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EDITORIAL COMMENT

Worsening Heart Failure

Challenges as a Therapeutic Target*

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Worsening heart failure (WHF) has been proposed over the years as a clinically relevant endpoint in assessing therapies for acute decompensated heart failure (ADHF) (1). Although varied across different studies, WHF was often defined as "either failure to improve (persistent symptoms and signs of HF during treatment) or worsening symptoms and signs of HF, pulmonary edema, or cardiogenic shock after initial stabilization and treatment of at least 24 h any of which requires rescue therapy" (1). This short-term endpoint (often within 7 days of admission) parallels early reinfarction after myocardial infarction as an indicator of initial treatment failure (2). As such, WHF has been used as a component of a primary or secondary endpoint in many clinical trials testing both novel medications (3-7) and new methods for established therapies for ADHF (8-10) as summarized in **Table 1**. In this issue

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of *JACC: Heart Failure*, Davison et al. (11) added another analysis to this growing body of literature on WHF during treatment for ADHF. They retrospectively analyzed a pooled contemporary ADHF cohort to identify baseline predictors of WHF and its associated outcomes. As with the previous studies (1,12-15), respiratory status, increased neurohormonal activation, and other familiar (and some less familiar such as "Western-like country") baseline markers of clinical severity were found to be significant, but modest, predictors in a multivariable model for incident WHF (C-statistic: 0.67, 95% confidence interval: 0.65 to 0.70). After adjusting for baseline risk factors, laboratory values with their changes, and physical examination changes, WHF was associated with increased length of stay, cardiovascular death, or heart failure/renal failure rehospitalization by 60 days, and death by 180 days ($p < 0.0001$ for all). When stratified by treatment type—additional intravenous loop diuretic drugs or inotropes or mechanical therapies—WHF remained associated with death by 180 days. As with other studies, the investigators concluded that WHF is an important clinical event during the clinical course of ADHF that is not fully explained by baseline risk factors and can track with adverse outcomes after ADHF.

Any clinician that has cared for patients with ADHF will no doubt recall their daunting encounters with patients not improving after initial treatment and will relate to the often-haunted-by-downward-spiraling nature of their clinical courses as portrayed in these studies. So far, the relentless effort to establish WHF as a potential therapeutic target or clinical endpoint should be highly commended. Yet, as tempting as it is to believe the appealing nomenclature, overcoming the following challenges is necessary, in part due to the fundamental assumptions being made in the conception of WHF.

The first challenge is to understand exactly *what* WHF is. Currently, WHF is arbitrarily defined by the clinician's therapeutic decisions rather than an underlying biologic process. Though easily ascertained and readily documented, this assumes that clinicians are capable of providing accurate, reproducible, and timely prescription of advanced therapies on the basis of their subjective assessment. The reality is that defining WHF can be unclear and quite inconsistent given the wide array of local and regional practice patterns as well as diverse range of clinical expertise and subjective bedside

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TABLE 1 Studies Evaluating WHF as a Clinical Event

	First Author (Ref. #)	WHF Definition	Incident WHF, n/N (%)	Follow-Up Period	Endpoints	Predictors
Single center	Weatherley et al. (1)	WHF was defined as unresolved or recurrent symptoms and signs of HF that required an increase in or institution of intravenous HF-specific therapy, or institution of mechanical ventilatory or circulatory support.	99/337 (29)	7 days	Associated with 6-month mortality	NA
Pooled cohorts from small RCT	Torre-Amione et al. (14)	Occurrence of new pulmonary edema or cardiogenic shock (investigator-defined); in the first 24 h, no resolution of symptoms and signs of HF despite therapy; or worsening of symptoms and signs of HF despite therapy.	50/120 (42)	30 days	Associated with 6-month mortality	CO, MAP, CPO, CPO change, and pacemaker
PROTECT-pilot	Cotter et al. (13)	WHF was a pre-specified endpoint that was evaluated daily by the treating physician on the basis of evaluation of the history, physical examination, laboratory evaluations and patients' medical records for worsening symptoms and/or signs of HF.	29/305 (9.6)	7 days	Increased length of stay, 60-day mortality, cardiovascular/renal rehospitalization, and death or cardiovascular/renal rehospitalization	NA
ADHERE	DeVore et al. (12)	Initiated inotropic medications or an intravenous vasodilator more than 12 h after hospital presentation, transferred to the intensive care unit, or received advanced medical therapy after the first inpatient day.	7,032/63,727 (11)	During hospitalization	Increased 30-day and 1-year mortality, and increased 30-day and 1-year heart failure and all-cause readmissions	NA
VERITAS	McMurray et al. (3)	The development of pulmonary edema, cardiogenic shock, or other evidence of WHF or as lack of improvement in the patient's HF with treatment (treatment failure). Both definitions required at least 1 of the following: 1) initiation of new intravenous therapy; 2) reinstitution of previous intravenous therapy; 3) increase in current intravenous therapy for HF; 4) implementation of mechanical circulatory (e.g., intra-aortic balloon pump) or ventilatory (including continuous positive airway pressure) support; or 5) use of ultrafiltration, hemofiltration, or hemodialysis.	175/1,435 (12)	7 days	NA	NA
REVIVE I and II	Packer et al. (4)	If the patient died; experienced persistent or unresponsive symptoms of HF after the first 24 h of randomized therapy or WHF at any time during the first 5 days, which required a rescue intervention specifically to relieve such symptoms; or considered themselves to have moderately or markedly worsened on global assessment at 6 h, 24 h, or 5 days.	124/710 (17)	5 days	NA	NA

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assessments. Although attempts have been made to standardize this definition (13) to include both worsening signs and symptoms and requiring additional therapy, it is still a situational outcome, and like incident heart failure (16), WHF may occur differently depending on how patients present and how clinicians respond.

The second challenge lies with the lack of understanding of just *who* these patients might be. A corollary and often overlooked question is whether or not the clinical course leading to WHF is directly related to the ADHF admission or the intended treatment. Calling it "worsening" itself implies a clear progression of disease course despite standard pharmacological therapy (mainly in the form of diuretic therapy to relieve congestion) shortly after hospital admission for ADHF. Yet, in most cases, we simply do not have adequate knowledge or understanding of why WHF occurs and whether the deterioration is in any way related to the treatment. Unlike reinfarction after myocardial infarction, there is no uniform pathophysiological process(es) leading to WHF. It is

TABLE 1 Continued

	First Author (Ref. #)	WHF Definition	Incident WHF, n/N (%)	Follow-Up Period	Endpoints	Predictors
PROTECT	Massie et al. (5)	Worsening symptoms and signs of HF occurring more than 24 h after the initiation of the study drug requiring intervention by day 7 or discharge (if earlier).	189/2,033 (9.2)	3–7 days	NA	NA
RELAX-AHF	Teerlink et al. (7)	Defined as worsening signs or symptoms of HF necessitating intensification of intravenous or mechanical HF treatment.	157/1,161 (13)	5 days	NA	NA
DOSE-AHF	Felker et al. (8)	Defined as the need for rescue therapy (additional open-label loop diuretic, addition of thiazide, IV vasoactive agent for HF treatment, ultrafiltration, mechanical circulatory or respiratory support) over 72 h after randomization.	72/299 (24)	3 days	NA	NA
ROSE-AHF	Chen et al. (10)	Defined as the need for rescue therapy (additional intravenous vasoactive agent for HF treatment, ultrafiltration, or mechanical or respiratory support).	22/360 (6.1)	3 days	NA	NA

ADHERE = Acute Decompensated Heart Failure National Registry; CO = cardiac output; CPO = coproporphyrinogen oxidase; DOSE-AHF = Diuretic Optimization Strategies Evaluation in Acute Heart Failure; HF = heart failure; IV = intravenous; MAP = mean arterial pressure; NA = not applicable; PROTECT = A Study of the Selective A1 Adenosine Receptor Antagonist KW-3902 for Patients Hospitalized With Acute HF and Volume Overload to Assess Treatment Effect on Congestion and Renal Function; RCT = randomized controlled trial; RELAX-AHF = Efficacy and Safety of Relaxin for the Treatment of Acute Heart Failure; REVIVE = Evaluation of Intravenous Levosimendan Efficacy in the Short Term Treatment of Decompensated Heart Failure; ROSE-AHF = Renal Optimization Strategies Evaluation in Acute Heart Failure; VERITAS = Value of Endothelin Receptor Inhibition With Tezosentan in Acute Heart Failure; WHF = worsening heart failure.

also important to remember that incident WHF is associated with worse presenting symptoms, more respiratory compromise (e.g., lower oxygen saturation and higher respiration rate), worse renal function, and more neurohormonal activation (higher natriuretic peptide and blood urea nitrogen levels) (1,12–15). Furthermore, patients with WHF have more hemodynamic perturbations, as exemplified by lower mean arterial pressure, higher pulmonary capillary wedge pressure, and lower cardiac power output (14). As these features are commonly observed in advanced stages of HF, this begs the question regarding whether the clinical manifestations of WHF are indeed "new" or "recurrent" (akin to that of reinfarction), or whether these are simply persistent exacerbations and even pre-existed before admission. In other words, it is questionable whether the clinical deterioration depicted by WHF may have evolved with or without ADHF admission. None of the published studies can adequately dissect these possibilities.

The third challenge is the lack of appreciation of *how* WHF evolved in those experiencing WHF. Whereas WHF may be influenced by underlying disease severity, it may also be due to inappropriate treatment (either overzealous vs. insufficient) or a lack of appropriate or adequate treatment response. These may be important confounders that may in part help to explain why adverse outcomes occur beyond physiologic measures or traditional risk factors. Furthermore, if a specific intervention is to be tested to counter such clinical deterioration that leads to WHF, it has to be capable of targeting the very mediators that promote such adverse processes. Among such heterogeneity of ADHF phenotypes, we simply do not have a good sense whether a broad endpoint such as WHF can be altered by a single therapeutic intervention.

Theoretically it makes good sense to consider WHF as a potential therapeutic target and to pursue strategies to prevent such devastating clinical situations. It is a telling story when an intervention can prevent WHF. Unfortunately, the current concept of WHF defies simple definition and has no easily quantitative attributes. Indeed, the 3 challenges described herein remained largely unanswered despite the wealth of supportive studies. It is unlikely that the concept of WHF will be any better clarified by this or any future contributions in the form of post-hoc analyses or observational studies. We therefore need to step back and critically ask ourselves how much we truly understand the underlying biology of ADHF and the factors that precipitate WHF. These are necessary insights if we seek to develop better heart failure therapies and design successful clinical trials to demonstrate their effectiveness.

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REFERENCES

1. Weatherley BD, Milo-Cotter O, Felker GM, et al. Early worsening heart failure in patients admitted with acute heart failure–a new outcome measure associated with long-term prognosis? Fundam Clin Pharmacol 2009;23:633–9.

2. The GUSTO Investigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. N Engl J Med 1993;329:673–82.

3. McMurray JJ, Teerlink JR, Cotter G, et al., for the VERITAS Investigators. Effects of tezosentan on symptoms and clinical outcomes in patients with acute heart failure: the VERITAS randomized controlled trials. JAMA 2007;298:2009–19.

4. Packer M, Colucci W, Fisher L, et al. Effect of levosimendan on the short-term clinical course of patients with acutely decompensated heart failure. J Am Coll Cardiol HF 2013;1:103–11.

5. Massie BM, O'Connor CM, Metra M, et al., for the PROTECT Investigators and Committees. Rolofylline, an adenosine A1-receptor antagonist, in acute heart failure. N Engl J Med 2010;363:1419–28.

6. O'Connor CM, Starling RC, Hernandez AF, et al. Effect of nesiritide in patients with acute decompensated heart failure. N Engl J Med 2011;365:32–43.

7. Teerlink JR, Cotter G, Davison BA, et al., for the RELAX-AHF Investigators. Serelaxin, recombinant human relaxin-2, for treatment of acute heart failure (RELAX-AHF): a randomised, placebo-controlled trial. Lancet 2013;381:29–39.

8. Felker GM, Lee KL, Bull DA, et al., for the NHLBI Heart Failure Clinical Research Network. Diuretic strategies in patients with acute decompensated heart failure. N Engl J Med 2011;364:797–805.

9. Bart BA, Goldsmith SR, Lee KL, et al., for the Heart Failure Clinical Research Network. Ultrafiltration in decompensated heart failure with cardiorenal syndrome. N Engl J Med 2012;367:2296–304.

10. Chen HH, Anstrom KJ, Givertz MM, et al., for the NHLBI Heart Failure Clinical Research Network. Low-dose dopamine or low-dose nesiritide in acute heart failure with renal dysfunction: the ROSE acute heart failure randomized trial. JAMA 2013;310:2533–43.

11. Davison BA, Metra M, Cotter G, et al., on behalf of the PROTECT and RELAX-AHF Executive Committees. Worsening heart failure following admission for acute heart failure: a pooled analysis of the PROTECT and RELAX-AHF studies. J Am Coll Cardiol HF 2015;3:395–403.

12. DeVore AD, Hammill BG, Sharma PP, et al. In-hospital worsening heart failure and associations with mortality, readmission, and healthcare utilization. J Am Heart Assoc 2014;3. pii:e001088.

13. Cotter G, Metra M, Weatherley BD, et al. Physician-determined worsening heart failure: a novel definition for early worsening heart failure in patients hospitalized for acute heart failure–association with signs and symptoms, hospitalization duration, and 60-day outcomes. Cardiology 2010;115:29–36.

14. Torre-Amione G, Milo-Cotter O, Kaluski E, et al. Early worsening heart failure in patients admitted for acute heart failure: time course, hemodynamic predictors, and outcome. J Card Fail 2009;15:639–44.

15. Cotter G, Metra M, Davison BA, et al. Worsening heart failure, a critical event during hospital admission for acute heart failure: results from the VERITAS study. Eur J Heart Fail 2014;16:1362–71.

16. Zannad F, Stough WG, Pitt B, et al. Heart failure as an endpoint in heart failure and non-heart failure cardiovascular clinical trials: the need for a consensus definition. Eur Heart J 2008;29:413–21.

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