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Management of Worsening Heart Failure With Reduced Ejection Fraction

JACC Focus Seminar 3/3

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ABSTRACT

Despite worsening heart failure (HF) being extremely common, expensive, and associated with substantial risk of death, there remain no dedicated clinical practice guidelines for the specific management of these patients. The lack of a management guideline is despite a rapidly evolving evidence-base, as a number of recent clinical trials have demonstrated multiple therapies to be safe and efficacious in this high-risk population. Herein, we propose a framework for treating worsening HF with reduced ejection fraction with the sense of urgency it deserves. This includes treating congestion; managing precipitants; and establishing a foundation of rapid-sequence, simultaneous, and/or in-hospital initiation of quadruple medical therapy for HF with reduced ejection fraction, with the top priority being at least low doses of all 4 medications. Moreover, to maximally reduce residual clinical risk, we further propose consideration of upfront simultaneous use of vericiguat (ie, quintuple medical therapy) and administration of intravenous iron for those who are iron deficient. (J Am Coll Cardiol 2023;82:559–571) © 2023 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/).

Heart failure (HF) is a progressive disease characterized by periods of clinical stability disrupted by episodes of worsening signs and symptoms.[1-3] These episodes of worsening are recognized as a distinct phase in the natural history of the disease, termed worsening heart failure (WHF).[1-3] Nonetheless, despite WHF being common, expensive, and associated with substantially reduced

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ABBREVIATIONS AND ACRONYMS

ARNI = angiotensin receptor-neprilysin inhibitor

HF = heart failure

HFrEF = heart failure with reduced ejection fraction

IV = intravenous

MRA = mineralocorticoid receptor antagonist

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

SGLT2 = sodium-glucose cotransporter-2

WHF = worsening heart failure

survival, there remain no dedicated clinical practice guidelines for the specific management of these patients. Indeed, the concept of WHF was only recognized in practice guidelines for the first time with the 2021 update of the European Society of Cardiology guidelines, but neither a specific definition nor recommendations were provided.[4] Likewise, the 2022 American College of Cardiology/American Heart Association/Heart Failure Society of America HF guidelines newly referred to WHF as a potential trajectory among patients with Stage C (symptomatic) HF, but specific and dedicated management recommendations were not included.[5] Concurrently, the evidence base for treating WHF has evolved, and a number of recent clinical trials have demonstrated multiple therapies to be safe and efficacious in this high-risk population (Table 1). In this paper, we review the available evidence for the management of patients with worsening HFrEF and seek to provide practical recommendations for the contemporary medical management of these patients. A specific focus of this paper is pharmacotherapy for worsening HFrEF, and considerations outlined here are distinguished from discussions related to WHF with preserved ejection fraction or device- or procedural-based therapies.

HIGHLIGHTS

- Clinical practice guidelines do not specifically address management of patients with worsening HFrEF.
- Management of patients with worsening HFrEF should include simultaneous or rapid sequence initiation of the 4 classes of medications that form the cornerstones of therapy.
- To reduce residual risk, simultaneous use of vericiguat and intravenous iron should be considered.

DIAGNOSIS OF WHF

WHF is defined by escalating signs and symptoms of HF in patients with chronic HF, despite previously stable therapy.[1,3] This definition also requires the need for an urgent escalation of therapy, usually centered on administration of intravenous (IV) diuretic agents or escalation of oral diuretic agents.[3] Although WHF has historically been synonymous with HF hospitalization, it is now recognized that WHF can occur across the spectrum of inpatient or outpatient settings.[1,3] Recommendations regarding the diagnosis and initial evaluation of WHF are outlined in Table 2. Further details regarding the definition and epidemiology of WHF have been discussed elsewhere.[3]

MANAGEMENT OF CONGESTION

AVAILABLE CLINICAL TRIAL EVIDENCE. There are limited data informing in-hospital management of congestion, and there remains large variability across clinicians. However, based on available data from modestly sized clinical trials, the following recommendations can be made (Table 3, Figure 1):

1. Based on the DOSE (Diuretic Optimization Strategies Evaluation) trial of 308 patients hospitalized for HF, to optimally treat congestion among hospitalized patients, a starting daily IV dose of loop diuretic that is 2.5 times the chronic daily oral dose should be routinely considered.[6] Although the DOSE trial did not meet the primary endpoints, at 72 hours, benefits with the high-dose loop diuretic strategy on secondary endpoints included less dyspnea, higher proportion of patients free of congestion, more weight loss, more net volume loss, and greater reduction in N-terminal pro–B-type natriuretic peptide (NT-proBNP).[6] The high-dose strategy did modestly increase the risk of a transient worsening of kidney function of >0.3 mg/dL (23% vs 14%), but there was no significant difference in 60-day kidney function or clinical outcomes. In the DOSE trial, there were no significant differences in the efficacy or safety of continuous vs bolus dosing of IV diuretic agents.[6]
2. Apart from benefits on clinical outcomes and patient-reported health status, sodium-glucose cotransporter-2 (SGLT2) inhibitor therapy should be routinely considered as an early addition to background loop diuretic therapy to improve diuretic efficiency and facilitate decongestion for patients with worsening HFrEF. The EMPAG-HF (Empagliflozin in Acute Decompensated Heart Failure) trial (n = 60) found that addition of empagliflozin 25 mg daily to standard medical therapy for patients within 12 hours of hospital admission for HF resulted in a 25% relative increase in urine output over 5 days (median 10.8 L vs 8.7 L) and more pronounced decrease in NT-proBNP (−1,861 pg/mL vs −727 pg/mL), without affecting markers of kidney function or noted

safety concerns.[7] Likewise, the EMPA-RESPONSE-AHF (Effects of Empagliflozin on Clinical Outcomes in Patients With Acute Decompensated Heart Failure) trial (n = 80), suggested that initiation of empagliflozin 10 mg daily within 24 hours of hospital admission increased urine output (estimated difference +3.45 L) and was well tolerated.[8] The EMPULSE (Empagliflozin in Patients Hospitalized With Acute Heart Failure Who Have Been Stabilized) trial (n = 530) also found incremental weight loss and hemoconcentration with empagliflozin compared with placebo among patients hospitalized for HF.[9] In-hospital initiation of empagliflozin was safe and well tolerated, with numerically fewer adverse events with SGLT2 inhibitor than placebo.[10]

3. Early initiation of intravenous acetazolamide can be considered in addition to background loop diuretic therapy to improve diuretic efficiency and facilitate decongestion. This recommendation is based on the ADVOR (Acetazolamide in Decompensated Heart Failure with Volume Overload) trial (n = 519) of patients hospitalized for HF, where intravenous acetazolamide (500 mg daily for 3 days) plus standardized IV loop diuretic therapy increased the likelihood of successful decongestion at day 3 (42% of patients) compared with IV loop diuretic therapy alone (30% of patients).[11] With regard to safety, during the treatment phase, there was no significant excess in worsening kidney function, hypokalemia, or hypotension compared with placebo.[11] However, ADVOR excluded patients receiving SGLT2 inhibitor therapy, leaving uncertainty regarding the combined effects of both therapies.
4. Addition of hydrochlorothiazide to IV loop diuretic therapy may be considered to improve diuretic response and decongestion among patients with WHF. This recommendation is based on the CLOROTIC (Safety and Efficacy of the Combination of Loop with Thiazide-type Diuretics in Patients with Decompensated Heart Failure) trial (n = 230), where addition of daily hydrochlorothiazide (dose adjusted to estimated glomerular filtration rate) for 5 days lost more weight at 72 hours (coprimary endpoint) than placebo (−2.3 kg vs −1.5 kg).[12] However, safety concerns included significantly higher risks of worsening kidney function (46.5% vs 17.2%) and hypokalemia ≤3.0 mmol/L (40.6% vs 16.1%).[12]
5. The pragmatic TRANSFORM-HF (Torsemide Comparison With Furosemide for Management of Heart Failure) trial of patients hospitalized with HF demonstrated no significant difference in long-term risk of mortality or hospitalization with a postdischarge strategy of oral torsemide vs oral furosemide.[13] These results suggest that in routine management following a WHF event, attention is better directed toward ensuring appropriate loop diuretic dosing, rather than focus on a particular agent.

TREAT CONGESTION BEYOND SIGNS AND SYMPTOMS. At hospital discharge, many patients continue to have clinical evidence of congestion with the associated heightened risks of postdischarge mortality and WHF. In general, decongestive therapy should continue despite modest increases in serum creatinine, as such episodes of worsening kidney function have been repeatedly shown to have no adverse prognostic consequences in the setting of active decongestion. Patients with persistent clinical or hemodynamic congestion during or immediately following a WHF event warrant strong consideration of continued aggressive therapy, including escalation of GDMT and/or diuretic therapy, as tolerated.

PHARMACOLOGICAL THERAPY FOR WHF

Based on the totality of evidence, we propose a framework for the management of worsening HFrEF that is practical and has substantial potential to improve patient outcomes (**Table 4**, **Central Illustration**).

CONSIDERATIONS FOR GDMT. Efficacy and safety of quadruple medical therapy for worsening HFrEF. Comprehensive disease-modifying quadruple medical therapy ("4 pillars") with an angiotensin receptor-neprilysin inhibitor (ARNI), beta-blocker (BB), mineralocorticoid receptor antagonist (MRA), and SGLT2 inhibitor is foundational therapy for all eligible patients with HFrEF.[4,5] Aside from benefits toward reducing risk of WHF, each of these classes of medication are proven to reduce all-cause mortality. Specifically, the estimated cumulative effect of these 4 medications includes a 73% relative reduction in mortality over 2 years.[14]

Although many of the registration trials for the 4 foundational medications were conducted among outpatients with "stable" chronic HFrEF at baseline, multiple lines of evidence strongly support the efficacy and safety of the 4 pillars of GDMT generalizing to patients with worsening HFrEF.

1. First, complementary to large outcome trials for initial regulatory labeling, there exist multiple subsequent dedicated trials proving that the benefits of the quadruple medical therapies apply to stabilized patients with WHF. In the PIONEER-HF (Comparison of Sacubitril-Valsartan versus

TABLE 1 Recent Clinical Trials Inclusive of Patients With WHF

Clinical Trial	Study Drugs	Inclusion Criteria/ Number of Patients	Primary Endpoint and Duration	Primary Endpoint Result	Select Secondary or Exploratory Endpoint Results
PIONEER-HF	Sacubitril-valsartan vs enalapril	Patients with HFrEF who were hospitalized for ADHF (n = 881)	Change in NT-proBNP from baseline through wks 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 wks:* • 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	Ferric carboxymaltose (up to 24 wks) 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 wks	• Ferric carboxymaltose event rate: 57.2 per 100 patient-y Placebo event rate: 72.5 per 100 patient-y • 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	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 of 10.8 mo	• Vericiguat event rate: 33.6 per 100 patient-y Placebo event rate: 37.8 per 100 patient-y • HR: 0.90 (95% CI: 0.82-0.98); $P = 0.02$	*Hospitalization for HF* • Vericiguat event rate: 25.9 per 100 patient-y Placebo event rate: 29.1 per 100 patient-y • HR: 0.90 (95% CI: 0.81-1.00) *Cardiovascular Death* • Vericiguat event rate: 12.9 per 100 patient-y Placebo event rate: 13.9 per 100 patient-y • 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	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 during a median of 21.8 mo	• Omecamtiv mecarbil event rate: 24.2 per 100 patient-y Placebo event rate: 26.3 per 100 patient-y • HR: 0.92 (95% CI: 0.86-0.99); $P = 0.03$	*WHF Event* • Omecamtiv mecarbil event rate: 18.7 per 100 patient-y Placebo event rate: 20.3 per 100 patient-y • HR: 0.93 (95% CI: 0.86-1.00) *Cardiovascular Death* • Omecamtiv mecarbil event rate: 10.9 per 100 patient-y Placebo event rate: 10.8 per 100 patient-y • HR: 1.01 (95% CI: 0.92-1.11); $P = 0.86$

Continued on the next page

Enalapril on Effect on NT-proBNP in Patients Stabilized from an Acute Heart Failure Episode) trial among patients hospitalized for HFrEF, compared with enalapril, treatment with sacubitril/valsartan resulted in incremental lowering of NT-proBNP and, in exploratory analysis, reduced the relative risk of cardiovascular death or HF hospitalization by 42% over 8-week follow-up, with no excess in safety events.[15] In the EMPULSE trial among patients hospitalized for HF, compared with placebo, patients randomized to empagliflozin were 36% more likely to have a clinical benefit at 90 days (as defined by hierarchical composite of death, HF events, and change from baseline in Kansas City Cardiomyopathy Questionnaire).[16]

2. Second, many patients in the landmark cardiovascular outcome trials of quadruple medical therapies had a recent history of a WHF event. For example, in the PARADIGM-HF (Prospective Comparison of ARNI with ACEI to Determine Impact on

TABLE 1 Continued

Clinical Trial	Study Drugs	Inclusion Criteria/ Number of Patients	Primary Endpoint and Duration	Primary Endpoint Result	Select Secondary or Exploratory Endpoint Results
SOLOIST-WHF	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 during a median of 9 mo	• Sotagliflozin event rate: 51.0 per 100 patient-y Placebo event rate: 76.3 per 100 patient-y • HR:, 0.67; 95% CI: 0.52 to 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	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 per 100 patient-y Placebo event rate: 80.45 per 100 patient-y • 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)

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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 = Empagliflozin in Patients Hospitalized With Acute Heart Failure Who Have Been Stabilized; GALACTIC-HF = Global Approach to Lowering Adverse Cardiac Outcomes through Improving Contractility in Heart Failure; 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; PIONEER-HF = Comparison of Sacubitril-Valsartan versus Enalapril on Effect on NT-proBNP in Patients Stabilized from an Acute Heart Failure Episode; VICTORIA = VericiguaT Global Study in Subjects With Heart Failure With Reduced Ejection Fraction; WHF = worsening heart failure.

Global Mortality and Morbidity in Heart Failure) trial of sacubitril/valsartan, nearly 1 in 5 patients (19%) had a prior HF hospitalization within 3 months of trial screening.[17] In the EMPHASIS-HF (Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure) trial of eplerenone, 55% of participants had a HF hospitalization in the prior 6 months.[18] In the COPERNICUS (Carvedilol Prospective Randomized Cumulative Survival) trial of carvedilol, 65% of patients had a history of HF hospitalization in the 12 months before randomization, and some patients were hospitalized at the time of screening or randomization.[19]

3. Third, the relative benefits and safety of each of the quadruple medical therapies are consistent across the spectrum of underlying patient risk.[20,21] However, these consistent relative benefits are accompanied by larger absolute benefits and lower numbers needed-to-treat among those with extreme underlying baseline risk.[20,21]

Simultaneous, rapid sequence, or in-hospital initiation of quadruple medical therapy. Quadruple medical therapy should be initiated for all patients with worsening HFrEF who do not have absolute contraindications or proven intolerance, without delay.[5,22] This emphasis on prompt initiation should be translated to in-hospital initiation among stabilized patients who are hospitalized, and rapid sequence or simultaneous initiation of quadruple medical therapy among outpatients.[22] To maximize tolerability and the ratio of benefit to safety, the top priority should be to rapidly or simultaneously initiate at least low doses for BB, ARNI, and MRA, understanding there is only a single dose for SGLT2 inhibitor (10 mg daily). Although shared decision-making with patients is critical, it is important to recognize that there is no evidence that routinely delaying initiation of any pillar of quadruple medical therapy accomplishes anything beneficial, including no evidence that it improves overall medication tolerability (**Figure 2**). Rather, there is strong evidence supporting simultaneous or rapid sequence optimization of quadruple therapy, as follows (**Figure 3**):

1. *Benefits of each therapy appear early after initiation:* For each of the 4 pillars, clinical event curves for death and WHF diverge within days to weeks following initiation.[22] For example, in EMPEROR-Reduced (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and Reduced Ejection Fraction), empagliflozin achieved a statistically significant 58% relative reduction in death, hospitalization for HF, or urgent HF visit at just

TABLE 2 Key Points and Summary Recommendations for Diagnosis and Evaluation of WHF

Diagnosis
• WHF is defined by escalating signs and symptoms of HF in a patient with established chronic HF, despite previously stable therapy. At present, this definition also requires the need for an urgent escalation of therapy, usually centered on administration of IV diuretic agents or escalation of oral diuretic agents.
• WHF is independent from the location of care and can occur across the spectrum of inpatient or outpatient settings.
• Apart from history and physical examination, measurement of natriuretic peptide concentration and comparison with prior values can be useful in diagnosing or confirming WHF.
Initial Evaluation and Triage
• Key priorities include the following: 1) address respiratory and hemodynamic stability; 2) treat signs and symptoms of congestion; and 3) identify and manage precipitants.
• Patients with WHF and stable hemodynamic and respiratory status may be considered for outpatient management at select centers.
• Every effort should be made to understand the precipitant of WHF, but many patients may have no clearly identifiable trigger for clinical worsening.
• Irrespective of whether an immediate precipitant is discovered, nonuse or underdosing of GDMTs proven to prevent WHF should be considered an overarching precipitant of a WHF event.

Abbreviations as in Table 1.

12 days following medication initiation.[23] Delaying initiation of any of these 4 medications in an eligible patient (whether defined by discharging an eligible patient from the hospital without therapy or delaying any medication several weeks to months between outpatient clinic visits) equates to needless exposure to excess clinical risk.[24]

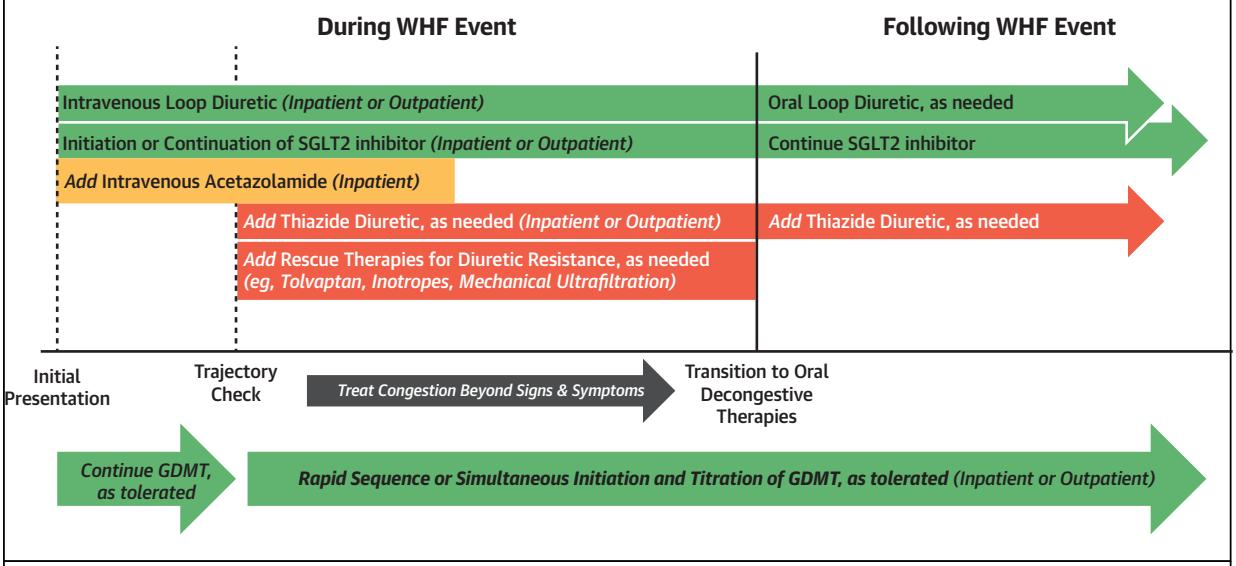
2. *Benefits of each therapy are fully additive:* All 4 of the foundational disease-modifying medications offer consistent incremental reductions in death and hospitalization irrespective of background therapy. Although the pros and cons of different sequencing strategies for the 4 therapies have been debated, specific sequencing is much less relevant with the compressed timelines recommended with simultaneous or rapid sequence initiation of all 4 therapies.[22] Importantly, it is key to recognize that low doses of GDMT provide major clinical benefits, and that timing of the early separation of event curves in the respective clinical trials coincided with patients receiving low starting doses of BB, ARNI, and MRA.
3. *Therapies may maximize tolerance of each other:* Simultaneous or rapid sequence initiation may better enable tolerance to the full set of quadruple medical therapies.[22] For example, switching an angiotensin-converting enzyme (ACE) inhibitor to ARNI decreases the risk of hyperkalemia and MRA discontinuation.[25] Likewise, SGLT2 inhibitor therapy prevents hyperkalemia, slows progression of renal disease, and reduces risk of MRA discontinuation.[26]
4. *Rapid sequence initiation of medications is routine in other common diseases:* Patients hospitalized with acute MI and new-onset left ventricular dysfunction are routinely initiated on 5 to 6 new medications over a typical 2- to 4-day hospitalization in the United States. Aside from statin, aspirin, and $P2Y_{12}$ inhibitor medications, therapies include ACE inhibitor, BB, and MRA therapy before discharge. Likewise, for patients with type 2 diabetes, hyperlipidemia, and hypertension, there are numerous combination drug formulations available and routinely used, including many where the specific agents exert complementary effects toward safety and tolerability (eg, hydrochlorothiazide-lisinopril and potassium balance). Yet, despite patients with worsening HFrEF having risks of death and hospitalization orders of magnitude higher than populations with acute MI and these other conditions, there is often hesitancy toward quickly initiating even low doses of multiple disease-modifying therapies at once or in rapid sequence.[16] This hesitancy exists despite large real-world populations of patients with WHF having median systolic blood pressure >120 mm Hg and estimated glomerular filtration rate >50 mL/min/1.73 m^2.[16]
5. *Deferring initiation of GDMT is associated with never initiation or substantial delay:* Data from routine clinical practice have repeatedly shown that changes in baseline GDMT are relatively rare among patients with chronic HFrEF, whether during longitudinal outpatient follow-up, during hospitalizations, or following WHF events.[16,27] Among patients hospitalized for HFrEF in U.S.

TABLE 3 Key Points and Summary Recommendations for Management of Congestion in WHF

• There are limited randomized trial data informing best practices for treatment of congestion and use of diuretic agents for WHF.
• Intravenous loop diuretic therapy is foundational therapy for decongestion. High doses (2.5× chronic daily oral dose) should be considered to improve the rate of decongestion.
• SGLT2 inhibitor therapy should be used in conjunction with loop diuretic therapy to improve short-term diuretic efficiency and decongestion, as well as clinical and patient-reported outcomes.
• Intravenous acetazolamide can be considered to improve diuretic efficiency and facilitate decongestion.
• Thiazide diuretic agents may be considered to improve diuretic efficiency and facilitate decongestion, but safety concerns include higher risk of worsening kidney function and hypokalemia.
• Furosemide, torsemide, or bumetanide are all reasonable oral loop diuretic options for the routine management of signs and symptoms of congestion following a WHF event. Appropriate dosing of loop diuretic agent is more important than routine use of a particular agent. However, for patients with refractory congestion or diuretic resistance on high-dose furosemide, switching to an oral loop diuretic with greater bioavailability (ie, torsemide, bumetanide) may be considered.

SGLT2 = sodium glucose co-transporter 2; WHF = worsening heart failure.

FIGURE 1 Approach to Decongestive Therapy for WHF



Intravenous loop diuretic and sodium-glucose cotransporter-2 (SGLT2) inhibitor are foundational therapies for decongestion among patients with worsening heart failure (WHF). Other adjunctive diuretic therapies can be considered in select patients. GDMT = guideline-directed medical therapy.

clinical practice and eligible for therapy, deferring in-hospital initiation of a given GDMT is associated with >75% chance therapy will not be started within the next year.[28]

6. *STRONG-HF provides direct randomized trial evidence supporting a routine approach of rapid sequence or simultaneous initiation and titration of GDMT for patients hospitalized for HF:* In 2022, the publication of the STRONG-HF (Safety, Tolerability and Efficacy of Rapid Optimization, Helped by NT-proBNP Testing, of Heart Failure Therapies) provided, for the first time, direct randomized clinical trial evidence that a routine strategy of simultaneous or rapid sequence initiation and titration of multiple GDMTs for patients hospitalized for HF is efficacious, safe, and well tolerated.[29] As compared with usual care, high-intensity simultaneous initiation and titration resulted in significantly greater use of ACE inhibitor/angiotensin receptor blocker (ARB)/ARNI (97.3% vs 73.4%) and BB (95.8% vs 54.2%) at 6-month follow-up. Likewise, patients randomized to high-intensity care were significantly more likely to achieve target doses (ACE inhibitor/ARB/ARNI 51.3% vs 2.3%; BB 45.0% vs 5.1%; MRA 88.3% vs 62.7%).[29] Despite these substantial differences in use and dosing of GDMT between study arms, there were no significant differences in the rate of serious adverse events.

STRONG-HF was terminated early by the data safety and monitoring board because of overwhelming efficacy. High-intensity care demonstrated a 34% relative risk reduction in the primary endpoint of 180-day death or HF readmission. This translated to a large absolute risk reduction of 8.1% (number-needed-to-treat over 6 months: 12).[29] Clinically and statistically significant benefits were seen across a

TABLE 4 Key Points and Summary Recommendations for Pharmacological Therapy for WHF

- Quadruple medical therapy (ARNI, BB, MRA, SGLT2 inhibitor), titrated to maximally tolerated or target doses, is foundational therapy for all eligible patients with worsening HFrEF (as tolerated) to extend survival, reduce hospitalizations, and improve patient-reported outcomes.
- Rapid sequence or simultaneous initiation of quadruple medical therapy is an evidence-based strategy to improve clinical and patient-reported outcomes, and overall medication use, following a WHF event.
- Early upfront use of vericiguat should be considered among patient with WHF, in combination with simultaneous/rapid sequence optimization of quadruple medical therapy as tolerated, to further reduce residual risk of adverse clinical outcomes (ie, quintuple medical therapy). Alternatively, it is also reasonable to initially optimize quadruple medical therapy alone in response to a WHF event, and reserve vericiguat for a subsequent WHF event despite optimal quadruple medical therapy.
- Early upfront use of vericiguat should be considered among patients with WHF who have contraindications or intolerance to 1 or more of the quadruple medical therapies.
- Intravenous iron should be administered to patients with iron deficiency to improve functional status and patient-reported outcomes, and reduce residual risk of HF hospitalization despite background quadruple or quintuple medical therapy.

ARNI = angiotensin receptor-neprilysin inhibitor; BB = beta-blocker; EF = ejection fraction; GDMT = guideline-directed medical therapy; MRA = mineralocorticoid receptor antagonist; SGLT2 = sodium-glucose cotransporter-2; WHF = worsening heart failure.

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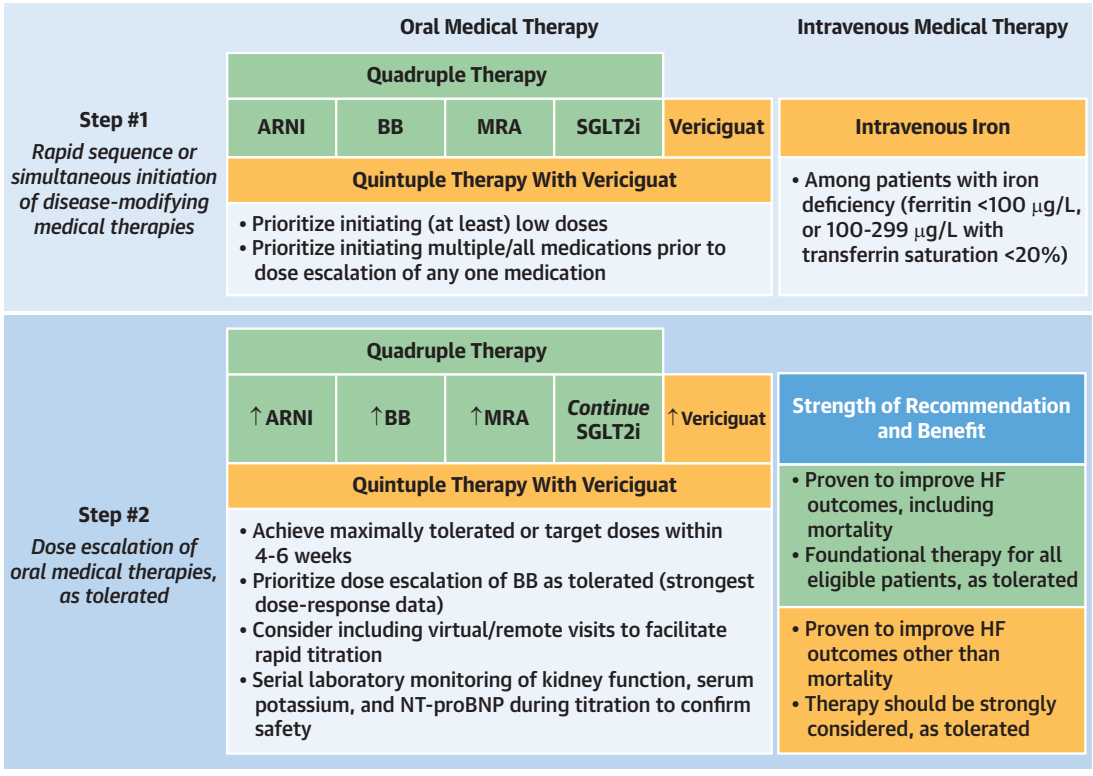
CENTRAL ILLUSTRATION **Medical Therapy for Worsening Heart Failure With Reduced Ejection Fraction**



Greene SJ, et al. J Am Coll Cardiol. 2023;82(6):559-571.

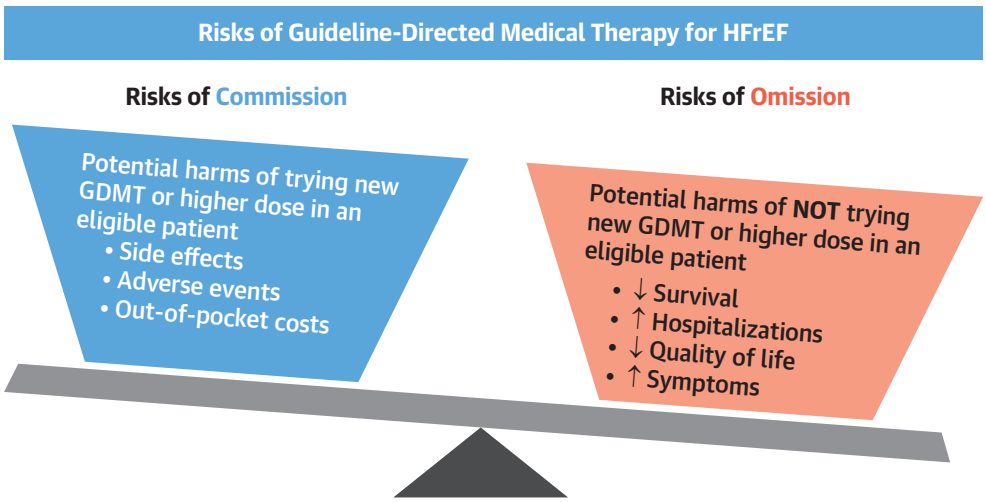
Quadruple medical therapy is foundational for all eligible patients with worsening heart failure with reduced ejection fraction (HFrEF) as tolerated, but additional therapies (vericiguat, intravenous [IV] iron) can be strongly considered to reduce residual clinical risk. Angiotensin-converting enzyme (ACE) inhibitor/angiotensin receptor blocker (ARB) is strongly recommended when use of angiotensin receptor-neprilysin inhibitor (ARNI) is not feasible. BB = beta-blocker; MRA = mineralocorticoid receptor antagonist; NT-proBNP = N-terminal pro–B-type natriuretic peptide; SGLT2i = sodium-glucose cotransporter-2 inhibitor.

spectrum of additional endpoints, with high-intensity care improving patient-reported health status, improving NYHA functional class, reducing clinical congestion, and incrementally reducing NT-proBNP. Limitations of STRONG-HF should be acknowledged, including no enrollment from North America and minimal use of SGLT2 inhibitors during the trial. Yet, routine inclusion of SGLT2 inhibitors would be expected to only further magnify the benefits of high-intensity care.

ADDITIONAL MEDICATIONS FOR WHF

Vericiguat, a soluble guanylate cyclase stimulator, has been approved for treatment of symptomatic chronic HF with ejection fraction <45% following a WHF event to reduce the risk of cardiovascular death and HF hospitalization. This approval was based on the results of the VICTORIA trial, where vericiguat reduced the relative risk of this endpoint by 10% among a population that had been hospitalized for HF in the preceding 6 months or received outpatient IV diuretic agents in the preceding 3 month despite high background use of GDMT.[30] Given the underlying high baseline risk of the worsening HFrEF population enrolled in VICTORIA, the modest relative risk reduction equated to a large annualized absolute risk reduction of 4.2%.[31] Vericiguat was also safe and well tolerated, with no significant effect on electrolytes or kidney function, little initial effect on blood pressure, and numerically fewer adverse events than placebo. Based on this collective efficacy and safety, vericiguat

FIGURE 2 **Contextualizing Risks and Shared Decision Making Regarding GDMT for HFrEF**



To make informed decisions, clinicians and patients need to be aware of both the risks of trying and not trying to escalate guideline-directed medical therapy (GDMT). Adapted and modified with permission from Greene and DeVore.[40] HFrEF = heart failure with reduced ejection fraction.

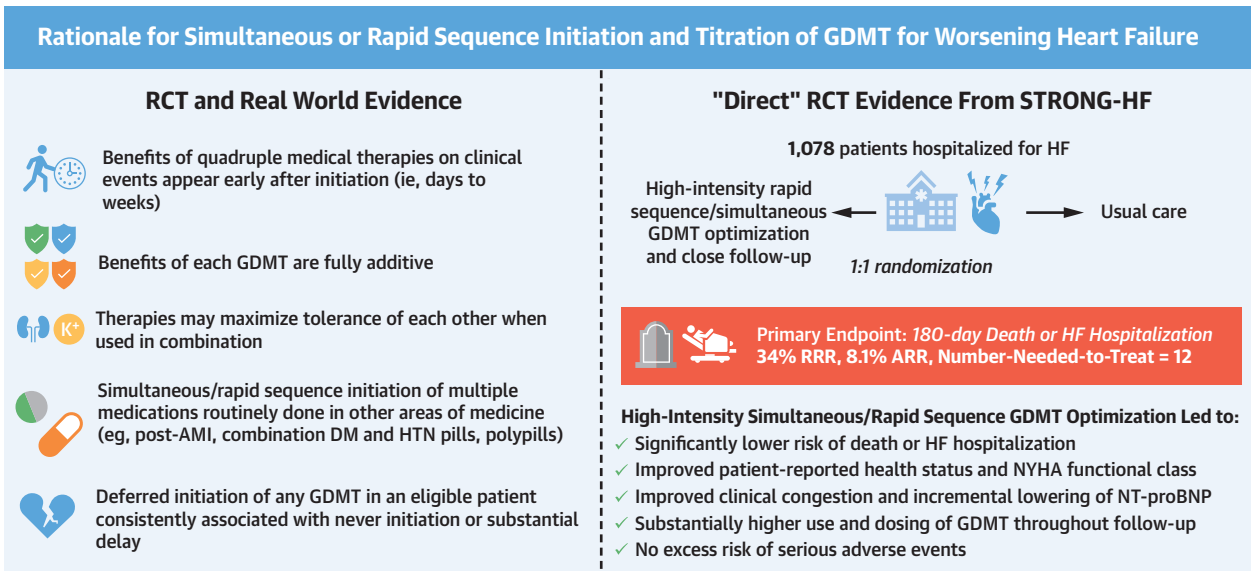
received a Class IIb recommendation in HF practice guidelines for consideration among patients with worsening HF despite background GDMT.[4,5]

QUINTUPLE MEDICAL THERAPY FOR WHF. Patients with worsening HFrEF face high residual risk of adverse clinical events, even with optimal treatment with quadruple medical therapy. For example, despite high background use of renin-angiotensin-system inhibitors, MRAs, and BB in EMPEROR-Reduced, patients randomized to empagliflozin experienced a rate of cardiovascular death or HF hospitalization of 15.8 per 100 patient-years, with absolute event rates even higher among those with a recent worsening HFrEF event (**Figure 4**).[32] Thus, despite excellent background treatment, the importance of additional therapies such as vericiguat that are well tolerated, safe, and reduce HF hospitalization should not be discounted.[30,33] Indeed, HF hospitalization is a consistent marker of disease progression, associated with step-wise declines in patient-reported health status, and equates to substantial patient time spent away from home. Likewise, prevention of HF hospitalization has been a consistent target for quality improvement across health systems, with HF hospitalizations accounting for substantial health care expenditure and driving HF as the costliest of common comorbidities.[34]

Given the high risks of mortality and morbidity among patients with worsening HFrEF, as well as the persistent residual risk despite quadruple therapy, use of vericiguat as an adjunct to quadruple medical therapy may be considered. The clinical trial evidence would suggest that this approach of "quintuple therapy" would maximally treat worsening HFrEF with every available oral medical therapy proven to be effective, thus treating this high-risk patient population with the sense of urgency it deserves.

As a practical consideration, patients already receiving quadruple medical therapy commonly receive subtarget doses, and key questions will involve whether to prioritize uptitration of existing medication vs initiation of vericiguat. Although randomized trial evidence shows dose-response clinical benefits with BB titration, the incremental benefits of low-dose vs high-dose ACE inhibitor/ARB therapy in dedicated dosing RCTs are modest.[35-37] Moreover, there are no such randomized trials comparing high vs low doses of ARNI and MRA. At the same time, the benefits of vericiguat on composite cardiovascular mortality or HF hospitalization appear generally consistent irrespective of background use and dose of GDMT, and benefits are additive. Thus, although simultaneous or rapid sequence initiation and escalation toward target doses of (at least) quadruple medical therapy as tolerated should continue to remain the goal for all eligible patients with HFrEF, it is unclear whether dose escalation of ARNI or MRA, vs initiation of vericiguat, offers greater clinical risk reduction. Thus, initiation of vericiguat before

FIGURE 3 Simultaneous or Rapid Sequence Optimization of GDMT for WHF



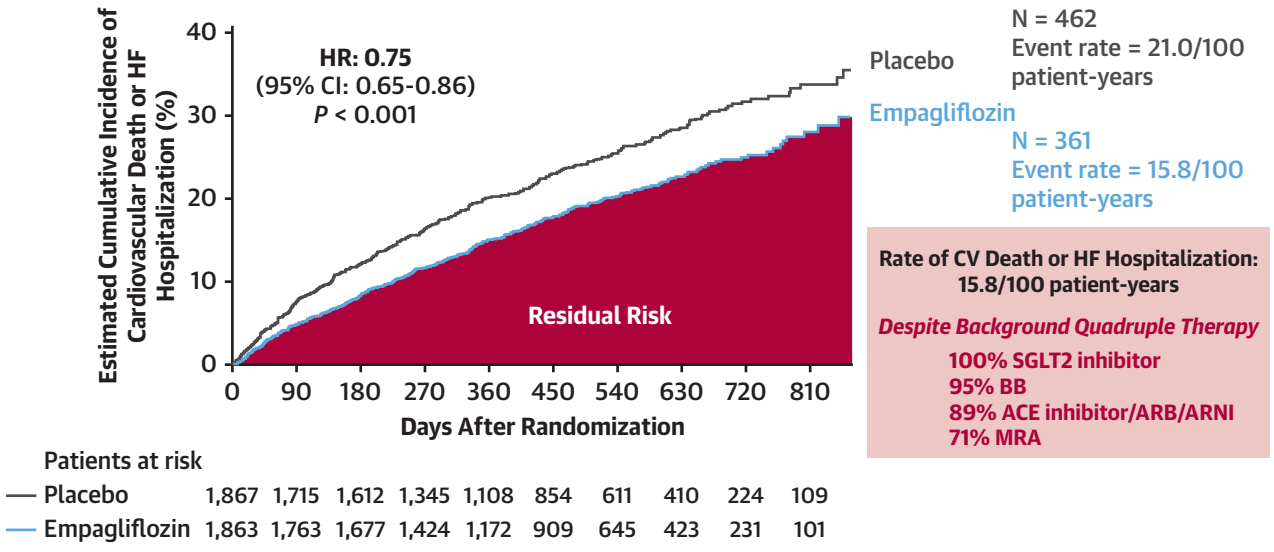
There is strong evidence from randomized clinical trials (RCTs) and real-world evidence supporting the efficacy, safety, and tolerability of simultaneous or rapid sequence initiation and titration of GDMT for WHF. AMI = acute myocardial infarction; ARR = absolute risk reduction; DM = diabetes mellitus; HTN = hypertension; RRR = relative risk reduction; other abbreviations as in Figure 1.

reaching target doses of ARNI and MRA, or initiation of vericiguat simultaneously with dose escalation of these therapies, may be considered. Further randomized trials are needed among patients on subtarget doses of baseline GDMT to definitively compare a strategy of "up-front" early initiation of vericiguat simultaneously with rapid optimization of quadruple therapy as tolerated ("quintuple therapy") vs rapid optimization of quadruple medical therapy alone. For now, clinicians should use judgment when deciding between these 2 approaches.

Although the scientific evidence can make the case for aggressive use of quintuple therapy for patients with worsening HFrEF, out-of-pocket patient costs and insurance coverage for vericiguat, combined with the other newer therapies (ie, ARNI and SGLT2 inhibitor), are barriers to this approach for select patients. In practice, initiating and up-titrating foundational quadruple therapy first and awaiting a second episode of worsening HFrEF (ie, an event "breaking through" optimized quadruple therapy) before initiating vericiguat is also a reasonable approach, though in principle, considering the residual risk on quadruple therapy and the further worsening of prognosis with each hospitalization, upfront therapy with vericiguat may be considered. It is also sensible to consider early upfront use of vericiguat among patients who have contraindications or intolerance to 1 or more of the foundational quadruple medical therapies.

INTRAVENOUS IRON THERAPY. In both the American College of Cardiology/American Heart Association/Heart Failure Society of America and European Society of Cardiology HF guidelines, intravenous iron replacement is recommended for patients with HFrEF and concomitant iron deficiency to improve functional status and patient-reported quality of life (Class IIa).[4,5] This recommendation was based on the FAIR-HF (Ferinject Assessment in Patients with Iron Deficiency and Chronic Heart Failure) (n = 459) and CONFIRM-HF (Ferric Carboxymaltose Evaluation on Performance in Patients with Iron Deficiency in Combination with Chronic Heart Failure) (n = 304) trials, both of which found IV administration of ferric carboxymaltose to improve patient global assessment, NYHA functional class, and 6-minute walk distance.[38] Subsequently, clinical benefits and safety of IV iron were proven to generalize to patients hospitalized for newly diagnosed or worsening chronic HFrEF in the AFFIRM-AHF (A Randomised, Double-blind Placebo Controlled Trial Comparing the Effect of Intravenous Ferric Carboxymaltose on Hospitalizations and Mortality in Iron Deficient Subjects Admitted for Acute Heart Failure) trial (n = 1,132), where over 52-week follow-up, ferric carboxymaltose therapy yielded a statistically borderline reduction

FIGURE 4 Residual Risk in HFrEF Despite Quadruple Medical Therapy



Given high rates of background therapy in the trial, patients randomized to empagliflozin in EMPEROR-Reduced provide an estimate of the residual risk of HFrEF, despite quadruple medical therapy. Reused with permission from Packer et al.[32] ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor-neprilysin inhibitor; CV = cardiovascular; other abbreviations as in Figures 1 and 2.

(which became statistically significant in prespecified sensitivity analysis account for COVID pandemic) in total HF hospitalization or CV death (rate ratio [RR]: 0.79; 95% CI: 0.62-1.01; $P = 0.059$), and a significant reduction in total HF hospitalizations (RR: 0.74; 95% CI: 0.58-0.94; $P = 0.013$) that were incremental to background oral GDMT.[39] Ferric carboxymaltose also afforded significant improvements in health-related quality of life, with the effect manifesting within 4 weeks following initiation of therapy. Based on these collective data, the ESC HF guidelines include a second recommendation for use of IV ferric carboxymaltose among patients hospitalized for HF and EF<45% with iron deficiency to reduce the risk of HF hospitalization (Class IIa).[4]

Like the rationale for quintuple medical therapy, there is a clear rationale for routine use of IV iron supplementation as part of an aggressive upfront treatment approach for patients with worsening HFrEF to maximally reduce clinical risk. Moreover, as a matter of practicality, patients hospitalized with worsening HFrEF or receiving outpatient IV diuretic agents already have IV access, which may further facilitate implementation of IV iron for worsening HFrEF in clinical practice.

CONCLUSIONS

Herein, we propose a framework for treating worsening HFrEF with the sense of urgency it deserves. This includes ensuring treatment of congestion while establishing a foundation of rapid-sequence, simultaneous, or in-hospital initiation of quadruple medical therapy for HFrEF, with the top priority being at least low doses of all 4 medications. However, to maximally reduce residual clinical risk, we further propose upfront simultaneous use of vericiguat (ie, quintuple medical therapy), administration of IV iron for those who are iron deficient, and aggressive treatment of clinical and hemodynamic congestion. Although cost and patient access to medications may be barriers for select patients, the totality of available scientific evidence supports the clinical community doing everything possible to follow an aggressive treatment approach for worsening HFrEF that removes or minimizes delays with initiation of therapy. Indeed, improving outcomes for patients with worsening HFrEF and preventing subsequent WHF events is likely to be the most efficient, efficacious, and cost-effective strategy for addressing the overall public health and economic burden of HF.

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