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JACC REVIEW TOPIC OF THE WEEK

Worsening Heart Failure: Nomenclature, Epidemiology, and Future Directions

JACC Review Topic of the Week

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ABSTRACT

Heart failure (HF) is a progressive disease characterized by variable durations of symptomatic stability often punctuated by episodes of worsening despite continued therapy. These periods of clinical worsening are increasingly recognized as a distinct phase in the history of HF, termed worsening HF (WHF). The definition of WHF continues to evolve from a historical focus solely on hospitalization to now include nonhospitalization events (eg, need for intravenous diuretic therapy in the emergency or outpatient setting). Most HF clinical trials to date have had HF hospitalization and death as primary endpoints, and only recently, some studies have included other WHF events regardless of location of care. This article reviews the evolution of the WHF definition, highlights the importance of considering the onset of WHF as an event that marks a new phase of HF, summarizes the latest clinical trials investigating novel therapies, and outlines unmet needs regarding identification and treatment of WHF. (J Am Coll Cardiol 2023;81:413–424)

Most patients with new-onset heart failure (HF) transition to chronic HF and can be symptomatically stabilized on therapy for a variable period ranging from months to years.[1] During this chronic phase, despite apparent clinical stability, a significant residual risk of clinical deterioration and death remains.[1] This risk is increased several fold if signs and symptoms consistent with worsening HF (WHF) develop (**Figure 1**).[1-3] WHF is defined by escalating signs and symptoms of HF in patients with chronic HF despite previously stable therapy.[4] At present, this definition requires the need for a hospitalization for HF, treatment of HF in the emergency department (ED), or receipt of intravenous (IV) diuretic therapy in the outpatient setting.[4,5] WHF is considered a phase in the natural history of

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ABBREVIATIONS AND ACRONYMS

ED = emergency department

HF = heart failure

HFrEF = heart failure with reduced ejection fraction

IV = intravenous

MRA = mineralocorticoid receptor antagonist

WHF = worsening heart failure

the disease that marks its progression, and it portends a substantially worse prognosis.[6] The concept of WHF is evolving and was mentioned in the 2021 update of the European Society of Cardiology guidelines, but without a clear explanation or definition.[7] Likewise, the 2022 American College of Cardiology/American Heart Association/Heart Failure Society of America guideline defined WHF as worsening symptoms, signs and/or functional capacity, and classified it as a potential stage C trajectory along with new-onset/de novo HF, resolution of symptoms, and persistent HF.[8] Although this guideline reinforces the progressive nature of the disease, this classification and the proposed WHF definition remain general and do not discuss the impact of varying phenotypes and disease trajectories on management decisions.

Despite its clinical importance and recent introduction within practice guidelines, WHF remains inadequately defined, particularly in the outpatient setting.[4] The management of WHF is challenging, limited by the lack of a clear biologic definition as well as the absence of robust evidence-based guidelines to inform the specific management. Likewise, from the perspective of clinical trial design, considerations exist for inclusion of WHF as either a study eligibility criterion and/or study endpoint. In this context, this review aims to define WHF as a distinct phase of HF, as well as summarize the current evidence and future directions for the identification and management of these patients.

TRADITIONAL DEFINITIONS OF WHF

HOSPITALIZATION FOR HF. The definition of WHF has evolved over time. For decades, WHF has been equated with the deterioration of HF signs and symptoms requiring hospitalization.[4] Similarly, terms such as *acute decompensated HF* and *acute HF* have often been used interchangeably with WHF to describe a HF hospitalization event.[4] This near synonymous use of all these terms coincided with substantial clinical, public health, and research investment in characterizing the profile and outcomes of patients hospitalized for HF. For example, there is relatively widespread appreciation of HF hospitalization as a sentinel event, with observational studies reporting mortality rates for patients hospitalized for HF as 3-fold higher than patients not hospitalized.[4,9] Similarly, data show that approximately 1 in 4 patients hospitalized for WHF die or are readmitted within 30 days of discharge.[10]

HIGHLIGHTS

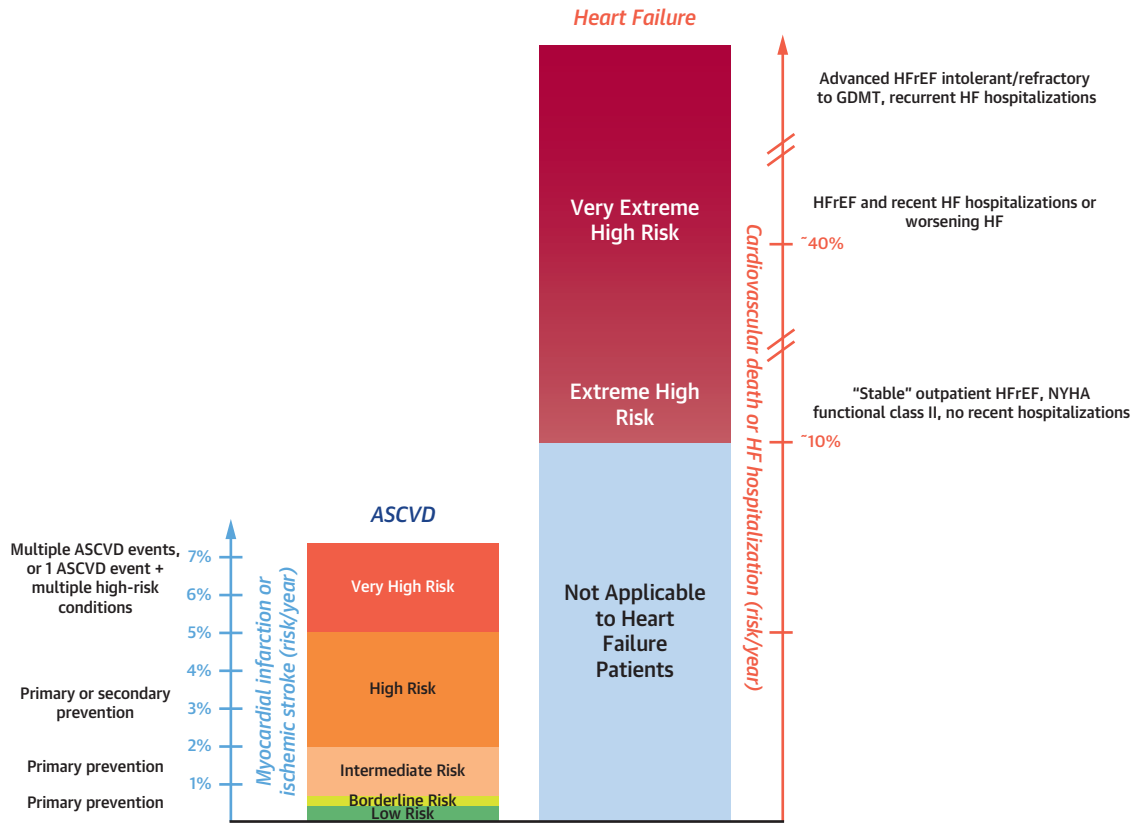
- Management of patients with worsening heart failure is limited by the lack of a clear biological definition and specific guidelines.
- It is important to recognize worsening heart failure as an indication that the disease has progressed to a new phase.
- Additional research is needed to define criteria for assessment of worsening heart failure and guide management.

WORSENING HF WITHOUT HOSPITALIZATION. It has been increasingly recognized that not all patients with HF decompensation are hospitalized and that many patients may receive treatment for WHF in the outpatient setting.[4] One of the reasons for the slow progress in understanding the biology of WHF is the paucity of research on this entity among patients not hospitalized for HF, including those who may be discharged from the ED setting, and an exclusive focus on the hospitalization episode, without taking into consideration the biological changes in the clinical condition. In this respect, there are at least 3 potential scenarios in which a patient may present with WHF and receive treatment without hospitalization: outpatient IV diuretic administration, escalation of outpatient oral diuretic therapy, and ED visit and discharge without hospitalization.

Outpatient intravenous diuretic therapy. Although hospitalization easily identifies patients at high risk for clinical events, a secondary analysis of the MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy Post Approval Registry) trial of patients with HF and reduced ejection fraction (HFrEF) was among the first large studies to show that those with WHF who were treated with IV diuretic therapy during urgent outpatient clinic visits had similar mortality to patients who were hospitalized.[11] Similar results were seen in a secondary analysis of PARADIGM-HF (Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial).[12]

By contrast, more recent analyses suggest that although outpatient IV diuretic treatment of WHF is associated with a high clinical event rate, the risk is lower than in patients who are hospitalized.[13,14] For example, a secondary analysis of the DAPA-HF

FIGURE 1 **Contextualizing Risk of WHF**



The 2018 American College of Cardiology/American Heart Association Cholesterol Guidelines applied terms (eg, "high risk") to describe patients based in part on absolute event rates. Although all subsets of patients with heart failure (HF) with reduced ejection fraction (HFrEF) generally face absolute rates of cardiovascular events much higher than patients with atherosclerotic cardiovascular disease (ASCVD), comparison of absolute event rates support worsening heart failure (WHF) as a "very extreme high risk" condition. Reused with permission from Greene et al.[33] NYHA = New York Heart Association.

(Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure) trial found that compared with patients without a WHF event, risk of death was ~3-fold higher following an urgent IV diuretic visit, but ~6-fold higher after HF hospitalization.[13] Nonetheless, given the strong prognostic significance of outpatient IV diuretic administration for WHF seen across studies, such urgent HF visits are now a formally defined clinical trial endpoint and are increasingly included as an outcome in large, randomized trials.[5]

Outpatient escalation of oral diuretic therapy. Historically, escalation of outpatient oral diuretic treatment has been poorly characterized. Although the escalation of oral diuretic treatment during a hospitalization is within the accepted definition of a HF hospitalization event, augmentation of oral diuretic treatment in the outpatient setting is not routinely considered a WHF event in clinical trials.[5] Accumulating data suggest that the need to increase oral diuretic therapy in the outpatient setting is not benign and is associated with substantial risk of morbidity and mortality.[13] For example, an analysis of the nationwide Danish registry found that outpatient intensification of oral diuretics was common (9 events per 100 patient-years) and was associated with a 75% higher relative risk of 1-year mortality.[15] Likewise, an analysis from the CHAMP-HF (Change the Management of Patients with Heart Failure) registry in the United States outpatient practice found that 1 in 4 patients with HFrEF may have outpatient escalation of oral diuretic therapy over longitudinal follow-up.[16] In the aforementioned secondary analysis of DAPA-HF, intensification of oral therapy, including diuretics, carried similar risk of subsequent mortality as outpatient IV diuretic visits, although

both the intensification of oral therapy and outpatient use of IV diuretic agents were associated with lower risk of mortality than HF hospitalization.[13] In a recent analysis of WHF events within an integrated health system, ED visits, observation stays, and outpatient encounters, including any new initiation and/or augmentation of oral diuretic therapy, comprised approximately one-half of all WHF events in the health system.[17] These data also inform the potential impact of including outpatient oral diuretic escalation within a clinical trial definition of WHF. Although recent clinical trials have shown that adding outpatient IV diuretic visits within a composite WHF endpoint has not substantially changed the event rate as compared with HF hospitalization alone, this is consistent with real-world evidence from the United States suggesting that outpatient IV diuretic administration may be relatively rare.[18] By contrast, addition of oral outpatient diuretic escalation could result in a large increase in the event rate for a WHF composite endpoint.

ED visit and discharge. In the United States alone, there are an estimated 1 million visits to the ED for HF annually, of which ~1 in 5 may be discharged without admission to the hospital or observation unit.[19,20] In the secondary analysis of the PARADIGM-HF trial, rates of all-cause death (25.1/100 patient-years) and cardiovascular death (19.9/100 patient-years) following ED visit and discharge were at a high level, but numerically lower than those following HF hospitalization (33.4/ and 30.3/100 patient-years, respectively).[12] Likewise, in a post-hoc analysis of the ASCEND-HF (Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure Trial) trial, rates of death over 150-day follow-up were 11.4% among those discharged from the ED and 21.0% among those who were hospitalized.[21]

DEFINITION AGNOSTIC TO LOCATION OF CARE. Although evidence suggests that the risk of death associated with WHF is highest following HF hospitalization, the prognosis following outpatient and ED care for WHF is nevertheless poor and substantially worse than HF patients without a WHF episode. These nonhospitalization events have only recently received attention in trials as markers of HF disease progression and subsequent poor outcomes.[11] Large variations in hospitalization rates across different regions have been documented, in part determined by nonclinical and nonbiological factors such as the availability of outpatient care options or financial disincentives of hospitalizations, and caregiver support, rather than the true severity of the disease.[4] A sole focus on HF hospitalization underestimates the burden and prognostic consequences of WHF.[12] Hence, the current definition of WHF has been refined to include worsening signs and symptoms requiring intensification of therapy regardless of location of care in patients with chronic HF after a period of clinical stability and stable background therapy (**Central Illustration**).[1,4] Specifically, a WHF event is an escalation of signs and symptoms leading to a HF decompensation event where the patient requires IV diuretic therapy, regardless of location of care. Despite prognostic value, further research may be required to operationalize outpatient escalation of oral therapy within the WHF definition.

LIMITATIONS AND UNCERTAINTIES OF THE CURRENT DEFINITION

Despite increasing recognition of WHF in trials and guidelines, the current definition has limitations and associated areas of uncertainty (**Central Illustration**).

SUBCLINICAL WORSENING. A limitation of the current WHF definition is that the absence of overtly worsening signs and symptoms is not always an indication of lower risk.[22] Biomarker levels are powerful predictors of morbidity and mortality, and illustrate the progressive nature of HF and ongoing cardiac structural and functional deterioration in many symptomatically "stable" patients.[23] This "silent worsening" can be unrecognized and undertreated, particularly as patients with worsening HF decrease their activity level which can potentially mask the development of overt symptoms. A future WHF definition may consider deterioration of HF signs *or* symptoms rather than signs *and* symptoms. Nonetheless, incorporating symptomatically silent, yet prognostically relevant, biologic worsening within a practical definition of WHF remains challenging. Routinely available parameters, such as ejection fraction, blood pressure, and heart rate have limitations and are not actionable for defining WHF in practice.[1] In the future, these may be refined by more comprehensive assessment of changes in biological characteristics using biomarker or omics profiling. For example, asymptomatic increases in N-terminal pro-B-type natriuretic peptide (NT-proBNP) (eg, >30%) or new-onset troponin elevation (without acute coronary syndrome) have shown prognostic value that may warrant further study within a "subclinical WHF" definition.[24] Likewise, the approach to assessing and defining therapeutic response in subclinical WHF may differ from that of clinical WHF. Although prior data suggest that most

CENTRAL ILLUSTRATION **Considering the Definition of Worsening Heart Failure**

Current Definition:
• Deterioration of HF signs and symptoms in a patient with chronic HF, despite previous stable background therapy
• Requires urgent escalation of therapy, including hospitalization, ED visit, or outpatient IV diuretic therapy, ± outpatient oral therapy*

Limitations & Uncertainties With the Current Definition

- Inability to detect asymptomatic but clinically meaningful worsening
- Definition anchored to treatment provided rather than biology
- Uncertain time horizon following WHF event to distinguish WHF vs return to "stable" persistent HF
- Unclear level of required background therapy to differentiate WHF from "untreated" HF
- No consensus on definition of escalated oral therapy

Potential Future Directions

- Continue efforts to establish an objective, reproducible, biologic definition of WHF (eg, biomarkers, omics, risk models, implantable hemodynamic monitoring)
- Perform clinical trials to inform management of WHF, including optimal escalation of existing therapies for chronic HF and use of novel therapies
- Consider routine inclusion of WHF across various locations of care (ie, inpatient and outpatient) within clinical trial eligibility criteria and endpoints

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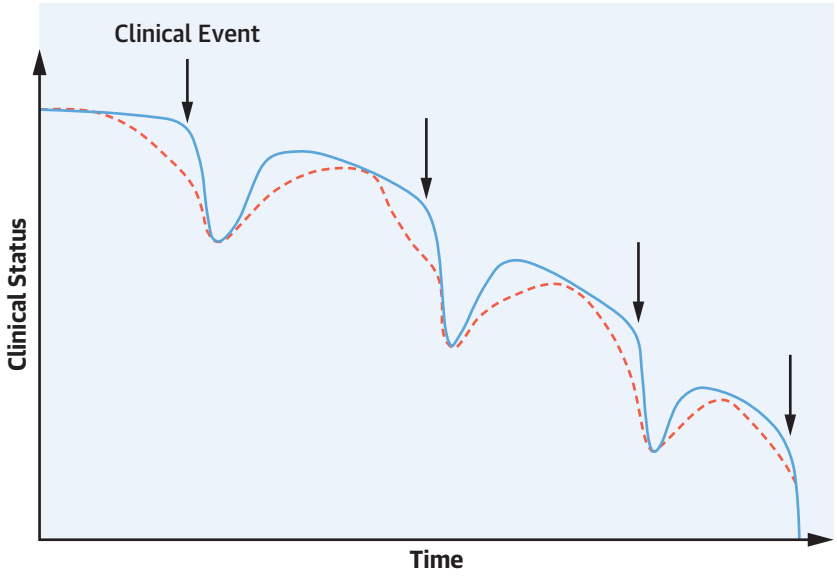
*Traditional definition focused on the receipt of intravenous (IV) diuretic therapy. Further data may be needed to operationalize outpatient escalation of oral therapies within a worsening heart failure (WHF) definition. ED = emergency department; HF = heart failure.

existing therapies for WHF offer consistent relative risk reductions in clinical events across a wide spectrum of underlying patient risk and functional limitation, for a given therapy, further studies are needed to confirm the consistency and nature of clinical benefit among patients with asymptomatic worsening.

DEFINITION ANCHORED TO TREATMENT RATHER THAN BIOLOGY. The current WHF definition is reliant on criteria based on treatment prescribed rather than underlying biology, which is vulnerable to subjective judgment and variability among clinicians, as well as factors that may influence provision of therapies independent of the clinical presentation such as resource availability or financial incentives. Future studies of WHF may leverage accumulating data by using implantable hemodynamic monitors. Such data have found the term *acute HF* to be a misnomer in many circumstances, because the transition from "stable" to decompensated status is most often gradual over days to weeks before patients receive urgent treatment.[4,25] At the same time, the assessment of congestion on clinical examination can experience interclinician variability, and objective and reproducible signs of worsening of HF may be useful for accurate and timely diagnosis. Detection of this early subclinical worsening may reflect an opportunity to treat worsening congestion and avoid the transition to a clinical event.[4] Data from the CHAMPION (CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III Heart Failure Patients) trial with CardioMEMS, an implantable pulmonary artery pressure sensor, suggest that early treatment of subclinical worsening of pulmonary artery pressure may reduce downstream risk of HF hospitalization.[26] Further confirmatory evidence is needed to operationalize this concept in light of the mixed data from implantable hemodynamic monitoring from other studies.[27] It will also be important to validate the magnitude of asymptomatic change in filling pressure that has a high probability of transitioning to a clinical event and warrants escalated treatment. Other potential markers of worsening biology that could be considered within a

FIGURE 2 Traditional and New Theories of HF Clinical Course and WHF



Blue line reflects the traditional view of the course of chronic HF with episodes of acute decompensation. **Red dotted line** reflects the newer theory that the worsening event is preceded by gradual progressive subclinical worsening, and a subclinical high-risk state that follows an apparent clinical recovery and discharge. Adapted with permission from Gheorghiade et al.[41,42] Abbreviations as in Figure 1.

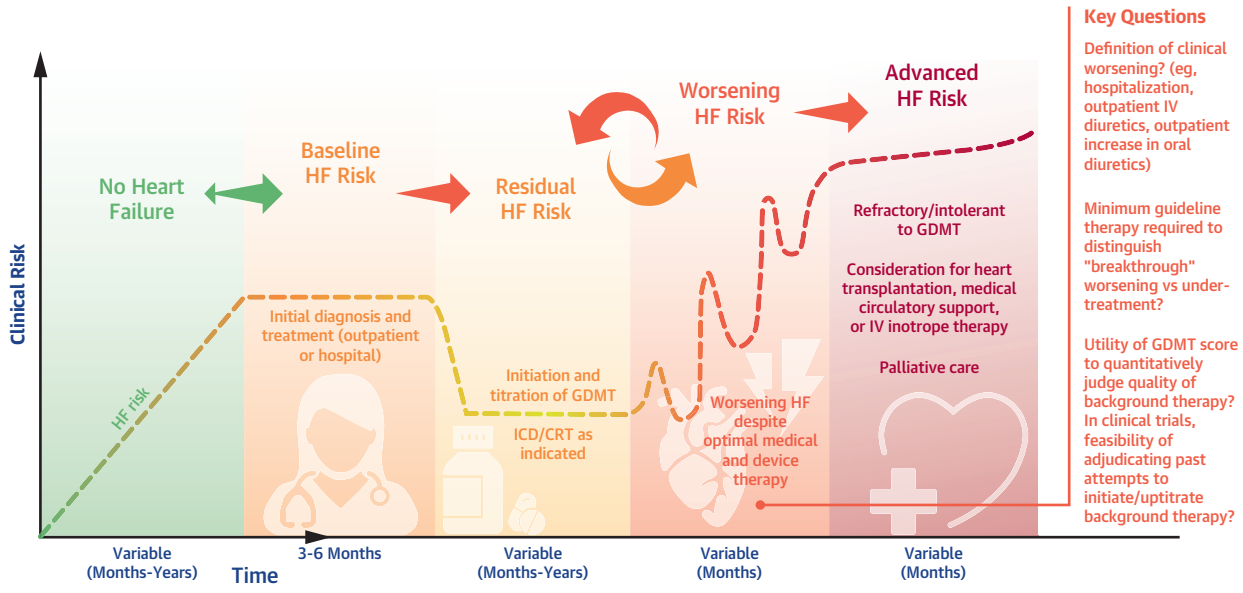
WHF definition may include HF-specific patient-reported outcomes (eg, Kansas City Cardiomyopathy Questionnaire), or alternative biomarkers such as bioimpedence.[28]

PROXIMITY TO THE PRIOR WHF EVENT. Although the *vulnerable phase* following a WHF event is widely recognized, there is no consensus on how long such a period may last.[2] Although patients with WHF may remain at greater absolute risk than those never hospitalized, it is possible for relative risk to decline over time in response to therapy. As such, although HF is generally recognized as a progressive disease, utilizing classification introduced in the recent guidelines, it is possible for patients to transition from WHF back to "persistent HF" (or less likely, remission of HF).[8]

Where to draw the line between WHF and persistent HF is uncertain. For example, a patient with most recent WHF event a year ago and with continuing HF symptoms may be termed *persistent HF*; however, the appropriate term for a patient with a WHF event 6 months ago is unclear. Even trials generally regarded as enrolling "stable" outpatient chronic HF have generally included a sizeable proportion of patients with prior HF hospitalization, with varying durations of time between prior hospitalization and trial enrollment. For example, among 8,399 patients in the PARADIGM-HF trial, 5,274 (63%) had a history of prior HF hospitalization. This included 1,611 (19%) with a HF hospitalization within the prior 3 months, and 1,009 (12%) with a HF hospitalization 3 to 6 months before enrollment.[29] For clinical trials, as a matter of practicality in order to operationalize a WHF eligibility criterion, a time duration following a WHF event must be set. The recent VICTORIA (VerICiguaT GlObal Study in Subjects With Heart Failure With Reduced EjectIon FrAction) trial defined the eligibility criterion for WHF as recent HF hospitalization within the past 6 months or outpatient IV diuretic visit within the past 3 months.[30] The arbitrary nature of such time horizons in defining WHF and the absence of guidance in guidelines should provide impetus for further efforts to define WHF by objective, reproducible, and biological measures that are reliably congruent with clinical risk.

DEFINING THE ADEQUATE LEVEL OF BACKGROUND MEDICAL THERAPY. Implicit in the definition of WHF is the assumption that patients have worsened despite background therapy.[1] Worsening of any chronic condition may be expected in the absence of

FIGURE 3 **Progression of HF Clinical Risk Over Time**



A heart failure (HF) diagnosis carries significant intrinsic clinical risk (baseline risk). This risk can be substantially reduced with aggressive use and titration of guideline-directed therapy (residual risk), although risk still remains high compared with patients without HF and compared with patients with other cardiovascular diseases. Many patients experience episodes of clinical worsening over time despite stable therapy (worsening risk), termed worsening HF (WHF). Key questions remain with regard to defining clinical worsening and distinguishing worsening status in the context of optimal and maximally tolerated background therapy vs undertreatment and underdosing of therapy. Adapted with permission from Greene et al.[1] CRT = cardiac resynchronization therapy; GDMT = guideline-directed medical therapy; ICD = implantable cardioverter-defibrillator; IV = intravenous.

appropriate therapy. However, there is no consensus on what level of background therapy or duration of stable background therapy is required to differentiate WHF breaking through reasonable medical therapy vs poorly treated chronic HF. Medication scores including use and dosing of available therapies may be considered in efforts to objectively grade and compare level of background therapy.[1,31] However, such scores do not account for the possibility of maximally tolerated but subtarget doses, prior intolerance, or absolute or relative contraindications. Intolerance or ineligibility for medical therapy reflect a high-risk patient population that should motivate efforts for developing alternative therapies that are efficacious and well-tolerated. At the same time, it is important to acknowledge the gaps in quality of care in clinical practice. For example, among eligible patients with HFrEF in U.S. clinical practice, 1 in 3 may not receive a beta-blocker and 2 in 3 may not receive a mineralocorticoid receptor antagonist (MRA).[32] Despite this, considering the challenges regarding intolerance, comorbidities, and contraindications, mandating that patients receive all available therapies at target doses in order to potentially qualify as having WHF is impractical. It is therefore a reasonable approach to require some background therapy and stability of clinical course before the development of WHF as a transition phase requiring further efforts to reduce the risk for future worsening events.

DEFINING CRITERIA FOR ESCALATED ORAL THERAPY. Although data have established a need for outpatient escalation of oral diuretic therapy as a predictor of clinical risk, the details of what magnitude of escalation to include as criteria for WHF remain uncertain. In the Danish cohort study, intensification was defined as: 1) newly prescribed oral loop diuretic of minimum 80 mg/day furosemide equivalent; 2) doubled dosage of loop diuretic to minimum 160 mg/day furosemide equivalent; or 3) newly prescribed thiazide diuretic in addition to ≥160 mg/day furosemide equivalent.[15] The CHAMP-HF study utilized a definition as either: 1) any change in total daily dose higher than previous dose; 2) addition of metolazone; or 3) switch from any dose of furosemide

TABLE 1 Recent Clinical Trials Inclusive of Patients With WHF

Clinical Trial	Study Drugs	Inclusion Criteria	Primary Endpoint and Duration	Primary Endpoint Result	Select Secondary or Exploratory Endpoint Results
PIONEER-HF[39]	Sacubitril-valsartan vs enalapril	Patients with HFrEF who were hospitalized for ADHF (N = 881)	Change in NT-proBNP from baseline through weeks 4 and 8	• Percent change in NT-proBNP concentration with sacubitril/valsartan: −46.7% Percent change with enalapril: −25.3% • Ratio of change: 0.71 (95% CI: 0.63-081); $P < 0.001$	Cardiovascular death or HF hospitalization over 8 wk: • Sacubitril/valsartan event rate: 9.2% Enalapril event rate: 15.2% • HR: 0.58 (95% CI: 0.39-0.87); $P = 0.007$
AFFIRM-AHF[40]	Ferric carboxymaltose (up to 24 wk) vs placebo	Patients with iron deficiency, LVEF <50%, and who were stabilized after an episode of AHF requiring hospitalization (N = 1,110)	Total hospitalizations for HF and CV death up to 52 wk	• Ferric carboxymaltose event rate: 57.2/100 patient-years Placebo event rate: 72.5/100 patient-years • Rate ratio: 0.79 (95% CI: 0.62-1.01); $P = 0.059$	Total HF hospitalizations • Ferric carboxymaltose: 217 Placebo: 294 • Rate ratio: 0.74 (95% CI: 0.58-0.94); $P = 0.013$ Cardiovascular death • Ferric carboxymaltose event rate: 14% Placebo event rate: 14% • HR: 0.96 (95% CI: 0.70-1.32); $P = 0.81$
VICTORIA[30]	Vericiguat vs placebo	Patients with CHF (NYHA functional class II, III, or IV), EF <45%, and evidence of WHF (N = 5,050). WHF was defined as HF hospitalization within the prior 6 mo, or receipt of IV diuretic therapy without hospitalization within the prior 3 mo	Composite of CV death or first hospitalization for HF, over a median follow-up of 10.8 mo	• Vericiguat event rate: 33.6/100 patient-years Placebo event rate: 37.8/100 patient-years • HR: 0.90 (95% CI: 0.82-0.98); $P = 0.02$	Hospitalization for HF • Vericiguat event rate: 25.9/100 patient-years Placebo event rate: 29.1/100 patient-years • HR: 0.90 (95% CI: 0.81-1.00) Cardiovascular death • Vericiguat event rate: 12.9/100 patient-years Placebo event rate: 13.9/100 patient-years • HR: 0.93 (95% CI: 0.81-1.06) Total HF hospitalizations • Vericiguat: 1,223 Placebo: 1,336 • HR: 0.91 (95% CI: 0.84-0.99); $P = 0.02$
GALACTIC-HF[43]	Omecamtiv mecarbil vs placebo	Inpatients and outpatients with symptomatic CHF and an EF ≤35% (N = 8,256)	Composite of a first heart-failure event (hospitalization or urgent visit for HF) or CV death, over a median follow-up of 21.8 mo	• Omecamtiv mecarbil event rate: 24.2/100 patient-years Placebo event rate: 26.3/100 patient-years • HR: 0.92 (95% CI: 0.86-0.99); $P = 0.03$	WHF event • Omecamtiv mecarbil event rate: 18.7/100 patient-years Placebo event rate: 20.3/100 patient-years • HR: 0.93 (95% CI: 0.86-1.00) Cardiovascular death • Omecamtiv mecarbil event rate: 10.9/100 patient-years Placebo event rate: 10.8/100 patient-years • HR: 1.01 (95% CI: 0.92-1.11); $P = 0.86$

Continued on the next page

to any dose of torsemide or bumetanide for ≥7 days.[16] Where to set the bar for magnitude of oral diuretic dose escalation required for the optimal specificity and sensitivity for defining WHF is challenging and requires further study. Likewise, relevant questions include how to account for baseline kidney function in relation to changes in diuretic dose, whether dose increases are defined by percent relative change vs absolute change, and how to account for dose changes in loop diuretic vs addition of adjunctive diuretics. Other uncertainties include how to consider nondiuretic oral medications, including dosing changes and new initiations.

RECOGNIZING WHF AS A DISTINCT PHASE

Until more refined biological underpinnings of the trajectory of the HF disease process are established, recognizing WHF as an event that marks the initiation of a new phase is imperative to guide the development

TABLE 1 Continued

Clinical Trial	Study Drugs	Inclusion Criteria	Primary Endpoint and Duration	Primary Endpoint Result	Select Secondary or Exploratory Endpoint Results
SOLOIST-WHF[37]	Sotagliflozin vs placebo	Patients with type 2 diabetes mellitus who were recently hospitalized for WHF (N = 1,222)	Total CV deaths, hospitalizations for HF, and urgent visits for HF, over a median follow-up of 9 mo	• Sotagliflozin event rate: 51.0/100 patient-years Placebo event rate: 76.3/100 patient-years • HR: 0.67; 95% CI: 0.52-0.85; $P < 0.001$	Hospitalizations or urgent visits for HF • Sotagliflozin: 194 Placebo: 297 • Rate ratio: 0.64 (95% CI: 0.49-0.83); $P < 0.001$ Cardiovascular death • Sotagliflozin: 51 Placebo: 58 • HR: 0.84 (95% CI: 0.58-1.22); $P = 0.36$
EMPULSE[38]	Empagliflozin vs placebo	Patients hospitalized for acute de novo or decompensated chronic HF (N = 530)	Composite of all-cause death, HF events, and ≥5-point change from baseline in KCCQ-TSS using a win ratio, at 90 d	Win ratio favored empagliflozin (1.36, [95% CI: 1.09-1.68]; $P = 0.005$)	Cardiovascular death or HF event • Empagliflozin event rate: 55.01/100 patient-years Placebo event rate: 80.45/100 patient-years • HR: 0.69 (95% CI: 0.45-1.08) Change from baseline in KCCQ-TSS • Empagliflozin: 36.19 Placebo: 31.73 • Adjusted mean difference: 4.45 (95% CI: 0.32-8.59)

ADHF = acute decompensated heart failure; AFFIRM-AHF = Study to Compare Ferric Carboxymaltose With Placebo in Patients With Acute Heart Failure and Iron Deficiency; AHF = acute heart failure; CHF = chronic heart failure; CV = cardiovascular; EF = ejection fraction; EMPULSE = A Study to Test the Effect of Empagliflozin in Patients Who Are in Hospital for Acute Heart Failure; GALACTIC-HF = Registrational Study With Omecamtiv Mecarbil (AMG 423) to Treat Chronic Heart Failure With Reduced Ejection Fraction; GDMT = guideline-directed medical therapy; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; IV = intravenous; KCCQ-TSS = Kansas City Cardiomyopathy Questionnaire total symptom score; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; PIONEER-HF = Comparison of Sacubitril/Valsartan Versus Enalapril on Effect on NT-proBNP in Patients Stabilized From an Acute Heart Failure Episode; SOLOIST-WHF = Effect of Sotagliflozin on Cardiovascular Events in Participants With Type 2 Diabetes Post Worsening Heart Failure; VICTORIA = VerICiguaT GlObal Study in Subjects With Heart Failure With Reduced EjectIon FrAction; WHF = worsening heart failure.

of therapies for this patient population. As per the proposed WHF definition, a progressive subclinical silent worsening followed by signs and symptoms requiring changes in medication represent the start of a different high-risk phase of HF (Figure 2). Figure 3 illustrates where the proposed WHF phase can be placed within the various risk profiles of chronic HF.

EVENTS THAT SHOULD NOT BE CONSIDERED WHF

Despite genuine worsening signs and symptoms of HF requiring escalation of HF therapies, three scenarios should not be considered as WHF in terms of defining it as a distinct phase of the disease process.

TABLE 2 Recommendations and Future Directions

1	Recognize WHF as an event that marks the start of a new phase in the natural history of HF
2	Distinguish patients with WHF from those having de novo HF, those not receiving background HF therapy, or those with major secondary precipitants (eg, acute coronary syndrome, infection)
3	Establish a biological definition of WHF that is agnostic to the setting of care or treatment administered
4	Acknowledge the potential for "silent" worsening of HF where signs and symptoms may be unchanged, but biomarkers and underlying biology are worsening
5	Increase recognition and incorporation of WHF management within clinical practice guidelines
6	Consider the routine inclusion of WHF across the locations of care (eg, hospitalization, emergency department, outpatient clinic) within eligibility criteria and/or endpoints in trials
7	Perform trials evaluating novel biomarkers, risk model performance, and implantable hemodynamic monitoring to predict the risk of a worsening HF event in patients with chronic HF
8	Develop a consensus on the changes in diuretics (dose, route of administration, duration, additions), and/or other medications that may be included within a WHF definition. Consider routine inclusion of outpatient escalation of oral diuretic within a WHF definition
9	Acknowledging that a complete lack of background medical therapy (despite eligibility) should be considered "untreated HF" rather than WHF, develop a consensus on the level of background therapy needed to reflect WHF and "breakthrough" progression of HF

Abbreviations as in Table 1.

GROSS LACK OF ADHERENCE. Some degree of nonadherence with HF chronic self-care recommendations and medication compliance is seen commonly in patients with HF or other chronic conditions, including those who tolerate medications well. It is misguided to blame intermittent medication lapses or dietary indiscretion as the sole precipitants for a WHF episode. If a patient's clinical status is so tenuous that a single missed medication dose or high-sodium meal is thought to be responsible for decompensation, this likely signals underlying worsening HF biology.

However, this situation of intermittent nonadherence should be differentiated from situations of gross lack of adherence. For example, patients may consistently forget or refuse to take medications, or have social or economic barriers that prevent reliable access to medications. The definition of WHF requires worsening signs and symptoms despite stable medical therapy. In the absence of true medication intolerance, patients with gross lack of adherence or access to stable medical therapy are best considered "untreated HF." Although these situations are critically important to address, different strategies are needed to improve outcomes for such patients as compared with patients with WHF.

ACUTE SECONDARY DISEASES. WHF definition should exclude patients with distinct precipitants, for example, decompensation related to acute coronary syndrome or infections.[7] In addition, patients with end-stage kidney disease receiving dialysis also warrant separate consideration.

DE NOVO HEART FAILURE. WHF requires a prior diagnosis of chronic HF and should not include patients with new HF diagnoses who are naive to therapy. This distinction between de novo and WHF is important because both may fall within the term *acute HF*. Nonetheless, the difference between these 2 categories of patients is relevant because patients with de novo HF have a better prognosis once initiated on standard of care medical therapies.[4,10]

NEED FOR NOVEL THERAPIES

Recent evidence suggests that patients with optimal medical therapy continue to have a residual risk of adverse outcomes (**Figure 3**).[33] For example, in the DAPA-HF trial, the rate of WHF or cardiovascular death in the group receiving optimal background medical therapy plus dapagliflozin was 16.3% over a median of 18.2 months.[34] A post hoc analysis of the GALACTIC-HF (Global Approach to Lowering Adverse Cardiac outcomes Through Improving Contractility in Heart Failure) trial identified an emerging patient population that included those receiving guideline-directed medical therapy (stage C HF) but with progressive severe symptoms that do not yet reach the threshold of advanced HF (stage D HF).[35,36] It was suggested that this patient population qualifies as a new stage C2.[35]

Despite residual risk and poor outcomes following WHF events, there are no dedicated guideline recommendations for how to manage these patients.[4] WHF has been variably defined for trial eligibility, for example, acute HF within 48 hours of hospital presentation vs poststabilization/prehospital discharge. Until more recently, WHF trials only recruited patients in the hospital setting and focused on short-term investigational therapies. Only some recent large studies involved patients regardless of inpatient or outpatient WHF.[30,37] **Table 1** summarizes the findings of the latest trials involving patients with HF and worsening symptoms. Although each of these trials demonstrated favorable results, many exclusively enrolled hospitalized patients.[38-40] On the basis of the VICTORIA trial, vericiguat is the only treatment that is specifically recognized for WHF in recent guidelines for HFrEF.[8,30] In the VICTORIA trial, the addition of vericiguat reduced the residual risk of cardiovascular death or HF hospitalization from 37.8 per 100 patient-years to 33.6 per 100 patient-years among patients already receiving guideline-directed medical therapy.[30]

FUTURE DIRECTIONS AND RECOMMENDATIONS

WHF remains under-recognized in trials and guidelines, with no consensus on definition, despite the high risk of poor outcomes associated with each worsening event. Recognizing the importance of WHF in clinical guidelines, establishing a biological definition, and designing trials targeting this high-risk patient population are unmet needs in HF management. The importance of post-WHF event management should be recognized to prevent further events. **Table 2** summarizes recommendations and future directions for optimizing management and research in WHF.

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