Fraction) program, semaglutide caused a 20% decrease in NT-proBNP, which was coupled with marked improvements in KCCQ-CSS and 6MWD.[111] In SUMMIT (Study to Understand Mortality and Morbidity in Heart Failure), a nominally significant 10% decrease in NT-proBNP was coupled with a 38% decrease in the risk for HFH or cardiovascular death.[112]

In those with acute HF, lower post-treatment natriuretic peptide concentrations are associated with better prognosis, typically when such values are accompanied by a pre- to post-treatment decrease of ≥30%,[108] which is similarly prognostic in both preserved and reduced ejection fraction. Recent clinical practice guidelines provided a class 2a recommendation for using a ≥30% post-treatment BNP or NT-proBNP to prognosticate postdischarge events.[92,113]

Thus, on the basis of the existing evidence, there are several considerations for the use of biomarkers in clinical practice. First, regardless of the percentage change noted, in all populations studied, lower natriuretic peptide levels are consistently associated with better prognosis, whereas higher levels are associated with worse outcomes. Failure to demonstrate natriuretic peptide lowering after treatment represents a high-risk population. Furthermore, change in natriuretic peptides is affected by numerous factors, including age, HF etiology, atrial fibrillation, and comorbidities, which should be contextualized when serially measuring BNP or NT-proBNP. Finally, although the reference change value for BNP and NT-proBNP may be as high as a 100% increase or a 50% reduction in apparently unaffected individuals and between 30% and 50% in those with HF, a clinically meaningful change value appears to be a rise or fall of ≥30%.

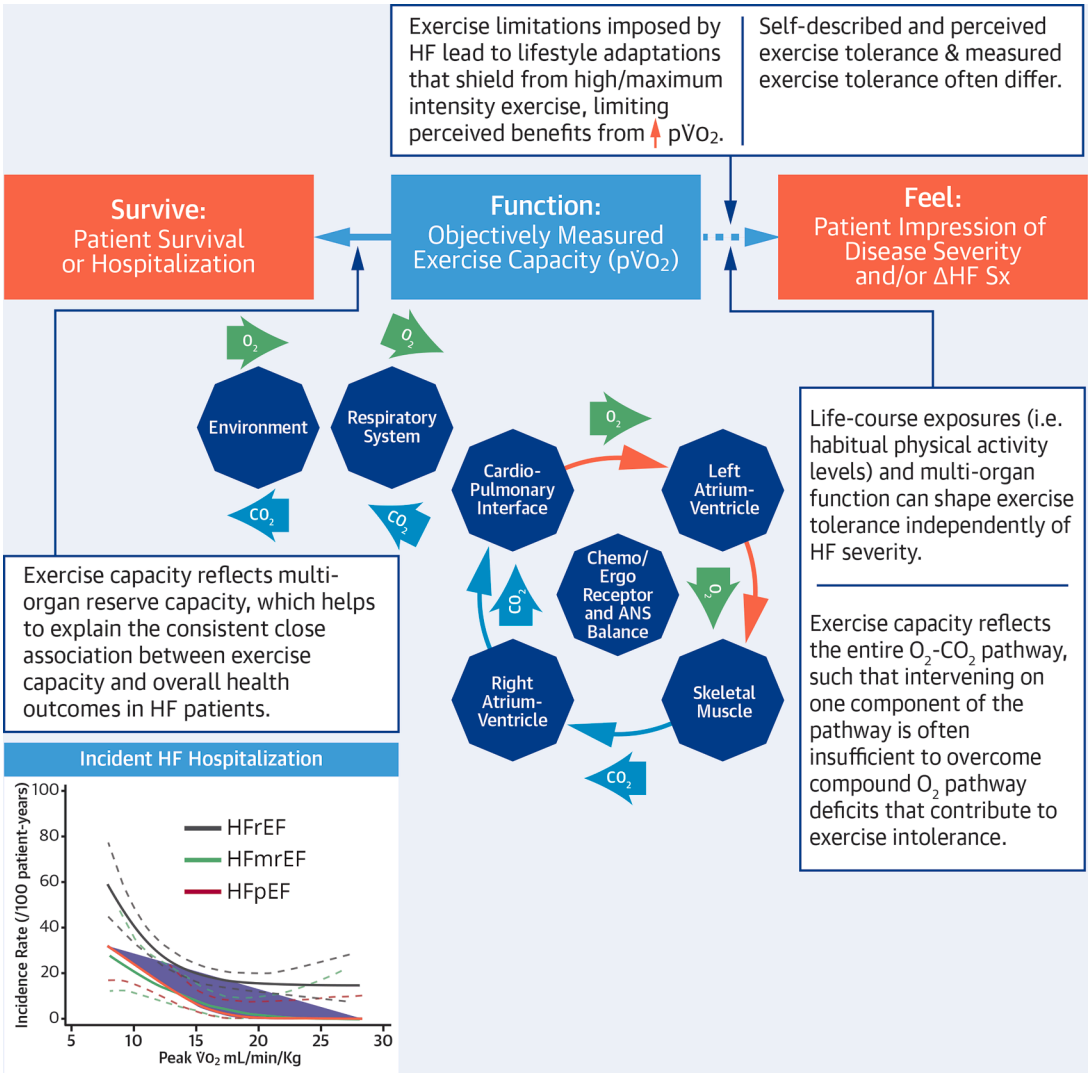
FUNCTIONAL ASSESSMENTS

Although the terms *exercise capacity* and *functional capacity* are often used interchangeably, they refer to the response to different levels of physical exertion.[114] Exercise capacity is typically defined as the "maximum amount of physical exertion that a subject can sustain," whereas functional capacity is the "ability to perform activities of daily living that require sustained, submaximal aerobic metabolism."[115] As outlined in a 2019 FDA document titled "Treatment for Heart Failure: Endpoints for Drug Development Guidance for Industry,"[116] changes in functional capacity, such as walking or performing activities of daily living, can be used to assess the effectiveness of HF therapies.

CPET. CPET is generally considered to be the gold-standard approach for assessing exercise capacity[117-119] (**Figure 3**). CPET can both risk-stratify subsequent HF events and evaluate exertional symptomatology and disease severity using peak $pV\dot{o}_2$.[117,118,120] At the average level of impairment in exercise experienced by patients with symptomatic HF, modest relative increments in exercise capacity markedly change what activities patients can "afford" to do (**Figure 4**).[121] Therefore, improvements beyond repeated measurement variance (~6% for peak $pV\dot{o}_2$),[122] of a magnitude associated with survival advantage (also ~6% for peak $pV\dot{o}_2$),[123] are often considered clinically important and used to design HF trials.[124]

On behalf of the Heart Failure Collaboratory-Academic Research Consortium Scientific Expert Panel, Psotka et al[125] reported on functional and clinical trial endpoints. Regarding CPET, and in particular peak $pV\dot{o}_2$, the panel concluded that: 1) "CPET measurements are established functional endpoints;" 2) remote capture of CPET data is

FIGURE 3 Inter-Relatedness of Functional Capacity to Other Clinically Important Assessment Domains in HF



Conceptual model for cardiovascular, pulmonary, and systemic circuits involved in gas exchange from the atmosphere to skeletal muscle. ANS = autonomic nervous system; HFmrEF = heart failure with mildly reduced ejection fraction; HFrEF = heart failure with reduced ejection fraction; $pV\dot{o}_2$ = peak oxygen consumption; $V\dot{o}_2$ = oxygen consumption; other abbreviations as in Figure 2.

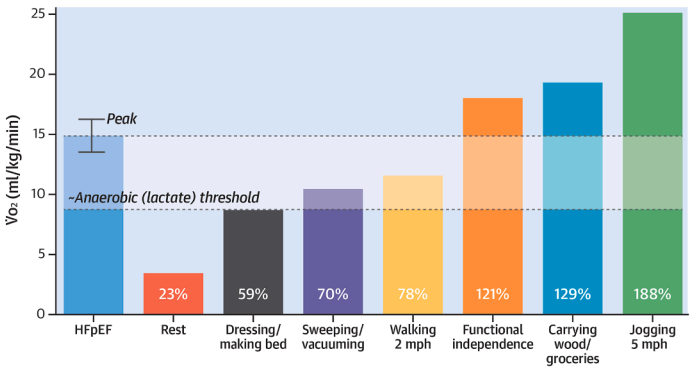
infeasible because of the specialized equipment required; and 3) "meaningful difference in peak VO_2 has been reported as a 6% change or 1 $mLO_2 \cdot kg^{-1} \cdot min^{-1}$ in patients with substantially reduced baseline exercise tolerance, based upon test-test variability of CPET assessment rather than clinical improvements that patients can detect as meaningful." The last statement highlights the paucity of data defining CMWPCs in peak $pV\dot{o}_2$ in relation to perceived symptoms of HF. There are several reasons for this. First, traditional anchoring measures, such patient's global impression of severity and patient's global impression of change, have not been routinely ascertained in HF trials focused on change in peak $pV\dot{o}_2$. Second, to perform symptom-linked CMWPC analyses, a correlation coefficient >0.3 between changes in the variable of interest and the anchor is advised. Although peak $pV\dot{o}_2$ is an important measure of cardiopulmonary function, its correlation with QoL metrics is modest. The HF-Action (Heart Failure—A Controlled Trial Investigating Outcomes of Exercise Training) trial in HFrEF was 1 of the few

studies to estimate the change in $pV\dot{o}_2$ associated with a CMWPC, defined as a 5-point change in KCCQ-Overall Summary Score (OSS). The correlation between changes in both measures was 0.31, and a 5-point change in KCCQ score was associated with a 2.5 mL/kg/min change in peak $pV\dot{o}_2$, substantially larger than the 6% CMWPC assessed by measurement variance and the association with mortality.[126] In contrast, in HFpEF, 1 trial showed that exercise training produced a much more modest 0.8 mL/kg/min improvement in peak $pV\dot{o}_2$ that was coupled with a 5.5-point improvement in KCCQ-OSS, suggesting that associations with aerobic capacity and QoL may differ by HF phenotype.[127]

Ventilatory efficiency is commonly assessed during CPET as the minute ventilation/carbon dioxide production slope. The minute ventilation/carbon dioxide production slope is resistant to variations in subject effort during CPET and may provide greater accuracy in assessing the magnitude of HF severity.[128] Currently, there are no studies defining the CMWPC of minute ventilation/carbon dioxide production slope in patients with HF. The modest correlation between how patients "feel" and how patients "function" underscores the importance of assessing both domains independently, as each provides clinically meaningful insights into HF prognosis.

6MWD AND ACTIGRAPHY. The 6MWD test is a widely used tool in clinical and research settings to assess functional capacity and monitor treatment responses in patients with HF. Importantly, it is reliable, reproducible, and inexpensive, and the personnel training required is minimal compared with CPET. An estimate for a CMWPC, on the basis of a 5-point change in KCCQ-OSS, was observed in HF-ACTION (CMWPC = 112 m; correlation between changes in both measures = 0.31),[126] but this may have been influenced by the intervention being exercise, with a baseline 6MWD of 365 m. In iron-deficient patients with HFrEF in the FAIR-HF (Ferinject Assessment in Patients With Iron Deficiency and Chronic Heart Failure) and CONFIRM-HF (Ferric Carboxymaltose Evaluation on Performance in Patients With Iron Deficiency in Combination With Chronic Heart Failure) trials,[129,130] changes in 6MWD were correlated with changes in patient global assessment at 24 weeks more so than 12 weeks ($r = 0.43$ and $r = 0.31$, respectively), with an estimated CMWPC in 6MWD of 14 to 15 m. Analyses from the STEP-HFpEF trial demonstrated that smaller changes in KCCQ-CSS and in 6MWD ($P < 0.0001$) were clinically meaningful, with a 5-point increase in KCCQ-CSS associated with an increase of about 5 m in 6MWD.[131]

FIGURE 4 $V\dot{o}_2$ **Requirements for Specific Physical Activities Relative to HFpEF Functional Capacity**



The bar graph depicts the $V\dot{o}_2$ required to perform common physical activities. Abbreviations as in Figures 2 and 3.

Despite its simplicity and ability to predict clinical events and detect treatment effects, 6MWD is likely not as sensitive as peak $pV\dot{o}_2$. For example, in the HF-ACTION trial, a 12-month exercise training program improved peak $pV\dot{o}_2$ and clinical outcomes in patients with HFrEF, whereas 6MWD remained unchanged.[132] A potential explanation may be the increased variability of 6MWD from the effects of variable patient effort and the motivation created by the testers. Heightened variability in repeated measures of 6MWD compared with peak $pV\dot{o}_2$ has also been observed in HFpEF trials that measured both 6MWD and peak $pV\dot{o}_2$, with variable relative effect sizes of exercise training observed on the 2 measures.[133] In addition to the 6MWD test, actigraphy via noninvasive wearable or implantable devices represents a promising method to estimate functional capacity.[134] In the NEAT (Nitrate's Effect on Activity Tolerance in Heart Failure With Preserved Ejection Fraction) trial, isosorbide mononitrate was shown to modestly decrease activity levels compared with placebo in patients with HFpEF, with an apparent dose response.[135] Actigraphy provides objective data on daily steps count, activity intensity (light, moderate, vigorous) and duration, sedentary behaviors,[136,137] and sleep patterns,[138] without reliance on self-reports. However, there is a lack of standardization across different actigraphy devices,[125] with a large data variability across studies. Exemplifying the challenge, step counts, but not floors climbed, on the Fitbit Versa 2 were associated with changes in KCCQ score but in a nonlinear fashion. There is a compelling need for additional rigorous actigraphy-related

research in HF to understand how routine activity can best be measured and interpreted.[139]

PATIENT-REPORTED HEALTH STATUS OUTCOMES

Quantifying the impact of novel treatments on health status outcomes, patients' symptoms, function, and QoL, has become increasingly common since the FDA clarified its role in drug approval and labeling.[140] This has been an important advance, given that patients often prioritize their health status outcomes as highly as, or even higher than, clinical events of mortality and hospitalizations.[141,142] Although there are many disease-specific PROs for patients with HF, KCCQ score has emerged as the most common PRO because of its qualification by both the drug and device divisions of the FDA.[143-145]

Although interpreting a continuous measure such as KCCQ score (range: 0-100, with higher scores indicating fewer symptoms, better function, and higher QoL) can be challenging, extensive work has been conducted over the past 20 years to translate scores into clinically meaningful concepts.[146] Cross-sectionally, the most common approach is to categorize KCCQ score into 25-point ranges (ie, 0-24, 25-49, 50-74, and 75-100) that represent very poor to poor, poor to fair, fair to good, and good to excellent health status and have been shown to be strongly associated with subsequent mortality and hospitalization.[146-150] Given the interphysician variability in assigning NYHA functional classifications, it is hard to exactly map KCCQ score to NYHA functional classes,[151,152] but KCCQ-OSSs of <45, 45 to 60, >60 to <80, and ≥ 80 roughly correlate with NYHA functional classes IV, III, II, and I, respectively.

More relevant to clinical trial outcomes is interpreting the change in KCCQ score to quantify the benefits of treatment. From clinicians' perspectives, changes of 5 to <10 points are considered small but clinically important changes, while changes of 10 to 15 points are moderate to large changes, and changes of >15 points are large to very large clinical changes in patients' health status.[5] From patients' perspective, even smaller changes are considered important.[6,153] A 5-point change in KCCQ score is also correlated with subsequent clinical events and other functional measures, such as changes in peak ventilatory capacity and 6MWD.[126,149,154] Importantly, these thresholds of clinically important change are consistent across multiple etiologies of HF, including those with reduced and preserved ejection fraction, valvular heart disease, and hypertrophic cardiomyopathy.[5,155-158]

In light of the work defining clinically important changes, it is recommended not only that clinical trials compare mean differences among groups but also that the distribution of clinically important changes be described, so that these mean differences can be clinically interpreted and shared with patients.[146,159] Underscoring the value of describing the distributions of clinically important change is that although the mean difference between groups may be smaller than the intraindividual thresholds that are clinically important, the underlying distribution of changes experienced by trial participants can be clinically significant. For example, a recent meta-regression of 11 trials demonstrated that a 2.5-point mean difference between groups, one-half the threshold considered to be a CMWPC for individual patients, was associated with an absolute difference of 6% (95% predicted interval: 4.0%-8.1%) in the proportion of patients experiencing $\geq$5-point improvements in KCCQ-OSS, with a corresponding NNT of 17 (95% predicted interval: 12-25) for 1 patient to be significantly better.[159]

Collectively, the KCCQ not only measures outcomes of great relevance to patients but also has extensive data supporting its interpretation, so that clinicians and patients can better understand the clinical impact of novel treatments. Ultimately, clinical trials should consider modeling the heterogeneity of treatment benefit on health status outcomes so that the data from these rigorous studies can be incorporated into evidence-based decision aids to improve the patient-centeredness of care.[160-162]

A PATIENT'S PERSPECTIVE

As an HF patient, I find it is sometimes difficult to think about what is meaningful and important because it means confronting my mortality and assessing it. Being diagnosed with HF interrupted my life plan and course and set me on a new trajectory. Shared decision-making became the new life path, tasking us with determining the balance between clinically meaningful information and data and individually meaningful decisions. On this difficult path it is important to make sure we—both clinicians and patients—are speaking the same language.

What does the trial outcome you are sharing offer me in terms of my own clinical care and decision-making? If you are asking me to make a change in my lifestyle, how does that change my longevity and/or QoL? What is the trade-off in my life? What new risks do I face? What do I lose if I don't make the

change? How important do you think the change we are discussing is to me individually? Are you as a clinician willing to sit with me and sort through these questions nonjudgmentally? Do you see me as a unique individual worthy of your time, worthy of saving?

When discussing clinically meaningful and individually meaningful outcomes, we patients find it helpful for you to share your understanding and interpretation of our personal trajectory with HF. For instance, if you are doing 6MWD testing, share how the current test demonstrates change or stability or improvement since the previous tests, and why it matters. If you are doing PROs, share how those have changed or remained stable. Help me as a patient to see any change as an opportunity for growth, even when it is a negative change. Work with me to stay clear of falling off the edge of my world.

Clinical trials are incredibly important; they guide us into the future. Patients and clinicians must see these trials as part of the continuum of care, not as side trips or last resorts. Show me how it fits me instead of how I fit into it. This helps both of us move the science forward while I move forward with my life.

A REGULATORY PERSPECTIVE ON THE INTERPRETATION OF CMWPC. This section is "a" regulatory perspective, not "the" regulatory perspective, authored by 1 current (M.A.P.) and 1 former (N.S.) staff member in the Division of Cardiology and Nephrology of the FDA's Center for Drug Evaluation and Research. Nothing further should be inferred.

We consider the clinical relevance of 3 general classes of HF outcomes.

"Events" are countable outcomes, but what should count as an event is seldom obvious. Deaths are often classified by judged cause and may include near deaths, such as resuscitation or persistent vegetative state. Hospitalizations are counted only for certain facilities and only if they last some arbitrarily determined time. Strokes and myocardial infarctions have complex and subjective definitions. In effect, all of these "events" are defined to reflect some assessment of what is clinically meaningful. In a regulatory context, effects on "events" need to outweigh an intervention's risks or harms, a calculus that may be complicated by "events" of disparate clinical meaningfulness, as evidenced by their subjective definitions and inclusions. Although mortality and hospitalization are generally accepted to be clinically meaningful, and reductions in hospitalizations alone may support approval as long as mortality is not adversely affected, events that require complicated definitions and infusion of greater subjective judgement in their definition and assessment lack the same face validity. Potential benefit demonstrated on such events may be harder to weigh against adverse safety signals, and events of unclear clinical meaningfulness may be unable to support the conclusion that a therapeutic is efficacious.

This same calculus can be applied to validated surrogates: outcomes that are not measures of survival, symptoms, or function but typically predict such outcomes with a robust and well-defined quantitative relationship. The clinical meaningfulness of these validated surrogates is dependent on the outcomes they predict. The predicted benefits have to outweigh risks or harms, including the risks of delaying achievement of a goal, but there is no other regulatory issue of clinical meaningfulness.

For observable "events" or those predicted by surrogates, it is meaningless to speak of individuals' benefiting. Labeling for "event" prevention seeks to identify the population apt to benefit from an intervention and to describe factors that affect the risks and benefits, but whether an individual benefits is down to chance.

The second class of HF outcomes assess how patients feel or function. Functional outcomes in HF include peak $pV\dot{o}_2$ (a measure of peak exercise ability), 6MWD (a measure of sustained moderate exercise), and potentially actigraphy (a measure of spontaneous activity). All of these have continuous outcomes. Symptoms or PROs can be single questions or complex survey instruments, and they can be discretized as Likert-type scales or continuous as visual analog scales. However, it is much more common to analyze discrete outcomes as if they were truly continuous and to treat a 1-step change the same regardless of where in a scale it occurs.

Large HF trials may have modest ability to detect small differences in "event" rates, because only the subjects with "events" are counted, but they have enormous power to resolve very small effects on symptoms or functional outcomes, because everyone's data contribute. FDA guidance calls for these outcomes to be clinically meaningful if they are, on average, large enough to be perceived by a patient as a benefit (within-patient change) against the background waxing and waning of the underlying disease (assessed as within-patient variability in response). The FDA's preferred approach to this problem is to develop a 1-question global assessment of change Likert-type scale, based on the core concept of the functional measure or the complex symptom score, and to set the clinically meaningful change (usually) as what corresponds to a 1-step change on the global assessment. For this to work,

the global and the symptom or functional endpoints must be well correlated, but we are unaware of analytical work that describes how the apparent meaningful effect size declines as correlation declines. A simple Likert-type scale could also serve as the basis for approval, perhaps with a complex survey used informally to explore why patients responded as they did.

Other approaches to setting what is clinically meaningful exist, including one that compares the observed mean effect with the within-subject variance. Although not supported by the agency, this may be a sensible alternative for calibrating a complex, multidomain survey.

Responder analyses are not recommended, because within-subject variability creates "responders" even when the true treatment effect is utterly trivial. Differences between the distributions of responses on the intervention and the control group may provide valid inferences about a true responder group, even if its characteristics are not determinable. A *Q*-*Q* plot may be useful to explore for this when the mean treatment effect is of dubious magnitude. It is also possible to test formally the difference in skewness of 2 distributions.

A third class of HF outcomes consists of biomarkers, in the broad sense of any objective, nonclinical measurement, that are not accepted as surrogates but may still be informative as to the clinical state. It seems difficult to justify what effects are clinically meaningful for such biomarkers outside of a model in which one can understand how, collectively, they affect some clinical outcome. In this context, the vast majority of biomarkers described in this paper (ie, laboratory, radiographic, echocardiographic, hemodynamic, and risk score measurements) are unvalidated surrogates that are not suitable to support regulatory approval because they lack a clear and established relationship between the biomarker and the expected consistent and predictable clinical benefit. Because this relationship is not known or proved for these unvalidated surrogates, the clinically meaningful magnitude of change cannot be known for them either and exists for the majority only as subjective inference or expert opinion.

CONCLUSIONS

Establishing the CMWPC for clinical outcomes requires a rigorous, mixed-method approach that integrates statistical, clinical, and patient-centered methodologies to understand measurement variability and to separate "signal" from "noise," ideally from patients' perspectives. It is important to convert commonly used measures of HF status into concepts that have clinical meaning to both providers and patients. More important than defining cross-sectional assessments that stratify disease severity are changes in these measures that reflect clinically important improvements (or deteriorations) in patients' health. Such changes are needed so that the continuous mean differences between groups can be translated into clinical interpretable treatment benefits, facilitating informed discussions between patients and providers as part of the shared decision-making.

Few of the outcomes, other than health status, have undergone rigorous estimates of CMWPC. Even traditionally accepted clinical events, such as HFH, have underappreciated variability and may be really measuring transient health status deteriorations and costs. Nevertheless, the pathophysiological insights offered by the outcomes described in this review can provide invaluable insights into disease processes and identify novel treatment mechanisms that can spur future treatment interventions. Many of the proposed cutpoints reflect the best available evidence, incorporating measurement variability, prognostic associations, and patient-anchored data where available; however, for several domains, linking specific magnitudes of change to patient-perceived benefit or hard clinical outcomes remains incomplete. Accordingly, these benchmarks should be viewed as provisional guides to aid interpretation, clinical communication, and trial design, rather than fixed treatment targets.

Future work is needed to interpret the clinical importance of almost all measures. A practical strategy would be to conduct anchor-based analyses for all outcomes discussed in this review, as has been done for the KCCQ. This can be done either through retrospective evaluation of prior trials or by prospectively implementing such analyses into future studies. Retrospective analyses of real-world data and landmark trials should begin describing measurement variability, leveraging changes in KCCQ scores or patient anchors to categorize thresholds of CMWPC, and describe potential patient-level factors associated with the heterogeneity in interpreting these measures. Prospective validation and replication of CMWPC estimates are needed, with attention to patient factors (eg, age, comorbidities) that may influence these thresholds. Moreover, as hierarchical analytical approaches, such as win ratios, become increasingly common, qualitative research and discrete choice experiments should be conducted to capture patient preferences when prioritizing outcomes such as death, hospitalization, and QoL. Only

with continued work to define and prioritize interpreting the numerous outcomes used in HF clinical trials can the evidence be generated to truly inform shared decision-making in clinical practice, the primary goal of clinical research.

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KEY WORDS biomarkers, clinical trials, CMWPC, heart failure, KCCQ, MCID, outcomes

APPENDIX For a supplemental table and references, please see the online version of this paper.